Original Investigation

Early Child Development and Exposure to Antiepileptic Drugs Prenatally and Through Breastfeeding

A Prospective Cohort Study on Children of Women With Epilepsy

Gyri Veiby, MD; Bernt A. Engelsen, MD, PhD; Nils Erik Gilhus, MD, PhD

IMPORTANCE Exposure to antiepileptic drugs during pregnancy is associated with adverse effects on psychomotor development.

OBJECTIVES To determine whether signs of impaired development appear already during the first months of life in children exposed prenatally to antiepileptic drugs, and to explore potential adverse effects of antiepileptic drug exposure through breastfeeding.

DESIGN, SETTING, AND PARTICIPANTS Mothers at 13 to 17 weeks of pregnancy were recruited in the population-based, prospective Norwegian Mother and Child Cohort Study from 1999 to 2009. The mothers reported on their child's motor and social skills, language, and behavior using items from standardized screening tools at 6 months (n = 78 744), 18 months (n = 61 351), and 36 months (n = 44 147) of age. The mothers also provided detailed information on breastfeeding during the first year.

MAIN OUTCOMES AND MEASURES The risk of adverse development in children according to maternal or paternal epilepsy was estimated as the odds ratio with corresponding 95% confidence interval, adjusted for maternal age, parity, education, smoking, breastfeeding, depression/anxiety, folate supplementation, and congenital malformation in the child.

RESULTS At age 6 months, infants of mothers using antiepileptic drugs (n = 223) had a higher risk of impaired fine motor skills compared with the reference group (11.5% vs 4.8%, respectively; odds ratio = 2.1; 95% CI, 1.3-3.2). Use of multiple antiepileptic drugs compared with the reference group was associated with adverse outcome for both fine motor skills (25.0% vs 4.8%, respectively; odds ratio = 4.3; 95% CI, 2.0-9.1) and social skills (22.5% vs 10.2%, respectively; odds ratio = 2.6; 95% CI, 1.2-5.5). Continuous breastfeeding in children of women using antiepileptic drugs was associated with less impaired development at ages 6 and 18 months compared with those with no breastfeeding or breastfeeding for less than 6 months. At 36 months, prenatal antiepileptic drug exposure was associated with adverse development regardless of breastfeeding status during the first year. Children of women with epilepsy who did not use antiepileptic drugs and children of fathers with epilepsy had normal development at 6 months.

CONCLUSIONS AND RELEVANCE Prenatal exposure to antiepileptic drugs was associated with impaired fine motor skills already at age 6 months, especially when the child was exposed to multiple drugs. There were no harmful effects of breastfeeding. Women with epilepsy should be encouraged to breastfeed their children irrespective of antiepileptic drug treatment.

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Author Affiliations: Department of Clinical Medicine, Section for Neurology, University of Bergen, Bergen, Norway (Veiby, Engelsen, Gilhus); Department of Neurology, Haukeland University Hospital, Bergen, Norway (Veiby, Engelsen, Gilhus).

Corresponding Author: Gyri Veiby, MD, Department of Neurology, Haukeland University Hospital, 5021 Bergen, Norway (gyri.veiby@hotmail.com).

Antiepileptic drugs potentially influence fetal development throughout the pregnancy.[1,2] Increasing evidence indicates that prenatal exposure to antiepileptic drugs has effects on cognition, motor function, and behavior.[3-7] Few studies have presented data on development during the first months in children of mothers with epilepsy. Early identification of children at risk could promote appropriate follow-up and intervention.[8]

Deleterious effects of breastfeeding in children of mothers using antiepileptic drugs are of special interest.[9] Breastfeeding is generally encouraged until at least 6 months of age, based on widely documented beneficial effects.[10,11] This is controversial concerning women with epilepsy as exposure to antiepileptic drugs through breastfeeding could harm the developing infant, similar to the teratogenic effects associated with in utero exposure.[1]

In the prospective Norwegian Mother and Child Cohort Study (MoBa), mothers have reported on their child's development at ages 6, 18, and 36 months using validated screening instruments and have provided detailed information on breastfeeding during the first year.

The primary aim of this study was to examine whether prenatal exposure to antiepileptic drugs has an effect on development already during the first 6 months. The secondary aim was to explore adverse effects of antiepileptic drug exposure through breastfeeding. Children of mothers using antiepileptic drugs were compared with a large reference group of children without parental epilepsy. Children of fathers and untreated mothers with epilepsy served as internal control groups, accounting for genetic and socioeconomic effects of parental epilepsy.

Methods

Norwegian Mother and Child Cohort Study

The Norwegian Institute of Public Health established MoBa.[12] Pregnant women in Norway attending routine ultrasonographic scanning were invited to participate, recruited from hospitals and maternity units. Provided the mother's consent, expecting fathers were also invited to participate. The women received a postal invitation prior to their scheduled ultrasonographic examination (pregnancy weeks 13-17) containing the first questionnaire, focusing on medical history before pregnancy. A questionnaire 6 months after delivery focused on child nutrition, health, and development, while questionnaires at 18 and 36 months further explored the child's developmental status.

From mid-1999 to December 2008, 108 976 children were registered in MoBa. The participation rate for invited pregnancies was 38.5%.[13] Subsequent response rates for the questionnaires at 6, 18, and 36 months were 84.8%, 73.0%, and 60.2%, respectively.[14] Fathers were invited to participate in 87.3% of the included pregnancies, with a response rate of 82.9%.[12]

In a substudy, hospital records for mothers with epilepsy residing in western Norway and participating in MoBa were examined, validating the self-reported epilepsy diagnosis and use of antiepileptic drugs.[15]

This study was approved by the Regional Committee for Medical Research Ethics in western Norway. Written informed consent was obtained from all the participants in MoBa.

Assessment of Parental Epilepsy

All 974 children of mothers or fathers with epilepsy in the MoBa cohort at 6 months formed the epilepsy group. The remaining 77 770 children of parents without epilepsy served as the reference group. Use of antiepileptic drugs during pregnancy was reported by the mother in the first MoBa questionnaire (weeks 13-17) as well as recorded in the compulsory Medical Birth Registry by the attending physician and midwife at delivery. In pregnancies with antiepileptic drug use, 93.7% had drug information from MoBa, whereas the remaining 6.3% had additional drug information from the Medical Birth Registry. For pregnancies with drug information from both registers (73.9%), there was 99.5% accordance with recorded type of monotherapy. Antiepileptic drug monotherapy was subgrouped into carbamazepine, lamotrigine, and valproate sodium. The polytherapy group included pregnancies in which more than 1 antiepileptic drug was reported.

Due to both ongoing data collection and loss to follow-up, the numbers of children of parents with and without epilepsy differ at 6, 18, and 36 months.

Measures of Development

The mothers' rating of the child's development and behavior provided the main outcome variables. The screening tools in MoBa are based on standardized and validated scales designed to identify difficulties within each developmental domain and are suited for research.[16-23] The instruments typically assess whether a child has reached critical developmental milestones.[19] Due to space limitations, some domains are represented with selected items from the original scales, aimed at items that are easily observable by parents. All included items are listed in the eAppendix in the Supplement.

Total scores on the developmental scales were dichotomized by cutoff values into adverse or normal range. For scales without predefined cutoff values, adverse outcome was defined as sum scores rarely observed in the reference group (90th-95th percentile range), corresponding to greater than 2 SDs of the mean. Such scores were regarded as representing clinically relevant impairment. Previous MoBa studies on the applied screening instruments have shown good reliability for developmental scores that are distant (>1.5-2.0 SDs) from the mean.[24-26]

At age 6 months, items measuring motor skills were obtained from the Ages and Stages Questionnaire.[22,27] Rating of social skills was based on the Ages and Stages Questionnaire, supplied by items from the Bayley Scales of Infant Development. Assessment of difficult temperament was obtained from the Infant Characteristics Questionnaire.[28]

At age 18 months, motor and communication skills were assessed by items from the Ages and Stages Questionnaire. Autistic traits were examined by a 23-item checklist based on the Modified Checklist for Autism in Toddlers, with a cutoff score at 2 or more of 6 critical items or any 3 items of the total scale.[17,19]

At age 36 months, language skills were based on criteria by Dale et al,[20] assessing the child's typical level of sentence completeness. Attention-deficit/hyperactivity disorder symptoms were measured by a MoBa-specific checklist, including items from the Child Behavior Checklist[23,29] and the attention-deficit/hyperactivity disorder criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition). Aggressiveness was assessed by items from the Child Behavior Checklist. The 40-item Social Communication Questionnaire was applied to investigate autistic traits at 36 months, with a cutoff score at 15 or more positive items.[19,30]

Perinatal Outcome and Child Weight

The Medical Birth Registry provided information on preterm delivery (<37 weeks), low birth weight (<2500 g), and major congenital malformations diagnosed during the neonatal period or pediatric follow-up within the first year. Low child weight at 6 weeks, 3 months, and 6 months was defined as weight below the 10th percentile based on the reference population.

Statistical Analysis

In the primary analyses, children of mothers with epilepsy were categorized according to prenatal antiepileptic drug exposure and according to postnatal antiepileptic drug exposure through breast milk. Antiepileptic drug exposure during the breastfeeding period was based on recorded medication during pregnancy, assuming continued treatment after delivery. Children of mothers starting antiepileptic drug treatment after delivery were excluded (n = 4). This ensured that adverse effects of antiepileptic drugs via breast milk were assessed only in children who had also been exposed in utero. Continuous breastfeeding required daily breastfeeding for a minimum of 6 months, whereas discontinued breastfeeding was defined as breastfeeding for less than 6 months or not at all.

The analyses were performed using IBM SPSS Statistics version 20 (IBM Corp). The risk of adverse outcomes was estimated as odds ratio (OR) with the corresponding 95% confidence interval, using unconditional logistic regression and adjustment for potential confounders. When the OR differed considerably from the relative risk, a generalized linear model estimated the adjusted relative risk. Two-sided $P \leq .05$ was considered statistically significant. Covariates included maternal age (years), maternal education (0-9, 10-12, 13-16, or ≥17 years), maternal depression/anxiety (Hopkins Symptom Checklist),[31] breastfeeding duration (months), smoking during pregnancy (yes or no), folate supplementation (preconception and/or during first trimester), child's birth order (first, second, or third or later), low birth weight, preterm delivery, and major malformation.

To avoid potential sample distortions caused by missing data in the developmental scales, a maximum likelihood estimation procedure was applied to impute missing values.[32] Developmental scores with 20% or more missing data were excluded.

Explorative analyses are presented in the eAppendix in the Supplement, including stratified analyses and propensity score matching (eTable 1 and eTable 2 in Supplement).[33]

Results

Epilepsy Group

Data 6 months after delivery included 503 children in 490 pregnancies by 441 women with epilepsy. Baseline characteristics of the epilepsy cohort in MoBa have been published previously.[15] Exposure to antiepileptic drugs during pregnancy was reported in 223 children (44.3%), with the majority as monotherapy (n = 182). The most common monotherapies were lamotrigine (n = 71), carbamazepine (n = 48), and valproate (n = 27). Exposure to polytherapy with antiepileptic drugs was recorded in 41 children (18.4%).

Another 471 children had a father with epilepsy, of whom 37.6% used antiepileptic drugs within 6 months prior to conception.

Child Health and Development

Referrals to a specialist owing to developmental delay were increased for children of mothers using antiepileptic drugs compared with the reference group (3.1% vs 1.5%, respectively; unadjusted OR = 2.2; 95% CI, 1.0-4.6). The same was not observed for children of untreated mothers with epilepsy or children of fathers with epilepsy. Other health problems (infant colic, febrile or nonfebrile convulsions, impaired vision or hearing, heart disorder, or asthma) at 6 months were not increased in any of the epilepsy groups.

Children of mothers using antiepileptic drugs scored more often outside the normal range for fine motor skills at 6 months, with similar risks for monotherapy with lamotrigine, carbamazepine, and valproate (**Table 1**). Children of mothers using multiple antiepileptic drugs had the highest risk for impaired fine motor skills and also had impaired social skills (Table 1). Difficult temperament was not more common in children of mothers with epilepsy compared with the reference group, including mothers using antiepileptic drugs (3.6% vs 5.2%, respectively; adjusted OR = 0.6; 95% CI, 0.3-1.2) and untreated mothers (5.5% vs 5.2%, respectively; adjusted OR = 1.0; 95% CI, 0.6-1.7).

Children of fathers with epilepsy were similar to the reference group for all the developmental outcomes: gross motor skills (9.9% vs 9.8%, respectively; adjusted OR = 1.0; 95% CI, 0.7-1.4), fine motor skills (5.4% vs 4.8%, respectively; adjusted OR = 1.1; 95% CI, 0.8-1.7), social skills (9.4% vs 10.2%, respectively; adjusted OR = 0.9; 95% CI, 0.7-1.2), and difficult temperament (5.6% vs 5.2%, respectively; adjusted OR = 1.1; 95% CI, 0.7-1.6).

Breastfeeding and Effects on Child Development and Weight

Breastfeeding rates varied within the epilepsy groups and were lowest for women using lamotrigine monotherapy (**Figure 1**). Exclusive breastfeeding was less common among women using antiepileptic drugs (eTable 3 in Supplement).

Continuous breastfeeding during the first 6 months was associated with a tendency toward improved outcome for all the developmental domains regardless of maternal antiepileptic drug treatment (**Figure 2**). For carbamazepine and valproate, the discontinuation rate was too low to sepa-

Table 1. Risk of Adverse Developmental Outcome at Age 6 Months in Children of Mothers With Epilepsy Compared With the Reference Group

		Fine Motor Impairment		Gross Motor Impairment		Social Impairment	
Child Group[a]	No.	No. (%)	OR (95% CI)[b]	No. (%)	OR (95% CI)[b]	No. (%)	OR (95% CI)[b]
Reference	77 770	3648 (4.8)	1 [Reference]	7507 (9.8)	1 [Reference]	7848 (10.2)	1 [Reference]
No antiepileptic drug	276	19 (6.9)	1.4 (0.8-2.2)	33 (12.0)	1.2 (0.8-1.8)	37 (13.4)	1.4 (1.0-2.0)
Antiepileptic drugs in total	223	25 (11.5)	2.1 (1.3-3.2)[c]	30 (13.7)	1.3 (0.9-1.9)	28 (12.7)	1.3 (0.9-1.9)
Monotherapy	182	15 (8.5)	1.6 (0.9-2.7)	21 (11.7)	1.1 (0.7-1.7)	19 (10.5)	1.0 (0.6-1.7)
Lamotrigine monotherapy	71	7 (10.1)	1.8 (0.8-3.9)	11 (15.7)	1.5 (0.8-2.9)	9 (12.7)	1.2 (0.6-2.5)
Carbamazepine monotherapy	48	5 (10.9)	2.3 (0.9-6.0)	6 (12.8)	1.3 (0.5-3.0)	6 (12.8)	1.4 (0.6-3.3)
Valproate sodium monotherapy	27	3 (11.5)	2.1 (0.6-7.3)	2 (7.4)	0.7 (0.2-2.8)	1 (3.7)	0.3 (0.1-2.4)
Polytherapy	41	10 (25.0)	4.3 (2.0-9.1)[c]	9 (23.1)	2.1 (1.0-4.4)	9 (22.5)	2.6 (1.2-5.5)[c]

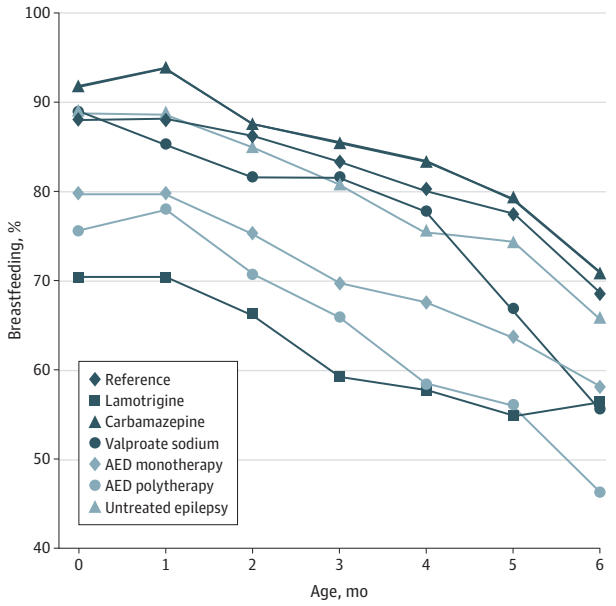
Abbreviation: OR, odds ratio.

[a] Categorized according to maternal antiepileptic drug use during pregnancy.

[b] The ORs with corresponding 95% CIs were adjusted for maternal age, parity, education, folate supplementation, smoking, depression/anxiety, breastfeeding (number of months), and child malformation.

[c] $P \leq .05$.

Figure 1. Exclusive or Mixed Breastfeeding at Ages 0 to 6 Months



Frequency of breastfeeding in epilepsy groups and the reference group at 0 to 6 months after delivery. AED indicates antiepileptic drug.

rately evaluate data concerning nonbreastfeeding. However, development in those who were breastfed compared favorably with other subgroups at 6 months (eTable 4 in Supplement).

At 18 months, children in the drug-exposed group had an increased risk of impaired development compared with the reference group (**Table 2**). The risks tended to be elevated particularly in children with discontinued breastfeeding. Within the drug-exposed group, this was only statistically significant for autistic traits, where 22.4% with discontinued breastfeeding were affected compared with 8.7% of those with prolonged breastfeeding (unadjusted OR = 3.0; 95% CI, 1.2-7.4). At 36 months, the risk of autistic traits was equally high for both groups (Table 2).

Not breastfeeding was associated with an increased risk of low child weight at 6 weeks and was significant for children of women using antiepileptic drugs (**Table 3**). At 6 months, the frequency of low child weight was similar for the epilepsy and reference groups regardless of breastfeeding status (Table 3).

Validation

Mothers of 40 children in the epilepsy group were included in the validation study.[15] In this study, MoBa mothers reported reliable information about their epilepsy, and there was 100% accordance with the mothers' reports of antiepileptic drug use during pregnancy and drug use registered in hospital records. All mothers treated with antiepileptic drugs continued their medication through the entire pregnancy, and none discontinued their medication within the first year after delivery.

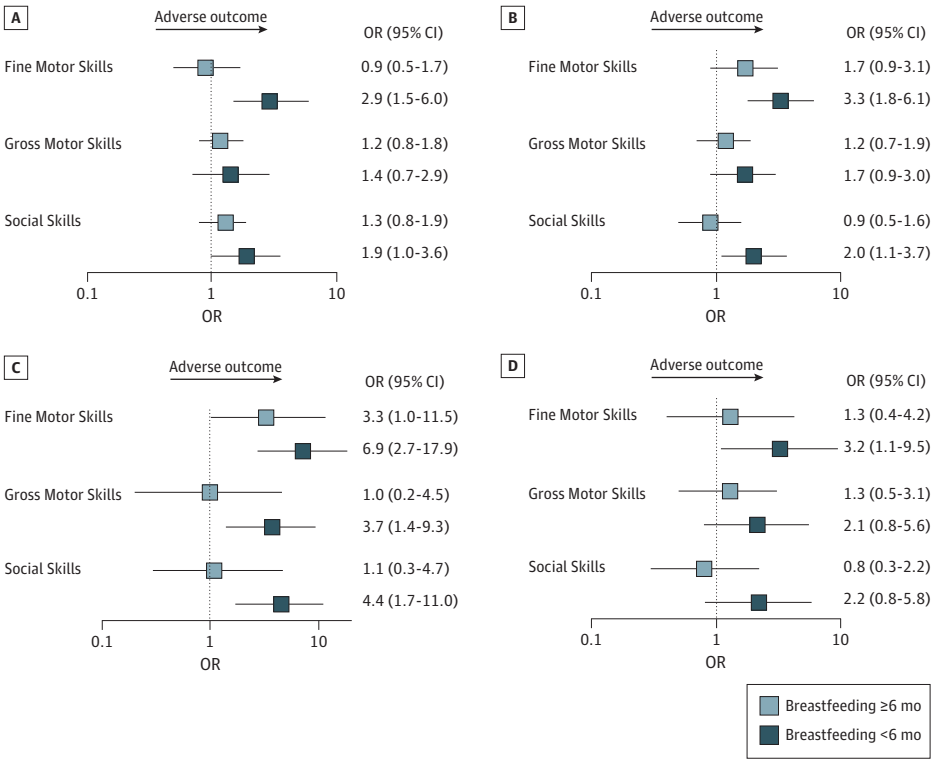
Discussion

Key Findings

Infants of mothers using antiepileptic drugs had an increased risk of delayed fine motor skills at 6 months, with similar risk estimates for monotherapy with lamotrigine, valproate, and carbamazepine. Children exposed to polytherapy had higher risks, with significant effects on both fine motor and social skills. Other developmental measures in the exposed group were within the normal range at this early age. Children of mothers with epilepsy who did not use antiepileptic drugs and children of fathers with epilepsy had normal development at 6 months, indicating that adverse effects in the drug-exposed group were not a result of genetic factors.

Breastfeeding was not associated with adverse development at ages 6 to 36 months in children of mothers using antiepileptic drugs. On the contrary, there was a trend toward a more favorable outcome in children who were continuously breastfed, especially for early autistic traits. Breastfeeding in the drug-exposed group was also associated with a lower risk of poor weight gain during the postnatal period.

Figure 2. Risk of Adverse Development Score at 6 Months in Children of Mothers With Epilepsy According to Breastfeeding



Epilepsy groups with no maternal antiepileptic drug use (A), maternal antiepileptic drug use (B), maternal antiepileptic drug polytherapy (C), and maternal lamotrigine monotherapy (D) were examined. Odds ratios (ORs) with 95% CIs were adjusted for maternal age, parity, smoking, folate use, education, anxiety/depression, and child malformation.

Table 2. Risk of Adverse Development at Ages 18 and 36 Months in Children of Antiepileptic Drug–Treated Mothers Categorized According to Breastfeeding

		Mother Treated With AED			
		Breastfeeding ≥6 mo		Breastfeeding <6 mo[b]	
Adverse Outcome[a]	Reference, %	No. (%)	OR (95% CI)[c]	No. (%)	OR (95% CI)[c]
Child aged 18 mo[d]					
Fine motor skills	12.4	22 (19.6)	1.7 (1.1-2.8)[e]	14 (20.6)	1.7 (0.9-3.1)
Gross motor skills	8.6	13 (11.5)	1.2 (0.7-2.3)	14 (20.0)	2.2 (1.2-4.1)[e]
Autistic traits	7.8	9 (8.7)	1.0 (0.5-2.0)	15 (22.4)	2.9 (1.6-5.2)[e]
Communication skills	10.6	20 (18.0)	1.7 (1.1-2.9)[e]	17 (24.3)	2.6 (1.5-4.5)[e]
Child aged 36 mo[f]					
Autistic traits	1.5	4 (5.0)	3.1 (1.1-8.7)[e]	4 (7.5)	3.8 (1.4-10.8)[e]
Sentence skills	4.8	9 (11.1)	2.3 (1.3-4.7)[e]	6 (11.3)	1.9 (0.8-4.6)
ADHD symptoms	4.0	7 (8.5)	2.2 (1.0-5.2)	1 (1.9)	0.3 (0.1-2.4)
Aggressive symptoms	4.1	4 (4.9)	1.3 (0.5-3.7)	7 (13.0)	2.9 (1.3-6.6)[e]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AED, antiepileptic drug; OR, odds ratio.

[a] More than 2 SDs from the mean.

[b] Absent or discontinued breastfeeding (median duration of breastfeeding, 1 month).

[c] The ORs with corresponding 95% CIs were adjusted for maternal age, parity, education, smoking, folate supplementation, depression/anxiety at assessment, and child malformation.

[d] A total of 184 children of mothers with epilepsy using AEDs were compared with a reference group of 60 583 children.

[e] $P \leq .05$.

[f] A total of 139 children of mothers with epilepsy using AEDs were compared with a reference group of 43 571 children.

Continuous breastfeeding during the first year was less common among women using antiepileptic drugs, especially regarding lamotrigine monotherapy, compared with both those not using drugs and the reference population. This may indicate that antiepileptic drugs are regarded by patients, midwives, and physicians as a relative contraindication for breastfeeding.

Table 3. Risk of Weight Less Than the 10th Percentile According to Breastfeeding Status in Children of Women With Epilepsy Compared With the Reference Group

		Low Weight					
		6 wk[c]		3 mo		6 mo	
Child Group[a]	Breastfeeding[b]	% (No.)	OR (95% CI)[d]	% (No.)	OR (95% CI)[d]	% (No.)	OR (95% CI)[d]
Reference		6606 (10.0)	1 [Reference]	7425 (10.0)	1 [Reference]	7101 (10.0)	1 [Reference]
No AED use	No	4 (15.4)	1.7 (0.5-5.7)	12 (18.8)	1.5 (0.7-3.0)	6 (9.7)	0.8 (0.3-2.0)
	Yes	20 (9.7)	0.9 (0.5-1.5)	30 (13.7)	1.4 (0.9-2.1)	19 (9.5)	1.0 (0.6-1.6)
AED use	No	14 (31.8)	2.7 (1.7-4.2)[e,f]	11 (16.4)	1.5 (0.7-3.0)	7 (10.4)	0.9 (0.4-2.1)
	Yes	21 (13.8)	1.4 (0.8-2.4)	18 (12.7)	1.3 (0.8-2.2)	14 (10.5)	1.1 (0.6-1.9)
AED monotherapy	No	8 (22.9)	1.9 (1.0-3.6)[e]	7 (13.0)	1.1 (0.5-2.8)	4 (7.7)	0.8 (0.3-2.2)
	Yes	14 (11.5)	1.3 (0.7-2.4)	13 (11.3)	1.2 (0.6-2.2)	12 (10.9)	1.1 (0.6-2.0)
AED polytherapy	No	6 (66.7)	5.6 (3.6-8.9)[e,f]	4 (33.3)	3.1 (1.4-6.8)[e,f]	3 (18.8)	1.4 (0.4-5.2)
	Yes	7 (25.0)	2.7 (1.4-5.0)[e,f]	5 (19.2)	2.0 (0.7-5.8)	2 (10.0)	1.1 (0.2-4.8)
Lamotrigine monotherapy	No	6 (30.0)	2.4 (1.1-5.1)[e,f]	4 (13.8)	1.1 (0.3-3.9)	2 (8.7)	0.9 (0.2-3.9)
	Yes	5 (10.6)	1.4 (0.5-3.8)	6 (15.8)	2.0 (0.8-5.0)	4 (9.8)	1.1 (0.4-3.1)

Abbreviations: AED, antiepileptic drug; OR, odds ratio.

[a] Categorized according to maternal AED use.

[b] Breastfeeding status (yes or no) at the time of weight assessment.

[c] Data available for 89.9% of the cohort.

[d] The ORs with corresponding 95% CIs were adjusted for low birth weight, preterm delivery, maternal education, age, parity, and smoking.

[e] Values are relative risks with corresponding 95% CIs, adjusted for low birth weight, preterm delivery, maternal education, age, parity, and smoking.

[f] $P < .05$.

Interpretation

Recent studies have provided new insights into the long-term effects of prenatal exposure to antiepileptic drugs, with the majority reporting some degree of adverse development.[3,6,7,34,35] According to our findings, assessment of fine motor skills may be especially suited for early identification of children at risk and could initiate the follow-up of these children. There are limited previous reports on development during infancy in children exposed in utero to antiepileptic drugs, and no reports systematically explore effects of breastfeeding during this early period. Evidence to determine whether maternal use of antiepileptic drugs has symptomatic effects on the infant has not been established earlier.[36] We could not identify any deleterious effects of breastfeeding on early development in children of mothers using antiepileptic drugs. Similarly, Meador et al[37] found no harmful effects of breastfeeding on child IQ at age 3 years. The beneficial role of breastfeeding is widely documented, including effects on cognition.[10] In maternal epilepsy, professional recommendations must balance such benefits against potential harmful effects of continued drug exposure through breast milk. This has been of concern especially for lamotrigine and other newer-generation antiepileptic drugs, which penetrate into breast milk in relatively substantial amounts.[36,38,39] Antiepileptic drugs cross the placenta in clinically relevant amounts,[36] with a dose-dependent teratogenicity.[40] However, ingested concentrations from breast milk are substantially lower than in utero exposure.[39] Whereas fetal exposure to antiepileptic drugs is similar to maternal plasma concentrations, infant and maternal plasma concentrations are highly variable and depend on a variety of factors.[41] Phenytoin, phenobarbital, carbamazepine, and valproate probably do not transfer to breast milk in significant amounts.[36] Antiepileptic drugs with low protein binding, such as levetiracetam and gabapentin, accumulate in breast milk but are probably efficiently eliminated by the infant.[39] For lamotrigine and oxcarbazepine, reduced hepatic elimination in the newborn combined with moderate transfer via breast milk can result in clinically relevant plasma concentrations in the infant.[39,41,42] Case reports describing withdrawal seizures as a result of discontinued breastfeeding[43] and serious apnea in a newborn exposed to lamotrigine via breast milk[44] underline the importance of cautious observation during the perinatal period. Previous Norwegian guidelines regarding lamotrigine probably explain the low rate of breastfeeding among MoBa mothers using lamotrigine. However, most reports on lamotrigine exposure via breast milk have not observed any adverse effects.[38,41] Our study supports that positive effects of breastfeeding outweigh any negative effects, including for mothers treated with lamotrigine or polytherapy.

In the drug-exposed group, the risk of autistic traits at age 18 months was substantially higher for children who discontinued breastfeeding compared with those with prolonged breastfeeding. Previous reports have described a link between autism spectrum disorders and suboptimal breastfeeding.[45,46] Potential mechanisms include nutritional and immunological factors, maternal comorbidity, socioeconomic status, and psychological effects of breastfeeding. Autistic traits at this early age can be associated with general cognitive delay and behavioral problems and not necessarily with true autism.[47]

At 36 months, children of drug-treated mothers with epilepsy had more autistic traits regardless of previous breastfeeding, indicating general and specific risks of autism at this age.

Study Strengths and Limitations

This study included children of mothers both with and without antiepileptic drug treatment and of fathers with epilepsy

recruited in an unselected manner and followed up prospectively in a large national cohort. The participation rate of 38.5% at first assessment is in accordance with the rate from similar registers.[48] Systematic bias due to nonparticipants is a potential concern. However, exposure and outcome associations were not biased in a previous MoBa study,[49] and the prevalence of epilepsy did not differ from the total population.[49,50] Mothers' ratings of the child were based on validated screening tools. Such ratings provide adequate information on the child's development[8,27,51] but do not correspond directly with medical diagnosis. Adjusting for maternal anxiety/depression should partly control for effects of maternal mood on rating of the child. Stratified analysis and propensity score matching showed that the results were not due to differences in baseline variables. Still, residual confounding due to unmeasured parameters such as severity and type of mothers' epilepsy may theoretically contribute to some of the observed drug-exposure associations. Breastfeeding status is strongly related to socioeconomic factors,[52] but such confounding has been accounted for in our study. Reported drug use during pregnancy was applied as a proxy for antiepileptic drug treatment after delivery. This could potentially lead to misclassification of drug exposure via breast milk, although most likely only for a minor percentage as discontinuation of antiepileptic drugs during the postnatal period is not recommended. No mothers in the validation study discontinued antiepileptic drugs during pregnancy or within the first year post partum. Thus, children in the drug-treated group were most likely exposed during the entire pregnancy. Limitations of this study were that specific trimester effects, antiepileptic drug dosages, and concentrations in breast milk could not be investigated.

Conclusions

Prenatal exposure to antiepileptic drugs was associated with a higher risk of impaired fine motor skills at age 6 months, especially in children exposed to multiple antiepileptic drugs. Awareness of such signs may promote early identification of children at risk. Breastfeeding in women using antiepileptic drugs was not associated with any harmful effects on child development at 6 to 36 months of age, and it protected against low weight during the postnatal period. Women with epilepsy should be encouraged to breastfeed their children irrespective of antiepileptic medication use.

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REFERENCES

1. Ikonomidou C, Turski L. Antiepileptic drugs and brain development. *Epilepsy Res*. 2010;88(1):11-22.

2. Kluger BM, Meador KJ. Teratogenicity of antiepileptic medications. *Semin Neurol*. 2008;28(3):328-335.

3. Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. Language skills of school-aged children prenatally exposed to antiepileptic drugs. *Neurology*. 2011;76(8):719-726.

4. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. *Drug Saf*. 2010;33(1):73-79.

5. Forsberg L, Wide K, Källén B. School performance at age 16 in children exposed to antiepileptic drugs in utero: a population-based study. *Epilepsia*. 2011;52(2):364-369.

6. Meador KJ, Baker GA, Browning N, et al; NEAD Study Group. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. *N Engl J Med*. 2009;360(16):1597-1605.

7. Meador KJ, Baker GA, Browning N, et al; NEAD Study Group. Effects of fetal antiepileptic drug exposure: outcomes at age 4.5 years. *Neurology*. 2012;78(16):1207-1214.

8. Rydz D, Shevell MI, Majnemer A, Oskoui M. Developmental screening. *J Child Neurol*. 2005;20(1):4-21.

9. Klein A. Antiepileptic drugs and breastfeeding: do we tell women "no"? *Neurology*. 2010;75(22):1948-1949.

10. Quigley MA, Hockley C, Carson C, Kelly Y, Renfrew MJ, Sacker A. Breastfeeding is associated with improved child cognitive development: a population-based cohort study. *J Pediatr*. 2012;160(1):25-32.

11. Renfrew MJ, McCormick FM, Wade A, Quinn B, Dowswell T. Support for healthy breastfeeding mothers with healthy term babies. *Cochrane Database Syst Rev*. 2012;5:CD001141.

12. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C; MoBa Study Group. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2006;35(5):1146-1150.

13. Roth C, Magnus P, Schjølberg S, et al. Folic acid supplements in pregnancy and severe language delay in children. *JAMA*. 2011;306(14):1566-1573.

14. Stoltenberg C, Schjølberg S, Bresnahan M, et al; ABC Study Group. The Autism Birth Cohort: a paradigm for gene-environment-timing research. *Mol Psychiatry*. 2010;15(7):676-680.

15. Veiby G, Daltveit AK, Schjølberg S, et al. Exposure to antiepileptic drugs in utero and child development: a prospective population-based study. *Epilepsia*. 2013;54(8):1462-1472.

16. Robins DL, Fein D, Barton ML, Green JA. The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders. *J Autism Dev Disord*. 2001;31(2):131-144.

17. Dumont-Mathieu T, Fein D. Screening for autism in young children: the Modified Checklist for Autism in Toddlers (M-CHAT) and other measures. *Ment Retard Dev Disabil Res Rev*. 2005;11(3):253-262.

18. Swinkels SH, Dietz C, van Daalen E, Kerkhof IH, van Engeland H, Buitelaar JK. Screening for autistic spectrum in children aged 14 to 15 months, I: the development of the Early Screening of Autistic Traits Questionnaire (ESAT). *J Autism Dev Disord*. 2006;36(6):723-732.

19. Snow AV, Lecavalier L. Sensitivity and specificity of the Modified Checklist for Autism in

Toddlers and the Social Communication Questionnaire in preschoolers suspected of having pervasive developmental disorders. *Autism*. 2008;12(6):627-644.

20. Dale PS, Price TS, Bishop DV, Plomin R. Outcomes of early language delay, I: predicting persistent and transient language difficulties at 3 and 4 years. *J Speech Lang Hear Res*. 2003;46(3):544-560.

21. Gollenberg AL, Lynch CD, Jackson LW, McGuinness BM, Msall ME. Concurrent validity of the parent-completed Ages and Stages Questionnaires, 2nd Ed. with the Bayley Scales of Infant Development II in a low-risk sample. *Child Care Health Dev*. 2010;36(4):485-490.

22. Richter J, Janson H. A validation study of the Norwegian version of the Ages and Stages Questionnaires. *Acta Paediatr*. 2007;96(5):748-752.

23. Nøvik TS. Validity of the Child Behaviour Checklist in a Norwegian sample. *Eur Child Adolesc Psychiatry*. 1999;8(4):247-254.

24. Brandlistuen RE, Stene-Larsen K, Holmstrom H, Landolt MA, Eskedal LT, Vollrath ME. Motor and social development in 6-month-old children with congenital heart defects. *J Pediatr*. 2010;156(2):265-269; e1.

25. Brandlistuen RE, Stene-Larsen K, Holmstrøm H, Landolt MA, Eskedal LT, Vollrath ME. Symptoms of communication and social impairment in toddlers with congenital heart defects. *Child Care Health Dev*. 2011;37(1):37-43.

26. Schjølberg S, Eadie P, Zachrisson HD, Oyen AS, Prior M. Predicting language development at age 18 months: data from the Norwegian Mother and Child Cohort Study. *J Dev Behav Pediatr*. 2011;32(5):375-383.

27. Squires J, Bricker D, Potter L. Revision of a parent-completed development screening tool: Ages and Stages Questionnaires. *J Pediatr Psychol*. 1997;22(3):313-328.

28. Bates JE, Freeland CA, Lounsbury ML. Measurement of infant difficultness. *Child Dev*. 1979;50(3):794-803.

29. Achenbach TM, Edelbrock C, Howell CT. Empirically based assessment of the behavioral/emotional problems of 2- and 3- year-old children. *J Abnorm Child Psychol*. 1987;15(4):629-650.

30. Rutter M. Autism: its recognition, early diagnosis, and service implications. *J Dev Behav Pediatr*. 2006;27(2)(suppl):S54-S58.

31. Strand BH, Dalgard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry*. 2003;57(2):113-118.

32. Croy CD, Novins DK. Methods for addressing missing data in psychiatric and developmental research. *J Am Acad Child Adolesc Psychiatry*. 2005;44(12):1230-1240.

33. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.

34. Bromley RL, Mawer G, Love J, et al; Liverpool and Manchester Neurodevelopment Group (LMNDG). Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia*. 2010;51(10):2058-2065.

35. Meador KJ, Baker GA, Browning N, et al; NEAD Study Group. Foetal antiepileptic drug exposure and verbal vs non-verbal abilities at three years of age. *Brain*. 2011;134(pt 2):396-404.

36. Harden CL, Pennell PB, Koppel BS, et al; American Academy of Neurology; American Epilepsy Society. Management issues for women with epilepsy: focus on pregnancy (an evidence-based review), III: vitamin K, folic acid, blood levels, and breast-feeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50(5):1247-1255.

37. Meador KJ, Baker GA, Browning N, et al; NEAD Study Group. Effects of breastfeeding in children of women taking antiepileptic drugs. *Neurology*. 2010;75(22):1954-1960.

38. Liporace J, Kao A, D'Abreu A. Concerns regarding lamotrigine and breast-feeding. *Epilepsy Behav*. 2004;5(1):102-105.

39. Sabers A, Tomson T. Managing antiepileptic drugs during pregnancy and lactation. *Curr Opin Neurol*. 2009;22(2):157-161.

40. Tomson T, Battino D, Bonizzoni E, et al; EURAP Study Group. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol*. 2011;10(7):609-617.

41. Newport DJ, Pennell PB, Calamaras MR, et al. Lamotrigine in breast milk and nursing infants: determination of exposure. *Pediatrics*. 2008;122(1):e223-e231.

42. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia*. 2000;41(6):709-713.

43. Rauchenzauner M, Kiechl-Kohlendorfer U, Rostasy K, Luef G. Old and new antiepileptic drugs during pregnancy and lactation: report of a case. *Epilepsy Behav*. 2011;20(4):719-720.

44. Nordmo E, Aronsen L, Wasland K, Småbrekke L, Vorren S. Severe apnea in an infant exposed to lamotrigine in breast milk. *Ann Pharmacother*. 2009;43(11):1893-1897.

45. Schultz ST, Klonoff-Cohen HS, Wingard DL, et al. Breastfeeding, infant formula supplementation, and autistic disorder: the results of a parent survey. *Int Breastfeed J*. 2006;1:16.

46. Tanoue Y, Oda S. Weaning time of children with infantile autism. *J Autism Dev Disord*. 1989;19(3):425-434.

47. Möricke E, Swinkels SH, Beuker KT, Buitelaar JK. Predictive value of subclinical autistic traits at age 14-15 months for behavioural and cognitive problems at age 3-5 years. *Eur Child Adolesc Psychiatry*. 2010;19(8):659-668.

48. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology*. 2006;17(4):413-418.

49. Nilsen RM, Vollset SE, Gjessing HK, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol*. 2009;23(6):597-608.

50. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. *Epilepsia*. 2009;50(9):2130-2139.

51. Sachse S, Von Suchodoletz W. Early identification of language delay by direct language assessment or parent report? *J Dev Behav Pediatr*. 2008;29(1):34-41.

52. Kristiansen AL, Lande B, Øverby NC, Andersen LF. Factors associated with exclusive breast-feeding and breast-feeding in Norway. *Public Health Nutr*. 2010;13(12):2087-2096.