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A META-ANALYSIS: DEPRESSION AS A RISK FOR THE ONSET OF DIABETES MELLITUS 2

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ABSTRACT

Objective: This study examined the latter association by reviewing the literature and conducting a meta-analysis of longitudinal studies on this topic. **Study design:** Meta analysis. **Setting:** Articles published on Medicine, Psychology, Human Behavioral changes, and Psychiatric Information were searched **Period:** December 2020. **Material and Method:** All studies that examined the relationship between depression and the onset of type 2 diabetes were included. Concluded relative risks were calculated using fixed and random effects models. To explore sources of heterogeneity between studies, subgroup analyses and meta-regression analyses were performed. **Results:**1099studies met our inclusion criteria for this meta-analysis. The concluded relative risk was 3.26 (3.13–3.39) using the fixed effects model and 3.37 (3.14–3.63) using the random-effects model. The differences and heterogeneity between studies could not be explained by the following1. whether studies controlled for undetected diabetes at baseline; 2. the method of diabetes assessment at follow-up; 3. the baseline overall risk of diabetes in the study population; and 4. follow-up duration. **Conclusions:** Depressed persons have a 41% increased risk of developing type 2 diabetes mellitus. The pathophysiological mechanisms underlying this relationship are still unclear and need further research. A randomized controlled study is needed to test whether effective prevention or treatment of depression can reduce the incidence of type 2 diabetes and its health consequences. **Abbreviations** HPA: Hypothalamic-pituitaryadrenocortical. PSAD: Psychosocial aspects of diabetes. PUFA: Polyunsaturated fatty acids

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INTRODUCTION

Diabetes and depression are both common health issues in today's society. There are currently about 200 million people with diabetes worldwide. If nothing is done to slow down the epidemic, the number will exceed 333 million by the year 2025.[1] Moreover, an estimated 121 million people currently suffer from depression: 9% of men and 14% of women will experience a depressive episode in any given year.[2] There is plenteous evidence that suggests that diabetes and depression are associated. According to a recent meta-analysis, the prevalence of depression is doubled in individuals with type 2 diabetes compared with those without diabetes.[3] However, the causal or temporal relationship between depression and type 2 diabetes remains unclear despite having a close association. Depression is often considered a co-existingcondition that results from the daily

burden of having diabetes and/or its complications. Interestingly, there are also indications that depression in turn is an independent risk factor for the development of type 2 diabetes.[4,5] This is an observation that dates back to 1684 when the English physician Thomas Willis noted that emotional factors such as grief or sadness could bring on diabetes.[6,7] About 10 years ago, Eaton and colleagues were the first to report the results of an epidemiological study that confirmed Willis' hypothesis.[6] Since then, several studies and researches have been done on finding the relation between depression and onset of type 2 diabetes longitudinally, with inconsistent findings. Recent studies report that depression is associated with an increased risk of developing type 2 diabetes, while other studies do not find a significant association.

This study aimed to examine the relationship between depression and the risk of the onset of type 2 diabetes by conducting a meta-analysis of longitudinal studies published on this subject in the peer-reviewed literature

MATERIALS AND METHODS

Retrieval of Data from Previous studies

To collect data on depression, human behavior, and diabetes mellitus type 2, studies were selected from PubMed, and Medline. The search was limited to the last 10 years' studies, studies written in English, and the availability of an abstract. Abstracts and titles of the retrieved studies were read out to exclude studies that were irrelevant and does not meet our inclusion criteria.

Inclusion and exclusion criteria

In this meta-analysis, we included all studies that explained and examined the relationship between depression and the onset of type 2 diabetes, irrespective of their study design. In case of availability of Multiple publications from the same study population, we included the most recent studies, regarding that study as an improvement of the older publication, and representing both studies. Data extraction was carried out on the following parameters, particularly regarding 1. name of the author; 2. publication year; 3. study design; 4. follow-up time in years; 5. The number of subjects in the analysis; 6. sex of subjects; 7. age of subjects; 8. method of depression assessment; 9. method of type 2 diabetes assessment; 10. relative risk and 95% Significance; 11. adjustment for confounders; 12. method of exclusion of diabetes patients at baseline; and 13. overall incidence per year.

The method of depression assessment was a diagnosis of depression assessed by a diagnostic psychiatric interview, the assessment of depressive symptoms by a self-reported questionnaire, or a diagnosis by a general practitioner (with an unknown method of diagnosis). The method of assessment of type 2 diabetes was either self-report or screening, i.e. measuring the blood glucose of all subjects. The method of exclusion of diabetes patients at baseline was also either self-report or screening; the latter correcting for undetected diabetes as well. If depressive symptoms were categorized in more than two groups, the relative risk of the highest vs the lowest depressive symptoms group was used. Overall incidence per year was extracted as the crude incidence of type 2 diabetes of the whole study population, divided by follow-up duration.

Statistical Analysis

For each study, the relative risk of the most adjusted model was used to estimate a collected relative risk. Both the fixed effects model and the random-effects model were used. With a fixed-effects model, the variability between studies is exclusively due to random variation, and individual studies are simply weighted by their precision. The random. effects model makes different underlying effects for each study thus making it an additional source of variation. A random-effectsmeta-analysis is more conservative than a fixed-effectsmeta-analysis, as it gives wider CIs around the point estimate, and is recommended for use when heterogeneity between studies exists.[8] In the fixed-effects model, the weight of each study is equal to the inverse variance of the natural logarithm of the

relative risk. In the random-effects model, an extra term is added to the variance according to the Der Simonian and Laird method.[9]

In trying to explain heterogeneity between studies we identified certain study characteristics and assessed whether there was an association between these characteristics and the relative risks of the included studies. Four study characteristics were identified: 1. whether studies controlled for undetected diabetes at baseline; 2. the method of diabetes assessment at follow-up; 3. the overall risk of diabetes of the particular study population; and 4. follow-up duration. The first two characteristics are categorical and therefore a stratified meta-analysis was performed. The last two characteristics are continuous and meta-regression analysis was performed. In these subgroup analyses, only the random-effects model was used. Finally, the influence of adjusting for certain confounders was investigated qualitatively. All statistical analyses were performed using STATA.

RESULTS

The literature search in PUBMED and MEDLINE using 'depression or depressive' and 'diabetes', limited to items with an abstract and written in English, resulted in 2720 articles. After careful selection, 1099 studies appeared to have studied the relationship between depression and the onset of type 2 diabetes longitudinally.[10,20] Searching the online Psyc Info database yielded no additional studies. One of the 1621 studies was excluded.[17] because there was insufficient information in the article to calculate relative risk.

The extracted data of the 2304 studies included in this meta-analysis.Few studies reported relative risks separately for men and women.[18] Those relative risks were pooled using the random-effects model and pooled relative risk (3.26) and its 95% CI (3.14–3.63) were used in further analyses.

Meta-Analysis

The forest plot shows the relative risk and 95% CI of each study and the pooled relative risk of both the fixed effects model and the random-effects model. The pooled relative risk was 3.26 (3.13–3.39) using the fixed effects model and 3.37 (3.14–3.63) using the random-effects model.

Studies with a large standard error (small sample size) and small relative risk are missed out. This could indicate publication bias as studies showing small (or no) associations and large CIs are probably less often submitted by authors and less often published by editors. The Begg-adjusted rank correlation test for publication bias resulted in a p-value of 0.10. Cochran's Q test was statistically significant ($Q=18.264$; $p=0.02$), indicating heterogeneity. Because of this heterogeneity, the pooled relative risk resulting from the fixed effects model should be disregarded. In further analyses, only random-effectsmodeling was performed.

Subgroup and sensitivity analyses

The pooled relative risk (95% CI) of studies that relied on self-reported diabetes to exclude prevalent diabetes at baseline, and thus did not control for undetected diabetes at baseline [10–13, 16, 18], was 2.32 (1.04–1.66). The pooled relative risk (95% CI) of studies that did control for undetected diabetes by screening all subjects for high blood glucose [14, 15, 19] was slightly higher, namely 3.54 (1.07–4.23). The four studies [10–13] that determined type 2 diabetes at follow-up using self-report had a pooled relative risk (95% CI) of 1.32 (1.98–3.78). The studies that assessed diabetes onset by measuring glucose levels.[14,16,18,19] instead of self-report, had a pooled relative risk (95% CI) of 1.43 (2.12–3.81). The overall risk of diabetes in each study, i.e. the overall incidence per year, was plotted against the natural logarithm of the relative risk of each study. The regression coefficient (95% CI) was 18.6 (−35.9 to 73.1) but not significantly different from zero, which means there is no relation between the overall risk of diabetes and relative risk. Also, no relation was found between follow-up duration and relative risk. The regression coefficient (95% CI) was −0.0018 (−0.045 to 0.042).The influence of adjusting for confounders presents an overview of the unadjusted and adjusted relative risks (95%

CI) which were reported by each study, with a detailed description of the different sets of confounders that were used. Unfortunately, as the studies adjusted for many different sets of confounders, it is impossible to quantify the exact influence of adjusting for certain confounders. Qualitatively, no association was seen between adjustment for certain confounders and the magnitudes of the relative risks, as some relative risks decreased after adjusting for certain confounders and others increased.

DISCUSSION

This study represents the application of a meta-analysis of literature regarding depression as a risk factor for the onset of type 2 diabetes mellitus. This meta-analysis is the result of those studies which suggest that adults with depression or high-depressive symptoms have a 41% increased risk of developing type 2 diabetes compared with those who are not depressed or have low-depressive symptoms. Heterogeneity between studies regarding relative risks could not be explained by: 1. whether studies controlled for undetected diabetes at baseline; 2. the method of diabetes assessment at follow-up; 3. the baseline overall risk of diabetes in the study population; or 4.follow-up duration. Also, adjustment for several confounders did not explain differences in effect sizes between studies. Before concluding the findings of this meta-analysis, we will discuss several biases which may have confounded our results. First, reversed causality could be an issue. In reversed causality, presymptomatic persons with diabetes develop depression. These subjects are more likely to develop symptomatic diabetes and this will overestimate the effect size. However, we believe that this hypothesis is less probable, as we have found that studies that exclude cases with undetected diabetes at baseline showed a pooled relative risk similar to the overall pooled relative risk. Second, ascertainment or diagnostic bias could play a role in explaining the results of the present meta-analysis. Subjects with depression tend to visit their doctor more often and may thus be more likely to be recognized as having diabetes.[21] This bias could have occurred particularly in studies that relied on self-reported diabetes at follow-up. However, the pooled relative risk of studies that assessed diabetes by measuring glucose levels (as opposed to self-report or doctor's diagnosis) appeared to be similar to the overall pooled relative risk. These findings do not support the notion that ascertainment bias explains the results of our study. Third, although all studies adjusted for multiple potential confounders, residual confounding may have influenced our findings. Given the fact that most of the studies adjusted for a considerable number of confounders (median 7, range 4–14), we consider this as less likely. In contrast, over correction may have occurred. It may be true that some studies adjusted for intermediate rather than confounding factors, resulting in underestimation of the concluded relative risk.

A fourth potential bias of the present meta-analysis is publication bias, which is a threat to the validity of every systematic review. We tried to minimize publication bias by asking members of relevant study groups whether they had any unpublished/rejected results of studies investigating the relationship between depression and the onset of type 2 diabetes. Still, the funnel plot drawn did show some asymmetry, as studies with a small sample size and low relative risk were missing, which indicates publication bias. However, even after excluding the three smallest studies.[13,16,19] a significant, pooled relative risk was found. In sum, reversed causality, ascertainment bias, confounding factors, and publication bias do not seem to explain the relationship found in this meta-analysis. Another potential problem in this meta-analysis is that each study used a different method to assess depression. These different methods can be categorized into four hierarchical groups. First, only a few studies used a diagnostic interview schedule [13], which is the gold standard for the diagnosis of major depression. Second, many studies used validated depression severity scales, the Zung Depression Scale, the General Health Questionnaire, the Beck Depression Inventory, and the Center for Epidemiological Studies Depression Scale.[14,16,18,19]

In these studies, validated cutoff scores were used to define levels of depressive affect. The sensitivity and specificity of these measures proved to be acceptable.[22] As a third measure of depression, three studies used semi-depression severity scales: the General Well-Being Depression Scale, the Mental Health Index of the SF-36, and the Vital Exhaustion Scale.[11,12,15] These measures were not designed to measure depression severity but are commonly used as a proximal measure of negative affect.

The relative risks found in the studies that used these semi-depression scales were similar to the relative risks of the studies that used the more sophisticated scales and showed the same direction of effect. Few studies from the early 20s used the general practitioner's diagnosis of depression.[10] It has been reported that depressive symptoms are not recognized in about half of attending patients with depressive disorders in general practice.[23] and this under-recognition of depression would result in an underestimation of the effect size between depression and onset of diabetes. Therefore, we performed a sensitivity analysis excluding this study, which resulted in a slightly higher pooled relative risk: 3.44 (2.21–3.71). A second issue in the method of assessment of depression is that some studies made three categories of depression levels.[12,16] and very few studies divided the depression scores into quartiles.[15] This might have influenced our results, as we used the relative risk of the highest vs the lowest group of depressive symptoms. It is seen, in these three studies, that the relative risk of the highest vs the lowest group is larger than the relative risks for the other categories. The additional stratified analysis also showed that the pooled relative risk for these three studies is somewhat higher (3.59 [2.16–4.17]) than the pooled relative risk of the other studies (2.26 [2.02–2.56]). However, we still believe that the relative risk of the lowest vs the highest category of depression represents best the difference between 'no/yes' depression.

In the literature, several hypotheses have been described regarding the pathophysiological mechanisms that could explain the increased risk of type 2 diabetes in depressed subjects.

First, the hypothesis of increased activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and sympathetic nervous system will be discussed. Depression is associated with increased activity of the HPA axis and the sympathetic nervous system.[24] resulting in increased cortisol release and increased release of the catecholamines epinephrine and norepinephrine. Cortisol is a stress hormone, which stimulates glucose production, increases lipolysis and circulating free fatty acids, decreases insulin secretion from beta cells, and decreases sensitivity to insulin.[24,27] It is postulated that a chronically high cortisol level, which is a feature of about 50% of depressed patients, results in obesity, insulin resistance, and type 2 diabetes.[24,28,29] Some studies found evidence for this hypothesis.[27,28] Epinephrine generates responses in glucose and fat metabolism similar to those of cortisol.[26] also possibly resulting in insulin resistance and type 2 diabetes.

The credibility of this hypothesis is further strengthened by findings on other medical problems that are accompanied by hypercortisolemia. For example, Cushing's syndrome, sleeping disorders, work stress, and schizophrenia.[30,33] appeared to be associated with an increased level of cortisol and also with an increased risk of type 2 diabetes and insulin resistance, although studies on sleep disorders showed inconsistent results regarding the risk of diabetes.[33,37]

A second hypothesis is that dysregulation of the immune system plays a role in the relationship between depression and increased risk of type 2 diabetes. Both depression and type 2 diabetes are found to be associated with increased C-reactive protein, TNF-α, and proinflammatory cytokines, including IL-6.[38,42] A contradiction between this hypothesis and the first hypothesis is that cortisol inhibits inflammation and the

immune response, whereas depression is associated with both elevated cortisol and increased inflammatory markers. A recent finding possibly explains this contradiction by showing that melancholic depressed patients had increased HPA axis activity and no signs of inflammation, whereas non-melancholic depressed patients did show signs of inflammation and normal HPA axis activity.[43]

Finally, a low intake or impaired metabolism of ω-3 polyunsaturated fatty acids (PUFA) could contribute to both depression and type 2 diabetes. ω-3 PUFA has direct and indirect actions on cerebral function and depletion of these fatty acids is associated with psychiatric illness, including depression.[44,45] In addition, there is evidence that a low intake of ω-3 PUFA is associated with an increased risk of type 2 diabetes, but these results were concluded to be less convincing.[44]

It is known that the most important risk factor for type 2 diabetes is obesity.[46,47] and that physical inactivity further increases the risk, independently of obesity.[48] Given the findings in our meta-analysis, the depressive effect could be regarded as an additional risk factor for type 2 diabetes, comparable in size to smoking and physical activity.[47,49] Clinicians should be made aware of the fact that the depressive effect might be an additional risk factor for type 2 diabetes as this makes adequate detection and treatment of depression even more important than it already is. Assessing fasting glucose and advising exercise in depressed patients might also prevent type 2 diabetes.

CONCLUSION

This meta-analysis suggests that depression is a risk factor for the onset of type 2 diabetes mellitus, comparable in size to smoking and physical activity. However, further well-designed research with adequate control for confounding factors is needed to establish the exact size of the relationship. The influence of the duration of depression or the change in depression over time on the risk of type 2 diabetes should be studied especially. Furthermore, research is warranted to elucidate the pathophysiological mechanisms underlying the association. With the expectation of more than 100 million new cases of type 2 diabetes in the coming two decades, prevention becomes more important every day. Whether the prevention of depression or the treatment of depressed people can truly prevent or delay the onset of type 2 diabetes mellitus remains to be tested in long-term intervention studies.

Conflict of interest:

Conflict of interest regarding the publication of this paper is none.

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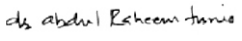
2	Abdul Raheem Tunio	Author	
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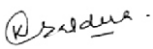
4	Kausar Abbas	Author	
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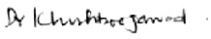
6	Khushboo Jawed	Author	
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