PREVALENCE AND COMORBIDITY OF DEPRESSION AND ANXIETY DISORDERS IN DIABETIC PATIENTS: A META-ANALYSIS

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Abstract

**Background:** Depressive and anxiety disorders are common among diabetic patients and are associated with high risk of diabetes-related complications and mortality. This study presents a meta-analysis of studies investigating depression and anxiety in diabetic patients.

**Aim:** To conduct a meta-analysis in order to estimate the prevalence and odds ratio of clinically diagnosed depression and anxiety in individuals with diabetes mellitus (type 1 and 2) compared to those without.

**Methods:** PubMed database was searched using MeSH terms to identify relevant studies that reported the prevalence of depression and/or anxiety in diabetes. Published reference lists of other meta-analyses on the subject were also examined. We used Event Rate (ER) to assess the prevalence rates and Odds Ratios (ORs) to assess the prevalence and likelihood (respectively) of depressive and anxiety disorders. Age and gender were checked as moderating factors.

**Results:** In total, 16 studies met the inclusion criteria; 5 (30%) studies included a non-diabetic control group. Prevalence rates for depression in diabetic patients based on 11 studies varied from 8.7% to 21.4%, while for anxiety disorders rates varied from 10.1% to 27.2%. Older patients manifested higher rates of depression and anxiety. Less female diabetic patients manifested depression in comparison to men, while more female diabetics had anxiety in comparison to male patients. In controlled studies, the odds of depression in the diabetic group were 1.7 times that of the non-diabetic control group (OR= 1.722, (95% CI= 1.347 to 2.202, p<0.001), while the odds ratio of anxiety in diabetic patients were not significant. Also, in the controlled studies there was no significant correlation of age or gender with the prevalence of depression in the diabetic group.
Conclusions: Analyses demonstrate a moderate to high prevalence of depression and anxiety among diabetic patients. Finally, diabetics have a higher risk to manifest depressive disorders in comparison to people without.
Introduction

1.1 Diabetes Mellitus

Diabetes Mellitus (DM), commonly referred to as diabetes, is a chronic, lifelong condition. Diabetes results from defects in insulin action, secretion or both (Alberti & Zimmet, 1998) meaning that the condition is due to the pancreas not producing the proper amount of insulin or the body cells not responding properly to the insulin produced (Shoback, 2011).

Diabetes consists of a group of metabolic diseases characterized by hyperglycemia, a condition in which there are high blood sugar levels over a prolonged period of time (Herman, 2007). Common symptoms of marked hyperglycemia include weight loss, increased thirst (polydipsia) and hunger (polyphagia), and frequent urination (polyuria) (Cooke, Plotnick, 2008).

Diabetes Mellitus is classified into two broad etiopathogenic categories; type 1 and type 2. Gestational diabetes is the third main form of diabetes, and it occurs in pregnant women with high blood sugar levels. Unlike diabetes 1 and 2, gestational diabetes is transient and may improve or disappear after delivery (Cash, 2014).

Diabetes type 1 is characterized by a deficiency of insulin secretion, and results from the autoimmune destruction of the insulin-producing beta-cells in the pancreas (Rother, 2007). This type was formerly known as juvenile diabetes, as it is usually diagnosed in children and young adults. Administration of insulin therapy is essential, life-long and usually doesn’t impair normal daily activities and function. Diabetes type 1 affects between 5% and 10% of diabetic cases (American Diabetes Association, 2014). Diabetes type 2 is characterized by hyperglycemia and insulin resistance, which may be combined with inadequate compensatory insulin secretion (Shoback, 2011). Diabetes type 2 is the most prevalent form of diabetes, as it accounts for almost 90% of diabetic cases (American Diabetes Association, 2014). Excessive body weight and
absence of physical exercise are the primary causes of this form of diabetes (Abdullah, Peeters, de Courten & Stoelwinder, 2010). This type is initially managed by exercise and diet and if blood sugar levels remain high, treatment with medication such as metformin or insulin may be used (Turner, Cull, Frighi, Holman, 2005).

The chronic high blood sugar of diabetes is related with long-term damage, dysfunction and failure of various organs (Alberti & Zimmet, 1998), commonly the kidneys, nerves, eyes, heart and blood vessels. Acute, life-threatening complications of uncontrolled or untreated diabetes include diabetic ketoacidosis and the nonketotic hyperosmolar syndrome (Kitabchi, Umpierrez, Miles, Fisher, 2009).

Long-term complications of diabetes include nephropathy, often resulting in kidney failure; retinopathy with potential damage to the eyes or loss of vision; proximal diabetic neuropathy that causes weakness and painful muscle atrophy; peripheral neuropathy associated with diabetes-related foot problems, such as foot ulcers or Charcot joints with risk of amputation; autonomic neuropathy leading to cardiovascular and gastrointestinal complications (Alberti & Zimmet, 1998). Also, diabetic patients are at greater risk for stroke, cardiovascular (Herman, 2006; Sarwar et al., 2010) and cerebrovascular disease (Sarwar et al., 2010), and about 75% of deaths in diabetic patients are due to coronary artery disease (O'Gara et al., 2013).

In 2013 the prevalence of diabetes was estimated at 382 million people worldwide, while according to the World Health Organization, diabetes was the 8th leading cause of death in 2012, resulting in 1.5 million deaths. Diabetes mellitus occurs throughout the world, both in developed and developing countries, but remains uncommon in the underdeveloped world. Globally, the prevalence of diabetes is similar amongst women and men (Vos et al., 2014). Gale and Gillespie
in their article on Diabetes and Gender in 2001, note that it is often considered to be little bias related to gender or sex differences within Type 1 or Type 2 diabetes mellitus. Specifically, diabetes type 1 diabetes is considered to be the only major organ-specific autoimmune disorder not to be more prevalent in female populations (Gale & Gillespie, 2011). Type 2 is equally prevalent among male and female populations, while some evidence suggests slight male preponderance in middle age (Gale & Gillespie, 2001). With regard to age, Wild et al. (2004), report that in developed countries the majority of diabetics are >64 years of age, while in developing countries the majority of diabetic people is in the 45-65 year range.

### 1.2 Depression and anxiety in diabetes mellitus

Depression refers to a state of low mood and indisposition to activity that can influence one’s thoughts, behavior, emotions and sense of well-being (Diagnostic and Statistical Manual of Mental Disorders, fifth edition, American Psychiatric Association 2013). Depressed mood can be a feature of major depressive disorder. Individuals with clinical depression can experience feelings of sadness, fatigue, guilt, worthlessness, lack of concentration, irritability, suicidality and changes in sleep, appetite and/or activity (Diagnostic and Statistical Manual of Mental Disorders, fifth edition, American Psychiatric Association 2013). Depressive mood disorder is a major cause of morbidity worldwide and as of 2010 affects approximately 4.3% of the global population (Vos et al. 2012). Population studies have consistently demonstrated clinical depression to be twice as common in females than in males (Kuehner, 2003).

Anxiety disorders constitute of a category of mental disorders characterized by feelings of fear and anxiety (Diagnostic and Statistical Manual of Mental Disorders, fifth edition, American Psychiatric Association 2013). Fear manifests as a reaction to current events, while anxiety is a worry concentrated on future events (Diagnostic and Statistical Manual of Mental
Disorders, fifth edition, American Psychiatric Association 2013). Common physical symptoms caused by these emotions are racing heart and shakiness (Diagnostic and Statistical Manual of Mental Disorders, fifth edition, American Psychiatric Association 2013). Among others, anxiety disorders include: generalized anxiety disorder, specific phobia, panic disorder, social anxiety disorder and post-traumatic stress disorder (Diagnostic and Statistical Manual of Mental Disorders, fifth edition, American Psychiatric Association 2013). Often, there is comorbidity of anxiety with other mental disorders, such as major depressive disorder and bipolar disorder. In 2010, anxiety disorders affected approximately 4.5% of the global population, and are more prevalent in women (5.2%) than men (2.8%) (Vos et al., 2012).

There are studies suggesting that depression and diabetes are comorbid to a significant extent and that depressive disorders are associated with high risk of diabetes-related complications and mortality (Vanderlip, Katon, Russo, Lessler, & Ciechanowski, 2014). It has been reported that depression affects about 20% to 25% of diabetic patients, is common in both type 1 and type 2 diabetes, and has significant effects on the course and outcome of this medical condition (Ladea, Barbu, & Rosu, 2013). Depressive disorders are a major factor causing hospital admissions among diabetic patients (Erkie, Feleke, Desalegne, Anbessie, & Shibre, 2013) and out-patient attendances and emergency department presentations with diabetes-related difficulties (Garrett & Doherty, 2014).

The interaction of depressive disorders and diabetes has been found to be synergistic, impairing overall functioning and quality of life. Depression has additional importance due to its association with poor outcomes in disease control (Joseph, Unnikrishnan, Babu,, Kotian, & Nelliyanil, 2013), poor metabolic control, low compliance with diabetes treatment and greater risk for micro- and macrovascular disease complications needs reference. In this case, metabolic
control refers to glycemic management (control of glucose levels) and disease control refers to the general management of the disease (i.e. self-care, exercise, adherence to diet, commitment to therapy, monitoring of glycemic levels).

The prevalence of Generalized Anxiety Disorder (GAD) in diabetic patients is estimated up to 14%, while anxiety symptoms can influence up to 40% of the diabetic population (Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002). Anxiety disorders, like depressive disorders are associated with poor adherence to treatment as well as inadequate glycemic control (Collins, Corcoran, & Perry, 2009).

Recent studies indicate that elevated glucose levels can influence the development of anxiety and depressive disorders (Wang, Tsai, Chou, & Chen, 2008). On the other hand, there is evidence that depression is a risk factor for the development of diabetes (Mezuk, Eaton, Albrecht, & Golden, 2008). These findings may suggest that there is a bidirectional association between the existence of diabetes and the occurrence of depressive disorders, although few studies have assessed or reviewed this hypothesis.

There are several meta-analyses that describe the relationship between diabetes and depression. In 2001, Anderson et al. found that the prevalence of comorbid depression was 28% in diabetic women and 18% in diabetic men. Another meta-analysis by Ali, Stones, Peters, Davies and Khunti in 2006 showed similar results with depression rates significantly higher in diabetic women than in diabetic men (23.8% and 12.8% respectively). Anderson et al. highlight that the prevalence of comorbid depression was notably higher in uncontrolled studies (30%) than in controlled studies (21%). A systematic review by Barnard, Skinner and Peveler (2006) indicates that the incidence of clinical depression in controlled studies was 12% and in studies with no control group the prevalence of clinical depression was 13.4%.
Evidence based on systematic reviews on this topic indicate that depression is a substantial risk factor for diabetes (Mezuk et al., 2008) and that depressive disorders are associated with increased risk of mortality in diabetic patients (Park, Katon, Wolf, 2013; Van Dooren, Nefs, Schram, Vehrhey, Denollet, Pouwer, 2013). There are fewer meta-analyses and articles researching the interaction between anxiety disorders and diabetes compared to those investigating the relationship between depression and diabetes.

It is documented that approximately one third of people with diabetes face psychological and/or social issues which interfere with their ability to self-manage their disease (Garrett & Doherty, 2014). This suggests that it is important for more studies to be carried out in order to examine in further detail the proportion and the components associated with the prevalence of depressive and anxiety disorders amongst people with diabetes.

1.4 Aim of the study

The primary objective of this study is to investigate the prevalence of clinically diagnosed depression and anxiety disorders among patients with diabetes mellitus (type 1 and 2) using a meta-analysis. A secondary aim of this report is to examine the role of age and gender in relation to depression and anxiety in the diabetic population. Scientific research has found depression and anxiety to be more prevalent in women than in men (Kuehner, 2003; Vos et al., 2012). Moreover, diabetes mellitus is considered to be an age-prevalent disease, with increased chances of diagnosis as one ages (Gambert & Pinkstaff, 2006). Therefore, this study evolves around the following research questions: a) What is the prevalence of depression and anxiety disorders in diabetic people? b) Are there differences in the prevalence of depression and anxiety disorders in diabetic patients compared to healthy controls? c) Are there effects of age and gender in the context of the comorbidity of diabetes and the aforementioned mental disorders?
Methods

2.1 Online search strategy and information sources

A systematic electronic research was conducted from December 2014 until January 2015 using the PubMed online search engine, in order to identify and scrutinize studies that investigated the comorbidity of depression and anxiety disorders with diabetes. The terms entered in the search engine were the following: (“diabetes”) AND (“depression” OR “depressive disorder”) and in a separate search, (“diabetes”) AND (“anxiety” OR “anxiety disorder”).

The initial search showed 10,492 articles that were screened based on their titles and abstracts, while papers that didn’t provide enough information in the abstract were read in full form.

Inclusion criteria were: a reported diagnosis of diabetes and diagnosis of depressive/anxiety disorders by a clinician. In addition the article should report the necessary data and all the results should be published in a peer reviewed journal.

Studies were excluded when data is reported in meta-analyses, when the studies report self-rated depressive/anxiety symptoms, when studies are performed on non-human subjects and finally when studies are not written in English, French, Spanish or Greek, German, Dutch or Italian.

Data collection

The data extracted for the writing of this meta-analysis include information on authors, year of publication, journal of publication, country that the study took place, study design, setting
of the research (i.e. hospital, institution, home doctors), diagnosis of diabetes and diagnosis of depression and/or anxiety (based on clinical interview). Other information included refer to the number of participants (cases/controls) or number of patients (in larger population-based studies), specific characteristics of the population in research (age, gender) and follow-up information, if such information was available.

**2.2 Study selection**

In the end of the first screening, studies were eligible when i) structured clinical interviews were used for the psychological assessment of depression and/or anxiety ii) depression or anxiety diagnosis was based on ICD (World Health Organization, 2014) diagnostic codes c) prevalence rates of depression and/or anxiety in patients with diabetes were reported iii) prevalence rates of diabetes in patients with depression and/or anxiety were reported iv) prevalence rates of depression and/or anxiety of diabetic samples were directly compared to those of healthy control groups v) cohort studies registered the incidence of depression and/or anxiety and diabetes.

The structured clinical interviews used for the assessment and diagnosis of depression and anxiety are the following: Composite International Diagnostic Interview (CIDI) (Robins et al., 1988), Structured Clinical Interview (SCID) (Spitzer, Williams, Gibbon, First, 1992), Diagnostic Interview Schedule (DIS) (Robins, Helzer, Croughan, Ratcliff, 1981), Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and the Computerized Diagnostic Interview Schedule (C-DIS) (Blouin, Perez, Blouin, 1988).

The International Classification of Diseases (ICD) is developed as a health care classification system in order to provide a system of diagnostic codes for the classification of
diseases (World Health Organization, 2014). The ICD is published by the World Health Organization (WHO) and is used globally for mortality and morbidity statistics and epidemiology, as well as in reimbursement systems and in automated decision support in health care. In the case of mental and behavioral disorders, the ICD code system is based on the Diagnostic and Statistical Manual of mental disorders (DSM) and is used to provide diagnostic assistance and statistically classify mental health disorders (World Health Organization, 2014).

2.2 Data Extraction

From the initial overview of the PubMed online results (10,492 articles) we concluded in 32 possibly relevant articles, of which 16 were found eligible for this study. A data extraction worksheet was developed and used to gather information on the author’s data; year of publication; country and setting where the study took place; sample sizes; method of psychiatric assessment or diagnosis of diabetes; adjusted and/or unadjusted odds ratios and confidence intervals (if applicable); prevalence of depression and/or anxiety in diabetic samples.

Data on the demographic characteristics of the diabetic samples were extracted as well, including the mean/median age and the percentage of female subjects in a particular study. When the mean age was not given but data on the age were presented in age bands, the median age was calculated using the age band with the larger amount of participants.

2.3 Statistics

The statistical analyses were performed using the Comprehensive Meta-Analyses program (CMA), version 2 (Borenstein, Hedges, Higgings & Rothstein, 2009). Random-effects models were applied in order to calculate i) the effect sizes of the prevalence of depression and/or anxiety between diabetic samples and healthy control groups ii) the point estimates of the
prevalence of the aforementioned psychiatric disorders in the diabetic samples. For the studies that provided data solely on diabetic samples, the prevalence of depression and anxiety was computed using the event-rates (ER), centered at 0.00 with 95% confidence intervals, while for the studies that provided data on diabetic samples and healthy controls, the comparison of prevalence of depression and anxiety between those groups was computed using the Odds-Ratio (OR), centered at 1.00 with 95% confidence intervals. Furthermore, meta-regression analyses were performed to illustrate possible effect of age and/or gender on the strength of the association between diabetes and depression and/or anxiety.

The variation in study outcomes between studies was measured by Cochran’s Q statistic value with 95% Confidence Interval CI, and the extent of heterogeneity was calculated by the I² statistic value, which illustrates the proportion of variation that is due to heterogeneity across the studies rather than chance (Higgins and Thompson, 2002; Higgins et al., 2003). To check for possible publication bias the Egger’s regression test was computed. Publication bias was also illustrated through funnel plots.

3. Results

3.1 Description of the sample

Overall, 16 studies met the criteria set for this meta-analysis. Sample sizes and demographic characteristics of the samples are summarized in Table 1. The sample size of the studies included ranged from $N = 46$ to $N = 782020$. In 9 out of 16 studies the percentage of females was larger than that of the males, in 4 studies there were more male participants and in another 3 studies men and women were equally represented in the sample. In total, 4 studies provided incomplete or missing data on the mean age and/or female percentage. The study of
Dowden et al. didn’t provide information on the mean age and female percentage of the sample. Also, information on gender distribution was not applicable for the study of Pibernik-Okanovic et al. (2004) and of Mayou et al. (1991). Data on the mean age of the sample was missing from the study of Egede (2004).

Furthermore, 11 studies examined the association of diabetes with depression, 1 study focused on anxiety in diabetic patients, while 7 studies reported data on both depressive and anxiety disorders in diabetic samples. The majority of the studies (7 studies) were conducted in Europe (France, Sweden, Finland, Poland, Spain, Croatia and Great Britain) and in USA (6 studies). Of the remaining studies, one was conducted in Taiwan, one in India and one in Australia.

<table>
<thead>
<tr>
<th>Author, Year of publication</th>
<th>Sample size (N)</th>
<th>Age (n)</th>
<th>Female percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wandell et al. 2014 a</td>
<td>96103</td>
<td>50, median</td>
<td>43</td>
</tr>
<tr>
<td>Lynch et al. 2014</td>
<td>625903</td>
<td>64, mean</td>
<td>2</td>
</tr>
<tr>
<td>Alonso-Moran et al. 2014</td>
<td>126894</td>
<td>65, median</td>
<td>74.2</td>
</tr>
<tr>
<td>Ali et al. 2013</td>
<td>122</td>
<td>47.2, mean</td>
<td>50.8</td>
</tr>
<tr>
<td>Lin et al. 2012</td>
<td>782020</td>
<td>57, median</td>
<td>50</td>
</tr>
<tr>
<td>Dowden et al. 2011</td>
<td>1592</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Kokoszka et al. 2009</td>
<td>101</td>
<td>64, mean</td>
<td>60</td>
</tr>
<tr>
<td>Pibernic-Okanovic et al. 2005</td>
<td>384</td>
<td>57, mean</td>
<td>*</td>
</tr>
<tr>
<td>Thomas et al. 2003 a</td>
<td>104</td>
<td>50.6, mean</td>
<td>73.1</td>
</tr>
<tr>
<td>Nichols &amp; Brown 2003</td>
<td>16190</td>
<td>61, mean</td>
<td>63</td>
</tr>
<tr>
<td>Cohen et al. 1997 a</td>
<td>49</td>
<td>36.3, mean</td>
<td>62</td>
</tr>
<tr>
<td>Mont-Marin et al. 1995 a</td>
<td>46</td>
<td>51, mean</td>
<td>63</td>
</tr>
<tr>
<td>Kokkonen at al. 1995 a.</td>
<td>63</td>
<td>20.9, mean</td>
<td>41.3</td>
</tr>
<tr>
<td>Mayou et al. 1991 a.</td>
<td>109</td>
<td>21.9, mean</td>
<td>*</td>
</tr>
<tr>
<td>Wells et al. 1989 a</td>
<td>154</td>
<td>39.5, mean</td>
<td>50.4</td>
</tr>
<tr>
<td>Lustman et al. 1986 a</td>
<td>114</td>
<td>40, mean</td>
<td>67</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wandell et al. 2014 b</td>
<td>96103</td>
<td>50, mean</td>
<td>43</td>
</tr>
</tbody>
</table>
3.2 Prevalence of depression and/or anxiety in diabetic patients.

The prevalence of depressive disorders in diabetic samples based on 11 studies (N=1633294) varied from 8.7% to 21.4% (see Figure 1.). Prevalence rates for anxiety disorders among diabetics based on data from 6 studies (N= 102085) varied from 10.1% to 27.2 % (see Figure 2.). The overall estimate of depressive disorders in diabetic samples is 13.9% while for anxiety disorders is 17.0%.

Table 1. Sample sizes of diabetic patients and demographics.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Sample Size</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al. 2011</td>
<td>5685</td>
<td>59</td>
<td>52</td>
</tr>
<tr>
<td>Thomas et al. 2003 b</td>
<td>104</td>
<td>50.6</td>
<td>73.1</td>
</tr>
<tr>
<td>Cohen et al. 1997 b</td>
<td>49</td>
<td>35.6</td>
<td>57</td>
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<tr>
<td>Mont-Marin et al. 1995 b</td>
<td>46</td>
<td>51</td>
<td>63</td>
</tr>
<tr>
<td>Kokkonen at al. b</td>
<td>63</td>
<td>20.9</td>
<td>41.3</td>
</tr>
<tr>
<td>Mayou et al. 1991 b</td>
<td>109</td>
<td>21.9</td>
<td>*</td>
</tr>
<tr>
<td>Wells et al. b</td>
<td>154</td>
<td>39.5</td>
<td>50.4</td>
</tr>
<tr>
<td>Lustman et al. 1986 b</td>
<td>93</td>
<td>40</td>
<td>67</td>
</tr>
</tbody>
</table>

Figure 1. Prevalence rates of depression in diabetic samples.
Figure 2. Prevalence rates of anxiety in diabetic samples.

Meta regression analyses

Analyses illustrate a significant association of age and gender with the prevalence of depression in diabetic patients ($p < 0.001$). There was a positive correlation between age and depressive disorders in diabetic patients, as older patients had higher depression prevalence ($slope = 0.099$, 95% $CI = 0.908$ to $0.100$, $p = < 0.001$) (see Figure 3). On the other hand, gender was negatively associated with depression ($slope = -0.015$, 95% $CI = -0.016$ to $-0.015$, $p = < 0.001$), as less female diabetic patients manifested depressive disorders in comparison to men.

Figure 3. Regression of Age in diabetics with comorbid depression.
Age was positively associated with the prevalence of anxiety disorders since older patients had higher anxiety rates \( (slope = 0.064, \ 95\% \ CI = 0.055 \text{ to } 0.072, \ p = < 0.001) \). Gender was also positively correlated with anxiety \( (slope = 0.098, \ 95\% \ CI = 0.090 \text{ to } 0.106, \ p = <0.001) \), as more female diabetics manifested anxiety disorders compared to male patients. Finally, both age and gender were significantly associated with anxiety disorders \( (p = < 0.001) \).
A high degree of heterogeneity was observed across the core analyses for depressive ($Q = 43899.662$, $df (Q) = 10$, $p = <0.001$, $I^2 = 99.977$) and anxiety disorders ($Q = 621.710$, $df (Q) = 5$, $p = <0.001$, $I^2 = 99.196$). Moreover, according to Egger’s test for depressive ($t = 0.31958$, $p = 0.75658$) and anxiety disorders ($t = 1.86714$, $p = 0.13528$) publication bias was not significant for these studies; for funnel plots see Figure 7,8.
3.3 Prevalence of depression and/or anxiety between diabetic samples and healthy control groups.

To estimate the association of depressive and/or anxiety disorders in diabetics compared with healthy controls, a pooled random effects meta-analysis was conducted using data from 5 studies, which examined the cross-sectional association between depression and/or anxiety in diabetics compared with those without diabetes. This analysis included data for 16623 patients with diabetes and 3313 individuals without diabetes.

The odds ratio for depression was significantly increased in patients with diabetes compared to those without. The overall effect size was $OR=1.722$ (95% CI= 1.347 to 2.202, $p<0.001$), meaning that diabetic patients were 1.7 times more likely to manifest depressive disorders than people without diabetes.

In contrast, the odds ratio for anxiety in diabetic patients was not significant ($p = 0.68$) with overall effect $OR=0.693$ (95% CI= 0.122 to 3.954).
Figure 9. Forest plot and effect sizes for random meta-analysis on the prevalence of depression in diabetic samples compared to healthy controls.

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Ali et al.</td>
<td>2.365</td>
<td>1.411</td>
<td>2.308</td>
</tr>
<tr>
<td>Thomas et al.</td>
<td>1.041</td>
<td>0.930</td>
<td>2.775</td>
</tr>
<tr>
<td>Nakhoi and Kikkursen</td>
<td>1.298</td>
<td>0.526</td>
<td>3.107</td>
</tr>
<tr>
<td>Wells et al.</td>
<td>2.269</td>
<td>1.372</td>
<td>3.716</td>
</tr>
<tr>
<td>Random</td>
<td>1.222</td>
<td>1.347</td>
<td>2.262</td>
</tr>
</tbody>
</table>

Figure 10. Forest plot and effect sizes for random meta-analysis on the prevalence of anxiety in diabetic samples compared to healthy controls.

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
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<tr>
<td>Thomas et al.</td>
<td>0.453</td>
<td>0.106</td>
<td>1.105</td>
</tr>
<tr>
<td>Korkonen</td>
<td>0.136</td>
<td>0.017</td>
<td>1.068</td>
</tr>
<tr>
<td>Wells et al.</td>
<td>2.922</td>
<td>2.006</td>
<td>4.464</td>
</tr>
<tr>
<td>Random</td>
<td>0.853</td>
<td>0.122</td>
<td>3.954</td>
</tr>
</tbody>
</table>

**Meta regression analyses**

To detect possible effect of age and gender in diabetic patients with co-morbid depressive or anxiety disorders, meta-regression analyses were conducted. There was a negative correlation of age with depressive disorders (slope = -0.007, 95% CI = -0.022 to 0.008, p = 0.359), as older diabetic patients reported lower rates of depression. Female percentage was also negatively associated with the prevalence of depression in diabetic samples (slope = -0.019, 95% CI = -0.044 to 0.006, p = 0.134), as less female diabetics manifested depressive disorders compared to male patients. The effect of gender and age was not significant.

Like depressive disorders, anxiety disorders were negatively and non-significantly associated with age. Specifically, older patients with diabetes reported lower rates of anxiety (slope = -0.037, 95% CI = -0.103 to 0.028, p = 0.268). In contrast, anxiety was significantly and
negatively associated with gender. Less female diabetics manifested anxiety disorders in comparison to men (slope = -0.063, 95% CI = -0.105 to -0.021, p = 0.002).

Heterogeneity and Publication bias

For the studies reporting data on depressive disorders ($Q = 5.518$, $df (Q) = 4$, $p = <0.238$, $I^2 = 27.513$) heterogeneity was not substantial or significant (as observed in funnel plot figure 11). For articles reporting data on anxiety disorders heterogeneity was substantial and significant ($Q = 21.093$, $df (Q) = 2$, $p = <0.001$, $I^2 = 90.518$). Furthermore, Egger’s test was run only for studies providing information on depression ($t = 0.64106$, $p = 0.56710$). The test could not be run for studies on anxiety, as there were only 3 articles on anxiety and there needs to be a larger amount of trials/strata in the meta-analysis for the bias assessment functions to work (see figure 11).

Figure 11. Funnel plot for studies reporting data on depression.
4. Discussion

4.1 Prevalence rates and Odds Ratios

The primary aim of the study was to investigate the prevalence of clinically diagnosed depression and anxiety amongst patients with diabetes mellitus (type 1 and type 2). For this purpose, there was sufficient data provided by the selected studies. Analyses demonstrate an aggregated prevalence rate of depression of 13.9% among diabetic patients, which illustrates a modest to strong association between depression and diabetes mellitus. The prevalence rates of depression (13.9%) in diabetic patients were higher than the depression rates reported for the global population in 2010, which was 4.5% (Vos et al., 2012).

We found fewer studies that showed the prevalence of anxiety disorders in diabetic samples, compared to those showing the prevalence of depression. Analyses indicate an aggregated prevalence of anxiety disorders of 17% in diabetic patients, higher than the prevalence of anxiety disorders in the general population, which was approximately 4.5% in 2010 (Vos et al. 2012).

The second objective of this meta-analysis was to estimate the odds ratio of depressive and anxiety disorders in individuals with diabetes compared to those without. Based on data from 5 studies, depressive disorders were found to be 1.7 times more likely in diabetics than in healthy populations. Previous meta-analyses present similar findings. Specifically, Anderson et al. (2001), who included 20 studies in their meta-analysis, report that the odds of depressive disorders in the diabetic population was twice that of the comparison group (OR = 2.0, 95% CI 1.8–2.2). Moreover, according to Ali et al. (2006), who included 10 studies, the prevalence rates of depression were significantly higher in comparison with the non-diabetic controls (17.6 vs.
9.8%, OR = 1.6, 95%, (CI) 1.2–2.0). Mezuk et al. (2008) describe in their meta-analysis (13 studies) that there is a 60% increased risk of type 2 diabetes in depressive disorder, while the latter is moderately associated with increased risk of depression. Finally, Nouwen et al. (2010) in their meta-analysis (11 studies) illustrate that compared with non-diabetic control groups, individuals with diabetes type 2 have increased risk of 24% of developing depression.

Unlike depression, there was no significant increased risk of anxiety disorders in diabetic patients compared to control groups, probably due to the very small number of studies (only 3 in total).

4.2 Age and Gender

According to our findings, age was positively correlated with depression and anxiety based on the ER analyses assessing the prevalence of the aforementioned mental illnesses with diabetes mellitus. This suggests that older patients had higher rates of depressive and anxiety disorders.

Our findings illustrate higher rates of depression in older diabetic patients and are in contrast with prior research, which suggests decline in depression and anxiety prevalence with age. Studies support that depression is more common in younger age both in diabetic samples (Katon et al., 2004) and healthy population samples (Gottfrieds, 1998) and that elderly people report less depressed mood (Gottfrieds, 1998).

Regarding the effect of gender on the association of diabetes with depressive and anxiety disorders, ER meta-regression analyses show a significant correlation of gender with both depressive and anxiety disorders. According to our findings, depression was more prevalent in male diabetic patients than in female ones. This outcome is not consistent with prior meta-
analyses on the comorbidity of diabetes with depression and anxiety. According to the meta-
analyses of Ali et al. (2006) and of Anderson et al. (2001), the prevalence of comorbid
depression was significantly higher in female diabetic patients in comparison to men.

Regarding anxiety disorders, our ER analyses present higher rates of anxiety in females
compared to males. There are similar results in prior research supporting that anxiety disorders
are more common in women (5.2 %) than in men (2.8 %) (Vos et al., 2012). Specifically, female
diabetics are more likely to report moderate-severe anxiety compared to male patients (Lloyd et
al. 2000; Grisby et al. 2002). In contrast, the OR meta-regression analyses investigating gender
as moderator in relation to anxiety in diabetic patients demonstrate that less women with diabetes
manifested anxiety disorders. This inconsistency with previous results could be attributed to the
small amount of studies included in the analyses.

4.3 Publication bias and Heterogeneity

Egger’s test suggested no evidence of publication bias for the studies reporting
prevalence data on depressive and anxiety disorders in diabetic samples. A high degree of
heterogeneity was observed across these studies, meaning there was significant variation in
outcomes between studies. The significant heterogeneity compromises the consistency of the
results and the combinability of the studies.

On the other hand, it worthy to note that there was no publication bias observed regarding
the studies that reported data on depression in diabetic groups compared with controls.
Moreover, there was no substantial heterogeneity observed across these studies.

4.4 Strengths and limitations
There are various strengths and limitations observed in the present meta-analysis. Firstly, only studies using diagnostic interviews were included in the final analyses. Previous meta-analyses and systematic reviews included also studies that used questionnaires as a diagnostic tool for depression. Psychiatric interviews consist of a more thorough mental examination compared to questionnaires. Furthermore, having one method of psychiatric assessment contributes to the homogeneity of the sample.

Nonetheless, there are various limitations to this meta-analysis. In this meta-analysis type 1 and type 2 diabetes are not distinguished, as most of the studies didn’t refer to the two types separately, but generally as ‘diabetes’. The publication bias displayed for studies reporting data on depressive and anxiety disorders is significant and compromises the validity and accuracy of the results describing the prevalence of depression and anxiety in diabetic patients. The presence of publication bias could be attributed to the small number of studies, small sample sizes and small effect sizes. Also, the small amount of studies limits our ability to generalize the outcomes and take the main confounding variables into account. Moreover, there was heterogeneity illustrated across these studies as well, indicating a significant variation among the studies. This variation could be due to the difference in the design of the studies, which included retrospective cohort studies, prospective, and cross-sectional.

Apart from the variation in study outcomes between studies, there was variation of the diabetic sample across the studies. For example, women and men were represented in different numbers in each study, some studies didn’t provide information on age or gender, age categories were defined differently in each study and some studies focused just on younger or older patients. In addition, some studies examined inpatients while other outpatients. Finally, the
studies differ in the diagnostic methods of diabetes, as some rely on diagnostic codes (ICD) and medical records, other on diagnosis by a physician and other on self-reports.

4.5 Conclusions

Although this meta-analysis aimed to describe an overall estimate of the prevalence of depression and anxiety in diabetic populations but also compared to healthy groups, a number of factors must be taken under consideration regarding the accuracy of this estimate. The publication bias detected jeopardizes the accuracy and validity of the findings on the prevalence of depressive and anxiety disorders in diabetic patients. Also, valid conclusions on the prevalence of this comorbidity cannot be made due to substantial heterogeneity.

Findings on the prevalence of depression in diabetics compared with healthy controls, indicates that diabetic patients are 1.7 times more likely to manifest depression than healthy individuals. These findings are in line with previous research. Our findings with regard to anxiety in diabetic individuals compared with healthy ones did not show an increased risk of anxiety disorders, and age and gender did not have a moderating effect.

4.6 Suggestions for further research

There is substantial need for high-quality research in order to direct a precise assessment of the unique association of diabetes mellitus and depressive as well as anxiety disorders. Research should include large population-based cohort studies, using diagnostic interviews for the assessment of mental disorders and appropriately matched control groups. Additionally, it is vital that type 1 and type 2 diabetes are distinguished and reported separately. Also, for a better illustration of the relationship of diabetes and depression or anxiety, there should be adequate data on moderating variables, such as age and gender.
References


