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Associations between maternal long-chain polyunsaturated fatty acid concentrations and child cognition at 7 years of age: The MEFAB birth cohort

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ABSTRACT

Introduction: Concentrations of the fish fatty acids EPA and DHA are low among Dutch women of reproductive age. As the human brain incorporates high concentrations of these fatty acids in utero, particularly during third trimester of gestation, these low EPA and DHA concentrations may have adverse consequences for fetal brain development and functioning.

Methods: Analyses were conducted using longitudinal observational data of 292 mother-child pairs participating in the MEFAB cohort. Maternal AA, DHA, and EPA were determined in plasma phospholipids - obtained in three trimesters - by gas-liquid chromatography. Cognitive function was assessed at 7 years of age, using the Kaufman Assessment Battery for Children, resulting in three main outcome parameters: sequential processing (short-term memory), simultaneous processing (problem-solving skills), and the mental processing composite score. Spline regression and linear regression analyses were used to analyse the data, while adjusting for potential relevant covariates.

Results: Only 2% of the children performed more than one SD below the mental processing composite norm score. Children with lower test scores (< 25%) were more likely to have a younger mother with a higher pre-gestational BMI, less likely to be breastfed, and more likely to be born with a lower birth weight, compared to children with higher test scores (≥25%). Fully-adjusted linear regression models did not show associations of maternal AA, DHA, or EPA status during any of the pregnancy trimesters with childhood sequential and simultaneous processing.

Conclusion: Maternal fatty acid status during pregnancy was not associated with cognitive performance in Dutch children at age 7.

1. Introduction

Fish consumption in the Dutch population is low [1]. As fish is the predominant source of the long-chain polyunsaturated fatty acids (LCPUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the intake of these fatty acids is low as well. Specifically, Dutch women aged 19–30 have reported a median (25th – 75th percentile) intake of 75 (41–133) mg EPA + DHA/day; those aged 31–51 years have reported an intake of 89 (49–155) mg EPA + DHA/day [1]. To put this into perspective, the European Food Safety Authority (EFSA) currently recommends pregnant women to consume 350–450 mg of EPA and DHA per day [2]. This low intake of these LCPUFAs, particularly DHA, in women of reproductive age is worrisome. Human studies namely indicate that the brain contains high concentrations of DHA [3], of which high quantities are already incorporated during the third trimester of gestation [4]. As the fetus principally depends on the DHA stores/intake of the mother, an adequate and balanced maternal DHA supply during gestation is assumed to be important for the developing fetal brain.

Besides DHA, another predominant LCPUFA in the human brain is

Abbreviations: AA, arachidonic acid, 20:4n-6; DHA, docosahexaenoic acid, 22:5n-3; EPA, eicosapentaenoic acid, 20:5n-3; LCPUFAs, long-chain poly unsaturated fatty acids; K-ABC, Kaufman-Assessment Battery; MEFAB, Maastricht Essential Fatty Acid Birth Cohort

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arachidonic acid (AA). As AA can be obtained from a more abundant spectrum of food sources than EPA and DHA, including vegetable oils, poultry, eggs, nuts, and whole-grain products, the intake of AA is assumed to be adequate in the Dutch population. Previous literature, however, does indicate an endogenous metabolic competition between n-3 fatty acids (e.g. EPA and DHA) and n-6 fatty acids (e.g. AA) [5]. Hence, not only the quantity of these LCPUFAs, but also their relative proportion may be of importance with respect to fetal brain development.

Studies investigating the impact of prenatal LCPUFA supplementation [6–12], intake [13,14], or maternal or cord blood concentrations [11,12,15–20] on child brain development and function are inconclusive. Whereas a study among 11-year-old Inuit children showed significant associations between higher umbilical cord DHA concentration and a better performance on the digit span forward and California Verbal Learning Test-Children's Version [16], no associations were observed between umbilical cord DHA concentrations and cognitive performance in 7-year-old Norwegian [6] and Dutch children [19]. Beneficial associations were observed for maternal third trimester DHA concentrations and sequential processing scores at age 7 in Norwegian boys and girls [6] and language and verbal ability in 5-year-old children living at the Seychelles [15]. On the contrary, no associations were observed between second or second/third trimester maternal DHA concentrations and cognitive performance of the child at the age of 3 [13] and 18 months [18]. Clearly, most studies investigated maternal LCPUFA concentrations in late gestation or at delivery in relation to childhood cognition. However, as fetal brain development is a highly complex process that already starts in the first trimester, research on potential LCPUFA effects throughout the whole gestational period is warranted to provide more insight regarding specific LCPUFA requirements during the various critical periods of brain development.

The Maastricht Essential Fatty Acid Birth (MEFAB) cohort provides the unique opportunity to study associations between maternal essential fatty acid status throughout gestation (i.e. < 16, 22, 32 gestational weeks) and childhood brain development and functioning. Previous analyses within the MEFAB cohort did not show associations between umbilical cord plasma AA and DHA and sequential and simultaneous processing at age 7 [19], but adverse associations were observed for maternal DHA status across trimesters and school performance based on arithmetic scores at age 7 [21]. Associations between fatty acid status across trimesters and cognitive performance at age 7 have not been explored yet. Therefore, the aim of this study was to examine the associations of maternal LCPUFA concentrations (i.e. AA, DHA, EPA, and DHA:AA) during gestation (i.e. < 16, 22, 32 weeks) with childhood cognitive performance at 7 years of age as assessed with the Kaufman-Assessment Battery (K-ABC) in the MEFAB cohort.

2. Patients and methods

2.1. Study population

This study was performed using data of the MEFAB cohort, a prospective study designed to study relationships of essential fatty acid status during gestation and birth with metabolic health and cognitive, visual and motor function in Dutch children. Recruitment took place from 1989 to 1995. Pregnant women (< 16 weeks) without any cardiovascular, neurological, renal or metabolic condition were eligible to participate. In total, $n = 1334$ women were screened; $n = 131$ (10%) were either excluded or dropped out before partus. At 7 years of age, $n = 305$ participated in the cognitive testing procedures. Excluding those with missing data on maternal fatty acid status in all three trimesters resulted in a sample size of $n = 292$ children for the analyses. More detailed information on the design and methods of the MEFAB cohort has been described elsewhere [22]. The Medical Ethics Committee of the University Hospital Maastricht/University Maastricht approved the study protocol and all families gave written informed consent.

2.2. LCPUFA status

Non-fasted blood samples were collected at study entry (< 16 gestational weeks), at 22 gestational weeks, 32 gestational weeks, and when the children were 7 years of age. Immediately after sampling, blood samples were stored at −80 °C until further analyses were conducted. In total, 41 different maternal fatty acids of plasma phospholipids (PL) were determined by gas-liquid chromatography [23], including C14:0, C15:0, C16:0, C17:0, C18:0, C20:0, C22:0, C23:0, C24:0, C16:1n-7, C18:1n-7, C20:1n-7, C18:1n-9, C18:2n-9, C20:1n9, C20:3n-9, C22:1n-9, C22:3n-9, C24:1n-9, C18:2n-6, C18:3n-6, C20:2n-6, C20:3n-6, C20:4n-6, C22:2n-6, C22:4n-6, C22:5n-6, C24:2n-6, C18:3n-3, C20:3n-3, C20:4n-3, C20:5n-3, C22:3n-3, C22:5n-3, C22:6n-3, C16:0 DMA, C18:0 DMA, C18:1 DMA, C18:2n-6tr, C16:1n-7tr, and C18:1n-9tr. For this study, maternal plasma phospholipid DHA (C22:6n-3), AA (C20:4n-6), and EPA (C20:5n-3) concentrations were selected, providing relative concentrations of DHA, AA, and EPA to total phospholipid-associated fatty acids (% wt/wt).

2.3. Cognitive performance

Cognitive function was assessed with the Kaufman Assessment Battery for Children (K-ABC) [24], which evaluates two different types of information processing: sequential processing (i.e. short-term memory) and simultaneous processing (i.e. problem-solving skills). The sequential processing score is based on a variety of assignments in which the child arranges items in serial or sequential order, such as reproducing hand taps on a table, recalling numbers, and recalling objects as presented by the researcher. The simultaneous processing score is based on a variety of assignments in which the child completes a facial recognition task, identifies objects or scenes in an unfinished picture, replicates an object using rubber triangles, selects a picture to finalize another picture or complement another picture, has to remember and recall the location of specific pictures, and arranges a variety of pictures in a meaningful order. Together the sequential and simultaneous processing scores form the mental processing composite score, a measure of intelligence. For all three scores, a score of 100 ± 15 points is considered average (i.e. norm score); a score of 85 is one standard deviation below the norm score of 100. Thus, higher scores indicate a better performance. The K-ABC was assessed according to a standard protocol, in a quiet room with blinded windows and by a single well-trained researcher.

2.4. Covariates

Information on child's sex (boy/girl, *n* (%)), gestational age at birth (weeks), birth weight (grams), birth order (first/second/third/fourth/fifth, *n* (%)),breastfeeding (no/yes, *n* (%) and duration), child's age at the time of the cognitive assessment (years), maternal age (years), maternal height (m), maternal pre-pregnancy weight (kg), maternal smoking during gestation (yes/no, *n* (%)), and maternal alcohol consumption during gestation (yes/no, *n* (%)) were collected by means of questionnaires. Bodyweight of the child was measured to the nearest 100 g using a digital scale (SECA) while wearing light underwear. Height of the child was measured to the nearest mm using a stadiometer (HoltainLTD, Crymych, UK). BMI was calculated as weight/height^2. APGAR scores 5 min after birth were extracted from hospital records. Maternal pre-gestational BMI was calculated as weight/height^2, using the measures of self-reported height and weight. Maternal intelligence was tested with Raven's Standard Progressive Matrices [25].

2.5. Statistical analyses

Participant characteristics are reported as mean with standard deviation (mean ± SD), or *n* with percentages (*n*, (%)). Medians with interquartile range (median (IQR)) were used to report skewed