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The global distribution of comorbid depression and anxiety in people with diabetes mellitus: Risk-adjusted estimates

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ABSTRACT

Background: Previous reports suffer from the problem that they simply pooled data using aggregate means or standard meta-analytic method. The aim of the current study was to re-estimate the point prevalence of comorbid depression and anxiety in people with diabetes.

Methods: The estimates were calculated using recently introduced directly standardized effect estimate method, which gives corrected risk-adjusted estimates for the population of interests. Reported are global and regional burden of prevalence, presented as risk-adjusted prevalence estimates with 95% confidence intervals.

Results: Globally, the burden of comorbid depression was higher than the burden of anxiety (23.36% vs. 17.58%) symptoms and/or disorder in people with diabetes. There was a higher burden of comorbid depression in people living in developing regions (26.32%), in women (15.41%), and when assessed by self-report scales (SRS) (22.66%). The burden of anxiety was higher in developed regions in people with Type 2 diabetes mellitus (20.15%) and when assessed by SRS (20.75%). No statistically significant differences were observed due to gross heterogeneity across countries.

Conclusions: There are wide-ranging differences in studies in developed and developing regions, regarding the burden of comorbid depression and of anxiety among people with diabetes and both conditions affect approximately a fifth of the diabetic population.

INTRODUCTION

Worldwide estimates of prevalence of depression and anxiety among people with diabetes seem to vary by diabetes type and where the study was conducted, including whether countries were developed or developing.[1-3] Depression and anxiety are two common mental health-related comorbidities in people with diabetes,[4] and their prevalence has been summarized in a number of systematic reviews.[5-8] A meta-analysis published in 2001 reported that 11% of the patients with diabetes had comorbid major depressive disorder and 31% experienced significant depressive symptoms.[6] Another meta-analysis published in 2006 reported that the prevalence of clinical depression was significantly higher among patients with diabetes (17.6%) compared to those without diabetes (9.8%).[5]

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Both studies reported that the prevalence of depression in women with diabetes was double that of men with diabetes; they also estimated that the prevalence in people with diabetes was nearly twice that of people without diabetes.[5,6] The only meta-analysis on the prevalence of anxiety was published in 2002 by Grigsby *et al.*, who reported that generalized anxiety disorder (GAD) was present in 14% of patients with diabetes; however, elevated symptoms of anxiety were found in 40% of the patients with diabetes who had participated in clinical studies.[7]

These previous reports suffer from the problem that they simply pooled data using aggregate means or standard meta-analytic methods,[5-8] which are inappropriate given that we are not seeking a common underlying estimate and therefore this approach could lead to biased prevalence estimates. What is actually more meaningful is a standardized rate, and the directly standardized rate is one of the most commonly used methods of standardization in epidemiologic studies,[9-11] but its use is limited to rates. Doi *et al.* recently introduced a directly standardized effect estimate (DSE) which can be used to standardize any effect size against the size of population at risk.[9] The aim of the current study was to re-estimate the point prevalence of comorbid depression and anxiety in people with diabetes using the DSE method which gives corrected risk-adjusted estimates for the population of interests.[9] We also stratified the estimates by the type of region (developed vs. developing), type of diabetes (Type 1 diabetes mellitus [T1DM] vs. T2DM), type of measurement (self-report vs. standard criteria), and gender (males vs. females).

METHODS

The databases PubMed, EMBASE, and PSYCINFO were systematically searched to identify relevant studies published between 2000 and 2014. The reason behind this search was to include more articles. Additional articles were sourced from the reference lists of relevant review articles and original research studies. Keywords included original terms, and synonyms related to diabetes, depression, and anxiety, and critical review were conducted by the principal investigator. The search strategy involved using the explode command with a search under the MeSH terms, for example, "depression/anxiety," "depressive/anxiety disorder," "major depressive disorder," and "dysthymic disorder" combined with "diabetes mellitus" or "Type 2 diabetes mellitus." This was supplemented with a keyword search of the terms "depression/anxiety," "depressive/anxiety disorder," and "depressive/anxiety symptoms" combined using Boolean operators with "diabetes" and "diabetes mellitus." We categorized the countries into developed and developing using the United Nations classification.[12] Developing world includes countries outside Europe, excluding Australia, Canada, Japan, New Zealand, the USA, Singapore, Hong Kong, and Taiwan.

Studies eligible for inclusion in this paper were required to assess T1DM and/or T2DM in an adult population with no limit on age. Studies were included only if they had a sample size ≥30, were published or available in English, and if a current estimate of proportion with depression or anxiety was available through self-reported diagnostic criteria. Included studies utilized both standard diagnostic criteria (SDC) as well as self-report scales (SRS) to measure these disorders and their symptoms. Standard criteria comprised structured or semi-structured interviews that were based on the Diagnostic and Statistical Manual of Mental Disorders. Elevated symptoms were assessed using self-report measures such as the Beck Depression Inventory or the hospital anxiety and depression scale.

Selection criteria were not restricted to studies comparing the occurrence of depression and/or anxiety disorders or elevated symptoms (using a clinically significant cutoff) in people with diabetes. Because there were many controlled studies that reported the prevalence of depression and anxiety in a nondiabetic group, prevalence in the latter studies was taken from the diabetic arm only. For studies that presented graded relationships such as low, medium, or high depressive symptoms, only the prevalence for the highest category was selected. Studies where the type of diabetes was not specified were included as T2DM because the ages of populations recruited suggested they would be predominantly subjects with T2DM.

The quality of the included studies was rated independently by the authors using criteria that include adequacy of the description of groups (T1DM and T2DM, diabetes mellitus, T1DM and T2DM with depression/anxiety, control without depression/anxiety, and control with depression/anxiety), control for confounding variables, and representativeness of sampling.

Statistical analysis

Each study was examined for information regarding the events of comorbid depression and anxiety in

people with diabetes. For studies that reported events separately by gender (males vs. females), type of assessment (SRS vs. SDC), and type of diabetes (T1DM vs. T2DM), events were extracted and burden of depression and anxiety within these subgroups were calculated.

In addition to comorbid depression and anxiety disorders, data on depression and anxiety symptoms as well as specific anxiety disorders were extracted (GAD, panic disorder, phobias, and post-traumatic stress disorder).

The country-specific prevalence of comorbid depression and anxiety was then used to pool the burden of these disorders in specific broad populations using the DSE approach.[9] This process involves adjustment for different sizes of populations at risk when computing summary measures across populations with diabetes. The population size at risk was the prevalence of diabetes across the different countries in the world obtained from the International Diabetes Federation.[13] Sensitivity analysis was also conducted by publication years to explore potential heterogeneity.

This approach is similar to direct standardization using the diabetes subpopulation size to adjust prevalence estimates such that larger populations contribute more to the pooled estimate for a region than smaller populations.[9] Thus, the DSE is a type of direct standardization and can be calculated as:

$$\text{DSE} = \frac{\sum \left(w_j^a \times \text{ES}_j \right)}{\sum w_j^a}$$

where the weight is defined as described by Doi *et al*. and j indexes the subpopulations and ES_j is the subpopulation effect estimate of interest (the double arcsine square root transformed proportion in this study with results back transformed for reporting).[9] This weighted averaging procedure does not use inverse variance weights and thus is not a meta-analysis.[9] For countries where more than one study was available, a single estimate was obtained through standard meta-analysis, thus ensuring that each country provided a single estimate. This meta-analysis (within country) was conducted using an inverse variance quasi likelihood-based alternative (IVhet) to the random effects model.[14] Data were analyzed using Stata 12 (StataCorp LP, TX, USA), MetaXL 2.0 (EpiGear International Pty Ltd, Queensland, Australia) and Microsoft Excel. Linear regression analysis was used to examine the trend of prevalence between 2000 and 2013.

RESULTS

The 103 studies selected for review generated 103 data sets, of which 71 examined the prevalence of depression in people with diabetes and 32 examined the prevalence of anxiety in people with diabetes. Of the 71 studies assessing the prevalence of depression in people with diabetes, 37 studies were from developed and 34 from developing countries. Similarly, to estimate the prevalence of anxiety in people with diabetes, a comprehensive review was conducted on 17 studies from developed and 15 studies from developing countries, as shown in Figure 1.

Burden of depression

Global

The burden of comorbid depression symptoms and/or disorder in people with diabetes was 23.36%, which was similar to the burden of symptoms only at 24.50% and the burden of any depressive disorder at 22.27% [Table 1].

Developed

The burden of comorbid depression in T1DM and T2DM was similar (13.47 vs. 17.9%). Subgroups by SDC (21.70%) or female gender (12.92%) made up a greater burden than self-reports and males, respectively [Table 1]. The sensitivity analysis by

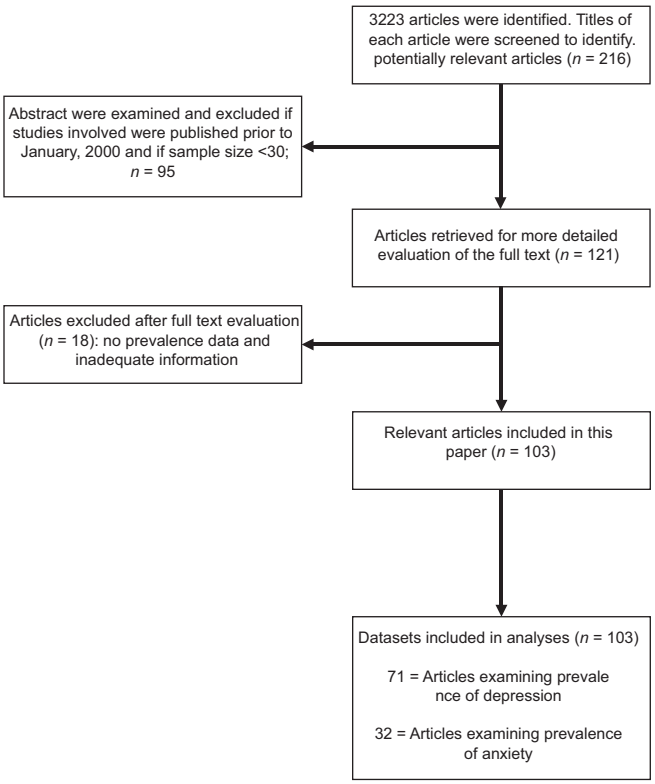

Figure 1: Flow diagram of study selection process

Table 1: The standardized prevalence estimates of comorbid depression and anxiety in people with diabetes by developed and developing countries

Region	Variable	Prevalence of depression (%)			Prevalence of anxiety (%)		
		ES	95% CI		ES	95% CI	
			LCI	UCI		LCI	UCI
Global	Symptoms or disorder	23.36	5.03	49.72	17.58	4.22	37.44
	Symptoms	24.50	5.27	51.86	20.16	5.17	41.68
	Any disorder	22.27	3.13	51.98	7.11	1.04	17.87
Developed	T2DM + T1DM	13.58	1.61	32.37	15.46	2.63	36.17
	T2DM	13.47	1.10	36.42	20.15	8.57	35.09
	T1DM	17.90	1.00	51.33	17.00	1.00	42.80
	Self-report	14.53	3.27	30.85	22.26	4.49	48.39
	Standard criteria	21.70	3.20	66.20	11.72	2.60	25.23
	Male	6.55	2.94	24.94	17.50	1.60	42.20
	Female	12.92	1.00	38.68	23.30	14.90	32.90
Developing	T2DM	26.32	1.00	64.93	18.19	2.15	44.90
	Self-report	30.79	9.64	57.51	19.24	2.72	45.71
	Standard criteria	2.20	2.00	52.20	2.50	0.70	5.10
	Male	10.30	0.20	28.80	8.27	1.27	41.16
	Female	17.90	4.70	36.30	15.21	1.20	50.99

DSE=Directly standardized effect estimate, T1DM=Type 1 diabetes mellitus, CI=Confidence interval, LCI=Lower confidence interval, UCI=Upper confidence interval, ES=Effect size, T2DM=Type 2 diabetes mellitus

publication years presented a declining trend in the prevalence of depression where prevalence was lowest in the recent years (2010 onward) [Figure 2].

Developing

Trends were similar to developed nations except that self-reports demonstrated exaggerated estimates of burden [Table 1]. The prevalence was higher in the recent years (2010 onward) compared to the prevalence between 2000 and 2009.

Burden of anxiety

Global

The burden of comorbid anxiety symptoms or disorder in people with diabetes was lower than that of depression (17.58%), the burden of symptoms was 20.16%, and the burden of any anxiety disorder was 7.11% [Table 1].

Developed

The burden of comorbid anxiety in people with T1DM (17.00%) was similar to T2DM (20.15%) [Table 1]. Again, subgroups by female gender and self-reports made up a higher burden than male gender and standard criteria, respectively [Table 1]. The prevalence was highest between 2005 and 2009, and almost same in other two groups (2000–2004 and 2010–2014).

Developing

Again, self-reports were associated with a much higher burden of anxiety than standard criteria. The sensitivity analysis by publication years showed

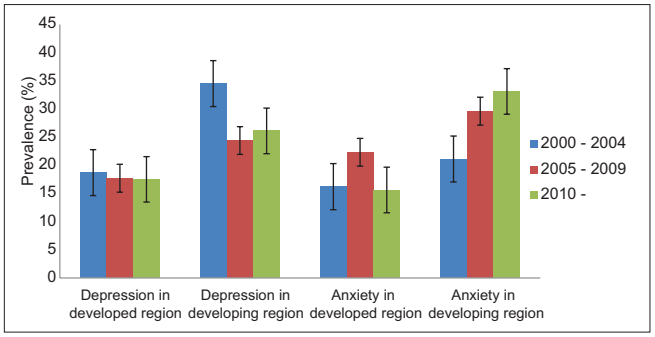

Figure 2: The prevalence percentages with standard errors of depression and anxiety in developed and developing countries by publication years (symptoms and disorders)

an increasing trend in the prevalence of anxiety where prevalence was highest in the years between 2010 and 2014 [Figure 2].

DISCUSSION

Our findings suggest that about one in eight people with diabetes living in developed regions and one in four people with diabetes living in developing region are likely to experience depression symptoms. We also notice that depression and anxiety demonstrate a greater burden in females with diabetes and by self-reports. The burden of depression in people with diabetes tended to be lower in developed regions compared to developing regions. However, a reverse trend was seen for anxiety, being higher in developed regions than developing regions, in people with T2DM. Baxter *et al*. also suggested that

anxiety was more common in general population living in high-income regions compared to low- or middle-income regions.[15]

Unlike the previous reviews,[5-7] one of the strengths of this study is the use of standardized prevalence estimates. Previous estimates seem to have been biased upward and for instance, the reported 40% prevalence of comorbid anxiety in people with diabetes[7] was revised downward to 20% in this study [Table 2].

This study was based on SRS and thus, their validity is of paramount importance. This does not seem to pose a problem because these scales used for screening for depression and anxiety have been shown to be reliable and valid,[16] and are often employed in epidemiological surveys such as those investigated in this study. However, the diagnosis of diabetes is also important and again it has been shown in a meta-analysis that the prevalence of depression varies little across assessments by blood glucose measures, physician diagnosis, or patient self-report.[17]

Regarding gender, our findings suggest that about one in eight females with diabetes living in developed region and one in six females with diabetes living in developing region are likely to report depression. This is consistent with the reports from earlier studies.[5,6] Similarly, the prevalence of gender difference between females and males has been previously reported.[7] Even in the general population, women are more likely to experience mood disorders compared to men,[18] so this is not unexpected.

The overall burden of any anxiety disorder in people with diabetes was within the range of 12–21% as reported for the general population.[19-21] Depression was however found to be higher (23%) compared to the general population (10%).[5] Finally, the prevalence of the GAD found in developed regions is comparable to the 3–4% observed in community studies in the United States.[22,23] Since this burden is within or close to the range of estimates reported for the general population, there is a possibility that the burden can be explained by factors other than diabetes *per se* that share a relationship with both diabetes and depression or anxiety. For instance, obesity has been shown to be associated with the former condition as well as with diabetes.[24,25]

Comorbid depression and anxiety disorders and elevated symptoms in people with diabetes have been shown to be associated with increased diabetes complications,[1] worsened blood glucose levels,[26,27] and reduced quality of life.[28] This is of particular concern to developing regions where resources to address depression and anxiety are not adequate.[29] Indeed, it has been reported that about 35–50% of serious cases in developed countries and about 76% to 85% in less-developed countries received no treatment in the 12 months preceding the interview.[30]

There were a limited number of studies using standard criteria to diagnose depression and anxiety disorders. It is possible that some estimates and confidence intervals may be unstable because of the small number of subjects used in the calculations, and there is a concern about variability in the methods used to identify cases of depression and anxiety. Various SRSs were used to measure depression and anxiety symptoms, and even in studies that employed the same scales, different threshold scores were used.

We had samples from a variety of settings including primary, secondary, and community settings. Patients with diabetes recruited from a secondary-care setting are likely to differ from those selected from primary-care and population settings with regard to

Table 2: Comparison of comorbid depression and anxiety in people with diabetes in percentage reported by different studies

Variables	Global burden (risk adjustment)	Burden in developed regions risk adjustment)	Burden in developing regions (risk adjustment)	Gavard *et al.*, 1993 - Burden (proportion)	Anderson *et al.*, 2001 - Burden (aggregate mean)	Grigsby *et al.*, 2002 - Burden (aggregate mean)	Ali *et al.*, 2006 - Burden (meta-analysis)
Depressive symptoms	24.50	14.53	30.79	26.0	31.0	-	17.60
Any depressive disorder	22.27	21.70	2.20	-	-		-
Anxiety symptoms	20.16	22.26	19.24	-	-	39.60	-
Any anxiety disorder	7.11	11.72	2.50	-	-	14.00	-
GAD	8.76	5.41	12.10	-	-	13.50	-
PTSD	2.30	3.10	1.50	-	-	1.20	-
Any phobia	9.82	13.27	6.37	-	-	10.10	-

GAD=Generalized anxiety disorder, PTSD=Post-traumatic stress disorder

disease stage and severity.[31] No statistically significant differences were seen due to gross heterogeneity across countries. Despite these limitations, this review presents significant findings regarding standardized prevalence of comorbid mental health conditions in people with diabetes living in different types of countries.

The association between depression and diabetes and anxiety and diabetes may have deleterious impact on public and individual health. Once depression or anxiety develops, it can represent a barrier to glycemic control.[32] Unfortunately, both conditions often remain unrecognized and thus untreated.[33] The burden of depression found in this study is higher in people with diabetes than in general population. However, the burden of anxiety seems to be similar in diabetes as in the general population. The burden of comorbid depression and anxiety tended to be higher in people with diabetes living in developing region compared to developed region, and in females relative to males with diabetes. The above findings that people with diabetes are at a higher risk of having depression and anxiety should alert clinicians to screen and treat anxiety and depression in people with diabetes.

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Conflicts of interest
There are no conflicts of interest.

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