Breastfeeding and Risk of Epilepsy in Childhood: A Birth Cohort Study

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Objective We asked whether breastfeeding reduces the risk of epilepsy in childhood.

Study design We included 69 750 singletons born between September 1997 and June 2003 in the Danish National Birth Cohort and observed them to August 2008. Information on breastfeeding was reported by mothers in two computer-assisted telephone interviews at 6 and 18 months after birth. Information on epilepsy (inpatients and outpatients) was retrieved from the Danish National Hospital Register. Cox proportional hazards regression models were used to estimate incidence rate ratios and 95% CIs.

Results Breastfeeding was associated with a decreased risk of epilepsy, with a dose-response like pattern. For example, children breastfed for 3 to 5, 6 to 8, 9 to 12, and ≥13 months had a 26%, 39%, 50%, and 59% lower risk of epilepsy after the first year of life, respectively, compared with children who were breastfed for <1 month. The association remained when we excluded children who had adverse neonatal conditions or children who were exposed to adverse maternal conditions during pregnancy.

Conclusions The observed protective effect of breastfeeding may be causal. Breastfeeding may decrease epilepsy in childhood, thereby adding another reason for breastfeeding. *(J Pediatr 2011;158:924-9)*.

Epilepsy affects 1% of children before 20 years of age.[1] Most cases have unknown etiology, but environmental factors operating prenatally such as preeclampsia and maternal infections may play etiologic roles.[2-4] The development of the human brain continues after birth,[5] and breast milk contains a near-optimal combination of nutrients for the growing infant.[6] A randomized trial showed that providing breast milk even for a short time to preterm babies improved cognitive function.[7] Breastfeeding has been associated with enhanced mental, cognitive, psychomotor development, and even with a decreased risk of schizophrenia.[8-11] A few studies have shown that children with epilepsy were less likely to be breastfed, but these findings could be confounded by maternal or neonatal complications related to both breastfeeding and epilepsy.[12,13]

We used a cohort approach to explore the association between duration of breastfeeding and the risk of epilepsy in early childhood by taking duration of breastfeeding and a number of potential confounders into consideration.

Methods

This study was based on data from the Danish National Birth Cohort (DNBC), a nation-wide population-based cohort including approximately 100 000 pregnancies and their offspring.[14] Enrollment into the cohort was between March 1996 and November 2002. Four computer-assisted telephone interviews (two during pregnancy and two after birth) were used to collect information on social, environmental, and health conditions of mothers and children during pregnancy and after birth. An English language version of the interviews is available at www.DNBC.dk. We identified all live-born singletons whose mothers took part in the first postpartum interview (n = 70 270). We excluded children with missing information on breastfeeding (n = 94) and on maternal smoking or parity (n = 426), leaving 69 750 children in the final analysis. The DNBC was approved by the ethics committees and the Data Protection Agency in Denmark.

Information on infant feeding practice was from two postpartum interviews conducted approximately 6 and 18 months after birth. At the interviews, information on breastfeeding, use of infant formula, complementary food, cow milk, and other kinds of bottle food were collected. Duration of breastfeeding in this study was defined according to the period during which the infants were breastfed, irrespective of whether they received formula or other complementary food in addition to breast milk. Infants who were breastfed <7 days were given a value of 0.5 week. The termination of the breastfeeding period was set to the date of the first postpartum interview for infants who were still breastfed at the first postpartum interview, but whose mothers did not participate in the second postpartum in-

BMI	Body mass index
DNBC	Danish National Birth Cohort
ICD-10	*International Classification of Diseases, 10th Revision*
IRR	Incidence rate ratio
LCPUFA	Long-chain polyunsaturated fatty acids

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terview (n = 9186) and for infants of mothers who did not report on breastfeeding in the second postpartum interview (n = 3318). The duration of breastfeeding was based on the date of the second postpartum interview (n = 2646) for children who were still breastfed at the time of the second postpartum interview. When the available data on duration of breastfeeding were not consistent for the two interviews, we used data from the first postpartum interview (n = 1206).

Exclusive breastfeeding in this study was defined as feeding with breast milk alone, only supplemental water was allowed. This is a slight modification of the definition of exclusive breastfeeding given by the World Health Organization (breastfeeding with no supplemental liquids or solid foods other than medications or vitamins).[15] Duration of exclusive breastfeeding was only reported by mothers at the 6-month interview. When the mother reported that she introduced infant formula, complementary food, cow milk, or other kinds of food ≥2 weeks before her report on exclusive breastfeeding (n = 3998), we corrected the duration of exclusive breastfeeding. There were two dates on the use of infant formula, the date of introduction and the date of regular use of infant formula. We used whichever date came first. When the duration of exclusive breastfeeding was longer than the duration of breastfeeding, the latter was used as the duration of exclusive breastfeeding (n = 2).

Information on epilepsy was obtained from the Danish National Hospital Register that stores information on all persons treated in any Danish non-psychiatric hospitals except private hospitals.[16] The coding of diseases is based on the Danish version of the *International Classification of Diseases, 10th revision* (ICD-10) from 1994. Both inpatients and outpatients with a diagnosis of epilepsy (ICD-10: G40-G41) were identified. Children with neonatal seizures only were not included as cases of epilepsy, but we included children who had neonatal seizures in whom epilepsy was diagnosed later. The time of onset of epilepsy was defined as the first day of admission or contact with the hospital when the children were first given a diagnosis of epilepsy.

Information on maternal age, gestational age at birth, birth weight, and Apgar score at 5 minutes was obtained from the Danish Medical Birth Registry.[17] Information on maternal weight and height before pregnancy, socioeconomic status, and smoking status at the time of interviews during pregnancy was obtained from the interviews during pregnancy. Coding of socioeconomic status was based on self-reported education and job titles at the time of recruitment. Women with a higher education (4 years beyond secondary school education) or in management were classified as having "high" socioeconomic status. Women with middle-range training (<3 years beyond secondary school education) and skilled workers were classified as having "middle" socioeconomic status, and unskilled workers and unemployed women were classified as having "low" socioeconomic status. Information on parity was obtained from the Danish Medical Birth Registry when unavailable from the DNBC interview (<1%). Information on parental history of epilepsy (ICD-8th Revision: 345; ICD-10: G40-G41), adverse conditions during the index pregnancy including preeclampsia (ICD-10: O14), diabetes mellitus (CD-10: O24), infection of genitourinary tract (ICD-10: O23), infection of amniotic sac and membranes (ICD-10: O41), premature rupture of membrane (ICD-10: O42), children with a diagnosis of congenital malformation (ICD-10: Q00-Q99), cerebral palsy (ICD-10: G80), adverse conditions originating in the perinatal period (ICD-10: P00-P96), and hospitalization or treatment as outpatients because of other disorders in the first 6 months of life (ICD-10: A00-T98) was obtained from the Danish National Hospital Register.[16] We used maternal weight and height before pregnancy to calculate maternal pre-pregnancy body mass index (BMI; weight in kg/height in m^2), and children with a missing maternal BMI (n = 3775) and socioeconomic status (n = 2944) were categorized in a separate group. Dietary information during pregnancy was collected by means of a food-frequency questionnaire covering dietary habits during the 4 weeks before the questionnaire was filled in at approximately 25 gestational weeks. We estimated energy-adjusted intakes (mg/day) of n-3 long-chain polyunsaturated fatty acids (LCPUFA) from the amount and type of fish in the maternal diet, which included docosahexaenoic acid (22:6 n-3), eicosapentaenoic acid (20:5 n-3), and docosapentaenoic acid (22:5 n-3).

Statistical Analyses

We used Cox proportional hazards models in STATA software version 9.2 (StataCorp, College Station, Texas) to estimate the incidence rate ratios (IRRs) of epilepsy. Because IRRs of epilepsy for breastfeeding duration differed between onset of epilepsy during the first year of life and later onset, we estimated the associations separately for epilepsy in the two periods. We used children who were breastfed <1 month (n = 5474, 8%), including children who were not breastfed at all (n = 1251, 2%), as a reference group in the analysis.

We checked whether the associations between duration of breastfeeding and risk of epilepsy were modified on a multiplicative scale by sex, gestational age, parity, and maternal intake of n-3 LCPUFA during pregnancy. When no effect measure modification was found, we adjusted for these factors in the analyses together with maternal age, socioeconomic status, smoking status at time of the interviews during pregnancy, pre-pregnancy BMI, time to pregnancy, and parental history of epilepsy. Robust SEs were used to adjust for dependency in different pregnancies (n = 7739, 11.1%) of woman who participated in the cohort two times or more.

In the estimation of IRR for epilepsy in the first year of life, breastfeeding was treated as a time-dependent variable, and we observed children from day 29 after birth until the onset of epilepsy, death, or the end of the first year, whichever came first. We estimated IRRs of epilepsy for breastfeeding duration of 1 to 2, 3 to 5, 6 to 8, or 9 to 12 months compared with children breastfed <1 month.

In the estimation of IRR for epilepsy after the first year of life, we observed children from the beginning of the 13th month of life until the onset of epilepsy, death, or Aug 31, 2008, whichever came first (n = 69 579). We estimated the

Table I. Characteristics of the study population according to duration of breastfeeding in 69 750 children in the Danish National Birth Cohort

Characteristics*	Breastfeeding					
	<1 month (n = 5474)		1-6 months (n = 20 946)		≥7 months (n = 43 330)	
	n	%	n	%	n	%
Mother's age (years)						
15-24	930	17.0	2708	12.9	2522	5.8
25-29	2281	41.7	8981	42.9	15 792	36.5
30-34	1641	30.0	6822	32.6	17 504	40.4
35-39	554	10.1	2181	10.4	6680	15.4
≥40	68	1.2	254	1.2	832	1.9
Parity						
Primiparous	2884	52.7	10 667	50.9	19 173	44.3
Multiparous	2590	47.3	10 279	49.1	24 157	55.8
Socioeconomic status						
High	1630	29.8	8544	40.8	25 296	58.4
Middle	2673	48.8	9289	44.4	13 717	31.7
Low	948	17.3	2332	11.1	2798	6.5
Missing	223	4.1	781	3.7	1519	3.5
Smoking at time of interview						
No	3352	61.2	14 131	67.5	34 831	80.4
Yes	2122	38.8	6815	32.5	8499	19.6
Prepregnancy BMI						
<18.5	228	4.2	895	4.3	1755	4.1
18.5-24.9	2755	50.3	12 495	59.7	29 530	68.2
25-29.9	1269	23.2	4378	20.9	7446	17.2
≥30	924	16.9	2153	10.3	2567	5.9
Missing	298	5.4	1025	4.9	2032	4.7
Parental history of epilepsy						
No	5283	96.5	20 451	97.6	42 514	98.1
Yes	191	3.5	495	2.4	816	1.9
Preeclampsia						
No	5221	95.4	20 169	96.3	42 100	97.2
Yes	253	4.6	777	3.7	1230	2.8
Diabetes during pregnancy						
No	5300	96.8	20 540	98.1	42 748	98.7
Yes	174	3.2	406	1.9	582	1.3
Infections of genitourinary tract						
No	5250	95.9	20 371	97.3	42 319	97.7
Yes	224	4.1	575	2.8	1011	2.3
Infections of amniotic sac and membranes						
No	5343	97.6	20 527	98.0	42 653	98.4
Yes	131	2.4	419	2.0	677	1.6
Premature rupture of membrane						
No	5063	92.5	19 443	92.8	40 514	93.5
Yes	411	7.5	1503	7.2	2816	6.5
Time to pregnancy						
≤12 months	3479	64.0	14 311	68.0	30 508	70.0
>12 months	877	16.0	2873	14.0	5381	12.0
Unplanned pregnancy or missing	1118	20.0	3762	18.0	7441	17.0
Gestational age (weeks)						
19-36	368	6.7	1068	5.1	1517	3.5
37-41	4601	84.1	17 972	85.8	38 040	87.8
≥42	505	9.2	1906	9.1	3773	8.7
Cerebral palsy						
No	5444	99.5	20 870	99.6	43 246	99.8
Yes	30	0.6	76	0.4	84	0.2
Congenital malformation diagnosed in the first year						
No	5067	92.6	19 960	95.3	41 703	96.3
Yes	407	7.4	986	4.7	1627	3.8
Epilepsy						
No	5385	98.4	20 721	98.9	43 006	99.3
Yes	89	1.6	225	1.1	324	0.8
Apgar score at 5 minutes						
7-10	5377	98.2	20 663	98.7	42 740	98.6
<7	97	1.8	283	1.4	590	1.4
Conditions originating in the perinatal period						
No	4019	73.4	16 645	79.5	35 895	82.8
Yes	1455	26.6	4301	20.5	7435	17.2

*χ^2 tests for all characteristics are statistically significant ($P < .05$) according to duration of breastfeeding.

IRRs of epilepsy for children breastfed for 1 to 2, 3 to 5, 6 to 8, 9 to 12, and ≥13 months compared with children breastfed <1 month. We also analyzed the trend of the IRRs by using the initial number of each category as the exposure score (0, 1, 3, 6, 9, 13 months).

Maternal conditions during pregnancy and child morbidity may influence both breastfeeding and epilepsy. We therefore conducted analyses in a subgroup (n = 42 118) by excluding children with a birth weight <2500 g (n = 1902), gestational age <37 completed weeks (n = 2953), congenital malformation diagnosed in the first year of life (n = 3020), a low or missing Apgar score (n = 970), cerebral palsy (n = 190), certain conditions originating in the perinatal period (n = 13 191), and a hospitalization or treatment as an outpatient because of other disorders in the first 6 months of life (n = 5136) and children exposed to maternal preeclampsia (n = 2260), diabetes mellitus during pregnancy (n = 1162), infections of genitourinary tract (n = 1810), infections of the amniotic sac and membranes (n = 1227), or premature rupture of membrane (n = 4730).

We further restricted the analyses to children with completed information on termination of breastfeeding (n = 53 509) by excluding children who were still breastfed at the time of interview (n = 15 150) and children with inconsistent data in the two interviews (n = 1206).

We also estimated the IRRs of epilepsy according to the duration of exclusive breastfeeding (<1, 1, 2, 3, ≥4 months) despite the duration of breastfeeding by using children who were breastfed <1 month as a reference group. Exclusive breastfeeding was treated as a time-dependent variable in the estimation of IRR for epilepsy in the first year of life.

Results

We identified 638 children in whom epilepsy was diagnosed in the National Hospital Register during as long as 11 years of follow-up (median, 7.7 years); 159 of these children (25%) received a diagnosis within the first year of life. In the study population, 68 499 children (98.2%) were breastfed and 43 330 children (62.1%) were breastfed for >6 months. Among breastfed children, 49 174 children (77.8%) were exclusively breastfed according to our definition.

Mothers who breastfed their children ≥6 months were more likely to be >30 years old, multiparous, of higher socioeconomic status, non-smokers, have a normal BMI, have fewer complications during pregnancy, and be without a history of epilepsy. Children who were breastfed <1 month were more likely to have a low gestational age at birth, a low Apgar score, congenital malformations, conditions originating in the perinatal period, and cerebral palsy (**Table I**).

The IRRs between duration of breastfeeding and risk of epilepsy were not modified by sex of the child, gestational age, parity, or maternal intake of n-3 LCPUFA during pregnancy. The association seemed to be stronger for girls than for boys and for children born to mothers with a low intake of n-3 LCPUFA compared with children born to mothers with a moderate intake of n-3 LCPUFA, although the test for effect measure modification was not statistically significant (data not shown).

Children who were breastfed for a longer duration had a lower risk of epilepsy both in the first year of life and later, when compared with children who were breastfed <1 month. The risk of epilepsy decreased with increasing duration of breastfeeding in a dose-response like pattern (**Table II**). When we excluded children with adverse neonatal conditions and children exposed to adverse maternal conditions, the association remained with a dose-response like pattern for epilepsy after 1 year of age. The IRRs for epilepsy were 0.94 (95% CI, 0.56 to 1.56) for breastfeeding 1 to 2 months, 0.53 (95% CI, 0.33 to 0.86) for 3 to 5 months, 0.52 (95% CI, 0.34 to 0.80) for 6 to 8 months, 0.41 (95% CI, 0.24 to 0.70) for 9 to 12 months, and 0.27 (95% CI, 0.13 to 0.57) for ≥13 months compared with children who were breastfed <1 month. The associations did not change when we restricted the analyses to children with complete information on termination of breastfeeding (data not shown).

Compared with children breastfed <1 month, the risk of epilepsy decreased with increasing duration of exclusive breastfeeding (**Table III**).

Discussion

Longer duration of breastfeeding was associated with a lower risk of epilepsy in childhood with a dose-response like pattern, and the associations remained when we excluded children who had adverse neonatal conditions and children who were exposed to adverse maternal conditions during pregnancy that may interfere with duration of breastfeeding and risk of epilepsy.

The study has several strengths and limitations. Results were derived from a population-based cohort, which represented 30% of all Danish pregnant women in the recruitment period.[18] All women in Denmark can receive benefits during a relatively long maternity leave (at least 32 weeks), and breastfeeding is common, encouraged, and supported by trained health nurses with similar rates in our study population compared with previously reported rates. The factors that influence breastfeeding, however, may differ from that of other countries, especially in less affluent countries.[19] The DNBC was established to provide a data source for epidemiological studies of the short- and long-term consequences of prenatal or perinatal exposure. Information on breastfeeding and epilepsy was collected independently and prospectively, reducing the risk of systematic bias. Epilepsy had been diagnosed in some children (n = 164) before the telephone interview was conducted, which could affect the response. However, we found no change in the estimates of risk for epilepsy after the first year of life when these children were excluded. Information on epilepsy was obtained from the hospital register from the ICD-10 diagnoses, and the positive predictive value of the epilepsy diagnosis in the Danish Hospital Registry has been estimated to be 81% (95% CI, 75% to 87%). However,

Table II. Incidence rate ratios for epilepsy according to duration of breastfeeding

Duration of breastfeeding (months)	Number of children	Person years	Total population			
			Epilepsy cases	IR	Crude IRR	Adjusted IRR* (95% CI)
Epilepsy onset in the first year of life†						
<1‡	5474	5039	30	595.4	1.00	1.00 (reference)
1-2	64 276	15 279	43	281.4	0.44	0.44 (0.23-0.84)
3-5	57 192	20 634	49	237.5	0.39	0.39 (0.21-0.72)
6-8	43 286	17 695	32	180.8	0.30	0.35 (0.17-0.71)
≥9	18 282	5668	5	88.2	0.23	0.42 (0.12-1.50)
P value of trend test						.052
Epilepsy onset after 1 year of age						
<1‡	5443	36 135	59	163.3	1.00	1.00 (reference)
1-2	7037	47 495	76	160.0	0.98	1.00 (0.66-1.51)
3-5	13 852	94 121	101	107.3	0.66	0.74 (0.50-1.09)
6-8	24 970	168 592	145	86.0	0.53	0.61 (0.42-0.88)
9-12	11 849	80 018	66	82.5	0.51	0.50 (0.32-0.77)
≥13	6428	43 891	32	72.9	0.45	0.41 (0.24-0.71)
P value of trend test						<.001

*Adjusted for sex of the child, gestational age at birth (<37, 37-41, ≥42 weeks), maternal age (15-24, 25-29, 30-34, 35-39, ≥40 years), socioeconomic status (high, middle, low, missing), smoking status at time of the interviews during pregnancy (yes, no), prepregnancy BMI (<18.5, 18.5-24.0, 25-29, ≥30, missing), parity (primiparous, multiparous), time to pregnancy (≤12 months, >12 months, unplanned pregnancy or missing), maternal intake of n-3 LCPUFA during pregnancy (low 1/3, middle 1/3, high 1/3), and parental history of epilepsy (yes, no).
†Breastfeeding was treated as a time-dependent variable; for example, a child who was breastfed for >2 months could contribute follow-up time in several categories.
‡Includes children without breastfeeding.

40% of the children who did not fulfill the criteria for epilepsy (at least 2 seizures) had experienced a single unprovoked seizure.[20] The completeness of the epilepsy registration in the registry is unknown, but few neurologists and pediatricians are working in private clinics in Denmark. The misclassification from register sources should be non-differential and will not affect the precision of the estimates. Children who were breastfed for a longer period, however, may spend more time with their mother and the mother may observe seizures activity that would otherwise not have been recognized, which tends to underestimate the association.

We did not examine whether the association was restricted to specific types of epilepsy because of limited information on the epilepsy subtypes in the Danish Hospital Register.[20] Our finding is consistent with findings from two earlier cohort studies,[12,13] but not the findings from a case-control study, in which information on breastfeeding was collected after epilepsy was diagnosed in the child.[21] We were able to adjust for many potential confounding factors, such as socioeconomic status, smoking, BMI, gestational age, parity, and maternal age, but residual confounding may come from factors for which we did not account, such as life style, diet, and maternal conditions after giving birth. Excluding children with adverse neonatal or prenatal conditions also showed an association between breastfeeding and risk of epilepsy with onset after 1 year of age. It is difficult to explain the dose-response-like pattern beyond influence of breastfeeding because the effect of the confounders would have to increase with the duration of breastfeeding, which we find unlikely. Still, caution is needed because breastfeeding may correlate with other conditions that we did not consider, for example, child head injuries or psychological disorders of mothers.

It is biologically plausible that breastfeeding may protect children from the development of epilepsy. The human brain increases dramatically in size and complexity in the first years of life.[22] Human milk contains essential nutritional factors, including docosahexaenoic acid, which is almost absent in cow milk.[23] More studies have indicated that lipids such as choline, cholesterol, and gangliosides, which are constituents of human milk, also play an important role in the early brain

Table III. Incidence rate ratios of epilepsy according to duration of exclusive breastfeeding

Duration of exclusive breastfeeding (months)	Epilepsy in the first year of life	Epilepsy after the first year of life
	Adjusted IRR*† (95% CI)	Adjusted IRR* (95% CI)
<1‡	1.00 (reference)	1.00 (reference)
1	0.38 (0.20-0.72)	0.98 (0.63-1.50)
2	0.29 (0.13-0.64)	0.84 (0.54-1.30)
3	0.36 (0.20-0.65)	0.65 (0.46-0.92)
≥4	0.35 (0.19-0.64)	0.56 (0.39-0.80)
P value for trend test	.002	<.001

*Adjusted for sex of the child, gestational age at birth (<37, 37-41, ≥42 weeks), maternal age (15-24, 25-29, 30-34, 35-39, ≥40 years), socioeconomic status (high, middle, low, missing), smoking status at time of the interviews during pregnancy (yes, no), prepregnancy BMI (<18.5, 18.5-24, 25-29, ≥30, missing), parity (primiparous, multiparous), time to pregnancy (≤12 months, >12 months, unplanned pregnancy or missing), and parental history of epilepsy (yes, no).
†Exclusive breastfeeding was treated as a time-dependent variable in the estimation of IRR for epilepsy in the first year of life.
‡Includes children without breastfeeding.

development.[24] Breast milk also contains antibodies, enzymes, and hormones, all which may have health effects on the child.[25-27] Physical mother-child contact may play a protective role because animal studies indicate that maternal behavior such as licking and grooming have effect on the neurodevelopment in early life, and can alter the offspring's response to stress.[28] ■

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