THE LANCET.com

The Lancet 2007; **369**:578-585

DOI:10.1016/S0140-6736(07)60277-3

Articles

Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study

Joseph R HibbelnMD [a], John M DavisMD [b], Colin SteerMSc [c], Pauline EmmettPhD [c], Imogen RogersPhD [c], Cathy WilliamsPhD [c] and Jean GoldingFMedSci [c]

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Summary

Background

Seafood is the predominant source of omega-3 fatty acids, which are essential for optimum neural development. However, in the USA, women are advised to limit their seafood intake during pregnancy to 340 g per week. We used the Avon Longitudinal Study of Parents and Children (ALSPAC) to assess the possible benefits and hazards to a child's development of different levels of maternal seafood intake during pregnancy.

Methods

11 875 pregnant women completed a food frequency questionnaire assessing seafood consumption at 32 weeks' gestation. Multivariable logistic regression models including 28 potential confounders assessing social disadvantage, perinatal, and dietary items were used to compare developmental, behavioural, and cognitive outcomes of the children from age 6 months to 8 years in women consuming none, some (1–340 g per week), and >340 g per week.

Findings

After adjustment, maternal seafood intake during pregnancy of less than 340 g per week was associated with increased risk of their children being in the lowest quartile for verbal intelligence quotient (IQ) (no seafood consumption, odds ratio [OR] 1·48, 95% CI 1·16–1·90; some, 1·09, 0·92–1·29; overall trend, p=0·004), compared with mothers who consumed more than 340 g per week. Low maternal seafood intake was also associated with increased risk of suboptimum outcomes for prosocial behaviour, fine motor, communication, and social development scores. For each outcome measure, the lower

the intake of seafood during pregnancy, the higher the risk of suboptimum developmental outcome.

Interpretation

Maternal seafood consumption of less than 340 g per week in pregnancy did not protect children from adverse outcomes; rather, we recorded beneficial effects on child development with maternal seafood intakes of more than 340 g per week, suggesting that advice to limit seafood consumption could actually be detrimental. These results show that risks from the loss of nutrients were greater than the risks of harm from exposure to trace contaminants in 340 g seafood eaten weekly.

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Introduction

Optimum fetal neurodevelopment is dependent on specific nutrients derived solely from dietary sources, including docosahexaenoic acid (DHA), an omega-3 essential fatty acid, of which seafood is a major source.[1] Low seafood intake during pregnancy could lead to fetal deficiency in essential long-chain omega-3 fatty acids such as DHA and eicosapentaenoic acid, (EPA) resulting in adverse effects on neurodevelopment.[2] DHA deficiency leads to reduced dendritic arborisation[3] and impaired gene expression for regulation of neurogenesis, neurotransmission, and connectivity.[4] In severe conditions of DHA deprivation, such as Zellweger disease and peroxisomal disorders, mental retardation is common, yet restoration of dietary DHA intake improves clinical outcomes and neuronal myelination.[5–7]

In 2004, advice[8] was issued jointly by two US Federal Government agencies for pregnant women or women likely to become pregnant to restrict their overall consumption of seafood to 340 g per week,[8] to avoid fetal exposure to trace amounts of neurotoxins. However, such control of seafood consumption could cause intake of long-chain omega-3 fatty acids to fall below quantities adequate for best fetal neurodevelopment.[9,10] We analysed an observational cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC), to assess whether the advice is successful in providing protection from adverse neurodevelopmental outcomes.

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Methods

ALSPAC was designed to assess environmental factors (including diet) during and after pregnancy that might affect the development, health, or wellbeing of the child. All pregnant women living in Bristol, UK, and surrounding areas, with an expected delivery date between April 1, 1991 and Dec 31, 1992 were eligible for inclusion.[11] Of 14 541 pregnancies, 13 988 children survived for at least 12 months. About 85% of eligible expectant mothers participated; recruitment, dropout, and other methodologies have been described elsewhere.[11,12] Mothers were sent postal questionnaires four times during pregnancy and then at specific time points[11,12] after birth of the child to obtain information about diet, education, social circumstances, behavioural, and developmental outcomes. The investigation used singleton and first-twin births for whom data were available for 28 key social, demographic, and other confounding variables (n=8946). Mothers answered questions about development or behaviour of their children at ages 6, 18, 30, 42, and 81 months (number completing at least one valid response and having all confounders=8801), and their children had their intelligence quotient (IQ) measured by the Weschler Intelligence Scale for Children III^{UK} (WISC-III^{UK}) at age 8 years (n=5449). All ALSPAC studies were done voluntarily under ethical review as previously described.[11] Mothers volunteeres to take part on the understanding that they were under no obligation and could drop out whenever they wished. The study had the approval of the ALSPAC Ethics and Law Advisory Committee and local ethics committees.

Seafood exposure

Data for food consumption were obtained at 32 weeks' gestation by a self-completed detailed food-frequency questionnaire, which was also used to calculate nutrient and energy intakes.[13] Three questions assessed seafood consumption: "How many times nowadays do you eat (a) white fish (cod, haddock, plaice, fish fingers, etc), (b) dark or oily fish (tuna, sardines, pilchards, mackerel, herring, kippers, trout, salmon, etc), and (c) shellfish (prawns, crabs, cockles, mussels etc)?”. Each response was chosen from five predefined categories: Never or rarely; once in 2 weeks; 1–3 times per week; 4–7 times per week; and more than once a day. These were scored as portions per week as follows: rarely or never=0; once in 2 weeks=0·5; 1–3 times per week=2; 4–7 times per week=5·5; or more than once a day=10.

Portion sizes were based on typical eating patterns in the UK with consideration of relative proportions of processed and fresh seafood commonly consumed (**webpanel 1**). Total seafood consumption per week was calculated as the total number of portions, multiplied by the portion size for each type of fish. A mother who ate seafood three times a week would typically have a fish intake of 347 g per week (range 297–358 g per week). Fatty acid values were based on profiles of typical species of British seafood (**webpanel 1**).[14] Intake of omega-3 fatty acids for each portion were estimated as follows: white fish, 0·32 g; oily fish, 0·89 g; shellfish, 0·34 g.[14] Derived estimates of the intake of omega-3 fats from seafood (α-linolenic, eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids) were calculated as total amounts and as proportions of total energy intake. The questionnaire also asked about intake of other foods (meats, poultry, vegetables, fruits, potatoes etc); the social variations in diet have been described previously.[15]

The frequency of seafood consumption has previously been validated in relation to two biochemical markers in subpopulations of ALSPAC.[16–18] First, seafood consumption association with predicted erythrocyte fatty acid composition was established in a thorough statistical analysis with smile plots to correct for multiple analyses of 40 fatty acids.[16] The frequency of oily-fish consumption positively correlated with erythrocyte DHA content in a dose-response effect ($p<0·0001$).[16,17] Second a further biochemical marker of seafood consumption is umbilical cord mercury content, since seafood is a major dietary source of methyl-mercury (MeHg). Umbilical MeHg concentrations also showed a positive relation to reported seafood intake.[18] These direct biochemical comparisons are consistent with other studies that validated the use of similar food frequency questionnaires and derived nutrient intake data (eg, those used in pregnancy).[19]

Outcome measures

An estimate of the child's abilities used a scale developed by ALSPAC, including items from the Denver Developmental Screening Test.[20] A set of questions completed by the mother at home was used to calculate a continuous score with four domains (gross motor, fine motor, communication, and social skills). The scales were completed by parents when the children were 6, 18, 30 and 42 months of age. A comparison of the self-completion results with the Griffiths scale[21] (administered under controlled conditions by trained psychologists) done on a representative subpopulation of the cohort (n=1045) at 18 months, gave a correlation coefficient of 0·54 ($p<0·0001$).

Suboptimum development was defined as scores at the lower end of the distribution closest to 25% for the total score and for each of the four component scores. Because the communication scores at age 6 months were clustered, the percentage with sub-optimum development deviated substantially from this target, being closer to 15%. Assessments from the questionnaires at 6 months of age were susceptible to small differences in ages, and we therefore corrected these scores for the age of the child.

The Strengths and Difficulties Questionnaire[22] was completed by the mothers for their children at age 81 months. The questionnaire has well-established consistency, reliability, and diagnostic predictability, surpassing the Child Behaviour Checklist for inattention and hyperactivity.[23,24] The scale consists of 25 questions with five subscales (prosocial [ie, positive social interactions], hyperactivity, emotional symptoms, conduct problems, and peer problems) and a total difficulties score. These scores were prorated according to Goodman's[22] instructions and as previously described for the cohort,[25] such that the low tails of the distribution of gender-specific scores (closest to 10%) were chosen to create the binary outcome, indicating sub-optimum behavioural outcomes for each subscale.

IQ was estimated with an abbreviated form of the WISC-III^{UK}, a well-standardised assessment of full-scale, verbal, and performance intelligence,[26] which was given to 8-year-old children at the ALSPAC research clinic with standard neuropsychological testing procedures.[12] Suboptimum cognitive outcomes were defined as the lowest 25% of scores for full scale, verbal, and performance subscales.

Statistical analyses

To evaluate the 2004 US advice, we used three categories of seafood consumption: none; consumption of 1–340 g per week (ie, up to three portions per week); and consumption of more than 340 g per week. Categories of intake of omega-3 fatty acids were created, with women whose estimated intake was zero as one category, and the remainder were divided into equal groups. The relation of these categories of omega-3 intake to each outcome measure to estimate dose-response was assessed for non-linearity by plotting residuals and iterative curve-fitting analyses including linear, power, exponential, quadratic, and logarithmic models (Sigma Plot version 8.02). We did logistic regression analyses with those who ate more than 340 g of seafood per week as the unity or reference category (SPSS version 11.0.1). p values are provided for trend.

We identified potential confounding variables by review of published data (**table 1**). Two continuous variables were used to assess the cumulative effects of adverse social and developmental factors during defined developmental periods: the family adversity index during pregnancy and a measure of parenting, one based on facilities for child care in the home[27] at 6 months of age. The family adversity index was calculated from the scores of 38 adverse factors (**webpanel 2**). Perinatal variables were birthweight (<2500 g; ≥2500 g), and gestation at delivery (<37 weeks, ≥37 weeks). Additionally, 12 individual categorical covariates were included: sex of the child, age of the mother (<20 years or ≥20 years), parity, highest maternal educational attainment, educational attainment (based on the UK examination system, and referred to qualifications that the parent might have obtained at school or at later ages,[28] catergorised as low, medium, or high), housing status (council [subsidised public housing], other rented, owned/mortgaged), crowding (≤1 or >1 person per room), stressful life events at 18 weeks of gestation (upper 10%, lower 90% of cohort), had partner at time of birth (no, yes), smoking status during pregnancy (never, smoked before but not at 18 weeks of gestation, or still smoking at 18 weeks of gestation), alcohol use during pregnancy (non-drinker, drank before 18 weeks of gestation, still drinking alcohol at 18 weeks of gestation), breastfeeding (none, some) and ethnicity (white, black, Asian). Perinatal variables were low birthweight (<2500 g, ≥2500 g), and preterm delivery (<37 weeks, ≥37 weeks).

***Table 1*. Characteristics of confounders used in the analyses by seafood intake groups (n=8916) with tests of the differences between the three groups**

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To investigate the possibility that seafood intake might be a marker for other differences in diet affected by social patterning, we also adjusted for 12 other food groups noted to be socially patterned in a previous analysis of diet in pregnancy in this cohort (sausages/burgers, pies/pasties, red meat, poultry, green leafy vegetables, other vegetables, salad, chips, fresh fruit, fruit juice, crisps, and biscuits).[15] All these 28 confounding variables (12 categorical and two continuous social variables, two perinatal variables, plus 12 dietary food groups) were used uniformly for all multivariable logistic regression analyses.

To assess whether the outcomes of families with social disadvantage who did not complete the study were different, we used the national test results (standardised assessment tasks) at age 7. These tests are administered to all children enrolled in British Government-funded schools.

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Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The US National Insititute of Alcohol Abuse and Alcoholism contributed to scientific review of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Results

Maternal seafood consumption ranged from 0 to 3268 g per week (mean 235 g per week, SD 202), resulting in estimated intakes of omega-3 fatty acids from seafood ranging from 0 to 15·6 g per week, (mean 1·06 g per week, SD 1·05). In total 12% of women were eating no fish during pregnancy, 65% 1–340 g per week, and 23% more than 340 g per week.

As shown in **table 1**, low seafood consumption by mothers was more likely in homes with evidence of social disadvantage (high level of family adversity, crowding, low maternal education levels, not being a home owner, and being a single parent) and less than ideal lifestyles (smoker, low parenting scores, and not breastfeeding).

The proportions of children with suboptimum behaviour and development scores by maternal seafood intake are shown in **table 2**. The unadjusted data consistently show that children of mothers who ate more than 340 g per week of seafood had outcomes that were no worse than children of women who ate less seafood. However, these unadjusted data clearly show that children of mothers who reported no seafood intake often had the greatest risk of adverse or suboptimum outcomes. Additionally, when seafood intake was moderate (1–340 g per week) the risk of suboptimum outcomes in the children were between those of no seafood consumption and those eating more than 340 g per week. This result can be seen for four outcomes in **figure 1**.

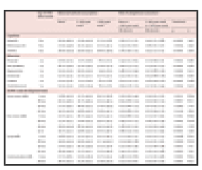

***Table 2*. Children with suboptimal outcomes and their corresponding maternal seafood consumption (unadjusted)**

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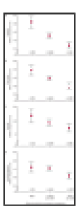

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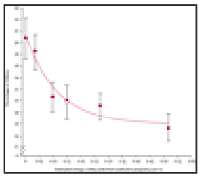
***Figure 1*. Suboptimum outcomes in children according to mothers' seafood consumption**

Means and 95% CI of the percentage of children with suboptimum outcomes. Suboptimum outcomes are defined as the lowest quartile for verbal IQ, fine motor control, and social skills and by scores in the suboptimum range for prosocial behaviour. A=suboptimum verbal IQ in 8-year-old children. B=suboptimum fine motor score in 42-month-old children. C=suboptimum prosocial score in 7-year-old children. D=suboptimum social development score in 42-month-old children.

Greater maternal intake of omega-3 fatty acids was associated with lower risk of suboptimum verbal IQ in a non-linear dose-response curve (**figure 2**). Much the same protective dose-response patterns were seen for nearly all of the outcomes significant in unadjusted and adjusted analyses (data not shown).

***Figure 2*. Prevalence of children with low verbal IQ according to mothers' omega-3 fatty acid from seafood**



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Estimated maternal consumption of long chain omega-3 fatty acids is expressed as proportion of total calories (en %). Maternal seafood consumption was grouped into six categories: mothers with no reported consumption plus five equal groups of remaining population. Means and 95% CI for proportion of children in the lowest quartile for verbal IQ. Best curve fit for categorical means was r=0·96, r^2=0·92, f=19·2, p=0·017, with the following equation: f=20·6229+12·7575*exp (−12·7934*x).

Table 3 shows results after adjustment for the factors shown in **table 1**, plus the two perinatal factors and 12 food categories. Consumption of seafood in pregnancy was significantly associated with nine of the 23 outcomes—in each case the higher the maternal seafood intake the less likely the infant was to have a suboptimum score.

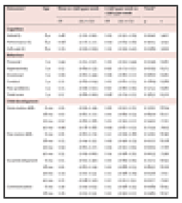

***Table 3*. Maternal seafood consumption and suboptimum childhood outcomes:logistic regression models adjusted for 28 factors**

Click to view table

Since specific nutrient deficiencies could contribute to deficits in verbal development, a separate analysis was done using 30 co-variates with maternal intakes of 14 specific nutrients, instead of 12 categories of food. The risks for low verbal IQ were greater when using the data for 14 specific nutrients (Odds ratio [OR] 1·67 [95% CI 1·28–2·13]) than when using the food category data (OR 1·48 [1·16–1·90]) in analyses comparing children whose mothers ate no seafood with children whose mothers ate more than 340 g seafood per week. These results suggest that our use of the food category data could lead to underestimation of the risks of low maternal seafood consumption; we chose to use food category data because it does not make assumptions about the nutrient content of food as does data for specific nutrients.

In a further attempt to allow for potential confounders, we repeated the earlier analysis with our standard 28 factors but included paternal seafood consumption as a proxy for social confounding. Even though this could be regarded as an over-control, maternal seafood consumption was still significantly associated with verbal IQ, although the effect sizes were slightly reduced (for no maternal fish compared with >340 g per week, OR dropped from 1·48 [1·16–1·90] to 1·39 [1·04–1·86].

We did not do a detailed analysis of fish oil supplements. They were consumed in pregnancy by only 205 (1·7%) women in the study. The outcomes of infants of mothers who took supplements, but did not eat seafood were close to those of mothers who did eat fish (data not shown). There was no trend toward benefit in any childhood outcome variable associated with a seafood intake less than 340 g per week, irrespective of statistical model used.

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Discussion

The information obtained in ALSPAC shows no evidence that consumption of more than three portions of seafood a week during pregnancy has an adverse effect on the behaviour or development of the child. By contrast, maternal consumption of more than 340 g seafood a week was beneficial for the child's neurodevelopment. These results were unexpected since the 2004 advisory[8] was formulated on the basis of an assessment of development in the verbal domain, the Boston naming test.[29] The relevant measures in ALSPAC were verbal IQ and communication skills. The relation between maternal seafood intake and the child's communication skills at ages 6 and 18 months and verbal IQ are the opposite to those anticipated by the US advisory.

In any observational study the possibility exists that relevant confounders have not been taken into account. As we show in **table 1**, there are notable social differences between groups. We tried to account for these differences by allowing for many factors. Another possibility is that by measuring seafood consumption, we are measuring only the effects of a healthy diet. For this reason, we also took account of 12 socially patterned food categories[15] but there was no change in the direction of the results (**table 3**). Further analyses allowed for all estimated nutrients in the mother's diet, but again this analysis made little difference to the outcomes.

Seafood intake in the ALSPAC cohort is unlikely to have resulted in a lower exposure to MeHg than in the US general population. ALSPAC is reasonably representative of the British population,[11] which has a higher mean consumption of mercury (0·05 μg/kg bodyweight[30]), than does the US population (0·02 μg/kg bodyweight[31]). Seafood eaten in Avon, UK, was therefore likely to have contained greater quantities of MeHg[32] than the species from the USA that were used to formulate the 2004 US advice.[29,31,33] Such seafood obtained in the UK would be expected to put children at greater risk of suboptimum development outcomes than in the USA, in contrast with the findings presented here. However, the UK has less contamination by polychlorinated biphenyls than other developed countries.[34]

Differences between the children who continued in the study and those who did not could provide a possible explanation for the discrepancy between our results and the outcomes anticipated when following the advisory. Attrition was disproportionately high in families with social disadvantage and lower seafood intake. To assess whether their outcomes were different we used the national test results (standardised assessment tasks) at age 7 years. These tests are administered to all children enrolled in British government funded schools (more than 90% of the cohort).

For attrition bias to have an effect in the direction of trend, the group of children who dropped out of the study must have had the highest standardised assessment scores of the children whose mothers who ate no seafood. However, the lower standardised test scores were in the same direction and more pronounced in children who dropped out of the cohort (n=2454): mothers who ate no seafood (mean 7·1; SD 3·8); mothers who ate 0–340 g per week (8·4; 3·7); mothers who ate more than the advisory limit (8·8; 3·8); compared with the scores of children who remained in the cohort (n=7081): mothers who ate no seafood (mean 9·2; SD 3·6); mothers who ate 0–340 g per week (9·7; 3·5); and mothers who ate more than the advisory limit (10·2; 3·4])(p=0·0091, unadjusted ANOVA by mother's consumption and attrition status).

We noted that the disproportionate attrition of socially disadvantaged participants probably caused an underestimation of the association of suboptimum development with low seafood consumption.

Nearly all assessments of dietary intakes are difficult. Here we did not have information about specific species of seafood or portion sizes. However, our food frequency questionnaire, which was specially developed for ALSPAC, has been validated in comparison with two biochemical markers for seafood consumption in a subpopulation of this cohort.[16–18] Food frequency questionnaires for seafood have also been validated in other studies.[19,35,36] Similarly, the maternal reports of child development and behaviour are prone to reporting bias. Although the ALSPAC development score that was completed by the parents does not have the sensitivity suitable for a screening test, it does have high specificity for detection of damage.[37] Additionally, when compared with development scores based on a different test administered by psychologists, the resulting correlation (*r*=0·54) was close to what is generally seen in comparisons between two different tests purporting to measure a similar trait.

Advice that limits seafood consumption might reduce the intake of nutrients necessary for optimum neurological development. Findings reported here are consistent with reports that lower omega-3 fatty acid intakes in pregnancy predict lower verbal IQ.[38,39] Adverse outcomes associated with insufficient intakes of long chain omega-3 fatty acids during pregnancy include: intrauterine growth retardation,[40] delayed or suboptimum depth perception,[17] adverse neurodevelopmental measures,[18] residual deficits in fine motor skills, speed of information processing in infants,[41] and irreversible deficits in serotonin and dopamine release.[42] Thus, other evidence suggests that omega-3 fatty acids in pregnancy could be directly responsible for the beneficial findings shown here. The 2004 US advisory[8] however, aimed to reduce the potential harm from pollutants in seafood, specifically methylmercury. Although methylmercury undoubtedly has harmful effects on the developing brain, the harm is unlikely to be greater than the overall benefits of nutrients at the concentrations usually present in seafood. These data show that the risks from losing the benefits of nutrients essential to neurodevelopment exceeds the risk of exposure to trace concentrations of contaminants in 340 g seafood eaten weekly.

In conclusion, we recorded no evidence to lend support to the warnings of the US advisory[8] that pregnant women should limit their seafood consumption. By contrast, we noted that children of mothers who ate small amounts (<340 g per week) of seafood were more likely to have suboptimum neurodevelopmental outcomes than children of mothers who ate more seafood than the recommended amounts.

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Contributors

P Emmett designed the food frequency questions. P Emmett and I Rogers developed the nutrient coding scheme. J Hibbeln, J M Davis, C Steer, and J Golding analysed data. All authors contributed to writing the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We thank all parents and children who took part and, the midwives for their cooperation and help in recruitment; the whole ALSPAC study team, including interviewers, computer technicians, laboratory technicians, clerical workers, research scientists, volunteers, and managers who continue to make our study possible. ALSPAC received financial support from the Medical Research Council, the Wellcome Trust, the University of Bristol, UK government departments, medical charities, and other sources. The statistical analyses presented here were supported by the Intramural Research Program of the National Institute on Alcohol Abuse and Alcoholism, NIH and National Institute of Mental Health Grant No 1 P01MH68580-01 CFDA#93.242 through John M Davis. The ALSPAC study is part of the WHO initiated European Longitudinal Study of Pregnancy & Childhood.

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Web Extra Material

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***Webpanel 1*. Estimated fish portion sizes in UK**

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***Webpanel 2*. The ALSPAC family adversity index in pregnancy**

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Affiliations

[a]. Laboratory of Membrane Biophysics and Biochemistry, US National Institute on Alcohol Abuse and Alcoholism, US National Institutes of Health, Bethesda, MD 20952, USA

[b]. University of Illinois at Chicago, Chicago, IL, USA

[c]. Department of Community Based Medicine, University of Bristol, UK

Correspondence to: Joseph R Hibbeln, Laboratory of Membrane Biophysics and Biochemistry, US National Institute on Alcohol Abuse and Alcoholism, US National Institutes of Health, 31 Center Drive Rm. 31/1B58, MSC 2088, Bethesda, MD 20952, USA