DOI: 10.1111/dme.14349

Research: Epidemiology

Biopsychosocial factors associated with a current depressive episode in diabetes: the ELSA-Brasil study

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Accepted 18 June 2020

Abstract

Aims Depression is more prevalent in people with diabetes, and is associated with worse diabetes outcomes. Depression in diabetes is more treatment resistant, and as underlying mechanisms are unknown, development of more effective treatment strategies is complicated. A biopsychosocial model may improve our understanding of the pathophysiology, and therewith help improving treatment options.

Methods Diabetes was diagnosed according to American Diabetes Association (ADA) criteria and a current depressive episode according to the International Classification of Diseases (ICD-10), based on the Clinical Interview Schedule Revised (CIS-R). From the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), we included 455 participants without diabetes with a current depressive episode and 10 900 without either diabetes or a current depressive episode. Furthermore, 2183 participants had diabetes alone and 106 had both diabetes and a current depressive episode. Variable selection was based on their relationship with depression and/or diabetes. Multinomial multivariate logistic regression was used to determine how the models differed between participants with and without diabetes.

Results A current depressive episode in diabetes was related to being older and female, having poorer education, financial problems, experiencing discrimination at work, home and school, higher waist circumference, albumin to creatinine ratio and insulin resistance, and the presence of hypertension and cardiovascular disease. In non-diabetes, a current depressive disorder was related to being female, not being black, low income, psychological and social factors, non-current alcohol use, lower HDL cholesterol, higher insulin resistance and the presence of cardiovascular disease.

Conclusions A current depressive episode in the presence compared with the absence of diabetes was related more to biological than to psychosocial factors.

Diabet. Med. 37, 1742–1751 (2020)

Introduction

Both diabetes mellitus and major depression are common disorders, with up to 451 million people worldwide currently having diabetes [1], and the 1-year incidence of major depression being 6.7% in the USA and 8.0% in Brazil [2,3]. Besides occurring separately, both disorders can cluster together, with an early meta-analysis of 20 case–control studies showing a prevalence of major depression in diabetes of 21% (22% for type 1 and 17% for type 2 diabetes) compared with 11% in control groups [4]. More recent meta-analyses reported an increased risk of major depression in people with diabetes of between 24 and 41% [5,6]. Interestingly, the relationship between diabetes and depression seems to be bidirectional and those with major depression also have a

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What's new?

- Diabetes is related to a higher prevalence of depression, which is more treatment resistant, and to angiopathy and morbidity.
- In individuals with diabetes, a current depressive episode was related to cardiovascular disease, hypertension, insulin resistance, higher waist circumference, triglyceride levels and albumin to creatinine ratio, being older and female, having lower education, financial problems in the past year, and experiencing discrimination at work, home and school.
- In participants without diabetes, a current depressive disorder was related to being female, not being of black race/ethnicity, having lower income, experiencing life events in the past year (assault/robbery, hospitalization, financial problems, divorce), discrimination at work, public places and at school, being an ex-smoker, non-current alcohol user, lower HDL cholesterol, higher γ-glutamyltransferase, insulin resistance, and presence of cardiovascular disease.
- The biopsychosocial model increases our understanding of the complex pathophysiology of depression in diabetes.

higher risk of type 2 diabetes [7], suggesting at least some shared mechanisms.

Major depression in diabetes has been shown to amplify the negative consequences of diabetes [8], such as an increase in the prevalence and severity of micro- and macroangiopathy [9], increased risk of cognitive disturbances and dementia [10], and a greater risk of all-cause, cardiovascular, non-cardiovascular and non-cancer mortality [11]. It is also related to poorer diabetes self-care, higher recurrence rate, and treatment of depression is less effective in people with diabetes [12].

A comprehensive understanding of the pathophysiology of depression in diabetes is lacking, which further complicates effective treatment, leaving people with diabetes at a higher risk of adverse outcomes. Although an interplay between psychological, social and biological factors may be likely, to date no studies have combined such factors into one model. Rather, studies have looked at biological (e.g. inflammation) [13] and psychological (including the hardship of living with a chronic disease) [4,14], factors separately. Social factors, including life events and discrimination have not been included, although it is known they are related to depression.

Integrating biological, psychological and social factors into a biopsychosocial model will help create a more complete picture of the pathophysiology of depression in diabetes, which in turn may help improve treatment options for people with diabetes. We aimed to create such a model using data of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). This model was then compared with the biopsychosocial model of participants with depression but without diabetes, evaluating their similarities and differences.

Participants and methods

Population

ELSA-Brasil is a longitudinal prospective cohort study, focused on diabetes, cardiovascular disease and other chronic diseases, including 15 105 civil servants aged 34–75 years. A detailed overview of all study measurements has been published previously [15]. This study was approved by the institutional review boards of all six participating institutions (reference number FioCruz: 343/06) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

For this study, data collected between August 2008 and December 2010, in the cities of Porto Alegre, São Paulo, Belo Horizonte, Rio de Janeiro, Vitória and Salvador, were used. Of all participants, 961 were excluded because of missing values. In addition, owing to low prevalence within ELSA-Brasil and impossibility of grouping with other ethnic groups, native Brazilians (n = 151) and those of Asian ethnicity (n = 349) were excluded from this study. The total sample consisted of 13 644 participants.

Diagnosis of diabetes

Diabetes status was established according to the American Diabetes Association (ADA) guidelines by using fasting (≥ 7.0 mmol/l) or 2-h (≥ 11.1 mmol/l) glucose levels obtained during a 75-g oral glucose tolerance test, or HbA_{1c} ≥ 48 mmol/mol (≥ 6.5%) [16], self-reported previous diabetes diagnosis or the use of anti-hyperglycaemic medication.

Evaluation of a current depressive episode

The Clinical Interview Schedule Revised (CIS-R), developed in 1992 [17], and translated into Brazilian Portuguese and adapted culturally [18], was used to diagnose a current depressive episode and applied by a trained professional. This instrument was shown to have high specificity, positive predictive value and a large overlap with other standardized diagnostic instruments [19,20].

Through an algorithm that uses the diagnostic criteria of the International Classification of Diseases (ICD-10), the presence or absence of a current depressive episode is calculated based on the F32.xx codes, excluding F32.8 and F32.9. Questions about onset, frequency, duration and severity over the last 7 days covering somatic symptoms, fatigue, concentration and forgetfulness, sleep problems, irritability, worry about physical health, depression,

depressive ideas, worry, anxiety, phobias, panic, compulsions and obsessions are included in the CIS-R to establish a diagnosis [21]. Psychotic symptoms are not included. The CIS-R categorizes depressive episodes according to the ICD-10 classification, including: (1) mild depressive episodes with or without somatic symptoms, (2) moderate depressive episodes with or without somatic symptoms, and (3) severe depressive episodes without psychotic symptoms. For the purpose of this study, these five categories were joined into one variable: presence or absence of a current depressive episode. During data collection, the CIS-R introductory questions about appetite and weight fluctuations were not included. Although these questions do not count towards the total score of common mental health disorders and are not necessary to reach an ICD-10 diagnosis, they can be considered in the CIS-R algorithm [21]. Therefore, the prevalence of depressive disorders might represent a slight underestimation.

Biopsychosocial model

The constructed model included variables available in ELSA-Brasil, which were chosen based on previous literature in depression and diabetes [4–6,8,13,14]. Blocks were created according to their theoretical proximity to a current depressive episode, starting from the more distal to the more proximal ones. The first block included classical predictors of depression, being age, sex, race/skin colour and education. The second group included other social and psychological factors: income in tertiles, marital status, major life events in the past year (assault/robbery, hospitalization, death of a relative, financial problems, divorce), and discrimination at work, home, school, in public places, and by the police. The third group included alcohol consumption, smoking, use of lipid-lowering medication, BMI, waist circumference and lipid profile. The fourth group included liver enzymes, urinary albumin to creatinine ratio, C-reactive protein (CRP) and HOMA2 insulin resistance. Insulin resistance was calculated using the HOMA2 calculator obtained from https://www.dtu.ox.ac.uk/homacalculator/. The use of HOMA2 insulin resistance in people using insulin is possible, but should be done when glucose and insulin are in a steady state [22]. In this study, glucose and insulin were determined after an overnight fast. The fifth block included hypertension (systolic $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg or the use of anti-hypertensive medication), and cardiovascular disease (stroke, angina pectoris, myocardial infarct, heart failure).

Statistical analyses

All analyses were performed in R version 3.3.4. Normality was checked visually by inspecting the histogram, boxplot, QQ-plot and kernel density plots. Group characteristics across all four groups were analysed using an analysis of variance (ANOVA) for normally distributed variables, a Kruskal–Wallis test for non-normally distributed variables and a χ^2 test for categorical variables. Based on these tests, variables were entered in a multivariate model when $P < 0.05$.

A multivariate multinomial logistic regression was used to determine which variables were related to a current depressive episode in participants with and without diabetes. Participants without diabetes and without a current depressive episode were used as a reference category. The first block, with more classical predictors of depression, was forced into the model. Next, the other blocks were entered one by one. In case a variable did not reach statistical significance, it was deleted before entering the next block, so that the final model contained only variables with statistically significant associations. Fasting plasma glucose and insulin, and HbA_{1c} were not included in this analysis as they will have naturally strong associations driven by diabetes and not a current depressive episode. These associations may also prevent the detection of other, more subtle associations.

As a secondary analysis, a biopsychosocial model, including the same blocks, was created comparing both groups with diabetes using multivariate logistic regression. This enabled us to determine effects of glucose control and psychosocial factors in diabetes, specific to the presence of a current depressive episode. This analysis included HbA_{1c}, and fasting plasma glucose and insulin. Variables were considered statistically significant when $P < 0.05$, no allowance was made for multiplicity of statistical tests.

Results

Participants

Table 1 presents an overview of the descriptive statistics of the sample, and the *P*-values on which inclusion into the multivariate multinomial regression analyses was based. In this sample, 2289 (17%) participants had diabetes, of whom 1017 (44%) were newly diagnosed by ELSA-Brasil. A small group of 49 participants with diabetes (2.1%) used only insulin, and 77 (3.4%) used a combination of oral medication and insulin. Of the participants without diabetes, 455 (4.0%) had a current depressive episode, compared with 106 (4.6%) individuals with diabetes. After adjustment for age, sex, education level and race/skin colour, this was statistically significantly higher [odds ratio (OR) 1.28, 95% confidence interval (CI) 1.02, 1.60; $P = 0.040$). In participants with diabetes, the prevalence of a mild depressive episode with somatic symptoms (31; 29%) was statistically higher than in those without diabetes (83; 18%; $P = 0.016$). There were no differences in the prevalence of the other subtypes (Table 1).

Multivariate multinomial regression model

As shown in Table 1, all variables, except for discrimination by the police ($P = 0.233$) and total cholesterol ($P = 0.587$),

Table 1 Group characteristics

	Without diabetes		With diabetes		Overall *P*-value	*P*-value diabetes
	No depression	Depression	No depression	Depression		
N	10 900	455	2183	106	—	
Demographic variables						
Age (years)	51.12 ± 8.90	50.01 ± 8.02	56.42 ± 8.52	55.08 ± 8.73	< 0.001	0.114
Sex M : F (% male)	4911 : 5989 (45)	113 : 342 (25)	1203 : 980 (55)	28 : 78 (26)	< 0.001	< 0.001
Education level					< 0.001	< 0.001
Low (%)	1142 (11)	56 (12)	472 (22)	32 (30)		
Medium (%)	3689 (34)	198 (44)	844 (39)	52 (49)		
High (%)	6069 (56)	201 (44)	868 (40)	22 (21)		
Race/skin colour					< 0.001	0.187
White (%)	6131 (56)	229 (50)	1000 (46)	39 (37)		
Mixed ('pardo' %)	3134 (29)	149 (33)	658 (30)	38 (36)		
Black (%)	1635 (15)	77 (17)	525 (24)	29 (27)		
Income (tertile)					< 0.001	< 0.001
R$726 or less (%)	2444 (22)	160 (35)	645 (30)	51 (48)		
Between R$727 and 2281 (%)	5603 (51)	225 (50)	1037 (48)	44 (42)		
R$2282 or higher (%)	2853 (26)	70 (15)	501 (23)	11 (10)		
Partnered (%)	7288 (67)	247 (54)	1463 (67)	56 (53)	< 0.001	0.003
Life events						
Assault/robbery (%)*	693 (6.4)	52 (11)	138 (6.3)	10 (9.4)	< 0.001	0.203
Hospitalization (%)*	921 (8.4)	75 (17)	274 (13)	19 (18)	< 0.001	0.106
Death relative (%)*	1174 (11)	53 (12)	283 (13)	14 (13)	0.025	0.942
Financial difficulty (%)*	2119 (19)	191 (42)	495 (23)	46 (43)	< 0.001	< 0.001
Divorce (%)*	684 (6.3)	70 (15)	95 (4.4)	8 (7.5)	< 0.001	0.121
Discrimination						
At work (%)	1849 (17)	143 (31)	399 (18)	36 (34)	< 0.001	< 0.001
At home (%)	585 (5.4)	47 (10)	117 (5.4)	16 (15)	< 0.001	< 0.001
By police (%)	966 (8.9)	53 (12)	201 (9.2)	10 (9.4)	0.233	0.937
In public places (%)	1910 (18)	157 (35)	441 (20)	30 (28)	< 0.001	0.044
At school (%)	807 (7.4)	92 (20)	152 (7.0)	18 (17)	< 0.001	< 0.001
Anthropometrical variables						
Waist circumference (cm)	89.71 ± 12.15	90.44 ± 12.86	98.75 ± 12.44	101.31 ± 13.00	< 0.001	0.039
BMI (kg/m^2)	26.53 ± 4.52	27.27 ± 4.85	29.24 ± 4.95	30.98 ± 5.39	< 0.001	< 0.001
Smoking					< 0.001	0.955
Never smoked (%)	6422 (59)	235 (52)	1,071 (49)	53 (50)		
Ex-smoker (%)	3101 (28)	131 (29)	814 (37)	38 (36)		
Current smoker (%)	1377 (13)	89 (20)	298 (14)	15 (14)		
Alcohol consumption					< 0.001	0.002
Never drank (%)	1071 (9.8)	56 (12)	263 (12)	21 (20)		
Ex-drinker (%)	2025 (19)	123 (27)	557 (26)	36 (34)		
Current drinker (%)	7804 (72)	276 (61)	1363 (63)	49 (46)		
Cardiometabolic and liver factors						
Hypertension (%)[†,‡]	3284 (30)	129 (28)	1368 (63)	72 (68)	< 0.001	0.273
Systolic blood pressure (mmHg)	119.67 ± 16.40	117.28 ± 15.24	129.66 ± 19.28	126.28 ± 16.72	< 0.001	0.077
Diastolic blood pressure (mmHg)	75.70 ± 10.57	74.46 ± 10.00	79.55 ± 11.27	79.92 ± 10.89	< 0.001	0.743
Antihypertensive medication (%)	2,644 (24)	117 (26)	1,204 (55)	67 (63)	< 0.001	0.103
Total cholesterol (mmol/l)	11.94 ± 2.26	11.97 ± 2.36	11.87 ± 2.66	12.08 ± 2.53	0.587	0.439
HDL (mmol/l)	3.20 ± 0.81	3.14 ± 0.76	2.91 ± 0.74	3.05 ± 0.70	< 0.001	0.065
LDL (mmol/l)	7.32 ± 1.92	7.34 ± 1.93	7.11 ± 2.11	7.16 ± 2.14	< 0.001	0.815
Triglycerides (mmol/l)	6.06 (1.44–95.22)	6.44 (1.61–67.89)	7.89 (1.67–172.06)	8.06 (2.67–46.56)	< 0.001	0.581
Lipid lowering medication (%)	1,128 (10)	36 (7.9)	552 (25)	26 (25)	< 0.001	0.861
CRP (mg/l)	1.35 (0.09–114.00)	1.61 (0.09–36.10)	2.27 (0.09–90.00)	2.95 (0.09–22.10)	< 0.001	0.009
Cardiovascular disease (%)[‡]	529 (4.9)	39 (8.6)	256 (12)	24 (23)	< 0.001	< 0.001
Myocardial infarct (%)	134 (1.2)	10 (2.2)	86 (3.9)	8 (7.5)	< 0.001	0.068
Angina pectoris (%)	271 (2.5)	22 (4.8)	130 (6.0)	16 (15)	< 0.001	< 0.001
Heart failure (%)	118 (1.1)	9 (2.0)	75 (3.4)	5 (4.7)	< 0.001	0.483
Stroke (%)	111 (1.0)	11 (2.4)	44 (2.0)	5 (4.7)	< 0.001	0.061
ASAT (U/l)	24 (6–484)	23 (10–123)	25 (8–232)	25 (13–197)	< 0.001	0.803
ALAT (U/l)	23 (4–730)	22 (7–148)	28 (5–400)	26.5 (10–177)	< 0.001	0.412
γ-glutamyltransferase (U/l)	25 (3–1185)	26 (4–832)	35 (6–1731)	36 (6–373)	< 0.001	0.334

Table 1 (*Continued*)

	Without diabetes		With diabetes		Overall *P*-value	*P*-value diabetes
	No depression	Depression	No depression	Depression		
Diabetes variables						
Diabetes					—	0.069
Newly diagnosed (%)	—	—	979 (45)	38 (36)		
Previously diagnosed (%)	—	—	1204 (55)	68 (64)		
Years since diagnosis (years)	—	—	0 (0–55)	2 (0–47)	—	0.142
Diabetes medication					—	0.675
None (%)	—	—	1,188 (54)	58 (55)		
Oral medication only (%)	—	—	876 (40)	41 (39)		
Insulin only (%)	—	—	45 (2.1)	4 (3.8)		
Oral medication and insulin (%)	—	—	74 (3.4)	3 (2.8)		
Fasting plasma glucose (mmol/l)	5.46 (3.37–6.97)	5.46 (4.47–6.97)	7.03 (2.82–24.51)	6.92 (4.13–19.78)	< 0.001	0.825
Fasting plasma insulin (pmol/l)	65.54 (8.45–389.22)	69.85 (19.94–397.19)	94.51 (14.20–398.56)	110.46 (32.21–396.47)	< 0.001	0.043
HbA1c (%)	5.2 (1.2–6.4)	5.2 (2.6–6.4)	6.4 (3.6–14.4)	6.6 (4.6–14.6)	< 0.001	0.049
HbA1c (mmol/mol)	33 (−10 to 46)	33 (5–46)	46 (16–134)	49 (27–136)	< 0.001	0.049
ACR (mg/mmol)	0.75 (0–408.51)	0.79 (0.07–39.54)	0.78 (0–555.67)	0.82 (0.26–485.40)	< 0.001	0.365
HOMA2 Insulin resistance	1.25 (0.16–6.90)	1.32 (0.37–7.09)	1.95 (0.27–45.45)	2.30 (0.62–7.30)	< 0.001	0.021
Laser treated diabetic retinopathy (%)[§]	—	—	47 (3.0)	6 (8.3)	—	0.013
Depressive episode variables						
Type of depressive episode						
Mild without somatic symptoms (%)	—	209 (46)	—	40 (38)	—	0.155[¶]
Mild with somatic symptoms (%)	—	83 (18)	—	31 (29)	—	0.016[¶]
Moderate without somatic symptoms (%)	—	77 (17)	—	16 (15)	—	0.756[¶]
Moderate with somatic symptoms (%)	—	19 (4.2)	—	6 (5.7)	—	0.685[¶]
Severe without psychotic symptoms (%)	—	67 (15)	—	13 (12)	—	0.618[¶]
Antidepressant use					< 0.001	< 0.001
None (%)	10 261 (94)	388 (85)	2079 (95)	92 (87)		
SSRI (%)	310 (2.8)	31 (6.8)	47 (2.2)	8 (7.5)		
Tricyclic (%)	153 (1.4)	12 (2.6)	25 (1.1)	2 (1.9)		
Other class (%)	141 (1.3)	19 (4.2)	27 (1.2)	4 (3.8)		
Multiple classes (%)	35 (0.3)	5 (1.1)	5 (0.2)	0 (0.0)		

Data are presented as means (± SD) for normally distributed variables, median (min–max) for non-normally distributed variables, and absolute value (%) for categorical variables.
[*]In the past year.
[†]Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher or the use of anti-hypertensive medication.
[‡]Hypertension and cardiovascular disease were entered in the multinomial and logistic regression models instead of their subcategories.
[§]Information on laser treatment for proliferative retinopathy was available for 1627 of the 2289 participants with diabetes included in the study.
[¶]The *P*-value represents the comparison between the group without diabetes with a current depressive episode and the participants with diabetes and a current depressive episode.

were statistically different between all four groups, and were thus included in the multinomial regression model. When entered into the model having a partner (block 2), death in family (block 2) and BMI (block 3) did not reach statistical significance and were removed. Table 2 shows the ORs of the statistically significant variables of the final biopsychosocial model for both groups with a current depressive episode. ORs of all variables and changes in odds as blocks were added to the model and can be found in Table S1.

The final biopsychosocial model of a current depressive episode in diabetes included higher age (OR 1.03, 95% CI 1.00, 1.06), sex (being female; OR 3.48, 95% CI 2.10, 5.76), middle (OR 2.38, 95% CI 1.35, 4.20) and lower (OR 3.49, 95% CI 1.79, 6.82) education, having financial problems in the past year (OR 1.63, 95% CI 1.07, 2.49) and having experienced discrimination at work (OR 1.70, 95% CI 1.08, 2.68), at home (OR 2.01, 95% CI 1.10, 3.67) and at school (OR 1.87, 95% CI 1.05, 3.35). It furthermore included

Table 2 Final block of the multivariate multinomial logistic regression, with participants without a current depressive episode and without diabetes as the reference group.

	Depression without diabetes (n = 455)	Depression with diabetes (n = 106)	Depression with diabetes without insulin users (n = 99)
Block 1			
Age (years)	—	1.03 (1.00, 1.06)	—¶
Sex (female)	2.97 (2.30, 3.84)	3.48 (2.10, 5.76)	3.44 (2.04, 5.81)
Education			
Higher	Reference		
Middle	—	2.38 (1.35, 4.20)	2.45 (1.37, 4.40)
Lower	—	3.49 (1.79, 6.82)	3.28 (1.64, 6.60)
Race/skin colour			
White	Reference		
Mixed (pardo)	—	—	—
Black	0.68 (0.51, 0.90)	—	—
Block 2			
Partnered (no)	—	—	—
Income (tertile)	Reference		
≥ R$2282			
R$727–R$2281	—	—	—
≤ R$726	1.70 (1.20, 2.42)	—	—
Life events last year			
Assault/robbery (yes)*	1.55 (1.14, 2.12)	—	—
Hospitalisation (yes)*	1.69 (1.29, 2.22)	—	—
Death in family (yes)*	—	—	—
Financial problems (yes)*	1.85 (1.50, 2.29)	1.63 (1.07, 2.49)	1.62 (1.05, 2.50)
Divorce (yes)*	2.04 (1.54, 2.71)	—	—
Discrimination			
At work (yes)†	1.45 (1.16, 1.82)	1.70 (1.08, 2.68)	1.70 (1.07, 2.71)
At home (yes)†	—	2.01 (1.10, 3.67)	2.08 (1.12, 3.86)
In public places (yes)†	1.58 (1.27, 1.98)	—	—
At school (yes)†	2.17 (1.66, 2.84)	1.87 (1.05, 3.35)	—¶
Block 3			
Smoking	Reference		
Never			
Ex-smoker	1.41 (1.16, 1.70)	—	—
Current smoker	—	—	—
Alcohol use			
Never	Reference		
Ex-drinker	—	—	—
Current drinker	0.80 (0.66, 0.98)	—	—
Waist circumference	—	1.04 (1.02, 1.06)	1.04 (1.02, 1.05)
BMI	—	—	—
Triglycerides	—	1.03 (1.01, 1.05)	1.03 (1.01, 1.06)
HDL cholesterol	0.84 (0.73, 0.97)	—	—
LDL cholesterol	—	—	—
Lipid lowering medication (yes)	—	—	1.96 (1.17, 3.27)‖
Block 4			
ASAT	—	—	—
ALAT	—	—	—
γ-glutamyltransferase	1.00 (1.00, 1.00)	—	—
Albumin to creatinine ratio	—	1.01 (1.00, 1.02)	—¶
C-reactive protein	—	—	
HOMA2 insulin resistance	1.17 (1.02, 1.34)	1.62 (1.45, 1.81)	1.66 (1.39, 1.98)
Block 5			
Hypertension (yes)‡	—	1.82 (1.16, 2.85)	1.77 (1.12, 2.81)
Cardiovascular disease (yes)§	1.54 (1.07, 2.22)	1.97 (1.18, 3.31)	2.00 (1.18, 3.39)

Data are presented as odds ratio (OR) with 95% confidence interval.
—, variables not statistically significant ($P > 0.05$).
*Life events were recorded as present or absent in the year before the interview.
†Discrimination is recorded as experienced over the course of life.
‡Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg or the use of anti-hypertensive medication.
§Cardiovascular disease is the combination of angina pectoris, heart failure, stroke, and myocardial infarct.
¶Due to loss of statistical power, these variables did not reach statistical significance.
Variable did reach statistical significance only in the analysis in which participants with diabetes using insulin were excluded.

higher waist circumference (OR 1.04, 95% CI 1.02, 1.06), triglycerides (OR 1.03, 95% CI 1.01, 1.05), albumin to creatinine ratio (OR 1.01, 95% CI 1.00, 1.02), HOMA2 insulin resistance (OR 1.62, 95% CI 1.45, 1.81), and having hypertension (OR 1.82, 95% CI 1.16, 2.85) and cardiovascular disease (OR 1.97, 95% CI 1.18, 3.31) (Table 2). Excluding participants with diabetes using insulin did not significantly alter the model (Table 2).

The final biopsychosocial model for participants without diabetes with a current depressive episode consisted of sex (being female; OR 2.97, 95% CI 2.30, 3.84), race/skin colour (being black: OR 0.68, 95% CI 0.51, 0.90) and the lowest income tertile (≤ R$726; OR 1.70, 95% CI 1.20, 2.42). Also included were assault/robbery (OR 1.55, 95% CI 1.14, 2.12), hospitalization (OR 1.69, 95% CI 1.29, 2.22), financial problems (OR 1.85, 95% CI 1.50, 2.29) and divorce in the past year (OR 2.04, 95% CI 1.54, 2.71), having experienced discrimination at work (OR 1.45, 95% CI 1.16, 1.82), in public places (OR 1.58, 95% CI 1.27, 1.98) and at school (OR 2.17, 95% CI 1.66, 2.84), being ex-smoker (OR 1.41, 95% CI 1.16, 1.70), current alcohol use (OR 0.80, 95% CI 0.66, 0.98), lower HDL cholesterol (OR 0.84, 95% CI 0.73, 0.97), higher γ-glutamyltransferase (OR 1.00, 95% CI 1.00, 1.00) and HOMA2 insulin resistance (OR 1.17, 95% CI 1.02, 1.34), and having cardiovascular disease (OR 1.54, 95% CI 1.07, 2.22) (Table 2).

The biopsychosocial model of the group without diabetes included more variables related to life events in the past year and discrimination, income, and smoking, but fewer cardiometabolic factors than the biopsychosocial model of a current depressive episode of the group with diabetes.

Multivariate logistic regression model

Based on Table 1 ($P < 0.05$), block 1 included age, sex, race/skin colour and education level. Block 2 included marital status, financial problems in the past year, income and discrimination at work, home, school and in public places. Block 3 included alcohol consumption, waist circumference and BMI. Block 4 included fasting plasma insulin, HbA_{1c}, CRP and HOMA2-IR. Block 5 included cardiovascular disease.

In the multivariate model of the whole diabetic group, a current depressive episode was related to being female (OR 3.90, 95% CI 2.46, 6.19), having middle (OR 2.26, 95% CI 1.31, 3.87) and lower (OR 3.49, 95% CI 1.91, 6.41) education, financial problems in the past year (OR 1.73, 95% CI 1.13, 2.65), discrimination at work (OR 1.86, 95% CI 1.18, 2.93), at home (OR 2.09, 95% CI 1.14, 3.86) and at school (OR 1.97, 95% CI 1.09, 3.55), higher waist circumference (OR 1.02, 95% CI 1.01, 1.04) and having cardiovascular disease (OR 2.13, 95% CI 1.28, 3.53) (Tables 3 and S2). Excluding participants with diabetes using insulin did not significantly alter the model (Table 3).

Table 3 Final block of the multivariate logistic regression, with participants with diabetes but without a current depressive episode as the reference group

	Diabetes with depression (n = 106)	Diabetes with depression without insulin users (n = 99)
Block 1 (forced)		
Age (years)	—	—
Sex (female)	3.90 (2.46, 6.19)	3.69 (2.29, 5.95)
Education		
Higher	Reference	
Middle	2.26 (1.31, 3.87)	2.28 (1.31, 3.97)
Lower	3.49 (1.91, 6.41)	3.34 (1.77, 6.27)
Race/skin colour		
White	Reference	
Mixed (pardo)	—	—
Black	—	—
Block 2 (forward)		
Partnered (no)	—	—
Income (tertile)		
≥ R$2282	Reference	
R$727–R$2281	—	—
≤ R$726	—	—
Life events last year		
Financial problems (yes)*	1.73 (1.13, 2.65)	1.86 (1.20, 2.89)
Discrimination		
At work (yes)†	1.86 (1.18, 2.93)	1.96 (1.23, 3.11)
At home (yes)†	2.09 (1.14, 3.86)	2.50 (1.33, 4.68)
In public places (yes)†	—	—
At school (yes)†	1.97 (1.09, 3.55)	—
Block 3 (forward)		
Alcohol use		
Never	Reference	
Ex-drinker	—	—
Current drinker	—	—
Waist circumference	1.02 (1.01, 1.04)	—
BMI	—	—
Block 4 (forward)		
Fasting plasma insulin	—	1.00 (1.00, 1.01)‡
HbA_{1c}	—	—
C-reactive protein	—	—
HOMA2 insulin resistance	—	—
Block 5 (forward)		
Cardiovascular disease (yes)	2.13 (1.28, 3.53)	2.25 (1.34, 3.79)

Data are presented as odds ratios (OR) with 95% confidence interval.
—, variables not carried over to the next block as they did not reach overall statistical significance ($P < 0.05$).
*Life events were recorded as present or absent in the year before the interview.
†Discrimination is recorded as experienced over the course of life.
‡Variable did reach statistical significance only in the analysis in which participants with diabetes using insulin were excluded.

Discussion

In this study, we aimed at building a biopsychosocial model of factors related to a current depressive episode in diabetes using data of the ELSA-Brasil study. First, the proportion of a current depressive episode in diabetes (4.6%) was slightly, but statistically significantly higher than in participants without diabetes (4.0%). The results of the multinomial regression showed that a current depressive episode in diabetes was related to being older and female, poorer education, financial problems in the past year, having experienced discrimination at work, home and school, higher waist circumference, triglycerides, albumin to creatinine ratio, and insulin resistance, and presence of hypertension and cardiovascular disease.

In the current study, those with diabetes had a 28% (95% CI 2, 60%) higher risk of a current depressive episode than those without diabetes. This percentage is comparable with that found in two recent meta-analyses, demonstrating risks of 24% and 32% [5,6]. Interestingly, the current depressive episodes diagnosed in our group with diabetes were not more severe compared with episodes in their counterparts without diabetes. Although for the mild episodes, somatic symptoms were more prevalent in those with than those without diabetes.

The biopsychosocial models of a current depressive episode in diabetes and participants without diabetes both consisted of psychosocial factors, although life events were more prevalent in the model of participants without diabetes. By contrast, cardiometabolic factors were more prevalent in the model including participants with diabetes compared with the model using the sample without diabetes. Furthermore, in the former, these associations were stronger than in the later model. These results support the hypothesis that in depression in diabetes, cardiometabolic processes play a more important role than in depression without diabetes. This hypothesis is further supported by a study identifying a melancholic type of depression that was related to classical depression symptoms and hypothalamus–pituitary–adrenal (HPA) axis dysregulation, and an atypical type, being related to BMI, metabolic syndrome factors and inflammation [23,24]. Although these constructs are not included in the ICD-10 categories of depression, and this hypothesis cannot be tested in the current study, the biopsychosocial model in diabetes contained all these cardiometabolic factors related to the atypical type, except for inflammation, which may be due to the unavailability of inflammation markers other than CRP. However, higher waist circumference, an independent factor in the model and related to higher inflammation levels [25], might indicate the presence of the inflammation pathway in the biopsychosocial model.

Depression in diabetes is more treatment resistant, highlighting the need for additional treatment strategies [12]. Such strategies might be focussed on factors presented in the biopsychosocial model, including insulin resistance. For example, a randomized controlled trial demonstrated light therapy as being effective in diminishing depressive symptoms, especially in participants with type 2 diabetes with a major depressive disorder with higher levels of insulin resistance [26]. Although promising, further studies are needed to provide additional therapy options for depression in diabetes.

Our secondary analysis showed that compared with participants with diabetes without a current depressive episode, the presence of an depressive episode was related to higher waist circumference and cardiovascular disease, but also to life events and discrimination. Metabolic factors, such as glycaemic control, were not independently related to a current depressive episode, corroborating some studies [27] but contradicting others [28]. Clinically, this indicates that identification of people with diabetes at risk of depression should not necessarily focus metabolic factors alone. Rather screening should focus strongly on psychological and social factors, in addition to cardiovascular and microvascular disease presence.

Strengths of this study include the large sample size, the ability to combine all factors to determine independent associations, ample availability of different psychological, social and biological factors, and diagnosis of diabetes and a current depressive episode on the basis of standardized tests. Limitations include the relatively low number of participants with a current depressive episode and diabetes, limiting the power of this study and increasing the width of the confidence intervals; not having information on lifetime depression history, which has been found to be a strong indicator for recurrence of depressive episodes; and not having measures of HPA axis functioning or inflammation markers other than CRP. Within the ELSA-Brasil study, no questions about type of diabetes were included. Thus, this could only be inferred from onset age and medication use. This would lead to inaccurate inference, as adult-onset type 1 diabetes is not uncommon [29], onset age of type 2 diabetes is getting progressively earlier [30], and people with type 2 diabetes can also be on insulin alone treatment. Because of this uncertainty and given the importance of identifying a biopsychosocial model that also serves for people with type 1 diabetes, we opted to include all participants with diabetes. Results of this study may have lower generalizability to the general population, as only civil servants were included.

In conclusion, we showed that the biopsychosocial model of a current depressive episode in diabetes contained mostly biological factors and only a limited number of psychosocial variables, whereas the opposite was true for the group without diabetes with a current depressive episode. Future research should focus on the longitudinal association between diabetes and depression, and could use these data to focus additional depression treatment on modifiable underlying factors to improve treatment options for people with diabetes and depression.

Funding sources

This study was funded by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science, Technology and Innovation (Financiadora de Estudos e Projetos and Conselho Nacional de Desenvolvimento Científico e Tecnológico). This study was partly funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior–Brasil (CAPES). Grant numbers: 01 06 0010.00 and 01.10.0643.03 (RS); 01 06 0212.00 and 01.10.0742-00 (BA); 01 06 0300.00 and 01.12.0284.00 (ES); 01 06 0278.00 and 01 10 0746 00 (MG); 01 06 0115.00 and 01.10.0773-00 (SP); and 01 06 0071.00 and 01.11.0093.01 (RJ). RHG, DC, PL, and SMB are research fellows of CNPq.

Competing interests

None declared.

Acknowledgements

This study was funded by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science, Technology and Innovation (Financiadora de Estudos e Projetos and Conselho Nacional de Desenvolvimento Científico e Tecnológico). This study was partly funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior–Brasil (CAPES).

Author contributions

E.v.D., A.B.M. and R.H.G. designed the study. E.v.D., A.B.M. and F.N.E. performed the statistical analyses and drafted the manuscript. All authors made meaningful contributions to the manuscript. E.v.D., A.B.M. and R.H.G. have full access to the data and take full responsibility for the contents of this article.

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Supporting Information

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

Table S1. Results of the multivariate multinomial regression, with participants without a current depressive episode and without diabetes as the reference group.
Table S2. All blocks of the multivariate logistic regression, with participants with diabetes but without a current depressive episode as the reference group.