BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020768
Article Type:	Research
Date Submitted by the Author:	24-Nov-2017
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Mental health, Epidemiology
Keywords:	Depression, Diabetes Mellitus, Type 2, Self-Care, Cohort Studies

The DIADEMA Study- Prevalence of depression in patients with Type 2 Diabetes Mellitus: Results from the MADiabetes Cohort.

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Abstract

Objective: To estimate the prevalence of depression in patients diagnosed with Type 2 Diabetes Mellitus, and to identify factors associated with the occurrence of depression. Additionally, we examine the one year incidence rate of depression among T2DM patients.

Methods: A prospective dynamic cohort study of patients with Type 2 Diabetes Mellitus from the Madrid Diabetes Study with two recruitments (n=3,443 patients and n=727). Data was collected since baseline visit and annually during the follow-up period.

Results: Depression was prevalent in 23.4% of patients, and was significantly associated with previous personal history of depression (OR, 8.039; 95%CI, 6.394 to 10.108), mental health status (OR, 1.935; 95%CI, 1.452-2.577), neuropathy (OR, 1.571; 95%CI, 1.146-2.154), treatment with insulin (OR, 1.568; 95%CI, 1.008-2.439), fair or poor self reported health status (OR, 1.473; 95%CI, 1.189-1.824), treatment with oral antidiabetic agents plus insulin (OR, 1.421; 95%CI, 1.075-1.878), female gender (OR, 1.398; 95%CI, 1.069-1.827), cardiovascular disease (OR, 1.273; 95%CI, 1.002-1.617), and blood cholesterol level (OR, 1.004; 95%CI, 1.001-1.008; p=0.016).

On the other hand, the variables inversely associated with depression were: status of workers employed (OR, 0.603; 95%CI, 0.409 to 0.890; p=0.011), foreign born (OR, 0.300; 95%CI, 0.124 to 0.729; p=0.008), moderate and vigorous physical activity (OR, 0.409; 95%CI, 0.241 to 0.694; p=0.001), systolic blood pressure (OR, 0.989; 95%CI, 0.978 to 0.999; p=0.029), and social support (network size) (OR, 0.978; 95%CI, 0.963 to 0.993; p=0.004).

Conclusions: Depression is very prevalent among patients with Type 2 Diabetes Mellitus and it was associated with several key diabetes-related outcomes. Our results suggest that previous mental status, self reported health status, gender and several complications related to diabetes express differences in depression of the patients. These findings should alert practitioner to the importance of detection of depression in patients with Diabetes Mellitus Type 2.

Strengths and limitations of this study

1.1. Strengths and limitations

- Time between both telephone interviews for depression screening was too short (12 months), making it difficult to compare cumulative incidence rates with most studies.
- The prescription of antidepressants takes place in diseases other than depression (i.e., sleeping disorders, migraine, neuropathic pain, obsessive-compulsive disorders, anxiety/panic disorder), and the use of a combined variable for the diagnosis of depression includes the prescription of antidepressant medication and could have therefore overestimated its prevalence.
- In order to compare multivariate models from different studies, it is possible that we just performed an unnecessary adjustment of variables. But, fortunately, there was no significant evidence for over-adjustment (changes >20% between crude and adjusted SE, data not shown).
- The prospective design of the study was a strength, which ensured that measurement of risk factors preceded the development of depression; and the assessment of information on potentially confounding variables, which reduces the potential selection and confusion biases.
- Also, we used an assessment of depression based on MINI 5.0, completed with having been diagnosed with depression, treatment with antidepressant medications or any of these conditions. Therefore, self-reported diagnosis was avoided.

Keywords: Depression; Diabetes Mellitus, Type 2; Self-Care; Cohort Studies.

2. Introduction

Currently, an estimated 8%-9% of the worldwide adult population has Type 2 Diabetes Mellitus (T2DM), with a substantial increase of the prevalence over time (1). Among the Spanish population, the prevalence is even higher (13.8%) (2).

Previous studies have shown that among people with T2DM, the coexistence of mental disorders such as depression is considerably higher than in the overall population (3) (4), with an prevalence from 15% to 24% (5) and an incidence rate of depression during the first year after oral antidiabetic drugs initiation of 12.61 per 1000 person-years (6). The coexistence of diabetes and mental disorders has a strong impact on the patient, with an increased risk of cardiovascular disease and all-cause (7) and cardiovascular mortality (7), especially as a result of cardiovascular complications (8) of T2DM. Also, patients with diabetes and mental disorders show less compliance with treatment recommendations than T2DM patients without depression, and more frequently have cardiovascular risk factors such as smoking, obesity, sedentary lifestyle or poor glycemic control (9), which can consequently impact on their health-related quality of life (10).

To our knowledge, research on common mental disorders affecting patients with T2DM is scarce in Spain (11) (12) (13). Recently, Alonso-Morán et al. found, (14) in their cross-sectional study in patients with T2DM, that 9.8% of the patients were diagnosed with depression (5.2% for males and 15.1% for females), and in a study by Nicolau et al. (12), 27.2% had symptoms of depression. However, in these studies data collection has often been based on Health Surveys (11) (15) or self-reported scales (16) (12), with a heterogeneous variability of the data. Thus, mental disorders have not been assessed using as “gold standard” a clinical interview.

The aims of the present study are to estimate the prevalence of depression in patients diagnosed with T2DM, and to identify sociodemographic, clinical, and psychological factors associated with the occurrence of depression in this population. Additionally, we examine the one year incidence rate of depression among T2DM patients.

3. Material and Methods

3.1. Design and participants

The Madrid Diabetes Study (MADiabetes Study), is a large prospective cohort study, focusing on the analysis of different clinical and psychosocial aspects of outpatients with T2DM living in the metropolitan area of Madrid, Spain. In 2007, a first recruitment process was performed, and 3,443 T2DM outpatients were enrolled in one of the 56 Primary Health Care Centers (PHCC) participating. Patients were selected by simple random sampling by participating general practitioners (n= 131), based on the list of patients with a diagnosis of T2DM in their Computerized Clinical Records (CCRs). A more complete description of this methodology can be found elsewhere (17).

Reasons not to continue till the study completion were leaving the participating practice, death or drop-out. Furthermore, the dynamic character of MADiabetes cohort, which means that new participants could enter over time, helped prevent vanishing of the study population sample. So, at the end of 2010, a second recruitment process was performed, with 41 PHCC including 727 new patients.

Inclusion criteria to participate in the study were: patients with a diagnosis of T2DM in the CCR (code T90 of International Classification of Primary Care [ICPC-2] (19), who were 30 years of age or older, who had visited their PHCC at least twice in the last year, and had agreed to take part in the study and provided written informed consent. Patients were excluded for the following reasons: diagnosis of gestational diabetes mellitus, institutionalized patients, subjects who could not understand Spanish, patients with severe chronic diseases or significant physical or psychic disabilities that might invalidate informed consent or interviews (according to clinical judgment), legal incompetence or legal guardianship, or participation in clinical trials.

For the purpose of evaluating the prevalence of depression (DIAbetes and DEpression in MAdrid-DIADEMA Study), we included those patients who participated in the interview

conducted between January 1st 2011 and 31th December 2011. Also, to estimate the annual incidence of depression, the data from the second interview was included. The original protocol of the study was published in advance (18). Therefore, for the main variable the MADiabetes cohort included a total of 2,955 patients (see the flow diagram in Figure 1).

3.2. Source of data

To achieve the goal of the MADiabetes Study, data was collected since 2007 (baseline visit) and annually during the follow-up period (since 2008), and four data collection strategies were combined.

Firstly, data concerning disease episodes (coded in ICPC-2) (19), prescription of medication (coded in Anatomical Therapeutic Chemical classification system), laboratory results, anthropometric variables, and use of care facilities were registered using data from CCR. The CCR for Primary Health Care in Madrid's Health Service was administered by OMI-AP© software. The CCR registration is continuously updated in the Primary Health Care Center under routine clinical practice conditions, and once a year, data was transferred to our central database.

Secondly, the general practitioner of each participating patient completed information about morbidity and mortality, collected under routine clinical practice conditions; this information was recorded on electronic case report forms (hosted on the website www.madiabetes.com. All the team of general practitioners received training to standardize their knowledge about project objectives, data collection techniques and field work procedures.

Thirdly, from 2011 onward, all patients were invited each year to undergo an interview to collect sociodemographic data, lifestyles, determinants of health, and psychosocial characteristics. This data collection was conducted using a previously standardized protocol designed in advance, and was done through a telephone interview performed by a clinical psychologist trained in the evaluation procedure of the study. Lastly, the vital status of the

patients was ascertained from two mortality records: *Índice Nacional de Defunciones* (https://www.msssi.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/IND_TipoDifusion.htm) and *Instituto Nacional de Estadística* (http://www.ine.es). This last record indicates the underlying cause of death recorded on the death certificates, which is coded according to the International Classification of Diseases, Tenth Revision (20).

3.3. Variables

The primary outcome variable was depression. The diagnosis of depression was considered as a combined variable, as suggested by other authors (21), consisting of a diagnosis based on the module of major depressive disorder of the International Neuro-psychiatric Interview (MINI 5.0.0) (22), and according to clinical judgment, use of antidepressant medication, and/or physician-diagnosed depression. In order to exclude those episodes that were not currently active at the moment of the evaluation, we included only those patients who had received a diagnosis of depression in the preceding last 12 months, or had a prescription of antidepressant medication within the previous four months.

The MINI is a short and efficient diagnostic interview to diagnose mental disorders, which was used in its Spanish version (23).

In addition, other *psychosocial variables* were evaluated:

- A personal history of psychiatric disorder was registered if patient reported a positive response to the question: “Has a clinician ever diagnosed you as having any psychiatric disorder?. Alternatively, whenever patients had formerly received a diagnosis of a psychiatric disorder before the last 12-month interval, as coded in the CCR.

- A family history of psychiatric disorder was registered if the patient reported a positive response to the question: “Has any family member (in first-degree relatives) ever been diagnosed of a psychiatric disorder?”

- Anxiety disorder was defined based on the module of generalized anxiety disorder of the MINI (23) and according to clinical judgment.

- Social support, such as network size, was measured by the question: "About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?", which corresponds to the first item of the Medical Outcomes Study-Social Support Survey (MOS-SSS) (24).

- Health-related quality of life was measured using the SF-12 questionnaire, a composite of 12 items that assess eight dimensions of health: physical functioning, role-physical, general health, bodily pain, vitality, social functioning, role-emotional and mental health (25). The SF-12 measures various aspects of physical and mental health, from which physical and mental summary scores are computed using the scores of twelve questions, and ranges from 0 to 100, where a zero score indicates the lowest level of health and 100 indicates the highest level of health. Both Physical and Mental Health Composite Scales combine the 12 items in such a way that they compare to a national norm with a mean score of 50.0 and a standard deviation of 10.0.

Sociodemographic variables included were: age (date of birth), gender, nationality, time of residence in Spain, marital status (single, unmarried partners, married, divorced, widowed), educational level (no studies, primary, high school, university), and employment status (employed, unemployed, retired, housewife and other).

Medical variables included the following:

- Comorbidity variables: hypertension, heart failure, myocardial infarction, stroke, peripheral artery disease, low limb amputations, erectile dysfunction, retinopathy, nephropathy, neuropathy and renal failure. Cardiovascular disease (CVD) was defined as one or more of the following: myocardial infarction, stroke or peripheral vascular disease.
- Other clinical variables: diabetes duration and family history (in the first-degree relatives) of diabetes.

- Anthropometric variables: height, weight, body mass index (BMI), hip circumference, waist circumference, systolic blood pressure, and diastolic blood pressure.
- Laboratory results: albuminuria, creatinine, lipid profile, HbA1c and glucose.
- Personal health habits: smoking (never, former or current smoker), physical activity level (sedentary, moderate-intensity, vigorous-intensity, competition-level), and drinking (0.1 through 4.9, or 5.0 or more g/d of alcohol).
- Treatment: statins, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, antiplatelets, antidiabetics, antidepressant drugs and anxiolytics that had been prescribed.

3.4. Statistical analysis

A descriptive analysis was conducted for each variable, as mean and standard deviation for quantitative variables, and as frequency distribution for qualitative variables. Normally distributed continuous variables were compared using the t test, non-normally distributed variables were compared using the Mann-Whitney test, and categorical variables were compared using the Chi-square test.

Multivariate logistic regressions models were constructed to identify variables that were independently associated with depression (prevalent). We report adjusted odds ratios (ORs) with their respective 95% confidence intervals (95%CIs). Variables that were statistically significant in the bivariate analysis and those shown to be predictors in previous studies were included in the multivariate analysis. We analyzed the possibility of over-adjustment, defined when after adjusting on the covariate it altered the adjusted OR of 10%–20% with a concomitant change of the standard error (SE) higher than 20%.

The annual incidence rate of depression was calculated by the standard method as follows: number of new cases of depression over a period (year 2011) / Population at risk of developing the disease at the begging of the period.

In all cases, the accepted level of significance was 0.05 or less, with a 95%CI. Statistical processing of the data was performed using the Statistical Package for the Social Sciences (SPSS for windows, version 21.0; IBM Corp, Armonk, New York, USA).

3.5. Ethical aspects

The study was approved by the Institutional Review Board of the Ramón y Cajal Hospital (Madrid) and conducted in accordance with the principles of the Declaration of Helsinki. All patients gave their written informed consent to participate in the study.

4. Results

4.1. Characteristics of the study population and prevalence of depression

At the first recruitment (January 2007), 3,443 patients were included at the study. A total of 3,217 were alive before the start of the survey (January 2013), and 2,228 agreed to the interview (participation rate: 69.3%), and of the second recruitment, 727 patients accept to participate (December 2010). Therefore, for the main objective of this study, the sample consisted of 2,955 people; 48.1% were women and the mean age was 70.2 years (SD 10.6).

Depression was prevalent in 23.4% (n=691; 95%CI, 21.9 to 24.9) Table 1 shows the characteristics of the sample, stratified by depression and anxiety status.

Compared with patients without depression, people with depression were more likely to be female (<0.001), older (p<0.004), widowed or divorced (p<0.001), had a lower educational level (p<0.001), were more frequently classified as housewife, unemployed or retired (p<0.001), and had a higher duration and intensity of diabetes treatment regimen (p=0.003). Also, patients with depression had lower BMIs (p<0.001), were lower consumers of alcohol (p<0.001) and, on the contrary, showed higher rates of never smoker (p<0.001), sedentary life (p<0.001), history of myocardial infarction (p=0.013), neuropathy (p<0.001), and renal failure

	TOTAL (n=2,955)	Without depression (n=2,264)	With depression (n=691)	p value

(p=0.005). 14.8% of the sample had anxiety (n= 438; 95%CI, 13.5 to 16.1), and coexistence of conditions, depression and anxiety, occurred in up to 8.2% (n=242) of the patients.

Also patients with depression had higher rates of previous episodes of depression (p<0.001) and anxiety (p<0.001), and fair or poor self-reported health status (p<0.001), as compared with patients without these disorders. In addition, patients with depression or anxiety, showed no significant differences when compared with psychically healthy subjects in the following aspects: family history of diabetes, level of HbA1c, triglycerides values, nephropathy, and retinopathy.

Table 1.Characteristics of the MADiabetes Cohort (n=2,955), stratified depression status.

Sociodemographic variables				
Gender (female); n (%; 95%CI)	1.421 (48.1; 46.3-49.9)	955 (42.2; 40.1-44.2)	466 (67.4;63.9-70.9)	<0.001
Age (years); mean (SD)	70.2 (10.6)	69.9 (10.7)	71.2 (10.3)	<0.004
Country of origin (foreign-born); n (%; 95%CI)	70 (2.4;1.8-2.9)	62 (2.8;2-3.4)	8 (1.2;0.3-1.9)	0.016
Marital status; n (%; 95%CI)				
Single without partner	4.6	4.8	3.9	<0.001
Married o with partner	70.4	73	61.6	
Divorced	4.4	4.2	4.4	
Widowed	20.8	18	30	
Educational level; n (%)				
No completed	613 (20.9)	439 (19.6)	174 (25.4)	<0.001
Primary	1367 (46.7)	1030 (45.9)	337 (49.1)	
Secondary	576 (19.7)	463 (20.6)	113 (16.5)	
University	374 (12.8)	312 (13.9)	62 (9)	
Employment status; n (%)				
Employed	459 (15.7)	394 (17.6)	65 (9.4)	<0.001
Unemployed	105 (3.6)	75 (3.3)	30 (4.4)	
Retired	1953 (66.6)	1492 (66.5)	461 (67)	
Housewife	372 (12.7)	252 (11.2)	120 (17.4)	
Other	43 (1.5)	31 (1.4)	12 (1.7)	
Variables related to diabetes				
Duration of diabetes (years); mean (SD)	15.4 (10.2)	15 (10.1)	16.4 (10.4)	0.003
Family history of diabetes (Yes); n (%; 95%CI)	1813 (61.7; 59.9-63.5)	1373 (61; 58.9-63)	440 (54.1; 60.5-67.7)	0.135
Type of diabetes treatment; n (%)				
Only diet	400 (16.8)	309 (17)	91 (16)	0.003
Oral antidiabetic agents	1453 (60.9)	1134 (62.4)	319 (56.3)	
Insulin	149 (6.2)	110 (6.1)	39 (6.9)	
Oral antidiabetic agents + insulin	383 (16.1)	265 (14.6)	118 (20.8)	
Lifestyle and self-care				
Smoking habit; n (%)				
Never smoker	1305 (45)	931 (41.6)	374 (56.3)	<0.001
Ex-smoker	1259 (43.4)	1034 (46.2)	225 (33.9)	
Smoker	336 (11.6)	271 (12.1)	65 (9.8)	
Current regular alcohol use; n (%; 95%CI)	883 (33.6; 31.9-35.44)	745 (36.6; 34.6-38.7)	138 (23.3; 19.9-26.7)	<0.001
Physical activity; n (%)				
Sedentary	333 (13.3)	211 (10.9)	122 (21.3)	<0.001
Low	1963 (78.2)	1540 (79.5)	423 (73.7)	
Moderate	209 (8.3)	180 (9.3)	29 (5.1)	
Vigorous activity	5 (0.2)	5 (0.3)	0 (0)	
Clinical risk factors				
BMI (Kg/m^2); mean (SD)	31.1 (5.6)	30.9 (5.5)	32 (5.9)	<0.001
Systolic blood pressure (mmHg); mean (SD)	131.5 (12.6)	131.9 (12.6)	129.9 (12.4)	<0.001
Diastolic blood pressure (mmHg); mean (SD)	73.9 (7.5)	74.1 (7.4)	73.2 (7.6)	0.005
Biochemical risk factors				
HbA1c (%); mean (SD)	7.1 (1.1)	7.1 (1.1)	7.2 (1.2)	0.349
Triglycerides; mean (SD)	142.4 (87.6)	141 (92.2)	146.8 (69.3)	0.122
Cholesterol; mean (SD)	175.7 (33.9)	174.2 (33.3)	180.6 (35.4)	<0.001
LDL-Cholesterol; mean (SD)	99.2 (27.3)	98.4 (26.6)	101.7 (29.4)	0.024
HDL-Cholesterol; mean (SD)	49.5 (13.2)	48.9 (12.7)	51.3 (14.7)	<0.001
Complications and comorbidities				
Acute myocardial infarction	570 (13.7; 12.6-14.7)	429 (13; 11.8-14.1)	141 (16.2; 13.8-18.7)	0.013
Nephropathy	522 (12.5; 11.5-13.5	401 (12.1; 11-13.3)	121 (13.9; 11.6-16.2)	0.155
Neuropathy	397 (9.5; 8.6-10.4)	271 (8.2; 7.3-9.1)	126 (14.5; 12.2-16.9)	<0.001
Retinopathy	567 (13.6; 12.6-14.6)	434 (13.1; 12-14.3)	133 (15.3; 12.9-17.7)	0.096
Renal failure	536 (12.9; 11.8-13.9)	400 (12.1; 11-13.2)	136 (15.7; 13.2-18.1)	0.005
Psychosocial variables				
Family history of depression (Yes); n (%; 95%CI)	197 (6.7; 5.8-7.6)	135 (6; 5-7)	62 (9.1; 7-11.3)	0.004
Personal history of depression (Yes); n (%; 95%CI)	557 (18.9; 17.5-20.3)	216 (9.6; 8.3-10.7)	341 (49.6; 45.9-53.4)	<0.001
Anxiety	438 (14.8;13.5-16.1)	196 (8.7;7.5-9.9)	242 (35;31.4-38.6)	<0.001
Family history of anxiety (Yes); n (%; 95%CI)	71 (2.4; 1.9-3)	47 (2.1; 1.5-2.7)	24 (3.5, 2.1-4.9)	0.033
Personal history of anxiety (Yes); n (%; 95%CI)	344 (11.7; 10.5-12.8)	157 (7; 5.9-8)	187 (27.2; 23.9-30.5)	<0.001

Self-reported Health status (Fair or poor); n (%; 95%CI)	992 (34.3; 32.5-36)	685 (30.8; 28.8-32.7)	307 (46; 42.2-49.8)	<0.001
Physical quality of life; mean (SD)	40.1 (11.4)	41.4 (10.8)	36.4 (12.1)	<0.001
Mental quality of life; mean (SD)	47.4 (10.9)	49.5 (9.3)	41.5 (12.7)	<0.001
Social support (network size); mean (SD)	10.2 (8.3)	10.7 (8.7)	8.6 (6.5)	<0.001
Sleep (AIS); mean (SD)	2.6 (3.7)	2.1 (3.1)	4.4 (4.9)	<0.001

OR	95% CI OR	P-value

4.2. Factors associated with prevalent depression

Table 2 shows the variables associated with depression after fully adjustment for potential confounding factors. The variable more strongly associated with depression was previous personal history of depression (OR, 8.039; 95%CI, 6.394 to 10.108; p≤0.001), followed by mental health score (SF-12) below mean (OR, 1.935; 95%CI, 1.452 to 2.577; P≤0.001), neuropathy (OR, 1.571; 95%CI, 1.146 to 2.154; p=0.005), treatment with insulin (OR, 1.568; 95%CI, 1.008 to 2.439; p=0.045), fair or poor self reported health status (OR, 1.473; 95%CI, 1.189 to 1.824; p=<0.001), treatment with oral antidiabetic agents plus insulin (OR, 1.421; 95%CI, 1.075 to 1.878; p=0.014), female gender (OR, 1.398; 95%CI, 1.069 to 1.827; p=0.014), cardiovascular disease (OR, 1.273; 95%CI, 1.002 to 1.617; p=0.049), and blood cholesterol level (OR, 1.004; 95%CI, 1.001 to 1.008; p=0.016).

On the other hand, the variables inversely associated with depression were: status of workers employed (OR, 0.603; 95%CI, 0.409 to 0.890; p=0.011), foreign born (OR, 0.300; 95%CI, 0.124 to 0.729; p=0.008), moderate and vigorous physical activity (OR, 0.409; 95%CI, 0.241 to 0.694; p=0.001), systolic blood pressure (OR, 0.989; 95%CI, 0.978 to 0.999; p=0.029), and social support (network size) (OR, 0.978; 95%CI, 0.963 to 0.993; p=0.004).

Table 2. Factors associated with prevalence of Depression (Logistic Regression Analysis)

Gender			
Male	1		
Female	1.398	1.069-1.827	0.014
Age			
<65 years	1		
≥65 years	0.821	0.606-1.114	0.205
Duration of DMT2 (y)[per unit of increment]	1.006	0.995-1.016	0.288
Educational level			
University	1		
Secondary	1.123	0.752-1.677	0.572
Primary	1.135	0.793-1.627	0.488
No completed	1.148	0.768-1.717	0.501
Country of origin			
Spain	1		
Foreign born	0.300	0.124-0.729	0.008
Employment status			
No Occupied	1		
Occupied	0.603	0.409-0.890	0.011
Smoking			
Never smoker	1		
Former smoker	0.836	0.644-1.085	0.177
Current smoker	0.901	0.614-1.321	0.592
Family history of DM			
No	1		
Yes	1.144	0.924-1.418	0.217
Current Alcohol use			
No	1		
Yes	0.814	0.629-1.054	0.119
Physical activity			
Sedentary	1		
Low	0.544	0.412-0.745	<0.001
Moderate-Vigorous	0.409	0.241-0.694	0.001
Diabetes Treatment			
Oral anti-diabetic agents	1		
Oral anti-diabetic agents + insulin	1.421	1.075-1.878	0.014
Insulin	1.568	1.008-2.439	0.045
Diet	1.015	0.694-1.485	0.939
Unknown	1.198	0.898-1.598	0.220
BMI (Kg/m^2)[per unit of increment]	1.012	0.993-1.031	0.233
Systolic BP (mmHg)[per unit of increment]	0.989	0.978-0.999	0.029
Diastolic BP (mmHg)[per unit of increment]	0.984	0.967-1.001	0.063
Cholesterol (mg/dl) [per unit of increment]	1.004	1.001-1.008	0.016
Neuropathy			
No	1		
Yes	1.571	1.146-2.154	0.005
Nephropathy			

	No	1		
	Yes	0.797	0.578-1.098	0.165
Retinopathy				
	No	1		
	Yes	0.958	0.716-1.282	0.772
Renal Failure				
	No	1		
	Yes	1.233	0.910-1.670	0.176
Self-reported Health status				
	Excellent-very good-good	1		
	Fair-poor	1.473	1.189-1.824	<0.001
Family history of depression				
	No	1		
	Yes	0.943	0.644-1.383	0.765
Personal history of depression				
	No	1		
	Yes	8.039	6.394-10.108	<0.001
Social support (network size)[per unit of increment]		0.978	0.963-0.993	0.004
Physical health score (SF-12)				
	Score ≥ mean	1		
	Score < mean	1.094	0.804-1.488	0.568
Mental health score (SF-12)				
	Score ≥ mean	1		
	Score < mea	1.935	1.452-2.577	<0.001
History of cancer				
	No	1		
	Yes	1.037	0.784-1.370	0.801
Cardiovascular disease				
	No	1		
	Yes	1.273	1.002-1.617	0.049
Heart failure				
	No	1		
	Yes	0.927	0.647-1.327	0.678
Lower limb amputation				
	No	1		
	Yes	0.918	0.387-2.182	0.847

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; BP: Blood Pressure; DMT2: Type 2 Diabetes Mellitus.

4.3. Incidence of depression and predictive factors

During a median of 12 months of follow-up, a total of 363 patients developed a new episode of depression, constituting an annual incidence of 12.3% (95%CI, 11.12 to 13.48). There were differences by gender and age group: 6.5% (95%CI, 5.27 to 7.73) in men and 18.5% (95%CI, 16.48 to 20.52) in women (p≤0.001); 9.8% (95%CI, 7.79 to 11.81) in <65 years and 13.3% (95%CI, 11.85 to 14.75) in ≥65 years (p=0.009).

As observed with the prevalence, a previous personal history of depression was the variable more strongly associated with incidence of depression (OR, 3.901; 95%CI, 3.017 to 5.045; p≤0.001). Other variables directly associated were: neuropathy (OR, 1.919; 95%CI, 1.351 to 2.726; p≤0.001), current smoking status (OR, 1.584; 95%CI, 1.025 to 2.448; p=0.038), age group ≥65 years (OR, 1.473; 95%CI, 1.013 to 2.142; P=0.043) and female gender (OR, 2.048; 95%CI, 1.474 to 2.847; p≤0.001). Low (OR, 0.565; 95% CI, 0.405 to 0.789; p≤0.001), or moderate/vigorous physical activity (OR, 0.543; 95%CI, 0.293 to 1.006; p=0.050) were protective factors for depression, as well as systolic blood pressure (per each unit of increment) (OR, 0.984; 95%CI, 0.972 to 0.997; p=0.014), and social support (network size) (OR, 0.972; 95%CI, 0.952 to 0.991; p=0.004) (Table 3).

Table 3. Predictive factors for the development of Depression (Logistic Regression Analysis)

	OR	95% CI OR	P-value
Gender			
Male	1		
Female	2.048	1.474-2.847	<0.001
Age			
<65 years	1		
≥65 years	1.473	1.013-2.142	0.043
Duration of DM2 (y)[per unit of increment]	0.995	0.982-1.008	0.441
Country of origin			
Spain	1		
Foreign born	0.611	0.243-1.535	0.295
Employment status			
No Occupied	1		
Occupied	0.926	0.578-1.482	0.748
Smoking			
Never smoker	1		
Former smoker	0.937	0.684-1.284	0.685
Current smoker	1.584	1.025-2.448	0.038
Physical activity			
Sedentary	1		
Low	0.565	0.405-0.789	0.001
Moderate-Vigorous	0.543	0.293-1.006	0.052
Systolic BP (mmHg)[per unit of increment]	0.984	0.972-0.997	0.014
Diastolic BP (mmHg)[per unit of increment]	1.005	0.985-1.026	0.633
Neuropathy			
No	1		
Yes	1.919	1.351-2.726	<0.001
Self-reported Health status			
Excellent-very good-good	1		
Fair-poor	1.212	0.941-1.562	0.136
Personal history of depression			
No	1		
Yes	3.901	3.017-5.045	<0.001
Social support (network size)[per unit of increment]	0.972	0.952-0.991	0.004
Lower limb amputation			
No	1		
Yes	0.918	0.387-2.182	0.847

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; BP: Blood Pressure; DM2: Type 2 Diabetes Mellitus; DM: Diabetes Mellitus.

Adjusted for educational level, family history of diabetes, alcohol use, nephropathy, retinopathy, renal failure, diabetes treatment, BMI, cholesterol, family history of depression, history of cancer, cardiovascular disease, heart failure, lower limb amputation and SF-12

5. Discussion

The association between diabetes and depression is well-known since at least three decades ago (4). The prevalence of depression in people with T2DM ranges widely due to various circumstances such as different depression assessment methods used (clinical interviews, questionnaires, self-report scales, or patient medical records), sample origin (clinical or outpatient screening population), ethnic subgroups, gender composition, and age intervals used. Two meta-analyses reported overall depression prevalence ranging from 17.6% to 27% (4). We analyzed the prevalence of depression in a cohort of patients with T2DM from the city of Madrid based on a clinical interview completed with prescribing and clinical data from CCRs. Depression was prevalent in 23.4% (n=691; CI 95%, 21.9 to 24.9) of our sample, a finding that is highly comparable to the recent estimates of 27.2% from Primary-Care settings and a Hospital Endocrinology Department in Mallorca (Spain) using the Beck Depression Inventory as screening tool (12). These figures represent a worrying clinical scenario, given the adverse impact of depression on the natural history of T2DM: poor metabolic control (26), non-adherence to treatment (27), and increased risk of vascular complications (8) .

Poor social support and negative life events (i.e., adverse socioeconomic circumstances, death of relatives) have been associated with depression in people with T2DM (29). These two factors are overrepresented in females in comparison with males (30) (31), and this phenomenon would explain the predominance of depression among females, as reported by a vast majority of studies (32) (33). However, not all the studies have confirmed this hypothesis (34).

After adjusting for gender and other known risk factors, our findings show that the risk of depression was reduced by 2.2% per unit of increment of network size, in the same line, the implementation of moderate or vigorous physical activity significantly reduced by 59.1% the risk of depression.

General practitioners should be encouraged to implement strategies designed to reduce the risk of depression in patients suffering from T2DM, especially in those with high-risk for depression for having chronic psychosocial stressors (28).

We have shown an inverse association between both moderate-vigorous physical activity (OR 0.409, p=0.001) and social support (OR 0.978; p=0.004) and depression; even though this association does not necessarily imply a causal relationship, it might urge the implementation of programs of physical activity and the creation of support groups focused on psychological well-being and the detection of depressive symptoms. Also, a better control of blood cholesterol levels might provide additional value (OR per unit of decrement, 0.996; p=0.016). Some of these aspects have proven to be effective and feasibility in older populations (35).

On the other hand, it is necessary to keep in mind that treatment of depression can be a prerequisite for good diabetes control because people with diabetes might follow their treatment plan more easily if their mood is improved first (36).

Other predictive factors of depression such as a previous depression episode or family history of depression are not modifiable factors for reducing the risk of developing depression, but health professionals must be alert to the presence of early symptoms of depression in order to treat this condition promptly. Indeed, routinely screening for psychosocial problems such as depression has supportive evidence from well-conducted cohort studies (37). In this sense, screening for depression with questionnaires has not enough specificity and needs to be complemented by a formal clinical assessment to confirm the diagnosis (36).

Occupied employment status was inversely associated with depression (OR, 0.603; p= 0.011), as other studies have previously shown (38). This aspect suggests that going to work might have a protective role against depression due to social support received from the co-workers.

After controlling for covariates, being foreign-born was negatively associated with depression (OR, 0.300; p=0.008). This finding could reveal a social resilience processes, with an optimal development of social relations and social networks in the immigrating population. However,

this hypothesis must be interpreted with caution, given that it is well-known that the immigrant population is more vulnerable to depression than the native population (39).

Of the classic complications of diabetes, neuropathy (OR, 1.571; P=0.005) and cardiovascular disease (OR, 1.273; p=0.049) were the only ones significantly associated with depression. These study findings were consistent with several previous studies (8) (33). It would be logical to think that micro- and macro-vascular complications of diabetes are associated with depression, but the lack of association between retinopathy and nephropathy with depression prevents the possibility of the so-called vascular depression, as has been reported in other studies (40). Also, limb amputation showed a tendency to be a protective factor for incident depression.

As it was logical to suppose, subjects with depression showed lower values in the mental health component score obtained from the SF-12, as other studies have reported (41).

The participants with depression self-rated their own health status significantly lower than those without depression, which is concordant with other studies (42). Given the known relationship between fair/poor perceived health status and mortality (43), especially in patients with chronic diseases (44), it would be advisable that patients with poor self-rated health were enrolled in a health coaching program similar to that used in the Royal North Shore Hospital, Sydney, Australia (45). In this program, those with diabetes who had the lowest self-reported health status at baseline improved their rating in the first question of the Short-Form 36 Quality of Life Instrument (SF-1) from 4.4 to 3.7 (P≤ 0.001), and improved in diabetes knowledge too, and their distress levels decreased significantly with respect to basal values.

Medications for lowering blood sugar (insulin alone or insulin plus oral anti-diabetic agents) showed a significant association with depression (OR, 1.568; p=0.045 and OR, 1.421; p≤0.001, respectively). Prior studies have highlighted the same phenomenon: the glucose lowering therapies that include insulin are strongly associated with depression (46). Two different

factors could be implicated in this link: first, the implementation of insulin therapy requires painful injections and frequent glucose measurements and it can constitute a stressful life event that is a potent risk factor for the onset of a depressive episode in the old age (47); second, usually the use of insulin is necessary for situations of poor glycemic control, and it could be that the non-optimal control of diabetes causes a worsening of mood, greater stress, and less life-satisfaction.

Regarding incidence of depression after one year of follow-up, the present study reveals a value of 12.3%, which is in the range of prior researches (48) (5) (49) (50). In a meta-analysis (51) that evaluated 16 studies to analyze the relationship between diabetes and depression, the cumulative incidence of depression among people with diabetes ranged from 11.9%, after two years of follow-up, (52) to 23.5%, after 5.9 years of follow-up (53). The conclusion of the referred meta-analysis (51) is that there is evidence to support the hypothesis that diabetes is a ''depressogenic'' condition. This affirmation implies a real public health problem that may be resolved only by a specific prevention strategy.

Current smoking status was a factor not associated with the prevalence of depression, but associated with its incidence. Other studies (54) had found the same association. In a recent meta-analysis (54), eleven longitudinal studies analyzed the current smoking status as a predictor factor for depression onset; five of them showed a significant risk of incidence of depression (pooled HR, 1.40; 95% CI, 1.18 to 1.65; p≤0.001), whereas six of them showed a non-significant association (pooled HR, 1.15; 95% CI, 0.94 to 1.41).

5.1. Conclusions

Depression is very prevalent among patients with Type 2 Diabetes Mellitus and it was associated with several key diabetes-related outcomes. Our results suggest that previous mental status, self reported health status, and several complications related to diabetes express differences in depression of the patients. We also found sex-related differences with respect to the prevalence of depression. Our study highlights that the implementation of

moderate or vigorous physical activity significantly reduced the risk of depression. These findings should alert practitioner to the importance of detection of depression in patients with Diabetes Mellitus Type 2, and to reduce the risk of depression with prevention group programs focused on improve the physical activity of the patients and creation support groups.

Acknowledgements

The authors thank to all health professionals of Primary Health Care of Madrid who have made its development possible.

Contributor Ship Statement

CBL and MASF designed the study and got funding. JCV, PGC, JCAH, and RCM contributed to data collection. FJSR, CBL, PGC and MASF analysed the data. PGC, MASF, and JMDY wrote the initial draft of the paper. RJG, ALA, CBL and ECS were involved in further drafting of the paper. All authors participated in interpreting the data, revising the paper for critically important intellectual content and gave final approval of the submitted version.

Data Sharing Statement

No additional data are available

Funding

This study forms part of research funded by the FIS (Fondo de Investigaciones Sanitarias—Health Research Fund, Instituto de Salud Carlos III) grants no.: PI10/02796, PI12/01806 and PI15/00259 and co-financed by the European Union through the Fondo Europeo de Desarrollo Regional (FEDER, “Una manera de hacer Europa”).

The members of the MADIABETES Group are as follows : AM Sobrado-de Vicente-Tutor; Mar Sanz-Pascual; M Arnalte-Barrera; S Pulido-Fernández; EM Donaire-Jiménez; C Montero-Lizana;

M Domínguez-Paniagua; P Serrano-Simarro; R Echegoyen-de Nicolás; P Gil-Díaz; I Cerrada-Somolinos; R Martín-Cano; A Cava-Rosado; T Mesonero-Grandes; E Gómez-Navarro; D Beamud-Victoria; A Maestro-Martín; A Muñoz-Cildoz; ME Calonge-García; M Martín-Bun; P Carreño-Freire; J Fernández-García; A Morán-Escudero; J Martínez-Irazusta; E Calvo-García; AM Alayeto-Sánchez; C Reyes-Madridejos; MJ Bedoya-Frutos; B López-Sabater; J Innerarity-Martínez; A Rosillo-González; AI Menéndez-Fernández; F Mata-Benjumea; P Vich-Pérez; C Martín-Madrazo; MJ Gomara-Martínez; C Bello-González; A Pinilla-Carrasco; M Camarero-Shelly; A Cano-Espin; J Castro Martin; B de Llama-Arauz; A de Miguel-Ballano; MA García-Alonso; JN García-Pascual; MI González-García; C López-Rodríguez; M Miguel-Garzón; MC Montero-García; S Muñoz-Quiros-Aliaga; S Núñez-Palomo; O Olmos-Carrasco; N Pertierra-Galindo; G Reviriego-Jaén; P Rius-Fortea; G Rodríguez-Castro; JM San Vicente-Rodríguez; ME Serrano-Serrano; MM Zamora-Gómez; and MP Zazo-Lázaro.

Competing interests

The authors declare that there is no duality of interest associated with this manuscript.

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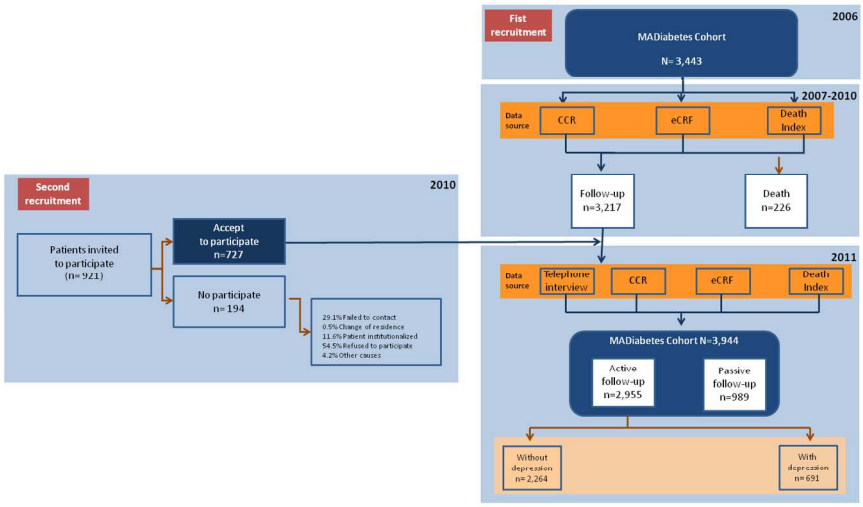
Figure 1- Flowchart



450x350mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 Pag. 1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 Pag. 5	Explain the scientific background and rationale for the investigation being reported
Objectives	3 Pag. 5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 Pag. 6	Present key elements of study design early in the paper
Setting	5 Pag. 6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 Pag. 6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 Pag. 8-10	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* Pag. 7-8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 Pag. 10	Describe any efforts to address potential sources of bias
Study size	10 Pag. 6	Explain how the study size was arrived at
Quantitative variables	11 Pag. 8-10	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 Pag. 10	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed

	Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The DIADEMA Study- Prevalence of depression in patients with Type 2 Diabetes Mellitus: Results from the MADiabetes Cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020768.R1
Article Type:	Research
Date Submitted by the Author:	13-Mar-2018
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Mental health, Epidemiology
Keywords:	Depression, Diabetes Mellitus, Type 2, Self-Care, Cohort Studies

The DIADEMA Study- Prevalence of depression in patients with Type 2 Diabetes Mellitus: Results from the MADiabetes Cohort.

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1. Abstract

Objective: To estimate the prevalence of depression in patients diagnosed with type 2 diabetes mellitus (T2DM), and to identify sociodemographic, clinical, and psychological factors associated with depression in this population. Additionally, we examine the annual incidence rate of depression among T2DM patients.

Methods: We performed a large prospective cohort study of patients with T2DM from MADIABETES Study. The first recruitment drive was included 3,443 patients. Aa second recruitment drive included 727 new patients. Data have been collected since 2007 (baseline visit) and annually during the follow-up period (since 2008).

Results: Depression was prevalent in 20.03% of patients (n=592; 95%CI, 18.6 to 21.5), and was associated with previous personal history of depression (OR, 6.482; 95%CI, 5.138 to 8.178), mental health status below mean (OR, 1.423; 95%CI, 1.452 to 2.577), neuropathy (OR, 1.951; 95%CI, 1.423 to 2.674), fair or poor self reported health status (OR, 1.509; 95%CI, 1.209 to 1.882), treatment with oral antidiabetic agents plus insulin (OR, 1.802; 95%CI, 1.364 to 2.380), female gender (OR, 1.333; 95%CI, 1.009 to 1.761), and blood cholesterol level (OR, 1.005; 95%CI, 1.002 to 1.009).

The variables inversely associated with depression were: being in employment (OR, 0.595; 95%CI, 0.397 to 0.894), low physical activity (OR, 0.552; 95%CI, 0.408 to 0.746), systolic blood pressure (OR, 0.982; 95%CI, 0.971 to 0.992), and social support (OR, 0.978; 95%CI, 0.963 to 0.993). In patients without depression at baseline, the incidence of depression after one year of follow-up was 1.20% (95%CI, 1.11 to 2.81).

Conclusions: Depression is very prevalent among patients with T2DM and is associated with several key diabetes-related outcomes. Our results suggest that previous mental status, self reported health status, gender and several diabetes-related complications are associated with differences in the degree of depression. These findings should alert practitioners to the importance of detecting depression in patients with T2DM.

Strengths and limitations of this study

- Time between both telephone interviews for depression screening was too short (12 months), making it difficult to compare cumulative incidence rates with those other studies.
- We preferred to exclude antidepressant agents from our combined variable for depression, because the antidepressants can be prescribed for diseases other than depression (i.e., sleeping disorders, migraine, neuropathic pain, obsessive-compulsive disorders, anxiety/panic disorderIn order to compare our findings with multivariable models from different studies, we may have adjusted variables unnecessary. However, fortunately, over-adjustment was avoided (changes >20% between crude and adjusted SE, data not shown).
- The strengths of our study include its prospective design, which ensured that measurement of risk factors preceded the development of depression, and the assessment of information on potentially confounding variables, which reduces potential selection and confusion biases.
- We also used an assessment of depression based on MINI 5.0, which was completed with the patient's general practitioner clinical who used his/her clinical judgment to determine whether the patient's symptoms and signs were compatible with a depressive disorder. Therefore, self-reported diagnosis was avoided.

Keywords: Depression; Diabetes Mellitus, Type 2; Self-Care; Cohort Studies.

1. Introduction

Currently, an estimated 8%-9% adults worldwide have type 2 diabetes mellitus (T2DM), and a substantial increase in prevalence over time has been observed (1). The prevalence of T2DM in the Spanish population is even higher (13.8%) (2).

Previous studies have shown that coexistence of mental disorders such as depression is considerably more frequent in people with T2DM than in the overall population (3) (4), with an prevalence ranging from 15% to 24% (5) and an incidence rate of depression during the first year after initiation of oral antidiabetic treatment of 12.61 per 1000 person-years (6). The coexistence of diabetes and mental disorders has a strong impact on the patient, with an increased risk of cardiovascular disease, all-cause mortality (7) and cardiovascular mortality (7), especially as a result of cardiovascular complications of T2DM (8). In addition, patients with diabetes and mental disorders show poorer compliance with treatment recommendations than T2DM patients without depression, and more frequently have cardiovascular risk factors such as smoking, obesity, sedentary lifestyle, and poor glycemic control (9), which can impact on their health-related quality of life (10).

To our knowledge, research on common mental disorders affecting patients with T2DM is scarce in Spain (11) (12) (13). In a recent cross-sectional study on patients with T2DM, Alonso-Morán et al. (14) reported that 9.8% of patients were diagnosed with depression (5.2% for males and 15.1% for females), and in a study by Nicolau et al. (12), 27.2% of patients had symptoms of depression. However, in these studies, data collection was often based on health surveys (11) (15) or self-reported scales (12,16), which yielded heterogeneous data. Thus, mental disorders have not been assessed using a clinical interview as the “gold standard”.

The aims of the present study were to estimate the prevalence of depression in patients diagnosed with T2DM, and to identify sociodemographic, clinical, and psychological factors associated with the occurrence of depression in this population. Additionally, we examine the one-year incidence rate of depression among T2DM patients.

2. Material and Methods

2.1. Design and participants

The Madrid Diabetes Study (MADIABETES Study), is a large prospective cohort study of various clinical and psychosocial aspects of outpatients with T2DM living in the metropolitan area of Madrid, Spain. The first recruitment drive was in 2007 and enrolled 3,443 T2DM outpatients from the 56 participating primary health care centers (PHCC). Patients were selected by simple random sampling by participating general practitioners (n= 131) based on the list of patients with a diagnosis of T2DM in their computerized clinical records (CCR). A more complete description of this methodology can be found elsewhere (17).

Reasons for not continuing till completion were leaving the participating PHCC, death or drop-out. Furthermore, the dynamic character of MADIABETES cohort, i.e. new participants could enter over time, helped prevent loss of the study population. Therefore, at the end of 2010, a second recruitment drive involving 41 PHCC included 727 new patients.

The inclusion criteria were: a diagnosis of T2DM in the CCR (code T90 of the International Classification of Primary Care [ICPC-2]) (18), age ≥ 30 years, visit to a PHCC at least twice in the previous year, and agreement to take part in the study and provided written informed consent. Patients were excluded for the following reasons: diagnosis of gestational diabetes mellitus, being in an institution, inability to understand Spanish, severe chronic diseases or significant physical or psychological disabilities that might invalidate informed consent or interviews (according to clinical judgment), legal incompetence or legal guardianship, and participation in clinical trials.

For the purpose of evaluating the prevalence of depression (DIAbetes and DEpression in MAdrid-DIADEMA Study), we included those patients who participated in the interview process conducted between January 1st 2011 and 31th December 2011. Furthermore, to estimate the annual incidence of depression, the data from the second interview were included. The original protocol of the study was published in advance (19). Therefore, for the

main variable the MADIABETES cohort included a total of 2,955 patients (see the flow diagram in Figure 1).

2.2. Patient and Public Involvement

Major depression is prevalent among patient with diabetes, especially older adults, and is a risk factor for self-care, complications and death. Therefore, our research question focuses on screening for depressive symptoms in all patients with diabetes, with particular emphasis on those with a self-reported history of depression. We use age-appropriate depression screening measures and are aware that further evaluation will be necessary for individuals with a positive result. Treatment is prescribed accordingly.

Patients were not involved in the design, recruitment or conduct of the study. We report our results annually at specific meeting, to which we invited the participating general practitioners and all the patients included in the MADIABETES Cohort.

2.3. Source of data

To achieve the goal of the MADIABETES Study, data began to be collected in 2007 (baseline visit) and then annually during the follow-up period (since 2008). Four data collection strategies were combined.

First, data concerning disease episodes (coded in ICPC-2) (18), prescription of medication (coded according to the Anatomical Therapeutic Chemical classification system), laboratory results, anthropometric variables, and use of care facilities were obtained from the CCR. The CCR for primary health care in the Madrid Health Service was administered by OMI-AP© software. CCR registration is continuously updated in the PHCC under routine clinical practice conditions, and once a year, data are transferred to our central database.

Second, the general practitioner of each participating patient collected information about morbidity and mortality, under routine clinical practice conditions using an electronic case report form (hosted on the website www.madiabetes.com. All general practitioners received

training to standardize their knowledge of project objectives, data collection techniques and field work procedures.

Third, from 2011 onward, all patients were invited each year to undergo an interview to provide sociodemographic data, lifestyle data, determinants of health, and psychosocial characteristics. Data were collected using a previously standardized protocol through a telephone interview with a clinical psychologist trained in the evaluation procedure of the study. Lastly, the vital status of the patients was ascertained from two mortality records: *Índice Nacional de Defunciones* (https://www.msssi.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/IND_TipoDifusion.htm) and *Instituto Nacional de Estadística* (http://www.ine.es). The latter indicates the underlying cause of death recorded on the death certificates, which is coded according to the International Classification of Diseases, Tenth Revision (20).

2.4. Variables

The primary outcome variable was depression. The diagnosis of depression was considered a combined variable, as suggested by other authors (21), consisting of a diagnosis based on the module of major depressive disorder of the International Neuro-psychiatric Interview (MINI 5.0.0) (22), The interview was applied by a trained psychologist, and the diagnosis was made with the patient's general practitioner clinical who used his/her clinical judgment to determine whether the patient's symptoms and signs were compatible with a depressive disorder.

The MINI is a short and efficient diagnostic interview to diagnose mental disorders, which was used in its Spanish version (23).

The other *psychosocial variables* evaluated included the following:

- A personal history of psychiatric disorder if the patient reported a positive response to the question: "Has a clinician ever diagnosed you as having any psychiatric disorder?. Alternatively,

patients could have been diagnosed with a psychiatric disorder before the last 12-month interval, as coded in the CCR.

- A family history of psychiatric disorder was registered if the patient reported a positive response to the question: "Has any family member (first-degree relatives) ever been diagnosed with a psychiatric disorder?"

- Anxiety disorder was defined based on the module of generalized anxiety disorder of the MINI (23) and according to clinical judgment.

- Social support, such as network size, was assessed based on the question: "About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?", which corresponds to the first item of the Medical Outcomes Study-Social Support Survey (MOS-SSS) (24).

- Health-related quality of life was measured using the SF-12 questionnaire, a composite of 12 items that assess eight dimensions of health: physical functioning, role-physical, general health, bodily pain, vitality, social functioning, role-emotional, and mental health (25). The SF-12 measures various aspects of physical and mental health, from which physical and mental summary scores are computed using the scores of 12 questions. The score ranges from 0 to 100, where a zero score indicates the lowest level of health and 100 indicates the highest level of health. Both Physical and Mental Health Composite Scales combine the 12 items in such a way that they compare with a national norm (mean score of 50.0 and a standard deviation of 10.0).

-Insomnia was assessed using the Spanish version of the eight-item Athens Insomnia Scale (AIS-8) (26) which is a self-reported questionnaire designed to measure the severity of insomnia based on the diagnostic criteria of the ICD-10 Classification of Mental and Behavioural Disorders.

Sociodemographic variables included age (date of birth), gender, nationality, length of residence in Spain, marital status (single, unmarried partners, married, divorced, widowed),

educational level (no studies, primary, high school, university), and employment status (employed, unemployed, retired, housewife and other).

Medical variables included the following:

- Comorbidity variables: hypertension, defined as systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg; heart failure, which was defined as symptoms of dyspnea or edema associated with bilateral rales, elevated venous pressure, or interstitial or alveolar edema on chest X-ray, and required the addition of diuretics or inotropic medications; myocardial infarction, defined as a history of chest pain/discomfort associated with elevation of ST segment in electrocardiographic in two or more contiguous leads and elevation of myocardial enzymes; stroke, defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function that lasted more than 24 hours; peripheral artery disease, defined as a symptomatic and documented obstruction of the distal arteries of the leg; low limb amputations, defined as the complete loss in the transverse anatomical plane of any part of the lower limb; erectile dysfunction, defined as the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance; retinopathy, defined as a documented diagnosis by an ophthalmologist of non-proliferative retinopathy, proliferative retinopathy or macular edema; nephropathy, defined as a history of renal disease due to diabetes mellitus or requiring dialysis; neuropathy, defined as diminished or lack of perception of touch or pain stimuli and loss of joint position sense and vibration sense, and renal failure, defined as an estimated glomerular filtration rate below 30 mL/1.73 m^2. Cardiovascular disease (CVD) was defined as one or more of the following: myocardial infarction, stroke or peripheral vascular disease.
- Other clinical variables: duration of diabetes (years) and family history of diabetes (in the first-degree relatives).

- Anthropometric variables: height, weight, body mass index (BMI), hip circumference, waist circumference, systolic blood pressure, and diastolic blood pressure.
- Laboratory results: albuminuria, creatinine, lipid profile, HbA1c and glucose.
- Personal health habits: 1. Smoking (never, former or current smoker). 2. Physical activity level which was measured using a short questionnaire based on the FAO/WHO/UNU Expert Consultation Report Energy and Protein Requirements (Geneva, 1985) and administered individually at a medical examination. The answers were coded from 1 to 3, with 1 representing inactivity or sedentary activity (remaining seated or at rest most of the time, sleeping, resting, sitting or standing, walking on flat ground, light housework, playing cards, sewing, cooking, studying, driving, typing, office duties, etc.), 2 representing low activity (walking at 5 km/h, heavy housework [cleaning windows, etc.], jobs such as carpenter, construction workers [except hard work], chemical industry, electrical, mechanized agricultural tasks, playing golf, child care, etc.), and 3, moderate or vigorous activity (non-mechanized agricultural tasks, mining, forestry, digging, chopping wood, hand mowing, climbing, mountaineering, playing football, tennis, jogging, dancing, skiing, etc.). 3. Drinking (0.1 through 4.9, or 5.0 or more g/d of alcohol).
- Treatment: statins, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, antiplatelet drugs, antidiabetics, antidepressant drugs and anxiolytics.

2.5. Statistical analysis

Quantitative variables were expressed as mean and standard deviation; qualitative variables were expressed as frequency distribution. Normally distributed continuous variables were compared using the *t* test, non-normally distributed variables were compared using the Mann-Whitney test, and categorical variables were compared using the chi-square test. Effect sizes

were calculated using Cohen's d for continuous measures and Cramer's V for categorical variables.

Given the hierarchical structure of our data, we used a logistic regression analysis with two levels: level 1, patients, and level 2, health centers (our sampling unit). However, in the initial step (null model), the variation in the prevalence of depression between centers was not significant ($\sigma 2u0 = 0.02$, SE = 0.02, $p = 0.115$), with an intraclass correlation coefficient of 0.007; therefore, we did not consider it necessary to adjust for a hierarchical model.

Explanatory multivariable logistic regressions models were constructed to identify variables that were independently associated with depression (prevalent). We report adjusted odds ratios (ORs) with their respective 95% confidence intervals (95%CIs). Variables that were statistically significant in the bivariate analysis and those shown to be predictors in previous studies were included in the multivariate analysis. We analyzed the possibility of over-adjustment, defined when after adjusting on the covariate it altered the adjusted OR of 10%–20% with a concomitant change in the standard error (SE) higher than 20%.

The annual incidence rate of depression was calculated by the standard method as follows: number of new cases of depression over a period (year 2011) / population at risk of developing the disease at the beginning of the period.

In all cases, the accepted level of significance was 0.05 or less, with a 95%CI. Data were processed using the Statistical Package for the Social Sciences (SPSS for windows, version 21.0; IBM Corp, Armonk, New York, USA).

2.6. Ethical aspects

The study was approved by the Institutional Review Board of Ramón y Cajal Hospital (Madrid) and conducted in accordance with the principles of the Declaration of Helsinki. All patients gave their written informed consent to participate in the study.

3. Results

3.1. Characteristics of the study population and prevalence of depression

A total of 3,443 patients were included in the study at the first recruitment drive (January 2007). Of these 3,217 were alive before the start of the survey (January 2013), and 2,228 agreed to the interview (participation rate: 69.3%). At the second recruitment, 727 patients agreed to participate (December 2010). Therefore, for the main objective of this study, the sample consisted of 2,955 people; 48.1% were women and the mean age was 70.2 years (SD 10.6).

Depression was prevalent in 20.03% (n=592; 95%CI, 18.6 to 21.5) Table 1 shows the characteristics of the sample, stratified by depression status.

Compared with patients without depression, people with depression were more likely to be female (<0.001), older (p=0.017), and widowed or divorced (p<0.001). They also, had a lower educational level (p<0.001), were less frequently classified as employed (p<0.001), and had been taking more intense diabetes treatment for longer (p=<0.001). Furthermore, patients with depression had higher BMIs (p<0.001), were lower consumers of alcohol (p<0.001), and had higher rates of never smoking (p<0.001), sedentary lifestyle (p<0.001), neuropathy (p<0.001), and renal failure (p=0.012). Anxiety was recorded in 14.8% of the sample (n= 438; 95%CI, 13.5 to 16.1). Coexistence of depression and anxiety was recorded in up to 8.6% (n=255) of the patients.

In addition, patients with depression more frequently had previous episodes of depression (p<0.001) and anxiety (p<0.001), and fair or poor self-reported health status (p<0.001) than patients without these disorders. No significant differences were observed between patients with depression and psychologically healthy subjects in the following: family history of diabetes, level of HbA1c, triglycerides values, nephropathy, and retinopathy.

Table 1. Baseline characteristics of the sample, with and without depression.

	TOTAL (n=2,955)	With depression (n=592)	Without depression (n=2,363)	p value	Effect size*
Sociodemographic variables					
Gender (female); % (n)	48.1 (1,421)	67.7 (401)	43.02 (1,020)	<0.001	0.197†
Age (years); mean (SD)	70.2 (10.6)	71.1 (10.3)	69.9 (10.7)	0.017	0.110‡
Country of origin (foreign-born); % (n)	2.4 (70)	2.9 (17)	2.2 (53)	0.368	0.017†
Marital status; % (n)				<0.001	0.123†
Single without partner	4.6 (136)	2.7 (16)	5.1 (120)		
Married or with partner	70.4 (2,077)	62 (366)	72.5 (1,711)		
Divorced	4.2 (124)	5.9 (35)	3.8 (89)		
Widowed	20.8 (614)	29.3 (173)	18.7 (441)		
Educational level; % (n)				<0.001	0.081†
Not completed	20.9 (613)	25.7 (152)	19.5 (461)		
Primary	46.7 (1,367)	48.6 (288)	46.7 (1,104)		
Secondary	19.7 (576)	16.4 (97)	20.3 (479)		
University	12.8 (374)	9.3 (55)	13.5 (319)		
Employment status; n (%)					
Employed	15.7 (459)	9.5 (56)	17 (403)	<0.001	0.084†
Variables related to diabetes					
Duration of diabetes (years); mean (SD)	15.4 (10.2)	16.5 (10.6)	15.06 (10)	0.002	0.143‡
Family history of diabetes (yes); % (n)	61.7 (1,813)	64.5 (382)	61.3 (1,448)	0.145	0.027†
Type of diabetes treatment; % (n)				<0.001	0.121†
Only diet	8.4 (248)	7.4 (44)	8.6 (204)		
Oral antidiabetic agents	53.2 (1,572)	47.3 (280)	54.7 (1,292)		
Insulin	5.4 (159)	6.9 (41)	5 (118)		
Oral antidiabetic agents + insulin	16.9 (498)	25.2 (149)	14.8 (349)		
Not specified	16.2 (478)	13.2 (78)	16.9 (400)		
Lifestyle and self-care					
Smoking habit; % (n)				<0.001	0.127†
Never smoker	46 (1,360)	58.6 (347)	42.9 (1,013)		
Ex-smoker	42.6 (1,259)	32.1 (190)	45.2 (1,069)		
Smoker	11.4 (336)	9.3 (55)	11.9 (281)		
Current regular alcohol use; % (n)	883 (33.6)	22 (111)	36.4 (772)	<0.001	0.120†
Physical activity; % (n)				<0.001	0.117†
Sedentary	11.3 (333)	18.4 (109)	9.5 (224)		
Low	81.5 (2,408)	76.5 (453)	82.7 (1,955)		
Moderate-vigorous	7.2 (214)	5.1 (30)	7.8 (184)		
Clinical risk factors					
BMI (kg/m^2); mean (SD)	31.1 (5.6)	32.4 (6.4)	31.2 (5.8)	<0.001	0.196‡
Systolic blood pressure (mmHg); mean (SD)	131.5 (12.6)	129.3 (12.6)	131.9 (11.9)	<0.001	0.208‡
Diastolic blood pressure (mmHg); mean (SD)	73.9 (7.5)	73.3 (7.6)	74.2 (7.4)	<0.001	0.120‡
Biochemical risk factors					
HbA1c (%); mean (SD)	7.1 (1.1)	7.1 (1.2)	7.3 (1.5)	0.703	0.110‡
Triglycerides; mean (SD)	142.4 (87.6)	148.9 (89.7)	140.7 (86.9)	0.070	0.092‡
Cholesterol; mean (SD)	175.7 (33.9)	181.1 (37.1)	174.3 (32.9)	<0.001	0.194‡
LDL-cholesterol; mean (SD)	99.2 (27.3)	101.6 (29.9)	98.3 (27.1)	0.064	0.115‡
HDL-cholesterol; mean (SD)	49.5 (13.2)	50.6 (12.9)	49.1 (13.3)	0.032	0.114‡
Complications and comorbidities					
Cardiovascular event; % (n)	29.7 (1,240)	31.9 (212)	29.3 (1,028)	0.178	0.021†
Heart failure; % (n)	11.5 (480)	13.7 (91)	11.1 (389)	0.053	0.030†
Lower limb amputation; % (n)	1.4 (60)	1.8 (12)	1.4 (48)	0.385	0.013†
Nephropathy; % (n)	13.5 (400)	16.2 (96)	12.9 (304)	0.033	0.039†
Neuropathy; % (n)	10.1 (299)	16.7 (99)	8.5 (200)	<0.001	0.111†
Retinopathy; % (n)	15 (442)	15.7 (93)	14.8 (349)	0.566	0.011†
Renal failure; % (n)	14.3 (424)	17.6 (104)	13.5 (320)	0.012	0.046†
Psychosocial variables					
Family history of depression (Yes); % (n)	197 (6.7)	10.6 (63)	5.7 (134)	<0.001	0.080†
Personal history of depression (Yes); % (n)	557 (18.8)	48.6 (288)	11.4 (269)	<0.001	0.381†
Self-reported health status (Fair or poor); % (n)	34.3 (992)	47 (269)	31.1 (723)	<0.001	0.133†
Physical quality of life; mean (SD)	40.1 (11.4)	35.3 (12.5)	41.5 (10.7)	<0.001	0.533‡
Mental quality of life; mean (SD)	47.4 (10.9)	41.3 (12.5)	49.1 (9.7)	<0.001	0.697‡
Social support (network size); mean (SD)	10.2 (8.3)	8.5 (7.3)	10.6 (8.5)	<0.001	0.217‡
Sleep (AIS); mean (SD)	2.6 (3.7)	5.3 (5.2)	2 (2.9)	<0.001	0.783‡

BMI, body mass index; AIS, Athens Insomnia Scale; HbA1c, glycated haemoglobin; †Cramer's V; ‡Cohen's d; *0.2 is the recommended minimum effect size; Cardiovascular event, includes nonfatal myocardial infarction, stroke, and peripheral artery disease.

3.2. Factors associated with prevalent depression

Table 2 shows the variables associated with depression after fully adjustment for potential confounding factors. The variable most strongly associated with depression was previous personal history of depression (OR, 6.482; 95%CI, 5.138 to 8.178; p=≤0.001), followed by neuropathy (OR, 1.951; 95%CI, 1.423 to 2.674; p≤0.001), treatment with oral antidiabetic agents plus insulin (OR, 1.802; 95%CI, 1.364 to 2.380; p≤0.001), fair or poor self reported health status (OR, 1.509; 95%CI, 1.209 to 1.882; p≤0.001), mental health score (SF-12) below the mean (OR, 1.423; 95%CI, 1.054 to 1.921; P=0.021), ≤female gender (OR, 1.333; 95%CI, 1.009 to 1.761; p=0.043), and blood cholesterol level (OR, 1.005; 95%CI, 1.002 to 1.009; p=0.002).

On the other hand, the variables inversely associated with depression were: being employed (OR, 0.595; 95%CI, 0.397 to 0.894; p=0.012), low physical activity (OR, 0.552; 95%CI, 0.408 to 0.746; p=<0.001), systolic blood pressure (OR, 0.982; 95%CI, 0.971 to 0.992; p=0.001), current alcohol use (OR, 0.726; 95%CI, 0.552 to 0.954) and social support (network size) (OR, 0.978; 95%CI, 0.962 to 0.993; p=0.005).

Table 2. Factors associated with prevalence of depression (logistic regression analysis)

(Hosmer-Lemeshow= 5.132; df=5; p=0.743)

	OR	95% CI	P-value
Gender			
Male	1		
Female	1.333	1.009-1.761	0.043
Age			
<65 years	1		
≥65 years	0.858	0.626-1.175	0.339
Duration of T2DM (y)[per unit of increment]	1.006	0.995-1.016	0.303
Educational level			
University	1		
Secondary	0.980	0.644-1.493	0.926
Primary	1.060	0.729-1.543	0.759
Not completed	1.118	0.735-1.699	0.602
Country of origin			
Spain	1		
Other	1.433	0.738-2.784	0.288
Employment status			
Not working	1		
Working	0.595	0.397-0.894	0.012
Smoking			
Never smoker	1		
Former smoker	0.854	0.652-1.119	0.252
Current smoker	0.874	0.585-1.306	0.510
Family history of DM			
No	1		
Yes	1.109	0.888-1.385	0.362
Current Alcohol use			
No	1		
Yes	0.726	0.552-0.954	0.022
Physical activity			
Sedentary	1		
Low	0.552	0.408-0.746	<0.001
Moderate-Vigorous	0.636	0.377-1.074	0.091
Diabetes treatment			
Oral antidiabetic agents	1		
Oral antidiabetic agents + insulin	1.802	1.364-2.380	<0.001
Insulin	1.476	0.938-2.323	0.092
Diet	0.932	0.623-1.394	0.731
Unknown	0.771	0.560-1.061	0.110
BMI (kg/m^2)[per unit of increment]	1.012	0.992-1.032	0.249
Systolic BP (mmHg)[per unit of increment]	0.982	0.971-0.992	0.001
Diastolic BP (mmHg)[per unit of increment]	0.992	0.974-1.009	0.358
Cholesterol (mg/dl) [per unit of increment]	1.005	1.002-1.009	0.002
Neuropathy			
No	1		
Yes	1.951	1.423-2.674	<0.001
Nephropathy			
No	1		

	Yes	1.077	0.782-1.483	0.649
Retinopathy				
	No	1		
	Yes	0.784	0.578-1.065	0.119
Renal failure				
	No	1		
	Yes	1.220	0.892-1.670	0.214
Self-reported health status				
	Excellent-very good-good	1		
	Fair-poor	1.509	1.209-1.882	<0.001
Family history of depression				
	No	1		
	Yes	1.419	0.975-2.066	0.067
Personal history of depression				
	No	1		
	Yes	6.482	5.138-8.178	<0.001
Social support (network size)[per unit of increment]		0.978	0.962-0.993	0.005
Physical health score (SF-12)				
	Score ≥ mean	1		
	Score < mean	1.243	0.910-1.699	0.171
Mental health score (SF-12)				
	Score ≥ mean	1		
	Score < mean	1.423	1.054-1.921	0.021
History of cancer				
	No	1		
	Yes	0.961	0.716-1.290	0.792
Cardiovascular disease				
	No	1		
	Yes	1.156	0.901-1.482	0.255
Heart failure				
	No	1		
	Yes	1.297	0.910-1.849	0.150
Lower limb amputation				
	No	1		
	Yes	1.765	0.798-3.904	0.160

3.3. Incidence of depression and predictive factors

During a median 12 months follow-up, 28 patients, without depression at baseline, developed an incident episode of depression, that is an annual incidence of 1.2% (95%CI, 1.11 to 2.81). There were differences by gender: 0.6% (95%CI, 0.13 to 1.07) in men and 2% (95%CI, 1.11 to 2.81) in women (p=0.002. Female gender was the variable most strongly associated with incidence of depression (OR, 2.620; 95%CI, 1.129 to 6.083); p=0.025). Other variables inversely associated with incidence of depression were: low physical activity (OR, 0.334; 95%CI, 0.136 to 0.818; p=0.018), diastolic blood pressure (pear each unit of increment) (OR, 0.937; 95%CI, 0.887 to 0.988; p=0.017), and social support (network sie) (OR, 0.875; 95% CI, 0.797 to 0.962;p=0.006).

Of the 592 patients initially identified as depressed, 394 (66.66%) had no symptoms or signs of depression after 1-year of follow-up, and 198 (33.33%) persisted with symptoms.

4. Discussion

The association between diabetes and depression has been well-known for at least three decades (4). The prevalence of depression in people with T2DM varies widely owing to circumstances such as differences in the methods used to assess depression (clinical interviews, questionnaires, self-report scales, and medical records), sample origin (clinical or outpatient screening), ethnic subgroups, gender composition, and age intervals. Two meta-analyses reported an overall prevalence of depression ranging from 17.6% to 27% (4). We analyzed the prevalence of depression in a cohort of patients with T2DM from the city of Madrid based on a clinical interview completed with prescribing and clinical data from CCR. Depression was prevalent in 20.03% (n=592; CI 95%, 18.6 to 21.5) of our sample, a finding that is lower than the 27.2% reported in primary-care settings and a hospital endocrinology department in Mallorca (Spain) using the Beck Depression Inventory as the screening tool (12). These findings are worrying, given the adverse impact of depression on the natural history of

T2DM, which takes the form of poor metabolic control (27), non-adherence to treatment (28,29), and increased risk of vascular complications (8) .

Poor social support and negative life events (i.e., adverse socioeconomic circumstances, death of relatives) have been associated with depression in people with T2DM (30). These two factors are more frequent in women (31) (32), thus explaining the predominance of depression among females, as reported by the vast majority of studies (33) (34). However, not all the studies have confirmed this hypothesis (35).

After adjusting for gender and other known risk factors, our findings show that the association with depression was reduced by 2.2% per unit of increment of network size. Similarly, the association with depression could be reduced by physical activity, as we found in patients with low physical activity compared with a sedentary lifestyle (OR, 0.552; 95%CI, 0.408 to 0.746;p≤0.001). However, we did not demonstrate a similar benefit in those who undertake moderate or vigorous physical activity. This phenomenon could be explained by the fact that very few had a high level of activity.

General practitioners should be encouraged to implement strategies designed to reduce the risk of depression in patients with T2DM, especially in those at high-risk of depression owing to exposure to chronic psychosocial stressors (29).

We found an inverse association between low physical activity and social support and depression. While this association does not necessarily imply a causal relationship, it might encourage the implementation of physical activity programs and the creation of support groups focused on psychological well-being and detection of depressive symptoms. Some of these suggestions have proven to be effective and feasible in older populations (36).

On the other hand, it is necessary to bear in mind that treatment of depression can be a prerequisite for good diabetes control because people with diabetes might follow their treatment plan more easily if their mood is improved first (37).

Other predictive factors of depression such as a previous depressive episode or family history of depression are not modifiable factors for reducing the risk of developing depression. However, health professionals must be alert to the presence of early symptoms of depression in order to treat this condition promptly. Indeed, routine screening for psychosocial problems such as depression is supported in well-conducted cohort studies (38). In this sense, screening for depression with questionnaires is insufficiently specific and needs to be complemented by a formal clinical assessment to confirm the diagnosis (37).

Being in employment was inversely associated with depression (OR, 0.595; p= 0.012), as shown elsewhere (39). This aspect suggests that going to work might have a protective role against depression owing to the social support received from co-workers.

Of the classic complications of diabetes, neuropathy was the only one significantly associated with depression (OR, 1.951;p≤0.001). Nephropathy, renal failure, heart failure, CVD, and lower limb amputation tended to have a positive association with depression. However, other studies have shown a significant and consistent association between complications of diabetes and depressive symptoms (8) As it was logical to suppose, subjects with depression had lower values in the mental health component score obtained from the SF-12, as reported elsewhere (40).

Consistent with other studies (41,42), we found that participants with depression self-rated their health status significantly lower than those without depression. Given the known relationship between fair/poor perceived health status and mortality (43), especially in patients with chronic diseases (44), it would be advisable for patients with poor self-rated health to be enrolled in a health coaching program similar to that used in the Royal North Shore Hospital, Sydney, Australia (45). In this program, patients with diabetes who had the lowest self-reported health status at baseline improved their rating in the first question of the Short-Form 36 Quality of Life Instrument (SF-1) from 4.4 to 3.7 (P≤ 0.001), and improved their

knowledge of diabetes. Their distress levels decreased significantly with respect to baseline values.

Medications for lowering blood sugar (insulin plus oral anti-diabetic agents) were significantly associated with depression (OR, 1.802; p≤0.001). Prior studies have highlighted the same phenomenon: the glucose-lowering therapies that include insulin are strongly associated with depression (46). Two different factors could explain this association: first, the implementation of insulin therapy requires painful injections and frequent glucose measurements, thus increasing stress and favoring the onset of a depressive episode in old age (47); second, since insulin is usually necessary for situations of poor glycemic control, it could be that non-optimal control of diabetes leads to worsening of mood, greater stress, and less life-satisfaction.

As for the incidence of depression after one year of follow-up, the present study reveals a value of 1.20% which is similar to that reported in the ZARADEMP Spanish Study (48), but lower than reported in other countries (5, 49-51). A possible explanation for this result could be that, compared with other European countries, the greater number of hours of sunlight in Spain protect against depression (50). In a meta-analysis (51) that evaluated 16 studies to analyze the relationship between diabetes and depression, the cumulative incidence of depression among people with diabetes ranged from 11.9%, after two years of follow-up, (52) to 23.5%, after 5.9 years of follow-up (53). The conclusion of the meta-analysis (54) is that there is evidence to support the hypothesis that diabetes is a ‘‘depressogenic’’ condition. This affirmation implies a real public health problem that may be resolved only by a specific prevention strategy.

4.1. Conclusions

Depression is very prevalent among patients with T2DM and it is associated with several key diabetes-related outcomes. Our results suggest that previous mental status, self-reported health status, and some diabetes-related complications are associated with differences in the degree of depression. We also found sex-related differences with respect to the prevalence of

depression. Our study shows that the risk of depression could be reduced by physical activity and social support. These findings should alert practitioners to the importance of detection of depression in patients with T2DM, and to the need to reduce the risk of depression with prevention programs focused on improving the physical activity of the patients and the creation of support groups. Our findings also suggest that the annual incidence rate of depression is low and that a high proportion of patients with T2DM who experience depression achieved full remission after one year of follow-up.

Acknowledgements

The authors thank to all health professionals of Primary Health Care of Madrid who have made its development possible.

Contributor Ship Statement

CBL and MASF designed the study and got funding. JCV, PGC, JCAH, RCM and DBV contributed to select the patients sampling by participating general practitioner, to data collection and combined the data collection strategies in a single database. FJSR, CBL, PGC and MASF analysed the data. PGC, MASF, and JMDY wrote the initial draft of the paper. RJG, ALA, CBL and ECS were involved in further drafting of the paper. All authors participated in interpreting the data, revising the paper for critically important intellectual content and gave final approval of the submitted version.

Data Sharing Statement

No additional data are available

Funding

This study forms part of research funded by the FIS (Fondo de Investigaciones Sanitarias—Health Research Fund, Instituto de Salud Carlos III) grants no.: PI10/02796, PI12/01806 and PI15/00259 and co-financed by the European Union through the Fondo Europeo de Desarrollo Regional (FEDER, "Una manera de hacer Europa").

The members of the MADIABETES Group are as follows : AM Sobrado-de Vicente-Tutor; Mar Sanz-Pascual; M Arnalte-Barrera; S Pulido-Fernández; EM Donaire-Jiménez; C Montero-Lizana; M Domínguez-Paniagua; P Serrano-Simarro; R Echegoyen-de Nicolás; P Gil-Díaz; I Cerrada-Somolinos; R Martín-Cano; A Cava-Rosado; T Mesonero-Grandes; E Gómez-Navarro; A Maestro-Martín; A Muñoz-Cildoz; ME Calonge-García; M Martín-Bun; P Carreño-Freire; J Fernández-García; A Morán-Escudero; J Martínez-Irazusta; E Calvo-García; AM Alayeto-Sánchez; C Reyes-Madridejos; MJ Bedoya-Frutos; B López-Sabater; J Innerarity-Martínez; A Rosillo-González; AI Menéndez-Fernández; F Mata-Benjumea; P Vich-Pérez; C Martín-Madrazo; MJ Gomara-Martínez; C Bello-González; A Pinilla-Carrasco; M Camarero-Shelly; A Cano-Espin; J Castro Martin; B de Llama-Arauz; A de Miguel-Ballano; MA García-Alonso; JN García-Pascual; MI González-García; C López-Rodríguez; M Miguel-Garzón; MC Montero-García; S Muñoz-Quiros-Aliaga; S Núñez-Palomo; O Olmos-Carrasco; N Pertierra-Galindo; G Reviriego-Jaén; P Rius-Fortea; G Rodríguez-Castro; JM San Vicente-Rodríguez; ME Serrano-Serrano; MM Zamora-Gómez; and MP Zazo-Lázaro.

Competing interests

The authors declare that there is no duality of interest associated with this manuscript.

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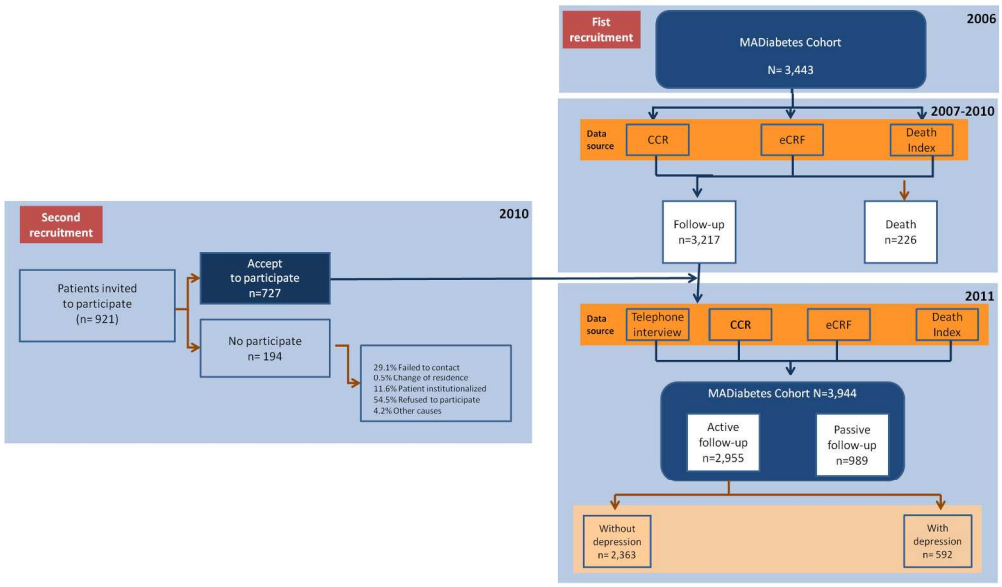
Figure 1- Flowchart



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 Pag. 1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 Pag. 5	Explain the scientific background and rationale for the investigation being reported
Objectives	3 Pag. 5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 Pag. 6	Present key elements of study design early in the paper
Setting	5 Pag. 6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 Pag. 6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 Pag. 8-10	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* Pag. 7-8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 Pag. 10	Describe any efforts to address potential sources of bias
Study size	10 Pag. 6	Explain how the study size was arrived at
Quantitative variables	11 Pag. 8-10	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 Pag. 10	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed

	Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The DIADEMA Study- Prevalence of depression in patients with Type 2 Diabetes Mellitus in Spain: Results from the MADiabetes Cohort.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020768.R2
Article Type:	Research
Date Submitted by the Author:	23-May-2018
Complete List of Authors:	SALINERO-FORT, MIGUEL; Servicio Madrileño de Salud, Gerencia de Atención Primaria GÓMEZ-CAMPELO, PALOMA; Fundación Investigación Biomédica Hospital Universitario La Paz, IdiPAZ; Universidad Antonio de Nebrija Ciencias de la Salud, Centro de Ciencias de la Salud San Rafael San Andrés-Rebollo, Javier; Servicio Madrileño de Salud Cárdenas-Valladolid, Juan; Comunidad de Madrid Servicio Madrileno de Salud ABANADES-HERRANZ, JUAN; Servicio Madrileño de Salud, Gerencia Adjunta Planificación y Calidad de Atención Primaria Carrillo de Santa Pau, Enrique; Centro Nacional de Investigaciones Oncologicas Chico-Moraleja, Rosa; Hospital Central de la Defensa Gomez Ulla Beamud-Victoria, Domingo; Comunidad de Madrid Servicio Madrileno de Salud, Centro de Salud Felipe II de Miguel-Yanes, Jose; Hospital General Universitario Gregorio Maranon, Internal Medicine Department Jimenez-Garcia, Rodrigo; Univ Rey Juan Carlos, Lopez-de-Andres, Ana ; Universidad Rey Juan Carlos, Preventive Medicine and Public Health Teaching and Research Unit. Ramallo-Fariña , Yolanda; Fundacion Investigacion Biomedica Del Hospital Universitario La Paz DE BURGOS-LUNAR, CARMEN; Hospital Universitario La Paz, Medicina Preventiva
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Mental health, Epidemiology
Keywords:	Depression, Diabetes Mellitus, Type 2, Self-Care, Cohort Studies

The DIADEMA Study- Prevalence of depression in patients with Type 2 Diabetes Mellitus in Spain: Results from the MADiabetes Cohort.

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1. Abstract

Objective: To estimate the prevalence of depression in patients diagnosed with type 2 diabetes mellitus (T2DM), and to identify sociodemographic, clinical, and psychological factors associated with depression in this population. Additionally, we examine the annual incidence rate of depression among T2DM patients.

Methods: We performed a large prospective cohort study of patients with T2DM from MADIABETES Study. The first recruitment drive was included 3,443 patients. A second recruitment drive included 727 new patients. Data have been collected since 2007 (baseline visit) and annually during the follow-up period (since 2008).

Results: Depression was prevalent in 20.03% of patients (n=592; 95%CI, 18.6 to 21.5), and was associated with previous personal history of depression (OR, 6.482; 95%CI, 5.138 to 8.178), mental health status below mean (OR, 1.423; 95%CI, 1.452 to 2.577), neuropathy (OR, 1.951; 95%CI, 1.423 to 2.674), fair or poor self reported health status (OR, 1.509; 95%CI, 1.209 to 1.882), treatment with oral antidiabetic agents plus insulin (OR, 1.802; 95%CI, 1.364 to 2.380), female gender (OR, 1.333; 95%CI, 1.009 to 1.761), and blood cholesterol level (OR, 1.005; 95%CI, 1.002 to 1.009).

The variables inversely associated with depression were: being in employment (OR, 0.595; 95%CI, 0.397 to 0.894), low physical activity (OR, 0.552; 95%CI, 0.408 to 0.746), systolic blood pressure (OR, 0.982; 95%CI, 0.971 to 0.992), and social support (OR, 0.978; 95%CI, 0.963 to 0.993). In patients without depression at baseline, the incidence of depression after one year of follow-up was 1.20% (95%CI, 1.11 to 2.81).

Conclusions: Depression is very prevalent among patients with T2DM and is associated with several key diabetes-related outcomes. Our results suggest that previous mental status, self-reported health status, gender and several diabetes-related complications are associated with differences in the degree of depression. These findings should alert practitioners to the importance of detecting depression in patients with T2DM.

Strengths and limitations of this study

- Time between both telephone interviews for depression screening was too short (12 months), making it difficult to compare cumulative incidence rates with those other studies.
- We preferred to exclude antidepressant agents from our combined variable for depression, because the antidepressants can be prescribed for diseases other than depression (i.e., sleeping disorders, migraine, neuropathic pain, obsessive-compulsive disorders, anxiety/panic disorderIn order to compare our findings with multivariable models from different studies, we may have adjusted variables unnecessary. However, fortunately, over-adjustment was avoided (changes >20% between crude and adjusted SE, data not shown).
- The strengths of our study include its prospective design, which ensured that measurement of risk factors preceded the development of depression, and the assessment of information on potentially confounding variables, which reduces potential selection and confusion biases.
- We also used an assessment of depression based on MINI 5.0, which was completed with the patient's general practitioner clinical who used his/her clinical judgment to determine whether the patient's symptoms and signs were compatible with a depressive disorder. Therefore, self-reported diagnosis was avoided.

Keywords: Depression; Diabetes Mellitus, Type 2; Self-Care; Cohort Studies.

1. Introduction

Currently, an estimated 8%-9% adults worldwide have type 2 diabetes mellitus (T2DM), and a substantial increase in prevalence over time has been observed (1). The prevalence of T2DM in the Spanish population is even higher (13.8%) (2).

Previous studies have shown that coexistence of mental disorders such as depression is considerably more frequent in people with T2DM than in the overall population (3) (4), with an prevalence ranging from 15% to 24% (5) and an incidence rate of depression during the first year after initiation of oral antidiabetic treatment of 12.61 per 1000 person-years (6). The coexistence of diabetes and mental disorders has a strong impact on the patient, with an increased risk of cardiovascular disease, all-cause mortality (7) and cardiovascular mortality (7), especially as a result of cardiovascular complications of T2DM (8). In addition, patients with diabetes and mental disorders show poorer compliance with treatment recommendations than T2DM patients without depression, and more frequently have cardiovascular risk factors such as smoking, obesity, sedentary lifestyle, and poor glycemic control (9), which can impact on their health-related quality of life (10).

To our knowledge, research on common mental disorders affecting patients with T2DM is scarce in Spain (11) (12) (13). In a recent cross-sectional study on patients with T2DM, Alonso-Morán et al. (14) reported that 9.8% of patients were diagnosed with depression (5.2% for males and 15.1% for females), and in a study by Nicolau et al. (12), 27.2% of patients had symptoms of depression. However, in these studies, data collection was often based on health surveys (11) (15) or self-reported scales (12,16), which yielded heterogeneous data. Thus, mental disorders have not been assessed using a clinical interview as the “gold standard”.

The aims of the present study were to estimate the prevalence of depression in patients diagnosed with T2DM, and to identify sociodemographic, clinical, and psychological factors associated with the occurrence of depression in this population. Additionally, we examine the one-year incidence rate of depression among T2DM patients.

2. Material and Methods

2.1. Design and participants

The Madrid Diabetes Study (MADIABETES Study), is a large prospective cohort study of various clinical and psychosocial aspects of outpatients with T2DM living in the metropolitan area of Madrid, Spain. The first recruitment drive was in 2007 and enrolled 3,443 T2DM outpatients from the 56 participating primary health care centers (PHCC). Patients were selected by simple random sampling by participating general practitioners (n= 131) based on the list of patients with a diagnosis of T2DM in their computerized clinical records (CCR). A more complete description of this methodology can be found elsewhere (17).

Reasons for not continuing still completion were leaving the participating PHCC, death or drop-out. Furthermore, the dynamic character of MADIABETES cohort, i.e. new participants could enter over time, helped prevent loss of the study population. Therefore, at the end of 2010, a second recruitment drive involving 41 PHCC included 727 new patients.

The inclusion criteria were: a diagnosis of T2DM in the CCR (code T90 of the International Classification of Primary Care [ICPC-2]) (18), age ≥ 30 years, visit to a PHCC at least twice in the previous year, and agreement to take part in the study and provided written informed consent. Patients were excluded for the following reasons: diagnosis of gestational diabetes mellitus, being in an institution, inability to understand Spanish, severe chronic diseases or significant physical or psychological disabilities that might invalidate informed consent or interviews (according to clinical judgment), legal incompetence or legal guardianship, and participation in clinical trials.

For the purpose of evaluating the prevalence of depression (DIAbetes and DEpression in MAdrid-DIADEMA Study), we included those patients who participated in the interview process conducted between January 1st 2011 and 31th December 2011. Furthermore, to estimate the annual incidence of depression, the data from the second interview were included. The original protocol of the study was published in advance (19). Therefore, for the

main variable the MADIABETES cohort included a total of 2,955 patients (see the flow diagram in Figure 1).

2.2. Patient and Public Involvement

Major depression is prevalent among patient with diabetes, especially older adults, and is a risk factor for self-care, complications and death. Therefore, our research question focuses on screening for depressive symptoms in all patients with diabetes, with particular emphasis on those with a self-reported history of depression. We use age-appropriate depression screening measures and are aware that further evaluation will be necessary for individuals with a positive result. Treatment is prescribed accordingly.

Patients were not involved in the design, recruitment or conduct of the study. We report our results annually at specific meeting, to which we invited the participating general practitioners and all the patients included in the MADIABETES Cohort.

2.3. Source of data

To achieve the goal of the MADIABETES Study, data began to be collected in 2007 (baseline visit) and then annually during the follow-up period (since 2008). Four data collection strategies were combined.

First, data concerning disease episodes (coded in ICPC-2) (18), prescription of medication (coded according to the Anatomical Therapeutic Chemical classification system), laboratory results, anthropometric variables, and use of care facilities were obtained from the CCR. The CCR for primary health care in the Madrid Health Service was administered by OMI-AP© software. CCR registration is continuously updated in the PHCC under routine clinical practice conditions, and once a year, data are transferred to our central database.

Second, the general practitioner of each participating patient collected information about morbidity and mortality, under routine clinical practice conditions using an electronic case report form (hosted on the website www.madiabetes.com. All general practitioners received

training to standardize their knowledge of project objectives, data collection techniques and field work procedures.

Third, from 2011 onward, all patients were invited each year to undergo an interview to provide sociodemographic data, lifestyle data, determinants of health, and psychosocial characteristics. Data were collected using a previously standardized protocol through a telephone interview with a clinical psychologist trained in the evaluation procedure of the study. Lastly, the vital status of the patients was ascertained from two mortality records: *Índice Nacional de Defunciones* (https://www.msssi.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/IND_TipoDifusion.htm) and *Instituto Nacional de Estadística* (http://www.ine.es). The latter indicates the underlying cause of death recorded on the death certificates, which is coded according to the International Classification of Diseases, Tenth Revision (20).

2.4. Variables

The primary outcome variable was depression. The diagnosis of depression was considered a combined variable, as suggested by other authors (21), consisting of a diagnosis based on the module of major depressive disorder of the International Neuro-psychiatric Interview (MINI 5.0.0) (22), The interview was applied by a trained psychologist, and the diagnosis was made with the patient's general practitioner clinical who used his/her clinical judgment to determine whether the patient's symptoms and signs were compatible with a depressive disorder.

The MINI is a short and efficient diagnostic interview to diagnose mental disorders, which was used in its Spanish version (23).

The other *psychosocial variables* evaluated included the following:

- A personal history of psychiatric disorder if the patient reported a positive response to the question: "Has a clinician ever diagnosed you as having any psychiatric disorder?. Alternatively,

patients could have been diagnosed with a psychiatric disorder before the last 12-month interval, as coded in the CCR.

- A family history of psychiatric disorder was registered if the patient reported a positive response to the question: "Has any family member (first-degree relatives) ever been diagnosed with a psychiatric disorder?"

- Anxiety disorder was defined based on the module of generalized anxiety disorder of the MINI (23) and according to clinical judgment.

- Social support, such as network size, was assessed based on the question: "About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?", which corresponds to the first item of the Medical Outcomes Study-Social Support Survey (MOS-SSS) (24).

- Health-related quality of life was measured using the SF-12 questionnaire, a composite of 12 items that assess eight dimensions of health: physical functioning, role-physical, general health, bodily pain, vitality, social functioning, role-emotional, and mental health (25). The SF-12 measures various aspects of physical and mental health, from which physical and mental summary scores are computed using the scores of 12 questions. The score ranges from 0 to 100, where a zero score indicates the lowest level of health and 100 indicates the highest level of health. Both Physical and Mental Health Composite Scales combine the 12 items in such a way that they compare with a national norm (mean score of 50.0 and a standard deviation of 10.0).

-Insomnia was assessed using the Spanish version of the eight-item Athens Insomnia Scale (AIS-8) (26) which is a self-reported questionnaire designed to measure the severity of insomnia based on the diagnostic criteria of the ICD-10 Classification of Mental and Behavioural Disorders.

Sociodemographic variables included age (date of birth), gender, nationality, length of residence in Spain, marital status (single, unmarried partners, married, divorced, widowed),

educational level (no studies, primary, high school, university), and employment status (employed, unemployed, retired, housewife and other).

Medical variables included the following:

- Comorbidity variables: hypertension, defined as systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg; heart failure, which was defined as symptoms of dyspnea or edema associated with bilateral rales, elevated venous pressure, or interstitial or alveolar edema on chest X-ray, and required the addition of diuretics or inotropic medications; myocardial infarction, defined as a history of chest pain/discomfort associated with elevation of ST segment in electrocardiographic in two or more contiguous leads and elevation of myocardial enzymes; stroke, defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function that lasted more than 24 hours; peripheral artery disease, defined as a symptomatic and documented obstruction of the distal arteries of the leg; low limb amputations, defined as the complete loss in the transverse anatomical plane of any part of the lower limb; erectile dysfunction, defined as the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance; retinopathy, defined as a documented diagnosis by an ophthalmologist of non-proliferative retinopathy, proliferative retinopathy or macular edema; nephropathy, defined as a history of renal disease due to diabetes mellitus or requiring dialysis; neuropathy, defined as diminished or lack of perception of touch or pain stimuli and loss of joint position sense and vibration sense, and renal failure, defined as an estimated glomerular filtration rate below 30 mL/1.73 m^2. Cardiovascular disease (CVD) was defined as one or more of the following: myocardial infarction, stroke or peripheral vascular disease.
- Other clinical variables: duration of diabetes (years) and family history of diabetes (in the first-degree relatives).

- Anthropometric variables: height, weight, body mass index (BMI), hip circumference, waist circumference, systolic blood pressure, and diastolic blood pressure.
- Laboratory results: albuminuria, creatinine, lipid profile, HbA1c and glucose.
- Personal health habits: 1. Smoking (never, former or current smoker). 2. Physical activity level which was measured using a short questionnaire based on the FAO/WHO/UNU Expert Consultation Report Energy and Protein Requirements (Geneva, 1985) and administered individually at a medical examination. The answers were coded from 1 to 3, with 1 representing inactivity or sedentary activity (remaining seated or at rest most of the time, sleeping, resting, sitting or standing, walking on flat ground, light housework, playing cards, sewing, cooking, studying, driving, typing, office duties, etc.), 2 representing low activity (walking at 5 km/h, heavy housework [cleaning windows, etc.], jobs such as carpenter, construction workers [except hard work], chemical industry, electrical, mechanized agricultural tasks, playing golf, child care, etc.), and 3, moderate or vigorous activity (non-mechanized agricultural tasks, mining, forestry, digging, chopping wood, hand mowing, climbing, mountaineering, playing football, tennis, jogging, dancing, skiing, etc.). 3. Drinking (0.1 through 4.9, or 5.0 or more g/d of alcohol).
- Treatment: statins, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, antiplatelet drugs, antidiabetics, antidepressant drugs and anxiolytics.

2.5. Statistical analysis

Quantitative variables were expressed as mean and standard deviation; qualitative variables were expressed as frequency distribution. Normally distributed continuous variables were compared using the *t* test, non-normally distributed variables were compared using the Mann-Whitney test, and categorical variables were compared using the chi-square test. Effect sizes

were calculated using Cohen's d for continuous measures and Cramer's V for categorical variables.

Given the hierarchical structure of our data, we used a logistic regression analysis with two levels: level 1, patients, and level 2, health centers (our sampling unit). However, in the initial step (null model), the variation in the prevalence of depression between centers was not significant ($\sigma 2u0 = 0.02$, SE = 0.02, $p = 0.115$), with an intraclass correlation coefficient of 0.007; therefore, we did not consider it necessary to adjust for a hierarchical model.

Explanatory multivariable logistic regressions models were constructed to identify variables that were independently associated with depression (prevalent). We report adjusted odds ratios (ORs) with their respective 95% confidence intervals (95%CIs). Variables that were statistically significant in the bivariate analysis and those shown to be predictors in previous studies were included in the multivariate analysis. We analyzed the possibility of over-adjustment, defined when after adjusting on the covariate it altered the adjusted OR of 10%–20% with a concomitant change in the standard error (SE) higher than 20%.

The annual incidence rate of depression was calculated by the standard method as follows: number of new cases of depression over a period (year 2011) / population at risk of developing the disease at the beginning of the period.

In all cases, the accepted level of significance was 0.05 or less, with a 95%CI. Data were processed using the Statistical Package for the Social Sciences (SPSS for windows, version 21.0; IBM Corp, Armonk, New York, USA).

2.6. Ethical aspects

The study was approved by the Institutional Review Board of Ramón y Cajal Hospital (Madrid) and conducted in accordance with the principles of the Declaration of Helsinki. All patients gave their written informed consent to participate in the study.

3. Results

3.1. Characteristics of the study population and prevalence of depression

A total of 3,443 patients were included in the study at the first recruitment drive (January 2007). Of these 3,217 were alive before the start of the survey (January 2013), and 2,228 agreed to the interview (participation rate: 69.3%). At the second recruitment, 727 patients agreed to participate (December 2010). Therefore, for the main objective of this study, the sample consisted of 2,955 people; 48.1% were women and the mean age was 70.2 years (SD 10.6).

Depression was prevalent in 20.03% (n=592; 95%CI, 18.6 to 21.5) Table 1 shows the characteristics of the sample, stratified by depression status.

Compared with patients without depression, people with depression were more likely to be female (<0.001), older (p=0.017), and widowed or divorced (p<0.001). They also, had a lower educational level (p<0.001), were less frequently classified as employed (p<0.001), and had been taking more intense diabetes treatment for longer (p=<0.001). Furthermore, patients with depression had higher BMIs (p<0.001), were lower consumers of alcohol (p<0.001), and had higher rates of never smoking (p<0.001), sedentary lifestyle (p<0.001), neuropathy (p<0.001), and renal failure (p=0.012). Anxiety was recorded in 14.8% of the sample (n= 438; 95%CI, 13.5 to 16.1). Coexistence of depression and anxiety was recorded in up to 8.6% (n=255) of the patients.

In addition, patients with depression more frequently had previous episodes of depression (p<0.001) and anxiety (p<0.001), and fair or poor self-reported health status (p<0.001) than patients without these disorders. No significant differences were observed between patients with depression and psychologically healthy subjects in the following: family history of diabetes, level of HbA1c, triglycerides values, nephropathy, and retinopathy.

Table 1. Baseline characteristics of the sample, with and without depression.

	TOTAL (n=2,955)	With depression (n=592)	Without depression (n=2,363)	p value	Effect size*
Sociodemographic variables					
Gender (female); % (n)	48.1 (1,421)	67.7 (401)	43.02 (1,020)	<0.001	0.197†
Age (years); mean (SD)	70.2 (10.6)	71.1 (10.3)	69.9 (10.7)	0.017	0.110‡
Country of origin (foreign-born); % (n)	2.4 (70)	2.9 (17)	2.2 (53)	0.368	0.017†
Marital status; % (n)				<0.001	0.123†
Single without partner	4.6 (136)	2.7 (16)	5.1 (120)		
Married or with partner	70.4 (2,077)	62 (366)	72.5 (1,711)		
Divorced	4.2 (124)	5.9 (35)	3.8 (89)		
Widowed	20.8 (614)	29.3 (173)	18.7 (441)		
Educational level; % (n)				<0.001	0.081†
Not completed	20.9 (613)	25.7 (152)	19.5 (461)		
Primary	46.7 (1,367)	48.6 (288)	46.7 (1,104)		
Secondary	19.7 (576)	16.4 (97)	20.3 (479)		
University	12.8 (374)	9.3 (55)	13.5 (319)		
Employment status; n (%)					
Employed	15.7 (459)	9.5 (56)	17 (403)	<0.001	0.084†
Variables related to diabetes					
Duration of diabetes (years); mean (SD)	15.4 (10.2)	16.5 (10.6)	15.06 (10)	0.002	0.143‡
Family history of diabetes (yes); % (n)	61.7 (1,813)	64.5 (382)	61.3 (1,448)	0.145	0.027†
Type of diabetes treatment; % (n)				<0.001	0.121†
Only diet	8.4 (248)	7.4 (44)	8.6 (204)		
Oral antidiabetic agents	53.2 (1,572)	47.3 (280)	54.7 (1,292)		
Insulin	5.4 (159)	6.9 (41)	5 (118)		
Oral antidiabetic agents + insulin	16.9 (498)	25.2 (149)	14.8 (349)		
Not specified	16.2 (478)	13.2 (78)	16.9 (400)		
Lifestyle and self-care					
Smoking habit; % (n)				<0.001	0.127†
Never smoker	46 (1,360)	58.6 (347)	42.9 (1,013)		
Ex-smoker	42.6 (1,259)	32.1 (190)	45.2 (1,069)		
Smoker	11.4 (336)	9.3 (55)	11.9 (281)		
Current regular alcohol use; % (n)	883 (33.6)	22 (111)	36.4 (772)	<0.001	0.120†
Physical activity; % (n)				<0.001	0.117†
Sedentary	11.3 (333)	18.4 (109)	9.5 (224)		
Low	81.5 (2,408)	76.5 (453)	82.7 (1,955)		
Moderate-vigorous	7.2 (214)	5.1 (30)	7.8 (184)		
Clinical risk factors					
BMI (kg/m^2); mean (SD)	31.1 (5.6)	32.4 (6.4)	31.2 (5.8)	<0.001	0.196‡
Systolic blood pressure (mmHg); mean (SD)	131.5 (12.6)	129.3 (12.6)	131.9 (11.9)	<0.001	0.208‡
Diastolic blood pressure (mmHg); mean (SD)	73.9 (7.5)	73.3 (7.6)	74.2 (7.4)	<0.001	0.120‡
Biochemical risk factors					
HbA1c (%); mean (SD)	7.1 (1.1)	7.1 (1.2)	7.3 (1.5)	0.703	0.110‡
Triglycerides; mean (SD)	142.4 (87.6)	148.9 (89.7)	140.7 (86.9)	0.070	0.092‡
Cholesterol; mean (SD)	175.7 (33.9)	181.1 (37.1)	174.3 (32.9)	<0.001	0.194‡
LDL-cholesterol; mean (SD)	99.2 (27.3)	101.6 (29.9)	98.3 (27.1)	0.064	0.115‡
HDL-cholesterol; mean (SD)	49.5 (13.2)	50.6 (12.9)	49.1 (13.3)	0.032	0.114‡
Complications and comorbidities					
Cardiovascular event; % (n)	29.7 (1,240)	31.9 (212)	29.3 (1,028)	0.178	0.021†
Heart failure; % (n)	11.5 (480)	13.7 (91)	11.1 (389)	0.053	0.030†
Lower limb amputation; % (n)	1.4 (60)	1.8 (12)	1.4 (48)	0.385	0.013†
Nephropathy; % (n)	13.5 (400)	16.2 (96)	12.9 (304)	0.033	0.039†
Neuropathy; % (n)	10.1 (299)	16.7 (99)	8.5 (200)	<0.001	0.111†
Retinopathy; % (n)	15 (442)	15.7 (93)	14.8 (349)	0.566	0.011†
Renal failure; % (n)	14.3 (424)	17.6 (104)	13.5 (320)	0.012	0.046†
Psychosocial variables					
Family history of depression (Yes); % (n)	197 (6.7)	10.6 (63)	5.7 (134)	<0.001	0.080†
Personal history of depression (Yes); % (n)	557 (18.8)	48.6 (288)	11.4 (269)	<0.001	0.381†
Self-reported health status (Fair or poor); % (n)	34.3 (992)	47 (269)	31.1 (723)	<0.001	0.133†
Physical quality of life; mean (SD)	40.1 (11.4)	35.3 (12.5)	41.5 (10.7)	<0.001	0.533‡
Mental quality of life; mean (SD)	47.4 (10.9)	41.3 (12.5)	49.1 (9.7)	<0.001	0.697‡
Social support (network size); mean (SD)	10.2 (8.3)	8.5 (7.3)	10.6 (8.5)	<0.001	0.217‡
Sleep (AIS); mean (SD)	2.6 (3.7)	5.3 (5.2)	2 (2.9)	<0.001	0.783‡

BMI, body mass index; AIS, Athens Insomnia Scale; HbA1c, glycated haemoglobin; †Cramer's V; ‡Cohen's d; *0.2 is the recommended minimum effect size; Cardiovascular event, includes nonfatal myocardial infarction, stroke, and peripheral artery disease.

3.2. Factors associated with prevalent depression

Table 2 shows the variables associated with depression after fully adjustment for potential confounding factors. The variable most strongly associated with depression was previous personal history of depression (OR, 6.482; 95%CI, 5.138 to 8.178; p=≤0.001), followed by neuropathy (OR, 1.951; 95%CI, 1.423 to 2.674; p≤0.001), treatment with oral antidiabetic agents plus insulin (OR, 1.802; 95%CI, 1.364 to 2.380; p≤0.001), fair or poor self reported health status (OR, 1.509; 95%CI, 1.209 to 1.882; p≤0.001), mental health score (SF-12) below the mean (OR, 1.423; 95%CI, 1.054 to 1.921; P=0.021), ≤female gender (OR, 1.333; 95%CI, 1.009 to 1.761; p=0.043), and blood cholesterol level (OR, 1.005; 95%CI, 1.002 to 1.009; p=0.002).

On the other hand, the variables inversely associated with depression were: being employed (OR, 0.595; 95%CI, 0.397 to 0.894; p=0.012), low physical activity (OR, 0.552; 95%CI, 0.408 to 0.746; p=<0.001), systolic blood pressure (OR, 0.982; 95%CI, 0.971 to 0.992; p=0.001), current alcohol use (OR, 0.726; 95%CI, 0.552 to 0.954) and social support (network size) (OR, 0.978; 95%CI, 0.962 to 0.993; p=0.005).

Table 2. Factors associated with prevalence of depression (logistic regression analysis)

(Hosmer-Lemeshow= 5.132; df=5; p=0.743)

	OR	95% CI	P-value
Gender			
Male	1		
Female	1.333	1.009-1.761	0.043
Age			
<65 years	1		
≥65 years	0.858	0.626-1.175	0.339
Duration of T2DM (y)[per unit of increment]	1.006	0.995-1.016	0.303
Educational level			
University	1		
Secondary	0.980	0.644-1.493	0.926
Primary	1.060	0.729-1.543	0.759
Not completed	1.118	0.735-1.699	0.602
Country of origin			
Spain	1		
Other	1.433	0.738-2.784	0.288
Employment status			
Not working	1		
Working	0.595	0.397-0.894	0.012
Smoking			
Never smoker	1		
Former smoker	0.854	0.652-1.119	0.252
Current smoker	0.874	0.585-1.306	0.510
Family history of DM			
No	1		
Yes	1.109	0.888-1.385	0.362
Current Alcohol use			
No	1		
Yes	0.726	0.552-0.954	0.022
Physical activity			
Sedentary	1		
Low	0.552	0.408-0.746	<0.001
Moderate-Vigorous	0.636	0.377-1.074	0.091
Diabetes treatment			
Oral antidiabetic agents	1		
Oral antidiabetic agents + insulin	1.802	1.364-2.380	<0.001
Insulin	1.476	0.938-2.323	0.092
Diet	0.932	0.623-1.394	0.731
Unknown	0.771	0.560-1.061	0.110
BMI (kg/m^2)[per unit of increment]	1.012	0.992-1.032	0.249
Systolic BP (mmHg)[per unit of increment]	0.982	0.971-0.992	0.001
Diastolic BP (mmHg)[per unit of increment]	0.992	0.974-1.009	0.358
Cholesterol (mg/dl) [per unit of increment]	1.005	1.002-1.009	0.002
Neuropathy			
No	1		
Yes	1.951	1.423-2.674	<0.001
Nephropathy			
No	1		

	Yes	1.077	0.782-1.483	0.649
Retinopathy				
	No	1		
	Yes	0.784	0.578-1.065	0.119
Renal failure				
	No	1		
	Yes	1.220	0.892-1.670	0.214
Self-reported health status				
	Excellent-very good-good	1		
	Fair-poor	1.509	1.209-1.882	<0.001
Family history of depression				
	No	1		
	Yes	1.419	0.975-2.066	0.067
Personal history of depression				
	No	1		
	Yes	6.482	5.138-8.178	<0.001
Social support (network size)[per unit of increment]		0.978	0.962-0.993	0.005
Physical health score (SF-12)				
	Score ≥ mean	1		
	Score < mean	1.243	0.910-1.699	0.171
Mental health score (SF-12)				
	Score ≥ mean	1		
	Score < mean	1.423	1.054-1.921	0.021
History of cancer				
	No	1		
	Yes	0.961	0.716-1.290	0.792
Cardiovascular disease				
	No	1		
	Yes	1.156	0.901-1.482	0.255
Heart failure				
	No	1		
	Yes	1.297	0.910-1.849	0.150
Lower limb amputation				
	No	1		
	Yes	1.765	0.798-3.904	0.160

3.3. Incidence of depression and predictive factors

During a median 12 months follow-up, 28 patients, without depression at baseline, developed an incident episode of depression, that is an annual incidence of 1.2% (95%CI, 1.11 to 2.81). There were differences by gender: 0.6% (95%CI, 0.13 to 1.07) in men and 2% (95%CI, 1.11 to 2.81) in women (p=0.002. Female gender was the variable most strongly associated with incidence of depression (OR, 2.620; 95%CI, 1.129 to 6.083); p=0.025). Other variables inversely associated with incidence of depression were: low physical activity (OR, 0.334; 95%CI, 0.136 to 0.818; p=0.018), diastolic blood pressure (pear each unit of increment) (OR, 0.937; 95%CI, 0.887 to 0.988; p=0.017), and social support (network sie) (OR, 0.875; 95% CI, 0.797 to 0.962;p=0.006).

Of the 592 patients initially identified as depressed, 394 (66.66%) had no symptoms or signs of depression after 1-year of follow-up, and 198 (33.33%) persisted with symptoms.

4. Discussion

The association between diabetes and depression has been well-known for at least three decades (4). The prevalence of depression in people with T2DM varies widely owing to circumstances such as differences in the methods used to assess depression (clinical interviews, questionnaires, self-report scales, and medical records), sample origin (clinical or outpatient screening), ethnic subgroups, gender composition, and age intervals. Two meta-analyses reported an overall prevalence of depression ranging from 17.6% to 27% (4). We analyzed the prevalence of depression in a cohort of patients with T2DM from the city of Madrid based on a clinical interview completed with prescribing and clinical data from CCR. Depression was prevalent in 20.03% (n=592; CI 95%, 18.6 to 21.5) of our sample, a finding that is lower than the 27.2% reported in primary-care settings and a hospital endocrinology department in Mallorca (Spain) using the Beck Depression Inventory as the screening tool (12). These findings are worrying, given the adverse impact of depression on the natural history of

T2DM, which takes the form of poor metabolic control (27), non-adherence to treatment (28,29), and increased risk of vascular complications (8) .

Poor social support and negative life events (i.e., adverse socioeconomic circumstances, death of relatives) have been associated with depression in people with T2DM (30). These two factors are more frequent in women (31) (32), thus explaining the predominance of depression among females, as reported by the vast majority of studies (33) (34). However, not all the studies have confirmed this hypothesis (35).

After adjusting for gender and other known risk factors, our findings show that the association with depression was reduced by 2.2% per unit of increment of network size. Similarly, the association with depression could be reduced by physical activity, as we found in patients with low physical activity compared with a sedentary lifestyle (OR, 0.552; 95%CI, 0.408 to 0.746;p≤0.001). However, we did not demonstrate a similar benefit in those who undertake moderate or vigorous physical activity. This phenomenon could be explained by the fact that very few had a high level of activity.

General practitioners should be encouraged to implement strategies designed to reduce the risk of depression in patients with T2DM, especially in those at high-risk of depression owing to exposure to chronic psychosocial stressors (29).

We found an inverse association between low physical activity and social support and depression. While this association does not necessarily imply a causal relationship, it might encourage the implementation of physical activity programs and the creation of support groups focused on psychological well-being and detection of depressive symptoms. Some of these suggestions have proven to be effective and feasible in older populations (36).

On the other hand, it is necessary to bear in mind that treatment of depression can be a prerequisite for good diabetes control because people with diabetes might follow their treatment plan more easily if their mood is improved first (37).

Other predictive factors of depression such as a previous depressive episode or family history of depression are not modifiable factors for reducing the risk of developing depression. However, health professionals must be alert to the presence of early symptoms of depression in order to treat this condition promptly. Indeed, routine screening for psychosocial problems such as depression is supported in well-conducted cohort studies (38). In this sense, screening for depression with questionnaires is insufficiently specific and needs to be complemented by a formal clinical assessment to confirm the diagnosis (37).

Being in employment was inversely associated with depression (OR, 0.595; p= 0.012), as shown elsewhere (39). This aspect suggests that going to work might have a protective role against depression owing to the social support received from co-workers.

Of the classic complications of diabetes, neuropathy was the only one significantly associated with depression (OR, 1.951;p≤0.001). Nephropathy, renal failure, heart failure, CVD, and lower limb amputation tended to have a positive association with depression. However, other studies have shown a significant and consistent association between complications of diabetes and depressive symptoms (8) As it was logical to suppose, subjects with depression had lower values in the mental health component score obtained from the SF-12, as reported elsewhere (40).

Consistent with other studies (41,42), we found that participants with depression self-rated their health status significantly lower than those without depression. Given the known relationship between fair/poor perceived health status and mortality (43), especially in patients with chronic diseases (44), it would be advisable for patients with poor self-rated health to be enrolled in a health coaching program similar to that used in the Royal North Shore Hospital, Sydney, Australia (45). In this program, patients with diabetes who had the lowest self-reported health status at baseline improved their rating in the first question of the Short-Form 36 Quality of Life Instrument (SF-1) from 4.4 to 3.7 (P≤ 0.001), and improved their

knowledge of diabetes. Their distress levels decreased significantly with respect to baseline values.

Medications for lowering blood sugar (insulin plus oral anti-diabetic agents) were significantly associated with depression (OR, 1.802; p≤0.001). Prior studies have highlighted the same phenomenon: the glucose-lowering therapies that include insulin are strongly associated with depression (46). Two different factors could explain this association: first, the implementation of insulin therapy requires painful injections and frequent glucose measurements, thus increasing stress and favoring the onset of a depressive episode in old age (47); second, since insulin is usually necessary for situations of poor glycemic control, it could be that non-optimal control of diabetes leads to worsening of mood, greater stress, and less life-satisfaction.

As for the incidence of depression after one year of follow-up, the present study reveals a value of 1.20% which is similar to that reported in the ZARADEMP Spanish Study (48), but lower than reported in other countries (5, 49-51). A possible explanation for this result could be that, compared with other European countries, the greater number of hours of sunlight in Spain protect against depression (50). In a meta-analysis (51) that evaluated 16 studies to analyze the relationship between diabetes and depression, the cumulative incidence of depression among people with diabetes ranged from 11.9%, after two years of follow-up, (52) to 23.5%, after 5.9 years of follow-up (53). The conclusion of the meta-analysis (54) is that there is evidence to support the hypothesis that diabetes is a ‘‘depressogenic’’ condition. This affirmation implies a real public health problem that may be resolved only by a specific prevention strategy.

Our findings have some limitations. First, the external validity of these results is limited because the study population may not be representative of the actual population of patients with diabetes. Second, the time between both telephone interviews for depression screening was too short (12 months), making it difficult to compare cumulative incidence rates with most studies. Third, the prescription of antidepressants takes place in diseases other than

depression (i.e., sleeping disorders, migraine, neuropathic pain, obsessive-compulsive disorders, anxiety/panic disorder), and the use of a combined variable for the diagnosis of depression includes the prescription of antidepressant medication and could have therefore overestimated its prevalence. Fourth, in order to compare multivariate models from different studies, it is possible that we just performed an unnecessary adjustment of variables. But, fortunately, there was no significant evidence for over-adjustment (changes >20% between crude and adjusted SE, data not shown).

Strengths of this study include: the prospective design, which ensured that measurement of risk factors preceded the development of depression; and the assessment of information on potentially confounding variables, which reduces the potential selection and confusion biases. We also used an assessment of depression based on MINI 5.0, completed with having been diagnosed with depression, treatment with antidepressant medications or any of these conditions. Therefore, self-reported diagnosis was avoided.

4.1. Conclusions

Depression is very prevalent among patients with T2DM and it is associated with several key diabetes-related outcomes. Our results suggest that previous mental status, self-reported health status, and some diabetes-related complications are associated with differences in the degree of depression. We also found sex-related differences with respect to the prevalence of depression. Our study shows that the risk of depression could be reduced by physical activity and social support. These findings should alert practitioners to the importance of detection of depression in patients with T2DM, and to the need to reduce the risk of depression with prevention programs focused on improving the physical activity of the patients and the creation of support groups. Our findings also suggest that the annual incidence rate of depression is low and that a high proportion of patients with T2DM who experience depression achieved full remission after one year of follow-up.

Acknowledgements

The authors thank to all health professionals of Primary Health Care of Madrid who have made its development possible.

Contributor Ship Statement

CBL and MASF designed the study and got funding. JCV, PGC, JCAH, RCM and DBV contributed to select the patients sampling by participating general practitioner, to data collection and combined the data collection strategies in a single database. FJSR, CBL, YRF, PGC and MASF analysed the data. PGC, MASF, and JMDY wrote the initial draft of the paper. RJG, ALA, CBL and ECS were involved in further drafting of the paper. All authors participated in interpreting the data, revising the paper for critically important intellectual content and gave final approval of the submitted version.

Data Sharing Statement

No additional data are available

Funding

This study forms part of research funded by the FIS (Fondo de Investigaciones Sanitarias—Health Research Fund, Instituto de Salud Carlos III) grants no.: PI10/02796, PI12/01806 and PI15/00259 and co-financed by the European Union through the Fondo Europeo de Desarrollo Regional (FEDER, "Una manera de hacer Europa"). Also, this article has been supported by the Foundation for Biomedical Research and Innovation of Primary Care FIIBAP through the call for aid for publications 2017.

(https://saluda.salud.madrid.org/atencionprimaria/investigacion/Paginas/fiibap.aspx)

The members of the MADIABETES Group are as follows : AM Sobrado-de Vicente-Tutor; Mar Sanz-Pascual; M Arnalte-Barrera; S Pulido-Fernández; EM Donaire-Jiménez; C Montero-Lizana; M Domínguez-Paniagua; P Serrano-Simarro; R Echegoyen-de Nicolás; P Gil-Díaz; I Cerrada-Somolinos; R Martín-Cano; A Cava-Rosado; T Mesonero-Grandes; E Gómez-Navarro; A Maestro-Martín; A Muñoz-Cildoz; ME Calonge-García; M Martín-Bun; P Carreño-Freire; J Fernández-García; A Morán-Escudero; J Martínez-Irazusta; E Calvo-García; AM Alayeto-Sánchez; C Reyes-Madridejos; MJ Bedoya-Frutos; B López-Sabater; J Innerarity-Martínez; A Rosillo-González; AI Menéndez-Fernández; F Mata-Benjumea; P Vich-Pérez; C Martín-Madrazo; MJ Gomara-Martínez; C Bello-González; A Pinilla-Carrasco; M Camarero-Shelly; A Cano-Espin; J Castro Martin; B de Llama-Arauz; A de Miguel-Ballano; MA García-Alonso; JN García-Pascual; MI González-García; C López-Rodríguez; M Miguel-Garzón; MC Montero-García; S Muñoz-Quiros-Aliaga; S Núñez-Palomo; O Olmos-Carrasco; N Pertierra-Galindo; G Reviriego-Jaén; P Rius-Fortea; G Rodríguez-Castro; JM San Vicente-Rodríguez; ME Serrano-Serrano; MM Zamora-Gómez; and MP Zazo-Lázaro.

Competing interests

The authors declare that there is no duality of interest associated with this manuscript.

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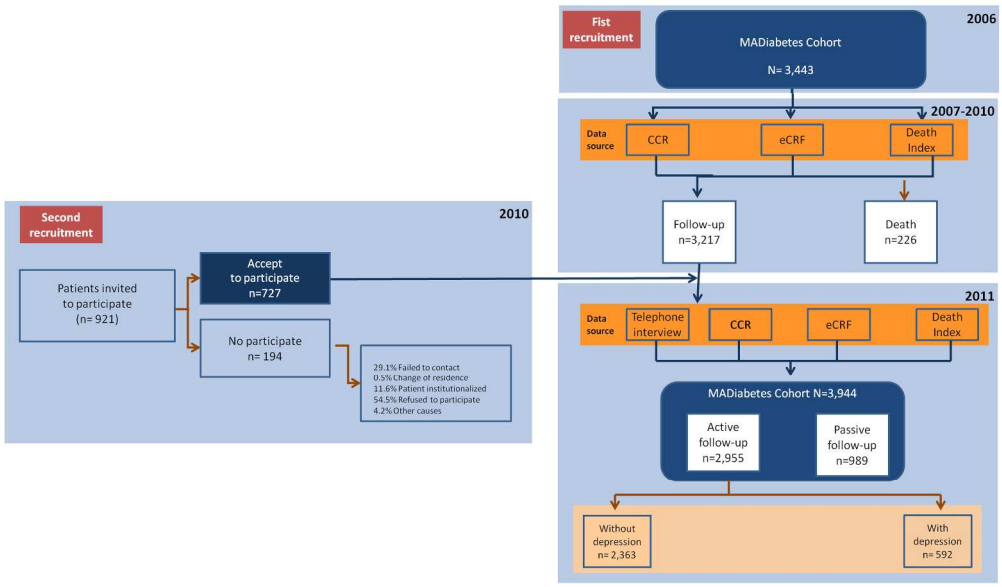
Figure 1- Flowchart



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 Pag. 1,3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 Pag. 5	Explain the scientific background and rationale for the investigation being reported
Objectives	3 Pag. 5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 Pag. 6	Present key elements of study design early in the paper
Setting	5 Pag. 6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 Pag. 6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 Pag. 8-11	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* Pag. 7-8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 Pag. 11-12	Describe any efforts to address potential sources of bias
Study size	10 Pag. 6	Explain how the study size was arrived at
Quantitative variables	11 Pag. 8-10	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 Pag. 11-12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13* Pag. 13-18	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* Pag. 13-14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* Pag. 15-18	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 Pag. 15-18	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 Pag. 18-22	Summarise key results with reference to study objectives
Limitations	19 Pag. 21-22	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 Pag-. 20-21	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 Pag-. 20-21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 Pag. 22-23	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.