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1 **Title: Macronutrient intake during infancy and neurodevelopment in preschool children from the**
2 **EDEN mother-child cohort**

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21

22

23 **Abstract**

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

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

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

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

41

42 **Keywords**

43 Nutrients; Fatty acids; Cognition; Childhood; intelligence quotient

44

45 **Introduction**

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

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

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

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

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

73 Therefore, if macronutrient intake at early stages of life may alter distinctively cognitive functions is
74 still unknown. In this context, the current study aimed to explore whether intake of macronutrient and

75 polyunsaturated fatty acids intake at 12 months was related to neurodevelopmental scores in preschool
76 children from the EDEN mother-child cohort. Our two main hypotheses were: (i) lower intake of protein,
77 and higher fat intake at 12 months is associated with higher neurodevelopmental scores at 3 and 5-6
78 years; (ii) a high omega-6/omega-3 ratio is negatively related to neurodevelopmental scores.

79

80 **Methods**

81 *Study Design*

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

88 Informed written consent was obtained from parents at enrolment, and consent for the child to be in the
89 study was obtained from both parents after the child's birth. The study received approval from the ethics
90 committee (CCPPRB) of the university hospital of Kremlin-Bicêtre hospital (ID 0270 of 12 December
91 2002), and data files were declared to the National Commission on Information Technology and Liberties
92 (Commission Nationale Informatique et Liberté) (CNIL, ID 902267 of 12 December 2002).

93

94 *Data collection*

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

102 Maternal dietary intake during the last three months of pregnancy was collected at delivery using a

103 validated food frequency questionnaire (23), including fruit and vegetable intake (times/day) and fish and

104 shellfish intake (split into terciles). Alcohol drinking during the last three months of pregnancy was also
105 collected and considered a binary variable (yes/no) due to its zero-inflated nature.

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

108

109 **Macronutrients intake.** At the 12-month follow-up, children's dietary intake was assessed by food
110 records reporting three non-consecutive days (two weekdays and one weekend day). Mothers were asked
111 to describe detailed information on their child's mealtime, each food provided, brand names (when
112 available) or the recipe in case of homemade foods, the quantity provided (grams, millilitres, or
113 household measures) and uneaten amount. The data were checked and computerised a posteriori by a
114 dietician, allowing the calculation of consumed quantity (25). Nutrient intake was calculated based on
115 food composition databases from the French baby foods industry group (SFAE 2005) or, in case of data
116 unavailability of certain foods, from the French Observatory of Food Nutritional Quality (CIQUAL
117 2020). Then, total energy intake, total intake of proteins, carbohydrates and lipids was obtained, and the
118 specific intake of α -linolenic (ALA, 18:3 n-3) and linoleic (LA, 18:2 n-6) acids. The LA/ALA ratio was
119 also determined. As breast milk intake could not be measured, nutrient intake was calculated only among
120 infants no longer breastfed at the 12-month follow-up.

121

122 **Neurodevelopment scores.** At the 3-year follow-up, neurodevelopment was assessed using the French
123 version of the Ages and Stages Questionnaire (ASQ) (26), which includes 30 items divided into 5
124 domains of child development: communication; gross motor; fine motor; problem solving; and personal-
125 social skills. For each item, the parents indicate whether the child was able to perform the task: "Yes"
126 (10 points), "Sometimes" (5 points) and "Not yet" (0 points). The score for each domain is obtained by
127 adding the scores of six items and ranges from 0 to 60 points. The total ASQ score is established by
128 combining the scores of the five domains and ranges from 0 to 300 points. At the 5-6-year follow-up,
129 children's overall cognitive and intellectual functioning was evaluated using the French version of the
130 Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III) (27), administered by
131 trained psychologists. The core subtests of the battery were assessed (Information, Vocabulary, Word
132 Reasoning, Block Design, Matrix Reasoning, Picture Concepts, and Coding) to obtain the age-adjusted
133 composite scores, namely verbal IQ, performance IQ, and full-scale IQ.

134

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

140

141 *Participants*

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

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

150

151 *Statistical Analysis*

152 Multivariable linear regression models (standardized beta coefficients, β , and 95% confidence intervals,
153 95% CI) were performed to assess the associations between dietary intake and child neurodevelopmental
154 scores (Full IQ, Verbal IQ, Performance IQ, total ASQ). Logistic regression models (odds ratio, OR, and
155 95% confidence intervals, 95% CI) were computed to evaluate associations of dietary intake with the 5
156 ASQ subscales. The ASQ subscales were considered dichotomous variables, using the first tercile as a
157 cut-off. Then, the risk of having a poor score for each domain was modelled. For both linear and logistic
158 regressions, dietary intake was considered in three different models, one considering simultaneously
159 proteins, carbohydrates, and lipids, the second one considering both ALA and LA and the last one
160 considering the LA/ALA ratio. Macronutrients were standardized to improve interpretability.

161 The covariates were firstly identified according to previous literature and selected using the directed
162 acyclic graph method (Supplementary figure S1) (29). Multivariable models were then adjusted for the
163 following covariates: maternal characteristics (age, educational level, parity, pre-pregnancy BMI,

164 smoking during pregnancy, alcohol drinking during pregnancy, fish, fruit, and vegetable intake during
165 pregnancy), child characteristics (birth weight z-scores, sex, gestational age, exclusive breastfeeding
166 duration, age at complementary food introduction), and recruitment centre. At both ages, a second model
167 was run, additionally adjusted for maternal home stimulation, at 3 years old, for the ASQ outcome and at
168 5-6 years old, for the IQ outcome. Missing data on covariates (Table 1) were imputed using multiple
169 imputation by chained equations since missing data was assumed at random (30), with 20 independent
170 datasets generated. Sensitivity analyses were performed based on the complete-case sample.

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

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

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

178

179 **Results**

180 In comparison with subjects excluded from the 3-year analysis (Supplementary Table S1), included
181 children were more likely to be born to older mothers (30.0 vs. 29.0 years), with a higher educational
182 level (64.4 vs. 39.7% with a University degree), being primiparous (49.6 vs. 36.2), less likely to smoke
183 during pregnancy (20.5 vs. 27.2%) and eating more frequently fish and shellfish intake during pregnancy
184 (>2 times/week: 30.7 vs. 24.8%). Included children had a higher birthweight (3304 vs. 3255 g),
185 gestational age (39.3 vs. 39.1 weeks) and lower duration of exclusive breastfeeding (1.4 vs. 1.8 months).
186 Similar differences were found for the sample included in the analysis at 5-6 years.

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

193 In both the imputed analyses (Table 3) and the complete-case analysis (Supplementary Table S2),
194 12-month macronutrient intake (proteins, lipids or carbohydrates) was not associated with any of the
195 neurodevelopmental scores at 3 or 5-6 years of age (Table 3).

196 When examining more specifically PUFA intake, 12-month ALA and LA intake were not related to
197 neurodevelopmental scores at 3 or 5-6 years in the imputed analyses (Table 4). In the complete-case
198 sample (Table S3), a higher 12-month LA intake was associated with a lower risk of having a poor
199 Personal-Social score (OR=0.75; 95% CI 0.57, 0.98, for 1 each SD of LA intake). After additional
200 adjustment for maternal home stimulation at 3 years old, the association was no longer significant, as
201 after accounting for multiple testing using the false discovery rate method. In the complete-case sample
202 (Table S3), a higher ALA intake at 12 months was associated with lower full-scale IQ ($\beta = -1.70$; 95% CI
203 $-3.12, -0.28$, for 1 each SD of ALA intake), even after adjustment for parental home stimulation, but the
204 association was no longer significant after accounting for multiple testing using the false discovery rate
205 method.

206 In the imputed analyses, the LA/ALA ratio was not related to any neurodevelopmental score (Table
207 5). However, in the complete-case analysis, an intermediate LA/ALA ratio (7.6 to 10.0) was associated
208 with a higher verbal IQ ($\beta = 2.72$; 95% CI 0.21, 5.22), compared to those with a lower LA/ALA ratio
209 (<7.6). The association was no longer significant after accounting for multiple testing using the false
210 discovery rate method.

211

212 **Discussion**

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

218 Macronutrients supply energy to the brain, but also essential nutrients/compounds to the physiological
219 system (35). The way the different macronutrients influence cognitive function or neurodevelopment may
220 relate to multiple pathways, i.e., affecting peripheral glucose and insulin, neurotransmitter synthesis,
221 oxidative stress and inflammation, leading to structural damage over time (36). Experimental and
222 observational studies on preterm infants supplied with higher energy-content formulas and macronutrient-

223 enriched formulas in the first weeks of life (protein, fat and carbohydrates) showed improvements in
224 neurodevelopmental scores in adolescence (37) or even adulthood (11), respectively, than those with a
225 regular formula intake. However, adjustment for neonatal complications significantly attenuated the
226 association between higher intakes of energy and nutrients and neurocognitive abilities in adulthood (11).

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

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

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

242 Regarding lipids, literature on the relationship between lipids intake during infancy and
243 neurodevelopment scores mainly focused on polyunsaturated fatty acids (19, 44, 45). In 2017, a Cochrane
244 review focused on PUFA supplementation in full-term formula-fed infants on neurodevelopmental
245 outcomes up to 2 years of age, did not show any beneficial effect of PUFA supplementation on
246 neurodevelopmental scores (44), in line with a previous meta-analysis of large clinical trials (45). Also, a
247 recent systematic review did not highlight any beneficial effect of PUFA enrichment of infant formula on
248 cognitive function among children aged >2.5 years (19). Our findings are in line with these reviews as we
249 did not highlight any association between PUFA intake and overall developmental scores, after
250 accounting for multiple testing. Besides the total PUFA intake, the LA/ALA ratio could be of interest, as
251 previous results from the EDEN study showed that maternal intake of LA/ALA ratio during pregnancy
252 was negatively associated with ASQ and other neurodevelopmental scores (46). A cross-sectional study

253 among 7-9 years old children reported that the effect of the ratio was moderated by total fatty acids
254 intake: the n-6 to n-3 ratio was related to cognitive performance negatively among children with high n-3
255 intake, whereas it was related positively among those with low n-3 intake (47). In the present study, an
256 intermediate LA/ALA ratio appeared positively related to 5-6-year verbal IQ, but only on the complete-
257 case sample and not anymore after accounting for multiple testing.

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

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

282

283 **Conclusion**

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

295

296

297

298 **Data availability**

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

306

307 **Authorship**

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

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

316

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332

333

334 **Conflicts of Interest**

335 None.

336

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476 **Figure legend**

477 **Figure 1.** Sample selection flow chart