The impact of hospital-diagnosed depression or use of antidepressants on treatment initiation, adherence and HbA_{1c}/LDL target achievement in newly diagnosed type 2 diabetes

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Abstract

Aims/hypothesis We aimed to assess whether current antidepressant therapy or a history of hospital-diagnosed depression affects diabetes treatment initiation, adherence, and HbA_{1c} and LDL-cholesterol target achievement.

Methods In this register-based study, we included all individuals from Central and Northern Denmark with newly diagnosed type 2 diabetes, defined as a first-ever HbA_{1c} measurement of ≥ 48 mmol/mol (6.5%), between 2000 and 2016. Individuals either diagnosed with depression at a psychiatric hospital in the 2 years prior to their diabetes diagnosis or currently receiving treatment with an antidepressant were compared with individuals with type 2 diabetes, but without depression treatment or previous history of depression. Outcome measures included initiation of glucose-lowering drugs and lipid-modifying agents, adherence to these medications (medication possession ratio $>80\%$), and HbA_{1c} (<53 mmol/mol [7%]) and LDL-cholesterol (<2.6 mmol/l) target achievement. The assessment of association between depression or antidepressant treatment and these outcomes was conducted using regression analyses with adjustment for potential confounders.

Results We included a total of 87,650 individuals with first-ever HbA_{1c}-diagnosed type 2 diabetes, of whom 0.9% ($n = 784$) had hospital-diagnosed depression and 11.4% ($n = 9963$) currently received antidepressant treatment. Compared with those without depression treatment, treatment with an antidepressant was associated with increased likelihood of glucose-lowering drug initiation (HR 1.39 [95% CI 1.34, 1.44]) and adherence (OR 1.27 [95% CI 1.18, 1.36]), lipid-modifying agent initiation (HR 1.17 [95% CI 1.11, 1.23]) and adherence (OR 1.25 [95% CI 1.09, 1.43]), and achievement of LDL (OR 1.08 [95% CI 1.03, 1.14]) but not HbA_{1c} target (OR 0.99 [95% CI 0.93, 1.06]). The findings were similar for individuals who had hospital-diagnosed depression.

Conclusions/interpretation In individuals with newly diagnosed type 2 diabetes, antidepressant treatment and depression were associated with improved diabetes treatment quality.

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Abbreviations

ATC	Anatomical Therapeutic Chemical
CCI	Charlson comorbidity index
DCRS	Danish Civil Registration System
DDD	Defined daily dosage
DNPatR	Danish National Patient Register
DNPreR	Danish National Prescription Register
DPCRR	Danish Psychiatric Central Research Register
GLD	Glucose-lowering drug
LABKA	Clinical Laboratory Information System
MPR	Medication possession ratio
SNRI	Serotonin–norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Research in context

What is already known about this subject?

- Depression developing during the course of type 2 diabetes is associated with poor diabetes treatment adherence and more treatment discontinuation
- The few published studies on adherence to treatment of diabetes in individuals with pre-existing depression have reached conflicting results
- No studies have investigated how pre-existing depression treatment in individuals with newly diagnosed type 2 diabetes affects time to glucose-lowering drug and lipid-modifying agent treatment initiation and achievement of early HbA_{1c} and LDL-cholesterol treatment targets

What is the key question?

- Does current antidepressant therapy or a history of hospital-diagnosed depression affect diabetes treatment initiation, adherence, and HbA_{1c} and LDL target achievement?

What are the new findings?

- Pre-existing hospital-diagnosed depression and antidepressant treatment were associated with an increased likelihood of glucose-lowering drug and lipid-modifying agent treatment initiation and adherence
- Those with hospital-diagnosed depression or antidepressant treatment were as likely to attain HbA_{1c} and LDL treatment targets as individuals without depression treatment

How might this impact on clinical practice in the foreseeable future?

- Treatment of pre-existing depression in individuals with newly diagnosed type 2 diabetes might be important to improve diabetes treatment quality

Introduction

While type 2 diabetes is associated with a number of physical comorbidities, including macro- and microvascular complications, cancer and infections, it also has important consequences for mental health, and depression in particular [1]. Specifically, depression affects one out of six individuals with type 2 diabetes [2], and converging evidence suggests that individuals with type 2 diabetes and comorbid depression are at increased risk of developing diabetes-related complications and of dying prematurely from non-communicable diseases [3–9]. The increased complication and mortality rates in those with depression comorbid to type 2 diabetes may be rooted in suboptimal adherence to diabetes treatment and poor self-care [10–14]. Relatedly, cohort studies have suggested that individuals with type 2 diabetes who later develop depression tend to have poor adherence to their diabetes treatment [15–20].

While the impact of depression developing during the course of type 2 diabetes has been widely studied, significantly less is known about diabetes treatment among individuals with depression who develop type 2 diabetes [17, 21, 22]. The few published studies on adherence to treatment of diabetes in individuals with pre-existing depression have reached conflicting results, with one study [21] finding no impact of pre-existing depression on diabetes treatment adherence, and two studies [17, 22] reporting poorer adherence and more treatment

discontinuation in individuals with pre-existing depression. However, so far, no studies in a population-based healthcare setting have investigated how pre-existing depression treatment in individuals with newly diagnosed type 2 diabetes affects diabetes treatment adherence. Furthermore, to our knowledge, no studies have investigated how pre-existing depression treatment affects time to glucose-lowering drug (GLD) and lipid-modifying agent treatment initiation and achievement of early HbA_{1c} and LDL-cholesterol treatment targets. We therefore conducted such a study based on data from Danish registers. In doing so, we hypothesised that, contrary to what has been suggested for having depressive symptoms in general [15–20], individuals currently receiving depression treatment (hospital-diagnosed depression or antidepressant treatment) might be equally, or even more likely, to initiate and be adherent to diabetes treatment and reach their treatment targets than others, as these individuals are already familiar with the healthcare system and are used to receiving treatment for their depression.

Methods

Data sources

We conducted a cohort study based on healthcare data from the Central and Northern Denmark Regions (1.8 million

inhabitants, 32% of Denmark's population). The Danish Civil Registration System (DCRS) was established in 1968 [23] and contains the unique personal registration numbers that are assigned to all residents in Denmark, either at birth or immigration, enabling linkage of data from several healthcare databases at the level of the individual [24]. Here, we linked data from the DCRS to data from the following four healthcare databases: the Danish National Prescription Register (DNPreR), which contains data on all prescriptions redeemed at Danish pharmacies since 1995 [25]; the Danish National Patient Register (DNPatR), which contains discharge diagnoses from all admissions to Danish non-psychiatric hospitals since 1977 and from emergency and outpatient hospital settings since 1995 [26]; the Danish Psychiatric Central Research Register (DPCRR), which contains discharge diagnoses from all psychiatric hospital admissions since 1969 and from emergency and outpatient hospital settings since 1995 [27]; and the Clinical Laboratory Information System (LABKA) database, which contains laboratory results from all general practitioners and hospitals in the Central and Northern Denmark Regions since the 1990s with full completeness since the early 2000s [28].

Definition of cohort with type 2 diabetes

We defined a cohort consisting of individuals diagnosed with incident type 2 diabetes in the period from 1 January 2000 to 31 October 2016. We chose this study period to ensure a sufficient cohort size for good statistical precision of our estimates, taking advantage of high completeness for laboratory results since the early 2000s and being able to follow all individuals for a full year after their diabetes diagnosis for drug treatment initiation and another year for adherence (we had complete register data until 31 October 2018). Incident type 2 diabetes was defined as the first-ever HbA_{1c} measurement of ≥ 48 mmol/mol (6.5%) in the LABKA database among individuals aged ≥ 30 [29, 30]. We excluded individuals that, prior to this date, had ever been diagnosed with diabetes at a hospital, had ever redeemed a prescription for a GLD (see the Anatomical Therapeutic Chemical [ATC] codes and the ICD-8/ICD-10 codes in electronic supplementary material [ESM] Table 1) or had an HbA_{1c} ≥ 48 mmol/mol (6.5%) before 1 January 2000, leaving a cohort of individuals with newly HbA_{1c}-diagnosed type 2 diabetes.

Definition of depression treatment

The majority of individuals with depression in the Danish healthcare system are treated by general practitioners or by private practicing psychiatrists [31], which do not report diagnoses to the DNPatR or DPCRR. Therefore, we defined depression treatment using data from both prescriptions (DNPreR) and hospital diagnoses (DNPatR and DPCRR) as

follows: First, we made a definition of antidepressant treatment based on redeemed prescriptions. For our main analyses, we defined 'current' users as those who had redeemed ≥ 1 prescription for an antidepressant in the 100 days prior to the diagnosis of type 2 diabetes. The current users were further divided into 'selective serotonin reuptake inhibitor (SSRI)', 'serotonin–norepinephrine reuptake inhibitor (SNRI)', 'tricyclic antidepressant (TCA)' and 'other' (mianserin, mirtazapine, reboxetine) users (see ESM Table 1). Subsequently, we defined three additional categories of antidepressant users, namely 'recent', 'persistent' and 'former' users. Recent users had redeemed ≥ 1 prescription for an antidepressant in the period from 101 to 365 days prior to the diagnosis of type 2 diabetes and were not current users. Persistent users of antidepressants were those who had redeemed ≥ 2 prescriptions for an antidepressant within the last 2 years before the diagnosis of type 2 diabetes, and at least one of these prescriptions in the year leading up to the diagnosis of type 2 diabetes. Former users of antidepressants were those who had redeemed ≥ 1 prescription for an antidepressant, but none in the year leading up to the diagnosis of type 2 diabetes.

Second, for our main analyses, we defined 'current hospital-diagnosed depression' as having a depression diagnosis (ICD-10 codes F32–F33) registered in the DNPatR or DPCRR following inpatient or outpatient treatment in the 2 years leading up to the diagnosis of type 2 diabetes. As an additional category, individuals that had not been diagnosed with depression within these 2 years, but had received a depression diagnosis in the period from 2 to 5 years prior to the diagnosis of type 2 diabetes, were labelled as 'former hospital-diagnosed depression'. Individuals with depression that had a diagnosis of bipolar disorder or any psychotic disorder diagnosis (see the ICD-8/ICD-10 codes in ESM Table 1) prior to the diagnosis of type 2 diabetes were excluded, as the exposure of interest in the current study was unipolar depression.

Individuals with newly diagnosed type 2 diabetes not included in any of the above-mentioned exposure groups (no current or former antidepressant treatment use, and no current or former hospital-diagnosed depression in the 5 years leading up to incident type 2 diabetes) were used as the control group for all analyses.

Baseline characteristics

We obtained information on sex, age and marital status at the time of the type 2 diabetes diagnosis from the DCRS. We used the following categories to categorise baseline HbA_{1c} levels: 48–53 mmol/mol (6.5–7.0%), 54–58 mmol/mol (7.1–7.5%), 59–69 mmol/mol (7.6–8.5%), 70–80 mmol/mol (8.6–9.5%), 81–91 mmol/mol (9.6–10.5%) and > 91 mmol/mol ($> 10.5\%$) [32]. We obtained information on comorbid conditions included in the Charlson comorbidity index (CCI) [33] prior

to type 2 diabetes diagnosis from the DNPatR (not counting diabetes). We defined three categories of comorbidity based on CCI total scores of 0, 1 and 2. We obtained information on macro- and microvascular complications, hospital-diagnosed obesity, alcohol-related diagnoses and smoking-associated disorders (see the ICD-8/ICD-10 codes in ESM Table 1). LABKA was used to obtain baseline eGFR (calculated from age, sex and creatinine), total cholesterol and LDL-cholesterol levels.

Outcomes

Time to GLD or lipid-modifying agent initiation We followed the cohort members from type 2 diabetes diagnosis until they initiated treatment (redeemed a prescription) with a GLD, died or emigrated, or until the end of follow-up (1 year after diabetes diagnosis), whichever came first. The same approach was used for initiation of treatment with a lipid-modifying agent.

GLD and lipid-modifying agent adherence Among the individuals with type 2 diabetes that initiated a GLD and/or a lipid-modifying agent, we assessed the extent to which they were adherent to this treatment. Specifically, we followed them from the time of their first GLD and/or lipid-modifying agent prescription redemption and for 1 year onwards. We used the medication possession ratio (MPR) for this year, i.e. the time under treatment divided by 1 year, to assess adherence. The time under treatment was calculated via the following formula: $(\text{dose} \times \text{number of pills per package} / \text{defined daily dosage [DDD]}) \times 1.15 + 7 \text{ days}$ [34]. Good adherence was defined as an MPR >80% [35].

HbA_{1c} and LDL-cholesterol treatment targets We defined HbA_{1c} <53 mmol/mol (7%) and LDL-cholesterol <2.6 mmol/l as treatment targets [36]. For each cohort member, we assessed whether their last measured HbA_{1c} or LDL-cholesterol value (in the 12 months following diabetes diagnosis) was below the treatment target cut-off [37, 38].

Changes in HbA_{1c} and LDL-cholesterol For each cohort member, we assessed the mean HbA_{1c} and LDL-cholesterol from all measurements (excluding the baseline value) in the year following the diagnosis of type 2 diabetes. We then calculated the difference between the baseline HbA_{1c} or LDL and the mean HbA_{1c} or LDL, respectively.

Statistical analyses

Time to GLD or lipid-modifying agent initiation Using time to treatment with a Cox regression, we assessed the association between antidepressant treatment or hospital-diagnosed depression and GLD or lipid-modifying agent initiation, respectively. We reported unadjusted HRs, partly adjusted HRs (adjusted for sex and age) and fully adjusted HRs

(adjusted for age, sex, baseline HbA_{1c}, LDL-cholesterol, eGFR, CCI, micro- and macrovascular complications, obesity, alcohol-related diagnoses, smoking-associated disorders, civil status and somatic medication use) with 95% CIs. The proportional assumptions were tested by plotting the observed survival curves with the estimated survival curves.

GLD and lipid-modifying agent adherence Using logistic regression, estimating prevalence rate ratios, we assessed the association between antidepressant treatment or hospital-diagnosed depression and GLD or lipid-modifying agent adherence (MPR >80%), respectively. We reported unadjusted ORs, partly adjusted ORs and fully adjusted ORs with 95% CIs (covariates as described above).

Achievement of HbA_{1c} and LDL-cholesterol treatment targets Using logistic regression, estimating prevalence rate ratios, we assessed the association between antidepressant treatment or hospital-diagnosed depression and achievement of HbA_{1c} and LDL treatment targets. We reported unadjusted ORs, partly adjusted ORs and fully adjusted ORs with 95% CIs (covariates as described above).

Changes in HbA_{1c} and LDL-cholesterol Using linear regression, we assessed whether antidepressant treatment or hospital-diagnosed depression was associated with changes in HbA_{1c} and LDL in the year following the diagnosis of type 2 diabetes. The model was checked by diagnostic plots of the residuals. We reported unadjusted coefficients, partly adjusted coefficients and fully adjusted coefficients with 95% CIs (covariates as described above).

Sensitivity analyses

Sensitivity analyses were performed using four different approaches.

First, according to guidelines, an HbA_{1c}-defined diabetes diagnosis should be based on two consecutive instances of elevated HbA_{1c} level in most patients [29]. Therefore, all analyses were repeated in a subcohort of that described above, consisting of individuals with two HbA_{1c} values ≥ 48 mmol/mol (6.5%) within half a year. In these analyses, the date of the second HbA_{1c} value ≥ 48 mmol/mol (6.5%) was considered as the incident type 2 diabetes diagnosis date and as the starting date for assessment of GLD or lipid-modifying agent initiation, adherence and target achievement. All individuals initiating a GLD or lipid-modifying agent between the two measurements were excluded from these analyses.

Second, until the mid-2000s, it was common clinical practice to initially treat an individual with newly diagnosed type 2 diabetes with only diet and physical activity. After 2006, metformin was recommended to be initiated promptly at the time of the diagnosis in most guidelines [39]. Analyses for

GLD/lipid-modifying agent initiation and adherence were therefore repeated for individuals diagnosed with type 2 diabetes after 1 January 2007.

Third, as an elevated HbA_{1c} (≥ 48 mmol/mol [6.5%]) was first officially approved as a diagnostic option for diabetes in 2012 in Denmark, we repeated all analyses for individuals diagnosed with type 2 diabetes after 1 January 2012.

Fourth, as some of the individuals without depression before type 2 diabetes diagnosis (control individuals) were likely to receive a depression diagnosis and/or treatment during follow-up, all analyses were repeated where we censored these individuals at the date of first depression diagnosis or antidepressant treatment initiation.

Results

Baseline characteristics for individuals with newly diagnosed type 2 diabetes

We identified 87,650 individuals with first incident HbA_{1c}-diagnosed type 2 diabetes. Among these, 784 (0.9%) had a current hospital-diagnosed depression within the 2 years leading up to the diagnosis of type 2 diabetes (Table 1). A total of 9963 (11.4%) currently received antidepressant treatment at the date of type 2 diabetes diagnosis, including 568 (72.4%) of the 784 with hospital-diagnosed depression. In addition, 4809 (5.5%) and 1606 (1.8%) had former antidepressant use or former hospital-diagnosed depression, respectively. A total of 65,101 individuals had no history of depression treatment and served as the control group (Table 1).

Individuals with current antidepressant treatment were more likely to be female and older than individuals without depression treatment. Individuals with hospital-diagnosed depression were more likely to be female and younger than individuals without depression treatment. In addition, individuals receiving antidepressant treatment or with hospital-diagnosed depression had a higher CCI score, a higher degree of macro- and micro-vascular complications, were more likely to live alone and had lower HbA_{1c} levels at baseline than individuals without depression treatment. In addition, individuals with hospital-diagnosed depression or current antidepressant treatment were more likely to be prescribed antipsychotic medication than individuals without depression treatment (Table 1).

An overview of treatment initiation and adherence outcomes within 1 year for all 87,650 individuals HbA_{1c}-diagnosed with type 2 diabetes in our study population can be found in Fig. 1.

Treatment initiation

A total of 36,722 (41.9%) individuals initiated a GLD within the first year after the HbA_{1c}-defined type 2 diabetes

diagnosis. Among GLD initiators, mean time to GLD initiation was 61.6 days (76.3 days for individuals with hospital-diagnosed depression, 67.2 days for individuals with current antidepressant treatment and 59.6 days for individuals with no depression treatment). Of these, 75.7% initiated metformin. In individuals with hospital-diagnosed depression or current antidepressant treatment, 363 (46.3%) and 4412 (44.3%) initiated a GLD, respectively. In the fully adjusted model, individuals with hospital-diagnosed depression (HR 1.41 [95% CI 1.26, 1.57]) and individuals with current antidepressant treatment (HR 1.39 [95% CI 1.34, 1.44]) were more likely to initiate a GLD, as seen especially after adjustment for baseline HbA_{1c} and the CCI score (Table 2). Similar findings were made for individuals with recent or persistent antidepressant treatment and for former depression (Table 2).

A total of 18,307 (29.4%) individuals initiated a lipid-modifying agent within the first year after HbA_{1c}-defined type 2 diabetes, out of the 62,234 individuals that did not already use lipid-modifying agents before they were diagnosed with type 2 diabetes. Among initiators, mean time to lipid-modifying agent initiation was 97.7 days (112.7 days for individuals with hospital-diagnosed depression, 98.1 days for individuals with current antidepressant treatment and 96.8 days for individuals with no depression treatment). Simvastatin (81.8%) and atorvastatin (15.3%) were the most commonly used lipid-modifying agents. In individuals with hospital-diagnosed depression or current antidepressant treatment, 163 (29.2%) and 1777 (28.1%) individuals initiated a lipid-modifying agent, respectively. Both individuals with hospital-diagnosed depression (HR 1.21 [95% CI 1.03, 1.41]) and individuals with current antidepressant treatment (HR 1.17 [95% CI 1.11, 1.23]) were more likely to initiate a lipid-modifying agent than individuals without depression treatment, as seen especially after adjustment for the CCI score (Table 2). Similar findings were made for individuals with former depression (Table 2).

Stratifying the analyses on sex did not materially change the associations found for GLD and lipid-modifying agent treatment initiation.

Treatment adherence

A total of 18,392 (50.1%) individuals were adherent to GLD treatment. In individuals with hospital-diagnosed depression or current antidepressant treatment, 186 (51.2%) and 2239 (50.7%) individuals were adherent to GLD treatment, respectively. In the fully adjusted model, individuals with hospital-diagnosed depression (OR 1.36 [95% CI 1.08, 1.71]) and individuals with current antidepressant treatment (OR 1.27 [95% CI 1.18, 1.36]) were more likely to be adherent to GLD than individuals without depression treatment, mainly explained by adjustment for baseline HbA_{1c} (Table 3). Individuals with former antidepressant treatment were less

Table 1 Clinical characteristics of individuals with incident newly diagnosed type 2 diabetes in Central and Northern Denmark from 1 January 2000 to 31 October 2016, stratified by depression diagnosis or treatment status

Characteristic	No depression treatment (<i>n</i> = 65,101) ^a	Current hospital-diagnosed depression within 2 years of type 2 diabetes diagnosis (<i>n</i> = 784) ^b	Current AD treatment at time of type 2 diabetes diagnosis (<i>n</i> = 9963) ^b
Women, <i>n</i> (%)	26,242 (40.3)	447 (57.0)	5799 (58.2)
Median age, years (IQR)	64.6 (54.9–73.9)	56.9 (46.8–70.4)	66.0 (55.4–77.0)
Current AD treatment, <i>n</i> (%)	X	568 (72.4)	X
Baseline HbA _{1c} , <i>n</i> (%)			
48–53 mmol/mol (6.5–7%)	38,831 (59.6)	515 (65.7)	6528 (65.5)
54–59 mmol/mol (7.1–7.5%)	7081 (10.9)	90 (11.5)	1136 (11.4)
60–69 mmol/mol (7.6–8.5%)	5811 (8.9)	74 (9.4)	843 (8.5)
70–80 mmol/mol (8.6–9.5%)	3363 (5.2)	31 (4.0)	421 (4.2)
81–91 mmol/mol (9.6–10.5%)	2869 (4.4)	25 (3.2)	303 (3.0)
>91 mmol/mol (>10.5%)	7146 (11.0)	49 (6.3)	732 (7.3)
Median HbA _{1c} , mmol/mol (IQR)	51 (49, 63)	51 (49, 57)	51 (49, 57)
Median HbA _{1c} , % (IQR)	6.82 (6.60, 7.91)	6.80 (6.60, 7.40)	6.80 (6.60, 7.40)
Baseline LDL-C, <i>n</i> (%)			
<1.8 mmol/l	5544 (8.5)	77 (9.8)	940 (9.4)
1.80–2.5 mmol/l	10,723 (16.5)	123 (15.7)	2028 (20.4)
2.51–3 mmol/l	9130 (14.0)	103 (13.1)	1339 (13.4)
3.01–4 mmol/l	31,290 (48.1)	371 (47.3)	4498 (45.1)
>4 mmol/l	8414 (12.9)	110 (14.0)	1158 (11.6)
Median LDL-C, mmol/l (IQR)	3.04 (2.50–3.50)	3.04 (2.50–3.55)	3.04 (2.40–3.30)
Blood tests			
Mean total cholesterol, mmol/l (95% CI)	5.29 (5.27, 5.30)	5.31 (5.21, 5.41)	5.24 (5.21, 5.27)
Mean eGFR, ml min ⁻¹ 1.73 m ⁻² (95% CI)	79.1 (78.9, 79.2)	82.5 (80.8, 84.2)	76.4 (75.9, 76.8)
CCI, <i>n</i> (%)			
CCI = 0	40,252 (61.8)	415 (52.9)	4354 (43.7)
CCI = 1	15,352 (23.6)	198 (25.3)	2806 (28.2)
CCI = 2	9497 (14.6)	171 (21.8)	2803 (28.1)
Acute myocardial infarction, <i>n</i> (%)	4436 (6.8)	49 (6.3)	778 (7.8)
Stroke, <i>n</i> (%)	4844 (7.4)	90 (11.5)	1717 (17.2)
Renal disease, <i>n</i> (%)	1571 (2.4)	25 (3.2)	312 (3.1)
Congestive heart failure, <i>n</i> (%)	3966 (6.1)	51 (6.5)	877 (8.8)
Diabetes-related complications, <i>n</i> (%)			
Macrovascular	14,326 (22.0)	210 (26.8)	2322 (23.3)
Microvascular	6849 (10.5)	86 (11.0)	1548 (15.5)
Lifestyle related, <i>n</i> (%)			
Obesity	4548 (7.0)	113 (14.4)	1095 (11.0)
Alcohol-related diagnoses	1761 (2.7)	106 (13.5)	861 (8.6)
Smoking-related disorders	4737 (7.3)	93 (11.9)	1392 (14.0)
Marital status, <i>n</i> (%)			
Married/partner	45,264 (69.5)	463 (59.1)	6118 (61.4)
Unmarried	5951 (9.1)	103 (13.1)	791 (7.9)
Divorced/ended partnership	5002 (7.7)	98 (12.5)	1034 (10.4)
Widow	6750 (10.4)	89 (11.4)	1690 (17.0)
Missing	2134 (3.3)	31 (4.0)	330 (3.3)
Medication, <i>n</i> (%)			
β-blockers	16,301 (25.0)	167 (21.3)	2943 (29.5)
Calcium channel blockers	12,240 (18.8)	133 (17.0)	2176 (21.8)

Table 1 (continued)

Characteristic	No depression treatment (<i>n</i> = 65,101) ^a	Current hospital-diagnosed depression within 2 years of type 2 diabetes diagnosis (<i>n</i> = 784) ^b	Current AD treatment at time of type 2 diabetes diagnosis (<i>n</i> = 9963) ^b
Renin–angiotensin system-acting agents	22,786 (35.0)	211 (26.9)	3608 (36.2)
Diuretics	21,451 (33.0)	248 (31.6)	4549 (45.7)
Antithrombotic agents	19,427 (29.8)	229 (29.2)	4084 (41.0)
Corticosteroids	6033 (9.3)	97 (12.4)	1542 (15.5)
Analgesics	13,588 (20.9)	314 (40.1)	4673 (46.9)
COPD and asthma inhalers	7726 (11.9)	131 (16.7)	1982 (19.9)
Antipsychotics, <i>n</i> (%)			
Overall	819 (1.3)	229 (29.2)	1309 (13.1)
Olanzapine	95 (0.2)	40 (5.1)	202 (2.0)
Quetiapine	52 (0.1)	96 (12.2)	302 (3.0)
Risperidone	117 (0.2)	38 (4.9)	177 (1.8)
Hospital diagnoses of other mental disorders, <i>n</i> (%)			
Anxiety disorder	697 (1.1)	342 (43.6)	1217 (12.2)
Personality disorder	593 (0.9)	162 (20.7)	778 (7.8)

For clinical characteristics, ICD-8/ICD-10 and ATC codes can be found in the [ESM](#)

^a Individuals with no history of depression treatment (no prior AD treatment, and no hospital-diagnosed depression in the 5 years leading up to incident type 2 diabetes)

^b Exposure groups are not mutually exclusive; 568 individuals (72.4%) of the 784 with current hospital-diagnosed depression also received current AD, while 216 individuals (27.6%) did not receive current AD; 9395 of the 9963 individuals (94.3%) with current AD had no current hospital-diagnosed depression

AD, Antidepressant

likely to be adherent to GLD treatment than individuals with hospital-diagnosed depression or current antidepressant treatment (Table 3).

As the official DDD for metformin (DDD = 2 g) is rather high, compared with clinical practice among metformin initiators, we repeated the analyses using the minimum recommended dose for metformin (500 mg). When using this approach, overall, 83% were adherent to GLD treatment in the first year; 87.1% for hospital-diagnosed depression and 85.7% for current antidepressant treatment. Also, individuals with hospital-diagnosed depression (OR 1.63 [95% CI 1.17, 2.27]) and current antidepressant treatment (OR 1.40 [95% CI 1.29, 1.54]) were more likely to be adherent to GLD than individuals without depression treatment.

A total of 14,643 (80.0%) individuals were adherent to lipid-modifying agent treatment. In individuals with hospital-diagnosed depression or current antidepressant treatment, 143 (87.7%) and 1467 (82.6%) individuals were adherent to lipid-modifying agent treatment. In the fully adjusted model, individuals with hospital-diagnosed depression (OR 1.93 [95% CI 1.20, 3.10]) and individuals with current antidepressant treatment (OR 1.25 [95% CI 1.09, 1.43]) were more likely to be adherent to lipid-modifying agent treatment than individuals without depression treatment, whereas

individuals with former depression were not more likely to be adherent to lipid-modifying agent treatment (Table 3).

Stratifying the analyses on sex did not materially change the observed associations, as both men and women with depression or current antidepressant treatment were more likely to be adherent than individuals without depression.

Achievement of HbA_{1c} and LDL-cholesterol treatment targets

A total of 68,887 (78.6%) individuals reached HbA_{1c} <53 mmol/mol (7%). In individuals with hospital-diagnosed depression or current antidepressant treatment, 611 (77.9%) and 7898 (79.3%) individuals reached HbA_{1c} treatment targets, respectively. In the fully adjusted model, individuals with hospital-diagnosed depression (OR 0.91 [95% CI 0.74, 1.11]) and individuals with current antidepressant treatment (OR 0.99 [95% CI 0.93, 1.06]) were as likely to achieve the HbA_{1c} treatment target as individuals without depression treatment (Table 4). Individuals with former depression were more likely to achieve the HbA_{1c} treatment target than individuals without depression treatment (Table 4).

When stratifying the analyses on sex, similar findings were made for men and women.

Fig. 1 All individuals diagnosed with type 2 diabetes and number of events (treatment initiation, adherence and treatment targets)

Table 2 The association between antidepressant treatment or hospital-diagnosed depression and initiation of treatment with GLDs and lipid-modifying agents

Variable	GLD initiation		
	Unadjusted HR	Partly adjusted HR ^a	Fully adjusted HR ^b
AD treatment			
Current	1.13 (1.10, 1.17)	1.20 (1.16, 1.24)	1.39 (1.34, 1.44)
SSRI	1.05 (1.00, 1.09)	1.13 (1.08, 1.18)	1.28 (1.22, 1.34)
SNRI	1.54 (1.43, 1.66)	1.47 (1.36, 1.58)	1.76 (1.63, 1.89)
TCA	1.09 (1.01, 1.19)	1.17 (1.08, 1.27)	1.34 (1.23, 1.46)
Other	1.11 (1.03, 1.19)	1.24 (1.15, 1.33)	1.45 (1.35, 1.56)
Recent	1.14 (1.10, 1.17)	1.19 (1.16, 1.23)	1.37 (1.32, 1.41)
Persistent	1.14 (1.11, 1.18)	1.20 (1.16, 1.24)	1.38 (1.33, 1.42)
Former	1.22 (1.18, 1.25)	1.21 (1.18, 1.25)	1.35 (1.31, 1.40)
Hospital-diagnosed depression			
Current	1.17 (1.05, 1.30)	1.09 (0.98, 1.21)	1.41 (1.26, 1.57)
Former	1.19 (1.11, 1.28)	1.16 (1.07, 1.25)	1.33 (1.24, 1.44)
Lipid-modifying agent initiation			
Variable	Lipid-modifying agent initiation		
	Unadjusted HR	Partly adjusted HR ^a	Fully adjusted HR ^b
AD treatment			
Current	0.98 (0.93, 1.03)	1.06 (1.00, 1.12)	1.17 (1.11, 1.23)
SSRI	0.93 (0.87, 1.00)	1.03 (0.95, 1.10)	1.12 (1.04, 1.20)
SNRI	1.32 (1.18, 1.48)	1.33 (1.18, 1.48)	1.47 (1.31, 1.65)
TCA	1.07 (0.95, 1.21)	1.11 (0.99, 1.26)	1.23 (1.09, 1.39)
Other	0.82 (0.73, 0.92)	0.93 (0.83, 1.05)	1.07 (0.95, 1.20)
Recent	0.99 (0.94, 1.04)	1.07 (1.02, 1.12)	1.17 (1.11, 1.23)
Persistent	0.99 (0.94, 1.03)	1.06 (1.01, 1.12)	1.17 (1.11, 1.23)
Former	1.12 (1.07, 1.17)	1.10 (1.06, 1.16)	1.17 (1.12, 1.22)
Hospital-diagnosed depression			
Current	1.00 (0.86, 1.17)	1.04 (0.89, 1.21)	1.21 (1.03, 1.41)
Former	1.19 (1.07, 1.32)	1.22 (1.10, 1.35)	1.39 (1.25, 1.54)

Data are shown as HR (95% CI)

Individuals with diabetes and hospital-diagnosed depression or AD treatment were compared with individuals with diabetes without depression treatment

^a Adjusted for sex and age

^b Adjusted for sex, age, baseline HbA_{1c}, marital status, CCI score, macro- and microvascular complications, obesity, alcohol-related diagnoses, smoking-related disorders, somatic medication use, baseline LDL-cholesterol and eGFR

AD, antidepressant; LDL-C, LDL-cholesterol

With regard to achievement of the LDL treatment target, a total of 40,453 (46.2%) individuals reached LDL-cholesterol <2.6 mmol/l. In individuals with hospital-diagnosed depression or current antidepressant treatment, 333 (42.5%) and 4735 (47.5%) individuals reached the LDL treatment target, respectively. In the fully adjusted model, individuals with current antidepressant treatment were more likely to reach treatment targets (OR 1.08 [95% CI 1.03, 1.14]) than individuals without depression treatment, whereas individuals with hospital-diagnosed depression were not more likely to reach treatment targets (OR 0.99 [95% CI 0.84, 1.17]). Former depression was associated with an increased likelihood of reaching the LDL treatment target (Table 4).

When stratifying the analyses on sex, men with current antidepressant treatment were more likely to reach the LDL treatment target (OR 1.14 [95% CI 1.06, 1.21]), whereas this association was not as clear for women (OR 1.04 [95% CI 0.96, 1.12]).

Changes in HbA_{1c} and LDL-cholesterol

Individuals without depression treatment had a larger decrease in HbA_{1c} in the first year (change in HbA_{1c}: −13.2 mmol/mol [−1.21%]) than individuals with hospital-diagnosed depression (change in HbA_{1c}: −7.5 mmol/mol [−0.69%]) or current antidepressant treatment (change in HbA_{1c}: −8.4 mmol/mol

Table 3 The association between antidepressant treatment or hospital-diagnosed depression and adherence to diabetes treatment

Variable	GLD		
	Unadjusted OR	Partly adjusted OR ^a	Fully adjusted OR ^b
AD treatment			
Current	1.00 (0.94, 1.06)	1.03 (0.97, 1.10)	1.27 (1.18, 1.36)
SSRI	1.01 (0.93, 1.11)	1.06 (0.97, 1.16)	1.28 (1.16, 1.41)
SNRI	0.94 (0.81, 1.08)	0.93 (0.80, 1.07)	1.29 (1.10, 1.51)
TCA	0.99 (0.84, 1.16)	1.03 (0.87, 1.21)	1.24 (1.04, 1.48)
Other	1.03 (0.90, 1.18)	1.10 (0.96, 1.27)	1.25 (1.07, 1.46)
Recent	0.98 (0.92, 1.04)	1.02 (0.95, 1.08)	1.24 (1.15, 1.33)
Persistent	0.99 (0.93, 1.05)	1.02 (0.96, 1.09)	1.25 (1.17, 1.34)
Former	0.82 (0.77, 0.87)	0.81 (0.76, 0.86)	0.96 (0.89, 1.02)
Hospital-diagnosed depression			
Current	1.02 (0.83, 1.25)	0.95 (0.77, 1.17)	1.36 (1.08, 1.71)
Former	1.01 (0.87, 1.17)	0.99 (0.85, 1.15)	1.22 (1.03, 1.43)
Lipid-modifying agent			
	Unadjusted OR	Partly adjusted OR ^a	Fully adjusted OR ^b
AD treatment			
Current	1.20 (1.05, 1.36)	1.24 (1.08, 1.41)	1.25 (1.09, 1.43)
SSRI	1.13 (0.95, 1.35)	1.17 (0.98, 1.39)	1.18 (0.97, 1.42)
SNRI	1.56 (1.13, 2.16)	1.65 (1.19, 2.28)	1.68 (1.21, 2.34)
TCA	1.32 (0.95, 1.82)	1.35 (0.97, 1.87)	1.37 (0.98, 1.91)
Other	1.10 (0.82, 1.48)	1.13 (0.84, 1.52)	1.13 (0.84, 1.54)
Recent	1.19 (1.05, 1.34)	1.23 (1.09, 1.39)	1.24 (1.09, 1.42)
Persistent	1.20 (1.07, 1.36)	1.25 (1.10, 1.41)	1.25 (1.10, 1.43)
Former	0.97 (0.87, 1.09)	0.98 (0.87, 1.09)	0.99 (0.89, 1.12)
Hospital-diagnosed depression			
Current	1.81 (1.13, 2.89)	1.94 (1.21, 3.11)	1.93 (1.20, 3.10)
Former	1.03 (0.80, 1.34)	1.08 (0.83, 1.40)	1.09 (0.83, 1.42)

Data are shown as OR (95% CI)

Individuals with diabetes and hospital-diagnosed depression or AD treatment were compared with individuals with diabetes without depression treatment

^a Adjusted for sex and age

^b Adjusted for sex, age, baseline HbA_{1c}, marital status, CCI score, macro- and microvascular complications, obesity, alcohol-related diagnoses, smoking-related disorders, somatic medication use, baseline LDL-cholesterol and eGFR

AD, antidepressant

[−0.77%]). Although not statistically significant, individuals without depression treatment had a larger decrease in HbA_{1c} than individuals with hospital-diagnosed depression (1.7 mmol/mol [0.16%] larger HbA_{1c} reduction) or antidepressant treatment (3.0 mmol/mol [0.27%] larger HbA_{1c} reduction) in the fully adjusted models.

Individuals without depression treatment had a 0.44 mmol/l decrease in LDL-cholesterol in the first year, whereas individuals with hospital-diagnosed depression or current antidepressant treatment had a decrease in LDL of 0.31 mmol/l or 0.40 mmol/l, respectively. In the fully adjusted model, individuals with hospital-diagnosed depression or current antidepressant treatment had a similar decrease in LDL to individuals without depression treatment.

Sensitivity analyses

When restricting to a cohort of individuals with two instances of elevated HbA_{1c} levels, similar findings were made (see ESM Tables 2–4). In these analyses, 29.0% of the individuals initiated a GLD and 24.7% initiated a lipid-modifying agent between the first and second elevated HbA_{1c} measurements and were therefore excluded.

Only including individuals diagnosed with type 2 diabetes after 1 January 2007 or 1 January 2012, respectively, did not change our results (see ESM Tables 5–10).

Out of the 65,101 individuals without pre-existing hospital-diagnosed depression or antidepressant treatment, 1420 (2.2%) individuals initiated antidepressant treatment or were diagnosed with depression. Censoring these individuals at the date of antidepressant treatment initiation or depression diagnosis did not materially change our results (see ESM Tables 11–13).

Discussion

Main findings

In this cohort study of 87,650 individuals with newly diagnosed type 2 diabetes, pre-existing hospital-diagnosed depression or antidepressant treatment was associated with an increased likelihood of GLD or lipid-modifying agent treatment initiation and adherence. In addition, those with hospital-diagnosed depression or antidepressant treatment were as likely to attain HbA_{1c} and LDL treatment targets as individuals without depression treatment.

Strengths and limitations

Although the findings from the current study are interesting, our findings should be interpreted in the light of several limitations. First, data on detailed clinical and lifestyle-related

factors and socioeconomic status were lacking. Thus, we could not assess whether having prevalent depression or receiving antidepressant treatment with newly diagnosed type 2 diabetes could reflect a distinct diabetes phenotype (e.g. particularly unhealthy lifestyle, severe obesity, severe insulin resistance) that called for more intensive diabetes treatment than in individuals without depression treatment. However, the baseline HbA_{1c} levels for individuals with depression or antidepressant treatment were lower, which contradicts that these individuals should have more severe type 2 diabetes. Accordingly, prevalent depression and antidepressant treatment might be associated with low socioeconomic status, and low socioeconomic status may negatively impact treatment adherence, meaning that the observed increased effect sizes might actually be an underestimation, not changing our conclusions. Second, we did not have information on individuals that received nonpharmacological treatment for depression from their general practitioner, meaning that some of the individuals classified as ‘individuals without depression treatment’ might have been misclassified. However, as our depression exposure was positively correlated with our outcome, such suboptimal completeness would be expected to decrease only the effect size of the association found between depression and diabetes treatment quality. Third, using hospital registers to define depression, some of the individuals with apparent depression might have been misdiagnosed. Nevertheless, depression diagnoses in the DPCRR have a documented moderate-to-high positive predictive value of 65% to 83%, depending on depression severity (mild to severe), indicating that hospital-admitted individuals were likely to have true depression [40]. Fourth, although pre-existing hospital-diagnosed depression or antidepressant treatment was associated with an increased likelihood of GLD adherence, it was not associated with increased likelihood of reaching glycaemic targets. This might indicate that direct biological effects of depression or antidepressant treatment adversely affect glucose metabolism, which might make it difficult to sustain well-controlled diabetes. Fifth, some SSRI users have other mental disorders than depression, anxiety disorders in particular, while some users of TCAs and SNRIs may have had early diabetes-related neuropathy or a chronic pain disorder and not depression. Sixth, not all individuals with an HbA_{1c} measurement of $\geq 6.5\%$ (48 mmol/mol) before 2012 may have been clinically recognised as having diabetes. However, since HbA_{1c} levels correlate closely, though not perfectly, with the blood glucose levels alternatively used to make the diabetes diagnosis, we expect that many patients will eventually have been diagnosed with diabetes. Moreover, restricting the analyses to diabetes patients diagnosed after 1 January 2012, or to those having at least two elevated HbA_{1c} measurements, did not change our findings. Seventh, the validity of some of the hospital-diagnosed disorders used as confounding factors in the fully adjusted model

Table 4 The association between antidepressant treatment or hospital-diagnosed depression and achievement of treatment targets (HbA_{1c} <53 mmol/mol (7%), LDL-cholesterol <2.6 mmol/l) within the first year

Variable	HbA _{1c}		
	Unadjusted OR	Partly adjusted OR ^a	Fully adjusted OR ^b
AD treatment			
Current	1.07 (1.01, 1.13)	1.02 (0.97, 1.08)	0.99 (0.93, 1.06)
SSRI	1.03 (0.96, 1.10)	0.98 (0.91, 1.05)	0.94 (0.87, 1.02)
SNRI	1.36 (1.18, 1.57)	1.40 (1.22, 1.62)	1.30 (1.10, 1.52)
TCA	1.12 (0.98, 1.28)	1.04 (0.91, 1.19)	0.99 (0.85, 1.15)
Other	1.00 (0.89, 1.11)	0.93 (0.83, 1.04)	0.98 (0.86, 1.12)
Recent	1.09 (1.04, 1.14)	1.04 (0.99, 1.10)	1.02 (0.96, 1.08)
Persistent	1.08 (1.03, 1.13)	1.03 (0.98, 1.09)	1.00 (0.95, 1.06)
Former	1.15 (1.09, 1.22)	1.14 (1.08, 1.20)	1.07 (1.01, 1.14)
Hospital-diagnosed depression			
Current	0.99 (0.83, 1.17)	1.07 (0.90, 1.28)	0.88 (0.72, 1.07)
Former	1.19 (1.05, 1.35)	1.23 (1.08, 1.39)	1.15 (1.00, 1.33)
	LDL-C		
	Unadjusted OR	Partly adjusted OR ^a	Fully adjusted OR ^b
AD treatment			
Current	1.13 (1.08, 1.18)	1.17 (1.12, 1.22)	1.08 (1.03, 1.14)
SSRI	1.10 (1.04, 1.17)	1.14 (1.07, 1.20)	1.04 (0.98, 1.12)
SNRI	1.26 (1.13, 1.40)	1.36 (1.22, 1.52)	1.26 (1.12, 1.42)
TCA	1.24 (1.11, 1.39)	1.30 (1.16, 1.45)	1.22 (1.08, 1.38)
Other	1.05 (0.96, 1.16)	1.07 (0.97, 1.17)	0.99 (0.89, 1.11)
Recent	1.10 (1.06, 1.15)	1.15 (1.10, 1.20)	1.05 (1.00, 1.10)
Persistent	1.10 (1.06, 1.15)	1.15 (1.10, 1.20)	1.06 (1.01, 1.11)
Former	1.10 (1.05, 1.15)	1.12 (1.07, 1.17)	1.06 (1.01, 1.11)
Hospital-diagnosed depression			
Current	0.89 (0.77, 1.03)	0.98 (0.84, 1.13)	0.99 (0.84, 1.17)
Former	1.08 (0.97, 1.19)	1.16 (1.05, 1.29)	1.14 (1.01, 1.27)

Data are shown as OR (95% CI)

Individuals with diabetes and hospital-diagnosed depression or AD treatment were compared with individuals with diabetes without depression treatment

^a Adjusted for sex and age

^b Adjusted for sex, age, baseline HbA_{1c}, marital status, CCI score, macro- and microvascular complications, obesity, alcohol-related diagnoses, smoking-related disorders, somatic medication use, baseline LDL-cholesterol and eGFR

AD, antidepressant; LDL-C, LDL-cholesterol

may vary, and completeness may be limited, e.g. for obesity, smoking and alcoholism, or for diabetic microvascular disease [26, 41, 42]. Nevertheless, although our study has several limitations, it is one of the first studies investigating how prevalent hospital-diagnosed depression or antidepressant treatment in newly diagnosed type 2 diabetes affects GLD and lipid-modifying agent treatment adherence, and the first investigating how hospital-diagnosed depression or antidepressant treatment affects GLD and lipid-modifying agent initiation and HbA_{1c} and LDL treatment targets. Our different definitions for depression likely reflected different degrees of depression, all providing similar results. Finally, the population-based nature of our study increases the generalisability of results.

Depression and diabetes-related treatment

Our findings seem to conflict with those of prior studies that have reported an association between depression and GLD treatment non-adherence among individuals with type 2 diabetes [14–20]. However, unlike the current study, most prior studies have reported individuals with prevalent type 2 diabetes who subsequently developed depression. The bidirectional nature of the relationship makes a strong case for also examining the quality of diabetes treatment in individuals with prevalent depression who develop type 2 diabetes. To our knowledge, only a few such studies exist. Kalsekar et al [17] and Hazel-Fernandez et al [22] established that prevalent depression is a predictor for GLD treatment non-adherence

and discontinuation, whereas Kostev and Jacob [21] found no difference in GLD treatment adherence between individuals with and without depression among individuals with newly diagnosed type 2 diabetes. Unlike the current population-based study population (approximately 12% depression), more than one-third (36%) of the study participants reported by Kalsekar et al had prevalent depression, which may reflect the selected nature of the cohort examined [43]. Instead, in a sample that is likely to be representative of the general population, we found that, among individuals with newly diagnosed type 2 diabetes, hospital-diagnosed depression and antidepressant treatment were associated with a better chance of both initiating and remaining adherent to diabetes treatment. These novel findings contradict the common understanding, namely that delayed treatment implementation and poor treatment adherence explain the excess mortality and amplified risk of diabetes-related complications in individuals with type 2 diabetes and comorbid depression [15–20]. Conversely, the findings may imply that these individuals are more likely to receive GLD and lipid-modifying agent treatment when redeeming prescriptions for antidepressants, and that diabetes treatment non-adherence first arrives when the antidepressant treatment stops. This hypothesis is supported by the finding that individuals who redeemed antidepressant prescriptions earlier, but with no current use, were less likely to be adherent to treatment with GLDs and lipid-modifying agents compared with individuals with current depression treatment.

Our findings could be attributable to four different, but not mutually exclusive, explanations: (1) individuals with depression or receiving antidepressant treatment may be more likely to take their diabetes medication as they are already used to receiving daily antidepressant therapy; (2) individuals with depression or receiving antidepressant treatment may be less likely to be adherent to lifestyle changes, which might lead to a lower physician threshold for initiating early GLD treatment; (3) individuals with depression or receiving antidepressant treatment and diabetes are followed up more closely by their general practitioner and other caregivers than individuals without depression treatment; and (4) treatment with antidepressants may increase adherence to GLD treatment.

Future research

Future studies should assess whether the effects of antidepressant treatment on diabetes-related outcomes are specific for individuals with depression, or whether the antidepressant treatment itself, regardless of medication indication, can improve diabetes medication implementation and adherence.

Conclusion

In conclusion, the findings of this study suggest that prevalent hospital-diagnosed depression or antidepressant treatment at

the time of type 2 diabetes development is not a predictor for delayed diabetes treatment implementation or poor adherence. Conversely, individuals with hospital-diagnosed depression or receiving antidepressant treatment with newly diagnosed type 2 diabetes were in fact more likely to implement and remain adherent to GLD and lipid-modifying agent treatment and to reach the LDL target within the first year after the type 2 diabetes diagnosis than individuals without depression treatment with newly diagnosed type 2 diabetes.

Data availability No additional data are available.

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References

1. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW (2019) Global trends in diabetes complications: a review of current evidence. *Diabetologia* 62(1):3–16. <https://doi.org/10.1007/s00125-018-4711-2>
2. Semenkovich K, Brown ME, Svrakic DM, Lustman PJ (2015) Depression in type 2 diabetes mellitus: prevalence, impact, and

- treatment. *Drugs* 75(6):577–587. <https://doi.org/10.1007/s40265-015-0347-4>
3. Katon WJ (2008) The comorbidity of diabetes mellitus and depression. *Am J Med* 121(Suppl 2):8–15. <https://doi.org/10.1016/j.amjmed.2008.09.008>
 4. Sullivan MD, O'Connor P, Feeney P et al (2012) Depression predicts all-cause mortality: epidemiological evaluation from the ACCORD HRQL substudy. *Diabetes Care* 35(8):1708–1715. <https://doi.org/10.2337/dc11-1791>
 5. Lin EH, Katon W, Von Korff M et al (2004) Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care* 27(9):2154–2160. <https://doi.org/10.2337/diacare.27.9.2154>
 6. Katon WJ, Rutter C, Simon G et al (2005) The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care* 28(11):2668–2672. <https://doi.org/10.2337/diacare.28.11.2668>
 7. Wu CY, Terhorst L, Karp JF, Skidmore ER, Rodakowski J (2018) Trajectory of disability in older adults with newly diagnosed diabetes: role of elevated depressive symptoms. *Diabetes Care* 41(10):2072–2078. <https://doi.org/10.2337/dc18-0007>
 8. Nouwen A, Adriaanse MC, van Dam K et al (2019) Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. *Diabet Med* 36(12):1562–1572. <https://doi.org/10.1111/dme.14054>
 9. Scherrer JF, Garfield LD, Chrusciel T et al (2011) Increased risk of myocardial infarction in depressed patients with type 2 diabetes. *Diabetes Care* 34(8):1729–1734. <https://doi.org/10.2337/dc11-0031>
 10. Capoccia K, Odegard PS, Letassy N (2016) Medication adherence with diabetes medication: a systematic review of the literature. *Diabetes Educ* 42(1):34–71. <https://doi.org/10.1177/0145721715619038>
 11. Kurlander JE, Kerr EA, Krein S, Heisler M, Piette JD (2009) Cost-related nonadherence to medications among patients with diabetes and chronic pain: factors beyond finances. *Diabetes Care* 32(12):2143–2148. <https://doi.org/10.2337/dc09-1059>
 12. Aikens JE (2012) Prospective associations between emotional distress and poor outcomes in type 2 diabetes. *Diabetes Care* 35(12):2472–2478. <https://doi.org/10.2337/dc12-0181>
 13. Osborn CY, Egede LE (2012) The relationship between depressive symptoms and medication nonadherence in type 2 diabetes: the role of social support. *Gen Hosp Psychiatry* 34(3):249–253. <https://doi.org/10.1016/j.genhosppsych.2012.01.015>
 14. Gonzalez JS, Peyrot M, McCarl LA et al (2008) Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care* 31(12):2398–2403. <https://doi.org/10.2337/dc08-1341>
 15. Gonzalez JS, Safren SA, Delahanty LM et al (2008) Symptoms of depression prospectively predict poorer self-care in patients with type 2 diabetes. *Diabet Med* 25(9):1102–1107. <https://doi.org/10.1111/j.1464-5491.2008.02535.x>
 16. Dirmaier J, Watzke B, Koch U et al (2010) Diabetes in primary care: prospective associations between depression, nonadherence and glycemic control. *Psychother Psychosom* 79(3):172–178. <https://doi.org/10.1159/000296135>
 17. Kalsekar ID, Madhavan SS, Amonkar MM et al (2006) Depression in patients with type 2 diabetes: impact on adherence to oral hypoglycemic agents. *Ann Pharmacother* 40(4):605–611. <https://doi.org/10.1345/aph.1G606>
 18. Katon W, Russo J, Lin EH et al (2009) Diabetes and poor disease control: is comorbid depression associated with poor medication adherence or lack of treatment intensification? *Psychosom Med* 71(9):965–972. <https://doi.org/10.1097/PSY.0b013e3181bd8f55>
 19. McKellar JD, Humphreys K, Piette JD (2004) Depression increases diabetes symptoms by complicating patients' self-care adherence. *Diabetes Educ* 30(3):485–492. <https://doi.org/10.1177/014572170403000320>
 20. Lunghi C, Zongo A, Moisan J, Gregoire JP, Guenette L (2017) The impact of incident depression on medication adherence in patients with type 2 diabetes. *Diabetes Metab* 43(6):521–528. <https://doi.org/10.1016/j.diabet.2017.07.003>
 21. Kostev K, Jacob L (2018) Association between depression and persistence with oral antihyperglycemic drugs in type 2 diabetes mellitus patients in Germany. *Psychiatry Res* 261:90–93. <https://doi.org/10.1016/j.psychres.2017.12.058>
 22. Hazel-Fernandez L, Xu Y, Moretz C et al (2015) Historical cohort analysis of treatment patterns for patients with type 2 diabetes initiating metformin monotherapy. *Curr Med Res Opin* 31(9):1703–1716. <https://doi.org/10.1185/03007995.2015.1067194>
 23. Schmidt M, Pedersen L, Sørensen HT (2014) The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 29(8):541–549. <https://doi.org/10.1007/s10654-014-9930-3>
 24. Pedersen CB (2011) The Danish Civil Registration System. *Scand J Public Health* 39(Suppl 7):22–25. <https://doi.org/10.1177/1403494810387965>
 25. Kildemoes HW, Sørensen HT, Hallas J (2011) The Danish National Prescription Registry. *Scand J Public Health* 39(Suppl 7):38–41. <https://doi.org/10.1177/1403494810394717>
 26. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT (2015) The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 7:449–490. <https://doi.org/10.2147/clep.S91125>
 27. Mors O, Perto GP, Mortensen PB (2011) The Danish Psychiatric Central Research Register. *Scand J Public Health* 39(Suppl 7):54–57. <https://doi.org/10.1177/1403494810395825>
 28. Grann AF, Erichsen R, Nielsen AG, Frøslev T, Thomsen RW (2011) Existing data sources for clinical epidemiology: the clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin Epidemiol* 3:133–138. <https://doi.org/10.2147/clep.S17901>
 29. American Diabetes Association (2020) 2. Classification and diagnosis of diabetes: *Standards of medical care in diabetes—2020*. *Diabetes Care* 43(Suppl 1):S14–S31. <https://doi.org/10.2337/dc20-S002>
 30. Ding L, Xu Y, Liu S, Bi Y, Xu Y (2018) Hemoglobin A_{1c} and diagnosis of diabetes. *J Diabetes* 10(5):365–372. <https://doi.org/10.1111/1753-0407.12640>
 31. Musliner KL, Liu X, Gasse C, Christensen KS, Wimberley T, Munk-Olsen T (2019) Incidence of medically treated depression in Denmark among individuals 15–44 years old: a comprehensive overview based on population registers. *Acta Psychiatrica Scand* 139(6):548–557. <https://doi.org/10.1111/acps.13028>
 32. American Diabetes Association (2015) (2) Classification and diagnosis of diabetes. *Diabetes Care* 38(Suppl):S8–S16. <https://doi.org/10.2337/dc15-S005>
 33. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT (2011) The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 11:83. <https://doi.org/10.1186/1471-2288-11-83>
 34. Gardarsdottir H, Heerdink ER, Egberts ACG (2006) Potential bias in pharmacoepidemiological studies due to the length of the drug free period: a study on antidepressant drug use in adults in the Netherlands. *Pharmacoepidemiol Drug Saf* 15(5):338–343. <https://doi.org/10.1002/pds.1223>
 35. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC (2009) Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 25(9):2303–2310. <https://doi.org/10.1185/03007990903126833>
 36. Melmer A, Laimer M (2016) Treatment goals in diabetes. *Endocr Dev* 31:1–27. <https://doi.org/10.1159/000439364>

37. Thomsen RW, Baggesen LM, Svensson E et al (2015) Early glycaemic control among patients with type 2 diabetes and initial glucose-lowering treatment: a 13-year population-based cohort study. *Diabetes Obes Metab* 17(8):771–780. <https://doi.org/10.1111/dom.12484>
38. Svensson E, Nielsen RB, Hasvold P, Aarskog P, Thomsen RW (2015) Statin prescription patterns, adherence, and attainment of cholesterol treatment goals in routine clinical care: a Danish population-based study. *Clin Epidemiol* 7:213–223. <https://doi.org/10.2147/CLEP.S78145>
39. Nathan DM, Buse JB, Davidson MB et al (2006) Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 49(8):1711–1721. <https://doi.org/10.1007/s00125-006-0316-2>
40. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV (2009) Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health* 5:4. <https://doi.org/10.1186/1745-0179-5-4>
41. Gribsholt SB, Pedersen L, Richelsen B, Thomsen RW (2019) Validity of ICD-10 diagnoses of overweight and obesity in Danish hospitals. *Clin Epidemiol* 11:845–854. <https://doi.org/10.2147/clep.S214909>
42. Dalsgaard EM, Witte DR, Charles M, Jørgensen ME, Lauritzen T, Sandbæk A (2019) Validity of Danish register diagnoses of myocardial infarction and stroke against experts in people with screen-detected diabetes. *BMC Public Health* 19(1):228. <https://doi.org/10.1186/s12889-019-6549-z>
43. Roy T, Lloyd CE (2012) Epidemiology of depression and diabetes: a systematic review. *J Affect Disord* 142(Suppl):8–21. [https://doi.org/10.1016/s0165-0327\(12\)70004-6](https://doi.org/10.1016/s0165-0327(12)70004-6)

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