

The Epidemiology of Depression and Diabetes

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In recent years there has been a heightened interest in the psychological well-being of people with diabetes. Current epidemiological evidence suggests that at least one third of them suffer from clinically relevant depressive disorders [1–3]. Furthermore, people with depressive disorders have an increased risk of developing diabetes [4].

Indeed, the prognosis of both diabetes and depression – in terms of severity of disease, complications, treatment resistance and mortality – as well as the costs to both the individual and society [5] is worse for either disease when they are comorbid than it is when they occur separately [6, 7]. However, in spite of the huge impact of comorbid depression and diabetes on the individual and its importance as a public health problem, questions still remain as to the nature of the relationship, its causes and consequences, as well as potential ways of preventing and treating these two conditions. This chapter aims to outline the epidemiological evidence as it stands, as well as point the way for future research in this area.

RATES OF DEPRESSION IN PEOPLE WITH DIABETES

Depression is usually defined by the number of symptoms present, usually within the past two weeks. In order to diagnose major depression using DSM-IV or ICD-10 criteria, a clinical interview is conducted and a number of symptoms have to be present (Table 1.1). Most epidemiological research on the prevalence of depression uses self-report instruments (for example the Centre for Epidemiologic Studies – Depression Scale [8] or the recently devised Patient Health Questionnaire – 9, PHQ-9 [9]) for detecting depression or depressive symptomatology, and most instruments that are used measure symptoms that approximate clinical levels of disorder (Table 1.1).

Rates of depression in people with diabetes are significantly increased and are thought to be at least doubled for those with diabetes compared to those without any chronic disease [1]. A recent report from the World Health Survey [10] estimated the prevalence of depression (based on ICD-10 criteria) in 245,404 individuals from 60 countries around the world. The overall one-year prevalence of self-reported symptoms of depression in individuals with diabetes was 9.3%. This study showed that the greatest decrements in self-reported health were observed in those with both depression and diabetes, more so than those with depression and any other chronic disease [10] (Figure 1.1).

Other studies have reported prevalence rates of depression of 24–30% [1, 2, 11]. Recently it has been suggested that although up to

Table 1.1 Symptoms listed in the DSM-IV criteria for major depressive disorder and symptoms of depression measured using self-report instruments

DSM-IV criteria (at least five symptoms present nearly every day for 2 wk and causing significant distress or functional impairment)

Depressed mood
Markedly diminished interest or pleasure in all or almost all activities
Significant weight loss/gain or decreased/increased appetite
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness/guilt
Diminished ability to concentrate/make decisions
Recurrent thoughts of death or suicide

Symptoms of depression measured using self-report instruments

Feeling sad/depressed mood
Inability to sleep
Early waking
Lack of interest/enjoyment
Tiredness/lack of energy
Loss of appetite
Feelings of guilt/worthlessness
Recurrent thoughts about death/suicide

DSM-IV criteria extracted from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, Copyright 2000. American Psychiatric Association.

30% of individuals with diabetes report depressive symptoms, only about 10% have major depression [12]. However, the published studies differ widely in terms of the methods used to measure depression, which makes any conclusions premature. Rates of depressive symptoms have been found to be higher in those studies where self-report instruments were used compared to diagnostic interviews [1]. Furthermore, in a recent report, Gendelman *et al.* [13] showed that prevalence rates were even higher if reports of elevated symptoms were combined with the use of antidepressant medication. This suggests that the available evidence should be considered with particular methodological differences in case ascertainment kept in mind.

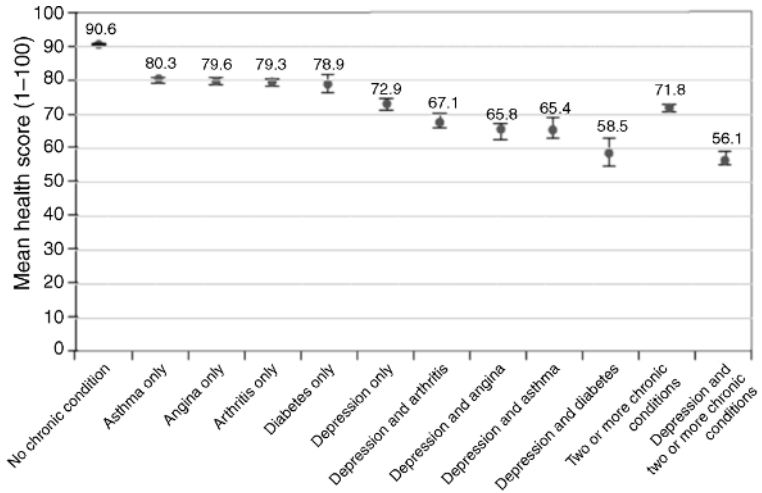


Figure 1.1 Global mean health by disease status. (Saba Moussavi et al., Depression, chronic diseases and decrements in health: results from the World Health Surveys, *The Lancet*, 2007, by permission of Elsevier)

Rates of depression have been found to be particularly high in individuals with type 2 diabetes, with less evidence to suggest that rates are also increased in those with type 1 diabetes [3]. Any potential differences are confounded by age, and it is known that older age is a risk factor for higher prevalence of depression in those with other health problems [14, 15]. There may also be an increased prevalence of psychological morbidity in young adults with type 1 diabetes [16–19]. Some reports have indicated that the prevalence of depression does not appear to differ according to type of diabetes [1, 20, 21]. One study [22] reported that those with major depression were more likely to be on insulin treatment rather than on oral agents or diet alone, and this may be related to the increased burden of the self-management regimen in these individuals.

INTERNATIONAL VARIATIONS IN RATES OF DEPRESSION IN PEOPLE WITH DIABETES

There may be regional/cultural differences in the prevalence of depression. However, this is difficult to establish with available data. Much of the research to date has been on the comparison of prevalence rates generally, and few published studies address culture or ethnicity as a specific factor within or across populations. Of those reports, studies have suggested that individuals from African American backgrounds have higher rates of diabetes and depression compared with Caucasian populations [23, 24]. Other studies have shown that Hispanic people have higher levels of comorbid depression compared with African Americans or Caucasian individuals [25–28]. Several studies have suggested that comorbid depression may also be much more common in native Americans with type 2 diabetes [29, 30].

In one of the few published studies of comorbid depression in the developing world, carried out in Bangladesh, Asghar *et al.* [29] reported that nearly one third (29% males, 30% females) of those with diabetes had clinically significant levels of depression, compared with only 6% of males and 15% of females without diabetes. In Pakistan, levels of depression have been reported to be lower, with prevalence rates of nearly 15% amongst those with diabetes compared to 5% amongst those without diabetes [31]. Prevalence rates in Europe have been shown to vary, although consistently higher in people with diabetes compared to those without [32, 33]. High rates of depression have also been observed in Australia in both individuals with type 1 and type 2 diabetes [11, 34].

It is clear that, although there may well be international variations in rates of comorbid depression and diabetes, there remains further work to be done to clarify whether those variations reflect socioeconomic/other environmental differences, whether race or culture play a part, or whether at least some of this difference is related to variations in assessment methods or the cultural applicability of those measurement tools. These possibilities still need to be fully examined in future studies.

RISK FACTORS FOR DEPRESSION IN PEOPLE WITH DIABETES

A range of factors may be implicated in increasing the risk of developing depressive symptoms, both in terms of an initial episode of depression and with regard to the persistence, recurrence and severity of depressive episodes. A number of risk factors identified in individuals without diabetes also apply to those with diabetes, although others may differ. Some of the key risk factors that have been identified are listed in Table 1.2. Elevated depression levels have been found in general populations in women, younger people and also those of older age (especially those with physical health problems), individuals living alone, those who report a lack of social support, and those who have lower socioeconomic status. In individuals with diabetes, the following additional risk factors for depression have been found to be important: occurrence of late or acute complications, persistently poor glycaemic control and insulin therapy in type 2 diabetes [35, 36] (Table 1.2).

In the general population, risk factors for an *initial* depressive episode include gender [37], major stressful life events [38–40] and socioeconomic conditions [41]. Maternal depression has been shown to increase the risk for depression in children and adolescents [42, 43], although this has not been confirmed in other studies [16]. Low birth weight and foetal undernutrition have also been associated with both depression and diabetes [44, 45]. Other factors, including lifestyle and health behaviours, may also play a part in increasing risk for depression in people with diabetes. However, the temporal association between these variables remains unclear and requires further investigation.

Table 1.2 Risk factors for depression in diabetes

Non-diabetes specific risk factors	Diabetes specific risk factors
Female gender	Manifestation of diabetes
Lack of social support	Occurrence of late complications
Low socioeconomic status	Persistent poor glycaemic control
Younger age; older age and physical health problems	Need for insulin therapy in type 2 diabetes
Occurrence of critical life events	Hypoglycaemia problems

A number of studies have reported a greater prevalence of depression in women with both type 1 diabetes and type 2 diabetes, similar to that observed in the general population [16, 21, 46]. A recent study showed even greater differences between men and women when use of antidepressant medication was included [13]. Indeed, medication use was almost twice as common in women with type 1 diabetes compared to men. There may be gender differences in the experience of depressive symptoms as well as in the reporting of symptoms and help-seeking behaviour. However, there are few studies that have examined these issues in depth [20, 47].

Although depression is not a part of normal ageing [48, 49], prevalence rates of severe depressive episodes/major depressive disorder are higher amongst certain groups of older people, in particular, individuals with a comorbid medical illness [50]. However, to date, little epidemiological data has been available with which to examine rates of depression in older people with diabetes [14, 15, 33, 51]. To further complicate the picture, several studies have reported that depressive symptoms are more common in younger individuals, in both type 1 and type 2 diabetes [16, 52]. Collins *et al.* [51] also reported lower rates of depression in older individuals with type 1 diabetes, suggesting that age might have a protective effect.

Recurrence of depression is common in people with diabetes, and episodes are likely to last longer [46, 53, 54]. In one five-year follow-up study, Lustman *et al.* [55] found that recurrence or persistence of major depression occurred in 23 (92%) participants, with an average of 4.8 episodes, after an eight-week treatment with nortriptyline. Kovacs *et al.* [53] found that episodes of major depressive disorder lasted longer in adolescents with type 1 diabetes than in control participants, although rates of recovery were similar.

The specific factors associated with recurrence of depression remain unclear. Gender has not been found to be associated with the number of episodes or the severity of recurrence or chronicity of depression [56], and the association between stress and depressive episodes appears to be less pronounced over time [57–60]. The evidence would suggest that stress is either no longer important in the triggering of subsequent depressive episodes or that weaker, and

therefore more frequent, stressors would suffice [61]. If confirmed, this would mean that the relatively minor stresses of living with diabetes may be enough to trigger a depressive episode in people vulnerable to depression. To date, both general stressors [27] and diabetes-related emotional problems and distress have been linked with higher levels of depressive symptoms [27, 32].

Diabetes-specific risk factors for depression include comorbidity of diabetes-related complications, in particular vascular complications [62–64]. Knowledge of having type 2 diabetes [65–67], longer duration of diabetes [68, 69], more demanding regimens, low levels of daily activities [70–72], higher dependency [73], nutrition (e.g. low intake of omega-3 fatty acids) [74], smoking [75], obesity [76] and perceived burden of diabetes [77, 78] have all been postulated as risk factors, but the epidemiological evidence remains limited. Potential risk factors for depression in people with diabetes often interact with each other and with other factors. For example, the relationship between duration of diabetes and depression may be confounded by the number of complications present.

A small number of studies has examined whether the presence of diabetes *per se* increases the risk of depression in people with type 2 diabetes [14, 33, 79–84]. A recent meta-analysis, which included these studies [85], demonstrated there was only a modest (15%) increased risk of developing depression in people with diabetes. However, this meta-analysis only contained seven studies and no distinction was made whether a diagnosis of depression was used or questionnaires. When examining studies where a diagnosis of depression was made separately from studies where self-reported symptoms were used, the risk of developing depression was 48% and only 20% in the questionnaire studies. Clearly the temporal association between diabetes and depression warrants further attention in long-term prospective studies.

DEPRESSION AS A RISK FACTOR FOR DIABETES

Mezuk *et al.* [85] reported data showing that depression may be an important risk factor for developing type 2 diabetes. Depression was associated with a 60% increased risk of developing type 2 diabetes.

The link between depression and diabetes was made as early as the seventeenth century, when the famous English physician T. Willis (1621–1675) noted that diabetes often appeared among patients who had experienced significant life stresses, sadness or long sorrow [86]. Whether depression increases the risk of type 1 diabetes is currently unknown. However, recent studies have suggested that people with depression are more vulnerable to the development of type 2 diabetes [85, 87], thereby confirming Willis' hypothesis.

It is important to recognize that depression is not only associated with an increased risk for the development of type 2 diabetes, but is also an established risk factor for cardiovascular disease [88, 89] and several features of the metabolic syndrome, particularly hypertension, abdominal obesity and low HDL cholesterol [90, 91]. Several hypotheses have been put forward regarding the pathophysiological mechanisms that could explain the increased risk of type 2 diabetes in depressed subjects. For example, increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system might play a role; these are examined elsewhere in this volume.

Depression may also increase the risk for type 2 diabetes via behavioural mechanisms. It is well known that the most important risk factor for type 2 diabetes is obesity [92], and that physical inactivity further increases this risk [93]. Interestingly, data from the Heart and Soul Study [89] showed that the association between depression and incident cardiovascular events was largely explained by behavioural factors, particularly physical inactivity.

In summary, the evidence to date suggests that depression may indeed increase the risk of developing type 2 diabetes. However, the mechanisms via which this may occur still require investigation. The link between depression and the development of type 1 diabetes remains unclear.

DEPRESSIVE SYMPTOMATOLOGY AND GLYCAEMIC CONTROL

People with diabetes are expected to carry out lifelong multiple self-care tasks (including self-monitoring of blood glucose, dietary modifications, exercising and managing medications) in order to achieve optimal glycaemic control and so reduce the risk of developing serious

complications. Intensive insulin and medication regimes and structured education programmes are effective in improving glycaemic control, decreasing cardiovascular risk and reducing diabetes complications in both type 1 and type 2 diabetes [94, 95]. However, for some individuals there are likely to be both psychological and social barriers to maintaining good glycaemic control over time.

Depression is associated with adverse outcomes in diabetes, and there is some evidence to suggest that depression worsens glycaemic control because it worsens self-care [96, 97]. For example, in one prospective study of approximately 4000 people with diabetes, depression was associated with poor concordance with oral medication taking, even in those with reasonable glycaemic control levels prior to the study [98]. Numerous studies, usually cross-sectional, suggest depression is associated with suboptimal glycaemic control, although in a systematic review the effect size was moderate [99]. Of the few prospective studies [100–103], only one [103] demonstrated a clear association between depression at baseline and persistently higher HbA1c levels over a four-year period. However, this study had some limitations, as it did not consider potential mediating factors, such as medication taking and diabetes self-management.

So far, the exact mechanism linking depression, glycaemic control, morbidity and mortality has not been established. The ‘depression leading to poor self-care’ hypothesis does not seem to tell the whole story. For example, when depression is treated in diabetes, whether by pharmacotherapy or using psychological techniques, depression is improved, but not necessarily glycaemic control [46, 104–110]. This suggests that depression could influence morbidity and mortality via other pathways, such as those involved in cardiovascular disease and lipid dysregulation. Future prospective studies measuring a range of biopsychosocial factors will allow us to unpick these complex interactions.

MILD DEPRESSION AND OTHER PSYCHOLOGICAL COMORBIDITIES IN PEOPLE WITH DIABETES

Having mild or subthreshold depression may have a disproportionate impact on people with diabetes. Owing to the effects on diabetes

self-management, what may be regarded as ‘subclinical’ in someone without diabetes may be seen as of great clinical importance when combined with diabetes [5]. This ‘mild’ depression may not just be the result of living with diabetes, but also a response to stresses and life events independent of diabetes (e.g. marital problems, work-related stresses) that may interact with diabetes.

Depressive symptoms commonly occur in other psychiatric disorders, such as eating and anxiety disorders. Depressive symptoms are common to young women with eating disorders: they are not separately diagnosed, but regarded as part of the illness/diagnosis, and affect approximately 30–50% of people with anorexia nervosa and 50% of those with bulimia nervosa [111]. Eating disorders associated with poor diabetes self-care, such as underdosing or omission of insulin to promote weight loss, occur disproportionately in pre-teen girls with diabetes [112–115].

Anxiety is common in diabetes populations and is frequently associated with depression [7, 20, 51, 52]. A recent systematic review found that around 14% of people with diabetes have generalized anxiety disorder, but subclinical anxiety and symptoms were more common and affected 27% and 40% respectively [116]. The presence of comorbid depression or anxiety has been associated with increased somatic symptoms of disease, which has important implications for treatment [7]. Diabetes-specific psychological problems, such as fear of self-injecting insulin or self-testing blood glucose (which may or may not be full-blown needle phobia) and fear of complications, are all associated with anxiety and depression [117–119]. Fears regarding hypoglycaemia and psychological insulin resistance are also common, but their relationship with depression is less clear [120, 121].

Several recent reports have indicated that psychosocial factors, including emotional problems related to diabetes, are associated with elevated levels of depression [32, 122]. These studies have used the Problem Areas in Diabetes (PAID) scale, which was developed to measure diabetes-related emotional distress, often referred to as ‘diabetes burn-out’, in individuals with either type 1 or type 2 diabetes [77]. Research has shown strong correlations between depressive symptomatology and diabetes-related distress. However, whilst many of those with high depression symptoms also report high

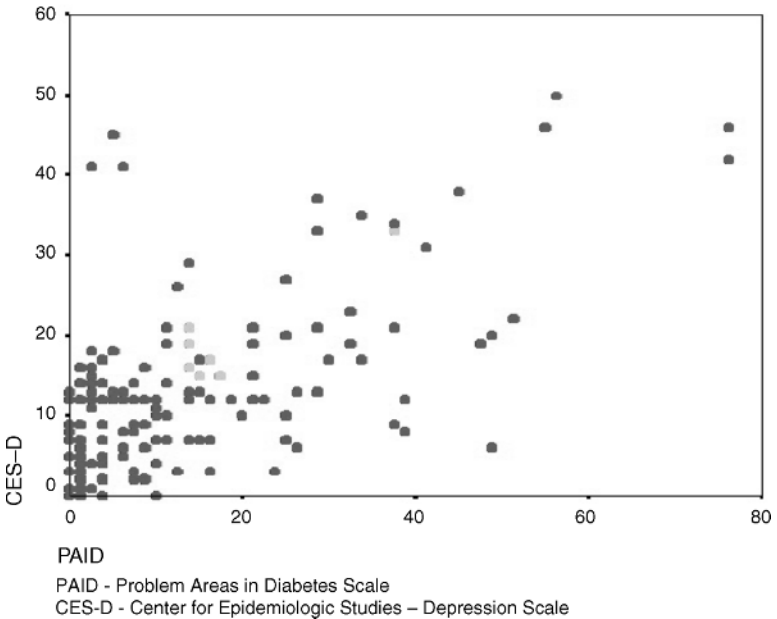


Figure 1.2 The overlap between symptoms of depression and diabetes-related distress. (With permission from Skinner TC, Combined Universities Centre for Rural Health, Australia)

diabetes-related emotional distress, there are also a significant number of individuals who only have either one or the other (Figure 1.2). Further studies are required in order to tease out the relative importance of different psychological morbidity and the impact on diabetes care.

LONGER-TERM OUTCOMES AND THE IMPACT OF DEPRESSION IN DIABETES

Depression in diabetes is associated with greater morbidity and mortality and poorer quality of life. Evidence shows that depressive symptoms are associated with less dietary self-care, poorer physical and mental functioning, increased use of health services and, in type 2 diabetes, poorer concordance with oral medication recommendations [96, 123].

As diabetes affects the economically active, there is the potential for loss of economic or social roles, affecting marital and family life, causing isolation and stigmatization, which may also engender depression. People who are depressed often have negative views regarding their diabetes, and these may perpetuate adverse coping behaviours and increase the likelihood of poor outcomes [124–126].

Depressive symptoms are more common in people with diabetes complications, although the causal direction of this relationship is unclear [33, 64]. Studies from an onset cohort of type 1 diabetes have demonstrated a prospective association between prior depressive symptoms and the onset of coronary artery disease [127, 128]. A similar association between depression and onset of retinopathy has also been identified in a study of children with diabetes [129]. Although depression is a risk factor for the onset of type 2 diabetes [87] and cardiovascular disease [130], people who experience diabetes complications suffer a loss of function that might lead to depression.

The wider literature supports a bidirectional relationship between depression and vascular disease [131]. Macro- and micro-vascular problems typically co-occur in diabetes, such as erectile dysfunction and diabetic foot disease, but it can be difficult to detect early signs of micro-vascular damage, so establishing the relationship between depression and the onset of conditions such as neuropathy is problematic.

There have been numerous prospective studies demonstrating an association between depression and mortality in people with (predominantly type 2) diabetes, which suggests a synergistic interactive effect of depression on cardiovascular mortality [100, 101, 132]. In a study in the United Kingdom, major and minor depressive episodes increased mortality risk threefold in a cohort of people with diabetes and their first foot ulcer at 18 months [101]. In the United States, the Pathways Study demonstrated a 1.67 and 2.30-fold increase in mortality at three years in those with minor and major depression, respectively [100]. Another study reported a 50% increased risk of death among people with diabetes, but no increased risk of death from cardiovascular disease [133].

The Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE) reported that depressed individuals were almost five times more likely to die and were significantly

more likely to develop early onset of diabetes complications at seven years follow-up [134]. Finally, the US National Health and Nutrition Examination Survey (NHANES) compared people with diabetes and depression to people with diabetes and no depression and other non-diabetes groups at eight years follow-up, and determined a 2.50-fold increase in all-cause mortality in the depressed diabetes group and a 2.43-fold increase in coronary heart disease mortality [5].

In another study using the NHANES data (Figures 1.3 and 1.4), Zhang *et al.* [132] also demonstrated a strong association between depressive symptoms and increased mortality in people with diabetes, which they did not observe in those without diabetes, even after adjusting for sociodemographic and lifestyle factors. These findings have important implications for the care of people with comorbid depression and diabetes.

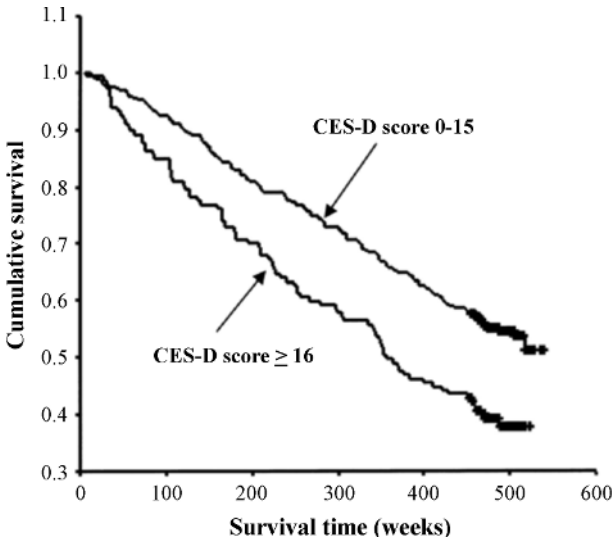


Figure 1.3 Survival functions in a diabetic population stratified by Center for Epidemiologic Studies-Depression (CES-D) Scale score. (Xuanping Zhang *et al.*, Depressive symptoms and mortality among persons with and without diabetes, American Journal of Epidemiology, 2005, by permission of Oxford University Press)

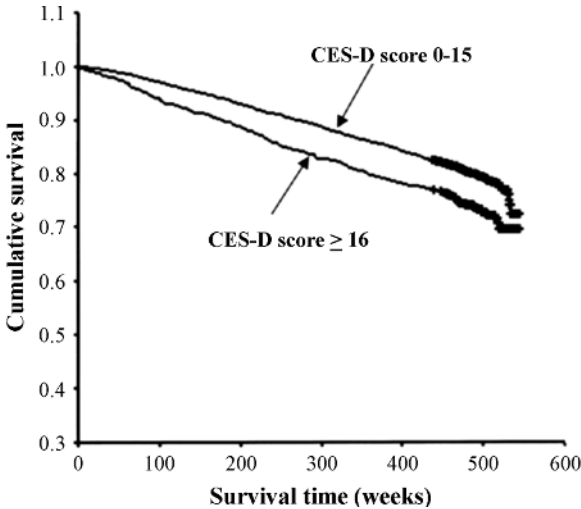


Figure 1.4 Survival functions in a non-diabetic population stratified by Centers for Epidemiologic Studies-Depression (CES-D) Scale score. (Xuanping Zhang *et al.*, Depressive symptoms and mortality among persons with and without diabetes, *American Journal of Epidemiology*, 2005, by permission of Oxford University Press)

CONCLUSIONS

Current epidemiological evidence demonstrates that people with diabetes have an increased risk of experiencing one or more depressive episodes in their lifetime and that this can have serious adverse consequences. This increased prevalence may be related to people with diabetes experiencing longer lasting or more recurrent depressive episodes, rather than an increased risk of developing depression *per se*.

A range of potential risk factors for this increased vulnerability has been postulated. However, much of the evidence cited is from cross-sectional studies and so the temporal relationship between the two conditions is yet to be fully determined. In particular, the role of a previous history of depression in future episodes remains unclear, and large population-based prospective studies are needed to examine this further.

The methods used to assess depressive symptoms have varied between studies and it is not clear whether different conclusions would be reached if more stringent diagnostic criteria were used. Given the known inter- and intra-national differences in prevalence rates, further research needs to be conducted in order to tease out whether these variations are due to the cultural inapplicability of particular measurement tools, or whether there are 'true' differences related to wider socioeconomic factors and/or cultural/ethnic marginalization.

People from ethnic minorities, lower socioeconomic status, or those who are obese also tend to have more mental health problems [135–137]. However, it is not clear how these factors exert their influence on diabetes outcomes, and this is an area where there has been little research.

Outcomes for people with depression and diabetes are frequently poor, and this includes the impact on self-management, glycaemic control and other comorbidities, including diabetes complications. However, the mechanisms mediating the associations between these and psychological and social factors remain poorly understood and require further investigation.

There is likely to be a complex biopsychosocial explanation. However, prospective evidence is not yet available. Further studies are required in order to tease out the relative importance of different psychological morbidities and their impact on glycaemic control, the development of diabetes complications, mortality and the management of diabetes.

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