Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism

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Abstract

Importance—Valproate is used for the treatment of epilepsy and other neuropsychological disorders and may be the only treatment option for women of childbearing potential. However, prenatal exposure to valproate may increase the risk of autism.

Objective—To determine whether prenatal exposure to valproate is associated with an increased risk of autism in offspring.

Design, Setting, and Participants—Population-based study of all children born alive in Denmark from 1996 to 2006. National registers were used to identify children exposed to valproate during pregnancy and diagnosed with autism spectrum disorders (childhood autism [autistic disorder], Asperger syndrome, atypical autism, and other or unspecified pervasive developmental disorders). We analyzed the risks associated with all autism spectrum disorders as well as childhood autism. Data were analyzed by Cox regression adjusting for potential

confounders (maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations, and parity). Children were followed up from birth until the day of autism spectrum disorder diagnosis, death, emigration, or December 31, 2010, whichever came first.

Main Outcomes and Measures—Absolute risk (cumulative incidence) and the hazard ratio (HR) of autism spectrum disorder and childhood autism in children after exposure to valproate in pregnancy.

Results—Of 655 615 children born from 1996 through 2006, 5437 were identified with autism spectrum disorder, including 2067 with childhood autism. The mean age of the children at end of follow-up was 8.84 years (range, 4-14; median, 8.85). The estimated absolute risk after 14 years of follow-up was 1.53% (95% CI, 1.47%-1.58%) for autism spectrum disorder and 0.48% (95% CI, 0.46%-0.51%) for childhood autism. Overall, the 508 children exposed to valproate had an absolute risk of 4.42% (95% CI, 2.59%-7.46%) for autism spectrum disorder (adjusted HR, 2.9 [95% CI, 1.7-4.9]) and an absolute risk of 2.50% (95% CI, 1.30%-4.81%) for childhood autism (adjusted HR, 5.2 [95% CI, 2.7-10.0]). When restricting the cohort to the 6584 children born to women with epilepsy, the absolute risk of autism spectrum disorder among 432 children exposed to valproate was 4.15% (95% CI, 2.20%-7.81%) (adjusted HR, 1.7 [95% CI, 0.9-3.2]), and the absolute risk of childhood autism was 2.95% (95% CI, 1.42%-6.11%) (adjusted HR, 2.9 [95% CI, 1.4-6.0]) vs 2.44% (95% CI, 1.88%-3.16%) for autism spectrum disorder and 1.02% (95% CI, 0.70%-1.49%) for childhood autism among 6152 children not exposed to valproate.

Conclusions and Relevance—Maternal use of valproate during pregnancy was associated with a significantly increased risk of autism spectrum disorder and childhood autism in the offspring, even after adjusting for maternal epilepsy. For women of childbearing potential who use antiepileptic medications, these findings must be balanced against the treatment benefits for women who require valproate for epilepsy control.

Antiepileptic drug exposure during pregnancy has been associated with an increased risk for congenital malformations and delayed cognitive development in the offspring,[1-3] but little is known about the risk of other serious neuropsychiatric disorders. Autistic symptoms have been described in case series of children exposed in utero to valproic acid,[4-7] and it has been suggested that valproate given to animals during pregnancy may constitute an experimental model of autism.[8-10]

Genes play a significant role in the risk of autism, and disease-related genes may be identified in up to 25% of children with autism.[11] However, a variety of environmental factors may increase the risk of autism,[12] and prenatal valproate exposure would be a modifiable environmental exposure.

Autism spectrum disorders are characterized by social and communication difficulties and by stereotyped or repetitive behaviors and interests.[13] The autism spectrum disorders include childhood autism (autistic disorder), Asperger syndrome, atypical autism, and other or unspecified pervasive developmental disorders. We analyzed the risks associated with all autism spectrum disorders and with the most severe of the autism spectrum disorders, childhood autism. A diagnosis of childhood autism requires symptoms related to (1) stereotyped patterns of behavior, (2) impaired social interaction, and (3) impaired

communication. Symptoms in at least 1 area must manifest before age 3 years. In this large population-based cohort study, we evaluated the association between maternal use of valproate during pregnancy and the risk of autism spectrum disorder and childhood autism in the offspring, taking parental history of epilepsy and psychiatric conditions into account.

METHODS

We conducted a population-based cohort study on the risk of autism in children exposed prenatally to valproate. The risk estimates were adjusted for known risk factors for autism. We also estimated the effects of valproate dose, trimester of exposure, valproate polytherapy, congenital malformations, and maternal history of epilepsy.

Ethical Approval

All data were analyzed at Statistics Denmark using encrypted identification numbers with no contact with the individuals. The study was approved by the Danish Data Protection Agency and a Danish Regional Ethical Committee. The requirement for informed consent was waived because of the use of deidentified data.

Study Population

We identified all children born alive in Denmark between January 1, 1996, and December 31, 2006, using data from the Danish Civil Registration System.[14] The unique personal identification number includes information on sex and age and was used to ensure complete linkage of individual information in all national registries used in this study.

Medication Exposure

The Danish Prescription Register holds information on all prescriptions filled since January 1, 1996. Information about medical treatment given only in hospitals is not part of the register. It is not possible to purchase antiepileptic drugs in Denmark without a prescription. We defined the exposure window from 30 days before the estimated day of conception to the day of birth and included children with an estimated time of conception after February 1, 1996, who were born up until December 31, 2006. Exposure for antiepileptic medication was defined as any filled prescription with Anatomical Therapeutic Classification codes N03A (antiepileptic drugs) and N05BA09 (clobazam).

Children were defined as having been exposed to monotherapy if their mothers had filled prescriptions for only 1 type of antiepileptic drug and as exposed to polytherapy if their mothers had filled prescriptions for more than 1 type of antiepileptic drug. For both monotherapy and polytherapy, the mothers may have filled prescriptions for other types of medicine. We also estimated the risk of autism spectrum disorder and childhood autism among the offspring of users of frequently used antiepileptic drugs other than valproate (carbamazepine, clonazepam, lamotrigine, and oxcarbazepine).

The estimated mean daily dose of antiepileptic drugs was calculated from the total amount of antiepileptic drug filled during the time from 30 days before pregnancy to birth divided by the number of days in the same period. The defined daily dose (DDD)[36] is the assumed

average maintenance dose per day for a drug used for its main indication in adults. Based on the DDD, the estimated daily antiepileptic drug dose was dichotomized into high (>50% of DDD) and low (50% of DDD).

Diagnostic and Covariate Information

The Danish Psychiatric Central Register was used to identify children diagnosed for the first time with autism spectrum disorder (*International Statistical Classification of Diseases, Tenth Revision* [*ICD-10*] codes F84.0, F84.1, F84.5, F84.8, and F84.9]) and with childhood autism (*ICD-10* code F84.0). The same register was used to identify parents diagnosed with psychiatric disorders before birth of the child (*International Statistical Classification of Diseases, Eighth Revision* [*ICD-8*] codes 290-315 and *ICD-10* codes F0.00-F99.9). Gestational age, birth weight, and parity information were obtained from the Danish Birth Register. We used the National Hospital Register to identify children diagnosed with congenital malformations (*ICD-10* codes Q0 to Q99 [except for Q53, undescended testicle, and Q65, congenital deformities of hip, because of low validity of these diagnoses])[15] and also to identify parents diagnosed with epilepsy before birth of the child (*ICD-8* code 345 and *ICD-10* codes G40 and G41).

Analytical Strategy

Children were followed up from birth to death, emigration, diagnosis of autism spectrum disorder or childhood autism, or December 31, 2010, whichever came first. Risk and prevalence estimates were reported with 95% CIs. *P* < .05 was used to define significance, using 2-sided testing.

The primary outcome was the hazard ratio (HR) of autism spectrum disorder and childhood autism after valproate exposure in pregnancy. We used Cox regression to estimate the HR for autism spectrum disorder, with age of the child as the underlying time scale and with separate baseline diagnostic rates (strata) for each birth year group to adjust for the increasing prevalence of autism spectrum disorder. The proportional hazards assumption was evaluated for all variables by comparing estimated log-minus-log survivor curves over the different categories of variables investigated. Control for the lack of independence of children within the same family was obtained using a robust (Huber-White) variance estimator. We adjusted for differences in both length of follow-up and autism spectrum disorder prevalence time trends. Importantly, the HR did not depend on age of the child; thus, age is not expected to bias the HR when the children are followed up into adulthood. Hazard ratios were adjusted for risk factors for autism (parental age at conception, parental psychiatric history, gestational age, birth weight, sex of the child, congenital malformations, and parity).

For the primary outcome we also estimated the cumulative incidence (absolute risk) of autism spectrum disorder and childhood autism in unexposed children using the Kaplan-Meier method and multiplied this estimate with the adjusted HR for the exposed children to estimate the absolute risk in exposed children. The absolute risk for the exposed children is valid under the proportional hazards assumption, because autism spectrum disorder is relatively rare (prevalence <10%).[16]

The secondary outcome was the risk of autism following valproate exposure after stratifying for maternal epilepsy prior to birth.

Stratified and Sensitivity Analyses

In a sensitivity analysis to assess possible confounding by indication, we compared the association between autism spectrum disorder and childhood autism in offspring of women who used valproate during pregnancy and women who were previous users of valproate but who stopped at least 30 days before the estimated day of conception. This analysis addresses whether the illness leading to valproate use, rather than valproate exposure, was associated with autism in the child. We also estimated the risk of autism after stratifying the risk according to dose, trimester of exposure (first vs later), and use of other antiepileptic drugs and polytherapy and after excluding children with congenital malformations. Because autism is more frequent in males, we calculated the sex ratio of exposed children adjusted for time to diagnosis of autism spectrum disorder and compared this sex ratio with that of unexposed children.

Data analyses were performed using Stata version 12 (StataCorp).

RESULTS

We identified children with an estimated time of conception after February 1, 1996, who were born up to December 31, 2006 (N=668 468). We excluded children with likely errors in gestational age (23 weeks or 45 weeks) (1489 [0.2%]), those with missing values for gestational age (6275 [0.9%]), those with missing information about the mother (5 [0.001%]), adopted children (3461 [0.5%]), and those who died during the first year of life (1623 [0.2%]). Children who died more than 1 year after birth (40 [0.01%]) and those who emigrated (14 492 [2.2%]) were included in the analyses and censored at time of death or emigration. After exclusion, the study cohort comprised 655 615 children born to 428 407 mothers, including multiple births of 26 418 children (4.0%).

The mean age of the children at end of follow-up was 8.84 years (range, 4-14; median, 8.85). During the study period, 5437 children were diagnosed with autism spectrum disorder, including 2067 with childhood autism. Characteristics of the study participants are shown in Table 1.

We identified 2644 children exposed to antiepileptic drugs during pregnancy, including 508 exposed to valproate. The overall use of antiepileptic drugs during pregnancy remained stable during the study period; however, valproate use decreased and lamotrigine use increased (Figure 1) (eTable 1, available at http://www.jama.com). The median number of valproate prescriptions filled during pregnancy was 4 (range, 1-15), and the median time between 2 successive filled valproate prescriptions during pregnancy was 6 weeks (range, 0-38).

The absolute risk after 14 years of follow-up was 1.53% (95% CI, 1.47%-1.58%) for autism spectrum disorder and 0.48% (95% CI, 0.46%-0.51%) for childhood autism.

Use of valproate during pregnancy was associated with an absolute risk of 4.42% (95% CI, 2.59%-7.46%) for autism spectrum disorder (adjusted HR, 2.9 [95% CI, 1.7-4.9]) and an absolute risk of 2.50% (95% CI, 1.30%- 4.81%) for childhood autism (adjusted HR, 5.2 [95% CI, 2.7-10.0]) (Table 2). We also found higher risks of autism spectrum disorder (adjusted HR, 2.2 [95% CI, 1.02-4.9]) and childhood autism (adjusted HR, 5.6 [95% CI, 1.7-18.1]) among children of women who used valproate during pregnancy compared with children of women who were previous users of valproate but who stopped at least 30 days before conception (eTable 2).

When restricting the analyses to offspring of women with epilepsy, the absolute risk of autism spectrum disorder in 432 children exposed to valproate was 4.15% (95% CI, 2.20%-7.81%) (adjusted HR, 1.7 [95% CI, 0.9-3.2]) and the absolute risk for childhood autism was 2.95% (95% CI, 1.42%-6.11%) (adjusted HR, 2.9 [95% CI, 1.4-6.0]), when compared with the absolute risk of 2.44% (95% CI, 1.88%-3.16%) for autism spectrum disorder and 1.02% (95% CI, 0.70%-1.49%) for childhood autism among 6152 children not exposed to valproate (Table 3).

There was also an increased risk among exposed children of mothers without a history of epilepsy when compared with those unexposed to valproate, but the number of exposed cases of mothers without epilepsy was low (Table 3).

In a sensitivity analysis, we changed the valproate exposure window prior to pregnancy. Compared with unexposed women, the adjusted HRs for autism spectrum disorder were 2.3 (95% CI, 1.4-3.9) for the window from 180 days prior to pregnancy, 2.7 (95% CI, 1.6-4.6) for the window from 90 days prior to pregnancy, and 3.0 (95% CI, 1.8-5.2) for the window from 0 days prior to pregnancy; the corresponding adjusted HRs for childhood autism were 4.1 (95% CI, 2.1-8.0), 4.8 (95% CI, 2.5- 9.3), and 5.4 (95% CI, 2.8-10.5), respectively.

The risk of autism spectrum disorder and childhood autism was increased among 441 valproate-exposed children whose mothers filled valproate prescriptions in the first trimester (adjusted HR, 2.9 [95% CI, 1.6-5.1] for autism spectrum disorder and 4.7 [95% CI, 2.2-9.9] for childhood autism). The adjusted HRs among 67 children whose mothers only filled valproate prescriptions later in pregnancy were 3.1 (95% CI, 0.8-12.2) for autism spectrum disorder and 8.3 (95% CI, 2.1-32.4) for childhood autism (eTable 3).

When compared with offspring not exposed to valproate, the adjusted HR of autism spectrum disorder among 388 children exposed to valproate monotherapy was 3.0 (95% CI, 1.7-5.4) and the adjusted HR of childhood autism was 4.9 (95% CI, 2.3-10.3). Among 120 children exposed to valproate polytherapy, the adjusted HR of autism spectrum disorder was 1.9 (95% CI, 0.5- 7.7) and the adjusted HR of childhood autism was 5.2 (95% CI, 1.3-21.3) (eTable 4).

Risks were similar for 183 children of women who used a high valproate dose (>750 mg/d) (adjusted HR, 2.5 [95% CI, 1.03-6.1] for autism spectrum disorder and 4.3 [95% CI, 1.4-13.4] for childhood autism) compared with those for 325 children of women who used a low valproate dose (750 mg/d) (adjusted HR, 3.2 [95% CI, 1.7-6.2] for autism spectrum disorder and 5.4 [95% CI, 2.4-12.1] for childhood autism) (eTable 5).

For other antiepileptic drugs, there was no increased risk of autism spectrum disorder or childhood autism among the offspring of women who used oxcarbazepine as monotherapy during pregnancy (Figure 2 and eTable 4). There were few (<5) exposed cases when stratifying the individual drugs by dose, especially when analyzing the risk of childhood autism (eTables 4 and 5).

After excluding the 25 619 children with congenital malformations from the analyses (Table 1), the adjusted HRs associated with valproate exposure (n=457), compared with those associated with nonexposure (n=629 539), were 2.8 (95% CI, 1.5-5.1) for autism spectrum disorder and 4.2 (95% CI, 1.9- 9.3) for childhood autism (eTable 6).

The sex ratio (boys to girls; adjusted for time to event) of autism spectrum disorder was 2.4 (95% CI, 0.8-7.7) (10 boys and 4 girls) for children exposed to valproate and 4.4 (95% CI, 4.1-4.7) (4449 boys and 974 girls) for children not exposed to valproate (P=.32 by χ^2 test). The sex ratio of childhood autism was 1.2 (95% CI, 0.3- 4.4) (5 boys and 4 girls) for children exposed to valproate and 4.6 (95% CI, 4.1-5.1) (1704 boys and 354 girls) for children not exposed to valproate (P=.04 by χ^2 test).

DISCUSSION

In this population-based cohort study, children of women who used valproate during pregnancy had a higher risk of autism spectrum disorder and childhood autism compared with children of women who did not use valproate. Their risks were also higher than those for children of women who were previous users of valproate but who stopped before their pregnancy. Our results are consistent with findings from previous case series, although the risk of autism spectrum disorder following valproate exposure in our study was slightly lower,[4-6] probably because our findings were based on a larger and unselected cohort of valproate-exposed women. Because autism spectrum disorders are serious conditions with lifelong implications for affected children and their families, even a moderate increase in risk may have major health importance. Still, the absolute risk of autism spectrum disorder was less than 5%, which is important to take into account when counseling women about the use of valproate in pregnancy.

Valproate is indicated for the treatment of epilepsy, manic episodes associated with bipolar disorder, and prophylaxis of migraine headaches. It was not possible from the prescriptions to identify the disorder for which the women received valproate treatment. However, we assume that women who had a diagnosis of epilepsy received valproate for this indication. An increased risk from valproate use was found in the offspring of mothers both with and without an epilepsy diagnosis, suggesting a biological effect of valproate. In the offspring of women with epilepsy, the risk associated with valproate use was lower compared with the overall risk from valproate. This suggests confounding effects of maternal epilepsy or interaction between genetic susceptibility and valproate. We cannot exclude the possibility that children of women who used valproate during pregnancy may be examined more carefully for autism spectrum disorders, because valproate has been associated with adverse effects.[4-6] This potential bias would lead to overestimation of the effect of valproate on the risk of autism in our study.

Risk of Autism According to the Timing of Exposure to Valproate

We found no difference in risk of autism spectrum disorder between offspring of women who redeemed prescriptions for valproate early vs later in pregnancy, but the number of women who redeemed valproate only in the later stages of pregnancy was low. The estimates were based on the trimester when the women redeemed a prescription and not on when the women actually ingested the tablets; therefore, misclassification of timing of the exposure may have occurred. Changing the exposure window prior to pregnancy had only minor influence on the association between valproate exposure and autism spectrum disorder. Misclassification of the timing of conception is also possible, but this misclassification is likely small.[17,18]

Risk of Autism by Antiepileptic Treatment Regimen

We found increased risks of autism spectrum disorder, both in offspring of women who filled prescriptions for valproate alone and offspring of those who filled prescriptions for valproate as well as other antiepileptic drugs during pregnancy; however, the number of women exposed to valproate polytherapy was low. We assume that women using valproate monotherapy did not change antiepileptic medication during pregnancy, but use of polytherapy may reflect a change.

Previous studies suggest that the teratogenic potential of valproate[19] is higher for high daily doses of valproate during pregnancy.[20] We found increased risks associated with both a high dose and a low dose. However, we did not have information on the actual dose of valproate or on whether the dose was changed during pregnancy, which may limit the validity of the analyses.

Exposures to carbamazepine, oxcarbazepine, lamotrigine, and clonazepam monotherapy were not associated with increased risks of autism spectrum disorder and childhood autism. Valproate is a fatty acid derivative and chemically different from the other antiepileptic drugs studied, which may explain the different results observed with different antiepileptic drugs.

Women who use valproate in pregnancy may use other types of drugs having a potential effect on the development of the nervous system. However, we did not adjust for use of other prescription medicines in pregnancy, because there is no consensus on what kinds of medicines may be associated with an increased risk of autism in the offspring.

Brain Development, Congenital Malformations, and Autism

The potential harmful effects of valproate on the developing brain give rise to health concerns.[1,2] Several animal studies describe autistic-like behavior in offspring of mothers exposed to valproate during pregnancy. In animal studies, some manifestations of autism were reproduced by administering valproate at various stages in pregnancy, eg, increased repetitive or stereotypic activity, higher anxiety, and decreased level of social interaction.[9,21] The precisemode of action of valproate is not established, but it may alter neurotransmitter functioning involved in cell migration and differentiation, neuronal apoptosis,[22] or synaptic plasticity[23] or act via other mechanisms including attenuation of folic acid metabolism,

inhibition of histone deacetylases, oxidative stress, and production of arene oxide intermediates.[24,25]

Like other studies,[19,20] ours found an increased risk of congenital malformations in children exposed to valproate, but the risk of autism spectrum disorder and childhood autism associated with valproate exposure persisted after restricting the analysis to children without congenital malformations.

Strengths and Weaknesses of the Data

We assessed a population-based cohort of all children born between 1996 and 2006 for up to 14 years and with less than 3% loss to follow-up, making selection bias an unlikely explanation for our results.[4-6]

We assumed that most women who filled a prescription for valproate also used themedication at least to some extent. A previous study showed high agreement between maternal report of antiepileptic medication use and filled prescriptions for antiepileptic drugs as registered by the Danish Prescription Register.[26]

We did not have information on the use of antiepileptic drugs by pregnant women while admitted to hospitals, and we therefore may not have included all valproate-exposed pregnancies. However, valproate is rarely given alone for shorter intervals such as hospital admissions, and failure to include valproate-exposed children in our exposed cohort would tend to underestimate an association with prenatal valproate exposure.

We did not adjust for multiple comparisons but specified a priori that the main outcome was the risk of autism spectrum disorder and childhood autism following prenatal exposure to valproate. Multiple comparisons increase the risk of incidental findings, and the results of the secondary analyses are therefore exploratory and subject to further studies.

The positive predictive value of an epilepsy diagnosis in the Danish Hospital Register was 81%[27]; therefore, some patients registered with epilepsy in our cohort do not have epilepsy. Also, patients registered with epilepsy in childhood and early adulthood may no longer have epilepsy. However, the associations between valproate exposure and autism spectrum disorders were found among offspring of mothers both with and without epilepsy, indicating an association with valproate exposure. Seizures may influence the well-being of the unborn child, but from the registers it was not possible to identify pregnant women experiencing seizures during pregnancy. We are not aware of studies that have assessed the contribution of seizures in pregnancy to the risk of autism in the offspring of women with epilepsy.

When evaluating the quality of the childhood autism diagnosis in the Danish Psychiatric Central Register, it was found that 94% of the childhood autism diagnoses met the *ICD-10* criteria for a correct diagnosis.[28] The other autism spectrum disorder diagnoses in the register have not been validated, but the quality is expected to be high. In this study, the prevalence estimate of autism spectrum disorder was 1.53% (95% CI, 1.47%-1.58%) at 14 years of follow-up, similar to the prevalence of 1.1% in US children aged 3 to 17 years

based on parent reports[29] or of approximately 1% among 8-year-old US children based on data from the Autism and Developmental Disabilities Monitoring Network.[30]

We adjusted for parental psychiatric history, which is a well-known risk factor for autism in the offspring,[31] but the estimates of the risk associated with valproate exposure changed little. We did not have information on use of alcohol in pregnancy, but we adjusted for diagnoses of alcohol abuse from the Danish Psychiatric Central Register. However, not all parents with alcohol abuse or psychiatric disorders were identified from the registers, and residual confounding by unmeasured psychiatric disorders in the mother or father can therefore not be entirely excluded. We did not have information on folic acid use in pregnant women (only high-dose [5 mg] folic acid requires a prescription in Denmark). Studies of folate status during the later stages of pregnancy did not find significant associations with mental and psychomotor development at age 5 years,[32] but periconceptional use of folic acid has been associated with a 39% reduced risk of autistic disorder (childhood autism) (adjusted odds ratio for autistic disorder in children of folic acid users, 0.61 [95% CI, 0.41-0.90]),[33] and use of folic acid may reduce the risk of autism spectrum disorder in mothers with inefficient folate metabolism.[34] However, we expect that pregnant women exposed to valproate would be more likely to take folic acid compared with those not exposed to valproate during pregnancy because of recommendations regarding the use of folic acid in fertile women with epilepsy, which would tend to underestimate the true risk associated with valproate.

CONCLUSIONS

Maternal use of valproate during pregnancy was associated with a significantly increased risk of autism in the offspring, even after adjusting for parental psychiatric disease and epilepsy. For women of childbearing potential who use antiepileptic medications, these findings must be balanced against the treatment benefits for women who require valproate for epilepsy control.

Acknowledgments

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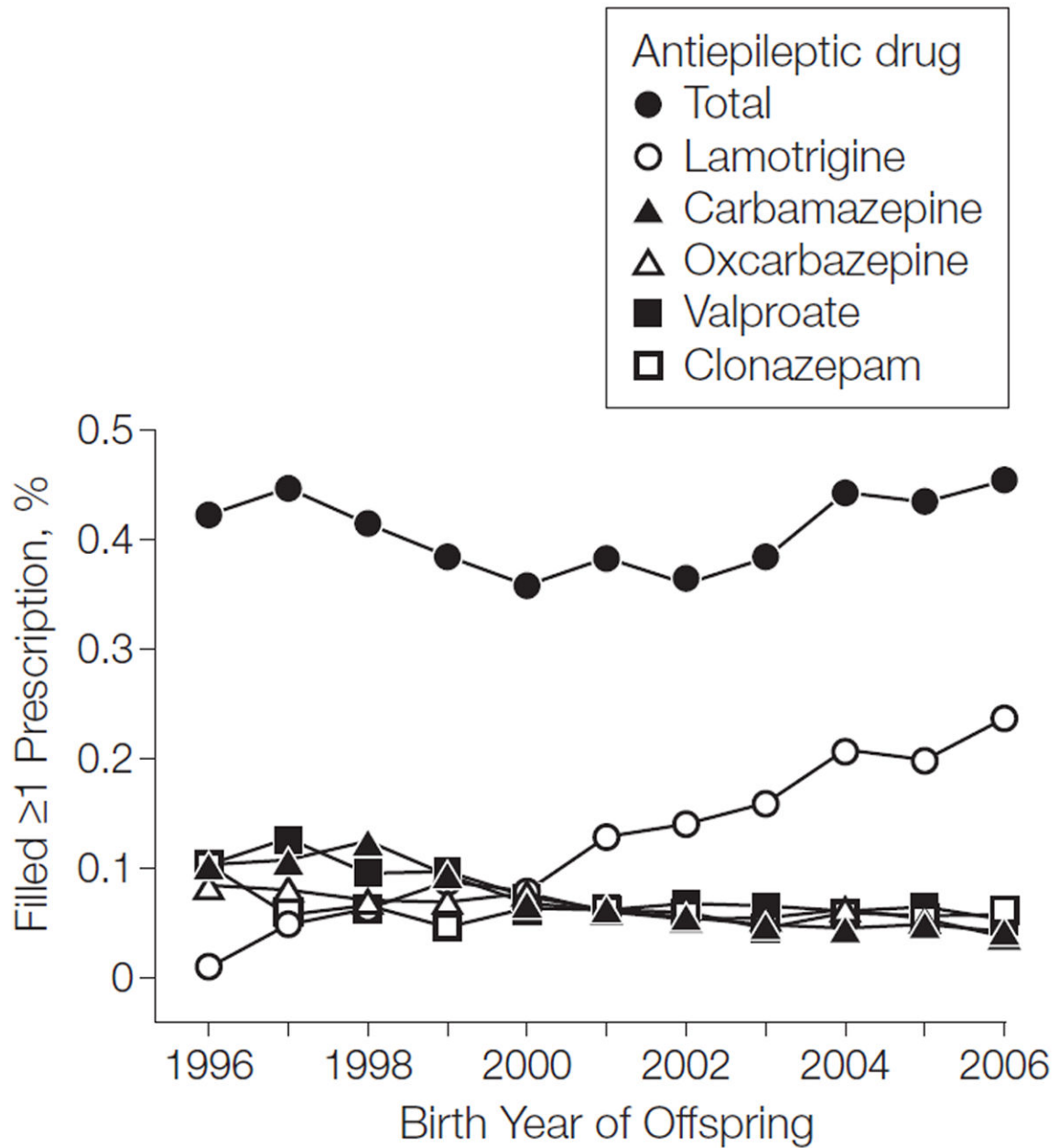
Figure 1.
Proportion of Women Who Filled at Least 1 Prescription for Antiepileptic Drugs During Pregnancy, by Birth Year of the Child See eTable 1 for number of live births, congenital malformations, autism spectrum disorder, chilhood autism, and antiepileptic use by the mother during pregnancy.

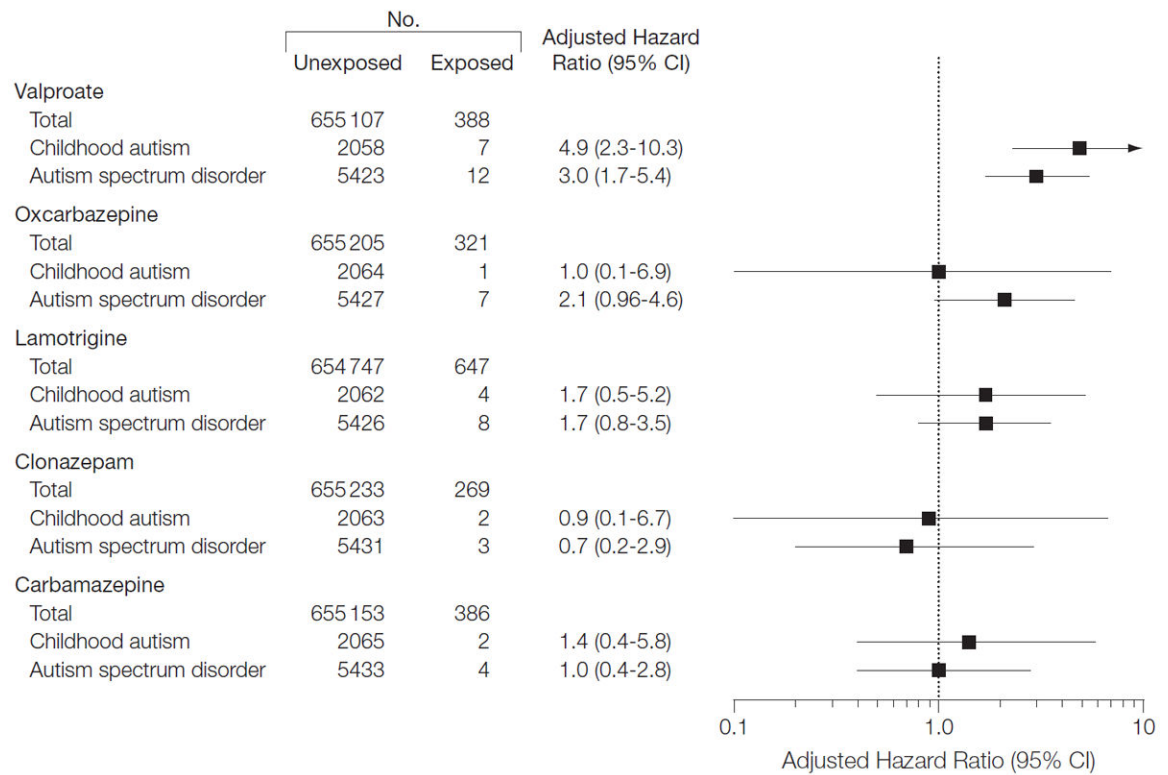|	No. Unexposed	No. Exposed	Adjusted Hazard Ratio (95% CI)
Valproate			
Total	655 107	388	
Childhood autism	2058	7	4.9 (2.3-10.3)
Autism spectrum disorder	5423	12	3.0 (1.7-5.4)
Oxcarbazepine			
Total	655 205	321	
Childhood autism	2064	1	1.0 (0.1-6.9)
Autism spectrum disorder	5427	7	2.1 (0.96-4.6)
Lamotrigine			
Total	654 747	647	
Childhood autism	2062	4	1.7 (0.5-5.2)
Autism spectrum disorder	5426	8	1.7 (0.8-3.5)
Clonazepam			
Total	655 233	269	
Childhood autism	2063	2	0.9 (0.1-6.7)
Autism spectrum disorder	5431	3	0.7 (0.2-2.9)
Carbamazepine			
Total	655 153	386	
Childhood autism	2065	2	1.4 (0.4-5.8)
Autism spectrum disorder	5433	4	1.0 (0.4-2.8)

Adjusted Hazard Ratio (95% CI)

Figure 2.
Autism Spectrum Disorder and Childhood Autism in Offspring of Mothers Who Used Antiepileptic Drugs as Monotherapy During Pregnancy Compared With Offspring of Women Who Did Not Use the Individual Antiepileptic Drug

Table 1

Characteristics of Study Participants

Characteristic	Valproate Exposure, No. (%)	
	Exposed (n = 508)	Not Exposed (n = 655 107)
Maternal age at conception, y		
<21	30 (5.9)	26 212 (4.0)
21-25	117 (23.0)	127 230 (19.4)
26-30	190 (37.4)	262 707 (40.1)
31-35	129 (25.4)	180 973 (27.6)
36	42 (8.3)	57985 (8.9)
Paternal age at conception, y		
25	67 (13.6)	76 700 (12.0)
26-30	171 (34.7)	213 912 (33.4)
31-35	149 (30.2)	211 993 (33.1)
36	106 (21.5)	138 337 (21.6)
Parental psychiatric history[a]		
Yes	43 (8.5)	22 854 (3.5)
No	465 (91.5)	632 253 (96.5)
Gestational age, wk		
<28	2 (0.4)	1230 (0.2)
28-31	9 (1.8)	4616 (0.7)
32-36	37 (7.3)	36 556 (5.6)
37	460 (90.6)	612 705 (93.5)
Birth weight, g		
<2500	46 (9.1)	32 225 (4.9)
2500-2999	69 (13.7)	72 735 (11.2)
3000-3499	147 (29.2)	199 583 (30.6)
3500	242 (48.0)	346 785 (53.2)
Sex		
Boys	267 (52.6)	335 843 (51.3)
Girls	241 (47.4)	319 249 (48.7)

Characteristic	Valproate Exposure, No. (%)	
	Exposed (n = 508)	Not Exposed (n = 655 107)
Congenital malformations[b]		
Yes	51 (10.0)	25 568 (3.9)
No	457 (90.0)	629 539 (96.1)
Parity		
0	239 (47.0)	283 054 (43.2)
1	269 (53.0)	372 047 (56.8)
Epilepsy (mother)		
Yes	432 (85.0)	6152 (0.9)
No	76 (15.0)	648 955 (99.1)

[a] One or both parents diagnosed with a psychiatric disorder before birth of the child (*International Classification of Diseases, Eighth Revision*: codes 290-315; International Classification of Diseases, Tenth Revision [*ICD-10*]: All F codes).

[b] Child diagnosed with congenital malformations (*ICD-10* codes Q0 to Q99, except for Q53 and Q65 [see Methods]).

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Table 2

Association Between Any Maternal Use of Valproate During Pregnancy and Autism Spectrum Disorder and Childhood Autism

Valproate Exposure	Live Births, No.	Person-Years at Risk	No. With Disorder	Hazard Ratio (95% CI)		Absolute Risk Over 14 y, % (95% CI)
				Crude	Adjusted[a]	
Autism Spectrum Disorder						
Yes	508	4880	14	3.0 (1.8-5.1)	2.9 (1.7-4.9)	4.42 (2.59-7.46)
No	655 107	5 793 387	5423	1 [Reference]	1 [Reference]	1.52 (1.47-1.58)
Childhood Autism						
Yes	508	4891	9	5.4 (2.8-10.4)	5.2 (2.7-10.0)	2.50 (1.30-4.81)
No	655 107	5 803 842	2058	1 [Reference]	1 [Reference]	0.48 (0.45-0.51)

[a] Adjusted for maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations, and parity.

Table 3

Association Between Epilepsy in the Mother, Valproate Exposure, and Autism Spectrum Disorder and Childhood Autism

Epilepsy in Mother	Valproate Exposure	Live Births, No.	No. With Disorder	Hazard Ratio (95% CI)		Absolute Risk Over 14 y, % (95% CI)
				Crude	Adjusted[a]	
Autism Spectrum Disorder						
Yes	Yes	432	11	1.7 (0.9-3.2)	1.7 (0.9-3.2)	4.15 (2.20-7.81)
	No	6152	83	1 [Reference]	1 [Reference]	2.44 (1.88-3.16)
No	Yes	76	3	4.2 (1.4-12.5)	4.4 (1.4-13.6)	6.67 (2.12-20.6)
	No	648 955	5340	1 [Reference]	1 [Reference]	1.52 (1.46-1.57)
Childhood Autism						
Yes	Yes	432	8	2.8 (1.3-6.1)	2.9 (1.4-6.0)	2.95 (1.42-6.11)
	No	6152	37	1 [Reference]	1 [Reference]	1.02 (0.70-1.49)
No	Yes	76	1	4.2 (0.6-30.0)	3.9 (0.5-28.9)	1.86 (0.24-13.8)
	No	648 955	2021	1 [Reference]	1 [Reference]	0.48 (0.45-0.51)

[a] Adjusted for maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations, and parity.