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Oily fish intake during pregnancy – association with lower hyperactivity but not with higher full-scale IQ in offspring

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Background: Long-chain omega-3 polyunsaturated fatty acids are thought to be important for fetal neurodevelopment. Animal studies suggest that a deficiency of omega-3 fatty acids may lead to behavioural or cognitive deficits. As oily fish is a major dietary source of omega-3 fatty acids, it is possible that low intake of fish during pregnancy may have adverse effects on the developing fetal brain. **Methods:** We used the Strengths and Difficulties Questionnaire and the Wechsler Abbreviated Scale of Intelligence to assess behavioural problems and intelligence in 217 nine-year-old children. The mothers of these children had participated in a study of nutrition during pregnancy during which fish intake was assessed in early and late gestation. **Results:** Children whose mothers had eaten oily fish in early pregnancy had a reduced risk of hyperactivity compared to those whose mothers did not eat oily fish: OR .34, 95% CI .15 to .78, after adjustment for potential confounding factors. Children whose mothers had eaten fish (whether oily or non-oily) in late pregnancy had a verbal IQ that was 7.55 points higher (95% CI .75 to 14.4) than those whose mothers did not eat fish. There were, however, no significant associations between fish intake in pregnancy and other behavioural problems or full-scale and performance intelligence, after adjustment for potential confounding factors. **Conclusions:** Although maternal fish intake in pregnancy was associated with hyperactivity scores and verbal IQ in children, in general, how much fish women ate during pregnancy appeared to have little long-term relation with neurodevelopmental outcomes in their child. **Keywords:** Intelligence, behaviour problems, diet, pregnancy, fish intake, hyperactivity, omega-3 fatty acids, nutrition, pre-natal.

Essential fatty acids, the omega-6 cis-linoleic acid (LA) and the omega-3 alpha-linolenic acid (ALA), are found in all cell membranes, along with their long-chain metabolites, arachidonic acid, derived from LA, and eicosapentaenoic acid and docosahexaenoic acid, derived from ALA (Das, 2006). As humans, together with other mammals, lack the enzymes needed to synthesise essential fatty acids, LA and ALA have to be obtained from the diet, primarily from unsaturated vegetable oils (Innis, 2007b). Humans and animals are able to convert LA to arachidonic acid (AA) and ALA to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Consequently, animal tissues are a major source of these long-chain metabolites: meat and egg yolks contain substantial amounts of AA (Bezard, Blond, Bernard, & Clouet, 1994), and fish, particularly oily fish, is by far the richest source of EPA and DHA (Scientific Advisory Committee on Nutrition (SACN), 2004). Humans convert less than 1% of dietary ALA into DHA (Goyens, Spilker, Zock, Katan, & Mensink, 2006), so a good dietary source of DHA may be essential if the body's needs for this fatty acid are to be met. This may be of particular relevance during pregnancy. All omega-6 and omega-3 fatty acids play a crucial role in regulating cell membrane function, influencing membrane lipid-protein interactions and facilitating inter- and intra-cellular signalling (Das, 2006; Innis, 2007b), but DHA appears to be of special importance for the developing brain (Innis, 2007a).

DHA is the principal omega-3 fatty acid in mammalian brain tissue, making up 10–20% of total fatty acid composition (McNamara & Carlson, 2006). The amount of DHA in the brain rises sharply during gestation in periods of neurogenesis, neuroblast migration and differentiation, synaptogenesis and axonal myelination (Green & Yavin, 1996; Schiefermeier & Yavin, 2002). Rats whose mothers were deficient in DHA during pregnancy show markedly lower concentrations of cortical DHA (McNamara & Carlson, 2006). This deficiency of DHA has adverse effects on the developing brain as regards neurogenesis (Coti, O'Kusky, & Innis, 2006), nerve growth factor expression, dendritic arborisation (Calderon & Kim, 2004; Ikemoto et al., 2000), and the expression of genes that are involved in synaptic plasticity, the cytoskeleton, and ion channel formation (Kitajka et al., 2004). There is also evidence that deficiency of DHA may cause changes in serotonin and dopamine neurotransmission (Kodas et al., 2004; Zimmer et al., 2000). Consistent with these findings, rats that experience a deficit in brain

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accrual of DHA during gestation are more likely to show problems with learning, memory, attention and emotion and display increased locomotor activity (Fedorova & Salem, Jr., 2006; Moriguchi, Greiner, & Salem, Jr., 2000; McCann & Ames, 2005).

But while the evidence from animal and in vitro studies confirms the importance of DHA accrual during gestation for neurodevelopment and function (Innis, 2007a), studies in humans have yet to establish whether the amount of DHA mothers obtain from their diet in pregnancy has any long-term influence on neurodevelopment in their offspring. There is evidence that the quantity of DHA in the mother's diet affects how much DHA is transferred via the placenta to the fetus (Innis, 2005) and data from randomised controlled trials show that supplementing mothers with fish oil during the last trimester results in higher concentrations of omega-3 fatty acids in umbilical cord blood (Velzing-Aarts et al., 2001; Krauss-Etschmann et al., 2007). Only a few randomised controlled trials of DHA supplementation during pregnancy have been published (Eilander, Hundscheid, Osendarp, Transler, & Zock, 2007). Two trials found that supplementation had no benefit as regards visual function or scores on Bayley Scales of Infant Development in the first year of life (Tofail et al., 2006; Malcolm, McCulloch, Montgomery, Shepherd, & Weaver, 2003). One trial found that babies of mothers who were supplemented scored significantly higher on a test of problem solving at age 9 months, though supplementation was not associated with performance on recognition memory tasks (Judge, Harel, & Lammi-Keefe, 2007). In a trial in which women were supplemented during pregnancy and lactation, there was a similar lack of association between maternal supplementation and recognition memory at 6 or 9 months of age (Helland et al., 2001), but follow-up of a subset of these children showed that by 4 years of age, those whose mothers had received the cod liver oil supplement during pregnancy and lactation had a significantly higher IQ (Helland, Smith, Saarem, Saugstad, & Drevon, 2003). Whether this effect was due to supplementation during gestation or lactation or both is unclear, but the findings of this study are at least partially consistent with those of the Avon Longitudinal Study of Parents and Children (ALSPAC). In this observational study, children whose mothers ate more seafood during pregnancy scored higher on tests of verbal, though not performance, IQ at age 8 years (Hibbeln et al., 2007).

No randomised controlled trials have examined whether maternal supplementation with DHA during pregnancy influences risk of behavioural problems in children, but there is evidence that mothers with higher red blood cell DHA concentrations at delivery have children who perform better on attention tasks in infancy and are less distractable at age 2 years (Colombo et al., 2004). In the only observational study to have examined the relation, risk of hyperactivity was lower in children in the ALSPAC cohort whose mothers had higher intakes of seafood during pregnancy, but the association ceased to be significant after adjustment for potential confounding factors (Hibbeln et al., 2007).

We investigated the relation between maternal consumption of fish during pregnancy and behavioural and cognitive outcomes in a cohort of children aged around 9 years whose mothers had taken part in a study of nutrition during pregnancy (Godfrey, Robinson, Barker, Osmond, & Cox, 1996). We hypothesised that as oily fish is particularly rich in omega-3 fatty acids (Scientific Advisory Committee on Nutrition (SACN), 2004), maternal intake of this type of fish might be more strongly associated with neurodevelopmental outcomes in the child than intake of fish overall. Fetal exposure to higher levels of omega-3 fatty acids may be particularly important in the last trimester of pregnancy, as this is a period when brain growth is at peak velocity and the need for DHA accrual is high (Clandinin et al., 1980; Levitt, 2003), though DHA is also involved in neurogenesis which is complete by 16 weeks. We therefore examined whether the relation between maternal fish consumption and child outcomes varied according to fish intake in early or late pregnancy.

Methods

In 1991–2 Caucasian women aged ≥16 years with singleton pregnancies of <17 weeks' gestation were recruited at the midwives' antenatal booking clinic at the Princess Anne Maternity Hospital in Southampton, UK; diabetics and those who had undergone hormonal treatment to conceive were excluded (Godfrey, Robinson, Barker, Osmond, & Cox, 1996). In early (15 weeks' gestation) and late (32 weeks' gestation) pregnancy, we administered a lifestyle questionnaire to the women that included questions about their smoking and alcohol habits. A food frequency questionnaire (FFQ) was administered which assessed frequency of consumption of 100 foods or food groups in the three preceding months. Participants were asked to indicate how often they ate a) white fish (grilled, poached, steamed, in crumbs or batter), b) fish pie, fish fingers, fish in sauces, c) oily fish (e.g. tuna, sardines, trout, salmon, mackerel) and d) shell fish (e.g. crab, prawns, mussels). Each response was chosen from 8 pre-defined categories: Never; once every 2–3 months; once a month; once a fortnight; 1–2 times per week; 3–6 times per week; once a day; more than once a day. Data were also collected on the women's parity, their highest educational qualifications and their most recent occupation. Anthropometric data on the child were collected at birth. Gestational age was estimated from menstrual history and scan data. Five hundred and fifty-nine children were followed up at age 9 months when data on infant feeding were recorded.

When these 559 children approached their 9th birthday, we asked the Community Paediatric Service in Southampton to write to their parents with an invitation to take part in a further follow-up study. All the children in the cohort had previously been flagged on the Service's child health computer. Letters were sent to all 461 families who were still living in the Southampton area. In total, 226 (49%) agreed to take part and were visited at home by a member of the research team. Cognitive function of the mother and her child was assessed using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Children's maladaptive behaviour was measured using the Strengths and Difficulties Questionnaire (Goodman, 1997). This questionnaire contains four subscales of maladaptive behaviour (hyperactivity, emotional symptoms, conduct problems and peer problems), a scale measuring prosocial behaviour, and a total difficulties score.

The Southampton and South West Hampshire Joint Local Research Ethics Committee approved the study. The children and their parents gave written informed consent.

Statistical analysis

We used *t*-tests or χ^2-tests to compare the characteristics of the participants and the non-participants. Spearman correlation coefficients were used to examine the relation between mothers' frequency of eating fish and characteristics of the participants. Owing to small numbers in some of the fish frequency categories, we collapsed the 8 categories into 4 for the analyses of overall fish intake and into 3 categories for the analyses of oily fish intake. The data on the maladaptive behaviour scales and the total difficulties scale were skewed and could not be transformed to normality. We therefore dichotomised each scale such that the reference category contained approximately 80–90% of the data, with the upper tail of the distribution constituting the adverse behavioural outcomes. We used binary logistic regression to examine the relation between mothers' frequency of eating fish in pregnancy and hyperactivity, conduct problems, peer problems, emotional symptoms and total difficulties in the children. We used linear regression to examine the relation between mothers' frequency of eating fish and children's intelligence. The analyses that follow are based on 217 children with complete data on behavioural and cognitive outcomes and potential confounding factors.

Table 1 Distribution of maternal and early life characteristics of the 217 study participants

Characteristic	No, % or Mean, SD	
Mother		
Social class		
Manual	54	24.9
Non-manual	163	75.1
Educational qualifications		
<A levels	126	58.1
≥A levels	91	41.9
Smoked in pregnancy	50	23.0
Drank in pregnancy	154	71.0
Frequency of eating fish in early pregnancy		
All types		
Never	19	8.76
Less than once per week	55	25.3
Once or twice per week	102	47.0
Three or more times per week	41	18.9
Oily fish		
Never	62	28.6
Less than once per week	100	46.1
Once or more per week	55	25.3
Frequency of eating fish in late pregnancy		
All types		
Never	19	8.76
Less than once per week	42	19.4
Once or twice per week	108	49.8
Three or more times per week	48	22.1
Oily fish		
Never	70	32.3
Less than once per week	97	44.7
Once or more per week	50	23.0
Age, yr	27.0	4.7
Full-scale IQ	104.2	13.0
Child		
Female	104	47.9
Male	113	52.1
No of older siblings		
0	120	55.8
1	70	32.4
2 or more	27	12.6
Duration of breast-feeding		
Never	59	28.5
<1 month	51	24.6
1–4 months	43	20.8
>4 months	54	26.1
Premature	14	6.45
Birthweight, kg	3.35	.57

Results

The characteristics of the 217 children and their mothers are shown in Table 1. Compared to those who took part in the previous follow-up when they were aged 9 months but were non-participants in the 9-year follow-up, the participants had mothers who were older (mean age at early pregnancy interview 27.0 vs. 26.1 years, $p = .03$), better educated (42% had A levels or higher level qualifications vs. 35%, $p = .01$) and more likely to come from a non-manual occupational social class (75% vs. 67%, $p = .02$). There were no differences between the participants and the non-participants as regards the frequency with which their mothers ate fish during pregnancy, their mothers' smoking or drinking habits in pregnancy, number of older siblings, sex, birthweight, proportion born before 37 weeks' completed gestation, or duration of breastfeeding.

Mothers who ate fish more frequently in pregnancy differed from those who never ate fish. These differences were most pronounced in respect of oily fish consumption. Mothers who ate oily fish more frequently in late pregnancy tended to be more highly educated ($r_s = .21$, $p = .002$), had a higher IQ ($r_s = .25$, $p < .001$), were older ($r_s = .25$, $p < .001$) and more likely to come from a non-manual social class ($r_s = -.18$, $p < .001$). Greater frequency of consumption of oily fish in late pregnancy was associated with a lower prevalence of smoking while pregnant (13% of mothers who never ate oily fish had smoked while pregnant compared with 5% of those who ate oily fish at least once a week, $p = .007$), but a higher prevalence of drinking alcohol while pregnant (85% vs.

95%, respectively, $p = .02$). Mothers who ate oily fish more frequently in late pregnancy had babies who weighed more at birth ($r_s = .18$, $p = .008$) and they tended to breastfeed for longer ($r_s = .16$, $p = .02$). There were no associations between frequency of fish eating in either early or late pregnancy and the sex of the child or number of previous births.

In unadjusted analyses, we found no significant associations between frequency of eating all types of fish in early or late pregnancy and risk of hyperactivity, conduct problems, peer problems or emotional symptoms (data not shown). Odds ratios for a high total difficulties score were significantly reduced in children whose mothers had eaten fish at least once a week in early pregnancy. Compared to those whose mothers never ate fish, the odds ratio (95% CI) for a high total difficulties score was .27 (.08 to .84) in those whose mothers ate fish once or twice a week and .17 (.04 to .78) in those whose mothers ate fish three or more times a week. Adjustment for the potential confounding factors, maternal social class, educational qualifications, IQ, age, smoking and alcohol use in pregnancy, duration of breastfeeding and birthweight, weakened this association and it ceased to be statistically significant. Compared to those whose mothers never ate fish, the multivariate-adjusted odds ratio (95% CI) for a high total difficulties score was .32 (.08 to 1.26) in those whose mothers ate fish once or twice a week and .23 (.04 to 1.24).

We repeated these analyses looking at intake of oily fish only (Table 2). Compared with children whose mothers never ate oily fish, those whose mothers ate oily fish less than once a week either in early (OR .33, 95% CI .15 to .75) or in late pregnancy (OR .41, 95% CI .18 to .91) had a significantly lower risk of hyperactivity. These associations were slightly strengthened after adjustment for potential confounding factors. Risk also tended to be lower in the much smaller group of children whose mothers had eaten oily fish once a week or more, particularly in early pregnancy (OR .48, 95% CI .19 to 1.18), but these relations were weaker and not statistically significant. We examined whether eating any oily fish in pregnancy, regardless of frequency, was associated with a reduced risk of hyperactivity: compared to those whose mothers never ate oily fish, children whose mothers ate oily fish in early pregnancy had an odds ratio for hyperactivity of .34 (95% .15 to .78), after adjustment for potential confounding factors. The equivalent risk associated with eating oily fish in late pregnancy was weaker and of borderline significance after adjustment: OR .49 (95% CI .22 to 1.10).

There were no significant associations between intake of oily fish either in early or late pregnancy and risk of peer problems, emotional symptoms or a higher total difficulties score. Risk of conduct disorders was significantly lower in children whose mothers had eaten oily fish in late pregnancy and the risk fell with increasing frequency of consumption, but this relation ceased to be statistically significant after adjustment for potential confounding factors.

The children's mean full-scale IQ was 106.9 (SD 14.2). Table 3 shows the results of linear regression analyses of the relation between frequency of fish consumption in pregnancy and full-scale IQ. As regards overall fish intake, there were no significant associations between frequency of eating fish in early pregnancy and children's full-scale IQ. Frequency of eating fish in late pregnancy, by contrast, was associated with higher full-scale IQ, such that IQ tended to be higher in children whose mothers had eaten fish more frequently. After adjustment for potential confounding factors, including mother's own IQ, there remained a significant association between eating fish in late pregnancy and children's full-scale IQ, though the effect was only present in children whose mothers ate fish once or twice a week or less; eating fish 3 or more times a week was not significantly associated with higher IQ in the child, though numbers in this group were relatively small. Compared to children whose mothers never ate oily fish, those whose mothers had eaten oily fish less than once a week either in early or in late pregnancy had a significantly higher full-scale IQ in unadjusted analyses, but these associations were weakened and ceased to be significant after adjustment for potential confounding factors. Eating oily fish once a week or more in early or late pregnancy was not associated with higher full-scale IQ scores, though numbers in these categories were small.

We repeated these analyses using children's performance IQ and verbal IQ as the outcomes (data not shown). As regards fish intake overall, there were no associations between frequency of eating fish either in early or late pregnancy and performance IQ. There was also no association between fish intake in early pregnancy and verbal IQ. However, there were significant trends between greater frequency of fish consumption in late pregnancy and verbal IQ and this persisted after adjustment for maternal IQ and other potential confounding factors: compared to those whose mothers ate no fish, verbal IQ was increased by 7.66 points (95% CI –.1 to 15.4) in those whose mothers ate fish less than once a week, 7.32 points (95% CI .26 to 14.4) in those whose mothers ate fish once or twice a week, and 8.07 points (95% CI .28 to 15.9) in those whose mothers ate fish three or more times per week. We calculated the relation between eating any fish in late pregnancy, regardless of frequency, and verbal IQ: compared to children whose mothers ate no fish, those whose mothers ate fish had a verbal IQ that was 7.55 points higher (95% CI .75 to 14.4). There were no significant associations between intake of oily fish either in early or late pregnancy and performance or verbal IQ.

Discussion

In this longitudinal study of 9-year-old children, we found that children whose mothers had eaten oily

Table 2 Odds ratios (95% CI) for behaviour problems according to maternal intake of oily fish in early or late pregnancy

	Early pregnancy		
	Never (n = 62)	Less than once per week (n = 100)	Once per week or more (n = 55)
Hyperactivity			
No (%) of cases	18 (29%)	6 (11%)	9 (16%)
Unadjusted OR (95% CI)	1.0	.33 (.15 to .75)	.48 (.19 to 1.18)
Adjusted* OR (95% CI)	1.0	.30 (.12 to .76)	.41 (.15 to 1.12)
Conduct problems			
No (%) of cases	14 (23%)	8 (15%)	5 (9%)
Unadjusted OR (95% CI)	1.0	.51 (.22 to 1.18)	.34 (.11 to 1.02)
Adjusted* OR (95% CI)	1.0	.58 (.22 to 1.53)	.36 (.11 to 1.21)
Peer problems			
No (%) of cases	15 (25%)	14 (26%)	13 (23%)
Unadjusted OR (95% CI)	1.0	.80 (.31 to 2.11)	1.28 (.50 to 3.43)
Adjusted* OR (95% CI)	1.0	.79 (.27 to 2.32)	1.44 (.47 to 4.80)
Emotional symptoms			
No (%) of cases	19 (31%)	10 (19%)	8 (14%)
Unadjusted OR (95% CI)	1.0	.52 (.21 to 1.31)	.46 (.15 to 1.43)
Adjusted* OR (95% CI)	1.0	.63 (.19 to 2.06)	.79 (.20 to 3.08)
Total difficulties			
No (%) of cases	19 (31%)	8 (15%)	13 (24%)
Unadjusted OR (95% CI)	1.0	.71 (.29 to 1.76)	.51 (.16 to 1.59)
Adjusted* OR (95% CI)	1.0	1.23 (.41 to 3.66)	.83 (.22 to 3.04)
	Late pregnancy		
	Never (n = 70)	Less than once per week (n = 97)	Once a week or more (n = 50)
Hyperactivity			
No (%) of cases	18 (26%)	12 (12%)	9 (18%)
Unadjusted OR (95% CI)	1.0	.41 (.18 to .91)	.63 (.26 to 1.55)
Adjusted* OR (95% CI)	1.0	.40 (.16 to .98)	.72 (.26 to 1.98)
Conduct problems			
No (%) of cases	17 (24%)	11 (11%)	4 (8%)
Unadjusted OR (95% CI)	1.0	.40 (.17 to .92)	.27 (.09 to .86)
Adjusted* OR (95% CI)	1.0	.46 (.18 to 1.17)	.31 (.08 to 1.10)
Peer problems			
No (%) of cases	12 (18%)	12 (12%)	7 (14%)
Unadjusted OR (95% CI)	1.0	.69 (.28 to 1.57)	.76 (.27 to 1.56)
Adjusted* OR (95% CI)	1.0	.68 (.25 to 1.82)	.82 (.27 to 2.57)
Emotional symptoms			
No (%) of cases	9 (13%)	12 (12%)	5 (10%)
Unadjusted OR (95% CI)	1.0	.96 (.40 to 2.41)	.77 (.24 to 2.46)
Adjusted* OR (95% CI)	1.0	2.32 (.73 to 7.43)	1.04 (.23 to 4.66)
Total difficulties			
No (%) of cases	11 (16%)	11 (11%)	5 (10%)
Unadjusted OR (95% CI)	1.0	.66 (.27 to 1.63)	.59 (.19 to 1.81)
Adjusted* OR (95% CI)	1.0	1.25 (.43 to 3.60)	1.20 (.32 to 4.49)

*Adjusted for maternal social class, educational qualifications, age, IQ, smoking and drinking in pregnancy, duration of breastfeeding and birthweight.

fish in early pregnancy had a reduced risk of hyperactivity compared with those whose mothers never ate oily fish. This relation persisted after adjustment for a range of potential confounding factors, including birthweight, maternal intelligence, education, social class, age, smoking or drinking habits during pregnancy, and duration of breastfeeding. Risk of hyperactivity also tended to be lower in children whose mothers had eaten oily fish in late pregnancy, but these associations were weaker. Fish intake in pregnancy, whether of all types or oily, showed no associations with risk of other behavioural problems after adjustment for potential confounding factors. We found no associations between the frequency with which mothers ate fish in pregnancy and full-scale or performance IQ in their children, but children whose mothers had eaten fish (all types) in late pregnancy had a verbal IQ that was around .5 of a standard deviation higher than those whose mothers never ate fish.

Women who have a higher dietary intake of fish tend to secrete higher concentrations of DHA in their breast milk (Innis, 2007c). Longer duration of breastfeeding has been linked with improved neurodevelopment in this cohort (Gale, O'Callaghan, Godfrey, Law, & Martyn, 2004) and in many other studies (Anderson, Johnstone, & Remley, 1999), though a recent large study, which included a meta-analysis, shows that breastfeeding has little or no effect on cognitive function, once the influence

Table 3 Regression coefficients (95% CI) for the relation between full scale IQ and maternal intake of all types of fish or oily fish in early or late pregnancy

	Regression coefficient (95% CI)	
	Unadjusted	Adjusted*
All types of fish – early pregnancy		
Never	Reference	Reference
Less than once per week	5.18 (–2.63 to 13.0)	5.12 (–1.95 to 12.2)
Once or twice a week	6.10 (–1.25 to 13.5)	3.07 (–3.74 to 9.88)
Three or more times a week	6.35 (–1.73 to 14.5)	1.19 (–6.24 to 8.61)
All types of fish – late pregnancy		
Never	Reference	Reference
Less than once per week	9.37 (1.42 to 17.3)	7.76 (.38 to 15.1)
Once or twice a week	11.0 (3.79 to 18.2)	6.91 (.19 to 13.6)
Three or more times a week	11.6 (2.81 to 18.4)	5.86 (–1.55 to 13.3)
Oily fish – early pregnancy		
Never	Reference	Reference
Less than once per week	5.03 (.45 to 9.59)	2.52 (–1.89 to 6.94)
Once per week or more	2.93 (–2.28 to 8.13)	–.99 (–6.01 to 4.02)
Oily fish – late pregnancy		
Never	Reference	Reference
Less than once per week	6.28 (1.89 to 1.7)	3.43 (–.80 to 7.65)
Once per week or more	4.37 (–.79 to 9.52)	–.29 (–5.34 to 4.76)

*Adjusted for maternal social class, educational qualifications, age, IQ, smoking and drinking in pregnancy, duration of breastfeeding and birthweight.

of maternal intelligence is removed (Der, Batty, & Deary, 2006). Adjustment for maternal intelligence, duration of breastfeeding and other potential confounding factors severely attenuated some of the associations we found with fish intake in pregnancy, but those described above persisted.

Only one previous study has examined the relation between maternal intake of fish in pregnancy and long-term neurodevelopmental outcomes in children. In the Avon Longitudinal Study of Parents and Children (ALSPAC), children whose mothers had eaten no seafood in late pregnancy had an increased risk of being in the lowest quartile of verbal IQ at age 8 years and were more likely to have sub-optimum scores for prosocial behaviour, fine motor skills, communication and social development earlier in childhood (Hibbeln et al., 2007). Our finding of higher verbal intelligence in children whose mothers had eaten fish in late pregnancy is consistent with the observations in ALSPAC. In the ALSPAC study, no association was found between maternal seafood consumption in late pregnancy and risk of hyperactivity. We found that risk of hyperactivity tended to be lower in children whose mothers had eaten oily fish either in early or late pregnancy, but it was only for oily fish consumption in early pregnancy that the association was statistically significant. ALSPAC had no dietary data relating to early pregnancy, and did not examine oily fish intake separately.

There has been growing interest in the role that omega-3 fatty acids might play in attention-deficit/hyperactivity disorder. Several studies have shown that children or adults with this condition have lower blood concentrations of DHA (Chen, Hsu, Hsu, Hwang, & Yang, 2004). There is some evidence from randomised controlled trials that supplementing children's diet with omega-3 fatty acids may alleviate the symptoms of the condition, at least in the short term (Richardson, 2006). It is not yet clear whether low prenatal accrual of DHA plays a role in its pathogenesis, but there is some support for the proposition that it may be a risk factor. Firstly, people with attention-deficit/hyperactivity disorder show deficits in frontal cortical dopamine synthesis and metabolism (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998). In rats, deficits in dopamine concentrations in the frontal cortex in adulthood can be caused by inadequate accrual of brain DHA during development (Kodas, Vancassel, Lejeune, Guilloteau, & Chalon, 2002; Zimmer et al., 2002). Secondly, in very young children, those whose mothers had lower blood concentrations of DHA at delivery showed poorer attention and greater distractability (Colombo et al., 2004). The finding in our study that children whose mothers ate oily fish during pregnancy had a reduced risk of hyperactivity provides further evidence that pre-natal DHA availability may play a part in the pathogenesis of this condition.

In common with ALSPAC, we found no evidence of any adverse neurodevelopmental outcomes in children whose mothers ate fish at least once a week. There has recently been some concern, particularly in the US, that fetal exposure to neurotoxins that accumulate in fish, such as methylmercury or polychlorinated biphenyls, might damage the developing brain (Scientific Advisory Committee on Nutrition (SACN), 2004; US Department of Health and Human Services, 2004).

Our study has some limitations. Firstly, we were unable to follow up all the children in the cohort. Some had moved away from the area and some declined to participate. Children who took part in this study were more likely to have mothers who were better educated and from non-manual occupational classes, but frequency of maternal fish consumption in pregnancy was similar in the groups who did and did not participate. We think it unlikely that bias will have been introduced. Secondly, our study was based on 217 children; it is possible that we lacked statistical power. Thirdly, we had no information on the children's diet after weaning. Whether the associations we observed are attributable solely to maternal fish intake in pregnancy or whether they reflect some influence of diet after weaning is unclear. Finally, although we were able to control for a range of potential confounding factors, it is possible that the associations we found were due to unmeasured factors in the children's home environment for which we were unable to control, such as quality of parenting or paternal education or IQ. The fact that some associations tended to be as strong or stronger in those children whose mothers had eaten fish least frequently as in those whose mothers ate fish often is surprising and raises the possibility of confounding by unmeasured factors. There were marked social and demographic differences in our study between mothers who ate fish and those who did not.

In this longitudinal study, we found that mothers who ate fish during pregnancy had children with a lower risk of hyperactivity and a higher verbal IQ at the age of 9 years. Eating fish during pregnancy was not significantly associated with other behavioural problems or with full-scale or performance IQ. Fish, and in particular oily fish, is a major source of omega-3 fatty acids that are known to be important for brain development (Innis, 2007a). Although we found links between maternal fish intake in pregnancy and hyperactivity scores and verbal IQ in children, in general, how much fish women ate during pregnancy appeared to have little long-term relation with neurodevelopmental outcomes in their child.

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References

Anderson, J.W., Johnstone, B.M., & Remley, D.T. (1999). Breast-feeding and cognitive development: A meta-analysis. *American Journal of Clinical Nutrition*, *70*, 525–535.

Bezard, J., Blond, J. P., Bernard, A., & Clouet, P. (1994). The metabolism and availability of essential fatty acids in animal and human tissues. *Reproduction Nutrition Development*, *34*, 539–568.

Calderon, F., & Kim, H.Y. (2004). Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *Journal of Neurochemistry*, *90*, 979–988.

Chen, J.R., Hsu, S.F., Hsu, C.D., Hwang, L.H., & Yang, S.C. (2004). Dietary patterns and blood fatty acid composition in children with attention-deficit hyperactivity disorder in Taiwan. *Journal of Nutritional Biochemistry*, *15*, 467–472.

Clandinin, M.T., Chappell, J.E., Leong, S., Heim, T., Swyer, P.R., & Chance, G.W. (1980). Extrauterine fatty acid accretion in infant brain: Implications for fatty acid requirements. *Early Human Development*, *4*, 131–138.

Colombo, J., Kannass, K.N., Shaddy, D.J., Kundurthi, S., Maikranz, J.M., Anderson, C.J., Blaga, O.M., & Carlson, S.E. (2004). Maternal DHA and the development of attention in infancy and toddlerhood. *Child Development*, *75*, 1254–1267.

Coti, B.P., O'Kusky, J.R., & Innis, S.M. (2006). Maternal dietary (n-3) fatty acid deficiency alters neurogenesis in the embryonic rat brain. *Journal of Nutrition*, *136*, 1570–1575.

Das, U.N. (2006). Essential Fatty acids – a review. *Current Pharmaceutical Biotechnology*, *7*, 467–482.

Der, G., Batty, G.D., & Deary, I.J. (2006). Effect of breast feeding on intelligence in children: Prospective study, sibling pairs analysis, and meta-analysis. *British Medical Journal*, *333*, 945.

Eilander, A., Hundscheid, D.C., Osendarp, S.J., Transler, C., & Zock, P.L. (2007). Effects of n-3 long chain polyunsaturated fatty acid supplementation on visual and cognitive development throughout childhood: A review of human studies. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *76*, 189–203.

Ernst, M., Zametkin, A.J., Matochik, J.A., Jons, P.H., & Cohen, R.M. (1998). DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18] fluorodopa positron emission tomographic study. *Journal of Neuroscience*, *18*, 5901–5907.

Fedorova, I., & Salem, N., Jr (2006). Omega-3 fatty acids and rodent behavior. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *75*, 271–289.

Gale, C.R., O'Callaghan, F.J., Godfrey, K.M., Law, C.M., & Martyn, C.N. (2004). Critical periods of brain growth and cognitive function in children. *Brain*, *127*, 321–329.

Godfrey, K., Robinson, S., Barker, D.J.P., Osmond, C., & Cox, V. (1996). Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. *British Medical Journal*, *312*, 410–414.

Goodman, R. (1997). Strengths and Difficulties Questionnaire: A research note. *Journal of Child Psychology and Psychiatry*, *38*, 581–586.

Goyens, P.L., Spilker, M.E., Zock, P.L., Katan, M.B., & Mensink, R.P. (2006). Conversion of alpha-linolenic acid in humans is influenced by the absolute amounts of alpha-linolenic acid and linoleic acid in the diet and not by their ratio. *American Journal of Clinical Nutrition*, *84*, 44–53.

Green, P., & Yavin, E. (1996). Fatty acid composition of late embryonic and early postnatal rat brain. *Lipids*, *31*, 859–865.

Helland, I.B., Saugstad, O.D., Smith, L., Saarem, K., Solvoll, K., Ganes, T., & Drevon, C.A. (2001). Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women. *Pediatrics*, *108*, E82.

Helland, I.B., Smith, L., Saarem, K., Saugstad, O.D., & Drevon, C.A. (2003). Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics*, *111*, e39–e44.

Hibbeln, J.R., Davis, J.M., Steer, C., Emmett, P., Rogers, I., Williams, C., & Golding, J. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): An observational cohort study. *Lancet*, *369*, 578–585.

Ikemoto, A., Nitta, A., Furukawa, S., Ohishi, M., Nakamura, A., Fujii, Y., & Okuyama, H. (2000). Dietary n-3 fatty acid deficiency decreases nerve growth factor content in rat hippocampus. *Neuroscience Letters*, *285*, 99–102.

Innis, S.M. (2005). Essential fatty acid transfer and fetal development. *Placenta*, *26*(Suppl. A), S70–S75.

Innis, S.M. (2007a). Dietary (n-3) fatty acids and brain development. *Journal of Nutrition*, *137*, 855–859.

Innis, S.M. (2007b). Fatty acids and early human development. *Early Human Development*, *83*, 761–766.

Innis, S.M. (2007c). Human milk: Maternal dietary lipids and infant development. *Proceedings of the Nutrition Society*, *66*, 397–404.

Judge, M.P., Harel, O., & Lammi-Keefe, C.J. (2007). Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: Benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. *American Journal of Clinical Nutrition*, *85*, 1572–1577.

Kitajka, K., Sinclair, A.J., Weisinger, R.S., Weisinger, H.S., Mathai, M., Jayasooriya, A.P., Halver, J.E., & Puskas, L.G. (2004). Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression. *Proceedings of the National Academy of Science of the United States of America*, *101*, 10931–10936.

Kodas, E., Galineau, L., Bodard, S., Vancassel, S., Guilloteau, D., Besnard, J.C., & Chalon, S. (2004). Serotoninergic neurotransmission is affected by n-3 polyunsaturated fatty acids in the rat. *Journal of Neurochemistry*, *89*, 695–702.

Kodas, E., Vancassel, S., Lejeune, B., Guilloteau, D., & Chalon, S. (2002). Reversibility of n-3 fatty acid deficiency-induced changes in dopaminergic neurotransmission in rats: Critical role of developmental stage. *Journal of Lipid Research*, *43*, 1209–1219.

Krauss-Etschmann, S., Shadid, R., Campoy, C., Hoster, E., Demmelmair, H., Jimenez, M., Gil, A., Rivero, M., Veszpremi, B., Decsi, T., & Koletzko, B.V. (2007). Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: A European randomized multicenter trial. *American Journal of Clinical Nutrition*, *85*, 1392–1400.

Levitt, P. (2003). Structural and functional maturation of the developing primate brain. *Journal of Pediatrics*, *143*, S35–S45.

Malcolm, C.A., McCulloch, D.L., Montgomery, C., Shepherd, A., & Weaver, L.T. (2003). Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: A double blind, prospective, randomised trial. *Archives of Disease in Childhood – Fetal and Neonatal Edition*, *88*, F383–F390.

McCann, J.C., & Ames, B.N. (2005). Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. *American Journal of Clinical Nutrition*, *82*, 281–295.

McNamara, R.K., & Carlson, S.E. (2006). Role of omega-3 fatty acids in brain development and function: Potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *75*, 329–349.

Moriguchi, T., Greiner, R.S., & Salem, N., Jr (2000). Behavioral deficits associated with dietary induction of decreased brain docosahexaenoic acid concentration. *Journal of Neurochemistry*, *75*, 2563–2573.

Richardson, A. (2006). Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. *International Review of Psychiatry*, *18*, 155–172.

Schiefermeier, M., & Yavin, E. (2002). n-3 Deficient and docosahexaenoic acid-enriched diets during critical periods of the developing prenatal rat brain. *Journal of Lipid Research*, *43*, 124–131.

Scientific Advisory Committee on Nutrition (SACN). (2004). *Advice on fish consumption: Benefits and risks*. London: TSO.

Tofail, F., Kabir, I., Hamadani, J.D., Chowdhury, S., Yesmin, F., Mehreen, E.L., & Hughes, E.L. (2006). Supplementation of fish oil and soy oil during pregnancy and psychomotor development of infants. *Journal of Health Population and Nutrition*, *24*, 48–56.

US Department of Health and Human Services, UEPA. (2004). *What you need to know about mercury in fish and shellfish. 2004 EPA and FDA advice for: Women who might become pregnant, women who are pregnant, nursing mothers, young children*. Rep. No. Report number EPA-823-R-04-005. Washington, DC. Available from http://www.cfsan.fda.gov/~dms/admehg3.html.

Velzing-Aarts, F.V., van der Klis, F.R., van der Dijs, F.P., van Beusekom, C.M., Landman, H., Capello, J.J., & Muskiet, F.A. (2001). Effect of three low-dose fish oil supplements, administered during pregnancy, on neonatal long-chain polyunsaturated fatty acid status at birth. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *65*, 51–57.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation.

Zimmer, L., Delpal, S., Guilloteau, D., Aioun, J., Durand, G., & Chalon, S. (2000). Chronic n-3 polyunsaturated fatty acid deficiency alters dopamine vesicle density in the rat frontal cortex. *Neuroscience Letters*, *284*, 25–28.

Zimmer, L., Vancassel, S., Cantagrel, S., Breton, P., Delamanche, S., Guilloteau, D., Durand, G., & Chalon, S. (2002). The dopamine mesocorticolimbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *American Journal of Clinical Nutrition*, *75*, 662–667.

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