Received: 21 February 2021 | Revised: 12 April 2021 | Accepted: 19 May 2021

DOI: 10.1002/brb3.2228

Brain and Behavior Open Access WILEY

ORIGINAL RESEARCH

Trend of recognizing depression symptoms and antidepressants use in newly diagnosed Parkinson's disease: Population-based study

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Abstract

Objectives: Although depression symptoms are common among patients with Parkinson's disease (PD), the medical literature still reports underrecognition of depression in patients with PD. Our main objective is to examine the trend of depression recognition during the first year of PD diagnosis using large population data.

Methods: We conducted a population-based study of residents in Wales, using the Secure Anonymized Information Linkage (SAIL) Databank. We included newly diagnosed patients with PD aged 40 years or older with a first PD diagnosis between 2000 and 2015. Depression and antidepressants related data were extracted from SAIL. A series of multilevel logistic regressions were run to determine the factors affecting depression recognition. The results were presented using odds ratios (ORs) with 95% confidence intervals (CI).

Results: The study included 6596 patients with PD. About 38% of patients had a recorded code of antidepressants, depression diagnosis, or both within the first year of PD diagnosis. There was a significant association of depression diagnosis, antidepressant use, or both with the year of PD diagnosis (OR 0.972, 95% CI 0.962–0.983). We also found that patients who used monoamine oxidase inhibitors (MAO-B inhibitors) were associated with a lower depression diagnosis, use antidepressants, or both, compared to those who did not use MAO-B inhibitors (OR 0.769, 95% CI 0.627–0.943).

Conclusion: There is a slight decrease in depression recognition in PD patients between 2000 and 2015, which could be due to an increase in depression recognition during the prodromal phase of PD.

KEYWORDS
depression, incidence, non-motor symptoms, Parkinson's disease, prodromal

1 | INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, with the elderly being the most affected age group (Aarsland et al., 2011). More than 1% of the population over the age of 60 is expected to have PD, and it could reach 5% for those over the age of 85 (Allain et al., 1993). Although in 1817, James Parkinson discussed in his original work "An Essay on the Shaking Palsy" the presence of

some non-motor symptoms of PD, such as depression, constipation, bladder dysfunction, and sleep problems (Alonso et al., 2009), it was not until the 1990s that those symptoms attracted researchers' attention (Becker et al., 2011). Neuropsychiatric, sensory, autonomic, and sleep-related symptoms are considered to be important in current practice, and they should be treated in patients with PD (Bega et al., 2014).

Depression is common in patients with PD. Recent reviews have estimated that 35% of patients with PD have depression (Byeon, 2020; Chaudhuri et al., 2006). Among them, about 20% developed depression within the first year of their PD diagnosis (Chaudhuri & Schapira, 2009). This depression may occur as a result of PD motor symptoms; however, in some cases, it precedes the motor symptoms of PD, which means it is not only a consequence of struggling with motor symptoms but also has a major role in disease progression (Byeon, 2020; Cummings, 1992). Despite the progressive recognition of depression in patients with PD in the late 1990s, some studies have found that depressed patients with PD were overlooked and undertreated, and many of them were not diagnosed with depression or still met the criteria of depressive disorders even though they used antidepressants (de Lau & Breteler, 2006; Erkkinen et al., 2018; Fang et al., 2010). Tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) are the most common medications for managing depression in PD (Fernandez et al., 2000). Despite clinical trials that have shown TCA (e.g., desipramine) as superior to SSRI in managing depression in patients with PD, SSRIs are more commonly used in practice (Jankovic, 2008).

In the last two decades, there was growing evidence that confirms the close connection between depression and PD, especially in its early stages. However, there were few studies that extrapolated this evidence to clinical settings by testing the improvement in recognizing depression symptoms in patients with PD across years. The purpose of this study is to determine the trend of depression incidence rates and antidepressant use in Wales between 2000 and 2015 and evaluate their relationship with different sociodemographic and comorbidities variables using large population-based data.

2 | MATERIALS AND METHODS

2.1 | Data source and databases used in the study

A retrospective repeated cross-sectional study that examined the depression and antidepressants incidence in patients with PD was carried out between 2000 and 2015. The data were obtained from the Secure Anonymized Information Linkage (SAIL) Databank, which contains the Welsh Longitudinal General Practice primary care dataset for at least 80% of patients in Wales. The data were collected since the year 2000 because of increased quality and consistency of coding and the quality of standard electronic health record (EHR) maintained thereafter. Using Read codes (version 2), a hierarchical coding system used to record clinical information (Table S1), data pertaining to patients who were diagnosed for the first time with PD and patients who are taking drugs for motor symptoms of PD were retrieved from the SAIL.

2.2 | Identifying depressed patients

Patients with depression following their PD diagnosis were identified if they have Read code entry for unipolar depression and/or prescribed a therapeutic dose of antidepressant for treatment of depression and were included in this study. The identified antidepressants were SSRIs, TCAs, and other antidepressants (Table S2).

The exclusion criteria included patients who were diagnosed with PD before the year 2000, less than 40 years of age, administered any PD medications prior to their PD diagnosis, not prescribed with any PD medications within a year after PD diagnosis, diagnosed with PD within 6 months from of their SAIL registration date, diagnosed with depression or prescribed antidepressants in the preceding year of PD diagnosis, or left SAIL or died within a year of PD diagnosis. Moreover, patients who were taking antipsychotics for 1 year or more before PD diagnosis were also excluded; since antipsychotics are known to cause extrapyramidal symptoms, which could be mistakenly diagnosed as PD (Jankovic & Poewe, 2012).

2.3 | Classification of patients with PD based on depression diagnosis and antidepressants use

In the primary analysis, patients were divided into two broad categories: patients with any sign of depression recognition (i.e., depression codes, antidepressants codes, or both), and patients with no sign of depression recognition (i.e., no depression or antidepressants codes).

To further analyze the trend of depression and antidepressants use incidence, patients were classified into four groups: patients with depression and antidepressants codes, in which the antidepressants were initiated within 1 year after depression diagnosis and last at least for 1 year (group 1); patients with depression code, but without antidepressant code up to 1 year after depression diagnosis (group 2); patients with antidepressant code within 1 year after PD diagnosis, but without depression code up to 1 year after the date of first antidepressant use (group 3); and patients without depression and antidepressant codes (group 4).

2.4 | Key variables

Socio-demographic characteristics included age at diagnosis, sex, social deprivation status, and geographical location of the health board. Health characteristics included the number and type of comorbidities and the prescribed first-line PD medications.

Patients were grouped into three categories based on their ages: 40–60 (a relatively early onset of PD), 61–80, and >80 years. The comorbidities identified among the patients were acute myocardial infarction, cancer, cerebral vascular accident, congestive heart failure, connective tissue disorder, dementia, diabetes, diabetes complications, liver disease, metastatic cancer, paraplegia, peptic ulcer, peripheral vascular disease, pulmonary disease, renal disease, and severe liver

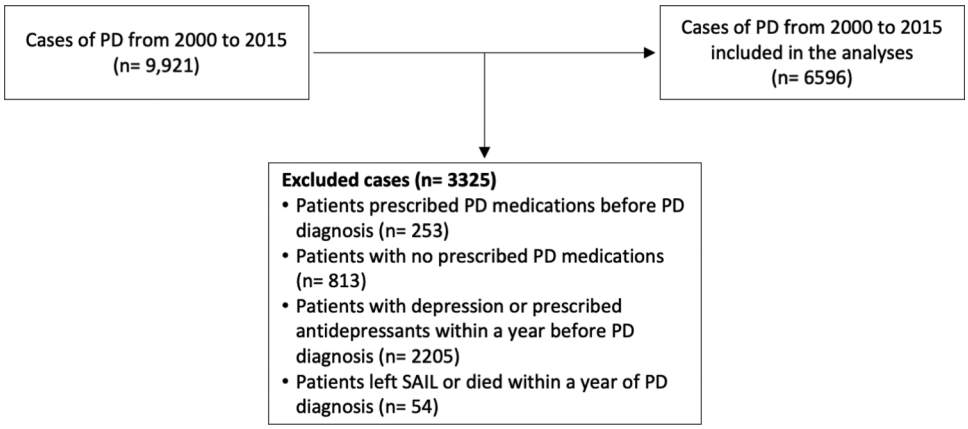

FIGURE 1 Cases selection and exclusion process

disease. Each condition was entered as a binary variable (i.e., presence or absence of the condition). First-line PD medication was defined as the first medication prescribed to the patient that lasted for at least 1 year following their PD diagnosis. The social deprivation status ranged from most deprived (quintile 1) to least deprived (quintile 5), based on the Welsh Index of Multiple Deprivation (WIMD; 2011) scale. The data were included from all the seven locations of Welsh Health Boards, which are Abertawe Bro Morgannwg, Aneurin Bevan, Betsi Cadwaladr, Cardiff and Vale, Cwm Taf, Hywel Dda, and Powys.

2.5 | Statistical analysis

The data were exported to Microsoft Excel and analyses were performed using the statistical package for social sciences, version 23. Binomial logistic regression was used to examine the association between the independent variables (e.g., age, sex, year of depression diagnosis, etc.) and the outcome of interest (i.e., depression and/or antidepressants incidence). Multinomial logistic regression was also performed to identify factors associated with the depression diagnosis and/or antidepressant use for groups 1, 2, and 3, compared to the absence of depression diagnosis and antidepressant use, group 4. The weighted Wald test was conducted to determine the effect significance of each independent variable in the model. Variables were included in the multivariate analysis if their p-value were $< .20$ and if a particular variable (a priori variable) had theoretical reasons for inclusion. Odd ratios (ORs) were calculated and presented with 95% confidence intervals (CIs). Statistical significance was set at $p < .05$. Aggregate numbers less than 5 were excluded from the analysis abiding by the rules of SAIL to protect the anonymity of the subjects.

2.6 | Ethical approval

The ethical approval was obtained from the independent Information Governance Review Panel (ref 0507) for the retrieval and usage of data from SAIL for the current research.

3 | RESULTS

The number of patients with PD included in the study was 6596 (Figure 1). About 61% of the patients were male. The mean age (SD) was 73.7 (9.8) years. Most patients (61.4%) were in the age group of 61–80 years. Among the seven different health boards at Welsh region, the most frequent health boards attended by the patients were Abertawe Bro Morgannwg (23.4%) and Betsi Cadwaladr (22.2%). Of the included patients with PD, 38.4% had a recorded code of depression diagnosis, antidepressants use code, or both within the first year of their PD diagnosis. Among antiparkinsonian medications, levodopa was the most commonly used (76.7%), while for the antidepressants, SSRIs (15.9%) were the most frequently used, followed by TCAs (7.3%). Table 1 shows the demographic and clinical characteristics of the included patients.

Throughout the majority of years from 2000 to 2015, the incidence of PD patients with depression and antidepressant code (group 1) remained higher than patients with depression or antidepressant code (groups 2 and 3; Figure 2). The trend of prescribing antidepressants is continued for the whole duration of the study, that is, from 2000 to 2015 (Figure 3(a)). There were only four antidepressants used by more than five patients per year (abiding by SAIL rules), and they constituted 69.6% of the total antidepressants used by patients with PD. They include citalopram ($n = 621$), amitriptyline ($n = 276$), fluoxetine ($n = 188$), and mirtazapine (n = 184; Figure 3(b)).

The results from logistic regression analysis, which examined factors that tend to affect the trend of depression diagnosis and/or antidepressant use in patients with PD, are shown in Table 2. The OR of depression diagnosis and/or antidepressant use was declined by 3% as the years from 2000 to 2015 passed by (OR 0.972, 95% CI 0.962–0.983), increased in patients aged 60 to 80 years (OR 1.831, 95% CI 1.297–2.582), decreased in patients using monoamine oxidase inhibitors (MAO-B inhibitors; OR 0.769, 95% CI 0.627–0.943). The associations were not significant for comorbidities and the different levels of WIMD.

The results of multinomial logistic regression examining potential factors affecting the trend of depression recognition in patients with

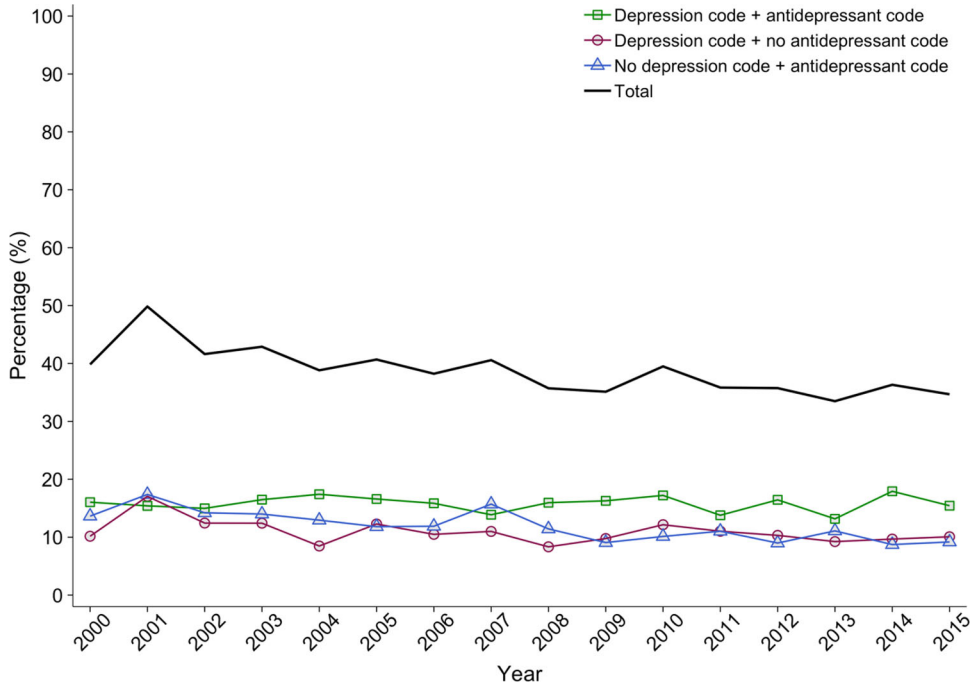

FIGURE 2 Depression incidence within the first year of the diagnosis of Parkinson's disease (PD), from 2000 to 2015

PD are shown in Table S3. The number of patients identified in each group was 1044, 713, and 778 in groups 1, 2, and 3, respectively. The ORs of both depression diagnosis (group 2; OR 0.973, 95% CI 0.957–0.990) and trend of antidepressant use (group 3; OR 0.950, 95% CI 0.934–0.996) have declined as years passed by. When the age group of 40–60 years was considered as a reference, the age group of 60–80 years had higher OR of depression recognition in the three groups; however, it was statistically significant for group 2 (OR 1.851, 95% CI 1.317–2.602) and group 3 (OR 1.881, 95% CI 1.312–2.698). Patients who were > 80 years old were more likely to use antidepressants but not necessarily diagnosed with depression (OR 1.806, 95% CI 1.291–2.527). Similarly, males were associated with a higher antidepressant use with no depression diagnosis ($p = .048$). Among the various comorbidities tested, cerebrovascular accidents ($p = .003$) and diabetes mellitus ($p = .007$) were associated with an increase in the use of antidepressants (group 3). The WIMD was not found to be a significant factor in all the three groups.

4 | DISCUSSION

To our knowledge, this is the first population-based study that examined the trend of depression recognition in patients with PD, with a substantial sample size representing the Welsh population. The main finding of this population-based study was identifying a slight decrease of 3% in depression recognition over the years. This finding is not necessarily reflecting the prevalence of depression in PD given the high number of reported cases of depression as the non-motor manifestation of PD in previous studies (Jankovic & Poewe, 2012; Kehagia et al., 2013; Lapane et al., 1999; Leentjens et al., 2003; Mann et al., 1989). All cases of depression that preceded the PD diagnosis were not recorded in our study, which may have affected the trend of depression recognition over years. Recent studies provided new insights on depression as prodromal to PD, and the occurrence of depression is increasingly recognized to precede the clinical appearance of motor symptoms of PD by 1–15 years before PD diagnosis (Parkinson, 2002; Poewe, 2008; Poewe et al., 2017).

Data are inconsistent regarding the associations of sex and age with the diagnosis of PD and the risk of depression. Unlike previous studies, we found that the diagnosis of depression was not associated with sex, although men were more likely to receive antidepressants (Chaudhuri & Schapira, 2009; Ranoux, 2000). Our study found a high frequency of depression diagnosis and/or antidepressant use among old-onset patients. In contrast to our finding, a previous study reported a high frequency of depression among young-onset patients (Richard & Kurlan, 1997).

Our study showed that patients on MAO-B inhibitors are less likely to be diagnosed with depression or prescribed antidepressants. It has been proposed by previous studies that depression in PD is mediated by the dopaminergic deficiency in limbic system pathways; therefore, replacing dopamine via MAO-B inhibitors might have improved depression symptoms (Riederer & Laux, 2011; Schapira et al., 2017; Schrag et al., 2003; Smith et al., 2015). The inherent antidepressant effect of MAO-B inhibitors might play a role in the incident of depression cases among patients taking MAO-B, especially if given at higher doses that are non-selective for MOA-B (Starkstein &

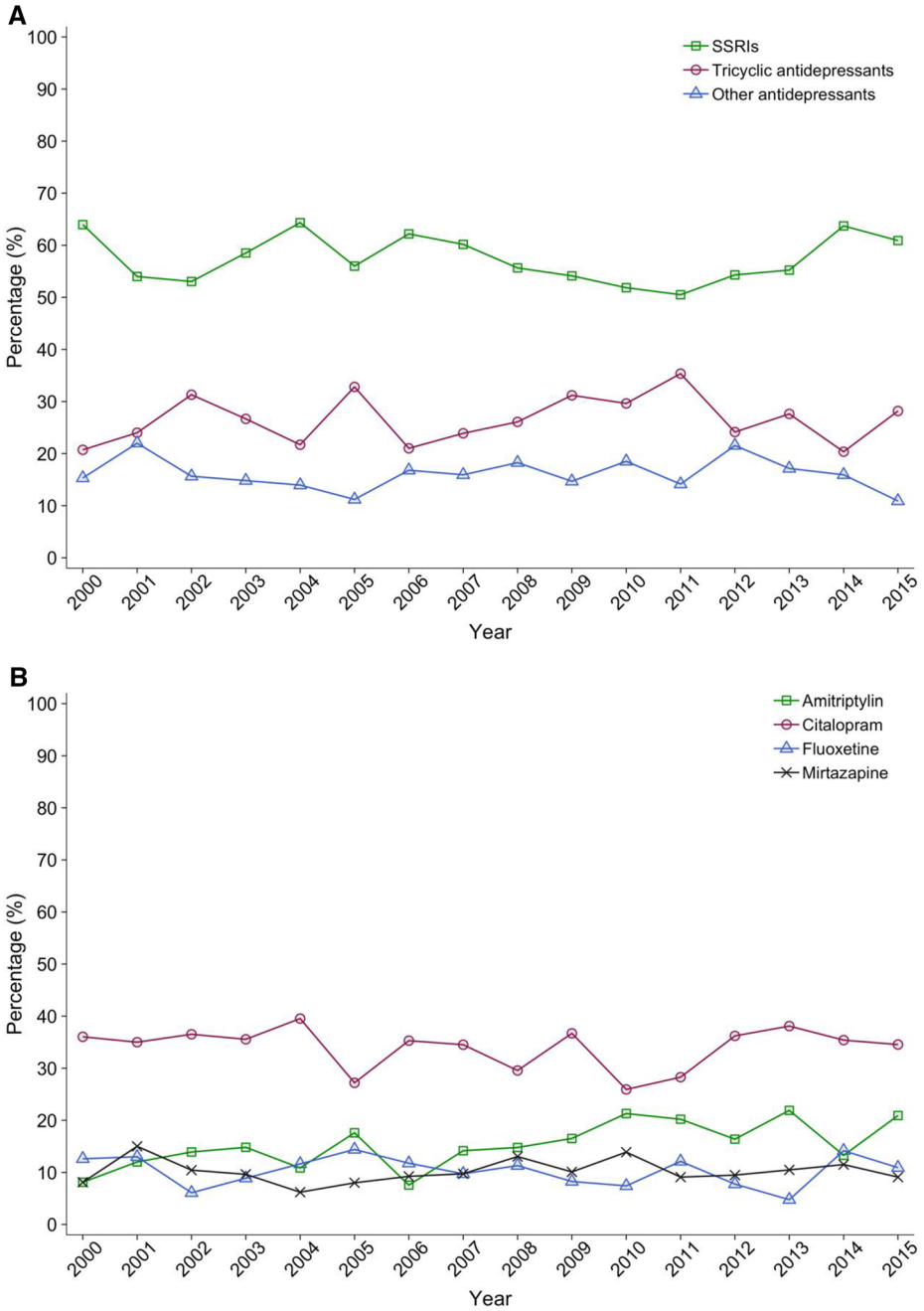

FIGURE 3 Prescribing pattern of antidepressant among patients with PD by class (A) and drug (B) from 2000 to 2015

Brockman, 2017; Sunderland et al., 1994; Thobois et al., 2013). Also, it is worth noting that the rate of prescribing antidepressants among patients taking MAO-B inhibitors might be affected by the potential drug–drug interaction and the safety concern of developing serotonin syndrome when combining MAO-B inhibitors with selective SSRI or TCA, although the frequency of serotonin syndrome has not been evaluated in controlled trials. In a randomized double-blind, placebo-controlled multicenter trial conducted by Smith et al., they have shown no serious adverse events suggestive of serotonin syndrome when combining an MAO-B inhibitor with antidepressants (Weintraub et al., 2003).

There is no consensus guideline in the treatment of depression in PD. A previous study reported an incidence rate of 51% for prescribing SSRIs and 41% prescribing TCAs (Wichowicz et al., 2006). This study finds a higher prescribing rate of SSRIs and a lower prescribing rate of TCAs that is more likely due to the favorable safety profile of SSRIs.

TABLE 1 Patient demographics

Demographic	Mean (SD) or *n* (%) *N* = 6596
Age, years (at PD incidence)	73.7 (9.8)
Age group	
40–60 years	620 (9.4)
61–80 years	4047 (61.4)
>80 years	1929 (29.2)
Sex, male	4041 (61.3)
Health board (geographical health board location)	
Abertawe Bro Morgannwg	1541 (23.4)
Aneurin Bevan	975 (14.8)
Betsi Cadwaladr	1462 (22.2)
Cardiff & Vale	933 (14.1)
Cwm Taf	584 (8.9)
Hywel Dda	861 (13.1)
Powys	240 (3.6)
Year of PD diagnosis	
2000–2005	1516 (23.0)
2004–2007	1676 (25.4)
2008–2011	1644 (24.9)
2012–2015	1760 (26.7)
PD medications	
Amantadine	17 (0.3)
Anticholenergics	179 (2.7)
COMT inhibitors	29 (0.4)
Ergot dopamine	81 (1.2)
Levodopa	5060 (76.7)
MAO-B inhibitors	467 (7.1)
Non-ergot dopamine	763 (11.6)
Antidepressant medications	
SSRI	1049 (15.9)
Tricyclic antidepressants	482 (7.3)
Other	291 (4.4)

Abbreviations: COMT inhibitors, catechol-O-methyltransferase inhibitors; MAO-B inhibitors, monoamine oxidase B inhibitors; PD, Parkinson's disease; SSRI, selective serotonin reuptake inhibitors.

This study has several limitations. The retrospective nature of the study is potentially biased by unmeasured or residual sources of confounding. We excluded all patients with depression diagnosis and/or antidepressant use precede the diagnosis of PD, which may affect the overall prevalence of depression in PD. All cases of depression that occur in the prodromal phase of PD were not recorded. The type of data retrieved from the data source is very limited and there is no data available on the severity of PD, severity of depression, and medication dosage.

TABLE 2 Multiple logistic regression examining potential factors affecting the trend of recognizing depression diagnosis and antidepressants use in patients with PD within the first year of their PD diagnosis

Variable	OR (95% CI)	*p*-value
Year of PD diagnosis	0.972 (0.962-0.983)	< **.001**
Age groups		
40–60	Reference	
60–80	1.831 (1.297–2.582)	< **.001**
>80	1.298 (0.940–1.790)	.088
Sex, male	1.063 (0.959–1.179)	.245
Comorbidities		
Cerebrovascular accident	0.762 (0.572–1.014)	.062
Dementia	0.818 (0.589–1.136)	.232
Diabetes mellitus	0.828 (0.672–1.020)	.077
Myocardial infarction	0.900 (0.670–1.209)	.485
Pulmonary disease	0.804 (0.634–1.018)	.071
WIMD (Welsh Index of Multiple Deprivation)		
WIMD 1 (most deprived)	Reference	
WIMD 2	0.963 (0.803–1.155)	.831
WIMD 3	0.870 (0.730–1.036)	.161
WIMD 4	0.965 (0.807–1.153)	.848
WIMD 5 (least deprived)	0.875 (0.735–1.042)	.183
PD medications		
Levodopa	0.965 (0.836–1.115)	.629
MAO-B inhibitors	0.769 (0.627–0.943)	**.012**

Abbreviations: CI, confidence interval; MAO-B inhibitors, monoamine oxidase B inhibitors; PD, Parkinson's disease.

5 | CONCLUSION

This study suggests that depression recognition in PD is slightly decreased over years (between 2000 and 2015). It is possible that this finding has been affected by the increase in depression recognition during the prodromal phase of PD. Further population-based studies are needed to better investigate the depression development in the course of PD.

ACKNOWLEDGMENTS

This work was funded by King Khalid University. The authors acknowledge and thank the SAIL technical team, without whom the work would not have been possible.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

DATA AVAILABILITY STATEMENT

Data may be obtained from a third party and are not publicly available. The electronic cohort is securely stored and maintained on the Secure

Anonymized Information Linkage (SAIL) databank at Swansea University Medical School. The authors welcome general enquiries and ideas for new collaborations.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/brb3.2228.

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SUPPORTING INFORMATION

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

How to cite this article: Orayj, K., Almeleebia, T., Vigneshwaran, E., Alshahrani, S., Alavudeen, S. S., Alghamdi, W. Trend of recognizing depression symptoms and antidepressants use in newly diagnosed Parkinson's disease: Population-based study. *Brain Behav*. 2021;*11*:e2228. https://doi.org/10.1002/brb3.2228