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Original Article

# Breast Milk and Brain: The Influence of Iodine and Neurotrophic and Growth Factors on Children's Neurodevelopment-A Secondary Analysis

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## Abstract

**Objective:** This study targeted to investigate the potential role of breast milk iodine concentration (BMIC), insulin-like growth factor-1 (IGF-I), and brain-derived neurotrophic factor (BDNF) during the early stage of lactation in child neurocognitive development.

**Materials and methods:** In this secondary analysis, we examined 122 breastfeeding mothers and their healthy children, all of whom were breastfed for at least six months. Levels of BDNF, IGF-1, and BMIC were assessed in breast milk samples obtained between the third and fifth days after lactation began (before any iodine supplementation intervention). Three-year-old children were administered the Bayley-III screening test to assess their cognitive, motor, and language development.

**Results:** The median (interquartile range) concentrations of iodine, BDNF, and IGF-1 in breast milk during the starting few days of lactation were 285.0 (181.0-366.0) µg/l, 0.59 (0.52-0.76) ng/ml, and 12.5 (9.6-18.3) ng/ml, respectively. The mean (standard deviation) cognitive, motor, and language scores were 101.0 (10.8), 93.4 (14.6), 100.1 (13.5) and, respectively. Linear regression models revealed a negative relation between breast milk iodine and children's cognitive development ((β unadjusted = -0.004 ($P$ = 0.010); β adjusted = -0.003 ($P$ = 0.024)). However, no associations were found between breast milk BDNF and IGF-1 and cognitive, language, or motor scores in three-year-olds.

**Conclusion:** Our findings indicate that early exposure to iodine, BDNF, and IGF-1 in breast milk, measured prior to iodine supplementation, has no substantial association with neurodevelopment in three-year-old children. The weak negative association between BMIC and cognitive scores may reflect prenatal iodine status, warranting further research to explore long-term effects of supplementation.

**Keywords:** Breast Milk Iodine Concentration; Brain-Derived Neurotrophic Factor; Insulin-Like Growth Factor-1; Child Neurocognitive Development

## Introduction

Early breastfeeding is crucial for optimal growth, development and health; its benefits persist into

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childhood, adolescence, and possibly beyond (1-4). According to the World Health Organization's recommendation, exclusively breastfeeding should be initiated within one hour of birth and continue up to 6 months after birth (5). This is due to several vital biological factors that influence gastrointestinal, immunological, and nervous system development in breastfed infants (6-8). Previous morphometric brain imaging studies have demonstrated that greater volumes and development of white matter and gray matter in various infant brain regions are associated with exclusive breastfeeding and its duration (9-11). Evidence suggests that formula-fed infants exhibit lower overall neurodevelopment in both measures of brain myelination and cognitive performance compared to breastfed infants (12, 13).

Several nutrients in breast milk, as well as lactose, amino acids, long-chain polyunsaturated fatty acids, choline, vitamins B9 and B12, zinc, and iron, have been recognized as critical for the neurocognitive development (14, 15). It is well-established that iodine is an important micronutrient for natural brain growth and cognitive development. Through the action of thyroid hormones, iodine affects the expression of neuronal proteins during the neurodevelopmental stage (16). However, data on the relation between breast milk iodine level (BMIC) and neurodevelopmental outcomes is limited (17). It remains unclear whether exposure to different amounts of iodine in breast milk can affect the neurocognitive development of infants. The precise mechanism through which iodine present in breast milk impacts an infant's neurodevelopmental status remains to be fully elucidated. Additionally, there is still much to learn about other bioactive compounds in breast milk that are involved in brain development and function. For instance, the brain-derived neurotrophic factor (BDNF), is a potential factor for enhanced cognition in breastfed infants (18). Additionally, insulin-like growth factor-1 (IGF-1) has been implicated in brain development and maturation as one of the most prevalent growth factors. (19). However, most available studies have focused on measuring BDNF and IGF-1 in serum (20-23), with only a few examining these components in breast milk (24-26). It remains unclear whether breast milk BDNF and IGF-1 could potentially contribute to child neurodevelopment.

To address the aforementioned research questions, this study is the first to investigate the role of early exposure to iodine, BDNF, and IGF-1 in the neurodevelopment of three-year-old children.

## Materials and methods

***Study design and Participants:*** This investigation, as a secondary analysis, is conducted on a subset of participants from our prior study, which evaluated the neurocognitive development of children following iodine supplementation during lactation (27). The study included 122 lactating mothers from whom breast milk samples were collected during the early days of lactation (prior to the initiation of supplementation), and their healthy children who participated in the neurodevelopmental study at the age of 3 years. This study included healthy mothers who had delivered a singleton with the intention of exclusively breastfeeding, as well as healthy infants with a normal birth weight of 2500-4200 grams, and who were exclusively or partially breastfed for at least six months after birth. Written informed consent was acquired from parents before enrolling their children. Our study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences.

***Measurements of breast milk components:*** Mothers were provided with sterile plastic bottles labeled (SUPA Medical Services, Tehran, Iran) for collecting a 10 ml sample of breast milk manually or with a breast pump during the first three to five days of lactation (before any iodine supplementation intervention). They were directed to obtain the sample during their usual feeding schedule and refrigerate it before sending it to the laboratory. At the Research Institute laboratory, all specimens were placed into labeled plastic vials with screw-top lids and stored at −80°C until analysis. Sandell-Kolthoff (acid-digestion) reaction method was applied to assessed the iodine concentration. The levels of neurotrophic and growth factors in breast milk were quantified utilizing a sandwich enzyme-linked immunosorbent assay (ELISA) technique for BDNF (ZellBio GmbH, Ulm, Germany) and IGF-1 (Mediagnost, Reutlingen, Germany).

There were 8.6%, 6.7%, and 9.3% intra-assay coefficient variations for BMIC values of 3.5, 12.7, and 36.2 g/dl, respectively. Correspondingly, the inter-assay CVs at concentrations of 3.3, 12.9, and 35.7 µg/dl were 9.8%, 8.6%, and 12.3%, respectively. BDNF's sensitivity and intra-assay CV were determined to be 0.1 ng/ml and 6.2%, whereas IGF-1's were 0.09 ng/ml and 5.9%.

***Child neurodevelopment status*:** At the age of 3 years, a child's neurocognitive development was

gauged using the Iranian version of the Bayley-III (the Bayley Scales of Infant and Toddler Development Third Edition), which is based on three key factors: cognitive, motor, and language. Once the Iranian version of the Bayley-III was verified for its accuracy and consistency, it was deemed suitable for assessing Persian-speaking minors (28). In summary, the cognition scale evaluated child's performance across various cognitive domains, including exploration and manipulation, object-relatedness skills, and memory. The receptive communication part comprised items assessing a child's vocabulary in relation to objects and images, social referencing, and verbal comprehension. The expressive communication component consists of items that evaluate a child's preverbal communication skills and the expansion of their vocabulary. The fine and gross motor sections focused on a child's movement quality, axial motor abilities, and coordination. The exact number of items can vary depending on the age of the child being assessed, but generally, each domain includes a substantial number of items to comprehensively cover the developmental milestones. There is no single overall maximum score for the Bayley-III, as it provides separate composite scores for each domain. The maximum scores for each domain depend on the specific items and the age of the child, but the composite scores typically range from 40 to 160, with a mean of 100 and a standard deviation of 15. Composite scores below 85 on the Bayley-III were considered indicative of neurodevelopmental delay (29).

***Statistical analysis:*** The mean (standard deviation), median (interquartile range), and frequency distribution (percentage) were used to express continuous and categorical variables. The normality of the variables was evaluated using the Kolmogorov–Smirnov test and by examining histogram charts. The Kruskal-Wallis and ANOVA tests were used to compare continuous variables with non-normal and normal distributions, respectively. Linear regression was applied to investigate the associations between breast milk components (i.e., iodine, BDNF, and IGF-1) and child neurocognitive development at age 3 years, with adjustments made for covariates. Unstandardized coefficients were reported in this analysis.

The covariates adjusted in the regression models included maternal age, education, use of iodine-containing supplements during lactation, gestational age, child's birth weight, age at the time of assessment, and sex. Data analysis was performed using SPSS IBM statistics (version 20.0, 2006, SPSS Inc., Chicago, IL), with statistical significance set at $P < 0.05$.

## Results

The mean (SD) age of mothers during the first few days of lactation was 28.4 (4.7) years; over half of them were multiparous (59.0%) and had undergone cesarean sections (59.5%). At the time of participation, all mothers were exclusively breastfeeding (Table 1).

**Table 1.** Basic characteristics of mothers and children, n= 122

| Characteristics | n | % | Mean | SD |
|---|---|---|---|---|
| Mothers | | | | |
| Age (year) | | | 28.4 | 4.7 |
| Occupation | | | | |
| Housewives | 115 | 94.3 | | |
| Employee | 7 | 5.7 | | |
| Education level | | | | |
| Primary | 16 | 13.3 | | |
| Secondary | 82 | 67.7 | | |
| Higher | 23 | 19.0 | | |
| Date of last pregnancy (year) | | | 3.6 | 4.2 |
| Gravidity | | | | |
| Primigravidity | 39 | 32.0 | | |
| Multigravidity | 83 | 68.0 | | |
| Parity | | | | |
| Primiparous | 50 | 41.0 | | |
| Multiparous | 72 | 59.0 | | |
| History of abortion | | | | |
| No | 99 | 81.1 | | |
| Yes | 23 | 18.9 | | |
| Mode of delivery | | | | |
| Natural vaginal delivery | 49 | 40.5 | | |
| Cesarean section | 72 | 59.5 | | |
| Gestational age (week) | | | 38.0 | 1.8 |
| Infants | | | | |
| Sex | | | | |
| Male | 70 | 57.4 | | |
| Female | 52 | 42.6 | | |
| Birth weight (g) | | | 3356 | 409 |
| Birth length (cm) | | | 50.2 | 2.1 |
| Birth head circumference (cm) | | | 35.1 | 1.3 |
| Age of children at assessment (month) | | | 39.7 | 1.2 |

The mean (SD) values for birth weight, length, and head circumference were 3356 (409) g, 50.2 (2.1) cm, and 35.1 (1.3) cm, correspondingly. At 6 months

of age, 79.5% of the children were exclusively breastfed. Although the age of 36 months was considered for assessing childhood neurodevelopment, the mean (SD) age of children was 39.7 (1.2) months due to logistical study delays. The baseline characteristics of mothers and children are presented in Table 1.

Out of the entire sample of 122 mother-neonate pairs enrolled in this study, breast milk samples from 117 mothers were available in sufficient amounts for measuring different components. The median (IQR) levels of iodine, BDNF, and IGF-1 in breast milk were 285.0 (181.0-366.0) µg/l, 0.59 (0.52-0.76) ng/ml, and 12.5 (9.6-18.3) ng/ml, respectively. When categorized into tertiles, iodine levels ranged from 154.0 (102.7-178.5) µg/l in T1 to 387.0 (354.0-532.0) µg/l in T3; BDNF levels ranged from 0.49 (0.45-0.53) ng/ml in T1 to 0.89 (0.75-2.30) ng/ml in T3; and IGF-1 levels ranged from 7.8 (6.8-9.8) ng/ml in T1 to 20.6 (17.9-23.8) ng/ml in T3 (Table 2).

The mean (SD) cognitive, motor, and language development of children according to tertiles of breast milk iodine, BDNF, and IGF-1 levels are given in Table 3. No significant differences were observed in cognitive, motor, and language scores among tertiles of breast milk components. There were no significant variances observed in the occurrence of neurodevelopmental delays across different domains concerning varying levels of breast milk iodine, BDNF, and IGF-1.

Table 4 illustrates the connections between BMIC, neurotrophic and growth factors, and the cognitive development of children at the age of 3, as determined by linear regression. In the linear regression analysis without adjustments, there was a significant decrease of 0.004 in child cognitive development for each 1 µg/l increase in BMIC (β= -0.004, *P*= 0.010). After further adjustment for maternal age, education, use of iodine containing supplement during lactation, gestational age, and child's birth weight, age at the time of assessment, and sex, the analysis indicated that for every 1 µg/l increase in BMIC, child cognitive significantly decreased by 0.003 (β= -0.003, *P*= 0.024). In both unadjusted and adjusted models, there were no observed connections between breast milk BDNF and IGF-1 levels and the cognitive, motor, or language scores of children.

## Discussion

To our knowledge, our study is among the first to explore the potential associations of certain breast milk components during the primary stage of lactation with child neurocognitive development at the age of 3 years. Our findings indicated that early exposure to iodine, BDNF and IGF-1 in breast milk does not have a significant association with neurodevelopment in three-year-old children.

A substantial body of evidence indicates that severe insufficient iodine levels in expectant mothers can lead to motor, cognitive, and auditory defects in their fetus, as observed in cretinism (29-31). However, the impact of the iodine levels in mothers during breastfeeding phase on the neurocognitive development of infants/children remains unclear. In a study conducted in China, the median colostrum iodine concentration suggested sufficient iodine status (median= 188 µg/L); no significant differences were found in the cognitive, language, or motor development of Chinese infants across different concentrations of colostrum iodine (17).

**Table 2.** Components of breast milk samples collected during the first few days of lactation

| | Breast milk components | | | | | |
|---|---|---|---|---|---|---|
| | Iodine (µg/l) | | BDNF (ng/ml) | | IGF-1 (ng/ml) | |
| Median (IQR) | 285.0 | 181.0-366.0 | 0.59 | 0.52-0.76 | 12.5 | 9.6-18.3 |
| Range | 34.0-798.0 | | 0.37-12.76 | | 5.2-57.6 | |
| Median (IQR) by tertile | | | | | | |
| T1 | 154.0 | 102.7-178.5 | 0.49 | 0.45-0.53 | 7.8 | 6.8-9.8 |
| T2 | 267.0 | 244.0-295.0 | 0.59 | 0.57-0.61 | 12.5 | 11.5-14.1 |
| T3 | 387.0 | 354.0-532.0 | 0.89 | 0.75-2.30 | 20.6 | 17.9-23.8 |
| Range by tertile | | | | | | |
| T1 | 34.0-210.0 | | 0.37-0.55 | | 5.2-10.5 | |
| T2 | 211.0-327.0 | | 0.56-0.63 | | 10.8-15.2 | |
| T3 | 329.0-798.0 | | 0.65-12.76 | | 15.7-57.6 | |

IGF-1, insulin-like growth factor-1; BDNF; brain-derived neurotrophic factor; IQR, interquartile range

**Table 3.** Neurocognitive development of children at age 3 years according to breast milk iodine, BDNF and IGF-1 concentrations

| | Bayley III score, mean (SD) | | | Bayley III score < 85, n (%) | | |
|---|---|---|---|---|---|---|
| | Cognitive | Language | Motor | Cognitive | Language | Motor |
| BMIC (µg/l) | | | | | | |
| T1 | 103.3±9.8 | 102.6±12.1 | 94.1±16.3 | 0 (0.0) | 3 (7.9) | 8 (21.1) |
| T2 | 100.1±10.0 | 100.8±11.3 | 94.5±12.4 | 2 (5.7) | 3 (8.6) | 6 (17.1) |
| T3 | 100.0±12.2 | 97.5±15.5 | 92.1±15.3 | 3 (6.8) | 6 (13.6) | 17 (29.5) |
| *P* | 0.219 | 0.204 | 0.325 | 0.277 | 0.643 | 0.403 |
| BDNF (ng/ml) | | | | | | |
| T1 | 100.3±10.1 | 99.0±13.3 | 91.2±14.0 | 2 (4.8) | 4 (9.5) | 10 (23.8) |
| T2 | 101.4±10.0 | 101.0±11.7 | 96.6±12.8 | 1 (2.9) | 4 (11.4) | 7 (20.0) |
| T3 | 101.6±12.4 | 100.7±14.8 | 93.3±17.0 | 2 (5.0) | 4 (10.0) | 10 (25.0) |
| *P* | 0.815 | 0.760 | 0.184 | 0.883 | 0.961 | 0.868 |
| IGF-I (ng/ml) | | | | | | |
| T1 | 103.4±8.1 | 100.3±12.0 | 94.0±13.7 | 0 (0.0) | 4 (10.3) | 8 (20.5) |
| T2 | 99.3±12.2 | 99.8±15.4 | 95.1±12.3 | 4 (10.3) | 3 (7.7) | 7 (17.9) |
| T3 | 103.6±11.5 | 100.5±12.8 | 91.4±18.0 | 1 (2.6) | 5 (12.8) | 12 (30.8) |
| *P* | 0.162 | 0.949 | 0.916 | 0.066 | 0.757 | 0.364 |

BDNF, brain-derived neurotrophic factor; IGF-1, insulin-like growth factor-1; SD, standard deviation; T, tertile

Consistently, in our current study with a median BMIC of 285 µg/L, no differences were observed in three neurodevelopmental areas in children at the age of 3 years among tertiles of BMIC. Similar results were observed for the frequency of neurodevelopmental delay in children. However, after adjusting for confounders, higher iodine concentrations in breast milk were associated with lower scores in child cognitive development, although its effect was very small. It is worth mentioning that there is no scientific consensus on the optimal BMIC for ensuring adequate iodine levels in infants. Different studies have proposed various cut-off values, ranging from 50 µg/L to 465 µg/L, to define sufficient iodine levels in breast milk (33-35). Additionally, BMICs typically peak during the initial days of lactation, then decline gradually over time (32, 33), as we observed in different treatment groups during 6 months of lactation in our primary study: 300 µg iodine/d group: 362 (293-511) µg/L to 160 (89-236) µg/L; 150 µg iodine/d group: 182 (151-297) µg/L to 97 (77-171) µg/L; and placebo group: 248 (177-327) µg/L to 100 (85-155) µg/L. Nevertheless, the effect of high iodine exposure during first few days of lactation on child neurocognitive development should be addressed in further studies. In a previous meta-analysis, the intelligence level of individuals (aged 7-14 years) who experienced elevated levels of iodine concentration in their drinking water significantly declined, which was aligned with our finding (34). The authors mentioned that in some studies, the absorption of a high amount of iodine in the nervous system has been proposed as an underlying mechanism of the impact of iodine excess on a child's cognitive behavior and psychomotor development, while in others, abnormal thyroid function caused by excess iodine intake has been claimed (34).

**Table 4.** Association between breast milk components during first few days of lactation and child neurocognitive development at age 3 years

| Bayley III scaled scores | BMIC (µg/l) | | | BDNF (ng/ml) | | | IGF-I (ng/ml) | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | SE | *P* | β | SE | *P* | β | SE | *P* |
| Cognitive | -0.003 | 0.001 | 0.024 | -0.051 | 0.093 | 0.584 | 0.036 | 0.026 | 0.175 |
| Receptive communication | -0.002 | 0.002 | 0.289 | -0.038 | 0.108 | 0.727 | 0.047 | 0.030 | 0.123 |
| Expressive communication | -0.001 | 0.002 | 0.473 | 0.030 | 0.124 | 0.809 | -0.017 | 0.035 | 0.634 |
| Fine motor | -0.001 | 0.002 | 0.654 | -0.036 | 0.120 | 0.765 | 0.002 | 0.034 | 0.945 |
| Gross motor | -0.002 | 0.002 | 0.277 | -0.176 | 0.128 | 0.172 | -0.014 | 0.036 | 0.696 |

BMIC, breast milk iodine concentration; IGF-I, insulin-like growth factor-I; BDNF, brain-derived neurotrophic factorData were analyzed using linear regression model and adjusted for maternal age, education, use of iodine containing supplement during lactation, gestational age, and child's birth weight, age at time of assessment, and sex. Unstandardized coefficients were reported in this analysis.

It has been shown that BDNF may play a potential role in neurodevelopment during breastfeeding or even long afterwards. For instance, in the study by Nassar *et al.*, infants (aged 4-6 months) who consumed breast milk had elevated serum BDNF levels compared to those who were fed formula. This showed a positive correlation with the overall behavior rating scale (23). However, the biological significance of BDNF in breast milk for infants and children is not well understood. To date, only a few studies have examined the prospective correlation of BDNF in serum or breast milk with child neurodevelopment. In the study by Ghassabian *et al.*, BDNF measured in newborn dried blood spots was not associated with children's neurodevelopment at age 3 years (35). Similarly, in our study, BDNF concentration in breast milk collected during the first 3-5 days of lactation ranged from 0.37-12.7 ng/ml but showed no association with child neurocognitive development at age 3 years. Different studies have reported a wide range of concentrations of BDNF in breast milk (24, 36, 37); Nevertheless, additional research is necessary to grasp the potential impact of BDNF in breast milk on the neurodevelopment of children.

Among the available studies addressing the association between IGF-1 and child growth and neurodevelopment, most have focused on serum measurements. In a study conducted in a disadvantaged area of Tanzania, serum IGF-1 was positively associated with the scores from the Malawi Developmental Assessment Tool, a measure of cognitive development in infants at 18 months of age (38). A comparable outcome was noted in preterm infants, where elevated serum IGF-1 levels during the first month were linked to greater total brain volume, white matter, gray matter, and cerebellar volume at term equivalent age (22). However, when we measured the IGF-1 concentration in breast milk, we found no associations between the three domains of the Bayley-III at 3 years of life and IGF-1 concentration. While it is true that physical development can contribute to cognitive development, the findings on breast milk IGF-1 and growth parameters in infants and children have remained inconsistent (39, 40).

This study provides the first evidence of prospective associations between certain components in breast milk (i.e., iodine, BDNF, and IGF-1) during the initial days of lactation and subsequent child neurodevelopment. Nonetheless, it is important to interpret the findings with caution due to certain limitations inherent in the current study. Firstly, we obtained a sole breast milk sample from breastfeeding mothers, which does not consider fluctuations in breast milk constituents over time. However, this initial data is valuable for identifying trends and guiding future research on iodine and other components exposure over longer durations. Secondly, we were unable to simultaneously measure the concentrations of neurotrophic and growth factors in both breast milk and infant serum, which could provide comprehensive data to better understand these associations. Although, there is no evidence to suggest that serum IGF-1 and BDNF levels are more important than their concentrations in breast milk for child neurodevelopment. Our findings provide foundational insights that can inform more comprehensive future studies, which could include simultaneous measurements of these important biomarkers in both breast milk and infant serum. Thirdly, we did not consider factors such as household income, parental intelligence, child nutritional status, etc., in the analysis, all of which can contribute to child neurocognitive development. The original study focused on the impact of iodine supplementation during lactation, and including additional variables would have required more resources and a larger sample size, which were beyond the study's scope. Fourthly, due to budget constraints, we did not assess urinary iodine levels as a marker of iodine status in children during the neurodevelopmental evaluation. Fifthly, due to the secondary nature of this analysis, which used a subset of participants from our prior study, the sample size was inherently limited. The original study's design and participant recruitment were focused on its primary objectives, thus constraining the subset available for this analysis.

## Conclusion

This study indicates that the association between iodine concentration in breast milk during the initial days of lactation, prior to iodine supplementation, and cognitive scores in children at the age of three is minimal and appears not to be clinically significant. This weak association may reflect the influence of prenatal iodine status rather than lactation-related exposure. Additionally, none of the neurodevelopmental domains showed associations with breast milk neurotrophic and growth factors (BDNF and IGF-1) measured before the intervention. Further investigations are warranted to determine the

potential biological role of breast milk components, including the effects of iodine supplementation during lactation, on both short- and long-term health outcomes for infants and young children.

## Conflict of Interests

Authors declare no conflict of interests.

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