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Prevalence and characteristics of antidepressant prescribing in adults with comorbid depression and type 2 diabetes mellitus: A systematic review and meta-analysis

Annie Jeffery[a,*], Lucy Maconick[a], Emma Francis[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

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ABSTRACT

Background: Treatment guidelines do not provide specific recommendations for antidepressant prescribing in people with type 2 diabetes mellitus (T2DM). It is important to understand the prevalence of antidepressant prescribing and associated patient characteristics, to recognise safety issues or inequalities related to treatment access.

Methods and Results: Seven databases were searched using terms related to depression, T2DM and antidepressant medication. From 14,389 reports retrieved, 9 met inclusion criteria. The prevalence of antidepressant prescribing varied considerably between studies from 18% to 87%. Where meta-analyses were possible, the pooled odds ratio for receiving an antidepressant were 1.52 (95% confidence intervals (CIs) 1.28 – 1.82) in women compared to men, 0.53 (95% CIs 0.23-1.20%) in Black and Ethnic Minorities compared to White ethnicity and 1.29 (95% CIs 0.92-1.80) in insulin users compared to individuals with non-insulin controlled T2DM.

Conclusions: Antidepressant prescribing is more common in women with T2DM compared to men, however, the difference is less than in the general population. Insulin users, representing individuals with more advanced T2DM, were as likely to be prescribed antidepressants as those who did not use insulin. There is a gap in the literature concerning which antidepressant agents are being prescribed, and alongside which concurrent medications and comorbidities.

1. Introduction

There is substantial evidence showing increased prevalence rates of depression in type 2 diabetes (T2DM) [1]. Depression can be linked to worsened self-care in diabetes [2,3] and has been shown to decrease adherence to diabetic treatments [4]. Furthermore, depression has been shown to be associated with poor glycaemic control [5] and the development of diabetic complications [6]. Thus, the successful treatment of depression in people with comorbid depression and T2DM can be important to improving both physical and mental health.

National and international healthcare guidelines [7–10] recommend antidepressant medication as a treatment option for people with moderate to severe depression. A number of antidepressants have been shown to be effective in the general population but differ substantially in terms of side-effects [11–13]. Guidelines addressing the treatment of depression in people with physical long-term conditions are non-specific and limited [14]. A review of clinical guidelines with respect to multimorbidity notes the difficulties of applying current guidelines to patients with multiple conditions [15].

A 2012 Cochrane review [16] of randomised-controlled trials (RCTs), and a 2016 systematic review including both RCTs and observational studies [17], both found antidepressant medication to have moderate effects on decreasing depressive symptoms in individuals with T2DM and small effects on improving glycaemic control. However, follow-up periods were limited, with no medium-long term evidence available regarding safety or effectiveness. It is known that a number of commonly prescribed antidepressants cause side-effects that poten-

* Corresponding author.
E-mail addresses: annie.jeffery.09@ucl.ac.uk (A. Jeffery), l.maconick@ucl.ac.uk (L. Maconick), emma.francis.19@ucl.ac.uk (E. Francis), k.walters@ucl.ac.uk (K. Walters), i.wong@ucl.ac.uk, wongick@hku.hk (I.C.K. Wong), d.osborn@ucl.ac.uk (D. Osborn), joseph.hayes@ucl.ac.uk (J.F. Hayes).

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tially exacerbate T2DM and/or its complications, such as weight gain [18], cardiac complications, arthralgia, gastrointestinal disturbances, sexual disfunction and visual impairment [19]. Furthermore, selective serotonin re-uptake inhibitors, which are recommended as first-line antidepressant choice [14] are cautioned for use in people with diabetes mellitus [19].

Polypharmacy is common in T2DM, given the number of metabolic factors that need to be controlled, in addition to the number of potential complications that need management [20]. The addition of one or more antidepressants adds to the potential burden and risks associated with polypharmacy. Patients with multimorbidity taking multiple medications are more likely to experience medication side-effects [21], medication interactions [22], have impaired medication adherence [23] and reduced quality of life [24]. There are no studies to the authors' knowledge that evaluate the prescribing of antidepressants in the context of the wider diabetic pharmacological regimen.

While there is a heightened need to successfully treat depression in people with T2DM, the lack of clarity from treatment guidelines, lack of medium-long-term evidence supporting antidepressant safety and effectiveness, and increased relevance of side effects and risks from polypharmacy, makes for difficult prescribing decisions. It is important to understand current trends in antidepressant prescribing in this group, including the patient characteristics associated with antidepressant treatment. This could highlight safety issues, or alternatively, the undertreatment of depression in patients with certain characteristics.

There is consistent evidence in the general population showing variation in the prevalence of antidepressant prescribing by ethnicity, gender and socioeconomic status [25–27]. These characteristics are all associated with variation in outcomes in T2DM and its associated complications, such as CVD and renal disease [28–30]. The sociodemographic treatment gap for antidepressants has the potential to contribute to worsening physical health, in groups of individuals who are already at increased risk. Conversely, there is evidence showing increased rates of antidepressant prescribing in individuals aged 60+ [25] who may be more susceptible to antidepressants side-effects [31] that can exacerbate T2DM and its complications. Therefore, additional caution may need to be exercised when prescribing in this group. Thus, it is important to know whether the sociodemographic differences seen in the general population with depression exist in individuals with comorbid depression and T2DM.

To our knowledge there is no systematic review at present investigating antidepressant prescribing trends in adults with comorbid depression and T2DM. Our objectives were, in adults with comorbid depression and T2DM:

1 To determine the prevalence of antidepressant prescribing
2 To determine patient characteristics associated with antidepressant prescribing
3 To determine the patient characteristics associated with the prescription of specific antidepressant agents

2. Methods

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [32] and registered the protocol on PROSPERO prior to the commencement of screening (CRD42020182581).

2.1. Study inclusion criteria

2.1.1. Types of study

We included observational studies from routinely collected data, registry studies, cohort studies, case-control studies and cross-sectional studies. We excluded randomised controlled trials, quasi-experimental trials where patients receive an antidepressant as part of the study, systematic reviews, case studies/reports, editorials, letters and opinion pieces.

2.1.2. Participants

We included studies investigating adults (18+ years) with comorbid depression and T2DM.

Depression could be identified by clinician diagnosis, medical records, standardised interviews, or self-reports. Where diagnostic criteria were not available, we used the authors' definition of depression, provided depression was explicitly stated for all participants or the subgroup being used for analysis. We did not include studies where definition of depression was the prescription of an antidepressant alone.

Type 2 diabetes could be defined as an in-study clinician diagnosis, medical records, or self-reports. The type of diabetes should have been explicitly verified as type 2, and we did not include studies where the diabetes type was ambiguous or mixed. If necessary, we accepted the authors' definition of type 2 diabetes.

We excluded participants with mental disorders other than depression, e.g. schizophrenia or bipolar disorder.

2.1.3. Outcome

Our primary outcome was the prescription of any antidepressant medication. We included antidepressant prescriptions defined through self-report, prescription records or clinician report. We excluded antidepressant prescriptions explicitly indicated for conditions other than depression.

Our secondary outcome was the individual antidepressant medication or medication class.

2.1.4. Comparison

Our comparison group for the primary outcome was no antidepressant treatment. For the secondary outcome a comparison was made between different antidepressant classes.

2.1.5. Exposures

We did not limit the potential patient characteristics that could be associated with antidepressant prescription: these included sociodemographic factors, depression severity, glycaemic control, comorbidities and polypharmacy.

2.2. Search strategy

We used the following sources from inception to 10-May-2021 for the identification of studies:

- MEDLINE
- EMBASE
- Scopus
- CINAHL Plus
- Web of Science
- PsychInfo
- PsycExtra
- Open Grey

Databases were searched using Medical Subject Headings (MeSH) and keywords for: depression AND type 2 diabetes AND antidepressant.

Articles in the following languages were eligible for inclusion: English, French, Spanish, Italian, Portuguese, Greek.

In addition, we reviewed references of all studies screened at full text stage and all relevant systematic reviews found during the search.

2.3. Data collection and analysis

2.3.1. Screening and extraction

The first (AJ) and third (EF) authors independently screened all titles and abstracts against the eligibility criteria. The first (AJ) and second (LM) review authors independently carried out full-text screening of studies that potentially met our inclusion criteria.

We included studies that used data from the same dataset, if they reported a unique outcome/exposure. If more than one study reported

Table 1
Study characteristics

Reference	Study Design/ Setting	Study Population	Study Aim	Study Size	Country	Average Age	Female %	Ethnicity	Education	Depression severity	Insulin dependent %	Case definition	Identification of outcome	Exposures
Binsalah 2018 [35]	NHANES[44] cross-sectional survey; home interviews and research centre assessment	Community dwelling	To evaluate "the association of antidepressant use with healthcare utilization in a nationally representative sample of patients with type 2 diabetes and mild to severe depressive symptoms in the United States population"	955	USA	58 ± (12-13)	66.1	Black (17.8%); hispanic (17.1%); other (6.5%); white (58.6%)	> high school 10.8%	Mild (60.6%); moderate-severe (39.4%)	20.0%	PHQ-9 [45]; self-reported T2DM	Self-report	Age; gender; ethnicity; education; insurance; depression severity; diabetes duration; glycaemic control; insulin use; oral antidiabetics; macrovascular/ microvascular complications
Brieler 2016 [36]	Retrospective cohort study; electronic medical records	Community dwelling; urban location	To determine whether the use of antidepressant medication is associated with glycaemic control in depressed patients with T2DM	265	USA	61-62 ± (11-12)	72.8	White (51.3%)	Not available	Not available	40.4%	ICD codes	Prescription	Age; gender; ethnicity; glycaemic control; insulin use; oral antidiabetics; hyperlipidemia; hypertension; obesity; vascular disease
Chen 2011 [37]	Secondary analysis of programme evaluation; data recorded by diabetes educator	Community dwelling; in diabetes education programme	To examine the effects of depression and antidepressant use on goal setting and barrier identification in patients with type 2 diabetes"	271	USA	55-57	72	BAME (14%); white (85.2%) [study reporting is missing 0.8%]	< high school 10%; > high school 41%	Not available	29.5%	Self-reported depression; participation in T2DM education programme	Documented by diabetes educator	Age; gender; ethnicity; education; diabetes duration; glycaemic control; insulin use; BMI; hypertension; heart disease; neuropathy; renal disease; retinopathy; sexual disfunction
Higgins 2007 [38]	Retrospective cohort study; electronic medical records	Community dwelling military veterens	To examine the association of heart disease with depression and the impact of treatment with anti-depressants on this association in older males with T2DM	691	USA	42% > 60	0	White (85.2%)	Not available	Not available	Not available	ICD codes	Prescription	None
Perez 2017 [39]	NHANES[44] cross-sectional survey; home interviews and research centre assessment	Community dwelling adults; white, black and hispanic	To determine antidepressant use among Mexican Americans and non-Hispanic blacks and whites with T2DM and depressive symptoms"	560	USA	45-64	65.6	Black (22.2%); hispanic (11.5%); white (66.3%)	< high school 32.8%; > high school 42.3%	Mild (59.9%); moderate-severe (40.1%)	Not available	PHQ-9 [45]; self-reported T2DM	Self-report	Ethnicity
Shrestha 2013 [40]	Cross-sectional; insurance claimes	Community dwelling; with employee insurance; not taking insulin	To estimate excess medical expenditures associated with major depressive disorder among working-age adults diagnosed with diabetes	10,881	USA	51.3-52.2	56.7	Not available	Not available	Not available	Not available	Primary/ secondary inpatient or outpatient encounters	Prescription	Age; gender; cerebrovascular disease; heart failure; liver disease; myocardial infarction; renal disease
Wagner 2009 [41]	Cross-sectional; phone interviews and research centre assessement	Community dwelling; with private insurance; urban location;	"To compare rates of discussion and treatment for depression among African Americans and Whites with diabetes"	56	USA	55.7 ± 7.2	56.6	White (40%)	Not available	Mean PHQ-9 = 11	55.4%	PHQ-9 [45]; ICD code or prescription for T2DM	Unclear - possible self-report	Ethnicity
Wang 2016 [42]	NHANES[44] cross-sectional survey; home interviews and research centre assessment	Community dwelling	To provide an updated, population-based estimate for the prevalence of depression in people with T2DM"	625	USA	50-64	66.5	Black (18.5%); hispanic (21.4%); other (17.0%); white (57.4%)	< high school 36.7%; > high school 39.0%	Mild (59.0%); moderate-severe	25.1%	PHQ-9 [45]; self-reported T2DM	Self-report	Depression severity
Whitworth 2017 [43]	Prospective cohort study; research centre assessment	Community dwelling	To describe the long-term trajectories of depression symptom severity in people with T2DM, and to identify predictors and associates of these trajectories	178	Australia	58-63 ± (11-12)	56.7	White (51.1%)	< high school 13.6%	Mild (49.4%); moderate-severe (50.6%)	29.7%	PHQ-9 [45]; clinical diagnosis	Unclear - possible self-report	Depression severity

the same outcome/exposure, we included the study with the most generalisable population for that outcome, larger sample size and lower risk of bias.

The first review author (AJ) carried out data extraction from included articles and data extraction tables were be checked by the second review author (LM).

Any disagreement was resolved through consensus.

2.3.2. Assessment of risk of bias

The first and second review authors (AJ, LM) used an adapted version of the Newcastle-Ottawa Scale [33] to independently assess the risk of bias for each study. We adapted the scale by combining criteria from both the cohort and case-control scales, to be appropriate for the design of the included studies.

Disagreement was resolved by consensus, or by consulting an additional reviewer (JH) when this was not possible. We decided not to exclude studies with higher risk of bias from the meta-analysis due to the strict inclusion criteria of the review; however, risk of bias was considered in the interpretation of the results.

2.3.2. Measures of effect

We calculated prevalence estimates based on the percentage of eligible participants who were reported as having been prescribed an antidepressant, and 95% CIs were calculated. For categorical exposures we extracted the odds ratio (OR) and 95% CIs; for continuous exposures we extracted the mean difference (MD) and standard deviation (SD). Where measures of effect were not provided, if possible, they were calculated from the data provided. For a comparison between different antidepressant classes, selective-serotonin reuptake inhibitors (SSRIs) were used as a reference category.

2.3.3. Assessment of heterogeneity

We assessed statistical heterogeneity by visual inspection of forest plots and by the I^2 statistic quantifying inconsistency across studies, where $I^2 > 75\%$ indicates considerable inconsistency [34].

2.3.4. Data synthesis

Where three or more studies that were sufficiently similar reported the same outcome/exposure of interest, we conducted random effects meta-analyses for each exposure to calculate a pooled effect size with 95% confidence intervals. Otherwise, we synthesised the results narratively.

3. Results

3.1. Description of studies

Our search yielded 14,389 unique abstracts, of which we assessed 96 full-text articles for eligibility, and selected nine studies for inclusion in the review [35–43]. Three studies used the same NHANES survey data [44], and so, are expected to have significant duplication of participants: Binsalah 2018 was chosen for inclusion for the primary outcome, however, did not report data on individual antidepressant medications or classes, and so, Perez 2017 and Wang 2016 were included for this outcome, each reporting on a different exposure. This resulted in at least 13,674 participants included overall (dependent on the extent of duplication between NHANES studies). A PRISMA flowchart showing study selection can be seen in Figure 1. All participants were community dwelling, with average ages ranging from 45 – 64. A summary of study characteristics and exposures can be seen in Table 1.

Risk of bias scores ranged from 2 to 5 out of 7, with 0 being highest risk of bias. A risk of bias summary for all included studies is shown in Figure 2.

3.2. Overall prevalence of antidepressant prescribing

There was considerable variation in the prevalence of antidepressant prescribing across studies, which ranged from 18% - 87%. The pooled prevalence estimate from the random effects meta-analysis was 56% (95% CIs 34 – 76%), however, statistical heterogeneity was considerable, at $I^2 = 99\%$ (Figure 3). Sensitivity analyses were performed according to study design, case and outcome identification, population setting, country and year. Three studies identified depression through clinical coding in health or insurance records – two of these studies had the highest prevalence rates of 85% and 87% [36,40]; the third had a relatively high prevalence rate of 0.57, however, this was recorded in a population of all-male military veterans [38]. The three studies with the lowest prevalence rates, ranging from 18% to 37% all identified depression in the community as part of the research study [35,41,43]. When combined in meta-analysis, these studies gave a pooled prevalence estimate of 29% (23% – 37%) and I^2 of 62%.

3.4. Depression severity

Two studies reported the prevalence of antidepressant prescribing across depression severities [35,43]. Only one of the studies showed evidence of a difference in antidepressant prescribing, with an OR of 2.30 (95% CIs 1.73-3.06) in moderate-severe compared to mild depression [35].

Only one study compared the prescription of different antidepressant classes by depression severity [42]. When comparing each antidepressant class to SSRIs there was no evidence of a difference between mild and moderate-to-severe depression.

3.5. Clinical features of diabetes

Two studies reported diabetes duration for participants prescribed antidepressants compared to those not, with no evidence of a difference [35,37].

Three studies reported the difference in glycaemic control for participants who were prescribed antidepressants compared to those not, with no evidence of a difference [35–37]. The heterogeneity of measures used meant that meta-analysis could not be performed.

Three studies reported the prevalence antidepressant use in participants who were treated with insulin, compared to those who were not [35–37]. None of the studies showed evidence of a difference in the odds of being prescribed an antidepressant in participants with insulin controlled T2DM, with a pooled OR estimate of 1.29 (95% CIs 0.92-1.80) (Figure 4). There was no evidence of statistical heterogeneity between studies (I^2 of 0%).

One study reported antidepressant prevalence in those prescribed oral antidiabetic medication compared to those not prescribed any antidiabetic medication, with no evidence of a difference [36].

3.6. Comorbidities and polypharmacy

Four studies reported antidepressant prevalence across different comorbidities, listed in Table 1 [35–37,40]. Due to the difference in comorbidities reported, it was not possible to synthesise these in meta-analysis. None of the studies showed evidence of a difference in antidepressant prescribing across any comorbidity.

No studies reported if there were differences in antidepressant prescribing because of other medications prescribed, other than antidiabetic medications described above.

3.7. Demographic factors

Four studies reported on the age of participants who were prescribed antidepressants compared to those who were not, with no statistical evidence of a difference [35–37,40]. The maximum difference in median

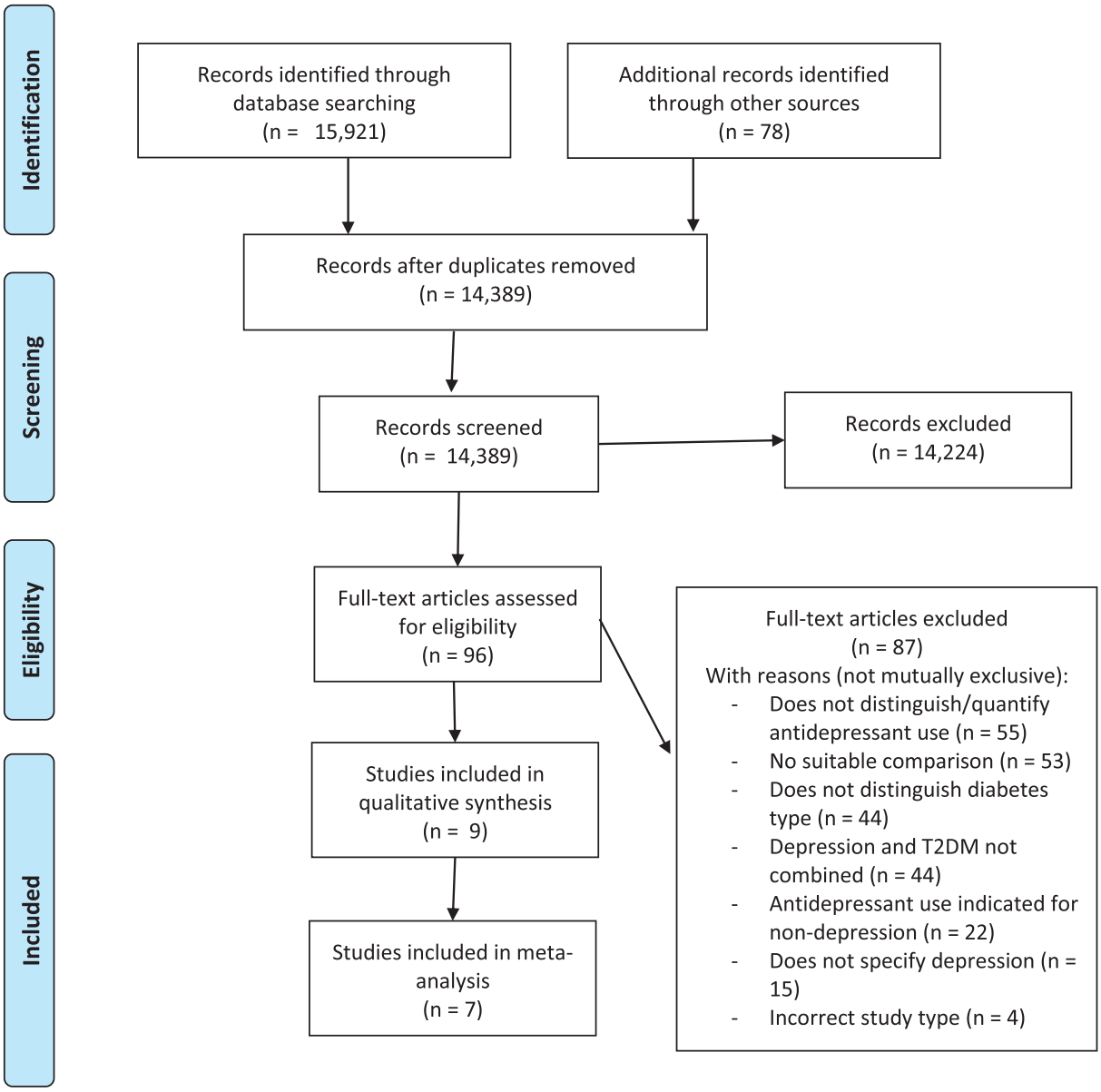

Figure 1. PRISMA Flow Diagram of study selection process

was 2 years. Insufficient information was available to perform a meta-analysis.

Four studies reported the prevalence of antidepressant prescription by gender [35–37,40]. All four studies found increased rates of antidepressant prescription in women, with a pooled OR estimate of 1.53 (95% CIs 1.28-1.82%) compared to men (Figure 4). There was low heterogeneity between studies with an I^2 of 24%.

Four studies reported the prevalence of antidepressant prescribing in Black and Ethnic Minorities compared to White ethnicity [35–37,41]. However, statistical inconsistency was high, at $I^2 = 84\%$, and the pooled OR estimate of 0.53 (95% CIs 0.23-1.20%) did not show evidence of a difference between ethnicities (Figure 4).

Only one study compared the prescription of different antidepressant classes between ethnicity groups [39]. When comparing each antidepressant class to SSRIs there was no evidence of a difference between ethnicities.

Two studies reported the prevalence of antidepressant prescription by educational status, with no evidence of a difference [35,37].

One study reported the prevalence of antidepressant prescribing by insurance status, with an odds ratio of 0.43 (95% CIs 0.27 – 0.68) for those without private medical insurance, compared to those with private insurance [35].

4. DISCUSSION

4.1. Summary of results

This systematic review investigated the prevalence of antidepressant prescribing in adults with comorbid depression and T2DM, and its association with sociodemographic factors, depression severity, clinical features of diabetes, other comorbidities and polypharmacy

However, The two highest prevalence rates of antidepressant prescribing were from studies where depression was identified through clinical coding, whereas the lowest three prevalence rates were in community screened populations. Populations with depression identified through clinical coding may have more severe depression than those

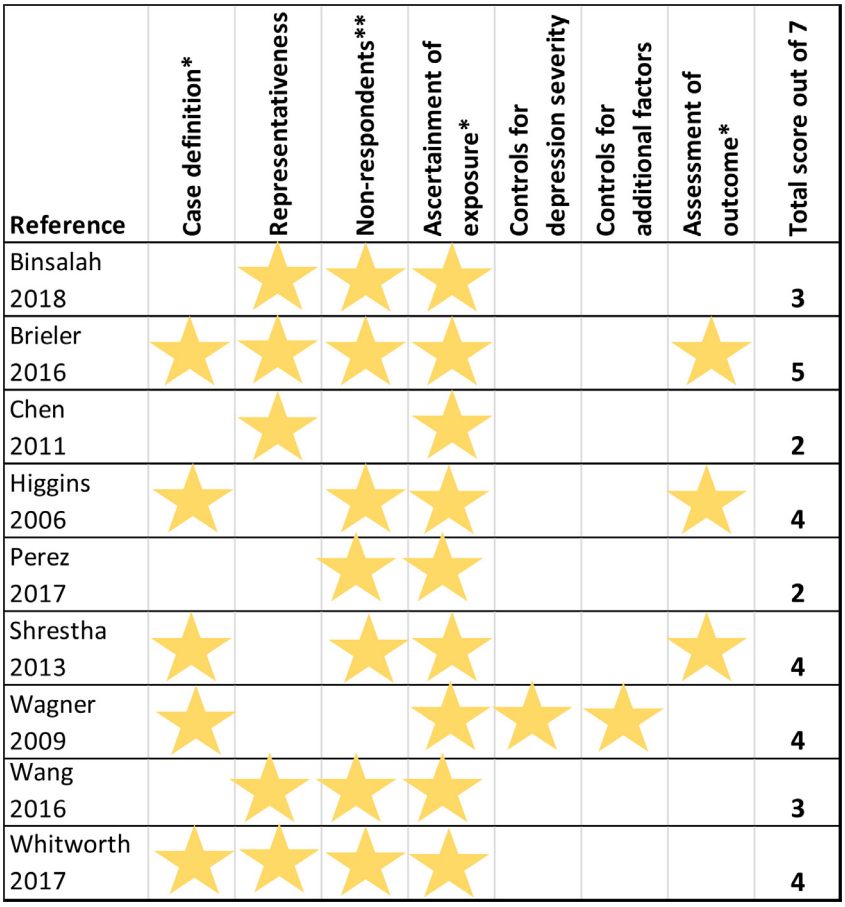

Figure 2. Risk of Bias Summary
Stars represent 1 point towards the total score, where studies met the criteria to have low risk of bias in each category. The higher the total score, the lower the risk of bias.
*Case definition, ascertainment of exposure and assessment of outcome all accepted in-study clinician diagnosis, validated questionnaires, medical records or prescriptions as meeting the criteria for low risk of bias. Self-report or no description did not meet the criteria for low risk of bias.
**Studies were considered to meet the criteria for low risk of bias if they made a reasonable attempt to manage non-respondents and described this

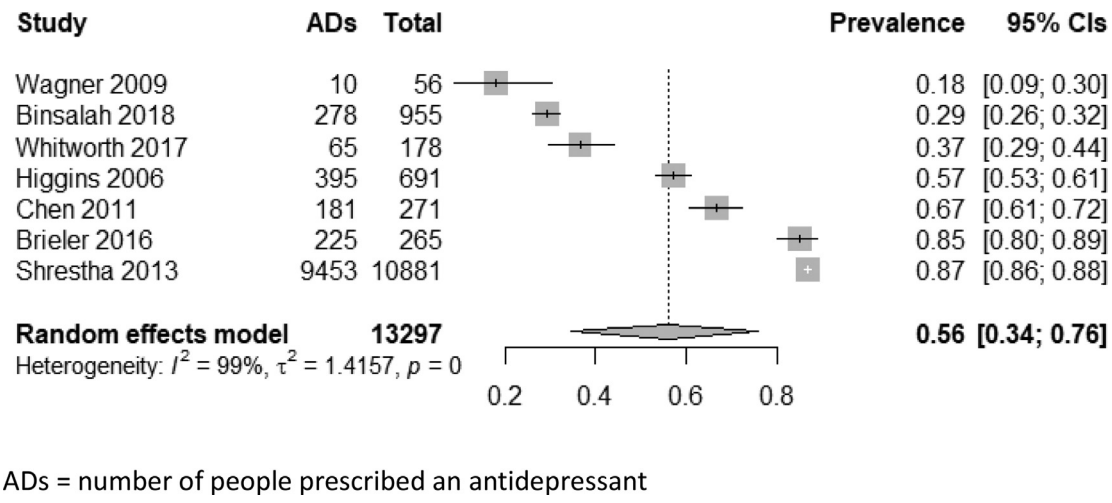

Figure 3. Forest plot and results of random effects model meta-analysis for prevalence of antidepressant prescribing
ADs = number of people prescribed an antidepressant

identified through community screening, as they may be more likely to access care [46]. Additionally, the decision to prescribe may drive the coding of depression diagnoses resulting in a tendency to see falsely high prevalence rates of prescribing using these data sources [47,48]. Thus, the prevalence estimate of 29% from the studies which identified depression through community screening, may be more representative.

An increase in antidepressant prescribing from mild to moderate-to-severe depression categories might be expected considering treatment guidelines recommend antidepressants only when depression severity is moderate-to-severe [7,8], however, this was only the case in one study. The two studies that did report antidepressant prescribing by depression severity were from different countries (USA and Australia) which may suggest a difference in prescribing practices between countries [26,27].

As no studies reported the gender difference in antidepressant prescribing adjusted for depression severity, it is not clear whether this indicates more severe depression in women, or whether more women are likely to be offered and/or accept pharmacological treatment for depression. This result is considerably lower than might be expected from the relative prevalence of antidepressant-prescribed individuals in men and women in the general population, which a large international

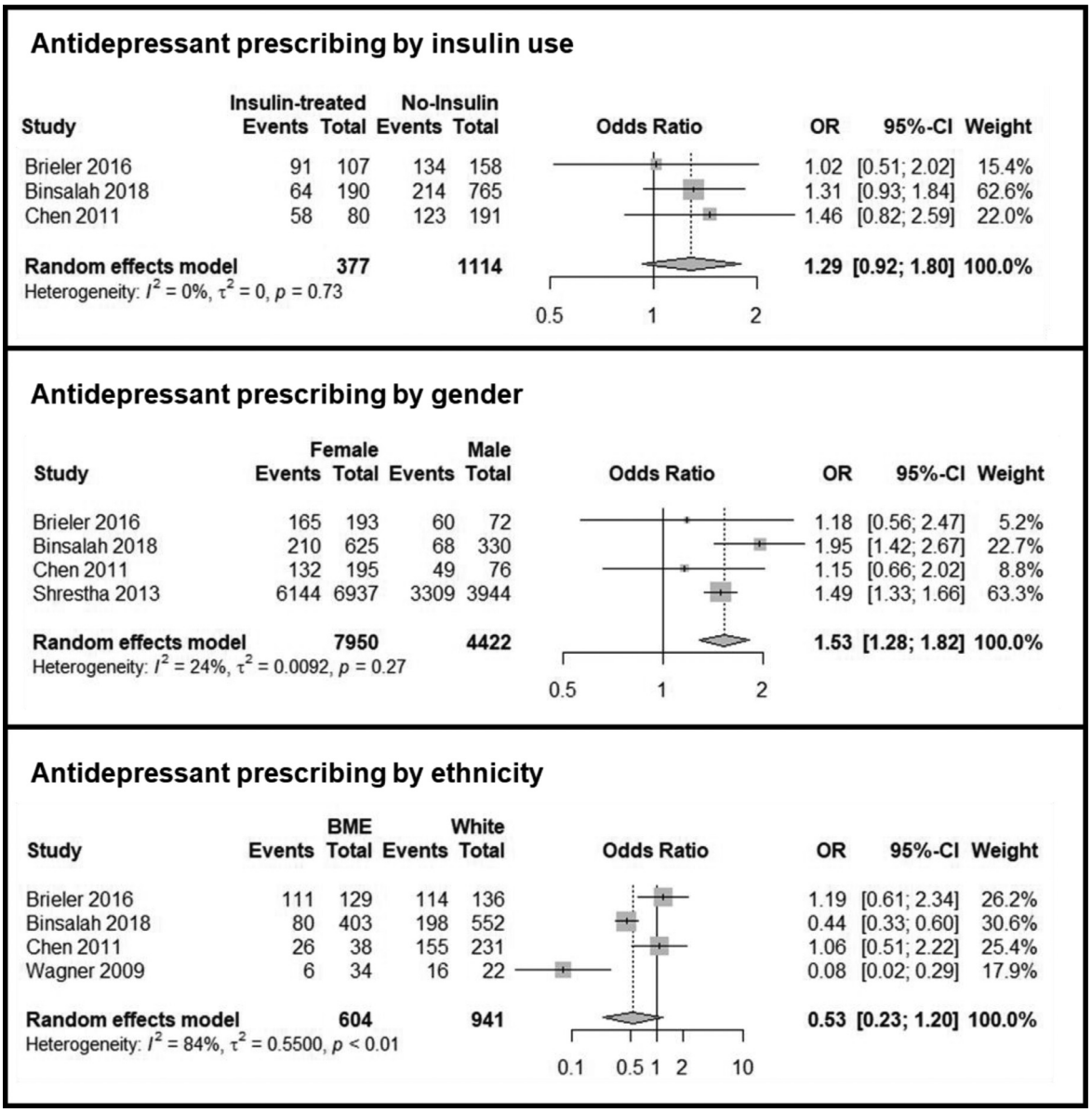

Figure 4. Forest Plots and results of meta-analysis for the odds ratio of being prescribed an antidepressant, comparing different exposures.

study [27] reported as being almost double for women compared to men. This may suggest reduced gender inequalities in access to antidepressant treatment for men with comorbid depression and T2DM compared to those without diabetes, perhaps due to the increased contact with healthcare services for people with diabetes of both genders compared to those without diabetes [49].

Evidence for the association between White ethnicity and antidepressant prescription was inconclusive due to statistical heterogeneity. There is consistent evidence in the general population of a positive association between white ethnicity and increased rates of antidepressant prescribing [25–27,50]. The variation from findings in the general population, was introduced in this review by two studies that showed no evidence of an association between white ethnicity and antidepressant prescription. A large survey across 27 European countries [26] found that a key factors in the variation in antidepressant prescribing rates were cultural factors concerning beliefs and attitudes about mental health. While all studies considered in this review for ethnic disparity in antidepressant prescription were from the USA, the population and culture of the USA is varied [51], and so different attitudes could be apparent in the different populations included in these studies. On the other hand, again, the increased contact with healthcare services experienced by people with diabetes could have a positive effect on access to antidepressant treatment – indeed, the two studies with no evidence of ethnicity association were conducted in patients identified through ambulatory care or in receipt of diabetic education intervention, while the other two studies showing a higher association for white ethnicity recruited patients from outside a care setting.

While there was limited evidence concerning socio-economic status, one study reported increased rates of antidepressant prescribing in participants with insurance coverage. This suggests that there may be social inequalities in prescribing in countries where healthcare is paid for or relies on insurance that may not be available to groups who have lower socio-economic status [26].

Higher odds of antidepressant prescribing may have been expected in insulin users compared to participants not using insulin, as a 2006 meta-analysis [52] showed that insulin use was associated with increased depression symptoms in T2DM. Insulin users represent participants with more complex T2DM, who may be more likely to have increased con-

tact time with healthcare services [49], which could provide increased opportunity to discuss antidepressant treatment. Again, however, this was not found to be the case.

4.2. Strengths and limitations

This is the first systematic review to our knowledge that investigates the prevalence and characteristics of antidepressant prescribing in adults with comorbid depression and T2DM. This review provides evidence from the first known studies to investigate patient characteristics associated with antidepressant prescription in this population.

The search terms used by the review were broad, searching seven databases to provide a wide range of coverage; this resulted in a large number (14,389) of references being screened. As the review was also exploratory, the range of potential characteristics was kept open, this enabled the review to identify evidence of a broad range of patient characteristics associated with antidepressant prescription.

Although the search terms were broad, the inclusion/exclusion criteria were strict. We only included studies that specifically identified patients as having depression, excluding those that made this assumption based on antidepressant prescription. Antidepressants can be used for conditions other than depression, such as neuropathic pain (particularly relevant to this population), sleep disorders or anxiety, and so antidepressant prescribing was not considered, for the purpose of this review, to be a confirmation of depression. Furthermore, as antidepressant prescription was the outcome of interest, this would not have been appropriate for participant inclusion criteria.

The review excluded any studies (n=22) where antidepressants were explicitly prescribed for a condition other than depression, however, while participants in the included studies met our criteria for depression, the indication of the antidepressant prescription was not always known (the exceptions being studies using NHANES data and Chen 2011). For individuals with T2DM, this is particularly relevant as a number of antidepressants could be indicated for diabetic neuropathic pain, as well as other comorbidities: This could have influenced the results for insulin use, because, as described above, insulin users have more complex disease and so are more likely to experience neuropathic pain which could lead to non-depression related prescription of antidepressants. However, this only applies to one of the studies included in our meta-analysis. Furthermore, there was no evidence of an association between insulin use or additional comorbidities and increased antidepressant prevalence.

For each exposure, only a small number of studies were identified with a maximum of four being suitable for each meta-analysis. Both meta-analyses covered a reasonable number of participants: 1,483 (insulin use) and 12,372 (gender). Despite the reasonable sample sizes, caution should be exercised when drawing conclusions from the results, taking into consideration the limited generalisability and high risk of bias of the included studies. No language restrictions were put on the literature searches and no studies were excluded based on language. However, search terms were in the English language and the databases searched primarily contain research in European languages, therefore this review may not have identified studies outside these limits.

All included studies, with one exception, were conducted in the USA. The USA operates an insurance-based healthcare system, where it has been shown that increased insurance coverage increases access to healthcare treatment [53]. The nature of an insurance-based health system is likely to impact sociodemographic inequalities [53]. The conclusions of this review, therefore, should be treated with caution, especially with regards to applicability to other types of healthcare system.

4.3. Implications

Effective treatment of depression is important in individuals with comorbid depression and T2DM. However, there was considerable variation in the prevalence of antidepressant prescribing between studies, with prevalence rates in the community considerably lower than in clinical populations. Female gender was the only predictor of antidepressant prescription for which we were able to find evidence from meta-analysis in this review, suggesting either that women with comorbid depression and T2DM are more likely to have depression requiring treatment than men, or that men are more likely to be undertreated. It is important to note, however, that the gender disparity for antidepressant prescribing is less than in the general population. White ethnicity was also not found to be associated with increased prevalence of antidepressant prescribing, while it is in the general population. This review has highlighted the gap in our knowledge about which antidepressant agents are being used in adults with comorbid depression and T2DM, and alongside which concurrent medications and comorbidities. Thus, we are unaware of the extent to which such individuals are at risk from the risks associated with polypharmacy and other adverse effects. With a lack of evidence to support the medium-long term use of antidepressants in individuals with T2DM, care should be taken when prescribing antidepressants in more complex patients, who have higher risks of potential adverse events. There is an urgent need for longitudinal studies to inform guidelines on the long-term safety and effectiveness of antidepressant prescription in persons with comorbid depression and T2DM.

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Conflict of interest

The authors declare no conflict of interest.

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