Macronutrient intake during infancy and neurodevelopment in preschool children from the EDEN mother–child cohort

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Abstract

Background: Although the deleterious effect of micronutrient deficiency at sensitive periods on neurodevelopment is well established, the potential influence of macronutrient intake on early life neurodevelopment of healthy term infants has been seldomly studied. We aimed to explore whether macronutrient intake at 12 months was related to neurodevelopmental scores in preschool children.

Methods: Analyses were based on data from the EDEN mother-child cohort. Macronutrient intake was assessed by 3-day food records at 12 months of age. Neurodevelopment was assessed at 3 years using the French version of the Ages and Stages Questionnaire (ASQ) (n=914), and at 5-6 years, using the French version of the Wechsler Preschool and Primary Scale of Intelligence – Third Edition (n=785). An association between macronutrient intake and neurodevelopmental scores were analysed by multivariable linear regression for 3-year Full Score ASQ or 5-6-year intelligence quotient scores and multivariable logistic regression for 3-year ASQ subdomains.

Results: Macronutrient intake in infancy was not associated with neurodevelopmental scores in preschool children. No association was found between PUFA intake and overall neurodevelopmental scores, after accounting for multiple testing.

Conclusion: In the present study, macronutrient intake at one year did not appear to influence the child's cognitive ability at 3 and 5-6 years. Further studies are needed to clarify the relationship between early fatty acid intake and neurodevelopment**.**

Keywords

Nutrients; Fatty acids; Cognition; Childhood; intelligence quotient

Introduction

The first years of life have been pointed as a relevant stage for cognitive development (1), marked by the onset of rapid structural changes and development of brain circuits, important for later developing structures and behaviours (2, 3). Considering this, nutrition plays a crucial role in brain development from foetal life onwards. Studies have shown associations of maternal diet during pregnancy (4, 5), breastfeeding practices (6) and single nutrients (7), with brain and cognitive development, suggesting that, since early life stages, adequate intake of key nutrients may have lasting effects on the brain.

Both cross-sectional and longitudinal observational studies also highlighted that poor diet quality or a Western dietary pattern during childhood was linked with poorer cognition in children and adolescents (8-10). However, in healthy infants, studies have reported inconsistent findings regarding macronutrient intake and later neurodevelopmental scores, possibly due to limited sample sizes, cross-sectional design, and discrepancies in dimensions of neurodevelopment (11-16).

Regarding carbohydrates, a higher intake of added sugar was associated with a lower score on hippocampal-dependent creativity in a cross-sectional study on 57 pre-adolescents (16), while in another cross-sectional study on 736 6-to-9-year children, a higher fructose intake was associated with a higher score on nonverbal reasoning (15).

Regarding proteins, a European multi-centre randomised controlled trial (RCT) (12) did not highlight any differences in mental performance in 8-year-old children who were fed with low- or high-protein-content formula during the first 12 months of life. In other RCTs, compared to infants consuming a regular formula, infants consuming up to 6 months of a low-energy low-protein formula supplemented with bovine milk-fat-globule membranes performed better than in the cognitive domain at 12 months (13). However, no differences were found between these two groups in any of the subscales of neurodevelopment assessment at 6.5 years old (14).

Given the association between fish intake in pregnancy or in childhood and neurodevelopmental scores (17, 18), and the role of omega-3 fatty acids in brain development, special attention has been given to polyunsaturated fatty acids (PUFAs) and the omega-6/omega-3 ratio. Nonetheless, systematic reviews and meta-analyses of RCTs showed no effect on cognition of supplementation PUFAs during infancy (19) or childhood (20).

Therefore, if macronutrient intake at early stages of life may alter distinctively cognitive functions is still unknown. In this context, the current study aimed to explore whether intake of macronutrient and polyunsaturated fatty acids intake at 12 months was related to neurodevelopmental scores in preschool children from the EDEN mother-child cohort. Our two main hypotheses were: (i) lower intake of protein, and higher fat intake at 12 months is associated with higher neurodevelopmental scores at 3 and 5-6 years; (ii) a high omega-6/omega-3 ratio is negatively related to neurodevelopmental scores.

Methods

Study Design

The EDEN study is an ongoing French mother-child cohort aiming to study pre- and postnatal determinants of the child's development and health, details on the study protocol have been published elsewhere (21). Between 2003 and 2006, pregnant women were invited to participate in the cohort at the university hospitals of Poitiers and Nancy, France, during their hospital visit before their 24th week of amenorrhea. Exclusion criteria were multiple pregnancies, diagnosis of diabetes prior to pregnancy, French illiteracy, and intention to move outside the region in the following 3 years.

Informed written consent was obtained from parents at enrolment, and consent for the child to be in the study was obtained from both parents after the child's birth. The study received approval from the ethics committee (CCPPRB) of the university hospital of Kremlin-Bicêtre hospital (ID 0270 of 12 December 2002), and data files were declared to the National Commission on Information Technology and Liberties (Commission Nationale Informatique et Liberté) (CNIL, ID 902267 of 12 December 2002).

Data collection

At 24–28 weeks of gestation, mothers had a clinical examination performed by research midwives assistants, where their height was measured, using a wall Seca 206 stadiometer (Hamburg, Germany) to the nearest 0.2 cm. Maternal education and pre-pregnancy weight, family income during pregnancy and smoking during pregnancy were obtained by interviewing the mother. Data were collected from obstetrical and paediatric records on sex, parity, gestational age at delivery, and birth weight. Birth weight customised z-scores were calculated according to Gardosi references taking into account physiological fetal (sex and gestational age) and maternal factors (weight, height, parity, country of birth) (22).

Maternal dietary intake during the last three months of pregnancy was collected at delivery using a validated food frequency questionnaire (23), including fruit and vegetable intake (times/day) and fish and shellfish intake (split into terciles). Alcohol drinking during the last three months of pregnancy was also collected and considered a binary variable (yes/no) due to its zero-inflated nature.

Exclusive breastfeeding duration (in months) and age at complementary food introduction (in months) were calculated from the data collected at ages 4, 8 and 12 months (24).

Macronutrients intake. At the 12-month follow-up, children's dietary intake was assessed by food records reporting three non-consecutive days (two weekdays and one weekend day). Mothers were asked to describe detailed information on their child's mealtime, each food provided, brand names (when available) or the recipe in case of homemade foods, the quantity provided (grams, millilitres, or household measures) and uneaten amount. The data were checked and computerised a posteriori by a dietician, allowing the calculation of consumed quantity (25). Nutrient intake was calculated based on food composition databases from the French baby foods industry group (SFAE 2005) or, in case of data unavailability of certain foods, from the French Observatory of Food Nutritional Quality (CIQUAL 2020). Then, total energy intake, total intake of proteins, carbohydrates and lipids was obtained, and the specific intake of α-linolenic (ALA, 18:3 n-3) and linoleic (LA, 18:2 n-6) acids. The LA/ALA ratio was also determined. As breast milk intake could not be measured, nutrient intake was calculated only among infants no longer breastfed at the 12-month follow-up.

Neurodevelopment scores. At the 3-year follow-up, neurodevelopment was assessed using the French version of the Ages and Stages Questionnaire (ASQ) (26), which includes 30 items divided into 5 domains of child development: communication; gross motor; fine motor; problem solving; and personal-social skills. For each item, the parents indicate whether the child was able to perform the task: ''Yes'' (10 points), ''Sometimes'' (5 points) and ''Not yet'' (0 points). The score for each domain is obtained by adding the scores of six items and ranges from 0 to 60 points. The total ASQ score is established by combining the scores of the five domains and ranges from 0 to 300 points. At the 5-6-year follow-up, children's overall cognitive and intellectual functioning was evaluated using the French version of the Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III) (27), administered by trained psychologists. The core subtests of the battery were assessed (Information, Vocabulary, Word Reasoning, Block Design, Matrix Reasoning, Picture Concepts, and Coding) to obtain the age-adjusted composite scores, namely verbal IQ, performance IQ, and full-scale IQ.

Parental stimulation. At the 3-year follow-up, maternal stimulation was assessed through the average frequencies of storytelling, singing and playing with the child (every day or almost, 3-5 times/week, 1-2 times/week and <1 time/week or never). At 5-6 years, cognitive stimulation at home was measured through three subscales of the Home Observation for the Measurement of the Environment Scale (HOME score): language stimulation, academic stimulation, and a variety of experimentations (28).

Participants

Of the 2002 recruited women, data on sex and birthweight were available for 1899 individuals (Figure 1). After the exclusion of children born very preterm (< 33 weeks, n=12) or with characteristics related to dietary intake such as having no dietary assessment, a food allergy or still being breastfed at the 12-month follow-up (n=754), a total of 1133 participants were included in the current study. Finally, children without data on neurodevelopmental outcomes (at 3 years, n=219; at 5-6 years, n=348) were excluded, leading to a sample of 914 children at 3 years and 785 children at 5-6 years.

For the complete-case analysis, we also excluded children with missing data on potential confounders ending up with a sample of 761 children at 3 years and 654 children at 5-6 years.

Statistical Analysis

Multivariable linear regression models (standardized beta coefficients, β, and 95% confidence intervals, *95% CI*) were performed to assess the associations between dietary intake and child neurodevelopmental scores (Full IQ, Verbal IQ, Performance IQ, total ASQ). Logistic regression models (odds ratio, *OR*, and 95% confidence intervals, *95% CI*) were computed to evaluate associations of dietary intake with the 5 ASQ subscales. The ASQ subscales were considered dichotomous variables, using the first tercile as a cut-off. Then, the risk of having a poor score for each domain was modelled. For both linear and logistic regressions, dietary intake was considered in three different models, one considering simultaneously proteins, carbohydrates, and lipids, the second one considering both ALA and LA and the last one considering the LA/ALA ratio. Macronutrients were standardized to improve interpretability.

The covariates were firstly identified according to previous literature and selected using the directed acyclic graph method (Supplementary figure S1) (29). Multivariable models were then adjusted for the following covariates: maternal characteristics (age, educational level, parity, pre-pregnancy BMI, smoking during pregnancy, alcohol drinking during pregnancy, fish, fruit, and vegetable intake during pregnancy), child characteristics (birth weight z-scores, sex, gestational age, exclusive breastfeeding duration, age at complementary food introduction), and recruitment centre. At both ages, a second model was run, additionally adjusted for maternal home stimulation, at 3 years old, for the ASQ outcome and at 5-6 years old, for the IQ outcome. Missing data on covariates (Table 1) were imputed using multiple imputation by chained equations since missing data was assumed at random (30), with 20 independent datasets generated. Sensitivity analyses were performed based on the complete-case sample.

For all models (imputed and complete-case analyses), an interaction between macronutrient intake and sex was tested and when significant ($p<0.05$), an interaction term was included in the model.

To account for multiple comparisons, the false discovery rate (FDR) correction was performed (31) with a q-value cut-off set at 0.10.

All statistical analyses were performed in R statistical software (The R Project for Statistical Computing, Vienna Austria), version 4.0.0 for MacOS, using the packages *stats (32), mice (33)* and *aod (34).* The significance level was set at 0.05.

Results

In comparison with subjects excluded from the 3-year analysis (Supplementary Table S1), included children were more likely to be born to older mothers (30.0 *vs.* 29.0 years), with a higher educational level (64.4 *vs.* 39.7% with a University degree), being primiparous (49.6 *vs*. 36.2), less likely to smoke during pregnancy (20.5 *vs.* 27.2%) and eating more frequently fish and shellfish intake during pregnancy (>2 times/week: 30.7 *vs.* 24.8%). Included children had a higher birthweight (3304 *vs.* 3255 g), gestational age (39.3 *vs.* 39.1 weeks) and lower duration of exclusive breastfeeding (1.4 *vs*. 1.8 months). Similar differences were found for the sample included in the analysis at 5-6 years.

Participants' characteristics are described in Table 1, and children's dietary intake and neurodevelopmental scores are represented in Table 2. Among the 3-year sample, the 12-month protein intake was on average 29.0 g/day, the 12-month carbohydrate intake on average 110.4 g/day, and the 12-month fat intake on average 30.2 g/day. The LA and ALA intakes were, on average, 3.0 g/day and 0.4 g/day, respectively. Children scored on average 270 points in the full ASQ score at 3 years and 104 points in the full IQ score at 5-6 years.

In both the imputed analyses (Table 3) and the complete-case analysis (Supplementary Table S2), 12-month macronutrient intake (proteins, lipids or carbohydrates) was not associated with any of the neurodevelopmental scores at 3 or 5-6 years of age (Table 3).

When examining more specifically PUFA intake, 12-month ALA and LA intake were not related to neurodevelopmental scores at 3 or 5-6 years in the imputed analyses (Table 4). In the complete-case sample (Table S3), a higher 12-month LA intake was associated with a lower risk of having a poor Personal-Social score (OR=0.75; 95% CI 0.57, 0.98, for 1 each SD of LA intake). After additional adjustment for maternal home stimulation at 3 years old, the association was no longer significant, as after accounting for multiple testing using the false discovery rate method. In the complete-case sample (Table S3), a higher ALA intake at 12 months was associated with lower full-scale IQ (β= -1.70; 95% CI -3.12, -0.28, for 1 each SD of ALA intake), even after adjustment for parental home stimulation, but the association was no longer significant after accounting for multiple testing using the false discovery rate method.

In the imputed analyses, the LA/ALA ratio was not related to any neurodevelopmental score (Table 5). However, in the complete-case analysis, an intermediate LA/ALA ratio (7.6 to 10.0) was associated with a higher verbal IQ (β= 2.72; 95% CI 0.21, 5.22), compared to those with a lower LA/ALA ratio (<7.6). The association was no longer significant after accounting for multiple testing using the false discovery rate method.

Discussion

In the EDEN mother-child cohort study, macronutrient intake during infancy was not associated with neurodevelopmental scores at preschool ages. Some associations were found between polyunsaturated fatty acids - linoleic acid and α-linolenic acid - and the personal-social and the IQ scores, but these associations were found only in the complete-case analysis and were not significant after accounting for multiple testing.

Macronutrients supply energy to the brain, but also essential nutrients/compounds to the physiological system (35). The way the different macronutrients influence cognitive function or neurodevelopment may relate to multiple pathways, i.e., affecting peripheral glucose and insulin, neurotransmitter synthesis, oxidative stress and inflammation, leading to structural damage over time (36). Experimental and observational studies on preterm infants supplied with higher energy-content formulas and macronutrientenriched formulas in the first weeks of life (protein, fat and carbohydrates) showed improvements in neurodevelopmental scores in adolescence (37) or even adulthood (11), respectively, than those with a regular formula intake. However, adjustment for neonatal complications significantly attenuated the association between higher intakes of energy and nutrients and neurocognitive abilities in adulthood (11).

In the present study, we did not find any association between macronutrient intake and neurodevelopmental scores, but our sample was mainly composed of well-nourished, healthy-term infants (only 8% had a gestational age between 33 and 37 weeks). Further studies are needed to clarify this relation as macronutrient influence on neurodevelopment during the first years of life may vary according to infant characteristics, particularly those with higher macronutrient needs, such as preterm infants or children affected by macro- and micronutrient deficiencies (38, 39).

Regarding carbohydrates, a systematic review reported inconsistent evidence on the influence of the quality and quantity of carbohydrates in meals and breakfasts (measured by the glycaemic index or glycaemic load) on executive function among children (more than 5 years old) and adolescents, mostly from studies with a cross-over design (40). A recent cross-sectional study among 6-8 years healthy old children showed no relation between total carbohydrates and cognition (15), as in the present study.

Regarding proteins, an RCT did not highlight any neuropsychological difference at 8 years old among term-born children consuming in infancy a low-protein formula or a high-protein formula (12). Even in a specific population, like preterm infants, RCTs have not highlighted any beneficial effect of protein-rich formulas on neurodevelopmental scores in childhood (41-43).

Regarding lipids, literature on the relationship between lipids intake during infancy and neurodevelopment scores mainly focused on polyunsaturated fatty acids (19, 44, 45). In 2017, a Cochrane review focused on PUFA supplementation in full-term formula-fed infants on neurodevelopmental outcomes up to 2 years of age, did not show any beneficial effect of PUFA supplementation on neurodevelopmental scores (44), in line with a previous meta-analysis of large clinical trials (45). Also, a recent systematic review did not highlight any beneficial effect of PUFA enrichment of infant formula on cognitive function among children aged >2.5 years (19). Our findings are in line with these reviews as we did not highlight any association between PUFA intake and overall developmental scores, after accounting for multiple testing. Besides the total PUFA intake, the LA/ALA ratio could be of interest, as previous results from the EDEN study showed that maternal intake of LA/ALA ratio during pregnancy was negatively associated with ASQ and other neurodevelopmental scores (46). A cross-sectional study among 7-9 years old children reported that the effect of the ratio was moderated by total fatty acids intake: the n-6 to n-3 ratio was related to cognitive performance negatively among children with high n-3 intake, whereas it was related positively among those with low n-3 intake (47). In the present study, an intermediate LA/ALA ratio appeared positively related to 5-6-year verbal IQ, but only on the complete-case sample and not anymore after accounting for multiple testing.

Based on the data from an established mother-child cohort, the strengths of the present study include its prospective design that limits memory bias for both exposure and outcome assessment. Data collection also allowed a detailed assessment of the infant's dietary intake with 3-day dietary records, but the food composition database did not allow the assessment of some PUFAs, such as DHA and AA for commercial complementary foods, and other macronutrient subtypes, such as free sugars. To facilitate comparisons with other studies, we used two validated tools, targeting different aspects of neurodevelopment. ASQ was a parent-completed tool, and we cannot exclude the social desirability bias, but the IQ was evaluated by trained psychologists, limiting this bias. Even though ASQ is a screening tool to detect a developmental delay in children, it is considered a useful tool for investigating risk factors of poor neurodevelopment (48). The ASQ and the WPPSI measure common constructs, i.e., language (Communication and Verbal IQ, respectively) and nonverbal skills (Problem-solving and Performance IQ), however, the ASQ puts greater emphasis on other domains of development, such as motor skills and personal-social abilities than the IQ. Nonetheless, a poor ASQ score (<270) at the age of 3 has been related to a higher risk of having a lower IQ (<85) at 5 to 6 years old (49).

Even though we could control for important confounding factors, like maternal dietary intake during pregnancy or parental home stimulation, residual confounding could not be excluded as we did not control for maternal IQ but only for maternal education level. Furthermore, mothers from the EDEN mother-child cohort had a higher educational level than the French national population (21) and the attrition enhanced this selection bias, which may also contribute to the lack of variability and inability to detect associations. Further studies would have to be conducted on more disadvantaged families, especially because poverty may increase the risk of nutrient deficiency that may impact the child's neurodevelopment (50). Performing multiple tests increases the chance of occurring Type-I errors, so we adjusted for multiple testing. No association remained significant after applying the false discovery rate correction, underlying the need to replicate the analyses in other studies.

Conclusion

In the EDEN mother-child cohort, macronutrient intake at 12 months did not appear as a strong determinant of neurodevelopmental scores at 3 and 5-6 years of age. As we cannot exclude that findings on PUFA were chance findings, the potential influence of PUFA intake at the end of the complementary feeding period should be further examined in a larger population, with a greater variability on polyunsaturated fatty acids intake and with more details on the different polyunsaturated fatty acids. Also, it would be essential to account for the influence of carbohydrate subtypes, like added sugar, and the influence of micronutrient intake, on child cognitive development in healthy term infants from different population settings, for instance low socioeconomic positions. From a public health perspective, prospectively studying the relationship between macronutrients and cognition/neurodevelopment may give insight into further recommendations aiming to improve diets for the developing child, at such a critical period of brain development.

Data availability

The data underlying the findings cannot be made freely available for ethical and legal restrictions imposed, because this study includes a substantial number of variables that, together, could be used to re-identify the participants based on a few key characteristics and then be used to have access to other personal data. Therefore, the French ethics authority strictly forbids making these data freely available. However, they can be obtained upon request from the EDEN principal investigator. Readers may contact barbara.heude@inserm.fr to request the data. The analytic code will be made available upon request pending application and approval.

Authorship

Ana Rita Marinho wrote the initial draft, performed data analysis, and had the final approval of the version to be published. Daniela Correia contributed to statistical analysis and data interpretation. Carla Lopes contributed to the conception of the study and interpretation of data. Blandine de Lauzon-Guillain supervised the analysis plan, assisted the statistical analysis and data interpretation. Barbara Heude was responsible of the EDEN mother-child cohort. Barbara Heude and Jonathan Bernard were involved in collection, cleaning, and interpretation of the data.

All authors reviewed drafts, provided critical feedback, read, and approved the final manuscript and were responsible for the final content of the paper.

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Conflicts of Interest

None.

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Figure legend

Figure 1. Sample selection flow chart