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Patterns of antidepressant prescribing around pregnancy: a descriptive analysis in CPRD

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HOW THIS FITS IN

Antidepressant use during pregnancy is increasing but up-to-date estimates of prevalence and patterns of prescribing are unknown. Mental health is important to maintain, particularly during pregnancy, so the risk of destabilisation when discontinuing is important to consider among this population. We showed that antidepressant prescribing during pregnancy has been increasing over time; discontinuation during pregnancy is common, as well as resumption in the 12 months after pregnancy. The results presented here highlight the benefit of counselling women of childbearing age upon initiation of antidepressants to support informed decision-making about their treatment if they were to become pregnant.

Short summary sentence

Antidepressant use during pregnancy is rising, with common patterns of discontinuation and resumption, underscoring the need for informed counselling at treatment initiation.

ABSTRACT

Background Antidepressant use is increasing during pregnancy but estimates of prevalence and patterns of prescribing are outdated.

Aim To describe the prevalence and patterns of antidepressant prescribing in and around pregnancy.

Design and setting Drug utilisation study in the UK's Clinical Practice Research Datalink (CPRD) GOLD Pregnancy Register.

Methods Using primary care prescription records, we identified individuals who had been prescribed antidepressants in and around pregnancy between 1996–2018 and described prevalence of prescribing during pregnancy over time. We defined 'prevalent' or 'incident' antidepressant prescribed, where 'prevalent' individuals were prescribed antidepressants both before and during pregnancy, and 'incident' individuals were newly prescribed antidepressants during pregnancy, then qualitatively compared patterns of prescribing between these two groups. We also investigated post-pregnancy prescribing, as well as characteristics associated with antidepressant discontinuation anytime during pregnancy.

Results A total of 1,033,783 pregnancies were eligible: 79,144 (7.7%) were prescribed antidepressants during pregnancy and 15,733 of these (19.9%) were 'incident'. Antidepressant prescribing during pregnancy increased from 3.2% in 1996 to 13.4% in 2018. Most women, both 'prevalent' and 'incident' prescribed, discontinued antidepressants anytime during pregnancy (54.8% and 59.9%, respectively). Over half of those who discontinued during pregnancy were prescribed antidepressants in the 12 months after pregnancy (53.0%). Younger age, previous stillbirth, and higher deprivation were associated with more frequent discontinuation anytime during pregnancy.

Conclusions Antidepressant prescribing during pregnancy has been increasing in the UK. Over half of the sample discontinued antidepressants at some point before the end of pregnancy, but post-pregnancy resumption of antidepressants was common.

Key words Antidepressants, drug utilisation, pregnancy, epidemiology.

INTRODUCTION

Antidepressants are widely prescribed medications (1, 2) and are used for a range of indications, predominantly depression and anxiety (3, 4). Pregnancy is not a contraindication for antidepressants; however, the UK's National Institute for Health and Care Excellence (NICE) lays out a series of recommendations for depression management before, during, and after pregnancy (5-8), mirrored by other recently updated guidelines (9, 10). The guidance refers to regimen changes such as discontinuation (for less severe illness), dose tapering, and product switching if the

risk of maternal condition destabilisation is lower than the potential risk to the fetus, assessed on an individual basis (5, 6). “Risk to the fetus” refers to both the uncertain effects of the medication *in utero* (11-13) and potential consequences of unmanaged maternal illness on the fetus, via physiological imbalances or characteristic differences, such as smoking and poor diet (14-16).

Antidepressant use is increasing globally among women of a childbearing age outside of pregnancy (17-20). During pregnancy, previous data from the UK (excluding Wales) suggested that 3.7% of women who had a delivery (either live or stillbirth) between 2004–2010 were exposed to selective serotonin reuptake inhibitors (SSRIs) during pregnancy, dropping from 8.8% in the year before pregnancy (21). This drop may reflect the clinical guidance, where discontinuation has been recommended (5), or reflect stigmatisation of antidepressant use during pregnancy and limited evidence for their safety (22). Similar patterns of discontinuation have been found in a previous study of antidepressant use during pregnancy (23). As guidelines are updated based on emerging evidence, so do prescribing patterns, and it is important to monitor them for research and clinical purposes.

The Clinical Practice Research Datalink (CPRD) GOLD is a repository of UK primary care data (24). Previous antidepressant utilisation during pregnancy studies have used the CPRD GOLD Mother-Baby Link, which includes all mother-baby pairs where both the mother and baby were registered with a CPRD GOLD practice (21, 23). Here, we used CPRD GOLD’s Pregnancy Register instead, capturing all pregnancy episodes in

the CPRD GOLD population, regardless of delivery type or child registration with a CPRD GOLD practice (25). We show the trend of antidepressant prescribing during pregnancy between 1996–2018, patterns of antidepressant prescribing in and around pregnancy, and characteristics associated with discontinuation during pregnancy.

METHODS

DATA SOURCES

CPRD is split into Aurum and GOLD. CPRD GOLD consists of primary care data from consenting general practices (GPs) that use Vision (24). It covers ~7% of the UK population and is broadly representative by age, sex, and ethnicity.(24) CPRD GOLD contains information on prescriptions using British National Formulary (BNF) codes and diagnoses using Read codes. The CPRD GOLD Pregnancy Register contains algorithmically derived information on all pregnancy episodes in the CPRD GOLD population (25). CPRD GOLD is linked to external data sources, including Hospital Episode Statistics (HES, for ~75% of English practices (24)) using International Classification of Diseases Tenth Revision (ICD-10) codes, Office for National Statistics (ONS), and Index of Multiple Deprivation (IMD) (24) (Methods S1.1).

All data in CPRD GOLD are pseudonymised which precludes the need for patient consent and details of CPRD's safeguarding processes can be found at https://cprd.com/safeguarding-patient-data. Patient and public engagement was not performed as part of this study.

POPULATION

Using the CPRD GOLD Pregnancy Register, we included patients with an estimated pregnancy start date within an enrolment period of January 1st, 1996 to December 31st, 2018, that ended in either a loss or delivery. Eligibility included registration with an 'up-to-standard' (UTS)(24) practice for at least 12 months prior to estimated pregnancy start (using last menstrual period, estimated due date, or imputed(25)) until the end of pregnancy, allowing sufficient time for collection of information prior to pregnancy. Each eligible pregnancy was followed up until the first of the following: transfer out of the practice, death, or the last collection date from the practice (the end of the study period, up to September 2021). The unit of measurement is 'a pregnancy'; multiple pregnancies were included, considered once, and individuals who had more than one eligible pregnancy were included for each pregnancy. Unknown outcomes and conflicting pregnancies were resolved where possible as per Campbell *et al.*'s approach(26) (Methods S1.2); unresolved pregnancies were dropped.

ANTIDEPRESSANT PRESCRIBING

Antidepressants were defined using validated codelists and divided into SSRIs, serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and 'other' antidepressants (Table S1). We identified prescriptions made in the 12 months before, during, and in the 12 months after pregnancy.

Prescription length was calculated by dividing the quantity of tablets prescribed by the number of tablets to be taken daily to estimate the prescription end date. We used hot-

decking imputation (27) where these were missing. We calculated daily dose in milligrams by multiplying the number of tablets prescribed per day by the number of milligrams delivered per dose. Daily dose in milligrams for each medication was then standardised to low, medium, or high based on dose distributions (Methods S1.3). Individuals with prescriptions of different products that overlapped by more than four weeks were defined as being on a 'multi-drug regimen'.

'Antidepressants prescribed' was defined as ≥1 prescription overlapping with the period of interest: the 12 months prior to pregnancy, during pregnancy (each week of gestation), and the 12 months post-pregnancy.

Pre-pregnancy discontinuation was defined by prescription for antidepressants in the 12 months before pregnancy but not during pregnancy (Figure 1).

Discontinuation during pregnancy was defined as antidepressant prescribing ending more than 2 weeks prior to the end of pregnancy. Discontinuation by trimester is described in Methods S1.4.

Among those who continued a single-drug regimen, antidepressant switching and dose changes were characterised; among those who continued a multi-drug regimen, product adding, product dropping, and dose changes were characterised (Figure S1, Methods S1.4). These patterns were explored among all individuals prescribed antidepressants, as well as 'prevalent' and 'incident prescribed' (Figure 1).

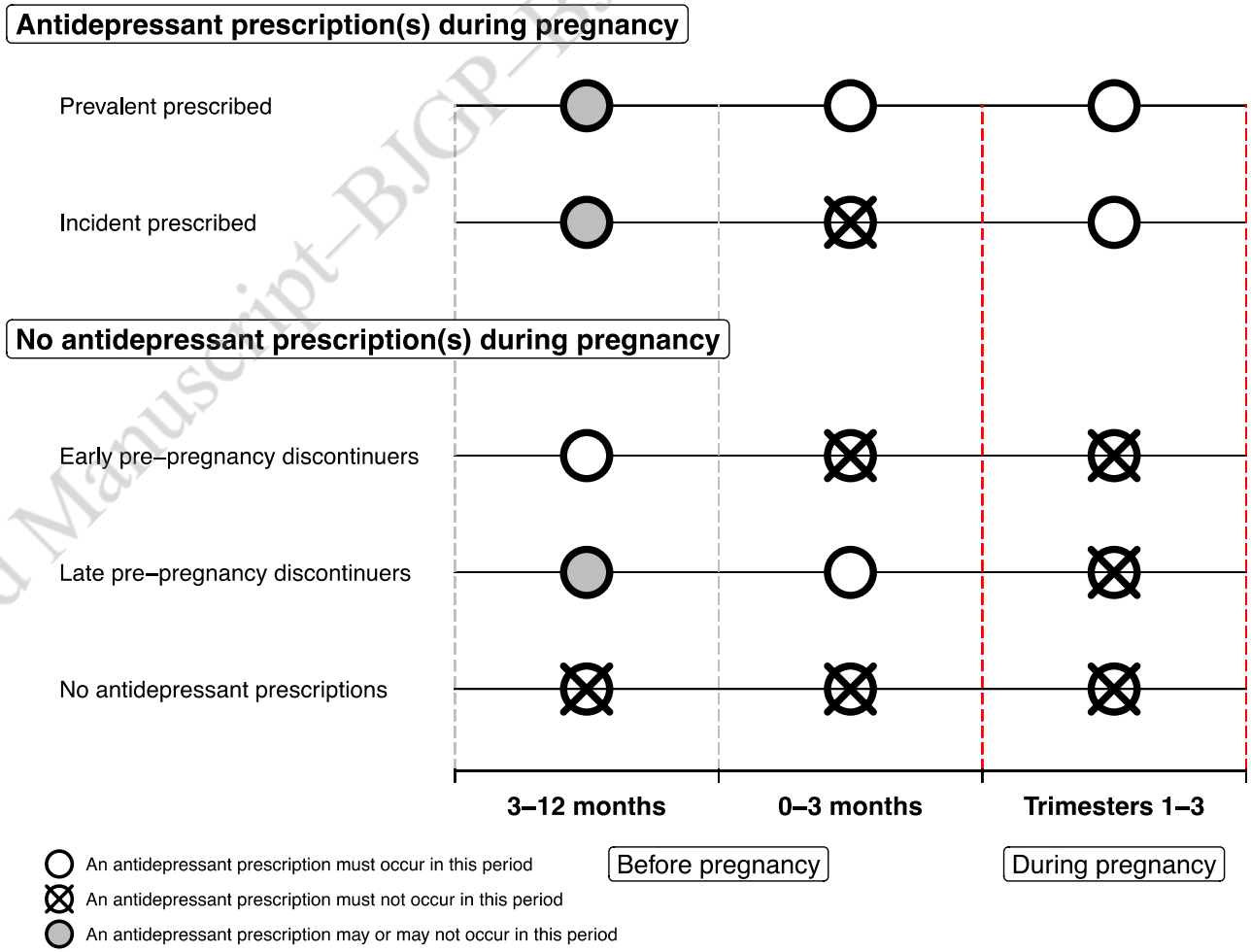


Figure 1 Prescription windows for pre- and during pregnancy.

Antidepressant prescribing after pregnancy was defined as those with at least one prescription in the 12 months post-pregnancy. Post-pregnancy prescribing was stratified by newly prescribed post-pregnancy and discontinuers from before and during pregnancy (follow-up sensitivity analysis described below).

POSSIBLE INDICATIONS

We compiled a list of licensed indications for antidepressants from the BNF and European Medicines Agency in the UK as of 2023. Then, we identified corresponding Read and ICD-10 codes (lists verified by clinical authors) which were applied to primary and secondary care data (where available) to identify the following: depression, anxiety, other mood disorders with a depressive element, eating disorders, pain, diabetic neuropathy, stress (urinary) incontinence, migraine prophylaxis, tension-type headache, and narcolepsy with cataplexy (Methods S1.5). Reporting indications for issued prescriptions is not a prerequisite of CPRD, so evidence of a possible indication may not denote the actual indication for which antidepressants were prescribed.

CHARACTERISTICS

Information on characteristics was abstracted for all eligible pregnancies. Demographics such as age (at the start of pregnancy), body mass index (BMI, around the start of pregnancy), ethnicity, socioeconomic position (SEP) (proxied using practice-level IMD quintile),(28) gravidity and parity (at the start of pregnancy), primary care consultations (in the 12 months before pregnancy), prescriptions of other

medications (in the 12 months before pregnancy), and other diagnoses (ever before the start of pregnancy), were captured from relevant data sources and defined per Table S2.

STATISTICAL ANALYSIS

We calculated the proportion of pregnancies in each year prescribed antidepressants during pregnancy and restricted to pregnancies ending in live births in sensitivity analysis. We showed antidepressant prescribing during pregnancy by UK region across the study period.

Among eligible pregnancies, we calculated the proportion of individuals who were prescribed antidepressants prior to pregnancy and of these, the proportion who discontinued prior to pregnancy.

Of those prescribed antidepressants during pregnancy, we described discontinuation and continuation of a single- and multi-drug regimen (i.e., switching and dose changes), repeating analyses stratified by 'prevalent' and 'incident prescribed'. We explored trimester of discontinuation by restricting to those with at least 29 completed weeks' gestation. We stratified the primary patterns analysis by nulliparity, stringency of 'incident' definition (>12 months without an antidepressant prescription before pregnancy), delivery type, either deliveries or losses, and restricted to those with linked secondary care data.

Of those who were prescribed antidepressants after pregnancy, we calculated the proportion of newly prescribed post-pregnancy and those resuming having discontinued prior to or during pregnancy. To explore 'post-pregnancy' compared to 'postnatal' prescribing, we stratified this analysis by delivery type in sensitivity analysis. We also restricted the sample to those with at least 12 months post-pregnancy follow-up.

We characterised timing of depression and anxiety and calculated the proportion of those prescribed antidepressants during pregnancy that had evidence of each possible antidepressant indication.

Logistic regression, minimally adjusted for pregnancy start year, was used to understand the relationship between characteristics and antidepressant discontinuation anytime during pregnancy. Each logistic regression model was a complete records analysis (CRA), so individuals were dropped in the event of missing data and the models were clustered by pregnant individual to account for those contributing more than one pregnancy to the analysis. We ran a sensitivity analysis investigating the association between record missingness and discontinuation during pregnancy to assess the potential bias introduced in a CRA.(29)

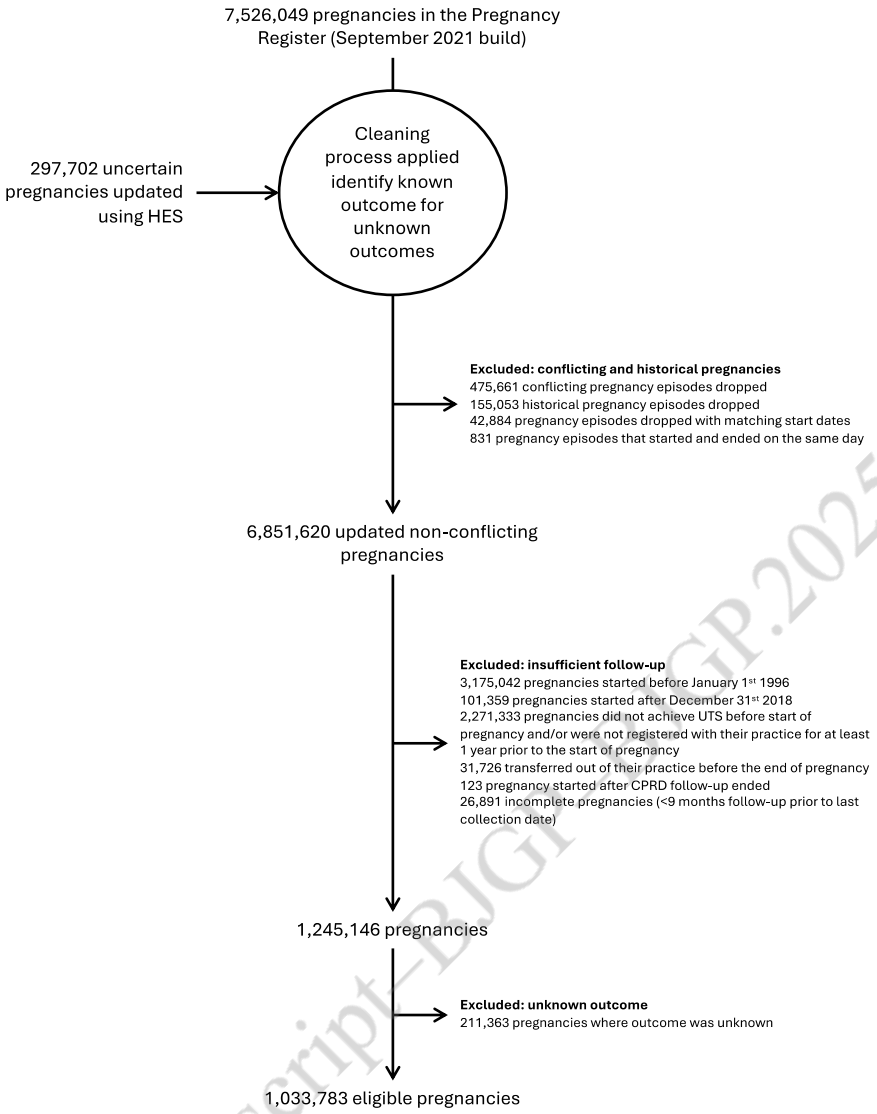
All analyses were performed in Stata 17.0 and R 4.3.1. This study was approved by CPRD's Independent Scientific Advisory Committee in 2021 [21_000362] and all scripts and codelists are open source: https://github.com/flozoemartin/Patterns/.

RESULTS

STUDY POPULATION

Of the pregnancies in the CPRD Pregnancy Register (September 2021), 1,033,783 were eligible. Pregnancies were excluded due to occurring outside the study window (*n*=3,276,401) or insufficient follow-up (*n*=2,271,333) (Figure 2). Most pregnancies in the sample ended in live birth (71.1%), with 12.3% ending in miscarriage and 13.5% ending in termination, among other outcomes (Table S3). Those with at least one pregnancy within which antidepressants were prescribed contributed more pregnancies to the analysis than those without any antidepressant prescriptions during pregnancy.

Figure 2 Detailed flow of pregnancies through the study.



Among eligible pregnancies, 79,144 (7.7%) were prescribed antidepressants anytime during pregnancy (Table 1). Those prescribed antidepressants during pregnancy were more likely to smoke (43.4% *v* 28.7%) and live in the most deprived IMD quintile (30.6% *v* 26.9%) than non-prescribed. Other mental health-related prescriptions were more commonly prescribed to women who were prescribed antidepressants during pregnancy (e.g., mood stabilisers in 6.7% *v* 0.7% of non-prescribed). High-dose folic acid and anti-emetics were more widely prescribed during pregnancy to those also prescribed antidepressants than those who were not (Table S5).

Table 1 Distribution of characteristics among those prescribed antidepressants during pregnancy (proportions of additional characteristics among those prescribed and not prescribed provided in Table S5).

Characteristics	Prescribed antidepressants during pregnancy[1] / Total n /N	%
Total	79,144 / 1,033,783	7.7
Pregnancy start year		
1996 – 2000	5,234 / 120,490	4.3
2001 – 2006	19,738 / 306,175	6.5
2007 – 2012	28,643 / 372,539	7.7
2013 – 2018	25,529 / 234,570	10.9
Age at start of pregnancy		
<18	1,117 / 38,836	2.9
18–24	19,196 / 234,583	8.2
25–29	20,632 / 265,993	7.8
30–34	20,545 / 287,482	7.2
≥35	17,654 / 206,889	8.5
Practice Index of Multiple Deprivation (IMD)		
1st quintile (least deprived)	10,316 / 163,727	6.3
2nd quintile	11,811 / 167,765	7.0

3rd quintile	14,390 / 189,474	7.6
4th quintile	18,433 / 231,787	8.0
5th quintile (most deprived)	24,194 / 281,030	8.6
Ethnicity		
White	51,322 / 639,193	8.0
South Asian	959 / 31,837	3.0
Black	513 / 16,920	3.0
Other	357 / 11,235	3.2
Mixed	429 / 6,657	6.5
Missing	25,564 / 327,941	7.8
History of pregnancy loss at the start of pregnancy		
Miscarriage	15,405 / 162,414	9.5
Stillbirth	722 / 6,345	11.4
Termination	19,360 / 174,264	11.1
Parity at the start of pregnancy		
0	29,080 / 489,830	5.9
1	26,667 / 348,858	7.6
2	14,754 / 132,186	11.2
3 or more	8,324 / 58,465	14.2
Number of GP visits in the 12 months before pregnancy		
0	5,177 / 116,218	4.5
1–3	5,291 / 266,266	2.0
4–10	26,633 / 426,917	6.2
≥10	42,043 / 224,382	18.7
Mental health problems ever before the end of pregnancy		
Depression	63,795 / 263,063	24.3
Anxiety	38,266 / 164,115	23.3
Schizophrenia	883 / 2,405	36.7
Eating disorders[3]	4,142 / 19,635	21.1

[1] A prescription made during or overlapping with pregnancy

[2] No prescription made during or overlapping with pregnancy

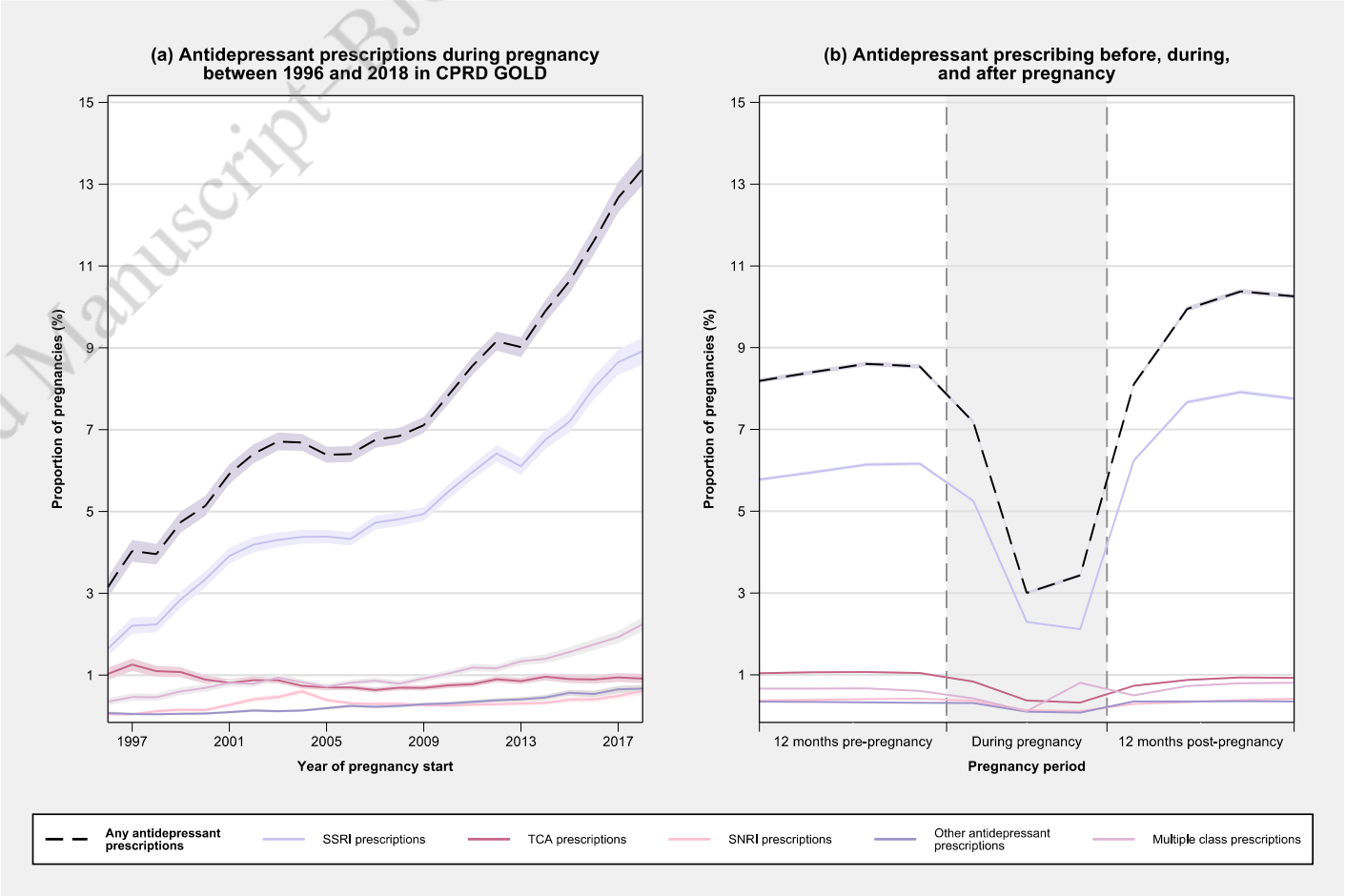
[3] Anorexia nervosa, bulimia, and other disordered eating codes (codelist in the supplement)

TRENDS OVER TIME

Antidepressant prescribing during pregnancy increased from 3.2% in 1996 to 13.4% in 2018. Exclusive treatment with SSRIs has dominated antidepressant prescribing during pregnancy (Figure 3a). We observed a similar increase when restricting to live

births (2.6% in 1996 to 12.6% in 2018) (Figure S3) and when restricting to pregnancies where at least two prescriptions were written during pregnancy (2.1% in 1996 to 11.1% in 2018).

Figure 3 (a) Antidepressant prescribing during pregnancy over time in CPRD GOLD and (b) Proportion of pregnancies in the sample who were prescribed antidepressants before, during, and after pregnancy. The denominator for trimesters two and three consists of those whose pregnancies reached trimesters two and three, respectively, i.e., pregnancy losses in trimester one do not contribute to the denominator for trimesters two and three.



Wales had the highest overall rate of antidepressant prescribing during pregnancy (9.5% of pregnancies, *n*=12,185) and London had the lowest rate (4.6% of pregnancies, *n*=77,744) (Table S6).

PATTERNS OF PRESCRIBING

Of the 142,817 individuals prescribed antidepressants in the 12 months before pregnancy (13.8% of pregnancies), 92,670 discontinued prior to the start of pregnancy (64.9% of pre-pregnancy antidepressant prescribed).

Of the 79,144 pregnancies among individuals who were prescribed antidepressants during pregnancy (7.7% of pregnancies) (Figure 3b), 63,411 were 'prevalent prescribed' (80.1% of antidepressant users during pregnancy). The remaining 15,733 (19.9%) were 'incident prescribed'.

Most 'prevalent prescribed' individuals discontinued antidepressants during pregnancy (54.9%). Of the 42.8% who continued a single-drug regimen throughout pregnancy, the majority appeared to continue their regimen with no changes (63.5%), 22.9% changed their dose, and 8.6% switched to a different product. The remaining 5.0% had evidence of multiple regimen changes during pregnancy (Table 2).

Many 'incident prescribed' individuals also discontinued during pregnancy (59.9%). Of the 'incident prescribed' who continued a single-drug regimen throughout pregnancy (39.7%), the majority did not make any changes to their regimen (80.0%). There was

evidence of dose changes for a further 10.9%, drug switching in 7.2%, and multiple changes for 1.8% (Table 2).

Table 2 Patterns of prescribing during pregnancy.

Pattern of prescribing during pregnancy	Total prescribed during pregnancy	'Prevalent prescribed'[a]	'Incident prescribed'[b]
All	79,144 (100.0)	63,411 (100.0)	15,733 (100.0)
Discontinued during pregnancy[c]	44,228 (55.9)	34,801 (54.9)	9,427 (59.9)
Continued[d] a single drug regimen throughout pregnancy	33,365 (42.2)	27,120 (42.8)	6,245 (39.7)
Continued[d] a multi-drug[e] regimen throughout pregnancy	1,551 (2.0)	1,490 (2.3)	61 (0.4)
Continued a single drug regimen throughout pregnancy	33,365 (100.0)	27,120 (100.0)	6,245 (100.0)
Antidepressant switched	2,776 (8.3)	2,329 (8.6)	447 (7.2)
Dose reduced	2,237 (6.7)	2,148 (7.9)	89 (1.4)
Dose increased	2,236 (6.7)	1,779 (6.6)	457 (7.3)
Dose fluctuated	2,422 (7.3)	2,282 (8.4)	140 (2.2)
More than one regimen change[f]	1,473 (4.4)	1,359 (5.0)	114 (1.8)
No changes to drug regimen	22,221 (66.6)	17,223 (63.5)	4,998 (80.0)
Continued a multi-drug[e] regimen throughout pregnancy	1,551 (100.0)	1,490 (100.0)	~60 (100.0)
Antidepressant added	225 (14.5)	215 (14.4)	10 (16.4)
Antidepressant dropped	207 (13.3)	193 (13.0)	14 (23.0)
Products added & dropped	294 (19.0)	281 (18.9)	13 (21.3)

Dose changes	83 (5.4)	83 (5.6)	<5
Multiple changes (to dose & product)	416 (26.8)	404 (27.1)	12 (19.7)
No changes to drug regimen	326 (21.0)	314 (21.1)	12 (19.7)

[a] Those who had at least one prescription for antidepressants in the 3 months prior to pregnancy and during pregnancy

[b] Those who did not have a prescription for antidepressants in the 3 months prior to pregnancy but at least one prescription during pregnancy

[c] Evidence of regimen changes before discontinuation *n*=6,998 (15.8%)

[d] Those who had an overlapping prescription with the end of pregnancy

[e] Those prescribed at least two, differing antidepressant products >5 days from the end of their current prescription

[f] Those who experienced a switch in product as well as at least one dose change

When restricting the patterns analysis to specific time windows, we observed a decrease in discontinuation (from 66.6% 1996–2000 to 50.5% 2013–2018) and a decrease in regimens with no changes (74.2%–63.0% over time) (Table S7). We observed a similar distribution of prescribing patterns when using a more stringent definition of incident prescribing (Table S8) and when stratifying by parity (Table S9). When restricting to discontinuers with at least 29 completed weeks' gestation, the majority discontinued in trimester one: 81.8% and 63.4%, 'prevalent' and 'incident prescribed', respectively (Table S10).

We restricted the primary analysis to deliveries, then to losses (Table S3). The patterns of prescribing during pregnancy among deliveries was similar to the primary analysis, with 65.4% discontinuing during pregnancy and 54.5% of the single-drug continuers making no changes to their regimen (Table S11). Conversely, most women who experienced a loss continued antidepressants throughout pregnancy (62.8%), reflecting the shorter length of gestation (Table S12). When restricting to those with >1 prescription in pregnancy and then to those with linked HES data, the distribution of patterns didn't change for either restriction (Table S13 and Table S14).

In the 12 months after pregnancy, 15.8% received ≥1 prescription for antidepressants (*n*=162,947, Table S15), representing a slight increase from pre-pregnancy (Figure 3b). Of those who discontinued within 12 months prior to pregnancy, 34.2% resumed antidepressant treatment in the 12 months after pregnancy (*n*=25,532). However, just over half of the 'during pregnancy discontinuers' resumed antidepressants in the 12

months after pregnancy (53.0%, *n*=23,457) (Table S15); when restricting to first pregnancies 47.3% of those who discontinued during pregnancy, resumed in the 12 months after pregnancy (Table S16).

By delivery type, 58.2% of discontinuers during a pregnancy that ended in a loss resumed post-pregnancy, compared to 51.5% of pregnancy discontinuers who had a delivery (Table S17). When restricting to those with at least 12 months of follow-up after the end of pregnancy, our proportions did not change (Table S18).

POSSIBLE INDICATIONS

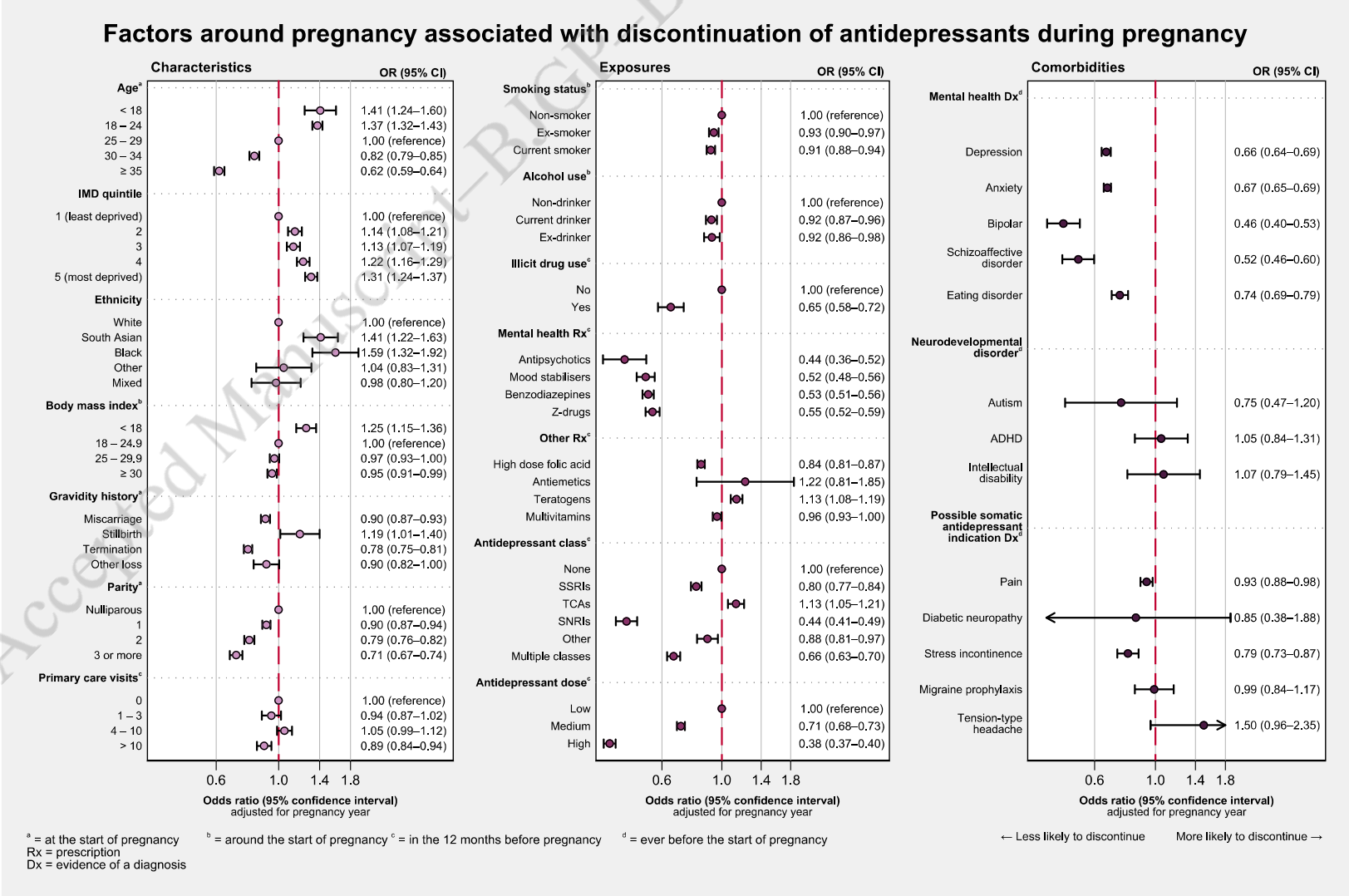
Of those prescribed antidepressants during pregnancy, 80.6% had evidence of depression ever before the end of pregnancy (Table 1), of which only 4.9% was incident antenatal depression (Table S19). Among the same group, 48.3% had evidence of anxiety before the end of pregnancy, of which 3.0% was incident antenatal anxiety during pregnancy (Table S19). Incident anxiety post-pregnancy was more common among those prescribed antidepressants during pregnancy, whereas incident post-pregnancy depression was more common among those not prescribed (Table S19). Among those prescribed antidepressants during pregnancy, 9.6% had no evidence of an antidepressant indication (Table S20).

CHARACTERISTICS ASSOCIATED WITH DISCONTINUATION

Younger (<18 years OR 1.41 95%CI 1.24–1.60) and 18–24 years OR 1.37 95%CI 1.32–1.43), underweight (OR 1.25 95%CI 1.15–1.36), and more deprived (most

deprived OR 1.31 95%CI 1.24–1.37) individuals were more likely to discontinue antidepressants than comparators. Ethnicity was associated with discontinuation during pregnancy, where Black and South Asian individuals were more likely to discontinue than white individuals (Figure 4).

Figure 4 Maternal factors associated with discontinuation of antidepressants during pregnancy.



Discontinuing during pregnancy increased the likelihood of having missing data in BMI, smoking, and alcohol use as compared to continuing throughout pregnancy (Table S21).

DISCUSSION

SUMMARY

The present study gives a detailed overview of antidepressant prescribing in and around pregnancy in the UK between 1996 and 2018, highlighting an increase from 3.2–13.4% between 1996–2018. Utilising all prescriptions made during pregnancy, we describe patterns of antidepressant prescribing during pregnancy and show the high resumption rate soon after the end of pregnancy among those who discontinued during pregnancy (53.0%).

Of both ‘prevalent’ and ‘incident prescribed’ , the majority discontinued their regimen at some point during pregnancy (54.9% and 59.9%, respectively). Of the ‘prevalent prescribed’ who continued their regimen throughout pregnancy, 51% continued their regimen with no regimen changes, as opposed to over 70% of ‘incident prescribed’. Most measured demographics were associated with discontinuation.

Those prescribed antidepressants during pregnancy have been shown to have greater needs and require more support during pregnancy.(30) It is important to understand this group to provide the best care in and around pregnancy.

STRENGTHS AND LIMITATIONS

The present study has several strengths. It is a large, population-based study that includes pregnancies of all known outcomes, not restricted to live birth, using a validated pregnancy register linked to primary and secondary care (25). It is the first study to discuss antidepressant prescribing alongside indication prevalence in and around the pregnancy period. Given that antidepressants are not sold over the counter in the UK and mostly prescribed in primary care, we are confident that we captured the majority of antidepressant prescribing.

The study does however have several limitations. The number of pregnancies has been dropping in CPRD GOLD in the last decade, likely due to more pregnant individuals self-referring to a midwife and circumventing the GP (31). It is possible that women on antidepressants are more likely to report their pregnancy to the GP than women who are not, which would artificially inflate the proportion of women on antidepressants during pregnancy after 2010 in the eligible sample and make the increase in antidepressant prescribing during pregnancy look greater than is true in the general population. However, antidepressant prescribing during pregnancy increased from 3.2–7.1% between 1996–2009 before these changes were enacted, reflecting trends outside of pregnancy among women of a child-bearing age.

Despite updating unknown outcome pregnancies and conflicts where possible (26), 9% of pregnancies were unresolved and thus dropped. This may have introduced selection bias, and we may have incorrectly estimated the prevalence of certain

prescribing practices or the associations between different demographics and discontinuation. Although gradual dose reduction is recommended when discontinuing antidepressants (32), there was limited evidence of this in the prescription data. However, it is plausible that dose reductions may have been described by the prescriber in the free text, that were then missed in the available structured data fields.

Pregnancy length was imputed for some pregnancies in the Pregnancy Register; this is more common for losses where less information on the pregnancy is available, potentially putting the study at risk of differential antidepressant exposure misclassification. We may have been more likely to misclassify losses as antidepressant prescribed when they weren't, thus have overestimated antidepressant exposure and certain patterns among this group. We used prescriptions of antidepressants to proxy exposure, but we had no information on dispensation or adherence, so some individuals may have been misclassified if they never filled or took their prescription. Identifying those on a multi-drug regimen was challenging; it was difficult to differentiate an antidepressant switch from a multi-drug regimen in many cases and some multi-drug regimens may have been misclassified as product switching.

Missing data was a problem in some of the covariates, such as smoking and BMI. In sensitivity analysis, we observed an association between missingness in ethnicity, BMI, smoking, and alcohol use and an increased likelihood to discontinue antidepressants, suggesting there may be a risk of bias in the CRA for these

characteristics (29), so should be interpreted with caution. Prescriptions made in hospital were not captured in these data, so pregnant women prescribed antidepressants solely in the hospital setting may have been misclassified as not prescribed during pregnancy.

Individuals may have contributed more than one pregnancy to the analysis, which is not accounted for in the patterns analysis; however, the logistic regression models are clustered on pregnant individual, and we included sensitivity analyses stratifying the patterns analysis on parity. Future studies may consider Poisson regression and other approaches to tackle this question.

COMPARISON WITH EXISTING LITERATURE

Our estimate of antidepressant prescribing during pregnancy is in line with the trajectory identified by Petersen *et al.* in 2011, who reported a 4-fold increase in antidepressant prescribing during pregnancies that ended in live birth between 1992–2006 in the UK (33). The upwards trend over time reflects the increased antidepressant prescribing in the general UK population over recent decades(19, 34) and shows the growing need for evidence-based advice on antidepressant use during pregnancy. Most individuals who were using antidepressants during pregnancy discontinued, predominantly in trimester one. NICE guidance notes that antidepressants can be used at any stage of pregnancy if clinically indicated, but that their risks and benefits should be person-centered (5-7). However, the evidence

regarding risks and the efficacy of these guidelines in reducing them, is mixed or unknown.

In relation to patterns of prescribing, the findings were in line with previous literature (21, 23). We found that continuation without dose changes was more common among 'incident' than 'prevalent' users, due to the likelihood that clinically, 'incident' users would be initiated on and maintain a low dose if symptoms were managed.

It is important to note the high post-pregnancy antidepressant resumption rate among those who discontinued antidepressants during pregnancy, which remained high when stratified by delivery and pregnancy loss (51.5% and 58.2%, respectively). A small study from France identified both benzodiazepine and anxiolytic use after pregnancy was higher than pre-pregnancy among those who discontinued antidepressants during pregnancy suggesting that symptoms may worsen when interrupting treatment (35). High antidepressant resumption rate may potentially reflect an exacerbation of illness during or after pregnancy.

Few studies have looked at characteristics associated with discontinuation of anti-depressants during pregnancy. Prady *et al*. reported similar percentages of discontinuation of medications for common mental disorders in white and non-white groups, but in a much smaller sample of 174 women who discontinued medication during pregnancy (36). Missing data and confounding should be factored into the interpretation of the analyses presented here, but are important findings nonetheless given the larger sample size and broad spectrum of characteristics explored.

IMPLICATIONS FOR RESEARCH AND PRACTICE

The importance of descriptive epidemiology, here in the context of drug utilisation, cannot be underestimated (37). It underpins subsequent studies aimed to assess causality in an observational setting by highlighting important measured demographics among exposure groups of interest, key differences between them and potential comparator groups, and data pitfalls that might hinder causal inference. The present study provides a useful resource for both researchers hoping to contribute high-quality evidence regarding the safety of antidepressant use during pregnancy and clinicians who are interested in the trends of different prescribing patterns in and around pregnancy.

The results presented here highlight the benefit of counselling women of childbearing age upon initiation of antidepressants, that contextualizes relative risk using absolute risks to support informed decision-making if they were to become pregnant. Although from this study we don't know why people discontinued (38), transparency surrounding the way antidepressants are being prescribed in primary care in turn advocates for enhanced monitoring and the provision of non-pharmacological mental health treatments for women who discontinue. The findings promote discussions about the use of antidepressants during pregnancy, allowing for safer discontinuation strategies, such as gradual tapering, where appropriate. The high rates of postpartum resumption of antidepressants emphasise the importance of thorough mental health discussions at the 6-week postnatal check, particularly regarding the safety of antidepressant use

during breastfeeding. The most recent MBRRACE-UK report showed that suicide is still the leading cause of direct death in the 6 weeks to 12 months postpartum (39), reinforcing the importance of mental healthcare during this period.

The identification of an association between younger age, previous stillbirth, non-white ethnicity, and higher deprivation with discontinuation during pregnancy highlight vulnerable groups that may require additional support in primary care and suggest areas of continued research focus to better understand patient groups.

CONCLUSION

Antidepressant use during pregnancy increased between 1996–2018 in the UK, from 3.2%–13.4%. Over half of individuals prescribed antidepressants during pregnancy discontinued at some point before the end of pregnancy (55.9%); resumption rate in the 12 months after pregnancy was high (53.0%) among these individuals. Future studies might leverage trajectory modelling to assess the impact of different antidepressant prescribing patterns on maternal health, primarily to address the dearth of evidence for antidepressant effectiveness during pregnancy.

AUTHOR CONTRIBUTIONS

FZM, DR, GCS, HF, and KEE proposed the original study, and FM provided the initial draft of the study. DR, VNS, and AS assisted with the clinical sign-off for the codelists; JLR provided expertise in codelist creation also. DR, LB, VNS, and AS provided clinical and topical expertise and interpretation of the findings. GCS, KEE, LB, PMD,

JLR, DR, and HR provided epidemiological expertise. PMD, HF and DR contributed methodological and data expertise to the design and write-up of the study. FZM performed the data analysis. All authors contributed to the preparation and editing of the manuscript and approved the final paper for submission.

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ETHICAL APPROVAL

This study was approved by the independent scientific advisory committee (ISAC number 21_000362) on May 13th 2021.

COMPETING INTERESTS

None.

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