The association between diabetes mellitus and incidence of depressive episodes is different based on sex: insights from ELSA-Brasil

Ther Adv Endocrinol Metab

2022, Vol. 13: 1–12

DOI: 10.1177/20420188221093212

Elizabeth Leite Barbosa, Arlinda B. Moreno, Eelco Van Duinkerken, Paulo Lotufo, Sandhi Maria Barreto, Luana Giatti, Maria Angélica Nunes, Maria Carmen Viana, Roberta Figueiredo, Dóra Chor and Rosane Harter Griep

Abstract

Objective: To investigate the association between diabetes mellitus (DM) and incidence of depressive episodes among men and women.

Methods: Data were used from 12,730 participants (5866 men and 6864 women) at baseline (2008–2010) and follow-up 1 (2012–2014) of the Longitudinal Study of Adult Health (ELSA-Brasil), a multicenter cohort of Brazilian civil servants. Participants were classified for diabetes using self-reported and clinical information, and evaluated for presence of depressive episodes by the Clinical Interview Schedule–Revised (CIS-R). Associations were estimated by means of logistic regression models (crude and adjusted for socio-demographic variables).

Results: Women classified as with DM prior to the baseline were at 48% greater risk (95% confidence interval (CI) = 1.03–2.07) of depressive episodes in the crude model and 54% greater risk (95% CI = 1.06–2.19) in the final adjusted model *compared to women classified as non-DM*. No significant associations were observed for men. The regression models for duration of DM and incidence of depressive episodes ($n = 2143$ participants; 1160 men and 983 women) returned no significant associations.

Conclusion: In women classified as with prior DM, the greater risk of depressive episodes suggests that more frequent screening for depression may be beneficial as part of a multi-factorial approach to care for DM.

Keywords: cohort studies, depression, diabetes mellitus

Received: 23 July 2021; revised manuscript accepted: 23 March 2022.

Correspondence to:
Rosane Harter Griep
Laboratory of Health and Environment Education, Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Av. Brasil, 4365, Campus Fiocruz – Manguinhos, Rio de Janeiro 21040-360, Brazil.
rohgriep@ioc.fiocruz.br; elsa@fiocruz.br

Elizabeth Leite Barbosa
Arlinda B. Moreno
Dóra Chor
National School of Public Health Sérgio Arouca, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

Eelco Van Duinkerken
Paulo Niemeyer State Brain Institute, Rio de Janeiro, Brazil

Graffée and Guinle University Hospital, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

Department of Medical Psychology, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, the Netherlands

Paulo Lotufo
University of São Paulo, Cidade Universitária, São Paulo, Brazil

Sandhi Maria Barreto
Luana Giatti
Medical School & Clinical Hospital, Federal University of Minas Gerais, Belo Horizonte, Brazil

Maria Angélica Nunes
Federal University of Rio Grande do Sul, Porto Alegre, Brazil

Maria Carmen Viana
Federal University of Espírito Santo, Vitória, Brazil

Roberta Figueiredo
Federal University of São João Del-Rei, São João Del-Rei, Brazil

Introduction

In 2019, Brazil ranked fifth worldwide in number of persons with diabetes mellitus (DM) (16.8 million),[1] which constitutes a serious public health problem, because of its chronic complications, leading to high morbidity, frequent hospitalisations and increasing mortality.[2,3] One comorbidity of DM reported by a number of studies is depression,[4–8] which affects around 5.8% of Brazil's entire population.[9] Increasing evidence indicates high rates of co-occurrence of the two diseases and supports that the relationships between diabetes and depression are bidirectional.[5] Despite the strong adverse impact on individual quality of life and its importance as a public health problem, little is understood of the pathophysiology, and the exact mechanisms of that association are still being investigated.[7]

Studies have pointed to possible shared pathways in the relationship between DM and incidence of depressive episodes. These include inflammatory pathways, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, metabolic effects (e.g. low leptin levels), as well as a series of environmental, genetic and behavioural factors.[6] Accordingly, biochemical, physiological and psychosocial burden-related factors provide some evidence of the two-way relationship between depression and DM.[5–7]

One recent meta-analysis of 248 cross-sectional studies, which investigated this association between DM and depression on all continents, showed a 28% prevalence of depressive disorders among persons with DM and when stratified by sex, the prevalence was 23% for men and 34% for women.[8] Few longitudinal studies have been performed, however, as shown in two meta-analyses of 16 and 24 studies, which revealed that individuals with DM were at greater risk of depression.[5,10] Meanwhile, in the meta-analysis by Tong *et al.*,[11] of five papers, only persons with self-reported diabetes prior to the start of the study were at greater risk of developing depression, suggesting a relationship with longer duration of DM. However, those studies that assessed incidence did not present stratified analyses or tested the interaction with sex.[5,10,11]

Characteristics such as lower socioeconomic status, being single, being female and being in the younger or older age groups are well recognized as factors associated with a greater predisposition to this association.[12,13] The role of sex in depression is well known, and depression is more common worldwide among women (5.1%) than men (3.6%).[9] Taken together, given the known cross-sectional association between depression and DM is greater in women, the lack of longitudinal studies stratified by sex, and studies that consider the time of diagnosis, the current study reported here hypothesized that women with DM and those with a longer reported diagnosis time would be more likely to present with incident depressive episodes. Therefore, the objective was to investigate, according to sex, the association between DM and the incidence of depressive episodes, as well as between the duration of DM and the incidence of depressive episodes, among participants of the Longitudinal Study of Adult Health (ELSA-Brasil), with a follow-up of approximately 4 years.

Methods

Study design, population and data collection

This longitudinal study used data from the baseline wave (2008–2010) that included 15,105 individuals and from the follow-up (2012–2014) that had 14,014 individuals, of ELSA-Brasil; a multicenter prospective cohort comprising active and retired civil servants aged 35–74 years from six public institutions of higher education and research in Brazil. At the beginning of the study, the following individuals were excluded: (1) having severe cognitive impairment or inability to communicate verbally, (2) having the intention of leaving the institution, (3) retirees who resided outside the metropolitan area of the respective study centre and (4) pregnant civil servants current or recent at the time of the interview, which constituted a temporary exclusion criterion, being rescheduled for 4 months after the delivery.[14] The selection of subjects took place before the follow-up period and the application of questionnaires and tests, and measures followed standardized protocols and was performed by trained and certified field researchers.[15] For a more detailed description of methodological aspects of ELSA-Brasil, see Aquino *et al.*,[14] Schmidt *et al.*,[16] Bensenor *et al.*[17] and Chor *et al.*[18]

In this study, 1037 individuals were lost to follow-up. In order to be eligible for this study, candidates had to have answered the Clinical Interview Schedule–Revised (CIS-R) at the baseline; responded, at the follow-up, on the variables of that instrument that comprise the classification of depressive episodes; and reported a medical diagnosis at both data collection instances or undergone laboratory tests in order to be classified as DM at baseline. Candidates were excluded for (1) depressive episodes at baseline, because the interest of the study was incidence of depressive episodes; (2) classification as DM at follow-up, because in order to ascertain incidence, exposure must precede the outcome, which was observed at follow-up; and (3) incomplete data on exposure, outcome or covariables. With loss to follow-up, the final sample comprised 12,730 participants, of whom 6864 were women and 5866, men (Figure 1).

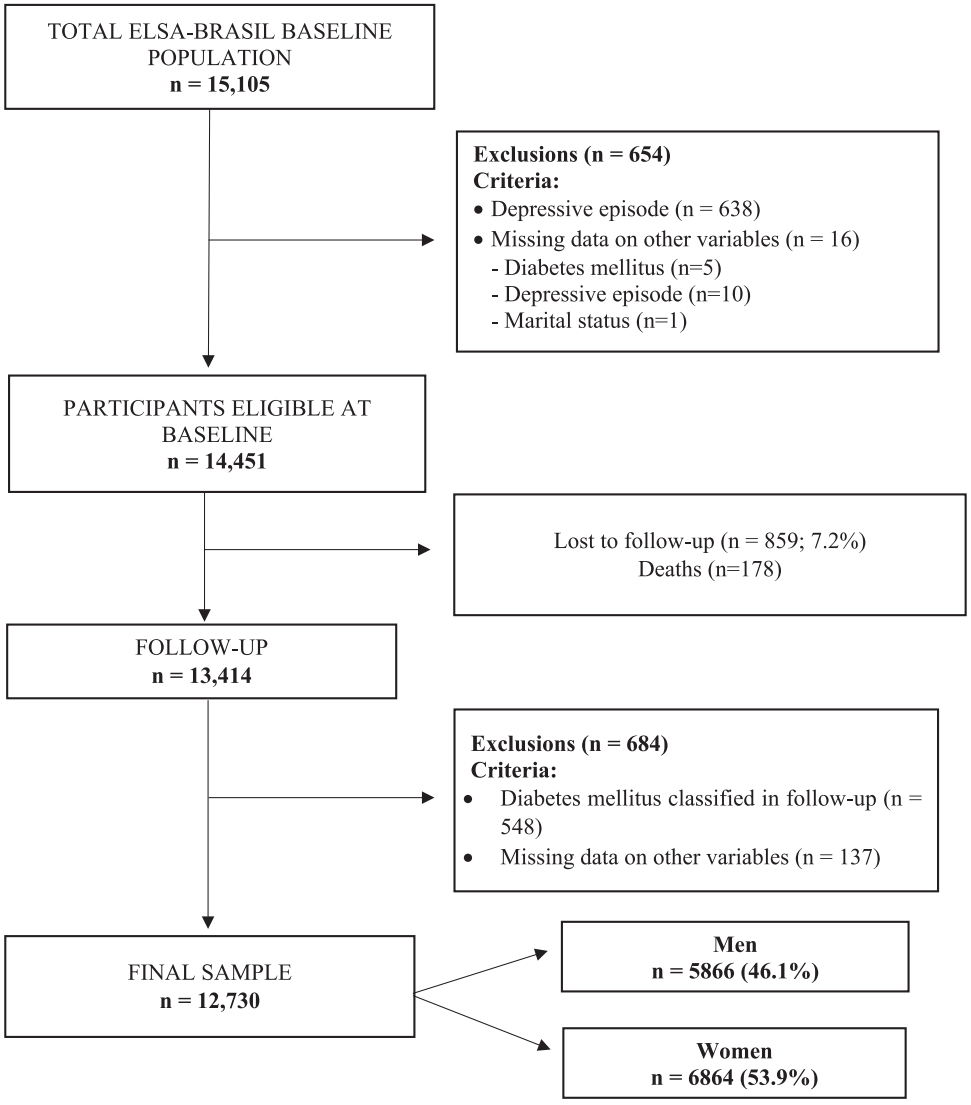

Figure 1. Selection criteria for the ELSA-Brazil study sample (2008–2014).

This study was approved by the research ethics committees of each research centre involved and by the ethics committee of the Escola Nacional de Saúde Pública (CEP-ENSP), with approval number CAAE 12596919.2.0000.5240. All participants signed a declaration of free and informed consent before being interviewed, tested or measured.

Study variables

Exposure variables: DM. Participants were classified for DM on the basis of self-reported and clinical information. The self-reported information was obtained in responses to either of the questions: 'Has a doctor ever told you that you had or have diabetes (sugar in the blood)?' or 'Have you used medication for diabetes in the past two weeks?' The response 'only when pregnant' was not considered a prior diagnosis.[19,20] The defining criteria for DM were: fasting plasma glucose (FPG) $\geqslant$ 126 mg/dl; 7.0 mmol/l or 2-hour oral glucose tolerance teste (OGTT) $\geqslant$ 200 mg/dl; 11.1 mmol/l or A1 C $\geqslant$ 6.5%; 48 mmol/mol.[19,20] Laboratory parameters were obtained by blood sample after 12-h nighttime fasting.[21]

In this study, the variable DM was categorized into (1) 'No' for participants who self-reported negative information and met no positive clinical criterion to be classified as DM and (2) 'Yes' for

participants who self-reported positive information or met one of the positive clinical criteria to be classified as DM. The variable was also categorized three ways into (1) 'Classified as non-DM'; (2) 'Classified as prior DM', for those who gave affirmative responses in self-reported information at baseline collection; and (3) 'Classified as DM after entering ELSA-Brazil', for those for whom laboratory alterations were identified at wave 1 or for those who gave positive responses in self-reported information at follow-up.

Secondary analyses were performed using the continuous exposure variable 'duration of DM', which was measured in years given by subtracting the follow-up reception date from the year of DM diagnosis/classification. The year of diagnosis was obtained (1) by asking: 'How old were you when the doctor informed you for the first time that you had or have diabetes?' for individuals classified as DM prior to the baseline; (2) from the variable 'wave 1 reception date', for those classified as DM at the baseline; and (3) from the variables 'wave 1 reception date' and time elapsed to onset of DM, for those who self-reported a diagnosis of DM between baseline wave and follow-up.

Outcome variable: depressive episodes. The variable 'depressive episode' was investigated by means of a psychiatric interview structured into sections corresponding to the presence and severity of 14 non-psychotic symptoms in the week prior to the interview, using a version of the CIS-R developed in 1992,[22] and cross-culturally adapted to the Brazilian language.[23] Somatic symptoms, fatigue, concentration and forgetfulness, sleep problems, irritability, worry about physical health, depression, depressive ideas, worry, anxiety, phobias, panic, compulsions and obsessions represent the sections of the CIS-R. This instrument has been used in several studies and is comparable with other structured interviews used in epidemiological surveys.[24]

Using an appropriated algorithm, the CIS-R classified a depressive episode (without psychotic symptoms) based on the F32.xx codes, excluding F32.8 and F32.9 of the International Classification of Diseases (ICD-10) as (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.[25]

In this study, depressive episodes were grouped into one dichotomous variable, as depressive episode present or absent, due to the relatively small number of participants with a current depressive episode and diabetes, causing a greater width of the confidence intervals (CIs), limiting the statistical power of this study. CIS-R introductory questions on appetite and weight variation were not included in the ELSA-Brasil questionnaire, which may have led to underestimation of diagnoses of depressive episodes.

Covariables. The variables used were those that the literature showed to be well recognized in association with onset of DM and of depression.[1,12,13,26] These were *Age* [continuous or categorical in age groups (35–44, 45–54, 55–65, and 65–74 years, depending on the analysis being performed], *sex* (male and female), *schooling* (up to incomplete lower secondary, complete lower secondary, complete upper secondary and complete higher education), *marital status* (separated, single, married/cohabiting and widowed), and *got pregnant after last visit* (yes and no) answered only by women who were still menstruating and who were under 55 years old.

Data analysis. The population was characterized by frequency distribution of categorical variables, and means and standard deviations (SDs) of continuous variables. Pearson's chi-square test was used to register significant differences between the variable 'depressive episode' and the other variables, to a 5% level of significance. All analyses were stratified by sex, given the influence of sex on the occurrence of both depression and of DM, as reported by previous studies.[9,27–29]

The associations between DM (with two or three categories) and incidence of depressive episodes, and between duration of DM (used for secondary analyses) and incidence of depressive episodes, were estimated by means of logistic regression models (crude and adjusted for socio-demographic variables). The associations were modelled as follows: Model 0, crude; Model 1, adjusted for age; Model 2, adjusted for age and schooling; and Model 3 adjusted for age, schooling and marital status. The adjustments to the models were evaluated by the Akaike information criterion (AIC). A complementary characterisation of the female sample classified as prior DM was conducted after observing the significant positive association of this group in the modelling.

All analyses were performed using the software R, version 3.4.2.[30]

Results

The study population was 53.9% female. Mean age at baseline was 51.8 years for both sexes (SD = 9.3 for men and SD = 8.8 for women), with most in the 45–64 years age range (65.1% of the men and 68.3% of the women). Most of the men and women had completed higher education, and only a small number had not completed lower secondary school (7.5% of the men and 3.3% of the women). More than 80% of the men were married, but only 53.7% of the women, with 25.4% of them divorced or separated (Table 1).

The frequency of diabetes in the study was 20.9% among men and 15.5% among women. Those classified as prior DM comprised 11.4% of the men and 8.2% of the women, while those classified as DM after entering the study were 9.5% of the men and 7.3% of the women.

Mean duration of DM was 7.8 (SD = 7.1) years in men and 7.4 (SD = 6.9) years in women. Incidence of depressive episodes over a mean monitoring period of 3.8 years was greater in women (4.9%) than men (2.3%), in women aged 45–54 years (5.7%), and in women with less schooling and widows, who returned the highest percentage incidences of depression (7.4% and 6.0%, respectively). Among persons classified as prior DM, incidence of depressive episodes was 2.1% in men and 6.9% in women and, of those classified as DM after entering the study, 2.0% in men and 4.8% in women. Mean duration of DM among individuals who had depressive episodes was 6.28 (SD = 4.0) years in men and 8.59 (SD = 7.0) years in women (Table 1).

The proportion of women who were pregnant during the study period was 114 (1.7%), and the incidence of depressive episodes in this group was 8 (7.0%) (Table 1). None of the pregnant women who had depressive episode had DM (data not shown in table).

In Table 2, it can be seen from the logistic regression model estimates that no statistically significant association was found, in either sex, between being classified as having diabetes and incidence of depressive episodes, despite the association observed in Model 1 among the women [odds ratio (OR) = 1.34; CI = 0.99–1.79]. When the AIC was considered in adjusting the models, the most parsimonious were Models 3 and 1, for women and men, respectively. In the results with three categories of DM, an association was found between individuals classified as prior DM and incidence of depressive episodes in women. By comparison with the women classified as non-DM, those classified as prior DM were at 48% greater risk (95% CI = 1.03–2.07) of depressive episodes in the crude model and 54% greater risk (95% CI = 1.06–2.19) in the final adjusted model (Table 3). By the AIC, the most parsimonious models were Model 1, for women, and Model 2, for men.

Complementary analysis was performed to further characterize the women classified as prior DM in the sample. Those who had depressive episodes were mostly married (59%), aged from 55 to 64 years (46.2%) and with less schooling (only 28.2% had completed higher education). However, these results showed no significant differences between the groups with or without depressive episodes.

In secondary analysis using the continuous variable 'duration of DM', no significant association was observed between duration of DM (n = 2143 participants; 1160 men and 983 women) and incidence of depressive episodes.

Discussion

In this study, it was observed that the women classified as prior DM were at 48% greater risk (95% CI = 1.03–2.07) of depressive episodes than the women classified as non-DM. After adjusting for potential confounders, that association not only continued to be significant, but increased in magnitude to 54% greater risk (95% CI = 1.06–2.19). Among men, a higher prevalence of DM was observed at baseline, but no significant associations were identified between DM and incidence of depressive episodes.

The summary measure of a recent meta-analysis with studies from all continents showed a higher prevalence of people with DM and depression in women (34%) than in men (24%).[8] Depression is more common worldwide among women (5.1%) than men (3.6%) and varies with age, peaking in older adulthood at 55–74 years (over 7.5% among women and 5.5% among men).[14] In the National

Table 1. Sample distribution by sex and incidence of depressive episodes, by sociodemographic variables and duration of DM: ELSA-Brasil (2008–2014).

	Men		Women	
	Total (%)	Depressive episodes (%)	Total (%)	Depressive episodes (%)
Sex	5866 (46.1)	136 (2.3)	6864 (53.9)	338 (4.9)
Age (years)[a]				
Mean (± SD)	51.8 (±9.3)	49.2 (±8.6)	51.8 (±8.8)	50.7 (±8.2)
Age group (years)[a]				
35–44	1392 (23.7)	43 (3.1)**	1558 (22.6)	73 (4.7)**
45–54	2319 (39.5)	57 (2.5)	2727 (39.7)	155 (5.7)
55–64	1529 (26.1)	28 (1.8)	1963 (28.6)	93 (4.7)
65–74	626 (10.7)	8 (1.3)	626 (9.1)	17 (2.7)
Schooling[a]				
Lower secondary incomplete	440 (7.5)	10 (2.3)†	229 (3.3)	17 (7.4)***
Lower secondary complete	446 (7.6)	15 (3.4)	342 (5.0)	21 (6.1)
Upper secondary complete	1920 (32.7)	53 (2.8)	2428 (35.4)	146 (6.0)
Higher complete	3060 (52.2)	58 (1.9)	3865 (56.3)	154 (4.0)
Marital status[a]				
Married/stable union	4808 (82.0)	105 (2.2)	3687 (53.7)	83 (5.0)†
Divorced/separated	680 (11.6)	21 (3.1)	1736 (25.3)	95 (5.5)
Single	315 (5.4)	8 (2.5)	1007 (14.7)	34 (3.4)
Widowed	63 (1.1)	2 (3.2)	434 (6.3)	26 (6.0)
Diabetes mellitus				
No	4641 (79.1)	111(2.4)	5799 (84.5)	277 (4.8)
Yes	1225 (20.9)	25(2.0)	1065 (15.5)	61 (5.7)
Diabetes mellitus				
Not classified as DM	4641 (79.1)	111 (2.4)	5799 (84.5)	277 (4.8)
Classified as DM prior to baseline	668 (11.4)	14 (2.1)	564 (8.2)	39 (6.9)
Classified as DM after entering the study	557 (9.5)	11 (2.0)	501 (7.3)	22 (4.8)
Duration of DM[b] (years)				
Mean (± SD)	7.8 (±7.1)	6.3 (±4.0)	7.4 (±6.9)	8.6 (±7.0)
Got pregnant after last visit				
Yes	–	–	114 (1,7)	8 (7,0)
No	–	–	6750 (98,3)	330(4,9)

DM: diabetes mellitus; ELSA-Brasil: Longitudinal Study of Adult Health.
[a]Baseline; Pearson's chi-square. †$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
[b]$n = 2143$ participants with known duration.

Health Survey (*Pesquisa Nacional de Saúde*, PNS) of Brazil carried out in 2013, the most affected age group was between 40–59 years and 70 years or more,[31] which represents the majority of the population in this study.

Previous studies by ELSA-Brasil have shown that being female is a risk factor for some psychological disorders.[32,33] Furthermore, some researchers argue that when compared with men, women may be more reliant on social support[34,35]; more likely to suffer sex prejudice and discrimination; to better report and recognize depressive symptoms and seek more help for mental health problems than men; and facing multiple journeys, including taking care of the family, work and study.[35,36] When considering the Disability Adjusted Life Years (DALY) indicator, type 2 diabetes mellitus (DM2) was ranked as the third most important cause for women and sixth for men,[37] which may explain why women tend to experience more depressive episodes. Accordingly, the association between DM and incidence of depressive episodes may be related to sex-related issues. However, the exact reasons for possible sex differences are still unclear and as far as we know, incidence studies have not offered stratified or tested analysis for interaction with sex[5,10,11] limiting the comparability of this study.

Another female-related factor is depression that occurs during or after pregnancy, known as prenatal depression and postpartum depression, respectively. Its occurrence is quite high and women with a history of depression before pregnancy have higher likeliness to experience depression again during pregnancy.[26] We observe that 7.0% of all women who became pregnant during the follow-up period had a depressive episode, but none of them had DM, not relating exposure to the outcome of this study. It is worth mentioning that, for the evaluation of depression in the prenatal and postpartum period, other instruments, approaching the specificities of common affective oscillations at pregnancy (more appropriated diagnostic criteria), should be used instead of the CIS-R. Besides this, we used the CIS-R as a screening instrument and not for a diagnosis (which should include clinical evaluation), which may explain a higher prevalence of depressive episode (7.0%) in this subgroup of women.

Partly corroborating the findings of our study, the meta-analysis by Tong *et al.*[11] also showed a higher risk of depressive episodes in people classified as having preexisting DM, but did not study the sample stratified by sex. Among the explanatory hypotheses are that psychological distress may be related to a longer duration of the disease, a greater number of chronic complications, greater difficulty in controlling blood glucose and more complex self-management of advanced stages of the disease.[11,38,39]

Taking into account the time since diagnosis measured in years, a mean duration of DM among individuals with depressive episodes was observed greater among women, but the association between this duration and the incidence of depressive episodes was not significant, which may have been influenced by the large variation in durations, leading to inaccuracy of duration and loss of duration information for 6.4% of participants classified as DM. In the English Longitudinal Study of Aging,[40] when the duration of diabetes in years was used, additional adjustment showed that it did not affect outcomes among participants diagnosed with diabetes compared with those who were normoglycemic.

Table 2. Association between DM and incidence of depressive episodes: ELSA-Brasil (2008–2014).

DM*	Depressive episodes			
	Men		Women	
	OR	95% CI	OR	95% CI
Model 0[a]				
Yes	0.85	(0.54–1.30)	1.21	(0.90–1.60)
Model 1[b]				
Yes	1.02	(0.64–1.58)	1.34	(0.99–1.79)
Model 2[c]				
Yes	0.97	(0.60–1.50)	1.24	(0.91–1.66)
Model 3[d]				
Yes	0.97	(0.60–1.50)	1.25	(0.92–1.67)

DM: diabetes mellitus; ELSA-Brasil: Longitudinal Study of Adult Health; OR: odds ratio; CI: confidence interval.
[a]Crude model.
[b]Model adjusted for age.
[c]Model 1 + schooling.
[d]Model 2 + marital status.
*Reference category: No.

Table 3. Association between DM prior to baseline, DM after entering the study and incidence of depressive episodes: ELSA-Brasil (2008–2014).

DM*	Depressive episodes			
	Men		Women	
	OR	95% CI	OR	95% CI
Model 0[a]				
Classified as DM prior to baseline	0.87	(0.48–1.48)	1.48	(1.03–2.07)
Classified as DM after entering the study	0.82	(0.41–1.47)	0.92	(0.57–1.39)
Model 1[b]				
Classified as DM prior to baseline	1.08	(0.58–1.85)	1.68	(1.16–2.38)
Classified as DM after entering the study	0.96	(0.48–1.73)	0.99	(0.62–1.52)
Model 2[c]				
Classified as DM prior to baseline	1.02	(0.55–1.76)	1.53	(1.05–2.18)
Classified as DM after entering the study	0.91	(0.45–1.64)	0.94	(0.58–1.43)
Model 3[d]				
Classified as DM prior to baseline	1.02	(0.55–1.76)	1.54	(1.06–2.19)
Classified as DM after entering the study	0.91	(0.46–1.65)	0.94	(0.58–1.44)

DM: diabetes mellitus; ELSA-Brasil: Longitudinal Study of Adult Health; OR: odds ratio; CI: confidence interval.
[a]Crude model.
[b]Model adjusted for age.
[c]Model 1 + schooling.
[d]Model 2 + marital status.
*Reference category: Not classified as DM.

The grouped result of 24 longitudinal studies showed that persons with DM (dichotomous variable without taking into account the time of diagnosis) have a 28% higher risk (95% CI = 1.15–1.42) of developing depression than those without DM, but the studies were significantly heterogeneous (I2 = 62, 5%), and 11 of them did not show a significant association as in our study.[8]

For mental health aspects to be better integrated into continuous, comprehensive individual care calls for early detection and intervention strategies. Depressive symptoms can be evaluated by way of a wide range of interview instruments and scales.[6] The Brazilian study that analysed data from the PNS used the Brazilian version of the Patient Health Questionnaire–9 (PHQ-9), a scale to screen for depression which has been widely used in Primary Health Care (PHC).[41] Another more recent study applied the CIS-R to the PHC population in order to examine the relationship between depression and bodily distress syndrome in order to enable new criteria for evaluating the syndrome to be included in the next edition of the ICD for use in PHC (ICD-11 PHC).[42]

In PHC, individuals are often at the onset of pathological processes and, accordingly, early detection and intervention and prevention of depressive episodes can help reduce disabilities and mortality from suicide, because depression is one of the main causes of disability worldwide and was the psychological condition that most contributed to deaths by suicide in 2015 (800,000 cases per year).[9,43,44]

Since 2001, the National Program on Arterial Hypertension and Diabetes Mellitus (HIPERDIA)

exists in Brazil, which aims to organize care, prevent and promote health by working in PHC to reduce the impact of morbidity and mortality related to these diseases.[44] However, even though DM receives much attention with regard to public policies and campaigns to provide guidance on the disease, the number of hospitalizations and the expenses for diabetes are high.[45] In this study, as it is a cohort of mostly highly educated voluntary civil servants from teaching and research institutions in Brazil, the participants might have greater and easier access to information about health and to private health services, leading to a greater availability of health care offered by both the private and public network. These characteristics may be related to a healthier population compared with the general Brazilian population.

Our study had several limitations. Failure to identify type of diabetes was one of them, although – according to the International Diabetes Federation (IDF)[1] – studies should generally be considered to reflect types 1 and type 2 combined. However, given that the data are drawn from adult populations where the incidence of type 2 diabetes is greater than that of type 1, any trend can be reasonably attributed to type 2 diabetes.

Another limitation was due to the fact that the CIS-R is an instrument that evaluates depressive episodes at specific times related to the last 7 days rather than long-term depression; therefore, the instrument did not capture depressive episodes occurring between the data collection waves. These limitations in the instrument may have led to underestimation of the diagnoses of incident depressive episodes. Furthermore, the variable family history of depression was not collected in the study, which is a strong indicator of recurrence of depressive episodes.

Due to the relatively small number of participants with a current depressive episode (characterized as mild, moderate or severe) and diabetes, a non-proportionality of odds was observed in the ordinal regression models for men and a greater width of the CIs in the regression models ordinal and multinomial for women was observed, limiting the power of this study. Thus, we chose to use depressive episodes as a dichotomous variable, rather than to explore the effect of depression severity. For a more in-depth analysis that will allow for a better understanding of the interaction between diabetes, sex and severity of depressive episodes, a longer follow-up time and more frequent assessments should be considered.

The results of this study may not be generalizable to the general population, as the sample consisted of public servants, mostly active and with a high level of education and socioeconomic status,[16] which is an advantage of this population, because, according to Librenza-Garcia *et al.*,[33] employment is a protective factor for depression. Another factor that must be considered in this population is the healthy worker bias (selection bias) and, therefore, the most severe cases of depressive episodes may have been underestimated.

Meanwhile, the study's strong points include its methodological rigour at all stages of data collection, and the size and diversity of the sample. Furthermore, as far as could be ascertained, this is the first Brazilian study to use longitudinal data and perform stratification by sex, allowing for inferences of causality.

The findings of this study contribute to the national and international literature with data on DM as a risk factor for depressive episodes stratified by sex. These data can inform the theoretical foundation that guides policy making. Considering that psychological distress is part of the multifactorial nature of care for people with DM, it is believed that evaluating individuals for possible early diagnosis and intervention is a necessity for planning the health of the population. Negative consequences can be avoided with the diagnosis and treatment of depression, such as poor adherence to treatment, sedentary lifestyle, social isolation, weight gain and lack of interest in self-care, directly influencing the risk of complications and the prognosis of DM. However, a deeper analysis considering a longer follow-up time and including more cases of incident depressive episodes will allow us to better understand this issue. There is also a need for more studies that take into account clinical conditions and glycaemic control and more longitudinal studies on sex differences.

Conclusion

Women classified as DM prior to the baseline were at 54% greater risk of incidence of depressive episodes than women classified as non-DM. Given the greater risk of depressive episodes in women with diabetes, it is suggested that this group of women be screened more often for depression.

Author contributions

Elizabeth Leite Barbosa: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft.

Arlinda B. Moreno: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – review & editing.

Eelco Van Duinkerken: Conceptualization; Investigation; Methodology; Project administration; Writing – review & editing.

Paulo Lotufo: Writing – review & editing.

Sandhi Maria Barreto: Writing – review & editing.

Luana Giatti: Writing – review & editing.

Maria Angélica Nunes: Writing – review & editing.

Maria Carmen Viana: Writing – review & editing.

Roberta Figueiredo: Writing – review & editing.

Dóra Chor: Writing – review & editing.

Rosane Harter Griep: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research: The Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) was funded by Brazil's Ministry of Health (Decit – Departamento de Ciência e Tecnologia) and by the Ministry of Science, Technology and Innovation (Finep – Financiadora de Estudos e Projetos e CNPq – Conselho Nacional de Desenvolvimento Científico e Tecnológico). Processes Nos. 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), 01 06 0071.00 and 01.11.0093.01 (RJ). Rosane Griep is a PQ-CNPq fellow and FAPERJ state scientist. Elizabeth Leite was a CNPq fellow.

ORCID iD

Elizabeth Leite Barbosa https://orcid.org/0000-0002-1829-2991

References

1. International Diabetes Federation. *IDF diabetes Atlas*. 9th ed., 2019, https://www.idf.org/e-library/epidemiology-research/diabetes-atlas.html
2. Flor LS and Campos MR. The prevalence of diabetes mellitus and its associated factors in the Brazilian adult population: evidence from a population-based survey. *Rev Bras Epidemiol* 2017; 20: 16–29.
3. Malta DC, França E, Abreu DMX, *et al*. Mortality due to noncommunicable diseases in Brazil, 1990 to 2015, according to estimates from the Global Burden of Disease study. *Medical J (São Paulo)* 2017; 135: 213–21.
4. Albertorio-Diaz JR, Eberhardt MS, Oquendo M, *et al*. Depressive states among adults with diabetes: findings from the National Health and Nutrition Examination Survey, 2007–2012. *Diabetes Res Clin Prac* 2017; 127: 80–88.
5. Zhuang QS, Shen L and Ji HF. Quantitative assessment of the bidirectional relationships between diabetes and depression. *Oncotarget* 2017; 8: 23389–23400.
6. Alzoubi A, Abunaser R, Khassawnwh A, *et al*. The bidirectional relationship between diabetes and depression: a literature review. *Korean J Fam Med* 2018; 39: 137–146.
7. van Sloten T and Schram M. Understanding depression in type 2 diabetes: a biological approach in observational studies. *F1000Res* 2018; 7: F1000.
8. Khaledi M, Haghighatdoos F, Feizi A, *et al*. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. *Acta Diabetol* 2019; 56: 631–650.
9. World Health Organization. *Depression and other common mental disorders: global health estimates*, 2017, https://apps.who.int/iris/handle/10665/254610
10. Rotella F and Mannucci E. Diabetes mellitus as a risk factor for depression. A meta-analysis of

longitudinal studies. *Diabetes Res Clin Prac* 2013; 99: 98–104.

11. Tong A, Wang X, Li F, *et al*. Risk of depressive symptoms associated with impaired glucose metabolism, newly diagnosed diabetes, and previously diagnosed diabetes: a meta-analysis of prospective cohort studies. *Acta Diabetol* 2016; 53: 589–598.
12. Lin EHB, Heckbert SR, Rutter CM, *et al*. Depression and increased mortality in diabetes: unexpected causes of death. *Ann Fam Med* 2009; 7: 414–421.
13. Demakakos P, Muniz-Terrera G and Nouwen A. Type 2 diabetes, depressive symptoms and trajectories of cognitive decline in a national sample of community-dwellers: a prospective cohort study. *PLoS ONE* 2017; 12: e0175827.
14. Aquino EML, Barreto SM, Bensenor IM, *et al*. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. *American J Epidemiol* 2012; 175: 315–324.
15. Schmidt MI, Griep RH, Passos VM, *et al*. Estratégias e desenvolvimento de garantia e controle de qualidade no ELSA-Brasil. *Rev Saúde Pública* 2013; 47: 105–112.
16. Schmidt MI, Hoffmann JF, Diniz FS, *et al*. Cohort profile: Longitudinal Study of Adult Health (ELSA-Brasil). *Int J Epidemiol* 2015; 44: 68–75.
17. Bensenor IM, Griep RH, Pinto KA, *et al*. Routines of organization of clinical tests and interviews in the ELSA-Brasil investigation center. *Rep Public Health* 2013; 47: 37–47.
18. Chor D, Alves MGM, Giatti L, *et al*. Questionnaire development in ELSA-Brasil: challenges of a multidimensional instrument. *Rep Public Health* 2013; 47: 27–36.
19. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2014; 37: S14–S80.
20. World Health Organization. Definition diagnosis of diabetes mellitus intermediate hyperglycaemia: report of a WHO/IDF consultation, 2006, https://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf
21. Fedeli LG, Vidigal PG, Leite CM, *et al*. Logistics of collection and transportation of biological samples and the organization of the central laboratory in the ELSA-Brasil. *Rep Public Health* 2013; 47: 63–71.
22. Lewis G, Pelosi AJ, Araya R, *et al*. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychol Med* 1992; 22: 465–486.
23. Nunes MA, Alves MGM, Chor D, *et al*. Cross-cultural adaptation of CIS-R (Clinical Interview Schedule–Revised Version) for the Portuguese in Longitudinal Study of Adult Health (ELSA). *Rev HCPA* 2011; 31: 487–490.
24. Robins LN, Wing J, Wittchen HU, *et al*. The composite international diagnostic interview. An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch Gen Psych* 1988; 45: 1069–1077.
25. Moreno AB, Chor D, Bensenor IM, *et al*. Dietary patterns and depression: first results in a cross-sectional study from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Psych* 2020; 2: 11–24.
26. Jahan N, Went TR, Sultan W, *et al*. Untreated depression during pregnancy and its effect on pregnancy outcomes: a systematic review. *Cureus* 2021; 13: e17251.
27. International Diabetes Federation. *IDF diabetes Atlas*. 8th ed., 2017, https://www.idf.org/e-library/epidemiology-research/diabetes-atlas.html
28. Ministry of Health. Vigitel Brazil 2016, 2017, https://bvsms.saude.gov.br/bvs/publicacoes/vigitel_brasil_2016_fatores_risco.pdf
29. Kautzky-Willer A, Harreiter J and Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr Rev* 2016; 37: 278–316.
30. R Core Team. *R: a language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing, 2018, https://www.R-project.org/.
31. Munhoz TN, Nunes BP, Wehrmeister FC, *et al*. A nationwide population-based study of depression in Brazil. *J Affect Disord* 2016; 192: 226–233.
32. Brunoni AR, Suen PJC, Bacchi PS, *et al*. Prevalence and risk factors of psychiatric symptoms and diagnoses before and during the COVID-19 pandemic: findings from the ELSA-Brasil COVID-19 mental health cohort. *Psychol Med*. Epub ahead of print 21 April 2021. DOI: 10.1017/S0033291721001719.
33. Librenza-Garcia D, Passos IC, Feiten JG, *et al*. Prediction of depression cases, incidence, and chronicity in a large occupational cohort using machine learning techniques: an analysis

of the ELSA-Brasil study. *Psychol Med*. Epub ahead of print 4 June 2020. DOI: 10.1017/S0033291720001579.

34. Afifi M. Gender differences in mental health. *Singapore Med J* 2007; 48: 385–391.
35. Salk RH, Hyde JS and Abramson LY. Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. *Psychol Bull* 2017; 143: 783–822.
36. Almeida-Filho N, Lessa I, Magalhães L, *et al*. Social inequality and depressive disorders in Bahia, Brazil: interactions of gender, ethnicity and social class. *Soc Sci Med* 2004; 59: 1339–1353.
37. Costa AF, Flor LS, Campos MR, *et al*. Burden of type 2 diabetes mellitus in Brazil. *Rep Public Health* 2017; 33: e00197915.
38. Wong EM, Afshar R, Qian H, *et al*. Diabetes distress, depression and glycemic control in a Canadian-based specialty care setting. *Can J Diabetes* 2017; 41: 362–365.
39. Liu SY, Huang J, Dong QL, *et al*. Diabetes distress, happiness and its associated factors among type 2 diabetes mellitus patients with different therapies. *Medicine* 2020; 99: e18831.
40. Demakakos P, Zaninotto P and Nouwen A. Is the association between depressive symptoms and glucose metabolism bidirectional? Evidence from the English longitudinal study of ageing. *Psychosomatic Med* 2014; 76: 555–561.
41. Lopes CS, Hellwig N, Silva GA, *et al*. Inequities in access to depression treatment: results of the Brazilian National Health Survey – PNS. *Int J Equity Health* 2016; 15: 154.
42. Fortes S, Ziebold C, Reed GM, *et al*. Studying ICD-11 Primary Health Care bodily stress syndrome in Brazil: do many functional disorders represent just one syndrome? *Braz J Psychiatry* 2019; 41: 15–21.
43. Vos T, Allen C, Arora M, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1545–1602.
44. Nicolau S, Batista KJD, Moura AA, *et al*. Práticas de educação em saúde realizadas por enfermeiros para pacientes do programa Hiperdia. *J Manag Prim Health Care* 2018; 9: e9.
45. Lima-Filho BF, Bessa NPOS, Fernandes ACT, *et al*. Internações por Diabetes Mellitus em idosos brasileiros e suas implicações regionais nos últimos 10 anos. *Res Soc Develop* 2020; 9: e40985106.