





RESEARCH ARTICLE

REVISED **Type 2 diabetes mellitus and anxiety symptoms: a cross-sectional study in Peru [version 2; peer review: 2 approved]**

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Abstract**Background:**

Information about the effect of type 2 diabetes mellitus (T2DM) awareness in the prevalence of anxiety disorders is scarce. Moreover, reports from resource-constrained and semiurban settings are usually focused on hospital-based data, instead of population-based surveys. We aimed to evaluate the association between T2DM and anxiety symptoms, with emphasis on T2DM awareness.

Methods:







A secondary data analysis was conducted using information from a population-based study. The outcome of interest was the presence of anxiety symptoms assessed by the Goldberg anxiety test, while the exposure variable was T2DM, defined using the oral glucose tolerance test. In addition, another definition was used based on self-reported T2DM awareness of previous diagnosis. Prevalence ratios (PR) and 95% confidence intervals (CI) were reported using Poisson regression models.



Results:

Data from 1,607 participants, of mean age 48.2 (SD: 10.6) years, and 809 (50.3%) females, were analyzed. Of all participants, 176 (11.0%; 95% CI: 9.5%–12.6%) had T2DM, 105 (59.7%) were aware of previous diagnosis, and 674 (41.9%; 95% CI: 39.5%–44.4%) had anxiety symptoms. In multivariable model, T2DM was not associated with anxiety symptoms (PR = 1.16; 95% CI: 0.99–1.36); however, individuals aware of T2DM diagnosis had a 36% (95% CI: 14%–64%) greater prevalence of anxiety symptoms compared to those without T2DM. Additionally, those aware of T2DM diagnosis had a 56% (95% CI: 13%–116%) higher probability to have anxiety symptoms compared to those not aware of T2DM diagnosis.

Conclusions:**Open Peer Review**

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Any reports and responses or comments on the article can be found at the end of the article.

The association between T2DM and anxiety symptoms was present among those participants who self-reported T2DM diagnosis, as opposed to those with T2DM but not aware and to those without T2DM. Evaluation of anxiety symptoms may be relevant among those with previous T2DM diagnosis.

Keywords

Anxiety, Type 2 diabetes mellitus, Awareness, Peru

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REVISED Amendments from Version 1

Changes in the Introduction, Statistical analysis, Results, and Discussion (limitations) sections have been done according to suggestions of the reviewers. In addition, we have added five new references as requested.

Any further responses from the reviewers can be found at the end of the article

Introduction

Anxiety is one of the most frequent psychiatric disorders worldwide¹, and is in the top three causes of disability-adjusted life-years (DALYs) among females². A systematic review of 87 studies from 44 countries estimated that the prevalence of anxiety disorders ranged between 0.9% and 28.3%, whilst past-year prevalence varied between 2.4% and 29.8%³. Moreover, anxiety has been reported to be more prevalent in Latin America, high income regions, and regions with a history of recent conflict⁴. For example, a population-based survey conducted in Lima, the capital of Peru, reported a prevalence of anxiety disorder between 10% and 15% among adults^{5,6}.

On the other hand, type 2 diabetes mellitus (T2DM) has been recognized as a major public health concern globally⁷. Thus, the worldwide prevalence of T2DM has doubled in the last 35 years⁸. In Peru, the prevalence of T2DM has been estimated to be 7% among adults over 25 years old, whereas this estimate increased to 8.4% in Lima⁹. Nevertheless, prevalence estimates in northern Peru are higher than national estimates, reaching, on average, a value of 10%¹⁰.

Although there is evidence supporting the bidirectional relationship between T2DM and some mental disorders, many of these studies have focused on depression and stress^{11–13}. Thus, the presence of T2DM may seem to be positively associated with increased depressive symptoms, and similarly, depression may increase the risk of diabetes^{14,15}, increasing at the same time the risk of complications, morbidity and death¹⁶. Nevertheless, a systematic review, using information from 18 studies, reported a 14% prevalence of anxiety disorder among individuals with T2DM compared to 5% among subjects without T2DM¹⁷; however, there is scant information about the impact of awareness of a T2DM diagnosis in the prevalence of anxiety disorders. In addition, reports from resource-constrained settings are usually focused on hospital settings, instead of population-based surveys.

As a result, this study aimed to explore the potential influence of the presence of T2DM on having anxiety symptoms, with a particular emphasis of those with T2DM but aware of their diagnosis, using a population-based survey conducted in the north of Peru.

Methods

Study design and setting

This study is a secondary analysis of a population-based survey conducted in the semiurban area of Tumbes, a region located in northern Peru, close to the border with Ecuador, between

December 2016 and November 2017. Tumbes has an area of approximately 4700 square kilometers and about 245,000 inhabitants¹⁸.

Study participants

Procedures utilized in the population-based study has previously been reported in detail¹⁹. A sex-stratified random sampling approach was used. Subjects between 30 and 69 years old, usual residents (≥ 6 months) of the study area, and able to consent, were invited to participate. Pregnant women, individuals with physical disabilities preventing anthropometric assessment, and those bedridden, were excluded.

Definition of variables

The outcome of interest in this study was the presence of anxiety symptoms evaluated using the Goldberg Anxiety test. This tool comprises nine items with dichotomic responses (no = 0 and yes = 1 point), and has been validated in Spanish to be used on adults in different countries^{20,21}, with a sensitivity and specificity of 85% and 65%, respectively. Each positive response adds a point to the total score; the first four items are usually utilized as screening questions, whereas the last five items only ask whether the participant scored two or more points in the first four items. For this study, the nine items were applied to all participants, and a score of ≥ 4 points was considered as having anxiety symptoms.

The exposure variable was the presence of T2DM, which was defined using the oral glucose tolerance test (OGTT), according to the procedures described by the World Health Organization²². Based on test results, study participants were split into two groups: (1) without type 2 diabetes, those with fasting glucose < 126 mg/dL and postprandial glucose < 200 mg/dL, and (2) with type 2 diabetes, those with fasting glucose ≥ 126 mg/dL or postprandial glucose ≥ 200 mg/dL. For specific sub-analysis, a second definition for the exposure variable was used, in which the type 2 diabetes group was divided into two subgroups depending on self-reported awareness of previous T2DM diagnosis; i.e., whether participants were aware or not of type 2 diabetes diagnosis.

Other variables were also considered in the analysis as potential confounders, including sociodemographic variables, lifestyle behaviors and cardiometabolic factors. Sociodemographic variables included sex (female or male), age (< 50 and ≥ 50 years), education level, collected as years of school accomplished and then divided into three group (< 7 , 7–11, and ≥ 12 years), socioeconomic status, evaluated using a wealth index based on family assets and possessions and then split into tertiles, and if the participant was currently working at the moment of the interview (yes or no). Lifestyle behaviors were smoking, defined as the self-report of the consumption of at least one cigarette per day, alcohol disorder, defined using the Alcohol Use Disorder Identification Test (AUDIT)²³; physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ) to estimate the metabolic equivalent of task (MET)²⁴, and split into low levels (< 600 MET-minutes/week) and moderate/high levels (those with at least 600 MET-minutes/week). Lastly, cardiometabolic factors considered were body mass index, divided according to

traditional cutoffs (<25 Kg/m², $25 - <30$ Kg/m², and ≥ 30 Kg/m²), and hypertension status, defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or self-report of previous hypertension diagnosis²⁵.

Study procedures

Questionnaires were administered face-to-face, using tablets with the Open Data Kit (ODK) software. The questionnaire was built using the STEPwise approach to surveillance developed by the World Health Organization (NCD WHO STEPS)²⁶. Information as well as anthropometric assessment were carried out by trained staff.

Regarding OGTT evaluation, individuals were asked to fast for eight to 12 hours before blood sampling. After verifying appropriate fasting period, the first blood sample was drawn, consisting of 7.5 ml of venous blood. After that, participants drank 75 g of anhydrous glucose diluted in 300 ml of water. Two hours later, the second blood sample was taken. During the two-hour period, the questionnaire and the anthropometric measures were performed.

Height (portable stadiometer) and weight (TBF-300A, TANITA Corporation, Tokyo, Japan) were measured using standard procedures. Blood pressure levels were measured in triplicate after a five-minute resting period. Each blood pressure measurement was separated by the other one for at least one minute and were done using an automatic monitor OMRON HEM-780, previously validated for adult populations²⁷.

Blood analyses were carried out by a certified laboratory located in Lima, Peru. Glucose was measured in plasma using a Cobas Modular Platform automated analyzer and reagents were supplied by Roche Diagnostics. Quality control for glucose measurements was provided by Bio-Rad, an independent assessment company.

Statistical analysis

Analyses were conducted using STATA 16 for Windows (StataCorp, College Station TX, US). Firstly, the characteristics of the study population were described by the exposure and outcome. Categorical variables were described as relative and absolute frequencies, whereas continuous variables were expressed using means and standard deviation (SD). Prevalence and 95% confidence intervals (95% CI) were calculated for variables of interest, and comparisons were carried out using Chi-squared test (two-sided p-values).

To assess the association of interest, crude and adjusted models using Poisson regression with robust variance were created²⁸. In these models, anxiety was considered the dependent variable, whereas the presence of T2DM was the exposure. In addition, a different Poisson regression model was also built to assess the difference on the prevalence of anxiety symptoms comparing those with T2DM but aware to those with T2DM unaware. In all the cases, prevalence ratios (PR) and 95% CI were reported, and collinearity was evaluated utilizing the variance inflation factor (VIF). Finally, because literature is consistent in results about gender as an effect modifier on

the potential effect of T2DM on mental health²⁹, we assessed such hypothesis using the likelihood ratio test.

Ethics

The original study was approved by the IRB at Universidad Peruana Cayetano Heredia, Lima, Peru, and the London School of Hygiene and Tropical Medicine, London, UK. Written informed consent was obtained from participants. This analysis was approved by the ethical committee of the Universidad Peruana de Ciencias Aplicadas, Lima, Peru. The database is available in Figshare³⁰, and did not contain identifying information, to guarantee appropriate anonymity and confidentiality.

Results

Characteristics of the study population

A total of 1,607 participant responses were analyzed, including 809 (50.3%) females, with a mean age of 48.2 (SD: 10.6) years; 518 (32.2%) had six or less years of education. Of all participants, 176 (11.0%; 95% CI: 9.5% - 12.6%) had T2DM, and 105 (59.7%) of them were aware of a previous diagnosis, with an average of 6.3 (SD: 6.1) years since diagnosis. Older age, low education, currently working, alcohol disorder, low physical activity levels, high body mass index, and hypertension were variables associated with having T2DM (Table 1).

Anxiety symptoms and associated factors

Overall, 674 (41.9%; 95% CI: 39.5% - 44.4%) individuals had anxiety symptoms. These were more frequent among females (56.0% against 27.7%) than males, and among those not working (53.4% against 36.5%) compared to those currently working (Table 2). In addition, daily smoking, alcohol disorder, physical activity and body mass index were behavioral variables associated with the presence of anxiety symptoms.

Association between type 2 diabetes and anxiety symptoms

In the multivariable model, and after controlling for different sociodemographic and behavioral factors, T2DM was not associated with the presence of anxiety symptoms (PR = 1.16; 95% CI: 0.99 - 1.36). Nevertheless, those individuals with T2DM, but aware of their diagnosis had a 36% (95% CI: 14% - 64%) greater prevalence of anxiety symptoms compared to those without T2DM (Table 3). Moreover, those aware of their T2DM diagnosis had a 56% (95% CI: 13% - 116%) higher probability to have anxiety symptoms compared to those not aware of their T2DM diagnosis. Finally, gender was not an effect modifier of the association of interest (p=0.48).

Discussion

Main findings

According to our results, there was no association between T2DM and the presence of anxiety symptoms at the population level; however, in our multivariable model, those individuals aware of their T2DM diagnosis had, on average, 37% and 57% greater prevalence of anxiety symptoms compared to those without T2DM and those not aware of T2DM diagnosis, respectively. Additionally, more than 40% of individuals from the general population had symptoms of anxiety and more than one in 10 had T2DM.

Table 1. Characteristics of the study population by type 2 diabetes mellitus (T2DM) status.

	Type 2 diabetes status			p-value
	No T2DM (n = 1431)	T2DM unaware (n = 71)	T2DM aware (n = 105)	
Sex				
Male	724 (50.6%)	29 (40.8%)	45 (42.9%)	0.10
Female	707 (49.4%)	42 (59.2%)	60 (57.1%)	
Age				
< 50 years	861 (60.2%)	36 (50.7%)	23 (21.9%)	< 0.001
50+ years	570 (39.8%)	35 (49.3%)	82 (78.1%)	
Education level				
< 7 years	438 (30.6%)	27 (38.0%)	53 (50.5%)	< 0.001
7 – 11 years	675 (47.2%)	32 (45.1%)	41 (39.0%)	
12+ years	318 (22.2%)	12 (16.9%)	11 (10.5%)	
Socioeconomic level				
Low	470 (32.8%)	25 (35.2%)	43 (41.0%)	0.34
Middle	497 (34.7%)	20 (28.2%)	33 (31.4%)	
High	464 (32.4%)	26 (36.6%)	29 (27.6%)	
Currently working				
Yes	992 (69.3%)	42 (59.2%)	56 (53.3%)	< 0.001
Daily smoking				
Yes	84 (5.9%)	2 (2.8%)	6 (5.7%)	0.56
Alcohol disorder				
Yes	113 (7.9%)	8 (11.3%)	0 (0.0%)	0.006
Physical activity				
Low levels	522 (36.5%)	27 (38.0%)	55 (52.4%)	0.005
Body mass index				
Normal	388 (27.1%)	11 (15.5%)	26 (24.8%)	0.02
Overweight	625 (43.7%)	28 (39.4%)	53 (50.5%)	
Obesity	418 (29.2%)	32 (45.1%)	26 (24.7%)	
Hypertension				
Yes	345 (24.1%)	25 (35.2%)	47 (44.8%)	< 0.001

Comparison with previous studies

Several studies have assessed the relationship between T2DM and anxiety. For example, a systematic review of 12 studies reported a significant positive association between T2DM and anxiety disorder and elevated anxiety symptoms assessing data from 12,626 individuals¹⁴. Nevertheless, a more recent review did not find a longitudinal association between baseline T2DM and incident anxiety, but instead an association between baseline anxiety and incident T2DM³¹.

Different cross-sectional studies have reported the association between T2DM and anxiety. Thus, a nationwide survey in Taiwan reported that the prevalence of anxiety disorders was higher among patients with T2DM than those in the general population³². In addition, a study conducted in Ireland showed that anxiety symptoms were considerably higher among cases of T2DM; nevertheless, the sample was enrolled from hospital/general practitioner shared care instead of the general population³³. In a study conducted in medical centers in Brazil

Table 2. Characteristics of the study population by anxiety symptoms.

	Anxiety symptoms		p-value
	No (n = 933)	Yes (n = 674)	
Sex			
Male	577 (61.8%)	221 (32.8%)	< 0.001
Female	356 (38.2%)	453 (67.2%)	
Age			
< 50 years	540 (57.9%)	380 (56.4%)	0.55
50+ years	393 (42.1%)	294 (43.6%)	
Education level			
< 7 years	295 (31.6%)	223 (33.1%)	0.55
7 - 11 years	445 (47.7%)	303 (44.9%)	
12+ years	193 (20.7%)	148 (22.0%)	
Socioeconomic level			
Low	306 (32.8%)	232 (34.4%)	0.68
Middle	318 (34.1%)	232 (34.4%)	
High	309 (33.1%)	210 (31.2%)	
Currently working			
No	241 (25.8%)	276 (40.9%)	< 0.001
Yes	692 (74.2%)	398 (59.1%)	
Daily smoking			
No	868 (93.0%)	647 (96.0%)	0.01
Yes	65 (7.0%)	27 (4.0%)	
Alcohol disorder			
No	847 (90.8%)	639 (94.8%)	0.003
Yes	86 (9.2%)	35 (5.2%)	
Physical activity			
Moderate/high levels	613 (65.7%)	390 (57.9%)	0.001
Low levels	320 (34.3%)	284 (42.1%)	
Body mass index			
Normal	265 (28.4%)	160 (23.7%)	0.03
Overweight	413 (44.3%)	293 (43.5%)	
Obesity	255 (27.3%)	221 (32.8%)	
Hypertension			
No	704 (75.5%)	486 (72.1%)	0.13
Yes	229 (24.5%)	188 (27.9%)	

Table 3. Effect of type 2 diabetes mellitus (T2DM) on the presence of anxiety symptoms: crude and adjusted models.

	Anxiety symptoms		Crude model	Adjusted model*
	No (n = 933)	Yes (n = 674)	PR (95% CI)	PR (95% CI)
T2DM				
No T2DM	846 (59.1%)	585 (40.9%)	1 (Reference)	1 (Reference)
With T2DM	87 (49.4%)	89 (50.6%)	1.24 (1.06 – 1.45)	1.16 (0.99 – 1.36)
T2DM and awareness				
No T2DM	846 (59.1%)	585 (40.9%)	1 (Reference)	1 (Reference)
With T2DM, but unaware	44 (62.0%)	27 (38.0%)	0.93 (0.69 – 1.26)	0.87 (0.66 – 1.16)
With T2DM, but aware	43 (41.0%)	62 (59.0%)	1.44 (1.22 – 1.71)	1.37 (1.14 – 1.64)

* Adjusted for sex, age, education level, socioeconomic status, daily smoking, alcohol disorder, and physical activity

found that some psychiatric disorders, i.e., generalized anxiety disorder, phobic-anxious disorder and mood disorders, were more frequent among those with T2DM than those without the condition³⁴.

Our results agree with these previous reports, but expand on showing that much of the association between T2DM and anxiety symptoms in a resource-constrained setting, is related to the awareness of that chronic condition. A study conducted in The Netherlands using a population-based cohort of 90,686 participants found that both diagnosed and undiagnosed T2DM were associated with the presence of anxiety disorders; however, the odds of experiencing anxiety were significantly higher among diagnosed (i.e., aware) compared with undiagnosed (i.e., unaware) cases³⁵.

Public health relevance

Our findings support the concept that awareness of T2DM explains the higher prevalence of anxiety symptoms among individuals with this condition. This association, especially among those aware of their T2DM diagnosis, may be related to having lived with this chronic condition and diabetes distress for longer³⁶. In addition, the need for continuous monitoring, taking antidiabetic medication, and the increased risk for future complications or other T2DM-related morbidities may induce anxiety among individuals with T2DM^{16,37}.

Some chronic conditions have been associated with mental health problems, depending on the time of diagnosis. Hypertension, for example, has been associated with depressive symptoms, especially in the first years after diagnosis³⁸. It is therefore necessary to guarantee appropriate mental health assessments of participants with noncommunicable conditions, especially common ones such as hypertension or T2DM. Different tools are available to assess mental health, including the Patient Health Questionnaire 9 (PHQ-9) for depression, and the Goldberg Anxiety test, with nine items, or the General Anxiety Disorder 7 (GAD-7) for anxiety. These tools are short, and can be easily implementable and used during clinical attention

to appropriately detect non-communicable disease cases with mental health problems that required adequate management.

Strength and limitations

The present analysis was conducted using a population-based survey conducted in an area with a high prevalence of T2DM. Cases with diabetes were detected using the OGTT, gold standard for T2DM diagnosis, and a valid tool for anxiety was utilized. Nevertheless, there are limitations that should be highlighted. First, because of the cross-sectional nature of the study, only associations can be reported. Although literature has shown bidirectional association between T2DM and mental health problems such as depression due to hypothalamic-pituitary-adrenal axis dysregulation³⁹, such relationship is controversial in the case of stress and anxiety. Second, some selection bias may have been introduced as the study sample was recruited in a setting with high prevalence of T2DM. Third, some recall bias may arise, especially for covariates such as smoking, alcohol disorder and physical activity. Finally, some variables, such as a previous history of, or treatment for, anxiety, as well as potential confounders, including, but not limited to, comorbidities or T2DM complications, were not assessed.

Conclusions

The association between T2DM and anxiety symptoms was only present among those aware of T2DM diagnosis, but not among those unaware. Evaluation and follow-up of anxiety symptoms may be relevant among those with previous T2DM diagnosis.

Data availability

Underlying data

Figshare:Bernabe-Ortiz, Antonio (2021): T2DM and anxiety, <https://doi.org/10.6084/m9.figshare.16862191.v2>³⁰

This project contains the following underlying data:

- T2DM and anxiety v11.csv (dataset)
- Dictionary (110521).txt (key to variable abbreviations)

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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Rosane Harter Griep 

Laboratório de Educação em Ambiente e Saúde, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

I am satisfied with the improvements made by the authors.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public health, occupational health, cardiovascular diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 16 May 2022

<https://doi.org/10.21956/wellcomeopenres.19823.r50527>

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Pilar Serrano-Gallardo 

Nursing Department, School of Medicine, IDIPHISA, INAECU, Autonomous University of Madrid, Madrid, Spain

No further comments.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health, Chronic diseases, Social Health Inequalities

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 May 2022

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**Pilar Serrano-Gallardo**

Nursing Department, School of Medicine, IDIPHISA, INAECU, Autonomous University of Madrid, Madrid, Spain

- The topic is of interest because both T2DM and anxiety are important public health problems with a major impact on people's health, as well as on health systems and at the societal level. Moreover, the relationship between the two problems remains a phenomenon that needs to be investigated to shed light on the causal pathways between anxiety and other mental health problems and T2DM. Precisely for this reason, the Introduction lacks a reflection on this issue, which would be necessary. The authors reflect that the presence of T2DM seems to be positively associated with an increase in depressive and anxiety symptoms (citation 12), suggesting that T2DM could be a risk factor for triggering depressive and anxiety symptoms. However, this temporal sequence is not clear in the literature, as are its pathogenic mechanisms, see for example the systematic review by Rotella and Mannuci¹ who identified an increased risk of developing diabetes in depressed versus non-depressed subjects, as well as in those taking antidepressant drugs and those with untreated depression.
- Although the method section states that the exposure variable is T2DM, the aim of the study should clarify whether the intention is to explore the influence of the presence of T2DM on having anxiety symptoms or vice versa. Also, within the Method, the statistical analysis should reflect which variable has been taken as the dependent variable for the regression model.
- In the same sense as mentioned in the previous point, table 3 should have a clearer title. In addition, and in relation to the results described in this table in the text, it would be more appropriate to include the PR and their 95%CI for the category "With T2DM, but aware". In the same paragraph, it is not clear where the data is derived from in the sentence: "In addition, those who were aware of their T2DM diagnosis were 56% (95% CI: 13% - 116%) more likely to have anxiety symptoms compared to those who were unaware of their T2DM diagnosis".

- The main limitation of the study is the cross-sectional nature of the design, which prevents capturing the temporal sequence, which is essential in the causal analysis. Although this is reflected in the Discussion, further explanation should be given in this section to support the authors' approach that relies on T2DM as an exposure variable for anxiety (see Joseph et al²).

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health, Chronic diseases, Social Health Inequalities

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 May 2022

Antonio Bernabe-Ortiz, Universidad Peruana Cayetano Heredia, Lima, Peru

The topic is of interest because both T2DM and anxiety are important public health problems with a major impact on people's health, as well as on health systems and at the societal level. Moreover, the relationship between the two problems remains a phenomenon that needs to be investigated to shed light on the causal pathways

between anxiety and other mental health problems and T2DM. Precisely for this reason, the Introduction lacks a reflection on this issue, which would be necessary. The authors reflect that the presence of T2DM seems to be positively associated with an increase in depressive and anxiety symptoms (citation 12), suggesting that T2DM could be a risk factor for triggering depressive and anxiety symptoms. However, this temporal sequence is not clear in the literature, as are its pathogenic mechanisms, see for example the systematic review by Rotella and Mannuci¹ who identified an increased risk of developing diabetes in depressed versus non-depressed subjects, as well as in those taking antidepressant drugs and those with untreated depression.

Response: We have changed the third paragraph of the Introduction to include this topic. Now it reads: *"Although there is evidence supporting the bidirectional relationship between T2DM and some mental health disorders, many of these studies have focused on depression and stress. Thus, the presence of T2DM may seem to be positively associated with increased depressive symptoms, and similarly, depression may increase the risk of diabetes^{11, 12}, increasing at the same time the risk of complications, morbidity and death¹³."*

Although the method section states that the exposure variable is T2DM, the aim of the study should clarify whether the intention is to explore the influence of the presence of T2DM on having anxiety symptoms or vice versa. Also, within the Method, the statistical analysis should reflect which variable has been taken as the dependent variable for the regression model.

Response: We have modified the aim of the study as suggested by the reviewer. Now it reads: *"...this study aimed to explore the potential influence of the presence of T2DM on having anxiety symptoms, with a particular emphasis on those aware of a previous T2DM diagnosis..."*

We have also clarified this in the *Statistical Analysis* section: *"In these models, anxiety was considered the dependent variable, whereas the presence of T2DM was the exposure."*

In the same sense as mentioned in the previous point, table 3 should have a clearer title. In addition, and in relation to the results described in this table in the text, it would be more appropriate to include the PR and their 95%CI for the category "With T2DM, but aware". In the same paragraph, it is not clear where the data is derived from in the sentence: "In addition, those who were aware of their T2DM diagnosis were 56% (95% CI: 13% - 116%) more likely to have anxiety symptoms compared to those who were unaware of their T2DM diagnosis".

Response: We have changed the title of Table 3. Now it reads: *"Effect of type 2 diabetes mellitus (T2DM) on the presence of anxiety symptoms: crude and adjusted models"*. In addition, we have added the PR and 95% CI as suggested: *"those individuals with T2DM, but aware of their diagnosis had a 37% (95% CI: 14% - 64%) greater prevalence of anxiety symptoms compared to those without T2DM"*.

Regarding the sentence: *"In addition, those who were aware of their T2DM diagnosis were 56% (95% CI: 13% - 116%) more likely to have anxiety symptoms compared to those who were unaware of their T2DM diagnosis"*, we compared those with T2DM but aware to those

with T2DM but unaware. So, the result is not in the table but instead in text only. This point is important because those unaware should be similar to those without T2DM. We have clarified that point in the *Statistical Analysis* section as this comparison was not included: "In addition, a different Poisson regression model was also built to assess the difference in the prevalence of anxiety symptoms comparing those with T2DM but aware to those with T2DM unaware".

The main limitation of the study is the cross-sectional nature of the design, which prevents capturing the temporal sequence, which is essential in the causal analysis. Although this is reflected in the Discussion, further explanation should be given in this section to support the authors' approach that relies on T2DM as an exposure variable for anxiety (see Joseph et al²).

Response: We have added some lines regarding this topic according to the reviewer's suggestion: "First, because of the cross-sectional nature of the study, only associations can be reported. Although literature has shown bidirectional association between T2DM and mental health problems such as depression due to hypothalamic-pituitary-adrenal axis dysregulation, such relationship is controversial in the case of stress and anxiety."

Competing Interests: No competing interest to disclose.

Reviewer Report 03 May 2022

<https://doi.org/10.21956/wellcomeopenres.19158.r48941>

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Rosane Harter Griep

Laboratório de Educação em Ambiente e Saúde, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

Thank you for the opportunity to review this interesting article. The article aimed to evaluate the association between type 2 diabetes mellitus (T2DM) and anxiety symptoms, with an emphasis on T2DM awareness. According to the authors, the information about the effect of T2DM awareness on the prevalence of anxiety disorders is scarce, especially in population-based studies. So, the analyses of the article are based on a secondary data analysis using information from a population-based study.

- Despite the relevance of the topic, my main concern with the article is related to the cross-sectional design for analyses. Some studies have shown that mental health could be a risk factor for diabetes. On the other side, some studies have indicated high rates of co-occurrence of the two diseases and support that the relationships between diabetes and depression are bidirectional (please see Zhuang *et al.*, 2017¹, van der Feltz-Cornelis *et al.*, 2021²). Please include this perspective in the introduction and justify the option of the

association between DM to anxiety symptoms. I also suggest testing the bi-directionality of the association between mental health and diabetes.

- Please consider including a recently published article about the same subject as the presented article, among the Latin American population (Barbosa *et al.*, 2022). The results are based on a relevant Brazilian cohort study. The article showed results by gender and observed that women classified with DM were at 54% greater risk (95% CI = 1.06-2.19) of depressive episodes compared to women classified as non-DM. No significant associations were observed for men. I'd like to suggest the authors evaluate gender as a modifier effect on the analyses. The literature is consistent in results about gender differences in the mental health issues (mental health is usually worse among women compared to men), and also the probability that T2DM awareness is different by gender (women presented higher chances of T2DM awareness). So, gender could be an important effect modifier variable.
- Have you collected the duration of T2DM diagnosis? Maybe the time of knowledge of diabetes could be an influencer on the association (more recent diagnosis, worse mental health).
- I am not sure if lifestyle behaviors could be considered potential confounders. For example, physical activities could be considered a mediator between T2DM and mental health (especially among those with a previous diagnosis of T2DM).
- The discussion section is well written.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public health, occupational health, cardiovascular diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 May 2022

Antonio Bernabe-Ortiz, Universidad Peruana Cayetano Heredia, Lima, Peru

Despite the relevance of the topic, my main concern with the article is related to the cross-sectional design for analyses. Some studies have shown that mental health could be a risk factor for diabetes. On the other side, some studies have indicated high rates of co-occurrence of the two diseases and support that the relationships between diabetes and depression are bidirectional (please see Zhuang *et al.*, 2017¹, van der Feltz-Cornelis *et al.*, 2021²). Please include this perspective in the introduction and justify the option of the association between DM to anxiety symptoms. I also suggest testing the bi-directionality of the association between mental health and diabetes.

Response: We have rephrased the third paragraph of the Introduction to include this topic and the references provided. Nevertheless, none of the references given by the reviewer studied the bidirectional association between T2DM and anxiety symptoms. Now it reads: "*Although there is evidence supporting the bidirectional relationship between T2DM and some mental health disorders, many of these studies have focused on depression and stress. Thus, the presence of T2DM may seem to be positively associated with increased depressive symptoms, and similarly, depression may increase the risk of diabetes...*".

We have decided not to test the bidirectionality of the association between T2DM and anxiety as temporality is not evaluable in cross-sectional studies. Anxiety was evaluated in the last 2 weeks prior to the application of the questionnaire, and as a result, anxiety cannot happen before type 2 diabetes.

Please consider including a recently published article about the same subject as the presented article, among the Latin American population (Barbosa *et al.*, 2022). The results are based on a relevant Brazilian cohort study. The article showed results by gender and observed that women classified with DM were at 54% greater risk (95% CI = 1.06-2.19) of depressive episodes compared to women classified as non-DM. No significant associations were observed for men. I'd like to suggest the authors evaluate gender as a modifier effect on the analyses. The literature is consistent in results about gender differences in the mental health issues (mental health is usually

worse among women compared to men), and also the probability that T2DM awareness is different by gender (women presented higher chances of T2DM awareness). So, gender could be an important effect modifier variable.

Response: We have added the reference as requested. On the other hand, we assessed the potential effect of modification of gender on the relationship between T2DM and anxiety. Our results were not significant, and as a result, we decided not to add such results. Based on the comment of the reviewer, we have added such finding in the Methods and Results section.

In the Methods, Statistical analysis section, we add: "Finally, because literature is consistent in results about gender as an effect modifier on the potential effect of T2DM on mental health, we assessed such hypothesis using the likelihood ratio test."

Similarly, we added the finding in the Results section: "Finally, gender was not an effect modifier of the association of interest ($p=0.48$)."

Have you collected the duration of T2DM diagnosis? Maybe the time of knowledge of diabetes could be an influencer on the association (more recent diagnosis, worse mental health).

Response: Unfortunately, that information was not collected, as the original study was centered on recruited participants with recent T2DM diagnoses (those unaware).

I am not sure if lifestyle behaviors could be considered potential confounders. For example, physical activities could be considered a mediator between T2DM and mental health (especially among those with a previous diagnosis of T2DM).

Response: This is a good point highlighted by the reviewer. We decided to include physical activity as a potential confounder as this variable is related to mental health outcomes. For example, high levels of physical activity are associated with a lower risk of depression or stress and potentially could be associated with anxiety. Similarly, evidence suggests that smoking and alcohol disorders are associated with mental health outcomes.

The discussion section is well written.

Response: Thanks.

Competing Interests: No competing interest to disclose.