

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Number of Live Births, Congenital Malformations, Autism Spectrum Disorder, Childhood Autism, and Antiepileptic Use in the Mother During Pregnancy by Birth Year

Birth year	Number of live births	Congenital malformations in child	Autism Spectrum Disorder	Childhood Autism	Use of antiepileptic drugs in the mother during pregnancy					
					Valproate	Carbamazepine	Clonazepam	Lamotrigine	Oxcarbazepine	Antiepileptic drug use ^a
1996	10,655	430	127	37	11	11	11	1	9	45
1997	66,020	2,208	803	200	84	71	38	32	53	295
1998	64,927	2,258	711	222	62	81	43	41	46	269
1999	64,956	2,425	756	272	63	61	30	57	45	250
2000	65,896	2,428	722	239	49	45	42	52	51	236
2001	64,450	2,409	621	259	40	40	40	83	39	247
2002	63,409	2,507	519	219	43	35	38	89	34	228
2003	63,954	2,576	477	234	42	31	29	102	35	245
2004	63,886	2,690	348	184	39	29	38	133	40	283
2005	63,348	2,796	237	141	41	31	36	126	34	275
2006	64,114	2,892	116	60	34	27	37	152	24	291
Total	655,615	25,619	5,437	2,067	508	462	382	868	410	2,664

^aMothers may have used more than one type of antiepileptic drugs and other types than those listed

eTable 2. Association Between Maternal Use of Valproate During Pregnancy and Autism Spectrum Disorder and Childhood Autism When Comparing With Offspring of Women Who Were Previous Users of Valproate But Stopped Before Pregnancy

Autism Spectrum Disorder						
Valproate exposure	Live births (Number)	Person years at risk	Autism Spectrum Disorder (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted ^a (95% CI)	Absolute risk (%) (95% CI)
Exposed to valproate in pregnancy	508	4,880	14	2.2 (1.03 – 4.9)	2.2 (1.02 - 4.9)	4.62 (2.10-10.3)
Mother used valproate prior to pregnancy	1,261	10,257	13	1.0 (ref)	1.0 (ref)	2.10 (1.06-4.13)
Childhood Autism						
Valproate exposure	Live births (Number)	Person years at risk	Childhood Autism (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted ^a (95% CI)	Absolute risk (%) (95% CI)
Exposed to valproate in pregnancy	508	4,891	9	3.7 (1.2–12.1)	5.6 (1.7-18.1)	5.19 (1.58-16.8)
Mother used valproate prior to pregnancy	1,261	10,276	5	1.0 (ref)	1.0 (ref)	0.93 (0.27-3.16)

a) Hazard Ratios were adjusted for maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations and parity.

eTable 3. Association Between First Trimester and Second/Third Trimester Valproate Exposure and Autism Spectrum Disorder and Childhood Autism

Autism Spectrum Disorder					
Valproate exposure	Time of exposure	Live births (Number)	Autism Spectrum Disorder (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted* (95% CI)
Valproate exposure	First trimester	441	12	3.0 (1.7-5.2)	2.9 (1.6-5.1)
	After first trimester only	67	2	3.5 (0.9-13.9)	3.1 (0.8-12.2)
No valproate exposure	Valproate exposure	655,107	5,423	1.0 (ref)	1.0 (ref)
Childhood Autism					
Valproate exposure	Time of exposure	Live births (Number)	Childhood Autism (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted* (95% CI)
Valproate exposure	First trimester	441	7	4.9 (2.3-10.2)	4.7 (2.2-9.9)
	After first trimester only	67	2	9.2 (2.3-36.3)	8.3 (2.1-32.4)
No valproate exposure	Valproate exposure	655,107	2,058	1.0 (ref)	1.0 (ref)

*Hazard Ratios were adjusted for maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations and parity.

eTable 4. Association between the use of antiepileptic drugs (AEDs) during pregnancy and Autism Spectrum Disorder and Childhood Autism.

Autism Spectrum Disorder									
AED	AED exposure	Live births (Number)	Autism Spectrum Disorder (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted* (95% CI)	Absolute Risk (%) (95% CI)			
Valproate	Monotherapy	388	12	3.4 (1.9-5.9)	3.0 (1.7-5.4)	4.57 (2.59-8.22)			
	Polytherapy	120	2	1.9 (0.5-7.6)	1.9 (0.5-7.7)	2.89 (0.76-11.7)			
	No exposure	655,107	5,423	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)			
Carbamazepine	Monotherapy	386	4	1.1 (0.4-3.0)	1.0 (0.4-2.8)	1.52 (0.61-4.26)			
	Polytherapy	76	0	NA NA	NA NA	NA (NA)			
	No exposure	655,153	5,433	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)			
Clonazepam	Monotherapy	269	3	1.3 (0.4-4.2)	0.7 (0.2-2.9)	1.07 (0.30-4.42)			
	Polytherapy	113	3	3.2 (1.03-10.0)	3.1 (0.99-9.7)	4.72 (1.52-14.8)			
	No exposure	655,233	5,431	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)			
Lamotrigine	Monotherapy	647	8	2.0 (0.98-3.9)	1.7 (0.8-3.5)	2.59 (1.22-5.33)			
	Polytherapy	221	3	1.7 (0.6-5.4)	1.1 (0.3-4.4)	1.68 (0.46-6.70)			
	No exposure	654,747	5,426	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)			
Oxcarbazepine	Monotherapy	321	7	2.5 (1.2-5.1)	2.1 (0.96-4.6)	3.20 (1.52-7.01)			
	Polytherapy	89	3	3.8 (1.2-11.8)	2.2 (0.5-9.0)	3.35 (0.76-13.7)			
	No exposure	655,205	5,427	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)			
Childhood Autism									
AED	AED exposure	Live births (Number)	Childhood Autism (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted* (95% CI)	Absolute risk (%) (95% CI)			
Valproate	Monotherapy	388	7	5.5 (2.6-11.6)	4.9 (2.3-10.3)	2.36 (1.11-4.95)			
	Polytherapy	120	2	5.1 (1.3-20.8)	5.2 (1.3-21.3)	2.50 (0.63-10.2)			
	No exposure	655,107	2,058	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)			
Carbamazepine	Monotherapy	386	2	1.6 (0.4-6.3)	1.4 (0.4-5.8)	0.67 (0.19-2.79)			
	Polytherapy	76	0	NA NA	NA NA	NA (NA)			
	No exposure	655,153	2,065	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)			
Clonazepam	Monotherapy	269	2	2.4 (0.6-9.6)	0.9 (0.1-6.7)	0.43 (0.05-3.22)			
	Polytherapy	113	2	5.6 (1.4-22.6)	5.1 (1.3-20.7)	2.45 (0.63-9.95)			
	No exposure	655,233	2,063	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)			
Lamotrigine	Monotherapy	647	4	2.2 (0.8-5.9)	1.7 (0.5-5.2)	0.82 (0.24-2.50)			
	Polytherapy	221	1	1.4 (0.2-10.3)	1.4 (0.2-9.9)	0.67 (0.10-4.76)			
	No exposure	654,747	2,062	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)			
Oxcarbazepine	Monotherapy	321	1	1.0 (0.1-6.8)	1.0 (0.1-6.9)	0.48 (0.05-3.32)			
	Polytherapy	89	2	6.8 (1.7-27.5)	6.2 (1.5-24.9)	2.98 (0.72-12.0)			
	No exposure	655,205	2,064	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)			

*Hazard Ratios were adjusted for maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations and parity.
AEDs: antiepileptic drug

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eTable 5. Low- and High-Dose Antiepileptic Drug (AED) Exposure During Pregnancy and Autism Spectrum Disorder and Childhood Autism

Autism Spectrum Disorder						
AED	AED exposure	Live births (Number)	Autism Spectrum Disorder (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted* (95% CI)	Absolute Risk (%) (95% CI)
Valproate	High dose (>750 mg)	183	5	2.9 (1.2-6.9)	2.5 (1.03-6.1)	3.81 (1.52-9.29)
	Low dose (≤750 mg)	325	9	3.1 (1.6-6.0)	3.2 (1.7-6.2)	4.87 (2.59-9.44)
	No exposure	655,107	5,423	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)
Carbamazepine	High dose (>500 mg)	280	3	1.1 (0.4-3.4)	1.1 (0.3-3.2)	1.68 (0.46-4.88)
	Low dose (≤500 mg)	182	1	0.6 (0.1-4.5)	0.6 (0.1-4.2)	0.91 (0.15-6.40)
	No exposure	655,153	5,433	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)
Clonazepam	High dose (>4 mg)	26	1	4.0 (0.6-28.8)	3.0 (0.4-22.5)	4.57 (0.61-34.3)
	Low dose (≤4 mg)	356	5	1.7 (0.7-4.1)	1.2 (0.5-3.2)	1.83 (0.76-4.87)
	No exposure	655,233	5,431	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)
Lamotrigine	High dose (>150 mg)	438	3	1.0 (0.3-3.2)	1.0 (0.3-3.0)	1.52 (0.46-4.57)
	Low dose (≤150 mg)	430	8	2.8 (1.4-5.5)	2.0 (0.9-4.6)	3.05 (1.37-7.01)
	No exposure	654,747	5,426	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)
Oxcarbazepine	High dose (>500 mg)	294	6	2.3 (1.04-5.1)	1.9 (0.8-4.6)	2.89 (1.22-7.01)
	Low dose (≤500 mg)	116	4	4.0 (1.5-10.6)	2.6 (0.8-8.0)	3.96 (1.22-12.2)
	No exposure	655,205	5,427	1.0 (ref)	1.0 (ref)	1.52 (1.47-1.58)
Childhood Autism						
AED	AED exposure	Live births (Number)	Childhood Autism (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted* (95% CI)	Absolute risk (%) (95% CI)
Valproate	High dose (>750 mg)	183	3	5.0 (1.6-15.6)	4.3 (1.4-13.4)	2.07 (0.67-6.44)
	Low dose (≤750 mg)	325	6	5.7 (2.6-12.6)	5.4 (2.4-12.1)	2.60 (1.15-5.82)
	No exposure	655,107	2,058	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)
Carbamazepine	High dose (>500 mg)	280	1	NA	NA	NA NA
	Low dose (≤500 mg)	182	1	NA	NA	NA NA
	No exposure	655,153	2,065	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)
Clonazepam	High dose (>4 mg)	26	1	NA	NA	NA NA
	Low dose (≤4 mg)	356	3	NA	NA	NA NA
	No exposure	655,233	2,063	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)
Lamotrigine	High dose (>150 mg)	438	1	NA	NA	NA NA
	Low dose (≤150 mg)	430	4	NA	NA	NA NA
	No exposure	654,747	2,062	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)
Oxcarbazepine	High dose (>500 mg)	294	1	NA	NA	NA NA
	Low dose (≤500 mg)	116	2	NA	NA	NA NA
	No exposure	655,205	2,064	1.0 (ref)	1.0 (ref)	0.48 (0.45-0.51)

*Hazard Ratios were adjusted for maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex, congenital malformations and parity. NA: not assessed due to low number of exposed cases.

eTable 6. Association Between the Use of Valproate During Pregnancy and Autism Spectrum Disorder and Childhood Autism After Excluding 25,619 Children With Congenital Malformations From the Analyses

Autism Spectrum Disorder						
Valproate exposure	Live births (Number)	Autism Sepctrum Disorder (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted* (95% CI)	Absolute Risk (%) (95% CI)	
Exposed to valproate	457	11	2.7 (1.5-4.9)	2.8 (1.5-5.1)	4.13	(2.21-7.52)
Not exposed to valproate	629,539	5,043	1.0 (ref)	1.0 (ref)	1.48	(1.42-1.53)
Childhood Autism						
Valproate exposure	Live births (Number)	Autism Sepctrum Disorder (Number)	Hazard Rate Crude (95% CI)	Hazard Rate Adjusted* (95% CI)	Absolute Risk (%) (95% CI)	
Exposed to valproate	457	6	4.1 (1.9-9.2)	4.2 (1.9-9.3)	1.97	(0.89-4.36)
Not exposed to valproate	629,539	1,913	1.0 (ref)	1.0 (ref)	0.46	(0.44-0.50)

*Hazard Ratios were adjusted for maternal age at conception, paternal age at conception, parental psychiatric history, gestational age, birth weight, sex and parity.