

Supplementary Table 1. Hospital discharge diagnoses, LTD diagnoses and ATC codes used to identify comorbidities and comedications

	Hospital discharge diagnoses (PD, RD and AD)	LTD	Specific drug reimbursements
Exclusion criterion			
Brain malformation	Q00-04, Q05.0-05.4 ^a		
Comorbidities			
History of mental and behavioral disorders	F00-99 (except F10, F17) ^b	F00-99 (except F10, F17) ^c	
Proxy for alcohol intake	E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, P04.3, Q86.0, R78.0, T51, X45, X65, Y15, Y57.3, Z50.2, Z71.4, Z72.1 ^d	F10, K70 ^e	Disulfiram, Acamprosate, Naltrexone, Nalmefene ^d
Proxy for smoking	F17, I73.1, J41-44, P04.2, T65.2, Z71.6, Z72.0 ^d	F17, J41-44 ^e	Nicotine replacement therapy Indacaterol, olodaterol, tiotropium bromide, umeclidinium bromide, glycopyrronium bromide ^d
Indication			
Epilepsy	G40, G41 ^d	G40, G41 ^e	Valproic acid as an AED, eslicarbazepine, ethosuximide, lacosamide, levetiracetam, perampanel, phenobarbital, phenytoin, retigabine, rufinamide, stiripentol, vigabatrin, zonisamide or lamotrigine, oxcarbazepine, primidone prescribed by a neurologist ^d
Comedications			
Folic acid supplementation			Reimbursed folic acid treatments [†]
SSRIs			Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram ^g
Antipsychotics			First- and second-generation antipsychotics ^b
Proxy for severity of mental disorder			Hypnotics, anxiolytics, antidepressants, antipsychotics ^b

Abbreviations: PD = primary diagnosis; RD = related diagnosis; AD = associated diagnosis; LTD = long-term disease; SSRIs = selective serotonin reuptake inhibitors

^a during the birth stay

- ^b in the year before pregnancy
- ^c beginning before pregnancy
- ^d in the year before or during pregnancy
- ^e beginning before birth
- ^f between one month before pregnancy and 3 months after the start of pregnancy
- ^g during pregnancy

Supplementary Table 2. Study drugs

Drug name	ATC code
Carbamazepine	N03AF01
Clonazepam	N03AE01
Eslicarbazepine	N03AF04
Ethosuximide	N03AD01
Gabapentin	N03AX12
Lacosamide	N03AX18
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Oxcarbazepine	N03AF02
Perampanel	N03AX22
Phenobarbital	N03AA02
Phenytoin	N03AB02
Pregabalin	N03AX16
Primidone	N03AA03
Retigabine	N03AX21
Rufinamide	N03AF03
Stiripentol	N03AX17
Tiagabine	N03AG06
Topiramate	N03AX11
Valproic acid ^a	N03AG01
Vigabatrin	N03AG04
Zonisamide	N03AX15

Abbreviation: ATC code = anatomical therapeutic chemical code

^aDivalproex sodium and valpromide are only indicated for the treatment of bipolar disorder in France and are therefore not considered to be AEDs.

Supplementary Table 3. Baseline characteristics according to AED use during pregnancy - study population limited to women considered to be treated for epilepsy

	Lamotrigine	Carbamazepine	Levetiracetam	Valproic acid
Number of exposed pregnancies	2,108	176	621	991
Maternal age at birth (years)				
< 25	349 (16.6)	21 (11.9)	119 (19.2)	137 (13.8)
[25 - 30[715 (33.9)	42 (23.9)	212 (34.1)	259 (26.1)
[30 - 35[679 (32.2)	60 (34.1)	181 (29.1)	310 (31.3)
≥ 35	365 (17.3)	53 (30.1)	109 (17.6)	285 (28.8)
Eligibility for CMU-C	340 (16.1)	30 (17.0)	134 (21.6)	311 (31.4)
Hospitalization for epilepsy	171 (8.1)	13 (7.4)	43 (6.9)	22 (2.2)
History of mental and behavioral disorders	150 (7.1)	18 (10.2)	51 (8.2)	96 (9.7)
Proxy for alcohol intake	18 (0.9)	0 (0.0)	13 (2.1)	22 (2.2)
Proxy for smoking	204 (9.7)	21 (11.9)	69 (11.1)	136 (13.7)
Folic acid supplementation	1,537 (72.9)	133 (75.6)	396 (63.8)	525 (53.0)
SSRIs during pregnancy	55 (2.6)	5 (2.8)	23 (3.7)	33 (3.3)
History of antipsychotic use	40 (1.9)	4 (2.3)	15 (2.4)	49 (4.9)
Number of psychiatric medications ^a				
0	1,286 (61.0)	105 (59.7)	366 (58.9)	653 (65.9)
1	522 (24.8)	51 (29.0)	138 (22.2)	180 (18.2)
2	167 (7.9)	11 (6.3)	54 (8.7)	67 (6.8)
3-4	91 (4.3)	4 (2.3)	39 (6.3)	45 (4.5)
≥ 5	42 (2.0)	5 (2.8)	24 (3.9)	46 (4.6)
Gestational age (weeks after LMP)				
< 32	8 (0.4)	2 (1.1)	7 (1.1)	7 (0.7)
[32 - 35[32 (1.5)	2 (1.1)	11 (1.8)	19 (1.9)
[35 - 37[91 (4.3)	5 (2.8)	33 (5.3)	45 (4.5)
≥ 37	1,977 (93.8)	167 (94.9)	570 (91.8)	920 (92.8)
Gender (male)	1,115 (52.9)	96 (54.5)	292 (47.0)	496 (50.1)
Birth weight				
< 2,500	128 (6.1)	14 (8.0)	60 (9.7)	88 (8.9)
[2,500 - 3,000[460 (21.8)	42 (23.9)	152 (24.5)	227 (22.9)
[3,000 - 3,500[872 (41.4)	63 (35.8)	251 (40.4)	389 (39.3)
≥ 3,500	648 (30.7)	57 (32.4)	158 (25.4)	287 (29.0)

Abbreviations: AED = antiepileptic drug; CMU- C = complementary universal health insurance for low-income people; SSRIs = selective serotonin reuptake inhibitors; LMP = last menstrual period

Figures are N (%)

^a Number of 5th level ATC classes of psychiatric medications to whom mothers were exposed in the year before pregnancy

*** p <0.0001; ** p <0.001; * p <0.05; NS: Not Significant

Supplementary Table 4. Number of children, number of events, crude event rates (per 1,000), crude IRRs and adjusted HRs for the four outcomes and each of the AEDs studied - exposure limited to dispensing during pregnancy

	Children	Events	Crude event rates	IRR	HR [95% CI]
Neurodevelopmental disorders					
Lamotrigine	2,832	49	4.9		
Carbamazepine	431	11	6.9	1.4 [0.7 - 2.7]	1.1 [0.6 - 2.3]
Clonazepam	876	21	5.4	1.1 [0.7 - 1.9]	0.7 [0.4 - 1.3]
Gabapentin	273	3	3.2	0.7 [0.2 - 2.1]	0.4 [0.1 - 1.7]
Levetiracetam	595	8	3.9	0.8 [0.4 - 1.7]	0.7 [0.3 - 1.6]
Oxcarbazepine	128	3	6.4	1.3 [0.4 - 4.2]	0.9 [0.2 - 3.6]
Pregabalin	951	19	5.8	1.2 [0.7 - 2.0]	0.7 [0.4 - 1.3]
Topiramate	338	6	4.9	1.0 [0.4 - 2.4]	1.0 [0.4 - 2.4]
Valproic acid	911	49	14.4	3.0 [2.0 - 4.4]	2.8 [1.9 - 4.2]
Pervasive developmental disorders					
Lamotrigine	2,832	10	1.0		
Carbamazepine	431	3	1.8	1.9 [0.5 - 6.8]	1.6 [0.4 - 6.3]
Clonazepam	876	5	1.3	1.3 [0.4 - 3.8]	0.8 [0.3 - 2.6]
Gabapentin	273	2	2.2	2.2 [0.5 - 10.0]	2.0 [0.4 - 9.3]
Levetiracetam	595	4	1.9	2.0 [0.6 - 6.2]	1.8 [0.5 - 6.2]
Oxcarbazepine	128	1	2.1	2.1 [0.3 - 16.6]	2.2 [0.3 - 16.9]
Pregabalin	951	5	1.5	1.5 [0.5 - 4.5]	1.5 [0.5 - 4.5]
Topiramate	338	0	0.0	N/A	N/A
Valproic acid	911	16	4.6	4.7 [2.1 - 10.4]	4.4 [2.0 - 9.6]
Mental retardation					
Lamotrigine	2,832	14	1.4		
Carbamazepine	431	2	1.2	0.9 [0.2 - 3.9]	0.6 [0.1 - 3.5]
Clonazepam	876	3	0.8	0.6 [0.2 - 1.9]	0.4 [0.1 - 1.7]
Gabapentin	273	0	0.0	N/A	N/A
Levetiracetam	595	1	0.5	0.3 [0.0 - 2.7]	0.4 [0.1 - 2.8]
Oxcarbazepine	128	0	0.0	N/A	N/A
Pregabalin	951	4	1.2	0.9 [0.3 - 2.7]	0.5 [0.1 - 2.2]
Topiramate	338	1	0.8	0.6 [0.1 - 4.5]	0.4 [0.0 - 4.7]
Valproic acid	911	14	4.0	2.9 [1.4 - 6.2]	3.0 [1.4 - 6.3]
Visits to a speech therapist					
Lamotrigine	2,832	152	15.1		
Carbamazepine	431	27	16.9	1.1 [0.7 - 1.7]	1.0 [0.6 - 1.5]
Clonazepam	876	63	16.3	1.1 [0.8 - 1.4]	0.8 [0.6 - 1.1]
Gabapentin	273	9	9.8	0.6 [0.3 - 1.3]	0.7 [0.4 - 1.3]
Levetiracetam	595	22	10.7	0.7 [0.5 - 1.1]	0.7 [0.5 - 1.2]
Oxcarbazepine	128	13	27.9	1.8 [1.0 - 3.3]	1.7 [1.0 - 3.1]
Pregabalin	951	38	11.6	0.8 [0.5 - 1.1]	0.6 [0.4 - 0.9]

Supplementary Table 4. Number of children, number of events, crude event rates (per 1,000), crude IRRs and adjusted HRs for the four outcomes and each of the AEDs studied - exposure limited to dispensing during pregnancy (continued)

	Children	Events	Crude event rates	IRR	HR [95% CI]
Topiramate	338	25	20.8	1.4 [0.9 - 2.1]	1.5 [0.9 - 2.2]
<i>Valproic acid</i>	<i>911</i>	<i>85</i>	<i>25.1</i>	<i>1.7 [1.3 - 2.2]</i>	<i>1.5 [1.1 - 1.9]</i>

Abbreviations: AED = antiepileptic drug; IRR = incidence rate ratio; HR = hazard ratio; N/A = not applicable
 Lines marked in bold and italics correspond to HRs for which the 95% CI does not include 1.

Supplementary Table 5. HRs for the four outcomes and each of the AEDs studied - propensity score excluding proxies for alcohol intake and smoking or gestational age and birth weight

	HR ^a [95% CI]	HR ^b [95% CI]
Neurodevelopmental disorders		
Carbamazepine	1.2 [0.6 - 2.2]	1.2 [0.6 - 2.3]
Clonazepam	0.7 [0.4 - 1.1]	0.7 [0.4 - 1.1]
Gabapentin	0.4 [0.1 - 1.3]	0.4 [0.1 - 1.4]
Levetiracetam	0.7 [0.3 - 1.5]	0.7 [0.3 - 1.5]
Oxcarbazepine	0.9 [0.2 - 3.3]	0.8 [0.2 - 3.2]
Pregabalin	0.6 [0.4 - 1.0]	0.7 [0.4 - 1.1]
Topiramate	0.8 [0.4 - 1.8]	0.8 [0.4 - 1.8]
<i>Valproic acid</i>	<i>2.7 [1.9 - 4.0]</i>	<i>2.7 [1.9 - 4.0]</i>
Pervasive developmental disorders		
Carbamazepine	1.3 [0.3 - 5.0]	1.4 [0.4 - 5.3]
Clonazepam	0.8 [0.3 - 2.1]	0.8 [0.3 - 2.1]
Gabapentin	1.7 [0.4 - 7.0]	1.5 [0.4 - 6.7]
Levetiracetam	1.5 [0.4 - 5.3]	1.7 [0.5 - 5.7]
Oxcarbazepine	2.1 [0.3 - 14.0]	2.0 [0.3 - 13.9]
Pregabalin	1.3 [0.5 - 3.3]	1.2 [0.5 - 3.1]
Topiramate	0.3 [0.0 - 4.8]	0.3 [0.0 - 4.5]
<i>Valproic acid</i>	<i>4.4 [2.1 - 9.2]</i>	<i>4.5 [2.1 - 9.6]</i>
Mental retardation		
Carbamazepine	0.6 [0.1 - 2.9]	0.6 [0.1 - 3.0]
Clonazepam	0.3 [0.1 - 1.2]	0.3 [0.1 - 1.2]
Gabapentin	N/A	N/A
Levetiracetam	0.3 [0.0 - 2.5]	0.4 [0.0 - 2.6]
Oxcarbazepine	N/A	N/A
Pregabalin	0.6 [0.2 - 1.8]	0.6 [0.2 - 1.7]
Topiramate	0.5 [0.1 - 3.3]	0.5 [0.1 - 3.3]
<i>Valproic acid</i>	<i>3.0 [1.5 - 6.1]</i>	<i>3.1 [1.5 - 6.2]</i>
Visits to a speech therapist		
Carbamazepine	0.9 [0.6 - 1.4]	1.0 [0.6 - 1.4]
Clonazepam	0.8 [0.6 - 1.0]	0.8 [0.6 - 1.1]
Gabapentin	0.7 [0.4 - 1.2]	0.7 [0.4 - 1.2]
Levetiracetam	0.7 [0.4 - 1.1]	0.7 [0.5 - 1.1]
Oxcarbazepine	1.3 [0.7 - 2.4]	1.3 [0.7 - 2.5]
<i>Pregabalin</i>	<i>0.7 [0.5 - 0.9]</i>	<i>0.7 [0.5 - 1.0]</i>
Topiramate	1.2 [0.8 - 1.8]	1.2 [0.8 - 1.8]
<i>Valproic acid</i>	<i>1.5 [1.2 - 1.9]</i>	<i>1.5 [1.2 - 1.9]</i>

Abbreviations: AED = antiepileptic drug; HR = hazard ratio; N/A = not applicable
 Lines marked in bold and italics correspond to HRs for which the 95% CI does not include 1.

^a adjusted for all covariates except proxies for smoking and alcohol

^b adjusted for all covariates except gestational age and birth weight

Supplementary Table 6. Baseline characteristics according to the dose of valproic acid dispensed during pregnancy - main analysis and sensitivity analysis restricted to women considered to be treated for epilepsy

	Lamotrigine - all indications	Lamotrigine - epilepsy	Valproic acid								
			[0-700 mg[[700-1500 mg[≥1500 mg		
			N (%)	N (%)	N (%)	Chi ² ^a	Chi ² ^b	N (%)	Chi ² ^a	Chi ² ^b	N (%)
Number of exposed pregnancies	2,916	2,108	308			520			163		
< 25	431 (14.8)	349 (16.6)	38 (12.3)			83 (16.0)			16 (9.8)		
Maternal age at birth (years)											
[25 - 30[927 (31.8)	715 (33.9)	81 (26.3)	*	**	135 (26.0)	**	***	43 (26.4)	***	***
[30 - 35[980 (33.6)	679 (32.2)	107 (34.7)			160 (30.8)			43 (26.4)		
≥ 35	578 (19.8)	365 (17.3)	82 (26.6)			142 (27.3)			61 (37.4)		
Eligibility for CMU-C	461 (15.8)	340 (16.1)	94 (30.5)	***	***	162 (31.2)	***	***	55 (33.7)	***	***
Hospitalization for epilepsy	N/A	171 (8.1)	5 (1.6)	N/A	***	12 (2.3)	N/A	***	5 (3.1)	N/A	*
History of mental and behavioral disorders	368 (12.6)	150 (7.1)	28 (9.1)	NS	NS	49 (9.4)	*	NS	19 (11.7)	NS	*
Proxy for alcohol intake	35 (1.2)	18 (0.9)	4 (1.3)	NS	NS	12 (2.3)	*	*	6 (3.7)	*	**
Proxy for smoking	311 (10.7)	204 (9.7)	33 (10.7)	NS	NS	69 (13.3)	NS	*	34 (20.9)	***	***
Folic acid supplementation	2,026 (69.5)	1,537 (72.9)	137 (44.5)	***	***	300 (57.7)	***	***	88 (54.0)	***	***
SSRIs during pregnancy	210 (7.2)	55 (2.6)	8 (2.6)	*	NS	15 (2.9)	*	NS	10 (6.1)	NS	*
History of antipsychotic use	227 (7.8)	40 (1.9)	16 (5.2)	NS	**	22 (4.2)	*	*	11 (6.7)	NS	***
0	1,641 (56.3)	1,286 (61.0)	209 (67.9)			351 (67.5)			93 (57.1)		
Number of psychiatric medications ^c											
1	669 (22.9)	522 (24.8)	50 (16.2)			95 (18.3)			35 (21.5)		
2	258 (8.8)	167 (7.9)	26 (8.4)	*	*	28 (5.4)	***	***	13 (8.0)	NS	**
3-4	211 (7.2)	91 (4.3)	14 (4.5)			21 (4.0)			10 (6.1)		
≥ 5	137 (4.7)	42 (2.0)	9 (2.9)			25 (4.8)			12 (7.4)		

Supplementary Table 6. Baseline characteristics according to the dose of valproic acid dispensed during pregnancy - main analysis and sensitivity analysis restricted to women considered to be treated for epilepsy (continued)

		Lamotrigine - all indications	Lamotrigine - epilepsy	Valproic acid								
				[0-700 mg[[700-1500 mg[≥1500 mg			
				N (%)	N (%)	N (%)	Chi ² ^a	Chi ² ^b	N (%)	Chi ² ^a	Chi ² ^b	N (%)
Gestational age (weeks after LMP)	< 32	11 (0.4)	8 (0.4)	1 (0.3)			4 (0.8)			2 (1.2)		
	[32 - 35[42 (1.4)	32 (1.5)	8 (2.6)	NS	NS	8 (1.5)	NS	NS	3 (1.8)	NS	NS
	[35 - 37[129 (4.4)	91 (4.3)	13 (4.2)			23 (4.4)			9 (5.5)		
	≥ 37	2,734 (93.8)	1,977 (93.8)	286 (92.9)			485 (93.3)			149 (91.4)		
Gender (male)		1,524 (52.3)	1,115 (52.9)	161 (52.3)	NS	NS	257 (49.4)	NS	NS	78 (47.9)	NS	NS
Birth weight	< 2,500	179 (6.1)	128 (6.1)	21 (6.8)			48 (9.2)			19 (11.7)		
	[2,500 - 3,000[630 (21.6)	460 (21.8)	71 (23.1)	NS	NS	119 (22.9)	*	*	37 (22.7)	*	*
	[3,000 - 3,500[1,196 (41.0)	872 (41.4)	112 (36.4)			212 (40.8)			65 (39.9)		
	≥ 3,500	911 (31.2)	648 (30.7)	104 (33.8)			141 (27.1)			42 (25.8)		

Abbreviations: AED = antiepileptic drug; Chi² = Chi-squared test; CMU- C = complementary universal health insurance for low-income people; SSRIs = selective serotonin reuptake inhibitors; LMP = last menstrual period; N/A = not applicable

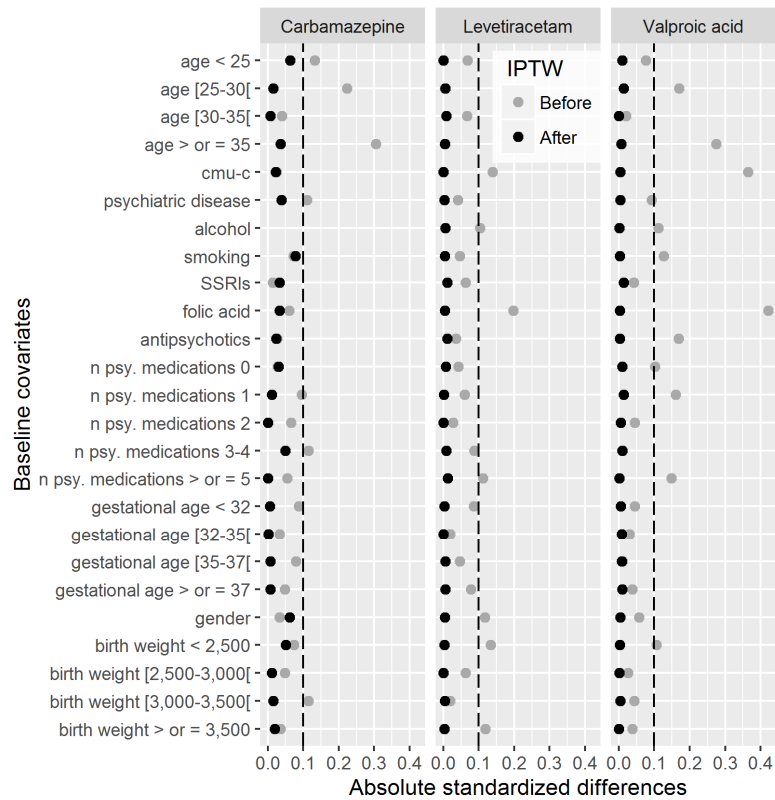
^a compared to women exposed to lamotrigine regardless of indication

^b compared to women exposed to lamotrigine and considered to be treated for epilepsy

^c number of 5th level ATC classes of psychiatric medications to whom mothers were exposed in the year before pregnancy

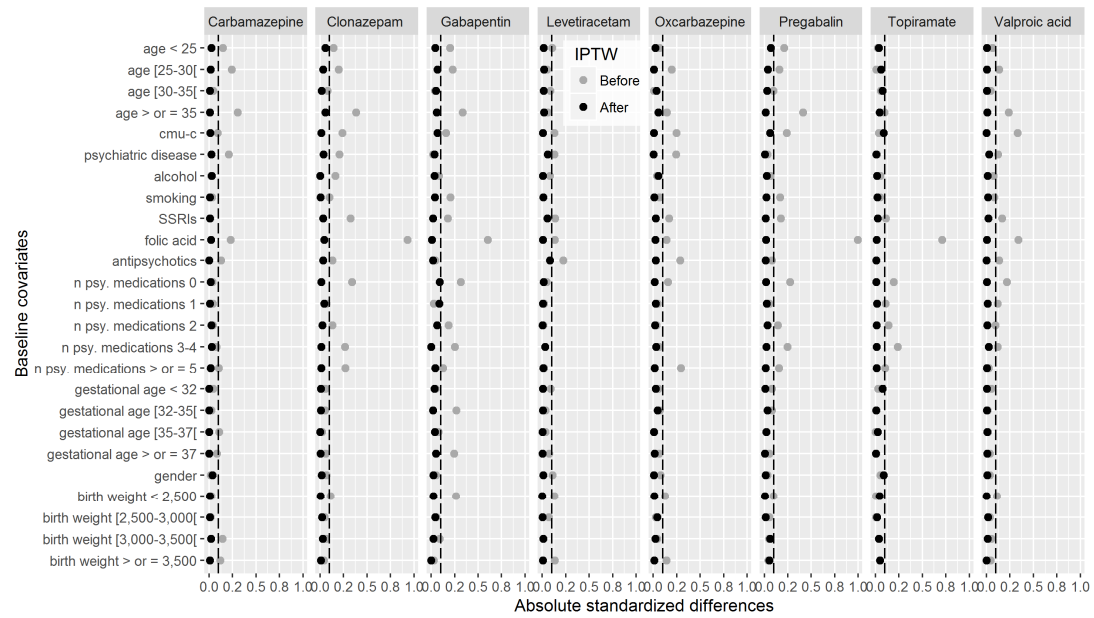
*** p <0.0001; ** p <0.001; * p <0.05; NS: Not Significant

Supplementary Figure 1. Differences in baseline covariates between children exposed to lamotrigine (reference group) and children exposed to the other AEDs studied before (grey dots) and after IPTW (black dots) - women considered to be treated for epilepsy



Abbreviations: AED = antiepileptic drug; IPTW = inverse probability of treatment weighting; cmu-c = complementary universal health insurance; n.psy. medications = number of ATC classes of psychiatric medications

Supplementary Figure 2. Differences in baseline covariates between children exposed to lamotrigine (reference group) and children exposed to the other AEDs studied before (grey dots) and after IPTW (black dots) - exposure limited to dispensing during pregnancy



Abbreviations: AED = antiepileptic drug; IPTW = inverse probability of treatment weighting; cmu-c = complementary universal health insurance; n.psy. medications = number of ATC classes of psychiatric medications