



## **The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT**

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# The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT

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## ABSTRACT

**Context:** Supplementation of breast milk is difficult once infants suckle the breast and is often discontinued at end of hospitalisation and after discharge. Thus, breastfed preterm infants are exposed to an increased risk of nutritional deficit with a possible consequence on neurodevelopmental outcome.

**Objective:** To assess the relationship between breast feeding at time of discharge, weight gain during hospitalisation and neurodevelopmental outcome.

**Design:** Observational cohort study.

**Setting:** Two large, independent population-based cohorts of very preterm infants: the Loire Infant Follow-up Team (LIFT) and the EPIPAGE cohorts.

**Patients:** 2925 very preterm infants alive at discharge.

**Main outcome measure:** Suboptimal neurodevelopmental outcome, defined as a score in the lower tercile, using Age and Stages Questionnaire at 2 years in LIFT and Kaufman Assessment Battery for Children Test at 5 years in EPIPAGE. Two propensity scores for breast feeding at discharge, one for each cohort, were used to reduce bias.

**Results:** Breast feeding at time of discharge concerned only 278/1733 (16%) infants in LIFT and 409/2163 (19%) infants in EPIPAGE cohort. Breast feeding is significantly associated with an increased risk of losing one weight Z-score during hospitalisation (LIFT: n=1463, adjusted odd ratio (aOR)=2.51 (95% CI 1.87 to 3.36); EPIPAGE: n=1417, aOR=1.55 (95% CI 1.14 to 2.12)) and with a decreased risk for a suboptimal neurodevelopmental assessment (LIFT: n=1463, aOR=0.63 (95% CI 0.45 to 0.87); EPIPAGE: n=1441, aOR=0.65 (95% CI 0.47 to 0.89) and an increased chance of having a head circumference Z-score higher than 0.5 at 2 years in LIFT cohort (n=1276, aOR=1.43 (95% CI 1.02 to 2.02)) and at 5 years in EPIPAGE cohort (n=1412, aOR=1.47 (95% CI 1.10 to 1.95)).

## ARTICLE SUMMARY

### Key messages

- The observed better neurodevelopment in spite of suboptimal initial weight gain could be termed the 'apparent breastfeeding paradox' in very preterm infants.
- Regardless of the mechanisms involved, the current data provide encouragement for the use of breast feeding in preterm infants.

### Strengths and limitations of this study

- The same effect was observed in two large distinct cohorts.
- Observational study: despite the use of propensity score, a few potential confounder can remain.

**Conclusions:** The observed better neurodevelopment in spite of suboptimal initial weight gain could be termed the 'apparent breastfeeding paradox' in very preterm infants. Regardless of the mechanisms involved, the current data provide encouragement for the use of breast feeding in preterm infants.

## INTRODUCTION

Breast feeding is universally recommended for the feeding of term infants.<sup>1</sup> Regarding very preterm infants, <32 weeks of gestation, exclusive breast feeding is a debated topic since supplementation is required to ensure optimal growth during initial hospitalisation but is difficult once the preterm infant can suckle the breast.<sup>2</sup>

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Suboptimal nutrition with insufficient growth during hospitalisation in neonatal intensive care unit is associated with later cognitive dysfunction.<sup>3 4</sup> In extremely preterm infants, growth velocity during hospitalisation exerts a significant, and possibly independent, effect on neurodevelopment and growth outcomes at 18–22 months of corrected age.<sup>3</sup> In preterm infants, follow-up studies showed that at 7 years of age, preterm infants fed standard formula demonstrated neurocognitive impairment with a significant reduction in IQ compared with infants fed with enriched formula.<sup>4</sup>

Breast feeding with supplementation during initial hospitalisation improves cognitive outcome at 30 months of corrected age in extremely preterm infants.<sup>5</sup> Human milk indeed requires nutrient fortification to meet the protein and mineral needs of the rapidly growing preterm infant.<sup>6</sup> During hospitalisation, as the baby receives mother's milk through a gastric tube, it is easy to use a milk fortifier to maintain adequate growth. Once the preterm infant can suckle the breast, however, the use of a milk fortifier is not easy, as it disrupts the routine of breast feeding. As a consequence, mother milk supplementation is often discontinued at the end of hospitalisation and hospital discharge, and this discontinuation exposes the infants to an increased risk of nutritional deficit.<sup>7</sup> Thus, breast feeding at time of discharge could be associated with less weight gain during neonatal hospitalisation and during the weeks following discharge. This is why exclusive breast feeding remains a matter of debate in preterm infants.

The aim of the current study was to assess the complex relationship between breast feeding at time of discharge, weight gain during neonatal hospitalisation and neurodevelopment at 2 or 5 years using data from two independent large cohorts of very preterm infants of

<33 weeks of gestation covering the late 1990s and mid-2000s. The secondary objective was assessment of growth (weight, height, head circumference) at 2 and 5 years.

### METHODS

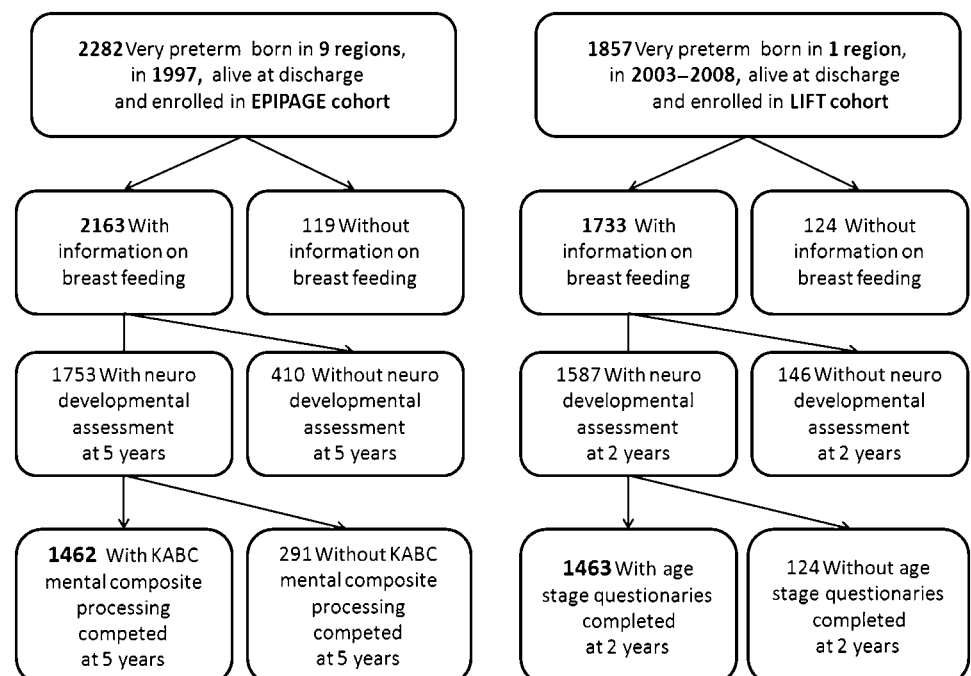
#### Data source and patients

Date source is constituted of two cohorts: EPIPAGE<sup>1</sup> and LIFT (Loire Infant Follow-up Team)<sup>8</sup> cohorts with recruitment over two distinct periods. EPIPAGE is a prospective population-based cohort study including all infants born between 22 and 32 weeks of gestation in 1997 in the maternity wards of nine French regions accounting for about one-third of all births in France. Among infants born in 1997, who survived and eligible for the follow-up (n=2282), we included all infants whose status regarding breast feeding at time of discharge was known (n=2163). LIFT cohort is a cohort of infants born in one region (Pays de la Loire, a region in Western France) and enrolled in the regional follow-up network. Among surviving very preterm infants with a gestational age <33 weeks of gestation, born between 1 January 2003 and 30 June 2008 and enrolled in LIFT cohort (n=1857), we included all children whose status regarding breast feeding at time of discharge was known (n=1733) (figure 1). Each cohort was registered to the French CNIL. For EPIPAGE cohort, parents were told about the study and given written information in the maternity or neonatal unit, and verbal consent was provided to the medical team in charge of the study at recruitment. For LIFT cohort, a written consent was obtained at enrolment.

#### Developmental assessment

In the EPIPAGE cohort, the neuropsychological assessment was performed using the Kaufman Assessment

**Figure 1** Flow charts.



Battery for Children (K-ABC) at 5 years of age.<sup>9</sup> Neuropsychological assessment was performed by trained psychologists when appropriate for the patient's condition and when accepted by the patient. The K-ABC yields four global test scores. The Mental Processing Composite (MPC) Scale, which is considered to be equivalent to IQ, is a global measure of cognitive ability. This scale is standardised to a mean of 100 (SD 15). An MPC in the lower tercile (score of <85) was considered as an index of suboptimal neurodevelopment.

In the LIFT cohort, neurodevelopmental assessment was performed using Age and Stages Questionnaires (ASQ),<sup>10</sup> a questionnaire completed by parents at a corrected age of 2 years. This questionnaire includes five parts, among which three are related to cognitive development: communication, problem solving and personal social interactions. The sum of the five partial scores was calculated, and subject population was split in three terciles of global ASQ score. Being in the lower tercile (ASQ score <220) was considered an index of suboptimal neurodevelopment.

### Growth assessment

To assess growth, we used measurements performed at birth, discharge and 6 months, 2 years and 5 years of age in EPIPAGE cohort and birth, discharge, 9 months and 2 years in LIFT cohort. We calculated Z-score by using LMS method.<sup>10a</sup> We used reference growth curves for which LMS parameters have been published for weight, height and head circumference. For birth and discharge (up to 41 weeks of postmenstrual age) measurements, we used Olsen's preterm infant growth chart.<sup>11</sup> For the few preterm infants discharged after 41 weeks of postmenstrual age and for follow-up period measurements, we used WHO growth curves.<sup>12</sup> Weight gain during hospitalisation was assessed as the difference of weight Z-score between discharge and birth.

### Statistical analysis

Means and SDs are reported for continuous variables and frequencies for categorical variables. ANOVA and  $\chi^2$  or *Fisher test* if necessary were used to compare infant characteristics and 5-year outcome between the groups of infants who were breast fed or formula fed at time of discharge.

The propensity score method was used to reduce bias in assessing the relation between breast feeding at discharge and cognitive outcomes.<sup>13 14</sup> The propensity score is defined as a conditional probability, between 0 and 1, that a subject will be 'breast fed at discharge' based on an observed group of covariates. This score is then used just as if it were the only confounding covariate. Thus, the collection of predictors is collapsed into a single predictor, which may better adjust covariates between the groups and reduce bias. Two full non-parsimonious logistic regression models were developed to derive a propensity score for breast feeding at

discharge, one for each cohort. These models included true confounders: variables that are potentially associated with both mode of feeding and with outcome.<sup>15 16</sup> These variables included for the EPIPAGE cohort: characteristics of the mothers (age, maternal body mass index,<sup>17</sup> level of maternal education, socioeconomic status, number of children at home), characteristics of the newborns (gestational age, Z-score of birth weight, presence of a congenital malformation), characteristics of pregnancy (antenatal corticosteroids, multiple pregnancy, complication of pregnancy), place of birth (inborn/outborn, region of birth) and characteristics of neonatal hospitalisation (cranial ultrasound abnormalities, patent ductus arteriosus, necrotising enterocolitis, neonatal surgery, bronchopulmonary dysplasia defined by supplemental oxygen requirement at 36 weeks, duration of mechanical ventilation, length of hospital stay). Patients with missing data were excluded from multivariable analysis. For the LIFT cohort, the variables included in propensity score calculation were similar but less numerous, including characteristics of the mother, characteristics of the newborn and neonatal hospitalisation. The Hosmer–Lemeshow goodness-of-fit test and the area under the curve were used to assess each model fit.

First, we studied crude associations between breast feeding at discharge and suboptimal neurodevelopment assessment and then the same associations after adjustment for the propensity score, gestational age and birthweight Z-score. Due to the known relationship between gestational age, weight gain and suboptimal development, these variables were included as confounding factors in the multivariable model even if they are already included in the calculation of propensity score, as suggested by other authors.<sup>14</sup> We used logistic regression models for univariate and multivariate analyses.<sup>16</sup> We estimated the crude and adjusted OR, and its 95% CI, of a suboptimal neurodevelopmental score, that is, to be in the lower tercile of MPC (<85) at 5 years in EPIPAGE cohort or ASQ (< 220) at 2 years corrected age in LIFT cohort, associated with breast feeding at discharge. Second, we studied crude associations between breast feeding and postnatal weight gain during neonatal hospitalisation and thereafter up to 2 years in LIFT cohort and 5 years in EPIPAGE cohort. Finally, we studied the relationship between weight gain during neonatal hospitalisation and suboptimal neurodevelopment assessment. Moreover, we assessed growth (weight, height, head circumference) at 6 months, 2 and 5 years in EPIPAGE and at 9 months and 2 years in LIFT cohort. A supplementary propensity–score matching analysis was performed comparing matched pairs of breast fed and not breast fed very preterm infants in each cohort. Matched pairs were created by their propensity score, and the outcomes of the two groups were compared in each cohort. All p values were based on two-sided tests. All analyses were performed using SPSS V.15.0 (SPSS Inc.).

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### RESULTS

#### Patients characteristics

The populations enrolled in EPIPAGE (n=2163) and LIFT cohorts (n=1733) were very similar with a small albeit significant difference in gestational age ( $29.9 \pm 2.0$  vs  $29.8 \pm 2.1$  weeks,  $p=0.01$ ), birth weight ( $1380 \pm 395$  vs  $1340 \pm 396$  g,  $p=0.01$ ) and postnatal weight gain ( $0.98 \pm 0.79$  vs  $0.83 \pm 0.82$  loss of weight Z-score,  $p=0.001$ ) but not in length of hospital stay ( $60.2 \pm 31.7$  vs  $58.7 \pm 32.2$  days,  $p=0.13$ ). The proportion of breastfed infants was a little bit higher in EPIPAGE cohort (19%) than in LIFT cohort (16%),  $p=0.02$ . In both cohorts, breast feeding was associated with some characteristics of the mothers, pregnancy, newborns and neonatal hospitalisation (table 1). Among the 2163 children of EPIPAGE cohort, 1753 (81%) were followed up to 5 years and 1462 (68%) assessed by trained psychologists. Among the 1733 of LIFT cohort, 1587 (85%) were followed up to 2 years of corrected age and we obtained ASQ for 1463 children (79%).

Propensity score was calculated in each cohort. In EPIPAGE cohort, it was possible to calculate the propensity score for 2130 of the 2163 very preterm infants who were alive at hospital discharge and whose status regarding breast feeding at time of discharge was known. The propensity scores ranged from 0.0005 to 0.722. The Hosmer–Lemeshow test was 7.2,  $p=0.51$ . The receiver operating characteristic (ROC) curve area was  $0.72 \pm 0.01$ . In LIFT cohort, the propensity score was calculated for all preterm infants. For each variable, if necessary, a subgroup with unknown data was constituted. The propensity scores ranged from 0.007 to 0.747. The Hosmer–Lemeshow test was 6.2,  $p=0.63$ . The ROC curve area was  $0.71 \pm 0.01$ . Variables significantly associated with breast feeding at discharge were very similar in both cohorts (table 2).

#### Exposure to breast feeding at time of discharge and neurodevelopmental outcome

In both cohorts, breast feeding was associated with a significant reduction of risk for a suboptimal

**Table 1** Demographic and clinical characteristics of very low gestational age infants breast fed or not at time of discharge

Characteristics	EPIPAGE cohort			LIFT cohort		
	Breast fed (n=409)	Not breast fed (n=1754)	p Value	Breast fed (n=278)	Not breast fed (n=1455)	p Value
<b>Characteristics of newborns</b>						
Gestational age, weight	30.4 (1.8)	29.8 (2.1)	0.001	30.3 (1.8)	29.8 (2.1)	0.001
Birth weight, g	1460 (400)	1360 (390)	0.001	1430 (280)	1330 (400)	0.001
Birth weight, Z-score	-0.23 (1.15)	-0.28 (1.05)	0.26	-0.26 (0.81)	-0.34 (0.81)	0.120
Male gender	212 (51.8)	952 (54.3)	0.36	155 (55.8)	788 (54.2)	0.62
<b>Characteristics of mothers</b>						
Age <25 years	49 (12.0)	372 (21.2)	0.001	—	—	—
Two or more children at home	57 (13.9)	349 (19.9)	0.005	121 (43.5)	675 (46.3)	0.013
Single	18 (4.4)	157 (9.0)	0.002	20 (7.2)	150 (10.3)	0.012
Upper level education	178 (43.5)	430 (24.5)	0.001	—	—	—
No professional activity	38 (9.3)	338 (19.3)	0.001	52 (18.7)	451 (31.0)	0.001
Health insurance for low financial income	—	—	—	12 (4.3)	146 (10.0)	0.001
Upper socio-demographic level	211 (51.6)	527 (30.0)	0.001	135 (48.6)	385 (26.5)	0.001
<b>Characteristics of pregnancy</b>						
Hypertension during pregnancy	99 (24.2)	381 (21.7)	0.276	31 (11.2)	253 (17.4)	0.010
Multiple pregnancy	101 (24.7)	572 (32.6)	0.002	61 (21.9)	415 (28.5)	0.024
<b>Neonatal hospitalisation</b>						
Duration of mechanical ventilation, days	3.1 (7.5)	5.6 (11.5)	0.001	4.0 (10.4)	6.8 (11.2)	0.002
Length of hospital stay, days	52.5 (24.1)	62.2 (32.6)	0.001	54.2 (29.2)	59.5 (32.7)	0.013
Change in weight Z-score during neonatal hospitalisation	-1.00 (0.63)	-0.95 (0.63)	0.170	-1.02 (0.60)	-0.80 (0.70)	0.001
<b>Follow-up and outcome</b>						
Lost to follow-up	49 (12.0)	361 (20.6)	0.001	22 (7.9)	124 (8.5)	0.738
Follow-up	<b>360</b> (88.0)	<b>1393</b> (79.4)	—	<b>256</b> (92.1)	<b>1331</b> (91.5)	—
Incomplete neurodevelopmental evaluation	44 (12.2)	247 (17.7)	0.001	14 (5.5)	110 (8.3)	0.001
Normal neurodevelopment	252 (70.0)	725 (52.0)	—	183 (71.5)	761 (57.2)	—
Non-optimal neurodevelopment	64 (17.8)	421 (30.2)	—	59 (23.0)	460 (34.5)	—

Bold values represent the denominator in each group to calculate percentage of each outcome.

Data are means (SD) or n (%). Non-optimal neurodevelopment was defined as Kaufman Assessment Battery for Children Mental Composite Processing <85 at 5 years in EPIPAGE cohort and Age and Stages Questionnaires score <220 at 2 years of corrected age in LIFT cohort. LIFT, Loire Infant Follow-up Team.



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**Table 2** Significant associations between the variables included in calculation of propensity score and breast feeding

	EPIPAGE cohort (n=2130)		LIFT cohort (n=1733)	
	aOR (95% CI)	p Value	aOR (95% CI)	p Value
Characteristics of the mothers				
Age <25 years	0.613 (0.42 to 0.89)	0.010	—	—
Upper socio-demographic level	1.77 (1.34 to 2.34)	0.001	2.32 (1.708 to 3.17)	0.001
Higher education	1.557 (1.17 to 2.06)	0.002	—	—
No professional activity	0.669 (0.44 to 1.00)	0.052	0.57 (0.35 to 0.75)	0.001
Mother of foreign origin	1.50 (1.05 to 2.14)	0.024	—	—
Characteristics of pregnancy				
Multiple pregnancy	0.51 (0.39 to 0.67)	0.001	0.69 (0.48 to 0.99)	0.047
Characteristics of the newborns				
Duration of neonatal hospitalisation (by week)	0.89 (0.84 to 0.94)	0.001	0.91 (0.85 to 0.97)	0.004
Gestational age (per week)	1.03 (0.92 to 1.16)	0.650	0.98 (0.86 to 1.10)	0.714
Birth weight (per Kg)	1.17 (0.66 to 2.08)	0.590	1.13 (0.701 to 1.83)	0.612

aOR, adjusted odd ratio; LIFT, Loire Infant Follow-up Team.

neurodevelopmental assessment at 2 years of corrected age (LIFT cohort) and at 5 years (table 3). Moreover, The K-ABC Mental Processing Composite score increased as a function of the corrected age at which infants were weaned off breast feeding (figure 2). In each cohort, breast feeding was consistently associated with a reduction in the risk for suboptimal neurodevelopmental assessment before and after adjustment for gestational age, birthweight Z-score and sex, and propensity score (table 3). We observed the same results in propensity—score matching analysis (supplemental table).

### Weight gain during neonatal hospitalisation and exposure to breast feeding

Breast feeding was associated with an increased risk of losing one weight Z-score during hospitalisation, before adjustment in LIFT cohort and after adjustment in both cohorts (table 4). The loss in weight Z-score during the NICU hospitalisation was similar in both cohorts in breastfed infants but not in non-breastfed infants: the loss was less pronounced in the most recent cohort (table 1). We observed a greater loss in weight Z-score in breastfed group in propensity—score matching analysis and this for each cohort (supplemental table).

### Weight gain during neonatal hospitalisation, exposure to breast feeding and neurodevelopmental outcome

Restricted intrauterine growth (ie, lower birthweight Z-score) was associated before and after adjustment for gestational age and sex with a suboptimal neurodevelopmental assessment in both cohorts. Postnatal weight gain during neonatal hospitalisation was significantly associated with a suboptimal neurodevelopmental assessment only in LIFT cohort but not in EPIPAGE cohort (table 5), with and without adjustment for gestational age, birthweight Z-score, sex, breast feeding and propensity score.

### Growth after neonatal hospitalisation

In contrast with data on initial growth, from 2 years of corrected age, weight, height and head circumference were significantly higher in preterm infants who had been breast fed at the time of discharge in both LIFT and EPIPAGE cohorts (figure 3). After adjustment for weight Z-score at birth, sex and propensity score, breast feeding at discharge was significantly associated to an increased chance of having a head circumference Z-score higher than 0.5 at 5 years in EPIPAGE cohort (n=1412, adjusted odd ratio (aOR)=1.47 (95% CI 1.10 to 1.95)) and at 2 years of corrected age in LIFT cohort (n=1276, aOR=1.43 (95% CI 1.02 to 2.02)).

**Table 3** Association between breast feeding at time of discharge and non-optimal neurodevelopmental performance

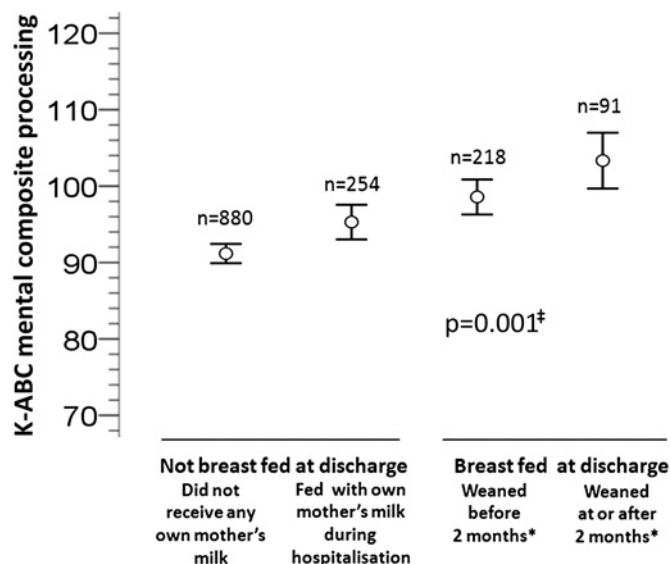
Adjustment	EPIPAGE cohort (n=1462)		LIFT cohort (n=1463)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
No adjustment	0.44 (0.33 to 0.60)	0.001	0.53 (0.39 to 0.73)	0.001
Adjusted for gestational age, birthweight Z-score and sex	0.46 (0.34 to 0.62)	0.001	0.57 (0.41 to 0.78)	0.001
Adjusted for gestational age, birthweight Z-score, sex and propensity score*	0.65 (0.47 to 0.89)	0.008	0.63 (0.45 to 0.87)	0.005

Non-optimal neurodevelopment was defined as Kaufman Assessment Battery for Children Mental Composite Processing <85 at 5 years in EPIPAGE cohort and Age and Stages Questionnaires score <220 at 2 years of corrected age in LIFT cohort.

\*n=1443.

LIFT, Loire Infant Follow-up Team.

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**Figure 2** The Kaufman Assessment Battery for Children (K-ABC) Mental Processing Composite score (mean, SD) at 5 years as a function of breastfeeding status at time of discharge and corrected age (\*) at which infants were weaned off breast feeding, in EPIPAGE cohort. †p adjusted for propensity score.

### DISCUSSION

In two independent cohorts of preterm infants, breast feeding at discharge was associated with a reduction in the risk for a suboptimal neurodevelopmental assessment at 2 (LIFT cohort) or 5 years of age (EPIPAGE cohort) despite a higher risk for suboptimal weight gain (loss of one weight Z-Score) during neonatal hospitalisation in these breastfed infants. The observed improved neurodevelopment in spite of suboptimal initial weight gain could be termed the 'apparent breastfeeding paradox' in very preterm infants.

Such an observation is indeed a paradox as several earlier studies have documented an association between suboptimal early postnatal nutrition with insufficient weight gain during hospital stay and later cognitive dysfunction. In extremely preterm infants, faster weight gain in the NICU was associated with improved outcome in terms of neurodevelopment and growth at 18–22 months of corrected age.<sup>3</sup> Nevertheless, this paradox is probably only an apparent paradox because weight gain

during hospitalisation is a poor predictor of the quality of growth, as it does not provide any insight into the changes in body composition. In infants with a very low birth weight, enhanced postnatal growth is also associated with a better later neurodevelopmental outcome,<sup>18</sup> especially regarding postnatal growth in head circumference, an index of brain growth.<sup>19 20</sup> Yet the 'neuro-protective' effects of improved growth may only be mild and mainly concern growth over the first few weeks of hospital stay.<sup>21</sup> In the two cohorts used in the current analysis, the role of postnatal weight gain was slightly different. In the EPIPAGE cohort, we did not observe any association between postnatal weight gain during hospitalisation and suboptimal neurodevelopmental score at 5 years of age (table 5). In the LIFT cohort, after adjustment for propensity score, a significant association was found between initial weight gain rate and neurodevelopment. In contrast, in both cohorts, a negative association was obvious between birthweight Z-score and suboptimal neurodevelopment (table 5). Such difference between the two cohorts could be in relation with the significantly better initial neonatal weight gain rate in the LIFT cohort compared with the EPIPAGE cohort, as a matter of fact, the loss in weight Z-score was less in the most recent cohort, presumably due to improvement in care routines between the two periods (1997 vs 2003) in the NICUs in France.<sup>22</sup> Thanks to the improvement in nutritional management in the second period, the role of postnatal nutrition may have become detectable in the more recent LIFT cohort before and after adjustment for breast feeding.

Beneficial effects of breast feeding on cognitive skills and behavioural scores have been demonstrated previously in term,<sup>23 24</sup> preterm<sup>25</sup> and extremely preterm infants.<sup>5</sup> Multiple biases may, however, interfere, particularly maternal socioeconomic and educational status: in the two cohorts, upper social status was obviously associated with a higher chance for being breast fed at discharge and for an optimal neurodevelopmental score. In term infants, after control for biases<sup>26</sup>—particularly using the method of sibling comparison which automatically controls for any confounding factors that are the same for each of the siblings in a pair<sup>27</sup>—the role of breast feeding has been found to be either not significant or modest. In preterm infants, observational studies

**Table 4** Association between breast feeding at time of discharge and slow postnatal growth defined as a loss of one Z-score unit for weight during neonatal hospitalisation

Adjustment	EPIPAGE cohort (n=1430)		LIFT cohort (n=1463)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
No adjustment	1.12 (0.87 to 1.43)	0.38	1.92 (1.49 to 2.49)	0.001
Adjusted for gestational age, sex, birthweight Z-score	1.32 (0.98 to 1.76)	0.07	2.66 (1.99 to 3.52)	0.001
Adjusted for gestational age, sex, birthweight Z-score and propensity score*	1.55 (1.14 to 2.12)	0.006	2.51 (1.87 to 3.36)	0.001

\*n=1417.

LIFT, Loire Infant Follow-up Team.

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**Table 5** Association between birth weight or postnatal growth and non-optimal neurodevelopment

	EPIPAGE cohort		LIFT cohort	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Birth weight (per one Z-score unit below the mean)	n=1460		n=1463	
No adjustment	1.19 (1.04 to 1.35)	0.01	1.12 (0.99 to 1.28)	0.08
Adjusted for gestational age, sex	1.23 (1.07 to 1.40)	0.003	1.24 (1.08 to 1.43)	0.001
Postnatal growth for weight (per one Z-score unit lost between birth and discharge)	n=1430		n=1463	
No adjustment	0.93 (0.78 to 1.11)	0.44	1.29 (1.10 to 1.51)	0.002
Adjusted for gestational age, sex, birthweight Z-score	0.97 (0.79 to 1.19)	0.74	1.21 (1.01 to 1.44)	0.038
Adjusted for gestational age, sex, birthweight Z-score, breast feeding and propensity score*	1.06 (0.85 to 1.31)	0.63	1.28 (1.07 to 1.53)	0.008

Non-optimal neurodevelopment was defined as Kaufman Assessment Battery for Children Mental Composite Processing <85 at 5 years in EPIPAGE cohort and Age and Stages Questionnaires score <220 at 2 years of corrected age in LIFT cohort.

\*n=1417.

LIFT, Loire Infant Follow-up Team.

have shown that preterm infants whose mothers chose to breast feed reached a higher IQ at 8 years of age. Interestingly, infants whose mothers were willing to breast feed but failed to do so had the same IQ as those whose mothers elected not to breast feed.<sup>25</sup> In preterm infants, observational studies found feeding with human milk to be associated with a better outcome.<sup>5</sup> Eight randomised studies were included in a Cochrane review.<sup>28</sup> Only two old randomised studies using unfortified donor human milk reported a comparison of developmental outcome between unfortified human milk and formula feeding. Follow-up of the infants who participated in these two trials did not find a significant effect on long-term growth parameters or neurodevelopmental outcomes. Most of other parameters reported by the randomised studies comparing formula to human milk were in favour of breastmilk, except for weight gain during hospitalisation. Moreover, among children who had been enrolled in one of such studies, Lucas *et al* observed 15 years later that breastmilk consumption was associated with a lower blood pressure in children born prematurely, suggesting a long-term beneficial effects of breastmilk in preterm infants.<sup>29</sup> Taken together, data from the literature and from the current study are consistent with a benefit of breastmilk consumption on developmental outcome.

At the time of discharge, very preterm infants have accumulated deficits in energy, protein and minerals, and, due to their early discharge, still have higher nutrient requirements than healthy appropriate-for-gestational age term infants. Despite the vast body of published recommendations on the nutrition of preterm infants, there is little data on optimal nutritional management after discharge of breastfed preterm infants.<sup>30</sup> No randomised studies can be ethically performed to determine whether feeding preterm infants following hospital discharge with nutrient-enriched formula milk versus human breast milk affects growth and development. The conclusion of a Cochrane review<sup>2</sup> is that 'mothers who wish to breast feed, and their healthcare advisors, would require very clear

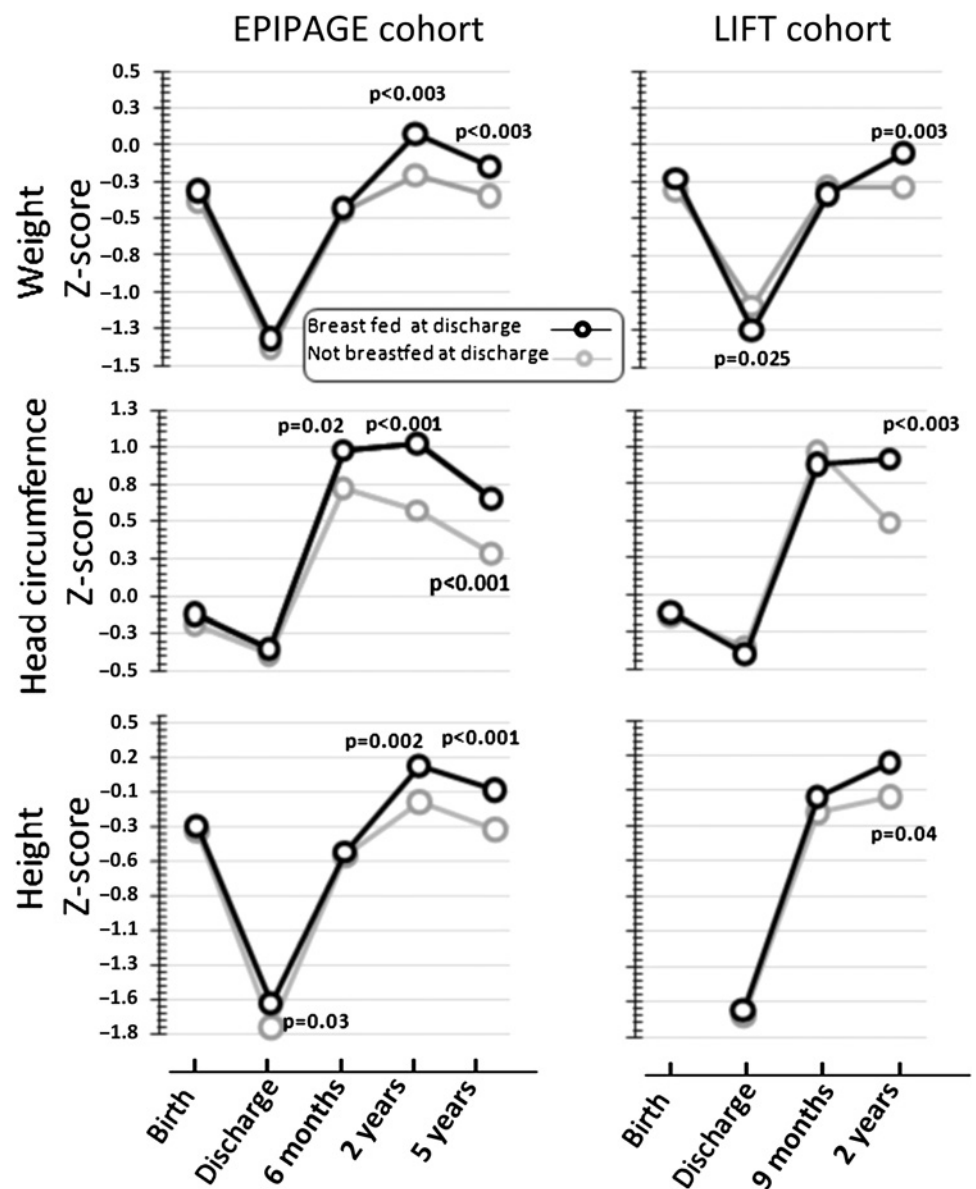
evidence that feeding with a nutrient-enriched formula milk had major advantages for their infants before electing not to feed (or to reduce feeding) with maternal breast milk, and that evidence from trials that compared feeding preterm infants following hospital discharge with nutrient-enriched versus standard formula milk demonstrating an effect on growth or development'. The need to contribute an answer to the nagging disturbing question, 'Does exclusive breastfeeding at the time of discharge influence outcome?' was the very incentive to perform the current study. Our analysis of two large cohorts of preterm infant with relatively long-term follow-up used the propensity score method as a means to control as much as possible for potential confounders. From such analysis, we obtained clear-cut evidence that despite an increased risk for suboptimal early weight gain (increased risk for the loss of one weight Z-score) during neonatal hospitalisation, breast feeding at discharge is associated with a better outcome after adjustment for potential confounders by using propensity score.

The main weakness of our study is the observational design. Despite the use of propensity score, we cannot ensure all potential confounders were eliminated. For instance, the very ability of an infant to suckle may be associated with a less sick infant, and the variables used in adjustment may not be entirely independent either of each other or of the outcome. Moreover, how much fortifier was given could not, unfortunately, be retrieved from either of the two databases, and thus, some important variable such as caloric intake during neonatal intensive care unit stay could not be included in the analysis. Similarly, we did not address the mechanisms. For instance, the effect of breast feeding for term infants has been attributed to bias,<sup>31</sup> including the complex relationship between weight gain and timing of weaning. Such bias is unlikely to be relevant for our population since the preterm infants with the slower weight gain rate were those who were not weaned at discharge. The slower weight gain during neonatal intensive care unit stay therefore likely reflects



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**Figure 3** Weight, head circumference and height expressed as Z-score at discharge, 6 or 9 months and 2 years of corrected age (EPIPAGE and Loire Infant Follow-up Team (LIFT) cohorts) and at 5 years (EPIPAGE cohort) according to breast feeding at discharge. Weight measurements was known for 1460, 1430, 973, 873 and 1447 infants at birth, discharge, 6 months, 2 and 5 years, respectively, in EPIPAGE and for 1463, 1463, 1341 and 1297 infants at birth, discharge, 9 months and 2 years, respectively, in LIFT cohort.



a biological effect rather than bias. Several potential mechanisms can be proposed to explain the better outcome in breastfed infants: mother–child interaction (better bonding, better care given by parents), the effect of specific nutrients contained in breastmilk such as polyunsaturated fatty acids, prebiotic oligosaccharides, etc. Regardless of mechanisms, we did observe the same fact in two distinct cohorts, with the same magnitude. By adjustment for propensity score, sex and birthweight Z-score, we were indeed able to observe the apparent paradox of a better neurodevelopmental outcome, despite a lower early weight gain. These adjustments are necessary because a complex relationship exists between breast feeding, birth weight, gestational age, birthweight Z-score and postnatal weight gain during hospitalisation.

In conclusion, the neurodevelopment of premature infants is likely to benefit from feeding supplemented mother milk during hospital stay and unsupplemented mother's milk after discharge, and these data from two cohorts are indeed reassuring because in spite of a lesser

weight gain during hospitalisation, we observed a better neurodevelopmental outcome in the breastfed groups. The present report suggests that breast feeding should be recommended at the time of discharge. As the rate of exclusive breast feeding at time of discharge is low—<30% in Europe<sup>32</sup>—strategies to facilitate breast feeding at discharge must be developed.<sup>33</sup> Moreover, when adjusted on breast feeding, postnatal weight gain has a positive effect on neurodevelopmental outcome as observed in LIFT cohort; so the question about the putative benefit of human milk supplementation after discharge remains open. Supplementation must be continued as long as possible, according to the state of knowledge, and this suggests also that more research is warranted about human milk composition and the potential benefit of human milk supplementation at time of discharge is warranted in the future.

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# The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT

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