



Contents lists available at ScienceDirect

## Diabetes Research and Clinical Practice

journal homepage: [www.elsevier.com/locate/diabres](http://www.elsevier.com/locate/diabres)

International  
Diabetes  
Federation



### Diabetes Atlas

## Diabetes and depression: Global perspectives

Leonard E. Egede<sup>a,b,\*</sup>, Charles Ellis<sup>b,c</sup>

<sup>a</sup> Department of Medicine, Center for Health Disparities Research, Medical University of South Carolina, Charleston, SC, United States

<sup>b</sup> Center for Disease Prevention and Health Interventions for Diverse Populations, Ralph H. Johnson VA Medical Center, Charleston, SC, United States

<sup>c</sup> Department of Health Professions, Medical University of South Carolina, Charleston, SC, United States

#### ARTICLE INFO

##### Article history:

Received 24 September 2009

Accepted 25 January 2010

##### Keywords:

Diabetes

Depression

Health care

Health outcomes

Global perspective

#### ABSTRACT

**Background:** Diabetes and depression are highly prevalent conditions and have significant impact on health outcomes. This study reviewed the literature on the prevalence, burden of illness, morbidity, mortality, and cost of comorbid depression in people with diabetes as well as the evidence on effective treatments.

**Methods:** Systematic review of the literature on the relationship between diabetes and depression was performed. A comprehensive search of the literature was performed on Medline from 1966 to 2009. Studies that examined the association between diabetes and depression were reviewed. A formal meta-analysis was not performed because of the broad area covered and the heterogeneity of the studies. Instead, a qualitative aggregation of studies was performed.

**Results:** Diabetes and depression are debilitating conditions that are associated with significant morbidity, mortality, and healthcare costs. Coexisting depression in people with diabetes is associated with decreased adherence to treatment, poor metabolic control, higher complication rates, decreased quality of life, increased healthcare use and cost, increased disability and lost productivity, and increased risk of death.

**Conclusion:** The coexistence of diabetes and depression is associated with significant morbidity, mortality, and increased healthcare cost. Coordinated strategies for clinical care are necessary to improve clinical outcomes and reduce the burden of illness.

© 2010 Elsevier Ireland Ltd. All rights reserved.

#### Contents

|   |     |
|---|-----|
| 1. Global burden of diabetes . . . . .  | 303 |
| 2. Global burden of depression . . . . .  | 303 |
| 3. Screening for depression . . . . .   | 304 |
| 4. The prevalence of depression in individuals with diabetes . . . . .  | 304 |
| 5. Causal pathways between depression and diabetes . . . . .  | 304 |
| 6. Effect of depression on glycemic control and self-care behaviors . . . . .                                       | 305 |
| 7. Effect of depression on risk for diabetes complications . . . . .  | 306 |
| 8. Effect of depression on disability, work productivity and quality of life in individuals with diabetes . . . . . | 306 |

\* Corresponding author at: Medical University of South Carolina, Center for Health Disparities Research, 135 Rutledge Avenue, Room 280H, Charleston, SC 29425, United States. Tel.: +1 843 792 2969; fax: +1 843 876 1201.

E-mail address: [egedel@musc.edu](mailto:egedel@musc.edu) (L.E. Egede).

0168-8227/\$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.

doi:10.1016/j.diabres.2010.01.024

|  |     |
|--|-----|
| 9. Effect of depression on healthcare utilization and costs in individuals with diabetes . . . . .     | 307 |
| 10. Effect of depression on mortality in individuals with diabetes . . . . .                           | 307 |
| 11. The effectiveness of treating depression in individuals with diabetes. . . . .                     | 308 |
| 12. The cost of treating depression in individuals with diabetes. . . . .                              | 308 |
| 13. Challenges and future directions for treatment of depression in individuals with diabetes. . . . . | 309 |
| References . . . . .   | 310 |

## 1. Global burden of diabetes

Reports from the International Diabetes Federation (IDF) indicate that the prevalence of diabetes mellitus has reached epidemic levels globally. Estimates for 2010 indicate that 285 million adults have diabetes in the seven regions of the IDF [1]. These numbers represent an increase of 39 million from 2007 and an expected continued increase to 439 million in 2030 [1]. Given prevalence figures approaching 290 million, the worldwide human, economic, and social costs of diabetes are staggering. For example, the IDF estimates that 3.9 million deaths will be caused by diabetes in 2010 which represents 6.8% of the total global mortality [1]. It is also believed that by 2025, more than 75% of the world population with diabetes will reside in developing countries and the countries with the largest populations of adults with diabetes will include: India, China and the United States [2]. In developing countries, the majority of adults with diabetes are between 45 and 64 years old, whereas in developed countries the majority of adults with diabetes are 65 years and older [2]. The IDF estimates that 23 million years of life are lost to disability and reduced quality of life as a result of complications associated with diabetes [3]. The costs associated with diabetes are difficult to accurately capture but some estimates suggest that the \$232 billion U.S. dollars were spent worldwide in 2007 to treat and prevent diabetes with this number expected to climb to a minimum of over \$300 billion in 2025 [3]. In the United States alone, the total cost of diabetes was reportedly \$132 billion in 2002 [4] while estimates from smaller and more economically disadvantaged countries such as Tanzania are \$2.5 billion [3].

## 2. Global burden of depression

Depression is another condition with high prevalence worldwide. Approximately 340 million people worldwide suffer from depression at any given time including 18 million in the United States [5]. According to the World Health Organization (WHO), depression is responsible for the greatest proportion of burden associated with non-fatal health outcomes accounting for approximately 12% total years lived with disability [6]. In 2000, it was estimated that depressive disorders were higher in women (4930 per 100,000) than men (3199 per 100,000) and that globally depressive disorders were the fourth leading cause of disease burden in women and seventh leading cause in men [7]. The World Mental Health Survey was conducted to estimate the 12-month prevalence rate of mood, anxiety and alcohol-use disorder among community samples of adults across 17 countries including: Europe, the Americas, the Middle East, Africa, Asia and the South Pacific [8]. Among more

than 85,000 adults surveyed, 42,697 self-reported the presence of diabetes. The risk of mood and anxiety disorders was higher among individuals with diabetes relative to those without. The odds ratio for depression was 1.38 (95% CI 1.14–1.66) after adjusting for age and gender.

Recent studies have reported that the lifetime prevalence of a major depressive disorder in the United States was 16.2% [9] whereas the lifetime prevalence in Europe was 14% [10]. Another study designed to examine the prevalence of mood disorders in 14 countries in the Americas, Europe, Middle East, Africa and Asia found that the 12-month prevalence of mood disorders was 0.8% in Nigeria, 3.1% in Japan, 6.6% in Lebanon, 6.8% in Columbia, 6.9% in the Netherlands, 8.5% in France, 9.1% in the Ukraine and 9.6% in the United States [11]. Studies show that depression is a major cause of morbidity, mortality and disability [12] and is associated with workplace absenteeism, diminished or lost work productivity and increased use of healthcare resources [13]. Finally, major depression is the second leading cause of disability-adjusted life years (DALYs) lost in women and the tenth leading cause of DALYs in men [12].

Depressive disorders include major depression, minor depression, and dysthymia. The clinical diagnosis of major depression is based on the presence of depressed mood and anhedonia during the same 2-week period and the presence of any five of the following symptoms [14]: (i) depressed mood; (ii) markedly diminished interest or pleasure in activities; (iii) significant weight loss when not dieting or weight gain; (iv) insomnia or hypersomnia; (v) psychomotor agitation or retardation; (vi) fatigue or loss of energy; (vii) feelings of worthlessness or excessive or inappropriate guilt; (viii) diminished ability to think or concentrate; and (ix) recurrent thoughts of death, suicidal ideation, or a suicide attempt. To meet criteria (i) these symptoms should represent a change from previous functioning and should occur most of the day.

Minor depression is similar to major depression in that patients experience depressed mood or anhedonia during the same 2-week period. However, the patient's symptoms are fewer than the five items required to make a diagnosis of major depression [14]. Dysthymia is characterized by depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years [14]. In addition, at least two of the following symptoms should be present while the patient is depressed (1): (i) poor appetite or overeating; (ii) low self-esteem; (iii) insomnia or hypersomnia; (iv) poor concentration or difficulty making decisions; (v) low energy or fatigue; and (vi) feelings of hopelessness. Patients with dysthymia typically have fewer symptoms (less than 5) than is required to make a diagnosis of major depression [14].

---

### 3. Screening for depression

The diagnosis of depression is based on clinical findings. Several valid and reliable screening instruments are available for use in primary care [15–20]. The 9-item Patient Health Questionnaire (PHQ-9) [20] is an easy to use depression screening instrument. The PHQ-9 is a brief questionnaire that scores each of the 9 DSM-IV criteria for depression as “0” (not at all) to “3” (nearly every day). PHQ-9 score  $\geq 10$  have a sensitivity of 88% and a specificity of 88% for major depression. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively [20]. The use of brief screening instruments to screen for depression in primary care patients is supported by the United States Preventive Services Task Force [21]. However, screening alone is not sufficient. It is important to have a system in place to confirm the diagnosis, offer guideline concordant treatment, and refer complex patients, or patients who do not respond to adequate dosage of two antidepressants.

---

### 4. The prevalence of depression in individuals with diabetes

More than 300 years ago Dr. Thomas Willis, a British physician made the observation that there was a relationship between diabetes and depression when he suggested that diabetes was the result of “sadness or long sorrow” [22]. Anderson et al. conducted a meta-analysis of 42 published studies that included 21,351 adults and found that the prevalence of major depression in people with diabetes was 11% and the prevalence of clinically relevant depression was 31% [23]. However, worldwide estimates of depression prevalence among individuals with diabetes appear to vary by diabetes type and among developed and developing nations. For example in the U.S., Li et al. examined data from the 2006 Behavioral Risk Factor Surveillance System (BRFSS), a standardized telephone survey of U.S. adults aged 18 and older and found that the age adjusted rate of depression was 8.3% (95% CI 7.3–9.3), ranging from a low of 2.0% to a high of 28.8% among the 50 states [24]. They also noted a 25-fold difference in the rates among racial/ethnic subgroups (lowest, 1.1% among Asians; highest, 27.8% among American Indians/Alaska Natives).

Li et al. also completed a second study using 2006 BRFSS data to estimate the prevalence of undiagnosed depression among individuals with diabetes. They found the adjusted and unadjusted prevalences of undiagnosed depression to be 8.7% and 9.2%, respectively. Their secondary finding was that about 45% of all diabetes patients had undiagnosed depression [25]. Asghar et al. found evidence of depressive symptoms in 29% of males and 30.5% of females with newly diagnosed diabetes in rural Bangladesh [26]. Similarly, Sotiropoulos et al. found that 33.4% of a cohort of Greek adults with type 2 diabetes reported elevated depressive symptoms [27]. Zahid et al. found a more modest depression prevalence (14.7%) among patients with diabetes in a rural area in Pakistan [28]. However, Khamseh et al. found major depression in 71.8% of a sample of 206 Iranian patients with type 1 and type 2 diabetes [29]. In a study of 143 patients with type-2 diabetes and 132 healthy controls

in Bahrain, an island country with a high prevalence of type-2 diabetes, Almawi et al. found a higher proportion of type 2 diabetes patients in both the mild-moderate and severe-extremely severe depression categories [30]. In a bi-national study of more than 300 patients designed to examine the prevalence of depression in Hispanics of Mexican origin, Mier et al. found that the rate of depression among Hispanic patients was 39% in South Texas (USA) and 40.5% in Northeastern Mexico [31]. Elevated depressive symptoms have also been reported in African Americans residing in rural counties in Georgia (USA) [32] and urban primary clinics in East Baltimore, Maryland (USA) [33].

In a systematic review designed to estimate the prevalence of clinically depressed patients with type 2 diabetes, Ali et al. found that the prevalence of depression was significantly higher among patients with type 2 diabetes (17.6%) than those without diabetes (9.8%) [34]. They also found that the prevalence among females with diabetes (23.8%) was higher than their male counterparts with diabetes (12.8%). Overall, studies have demonstrated that individuals with diabetes are more likely to have depression than in individuals who do not have diabetes. It should be noted however that the mechanisms linking these conditions are not entirely clear. Additional research is needed to further delineate the relationship between these two comorbid conditions.

---

### 5. Causal pathways between depression and diabetes

Evidence suggests a bi-directional relationship between depression and type 2 diabetes. For example research by Knol et al. suggests that in addition to depression being a consequence of diabetes, depression may also be a risk factor for the onset of diabetes [35]. Mezuk et al. completed a review of studies from 1950 to 2007 of diabetes and depression to examine the bi-directional relationship between diabetes and type 2 diabetes [36]. The pooled relative risk for incident depression associated with baseline diabetes was 1.15 (95% CI 1.02–1.30) while the relative risk for incident diabetes associated with baseline depression was 1.60 (95% CI 1.37–1.88). In summary, depression was associated with a 60% increase of type 2 diabetes while type 2 diabetes was only associated with a moderate (15%) risk of depression. This bi-directional relationship was confirmed in a recent study by Golden et al. in which they found that among individuals without elevated depressive symptoms at baseline, patients treated for diabetes had higher odds of developing depressive symptoms during the follow-up period [37]. In contrast, individuals with impaired fasting glucose and those with untreated diabetes had reduced risk of incident depressive symptoms. The authors found that these findings were comparable across racial/ethnic groups.

Two major hypotheses currently exist to explain the causal pathway between diabetes and depression. One hypothesis asserts that depression precedes type 2 diabetes (i.e. depression increases the risk of developing diabetes). Unfortunately, the mechanisms underlying the association between diabetes and depression are not clearly understood. In theory, the increased risk of type 2 diabetes in individuals

with depression is believed to result from increased counter-regulatory hormone release and action, alterations in glucose transport function, and increased immunoinflammatory activation [38]. These physiologic alterations are thought to contribute to insulin resistance and beta islet cell dysfunction, which ultimately lead to the development of type 2 diabetes. The second hypothesis is that depression in patients with both type 1 and type 2 diabetes results from chronic psychosocial stressors of having a chronic medical condition [39]. This hypothesis is supported by at least two important studies. First, 8870 participants from the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Survey who were free of diabetes at baseline were assessed for depression and followed for 9 years [40]. Compared with those with no depressive symptoms at baseline, those with high or moderate depressive symptoms did not have significantly higher incidence of diabetes over the study period. Second, 1586 older adults from the Rancho Bernardo study were screened for type 2 diabetes with a 75 g oral glucose tolerance test and screened for depression with a modified Beck's Depression Inventory [41]. There was no evidence that depression was associated with incident diabetes, instead, the study showed that there was a 3.7-fold increased odds of depression in those with a prior diagnosis of diabetes.

## 6. Effect of depression on glycemic control and self-care behaviors

There is substantial evidence that comorbid depression among individuals with diabetes is associated with poor diabetes outcomes such as glycemic control. Lustman et al. completed a meta-analysis of 24 studies and found that depression was significantly associated with poor glycemic control in individuals with type 1 and type 2 diabetes [42]. The standard effect size was 0.17 (small to moderate) and was consistent (95% CE 0.13–0.21). Similar effect sizes were noted for type 1 and type 2 diabetes but were larger when standardized interviews and diagnostic criteria were used rather than self-report questionnaire. Richardson et al. went a step further and assessed the longitudinal effects of depression on glycemic control [43]. They found that over 4 years of follow-up there was a significant longitudinal relationship between depression and glycemic control and that depression was associated with persistently higher HbA1c levels over the time period (see Fig. 1). Wagner et al. also found higher HbA1c and more diabetes complications in African Americans with higher depressive symptoms after controlling for confounders [44]. In this study, diabetes self-care did not fully account for the relationship between depression and HbA1c levels. Finally, Miranda et al. reported that variations in depressive mood

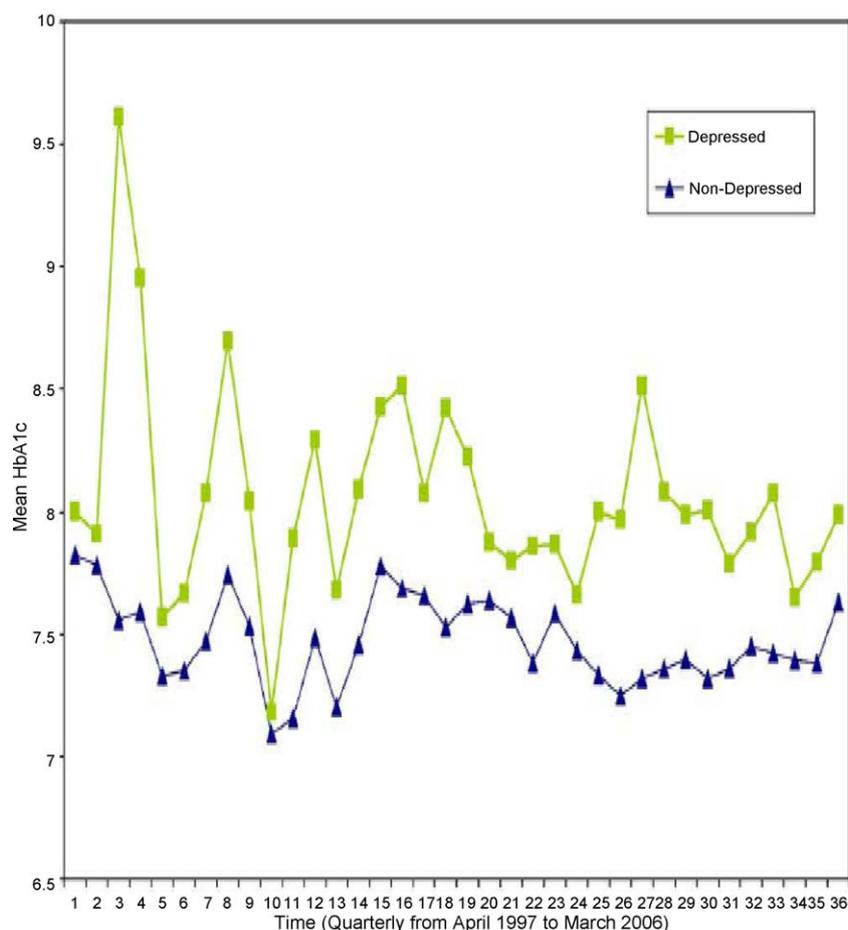


Fig. 1 – Comparison of unadjusted mean HbA1c over time among depressed and non-depressed adults with diabetes (adapted with permission from Ref. [43]).

below the level of clinical depression were associated with differences in glycemic control among patients with type 1 diabetes [45].

A number of appropriate self-care behaviors are critical to good diabetes care and consequently short and long term outcomes. Clinical management guidelines emphasize the importance of medication adherence, physical activity, diet and self-monitoring of blood glucose [46]. Gonzalez et al. proposed that the presence of depressive symptoms are good predictors of poor adherence to self-care particularly in adherence to medications and diet and exercise regimens [47]. Therefore, interventions should simultaneously address depression and self-care skills to achieve optimal diabetes outcomes. A systematic review of treatment adherence among individuals with diabetes and depression indicated that there was a significant relationship between depression and treatment nonadherence [48]. Effects sizes in the study were largest for medical appointments and composite measures of self-care ( $r = 0.31, 0.29$ ). Similarly, a systematic review of studies of medication adherence found that many patients did not adhere properly to diabetic medications [49]. A second review of self-management behaviors also concluded that comorbid depression in individuals with diabetes is associated with not only decreased adherence to medications but also decreased adherence to dietary recommendations [46]. Comorbid depression among individuals with diabetes generally has a negative impact on patient initiated activities such as less physical activity, unhealthy diet, and lower adherence to oral medications (hypoglycemic, antihypertensive, and lipid lowering) [50]. Gonzalez et al. found that after controlling for relevant covariates, patients with major depression reported significantly fewer days of adherence to diet, exercise and glucose self-monitoring self-management strategies and a 2.3-fold greater odds of missing medication doses compared with other respondents [51]. It is possible that patient attitudes play a critical role in self-care behaviors and depression impairs good self-care practices by influencing good self-care practices and perceived self-control [52]. Table 1 shows the association between depression and diabetes self-care behaviors.

### 7. Effect of depression on risk for diabetes complications

Diabetes complications are also greater among individuals with depression. In a meta-analysis of 27 studies including adults with type 1 and type 2 diabetes, de Groot et al. found significantly greater diabetes complications including: diabet-

ic retinopathy, nephropathy, neuropathy, microvascular complications and sexual dysfunction [53]. Effect sizes were in the small to moderate range (0.17–0.32). Clouse et al. found that the onset and prevalence of coronary heart disease was affected in women with diabetes who were depressed [54]. Studies have also shown a negative relationship between depression and poor glycemic control and diabetes complications in ethnic minorities. In a 6-year longitudinal study of depression in relationship to glycemic control as risk factor for diabetic retinopathy, Roy et al. found that depression was significantly associated with proliferative diabetic retinopathy in a cohort of approximately 500 African Americans with type 1 diabetes [55]. Worse glycemic control was also observed in depressed adults with diabetes in an American Indian community in Arizona (USA) [56] and among a cohort of Hispanic American patients residing in New York (USA) [57]. Similarly, results from the Hispanic Established Population for Epidemiologic Study of Elderly (EPESE) Survey concluded that depression in individuals with diabetes was significantly associated with increased microvascular and macrovascular complications in elderly Mexican Americans with type 2 diabetes [58].

### 8. Effect of depression on disability, work productivity and quality of life in individuals with diabetes

Diabetes and depression are common chronic conditions that are significantly associated with increased odds of disability [59]. In a study of more than 30,000 adults  $\geq 18$  years of age from the National Health Interview Survey (NHIS) conducted in the U.S., Egede found that the odds of functional disability was more than 7-fold greater among adults with diabetes and major depression compared with adults without diabetes and depression [59]. Results from the Hispanic Established Population for Epidemiologic Study of Elderly (EPESE) Survey also demonstrated greater disability among depressed adults with diabetes [58]. Patients with diabetes and coexisting depression had a 4.1-fold increase odds of disability compared with a 1.7-fold increase among adults with diabetes only and a 1.3-fold increase among adults with depression alone. Decreased work productivity has also been associated with the presence of depression in adults with diabetes. In a second study, Egede found that adults with diabetes and depression were more likely to miss more than 7 workdays in any given year [60]. Erin et al. found that the presence of depression resulted in a significant deterioration in quality of life in individuals with diabetes [61]. In a second population-based

**Table 1 – Relationship of depression and diabetes self-care behaviors (adapted with permission from Ref. [50]).**

| Self-care activities (past 7 days)                      | Major depression (%) | No major depression (%) | Odds ratio | 95% CI    |
|---|----------------------|-------------------------|------------|-----------|
| Healthy eating once weekly or less                      | 17.2                 | 8.8                     | 2.1        | 1.59–2.72 |
| 5 servings of fruits and vegetables once weekly or less | 32.4                 | 21.1                    | 1.8        | 1.43–2.17 |
| High fat foods $\geq 6$ times weekly                    | 15.5                 | 11.9                    | 1.3        | 1.01–1.73 |
| Physical activity ( $\geq 30$ min) once weekly or less  | 44.1                 | 27.3                    | 1.9        | 1.53–2.27 |
| Specific exercise session once weekly or less           | 62.1                 | 45.8                    | 1.7        | 1.43–2.12 |
| Smoking: Yes  | 16.1                 | 7.7                     | 1.9        | 1.42–2.51 |

**Table 2 – Comparison of mean health care use among depressed and non-depressed individuals with diabetes, U.S. 1996 (adapted with permission from Ref. [67]).**

| Utilization category            | Depressed |                  | Non-depressed |                  | P <sup>*</sup> |
|---------------------------------|-----------|------------------|---------------|------------------|----------------|
|                                 | n         | Mean utilization | n             | Mean utilization |                |
| Ambulatory visits               | 85        | 12               | 708           | 7                | 0.0001         |
| Emergency department visits     | 29        | 1                | 144           | 1                | 0.1624         |
| Hospital in-patient days        | 23        | 1                | 147           | 1                | 0.8983         |
| Use of prescription medications | 85        | 43               | 717           | 21               | <0.0001        |

\* P-value for mean log 10-transformed utilization adjusted for age, gender, race/ethnicity, health insurance, and comorbidity.

**Table 3 – Comparison of mean health care expenditures among depressed and non-depressed individuals with diabetes, U.S. 1996 (adapted with permission from Ref. [67]).**

| Expenditure categories               | Depressed |                                     | Non-depressed |                                     | P-value <sup>*</sup> |
|--------------------------------------|-----------|-------------------------------------|---------------|-------------------------------------|----------------------|
|                                      | n         | Mean expenditures <sup>a</sup> (\$) | n             | Mean expenditures <sup>a</sup> (\$) |                      |
| Ambulatory expenditures              | 85        | 920                                 | 708           | 666                                 | 0.1235               |
| Emergency department expenditures    | 26        | 350                                 | 130           | 383                                 | 0.8524               |
| Hospital in-patient expenditures     | 23        | 10,082                              | 147           | 7,648                               | 0.1802               |
| Prescription medication expenditures | 85        | 1,392                               | 717           | 666                                 | <0.0001              |
| Other medical expenditures           | 35        | 188                                 | 239           | 211                                 | 0.7883               |
| Total expenditure                    | 85        | 247,492,008                         | 732           | 55,406,559                          | <0.0001              |

<sup>a</sup> Expenditures are adjusted for inflation with the Consumer Price Index to reflect August 2001 dollars.

\* P-value for mean log 10-transformed expenditures adjusted for age, gender, race/ethnicity, health insurance, and comorbidity.

U.S. survey in 2004, lower health-related quality of life was observed in patients with diabetes and those at high risk for diabetes (3–5 diabetes-related risk factors) [62]. These findings suggest that the coexistence of diabetes and depression has a synergistic effect on the odds of disability and in turn reduced work productivity and quality of life.

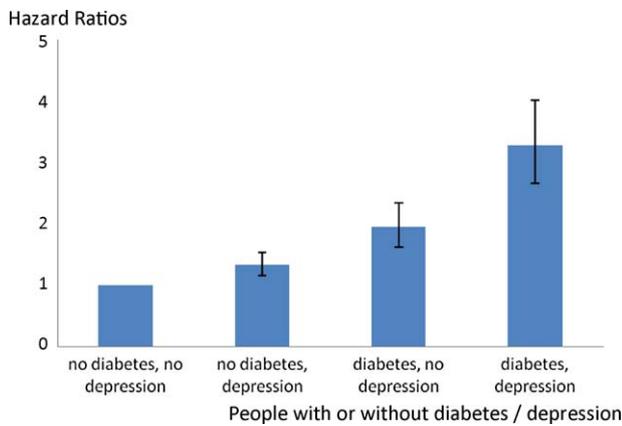
## 9. Effect of depression on healthcare utilization and costs in individuals with diabetes

Recent studies indicate increased healthcare utilization and healthcare costs among individuals with diabetes and coexisting depression. In a study of 55,972 adults with diabetes, Le et al. found that patient with diabetes and depression had higher diabetes-related medical costs (\$3264) than patients with diabetes alone (\$1297) [63]. They also found that depressed patients with diabetes had higher total medical costs (\$19,298) than patients without depression (\$4819). Ciechanowski et al. found that individuals with diabetes and depression had a 2-fold increase in health care costs compared with those who did not have depression [64]. In a third study, Finkelstein et al. found that U.S. Medicare beneficiaries with diabetes and major depression sought more treatment for more services, spent more time in in-patient facilities and incurred higher medical costs than adults with diabetes alone [65]. Nichols et al. found that in adjusted analyses, individuals with diabetes and minor depression used more ambulatory care visits and prescriptions than non-depressed adults even though depression alone was not associated with higher resource use [66]. Similar findings were reported in another study that used a U.S. nationally representative sample in which individuals with diabetes and depression had higher

ambulatory care use and filled more prescriptions than their non-depressed counterparts [67]. In the same study, Egede et al. also found that among individuals with diabetes, total health care expenditures were 4.5 times greater among those who were depressed than those who were not depressed (see Tables 2 and 3). Studies of healthcare utilization and healthcare costs confirm that the coexistence of depression among individuals with diabetes is associated with greater healthcare service utilization and costs.

## 10. Effect of depression on mortality in individuals with diabetes

Recent studies have shown that coexisting depression increases the risk of death among people with diabetes [68–70]. In a study of 10,704 Medicare beneficiaries in the U.S., Katon et al. reported that beneficiaries with diabetes and comorbid depression had a 36–38% increased risk for all-cause mortality over a 2-year period [69]. In a study using the first National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study, results indicated that diabetic individuals with depression had a 54% greater mortality than those without depression [68]. In a third study of 10,025 patients from the NHANES I Epidemiologic Follow-up Study who were followed for 8 years, Egede et al. found that hazard rates for all-cause mortality for individuals who had diabetes and depression were 2.50 (95% CI 2.04–3.08) compared with those without diabetes or depression [70]. In that study, the authors concluded that the coexistence of diabetes and depression is associated with significantly higher risk of death and this risk is beyond that due to having either diabetes or depression alone (see Fig. 2).



**Fig. 2 – Effect of depression on all-cause mortality in patients with diabetes (adapted with permission from Ref. [70]).**

### 11. The effectiveness of treating depression in individuals with diabetes

Evidence suggests that recognition and treatment for depression is less than ideal, particularly in primary care settings where most patients with diabetes receive care [71].

Despite increased efforts to identify and manage depression among patients with diabetes, several important questions remain. First, does recognition of depression improve patient outcomes? Second, is recognition of depression based on a single visit appropriate? Third, what is a reasonable timeframe to determine failure of recognition? The answers to each of these questions remain generally unanswered therefore significant gaps currently remain in the literature regarding the reliability of depression recognition.

There is an emerging literature regarding the efficacy and cost-effectiveness of treatments for depression. Both pharmacological and non-pharmacological approaches to treatment of depression have been considered. At least three major pharmacological clinical trials have been conducted to determine the effectiveness of treatment of depression on depression and diabetes outcomes. In the first study, 68 patients with diabetes and depression were randomly assigned to 8 weeks of treatment with nortriptyline to achieve plasma levels of 50–150 ng/ml [72]. Patients demonstrated significant improvements in mood however significant improvements were not observed in glycemic control. In the second study, 60 subjects with diabetes and depression were randomly assigned to treatment with fluoxetine (up to 40 mg per day) [73]. Treatment with fluoxetine was associated with significant improvement in mood but not glycemic control. A third study by Williams et al. was designed to assess whether enhancing treatment for depression improved mood and glycemic control in 417 elderly subjects (age  $\geq 60$  years) with diabetes and depression [74]. Patients were treated with antidepressants or psychotherapy; a care manager offered education, problem solving, and assistance with medication management; and patients were followed for 12 months. Collaborative care for depression in the elderly improved mood and function but had no significant effect on glycemic control.

A systematic review of the efficacy of non-pharmacological treatments for depression concluded that depression-focused interventions reduce depressive symptoms in patients with diabetes, although they might not be associated with optimal diabetes outcomes (e.g. glycemic control) [75]. At least three studies have examined whether psychotherapy alone or in combination with pharmacotherapy improve depression and diabetes outcomes. In the first study, 51 subjects with diabetes and depression were randomized to cognitive behavioral therapy (CBT) plus diabetes education vs. diabetes education alone [76]. CBT was associated with significant improvements in both mood and glycemic control. The second study randomized 329 patients with diabetes and depression to a case management intervention or usual care to determine whether enhancing the quality of depression care improved depression and diabetes outcomes [77]. The collaborative model of care for depression improved depression care and outcomes but did not have significant effects on glycemic control. The third study was designed to test the effectiveness of 6-month and 12-month follow-up of CBT compared with blood glucose awareness training (CGAT) in patients with type 1 diabetes [78]. Snoek et al. found that both interventions resulted in lower depressive symptoms up to 12 months but only the CBT was effective in lowering HbA1c in patients with high baseline depression scores.

Finally, the most recent comprehensive review of published randomized controlled trials of treatment of depression among individuals with diabetes by Petrak and Herpertz concluded that good scientific evidence exists that suggests that treatments for depression in patients with diabetes are effective [79]. Conclusions of the review indicated that treatments for depression in patients with diabetes can include: antidepressants, psychotherapy or combination therapies emphasizes medications and psychotherapy. Unfortunately, the findings of the review also concluded that neither led to significantly better outcomes.

### 12. The cost of treating depression in individuals with diabetes

Studies of the economics of treatments of depressed individuals with diabetes have yielded positive results. A recent study of the cost-effectiveness of treatment of depression among individuals with diabetes by Simon et al. concluded that systematic depression treatment significantly increased time free of depression resulting in an economic benefit from the perspective of the health plan [80]. Patients who received the systematic depression treatment accumulated a mean of 61 additional days free of depression (95% CI, 11–82 days) and had on average \$314 less costs associated with outpatient services. The net economic benefit was \$952 per treated patient when each day free of depression was valued at \$10 [80]. Similarly, patients participating in at least one clinical trial improved measures of depression outcomes while also experiencing reduced medical costs. Katon et al. completed the Pathways depression intervention program as a comparison with usual care and found that patients in the intervention arm of the study experienced improved depression outcomes and reduced 5-year mean costs of \$3907 compared to patients

in the usual source of care arm [81]. In summary, these studies suggest that treatment of depression in people with diabetes is both efficacious and cost-effective and can result in improved overall outcomes.

### 13. Challenges and future directions for treatment of depression in individuals with diabetes

Most people with diabetes who have depression are treated in primary care settings [4]. However, studies suggest that consistent recognition and treatment of depression is less than optimal in primary care settings [71]. One barrier to early recognition and treatment of depression among individuals with diabetes is the difficulty in separating the symptoms of depression from the symptoms of poor management of diabetes. For example, fatigue, gain or loss of weight, change in appetite, and sleep disturbances are common symptoms of both depression and poor diabetes management. The difficulties of distinguishing diabetes-related symptoms from depression were highlighted in a recent study which showed that the depression-diabetes symptom association is stronger than the association of diabetes symptoms with measures of glycemic control and diabetes complications [82]. Ludman et al. studied patients with major depression and found significantly more diabetes symptoms and that the overall number of diabetes symptoms was highly correlated with the number of depressive symptoms (see Table 4). Similarly, in a targeted screening study of 246 patients with high-risk profile for diabetes, Adriaanse et al. found that diabetic patients exhibited more symptoms of hyperglycemia and fatigue in the first year following diagnosis of type 2 diabetes than those patients who were not diagnosed with diabetes [83]. They concluded that symptom distress is associated with increased likelihood of negative mood in both patients with and without diabetes.

Unfortunately, the challenges of treating individuals with diabetes and depression are influenced by both patient-related and healthcare system-related factors. Patient-related factors include stigma and negative perceptions of any aspect of mental illness such as depression. Consequently, patients may not acknowledge their depression or their lack of adherence to treatment recommendations as these may reflect personal failure. In addition, financial constraints, side

effects of antidepressants, and implication of a mental health diagnosis on employment and insurability are among a host of other patient-related factors. Similarly, healthcare provider and healthcare systems may provide additional barriers resulting from poor provider knowledge of evidence-based guidelines, reimbursement issues associated with mental health diagnoses in primary care settings, insufficient referral networks in rural and suburban communities and negative perceptions of the time necessary to deal with depression [84]. Further, healthcare systems are burdened by fragmented care between general health and mental health services and the long standing practice of packaging mental health services as a “carve-out” program also reduce the overall effectiveness of care [4]. Unfortunately, services for mental health and substance use conditions have been separated from services for general medical conditions. Compounding this issue, many patients do not have adequate coverage for mental health conditions because health care payers have typically sold mental health coverage as separate products to employers and managed care programs. Together, these patient-related and healthcare system-related factors have limited the effectiveness of treatments for depression and decreased the chances of patients with diabetes and depression receiving optimal quality care.

Practice guidelines from the International Diabetes Federation indicate that because patients with diabetes are more likely affected by depression, periodic assessment and monitoring of depression and other mental health conditions is required in the management of patients with diabetes [85]. These guidelines also note that detection in brief encounters are problematic, and as such diabetes health professionals require basic training in identification and management of depression in patients with diabetes [85]. Additionally, there is a need for adequate communication/interview skills, motivational techniques and counseling skills for health professionals treating individuals with diabetes. Further, collaboration among mental health specialists with an interest in diabetes could facilitate optimal outcomes. Therefore, effective management of patients with diabetes and depression requires collaborative efforts between a number of health care disciplines including: primary care, endocrinology, psychiatry, psychology, nursing, pharmacy, and allied health professions. Unfortunately, in most clinical settings, patient care is fragmented and requires referral to practitioners in the different disciplines, who in most cases are located at a

**Table 4 – Relationship of major depression to diabetes symptoms adjusted for complications and glycohemoglobin level (adapted with permission from Ref. [82]).**

| Diabetes symptom          | Major depression (%) | No major depression (%) | Odds ratio | 95% CI    |
|---------------------------|----------------------|-------------------------|------------|-----------|
| Cold hands and feet       | 49.4                 | 32.4                    | 1.93       | 1.57–2.38 |
| Numbness in hands or feet | 51.3                 | 32.6                    | 1.98       | 1.61–2.43 |
| Pain in hands or feet     | 46.0                 | 25.2                    | 2.23       | 1.81–2.75 |
| Polyuria                  | 54.5                 | 33.7                    | 2.24       | 1.82–2.75 |
| Excessive hunger          | 44.7                 | 20.3                    | 2.66       | 2.16–3.28 |
| Abnormal thirst           | 46.2                 | 16.9                    | 3.30       | 2.67–4.08 |
| Shakiness                 | 39.2                 | 14.0                    | 3.33       | 2.66–4.17 |
| Blurred vision            | 38.2                 | 14.2                    | 3.42       | 2.74–4.27 |
| Feeling faint             | 10.9                 | 2.7                     | 4.00       | 2.74–5.86 |
| Daytime sleepiness        | 84.4                 | 52.3                    | 4.96       | 3.79–6.48 |

distance from each other. Fragmented clinical care subsequently creates substantial obstacles to achieving optimal clinical outcomes for patients. A coordinated approach to the provision of quality care to people with diabetes and coexisting depression is needed [4]. Coordinated clinical care could only occur in the context of extensive implementation of effective strategies to increase recognition of depression, adoption of effective interventions to provide guideline concordant care, and integration of performance measures for depression into diabetes clinical guidelines. Currently, recognition of depression among individuals with diabetes is suboptimal, therefore global approaches to establish coordinated, multifaceted interventions to improve early recognition of depression and early initiation of treatment for depression are required to reduce the worldwide burden of depression among individuals with diabetes.

### Conflict of interest

The authors declare that they have no conflict of interest.

### REFERENCES

- [1] International Diabetes Federation, Diabetes Atlas, 4th ed., International Diabetes Federation, Brussels, 2009.
- [2] H. King, R.E. Aubert, W.H. Herman, Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections, *Diabetes Care* 21 (9) (1998) 1414–1431.
- [3] International Diabetes Federation, The human, social and economic impact of diabetes. Available at: <http://www.idf.org/home/index.cfm?node=41>. 2008.
- [4] L.E. Egede, Disease-focused or integrated treatment: diabetes and depression, *Med. Clin. North Am.* 90 (4) (2006) 627–646.
- [5] J.F. Greden, Physical symptoms of depression: unmet needs, *J. Clin. Psychiatry* 64 (Suppl. 7) (2003) 5–11.
- [6] World Health Organization, Revised global burden of disease (GBD) 2002 estimates. Available from: <http://www.who.int/healthinfo/bodgbd2002revised/en/index.html>. 2005.
- [7] T.B. Ustun, J.L. Ayuso-Mateos, S. Chatterji, C. Mathers, C.J. Murray, Global burden of depressive disorders in the year 2000, *Br. J. Psychiatry* 184 (2004) 386–392.
- [8] E.H. Lin, M.V. Korff, J. Alonso, M.C. Angermeyer, J. Anthony, E. Bromet, et al., Mental disorders among persons with diabetes—results from the World Mental Health Surveys, *J. Psychosom. Res.* 65 (6) (2008) 571–580.
- [9] R.C. Kessler, P. Berglund, O. Demler, R. Jin, D. Koretz, K.R. Merikangas, et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R), *JAMA* 289 (23) (2003) 3095–3105.
- [10] J. Alonso, M.C. Angermeyer, S. Bernert, R. Bruffaerts, T.S. Brugha, H. Bryson, et al., Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project, *Acta Psychiatr. Scand. Suppl.* 420 (2004) 21–27.
- [11] K. Demyttenaere, R. Bruffaerts, J. Posada-Villa, I. Gasquet, V. Kovess, J.P. Lepine, et al., Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys, *JAMA* 291 (21) (2004) 2581–2590.
- [12] C.M. Michaud, C.J. Murray, B.R. Bloom, Burden of disease—implications for future research, *JAMA* 285 (5) (2001) 535–539.
- [13] US Department of Health and Human Services, Mental health: a report of the surgeon general Rockville, MD: US Department of Health and Human Services, Substance Abuse and Mental Health Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institute of Mental Health, 1999.
- [14] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders. Fourth ed. 2000, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association.
- [15] R.L. Spitzer, J.B. Williams, K. Kroenke, M. Linzer, F.V.R. deGuy, S.R. Hahn, et al., Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study, *JAMA* 272 (22) (1994) 1749–1756.
- [16] A. Beck, C. Ward, M. Mendelson, An inventory for measuring depression, *Arch. Gen. Psychiatry* 4 (1961) 53–63.
- [17] W. Zung, A self-rating depression scale, *Arch. Gen. Psychiatry* 12 (1965) 63–70.
- [18] L.S. Radloff, The CES-D scale: a self-report depression scale for research in the general population, *Appl. Psychol. Meas.* 1 (1977) 385–401.
- [19] M.A. Whooley, A.L. Avins, J. Miranda, W.S. Browner, Case-finding instruments for depression. Two questions are as good as many, *J. Gen. Intern. Med.* 12 (1997) 439–445.
- [20] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, *J. Gen. Intern. Med.* 16 (9) (2001) 606–613.
- [21] U.S. Preventative Services Task Force (USPSTF), Screening for depression: recommendations and rationale, *J. Gen. Intern. Med.* 136 (10) (2002) 760–764.
- [22] T. Willis, *Diabetes: A Medical Odyssey*, Tuckahoe, New York, 1971.
- [23] R.J. Anderson, K.E. Freedland, R.E. Clouse, P.J. Lustman, The prevalence of comorbid depression in adults with diabetes: a meta-analysis, *Diabetes Care* 24 (6) (2001) 1069–1078.
- [24] C. Li, E.S. Ford, T.W. Strine, A.H. Mokdad, Prevalence of depression among U.S. adults with diabetes: findings from the 2006 behavioral risk factor surveillance system, *Diabetes Care* 31 (1) (2008) 105–107.
- [25] C. Li, E.S. Ford, G. Zhao, I.B. Ahluwalia, W.S. Pearson, A.H. Mokdad, Prevalence and correlates of undiagnosed depression among U.S. adults with diabetes: the Behavioral Risk Factor Surveillance System, *Diabetes Res Clin Pract* 83 (2) (2009) 268–279.
- [26] S. Asghar, A. Hussain, S.M. Ali, A.K. Khan, A. Magnusson, Prevalence of depression and diabetes: a population-based study from rural Bangladesh, *Diabet. Med.* 24 (8) (2007) 872–877.
- [27] A. Sotiropoulos, A. Papazafropoulou, O. Apostolou, A. Kokolaki, A. Gikas, S. Pappas, Prevalence of depressive symptoms among non insulin treated Greek type 2 diabetic subjects, *BMC Res. Notes* 1 (2008) 101.
- [28] N. Zahid, S. Asghar, B. Claussen, A. Hussain, Depression and diabetes in a rural community in Pakistan, *Diabetes Res. Clin. Pract.* 79 (1) (2008) 124–127.
- [29] M.E. Khamseh, H.R. Baradaran, H. Rajabali, Depression and diabetes in Iranian patients: a comparative study, *Int. J. Psychiatry Med.* 37 (1) (2007) 81–86.
- [30] W. Almawi, H. Tamim, N. Al-Sayed, M.R. Arekat, G.M. Al-Khateeb, A. Baqer, et al., Association of comorbid depression, anxiety, and stress disorders with Type 2 diabetes in Bahrain, a country with a very high prevalence of Type 2 diabetes, *J. Endocrinol. Invest.* 31 (11) (2008) 1020–1024.

- [31] N. Mier, A. Bocanegra-Alonso, D. Zhan, S. Wang, S.M. Stoltz, R.I. Acosta-Gonzalez, et al., Clinical depressive symptoms and diabetes in a binational border population, *J. Am. Board Fam. Med.* 21 (3) (2008) 223–233.
- [32] S.M. Kogan, G.H. Brody, C. Crawley, P. Logan, V.M. Murry, Correlates of elevated depressive symptoms among rural African American adults with type 2 diabetes, *Ethn. Dis.* 17 (1) (2007) 106–112.
- [33] T.L. Gary, R.M. Crum, L. Cooper-Patrick, D. Ford, F.L. Brancati, Depressive symptoms and metabolic control in African-Americans with type 2 diabetes, *Diabetes Care* 23 (1) (2000) 23–29.
- [34] S. Ali, M.A. Stone, J.L. Peters, M.J. Davies, K. Khunti, The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis, *Diabet. Med.* 23 (11) (2006) 1165–1173.
- [35] M.J. Knol, J.W. Twisk, A.T. Beekman, R.J. Heine, F.J. Snoek, F. Pouwer, Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis, *Diabetologia* 49 (5) (2006) 837–845.
- [36] B. Mezuk, W.W. Eaton, S. Albrecht, S.H. Golden, Depression and type 2 diabetes over the lifespan: a meta-analysis, *Diabetes Care* 31 (12) (2008) 2383–2390.
- [37] S.H. Golden, M. Lazo, M. Carnethon, A.G. Bertoni, P.J. Schreiner, A.V. Roux, et al., Examining a bidirectional association between depressive symptoms and diabetes, *JAMA* 299 (23) (2008) 2751–2759.
- [38] D.L. Musselman, E. Betan, H. Larsen, L.S. Phillips, Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment, *Biol. Psychiatry* 54 (3) (2003) 317–329.
- [39] F. Talbot, A. Nouwen, A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care* 23 (10) (2000) 1556–1562.
- [40] S.H. Saydah, F.L. Brancati, S.H. Golden, J. Fradkin, M.I. Harris, Depressive symptoms and the risk of type 2 diabetes mellitus in a US sample, *Diabetes Metab. Res. Rev.* 19 (2003) 202–208.
- [41] L.A. Palinkas, E. Barrett-Connor, D.L. Wingard, Type 2 diabetes and depressive symptoms in older adults: a population-based study, *Diabet. Med.* 8 (6) (1991) 532–539.
- [42] P.J. Lustman, R.J. Anderson, K.E. Freedland, M. de Groot, R.M. Carney, R.E. Clouse, Depression and poor glycemic control: a meta-analytic review of the literature, *Diabetes Care* 23 (7) (2000) 934–942.
- [43] L.K. Richardson, L.E. Egede, M. Mueller, C.L. Echols, M. Gebregziabher, Longitudinal effects of depression on glycemic control in veterans with Type 2 diabetes, *Gen. Hosp. Psychiatry* 30 (6) (2008) 509–514.
- [44] J.A. Wagner, G.L. Abbott, A. Heapy, L. Yong, Depressive symptoms and diabetes control in African Americans, *J. Immigr. Minor. Health* 11 (1) (2009) 66–70.
- [45] M.A. Van Tilburg, C.C. McCaskill, J.D. Lane, C.L. Edwards, A. Bethel, M.N. Feinglos, et al., Depressed mood is a factor in glycemic control in type 1 diabetes, *Psychosom. Med.* 63 (4) (2001) 551–555.
- [46] L.E. Egede, Effect of depression on self-management behaviors and health outcomes in adults with type 2 diabetes, *Curr. Diabetes Rev.* 1 (2005) 235–243.
- [47] S. Gonzalez, S.A. Safren, L.M. Delahanty, E. Cagliero, D.J. Wexler, J.B. Meigs, et al., Symptoms of depression prospectively predict poorer self-care in patients with Type 2 diabetes, *Diabet. Med.* 25 (9) (2008) 1102–1107.
- [48] J.S. Gonzalez, M. Peyrot, L.A. McCarl, E.M. Collins, L. Serpa, M.J. Mimiaga, et al., Depression and diabetes treatment nonadherence: a meta-analysis, *Diabetes Care* 31 (12) (2008) 2398–2403.
- [49] J.A. Cramer, A systematic review of adherence with medications for diabetes, *Diabetes Care* 27 (5) (2004) 1218–1224.
- [50] E.H. Lin, W. Katon, M. Von Korff, C. Rutter, G.E. Simon, M. Oliver, et al., Relationship of depression and diabetes self-care, medication adherence, and preventive care, *Diabetes Care* 27 (9) (2004) 2154–2160.
- [51] J.S. Gonzalez, S.A. Safren, E. Cagliero, D.J. Wexler, L. Delahanty, E. Wittenberg, et al., Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity, *Diabetes Care* 30 (9) (2007) 2222–2227.
- [52] L.E. Egede, C. Ellis, The effects of depression on diabetes knowledge, diabetes self-management, and perceived control in indigent patients with type 2 diabetes, *Diabetes Technol. Ther.* 10 (3) (2008) 213–219.
- [53] M. de Groot, R. Anderson, K.E. Freedland, R.E. Clouse, P.J. Lustman, Association of depression and diabetes complications: a meta-analysis, *Psychosom. Med.* 63 (4) (2001) 619–630.
- [54] R.E. Clouse, P.J. Lustman, K.E. Freedland, L.S. Griffith, J.B. McGill, R.M. Carney, Depression and coronary heart disease in women with diabetes, *Psychosom. Med.* 65 (3) (2003) 376–383.
- [55] M.S. Roy, A. Roy, M. Affouf, Depression is a risk factor for poor glycemic control and retinopathy in African-Americans with type 1 diabetes, *Psychosom. Med.* 69 (6) (2007) 537–542.
- [56] P.K. Sahota, W.C. Knowler, H.C. Looker, Depression, diabetes, and glycemic control in an American Indian community, *J. Clin. Psychiatry* 69 (5) (2008) 800–809.
- [57] R. Gross, M. Olfson, M.J. Gameroff, O. Carasquillo, S. Shea, A. Feder, et al., Depression and glycemic control in Hispanic primary care patients with diabetes, *J. Gen. Intern. Med.* 20 (5) (2005) 460–466.
- [58] S.A. Black, K.S. Markides, L.A. Ray, Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes, *Diabetes Care* 26 (10) (2003) 2822–2828.
- [59] L.E. Egede, Diabetes, major depression, and functional disability among U.S. adults, *Diabetes Care* 27 (2) (2004) 421–428.
- [60] L.E. Egede, Effects of depression on work loss and disability bed days in individuals with diabetes, *Diabetes Care* 27 (7) (2004) 1751–1753.
- [61] I. Eren, O. Erdi, M. Sahin, The effect of depression on quality of life of patients with type II diabetes mellitus, *Depress. Anxiety* 25 (2) (2008) 98–106.
- [62] S. Grandy, R.H. Chapman, K.M. Fox, Quality of life and depression of people living with type 2 diabetes mellitus and those at low and high risk for type 2 diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD), *Int. J. Clin. Pract.* 62 (4) (2008) 562–568.
- [63] T.K. Le, S.L. Able, M.J. Lage, Resource use among patients with diabetes, diabetic neuropathy, or diabetes with depression, *Cost Eff. Resour. Alloc.* 4 (2006) 18.
- [64] P.S. Ciechanowski, W.J. Katon, J.E. Russo, Depression and diabetes: impact of depressive symptoms on adherence, function, and costs, *Arch. Intern. Med.* 160 (21) (2000) 3278–3285.
- [65] E.A. Finkelstein, J.W. Bray, H. Chen, et al., Prevalence and costs of major depression among elderly claimants with diabetes, *Diabetes Care* 26 (2) (2003) 415–420.
- [66] L. Nichols, P.L. Barton, J. Glazner, M. McCollum, Diabetes, minor depression and health care utilization and expenditures: a retrospective database study, *Cost Eff. Resour. Alloc.* 5 (2007) 4.

- [67] L.E. Egede, D. Zheng, K. Simpson, Comorbid depression is associated with increased health care use and expenditures in individuals with diabetes, *Diabetes Care* 25 (3) (2002) 464–470.
- [68] X. Zhang, S.L. Norris, E.W. Gregg, Y.J. Cheng, G. Beckles, H.S. Kahn, Depressive symptoms and mortality among persons with and without diabetes, *Am. J. Epidemiol.* 161 (7) (2005) 652–660.
- [69] W. Katon, M.Y. Fan, J. Unutzer, et al., Depression and diabetes: a potentially lethal combination, *J. Gen. Intern. Med.* 23 (10) (2008) 1571–1575.
- [70] L.E. Egede, P.J. Nietert, D. Zheng, Depression and all-cause and coronary heart disease mortality among adults with and without diabetes, *Diabetes Care* 28 (6) (2005) 1339–1345.
- [71] L.E. Egede, Failure to recognize depression in primary care: issues and challenges, *J. Gen. Intern. Med.* 22 (5) (2007) 701–703.
- [72] P.J. Lustman, L.S. Griffith, R.E. Clouse, K.E. Freedland, S.A. Eisen, E.H. Rubin, et al., Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial, *Psychosom. Med.* 59 (3) (1997) 241–250.
- [73] P.J. Lustman, K.E. Freedland, L.S. Griffith, R.E. Clouse, Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial, *Diabetes Care* 23 (5) (2000) 618–623.
- [74] J.W. Williams Jr., W. Katon, E.H. Lin, P.H. Noel, J. Worchel, J. Cornell, et al., The effectiveness of depression care management on diabetes-related outcomes in older patients, *Ann. Intern. Med.* 140 (12) (2004) 1015–1024.
- [75] M.Y. Wang, P.S. Tsai, K.R. Chou, C.M. Chen, A systematic review of the efficacy of non-pharmacological treatments for depression on glycaemic control in type 2 diabetics, *J. Clin. Nurs.* 17 (19) (2008) 2524–2530.
- [76] P.J. Lustman, L.S. Griffith, K.E. Freedland, S.S. Kissel, R.E. Clouse, Cognitive behavior therapy for depression in type 2 diabetes mellitus. A randomized, controlled trial, *Ann. Intern. Med.* 129 (8) (1998) 613–621.
- [77] W.J. Katon, M. Von Korff, E.H. Lin, G. Simon, E. Ludman, J. Russo, et al., The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression, *Arch. Gen. Psychiatry* 61 (10) (2004) 1042–1049.
- [78] F.J. Snoek, N.C. van der Ven, J.W. Twisk, M.H. Hogenelst, A.M. Tromp-Wever, H.M. van der Ploeg, et al., Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic patients: long-term effects on HbA moderated by depression. A randomized controlled trial, *Diabet. Med.* 25 (11) (2008) 1337–1342.
- [79] F. Petrak, S. Herpertz, Treatment of depression in diabetes: an update, *Curr. Opin. Psychiatry* 22 (2) (2009) 211–217.
- [80] G.E. Simon, W.J. Katon, E.H. Lin, et al., Cost-effectiveness of systematic depression treatment among people with diabetes mellitus, *Arch. Gen. Psychiatry* 64 (1) (2007) 65–72.
- [81] W.J. Katon, J.E. Russo, M. Von Korff, E.H. Lin, E. Ludman, P.S. Ciechanowski, Long-term effects on medical costs of improving depression outcomes in patients with depression and diabetes, *Diabetes Care* 31 (6) (2008) 1155–1159.
- [82] E.J. Ludman, W. Katon, J. Russo, M. Von Korff, G. Simon, P. Ciechanowski, et al., Depression and diabetes symptom burden, *Gen. Hosp. Psychiatry* 26 (6) (2004) 430–436.
- [83] M.C. Adriaanse, J.M. Dekker, A.M. Spijkerman, J.W. Twisk, G. Nijpels, H.M. van der Ploeg, et al., Diabetes-related symptoms and negative mood in participants of a targeted population-screening program for type 2 diabetes: the Hoorn Screening Study, *Qual. Life Res.* 14 (6) (2005) 1501–1509.
- [84] P.A. Nutting, K. Rost, M. Dickinson, J.J. Werner, P. Dickinson, J.L. Smith, et al., Barriers to initiating depression treatment in primary care practice, *J Gen Intern. Med.* 17 (2) (2002) 103–111.
- [85] IDF Clinical Guidelines Task Force, Global guideline for Type 2 diabetes. 2005, Brussels: International Diabetes Federation.