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Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study

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Abstract

Objective: To assess the association between prenatal exposure to monotherapy with the antiepileptic drugs (AEDs) most commonly used during pregnancy and the risk of various neurodevelopmental outcomes compared to lamotrigine.

Methods: This population-based cohort study, based on the French national health care databases, included children born alive between 2011 and 2014 and prenatally exposed to AED monotherapy. Women were considered to be exposed to an AED during the 30 days following each dispensing. The reference group comprised children prenatally exposed to lamotrigine. Outcomes included neurodevelopmental disorders (NDD), defined with ICD-10 codes F70-F98, – pervasive developmental disorders (PDD, F84) and mental retardation (MR, F70-F79) were studied separately – and visits to speech therapists. Children were followed until outcome, loss to follow-up, death or 31 December 2016. We performed inverse probability of treatment weighting analyses using the propensity score, which included maternal and infant characteristics. Hazard ratios (HRs) were calculated using Cox models.

Results: The cohort comprised 9,034 children, 2,916 of which were exposed to lamotrigine, 1,627 to pregabalin, 1,246 to clonazepam, 991 to valproic acid (VPA), 621 to levetiracetam, 502 to carbamazepine, 477 to topiramate, 378 to gabapentin and 143 to oxcarbazepine. None of these AEDs, except VPA, were associated with an increased risk of any of the four neurodevelopmental outcomes investigated. Exposure to VPA was associated with increased risks of NDDs (HR=2.7[1.8-4.0]), PDD (HR=4.4[2.1-9.3]), MR (HR=3.1[1.5-6.2]) and visits to speech therapists (HR=1.5[1.1-1.9]), with a dose-response relationship.

Conclusions: No increased risk of any of the neurodevelopmental outcomes investigated in this study was observed with prenatal exposure to levetiracetam, pregabalin, oxcarbazepine, topiramate, gabapentin, clonazepam or carbamazepine, compared to lamotrigine. However,

this study corroborates the well-known association between maternal use of VPA during pregnancy and the risk of neurodevelopmental disorders in the offspring. Longer follow-up is necessary to confirm these findings.

Keywords: antiepileptic drugs; pregnancy; neurodevelopmental disorders; health care databases; France

Strengths and limitations of this study

This nationwide cohort study based on the French health care databases is the largest study to date to assess the association between AED exposure during pregnancy and neurodevelopmental outcomes in the offspring.

This study investigated a wide range of AEDs, including some drugs for which little or no information is available in the literature.

Although residual confounding by unmeasured covariates cannot be excluded, the choice of lamotrigine as the reference group and the sensitivity analysis restricted to women considered to be treated for epilepsy should mitigate confounding.

The maximum length of follow-up was 6 years, allowing only early diagnoses of neurodevelopmental disorders to be identified.

INTRODUCTION

Antiepileptic drugs (AEDs) are commonly prescribed during pregnancy to treat epilepsy and various other conditions, such as neuropathic pain syndromes, psychiatric disorders and chronic migraine[1]: between 0.4 and 0.7% of women are exposed to AEDs during pregnancy in Europe,[2,3] while this prevalence is as high as 2% in the US.[4]

Some of these AEDs are known to be teratogens.[5] Of all AEDs, prenatal exposure to valproic acid has been most clearly associated with poor neurodevelopmental outcomes,[6] which led the US Food and Drug Administration to issue a warning in 2011[7] and stringent guidance in 2013 for clinicians prescribing valproic acid to pregnant women or women of childbearing potential.[8] The European Medicines Agency also strengthened warnings on the use of valproate-containing medicines in women and girls in 2014[9] and issued a ban in 2018 on the use of such medicines during pregnancy for migraine or bipolar disorder, and for epilepsy except when no other effective treatment is available.[10]

Lamotrigine has generally been associated with favorable neurodevelopmental outcomes.[6] Discordant but mainly reassuring data have been published for carbamazepine, while evidence for levetiracetam and topiramate remains limited and almost no information is available concerning the other AEDs, particularly clonazepam, oxcarbazepine, gabapentin and pregabalin.[6] Furthermore, most of the studies conducted to date have been based on small sample sizes and may be prone to selection bias.

We therefore conducted a large-scale nationwide cohort study using the French health care databases to assess various early neurodevelopmental outcomes among children prenatally exposed to monotherapy with individual AEDs compared to lamotrigine-exposed children.

METHODS

Study design and data sources

The French national health insurance database (SNIIRAM) and the French hospital discharge database (PMSI) linked by a unique patient identifier were used to conduct this nationwide population-based cohort study.[11]

The DCIR database contains all individualized and anonymous health care claims reimbursed by French National Health Insurance, in particular all dispensed drugs and medical procedures in the outpatient setting. The DCIR database also collects patient data such as age, gender, vital status and eligibility for complementary universal health insurance (CMU-C), which provides free access to health care for low-income people.[12] Eligibility for 100% health insurance coverage for serious and costly long-term diseases (LTD) is also recorded in the DCIR database.

The PMSI database provides detailed medical information on all admissions to public and private hospitals in France, including primary, related and associated discharge diagnoses, medical procedures and data related to pregnancy such as gestational ages and birth weights.

Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification and medical procedures are coded according to the French medical classification of clinical procedures (CCAM). LTD and hospital discharge diagnoses are coded according to the International Classification of Diseases, 10th Revision (ICD-10).

This linkage has previously been used to conduct epidemiological studies in pregnancy research.[3,13–15]

Study population

All live births between January 2011 and December 2014 were eligible for inclusion. These live births were identified by using a published algorithm based on discharge diagnoses and medical procedures indicative of completion of pregnancy.[3]

The mother had to be enrolled in the national health insurance general scheme (75% of the French population), during the penultimate year before pregnancy. Pregnancies that could not be linked to neonatal data and twin pregnancies were excluded, as well as pregnancies for which the child had no valid identifier allowing follow-up and pregnancies for which gestational ages or birth weights were not available. Children with a hospital discharge diagnosis of brain malformation documented at birth were also excluded (see supplementary Table 1 for ICD-10 codes). For each woman, only the first birth occurring during the study period was considered.

Finally, only pregnancies exposed to AED monotherapy were included in the study population.

These exclusion criteria are reported in the study population flowchart (Figure 1).

Patient and Public Involvement

Patients or the public were not involved in the design and the conduct of the study.

Exposure

All AEDs were studied (supplementary Table 2). Women were considered to be exposed during the 30 days following dispensing of an AED, as AED prescriptions are dispensed with a 30-day supply in France. Women were therefore exposed during pregnancy when an AED had been dispensed between 30 days before the beginning of pregnancy and the end of

pregnancy. Monotherapy was defined as the absence of any other AED dispensed during the same period. Results related to AEDs rarely used as monotherapy during pregnancy (< 100 exposed pregnancies) were not reported. The reference group included pregnant women exposed to lamotrigine monotherapy for the following reason: active-comparator designs minimize confounding by indication compared to the use of an unexposed control group[16] ; lamotrigine is the most commonly used AED in France for the treatment of epilepsy ; prenatal exposure to lamotrigine has been mostly shown to be associated with favorable neurodevelopmental outcomes ; comparing all individual AEDs to lamotrigine addresses a clinically relevant question: which is the safest AED?

Mean daily doses were calculated by dividing cumulative doses by the number of days covered. Cumulative doses were assessed by equally distributing the dose of AED dispensed over the 30 days following dispensing and then by adding these daily doses overlapping with the pregnancy period. The number of days covered was defined as the sum of the 30-day periods of exposure corresponding to each refill minus the number of days of overlap between two consecutive refills. Only the days overlapping with the pregnancy period were taken into account.

Outcomes

Four outcomes were considered, based on the literature but also on their availability in the French health care databases. The primary outcomes were hospitalization or LTD for neurodevelopmental disorders (ICD-10 diagnosis codes F70 to F98), but also for two specific subcategories: pervasive developmental disorders (F84) and mental retardation (F70-F79). The secondary outcome was “visits to a speech therapist”, as a proxy for communication-related disorders.

Follow-up

Children were followed from birth until any of the predefined outcomes, loss to follow-up (more than one year with no reimbursement), death from any cause or end of the study period defined as the 31st December 2016, whichever came first.

Covariates

Potential confounders related to the mother and considered in this study included sociodemographic covariates (maternal age at birth and eligibility for CMU-C), as well as comedications and comorbidities. Comedications included (1) pre-conception folic acid supplementation, defined as at least one dispensing between one month before pregnancy and 3 months after the start of pregnancy, (2) exposure to selective serotonin reuptake inhibitors (SSRIs) during pregnancy, (3) exposure to antipsychotics in the year before pregnancy, (4) a proxy for severity of mental disorders (the number of 5th level ATC classes of psychiatric medications dispensed in the year before pregnancy). History of mental and behavioral disorders not related to alcohol or smoking, which was identified by using hospital discharge and LTD diagnoses, was also considered to be potential confounder. Alcohol intake and smoking were not directly available in the databases and proxies were calculated using modified versions of previously published algorithms.[17] These proxies were constructed on the basis of hospital discharge diagnoses, LTD diagnoses and the child's hospital discharge diagnoses at birth. We also used specific drug reimbursements for alcohol intake and nicotine replacement therapy reimbursements for smoking. Potential confounders related to the child and considered in this study were gender, gestational age and birth weight.

All drugs and ICD-10 codes related to hospital discharge and LTD diagnoses used to define covariates are presented in supplementary Table 1.

Statistical analyses

Baseline covariates were compared between pregnancies exposed to each AED studied and lamotrigine-exposed pregnancies using $\chi 2$ tests. Number of events, crude event rates and crude incidence rate ratios (IRRs) were calculated. Potential confounders were controlled for by performing inverse probability of treatment weighting (IPTW) analyses using the propensity score. These analyses were conducted separately according to the type of AED. Propensity scores were determined by using logistic regression models including the covariates listed above, with maternal age as a categorical variable ($\leq$ 25 years, [25 - 30[, [30 - 35[and $\geq$ 35). Weights were trimmed at the 0.1 and 99.9 percentiles. Absolute standardized differences were calculated to assess the balance in baseline covariates before and after weighting. Groups were considered to be balanced when standardized differences were less than 0.1.[18] Cox models with robust sandwich estimates were used to calculate hazard ratios (HR) and their 95% confidence intervals.

As AEDs can be prescribed for a wide range of medical conditions other than epilepsy, a first sensitivity analysis in which the study population was restricted to women considered to be treated for epilepsy (see supplementary Table 1 for definition) was conducted. In this sensitivity analysis, HRs were further adjusted for hospitalization (primary and related diagnoses only) for epilepsy during pregnancy. A second sensitivity analysis, requiring at least one dispensing during pregnancy to consider a woman to be exposed, was also conducted to account for possible misclassification of exposure at the beginning of pregnancy. In a third sensitivity analysis, two other propensity scores were calculated: one excluding proxies for alcohol intake and smoking and another one excluding gestational age and birth weight.

Data extraction and statistical analysis were performed by using SAS Enterprise Guide 4.3 software (SAS Institute, Inc., Cary, NC). Graphics were performed by using R 3.5 statistical software.

RESULTS

Main analysis

From a total of 1,721,990 births satisfying all inclusion and exclusion criteria, 9,034 children were prenatally exposed to AED monotherapy (Figure 1), 32 (0.4%) of whom were censored at death and 1,224 (13.5%) were lost to follow-up. The median follow-up was 3.7 years (interquartile range, 2.7-4.7 years). Of these 9,034 children, 2,916 were exposed to lamotrigine, 1,627 were exposed to pregabalin, 1,246 were exposed to clonazepam, 991 were exposed to valproic acid, 621 were exposed to levetiracetam, 502 were exposed to carbamazepine, 477 were exposed to topiramate, 378 were exposed to gabapentin and 143 were exposed to oxcarbazepine (Table 1). A total of 133 children were exposed to another AED monotherapy, including phenobarbital (N=84), phenytoin (N=13), lacosamide (N=9), zonisamide (N=8), ethosuximide (N=7) and vigabatrin (N=6). The median follow-up ranged from 3.3 to 4.0 years across all AEDs except clonazepam (4.8 years).

Table 1 also reports baseline patient characteristics according to the type of AED prior to IPTW, showing some significant differences between the various AEDs studied and lamotrigine. Before weighting, across all variables included in the propensity score and all AEDs studied, the absolute standardized differences ranged from 0.00 to 0.94. After weighting, all standardized differences were less than 0.1, indicating a good balance between treatment groups (Figure 2).

Table 2 presents the number of events, crude event rates, IRRs and adjusted HRs for the four outcomes and each of the AEDs studied. Compared to prenatal exposure to lamotrigine, prenatal exposures to all of the AEDs studied, excluding valproic acid, were not found to be associated with an increased risk of any of the four outcomes investigated. By contrast,

valproic acid was associated with an increased risk of visits to a speech therapist (HR=1.5[1.1-1.9]) and neurodevelopmental disorders (HR=2.7[1.8-4.0]), particularly pervasive developmental disorders (HR=4.4[2.1-9.3]) and mental retardation (HR=3.1[1.5-6.2]).

Sensitivity analyses

In the first sensitivity analysis restricting the study population to women considered to be treated for epilepsy, only results related to carbamazepine, levetiracetam and valproic acid are reported. The number of women considered to be treated for epilepsy and exposed to monotherapy with each of the other AEDs was less than 100. Baseline patient characteristics and absolute standardized differences are available in supplementary Table 3 and supplementary Figure 1, respectively. Prenatal exposure to levetiracetam was not found to be associated with any of the four outcomes investigated and prenatal exposure to valproic acid was associated with all four outcomes, which is in line with the results of the main analysis. Results were different from the main analysis for the association between carbamazepine and the risk of visits to a speech therapist (HR=0.2[0.1-0.7]) (Table 3).

The results of the second (see supplementary Figure 2 for standardized differences) and third sensitivity analyses were comparable to those of the main analysis (see supplementary Table 4 and supplementary Table 5, respectively).

Dose

Baseline patient characteristics according to the dose of valproic acid dispensed during pregnancy are reported in supplementary Table 6. A dose-response relationship was observed for the association between prenatal exposure to valproic acid and the risks of visits to a speech therapist (< 700 mg: HR=0.6[0.3-1.0], [700-1500 mg[: HR=1.6[1.2-2.1], ≥ 1500 mg: HR=2.6[1.7-4.0]) and neurodevelopmental disorders (< 700 mg: HR=1.3[0.6-2.8], [700-1500

mg[: HR=2.1[1.3-3.5], ≥ 1500 mg: HR=7.0[4.3-11.5]), including pervasive developmental disorders (< 700 mg: HR=2.2[0.5-8.5], [700-1500 mg[: HR=2.7[1.0-7.1], ≥ 1500 mg: HR=14.7[6.2-34.7]). The highest HR of mental retardation was also observed for the highest mean daily dose (≥ 1500 mg: HR=7.3[3.0-17.7]). Comparable results were observed when the study population was limited to women considered to be treated for epilepsy (Table 4).

DISCUSSION

Main Findings

In this nationwide observational study based on the French health care databases, prenatal exposures to levetiracetam, pregabalin, oxcarbazepine, topiramate, gabapentin, clonazepam and carbamazepine were not associated with an increased risk of any of the early neurodevelopmental outcomes investigated compared to lamotrigine. The decreased risk of visits to a speech therapist observed with carbamazepine when the population was restricted to women with epilepsy may be a chance finding. This association is based on only 4 children and has never been observed in psychometric studies with detailed language assessments. Prenatal exposure to valproic acid was found to be associated with increased risks of all neurodevelopmental outcomes investigated compared to lamotrigine, ranging from pervasive mental disorders to possible communication-related disorders. A dose-response relationship was observed for most of these outcomes.

Comparison with Previous Studies

Prenatal exposure to lamotrigine has been mostly shown not to be associated with poorer neurodevelopmental outcomes, although limited data are available, with no dose-response relationship.[6] Only three studies have shown that prenatal exposure to lamotrigine was

associated with impaired specific cognitive skills[19,20] and parental concerns about autistic traits and sentence skills.[21]

The results of the present study concerning valproic acid, carbamazepine, levetiracetam and topiramate are consistent with those of previous studies. Prenatal exposure to valproic acid has been associated with poorer cognitive outcomes[19,22–24] and particularly poorer executive functions and memory abilities[23] compared to lamotrigine. Children prenatally exposed to valproic acid also show impaired adaptive behavior[25,26] and school performance[27] compared to lamotrigine-exposed children. Impaired language skills[28] and autism spectrum disorder have been reported to be more frequent among children exposed to valproic acid than among unexposed children.[29,30] A dose-response relationship has also been observed for most of these outcomes.[19,22,23,25,26,28]

Few studies have directly compared prenatal exposure to carbamazepine *versus* lamotrigine and these studies did not find any differences in terms of cognitive development[19,31] and adaptive behavior.[26] Data concerning levetiracetam and topiramate are more limited and no direct comparison with lamotrigine has been published. No increased risk of neurodevelopmental outcomes was found among levetiracetam-exposed children compared to unexposed children[32–34] and, although prenatal exposure to topiramate was associated with poorer neurodevelopmental outcomes in one study,[35] this association was not confirmed by a larger study.[33] Little or no information is available concerning the other AEDs, particularly clonazepam, oxcarbazepine, gabapentin and pregabalin.[29,33,36]

Strengths

This nationwide cohort study based on the French health care database is the largest study to date to assess the association between AED exposure during pregnancy and neurodevelopmental outcomes in the offspring. This study investigated a wide range of

AEDs, including some drugs for which little or no information is available in the literature. The strengths of this study also include the use of propensity score methods to mitigate confounding, as well as the advantages of the French health care databases, such as the independence between ascertainment of medication and outcomes, the absence of recall bias, and the possibility to study the dose-response relationship, which is a key concept in terms of teratogenicity.[33]

Limitations

Exposure misclassification constitutes a first limitation. Exposure assessment was based on pharmacy claims, which do not indicate whether the medication is actually taken. Exposure misclassification is more likely for AED classes that are often discontinued before conception.[37] However, the results of the sensitivity analysis regarding exposure measurement suggest that this bias is likely minimal.

Although we used an active-comparator design, residual confounding by unmeasured or insufficiently well measured covariates cannot be excluded. For instance, maternal education and IQ were not available in the databases. Data related to the father could not be linked to the child, not allowing any adjustment for paternal characteristics. Lifestyle factors such as alcohol intake and smoking could also not be exhaustively assessed.

As some AEDs can be prescribed to treat conditions other than epilepsy, the analyses were replicated in a population restricted to women considered to be treated for epilepsy, providing comparable results to those of the main analysis. However, the indication for which an AED is prescribed was not directly available in the databases. We therefore used LTD diagnoses, hospital diagnoses and specific drug reimbursements to identify women with epilepsy. Some studies,[34,38,39] unlike other studies,[19,22–24] have also reported an association between the severity of maternal epilepsy, particularly seizure type and frequency, and poorer

developmental outcomes in the child. As this confounder was not available in the databases, we considered at least one admission to hospital for epilepsy during pregnancy to be a proxy for epilepsy severity. Similar results were observed whether or not this proxy was included in the propensity score.

Outcome misclassification also cannot be ruled out, as the diagnosis codes used to identify neurodevelopmental outcomes have not been externally validated. However, the PMSI database is used for planning and funding purposes and is subject to coding quality control, and LTD registration, which is requested by the patient's general practitioner, must be validated by a medical consultant of the beneficiary's health insurance scheme. In addition, as hospital discharge and LTD diagnoses were used to define outcomes, children not reaching diagnostic thresholds but still having some evidence of impairment were not considered to have experienced the outcomes of interest.[40] Moreover, some of the outcomes studied may not have been exhaustively assessed, as data related to a large share of medical and social welfare services are not available in the French health care databases. Results related to visits to a speech therapist must also be interpreted with caution, as a visit to a speech therapist does not necessarily imply pathology. Speech therapists can also be consulted for various medical reasons, and access to speech therapists is associated with socioeconomic status.[41] Further, because the study outcomes were limited to three subtypes of neurodevelopmental disorders (pervasive developmental disorders, mental retardation and visits to a speech therapist as a proxy for communication-related disorders), no conclusion can be drawn concerning all of the other subtypes of neurodevelopmental disorders.

The short follow-up period constitutes another limitation: the median and maximum lengths of follow-up were 3.7 and 6 years, respectively. In particular, a diagnosis of autism spectrum disorders is considered to be stable at age 2[42] and is made at an average age of 3 years and 5 months in France,[43] but speech therapy is more frequent among school-aged children.

Therefore, only early diagnoses, probably corresponding to more severe disorders, were identified. This is especially true for mental retardation: although severe and profound mental retardation can be diagnosed before 3 years old, moderate mental retardation cannot be diagnosed before 4 or 5 years old.[44] Further assessment of children at older developmental stages would be useful to study a broader range of neurodevelopmental disorders. Except clonazepam for which French health authorities took measures to limit off-label use in November 2011,[45] lengths of follow-up were quite comparable across all AEDs. Children exposed to second-generation AEDs had only slightly shorter follow-ups than children exposed to first-generation AEDs, which should not have influenced the results of this study.

CONCLUSION

Despite the limitations inherent to health care claims databases, this study, based on 9,034 exposed children, confirms that valproic acid is associated with an increased risk of various neurodevelopmental outcomes compared to lamotrigine, with a dose-response relationship, while no association was observed for the other AEDs including carbamazepine, levetiracetam or topiramate. However, this study needs to be replicated with a longer follow-up period.

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Data sharing statement: Permanent access to the French health care databases is automatically granted to certain government agencies, public institutions and public service authorities. Temporary access for studies and research is possible upon request from the national health data institute (INDS).

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Table 1. Baseline characteristics according to AED use during pregnancy

		Lamotrigine		Carbamazepine		Clonazepam		Gabapentin		Levetiracetam	
Number of exposed pregnancies		2,916		502		1,246		378		621	
Median follow-up (years) (IQR)		3.5 (2.7-4.5)		3.8 (2.8-4.7)		4.8 (4.1-5.3)		3.4 (2.5-4.3)		3.4 (2.6-4.4)	
Maternal age at birth (years)	< 25	431 (14.8)		51 (10.2)		118 (9.5)		32 (8.5)		119 (19.2)	
	[25 - 30[	927 (31.8)		119 (23.7)		302 (24.2)		90 (23.8)		212 (34.1)	
	[30 - 35[	980 (33.6)		168 (33.5)		380 (30.5)		125 (33.1)		181 (29.1)	
	≥ 35	578 (19.8)		164 (32.7)		446 (35.8)		131 (34.7)		109 (17.6)	
			***		***		***		***		*
Eligibility for CMU-C		461 (15.8)		98 (19.5)	*	303 (24.3)	***	82 (21.7)	*	134 (21.6)	**
History of mental and behavioral disorders		368 (12.6)		104 (20.7)	***	216 (17.3)	***	43 (11.4)	NS	51 (8.2)	*
Proxy for alcohol intake		35 (1.2)		7 (1.4)	NS	35 (2.8)	**	6 (1.6)	NS	13 (2.1)	NS
Proxy for smoking		311 (10.7)		59 (11.8)	NS	165 (13.2)	*	66 (17.5)	***	69 (11.1)	NS
Folic acid supplementation		2,026 (69.5)		281 (56.0)	***	360 (28.9)	***	139 (36.8)	***	396 (63.8)	*
SSRIs during pregnancy		210 (7.2)		42 (8.4)	NS	201 (16.1)	***	42 (11.1)	*	23 (3.7)	*
History of antipsychotic use		227 (7.8)		64 (12.7)	**	123 (9.9)	*	24 (6.3)	NS	15 (2.4)	***
Number of psychiatric medications[a]	0	1,641 (56.3)		265 (52.8)		492 (39.5)		157 (41.5)		366 (58.9)	
	1	669 (22.9)		107 (21.3)		283 (22.7)		91 (24.1)		138 (22.2)	
	2	258 (8.8)		42 (8.4)		149 (12.0)		49 (13.0)		54 (8.7)	
	3-4	211 (7.2)		52 (10.4)		183 (14.7)		54 (14.3)		39 (6.3)	
	≥ 5	137 (4.7)		36 (7.2)		139 (11.2)		27 (7.1)		24 (3.9)	
					*		***		***		NS
Gestational age (weeks after LMP)	< 32	11 (0.4)		3 (0.6)		10 (0.8)		2 (0.5)		7 (1.1)	
	[32 - 35[	42 (1.4)		8 (1.6)		28 (2.2)		23 (6.1)		11 (1.8)	
	[35 - 37[	129 (4.4)		14 (2.8)		55 (4.4)		21 (5.6)		33 (5.3)	
	≥ 37	2,734 (93.8)		477 (95.0)		1,153 (92.5)		332 (87.8)		570 (91.8)	
			NS		NS		***		NS		NS
Gender (male)		1,524 (52.3)		265 (52.8)	NS	597 (47.9)	*	206 (54.5)	NS	292 (47.0)	*
Birth weight	< 2,500	179 (6.1)		35 (7.0)		105 (8.4)		47 (12.4)		60 (9.7)	
	[2,500 - 3,000[	630 (21.6)		110 (21.9)		278 (22.3)		73 (19.3)		152 (24.5)	
	[3,000 - 3,500[	1,196 (41.0)		182 (36.3)		485 (38.9)		140 (37.0)		251 (40.4)	
	≥ 3,500	911 (31.2)		175 (34.9)		378 (30.3)		118 (31.2)		158 (25.4)	
			NS		*		***		**		

Table 1. Baseline characteristics according to AED use during pregnancy (continued)

		Oxcarbazepine		Pregabalin		Topiramate		Valproic acid	
Number of exposed pregnancies		143		1,627		477		991	
Median follow-up (years) (IQR)		4.0 (2.7-4.8)		3.3 (2.5-4.3)		3.6 (2.6-4.6)		3.9 (2.8-4.8)	
Maternal age at birth (years)	< 25	23 (16.1)	NS	139 (8.5)	***	66 (13.8)	NS	137 (13.8)	***
	[25 - 30[	32 (22.4)		414 (25.4)		144 (30.2)		259 (26.1)	
	[30 - 35[	52 (36.4)		495 (30.4)		153 (32.1)		310 (31.3)	
	≥ 35	36 (25.2)		579 (35.6)		114 (23.9)		285 (28.8)	
Eligibility for CMU-C		36 (25.2)	*	404 (24.8)	***	79 (16.6)	NS	311 (31.4)	***
History of mental and behavioral disorders		36 (25.2)	***	169 (10.4)	*	54 (11.3)	NS	96 (9.7)	*
Proxy for alcohol intake		1 (0.7)	NS	21 (1.3)	NS	7 (1.5)	NS	22 (2.2)	*
Proxy for smoking		13 (9.1)	NS	257 (15.8)	***	43 (9.0)	NS	136 (13.7)	*
Folic acid supplementation		89 (62.2)	NS	440 (27.0)	***	179 (37.5)	***	525 (53.0)	***
SSRIs during pregnancy		22 (15.4)	**	172 (10.6)	***	55 (11.5)	*	33 (3.3)	***
History of antipsychotic use		31 (21.7)	***	79 (4.9)	**	30 (6.3)	NS	49 (4.9)	*
Number of psychiatric medications[a]	0	65 (45.5)	***	701 (43.1)	***	217 (45.5)	***	653 (65.9)	***
	1	33 (23.1)		355 (21.8)		92 (19.3)		180 (18.2)	
	2	14 (9.8)		227 (14.0)		69 (14.5)		67 (6.8)	
	3-4	9 (6.3)		216 (13.3)		68 (14.3)		45 (4.5)	
	≥ 5	22 (15.4)		128 (7.9)		31 (6.5)		46 (4.6)	
Gestational age (weeks after LMP)	< 32	1 (0.7)	NS	12 (0.7)	*	7 (1.5)	*	7 (0.7)	NS
	[32 - 35[	3 (2.1)		37 (2.3)		10 (2.1)		19 (1.9)	
	[35 - 37[	6 (4.2)		61 (3.7)		19 (4.0)		45 (4.5)	
	≥ 37	133 (93.0)		1,517 (93.2)		441 (92.5)		920 (92.8)	
Gender (male)		65 (45.5)	NS	847 (52.1)	NS	254 (53.2)	NS	496 (50.1)	NS
Birth weight	< 2,500	12 (8.4)	NS	118 (7.3)	NS	32 (6.7)	NS	88 (8.9)	*
	[2,500 - 3,000[	30 (21.0)		324 (19.9)		90 (18.9)		227 (22.9)	

	[3,000 - 3,500[	60 (42.0)		630 (38.7)		203 (42.6)		389 (39.3)	
	≥ 3,500	41 (28.7)		555 (34.1)		152 (31.9)		287 (29.0)	

Abbreviations: AED = antiepileptic drug; IQR = interquartile range; 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

Table 2. Number of events, crude event rates (per 1,000), crude IRRs and adjusted HRs for the four outcomes and each of the AEDs studied - main analysis

	Events	Crude event rates	IRR	HR [95% CI]
Neurodevelopmental disorders				
Lamotrigine	51	4.9		
Carbamazepine	13	7.0	1.4 [0.8 - 2.6]	1.2 [0.6 - 2.2]
Clonazepam	28	5.1	1.0 [0.6 - 1.6]	0.6 [0.4 - 1.1]
Gabapentin	4	3.1	0.6 [0.2 - 1.7]	0.4 [0.1 - 1.3]
Levetiracetam	8	3.7	0.8 [0.4 - 1.6]	0.7 [0.3 - 1.5]
Oxcarbazepine	3	5.6	1.1 [0.4 - 3.7]	0.8 [0.2 - 3.2]
Pregabalin	28	5.0	1.0 [0.6 - 1.6]	0.6 [0.4 - 1.0]
Topiramate	7	4.1	0.8 [0.4 - 1.8]	0.8 [0.4 - 1.9]
Valproic acid	**50**	**13.5**	**2.7 [1.9 - 4.0]**	**2.7 [1.8 - 4.0]**
Pervasive developmental disorders				
Lamotrigine	11	1.1		
Carbamazepine	3	1.6	1.5 [0.4 - 5.4]	1.3 [0.3 - 5.0]
Clonazepam	8	1.4	1.4 [0.5 - 3.4]	0.8 [0.3 - 2.1]
Gabapentin	3	2.3	2.2 [0.6 - 7.9]	1.8 [0.4 - 7.0]
Levetiracetam	4	1.8	1.8 [0.6 - 5.5]	1.6 [0.5 - 5.4]
Oxcarbazepine	1	1.9	1.8 [0.2 - 13.6]	2.0 [0.3 - 13.8]
Pregabalin	7	1.2	1.2 [0.5 - 3.1]	1.1 [0.4 - 3.0]
Topiramate	1	0.6	0.6 [0.1 - 4.3]	0.3 [0.0 - 4.9]
Valproic acid	**17**	**4.5**	**4.3 [2.0 - 9.1]**	**4.4 [2.1 - 9.3]**
Mental retardation				
Lamotrigine	15	1.4		
Carbamazepine	2	1.1	0.7 [0.2 - 3.2]	0.6 [0.1 - 2.9]
Clonazepam	3	0.5	0.4 [0.1 - 1.3]	0.3 [0.1 - 1.2]
Gabapentin	0	0.0	N/A	N/A
Levetiracetam	1	0.5	0.3 [0.0 - 2.4]	0.3 [0.0 - 2.5]
Oxcarbazepine	0	0.0	N/A	N/A
Pregabalin	7	1.2	0.9 [0.4 - 2.1]	0.6 [0.2 - 1.8]
Topiramate	2	1.2	0.8 [0.2 - 3.5]	0.5 [0.1 - 3.3]
Valproic acid	**15**	**4.0**	**2.8 [1.3 - 5.6]**	**3.1 [1.5 - 6.2]**
Visits to a speech therapist				
Lamotrigine	157	15.2		
Carbamazepine	31	16.7	1.1 [0.8 - 1.6]	0.9 [0.6 - 1.4]
Clonazepam	97	17.7	1.2 [0.9 - 1.5]	0.8 [0.6 - 1.0]
Gabapentin	11	8.5	0.6 [0.3 - 1.0]	0.7 [0.4 - 1.2]
Levetiracetam	22	10.2	0.7 [0.4 - 1.1]	0.7 [0.5 - 1.1]
Oxcarbazepine	13	24.6	1.6 [0.9 - 2.9]	1.3 [0.7 - 2.5]
Pregabalin	**61**	**11.0**	**0.7 [0.5 - 1.0]**	**0.7 [0.5 - 1.0]**
Topiramate	33	19.4	1.3 [0.9 - 1.9]	1.2 [0.8 - 1.8]
Valproic acid	**93**	**25.1**	**1.7 [1.3 - 2.1]**	**1.5 [1.1 - 1.9]**

Abbreviations: AED = antiepileptic drug; IRR = incidence rate ratio; HR = hazard ratio; N/A = not applicable

Lines marked in bold correspond to HRs for which the 95% CI does not include 1.

Table 3. Number of events, crude event rates (per 1,000), crude IRRs and adjusted HRs for the four outcomes and each of the AEDs studied - study population limited to women considered to be treated for epilepsy

	Events	Crude event rates	IRR	HR[a] [95% CI]	HR[b] [95% CI]
Neurodevelopmental disorders					
Lamotrigine	32	4.2			
Carbamazepine[c]	1	1.5	0.4 [0.0 - 2.7]	0.2 [0.0 - 2.7]	0.2 [0.0 - 2.7]
Levetiracetam	8	3.7	0.9 [0.4 - 1.9]	0.8 [0.4 - 1.8]	0.8 [0.4 - 1.8]
Valproic acid	**50**	**13.5**	**3.2 [2.0 - 5.0]**	**3.2 [2.0 - 4.9]**	**3.5 [2.3 - 5.4]**
Pervasive developmental disorders					
Lamotrigine	7	0.9			
Carbamazepine[c]	0	0.0	N/A	N/A	N/A
Levetiracetam	4	1.8	2.0 [0.6 - 6.8]	1.8 [0.5 - 6.6]	1.8 [0.5 - 6.6]
Valproic acid	**17**	**4.5**	**4.9 [2.0 - 11.8]**	**4.9 [2.0 - 11.8]**	**4.7 [1.9 - 11.4]**
Mental retardation					
Lamotrigine	10	1.3			
Carbamazepine[c]	0	0.0	N/A	N/A	N/A
Levetiracetam	1	0.5	0.3 [0.0 - 2.7]	0.4 [0.1 - 2.9]	0.4 [0.1 - 2.9]
Valproic acid	**15**	**4.0**	**3.0 [1.4 - 6.7]**	**3.1 [1.4 - 7.0]**	**4.0 [1.9 - 8.6]**
Visits to a speech therapist					
Lamotrigine	122	16.2			
Carbamazepine[c]	**4**	**6.1**	**0.4 [0.1 - 1.0]**	**0.2 [0.1 - 0.7]**	**0.2 [0.1 - 0.7]**
Levetiracetam	22	10.2	0.6 [0.4 - 1.0]	0.7 [0.4 - 1.1]	0.7 [0.4 - 1.1]
Valproic acid	**93**	**25.1**	**1.6 [1.2 - 2.0]**	**1.4 [1.1 - 1.8]**	**1.5 [1.1 - 1.9]**

Abbreviations: AED = antiepileptic drug; IRR = incidence rate ratio; HR = hazard ratio; N/A = not applicable

Lines marked in bold correspond to HRs for which the 95% CI does not include 1.

[a] adjusted for all covariates except hospitalization for epilepsy during pregnancy

[b] adjusted for all covariates including hospitalization for epilepsy during pregnancy

[c] no possible adjustment for the proxy for alcohol

Table 4. Number of events, crude event rates (per 1,000), crude IRRs and adjusted HRs for the four outcomes according to the dose of valproic acid dispensed during pregnancy - main analysis and sensitivity analysis restricted to women considered to be treated for epilepsy

				Main analysis		Women with epilepsy		
		Events	Crude event rates	IRR	HR[a] [95% CI]	IRR	HR[a] [95% CI]	HR[b] [95% CI]
Neuro-developmental disorders	< 700 mg	7	6.3	1.3 [0.6 - 2.8]	1.3 [0.6 - 2.8]	1.5 [0.7 - 3.4]	1.6 [0.7 - 3.6]	1.6 [0.7 - 3.6]
	[700-1500 mg[	23	11.5	2.3 [1.4 - 3.8]	2.1 [1.3 - 3.5]	2.7 [1.6 - 4.6]	2.5 [1.5 - 4.3]	2.7 [1.6 - 4.6]
	≥ 1500 mg	20	33.5	6.8 [4.1 - 11.5]	7.0 [4.3 - 11.5]	7.9 [4.5 - 13.8]	8.6 [5.1 - 14.5]	8.7 [5.2 - 14.6]
Pervasive developmental disorders	< 700 mg	2	1.8	1.7 [0.4 - 7.6]	2.2 [0.5 - 8.5]	1.9 [0.4 - 9.3]	2.9 [0.7 - 11.6]	2.7 [0.7 - 11.4]
	[700-1500 mg[	7	3.4	3.3 [1.3 - 8.4]	2.7 [1.0 - 7.1]	3.7 [1.3 - 10.7]	3.1 [1.1 - 9.0]	3.0 [1.0 - 8.9]
	≥ 1500 mg	8	12.8	12.2 [4.9 - 30.4]	14.7 [6.2 - 34.7]	14.0 [5.1 - 38.5]	17.0 [6.5 - 44.6]	15.4 [5.7 - 41.1]
Mental retardation	< 700 mg	5	4.4	3.1 [1.1 - 8.5]	1.5 [0.4 - 5.9]	3.4 [1.2 - 9.9]	1.8 [0.4 - 7.0]	1.6 [0.4 - 6.7]
	[700-1500 mg[	5	2.5	1.7 [0.6 - 4.7]	1.8 [0.7 - 4.9]	1.9 [0.6 - 5.5]	1.9 [0.7 - 5.7]	2.6 [1.0 - 6.7]
	≥ 1500 mg	5	7.9	5.5 [2.0 - 15.2]	7.3 [3.0 - 17.7]	6.0 [2.1 - 17.6]	7.1 [2.7 - 18.7]	8.4 [3.4 - 20.4]
Visits to a speech therapist	< 700 mg	13	11.6	0.8 [0.4 - 1.3]	0.6 [0.3 - 1.0]	0.7 [0.4 - 1.3]	0.6 [0.3 - 1.0]	0.5 [0.3 - 0.9]
	[700-1500 mg[	54	27.3	1.8 [1.3 - 2.5]	1.6 [1.2 - 2.1]	1.7 [1.2 - 2.3]	1.5 [1.1 - 2.0]	1.5 [1.1 - 2.1]
	≥ 1500 mg	26	43.4	2.9 [1.9 - 4.3]	2.6 [1.7 - 4.0]	2.7 [1.8 - 4.1]	2.6 [1.7 - 4.0]	2.7 [1.8 - 4.1]

Abbreviations: IRR = incidence rate ratio; HR = hazard ratio

[a] adjusted for all covariates except hospitalization for epilepsy during pregnancy

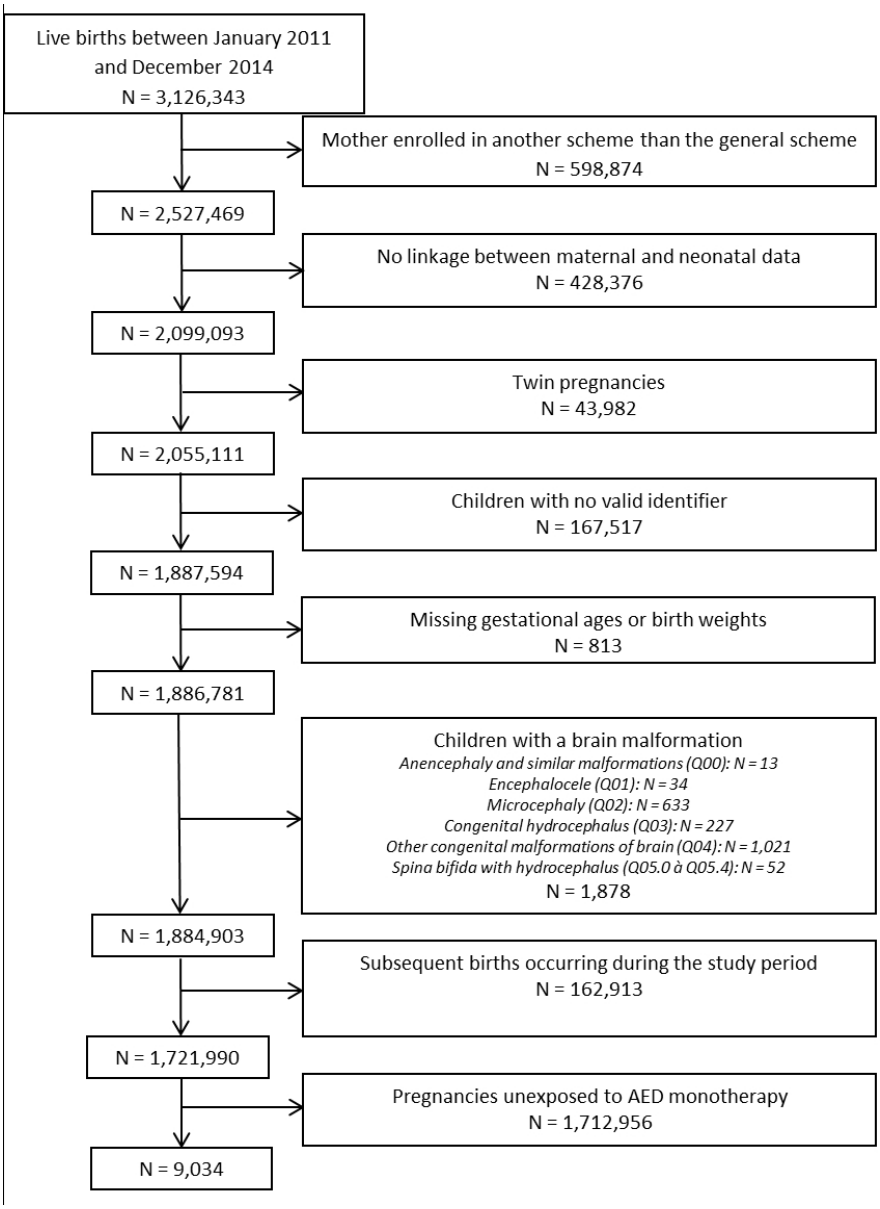
[b] adjusted for all covariates including hospitalization for epilepsy during pregnancy

Figure 1. Inclusion flow chart

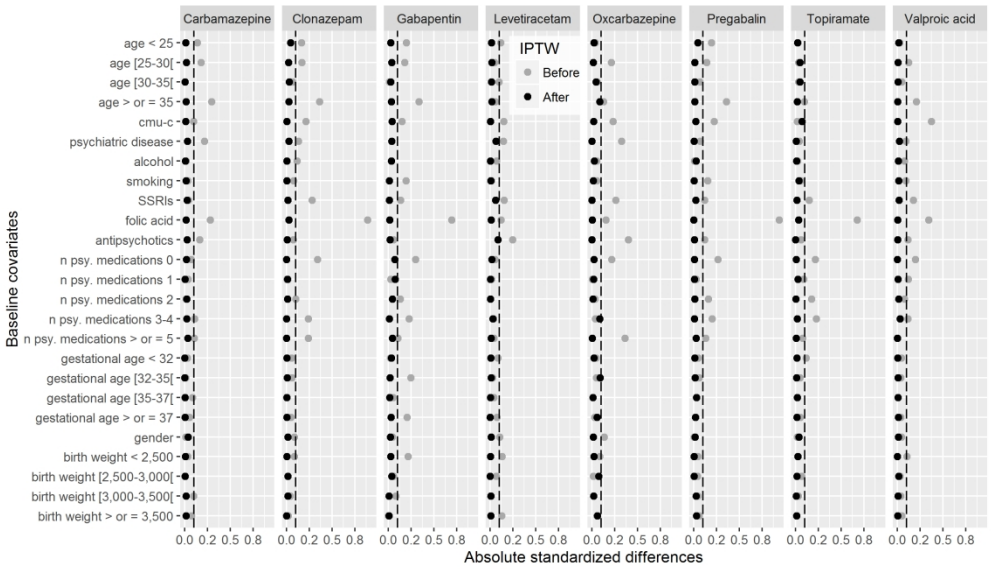
Abbreviation: AED = antiepileptic drug

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)

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



152x195mm (150 x 150 DPI)


Carbamazepine
Clonazepam
Gabapentin
Levetiracetam
Oxcarbazepine
Pregabalin
Topiramate
Valproic acid
IPTW
Before
After
Baseline covariates
age < 25
age [25-30[
age [30-35[
age > or = 35
cmu-c
psychiatric disease
alcohol
smoking
SSRIs
folic acid
antipsychotics
n psy. medications 0
n psy. medications 1
n psy. medications 2
n psy. medications 3-4
n psy. medications > or = 5
gestational age < 32
gestational age [32-35[
gestational age [35-37[
gestational age > or = 37
gender
birth weight < 2,500
birth weight [2,500-3,000[
birth weight [3,000-3,500[
birth weight > or = 3,500
0.0 0.2 0.5 0.8
Absolute standardized differences

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[f]
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
[a]Divalproex 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)	NS	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)	NS	134 (21.6)	*	311 (31.4)	***
Hospitalization for epilepsy		171 (8.1)	13 (7.4)	NS	43 (6.9)	NS	22 (2.2)	***
History of mental and behavioral disorders		150 (7.1)	18 (10.2)	NS	51 (8.2)	NS	96 (9.7)	*
Proxy for alcohol intake		18 (0.9)	0 (0.0)	NS	13 (2.1)	*	22 (2.2)	*
Proxy for smoking		204 (9.7)	21 (11.9)	NS	69 (11.1)	NS	136 (13.7)	**
Folic acid supplementation		1,537 (72.9)	133 (75.6)	NS	396 (63.8)	***	525 (53.0)	***
SSRIs during pregnancy		55 (2.6)	5 (2.8)	NS	23 (3.7)	NS	33 (3.3)	NS
History of antipsychotic use		40 (1.9)	4 (2.3)	NS	15 (2.4)	NS	49 (4.9)	***
Number of psychiatric medications[a]	0	1,286 (61.0)	105 (59.7)	NS	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)	NS	7 (1.1)	NS	7 (0.7)	NS
	[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)	NS	292 (47.0)	*	496 (50.1)	NS
Birth weight	< 2,500	128 (6.1)	14 (8.0)	NS	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]
Valproic acid	***911***	***85***	***25.1***	***1.7 [1.3 - 2.2]***	*1.5 [1.1 - 1.9]*

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]
Valproic acid	***2.7 [1.9 - 4.0]***	***2.7 [1.9 - 4.0]***
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]
Valproic acid	***4.4 [2.1 - 9.2]***	***4.5 [2.1 - 9.6]***
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]
Valproic acid	***3.0 [1.5 - 6.1]***	***3.1 [1.5 - 6.2]***
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]
Pregabalin	***0.7 [0.5 - 0.9]***	***0.7 [0.5 - 1.0]***
Topiramate	1.2 [0.8 - 1.8]	1.2 [0.8 - 1.8]
Valproic acid	***1.5 [1.2 - 1.9]***	***1.5 [1.2 - 1.9]***

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 (%)	Chi$^{2\ a}$	Chi$^{2\ b}$
Number of exposed pregnancies		2,916	2,108	308			520			163		
Maternal age at birth (years)	< 25	431 (14.8)	349 (16.6)	38 (12.3)			83 (16.0)			16 (9.8)		
	[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	***
Number of psychiatric medications[c]	0	1,641 (56.3)	1,286 (61.0)	209 (67.9)			351 (67.5)			93 (57.1)		
	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 (%)	Chi$^{2\ a}$	Chi$^{2\ b}$
Gestational age (weeks after LMP)	< 32	11 (0.4)	8 (0.4)	1 (0.3)	NS	NS	4 (0.8)	NS	NS	2 (1.2)	NS	NS
	[32 - 35[	42 (1.4)	32 (1.5)	8 (2.6)			8 (1.5)			3 (1.8)		
	[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)	NS	NS	48 (9.2)	*	*	19 (11.7)	*	*
	[2,500 - 3,000[	630 (21.6)	460 (21.8)	71 (23.1)			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; Chi^2 = 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

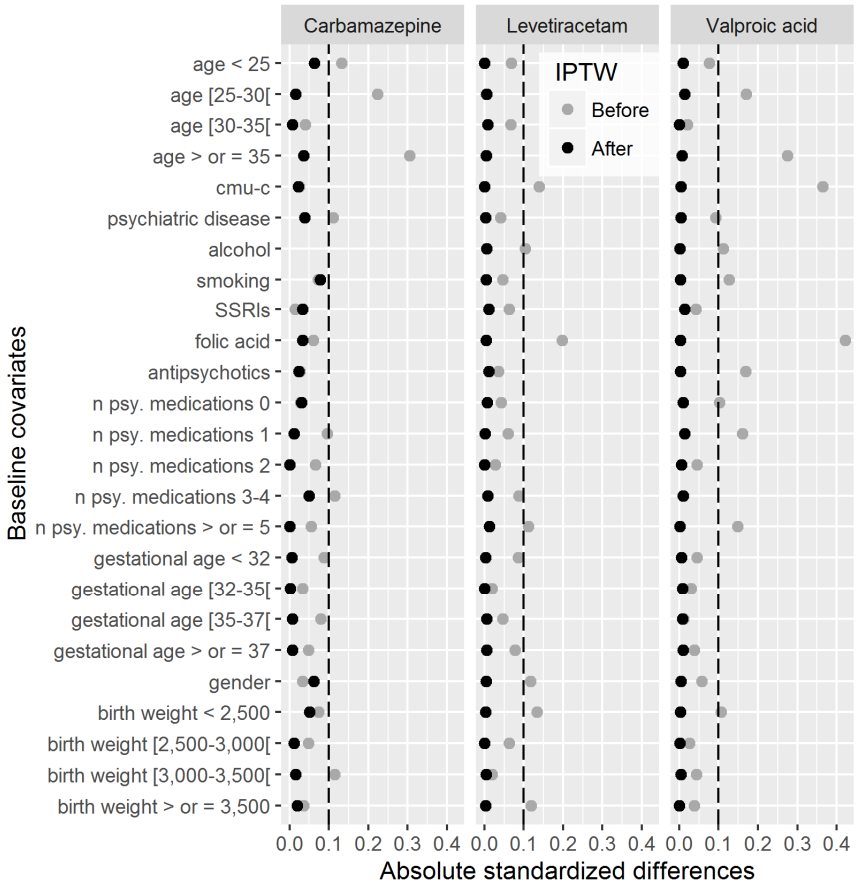
[a] compared to women exposed to lamotrigine regardless of indication

[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

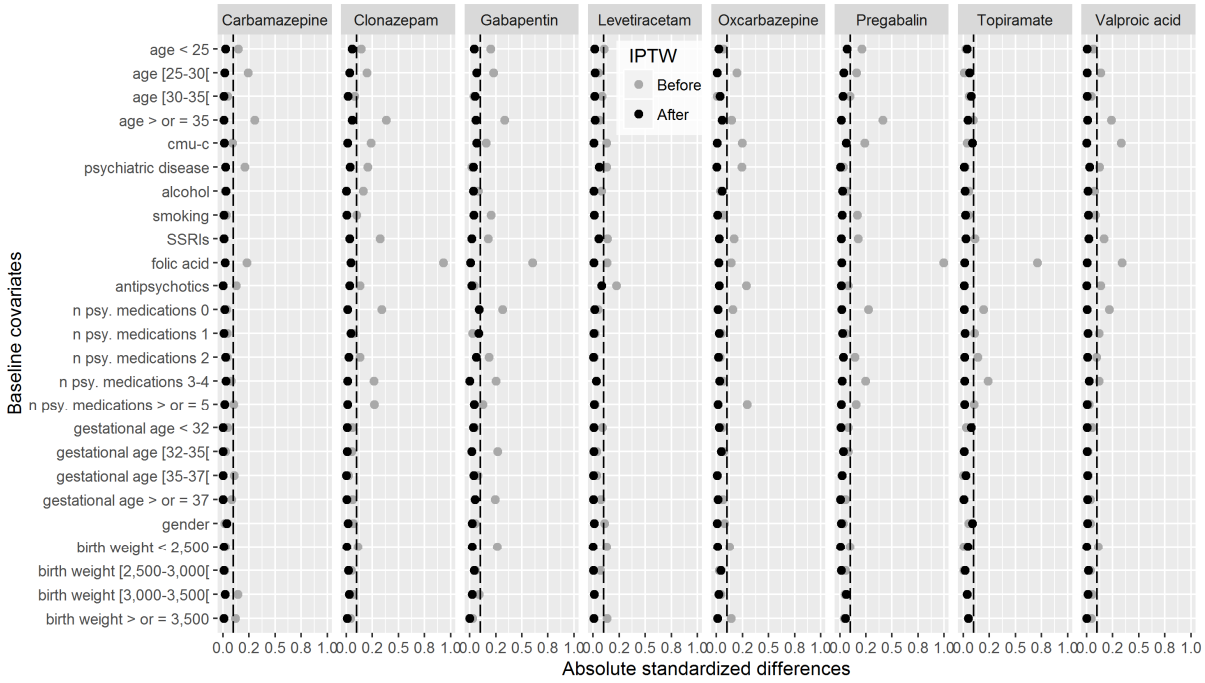
*** p <0.0001; ** p <0.001; * p <0.05; NS: Not Significant

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

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p. 1, 5, 6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p. 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p. 5
Objectives	3	State specific objectives, including any prespecified hypotheses	p. 5
Methods			
Study design	4	Present key elements of study design early in the paper	p. 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p. 6, 7, 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p. 6, 7, 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p. 7, 8, 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p. 8
Bias	9	Describe any efforts to address potential sources of bias	p. 9, 10
Study size	10	Explain how the study size was arrived at	p. 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p. 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p. 9
		(*b*) Describe any methods used to examine subgroups and interactions	p. 10
		(*c*) Explain how missing data were addressed	p. 7
		(*d*) If applicable, explain how loss to follow-up was addressed	p. 8
		(*e*) Describe any sensitivity analyses	p. 10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p. 10, 29
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	p. 29
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p. 10, 11, 22, 23
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	p. 10
Outcome data	15*	Report numbers of outcome events or summary measures over time	p. 25, 27, 28
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p. 11, 12, 25, 27, 28
		(*b*) Report category boundaries when continuous variables were categorized	p. 12, 28
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p. 11, 12 27
Discussion			
Key results	18	Summarise key results with reference to study objectives	p. 12, 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p. 14, 15, 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p. 14, 15, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	n/a
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p. 17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study

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Keywords:	Epilepsy < NEUROLOGY, Paediatric neurology < PAEDIATRICS, Child & adolescent psychiatry < PSYCHIATRY

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Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study

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Manuscript word count: 3,344

Abstract

Objectives: To assess the association between prenatal exposure to monotherapy with the antiepileptic drugs (AEDs) most commonly used during pregnancy and the risk of various neurodevelopmental outcomes compared to lamotrigine.

Design: Nationwide population-based cohort study.

Setting: French national health care databases.

Participants: Children born alive between 2011 and 2014 and prenatally exposed to AED monotherapy.

Primary and secondary outcome measures: Outcomes included neurodevelopmental disorders (NDD), defined with ICD-10 codes F70-F98, – pervasive developmental disorders (PDD, F84) and mental retardation (MR, F70-F79) were studied separately – and visits to speech therapists. The reference group comprised children prenatally exposed to lamotrigine. Children were followed until outcome, loss to follow-up, death or 31 December 2016. We performed inverse probability of treatment weighting analyses using the propensity score, which included maternal and infant characteristics. Hazard ratios (HRs) were calculated using Cox models.

Results: The cohort comprised 9,034 children, 2,916 of which were exposed to lamotrigine, 1,627 to pregabalin, 1,246 to clonazepam, 991 to valproic acid (VPA), 621 to levetiracetam, 502 to carbamazepine, 477 to topiramate, 378 to gabapentin and 143 to oxcarbazepine. None of these AEDs, except VPA, were associated with an increased risk of any of the four neurodevelopmental outcomes investigated. Exposure to VPA was associated with increased risks of NDDs (HR=2.7[1.8-4.0]), PDD (HR=4.4[2.1-9.3]), MR (HR=3.1[1.5-6.2]) and visits to speech therapists (HR=1.5[1.1-1.9]), with a dose-response relationship.

Conclusions: No increased risk of any of the neurodevelopmental outcomes investigated in this study was observed with prenatal exposure to levetiracetam, pregabalin, oxcarbazepine, topiramate, gabapentin, clonazepam or carbamazepine, compared to lamotrigine. However, this study corroborates the well-known association between maternal use of VPA during pregnancy and the risk of neurodevelopmental disorders in the offspring. Longer follow-up is necessary to confirm these findings.

Keywords: antiepileptic drugs; pregnancy; neurodevelopmental disorders; health care databases; France

Strengths and limitations of this study

This nationwide cohort study based on the French health care databases is the largest study to date to assess the association between AED exposure during pregnancy and neurodevelopmental outcomes in the offspring.

This study investigated a wide range of AEDs, including some drugs for which little or no information is available in the literature.

Although residual confounding by unmeasured covariates cannot be excluded, the choice of lamotrigine as the reference group and the sensitivity analysis restricted to women considered to be treated for epilepsy should mitigate confounding.

The maximum length of follow-up was 6 years, allowing only early diagnoses of neurodevelopmental disorders to be identified.

INTRODUCTION

Antiepileptic drugs (AEDs) are commonly prescribed during pregnancy to treat epilepsy and various other conditions, such as neuropathic pain syndromes, psychiatric disorders and chronic migraine[1]: between 0.4 and 0.7% of women are exposed to AEDs during pregnancy in Europe,[2,3] while this prevalence is as high as 2% in the US.[4]

Some of these AEDs are known to be teratogens.[5] Of all AEDs, prenatal exposure to valproic acid has been most clearly associated with poor neurodevelopmental outcomes,[6] which led the US Food and Drug Administration to issue a warning in 2011[7] and stringent guidance in 2013 for clinicians prescribing valproic acid to pregnant women or women of childbearing potential.[8] The European Medicines Agency also strengthened warnings on the use of valproate-containing medicines in women and girls in 2014[9] and issued a ban in 2018 on the use of such medicines during pregnancy for migraine or bipolar disorder, and for epilepsy except when no other effective treatment is available.[10]

Lamotrigine has generally been associated with favorable neurodevelopmental outcomes.[6] Discordant but mainly reassuring data have been published for carbamazepine, while evidence for levetiracetam and topiramate remains limited and almost no information is available concerning the other AEDs, particularly clonazepam, oxcarbazepine, gabapentin and pregabalin.[6] Furthermore, most of the studies conducted to date have been based on small sample sizes and may be prone to selection bias.

We therefore conducted a large-scale nationwide cohort study using the French health care databases to assess various early neurodevelopmental outcomes among children prenatally exposed to monotherapy with individual AEDs compared to lamotrigine-exposed children.

METHODS

Study design and data sources

The French national health insurance database (SNIIRAM) and the French hospital discharge database (PMSI) linked by a unique patient identifier were used to conduct this nationwide population-based cohort study.[11]

The DCIR database contains all individualized and anonymous health care claims reimbursed by French National Health Insurance, in particular all dispensed drugs and medical procedures in the outpatient setting. The DCIR database also collects patient data such as age, gender, vital status and eligibility for complementary universal health insurance (CMU-C), which provides free access to health care for low-income people.[12] Eligibility for 100% health insurance coverage for serious and costly long-term diseases (LTD) is also recorded in the DCIR database.

The PMSI database provides detailed medical information on all admissions to public and private hospitals in France, including primary, related and associated discharge diagnoses, medical procedures and data related to pregnancy such as gestational ages and birth weights.

Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification and medical procedures are coded according to the French medical classification of clinical procedures (CCAM). LTD and hospital discharge diagnoses are coded according to the International Classification of Diseases, 10th Revision (ICD-10).

This linkage has previously been used to conduct epidemiological studies in pregnancy research.[3,13–15]

Study population

All live births between January 2011 and December 2014 were eligible for inclusion. These live births were identified by using a published algorithm based on discharge diagnoses and medical procedures indicative of completion of pregnancy.[3]

The mother had to be enrolled in the national health insurance general scheme (75% of the French population), during the penultimate year before pregnancy. Pregnancies that could not be linked to neonatal data and twin pregnancies were excluded, as well as pregnancies for which the child had no valid identifier allowing follow-up and pregnancies for which gestational ages or birth weights were not available. Children with a hospital discharge diagnosis of brain malformation documented at birth were also excluded (see supplementary Table 1 for ICD-10 codes). For each woman, only the first birth occurring during the study period was considered.

Finally, only pregnancies exposed to AED monotherapy were included in the study population.

These exclusion criteria are reported in the study population flowchart (Figure 1).

Patient and Public Involvement

Patients or the public were not involved in the design and the conduct of the study.

Exposure

All AEDs were studied (supplementary Table 2). Women were considered to be exposed during the 30 days following dispensing of an AED, as AED prescriptions are dispensed with a 30-day supply in France. Women were therefore exposed during pregnancy when an AED had been dispensed between 30 days before the beginning of pregnancy and the end of

pregnancy. Monotherapy was defined as the absence of any other AED dispensed during the same period. Results related to AEDs rarely used as monotherapy during pregnancy (< 100 exposed pregnancies) were not reported. The reference group included pregnant women exposed to lamotrigine monotherapy for the following reason: active-comparator designs minimize confounding by indication compared to the use of an unexposed control group[16] ; lamotrigine is the most commonly used AED in France for the treatment of epilepsy ; prenatal exposure to lamotrigine has been mostly shown to be associated with favorable neurodevelopmental outcomes ; comparing all individual AEDs to lamotrigine addresses a clinically relevant question: which is the safest AED?

Mean daily doses were calculated by dividing cumulative doses by the number of days covered. Cumulative doses were assessed by equally distributing the dose of AED dispensed over the 30 days following dispensing and then by adding these daily doses overlapping with the pregnancy period. The number of days covered was defined as the sum of the 30-day periods of exposure corresponding to each refill minus the number of days of overlap between two consecutive refills. Only the days overlapping with the pregnancy period were taken into account.

Outcomes

Four outcomes were considered, based on the literature but also on their availability in the French health care databases. The primary outcomes were hospitalization or LTD for neurodevelopmental disorders (ICD-10 diagnosis codes F70 to F98), but also for two specific subcategories: pervasive developmental disorders (F84) and mental retardation (F70-F79). The secondary outcome was “visits to a speech therapist”, as a proxy for communication-related disorders.

Follow-up

Children were followed from birth until any of the predefined outcomes, loss to follow-up (more than one year with no reimbursement), death from any cause or end of the study period defined as the 31st December 2016, whichever came first.

Covariates

Potential confounders related to the mother and considered in this study included sociodemographic covariates (maternal age at birth and eligibility for CMU-C), as well as comedications and comorbidities. Comedications included (1) pre-conception folic acid supplementation, defined as at least one dispensing between one month before pregnancy and 3 months after the start of pregnancy, (2) exposure to selective serotonin reuptake inhibitors (SSRIs) during pregnancy, (3) exposure to antipsychotics in the year before pregnancy, (4) a proxy for severity of mental disorders (the number of 5th level ATC classes of psychiatric medications dispensed in the year before pregnancy). History of mental and behavioral disorders not related to alcohol or smoking, which was identified by using hospital discharge and LTD diagnoses, was also considered to be potential confounder. Alcohol intake and smoking were not directly available in the databases and proxies were calculated using modified versions of previously published algorithms.[17] These proxies were constructed on the basis of hospital discharge diagnoses, LTD diagnoses and the child's hospital discharge diagnoses at birth. We also used specific drug reimbursements for alcohol intake and nicotine replacement therapy reimbursements for smoking. Potential confounders related to the child and considered in this study were gender, gestational age and birth weight.

All drugs and ICD-10 codes related to hospital discharge and LTD diagnoses used to define covariates are presented in supplementary Table 1.

Statistical analyses

Baseline covariates were compared between pregnancies exposed to each AED studied and lamotrigine-exposed pregnancies using $\chi 2$ tests. Number of events, crude event rates and crude incidence rate ratios (IRRs) were calculated. Potential confounders were controlled for by performing inverse probability of treatment weighting (IPTW) analyses using the propensity score. These analyses were conducted separately according to the type of AED. Propensity scores were determined by using logistic regression models including the covariates listed above, with maternal age as a categorical variable ($\leq$ 25 years, [25 - 30[, [30 - 35[and $\geq$ 35). Weights were trimmed at the 0.1 and 99.9 percentiles. Absolute standardized differences were calculated to assess the balance in baseline covariates before and after weighting. Groups were considered to be balanced when standardized differences were less than 0.1.[18] Cox models with robust sandwich estimates were used to calculate hazard ratios (HR) and their 95% confidence intervals.

As AEDs can be prescribed for a wide range of medical conditions other than epilepsy, a first sensitivity analysis in which the study population was restricted to women considered to be treated for epilepsy (see supplementary Table 1 for definition) was conducted. In this sensitivity analysis, HRs were further adjusted for hospitalization (primary and related diagnoses only) for epilepsy during pregnancy. A second sensitivity analysis, requiring at least one dispensing during pregnancy to consider a woman to be exposed, was also conducted to account for possible misclassification of exposure at the beginning of pregnancy. In a third sensitivity analysis, two other propensity scores were calculated: one excluding proxies for alcohol intake and smoking and another one excluding gestational age and birth weight.

Data extraction and statistical analysis were performed by using SAS Enterprise Guide 4.3 software (SAS Institute, Inc., Cary, NC). Graphics were performed by using R 3.5 statistical software.

RESULTS

Main analysis

From a total of 1,721,990 births satisfying all inclusion and exclusion criteria, 9,034 children were prenatally exposed to AED monotherapy (Figure 1), 32 (0.4%) of whom were censored at death and 1,224 (13.5%) were lost to follow-up. The median follow-up was 3.7 years (interquartile range, 2.7-4.7 years). Of these 9,034 children, 2,916 were exposed to lamotrigine, 1,627 were exposed to pregabalin, 1,246 were exposed to clonazepam, 991 were exposed to valproic acid, 621 were exposed to levetiracetam, 502 were exposed to carbamazepine, 477 were exposed to topiramate, 378 were exposed to gabapentin and 143 were exposed to oxcarbazepine (Table 1). A total of 133 children were exposed to another AED monotherapy, including phenobarbital (N=84), phenytoin (N=13), lacosamide (N=9), zonisamide (N=8), ethosuximide (N=7) and vigabatrin (N=6). The median follow-up ranged from 3.3 to 4.0 years across all AEDs except clonazepam (4.8 years).

Table 1 also reports baseline patient characteristics according to the type of AED prior to IPTW, showing some significant differences between the various AEDs studied and lamotrigine. Before weighting, across all variables included in the propensity score and all AEDs studied, the absolute standardized differences ranged from 0.00 to 0.94. After weighting, all standardized differences were less than 0.1, indicating a good balance between treatment groups (Figure 2).

Table 2 presents the number of events, crude event rates, IRRs and adjusted HRs for the four outcomes and each of the AEDs studied. Compared to prenatal exposure to lamotrigine, prenatal exposures to all of the AEDs studied, excluding valproic acid, were not found to be associated with an increased risk of any of the four outcomes investigated. By contrast,

valproic acid was associated with an increased risk of visits to a speech therapist (HR=1.5[1.1-1.9]) and neurodevelopmental disorders (HR=2.7[1.8-4.0]), particularly pervasive developmental disorders (HR=4.4[2.1-9.3]) and mental retardation (HR=3.1[1.5-6.2]), compared to lamotrigine.

Sensitivity analyses

In the first sensitivity analysis restricting the study population to women considered to be treated for epilepsy, only results related to carbamazepine, levetiracetam and valproic acid are reported. The number of women considered to be treated for epilepsy and exposed to monotherapy with each of the other AEDs was less than 100. Baseline patient characteristics and absolute standardized differences are available in supplementary Table 3 and supplementary Figure 1, respectively. Compared to lamotrigine, prenatal exposure to levetiracetam was not found to be associated with any of the four outcomes investigated and prenatal exposure to valproic acid was associated with all four outcomes, which is in line with the results of the main analysis. Results were different from the main analysis for the association between carbamazepine and the risk of visits to a speech therapist (HR=0.2[0.1-0.7]) (Table 3).

The results of the second (see supplementary Figure 2 for standardized differences) and third sensitivity analyses were comparable to those of the main analysis (see supplementary Table 4 and supplementary Table 5, respectively).

Dose

Baseline patient characteristics according to the dose of valproic acid dispensed during pregnancy are reported in supplementary Table 6. A dose-response relationship was observed for the association between prenatal exposure to valproic acid and the risks of visits to a speech therapist (< 700 mg: HR=0.6[0.3-1.0], [700-1500 mg[: HR=1.6[1.2-2.1], ≥ 1500 mg:

HR=2.6[1.7-4.0]) and neurodevelopmental disorders (< 700 mg: HR=1.3[0.6-2.8], [700-1500 mg[: HR=2.1[1.3-3.5], ≥ 1500 mg: HR=7.0[4.3-11.5]), including pervasive developmental disorders (< 700 mg: HR=2.2[0.5-8.5], [700-1500 mg[: HR=2.7[1.0-7.1], ≥ 1500 mg: HR=14.7[6.2-34.7]). The highest HR of mental retardation was also observed for the highest mean daily dose (≥ 1500 mg: HR=7.3[3.0-17.7]). Comparable results were observed when the study population was limited to women considered to be treated for epilepsy (Table 4).

DISCUSSION

Main Findings

In this nationwide observational study based on the French health care databases, prenatal exposures to levetiracetam, pregabalin, oxcarbazepine, topiramate, gabapentin, clonazepam and carbamazepine were not associated with an increased risk of any of the early neurodevelopmental outcomes investigated compared to lamotrigine. The decreased risk of visits to a speech therapist observed with carbamazepine when the population was restricted to women with epilepsy may be a chance finding. This association is based on only 4 children and carbamazepine was associated with reduced verbal abilities in one study.[19] Prenatal exposure to valproic acid was found to be associated with increased risks of all neurodevelopmental outcomes investigated compared to lamotrigine, ranging from pervasive mental disorders to possible communication-related disorders. A dose-response relationship was observed for most of these outcomes.

Comparison with Previous Studies

Prenatal exposure to lamotrigine has been mostly shown not to be associated with poorer neurodevelopmental outcomes, although limited data are available, with no dose-response

relationship.[6] Only two studies have shown that prenatal exposure to lamotrigine was associated with impaired specific cognitive skills[20] and parental concerns about autistic traits and sentence skills.[21]

The results of the present study concerning valproic acid, carbamazepine, levetiracetam and topiramate are consistent with those of previous studies. Prenatal exposure to valproic acid has been associated with poorer cognitive outcomes[19,22–24] and particularly poorer executive functions and memory abilities[23] compared to lamotrigine. Children prenatally exposed to valproic acid also show impaired adaptive behavior[25,26] and school performance[27] compared to lamotrigine-exposed children. Impaired language skills[28] and autism spectrum disorder have been reported to be more frequent among children exposed to valproic acid than among unexposed children.[29,30] A dose-response relationship has also been observed for most of these outcomes.[19,22,23,25,26,28]

Few studies have directly compared prenatal exposure to carbamazepine *versus* lamotrigine and these studies did not find any differences in terms of cognitive development[22,31] and adaptive behavior.[26] Data concerning levetiracetam and topiramate are more limited and no direct comparison with lamotrigine has been published. No increased risk of neurodevelopmental outcomes was found among levetiracetam-exposed children compared to unexposed children[32–34] and, although prenatal exposure to topiramate was associated with poorer neurodevelopmental outcomes in one study,[35] this association was not confirmed by a larger study.[33] Little or no information is available concerning the other AEDs, particularly clonazepam, oxcarbazepine, gabapentin and pregabalin.[29,33,36]

Strengths

This nationwide cohort study based on the French health care database is the largest study to date to assess the association between AED exposure during pregnancy and

neurodevelopmental outcomes in the offspring. This study investigated a wide range of AEDs, including some drugs for which little or no information is available in the literature. The strengths of this study also include the use of propensity score methods to mitigate confounding, as well as the advantages of the French health care databases, such as the independence between ascertainment of medication and outcomes, the absence of recall bias, and the possibility to study the dose-response relationship, which is a key concept in terms of teratogenicity.[33]

Limitations

Exposure misclassification constitutes a first limitation. Exposure assessment was based on pharmacy claims, which do not indicate whether the medication is actually taken. Exposure misclassification is more likely for AED classes that are often discontinued before conception.[37] However, the results of the sensitivity analysis regarding exposure measurement suggest that this bias is likely minimal.

Although we used an active-comparator design, residual confounding by unmeasured or insufficiently well measured covariates cannot be excluded. For instance, maternal education and IQ were not available in the databases. Data related to the father could not be linked to the child, not allowing any adjustment for paternal characteristics. Lifestyle factors such as alcohol intake and smoking could also not be exhaustively assessed.

As some AEDs can be prescribed to treat conditions other than epilepsy, the analyses were replicated in a population restricted to women considered to be treated for epilepsy, providing comparable results to those of the main analysis. However, the indication for which an AED is prescribed was not directly available in the databases. We therefore used LTD diagnoses, hospital diagnoses and specific drug reimbursements to identify women with epilepsy. Some studies,[34,38,39] unlike other studies,[19,22–24] have also reported an association between

the severity of maternal epilepsy, particularly seizure type and frequency, and poorer developmental outcomes in the child. As this confounder was not available in the databases, we considered at least one admission to hospital for epilepsy during pregnancy to be a proxy for epilepsy severity. Similar results were observed whether or not this proxy was included in the propensity score.

Outcome misclassification also cannot be ruled out, as the diagnosis codes used to identify neurodevelopmental outcomes have not been externally validated. However, the PMSI database is used for planning and funding purposes and is subject to coding quality control, and LTD registration, which is requested by the patient's general practitioner, must be validated by a medical consultant of the beneficiary's health insurance scheme. In addition, as hospital discharge and LTD diagnoses were used to define outcomes, children not reaching diagnostic thresholds but still having some evidence of impairment were not considered to have experienced the outcomes of interest.[40] Moreover, some of the outcomes studied may not have been exhaustively assessed, as data related to a large share of medical and social welfare services are not available in the French health care databases. Results related to visits to a speech therapist must also be interpreted with caution, as a visit to a speech therapist does not necessarily imply pathology. Speech therapists can also be consulted for various medical reasons, and access to speech therapists is associated with socioeconomic status.[41] Further, because the study outcomes were limited to three subtypes of neurodevelopmental disorders (pervasive developmental disorders, mental retardation and visits to a speech therapist as a proxy for communication-related disorders), no conclusion can be drawn concerning all of the other subtypes of neurodevelopmental disorders.

The short follow-up period constitutes another limitation: the median and maximum lengths of follow-up were 3.7 and 6 years, respectively. In particular, a diagnosis of autism spectrum disorders is considered to be stable at age 2[42] and is made at an average age of 3 years and

5 months in France,[43] but speech therapy is more frequent among school-aged children. Therefore, only early diagnoses, probably corresponding to more severe disorders, were identified. This is especially true for mental retardation: although severe and profound mental retardation can be diagnosed before 3 years old, moderate mental retardation cannot be diagnosed before 4 or 5 years old.[44] Further assessment of children at older developmental stages would be useful to study a broader range of neurodevelopmental disorders. Except clonazepam for which French health authorities took measures to limit off-label use in November 2011,[45] lengths of follow-up were quite comparable across all AEDs. Children exposed to second-generation AEDs had only slightly shorter follow-ups than children exposed to first-generation AEDs, which should not have influenced the results of this study.

CONCLUSION

Despite the limitations inherent to health care claims databases, this study, based on 9,034 exposed children, confirms that valproic acid is associated with an increased risk of various neurodevelopmental outcomes compared to lamotrigine, with a dose-response relationship, while no association was observed for the other AEDs including carbamazepine, levetiracetam or topiramate. However, this study needs to be replicated with a longer follow-up period.

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Data sharing statement: Permanent access to the French health care databases is automatically granted to certain government agencies, public institutions and public service authorities. Temporary access for studies and research is possible upon request from the national health data institute (INDS).

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Table 1. Baseline characteristics according to AED use during pregnancy

		Lamotrigine		Carbamazepine		Clonazepam		Gabapentin		Levetiracetam	
Number of exposed pregnancies		2,916		502		1,246		378		621	
Median follow-up (years) (IQR)		3.5 (2.7-4.5)		3.8 (2.8-4.7)		4.8 (4.1-5.3)		3.4 (2.5-4.3)		3.4 (2.6-4.4)	
Maternal age at birth (years)	< 25	431 (14.8)		51 (10.2)		118 (9.5)		32 (8.5)		119 (19.2)	
	[25 - 30[	927 (31.8)		119 (23.7)		302 (24.2)		90 (23.8)		212 (34.1)	
	[30 - 35[	980 (33.6)		168 (33.5)		380 (30.5)		125 (33.1)		181 (29.1)	
	≥ 35	578 (19.8)		164 (32.7)		446 (35.8)		131 (34.7)		109 (17.6)	
			***		***		***		***		*
Eligibility for CMU-C		461 (15.8)		98 (19.5)	*	303 (24.3)	***	82 (21.7)	*	134 (21.6)	**
History of mental and behavioral disorders		368 (12.6)		104 (20.7)	***	216 (17.3)	***	43 (11.4)	NS	51 (8.2)	*
Proxy for alcohol intake		35 (1.2)		7 (1.4)	NS	35 (2.8)	**	6 (1.6)	NS	13 (2.1)	NS
Proxy for smoking		311 (10.7)		59 (11.8)	NS	165 (13.2)	*	66 (17.5)	***	69 (11.1)	NS
Folic acid supplementation		2,026 (69.5)		281 (56.0)	***	360 (28.9)	***	139 (36.8)	***	396 (63.8)	*
SSRIs during pregnancy		210 (7.2)		42 (8.4)	NS	201 (16.1)	***	42 (11.1)	*	23 (3.7)	*
History of antipsychotic use		227 (7.8)		64 (12.7)	**	123 (9.9)	*	24 (6.3)	NS	15 (2.4)	***
Number of psychiatric medications[a]	0	1,641 (56.3)		265 (52.8)		492 (39.5)		157 (41.5)		366 (58.9)	
	1	669 (22.9)		107 (21.3)		283 (22.7)		91 (24.1)		138 (22.2)	
	2	258 (8.8)		42 (8.4)		149 (12.0)		49 (13.0)		54 (8.7)	
	3-4	211 (7.2)		52 (10.4)		183 (14.7)		54 (14.3)		39 (6.3)	
	≥ 5	137 (4.7)		36 (7.2)		139 (11.2)		27 (7.1)		24 (3.9)	
					*		***		***		NS
Gestational age (weeks after LMP)	< 32	11 (0.4)		3 (0.6)		10 (0.8)		2 (0.5)		7 (1.1)	
	[32 - 35[	42 (1.4)		8 (1.6)		28 (2.2)		23 (6.1)		11 (1.8)	
	[35 - 37[	129 (4.4)		14 (2.8)		55 (4.4)		21 (5.6)		33 (5.3)	
	≥ 37	2,734 (93.8)		477 (95.0)		1,153 (92.5)		332 (87.8)		570 (91.8)	
			NS		NS		***		NS		NS
Gender (male)		1,524 (52.3)		265 (52.8)	NS	597 (47.9)	*	206 (54.5)	NS	292 (47.0)	*
Birth weight	< 2,500	179 (6.1)		35 (7.0)		105 (8.4)		47 (12.4)		60 (9.7)	
	[2,500 - 3,000[	630 (21.6)		110 (21.9)		278 (22.3)		73 (19.3)		152 (24.5)	
	[3,000 - 3,500[	1,196 (41.0)		182 (36.3)		485 (38.9)		140 (37.0)		251 (40.4)	
	≥ 3,500	911 (31.2)		175 (34.9)		378 (30.3)		118 (31.2)		158 (25.4)	
			NS		*		***		**		

Table 1. Baseline characteristics according to AED use during pregnancy (continued)

		Oxcarbazepine		Pregabalin		Topiramate		Valproic acid	
Number of exposed pregnancies		143		1,627		477		991	
Median follow-up (years) (IQR)		4.0 (2.7-4.8)		3.3 (2.5-4.3)		3.6 (2.6-4.6)		3.9 (2.8-4.8)	
Maternal age at birth (years)	< 25	23 (16.1)	NS	139 (8.5)	***	66 (13.8)	NS	137 (13.8)	***
	[25 - 30[	32 (22.4)		414 (25.4)		144 (30.2)		259 (26.1)	
	[30 - 35[	52 (36.4)		495 (30.4)		153 (32.1)		310 (31.3)	
	≥ 35	36 (25.2)		579 (35.6)		114 (23.9)		285 (28.8)	
Eligibility for CMU-C		36 (25.2)	*	404 (24.8)	***	79 (16.6)	NS	311 (31.4)	***
History of mental and behavioral disorders		36 (25.2)	***	169 (10.4)	*	54 (11.3)	NS	96 (9.7)	*
Proxy for alcohol intake		1 (0.7)	NS	21 (1.3)	NS	7 (1.5)	NS	22 (2.2)	*
Proxy for smoking		13 (9.1)	NS	257 (15.8)	***	43 (9.0)	NS	136 (13.7)	*
Folic acid supplementation		89 (62.2)	NS	440 (27.0)	***	179 (37.5)	***	525 (53.0)	***
SSRIs during pregnancy		22 (15.4)	**	172 (10.6)	***	55 (11.5)	*	33 (3.3)	***
History of antipsychotic use		31 (21.7)	***	79 (4.9)	**	30 (6.3)	NS	49 (4.9)	*
Number of psychiatric medications[a]	0	65 (45.5)	***	701 (43.1)	***	217 (45.5)	***	653 (65.9)	***
	1	33 (23.1)		355 (21.8)		92 (19.3)		180 (18.2)	
	2	14 (9.8)		227 (14.0)		69 (14.5)		67 (6.8)	
	3-4	9 (6.3)		216 (13.3)		68 (14.3)		45 (4.5)	
	≥ 5	22 (15.4)		128 (7.9)		31 (6.5)		46 (4.6)	
Gestational age (weeks after LMP)	< 32	1 (0.7)	NS	12 (0.7)	*	7 (1.5)	*	7 (0.7)	NS
	[32 - 35[	3 (2.1)		37 (2.3)		10 (2.1)		19 (1.9)	
	[35 - 37[	6 (4.2)		61 (3.7)		19 (4.0)		45 (4.5)	
	≥ 37	133 (93.0)		1,517 (93.2)		441 (92.5)		920 (92.8)	
Gender (male)		65 (45.5)	NS	847 (52.1)	NS	254 (53.2)	NS	496 (50.1)	NS
Birth weight	< 2,500	12 (8.4)	NS	118 (7.3)	NS	32 (6.7)	NS	88 (8.9)	*
	[2,500 - 3,000[	30 (21.0)		324 (19.9)		90 (18.9)		227 (22.9)	

	[3,000 - 3,500[	60 (42.0)		630 (38.7)		203 (42.6)		389 (39.3)	
	≥ 3,500	41 (28.7)		555 (34.1)		152 (31.9)		287 (29.0)	

Abbreviations: AED = antiepileptic drug; IQR = interquartile range; 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

Table 2. Number of events, crude event rates (per 1,000), crude IRRs and adjusted HRs for the four outcomes and each of the AEDs studied - main analysis

	Events	Crude event rates	IRR	HR [95% CI]
Neurodevelopmental disorders				
Lamotrigine	51	4.9		
Carbamazepine	13	7.0	1.4 [0.8 - 2.6]	1.2 [0.6 - 2.2]
Clonazepam	28	5.1	1.0 [0.6 - 1.6]	0.6 [0.4 - 1.1]
Gabapentin	4	3.1	0.6 [0.2 - 1.7]	0.4 [0.1 - 1.3]
Levetiracetam	8	3.7	0.8 [0.4 - 1.6]	0.7 [0.3 - 1.5]
Oxcarbazepine	3	5.6	1.1 [0.4 - 3.7]	0.8 [0.2 - 3.2]
Pregabalin	28	5.0	1.0 [0.6 - 1.6]	0.6 [0.4 - 1.0]
Topiramate	7	4.1	0.8 [0.4 - 1.8]	0.8 [0.4 - 1.9]
Valproic acid	**50**	**13.5**	**2.7 [1.9 - 4.0]**	**2.7 [1.8 - 4.0]**
Pervasive developmental disorders				
Lamotrigine	11	1.1		
Carbamazepine	3	1.6	1.5 [0.4 - 5.4]	1.3 [0.3 - 5.0]
Clonazepam	8	1.4	1.4 [0.5 - 3.4]	0.8 [0.3 - 2.1]
Gabapentin	3	2.3	2.2 [0.6 - 7.9]	1.8 [0.4 - 7.0]
Levetiracetam	4	1.8	1.8 [0.6 - 5.5]	1.6 [0.5 - 5.4]
Oxcarbazepine	1	1.9	1.8 [0.2 - 13.6]	2.0 [0.3 - 13.8]
Pregabalin	7	1.2	1.2 [0.5 - 3.1]	1.1 [0.4 - 3.0]
Topiramate	1	0.6	0.6 [0.1 - 4.3]	0.3 [0.0 - 4.9]
Valproic acid	**17**	**4.5**	**4.3 [2.0 - 9.1]**	**4.4 [2.1 - 9.3]**
Mental retardation				
Lamotrigine	15	1.4		
Carbamazepine	2	1.1	0.7 [0.2 - 3.2]	0.6 [0.1 - 2.9]
Clonazepam	3	0.5	0.4 [0.1 - 1.3]	0.3 [0.1 - 1.2]
Gabapentin	0	0.0	N/A	N/A
Levetiracetam	1	0.5	0.3 [0.0 - 2.4]	0.3 [0.0 - 2.5]
Oxcarbazepine	0	0.0	N/A	N/A
Pregabalin	7	1.2	0.9 [0.4 - 2.1]	0.6 [0.2 - 1.8]
Topiramate	2	1.2	0.8 [0.2 - 3.5]	0.5 [0.1 - 3.3]
Valproic acid	**15**	**4.0**	**2.8 [1.3 - 5.6]**	**3.1 [1.5 - 6.2]**
Visits to a speech therapist				
Lamotrigine	157	15.2		
Carbamazepine	31	16.7	1.1 [0.8 - 1.6]	0.9 [0.6 - 1.4]
Clonazepam	97	17.7	1.2 [0.9 - 1.5]	0.8 [0.6 - 1.0]
Gabapentin	11	8.5	0.6 [0.3 - 1.0]	0.7 [0.4 - 1.2]
Levetiracetam	22	10.2	0.7 [0.4 - 1.1]	0.7 [0.5 - 1.1]
Oxcarbazepine	13	24.6	1.6 [0.9 - 2.9]	1.3 [0.7 - 2.5]
Pregabalin	**61**	**11.0**	**0.7 [0.5 - 1.0]**	**0.7 [0.5 - 1.0]**
Topiramate	33	19.4	1.3 [0.9 - 1.9]	1.2 [0.8 - 1.8]
Valproic acid	**93**	**25.1**	**1.7 [1.3 - 2.1]**	**1.5 [1.1 - 1.9]**

Abbreviations: AED = antiepileptic drug; IRR = incidence rate ratio; HR = hazard ratio; N/A = not applicable

Lines marked in bold correspond to HRs for which the 95% CI does not include 1.

Table 3. Number of events, crude event rates (per 1,000), crude IRRs and adjusted HRs for the four outcomes and each of the AEDs studied - study population limited to women considered to be treated for epilepsy

	Events	Crude event rates	IRR	HR[a] [95% CI]	HR[b] [95% CI]
Neurodevelopmental disorders					
Lamotrigine	32	4.2			
Carbamazepine[c]	1	1.5	0.4 [0.0 - 2.7]	0.2 [0.0 - 2.7]	0.2 [0.0 - 2.7]
Levetiracetam	8	3.7	0.9 [0.4 - 1.9]	0.8 [0.4 - 1.8]	0.8 [0.4 - 1.8]
Valproic acid	**50**	**13.5**	**3.2 [2.0 - 5.0]**	**3.2 [2.0 - 4.9]**	**3.5 [2.3 - 5.4]**
Pervasive developmental disorders					
Lamotrigine	7	0.9			
Carbamazepine[c]	0	0.0	N/A	N/A	N/A
Levetiracetam	4	1.8	2.0 [0.6 - 6.8]	1.8 [0.5 - 6.6]	1.8 [0.5 - 6.6]
Valproic acid	**17**	**4.5**	**4.9 [2.0 - 11.8]**	**4.9 [2.0 - 11.8]**	**4.7 [1.9 - 11.4]**
Mental retardation					
Lamotrigine	10	1.3			
Carbamazepine[c]	0	0.0	N/A	N/A	N/A
Levetiracetam	1	0.5	0.3 [0.0 - 2.7]	0.4 [0.1 - 2.9]	0.4 [0.1 - 2.9]
Valproic acid	**15**	**4.0**	**3.0 [1.4 - 6.7]**	**3.1 [1.4 - 7.0]**	**4.0 [1.9 - 8.6]**
Visits to a speech therapist					
Lamotrigine	122	16.2			
Carbamazepine[c]	**4**	**6.1**	**0.4 [0.1 - 1.0]**	**0.2 [0.1 - 0.7]**	**0.2 [0.1 - 0.7]**
Levetiracetam	22	10.2	0.6 [0.4 - 1.0]	0.7 [0.4 - 1.1]	0.7 [0.4 - 1.1]
Valproic acid	**93**	**25.1**	**1.6 [1.2 - 2.0]**	**1.4 [1.1 - 1.8]**	**1.5 [1.1 - 1.9]**

Abbreviations: AED = antiepileptic drug; IRR = incidence rate ratio; HR = hazard ratio; N/A = not applicable

Lines marked in bold correspond to HRs for which the 95% CI does not include 1.

[a] adjusted for all covariates except hospitalization for epilepsy during pregnancy

[b] adjusted for all covariates including hospitalization for epilepsy during pregnancy

[c] no possible adjustment for the proxy for alcohol

Table 4. Number of events, crude event rates (per 1,000), crude IRRs and adjusted HRs for the four outcomes according to the dose of valproic acid dispensed during pregnancy - main analysis and sensitivity analysis restricted to women considered to be treated for epilepsy

				Main analysis		Women with epilepsy		
		Events	Crude event rates	IRR	HR[a] [95% CI]	IRR	HR[a] [95% CI]	HR[b] [95% CI]
Neuro-developmental disorders	< 700 mg	7	6.3	1.3 [0.6 - 2.8]	1.3 [0.6 - 2.8]	1.5 [0.7 - 3.4]	1.6 [0.7 - 3.6]	1.6 [0.7 - 3.6]
	[700-1500 mg[	23	11.5	2.3 [1.4 - 3.8]	2.1 [1.3 - 3.5]	2.7 [1.6 - 4.6]	2.5 [1.5 - 4.3]	2.7 [1.6 - 4.6]
	≥ 1500 mg	20	33.5	6.8 [4.1 - 11.5]	7.0 [4.3 - 11.5]	7.9 [4.5 - 13.8]	8.6 [5.1 - 14.5]	8.7 [5.2 - 14.6]
Pervasive developmental disorders	< 700 mg	2	1.8	1.7 [0.4 - 7.6]	2.2 [0.5 - 8.5]	1.9 [0.4 - 9.3]	2.9 [0.7 - 11.6]	2.7 [0.7 - 11.4]
	[700-1500 mg[	7	3.4	3.3 [1.3 - 8.4]	2.7 [1.0 - 7.1]	3.7 [1.3 - 10.7]	3.1 [1.1 - 9.0]	3.0 [1.0 - 8.9]
	≥ 1500 mg	8	12.8	12.2 [4.9 - 30.4]	14.7 [6.2 - 34.7]	14.0 [5.1 - 38.5]	17.0 [6.5 - 44.6]	15.4 [5.7 - 41.1]
Mental retardation	< 700 mg	5	4.4	3.1 [1.1 - 8.5]	1.5 [0.4 - 5.9]	3.4 [1.2 - 9.9]	1.8 [0.4 - 7.0]	1.6 [0.4 - 6.7]
	[700-1500 mg[	5	2.5	1.7 [0.6 - 4.7]	1.8 [0.7 - 4.9]	1.9 [0.6 - 5.5]	1.9 [0.7 - 5.7]	2.6 [1.0 - 6.7]
	≥ 1500 mg	5	7.9	5.5 [2.0 - 15.2]	7.3 [3.0 - 17.7]	6.0 [2.1 - 17.6]	7.1 [2.7 - 18.7]	8.4 [3.4 - 20.4]
Visits to a speech therapist	< 700 mg	13	11.6	0.8 [0.4 - 1.3]	0.6 [0.3 - 1.0]	0.7 [0.4 - 1.3]	0.6 [0.3 - 1.0]	0.5 [0.3 - 0.9]
	[700-1500 mg[	54	27.3	1.8 [1.3 - 2.5]	1.6 [1.2 - 2.1]	1.7 [1.2 - 2.3]	1.5 [1.1 - 2.0]	1.5 [1.1 - 2.1]
	≥ 1500 mg	26	43.4	2.9 [1.9 - 4.3]	2.6 [1.7 - 4.0]	2.7 [1.8 - 4.1]	2.6 [1.7 - 4.0]	2.7 [1.8 - 4.1]

Abbreviations: IRR = incidence rate ratio; HR = hazard ratio

[a] adjusted for all covariates except hospitalization for epilepsy during pregnancy

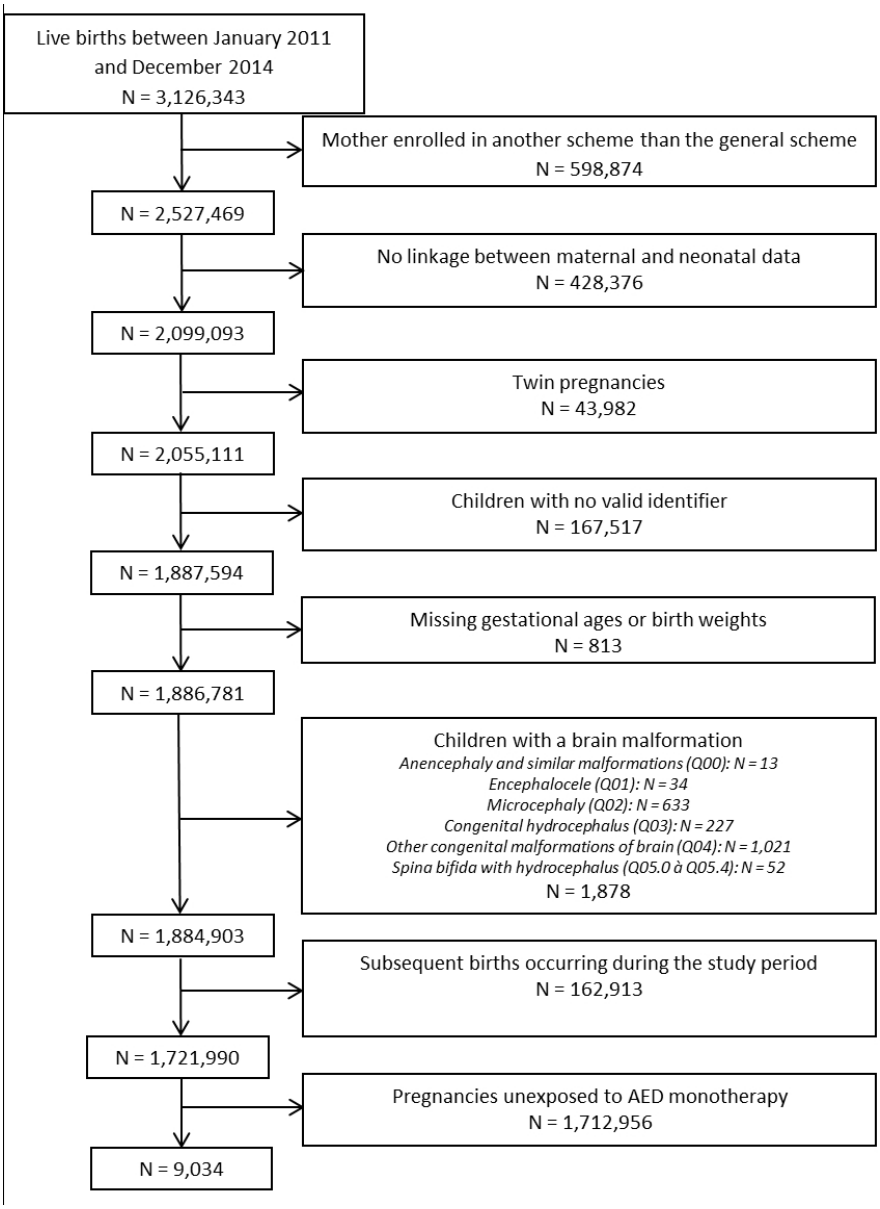
[b] adjusted for all covariates including hospitalization for epilepsy during pregnancy

Figure 1. Inclusion flow chart

Abbreviation: AED = antiepileptic drug

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)

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



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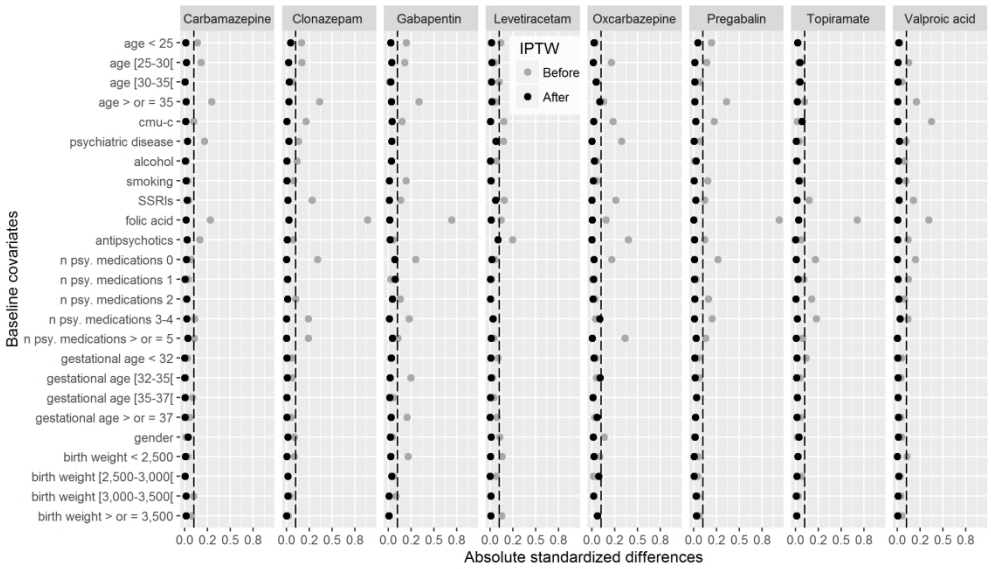

Carbamazepine
Clonazepam
Gabapentin
Levetiracetam
Oxcarbazepine
Pregabalin
Topiramate
Valproic acid
IPTW
Before
After
Baseline covariates
age < 25
age [25-30[
age [30-35[
age > or = 35
cmu-c
psychiatric disease
alcohol
smoking
SSRIs
folic acid
antipsychotics
n psy. medications 0
n psy. medications 1
n psy. medications 2
n psy. medications 3-4
n psy. medications > or = 5
gestational age < 32
gestational age [32-35[
gestational age [35-37[
gestational age > or = 37
gender
birth weight < 2,500
birth weight [2,500-3,000[
birth weight [3,000-3,500[
birth weight > or = 3,500
0.0 0.2 0.5 0.8
Absolute standardized differences

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[f]
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
[a]Divalproex 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)	NS	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)	NS	134 (21.6)	*	311 (31.4)	***
Hospitalization for epilepsy		171 (8.1)	13 (7.4)	NS	43 (6.9)	NS	22 (2.2)	***
History of mental and behavioral disorders		150 (7.1)	18 (10.2)	NS	51 (8.2)	NS	96 (9.7)	*
Proxy for alcohol intake		18 (0.9)	0 (0.0)	NS	13 (2.1)	*	22 (2.2)	*
Proxy for smoking		204 (9.7)	21 (11.9)	NS	69 (11.1)	NS	136 (13.7)	**
Folic acid supplementation		1,537 (72.9)	133 (75.6)	NS	396 (63.8)	***	525 (53.0)	***
SSRIs during pregnancy		55 (2.6)	5 (2.8)	NS	23 (3.7)	NS	33 (3.3)	NS
History of antipsychotic use		40 (1.9)	4 (2.3)	NS	15 (2.4)	NS	49 (4.9)	***
Number of psychiatric medications[a]	0	1,286 (61.0)	105 (59.7)	NS	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)	NS	7 (1.1)	NS	7 (0.7)	NS
	[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)	NS	292 (47.0)	*	496 (50.1)	NS
Birth weight	< 2,500	128 (6.1)	14 (8.0)	NS	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]
Valproic acid	***911***	***85***	***25.1***	***1.7 [1.3 - 2.2]***	*1.5 [1.1 - 1.9]*

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]
Valproic acid	***2.7 [1.9 - 4.0]***	***2.7 [1.9 - 4.0]***
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]
Valproic acid	***4.4 [2.1 - 9.2]***	***4.5 [2.1 - 9.6]***
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]
Valproic acid	***3.0 [1.5 - 6.1]***	***3.1 [1.5 - 6.2]***
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]
Pregabalin	***0.7 [0.5 - 0.9]***	***0.7 [0.5 - 1.0]***
Topiramate	1.2 [0.8 - 1.8]	1.2 [0.8 - 1.8]
Valproic acid	***1.5 [1.2 - 1.9]***	***1.5 [1.2 - 1.9]***

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 (%)	Chi$^{2\ a}$	Chi$^{2\ b}$
Number of exposed pregnancies		2,916	2,108	308			520			163		
Maternal age at birth (years)	< 25	431 (14.8)	349 (16.6)	38 (12.3)			83 (16.0)			16 (9.8)		
	[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	***
Number of psychiatric medications[c]	0	1,641 (56.3)	1,286 (61.0)	209 (67.9)			351 (67.5)			93 (57.1)		
	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 (%)	Chi$^{2\ a}$	Chi$^{2\ b}$
Gestational age (weeks after LMP)	< 32	11 (0.4)	8 (0.4)	1 (0.3)	NS	NS	4 (0.8)	NS	NS	2 (1.2)	NS	NS
	[32 - 35[	42 (1.4)	32 (1.5)	8 (2.6)			8 (1.5)			3 (1.8)		
	[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)	NS	NS	48 (9.2)	*	*	19 (11.7)	*	*
	[2,500 - 3,000[	630 (21.6)	460 (21.8)	71 (23.1)			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; Chi^2 = 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

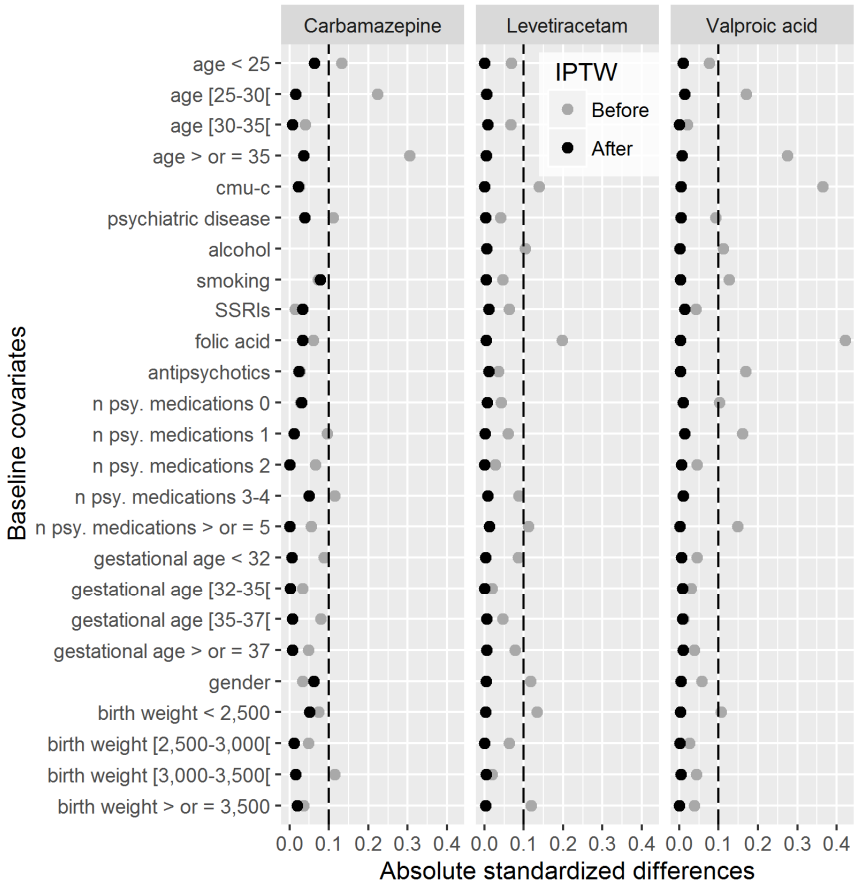
[a] compared to women exposed to lamotrigine regardless of indication

[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

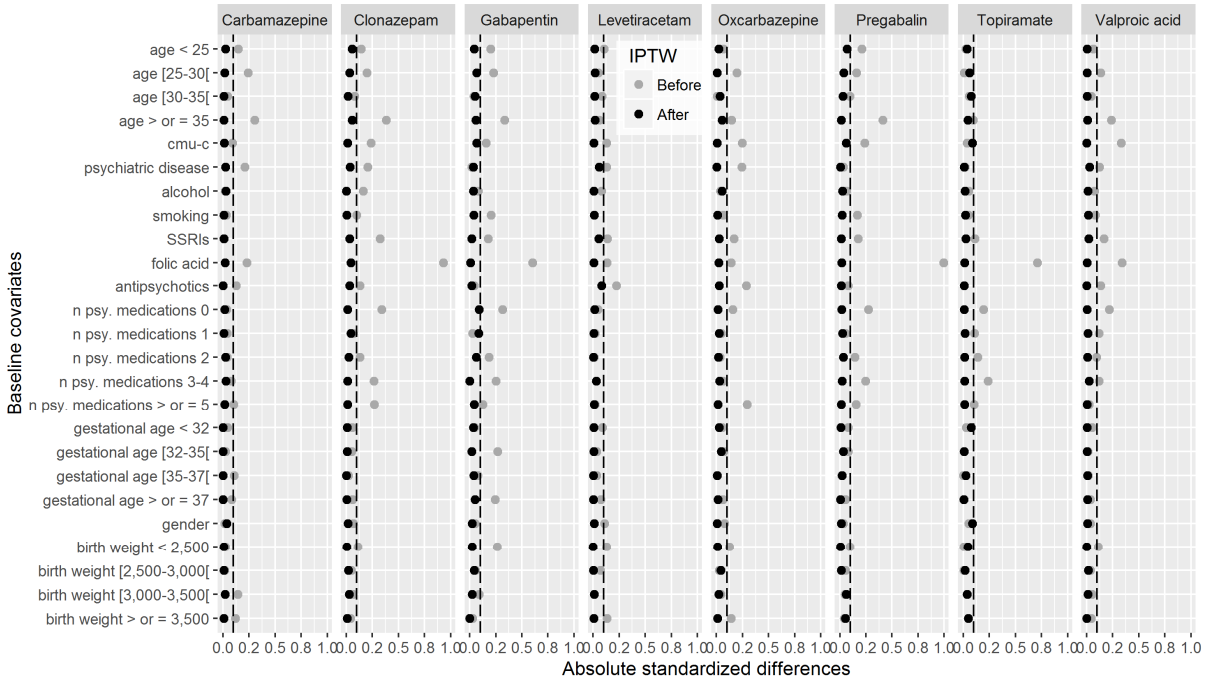
*** p <0.0001; ** p <0.001; * p <0.05; NS: Not Significant

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

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p1 l1 p3 l5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p7 l14-19
Objectives	3	State specific objectives, including any prespecified hypotheses	p7 l20-23
Methods			
Study design	4	Present key elements of study design early in the paper	p8 l4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p9-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p8-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.10-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p10 l17-23
Bias	9	Describe any efforts to address potential sources of bias	p12
Study size	10	Explain how the study size was arrived at	p9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p12 l7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p12
		(*b*) Describe any methods used to examine subgroups and interactions	p12 l13-17
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	p11 l1-3
		(*e*) Describe any sensitivity analyses	p12 l13-22
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p13 l3-5 Figure 1 p.33
		(b) Give reasons for non-participation at each stage	Figure 1 p33
		(c) Consider use of a flow diagram	Figure 1 p33
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1-2 p26-28
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	p13 l5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2 p29
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2 p29 p14-15
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	p15 l8-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p17-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p15-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p20 l13-17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.