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Association Between Prenatal Valproate Exposure and Performance on Standardized Language and Mathematics Tests in School-aged Children

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IMPORTANCE Valproate sodium is used for the treatment of epilepsy and other neuropsychiatric disorders in women of childbearing potential. However, there are concerns about impaired cognitive development in children who have been exposed to valproate during pregnancy.

OBJECTIVE To estimate the association between long-term school performance and prenatal exposure to valproate and a number of other antiepileptic drugs (AEDs).

DESIGN, SETTING, AND PARTICIPANTS In a prospective, population-based cohort study conducted from August 1, 2015, to May 31, 2017, data used in the study were provided by Statistics Denmark on April 15, 2016. All children born alive in Denmark between 1997 and 2006 (n = 656 496) were identified. From this cohort, children who did not participate in the national tests, with presumed coding errors in gestational age and children missing information on their mother's educational level or household income were excluded (n = 177 469) leaving 479 027 children for the analyses. Children were identified and linked across national registers that had information on exposure, covariates, and outcome. The primary outcome was performance in national tests, an academic test taken by students in Danish primary and lower secondary state schools. We assessed performance in Danish and mathematics at different grades among valproate-exposed children and compared their performance with that of unexposed children and children exposed to another AED (lamotrigine). Test scores were standardized to *z* scores and adjusted for risk factors.

MAIN OUTCOME AND MEASURES Difference in standardized *z* scores in Danish and mathematics tests among valproate-exposed children compared with unexposed and lamotrigine-exposed children.

RESULTS Of the 656 496 children identified, 479 027 children who participated in the national tests were evaluated, including children exposed to the following AEDs in monotherapy: valproate, 253; phenobarbital, 86; oxcarbazepine, 236; lamotrigine, 396; clonazepam, 188; and carbamazepine, 294. The mean (SD) age of the 244 095 children completing the sixth grade Danish test was 12.9 (0.39) years; 122 774 (50.3%; 95% CI, 50.1% to 50.5%) were boys and 121 321 (49.7%; 95% CI, 49.5% to 49.9%) were girls. Valproate-exposed children scored worse on the sixth-grade Danish tests (adjusted difference, −0.27 SD; 95% CI, −0.42 to −0.12) and sixth-grade mathematics tests (adjusted difference, −0.33 SD; (95% CI, −0.47 to −0.19) compared with unexposed children and children exposed to lamotrigine (adjusted difference, −0.33 SD; 95% CI, −0.60 to −0.06). Also, children exposed to clonazepam scored worse in the sixth-grade Danish tests (adjusted difference, −0.07 SD; 95% CI, −0.12 to −0.02). Carbamazepine, lamotrigine, phenobarbital, and oxcarbazepine were not linked to poor school performance compared with unexposed children.

CONCLUSIONS AND RELEVANCE Maternal use of valproate was associated with a significant decrease in school performance in offspring compared with children unexposed to AEDs and children exposed to lamotrigine. Findings of this study further caution against the use of valproate among women of childbearing potential.

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Editorial
Supplemental content

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There is concern regarding the possible teratogenic effects of antiepileptic drugs (AEDs),[1] and numerous studies demonstrate increased risk of malformations after prenatal exposure, especially to valproate sodium.[1-3] In addition, growing evidence indicates reduced IQ in young children after valproate exposure,[4-7] and increased risk of autism spectrum disorders has been reported.[8,9] Animal studies of prenatal and postnatal exposure also indicate affected brain development.[10,11] However, knowledge of the long-term consequences of prenatal exposure to valproate and newer generations of AEDs is scarce.[12] We therefore conducted a register-based cohort study to estimate school performance in primary and lower secondary state schools in Denmark.

Key Points

Question What is the association between long-term school performance and prenatal exposure to valproate sodium and other antiepileptic drugs?

Findings In this population-based cohort study including 479 027 children, 1865 children were exposed to different antiepileptic drugs in pregnancy. Prenatal exposure to valproate was associated with impaired school performance in both primary and lower secondary schooling compared with children unexposed to antiepileptic drugs and children exposed to lamotrigine.

Meaning Prenatal valproate exposure may be associated with long-term impairment of school performance.

Methods

Study Population

The Danish Civil Registration System[13] includes information on the personal identification number given at birth or immigration, which makes it possible to link population data across national registers. We identified all children born alive in Denmark between 1997 and 2006 (n = 656 496) using the Danish Medical Birth Registry; the present study was conducted from August 1, 2015, to May 31, 2017.[14] We excluded children who did not participate in the national tests (n = 115 175). Children who had participated in testing only in 2015 were also excluded because the tests performed in 2015 could not be compared with those of previous years (n = 56 573). We excluded children with presumed coding errors in gestational age (≤21 or ≥45 weeks) (n = 2336) and children for whom information on the mother's education (n = 3260) and household income (n = 125) was missing. After these exclusions (n = 177 469), the study cohort included 479 027 children, including 1865 children exposed prenatally to different types of AEDs. In the AED-unexposed group, 477 162 (73.9%) of the original population remained; and in the valproate monotherapy–exposed group, 253 (67.8%) of the original population remained, and in the lamotrigine monotherapy-exposed group, 396 (63.4%) of the original population remained. In accordance with Denmark's Act on Processing of Personal Data, this study maintained anonymity and confidentiality. The study was approved by the Danish Data Protection Agency (2012-41-0328), and data access was established by Statistics Denmark and the Danish Ministry of Education. Because this study used only registry data, it did not need approval from the Danish National Committee on Health Research Ethics. Patient informed consent is not necessary because registry information is routinely collected, and Danish legislation allows the use of this information for research purposes.

Medical Exposure

Information on medical exposure was retrieved from the Danish Register of Medicinal Product Statistics.[15] In Denmark, a prescription is required to buy any AED, but the register does not include AEDs prescribed for patients admitted to hospitals. Drugs in the register are coded by *Anatomical Therapeutic Classification* (*ATC*) codes. We identified AEDs with *ATC* codes N03A (AEDs) and N05BA09 (clobazam).

The exposure window was defined from 30 days before the first day of the last menstrual period (LMP) to 1 day before birth. The first day of the LMP was estimated by subtracting the gestation length from the date of birth (both variables obtained from the Danish Medical Birth Registry[14]). If only 1 type of AED was prescribed and redeemed within the exposure window, the child was defined as having been exposed to monotherapy. If more than 1 type of AED was prescribed and redeemed within the exposure window, the child was defined as having been exposed to polytherapy.

School Performance and Cognitive Abilities

Information on school performance was provided by the Danish Agency for Information Technology and Learning (http://www.stil.dk). The primary outcome was the measurements of cognitive abilities assessed using academic tests conducted in Danish primary (grades 1-6) and lower secondary (grades 7-9/10) state schools from 2010 to 2014. All students enrolled in Danish primary and lower secondary state schools are required by law to participate in these tests. Danish tests are carried out 4 times: in the second, fourth, sixth, and eighth grades. Mathematics tests are performed twice: in the third and sixth grades. The answers are assessed directly during testing, thereby adapting to the student's individual skill level during the test run. The test's adaptive function follows the Rasch model.[16,17] The adaptive testing process finds and asks a question from a comprehensive question database. Each question corresponds to the student's calculated ability level, and after each answer, a new ability level is calculated. Therefore, the student should be given questions with equal probability of a correct or false answer each time. As the estimation of ability level becomes increasingly certain, it ends when the SE of measurement reaches 0.55.[18] The final estimated skill level is presented on a logit scale, ranging from –7 to 7, which was normally distributed in our study population. Information on special needs was not available in the data.

Covariates

Information on maternal epilepsy diagnoses was retrieved from the National Patient Register.[19] From 1977 to 1994, the *International Classification of Diseases, Eighth Revision* classification was used (codes 345.00 to 345.99; excluding 345.29 [status epilepticus]) and from 1994, the *International Statistical*

Classification of Diseases and Related Health Problems, Tenth Revision (*ICD-10*) codes were used (G40). The date of the first registered epilepsy diagnosis was used to distinguish between maternal epilepsy diagnosed before or after birth of the child. *Congenital malformations* were defined as diagnoses based on *ICD-10* Q0 to Q99, excluding Q53 (undescended testicle) and Q65 (deformities of hip) because of low validity of these diagnoses.[20]

Information on parents' income (quartiles) and maternal education at birth (<10 years, 10-15 years, ≥16 years of education) was provided by Statistics Denmark on April 15, 2016.[21] Not all persons with psychiatric disorders are captured in the national patient registers, and we therefore used data on redemption of a prescription for antidepressants (N06A), antipsychotics (N05A), or anxiolytics (N05B) (excluding N05BA09 [clobazam]) as a proxy for psychiatric disorders in the parents.

Statistical Analysis

The outcomes of the national tests were presented as *z* scores to be comparable. The test scores were standardized according to the 3 cognitive areas of both subjects (Danish and mathematics). This method has previously been used in other studies using results of the national tests as an outcome of interest.[18,22,23] Concern for possible lack of independence owing to testing of several children at the same school was addressed by analyzing data as clustered at school level with robust SEs.

Linear regression was used to examine differences in school performance among children prenatally exposed to valproate and unexposed children. Score differences were reported with 95% CIs, and *P* values <.05 were used to define statistical significance using 2-sided testing. First, we examined the crude difference in both Danish and mathematics tests in all grades. We then adjusted the analyses for calendar year, sex, maternal education, and parents' income since these factors have been shown to be important estimators of school performance.[18,24] Calendar year was adjusted for using 1-year time markers according to test year.

As repeated measurements of academic performance were available for a large proportion of the children, we applied an additional 3-level, hierarchical, multilevel linear regression to the analysis. The measurements were considered as being nested within the child and the children as being nested within the mothers. The models included random intercepts at the child and maternal level and random slope for the age at the time of the assessment at the child level. The age of the child at the assessment was centered to the mean.

Sensitivity Analysis

Previous studies have indicated that lamotrigine use in pregnancy may not be associated with adverse cognitive outcomes,[2,3] and we therefore compared school performance among children prenatally exposed to valproate and lamotrigine monotherapy. To assess the influence of maternal disease, we estimated the difference in school performance after valproate exposure, stratifying on maternal epilepsy diagnosis before birth, epilepsy subtypes, and use of psychiatric medication in pregnancy.

We addressed possible confounding by indication in sensitivity analyses of children born to women who had received valproate monotherapy at some point from 6 months before the LMP to 30 days before the LMP (but not during pregnancy), comparing their children's school performance with that of children whose mothers used valproate monotherapy during pregnancy. We analyzed the school performance among children whose fathers used valproate during pregnancy and compared their performance with children whose mothers used valproate during pregnancy.

Information on dosage of AEDs reimbursed during the exposure window was obtained from the Danish Register of Medicinal Product Statistics.[15] The total redeemed dosages of AEDs during pregnancy were divided by the gestation length to calculate the mean daily dose. The influence of valproate dosage was investigated by categorizing the estimated daily exposure of valproate into doses below 1000 mg/d or equal to 1000 mg/d or above. Influence of exposure at different stages of the pregnancy was investigated by stratifying into valproate exposure in the first trimester or exposure only in the second to third trimesters.

Information on academic performance was missing on excluded children, and our results could be biased owing to nonparticipation. We used inverse probability weighting in a sensitivity analysis to assess this problem.[25] Data were analyzed using Stata, version 14 (StataCorp LLC).

Results

Among the 479 027 children who participated in the national tests, 1865 were prenatally exposed to 1 or more AED: 331 were exposed to valproate, 99 to phenobarbital, 301 to oxcarbazepine, 555 to lamotrigine, 269 to clonazepam, 357 to carbamazepine, and 296 to other drugs (eTable 1 in the Supplement). Among the 1576 children exposed to AED monotherapy, 253 were exposed to valproate, 86 to phenobarbital, 236 to oxcarbazepine, 396 to lamotrigine, 188 to clonazepam, 294 to carbamazepine, and 123 to other AEDs.

The highest number of valproate-exposed children completed the Danish and mathematics tests in sixth grade. The mean (SD) age of the 244 095 children completing the sixth-grade Danish test was 12.9 (0.39) years, of whom 122 774 (50.3%; 95% CI, 50.1% to 50.5%) were boys and 121 321 (49.7%; 95% CI, 49.5% to 49.9%) were girls. Women receiving valproate in pregnancy had a lower educational level, lower household income, and more often received antidepressants, antipsychotics, and anxiolytics compared with women not using any AEDs (**Table 1**).

Children exposed to valproate monotherapy performed significantly worse than AED-unexposed children in all tests administered between the third and eighth grades in the crude analyses (crude difference in sixth-grade Danish, −0.41; 95% CI, −0.57 to −0.25; *P* < .001), and the difference remained significant after adjusting for socioeconomic factors, including maternal educational level and parents' income, except for the mathematics test in the third grade (adjusted difference sixth-grade Danish, −0.27; 95% CI, −0.42 to −0.12; *P* < .001) (**Table 2**).

Table 1. Characteristics of the Study Population

Characteristic	No. (%)		
		Monotherapeutic Drug Exposure	
	Unexposed (n = 477 162)	Valproate Sodium (n = 253)	Lamotrigine (n = 396)
Sex			
Male	242 875 (50.9)	140 (55.3)	210 (53.0)
Female	234 287 (49.1)	113 (44.7)	186 (47.0)
Maternal educational level at birth, y			
<10	41 990 (8.8)	36 (14.2)	47 (11.9)
10-15	306 815 (64.3)	183 (72.3)	272 (68.6)
≥16	128 357 (26.9)	34 (13.4)	77 (19.5)
Family income quantiles			
Low	118 336 (24.8)	88 (34.8)	111 (28.0)
Low-medium	114 996 (24.1)	74 (29.2)	127 (32.1)
Medium-high	118 336 (24.8)	52 (20.6)	76 (19.1)
High	125 494 (26.3)	39 (15.4)	82 (20.8)
Maternal age at birth, y			
<35	405 111 (84.9)	222 (87.7)	352 (88.9)
≥35	72 051 (15.1)	31 (12.3)	44 (11.1)
Parity			
First child	208 043 (43.6)	120 (47.4)	200 (50.5)
>1 Child	269 119 (56.4)	133 (52.6)	196 (49.5)
Maternal civil status			
Married	255 759 (53.6)	142 (56.1)	185 (46.7)
Other	221 403 (46.4)	111 (43.9)	211 (53.3)
Maternal epilepsy diagnosis before birth			
Yes	1909 (0.4)	147 (58.1)	243 (61.4)
No	475 253 (99.6)	106 (41.9)	153 (38.6)
Malformation in child within first year of life			
Yes	23 858 (5.0)	31 (12.3)	24 (6.1)
No	453 304 (95.0)	222 (87.7)	372 (93.9)
Redeemed prescriptions			
Antidepressants			
Yes	134 560 (28.2)	99 (39.1)	133 (33.6)
No	342 602 (71.8)	154 (60.9)	263 (66.4)
Antipsychotics			
Yes	30 061 (6.3)	25 (9.9)	34 (8.6)
No	447 101 (93.7)	228 (90.1)	362 (91.4)
Anxiolytics			
Yes	68 234 (14.3)	73 (28.9)	124 (31.3)
No	408 928 (85.7)	180 (71.1)	272 (68.7)

Children exposed to lamotrigine monotherapy showed similar performance compared with the unexposed children (adjusted difference sixth-grade Danish, −0.01; 95% CI, −0.02 to 0.04; P = .33) (Table 2). Using lamotrigine as the active comparator, the valproate-exposed children performed significantly worse in all tests between the fourth and eighth grades (adjusted difference sixth-grade Danish, −0.33; 95% CI, −0.60 to −0.06; P = .02) (Table 2).

After excluding 10 586 children with malformations (15 of whom were exposed to valproate), valproate-exposed children still performed worse than AED-unexposed children (adjusted difference sixth-grade Danish, −0.27; 95% CI, −0.43 to −0.11; P < .001) and worse than lamotrigine-exposed children (adjusted difference sixth-grade Danish, −0.36; 95% CI, −0.63 to −0.09; P = .009) (eTable 2 in the Supplement).

Children exposed to other AED monotherapy did in general not perform worse than the unexposed children: phenobarbital (adjusted difference sixth-grade Danish, 0.06; 95% CI, −0.07 to 0.19; P = .39), carbamazepine (adjusted difference sixth-grade Danish, −0.02; 95% CI, −0.05 to 0.01; P = .30), and oxcarbazepine (adjusted difference sixth-grade Danish, −0.01; 95% CI, −0.04 to 0.02; P = .34). Children exposed to clonazepam scored lower than unexposed children (adjusted difference sixth-grade Danish, −0.07; 95% CI, −0.12 to −0.02; P = .005) (Table 2). Similar results were found for the sixth-grade mathematics test except for carbamazepine (adjusted dif-

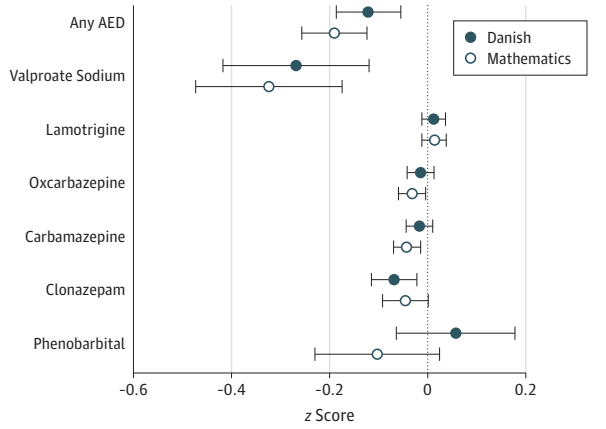
Table 2. School Performance Among Children Exposed to AED Monotherapy Compared With Children Unexposed to AEDs in Pregnancy

	Crude Analysis		Adjusted Analyses[a]			
			Reference Group Prenatally Unexposed to AED		Reference Group Prenatally Exposed to Lamotrigine	
Outcome	No.	*z* Score Difference (95% CI)	*z* Score Difference (95% CI)	*P* Value	*z* Score Difference (95% CI)	*P* Value
Unexposed						
Danish at 2nd grade	252 787					
Danish at 4th grade	251 886					
Danish at 6th grade	242 148					
Danish at 8th grade	133 667					
Mathematics at 3rd grade	253 430					
Mathematics at 6th grade	241 647					
Lamotrigine						
Danish at 2nd grade	301	−0.01 (−0.02 to 0.01)	−0.01 (−0.02 to 0.01)	.45		
Danish at 4th grade	186	0.00 (−0.02 to 0.02)	0.00 (−0.02 to 0.02)	.84		
Danish at 6th grade	117	0.01 (−0.02 to 0.04)	0.01 (−0.02 to 0.04)	.33		
Danish at 8th grade	44	0.02 (−0.03 to 0.06)	0.02 (−0.03 to 0.07)	.25		
Mathematics at 3rd grade	246	0.00 (−0.01 to 0.02)	0.00 (−0.02 to 0.02)	.82		
Mathematics at 6th grade	115	0.01 (−0.01 to 0.04)	0.01 (−0.01 to 0.04)	.30		
Valproate sodium						
Danish at 2nd grade	106	−0.17 (−0.35 to 0.02)	−0.06 (−0.25 to 0.12)	.50	−0.08 (−0.30 to 0.14)	.48
Danish at 4th grade	118	−0.44 (−0.64 to −0.25)	−0.33 (−0.52 to −0.14)	<.001	−0.36 (−0.59 to −0.13)	.003
Danish at 6th grade	151	−0.41 (−0.57 to −0.25)	−0.27 (−0.42 to −0.12)	<.001	−0.33 (−0.60 to −0.06)	.02
Danish at 8th grade	96	−0.33 (−0.53 to −0.13)	−0.22 (−0.41 to −0.03)	.03	−0.39 (−0.77 to 0.00)	.048
Mathematics at 3rd grade	104	−0.23 (−0.42 to −0.03)	−0.13 (−0.32 to 0.05)	.16	−0.12 (−0.35 to 0.12)	.32
Mathematics at 6th grade	151	−0.45 (−0.60 to −0.30)	−0.33 (−0.47 to −0.19)	<.001	−0.48 (−0.70 to −0.25)	<.001
Oxcarbazepine						
Danish at 2nd grade	123	−0.01 (−0.04 to 0.02)	−0.01 (−0.04 to 0.02)	.70		
Danish at 4th grade	126	−0.02 (−0.05 to 0.01)	−0.01 (−0.04 to 0.02)	.48		
Danish at 6th grade	125	−0.03 (−0.06 to 0.00)	−0.01 (−0.04 to 0.02)	.34		
Danish at 8th grade	71	−0.04 (−0.09 to 0.01)	−0.02 (−0.07 to 0.03)	.39		
Mathematics at 3rd grade	123	−0.02 (−0.05 to 0.01)	−0.01 (−0.04 to 0.02)	.47		
Mathematics at 6th grade	124	−0.04 (−0.07 to −0.01)	−0.03 (−0.06 to 0.00)	.03		
Carbamazepine						
Danish at 2nd grade	109	−0.03 (−0.07 to 0.01)	−0.01 (−0.05 to 0.03)	.57		
Danish at 4th grade	143	−0.04 (−0.07 to 0.00)	−0.02 (−0.05 to 0.01)	.30		
Danish at 6th grade	182	−0.04 (−0.07 to −0.01)	−0.02 (−0.05 to 0.01)	.30		
Danish at 8th grade	121	−0.04 (−0.08 to 0.00)	−0.03 (−0.07 to 0.01)	.11		
Mathematics at 3rd grade	123	−0.05 (−0.10 to −0.01)	−0.04 (−0.08 to 0.01)	.11		
Mathematics at 6th grade	184	−0.06 (−0.09 to −0.03)	−0.04 (−0.07 to −0.01)	.005		
Clonazepam						
Danish at 2nd grade	96	−0.06 (−0.11 to 0.00)	−0.03 (−0.08 to 0.03)	.37		
Danish at 4th grade	95	−0.05 (−0.10 to 0.00)	−0.03 (−0.08 to 0.02)	.27		
Danish at 6th grade	101	−0.08 (−0.12 to −0.03)	−0.07 (−0.12 to −0.02)	.005		
Danish at 8th grade	51	−0.04 (−0.09 to 0.02)	−0.04 (−0.10 to 0.01)	.13		
Mathematics at 3rd grade	109	−0.08 (−0.13 to −0.02)	−0.06 (−0.11 to −0.01)	.03		
Mathematics at 6th grade	100	−0.05 (−0.10 to 0.00)	−0.05 (−0.09 to 0.00)	.06		
Phenobarbital						
Danish at 2nd grade	31	−0.17 (−0.32 to −0.02)	−0.05 (−0.19 to 0.09)	.49		
Danish at 4th grade	45	−0.08 (−0.22 to 0.07)	0.00 (−0.12 to 0.12)	.98		
Danish at 6th grade	59	0.00 (−0.15 to 0.15)	0.06 (−0.07 to 0.19)	.39		
Danish at 8th grade	33	0.00 (−0.20 to 0.20)	0.06 (−0.12 to 0.24)	.51		
Mathematics at 3rd grade	34	−0.22 (−0.40 to −0.05)	−0.14 (−0.30 to 0.02)	.09		
Mathematics at 6th grade	54	−0.17 (−0.30 to −0.05)	−0.10 (−0.21 to 0.01)	.07		

Abbreviation: AEDs indicates antiepileptic drugs.

[a] Estimates were adjusted for test year, child sex, and maternal education and household income at birth.

Figure. *z* Score Difference in Sixth-Grade Danish and Mathematics Tests for Children Prenatally Exposed to Different Monotherapy With Antiepileptic Drugs (AEDs)



Comparison of children receiving AED monotherapy vs unexposed children, including children who completed the sixth-grade Danish test and were exposed to any AED (n = 795), valproate (n = 151), lamotrigine (n = 117), oxcarbazepine (n = 125), clonazepam (n = 101), carbamazepine (n = 182), and phenobarbital (n = 59). The any AED group contains children exposed to monotherapy with 1 of the following drugs: phenobarbital, primidone, clonazepam, carbamazepine, oxcarbazepine, valproate, vigabatrin, lamotrigine, topiramate, gabapentin, clobazam, phenytoin, levetiracetam, or pregabalin. The vertical line represents the reference of unexposed children. The school performance was adjusted for the sex of the child, calendar year, and maternal education and household income at birth. Error bars indicate 95% CI.

ference sixth-grade mathematics, −0.04; 95% CI, −0.07 to −0.01; *P* = .005) and oxcarbazepine (adjusted difference sixth-grade mathematics, −0.03; 95% CI, −0.06 to 0.00; *P* = .03). The Danish and mathematics sixth-grade results for all monotherapeutic AED groups are illustrated in the **Figure.**

Among children born to mothers with epilepsy, there was a tendency for valproate-exposed children to score worse than valproate-unexposed children (adjusted difference sixth-grade Danish, −0.12; 95% CI, −0.38 to 0.13; *P* = .34) (**Table 3**). Among children born to women without epilepsy, children exposed to valproate performed worse than children unexposed to valproate (adjusted difference sixth-grade Danish, −0.28; 95% CI, −0.49 to −0.08; *P* = .008) (Table 3).

Exposure to valproate was stratified on maternal epilepsy diagnosis and use of psychiatric medication during pregnancy. There was a tendency for children born to women with epilepsy who were prenatally exposed to valproate to perform worse than children born to women with epilepsy unexposed to valproate (adjusted difference sixth-grade Danish, −0.29 (95% CI, −0.63 to 0.05; *P* = .09) (eTable 3 in the Supplement). Children born to women using psychiatric medication who were prenatally exposed to valproate tended to perform worse than valproate-unexposed children born to women using psychiatric medication (adjusted difference sixth-grade Danish, −0.30; 95% CI, −0.61 to 0.00; *P* = .05) (eTable 3 in the Supplement). Using the only epilepsy group as reference, an adjusted comparison between the 2 groups of indications for receiving valproate showed no statistically significant difference (adjusted difference sixth-grade Danish, −0.01; 95% CI, −0.42 to 0.40; *P* = .95). There was no significant difference between children born to women with both epilepsy and use of psychiatric medication who were exposed prenatally to valproate compared with children born to women with both epilepsy and use of psychiatric medication unexposed to valproate (adjusted difference sixth-grade Danish, 0.12; 95% CI, −0.30 to 0.55; *P* = .57) (eTable 3 in the Supplement).

After stratifying on maternal epilepsy subtype, there was a tendency for children of mothers with focal epilepsy exposed to valproate to perform slightly better than unexposed children born to mothers without epilepsy (adjusted difference sixth-grade Danish, 0.09; 95% CI, −0.67 to 0.85; *P* = .81), whereas there was a tendency for children of mothers with generalized epilepsy exposed to valproate to perform worse than unexposed children born to mothers without epilepsy (adjusted difference sixth-grade Danish, −0.23; 95% CI, −0.50 to 0.05; *P* = .10). Valproate-exposed children born to mothers with epilepsy categorized as other performed worse than valproate-unexposed children (adjusted difference sixth-grade Danish, −0.39; 95% CI, −0.77 to −0.01; *P* = .046) (eTable 4 in the Supplement).

Children who were exposed to valproate during pregnancy scored worse than children born to women who discontinued the use of valproate before pregnancy (adjusted difference sixth-grade Danish, −0.27; 95% CI, −0.53 to 0.00; *P* = .046) (**Table 4**). When this analysis was restricted to women with epilepsy, the difference for worse outcomes in children who were exposed to valproate during pregnancy compared with children whose mothers discontinued valproate before pregnancy remained (adjusted difference sixth-grade Danish, −0.39; 95% CI, −0.77 to 0.00; *P* = .047) (eTable 5 in the Supplement).

The test results in sixth-grade Danish showed that children whose fathers used valproate during pregnancy scored higher than children whose mothers used valproate during pregnancy (adjusted difference sixth-grade Danish, −0.21, 95% CI, −0.38 to −0.04; *P* = .01) (eTable 6 in the Supplement).

There was a tendency for worse performance among children exposed to valproate only in the first trimester compared with children exposed to valproate in the second or third trimester (adjusted difference sixth-grade Danish, −0.53; 95% CI, −1.18 to 0.11; *P* = .11) (eTable 7 in the Supplement).

Compared with unexposed children, there was no significant difference in school performance between children exposed to valproate in high doses (≥1000 mg, n = 54) or low doses (<1000 mg, n = 97) (high-dose adjusted difference, −0.29 SD; 95% CI, −0.55 to −0.04; *P* = .02; low-dose adjusted difference, −0.26 SD; 95% CI, −0.44 to −0.07; *P* = .007). Similar analysis of other drugs is included in eTable 8 in the Supplement.

The results from the inverse probability-weighted analysis are almost identical to the unweighted analyses (eTable 9 in the Supplement). Results of the adjusted multilevel linear regression model are similar to the results of the adjusted linear regression model; for example, children prenatally exposed to valproate perform worse on the Danish academic tests compared with unexposed children (−0.26 SD; 95% CI, −0.38 to −0.14; *P* < .001) (eTable 10 in the Supplement).

Table 3. Danish Sixth-Grade Performance Among Children Exposed in Pregnancy to Valproate Sodium Monotherapy Compared With Children Unexposed to AEDs, Stratified on Epilepsy Diagnosis in the Mother

Maternal Epilepsy	AED Exposure in Pregnancy	No.	z Score (95% CI)[a]	z Score Difference			
				Crude (95% CI)	P Value	Adjusted (95% CI)[b]	P Value
Yes	Valproate	76	−0.39 (−0.61 to −0.16)	−0.17 (−0.43 to 0.09)	.22	−0.12 (−0.38 to 0.13)	.34
Yes	No AED	296	−0.22 (−0.33 to −0.11)	0 [Reference]	[Reference]	0 [Reference]	[Reference]
Yes	Valproate	76	−0.39 (−0.61 to −0.16)	−0.22 (−0.46 to 0.02)	.07	−0.16 (−0.40 to 0.07)	.19
Yes	No Valproate	713	−0.16 (−0.24 to −0.10)	0 [Reference]	[Reference]	0 [Reference]	[Reference]
No	Valproate	75	−0.40 (−0.61 to −0.18)	−0.40 (−0.61 to −0.18)	<.001	−0.28 (−0.49 to −0.08)	.008
No	No AED	241 852	0.00 (−0.01 to 0.01)	0 [Reference]	[Reference]	0 [Reference]	[Reference]

Abbreviation: AEDs, antiepileptic drugs.

[a] z Score describes crude difference with the reference group of children unexposed to any AEDs.

[b] Adjusted for test year, child sex, and maternal education and household income at birth.

Table 4. Danish and Mathematics Sixth-Grade Performance Stratified on Maternal Use of Valproate Sodium Before or During Pregnancy

School Age	Valproate Use in Pregnancy[a]	Valproate Use Before Pregnancy[b]	No.	z Score Difference (95% CI)	Adjusted z Score Difference (95% CI)	P Value
Danish in 6th grade						
	No	No	242 102	0 [Reference]	NA	NA
	Yes	Yes	151	−0.41 (−0.57 to −0.25)	−0.27 (−0.53 to 0.00)	.046
	No	Yes	99[c]	−0.14 (−0.36 to 0.08)	0 [Reference]	
Mathematics in 6th grade						
	No	No	241 600	0 [Reference]	NA	NA
	Yes	Yes	151	−0.45 (−0.60 to −0.30)	−0.25 (−0.50 to −0.01)	.04
	No	Yes	102[d]	−0.19 (−0.42 to 0.03)	0 [Reference]	

Abbreviation: NA, not applicable.

[a] All valproate-exposed children were exposed to monotherapy.

[b] A woman reimbursing a prescription for valproate at any point between 183 and 30 days before the last menstrual period was defined as using valproate before pregnancy.

[c] Fifty-three individuals redeemed a prescription for an antiepileptic drug other than valproate during pregnancy.

[d] Fifty-five individuals redeemed a prescription for an antiepileptic drug other than valproate during pregnancy.

Discussion

This large, population-based, observational cohort study identified cognitive difficulties in children following prenatal exposure to valproate. Children exposed prenatally to valproate performed worse on academic tests throughout the entire primary and lower secondary state schooling compared with children unexposed to AEDs. Consistent with previously described cognitive deficits in school-aged children,[4,5,26] impaired performance in a real-life school setting underlines the significant implication of prenatal valproate exposure in the children's everyday life. In contrast to most other studies, our study was able to compare the school performance of valproate-exposed children with that of children unexposed to AEDs. However, in the comparison with children prenatally exposed to lamotrigine as the reference group, children prenatally exposed to valproate still showed significant impairment.

We found no signs of cognitive impairment after prenatal exposure to lamotrigine, which is consistent with previous studies,[4,5,26] nor was phenobarbital exposure in pregnancy associated with lower school performance, although the sample size was small. Oxcarbazepine- and carbamazepine-exposed children generally did not show signs of impairment; however, results on sixth-grade Danish tests were significantly lower, but the absolute difference was small and possibly clinically irrelevant. Consistent with findings in previous studies,[27,28] we found signs of impaired school performance after prenatal clonazepam exposure, but the findings were not consistent and the absolute difference was small.

We were able to obtain results from all tests performed between 2010 and 2014 at primary and lower secondary state schools in Denmark. However, none of the private schools or their students were included in the study, which limits the interpretation to the population represented by children attending state schools. The proportion of students enrolled in state schools in Denmark was 80.8% in 2014.[29] Since the proportion of children who attended state schools was high during the study period, we expect that selection bias is an unlikely explanation for our findings. However, as described in the Methods section, a larger proportion of exposed children were excluded because they had not completed a test. Every child was required to participate in the tests regardless of proficiency level, and assistance for participating was allowed if needed. Still, tests were missed by a relatively high proportion of students with special education needs.[18] This exclusion might lead to an underestimation of the association between AED exposure and cognitive deficiency as measured by school performance.

A major strength of the present study is the objectivity of the results, as no teacher or evaluator assessment was required, making the outcome unlikely to be affected by information bias. Information on AED exposure came from the Danish Register of Medicinal Product Statistics; hence, we only had information on redeemed AED prescriptions. However, a previous study has shown high adherence in pregnant women,[30] making misclassification in the exposed group unlikely. The timing of exposure was based on the day that the prescription was redeemed and not on the day that the women consumed the medication. Inaccuracy in the estimation of the LMP date is possible, but the registers used have high validity,[31] and misclassification is unlikely and would most likely be nondifferential.

Limitations

A limitation of our study is the missing information about folic acid used during pregnancy. In addition, our lack of information on covariates could constitute a limitation to the study, such as AED blood levels during pregnancy; maternal seizure frequency; obstetric complications; use of alcohol, smoking, or illicit drugs; and breastfeeding.

Information on epilepsy diagnoses was obtained from the National Patient Register. Previous studies have reported a positive predictive value of an epilepsy diagnosis at 81%,[32] indicating that some women without epilepsy could be misclassified as having epilepsy. However, the combination of an epilepsy diagnosis and a prescription for an AED will identify a person with epilepsy with high validity.[33] Classification of epilepsy subtype is not recorded with the same validity, and the analyses were based on the first recorded epilepsy diagnosis.[32]

The school performance in valproate-exposed offspring of mothers with epilepsy with focal seizures tended to be better than the performance in offspring of mothers with epilepsy with generalized seizures and may indicate that the effects of valproate are lower in this group of children or subject to confounding by the underlying disorder. However, the number of exposed children was low, and differences observed were not significant. Also, these secondary analyses were not controlled for multiple comparisons.

Maternal education, IQ, and socioeconomic status are predictors of a child's cognitive abilities and educational achievements.[18,34] The association between IQ and educational achievements is documented, but school performance reflects different aspects of cognitive function, and the results are a product of the surroundings and the children's concentration, knowledge, and motivation for the given tests. Consequently, school grades and IQ are not completely correlated. Because information on maternal IQ was not accessible in our study, we adjusted only for educational achievements, which constitutes a limitation of this study. Educational achievements are likely to underestimate maternal IQ, as epilepsy could throw people off track in their educational and professional achievements; however, this problem would most likely result in overadjusting the estimates among the exposed children.

We found that children of women with epilepsy unexposed to valproate performed worse than unexposed children born of women without epilepsy. This finding could indicate that epilepsy in the mother accounts for some of the impairment observed.

We tried to control for confounding by indication by using different sensitivity analyses, including comparing the outcome in children after paternal valproate use during pregnancy with that seen after maternal use, with maternal use still indicating adverse outcomes after valproate exposure. However, it is impossible to rule out that results are affected by confounding by indication, even though many of our sensitivity analyses supported our main finding. In addition, it is possible that the family's genetic traits at some level are contributing to the impaired neurodevelopment. Further studies investigating this subject and confirming our findings are therefore needed.

Conclusions

Prenatal maternal use of valproate was associated with poor school performance in primary and lower secondary state education compared with children unexposed to AEDs and children exposed to lamotrigine. Findings of this study further caution against the use of valproate among women of childbearing potential.

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