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Title of article

Breastfeeding duration and cognitive development at 2 and 3 years of Age in the EDEN mother-child cohort

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Key words

Early childhood, Ages and Stages Questionnaire, MacArthur Communicative Development Inventory

Abbreviations

ASQ: Ages and Stages Questionnaire

CDI: MacArthur Communicative Development Inventory

IQ: Intelligence Quotient

LCPUFA: Long-Chain Poly-Unsaturated Fatty Acids

Contributions of each author

The authors' responsibilities were as follows: JYB performed the statistical analyses and wrote the first draft of the manuscript under the supervision of BH, MD and M-AC; M-AC coordinated the EDEN study and is the guarantor of the present study; MD, M-AC and BH designed the current study; BH provided statistical insight; JYB, AF, TA, MB, VC, MK and BLG greatly contributed to the database. All authors reviewed the manuscript, had full access to all the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analyses.

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STRUCTURED ABSTRACT

Objective: To investigate the dose-response relationship between breastfeeding duration and cognitive development in French preschool children.

Study design: In the French EDEN mother-child cohort study, we evaluated language ability with the Communicative Development Inventory (CDI) in 1387 two-year-old children and overall development with the Ages and Stages Questionnaire (ASQ) in 1199 three-year-old children. Assessments were compared between breastfed and non-breastfed children and also according to breastfeeding duration in multivariable linear models, controlling for a wide range of potential confounders. We tested departure from linearity.

Results: After adjustments, ever-breastfed children scored 3.7 ± 1.8 ($P = 0.038$) points higher than never-breastfed children on the CDI and 6.2 ± 1.9 ($P = 0.001$) points higher on the ASQ. Among breastfed children, exclusive and any-breastfeeding durations were positively associated with both CDI and ASQ scores. The fine motor domain of ASQ was associated with any-breastfeeding duration, and the problem solving domain with exclusive-breastfeeding duration. We did not observe significant departures from linearity. No interactions were found between the child's gender, parental education or socioeconomic status, and breastfeeding duration.

Conclusion: Our results show that longer breastfeeding duration was associated with better cognitive and motor development in two- and three-year-old children and suggest a dose-response relationship.

Since the original report in 1929,¹ many observational studies have shown that breastfeeding was associated with better language ability in middle childhood² that breastfed children have higher scores at tests on cognitive abilities than never-breastfed children by meta-analysis.³ However, some authors suggested that these results were due to the difference between the socio-demographic and occupational characteristics of mothers who breastfed and those who did not, and that breastfeeding itself had little or no effect on the intelligence quotient (IQ) score, after controlling for confounding variables about the child, the mother, and the household environment.⁴ In order to provide evidence for causality, Kramer et al performed a large trial,⁵ where maternity centers were randomized to the promotion or not, of breastfeeding. They concluded that the promotion of breastfeeding, resulting in a longer exclusive-breastfeeding duration, improved children's cognitive development.

Most authors have used a binary variable (breastfed vs bottle-fed children)^{3,6} or categorized breastfeeding duration,¹⁻³ and few prospective cohorts have studied quantitatively evaluated breastfeeding duration in relation to cognitive scores.⁶⁻⁸ Thus, the dose-response relationship between breast milk consumption and cognitive development, which is a further argument for causality, deserves to be further examined with an accurate, prospective data collection of breastfeeding from larger cohorts. To our knowledge, only 1 study tested the hypothesis of linearity and found a nonlinear association with 2 IQ tests, but this study was among adults.⁹

Few studies on breastfeeding have been published in France,¹⁰ where breastfeeding prevalence and duration remain slightly lower than in the US¹¹ and much lower than in other European countries.¹² New data on the relationship between breastfeeding duration and the child's cognitive development are necessary for national public health policies. The aim of the present study was to investigate the dose-response relationship between breastfeeding duration and child cognitive development at 2 and 3 years.

Methods

The EDEN study is an ongoing birth-cohort study that aims to investigate the role of pre- and post-natal determinants on child growth, development, and health. Between 2003 and 2006, a total of 2002 pregnant women were recruited before 24 weeks of amenorrhea, in 2 French university hospitals in Nancy and Poitiers. Exclusion criteria were multiple pregnancies, known diabetes prior to pregnancy, illiteracy, and plans to move outside the region in the next 3 years. Among women who fulfilled these inclusion criteria, 55% agreed to participate. Details of the EDEN study protocol have been published.¹³ The study was approved by the ethical research committee (Comité Consultatif de protection des personnes dans la recherche biomédicale) of the Hospital of Bicêtre, and by the Data Protection Authority (Commission Nationale de l'Informatique et des Libertés). Informed written

consents were obtained from the parents at enrolment for themselves and for the newborn after delivery.

½F1_ The Figure shows the flow chart of the EDEN population from the pregnant mother's inclusion to the child's cognitive assessments. In total, 1106 children were evaluated by both the Communicative Development Inventory (CDI) and Ages and Stages Questionnaire (ASQ) scores.

During the first visit performed between 24 and 28 weeks of amenorrhea, research midwives measured maternal height and mothers declared weight before pregnancy, highest diploma obtained, and household income. We determined obesity status (body mass index ≥ 30 kg/m²) and smoking status (yes/no). Household income in Euros per month was categorically ordered: 1: <800, 2: 800-1500, 3: 1500-2300, 4: 2300-3000, 5: 3000-3800, 6: >3800. Mothers also completed a food frequency questionnaire including their weekly alcohol consumption. The number of siblings was obtained by interview. During the mother's pregnancy, the father also reported his highest diploma obtained, and parental education was defined as the average number of years of education of the mother and father. From obstetric and pediatric records, we recorded data on birth weight, offspring's sex, gestational age at delivery, and congenital anomalies. In mailed questionnaires at 4 and 8 months and at 1, 2, and 3 years, parents reported reasons for the child's hospitalizations or medical consultations. In the 2-year questionnaire, mothers reported the child's caretaker: mother, family (father, grandparents), nursery, or other (childminder, neighbor). By averaging the weekly frequencies of storytelling, singing, and playing with the child reported by mothers at 2 years, we estimated the frequency of maternal stimulations. Then, in the 3-year questionnaire, mothers reported the date of the child's entry to pre-elementary school, if applicable, and we calculated the child's school attendance.

Breastfeeding

Feeding modes during the hospital maternity stay and at discharge were from medical records. In the 4-month questionnaire, parents reported the infant's consumption of breast milk, formula, cow's milk, water and other fluids, and solids during the first week, the second-fourth weeks, and the second, third, and fourth months. In the 8-month, 1-year, and 2-year questionnaires, mothers answered the question: "Do you still breastfeed your infant?" and their use of infant formula was also recorded. After full weaning, mothers reported the date of the end of breastfeeding. The duration of 'any-breastfeeding' (including partial and exclusive-breastfeeding) in days was from the dates at the end of breastfeeding. We determined the 'exclusive-breastfeeding' duration in months from answers about the infant's consumption. We defined 'exclusive-breastfeeding' as not receiving formulas, as few infants (5%) received

other liquids or food in addition to breast milk. Some infants (n = 166) received formula at the hospital maternity because of medical reasons, but were exclusively breastfed after discharge: we considered them as exclusively breastfed. We defined 'ever-breastfed' as having received breast milk at some time or other.

Neurodevelopment Assessments

In the 2-year questionnaire, the child's language ability was evaluated with the short French version of the MacArthur CDI.¹⁴ Parents reported, from a list of 100 words, those that the child was able to voice spontaneously. CDI scores ranged between 0 and 100. Overall development was investigated at 3 years, with the second French edition of the ASQ.¹⁵ This parent-completed assessment includes 5 domains of development (communication, gross motor, fine motor, problem solving, and personal-social) with 6 questions by domain. For each question, a child scored 10 points when parents reported the child had this ability, 5 points when the behavior was occasionally observed by parents, and 0 points otherwise. Each domain score goes from 0 to 60 points and ASQ total scores, from 0 to 300 points. In the case of 1 or 2 missing data in a domain, the mean value of the non-missing items was used.

Statistical Analyses

Student t and c2 tests were used to test differences between breastfed and never-breastfed children, and to compare included and non-included mother-child pairs. The Spearman correlation was used to quantify the association between the cognitive assessment scores.

We evaluated effects of breastfeeding as a binary variable (ever- vs never-breastfed), and other predictors on both scores of cognitive assessment, by multiple linear regression analyses. We adjusted for confounding variables concerning the child (sex, gestational age, birth weight, and age at assessment), the mother (age at inclusion, obesity, tobacco and alcohol consumption) and social environment (parental education, household income, sibling number, caretaker and maternal stimulations). In the ASQ analyses for 3-year olds, we also adjusted for pre-elementary school attendance.

Nonadjusted and adjusted associations between quantitative durations of breastfeeding and cognitive assessment scores were performed among breastfed children only, using simple and multiple linear regression models. Models were adjusted for the covariates listed above.

We tested deviation from linearity of the relation between breastfeeding durations and cognitive development by introducing and testing the square of breastfeeding duration in our

models. We also tested interactions by adding to our models the interaction terms between breastfeeding duration with the child's sex, gestational age, education level, and household income. Model residuals were tested for normality.

All P values were considered as significant when $<.05$. Analyses were performed with SAS 9.3 (SAS Institute, Inc, Cary, North Carolina).

Results

Breastfeeding mothers were less likely to be a smoker or obese, parents had a higher education, a higher socioeconomic status, and mothers had more frequent activities with their child (Table I).

In the whole population, mean CDI and ASQ scores were, respectively, 60.9 ± 29.3 (mean \pm SD) and 270.3 ± 28.6 . The Spearman correlation coefficient between the CDI and ASQ scores was 0.42 ($P < .0001$). In each sample, 74% of children were ever-breastfed: at 3 months, 41% were still breastfed of whom 16% exclusively, and at 6 months, 19% were breastfed of whom 7% exclusively.

We compared mother-child pairs included and non-included (due to attrition and exclusions) in the analysis (results not shown): the characteristics of included and non-included children were not significantly different. At 2- and 3 years, mothers included were significantly older (both $P < .001$), more often not a smoker (both $P < .0001$) and primiparous (both $P < .05$). Included mother-child pairs were from higher-income (both $P < .0001$) and more highly educated (both $P < .0001$) households than those not included.

After adjustments, ever-breastfed children scored 3.7 ± 1.8 (mean \pm SE, $P = .038$) points higher than never-breastfed on the CDI and 6.2 ± 1.9 ($P = .001$) points higher on the ASQ (Table II). The CDI score was positively associated with gestational age, birth weight, the child's age at the test, and the frequency of maternal stimulations, and negatively associated with the number of siblings. Girls scored 9.0 ± 1.5 ($P < .0001$) points and 11.1 ± 1.6 ($P < .0001$) points higher than boys on the CDI and on the ASQ, respectively. The ASQ score was positively associated with parental education, household income, and the frequency of maternal stimulations. One additional month of preelementary school attendance was associated with an increase of 0.9 ± 0.6 ($P = .0004$) ASQ-points.

Among breastfed children, non-adjusted linear relationships between breastfeeding durations and cognitive assessments were significant and positive (results not shown). An additional month of exclusive-breastfeeding was associated with an increase of 0.75 ± 0.33 ($P = .02$) CDI points, and 1.00 ± 0.33 ($P = .002$) ASQ points. For any-breastfeeding duration, an additional month was related with an increase of 0.58 ± 0.20 ($P = .004$) CDI points and 0.60 ± 0.20 ($P = .003$) ASQ points. Associations persisted, after adjustment for potential confounders (Table III). The duration of exclusive-breastfeeding was positively associated

with both cognitive scores, and longer any-breastfeeding duration was related with higher CDI and ASQ scores. Exclusive-breastfeeding duration was also associated with problem solving and tended to be associated with both gross and fine motor domains. The fine motor domain was the domain most strongly associated with any-breastfeeding duration.

Among ever-breastfed children, tests of hypotheses of non-linearity of the association between breastfeeding durations and cognitive assessments were rejected (any-breastfeeding: with CDI: $P = .91$; with ASQ: $P = .44$; exclusive-breastfeeding: with CDI: $P = .61$; with ASQ: $P = .23$). We found no interaction between breastfeeding durations and sex, gestational age, parental education, or household income.

Discussion

In the EDEN Mother–Child Cohort Study, children who were ever-breastfed scored higher than those never-breastfed on both the CDI and ASQ assessments, at 2 and 3 years, respectively. We also found among breastfed children, that both exclusive and any-breastfeeding durations were positively associated with cognitive development in early childhood. After adjusting for many confounding factors associated with breastfeeding in France,¹⁶ the associations were somewhat weaker but persisted. Exclusive-breastfeeding duration was also more strongly associated with both cognitive development assessments than any-breastfeeding duration, which is a further argument in favor of a dose–response relationship.

The prospective design of EDEN is the main strength of our study. The data collection about children at birth, 4 and 8 months, and at 1 and 2 years allowed the evaluation of the exclusive-breastfeeding duration in months and any-breastfeeding duration with a precision in days. The quality of breastfeeding data is a major limitation of studies in relation with intelligence research.¹⁷ Moreover, a greater precision in breastfeeding duration provides reliability for nonlinearity testing. In our study, we found that breastfeeding duration was related linearly with both scores in contrast to another study on breastfeeding and adult IQ, where many other factors might be involved.⁹

Many studies have investigated feeding mode and duration on later development in childhood among term and preterm newborns. Our findings are in agreement with most of them.³ Lucas et al highlighted the nutritional benefits of breast milk for preterm infants in a clinical trial¹⁸ and, recently, large epidemiological studies have confirmed that breastfeeding is positively associated with cognitive development.¹⁹⁻²⁰ We also found a significant association between breastfeeding duration and the child's motor abilities, association not clearly demonstrated so far in the literature.²¹

To our knowledge, no study has found a negative association between breastfeeding and cognitive development, although some reported no association after adjustment for

socioeconomic characteristics²²⁻²³ (parental education, social class, home environment, parenting behaviors), suggesting that the central issue still remains residual confounding due to inadequate or insufficient adjustments on covariates. Actually, most of the previous studies were from Western countries, where maternal education and high socioeconomic status were positively associated with the prevalence and duration of breastfeeding. However, Daniels et al conducted a study in Filipino children, where the prevalence of breastfeeding was lower in high socioeconomic households, and still found a positive association between breastfeeding duration and cognitive development after controlling for socioeconomic status.²⁴ Nevertheless, Jacobson et al reported that the association between breastfeeding and cognitive development was no longer significant after controlling for maternal IQ,⁶ a proxy for both genetic inheritance and familial exposure. Maternal intelligence was not available in the EDEN study and this is the main limitation of our study.

The main biological hypothesis to explain this association between breastfeeding and child cognitive development is based on the content of breast milk, especially long-chain poly-unsaturated fatty acids (LCPUFA) that may be essential for brain maturation in the newborn.²⁵ In the context of the developmental origins of health and diseases, LCPUFA and especially the omega-3 included in breast milk could have a structural role and a protective function for the neuronal cells of the child, from breastfeeding initiation to weaning. The cord plasma docosahexaenoic acid concentration has already been associated with infant cognitive development.²⁶ Two randomized trials also showed a positive impact of LCPUFA-supplemented²⁷ and docosahexaenoic acid-supplemented²⁸ formulas in infants. However, the Cochrane database systematic review of Simmer et al concluded that LCPUFA-supplemented formulas have no clear benefit on infant cognition.²⁹ However, a recent study measured LCPUFA contents in mother's milk and related it with breastfeeding duration to investigate infant mental development.³⁰ They found that children breastfed with high LCPUFA level milk for a longer time had better scores than those breastfed for a shorter duration or with lower LCPUFA level milk.

Another limitation of our study was that the EDEN population was not representative of the population at inclusion, with 29% lost to follow-up at 3 years. EDEN mothers were more educated than average French mothers, but there is no reason to think that this selection would have been differential and biased our results: actually it may have reduced the data variability and the power of the study. Even if a recent French study also observed a better cognitive development in very preterm children (<3 weeks) who were breastfed,³¹ we chose to exclude very premature infants from our study. Indeed, very preterm children present higher risks of mental retardation and may have very specific nutritional needs after birth. However, in order to maximize statistical power, we chose to keep late preterm (<37

weeks) children. Exclusion of late preterm children in sensitivity analyses did not change the direction and the strength of the associations.

CDI and ASQ are parent-reported questionnaires and their validity has been confirmed for the assessment of child development.³²⁻³⁴ Strong correlations between vocabulary measured with CDI at 25 months and the performances of 3 standardized tests later in childhood have been published.³² ASQ is a screening tool initially used to detect developmental delay among young children. The French version of the ASQ has been compared with the Brunet–Lezine test performed by a psychologist in 2-year-old premature infants.³³ The ASQ was shown to be a reliable tool to predict normal neurologic outcomes in follow-up programs. The use of quantitative scores had already been debated and explored.³⁴ Despite the ceiling effects of the ASQ, the residuals of the modeled scores tended to be normally distributed and, thus, appropriate to interpret multiple linear regression results. Our study is strengthened by similar results from 2 different cognitive assessments, even though they were not very strongly correlated. Results obtained using both assessments remained consistent, even if CDI specifically evaluates language ability, and ASQ other aspects such as motor development, one year further away from the exposure period.

To conclude, our results agree with previous studies showing a relationship between breastfeeding and cognitive and motor development in early childhood. In addition, by suggesting a dose–response relationship, our study brings new evidence to the possible benefits of breastfeeding. This could provide stronger arguments to public health professionals to promote not only the initiation but also a longer duration and continuation of breastfeeding.

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