Diabetes, depression and cognitive disorders

Richard IG Holt

Human Development and Health Academic Unit

Faculty of Medicine

University of Southampton

Southampton

UK

Email: r.i.g.holt@soton.ac.uk

**Abstract**

The interactions between diabetes and the mind are complex: physical illness increases the risk of a number of psychiatric disorders, while mental illness and its treatment also alter the risks of diabetes and worsen both acute metabolic and long-term outcomes of diabetes.

The prevalence of depression is approximately 1.5 to 2-fold higher in people with diabetes compared with the general population. Approximately 10% of people with diabetes will have a formal diagnosis of depression and around a quarter have significant depressive symptoms. Microvascular and macrovascular complications and treatment with insulin are associated with higher rates of depressive symptoms. The underlying mechanisms are multifactorial and include genetic and environmental factors as well as disease and treatment effects. The presence of depression adversely affects diabetes outcomes; quality of life and glycaemic control are worsened while the rates of microvascular and macrovascular complications and mortality are increased in people with depression. Screening for depression in people with diabetes and prompt treatment, where necessary, is recommended.

Diabetes has modest effects certain aspects of cognition, including general intelligence, psychomotor speed, and mental flexibility, particularly when diagnosed in children under the age of 7 years.

Diabetes increases the risk of vascular dementia and Alzheimer’s disease, even after adjustment for traditional cardiovascular risk factors. Approximately 1 in 15 cases of dementia is attributable to diabetes. Insulin directly affects amyloid β formation. Dementia impedes the person with diabetes’ ability to self-manage their diabetes and mandates a change in glycaemic targets and management strategies.

Keywords: Diabetes, depression, diabetes-related distress, cognitive function, dementia, Alzheimer’s disease

**Introduction**

An effect of diabetes on the mind and vice versa has been recognised for many centuries; in the 17th century, Thomas Willis discussed how *“diabetes is a consequence of prolonged sorrow”* (1). As the brain is highly vascular and dependent on glucose for its normal functioning, it is perhaps unsurprising that diabetes affects cognitive function and the risk of mental illness. What is surprising is that clinicians looking after people with diabetes frequently ignore this association. Nevertheless, the effects of comorbid mental illness on someone with diabetes may be profound as the comorbidity worsens the clinical outcomes of both conditions. Quality of life across a broad range of domains is worsened, while the individual’s ability to self-manage their diabetes is impaired, ultimately leading to a higher incidence of complications and reduced life expectancy (2).

Despite the pressing clinical need to consider the comorbidity, in many countries, mental and physical health services are not properly integrated; this leaves diabetes services poorly equipped and organized to address both the physical and psychological needs of patients in the same setting (3). Over the last decade, however, there have been increasing levels of interest in the comorbidity from researchers, who have made considerable progress in understanding the epidemiology and underlying mechanisms explaining the association. This is beginning to change clinical practice with national and international guidelines highlighting the importance of assessing and treating the psychological sequelae of diabetes (4-6).

This chapter will first describe the complex relationship between diabetes and depression before considering the effects of diabetes on cognitive function, with particular reference to the association between diabetes and dementia.

**Diabetes and Depression**

Depression is a mood disorder, which is characterised by persistent low mood and loss of interest or pleasure in life. Other symptoms include weight loss or gain, change in sleep patterns, agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate and recurrent thoughts of death including suicidal ideation.

Depressive symptoms are common in the general population and vary considerably in severity. Consequently a clinical diagnosis of depression is defined by the number, severity and duration of symptoms; the most widely used diagnostic criteria in current practice are those of the Diagnostic and Statistical Manual of Mental Disorders 5th edition (7) (table 1). This degree of symptomatology is associated with significant disability and dysfunction, but it is important to recognise that less severe depressive symptoms may still adversely affect diabetes self-care and outcomes.

**Epidemiology of diabetes and depression**

Depression within the general population is common and its prevalence is increasing. It is predicted to become the second leading global cause of disability after heart disease by 2020 (8). The lifetime prevalence varies widely across the globe from 3% in Japan to 17% in the USA, falling between 8-12% in most countries. At any one time, approximately 3-5% of men and 8-10% of women have depression. Given the high prevalence of diabetes and depression, one would expect a degree of comorbidity but the current evidence suggests that depression occurs more frequently in people with diabetes and vice versa than would be expected by chance (9).

Recent meta-analyses have demonstrated that significant depressive symptoms affect approximately 1 in 3-4 adults with diabetes while a formal diagnosis of depressive disorders is made in approximately 10-15%, equivalent to a 1.5-2.0 fold increased prevalence (10;11). Longitudinal cohort studies report the incidence of depression to be 15-24% higher in people with diabetes compared with those without diabetes (12;13). On the other hand, the incidence of type 2 diabetes is also increased by 15-37% among people with depression (13;14), indicating the bi-directional nature of the relationship between these conditions. Episodes of depression appear to be more persistent and more likely to relapse among people with diabetes (15), which may in part explain the discrepancy between the relative incidence and prevalence figures.

Although the literature is consistent in showing an increased prevalence of depression in people with diabetes and vice versa, within each of the meta-analyses, there is considerable variation in risk estimates. This variation stems in part from the meaning of the word “*depression*”, which spans from relatively minor, occasional negative mood symptoms to life-threatening disabling conditions (9). More recently, papers have started to differentiate between “*depressive symptoms*” and “*depression*” and this change in definition partly explains why current risk estimates of “*depression*” are lower than former ones. Another reason why earlier studies reported higher prevalence rates is because the studies recruited selected patient populations, often drawing from specialist diabetes clinics, where referral patterns and other differences in demographic characteristics, such as ethnicity, may increase the likelihood of depression.

The gold standard diagnostic procedure is a diagnostic interview, such as the Structured Clinical Interview for DSM-IV-TR Axis I Disorders SCID interview (16) or the Schedule for Clinical Assessment in Neuropsychiatry 2.1 (17), but these are time-consuming and are unfeasible in most large epidemiological studies. Consequently, many studies have relied on self-rating scores, which tend to overestimate the true prevalence of depression and only provide an estimate of true caseness. These questionnaires may further exaggerate the prevalence of depression because of the overlap of the symptoms of diabetes and depression (18).

**Depression or distress**

Some authors have argued that much of the psychopathology previously identified as depression is in fact ‘diabetes-related distress’ (19). This concept captures the emotional distress associated with living with diabetes (20), with the top most frequently reported problems including:

* ‘worries about the future and the possibility of serious complications’,
* ‘feeling guilty or anxious when you get off track with your diabetes management’,
* ‘feeling scared when you think about living with diabetes’,
* ‘feeling discouraged with your diabetes regimen’ and
* ‘feeling depressed with you think about living with diabetes’.

These symptoms are recognised in up to 60% of people with type 1 diabetes or insulin-treated type 2 diabetes (21;22) and are negatively associated with diabetes self-care and optimal glycaemic control (21). Indeed HbA1c correlates more closely with diabetes-related distress than depression. These feelings are more likely to develop in those with long-standing diabetes and in those with recurrent severe hypoglycaemia. Given the commonality of some symptoms, e.g. low mood and guilt, it is unsurprising that many people are reported to display both diabetes-related distress and depressive symptoms with ~30% overlapping variance. Nevertheless as well as the distinct association with glycaemic control, the association with self-management also differs between distress and depression, strengthening the view that these are two distinct entities.

**Specific Populations**

Many studies examining the prevalence of depression in people with diabetes have not differentiated between the type of diabetes. This limitation is important because people with type 2 diabetes are generally older and depression prevalence varies with age, the rates of various diabetic complications and other co-morbid conditions (e.g. obesity, heart disease) differ and management strategies are different. Because the prevalence of type 1 diabetes is so much lower than type 2 diabetes, people with type 1 diabetes are under-represented in depression association studies. One review of depression in type 1 diabetes (23), however, reported that depression was present in 12%, compared with 3.2% in people without diabetes. However, if studies without control groups and interview ascertainment were excluded, the estimated prevalence fell to 7.8%, which was no longer statistically significantly different from people without diabetes (OR 2.4, 95% CI -0.7 to 5.4). A recent study of 368 individuals with type 1 diabetes found an unexpectedly low rate of major depressive disorder (3.5%) and highlighted the marked difference in estimated prevalence rates using self-rated questionnaires (11.4%) compared with diagnostic interviews, again perhaps reflecting an effect of the overlap with diabetes-related distress (19).

Although many of the early studies were undertaken in Western Europe and North America, a recent report including 231,797 adults from 47 countries using data from the World Health Organisation World Health Survey found a two-fold increase in episodes of depressive symptoms in people with diabetes living in South America, Asia and Europe (table 2) (24). No increase in depressive symptoms was seen in people living in Africa but this may reflect less complete case ascertainment because of cultural differences in the understanding of depression.

Although there are few data, depression rates (9-26%) also appear elevated in children and adolescents with diabetes (9).

**Aetiology of diabetes and depression**

**Which people with diabetes are at risk of depression?**

Female sex, marital status, childhood adversity and social deprivation are all risk factors for depression in otherwise healthy individuals and these appear to operate equally in people with diabetes. However, in addition, there are a number of diabetes specific and treatment risk factors associated with the development of depression.

Poor glycaemic control and recurrent hypoglycaemia are risk factors for depression, in part as a direct effect of hypoglycaemia and hyperglycaemia on brain function as well as the psychological effects of abnormal glucose levels. Animal models of diabetes have loss of hippocampal integrity and neurogenesis (25), while hippocampal atrophy has also been shown in MRI studies of people with diabetes (26). These structural changes are associated with neurotransmitter abnormalities, including increased prefrontal glutamate-glutamine-gamma-aminobutyric acid levels, which have been observed in people with type 1 diabetes in a manner that correlates with mild depressive symptoms.

Diabetes is not the only chronic physical condition associated with the development of depression, which occurs also more commonly in people with cardiovascular disease (27), cancer (28) and inflammatory arthropathies among others (29). As disease burden increases, so does the prevalence of depressive symptoms. It is therefore unsurprising that depressive symptoms are more common in people with diabetes who have developed either macrovascular or microvascular complications (30). In a specialized outpatient clinic, people with two or more diabetes complications had twice the risk of depression, with neuropathy and nephropathy showing the strongest association with depression (31). Sexual dysfunction and painful peripheral neuropathy also appear to be particularly associated with depression (30).

People with insulin treated type 2 diabetes have higher rates of depression compared to those treated with lifestyle interventions or non-insulin medications (32;33). Exactly why this is the case is uncertain but probably has more to do with the increased treatment demands including intensive self-monitoring of blood glucose, longer duration of disease and higher rates of diabetes complications than a direct effect of insulin *per se* (33).

**Why do people with diabetes develop depression?**

The traditional view is that people with diabetes develop depression because of the psychological response to living with a chronic condition that is associated with unpleasant consequences and treatment that places heavy behavioural demands on the individual. There is support for this hypothesis as a meta-analysis indicated that the rates of depression were only increased among people with diagnosed diabetes while those with undiagnosed diabetes or impaired glucose regulation had no difference in depressive symptoms compared to those with normal glucose metabolism (34). This finding is important for clinicians who have the responsibility of communicating the diagnosis and its implications to people with new onset diabetes in a sensitive and compassionate manner to help people adjust to the diagnosis.

According to one German study, adults with new onset type 1 diabetes were more than twice as likely to develop a major depressive episode (5.8% vs 2.7%), although the difference was only statistically significant in women (35). By contrast, the situation appears less clear cut in people with type 2 diabetes where several studies have shown that the diagnosis has little impact on well-being (36;37); the higher rates of depression only start to appear as the disease moves from being asymptomatic to one where complications begin to occur and where treatment demands increase.

This psychological model does not preclude other biological mechanisms and it is important to recognise that acute changes in glucose may lead to a change in mood (38). Whether long-term changes or glucose variability may trigger depression directly is uncertain but changes in brain structure and function have been seen in the areas responsible for mood in people with type 1 diabetes (26).

**Why do people with depression develop diabetes?**

The low mood and loss of interest in pleasurable activities may lead to changes in behaviour that increase the risk of diabetes. People with depression tend to eat less prudent diets (comfort eating is a readily understandable concept), are less likely to undertake regular physical activity and are more likely to be smokers, all of which increase the risk of diabetes (39-41).

Depression is associated with poorer self-care management. This has been studied in more depth in people with established diabetes when people with comorbid depression are more likely to miss medical appointments and are less likely to follow advice about medication use, glucose monitoring and foot care (42). In people with established diabetes, this is associated with poorer diabetes outcomes but if similar patterns of behaviour pre-dated the diagnosis of diabetes, this may have contributed to its onset.

Several biological changes occur in depression, including alterations in the hypothalamic pituitary axis (HPA) and inflammatory markers that could lead to increased insulin resistance and consequently risk of diabetes (43). Subclinical hypercortisolism, blunted diurnal cortisol rhythm, or hypocortisolism with impaired glucocorticoid sensitivity have all been observed in depression while inflammatory changes include elevated concentrations of C-reactive protein, TNF-α and proinflammatory cytokines, which have been implicated in causing sickness behaviour in animal models and depression in humans (44;45). Disrupted sleep, which is common in depression, may be a further biological mechanism linking to diabetes as poor sleep quality and altered circadian rhythms are associated with an increased risk of diabetes through insulin resistances (46).

There have been concerns that the use of at least some antidepressants may worsen the risk of diabetes (47) as substantial weight gain may occur with certain antidepressants, including mirtazapine, amitriptyline and paroxetine (48). Case reports and early observational studies demonstrated a consistent association between antidepressant usage and risk of diabetes; however, more recent cohort studies have shown much lower odds ratios, to the point where the association could be explained by confounding and the antidepressant use is merely a marker of individuals at high risk of diabetes. Randomized controlled trials have reported both hyperglycaemic and hypoglycaemic effects suggesting that not all antidepressants are alike (47).

**Do common antecedents explain the association between diabetes and depression?**

Both diabetes and depression occur more frequently among people from lower socio-economic classes raising the possibility that both conditions occur because of shared environmental risk factors. The importance of social status was demonstrated in a recent study from Denmark, which showed that, while all people with diabetes were more likely to develop depression than those without diabetes, those from lower employment and income groups were disproportionately affected (49).

It is uncertain how the adult environment increases the risk of diabetes but poor physical (e.g. traffic, noise, decreased walkability) and social environments (e.g. lower social cohesion, increased violence, decreased residential stability) are associated with worse diet and lower physical activity levels that predispose to obesity, diabetes and depression (50). Although it is impossible to determine causality from these observational studies, dysfunctional HPA axis activity and disruption of its normal circadian rhythm (i.e. blunted profile) (51-55) as well as enhanced inflammation have all been observed in people living in adverse neighbourhood environments providing a potential biological mechanism to explain the association (56;57). Similar mechanisms may also operate in childhood adversity.

An adverse fetal environment may also predispose an individual to both type 2 diabetes and depression. There is a J-shaped relationship between birth weight and plasma glucose, insulin concentrations and type 2 diabetes while some but not all studies have shown that fetal under-nutrition is associated with adult depression (9). Again programming of the HPA axis may be one biological mechanism to explain the association (43).

**Consequences of depression in diabetes**

People with comorbid depression experience worsened diabetes outcomes and poorer quality of life (58-60). While it is clear that those with microvascular complications are more likely to develop depression, recent work has also shown that those with depression are more likely to develop complications. In one 10-year cohort study of individuals with childhood-onset diabetes, in addition to longer duration of diabetes and poor glycaemic control, the overall proportion of time that an individual was depressed predicted retinopathy severity (61). Similarly, in a longitudinal study of people with type 2 diabetes, progression to diabetic retinopathy and to proliferative diabetic retinopathy was more likely in those with high depressive symptom scores at both baseline and 6-year follow-up (62). Depression may worsen the pain experienced by those with painful peripheral neuropathy (63). Poor glycaemic control is not the explanation for the increase in microvascular complications seen in people with comorbid depression as studies have not reported a consistent association between depressive symptoms and HbA1c (64-66). Nevertheless, impaired self-care among people with depression may play a role.

Cardiovascular morbidity and mortality is increased in people with comorbid diabetes and depression (67); in one study those with diabetes and depression has an annual mortality rate of 8%, which was 2.5 fold higher than those without either condition (68).

**Management of people with diabetes and depression**

A greater awareness of the link between diabetes and depression have led several national and international guideline bodies to recommend action to improve the psychological well-being of people with diabetes (4-6). There is a responsibility for healthcare professionals caring for those with diabetes to identify depression when it occurs and then institute prompt treatment in order to reduce depressive symptoms and to improve self-care, glycaemic control and diabetes outcomes (69).

**Screening and diagnosis of Depression**

It goes without saying that before treatment can be offered, depression must be recognised and diagnosed. A formal diagnosis of depression requires a time consuming validated interview and so this is impractical for routine clinical care. Consequently, quicker and cheaper screening methods are needs to identify those in primary and secondary care with depressive symptoms who should then go forward for a diagnostic interview (70).

Many easy-to-use questionnaires that can be self-completed have been developed for routine use in clinical care but because of the overlap between symptoms of diabetes and depression, only validated questionnaires should be used for people with diabetes (18). The Patient Health Question-9 (PHQ-9), which contains 9 questions, is the most widely used and validated questionnaire in type 2 diabetes but even this overestimates the prevalence of depression (19). A score of ≥10 reliably identifies those with major depression is in community populations but a higher cut-off of ≥12 has been suggested for people with diabetes in order to improve the discrimination between diabetes related symptoms and depressive symptoms (71). The Beck Depression Inventory, the Centre for Epidemiologic Studies Depression Scale and the Hospital Anxiety and Depression Scale (HADS) are other examples of well-validated questionnaires for people with diabetes.

An even simpler approach that can be used by diabetes healthcare professionals is to ask two questions:

* “During the past month, have you been bothered by having little interest or pleasure in doing things?”
* During the past month, have you been bothered by feeling down, depressed, or hopeless?”

If the answer to either is “yes,” the healthcare professional should ask patient if they want help with this problem. If the answer to this is also “yes,” a diagnostic interview should be undertaken followed by appropriate referral and treatment.

Although diagnosis of depression is necessary to instigate treatment, there is debate as to whether screening for depression should be undertaken (70). Depression screening in the general population has little or no impact on the detection and management of depression if used alone and robust clinical pathways are essential to ensure that appropriate treatment can be offered if a diagnosis is made (72). The importance of this in the context of diabetes was demonstrated in a Dutch randomized controlled trial, which investigated the benefits of depression screening in people with type 2 diabetes (73). Following screening, although written feedback was provided to both participant and doctor, neither utilisation of mental health services nor depression scores improved. A further study from the USA also failed to demonstrate any improvement in depressive symptoms despite a modest increase in mental health care utilization (74). Low acceptance of screening and subsequent referral to further care by people with diabetes, failure to screen those at highest risk of depression, reluctance by healthcare professionals to undertake screening and treatment and generally poor quality of depression care in primary care systems may all contribute to these findings (69).

Thus, while there is a strong imperative to identify people with depression, better integration with care pathways is needed, before screening can be wholeheartedly adopted, not least because screening without appropriate follow-up could lead to harm, by increasing the stigma and discrimination associated with depression and the risk of labelling transient distress as illness (69).

**Treatment of depression in people with diabetes**

As depression adversely affects psychological well-being and diabetes outcomes, the best treatment approaches focus on both improving depressive symptoms and diabetes self-management. The aim of depression treatment is to achieve complete remission of symptoms with the further goals of improving health-related quality of life and psychosocial functioning (69). Over the last decade, a number of randomized controlled trials have demonstrated the effectiveness of both psychological and pharmacological treatments of depression in people with diabetes (69). Most of these trials have been undertaken in people with type 2 diabetes and so there is still a paucity of evidence for type 1 diabetes.

**Psychological treatment**

Psychological interventions are heterogeneous incorporating various techniques (e.g. cognitive behavioural therapy, problem-solving and psychodynamic), different settings (primary and secondary care) and media (face-to-face, group, web based and telephone contacts) (69). Given this level of variability, it is perhaps unsurprising that the effectiveness of interventions differs and comparisons between trials are challenging. Nevertheless, meta-analyses suggest psychological interventions improve depressive symptoms, with a moderate to large effect size (standardised mean difference (SMD) ranging from -0·14 to -1·47). The effect on glycaemic control, however, is more modest with one systematic review reporting a reduced HbA1c of ~0.6% (6 mmol/mol) (75) and another indicating a non-significant improvement (SMDs from 0.40 to –1.40) (76). Four recent trials on psychological interventions found an improvements in glycaemic control (SMD -0.25 to -0.68) (69). Web-based psychological therapies appear less effective than face-to-face contact, particularly for glycaemic outcomes (77). The most effective psychological interventions combine diabetes self-management education with psychological support (78).

**Pharmacotherapy**

There are several classes of effective and well-tolerated antidepressants and these form an integral component of depression management. Randomised clinical trials in people with diabetes have been undertaken for only a relatively small group of antidepressants, including nortriptyline, fluoxetine, buproprion, sertraline, paroxetine, and citalopram (69); however, these trials show that these antidepressants improve depressive symptoms to a similar extent in people with diabetes and the general population. All antidepressants studied appear to have similar efficacy and as long as adequate doses are used, the effect sizes are ‑0.61 SMD (76). However, there are gaps in our evidence base, with regards to glycaemic control and the medium- and long-term sustainability of pharmacological interventions after treatment cessation. Furthermore, a number of new antidepressants have recently been approved, including vilazodone, vortioxetine, and levomilnacipran, which have not been formally assessed in people with diabetes.

Given the comparable effectiveness, the treatment of choice depends largely on the side effect profile, patient preference and individual response. Selective serotonin reuptake inhibitors (SSRIs) are widely regarded as first choice agents because they are less cardiotoxic than the older tricyclic antidepressants and are safer in overdose.

Some antidepressants, including mirtazapine, paroxetine and some tricyclic antidepressants, may cause unwanted weight gain (48) while buproprion, which is available in the USA but not Europe, is associated with weight loss.

Several antidepressants may interact with oral hypoglycaemic agents through inhibition of the cytochrome P450 3A4 and 2C9 isoenzyme. For example, the use of fluoxetine may potentiate the effect of sulfonylureas precipitating hypoglycaemia (79).

Antidepressant treatment should be continued at an adequate dose for at least 4-6 months after complete remission of depressive symptoms to reduce the risk of relapse and recurrence. This is particularly important in people with diabetes, in whom the risk of relapse and persistence of symptoms is greater than the general population.

Clinical trials demonstrate that SSRIs lead to a modest improvement in glycaemic control (SMD -0.38) but there is a mixed effect on glycaemic control with other antidepressants ranging from hyperglycaemic effects with tricyclic antidepressant medications to euglycaemic or slightly hypoglycaemic effects with serotonin–noradrenaline reuptake inhibitors. The diversity of effect implies that any finding of improved glycaemic control with individual antidepressants should not be extrapolated to other untried antidepressants (69).

The treatment of depression may lead to a change in the patient’s behaviour and routine requiring a change in diabetes self-management. For example, should the patient’s appetite improve, more insulin may be required; by contrast, if the patient becomes more physical active, less may be needed.

**Models of Care**

Many health care systems are poorly equipped to manage comorbidity, particularly where this involves mental and physical illness. The Cartesian split of mind and body affects the delivery of care, leading healthcare professionals to consider one or other illness rather than making holistic decisions. In order to overcome this, the late Wayne Katon and colleagues in Seattle pioneered a model of care, known as “Collaborative Care” (80). This model encourages interdisciplinary cooperation between health care providers and shared decision making to facilitate appropriate provision of evidence-based treatment options, regular follow-up, self-management training and support for people with co-morbid diabetes and depression. The first study of this model showed improvements in depression symptoms but no change in glycaemic control (81); however, in later studies, greater attention was paid to diabetes and blood pressure interventions, leading to improved biomedical outcomes as well as improved depressive symptoms (80). These models of care are also highly cost-effective (82;83).

**Cognitive Function**

Cognitive function can be defined as an intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves aspects of perception, thinking, reasoning, and remembering. Given the multifaceted nature of cognition, a full assessment of cognitive functioning requires a battery of psychometric tests to obtain an overview of an individual's thinking skills. These tests assess how a person processes information, reasons and learns in different ways. Cognitive function may be impaired globally or specific components of cognitive function may be affected.

**Diabetes and cognition**

As cognitive and affective processes occur in highly linked regions of the brain, it is unsurprising that people with diabetes also experience cognitive deficits. These are relatively modest in most individuals but particularly affect general intelligence, psychomotor speed, and mental flexibility; on average performance in these domains is 0.3 – 0.7 standard deviations below the population mean (84-86) and has been likened to the change in cognitive function experienced after a 6-8 hour jetlag (figure 1). The effects of diabetes on the brain appear to be age related with children and older adults being most vulnerable, with effects being attributable to both hypoglycaemia and chronic hyperglycaemia.

**Cognitive dysfunction in children and adolescents**

The age of onset of diabetes is a major determining factor for its effect on cognitive function in children. In those diagnosed before the age of 7 years, there is an increased risk of developing cognitive impairment across a range of cognitive domains, including attention, mental flexibility, psychomotor efficiency, learning, memory, problem-solving and overall intelligence, and which start to be apparent within 2-3 years of diagnosis (87-91). For children diagnosed after this age, the effect is much more modest and is confined primarily to overall intelligence and speed related tasks, particularly those with a visual-perceptual aspect (88). The cognitive impairment seen in children diagnosed before the age of 7 years persists into adulthood and manifests as lower IQ scores and slower information processing (92).

Academic achievement is lower in children with diabetes, irrespective of the age of diagnosis but this could relate to school absences or hypoglycaemia interfering with learning as much as a direct effect on the developing brain (93). However, there is evidence from older studies that severe hypoglycaemia causes neuropsychological deficits, particularly in children whose onset of diabetes occurred below the age of 6 years (94;95). Part of the problem is that younger children may not be able to describe their hypoglycaemic symptoms thereby increasing the likelihood of prolonged and severe hypoglycaemia. Some support for the hypoglycaemia hypothesis comes from a meta-analysis of data from 441 children with recurrent severe hypoglycaemia and 560 children without recurrent severe hypoglycaemia (96). This study found that those with recurrent severe hypoglycaemia had a modestly reduced performance in the domains of intelligence, language and memory and learning but motor speed was unaffected (96). This effect appears to be limited to children because there was no difference in the cognitive function in adults with type 1 diabetes in the Diabetes Control and Complications Trial with and without a history of severe hypoglycemia after an 18-years follow-up period (97). Similarly, the ACCORD MIND study, which recruited adults with type 2 diabetes, found no difference in cognitive function after 20 months and 40 months follow-up between those treated intensively compared with standard care despite a three-fold increase in the rates of hypoglycaemia (98).

**Cognitive dysfunction in adults with diabetes**

Adults with type 1 diabetes show modest non-progressive cognitive deficits in measures of intelligence, attention, psychomotor speed, cognitive flexibility and visual perception but measures of language, learning and memory are unaffected despite long duration of diabetes (85;99). With the exception of “crystallized intelligence”, the affected domains require a rapid response indicating that diabetes affects mental agility rather than accuracy.

These changes are accompanied by structural changes that are characterised by reduced grey matter volumes in the frontal lobe and the adjacent supramarginal and postcentral gyri (100). These MRI alterations have been linked to disrupted integrity of fibre tracts connecting the main cortical areas of the brain (101). Functional studies have demonstrated altered cerebral perfusion with both decrease and increased blood flow (102-104).

Adults with type 2 diabetes also show mild cognitive deficits affecting memory, processing speed, and executive function, which may lead to the individual to be less able to process unstructured information (84;86). Interestingly similar deficits are also present in people with newly diagnosed type 2 diabetes and impaired glucose regulation as well as those with features of the metabolic syndrome (105-107). Type 2 diabetes is also associated with structural changes in the brain, characterised by a loss of grey matter loss in the medial temporal, anterior cingulate, and medial frontal lobes, while white matter is lost in the frontal and temporal regions (108).

The mechanisms underlying these changes are not fully understood although studies have not consistently demonstrated an association with cerebral small vessel disease (101). The link between glycaemic control and cognitive dysfunction in adults with diabetes is less obvious than for children. As previously described, hypoglycaemia does not appear to be a major risk factor for cognitive decline in young and middle aged adults with diabetes but hyperglycaemia appears to be more important, at least in the case of type 1 diabetes. A recent meta-analysis found a weak negative association between HbA1c and cognitive function, with HbA1c explaining at most 10-15% of the variance in cognitive function (109).

The presence of microvascular complications, especially retinopathy and nephropathy, is associated with accelerated cognitive decline (110;111). Cardiovascular disease and its risk factors are also associated with cognitive decline as they are in the general population but whether there is any specific interaction with diabetes is uncertain (101;110).

**Dementia**

The term dementia encompasses a broad category of brain disorders that lead to a gradual and progressive decline in cognitive function to the extent that an individual’s ability to function on a day-to-day is impaired. There are a number of types of dementia of which the most common are Alzheimer’s disease (50-70% of cases) and vascular dementia (up to 25%). Other causes of dementia are shown in table 3. There has been a rapid increase in the prevalence of dementia in recent years, with a global prevalence of 22.7 million in 2015. The World Alzheimer Report predicts the prevalence of dementia to rise to 38.5 million by 2030 and 131.5 million by 2050. This increase is largely being driven by an ageing population as the prevalence rises from 1.4% in men and 1.9% in women aged 60-64 years to 33.4% in men and 48.3% in women aged >90 years. In 2013, approximately 1.7 million people died as a result of dementia.

**Diabetes and Dementia**

The rate of cognitive decline in older individuals with type 2 diabetes appears to be up to two-fold quicker than the general population and a number of studies have indicated that the risk of dementia is increased by approximately 50% in people with diabetes (112). The commonest cause of dementia in people with diabetes is Alzheimer’s disease, which is increased by 46%, while vascular dementia is increased 2.38 fold (112). It is estimated that the diabetes-attributable risk of dementia is 6-7%; in other words, 1 in 15 cases of dementia is attributable to diabetes (101). An increased risk of dementia has also been reported in people with pre-diabetes and metabolic syndrome (105). Diabetes worsens the outcome for people with dementia and is associated with 90% increase in mortality compared with those without diabetes (113).

Part of the explanation for this increased incidence of dementia risk stems from a higher prevalence of risk factors for dementia among people with diabetes (Table 4). Many of these cardiovascular risk cluster in people with diabetes and those at risk of diabetes. Interestingly glycaemia *per se* appears to have little impact on the risk (109). Only one study has linked elevated HbA1c with the risk of dementia and only in those with markedly elevated levels (10-12%, 86 – 108 mmol/mol). No association between fasting or post-prandial glucose or measures of glucose variability with dementia has been found.

Unlike in younger adults, recurrent hypoglycaemia is an important risk factor for cognitive decline in those with dementia (114;115). In a retrospective study of 16,667 older people with diabetes, a history of one, two and three or more severe hypoglycaemic episodes increased the risk of dementia increased by 26%, 80% and 94% respectively independent of glycaemic control, medications and other comorbidities (114). The relationship, however, appears to be bi-directional as cognitive dysfunction increases risk of hypoglycaemia, thereby creating a vicious cycle.

Impaired insulin signalling in the brain may also play a role in the development of Alzheimer’s disease (116). Briefly, the pathology of Alzheimer’s disease is characterised by the deposition of β-amyloid plaques and tangles in the brain (117;118). β-amyloid is derived from the cleavage of amyloid precursor protein, an extracellular protein which is critical to neurone growth, survival and post-injury repair. The formation of β-amyloid is regulated with several genes but is increased in ageing and by obesity and less prudent diet (118). Insulin inhibits the production and accumulation of β-amyloid and so in situations where there is insulin deficiency or impaired action, β-amyloid accumulates (116). Supporting this hypothesis is the observation of reduced brain insulin and its receptor in people with Alzheimer’s disease.

**Clinical Implications of Dementia in people with diabetes**

**Prevention of dementia**

Several large randomised controlled trials in both type 1 diabetes and type 2 diabetes have investigated whether improved glycaemic control can reduce the risk of dementia. To date, no difference in the rate of cognitive decline, cognitive performance or incidence of dementia has been seen in those with tighter glycaemic control (97;98;119;120). The ACCORD-MIND study also assessed whether better blood pressure and lipid control could improve cognition but again no benefit was seen in those treated with a combination of statin and fibrate while intensive blood pressure lowering actually accelerated brain atrophy (121).

**Diagnosis of dementia**

Once dementia develops, the person’s ability to self-manage their diabetes progressively deteriorates. Exercise and diet appear to be particularly affected but the real danger lies in the increased risk of adverse events in people taking hypoglycaemic drugs. The risk of hypoglycaemia is exacerbated further because dementia may impair language and lead to disorientation and personality changes, all of which may mimic the symptoms of hypoglycaemia (122). When lack of engagement with self-management occurs in older people, clinicians should consider cognitive dysfunction as a cause.

A risk score which includes age, microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic events, depression and education, has been developed to help predict the risk of developing dementia. In a prospective study over 10 years, the risk of developing dementia was 5.3% in those with the lowest score compared with 73.3% for the top scores (123). Other authors have advocated the use of the easy-to-perform Mini Cog test as a simple screening tool for dementia. This test has a sensitivity of 86.4% and a specificity of 91.1% (124).

A formal diagnosis of dementia involves a combination of history, examination, including tests of mental investigation and investigation. It is important to obtain corroborating information from a friend or relative who knows the patient well. Unfortunately, the diagnosis is not always straightforward particularly in the early stages and time may be an important diagnostic tool.

**Treatment of dementia**

A detailed description of the treatment of Alzheimer’s disease is beyond the scope of this chapter as treatment is usually initiated in specialist memory clinics. The most commonly used drugs are the acetylcholinesterase inhibitors, such as donepezil, which are licensed for the treatment of mild to moderate Alzheimer’s disease (125). This class of agents can cause bradycardia and exacerbate symptoms of gastric and duodenal ulcers, precipitate bronchospasm and may cause convulsions. Dizziness, headache and nausea are the most common side effects with abdominal disturbance and nightmares also commonly reported. Because of the cardiovascular effects, they should be used with caution in those whose baseline pulse is <60 beats per minute. An ECG is recommended if the pulse is <70 beats per minute or if it is irregular.

Given the relationship between cerebral insulin action and Alzheimer’s disease, the use of several anti-diabetes drugs has been examined in people with dementia (101;116). Small studies have suggested that intra-nasal insulin improves delayed memory and cognitive function (126;127) but the results of larger on-going trials people with Alzheimer’s disease, with and without diabetes are awaited (101). Studies of thiazolidinediones have shown mixed effects on cognitive function but a possible benefit has been reported in those whose genotype is APOE-ε4-negative (128-130). As well as insulin, GLP-1 also appears to play an important role in the control of synaptic plasticity and in some forms of memory formation and two trials of GLP-1 receptor agonists are on-going (116).

**Management of diabetes in someone with dementia**

As dementia affects self-management, it is important that glycaemic targets are adjusted appropriately taking into account overall health and life expectancy. Several guidelines now recommend HbA1c targets of <8.5% (69 mmol/mol) for older dependent people with dementia (131). In these individuals, avoidance of symptomatic hypoglycaemia is more important than tight glycaemic control, which may reduce the quality of life. Glycaemic targets should be regularly reviewed and medications as appropriate.

Many older people with diabetes and dementia are over-treated with multiple drugs. In a retrospective cohort study of 15,880 people with type 2 diabetes and dementia from the Veterans Affairs Healthcare System, 52% of participants had an HbA1c <7% (53 mmol/mol) and within this group, 75% were treated either with sulfonylureas, insulin or both placing them at a high risk of hypoglycaemia (132). Declining weight, malnutrition and frailty may lead to a reduced need for antidiabetes medications and these have been safely withdrawn in several studies (133) without a deterioration of their glycaemic control (134). Drugs with a lower risk of hypoglycaemia should be preferentially used.

**Conclusions**

This chapter has highlighted some of the many and various ways in which diabetes interacts with the brain. It is clear that these connections can have a major impact on diabetes outcomes, and health professionals who work with people with diabetes requiregood knowledge and awareness of these issues to be able to provide optimal care. There is clearly also a great need for closerworking between diabetes services and mental health services while further research on these topics is also required.

**Acknowledgements**

The section on depression draws heavily from two of my previous review articles and I would like to acknowledge Sherita Golden, Mary de Groot, Frank Petrak, Harald Baumeister, Timothy Skinner and Alex Brown, my co-authors from these (9;69). The section on cognitive function summarises the excellent chapter by Jane Speight and Frans Pouwer, which is about to appear in the 5th edition of the Textbook of Diabetes. The section on dementia was inspired by the work of Geert Jan Biessels and his team who have made major contributions to this field (101).

**Conflict of Interest**

RH has received fees for lecturing and consultancy from the following companies: Eli Lilly, Janssen, Lundbeck, Novo Nordisk, Novartis, Otsuka, Sanofi, Takeda, MSD.

Reference List

(1) Willis T. Pharmaceutice rationalis sive diabtriba de medicamentorum operantionibus in humano corpore. Oxford; 1675.

(2) Holt RI, Katon WJ. Dialogue on Diabetes and Depression: Dealing with the double burden of co-morbidity. J Affect Disord 2012 Oct;142 Suppl:S1-S3.

(3) Mitchell AJ, Malone D, Doebbeling CC. Quality of medical care for people with and without comorbid mental illness and substance misuse: systematic review of comparative studies. Br J Psychiatry 2009 Jun;194(6):491-9.

(4) International Diabetes Federation. Global Guideline for Type 2 Diabetes. http://www.idf.org/guideline-type-2-diabetes. 2012. Last accessed 17 September 2016

(5) National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management, NICE guidelines (NG17). https://www nice org uk/guidance/ng17 2015 August. Last accessed 17 September 2016

(6) National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. NICE guidelines (NG28). https://www nice org uk/guidance/ng28 2015 December. Last accessed 17 September 2016

(7) American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition. Washington DC: American Psychiatric Association; 2005.

(8) Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997 May 24;349(9064):1498-504.

(9) Holt RI, de Groot M, Golden SH. Diabetes and depression. Curr Diab Rep 2014 Jun;14(6):491.

(10) Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001 Jun;24(6):1069-78.

(11) Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med 2006 Nov;23(11):1165-73.

(12) Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia 2010 Dec;53(12):2480-6.

(13) Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care 2008 Dec;31(12):2383-90.

(14) Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006 May;49(5):837-45.

(15) Nefs G, Pouwer F, Denollet J, Pop V. The course of depressive symptoms in primary care patients with type 2 diabetes: results from the Diabetes, Depression, Type D Personality Zuidoost-Brabant (DiaDDZoB) Study. Diabetologia 2012 Mar;55(3):608-16.

(16) First MB, Spitzer RL, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P) . 2002. New York: Biometrics Research, New York State Psychiatric Institute.

(17) World Health Organisation. Schedule for Clinical Assessment in Neuropsychiatry 2.1. <http://whoscan> org/wp-content/uploads/2014/10/xinterview pdf 1999. Last accessed 17 September 2016

(18) Roy T, Lloyd CE, Pouwer F, Holt RI, Sartorius N. Screening tools used for measuring depression among people with Type 1 and Type 2 diabetes: a systematic review. Diabet Med 2012 Feb;29(2):164-75.

(19) Fisher L, Hessler DM, Polonsky WH, Masharani U, Peters AL, Blumer I, et al. Prevalence of depression in Type 1 diabetes and the problem of over-diagnosis. Diabet Med 2015 Oct 3.

(20) Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with glycemic control among patients with type 2 diabetes. Diabetes Care 2010 May;33(5):1034-6.

(21) Polonsky WH, Anderson BJ, Lohrer PA, Welch G, Jacobson AM, Aponte JE, et al. Assessment of diabetes-related distress. Diabetes Care 1995 Jun;18(6):754-60.

(22) Sturt J, Dennick K, Due-Christensen M, McCarthy K. The detection and management of diabetes distress in people with type 1 diabetes. Curr Diab Rep 2015 Nov;15(11):101.

(23) Barnard KD, Skinner TC, Peveler R. The prevalence of co-morbid depression in adults with Type 1 diabetes: systematic literature review. Diabet Med 2006 Apr;23(4):445-8.

(24) Mommersteeg PM, Herr R, Pouwer F, Holt RI, Loerbroks A. The association between diabetes and an episode of depressive symptoms in the 2002 World Health Survey: an analysis of 231,797 individuals from 47 countries. Diabet Med 2013 Jun;30(6):e208-e214.

(25) Ho N, Sommers MS, Lucki I. Effects of diabetes on hippocampal neurogenesis: links to cognition and depression. Neurosci Biobehav Rev 2013 Sep;37(8):1346-62.

(26) Lyoo IK, Yoon SJ, Musen G, Simonson DC, Weinger K, Bolo N, et al. Altered prefrontal glutamate-glutamine-gamma-aminobutyric acid levels and relation to low cognitive performance and depressive symptoms in type 1 diabetes mellitus. Arch Gen Psychiatry 2009 Aug;66(8):878-87.

(27) Carney RM, Freedland KE. Depression, mortality, and medical morbidity in patients with coronary heart disease. Biol Psychiatry 2003 Aug 1;54(3):241-7.

(28) Sellick SM, Crooks DL. Depression and cancer: an appraisal of the literature for prevalence, detection, and practice guideline development for psychological interventions. Psychooncology 1999 Jul;8(4):315-33.

(29) Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology (Oxford) 2013 Dec;52(12):2136-48.

(30) de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001 Jul;63(4):619-30.

(31) van Steenbergen-Weijenburg KM, van Puffelen AL, Horn EK, Nuyen J, van Dam PS, van Benthem TB, et al. More co-morbid depression in patients with Type 2 diabetes with multiple complications. An observational study at a specialized outpatient clinic. Diabet Med 2011 Jan;28(1):86-9.

(32) Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. Affective and anxiety disorders in a German sample of diabetic patients: prevalence, comorbidity and risk factors. Diabet Med 2005 Mar;22(3):293-300.

(33) Li C, Ford ES, Strine TW, Mokdad AH. Prevalence of depression among U.S. adults with diabetes: findings from the 2006 behavioral risk factor surveillance system. Diabetes Care 2008 Jan;31(1):105-7.

(34) Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE, et al. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. Diabetes Care 2011 Mar;34(3):752-62.

(35) Petrak F, Hardt J, Wittchen HU, Kulzer B, Hirsch A, Hentzelt F, et al. Prevalence of psychiatric disorders in an onset cohort of adults with type 1 diabetes. Diabetes Metab Res Rev 2003 May;19(3):216-22.

(36) Adriaanse MC, Snoek FJ, Dekker JM, Spijkerman AM, Nijpels G, Twisk JW, et al. No substantial psychological impact of the diagnosis of Type 2 diabetes following targeted population screening: The Hoorn Screening Study. Diabet Med 2004 Sep;21(9):992-8.

(37) Pibernik-Okanovic M, Roglic G, Prasek M, Metelko Z. Emotional adjustment and metabolic control in newly diagnosed diabetic persons. Diabetes Res Clin Pract 1996 Oct;34(2):99-105.

(38) Hermanns N, Scheff C, Kulzer B, Weyers P, Pauli P, Kubiak T, et al. Association of glucose levels and glucose variability with mood in type 1 diabetic patients. Diabetologia 2007 May;50(5):930-3.

(39) McMartin SE, Jacka FN, Colman I. The association between fruit and vegetable consumption and mental health disorders: evidence from five waves of a national survey of Canadians. Prev Med 2013 Mar;56(3-4):225-30.

(40) Payne ME, Steck SE, George RR, Steffens DC. Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. J Acad Nutr Diet 2012 Dec;112(12):2022-7.

(41) Weyerer S. Physical inactivity and depression in the community. Evidence from the Upper Bavarian Field Study. Int J Sports Med 1992 Aug;13(6):492-6.

(42) Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care 2008 Dec;31(12):2398-403.

(43) Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. Curr Diab Rep 2010 Dec;10(6):396-405.

(44) Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiatry 2003 Aug 1;54(3):317-29.

(45) Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008 Jan;9(1):46-56.

(46) Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. Obes Rev 2009 Nov;10 Suppl 2:37-45.

(47) Barnard K, Peveler RC, Holt RI. Antidepressant medication as a risk factor for type 2 diabetes and impaired glucose regulation: systematic review. Diabetes Care 2013 Oct;36(10):3337-45.

(48) Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 2010 Oct;71(10):1259-72.

(49) Cleal B, Panton UH, Willaing I, Holt RI. Diabetes and depression in Denmark 1996-2010: national data stratified by occupational status and annual income. Diabet Med 2016 Jul 18.

(50) de Vet E, de Ridder DT, de Wit JB. Environmental correlates of physical activity and dietary behaviours among young people: a systematic review of reviews. Obes Rev 2011 May;12(5):e130-e142.

(51) Skinner ML, Shirtcliff EA, Haggerty KP, Coe CL, Catalano RF. Allostasis model facilitates understanding race differences in the diurnal cortisol rhythm. Dev Psychopathol 2011 Nov;23(4):1167-86.

(52) Brenner AB, Zimmerman MA, Bauermeister JA, Caldwell CH. The physiological expression of living in disadvantaged neighborhoods for youth. J Youth Adolesc 2013 Jun;42(6):792-806.

(53) Karb RA, Elliott MR, Dowd JB, Morenoff JD. Neighborhood-level stressors, social support, and diurnal patterns of cortisol: the Chicago Community Adult Health Study. Soc Sci Med 2012 Sep;75(6):1038-47.

(54) Do DP, Diez Roux AV, Hajat A, Auchincloss AH, Merkin SS, Ranjit N, et al. Circadian rhythm of cortisol and neighborhood characteristics in a population-based sample: the Multi-Ethnic Study of Atherosclerosis. Health Place 2011 Mar;17(2):625-32.

(55) Dulin-Keita A, Casazza K, Fernandez JR, Goran MI, Gower B. Do neighbourhoods matter? Neighbourhood disorder and long-term trends in serum cortisol levels. J Epidemiol Community Health 2012 Jan;66(1):24-9.

(56) Browning CR, Cagney KA, Iveniuk J. Neighborhood stressors and cardiovascular health: crime and C-reactive protein in Dallas, USA. Soc Sci Med 2012 Oct;75(7):1271-9.

(57) Broyles ST, Staiano AE, Drazba KT, Gupta AK, Sothern M, Katzmarzyk PT. Elevated C-reactive protein in children from risky neighborhoods: evidence for a stress pathway linking neighborhoods and inflammation in children. PLoS One 2012;7(9):e45419.

(58) Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, depression, and quality of life: a population study. Diabetes Care 2004 May;27(5):1066-70.

(59) Jacobson AM, de Groot M, Samson JA. The effects of psychiatric disorders and symptoms on quality of life in patients with type I and type II diabetes mellitus. Qual Life Res 1997 Jan;6(1):11-20.

(60) Carper MM, Traeger L, Gonzalez JS, Wexler DJ, Psaros C, Safren SA. The differential associations of depression and diabetes distress with quality of life domains in type 2 diabetes. J Behav Med 2013 Mar 21.

(61) Kovacs M, Mukerji P, Drash A, Iyengar S. Biomedical and psychiatric risk factors for retinopathy among children with IDDM. Diabetes Care 1995 Dec;18(12):1592-9.

(62) Roy MS, Roy A, Affouf M. Depression is a risk factor for poor glycemic control and retinopathy in African-Americans with type 1 diabetes. Psychosom Med 2007 Jul;69(6):537-42.

(63) Katona C, Peveler R, Dowrick C, Wessely S, Feinmann C, Gask L, et al. Pain symptoms in depression: definition and clinical significance. Clinical Medicine 2005 Jul;5(4):390-5.

(64) Lustman PJ, Anderson RJ, Freedland KE, de GM, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000 Jul;23(7):934-42.

(65) Hislop AL, Fegan PG, Schlaeppi MJ, Duck M, Yeap BB. Prevalence and associations of psychological distress in young adults with Type 1 diabetes. Diabet Med 2008 Jan;25(1):91-6.

(66) Aikens JE, Perkins DW, Piette JD, Lipton B. Association between depression and concurrent Type 2 diabetes outcomes varies by diabetes regimen. Diabet Med 2008 Nov;25(11):1324-9.

(67) Park M, Katon WJ, Wolf FM. Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. Gen Hosp Psychiatry 2013 May;35(3):217-25.

(68) Egede LE, Nietert PJ, Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. Diabetes Care 2005 Jun;28(6):1339-45.

(69) Petrak F, Baumeister H, Skinner TC, Brown A, Holt RI. Depression and diabetes: treatment and health-care delivery. Lancet Diabetes Endocrinol 2015 Jun;3(6):472-85.

(70) Holt RI, van der Feltz-Cornelis CM. Key concepts in screening for depression in people with diabetes. J Affect Disord 2012 Oct;142 Suppl:S72-S79.

(71) van Steenbergen-Weijenburg KM, de Vroege L, Ploeger RR, Brals JW, Vloedbeld MG, Veneman TF, et al. Validation of the PHQ-9 as a screening instrument for depression in diabetes patients in specialized outpatient clinics. BMC Health Serv Res 2010;10:235.

(72) Gilbody S, Sheldon T, House A. Screening and case-finding instruments for depression: a meta-analysis. CMAJ 2008 Apr 8;178(8):997-1003.

(73) Pouwer F, Tack CJ, Geelhoed-Duijvestijn PH, Bazelmans E, Beekman AT, Heine RJ, et al. Limited effect of screening for depression with written feedback in outpatients with diabetes mellitus: a randomised controlled trial. Diabetologia 2011 Apr;54(4):741-8.

(74) Scollan-Koliopoulos M, Herrera I, Romano K, Gregory C, Rapp K, Bleich D. Healthcare technician delivered screening of adults with diabetes to improve primary care provider recognition of depression. J Family Med Prim Care 2012 Jul;1(2):97-102.

(75) Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet 2004 May 15;363(9421):1589-97.

(76) Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. Cochrane Database Syst Rev 2012;12:CD008381.

(77) van der Feltz-Cornelis C.M. Comorbid diabetes and depression: do E-health treatments achieve better diabetes control? Diabetes Management 2013;3(5):379-88.

(78) van der Feltz-Cornelis CM, Nuyen J, Stoop C, Chan J, Jacobson AM, Katon W, et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. Gen Hosp Psychiatry 2010 Jul;32(4):380-95.

(79) Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. Biol Psychiatry 2003 Aug 1;54(3):317-29.

(80) Katon WJ, Lin EH, Von Korff M, Ciechanowski P, Ludman EJ, Young B, et al. Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010 Dec 30;363(27):2611-20.

(81) Katon WJ, Von Korff M, Lin EH, Simon G, Ludman E, Russo J, et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. Arch Gen Psychiatry 2004 Oct;61(10):1042-9.

(82) Simon GE, Katon WJ, VonKorff M, Unutzer J, Lin EH, Walker EA, et al. Cost-effectiveness of a collaborative care program for primary care patients with persistent depression. Am J Psychiatry 2001 Oct;158(10):1638-44.

(83) Simon GE, Katon WJ, Lin EH, Rutter C, Manning WG, Von KM, et al. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. Arch Gen Psychiatry 2007 Jan;64(1):65-72.

(84) van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. Biochim Biophys Acta 2009 May;1792(5):470-81.

(85) Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP. The effects of type 1 diabetes on cognitive performance: a meta-analysis. Diabetes Care 2005 Mar;28(3):726-35.

(86) Palta P, Schneider AL, Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. J Int Neuropsychol Soc 2014 Mar;20(3):278-91.

(87) Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. Lancet Neurol 2008 Feb;7(2):184-90.

(88) Gaudieri PA, Chen R, Greer TF, Holmes CS. Cognitive function in children with type 1 diabetes: a meta-analysis. Diabetes Care 2008 Sep;31(9):1892-7.

(89) Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, Werther GA. Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. Diabetes Care 2001 Sep;24(9):1541-6.

(90) Northam EA, Rankins D, Cameron FJ. Therapy insight: the impact of type 1 diabetes on brain development and function. Nat Clin Pract Neurol 2006 Feb;2(2):78-86.

(91) Hershey T, Lillie R, Sadler M, White NH. A prospective study of severe hypoglycemia and long-term spatial memory in children with type 1 diabetes. Pediatr Diabetes 2004 Jun;5(2):63-71.

(92) Ferguson SC, Blane A, Wardlaw J, Frier BM, Perros P, McCrimmon RJ, et al. Influence of an early-onset age of type 1 diabetes on cerebral structure and cognitive function. Diabetes Care 2005 Jun;28(6):1431-7.

(93) McCarthy AM, Lindgren S, Mengeling MA, Tsalikian E, Engvall J. Factors associated with academic achievement in children with type 1 diabetes. Diabetes Care 2003 Jan;26(1):112-7.

(94) Ryan C, Vega A, Drash A. Cognitive deficits in adolescents who developed diabetes early in life. Pediatrics 1985 May;75(5):921-7.

(95) Rovet JF, Ehrlich RM. The effect of hypoglycemic seizures on cognitive function in children with diabetes: a 7-year prospective study. J Pediatr 1999 Apr;134(4):503-6.

(96) Blasetti A, Chiuri RM, Tocco AM, Di GC, Mattei PA, Ballone E, et al. The effect of recurrent severe hypoglycemia on cognitive performance in children with type 1 diabetes: a meta-analysis. J Child Neurol 2011 Nov;26(11):1383-91.

(97) Jacobson AM, Musen G, Ryan CM, Silvers N, Cleary P, Waberski B, et al. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 2007 May 3;356(18):1842-52.

(98) Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol 2011 Nov;10(11):969-77.

(99) Brands AM, Kessels RP, Hoogma RP, Henselmans JM, van der Beek Boter JW, Kappelle LJ, et al. Cognitive performance, psychological well-being, and brain magnetic resonance imaging in older patients with type 1 diabetes. Diabetes 2006 Jun;55(6):1800-6.

(100) Hughes TM, Ryan CM, Aizenstein HJ, Nunley K, Gianaros PJ, Miller R, et al. Frontal gray matter atrophy in middle aged adults with type 1 diabetes is independent of cardiovascular risk factors and diabetes complications. J Diabetes Complications 2013 Nov;27(6):558-64.

(101) Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol 2015 Mar;14(3):329-40.

(102) Kodl CT, Franc DT, Rao JP, Anderson FS, Thomas W, Mueller BA, et al. Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. Diabetes 2008 Nov;57(11):3083-9.

(103) Franc DT, Kodl CT, Mueller BA, Muetzel RL, Lim KO, Seaquist ER. High connectivity between reduced cortical thickness and disrupted white matter tracts in long-standing type 1 diabetes. Diabetes 2011 Jan;60(1):315-9.

(104) van Duinkerken E, Schoonheim MM, Sanz-Arigita EJ, IJzerman RG, Moll AC, Snoek FJ, et al. Resting-state brain networks in type 1 diabetic patients with and without microangiopathy and their relation to cognitive functions and disease variables. Diabetes 2012 Jul;61(7):1814-21.

(105) Crichton GE, Elias MF, Buckley JD, Murphy KJ, Bryan J, Frisardi V. Metabolic syndrome, cognitive performance, and dementia. J Alzheimers Dis 2012;30 Suppl 2:S77-S87.

(106) Lamport DJ, Lawton CL, Mansfield MW, Dye L. Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review. Neurosci Biobehav Rev 2009 Mar;33(3):394-413.

(107) Ruis C, Biessels GJ, Gorter KJ, van den Donk M, Kappelle LJ, Rutten GE. Cognition in the early stage of type 2 diabetes. Diabetes Care 2009 Jul;32(7):1261-5.

(108) Moran C, Phan TG, Chen J, Blizzard L, Beare R, Venn A, et al. Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. Diabetes Care 2013 Dec;36(12):4036-42.

(109) Geijselaers SL, Sep SJ, Stehouwer CD, Biessels GJ. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol 2015 Jan;3(1):75-89.

(110) Ryan CM, Geckle MO, Orchard TJ. Cognitive efficiency declines over time in adults with Type 1 diabetes: effects of micro- and macrovascular complications. Diabetologia 2003 Jul;46(7):940-8.

(111) Jacobson AM, Ryan CM, Cleary PA, Waberski BH, Weinger K, Musen G, et al. Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. Diabetologia 2011 Feb;54(2):245-55.

(112) Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J 2012 May;42(5):484-91.

(113) Zilkens RR, Davis WA, Spilsbury K, Semmens JB, Bruce DG. Earlier age of dementia onset and shorter survival times in dementia patients with diabetes. Am J Epidemiol 2013 Jun 1;177(11):1246-54.

(114) Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Jr., Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009 Apr 15;301(15):1565-72.

(115) Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012 Apr;35(4):787-93.

(116) Li X, Song D, Leng SX. Link between type 2 diabetes and Alzheimer's disease: from epidemiology to mechanism and treatment. Clin Interv Aging 2015;10:549-60.

(117) Turner PR, O'Connor K, Tate WP, Abraham WC. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. Prog Neurobiol 2003 May;70(1):1-32.

(118) Niedowicz DM, Nelson PT, Murphy MP. Alzheimer's disease: pathological mechanisms and recent insights. Curr Neuropharmacol 2011 Dec;9(4):674-84.

(119) Koekkoek PS, Ruis C, van den Donk M, Biessels GJ, Gorter KJ, Kappelle LJ, et al. Intensive multifactorial treatment and cognitive functioning in screen-detected type 2 diabetes--the ADDITION-Netherlands study: a cluster-randomized trial. J Neurol Sci 2012 Mar 15;314(1-2):71-7.

(120) de Galan BE, Zoungas S, Chalmers J, Anderson C, Dufouil C, Pillai A, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia 2009 Nov;52(11):2328-36.

(121) Williamson JD, Launer LJ, Bryan RN, Coker LH, Lazar RM, Gerstein HC, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. JAMA Intern Med 2014 Mar;174(3):324-33.

(122) Sinclair AJ, Armes DG, Randhawa G, Bayer AJ. Caring for older adults with diabetes mellitus: characteristics of carers and their prime roles and responsibilities. Diabet Med 2010 Sep;27(9):1055-9.

(123) Exalto LG, Biessels GJ, Karter AJ, Huang ES, Katon WJ, Minkoff JR, et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. Lancet Diabetes Endocrinol 2013 Nov;1(3):183-90.

(124) Sinclair AJ, Gadsby R, Hillson R, Forbes A, Bayer AJ. Brief report: Use of the Mini-Cog as a screening tool for cognitive impairment in diabetes in primary care. Diabetes Res Clin Pract 2013 Apr;100(1):e23-e25.

(125) Cummings JL, Isaacson RS, Schmitt FA, Velting DM. A practical algorithm for managing Alzheimer's disease: what, when, and why? Ann Clin Transl Neurol 2015 Mar;2(3):307-23.

(126) Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 2008 Feb 5;70(6):440-8.

(127) Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012 Jan;69(1):29-38.

(128) Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, et al. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. Am J Geriatr Psychiatry 2005 Nov;13(11):950-8.

(129) Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J 2006 Jul;6(4):246-54.

(130) Gold M, Alderton C, Zvartau-Hind M, Egginton S, Saunders AM, Irizarry M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement Geriatr Cogn Disord 2010;30(2):131-46.

(131) Sinclair A, Morley JE, Rodriguez-Manas L, Paolisso G, Bayer T, Zeyfang A, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc 2012 Jul;13(6):497-502.

(132) Thorpe CT, Gellad WF, Good CB, Zhang S, Zhao X, Mor M, et al. Tight glycemic control and use of hypoglycemic medications in older veterans with type 2 diabetes and comorbid dementia. Diabetes Care 2015 Apr;38(4):588-95.

(133) Sjoblom P, Tengblad A, Lofgren UB, Lannering C, Anderberg N, Rosenqvist U, et al. Can diabetes medication be reduced in elderly patients? An observational study of diabetes drug withdrawal in nursing home patients with tight glycaemic control. Diabetes Res Clin Pract 2008 Nov;82(2):197-202.

(134) Abdelhafiz AH, Chakravorty P, Gupta S, Haque A, Sinclair AJ. Can hypoglycaemic medications be withdrawn in older people with type 2 diabetes? Int J Clin Pract 2014 Jun;68(6):790-2.

**Tables**

Table 1. The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) Definition of a “Major” Depressive Episode

1. Five (or more) of the following symptoms have been present during the same 2- week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

* Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
* Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
* Significant weight loss when not dieting or weight gain (e.g., a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day.
* Insomnia or hypersomnia nearly every day.
* Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
* Fatigue or loss of energy nearly every day.
* Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
* Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
* Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

1. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
2. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

**Table 2: Increased risk of depressive episodes in people with and without diabetes in four continents after adjustment for age, sex, education, BMI, smoking and physical activity (24).**

|  |  |  |
| --- | --- | --- |
|  | **OR** | **95% CI** |
| **World** | 2.36 | 1.91 - 2.92 |
| **Africa** | 0.86 | 0.54 - 1.37 |
| **South-America** | 1.98 | 1.46 - 2.68 |
| **Asia** | 2.16 | 1.38 - 3.37 |
| **Europe** | 2.47 | 1.73 - 3.52 |

**Table 3: Causes of dementia in people with diabetes**

Alzheimer’s disease 62%

Vascular dementia 17%

Mixed 10%

Lewy body dementia 4%

Parkinson’s disease 2%

Fronto-temporal 2%

Other 3%

**Table 4: Risk factors for Alzheimer’s disease and Vascular dementia**

|  |  |
| --- | --- |
| Alzheimer’s disease | Vascular dementia |
| Dyslipidaemia  Smoking  Hypertension  Obesity  Physical inactivity  Depression  Alcohol  Head injury | Dyslipidaemia  Smoking  Hypertension  Obesity  Atrial Fibrillation  Previous coronary heart disease, stroke of transient ischaemic event |

**Figure 1:**

**Trajectories of cognitive dysfunction in type 1 and type 2 diabetes**

(A) Cognitive dysfunction in patients with type 1 diabetes. Cognitive decrements can be detected soon after onset of diabetes, often in childhood. The width of the shaded area indicates the uncertainty of the estimates, which is larger in older age groups (>65 years for type 1, >80 years for type 2 diabetes) because of the small number of studies. In young adults with type 1 diabetes, cognitive decrements are largest in individuals with an early diabetes onset (black arrow E), and smaller in individuals with a later onset (arrow L). Estimates of the diabetes-associated decrements do not clearly increase with age, consistent with slow progression of the decrements over time. However, some individuals, particularly those with severe microvascular complications (arrow C), might show accelerated decline. (B) In people with type 2 diabetes, estimates of mean cognitive decrements are likewise mostly independent of age. By contrast, the incidence of dementia (blue lines), which is increased in people with diabetes, is strongly dependent on age.

Reprinted from Lancet Neurology, Vol 14. Number 3, Paula S Koekkoek, L Jaap Kappelle, Esther van den Berg, Guy E H M Rutten, Geert Jan Biessels, Cognitive function in patients with diabetes mellitus: guidance for daily care, Copyright (2015), with permission from Elsevier.

