



The association between antidepressant treatment and rates of insulin initiation in comorbid depression and type 2 diabetes: A UK electronic health record nested case-control study

Annie Jeffery^{a,*}, Kate Walters^b, Ian C.K. Wong^{c,d}, David Osborn^a, Joseph F. Hayes^a

^a Epidemiology and Applied Clinical Research Department, Division of Psychiatry, University College London (UCL), London, United Kingdom

^b Department of Primary Care & Population Health, Institute of Epidemiology & Health, University College London (UCL), London, United Kingdom

^c Research Department of Practice and Policy, School of Pharmacy, University College London (UCL), London, United Kingdom

^d Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

ARTICLE INFO

Keywords:

Depression
Type 2 Diabetes
Insulin therapy
Antidepressant
Long-term outcomes
Primary Care
Epidemiology

ABSTRACT

Aims: To investigate the association between antidepressant prescribing and the rate of insulin initiation in type 2 diabetes.

Methods: Using UK primary care records we completed a nested-case control study in a individuals with comorbid depression and type 2 diabetes. Cases were defined as individuals initiating insulin, controls were individuals remaining on oral antidiabetic medication. We used conditional logistic regression to estimate incident rate ratios (IRR) and the 95% confidence intervals (CI) for the association between antidepressant prescribing and initiating insulin. We adjusted for demographic characteristics, comorbidities, health service and previous medication use.

Results: We included 11,862 cases who initiated insulin, and 43,452 controls. Increased rates of insulin initiation were associated with any antidepressant prescription (IRR 3.78, 95% CI 3.53–4.04), longer (24+ months) durations of antidepressant treatment (IRR 5.61, 95% CI 5.23–6.03), and higher numbers (3+) of different antidepressant agents prescribed (IRR 5.72, 95% CI 5.25–6.24). There was no difference between recent and non-recent antidepressant prescriptions, or between different antidepressant agents.

Conclusions: Antidepressant prescribing was highly associated with the initiation of insulin therapy. However, this may not indicate a direct causal effect of the antidepressant medication itself, and may be a marker of more severe depression influencing diabetic control.

1. Introduction

It is estimated that one in four people with type 2 diabetes have comorbid depression [1]. Depression has been shown to be associated with poor glycaemic control [2] and the development of diabetic complications [3]. Depression symptoms, such as loss of motivation, can impede diabetic self-care [4] and adherence to diabetic treatments [5]. Depression can also lead to unhealthy lifestyle behaviours, such as poor diet [6] and low physical activity [7] – both of which can exacerbate type 2 diabetes [8]. Thus, conceptually, the successful treatment of comorbid depression could improve diabetic health in individuals with type 2 diabetes.

Antidepressant medication is recommended by national and international healthcare guidelines as a treatment option for individuals with moderate to severe depression [9–12]. For individuals with type 2 diabetes, there is evidence that antidepressant treatment is effective in improving depression symptoms and glycaemic control in the short-term [13–15]. However, there is a lack of evidence concerning the long-term impact of antidepressant treatment in comorbid depression and type 2 diabetes. A 2022 systematic review [16] investigated the impact of antidepressant treatment, meeting the minimum recommended treatment duration of 6 months, on long-term diabetic outcomes in adults with comorbid depression and type 2 diabetes. However, no studies fulfilling these criteria were found. There are a small number of relevant studies

* Corresponding author at: Maple House, Tottenham Court Road, London, United Kingdom.

E-mail addresses: annie.jeffery.09@ucl.ac.uk (A. Jeffery), k.walters@ucl.ac.uk (K. Walters), i.wong@ucl.ac.uk (I.C.K. Wong), d.osborn@ucl.ac.uk (D. Osborn), joseph.hayes@ucl.ac.uk (J.F. Hayes).

<https://doi.org/10.1016/j.diabres.2023.111083>

Received 30 August 2023; Received in revised form 5 December 2023; Accepted 25 December 2023

Available online 29 December 2023

0168-8227/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

investigating the long-term impact of antidepressant treatment on glycaemic control in less specific patient groups, described below, however, the findings are mixed. One study investigating reports listed in the World Health Organisation (WHO) Adverse Drug Reaction database, found long-term antidepressant use (greater than 1 year) to be associated with both hyperglycaemia and hypoglycaemia [17]. However, this was not limited to individuals with depression or type 2 diabetes, both of which may have confounded the study's findings. A large cohort study in Taiwan of 26,746 patients with diabetes and depression found that long-term antidepressant use prior to baseline was associated with a reduction in hyperglycaemic crisis episodes over time [18]. However, the antidepressant treatment may have been up to 12 years prior to the hyperglycaemic crisis, and ongoing antidepressant status between baseline and the event was unknown, making it difficult to attribute the association to any direct biological effect. The study was also not specific to type 2 diabetes, and did not differentiate between different antidepressant agents. Conversely, a cross-sectional study in the Netherlands found that SSRIs were associated with using insulin, and thereby potentially worse glycaemic control [19]. However, this study was unable to investigate the effect of treatment duration, or to make assumptions of causality due to its cross-sectional design. Furthermore, it was not specified that participants had a diagnosis of depression, and so, the true association may have been with the depressive disorder itself.

Insulin initiation, which may be defined as the initiation of insulin therapy in type 2 diabetes, represents a long-term decline in glycaemic control, and the failure of oral antidiabetic treatment. We aimed to investigate the association between antidepressant prescribing and the rate of insulin initiation in adults with comorbid depression and type 2 diabetes.

We hypothesised that antidepressant prescribing would be associated with a decreased rate of insulin initiation, due to the positive impact of treating depression on an individual's diabetic health and self-care.

2. Research design and methods

2.1. Study design and setting

We carried out a nested case-control study using longitudinal data from the UK Clinical Practice Research Datalink (CPRD). The CPRD contains electronic health records (EHRs) for over 60 million people, across 2000 primary care practices [20], and has been shown to be representative of the UK population with respect to age, gender and ethnicity [21–22]. The CPRD includes two separate databases which we combined, CPRD Gold and CPRD Aurum, based on different computer software packages used for the EHRs. The datasets are similar and include all demographic information, diagnoses, symptoms, laboratory tests and other health indicators recorded by the general practitioner, as well as all prescriptions issued.

We used the nested case-control approach because of the time varying nature of both depression and of antidepressant use [23–24], the large sample size and long duration of follow-up [23–24], and the examination of multiple exposures. The nested case-control study is an efficient alternative to cohort analysis when studying time-varying exposures, as it has superior computational efficiency to Cox regression and has been found to yield similar results [25].

Our study period ran from 1 January 2000, to 31 December 2018.

2.2. Participants

The cohort within which our case-control study was nested, included individuals with comorbid depression and type 2 diabetes, who had started oral antidiabetic medication during their EHR follow-up, as below:

1 – Depression.

Including: Individuals with any clinical code for depression

symptom, diagnosis or process of care, with at least one record for depression after the first record related to type 2 diabetes;

Excluding: Individuals who only had depression codes related to dementia, maternity, schizophrenia or bipolar disorder (as these are distinct disorders to depression);

2 – Type 2 diabetes:

Including: Individuals with at least one oral antidiabetic medication prescription code during their EHR follow-up, with the first oral antidiabetic prescription dated at least 6 months after the individual's date of registration to ensure we were capturing the start of oral antidiabetic treatment; also, two blood/serum glucose/HbA1C tests recorded above the threshold for type 2 diabetes; these inclusion criteria are based on previous research which shows the necessity of cross-validation for type 2 diabetes identification in EHRs [26–27]

Excluding: Individuals with less than 6 months between the date of the first recorded oral antidiabetic prescription and the first recorded insulin prescription (possible type 1 diabetes or gestational diabetes), or individuals who only had codes or medication for type 2 diabetes present during periods of pregnancy (possible gestational diabetes only);

We defined the date of a participant's first oral antidiabetic prescription as their study entry date. We considered this to be the start of pharmacological treatment for type 2 diabetes. Participants were observed until the date of their first insulin prescription, date of death, end of registration with the general practice, or end of the study period (31 December 2018), whichever was first.

The study design for cases and controls is illustrated in Fig. 1.

2.3. Selection of cases (individuals who initiated insulin treatment)

We identified any participant who received a prescription of insulin during the study period as a case and used the date of the first insulin prescription as the index date. We calculated the observation period duration for cases as the number of days between initiating oral antidiabetic medication (study entry date) and the date of the first insulin prescription (index date).

We excluded any cases who did not have one or more controls, or who did not have a code for depression between entering the study (the date of starting oral antidiabetic medication) and the index date (the date of insulin initiation).

2.4. Selection of controls (individuals who had not yet initiated insulin treatment)

We matched all cases to up to 4 randomly selected eligible controls. Eligible controls were participants who met the following criteria:

1. Had not started insulin by the time they reached the same number of days in the observed period as the case;
2. Had a code for depression within the same number of days in the observed period as the case;
3. Were exact matches for the case based on the 5 year age group at study entry, gender and GP practice.

We included all participants in the risk-set from which potential controls were selected, regardless of whether or not they later became a case.

For controls the index date was the same as their matched case, with respect to the number of days in the observed period from study entry to insulin initiation.

2.5. Primary exposure

We defined the primary exposure as being prescribed one or more antidepressant recorded between the study entry and the index date. We included the following antidepressant medications which have been licensed for use in treating depression in the UK during the follow-up

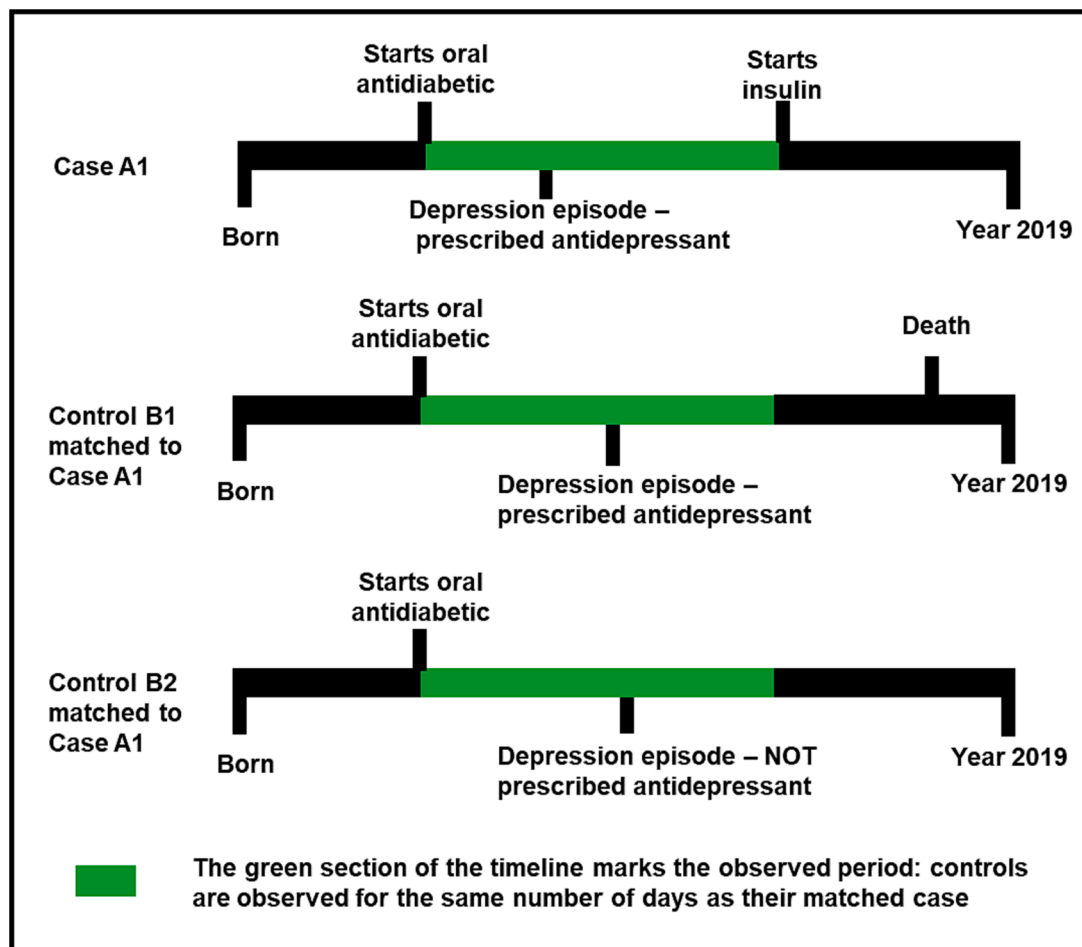


Fig. 1. Study cohort and observed period to investigate the association between antidepressant prescribing and insulin initiation.

period.

SSRIs: Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline;

SNRIs: Duloxetine, venlafaxine;

TCAs: Amitriptyline ≥ 50 mg per day*, amoxapine, clomipramine, dosulepin, oral doxepin, imipramine, lofepramine, maprotiline, nortriptyline ≥ 50 mg per day*, trimipramine;

MAOIs: Isocarboxazid, phenelzine, tranylcypromine;

Atypical: Agomelatine, mianserin, mirtazapine, moclobemide, nefazodone, reboxetine, trazodone, tryptophan, vortioxetine.

*Amitriptyline and nortriptyline were included only at the antidepressant dose of ≥ 50 mg per day, rather than lower hypnotic or neuralgia doses.

2.6. Secondary analyses

We performed secondary analyses on four subcategories exposures of our primary exposure:

i) Recent or past antidepressant use: We defined recent antidepressant users as any antidepressant prescription within 182 days [6] of the index date. We defined participants who only had a previous antidepressant prescription more than 182 days before the index date, as past antidepressant users. The reference category was no antidepressant prescription.

ii) Cumulative duration of antidepressant use: We calculated a participant's cumulative duration of antidepressant use as the sum of the duration of each antidepressant course. We calculated the duration of

each antidepressant course as the number of days between the first and last prescription of any antidepressant, plus the duration of that last prescription. If a participant had a gap of >90 days after a prescription without any antidepressant, that was considered to be the last prescription in that treatment episode, and any subsequent prescriptions were counted as subsequent treatment episodes. We categorised the cumulative duration of antidepressant use as < 6 months, 6–12 months, 13–24 months and >24 months. The reference category was no antidepressant prescription.

iii) Number of different antidepressant agents prescribed: We counted the number of different antidepressant agents, as listed in the main exposure, an individual received prescriptions for during the study follow-up period. We categorised these as: 0 (reference category), 1, 2 and 3+.

iv) For individuals who were prescribed only one antidepressant during the study follow-up period, we performed a subgroup analysis, with the specific antidepressant agent as the exposure, to compare the effect of different antidepressant agents. We used citalopram as the reference category as this is the most commonly prescribed antidepressant in the England [28]. We performed a Bonferroni correction of the p-values to account for the increased risk of type 1 error when making multiple statistical tests. Bonferroni correction multiplies the p-value by the number of exposures and covariates to a maximum of 1 – statistical significance is set at 0.05.

We also performed subgroup analyses for the main exposure by gender and ethnicity.

2.7. Covariates

We included the following covariates, measured at or before the study entry date, as potential confounders associated with both antidepressant treatment and insulin initiation.

Demographic characteristics: In addition to the variables used for matching, we also included ethnicity. Where ethnicity was missing, we recoded this as “White”, as it has been found in previous studies that more than 90% of individuals in the UK EHRs with missing ethnicity are of White ethnicity [29]. Socioeconomic status is recorded at primary care practice level, and so was accounted for inclusion of the primary care practice ID.

Health characteristics: We included a range of health characteristics that may be confounders through an association with antidepressant use (either directly or indirectly through an association with depression) and insulin initiation (either directly or indirectly through an association with poor overall physical health, or health behaviours):

- The following comorbidities based on codes Elixhauser comorbidity codelist [30]: alcohol abuse, blood loss anaemia, cardiac arrhythmia, chronic pulmonary disease, coagulopathy, deficiency anaemia, drug abuse, fluid and electrolyte disorders, hypertension (uncomplicated), hypertension with end organ damage, hypothyroidism, liver disease, lymphoma, metastatic cancer, other neurological disorders, paralysis, peptic ulcer disease, peripheral vascular disease, psychoses, pulmonary circulation disorders, renal disease, rheumatoid arthritis and collagen diseases, solid tumor or leukaemia, valvular disease – we coded the presence of each individual condition for participants who had a relevant code recorded prior to the study entry date;
- The most recent recorded BMI value categorised into “normal” (<25), “overweight” (25 to < 30), and “obese” (30+); where no value for BMI was available, we estimated the value using multiple imputation;
- Smoking status categorised into “current smoker” (most recent smoking code related to current smoking within 12 months before study entry), “ex-smoker” (most recent smoking code related to historic smoking, or most recent code related to current smoking more than 12 months before study entry, or most recent code related to non-smoking with prior codes related to current or historic smoking), “non-smoker” (no codes related to smoking, or non-smoking codes only);
- Diabetes duration, defined as the number of months between the first diabetes related code (this could include diagnosis, symptom, process of care, or medication) and the date of the first oral antidiabetic medication prescription;
- Number of GP consultations (any contact with a primary care professional in person or over the telephone) recorded in the 12 months prior to the study entry date.

We did not include glycaemic control as a covariate as all participants would be expected to have hyperglycaemia at the time of starting oral antidiabetic medication, which was when participants entered the study and all covariates were measured, and by definition on reaching the outcome of insulin initiation.

Medication history: We included the number of different pharmacological medications prescribed (excluding vaccinations, topical medications and supplements) in the 90 days before the study entry. As it was not possible to account for markers of depression and depression severity at study entry, we included any previous antidepressant prescription in the 12 months prior to study entry, to indicate previous depression at a severity requiring pharmacological treatment.

2.8. Statistical analysis

We reported sample characteristics, stratified by cases (who started

insulin) and controls (who did not start insulin). We reported numbers and proportions for categorical variables (sex, comorbidities, previous antidepressant use, smoking status, BMI), and performed chi-squared tests to assess differences between cases and controls. We reported medians and interquartile ranges for continuous variables (age, poly-pharmacy count, service contacts, diabetes duration, follow-up time), and performed Mann-Whitney U tests to assess differences between cases and controls.

We used conditional logistic regression to estimate adjusted incident rate ratios (IRR) and corresponding 95% confidence intervals (CI) for the association between each of our antidepressant prescribing exposures and the risk of initiating insulin therapy. As we have used a nested case-control design, with incident rate sampling and individual matching, the odds ratios computed by conditional logistic regression are unbiased estimates of incident rate ratios [31] with little or no loss in precision [25]. We report the results of our analyses as incident rate ratios (IRR). We initially performed univariable analyses, and then multivariable analyses adjusting for all aforementioned covariates.

All analysis was performed using R version 4.0.5.

3. Results

The base cohort consisted of 105,826 individuals with comorbid depression and type 2 diabetes, who started oral antidiabetic medication between the years 2000–2018. From this, we identified 11,862 cases who initiated insulin treatment, and matched these with 43,452 controls who did not initiate insulin. Table 1 shows baseline characteristics of cases and controls. The two groups were balanced in terms of demographic characteristics with the exception of a higher proportion of Asian and Mixed ethnicities in the control group. Cases had a higher prevalence of each comorbidity at baseline, with the exception of alcohol abuse, blood loss anaemia, drug abuse and psychosis.

Table 2 shows univariable and multivariable analysis results for each exposure and Table 3 shows univariable and multivariable analysis results for the subgroup analysis that compared individual antidepressant agents.

After adjusting for demographic characteristics, comorbidities and prescription history at baseline, the incident rate ratio (IRR) for the rate of insulin initiation in individuals who were prescribed at least one antidepressant prescription during the follow-up period compared to those without any antidepressant prescription was 3.78 (95% confidence intervals (CI) 3.53–4.04).

There was no statistically significant evidence of a difference between individuals who had recent antidepressant prescriptions (in the 6 month time period before the index date/date of insulin initiation or not) and those who only had non-recent antidepressant prescriptions.

There was a positive association between the cumulative duration of antidepressant treatment and insulin initiation: the adjusted IRR for the shortest durations of treatment (<6 months) compared to no antidepressant prescription was 3.94 (95% CI 3.64–4.27), while in the longest durations of treatment (>24 months) the adjusted IRR compared to no antidepressant treatment was 5.61 (95% CI 5.23–6.03).

There was a positive association between the number of antidepressant agents prescribed and insulin initiation: the adjusted IRR for only one antidepressant agent compared to none was 3.93 (95% CI 3.69–4.19), while the adjusted IRR for 3+ antidepressant agents compared to none was 5.72 (95% CI 5.25–6.24).

In our subgroup analysis of individuals who only received only one antidepressant agent during the study follow-up period, there was no statistically significant difference between the rates of insulin initiation for different antidepressant agents, after adjustment for covariates and Bonferroni correction.

The following comorbidities were associated with an increased rate of insulin initiation: cardiac arrhythmia, chronic pulmonary diseases, chronic heart failure, deficiency anaemia, fluid and electrolyte disorders, liver disease, metastatic cancer, other neurological disorders,

Table 1
Characteristics of cases and controls, at the time of study entry.

	Cases	Controls	Test of association**
Sample size	11,862	43,452	-
Female (%)	6,378 (53.77)	23,404 (53.86)	p = 0.8647
Median age (IQR)	53 (45-62)	53 (46-61)	p < 0.0001
Ethnicity:			
Asian (%)	433 (3.65)	2,298 (5.29)	
Black (%)	249 (2.10)	1,077 (2.48)	
Missing* (%)	4,247 (35.80)	14,766 (33.98)	p < 0.0001
Mixed (%)	49 (0.09)	239 (0.55)	
Other (%)	36 (0.41)	229 (0.53)	
White (%)	6,848 (57.73)	24,843 (57.17)	
Median (IQR) polypharmacy count	6 (3-9)	6 (3-9)	p = 0.0350
Number of service contacts in last 12 months	25 (11-35)	23 (13-36)	p < 0.0001
Prescribed antidepressants, n (%), in last 12 months	4,703 (39.65)	17,887 (41.16)	p = 0.0030
Median diabetes duration in months (IQR)	2 (0-23)	2 (0-23)	p < 0.0001
Comorbidity:			
Alcohol abuse	616 (5.19)	2,307 (5.31)	p = 0.6323
Blood loss anemia	43 (0.36)	190 (0.44)	p = 0.3010
Cardiac arrhythmia	1,316 (11.09)	3,375 (7.77)	p < 0.0001
Chronic heart failure	1,103 (9.30)	1,899 (4.37)	p < 0.0001
Coagulopathy	172 (1.45)	440 (1.01)	p < 0.0001
Chronic Pulmonary Disease	3,107 (26.19)	9,876 (22.73)	p < 0.0001
Deficiency anemia	1,523 (12.84)	4,249 (9.78)	p < 0.0001
Drug abuse	293 (2.47)	1,025 (2.36)	p = 0.5032
Fluid and electrolyte disorders	805 (6.79)	1,817 (4.18)	p < 0.0001
Hypertension (uncomplicated)	5,157 (43.47)	17,705 (40.75)	p < 0.0001
Hypertension with end organ damage	33 (0.28)	80 (0.18)	p = 0.0579
Hypothyroidism	1,026 (8.65)	3,369 (7.75)	p = 0.0015
Liver disease	454 (3.83)	1,072 (2.47)	p < 0.0001
Lymphoma	87 (7.33)	232 (0.53)	p = 0.0133
Metastatic cancer	199 (1.68)	339 (0.78)	p < 0.0001
Other neurological disorders	1,742 (14.69)	4,795 (11.04)	p < 0.0001
Paralysis	87 (7.33)	259 (0.60)	p < 0.0001
Peptic ulcer disease	415 (3.50)	1,084 (2.49)	p < 0.0001
Peripheral vascular disease	765 (6.45)	1,686 (3.88)	p < 0.0001
Psychosis	359 (3.03)	1,221 (2.81)	p = 0.2212
Pulmonary circulation disorders	333 (2.81)	779 (1.79)	p < 0.0001
Rheumatoid arthritis and collagen diseases	590 (4.97)	1,740 (4.00)	p < 0.0001
Renal disease	2,212 (18.65)	5,246 (12.07)	p < 0.0001
Solid tumour or leukaemia	1,408 (11.87)	3,817 (8.78)	p < 0.0001
Valvular disease	402 (3.39)	1,014 (2.33)	p < 0.0001

Table 1 (continued)

	Cases	Controls	Test of association**
Smoking Status:			
Non-smoker	6,148 (51.83)	2,1430 (49.32)	
Current smoker	3,559 (30.00)	12,566 (28.92)	p < 0.0001
Ex-smoker	2,155 (18.17)	9,456 (21.76)	
BMI category:			
Missing*	1,701 (14.34)	5,936 (13.66)	
Normal	752 (6.34)	2,391 (5.50)	p < 0.0001
Overweight	2,386 (20.11)	8,081 (18.60)	
Obese	7,023 (59.21)	27,044 (62.24)	
Median follow-up time, years (IQR)	6.80 (4.12-9.79)	6.81 (4.14-9.79)	p = 0.7559

*Missing data imputed – for ethnicity as “White”; for BMI using multiple imputation.

** Tests of association included chi-squared test for categorical/binary variables and Mann-Whitney *U* test for continuous variables.

Table 2

Univariable and Multivariable Analysis Results for the Association Between Antidepressant Prescribing and Insulin Initiation.

Antidepressant prescription:	Cases n (%)	Controls n (%)	Univariable IRR (95% CI)	Multivariable IRR (95% CI)
None	2,636 (22.18)	23,581 (54.27)	Reference	
Any	9,226 (77.78)	19,871 (45.73)	4.79 (4.55-5.05)	3.78 (3.53-4.04)
Recent	6,426 (54.17)	13,925 (32.05)	4.80 (4.54-5.06)	4.04 (3.74-4.37)
Non-recent only	2,800 (1.06)	5,946 (13.68)	4.79 (4.49-5.10)	3.47(3.19-3.77)
Duration:				
<6 months	1,984 (21.50)	4,515 (22.72)	4.35 (4.05-4.66)	3.94 (3.64-4.27)
6-12 months	964 (10.45)	2,178 (10.96)	4.39 (4.01-4.80)	4.35 (3.92-4.82)
13-24 months	1,292 (14.00)	2,821 (14.20)	4.68 (4.31-5.07)	4.93 (4.49-5.42)
>24 months	4,984 (54.02)	10,354 (52.11)	5.16 (4.87-5.46)	5.61 (5.23-6.03)
N antidepressant agents:				
0	2,636 (22.18)	23,581	Reference	Reference
1	4,874 (41.09)	11,748	4.23 (4.00-4.47)	3.93 (3.69-4.19)
2	2,486 (20.96)	4,878	5.40 (5.05-5.78)	5.03 (4.66-5.44)
3+	1,871 (15.77)	3,272	6.20 (5.75-6.68)	5.72 (5.25-6.24)

peptic ulcer disease, peripheral vascular disease, renal disease and solid tumours or leukaemia. The following covariates associated with a decreased rate of insulin initiation: Asian ethnicity, increased count of GP consultations, being an ex-smoker and obesity. There were no statistically significant differences in the subgroup analyses performed for gender and ethnicity.

Table 3
Univariable and Multivariable Analysis Results for the Association Between Antidepressant Agent and Insulin Initiation.

Antidepressant prescription:	Cases	Controls	Univariable	Multivariable
	n (%)	n (%)	IRR (95% CI)	IRR (95% CI)
Citalopram	1,656	3,985	Reference	Reference
Amitriptyline	116	305	0.75 (0.55-1.03)	0.80 (0.54-1.12)
Clomipramine	30	74	1.07(0.57-1.99)	1.24 (0.61-2.54)
Dosulepin	191	372	1.4 (1.08-1.82)	1.38 (1.02-1.86)
Doxepin	8	13	1.33 (0.26-6.80)	2.14 (0.34-13.51)
Duloxetine	123	319	1.04 (0.77-1.40)	0.98 (0.69-1.39)
Escitalopram	55	249	1.19 (0.84-1.67)	1.11 (0.74-1.68)
Fluoxetine	1,173	2,602	1.05 (0.92-1.19)	1.00 (0.86-1.17)
Fluvoxamine	2	10	0.89 (0.15-5.49)	0.51 (0.05-5.24)
Imipramine	17	44	0.77 (0.32-1.85)	0.77 (0.28-2.09)
Lofepramine	55	105	0.72 (0.43-1.20)	0.78 (0.44-1.38)
Mirtazapine	290	793	1.03 (0.84-1.27)	1.05 (0.82-1.33)
Moclobemide	3	8	0.77 (0.14-4.28)	0.27 (0.03-2.58)
Nortriptyline	4	21	0.34 (0.07-1.64)	0.44 (0.08-2.41)
Paroxetine	213	492	0.98 (0.77-1.25)	1.09 (0.82-1.44)
Phenelzine	7	4	10.34 (1.26-85.02)	11.3 (1.34-95.68)
Sertraline	546	1,650	0.83 (0.71-0.97)	0.84 (0.70-1.01)
Trazadone	46	100	1.00 (0.61-1.62)	0.90 (0.50-1.62)
Trimipramine	5	19	0.53 (0.14-2.03)	0.34 (0.08-1.47)
Venlafaxine	257	567	1.12 (0.90-1.39)	1.24 (0.95-1.61)

Results were not reported for the following antidepressants due to insufficient numbers: maprotiline, mianserin, reboxetine, tranlycypromine. The Bonferroni corrected p-value for all antidepressant agents was 1.00.

4. Discussion

This is the first study, to the best of our knowledge, to investigate the association between antidepressant treatment and insulin initiation, in adults with comorbid depression and type 2 diabetes.

We had hypothesised that antidepressant prescribing would be associated with a reduced rate of insulin initiation, based on the theory that successfully treating depression would improve an individual's diabetic health and self-care. On the contrary, we found that individuals who had one or more antidepressant prescriptions, prescribed after starting oral antidiabetic treatment were at considerably increased risk of initiating insulin, compared to those who did not have any antidepressant prescriptions during the follow-up period.

We considered that a preference for pharmacological treatment may lead to individuals who receive antidepressant medication to be more inclined to initiate insulin therapy. However, controlling for polypharmacy at baseline had no statistically significant effect on the association between antidepressant prescribing during follow-up and insulin initiation.

Individuals who were prescribed an antidepressant may represent a group of people who potentially have more severe depression and worse physical health. Indeed there is considerable evidence from previous studies that depression is associated with worsened glycaemic control

[2]. While we were unable to adjust for depression severity directly, we adjusted for a number of covariates that are known to be associated with depression severity, and still a considerable effect size remained for the association between any antidepressant prescription after starting oral antidiabetics, and the subsequent initiation of insulin therapy. Nevertheless, it is important to note that all covariates were measured at baseline, while the median duration of follow-up was 8 years. Participants who were prescribed antidepressants may have seen a decline in physical and mental health since baseline, due to factors that were not available from electronic health record data, such as lifestyle or life events. There are no previous studies to the best of our knowledge that included such covariates, or indeed other markers of physical or mental health beyond a baseline date.

We also found a positive association between the rate of insulin initiation and both the cumulative duration of antidepressant treatment and the number of different antidepressant agents prescribed. Individuals who remained on antidepressant treatment for longer durations and those who have trialled multiple different antidepressant agents are likely to represent individuals with more severe depression. This supports our theory that the association we found between any antidepressant prescribing and insulin initiation may largely be attributable to depression severity. Nevertheless, it should be noted that even individuals with the shortest antidepressant treatment durations (<6 months) and who were prescribed only one antidepressant agent during the course of study follow-up still showed significantly higher rates of insulin initiation than those who never received an antidepressant prescription.

There was no statistically significant difference in the rate of initiating insulin in individuals who had a recent antidepressant prescription (recorded 6 months prior to the date of starting insulin for cases or the index date where controls had not started insulin), and participants who only had antidepressant prescriptions more than 6 months before the index date. This suggests that there is no immediate, short-term, biological impact of antidepressant prescribing that leads to the initiation of insulin therapy. Furthermore, in our subgroup analysis of individuals who only received one antidepressant agent, there was no statistically significant difference between different antidepressant agents. As different antidepressant agents have different mechanisms of action and side effects [32–35], it is unlikely that the impact on insulin initiation would be directly attributable to antidepressant medication, without seeing differences between different agents.

4.1. Strengths and limitations

Our study is the first to investigate long-term diabetic outcomes in a group with comorbid depression and type 2 diabetes. Our use of primary care data, unlike RCTs, enables the observation of real-world pharmacological treatment, including and accounting for individuals with comorbidities and co-prescriptions, and where prescribing decisions are based to a large extent on the patient and clinician preference [36–37]. Our use of large scale primary care data, enabled a sample size of 55,314, allowing us to account for a generalisable population, and to investigate a range of outcomes, such as the timing and duration of antidepressant treatment and differences between different antidepressant agents. In addition, our long follow-up duration which would be untenable in clinical trials, with a median of 7 years, allowed for the natural observation of long-term outcomes, contributing to the understanding of long-term diabetic prognosis.

We specifically included only individuals with type 2 diabetes, due to the bidirectional relationship between depression and type 2 diabetes, which not only makes the treatment of depression in this patient group of particular importance, but also comes with distinct challenges, such as concerns about antidepressant side effects. Similarly, we only included individuals who received a GP code for depression during the follow-up period, ensuring that all individuals were depressed to the point of seeking help.

The CPRD does not record prescription indications, therefore, it was not possible to be certain that any antidepressant was prescribed to treat depression. This is particularly relevant for amitriptyline, nortriptyline and duloxetine, which are also indicated in the UK to treat diabetic neuropathic pain. For amitriptyline and nortriptyline, we included only prescriptions that were issued at a dosage ≥ 50 mg, which is indicated for depression, while neuropathic pain dosages are typically lower [34,38]. However, this is not always the case, and was not possible for duloxetine, which uses the same therapeutic doses for both depression and neuropathic pain. Similarly some TCAs or trazodone, for example, may be used to treat sleeplessness. However, we had included in the study only participants who had a diagnosis, symptom or process of care code for depression recorded during the follow-up period for which antidepressant treatment was measured, therefore, all participants were at risk of antidepressant prescribing during this time.

While we were able to adjust for a large number of health related covariates that may be associated with depression severity, we could not adjust for depression severity itself as there is no sufficiently completed variable in the database relating to this, nor for specific symptoms and characteristics of depression that may be associated with both antidepressant prescribing and insulin initiation. Furthermore, due to the study design, we were only able to adjust for covariates at baseline which may be subject to change over the average 7 year follow-up period.

4.2. Implications

After adjusting for demographic characteristics, physical health, medication use, and markers of depression severity at the time of the first oral antidiabetic prescription, subsequent antidepressant prescribing was highly associated with the initiation of insulin therapy, suggesting a decline in diabetic health. There was no evidence of an immediate effect of recent antidepressant treatment on insulin initiation, or of any difference between agents with different mechanisms of action and known physical side effects. This leads us to suggest that the association with insulin initiation was likely to be attributable to increased depression severity. Indeed, this is further confirmed by the still higher rates of insulin initiation seen in individuals with antidepressant prescribing patterns typical of those with more severe depression. Our study identifies a sub-population of people with depression and type 2 diabetes who are at very high risk of worse diabetic outcomes. Although these individuals are being treated with antidepressant medication, this does not appear to be sufficient in improving depression symptoms to negate the negative effects of depression on physical health. These individuals could be targeted earlier for holistic interventions to improve their mental well-being and glycaemic control and reduce the need for insulin. Further research is required whereby time-varying depression severity can be accounted for. Additionally, further research is needed into the specific characteristics of depression that cause long-term diabetic decline and potential interventions that can prevent this.

CRediT authorship contribution statement

Annie Jeffery: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualisation, Writing - original draft, Writing - review & editing. **Kate Walters:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Ian C.K. Wong:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **David Osborn:** Conceptualization, Funding acquisition, Resources, Software, Supervision, Writing - review & editing. **Joseph F. Hayes:** Conceptualization, Funding acquisition, Resources, Software, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Funding and conflict of interests statement:

Annie Jeffery reports financial support was provided by National Institute for Health Research. Joseph Hayes is supported by UKRI grant MR/V023373/1 and the University College London Hospitals NIHR Biomedical Research Centre and the NIHR North Thames Applied Research Collaboration. Joseph Hayes has received consultancy fees from Wellcome Trust and Juli Health: funding grants. Ian Wong, David Osborn, Joseph Hayes reports a relationship with National Institute for Health Research that includes: funding grants. David Osborn, Ian Wong reports a relationship with NIHR University College London Hospitals Biomedical Research Centre that includes: funding grants. Ian Wong reports a relationship with Amgen Inc that includes: funding grants. Ian Wong reports a relationship with BristolMyers Squibb that includes: funding grants. Ian Wong reports a relationship with Pfizer that includes: funding grants. Ian Wong reports a relationship with Janssen Pharmaceuticals Inc that includes: funding grants and speaking and lecture fees. Ian Wong reports a relationship with Bayer Corporation that includes: funding grants. Ian Wong reports a relationship with GSK that includes: funding grants. Ian Wong reports a relationship with Novartis that includes: funding grants. Ian Wong reports a relationship with Hong Kong Research Grants Council that includes: funding grants. Ian Wong reports a relationship with the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region that includes: funding grants. Ian Wong reports a relationship with National Health and Medical Research Council in Australia that includes: funding grants. Ian Wong reports a relationship with European Commission that includes: funding grants. Ian Wong reports a relationship with Medice that includes: funding grants. Ian Wong reports a relationship with Jacobson Medical that includes: board membership. Joseph Hayes is an Associate Editor on the Editorial Board for the British Journal of Psychiatry. None of the reported relationships had any role in study design, data collection and analysis, data interpretation, decision to publish, or preparation of the manuscript. The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

References

- [1] Khaledi M, Haghghatdoost F, Feizi A, Aminorroaya A. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. *Acta Diabetol* [Internet] 2019;56(6). <https://pubmed.ncbi.nlm.nih.gov/30903433/>.
- [2] Lustman PJ, Anderson RJ, Freedland KE, De Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* [Internet] 2000;23(7):934–42. <http://diabetesjournals.org/care/article-pdf/23/7/934/450641/10895843.pdf>.
- [3] de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. *Psychosom Med* 2001; 63(4):619–30.
- [4] Egede LE, Osborn CY. Role of motivation in the relationship between depression, self-care, and glycemic control in adults with type 2 diabetes. *Diabetes Educ* [Internet] 2010;36(2):276–83. <https://pubmed.ncbi.nlm.nih.gov/20179250/>.
- [5] Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care* [Internet] 2008;31(12):2398–403. Available from: 10.2337/dc08.
- [6] Dakanalis A, Mentzelou M, Papadopoulou SK, Papandreou D, Spanoudaki M, Vasios GK, et al. The Association of Emotional Eating with Overweight/Obesity, Depression, Anxiety/Stress, and Dietary Patterns: A Review of the Current Clinical Evidence. *Nutrients* [Internet]. 2023 Mar 1 [cited 2023 Nov 28];15(5). Available from: <https://pubmed.ncbi.nlm.nih.gov/36904172/>.
- [7] Glowacki K, Duncan MJ, Gainforth H, Faulkner G. Barriers and facilitators to physical activity and exercise among adults with depression: A scoping review. *Mental Health Phys Act* 2017 Oct;1(13):108–19.

- [8] Association AD. 4. Lifestyle Management. *Diabetes Care* [Internet]. 2017 Jan 1 [cited 2022 Apr 14];40(Supplement 1):S33–43. Available from: https://diabetesjournals.org/care/article/40/Supplement_1/S33/36913/4-Lifestyle-Management.
- [9] National Institute for Health and Care Excellence [Internet]. 2009 [cited 2022 Jan 4]. Recommendations | Depression in adults: recognition and management | Guidance | NICE. Available from: <https://www.nice.org.uk/guidance/cg90/chapter/Recommendations>.
- [10] Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. *Pharmacological Treatments Can J Psychiatry* [Internet] 2016;61(9):540–60. <https://pubmed.ncbi.nlm.nih.gov/27486148/>.
- [11] mhGAP Intervention Guide Mental Health Gap Action Programme Version 2.0 for mental, neurological and substance use disorders in non-specialized health settings. World Health Organisation [Internet]. 2016 [cited 2022 Jan 4];(2.0). Available from: <http://www.who.int>.
- [12] Psychological Association A. APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts Guideline Development Panel for the Treatment of Depressive Disorders Approved by APA Council of Representatives. 2019 [cited 2022 Jan 4]; Available from: <https://www.apa.org/depression-guideline>.
- [13] Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database of Systematic Reviews* [Internet] 2011. <http://doi.wiley.com/10.1002/14651858.CD008012.pub3>.
- [14] Roopan S, Larsen ER. Use of antidepressants in patients with depression and comorbid diabetes mellitus: a systematic review. 2016 [cited 2019 Nov 26]; Available from: <https://doi.org/10.1017/neu.2016.54>.
- [15] van der Feltz-Cornelis CM, Nuyen J, Stoop C, Chan J, Jacobson AM, Katon W, et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. *Gen Hosp Psychiatry* 2010;32(4):380–95.
- [16] Jeffery A, Buckman JEJ, Francis E, Walters K, Wong ICK, Osborn D, et al. A Systematic Review of Long-term Antidepressant Outcomes in Comorbid Depression and Type 2 Diabetes. *medRxiv* [Internet]. 2022 Apr 16 [cited 2022 May 3]; 2022.04.11.22273519. Available from: <https://www.medrxiv.org/content/10.1101/2022.04.11.22273519v1>.
- [17] Derijks HJ, Heerdink ER, De Koning FH, Janknegt R, Klungel OH, Egherts AC. The association between antidepressant use and hypoglycaemia in diabetic patients: a nested case-control study. *Pharmacopidemiol Drug Saf* [Internet]. 2008 Apr [cited 2022 Feb 7];17(4):336–44. Available from: <https://pubmed.ncbi.nlm.nih.gov/18302302/>.
- [18] Lee HM, Yang YC, Chen SF, Hsu CY, Shen YC. Risk of hyperglycemic crisis episode in diabetic patients with depression: A nationwide population-based cohort study. *J Diabetes Complications* 2020 Mar 1;34(3):107509.
- [19] Noordam R, Aarts N, Peeters RP, Hofman A, Stricker BH, Visser LE. Selective Serotonin Reuptake Inhibitors Decrease Pancreatic Insulin Secretion in Older Adults and Increase the Risk of Insulin Dependence in Type 2 Diabetes Patients. *J Clin Psychiatry* [Internet] 2016;77(9):e1124–9. <https://pubmed.ncbi.nlm.nih.gov/27487004/>.
- [20] Clinical Practice Research Datalink | CPRD [Internet]. [cited 2022 Jan 13]. Available from: <https://www.cprd.com/>.
- [21] 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* [Internet] 2015;44(3):827–36. <https://pubmed.ncbi.nlm.nih.gov/26050254/>.
- [22] Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol* 2019 Dec 1;48(6). 1740-1740G.
- [23] Suissa S. Novel Approaches to Pharmacoepidemiology Study Design and Statistical Analysis. *Textbook of Pharmacoepidemiology* 2013 May;31:383–95.
- [24] Breslow N, Day N, Heseltine E. Statistical methods in cancer research. 1980 [cited 2022 Apr 12]; Available from: http://publications.iarc.fr/_publications/media/download/3469/3be6599f0227fbc06d00d91a99aa5ce007090018.pdf.
- [25] Essebag V, Platt RW, Abrahamowicz M, Pilote L. Comparison of nested case-control and survival analysis methodologies for analysis of time-dependent exposure. *BMC Med Res Methodol* 2005 Jan;25:5.
- [26] Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. *e0162388 PLoS One* [Internet] 2016;11(9). <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162388>.
- [27] Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: A cohort study in the Clinical Practice Research Datalink 2004–2014. *BMJ Open* 2017 Feb 1;7(2).
- [28] Walker AJ, Croker R, Curtis HJ, MacKenna B, Goldacre B. Trends in antidepressant prescribing in England. *Lancet Psychiatry* 2021 Apr 1;8(4):278–9.
- [29] Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* [Internet] 2008;336(7659):1475–82. <https://pubmed.ncbi.nlm.nih.gov/18573856/>.
- [30] Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* [Internet]. 1998 [cited 2022 Apr 12];36(1):8–27. Available from: <https://pubmed.ncbi.nlm.nih.gov/9431328/>.
- [31] Labrecque JA, Hunink MMG, Ikram MA, Ikram MK. Do Case-Control Studies Always Estimate Odds Ratios? *Am J Epidemiol* [Internet]. 2021 Feb 1 [cited 2022 Jul 12];190(2):318. Available from: <https://pmc/articles/PMC7850067/>.
- [32] British National Formulary [Internet]. 2022 [cited 2022 Jan 4]. SERTRALINE | Drug | BNF content published by NICE. Available from: <https://bnf.nice.org.uk/drug/sertraline.html>.
- [33] British National Formulary [Internet]. 2022 [cited 2022 Jan 4]. MIRTAPAZINE | Drug | BNF content published by NICE. Available from: <https://bnf.nice.org.uk/drug/mirtazapine.html>.
- [34] AMITRIPTYLINE HYDROCHLORIDE | Drug | BNF content published by NICE [Internet]. [cited 2022 Apr 28]. Available from: <https://bnf.nice.org.uk/drug/amitriptyline-hydrochloride.html>.
- [35] Antidepressant drugs | Treatment summary | BNF content published by NICE [Internet]. [cited 2022 Apr 13]. Available from: <https://bnf.nice.org.uk/treatment-summary/antidepressant-drugs.html>.
- [36] Silverman SL. From randomized controlled trials to observational studies. *Am J Med* [Internet]. 2009 Feb [cited 2022 Jan 4];122(2):114–20. Available from: <https://pubmed.ncbi.nlm.nih.gov/19185083/>.
- [37] Sorensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. *Hepatology* [Internet] 2006;44(5):1075–82. <https://pubmed.ncbi.nlm.nih.gov/17058242/>.
- [38] Nortriptyline | Drugs | BNF | NICE [Internet]. [cited 2022 Jul 12]. Available from: <https://bnf.nice.org.uk/drugs/nortriptyline/>.