

## RESEARCH ARTICLE

# Trends and patterns of antiseizure medication prescribing during pregnancy between 1995 and 2018 in the United Kingdom: A cohort study

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## Abstract

**Objective:** To examine antiseizure medication (ASM) prescription during pregnancy.

**Design:** Population-based drug utilisation study.

**Setting:** UK primary and secondary care data, 1995–2018, from the Clinical Practice Research Datalink GOLD version.

**Population or Sample:** 752 112 completed pregnancies among women registered for a minimum of 12 months with an ‘up to standard’ general practice prior to the estimated start of pregnancy and for the duration of their pregnancy.

**Methods:** We described ASM prescription across the study period, overall and by ASM indication, examined patterns of prescription during pregnancy including continuous prescription and discontinuation, and used logistic regression to investigate factors associated with those ASM prescription patterns.

**Main Outcome Measures:** Prescription of ASMs during pregnancy and discontinuation of ASMs before and during pregnancy.

**Results:** ASM prescription during pregnancy increased from 0.6% of pregnancies in 1995 to 1.6% in 2018, driven largely by an increase in women with indications

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other than epilepsy. Epilepsy was an indication for 62.5% of pregnancies with an ASM prescription and non-epilepsy indications were present for 66.6%. Continuous prescription of ASMs during pregnancy was more common in women with epilepsy (64.3%) than in women with other indications (25.3%). Switching ASMs was infrequent (0.8% of ASM users). Factors associated with discontinuation included age  $\geq 35$ , higher social deprivation, more frequent contact with the GP and being prescribed antidepressants or antipsychotics.

**Conclusions:** ASM prescription during pregnancy increased between 1995 and 2018 in the UK. Patterns of prescription around the pregnancy period vary by indication and are associated with several maternal characteristics.

#### KEY WORDS

antiseizure medication, bipolar disorder, epilepsy, neuropathic pain, pregnancy

## 1 | INTRODUCTION

Antiseizure medications (ASMs) are prescribed for epilepsy, psychiatric disorders, pain and migraine. Continuous treatment throughout pregnancy is often recommended, as uncontrolled epilepsy and mood disorder could be detrimental to both the mother and baby.<sup>1,2</sup> However, some ASMs, including sodium valproate and topiramate, are teratogenic.<sup>3,4</sup> The latest evidence indicates lamotrigine and levetiracetam are the safest,<sup>3</sup> and prescribing advice suggests using monotherapy and lowest effective dose; however, the safety profile of many ASMs is poorly understood.

ASM prescription during pregnancy has risen in the past two decades internationally.<sup>5,6</sup> In the UK, despite reductions in sodium valproate prescriptions, the prevalence of ASM prescribing during pregnancy in the general population rose from around 6 to 12 per 1000 pregnancies between 2007 and 2016, largely due to increases in prescriptions of pregabalin, gabapentin and lamotrigine.<sup>5</sup> Evidence also indicates that discontinuation of ASMs before or during pregnancy is common (19%–38% of women prescribed any ASM before pregnancy are not prescribed during pregnancy,<sup>6</sup> and the prevalence of prescription declines between the first and later trimesters of pregnancy),<sup>5,6</sup> despite dangers associated with stopping treatment.<sup>1</sup> Discontinuation of ASMs is more common among women with bipolar disorder<sup>7</sup> and among women taking ASMs for less than 12 months prior to the start of pregnancy.<sup>8</sup>

Few studies to date have been able to leverage large-scale health registries and examine prescriptions for multiple indications for ASM. Furthermore, analyses assessing which factors are associated with ASM discontinuation have been limited by small sample sizes. The purpose of this study is to provide an overview of current clinical practice of ASM prescriptions during pregnancy from 1995 to 2018 using the UK Clinical Practice Research Datalink (CPRD) and the newly developed pregnancy register. We further aim to describe the patterns of ASM prescription (i.e. continuation, discontinuation, initiation) that reflect the decisions made by women and their doctors with respect to ASM exposure in pregnancy, and identify potential associations with discontinuation.

## 2 | METHODS

We carried out a population-based drug prescription study using UK electronic healthcare records. All code lists and scripts can be found at <https://github.com/pmadleydowd/PREPARe-ASM-trends-1995-2018>.

### 2.1 | Data sources

We used data from CPRD GOLD,<sup>9</sup> which holds primary care data for around 9% of the UK population; patients are broadly representative of the UK population in terms of age and sex. CPRD GOLD records diagnoses using Read codes<sup>10</sup> and prescriptions using British National Formulary codes. The CPRD GOLD Pregnancy Register identified pregnancy episodes in women aged 11–49 years using an algorithm,<sup>11</sup> providing pregnancy outcomes and timing estimates derived from all available pregnancy data in CPRD including estimated delivery dates, last menstrual period dates, ultrasound dating scans and prematurity records. Using a patient identifier, data have been linked to hospital admissions and hospital outpatient data from the Hospital Episode Statistics database (HES), Office for National Statistics (ONS) death certificate data and Index of Multiple Deprivation (IMD) data. Details of the datasets used are provided in Methods S1. Informed consent by patients was not sought, as all CPRD data are anonymised. Details of CPRD's safeguarding of patient data can be found at <https://cprd.com/safeguarding-patient-data>. Patient and public involvement was not employed for this study.

### 2.2 | Study population

We selected completed pregnancies from the pregnancy register; these included pregnancies ending in either a live or stillbirth (i.e. early pregnancy losses were excluded). The estimated pregnancy start date was between 1995 and 2018. Validation work, comparing the Pregnancy Register against linked electronic maternity records in HES, has indicated

overall good agreement, suggesting most pregnancies are well captured in the register.<sup>11</sup> We required each woman to be registered for a minimum of 12 months with an ‘up to standard’ practice prior to the estimated start of pregnancy. This ensured sufficient time to record underlying health conditions and ensured pregnancies represented current pregnancies, rather than retrospective recording of historical pregnancies soon after women join a new general practice.<sup>11</sup> Multiple pregnancies were included, and an individual woman could contribute several pregnancies.

A substantial proportion of pregnancies in the Pregnancy Register are uncertain, either having no identified outcome or overlapping (referred to as ‘conflict’) with other pregnancies. In line with recommendations, we developed an algorithm to clean and recover some of these pregnancies.<sup>12</sup> Full details can be found in Methods S2.

### 2.3 | ASM prescribing

We gathered information on ASM prescriptions from primary care records from 12 months prior to the estimated pregnancy start date, throughout pregnancy, and 12 months after pregnancy end date. Prescriptions came only from primary care records and do not include prescriptions written by specialists. It is not possible to purchase ASMs in the UK without a prescription. We defined the prescription of ASM as any prescription with the Anatomical Therapeutic Chemical codes N03A (antiseizure medications). Implausible values for number of tablets taken per day and total quantity of tablets prescribed were changed to missing, and a hot-decking approach was used to singly impute missing values for quantity and number of tablets taken per day (see Methods S3 for more details). Prescription length was calculated by dividing the quantity of tablets by number taken per day. Daily dose in milligrams was calculated for each prescription by multiplying the number of tablets taken per day by the dose per tablet.

We classified ASM prescriptions during the first trimester of pregnancy by daily dose (low, medium, high; derivation of cut-offs described in Methods S4), poly- or monotherapy (polytherapy was defined as prescriptions of  $\geq 2$  distinct ASMs prescribed in the first trimester). For monotherapies, we separately describe patterns by individual drugs (lamotrigine, valproate, carbamazepine, pregabalin, levetiracetam, gabapentin, levetiracetam, other).

Exposure was also categorised according to 3-month windows from 12 months prior to pregnancy start until the end of pregnancy. First-, second- and third-trimester windows are defined in the Pregnancy Register as the pregnancy start (presumed last menstrual period) through week 13, weeks 14–26, and week 27 through the pregnancy end, respectively. We considered a woman exposed to an ASM drug in any specific period if the prescription start or end date fell within the window.

Pre-pregnancy prescription was defined as two prescriptions of the same drug in the year before pregnancy, with

at least one prescription in the 12 to 6 months before pregnancy and at least one prescription in the 6 to 0 months before pregnancy to exclude inconsistent or temporary users.

Continuous prescription during pregnancy was defined as pre-pregnancy prescription and prescription of the same individual drug in the first, second and third trimester.

Pre-pregnancy discontinuation was defined as pre-pregnancy prescription but not in the pregnancy period.

Late discontinuation was defined as pre-pregnancy and first-trimester prescription, but no prescription in the third trimester (there may or may not have been prescription during the second trimester).

Initiators of ASMs during pregnancy were those with an ASM prescription during any trimester, but no prescription in the 12 months prior to pregnancy start.

Finally, we counted the number of women switching ASMs; this was defined as receiving a particular ASM in the 12 months prior to pregnancy start but not in the pregnancy period, and initiation of a different ASM in one of the three trimesters (see Methods S5).

### 2.4 | ASM indication

A first diagnosis of each indication was identified using information prior to pregnancy start. We identified European Medicines Agency (EMA)-approved indications for ASM prescription. Identification of epilepsy used a previously developed algorithm<sup>13</sup> based on a single diagnosis of epilepsy OR two seizure codes  $>24$  h apart (see Figure S4). Previous work using primary care electronic healthcare records from Wales showed a single epilepsy diagnosis accurately identified patients with epilepsy (sensitivity 86% and specificity 97%).<sup>14</sup> In psychiatry, ASMs are also approved for use in generalised anxiety disorder (GAD), yet there is widespread off-label use for many other conditions; as such we created an indication of ‘other psychiatric conditions’. Finally, we created an indication of ‘other somatic conditions’, which included restless leg syndrome, recurrent migraines and neuropathic pain. Each patient could have multiple indications. See Methods S6 and S7 for full definition of indications.

### 2.5 | Other characteristics

Characteristics investigated for association with discontinuation of ASMs included: age in years, ethnicity, social deprivation; smoking; body mass index (BMI), records of alcohol problems, GP consultation frequency in the year prior to pregnancy start, co-prescription of antidepressants and antipsychotics in the year prior to pregnancy; estimated gravidity, illicit drug use, number of hospitalisations in the year before pregnancy, number of seizures in year prior to pregnancy, ASM dose in first trimester and ASM drug (see above for categories). Methods S8 provides full definitions of all variables and the timing of ascertainment. Most variables

were captured prior to or during pregnancy, but social deprivation was captured at a single time point.

## 2.6 | Statistical analysis

All analyses were performed in STATA 17.<sup>15</sup>

### 2.6.1 | Secular trends in prescription of ASMs during pregnancy

We described the annual prevalence of ASM prescribing any time before and during pregnancy, for each calendar year between 1 January 1995 and 31 December 2018, overall and by indication. We calculated a period prevalence for each year by dividing the number of women prescribed ASMs during pregnancy in that year by the total number of pregnant women under follow-up during that year. We then described the proportion of pregnancies where there was evidence of polytherapy and high-dose prescribing in the first trimester for each year between 1995 and 2018, overall and by indication. We calculated the proportion of women prescribed each ASM drug type at any time in pregnancy, overall and by indication.

### 2.6.2 | Patterns of prescription before and during pregnancy

We described the proportion of pregnancies where ASMs were prescribed before and during pregnancy, in 3-month time periods, overall and by ASM indication. We assessed the proportion that were high dose across different trimesters. We calculated the proportion of pregnancies where ASMs were continued, discontinued pre-pregnancy and late into pregnancy, and initiated or switched during pregnancy, overall and by ASM indication. We repeated this among women prescribed valproate to investigate changes by indication and over time.

### 2.6.3 | Factors associated with discontinuation of ASMs

Logistic regression was used to investigate factors associated with ASM pre-pregnancy discontinuation or late discontinuation during pregnancy, adjusted for year of pregnancy start. We accounted for women contributing several pregnancies by using cluster-robust standard errors. We compared women who discontinued at any time during pregnancy with women who continued ASM prescription. There were missing data for ethnicity, BMI and smoking. As these data are unlikely to be missing at random, we used complete case analysis, which is valid providing that the probability of having complete data is independent of the outcome (discontinuation of ASMs) conditional on the covariate year of pregnancy start.<sup>16</sup>

## 3 | RESULTS

We identified 752 112 eligible pregnancies between 1995 and 2018 (Figure S4), of which 5783 were exposed to ASMs in pregnancy. Compared with unexposed pregnancies, pregnancies exposed to ASMs were more likely to be among women who were older, of lower socio-economic position, currently smoked, were obese, had alcohol problems, and used illicit drugs, antipsychotics or antidepressants in the year before pregnancy (Table 1). Tables S1 and S2 respectively present changes in characteristics over time for the entire cohort and for mothers exposed to ASMs in the year before or during pregnancy.

Prescription of ASMs in pregnancy during the study period increased by 250% from 0.6% in 1995 to 1.6% in 2018 (Figure 1A), with increases in prescription seen in women with bipolar disorder, other somatic conditions and other psychiatric conditions (Figure 1B). Prescription of ASMs was stable over time among women with epilepsy (Figure 1B). Across the study period, of pregnancies exposed to an ASM, the (not mutually exclusive) indication was epilepsy for 62.5%, bipolar disorder for 4.8%, other psychiatric conditions for 60.95% and somatic conditions for 29.2% of pregnancies.

Valproate prescription declined over time (Figure 2). In women with epilepsy, valproate prescription during pregnancy decreased from 23.1% in 1995 to 2.4% in 2018. Carbamazepine also decreased in women with epilepsy (26.9% in 1995 to 5.5% in 2018), whereas prescription of lamotrigine (2.3%–17.9%), pregabalin (0%–1.0%) and gabapentin (0.8%–2.7%) increased. Among women with bipolar disorder, carbamazepine prescriptions declined (28.6% in 1995 to 0% in 2018), whereas prescription of lamotrigine increased (0%–19.3%), and valproate prescriptions varied (0% in 1995, 3.6% in 2018; peaking at 10.5% in 2007). Trends in high-dose ASM prescriptions or polytherapy during the first trimester were inconclusive over the study period (Figure S1). Polytherapy was seen in 10.3% of women with first-trimester ASM prescriptions, with the most common combinations, in order, being lamotrigine and levetiracetam, lamotrigine and other, lamotrigine and valproate, carbamazepine and valproate, and carbamazepine and lamotrigine.

In all indications, prescription of ASMs declined throughout pregnancy, with the greatest drop between the first and second trimester (Figure 3). Continuous ASM prescription during pregnancy was more common in women with epilepsy (64.3%) than other indications, including bipolar disorder (20.6%), other somatic conditions (20.7%) and psychiatric illnesses (24.9%) (Figure 4; see Table S3 for exact numbers of pregnancies per prescription pattern; denominator: pregnancies with prescription in the year before or during pregnancy and relevant indication). Bipolar disorder had higher rates of pre-pregnancy and late discontinuation (16.3% and 24.8%, respectively) than other indications. Users who had  $\geq 1$  prescription in the 12 to 6 months pre-pregnancy, but no prescription in

**TABLE 1** Characteristics of eligible pregnancies included in analyses, overall and among those with ASM prescription during pregnancy.

	Unexposed to ASM in pregnancy, n (%)	Exposed to ASM in pregnancy, n (%)
Total	N=746 329	N=5783
<b>Maternal age (years)</b>		
<18	19 817 (2.7)	95 (1.6)
18–24	157 535 (21.1)	1164 (20.1)
25–29	208 362 (27.9)	1613 (27.9)
30–34	225 993 (30.3)	1669 (28.9)
≥35	134 622 (18.0)	1242 (21.5)
<b>Ethnicity</b>		
White	474 799 (63.6)	3691 (63.8)
South Asian	24 921 (3.3)	114 (2.0)
Black	12 127 (1.6)	50 (0.9)
Other	8618 (1.2)	51 (0.9)
Mixed	4788 (0.6)	29 (0.5)
Missing	221 076 (29.6)	1848 (32.0)
<b>ASM indication pre-pregnancy. Women may have &gt;1 indication</b>		
Epilepsy	5956 (0.8)	3614 (62.5)
Bipolar	1749 (0.2)	279 (4.8)
Other somatic conditions	96 142 (12.9)	1688 (29.2)
Other psychiatric indications	257 708 (34.5)	3525 (61.0)
No recorded indication	440 485 (59.0)	197 (3.4)
<b>Maternal IMD status</b>		
1 – Least deprived	144 136 (19.3)	867 (15.0)
2	132 372 (17.7)	881 (15.2)
3	142 519 (19.1)	1050 (18.2)
4	149 706 (20.1)	1272 (22.0)
5 – Most deprived	177 596 (23.8)	1713 (29.6)
<b>Smoking status</b>		
Non-smoker	313 305 (42.0)	2026 (35.0)
Current smoker	210 240 (28.2)	2028 (35.1)
Ex-smoker	188 689 (25.3)	1575 (27.2)
Missing	34 095 (4.6)	154 (2.7)
<b>BMI</b>		
Underweight, <18 kg/m <sup>2</sup>	22 835 (3.1)	166 (2.9)
Normal weight, 18 to <25 kg/m <sup>2</sup>	339 169 (45.4)	2132 (36.9)
Overweight, 25 to <30 kg/m <sup>2</sup>	177 309 (23.8)	1350 (23.3)
Obese, ≥35 kg/m <sup>2</sup>	136 055 (18.2)	1669 (28.9)
Missing	70 961 (9.5)	466 (8.1)

(Continues)

**TABLE 1** (Continued)

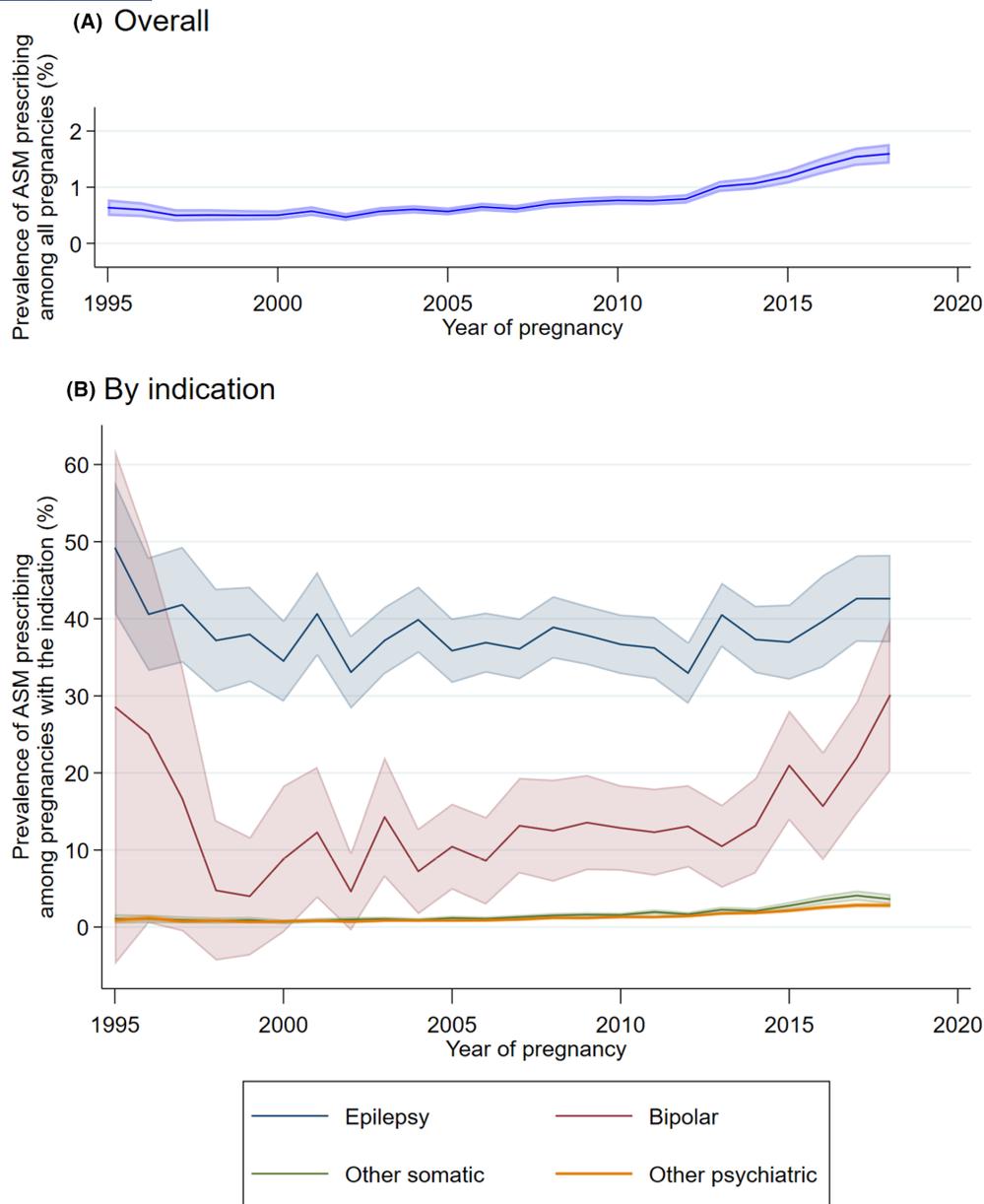
	Unexposed to ASM in pregnancy, n (%)	Exposed to ASM in pregnancy, n (%)
Evidence of alcohol problems	6709 (0.9)	105 (1.8)
Evidence of illicit drug use	1585 (0.2)	76 (1.3)
<b>Parity</b>		
0	548 137 (73.4)	4153 (71.8)
1	160 578 (21.5)	1230 (21.3)
2	30 403 (4.1)	296 (5.1)
3+	7211 (1.0)	104 (1.8)
<b>Number CPRD consultations in year before pregnancy</b>		
0	59 380 (8.0)	162 (2.8)
1–3	200 762 (26.9)	420 (7.3)
4–10	324 487 (43.5)	1792 (31.0)
>10	161 700 (21.7)	3409 (58.9)
Antipsychotic use in the year before pregnancy	500 (0.1)	28 (0.5)
Antidepressant use in the year before pregnancy	67 330 (9.0)	1814 (31.4)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation.

the 6 to 0 months pre-pregnancy, or vice versa, made up a large proportion of those with ASM prescription in the pre-pregnancy or pregnancy period (labelled as 'other' in Figure 4). Evidence of ASM switching during pregnancy was observed in 68 pregnancies (0.83% of those prescribed any ASM in the pre-pregnancy period).

Further analysis focused on women taking valproate. Among these women, 47.4% continued valproate during pregnancy, whereas 21.9% discontinued (Figure S2, Table S4). Pre-pregnancy and late discontinuation rates were comparable between women prescribed valproate and any ASM for all indications. Patterns of prescription for valproate changed over time, with an increase in discontinuation rates and no valproate initiation during pregnancy from 2015 (Figure S3).

We found evidence of increased odds of discontinuation versus continuation of ASMs in certain subgroups: women aged ≥35, nulliparous women, those prescribed ASMs for non-epilepsy conditions, with mixed ethnic background, higher social deprivation scores, current or ex-smokers, >10 GP consultations in the year prior to pregnancy, and prescribed antidepressants or antipsychotics in the year prior to pregnancy (Table S5). Women with one or more seizure events in the year before pregnancy were less likely to discontinue. Discontinuation was more likely for valproate, carbamazepine, pregabalin, gabapentin or topiramate than for lamotrigine, and higher ASM doses were associated with lower odds of discontinuation.



**FIGURE 1** Annual prevalence of ASMs prescribing during pregnancy between 1995 and 2018, (A) overall and (B) by indication at pregnancy start.

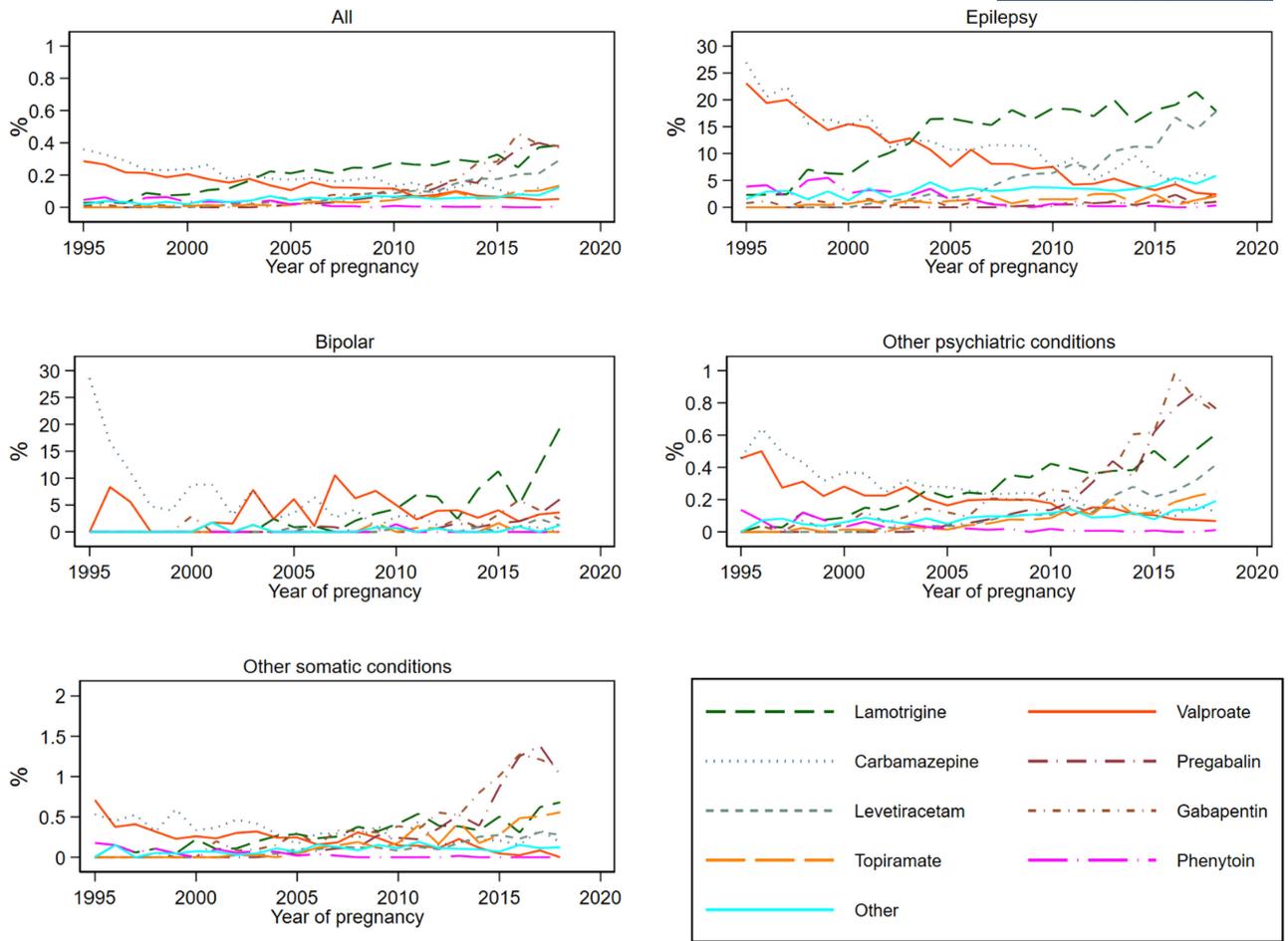
## 4 | DISCUSSION

### 4.1 | Main findings

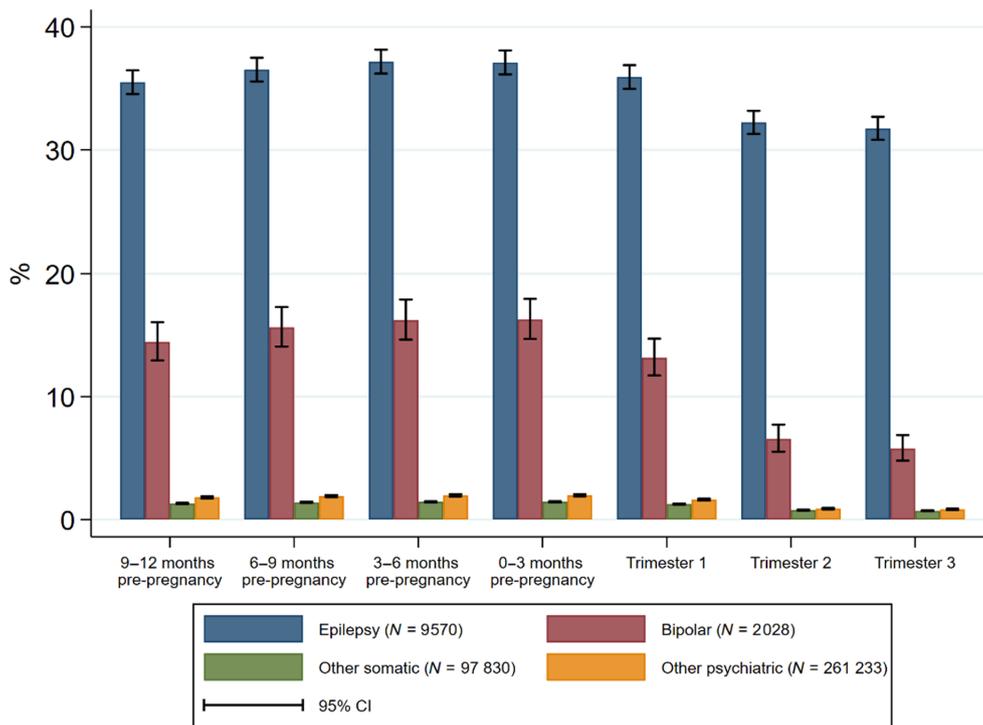
ASM prescribing during pregnancy increased 250% between 1995 and 2018. By 2018, the most prescribed ASM during pregnancy was lamotrigine, followed by pregabalin and gabapentin; valproate prescribing declined substantially. Towards the end of the study period, lamotrigine was the most common ASM in women with epilepsy and bipolar disorder, and gabapentin and pregabalin were more common in women with other indications. Similar rates of ASM prescription during pregnancy have been found in other western countries, with increasing prevalence

in recent time periods.<sup>6,17–20</sup> The overall increase in ASM prescription, in this study and others, was driven by prescription for indications other than epilepsy,<sup>20,21</sup> and prescription of ASMs with more evidence of teratogenicity decreased (specifically valproate, phenytoin, and carbamazepine).<sup>6,19,22–24</sup>

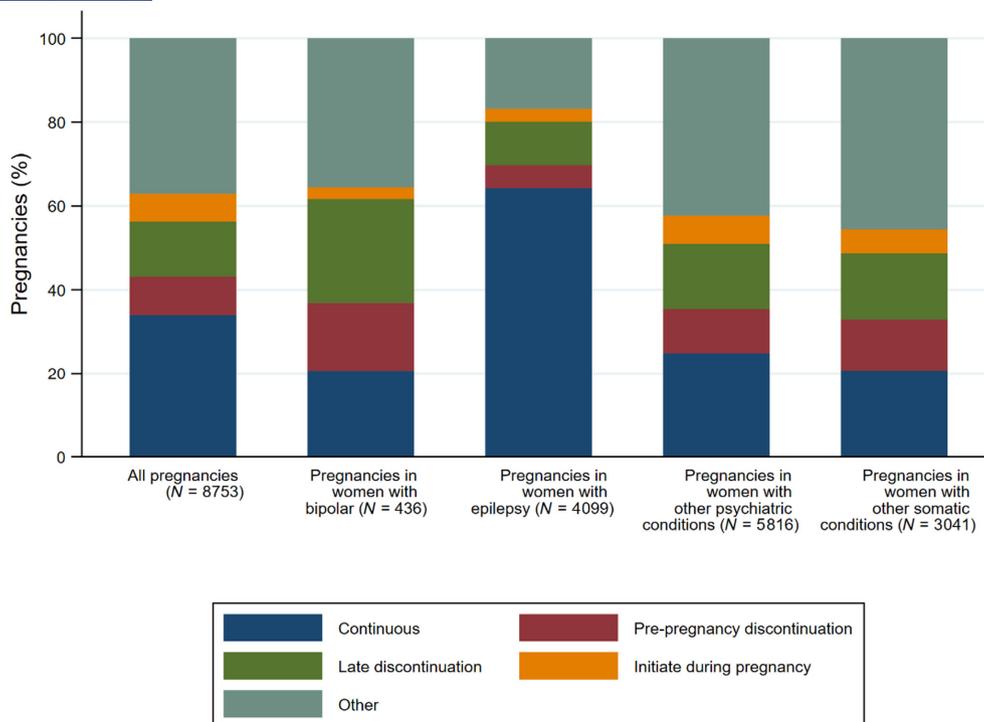
Discontinuation of ASMs during pregnancy was common, particularly among women with indications other than epilepsy. Factors with evidence for an association with discontinuation of ASMs included older age at conception and greater social deprivation. Discontinuation was most common during the second trimester, which may identify women who discontinued ASM use after they identified they were pregnant, as opposed to in anticipation of pregnancy.



**FIGURE 2** Proportion of pregnant women prescribed each ASM anytime in pregnancy during the study period, by indication.



**FIGURE 3** Percentage of pregnancies where ASMs were prescribed before and during pregnancy by ASM indication.



**FIGURE 4** Proportion of pregnancies with different patterns of prescription among women prescribed ASMs in the pre-pregnancy period or during pregnancy.

A previous UK-based study found higher discontinuation rates among women who did not have epilepsy, among which more than half discontinued ASM prescription in the first 6 weeks of pregnancy.<sup>7</sup> We found that nearly two-thirds of women with epilepsy continued to be prescribed ASMs during pregnancy, compared with a quarter of women with other indications.

ASM polypharmacy was observed in 10% of women using ASMs during the first trimester of pregnancy, similar to findings using Dutch data that showed 12% of pregnancies exposed to ASMs included polytherapy.<sup>19</sup>

## 4.2 | Interpretation

We found 7.7 per 1000 pregnancies are exposed to an ASM, equivalent to around 7000 pregnancies each year in England and Wales.<sup>25</sup> The increasing prescription of ASMs during pregnancy highlights the importance of understanding the risks and benefits of different ASMs during pregnancy.

The growth in ASM prescription in this and other studies is driven by increased prescription in women with indications other than epilepsy, yet these women are more likely to discontinue ASMs during pregnancy. Various factors may contribute to this difference, including lack of pre-pregnancy planning in women with non-epilepsy conditions, and different considerations for mental health management versus seizure control.

Guidelines regarding the prescription of valproate have emerged due to concerns about its teratogenicity. In 2018, the UK Medicines and Healthcare products Regulatory Agency advised that valproate not be prescribed to any 'woman or girl able to have children unless she has a pregnancy prevention programme in place'.<sup>26</sup> At a similar time, the European Medicines Agency ruled that valproate should not be used to treat bipolar disorder or migraine in pregnant women and should only be used in pregnant women with epilepsy if other treatments are ineffective.<sup>27</sup> Use of valproate during pregnancy declined in 2006–2016 in Denmark, Finland, Iceland, Norway, Sweden and the USA but not in Australia.<sup>6</sup> Within our data, valproate was prescribed in around 20% of pregnancies among women with epilepsy in 1995, whereas in 2018 it was prescribed in fewer than 1%. These patterns suggest that awareness of valproate teratogenicity had been guiding prescribing decisions pertaining to pregnancy in women with epilepsy for some time before clinical guidance was issued.

## 4.3 | Strengths and limitations

The study's strengths include the use of CPRD, which provides data over a 20-year period and represents the UK in terms of age, sex and ethnicity.<sup>9</sup> The dataset includes comprehensive health and prescription information with a validated source of pregnancy information.

There are several limitations. First, indication for treatment is not automatically recorded in CPRD, therefore there may be misclassification or missingness of underlying indication. Some characteristic information, including body mass index, ethnicity and smoking status was also missing for mothers in our sample. Estimates for the association with the discontinuation of ASMs for these variables may be biased as a result.

Secondly, prescriptions in CPRD do not equate with actual drug exposure; there are no data on dispensing or adherence, therefore we may have overestimated the proportion of women exposed to ASMs during pregnancy and cannot be certain that the dosage prescribed reflects the dosage taken. Further, CPRD only captures prescriptions from primary care, but some prescriptions may have been given in secondary care. This likely results in misclassification of some ASM users; however, prescription by a specialist is more likely for new users, or off-label uses, as ASM prescriptions in the UK tend to be initiated by a specialist and then ongoing management is carried out in primary care.<sup>28</sup> A major limitation of HES data is accuracy and completeness of diagnostic and procedure codes: a 2009 study found that 12% of primary diagnostic and 15% of primary procedure codes were incorrect. HES record reporting varies by provider institution, but national efforts to improve data quality include payment incentives and quality checks.<sup>29</sup> We only examined the year prior to pregnancy for prescription patterns; some women planning pregnancy well in advance may have discontinued or switched treatment earlier, thus we may have underestimated these numbers.

Thirdly, the study was based on completed pregnancies and not all pregnancies with ASM exposure, including spontaneous and elective abortions. Exclusion of spontaneous and elective abortions could impact the observed patterns of use, as use of some ASMs may lead to these outcomes. Investigating this was beyond the scope of this study. ASM prescription may be substantially different in women who experience these events. The outcome for a substantial proportion of pregnancies in the pregnancy register is unknown, potentially due to spontaneous abortion leading to records never being updated, meaning that the number of affected pregnancies may be larger than just those identified as incomplete.

Finally, we calculated duration and dose of the prescription utilising information in the primary care record; as some of this information was missing, and thus imputed, there may be some misclassification of prescription data. As concentrations of some ASMs vary<sup>30</sup> this may have led to further misclassification.

#### 4.4 | CONCLUSIONS

In this study, 7.7 per 1000 pregnancies were prescribed an ASM, and prescription was common among women with epilepsy (38% of pregnancies with epilepsy exposed) and

bipolar disorder (14% of pregnancies with bipolar disorder exposed). ASM prescription during pregnancy varied over time according to indication and drug. Patterns of ASM prescription around the time of pregnancy differed by indication and discontinuation rates were higher among women without epilepsy. Future research should investigate the impact of ASM prescribing patterns around pregnancy on maternal and fetal health to inform indication-specific guidelines.

#### AUTHOR CONTRIBUTIONS

HF and JR proposed the original study, and HF, JR and PM-D provided initial drafts of study findings. TT and DR contributed clinical and topical expertise in design and interpretation of findings. BKL, CM, KL, CN, VHA, CZ, FZM and NMD contributed methodological expertise to the design and write-up of study findings. FZM, NMD, PM-D and HF contributed data expertise in study conceptualisation and interpretation. PM-D and HF performed data analysis. All authors approved the final paper for submission and contributed to preparation and editing.

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#### CONFLICT OF INTEREST STATEMENT

None declared.

#### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

#### ETHICS STATEMENT

This study was approved by the independent scientific advisory committee (ISAC number 20\_000228).

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## REFERENCES

- Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Remnick A, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry*. 2007;164(12):1817–24; quiz 1923.
- Tomson T, Battino D, Bromley R, Kochen S, Meador K, Pennell P, et al. Executive summary: management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. *Epilepsia*. 2019;60(12):2343–5.
- Medicines and Healthcare Products Regulatory Agency (MHRA). Drugs safety update Vol 14, issue 6. London: UK Government; 2021 [cited 2023 Mar 2]. Available from: <https://www.gov.uk/drug-safety-update/antiepileptic-drugs-in-pregnancy-updated-advice-following-comprehensive-safety-review#valproate-reminder-of-the-known-risks-and-requirements>
- Bjork M-H, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. *JAMA Neurol*. 2022;79(7):672–81.
- Hurault-Delarue C, Morris JK, Charlton R, Gini R, Loane M, Pierini A, et al. Prescription of antiepileptic medicines including valproate in pregnant women: a study in three European countries. *Pharmacoepidemiol Drug Saf*. 2019;28(11):1510–8.
- Cohen JM, Cesta CE, Furu K, Einarsdóttir K, Gissler M, Havard A, et al. Prevalence trends and individual patterns of antiepileptic drug use in pregnancy 2006–2016: a study in the five Nordic countries, United States, and Australia. *Pharmacoepidemiol Drug Saf*. 2020;29(8):913–22.
- Man S-L, Petersen I, Thompson M, Nazareth I. Antiepileptic drugs during pregnancy in primary care: a UK population based study. *PLoS One*. 2012;7(12):e52339.
- Petersen I, McCrea RL, Sammon CJ, Osborn DPJ, Evans SJ, Cowen PJ, et al. Risks and benefits of psychotropic medication in pregnancy: cohort studies based on UK electronic primary care health records. *Health Technol Assess*. 2016;20(23):1–176.
- Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827–36.
- Chisholm J. The read clinical classification. *BMJ*. 1990;300(6732):1092.
- Minassian C, Williams R, Meeraus WH, Smeeth L, Campbell OMR, Thomas SL. Methods to generate and validate a pregnancy register in the UK clinical practice research datalink primary care database. *Pharmacoepidemiol Drug Saf*. 2019;28(7):923–33.
- Campbell J, Bhaskaran K, Thomas S, Williams R, McDonald HI, Minassian C. Investigating the optimal handling of uncertain pregnancy episodes in the CPRD GOLD pregnancy register: a methodological study using UK primary care data. *BMJ Open*. 2022;12(2):e055773.
- Powell G. An assessment of the use of routinely recorded data in the UK in a randomised controlled trial. Liverpool, UK: Liverpool University; 2018.
- Fonferko-Shadrach B, Lacey AS, White CP, Powell HWR, Sawhney IMS, Lyons RA, et al. Validating epilepsy diagnoses in routinely collected data. *Seizure*. 2017;52:195–8.
- StataCorp L. Stata 17. College Station: StataCorp LP; 2021 [cited 2023 Mar 02]. Available from: <http://www.stata.com>
- Hughes RA, Heron J, Sterne JAC, Tilling K. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. *Int J Epidemiol*. 2019;48(4):1294–304.
- Blotière PO, Weill A, Dalichampt M, Billionnet C, Mezzarobba M, Raguideau F, et al. Development of an algorithm to identify pregnancy episodes and related outcomes in health care claims databases: an application to antiepileptic drug use in 4.9 million pregnant women in France. *Pharmacoepidemiol Drug Saf*. 2018;27(7):763–70.
- Bobo WV, Davis RL, Toh S, Li DK, Andrade SE, Cheetham TC, et al. Trends in the use of antiepileptic drugs among pregnant women in the US, 2001–2007: a medication exposure in pregnancy risk evaluation program study. *Paediatr Perinat Epidemiol*. 2012;26(6):578–88.
- Houben E, Benson RJ, Steegers EAP, Herings RMC. Twenty-year trends in the use of antiseizure medication among pregnant women in the Netherlands. *Epilepsy Behav*. 2022;127:108549.
- Shouman W, Delaney JA, Kowalec K, Ng M, Ruth C, Falk J, et al. Trends of utilization of antiseizure medications among pregnant women in Manitoba, Canada: a 20-year population-based study. *Front Pharmacol*. 2022;13:871136.
- Bialer M. Why are antiepileptic drugs used for nonepileptic conditions? *Epilepsia*. 2012;53(Suppl 7):26–33.
- Kinney MO, Morrow J, Patterson CC, Campbell E, Russell A, Smithson HW, et al. Changing antiepilepsy drug-prescribing trends in women with epilepsy in the UK and Ireland and the impact on major congenital malformations. *J Neurol Neurosurg Psychiatry*. 2018;89(12):1320–3.
- Charlton R, Garne E, Wang H, Klungsoyr K, Jordan S, Neville A, et al. Antiepileptic drug prescribing before, during and after pregnancy: a study in seven European regions. *Pharmacoepidemiol Drug Saf*. 2015;24(11):1144–54.
- Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Declining malformation rates with changed antiepileptic drug prescribing: an observational study. *Neurology*. 2019;93(9):e831–40.
- Office for National Statistics. Births in England and Wales: 2020. Live births, stillbirths and the intensity of childbearing, measured by the total fertility rate. 2021 [cited 2023 Mar 02]. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2020#:~:text=Main%20points,decreased%20across%20all%20age%20groups>
- Medicines & Healthcare Products Regulatory Agency (MHRA). Guidance: valproate use by women and girls. London, UK: UK Government; 2018 [cited 2021 Feb 11]. Available from: <https://www.gov.uk/guidance/valproate-use-by-women-and-girls>
- Agency EM. Assessment report. Referral under Article 31 of Directive 2001/83/EC: medicinal products containing substances related to valproate. 2018.
- Personal Correspondence. Personal correspondence with a Consultant Neurologist (Dr Graham Powell), a General Practitioner (Dr Polly Duncan) and an Specialist Epilepsy Nurse. 2021.
- Boyd A, Cornish R, Johnson L, Simmonds S, Syddall H, Westbury L. Understanding hospital episode statistics (HES). London: CLOSER; 2017.

30. Pennell PB, Karanam A, Meador KJ, Gerard E, Kalayjian L, Penovich P, et al. Antiseizure medication concentrations during pregnancy: results from the maternal outcomes and neurodevelopmental effects of antiepileptic drugs (MONEAD) study. *JAMA Neurol.* 2022;79(4):370–9.

### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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