Type 2 diabetes mellitus and psychological stress - a modifiable risk factor

Ruth A. Hackett[1] and Andrew Steptoe[1]

[1] Department of Behavioural Science and Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK.

Correspondence to A.S.

a.steptoe@ucl.ac.uk

Abstract

Psychological stress is common in many physical illnesses and is increasingly recognized as a risk factor for disease onset and progression. An emerging body of literature suggests that stress has a role in the aetiology of type 2 diabetes mellitus (T2DM) both as a predictor of new onset T2DM and as a prognostic factor in people with existing T2DM. Here, we review the evidence linking T2DM and psychological stress. We highlight the physiological responses to stress that are probably related to T2DM, drawing on evidence from animal work, large epidemiological studies and human laboratory trials. We discuss population and clinical studies linking psychological and social stress factors with T2DM, and give an overview of intervention studies that have attempted to modify psychological or social factors to improve outcomes in people with T2DM.

Key points

- Psychological stress mobilizes biological responses implicated in type 2 diabetes mellitus (T2DM), including the release of glucose and lipids into the circulation, inflammatory cytokine expression and increased blood pressure
- Repeated or sustained stress exposure leads to chronic allostatic load, with dysregulation of glucose metabolism and neuroendocrine function and chronic low grade inflammation. Dysregulation of the diurnal profile of cortisol release predicts incident T2DM in population studies
- Epidemiological studies implicate depression, chronic work stress and early life adversity as risk factors for T2DM
- The adverse effect of psychological stress on health behaviours such as food choice, physical activity and adherence to medication also contributes to T2DM risk
- Among individuals with established diabetes mellitus, depression and diabetes mellitus-related distress are associated with poor glycaemic control and cardiovascular complications
- Stress management interventions seem to alleviate stress symptoms in T2DM, but effects on disease progression have not been established

When faced with a threat, animals and humans respond rapidly with sympathetic nervous system activation coupled with upregulation of the hypothalamic–pituitary– adrenal (HPA) axis[1, 2,] which results in increased release of the glucocorticoid cortisol from the adrenal cortex **(FIG. 1).** Corticotropin-releasing hormone, which is released from the hypothalamus in response to stress, activates the HPA axis and stimulates the release of adrenocorticotropic hormone from the pituitary gland into the systemic circulation. The principle target of adrenocorticotropic hormone is the adrenal cortex, where it stimulates the release of cortisol, a glucocorticoid hormone. Cortisol has vital physiological functions, many of which are relevant to diabetes mellitus; indeed, glucocorticoid hormones are so named owing to their influence on glucose homeostasis[3.]

In response to stress, cortisol promotes the mobilization of energy stores, which induces the release of glucose and lipids into the circulation. The release of cortisol suppresses inflammatory responses and stimulates the cardiovascular system, which increases blood pressure by working with the sympathetic system[1, 2.] The sympathetic nervous system innervates multiple tissues, and acts in conjunction with the release of adrenaline from the adrenal medulla to increase heart rate and blood pressure, decrease heart rate variability and induce energy mobilization and the release of pro-inflammatory cytokines[1, 2.]

Psychological stress is an umbrella term that encompasses a range of phenomena. It can include exposure to stressful conditions such as work stress, *psychological distress*, including emotional disorders like depression and anxiety, as well as negative personality traits such as anger or hostility. The physiological response to psychological stress is adaptive and designed to mobilize the organism for action and bolster immune mechanisms. Allostasis is the term used to describe this dynamic regulatory process whereby the maintenance of homeostasis occurs through the production of mediators such as adrenaline and cortisol. In

the context of diabetes mellitus, glucose allostasis refers to the feedback loop that controls glucose metabolism. This regulatory process maintains glucose concentrations in a narrow range such that an increase in levels of glucose usually causes a corresponding increase in insulin secretion to restore equilibrium[4]. Allostatic load refers to the repeated or sustained stimulation of an allostatic system through exposure to psychological stress, which ultimately results in a regulatory system failing to operate within adaptive limits. In the context of type 2 diabetes mellitus (T2DM), overabundance of glucose or lipids relative to cellular energy demands constitutes a form of metabolic stress that can promote insulin resistance and weight over time[7]. Components of the biological response to stress that plausibly contribute to T2DM include dysregulation of the cardiovascular system, changes in neuroendocrine parameters, such as cortisol, and heightened inflammation.

Here, we focus on psychological stress as a modifiable risk factor for T2DM, as stress in T1DM is a separate issue[8]. This Review aims to summarize the evidence linking T2DM and psychological stress, with a focus on the physiological processes involved.

Stress-related processes and T2DM

Animal studies.

Studying the relationship between stress and disease outcomes in humans is somewhat limited, as randomization to chronic stress exposure and comparison conditions is not ethical. Animal models therefore offer a useful methodology to help to understand the pathways linking chronic stress and stress-related biological processes with T2DM. Corticosterone is the primary glucocorticoid involved in the rodent physiological stress-response system[9]. Chronic administration of corticosterone in drinking water leads to hyperglycaemia, insulin resistance and dyslipidaemia in rodents[10, 11]. Feeding with a high-fat diet might exacerbate the

effects of chronic administration of glucocorticoid[12,] which is interesting considering that changes in eating behaviour are a potential response to chronic stress in humans[13.] Conversely, removal of the adrenal gland in rodents sensitizes the brain to insulin, suggesting that the absence of circulating glucocorticoids improves insulin sensitivity[14.]

Researchers have developed several animal models to study the link between early life stress and diabetes-related parameters in animals. In rodents, some evidence suggests that brief maternal separation in the neonatal period is associated with heightened levels of glucose and insulin[15, 16;] however, others have reported that fragmented nesting behaviour in early life has no effect on levels of glucose and insulin, and could even improve insulin sensitivity[17, 18.] The type, severity and length of the stress exposure could account for these varying results. For example, varied methods were used to gain[5.] Chronically heightened levels of glucose can damage mitochondria and mitochondrial DNA, which in turn can promote inflammation and telomere shortening[6].

Chronic activation of the biological systems involved in stress response can promote dysregulated physiological reactivity, resulting in heightened, prolonged or diminished responses to stress, increasing vulnerability to disease and contributing to negative health outcomes induce stress, including maternal separation[15,16,18,] as well as limited access to nesting materials17. Furthermore, in the studies that used maternal separation stress[15–17,] the length of separation varied from 10 min per day[15, 16] to 180 min18 per day for up to 21 days. The characteristics of the rodents used in the different studies also varied. Some studies used males rats[15, 16,] and others females rats[17, 18,] some rats assessed from birth[15, 16,] and others from day 2 of life[17]. The breeds used also varied, with CD-1[15, 16], Sprague Dawley[17] and Wistar[18] rats included across the different studies.

The notion that one period of stress exposure in early life might not be sufficient to induce metabolic change was noted in a 2015 study, which induced stress using footshock. The authors reported that early life stress at 2 weeks of age did not affect glucose and insulin parameters in rats; however, when this stress was combined with a second bout of stress at 8–10 weeks of age, levels of glucose and insulin were observed to increase, and insulin sensitivity and glucose tolerance became poorer19. In bonnet macaques, difficulty in foraging and obtaining food during nursing is used as a model of early life stress[20.] Under this procedure when offspring are 3–5 months old, the mothers are exposed to scenarios in which the effort to access food alternates from easy to difficult over a period of 16 weeks. Compared with normally reared monkeys, those exposed to this form of juvenile stress have significantly greater body weight and waist circumference, as well as impaired insulin resistance as measured using a glucose clamp[21.]

In summary, chronic administration of glucocorticoids leads to hyperglycaemia and insulin resistance in rodents, whereas the evidence for early life stress causing changes in metabolic parameters is mixed. One explanation for the conflicting data is that several stress exposures are necessary to induce changes in levels of insulin and glucose in rodents. In bonnet macaques, research suggests that stress related to food availability early in life reduces insulin sensitivity.

Human epidemiological studies.

Investigators can use observational cohort studies to study the relationship between stress-related biological processes and diabetes in humans; however, one should note that not all biological processes lend themselves to being studied in large population studies owing to

sampling difficulty and expense. Numerous pathways, through which stress-related biological processes act, have been hypothesized to contribute to T2DM aetiology **(FIG. 2).**

Chronic activation of the HPA axis can lead to dysregulated cortisol output[22.] Furthermore, neuroendocrine dysfunction has been implicated in the pathogenesis of T2DM; glucocorticoid receptors are expressed on pancreatic β cells, and cortisol stimulation directly influences insulin sensitivity and decreases insulin secretion[23.] Patients with long-term cortisol excess, as seen in those with Cushing syndrome[24], and patients treated with glucocorticoids often have increased susceptibility to hyperglycaemia and manifest diabetes mellitus[25]. Early research investigating the link between neuroendocrine dysfunction and diabetes mellitus assessed levels of plasma cortisol from single samples[26, 27]; however, cortisol shows marked circadian and diurnal rhythms that are better captured with multiple samples across the day[28.]

The pattern of daily cortisol release is characterized by high levels of cortisol on waking, followed by an increase that reaches a peak 30–45 min after waking (termed the cortisol awakening response (CAR)) and subsequent decline over the day[28] **(FIG. 3).** Dysregulation of the HPA axis can cause a reduction in the amplitude of the *diurnal cortisol pattern* or a flatter slope in the decline of levels of cortisol across the day[28.] Dysregulation in cortisol secretion can result in changes to the marked increase in cortisol concentrations after waking[29.] The CAR and the slope are thought to reflect separate neurobiological control systems; therefore, experimental samples of cortisol taken 30 min after waking, which reflect the CAR, are conventionally not included when calculating the cortisol slope[28.]

Several studies have investigated the cross-sectional association between diurnal cortisol release and T2DM. The largest study to date, which included over 3,500 individuals from the Whitehall II epidemiological cohort, reported that people with T2DM had a flatter slope in

levels of cortisol across the day and raised evening concentrations of cortisol compared with healthy individuals[30,] which corroborates previous evidence from another community cohort study[31]. Elevated levels of cortisol in the evening are associated with increased mortality risk from cardiovascular disease[32.] However, other findings in the area have been inconsistent[33–35,] with two studies reporting a lower CAR in participants with T2DM than in controls[33, 34] but no association with the cortisol slope[33,] and the other study finding no association between T2DM and any cortisol parameter across the day[35]. Differences in study samples or in the timing or number of cortisol samples might account for these conflicting findings. Few studies have linked neuroendocrine dysfunction with future changes in glucose metabolism. To the best of our knowledge, only one study has examined the relationship between the complete diurnal cortisol profile, which is morning cortisol, the CAR, the cortisol slope and evening cortisol and incident T2DM in an initially healthy population[36]. In this analysis of 3,270 initially healthy individuals from the Whitehall II cohort, raised evening levels of cortisol predicted new onset T2DM over a 9 year follow-up period independent of covariates. When the analysis was expanded to a broader category of glucose disturbance to include prediabetes, raised evening concentrations of cortisol and a flatter slope in cortisol across the day were found to predict the combined outcome. No associations were detected between morning levels of cortisol or the CAR and T2DM onset.

Another mechanism by which stress might influence the risk of developing diabetes mellitus is through activation of the immune system. T2DM has been characterized as a chronic low-grade inflammatory state involving multiple inflammatory mechanisms and metabolic pathways[37.] Obesity is common in patients with T2DM, and visceral adipose tissue is a major source of inflammatory factors — collectively termed *adipokines*[38] — that include: cytokines such as C-reactive protein (CRP); IL-6; IL-1β; tumour necrosis factor; and

hormone-like factors such as leptin, adiponectin, resistin, chemokines and acute phase proteins38. Adipokines are released into the circulation to affect many tissues including the β cells of the pancreas, which in turn affects insulin sensitivity[39, 40.]

Data from epidemiological studies indicate that circulating concentrations of pro-inflammatory adipokines are elevated in patients with T2DM. For example, a German study of over 15,000 individuals documented a dose– response relationship between impaired glucose status and adipokine concentrations[41]. Increased concentrations of inflammatory cytokines are also predictive of the development of T2DM in initially healthy populations. Prospective studies indicate that raised concentrations of IL-6 and CRP in the circulation are associated with increased risk of future T2DM[42.]

Taken together, the observational evidence supports a link between T2DM and inflammation. However, causality cannot be determined from observational studies owing to potential issues of confounding and reverse causality. Another type of epidemiological study known as Mendelian randomization uses the properties of common genetic variation (random allocation of alleles at the time of conception) to estimate the causal contribution of a biological factor of choice with disease outcomes[43.] One large study reported a near significant effect (P = 0.06) of a functional variant causing impaired signalling at the IL-6 receptor with reduced risk of developing diabetes mellitus[44.] Studies investigating variants in the genes that encode CRP and IL-1 have not detected statistically significant associations with T2DM[45.] This area of research has not yet been widely investigated, and thus future studies might detect associations[45].

Stress-induced sympathetic activation of the autonomic nervous system causes changes in blood pressure, heart rate and cardiac output, whereas parasympathetic activation results in changes in heart rate variability. High blood pressure is a recognized risk factor for diabetes

mellitus[46.] For example, a 2015 study investigated the link between objectively measured blood pressure and risk of diabetes mellitus using linked electronic health records from a UK primary care population[47]. In this cohort of 4.1 million adults who did not have diabetes mellitus or cardiovascular disease at baseline, both systolic and diastolic blood pressure were found to have a dose–response relationship with the risk of developing diabetes mellitus, independent of a range of covariates. The paper also included a meta-analysis of 30 previously published prospective studies. The pooled results indicated that, for an increase of 20 mmHg in systolic blood pressure, the relative risk of diabetes mellitus was 1.77 (95% CI 1.53–2.05). Proposed pathways through which blood pressure might increase the risk of diabetes mellitus include insulin resistance[47] and inflammation[48] **(FIG. 2).**

Raised resting heart rate is also a hypothesized risk factor for new onset T2DM. A review of 10 cohort studies, which included almost 120,000 participants, found a dose–response relationship between resting heart rate and incident T2DM, with a 19% increased risk of T2DM for every 10 beats per min increment in resting heart rate[49]. As resting heart rate is a marker of autonomic regulation, an imbalance between the sympathetic and parasympathetic nervous systems might contribute to the association between increased heart rate and diabetes mellitus. Autonomic regulation is also associated with inflammation and components of the *metabolic syndrome*, such as central fat accumulation[50, 51,] all of which increase T2DM risk. A bidirectional association exists between inflammation and autonomic function in the context of the metabolic syndrome. Reduced heart rate variability, a marker of autonomic regulation, is associated with increased fasting glucose, increased cortisol and expression of pro-inflammatory cytokines[52,] whereas inflammation contributes to vasoconstriction and sodium retention in the context of stress-related high blood pressure[53.]

Evidence from epidemiological studies with repeated measures of glucose and insulin parameters over many years suggests that the development of T2DM is a gradual process[54, 55.] For example, data from over 6,500 initially healthy individuals suggest that fasting levels of glucose and post-load glucose concentrations are higher among individuals who develop T2DM than in those who do not develop it up to 13 years before disease onset[55.] The glucose values of the incident T2DM cases increased in a linear manner (average fasting value of 5.47 mmol/l at baseline), until 2–6 years before T2DM diagnosis when abrupt elevations in glucose concentrations (average fasting value ranging from 5.79 mmol/l 3 years before diagnosis to 7.40 mmol/l at the end of follow-up) were observed. In the control participants who did not develop T2DM, glucose parameters increased slightly over time (average fasting value of 5.26 mmol/l at baseline, increasing to 5.31 mmol/l at the end of follow-up) but no abrupt rises in concentrations were detected. Individuals who developed T2DM had lowered insulin sensitivity at baseline and showed a marked decrease in insulin sensitivity in the 5 years before onset of the disease. These participants also had elevated insulin secretion until 3–4 years before diagnosis when the levels of insulin declined steeply. Conversely, control participants did not experience a change in insulin parameters during the study period.

As previously mentioned, changes in many stress-responsive biological systems influence glucose metabolism and insulin release; however, importantly, glucose and insulin are themselves stress responsive[5, 56.] Therefore, chronic psychological stress can act directly on glucose and insulin parameters, as well as affecting these processes indirectly through the other pathways discussed in this Review.

Human laboratory stress studies and allostatic load.

Epidemiological studies investigating the link between stress-related biological processes and T2DM have for the most part focused on single system measures of stress, such as cardiovascular measures alone, inflammatory markers alone or HPA axis measures alone. However, the stress response is dynamic and involves multiple biological processes. Repeated stimulation of the stress system as a result of chronic stress is thought to lead to dysregulation across several inter-related systems[22]. Typically, the concept of allostatic load is quantified by assessing a range of biomarkers, including cardiovascular, inflammatory and neuroendocrine measures, as well as glucose metabolism and anthropometric measures, but available evidence on T2DM is mixed. One study of 1,000 individuals reported that high allostatic load was associated with increased T2DM risk[57;] however, another investigation of 53 individuals failed to detect an association[58.]

Both aforementioned studies assessed allostatic load using biological measures taken at rest, which could present an issue. Allostasis is a dynamic process, and it manifests in response to challenge[22,] whereby a brisk biological activation occurs as the body mobilizes to deal with the stressor, a process that is followed by a swift recovery back to baseline values. Allostatic load dysregulates this dynamic process, which can result in inadequate biological responses to stress, with failure to mount an appropriate stress response and/or poor stress recovery, with diminished ability to return to pre-stress values across various parameters[7, 22.]

To study stress-induced changes across multiple biological systems, investigators can use acute laboratory stress testing. To date, only a single study has investigated the dynamics of the multiple systems that are potentially involved in the stress–diabetes mellitus relationship[59]. In the analysis, 140 individuals with T2DM and 280 healthy controls who were matched for age, sex and income underwent an identical acute stress testing procedure. The protocol involved tracking participants' biological responses to stress before, during and up

to 75 min after undertaking two 5-min standardized stress tasks. The investigators reported that people with T2DM experience chronic allostatic load, which manifested as alterations in biological responses to acute mental stress. Notably, participants with T2DM displayed reduced cardiovascular, neuroendocrine, inflammatory and metabolic responses to acute stress, coupled with impaired post-stress recovery. This study was cross-sectional, precluding inferences about causality. Therefore, whether heightened allostatic load precedes the development of T2DM and is a mechanism through which stress contributes to T2DM risk or whether allostatic load is secondary to the dysregulation of glucose metabolism in people with T2DM remains unclear.

Of note, biological reactivity to stress differs between individuals. The magnitude of the stress response and the ability to recover effectively are believed to be determined by multiple factors including genetics, personal perception of the specific stressor and coping resources[60]. Whether or not psychological stress promotes incident T2DM or complications in those individuals with existing diabetes mellitus will depend on the interaction between an individual's intrinsic stress responsivity and stress exposure in daily life, set against other health risk factors.

Stress and health behaviours

The biological changes that occur as a result of chronic stress do not happen in isolation and are often exacerbated by unhealthy behaviours such as poor diet, physical inactivity, smoking and reduced adherence to medication[13]. A detailed examination of this literature is beyond the scope of this Review, but it is important to acknowledge that psychological stress might decrease motivation for healthy lifestyle behaviours both before and after T2DM onset. For example, in a Danish study of over 7,000 initially healthy adults with a 10-year follow-up

period, perceived stress was linked with physical inactivity and unsuccessful smoking cessation or alcohol reduction attempts, as well as T2DM development in men[61]. In people with existing diabetes mellitus, evidence from a meta-analysis indicates that comorbid depression increases non-adherence to a range of behaviours including diet, medication usage and exercise[62]. Unhealthy behaviours influence stress-related biological pathways. For example, the HPA axis is involved in the regulation of appetite and energy balance, and stress is associated with increased food intake in some individuals[63]. In addition, an inverse association between inflammation and physical activity has been reported in people with T2DM[64]; however, more research investigating the potential synergies between behavioural and biological pathways is needed to further understand the complex links between psychological stress and T2DM.

Psychological stress and T2DM

Psychological stress comes in three forms; emotional disorders or states of distress such as depression and anxiety; personal traits, including anger or hostility; and external stressors, such as exposure to stressful conditions in adult or earlier life. A growing body of literature indicates that psychological stress might have a role in the development of diabetes mellitus in initially healthy populations and could affect outcomes in people with an existing diagnosis.

Psychological and social factors and T2DM risk

Depression is the most commonly researched psychological factor in the diabetes mellitus field. Results from meta-analyses and prospective cohort studies indicate that depression is associated with an increased risk of diabetes mellitus[65–68] **(TABLES 1, 2)**. Depressive

symptoms, such as loss of pleasure and feelings of hopelessness, and a diagnosis of clinical depression are predictive of future development of diabetes mellitus[67, 68]. Anxiety is not as well researched as depression, and reported links with new onset diabetes mellitus have been equivocal[69–74]. Several possible explanations exist for these mixed findings. First, the symptoms of depression and anxiety could overlap, and an independent association between anxiety and diabetes mellitus might not exist. Second, differences in measurements across studies or sex differences in the association might account for the results. Three studies have investigated the link between psychological distress and new onset diabetes mellitus. The largest study found an association between psychological distress and future development of diabetes mellitus, but the finding was attenuated after controlling for health behaviours[75]. Another study only detected the association in a subset of participants who had a high risk of developing T2DM at baseline[76], whereas a third reported a sex difference in the association, with psychological distress predicting new onset T2DM in men but not in women[77].

Most research on external stressors has focused on how measures of work-related stress can increase one's risk of developing T2DM. Meta-analytic evidence indicates that job strain, which is defined as high job demands coupled with low control at work, is associated with an increased risk of T2DM[78] **(TABLE 1).** Long work hours (≥55 h per week) have also been related to increased risk of diabetes mellitus but only in low socioeconomic groups[79]. Perceived stress has been investigated in relation to the development of T2DM in several studies[61, 80–85.] Considering the evidence as a whole, a link seems to exist between perceived stress and development of T2DM. However, this association has been shown in some studies to vary by sex or socioeconomic status (as measured by occupational status), which indicates that these factors might moderate this relationship.

Little prospective research has investigated the association between diabetes mellitus and personality traits **(TABLE 2)**. Two studies have investigated the link between anger as assessed by questionnaire (Spielberger Trait Anger Scale) and subsequent development of T2DM[70, 86]. In the Atherosclerosis Risk in Communities Study of 11,615 participants, trait anger was associated with an increased risk of future T2DM independent of covariates[86]. A later study of 5,598 individuals also found that this characteristic significantly increased T2DM risk; however, statistical adjustment for waist circumference attenuated the association[70].

Individuals who report adverse childhood experiences, such as neglect or physical abuse, seem to be at increased risk of diabetes mellitus in adulthood (combined odds ratio of 1.32 (95% CI 1.16–1.51))[87]. The methodological approaches adopted by researchers in the field have varied. In some studies, adult participants recalled early life experiences via self-report questionnaires, whereas, in others, data were based on review of court records taken over an individual's life course[87]. Little research has investigated the association between potentially protective, positive psychological traits, such as optimism and life satisfaction, and T2DM risk. One interesting study of 1.5 million Swedish military recruits with a 25.7 years of follow-up reported that low stress resilience (as assessed by semi-structured interview) was a predictor of the development of T2DM[88]. This association was robust to adjustment for a range of risk factors for T2DM. A 2016 analysis of the English Longitudinal Study of Ageing found that high quality of life was associated with a reduced risk of T2DM over a 6-year follow-up period in participants who were <65 years of age[89]. However, the evidence for a link between life satisfaction and reduced T2DM risk is weak. In a large European cohort, no association between life satisfaction and T2DM risk was detected in men, whereas, in women, the relationship did not remain after adjustment for covariates[90]. An

analysis of the Whitehall II cohort found no association between optimism, life satisfaction or well-being and T2DM risk over 13 years of follow-up[91].

Taken together, negative psychological factors (for the most part) have been prospectively associated with an increased risk of developing T2DM in initially healthy individuals; however, more research on positive psychological factors is needed. The most convincing evidence in the area of positive psychological factors comes from meta-analytic studies of depression and work stress[65, 66, 68, 74,78,79,87.] Nevertheless, it should be emphasized that these studies do not prove causality, and alternative non-causal explanations are plausible. In epidemiological studies, covariates are included to limit non-causal explanations **(TABLES 1, 2**); however, adjusting for potentially confounding factors does not exclude the possibility that unmeasured or poorly measured factors account for the relationship.

Psychological factors in diagnosed T2DM

As well as increasing the risk of new onset diabetes in initially healthy populations, a growing body of literature indicates that psychological factors such as depression and anxiety have a role in the aetiology of T2DM and its complications after the condition has been diagnosed.

Prevalence of psychological stress in T2DM.

The prevalence of many stress-related conditions is increased in people with diabetes mellitus, as has been recognized in diabetes mellitus care guidelines[92]. Depression is notably more common in patients with diabetes mellitus than in the general population[93–96]. Even though estimates vary between studies, from 8.7%[96] to 17.6%[93] depending on the criteria used to assess depression (such as depressive symptoms versus major depressive disorder), rates of

depression are consistently higher among people with diabetes mellitus than in the diabetes-free population.

The prevalence of anxiety is also raised in people with diabetes mellitus relative to the general population[97, 98]. As with studies investigating depression, rates vary depending on the definition of anxiety, but a 2013 meta-analysis found that individuals with diabetes mellitus have a 20% increased risk of having an anxiety disorder and a 48% increased risk of experiencing anxiety symptoms[98]. Growing evidence suggests that one particular type of anxiety, post-traumatic stress disorder, is more prevalent in people with T2DM than in healthy controls[74].

Diabetes-related distress is another common stress condition. This concept goes beyond general low mood and emotional distress and refers to the unique burden of living with and managing this chronic condition[99]. Diabetes-related distress encompasses distress related to self-management, regimen adherence and complications associated with diabetes mellitus[99, 100]. A study of almost 9,000 people with diabetes mellitus found that 44.6% report considerable diabetes-related distress[101].

Diagnosis with T2DM might also be a prognostic factor for cases of new onset depression. A number of prospective studies indicate that diabetes mellitus is a risk factor for incident depression[66,102,103], with a 25% greater risk of new onset depression in patients with diabetes mellitus than in controls[102]. However, it should be noted that the increased risk of depression in response to a disease diagnosis is not exclusive to diabetes mellitus and that this relationship has been observed in many other chronic conditions[104].

Psychological factors and disease management in T2DM.

Comorbid depression can negatively affect quality of life in people with T2DM[105, 106]. Depression in diabetes mellitus affects the patient's ability to control the disease, as well as *self-care behaviours*. For example, depression has been associated with suboptimal glycaemic control in people with diabetes mellitus, with stronger effects observed in patients with interview-diagnosed depression than in patients with self-reported depression[107]. A 2008 meta-analysis that included both cross-sectional and longitudinal evidence found that depression was associated with non-adherence to various treatment regimens[62]. Longitudinal research published after this meta-analysis has also reported poorer treatment adherence in people with diabetes mellitus and depressive symptoms[108].

The clinical significance of diabetes-related distress is exemplified by its association with poor glycaemic control and the greater effect that it has on glycaemic management compared with depression[99, 109]. Diabetes-related distress can also predict medication adherence in T2DM[109], such that those with greater levels of distress have poorer medication adherence.

Few studies have looked at the relationship between anxiety and self-care behaviours in T2DM; however, it is worth noting that fear of hypoglycaemia, as well as anxiety regarding glucose-lowering treatments, is commonly observed in around 25% of patients110. This form of anxiety can manifest as non-adherence to medication resulting in poor glycaemic control and raised levels of glucose[110]. One early meta-analysis of cross-sectional studies reported an inverse association between anxiety and poor glycaemic control[111]. Longitudinal research is lacking, but subsequent research in small cross-sectional studies has generally supported a link between anxiety and worse glucose control[112–114], and one prospective study of 1,691 individuals related anxiety to functional disability in T2DM[115].

Limited research has investigated the relationship between potentially protective psychological factors and glycaemic control in people with T2DM, and most research has been cross-sectional. One prospective study of 97 elderly women looked at the relationship between positive well-being (as defined by questionnaire measures of positive affect, purpose in life and personal growth) and glycaemic control[116]. Those with greater positive well-being at baseline had significantly lower levels of HbA1c at 2-year follow-up adjusting for age, income, marital status, waist–hip ratio and statin usage than those with lower positive well-being. Unfortunately, the significance of this finding is limited because the study did not include people with T2DM. The longitudinal relationship between resilience (the ability to maintain psychological well-being in situations of adversity) and glycaemic control was assessed in a study of 111 individuals with either T1DM or T2DM[117]. In this study, low stress resilience was associated with worsening levels of HbA1c over the 1-year follow-up period in both types.

Taken together, these data suggest that depression and diabetes-related distress are associated with glycaemic control and treatment adherence in T2DM. The use of cross-sectional studies and small sample sizes has limited the research on anxiety and potentially protective psychological factors.

Psychological factors and complications

Chronic hyperglycaemia is associated with long-term damage in multiple systems. The harmful effects of T2DM include microvascular (damage to the small blood vessels) and macrovascular (damage to the large blood vessels) complications. Microvascular complications include retinopathy (which can lead to blindness), nephropathy (which can lead to renal failure) and neuropathy (which can lead to impotence, foot ulcers and amputation) [46].

The macrovascular complications of T2DM include various cardiovascular diseases[118]. Emerging evidence suggests that psychological factors might increase the risk of complications resulting from T2DM **(TABLES 3, 4).**

The most commonly researched psychological factor in the context of complications resulting from T2DM is depression. Prospective evidence indicates that patients with a diagnosis of T2DM and depression have an increased risk of a myriad of microvascular complications, including foot ulcers, retinopathy and chronic kidney disease[119–123], as well as macrovascular complications, such as myocardial infarction and stroke[121, 124–127]. Depression in T2DM is associated with an increased risk of cardiovascular and all-cause mortality[128–130]. A limited number of studies have assessed the association between anxiety and T2DM complications but have failed to detect an association[131, 132]. One study looked at psychological distress and outcomes in T2DM and found that psychological distress predicted cardiovascular and all-cause mortality[133]. With regard to positive psychological traits, one study assessed positive well-being and risk of mortality in people with diabetes mellitus over a 10-year follow-up period[134], but protective effects did not remain once covariates were taken into consideration. Nevertheless, sub-analyses from this study indicated that enjoyment of life (a component of positive affect) reduced the risk of mortality in people with diabetes mellitus.

Stress modification in T2DM

If stress is relevant to T2DM, does stress management or stress modification have a therapeutic benefit? One study reported that group-based stress management training for people with T2DM could improve glycaemic control over a 1-year follow-up period[135]. A 2016 randomized control trial (RCT) including US-based Latino people found that stress

management improved self-reported depression, anxiety and self-rated health scores; however, the intervention and control groups did not differ in levels of HbA1c at 3-month follow-up[136]. Some evidence suggests that cognitive behavioural interventions and self-management programmes improve diabetes-related distress[137, 138], but reducing diabetes-related distress might not result in improvements in levels of HbA1c or inflammatory markers[137, 138].

Mindfulness has also been applied in an attempt to modify psychological stress in people with T2DM and seems to reduce symptoms of depression, anxiety, general stress and diabetes-related stress. A systematic review of the effectiveness of mindfulness-based interventions on glycaemic control identified seven studies: four interventions were found to improve levels of HbA1c, but the remaining three studies, which had larger sample sizes, reported no effect[139]. As mindfulness-based interventions for T2DM are fairly new, more studies with longer follow-up periods are needed to fully understand how this intervention affects glucose control.

The bulk of research on stress modification in T2DM has assessed whether treating depression in patients with T2DM improves psychological and physical outcomes. A 2012 Cochrane Review assessed the results from 19 RCTs of pharmacological and psychological interventions for depression in diabetes mellitus[140]. Antidepressant usage (including selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants) as a pharmacological intervention had a moderate effect on short-term (defined as end of treatment) depression severity, as well as depression remission. In addition, antidepressant usage notably improved glycaemic control at the end of the study period. Most pharmacological RCTs used SSRIs as a therapy, and, in sensitivity analyses, the associations remained when only these studies were included. Psychological interventions including cognitive behavioural therapies and psychodynamic supportive therapies improved depression severity and had a beneficial effect

on depression remission at the end of the study period and up to 6 months later; however, it was unclear whether psychological intervention was beneficial for glycaemic control as the study findings were mixed.

The gold standard for the management of comorbid depression in adults with chronic disease is collaborative care[141]. A 2014 meta-analysis pooled the results from seven RCTs of collaborative care for patients with depression and diabetes mellitus[142]. The results suggest that collaborative care reduces depression scores and levels of HbA1c in people with diabetes mellitus. However, the reductions in depression severity were not correlated with reductions in levels of HbA1c. The authors of the meta-analysis suggest that collaborative care for depression in diabetes mellitus could improve glucose control through other means, such as improved self-management, independent of depression.

Taken together, these findings indicate that therapies to modify psychological factors in people with diabetes mellitus have been reasonably effective in reducing the severity of depression and diabetes-related distress, but evidence for an effect on glycaemic control is mixed. Treating patients with comorbid T2DM and depression with antidepressants improves glycaemic control in the short term, and collaborative care is beneficial for reducing levels of HbA1c. However, the reductions reported in the severity of depression following collaborative care were not statistically significantly associated with reductions in HbA1c.

The evidence linking mindfulness-based intervention with improvements in levels of HbA1c is mixed. To our knowledge, no studies have assessed the effect of psychological stress modification on the microvascular and macrovascular complications that are associated with T2DM. As hyperglycaemia is linearly associated with increased cardiovascular disease risk[143, 144], interventions that improve glycaemic control might also affect hard clinical

outcomes, but this effect remains to be tested. Links between psychological interventions and the biological pathways detailed earlier in this Review have yet to be explored in detail.

Conclusion

Emerging evidence from animal studies, epidemiological studies and human laboratory stress trials indicates that stress-related biology is altered in T2DM and that disturbances across multiple biological systems reflecting chronic allostatic load might be present. Most of the evidence linking biological stress processes comes from observational studies, so we are unable to draw causal conclusions. Accumulating evidence, for the most part, has linked various psychological stress factors with new onset T2DM. Comorbid depression in T2DM increases the risk of early onset and progression of microvascular and macrovascular complications and increases mortality. Various interventions to improve symptoms of depression and diabetes-related distress seem to have a favourable impact on these outcomes. The effect of these interventions on glycaemic control is less certain, and research on the effect of stress modification on complications in T2DM is lacking.

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Author contributions

The authors contributed equally to all aspects of the preparation of this article

Competing interests statement

The authors declare no competing interests.

Publisher's note

Review criteria

We searched for articles on PubMed, focusing where possible on prospective studies and meta-analyses published up until November 2016. The following terms were used to obtain the literature on the biological aspects of stress in diabetes: "stress" and "blood pressure", "heart rate", "cardiovascular", "cortisol", "glucocorticoid", "inflammation", "inflammatory" "allostatic', together with "diabetes" and "type 2 diabetes". The following terms were used to obtain the literature on the link between psychological stress and diabetes: "stress", "depres-

sion", "depressive", "anxiety", "distress", "work stress", "job strain", "hostility", "anger", "optimism" together with "diabetes", "type 2 diabetes" and "prospective". In addition, we scrutinized the reference sections of all articles. The papers included are all full-text, English-language papers.

Glossary

Psychological stress: A broad term referring to a range of psychological phenomena including exposure to external challenges (stress conditions in adult or earlier life), psychological distress (including depression and anxiety) and personal traits, such as anger or hostility.

Diurnal cortisol pattern: The distinct pattern of daily cortisol output in humans

Adipokines: An umbrella term for inflammatory factors expressed in adipose tissue.

The metabolic syndrome: A combination of factors (including central obesity, raised blood pressure and raised cholesterol levels) that increases the risk of type 2 diabetes mellitus.

Psychological distress: A measure that encompasses depressive symptoms, anxiety, general stress and sleep disturbance.

Self-care behaviours: In type 2 diabetes mellitus these include behaviours such as glucose monitoring, managing complications and adhering to medication and lifestyle recommendations.

Collaborative care: A multidisciplinary form of management that can include a combination of lifestyle, pharmacological and psychological therapies as well as patient education and regular practitioner monitoring.

Table 1 | Meta-analyses linking psychological factors with T2DM risk

Population (sample size, follow-up)	Psychological measure	Association with T2DM risk	Refs
Nine studies (*n* = 174,035; average 9.4 year follow-up)	Depression	*RR 1.37 (95% CI 1.14–1.63).	Knol (2006)[59]
13 studies (*n* = 6,916 incident cases of diabetes mellitus; average 9.4 year follow-up)	Depression	*RR 1.60 (95% CI 1.37–1.88).	Mezuk (2008)[60]
23 studies (*n* = 19,977 incident cases of diabetes mellitus, average 8 year follow-up)	Depression	*Unadjusted RR 1.56 (95% CI 1.37–1.77) Adjusted RR 1.38 (95% CI.23–1.55).	Rotella (2013)[62]
Five studies (four longitudinal; healthy *n* = 125,723, PTSD (*n* = 23,203)	PTSD	*RR1.49 (95% CI 1.17–1.89).	Vancampfort (2016)[68]
13 European studies (*n* = 124,808; *n* = 3703 incident cases of diabetes mellitus; 10.3 year follow-up)	Work stress defined by job strain	*HR 1.15 (95% CI 1.06–1.25).	Nyberg (2014)[72]
19 cohort studies from the USA, Europe, Japan and Australia	Work stress defined by long working hours >55 h a week	‡Association only in low SES groups RR 1.29 (95% CI 1.06–1.57).	Kivimäki (2015)[73]

(*n* = 222,120, *n* = 4,963 incident cases of diabetes mellitus; average 7.6 year follow-up)			
Seven studies, four prospective (*n* = 87,251, *n* = 5,879 incident cases of diabetes mellitus)	Adverse childhood experiences	*OR 1.32 (95% CI 1.16 –1.51).	Huang (2015)[81]

***positive association; ‡some association; §no association.** CI, confidence interval; HR, hazard ratio; OR, odds ratio; PTSD, post-traumatic stress disorder; RR, relative risk.

Table 2 | Prospective studies linking psychological factors with T2DM risk

Population (sample size, follow-up)	**Psychological measure**	**Association with diabetes mellitus risk**	**Refs**
ELSA cohort (*n* = 4,238; 6 year follow-up)	Depressive symptoms using the eight-item centre for epidemiologic studies-depression scale (CES-D)	OR 1.53 (95% CI 0.80-2.93)*.	Demakakos (2014)[61]
Norwegian cohort (*n* = 37,291; 10 year follow-up)	Anxiety using the hospital anxiety and depression scale, seven-items for anxiety	OR 1.5 (95% CI 1.3–1.8)‡ Did not control for depression.	Engum (2007)[63]
NESDA cohort (*n* = 2,460; 2 year follow-up)	Anxiety using composite interview diagnostic instrument	OR 1.6 (95% CI 1.2–2.1).	Atlantis (2012)[66]
US adults (n=1920; 11 year follow-up)	Anxiety using the Diagnostic Interview Schedule	§OR 1.00 (95% CI 0.53–1.89).	Edwards (2012)[126]
3 prospective cohorts; Health Professional's follow-up study (*n* = 30,791 men); Nurses' Health Study (*n* = 68,904 women); Nurses' Health Study II (*n* = 79,960 women). Total *n* = 12,831 incident cases, 18–20 years follow-up	Phobic anxiety symptoms using the eight-item Crown–Crisp index	‡No association in the male cohort after adjustment in Health Professional's follow-up study but associations reported in women. In the Nurses' Health Study HR 1.02 (95% CI 1.01–1.03). In the Nurses' Health Study II HR 1.04 (95% CI 1.02–1.05).	Farvid (2014)[65]

Two prospective cohorts; NHANES cohort (*n* = 3,233; 17 year follow-up); The Detroit Neighbourhood Study (*n* = 1,054; 18 year follow-up)	Anxiety using the generalized anxiety disorder-seven item questionnaire	‡No association in the overall sample. Dividing the groups by sex, in both studies association found in women only. In the NHANES cohort, RR 2.19 (95% CI 1.17–4.09) In the Detroit Neighbourhood Study, RR 1.62 (95% CI 0.61–4.32).	Demmer (2015)[67]
MESA cohort (*n* = 5,598; 11.4 year follow-up)	Anxiety using the Spielberger trait anxiety scale	§HR 1.16 (95% CI 0.87–1.54).	Abraham (2015)[64]
Swedish adults (*n* = 5,227; 8–10 year follow-up)	Psychological distress using an index of five questions on anxiety, apathy, depression, fatigue and insomnia	‡Association only in males OR 2.2 (95% CI 1.2–4.1).	Eriksson (2008)[71]
UK adults (*n* = 9,514; 18 year follow-up)	Psychological distress using the 12- item general health questionnaire	*HR 1.33 (95% CI 1.10–1.61). Attenuated controlling for health behaviours.	Mommersteeg (2012)[69]
Whitehall cohort (*n* = 5,932; average follow-up 5.46 years)	Psychological distress using the 30-item general health questionnaire	‡No association in the overall sample, only in those at high risk of diabetes mellitus at baseline OR 2.07 (95% CI 1.19–3.62).	Virtanen (2014)[70]
Japanese men (*n* = 128; mean follow-up 3.2 years)	Perceived stress using 15-item stress in daily life questionnaire developed for Japanese individuals	*HR 3.81 (95% CI 1.09–13.35).	Toshihiro (2008)[75]
Danish adults (*n* = 7,066; 10 year follow-up)	Perceived stress intensity on seven-point scale (one-item) and stress frequency on seven-point scale (one-item).	‡Association only in men OR 2.36 (95% CI 1.22– 4.59).	Rod (2009)[55]
Japanese adults (*n* = 55,826, *n* = 1,601 incident cases of diabetes mellitus; 10 year follow-up)	Perceived stress based on one item ‘How much stress to feel in daily life?’ (three point scale)	*Overall association but effects were stronger among male OR 1.39(95% CI 1.15–1.65) than in female participants OR 1.25 (95% CI 1.01-1.56).	Kato (2009)[77]

Australian adults (*n* = 3,759; 5 year follow-up)	Perceived stress in 30-item questionnaire	‡Outcome was abnormal glucose tolerance rather than overt diabetes mellitus. Association only in women OR 1.72 (95% CI 1.07-2.76).	Williams (2013)[76]
Swedish men (*n* = 7,251; *n* = 899 incident cases of diabetes mellitus; 35 year follow-up)	Perceived permanent stress (self-reported stress related to work or home life ongoing for >1 year)	*HR 1.52 (95% CI 1.26–1.82).	Novak (2013)[74]
French adults (*n* = 22,567, n=527 incident cases of diabetes mellitus; 5.3 year follow-up)	Perceived stress using the four-item perceived stress Scale	‡Association only in those of low occupational status OR 1.39 (95% CI 1.02–1.90).	Wiernik (2016)[78]
Israeli defence forces (*n* = 32,584 men, *n* = 723 incident cases of diabetes mellitus; mean follow-up 6.3 years)	Perceived emotional distress based on one item 'Are you preoccupied by worries or concerns that affect your overall wellbeing?'	*HR 1.53(95% CI 1.08–2.18).	Twig (2016)[79]
Danish cohort (*n* = 1.9 million, *n* = 45,302 who experienced pre-natal stress)	Pre-natal stress measured by mother's experience of bereavement	*Incidence rate ratio 1.31 (95% CI 1.01–1.69).	Virk (2012)[139]
ARIC cohort (*n* = 11,615; 6 year mean follow-up)	Anger using the Spielberger trait anger scale (ten item)	*HR 1.34 (95% CI 1.10– 1.62).	Golden (2006)[80]
MESA cohort (*n* = 5,598; 11.4 year mean follow-up)	Anger using the Spielberger trait anger scale	*The trait anger HR 1.48 (95% CI 1.04–.12). Attenuated after adjustment for waist circumference. Analysis of the Spielberger anger reactivity sub-scale HR 1.07 (95% CI 1.03–1.11) robust to all covariates.	Abraham (2015)[64]
Swedish male military conscripts (*n* = 1.5 million; average mean follow-up 25.7 years)	Low stress resilience assessed by semi-structured interview	*HR 1.51 (95% CI 1.46–1.57).	Crump (2016)[82]
EPIC cohort (*n* = 50,358, n incident	Life satisfaction assessed with one item 'how	§Women with high life satisfaction had reduced	Feller (2013)[84]

diabetes = 1840; average mean follow-up 8 years)	satisfied are you with your life?'	risk of diabetes mellitus 1.53 (95% CI 1.19–1.97). Not robust to adjustment for covariates. (95% CI 1.27 (0.98–1.64)). No associations in men.	
Whitehall cohort (*n* = 7800; 13 year mean follow-up)	• Life satisfaction measured by self-report satisfaction with seven life domains. • Emotional vitality measured using three items from the Short-form 36 • Optimism measured using one item "Over the next 5–10 years, I expect to have many more positive than negative experiences" (six point scale)	‡No associations in overall sample. Sub-analyses by diabetes mellitus type (doctor diagnosed or Whitehall assessment) people with high life satisfaction OR 0.85(95% CI 0.76–0.95) and emotional vitality OR 0.86 (95% CI 0.77–0.97) were less likely to report doctor-diagnosed diabetes mellitus.	Boehm (2015)[85]
ELSA (*n* = 8,182 and *n* = 451 new cases of diabetes mellitus; median mean follow-up of 6 year)	CASP-19 quality of life scale.	‡Greater quality of life was associated with decreased diabetes mellitus risk HR 0.82 (95% CI 0.70–0.95) but only in those aged <65 years.	Okely (2016)[83]

***positive association; ‡some association; §no association.** ARIC, *Atherosclerosis Risk in Communities Study;* CASP, Control, Autonomy, Self-realisation and Pleasure; CES-D, Centre for Epidemiologic Studies-Depression scale; CI, confidence interval; ELSA, English Longitudinal Study of Ageing; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis; NESDA, Netherlands Study of Depression and Anxiety; NHANES, *National Health and Nutrition Examination Survey;* OR, odds ratio; RR, relative risk; SES, socioeconomic status.

Table 3 | Meta-analyses linking psychological factors with incident microvascular and macrovascular complications in diabetes mellitus

Population (sample size, follow-up)	Psychological measure	Association with diabetes mellitus complications and mortality	Refs
27 cross-sectional studies (*n* = 5374)	Depression	*Depression associated with retinopathy, nephropathy, neuropathy, sexual dysfunction and macrovascular complications. Effect size small to moderate (*r* = 0.17–0.32). Limited by lack of prospective evidence and the inclusion of studies of both T1DM and T2DM.	De Groot (2001)[140]
13 cross-sectional studies (*n* = 3,898 with diabetes mellitus)	Depression	*Depression in diabetes mellitus associated with neuropathy OR 2.01 (95% CI 1.60–2.54). Limited by use of cross-sectional evidence.	Bartoli (2016)[141]
16 prospective studies (eight studies on T2DM); 6 year follow-up. (*n* = 109,046 with diabetes mellitus; *n* = 21,443 with diabetes mellitus and depression).	Depression	*Increased risk of all-cause mortality HR 1.46 (95% CI 1.29–1.66). Increased risk of cardiovascular mortality HR 1.39 (95% CI 1.11–1.73).	Van Dooren (2013)[123]
16 prospective studies (nine studies on T2DM); 6 year follow-up (*n* = 107,944 with diabetes mellitus; *n* = 19,589 with diabetes mellitus and depression).	Depression by self-report and by clinical interview	*Self-reported depression: increased risk of all-cause mortality HR 1.76 (95% CI 1.45–2.14). Clinically diagnosed depression: increased risk of all-cause mortality HR 1.49(95% CI 1.15–1.93)	Hofmann (2013)[124]
Ten prospective studies (*n* = 42,363 with diabetes mellitus; *n* = 5,325with diabetes	Depression	*Increased risk of mortality HR 1.50 (95% CI 1.35–1.66)	Park (2013)[122]

mellitus and depression). 2–10 year follow-up. Studies of both T1DM and T2DM included.			

***positive association; ‡some association; §no association.** CI, confidence interval; HR, hazard ratio; OR, odds ratio; PTSD, post-traumatic stress disorder; r, correlation coefficient; RR, relative risk; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table 4 | Prospective studies linking psychological factors with incident microvascular and macrovascular complications in diabetes mellitus

Population (sample size, follow-up)	Psychological measure	Association with diabetes mellitus outcome	Refs
Americans of Mexican origin (*n* = 2,830, 23% with diabetes); 7 year follow-up	Depressive symptoms measured by CES-D, clinical depression assessed by diagnostic interview	*Depressive symptoms and major depression associated with increased risk microvascular and macrovascular complications of diabetes mellitus as well as mortality.	Black (2003)[142]
Pathways Epidemiological Follow-up study (*n* = 3,473 with diabetes mellitus; mean follow-up 4.1 years)	Depressive symptoms assessed by the PHQ-9	*Major depression associated with increased risk of incident diabetic foot ulcers 2.00 (95% CI, 1.24–3.25). No association with minor depressive symptom.	Williams (2010)[113]
Pathways Epidemiological Follow-up study (*n* = 4,623 with diabetes mellitus; 5 year follow-up)	Depressive symptoms assessed by the PHQ-9	*Major depression associated with increased risk of microvascular HR 1.36 (95% CI 1.05–1.75) and macrovascular outcomes HR1.24 (95% CI 1.0 –1.54).	Lin (2010)[120]
UK and USA collaborative study; *n* = 333 with peripheral neuropathy (73% with T2DM) 18 month follow-up	Depression assessed by the HADS	‡Increased risk of first diabetic foot ulcer HR 1.68 (95% CI 1.20–2.35). No association for recurrent ulceration. Study limited by use of sample with existing peripheral neuropathy.	Gonzalez (2010)[116]
Pathways Epidemiological Follow-up study (*n*= 2,359 with diabetes mellitus; 5 year follow-up)	Depressive symptoms assessed by the PHQ-9	*Increased risk of incident retinopathy OR 1.03 (95% CI 1.01–1.05). 5 point increase on PHQ-9, 15% increased risk of retinopathy.	Sieu (2011)[114]
US Veterans *n* = 345,	Diagnosed major	*Patients with diabetes	Scherrer (2011)[119]

949 (depression and diabetes free *n* = 214,749; depression only *n* = 77,568; diabetes mellitus only *n* = 40,953; depression and diabetes mellitus *n* =12,679; 7 year follow-up)	depressive disorder	mellitus and depression had an 83% increased for myocardial infarction HR 1.82 (95% CI 1.69–1.97).	
Chinese adults with diabetes mellitus *n* = 7,835; 7.4 year follow-up).	Depression assessed by psychiatrist diagnosis	*Increased risk of CVD HR 2.18 (95% CI 1.45–3.27), sub-analysis indicated stroke accounted for most of the risk HR 3.55 (95% CI 2.15– 5.84).	Ting (2013)[118]
Norwegian adults (*n* = 36,031; *n* = 1,331with diabetes mellitus and foot ulcer; mean follow-up 7.6 years)	Depression assessed by the HADS	‡Depression increased risk of foot ulceration *HADS score 8-10 OR1.95 (95% CI 1.02–3.74); HADS score ≥11 OR 3.06 (95% CI, 1.24–7.54).	Iversen (2015)[117]
US veterans (*n* = ~3 million, *n* = 933.211 with diabetes mellitus) The median follow-up was 2,659, 2,916, 2,451, and 2,453 days for chronic kidney disease, mortality, coronary heart disease, and stroke, respectively.	Depression assessed by clinical diagnosis or anti-depressant usage	Depression associated with increased risk of chronic kidney disease HR 1.20 (95% CI 1.19–1.20); coronary heart disease HR 1.22 (95% CI 1.19–1.24); stroke HR 1.32 (95% CI 1.28–1.36); all-cause mortality HR 1.25 (95% CI 1.24–1.26).	Novak (2016)[115]
Swedish drug register (*n* = ~4 million; depression and diabetes *n* = 47,856; 3 year follow-up).	Depression assessed by anti-depressant usage	*Sex stratified analysis of risk of myocardial infarction. Women HR 7.4 (95% CI 6.3–8.6). Men HR 3.1 (95% CI 2.8–3.6). Study limited by lack of information on BMI, smoking or lipids.	Radholm (2016)[121]
US adults REGARDS cohort (*n* = 22,003; *n* = 4,090 with diabetes mellitus; 5.95 year follow-up)	Depressive symptoms assessed by the CES-D (four item questionnaire) and perceived stress assessed by Cohen Perceived Stress Scale (four item questionnaire)	‡Depressive symptoms or perceived stress increased risk of stroke (HR 1.57; 95% CI 1.–2.33) and myocardial infarction (HR 1.57; 95% CI 1.02–2.40) and CVD death (HR 1.53; 95% CI 1.08–2.17.	Cummings (2016)[143]

		Association for myocardial infarction attenuated when adjusting for health behaviours. Limited by assessing depressive symptoms and perceived stress together.	
Baltimore Epidemiologic Catchment Area Study (*n* = 1,920; 8.6% had diabetes mellitus and anxiety; 11 year follow-up)	Anxiety assessed by diagnostic interview	§No statistically significant relationship between anxiety and incident diabetes complications (OR 2.02; 95% CI 0.61–6.74).	Edwards (2012)[126]
Norwegian adults with diabetes mellitus *n* = 948. 17 years follow-up; mean follow-up 12 years. Participants were insulin naive.	Anxiety symptoms assessed by the HADS Depression symptoms assessed by the HADS	‡Anxiety not associated with mortality HR 0.73 (95% CI 0.50–1.07). Depression associated with increased mortality risk HR 1.39 (95% CI 1.05–1.84). Depressive and anxiety symptoms together were not associated with mortality HR 1.30 (95% CI 0.96–1.74).	Iversen (2016)[125]
Australian adults with diabetes *n* = 1,337. 4 year follow-up.	Depression assessed by the PHQ Anxiety assed by the Generalised Anxiety Disorder scale.	‡Major depression increased risk of CVD events HR 2.10 (95% CI 1.22–3.62) and cardiovascular mortality HR 3.56 (95% CI 1.03–12.35). Anxiety disorder predicted cardiovascular mortality HR 5.92; (95% CI 1.84–19.08) but not CVD events. Combined outcome major anxious depression predicted CVD events HR 1.90 (95% CI 1.11–3.25) and cardiovascular mortality HR 4.32(95% CI 1.35–13.86).	Bruce (2016)[144]
Danish adults with diabetes (*n* = 1,533; average follow-up 5.4 years).	Psychological distress measured with the MHI-5	*Increased risk of a CVD event HR 1.69 (95% CI 1.05–2.70) and increased risk of all-cause mortality HR 1.76	Dalsgaard (2014)[127]

		(95% CI 1.23–2.53)	
NHEFS cohort *n* = 3,388 (*n* = 715 with diabetes mellitus); 10 year follow-up	Positive affect sub-scale of the CES-D (assessed by four components: self-esteem; hopeful; happy; and life enjoyment)	‡Positive affect reduced risk of mortality HR 0.87 (95% CI 0.76–0.99). Not robust to adjustment for covariates. Sub-analysis of the positive affect scale only enjoyment of life was a significant predictor of reduced mortality controlling for covariates HR 0.89 (95% CI 0.79–0.99).	Moskowitz (2008)[128]

***positive association; ‡some association; §no association.** CES-D, Center for Epidemiologic Study of Depression; CI, confidence interval; CVD, Cardiovascular Disease; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; MHI-5, Mental Health Inventory 5; NHEFS= NHANES I Epidemiologic Follow-up Study PHQ-9, Patient Health Questionnaire; REGARDS, Reasons for Geographic And Racial Differences in Stroke; T2DM, type 2 diabetes mellitus.

Figure 1

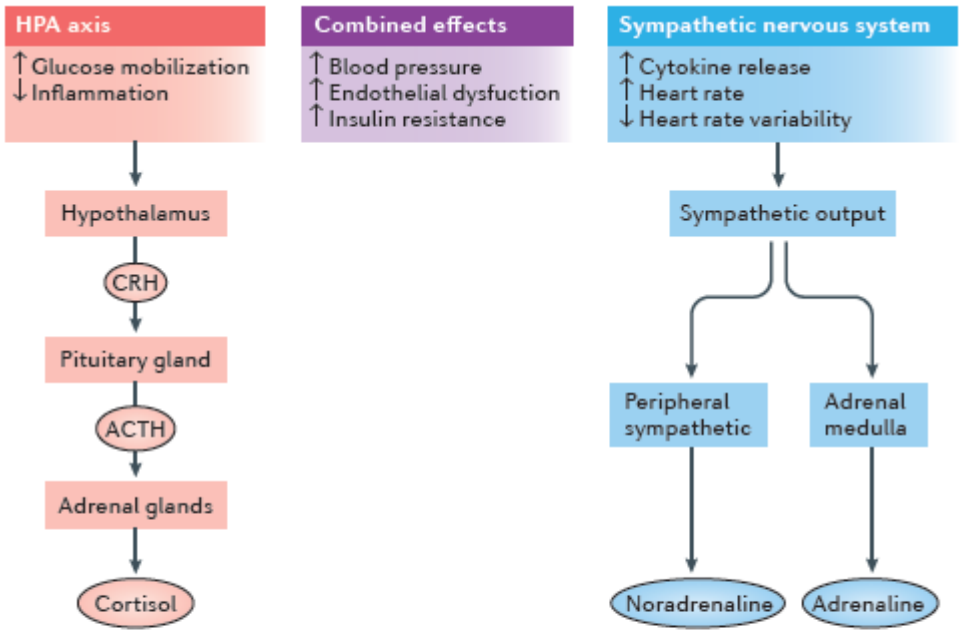

Figure 1 | **Overview of the human stress system.** The red pathway (left-hand side) represents the hypothalamic–pituitary–adrenal (HPA) axis. The purple shading (centre) represents the combined effects of the HPA axis and sympathetic nervous system. The blue shading (right-hand side) represents the sympathetic nervous system. The circles represent the physiological effects of these systems. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

Figure 2

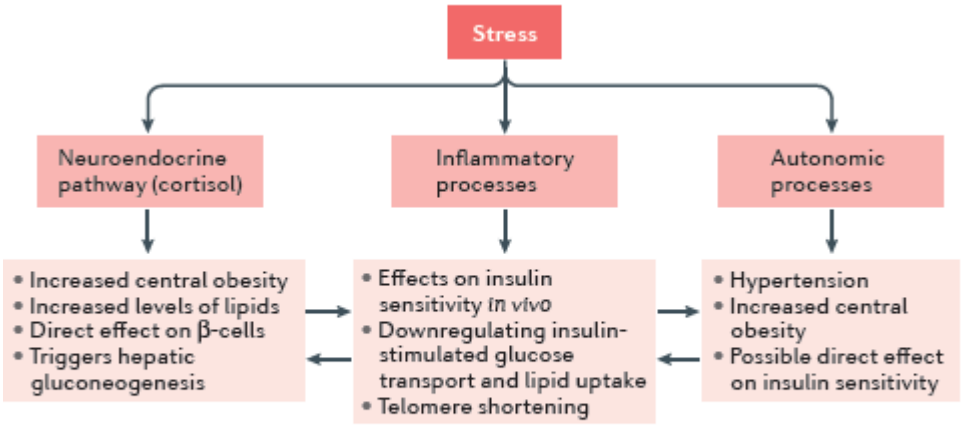

Figure 2 | **Stress-related biological pathways and their effect on diabetes mellitus processes.** An overview of neuroendocrine, inflammatory and autonomic pathways and their impact on diabetes-related processes is shown.

Figure 3

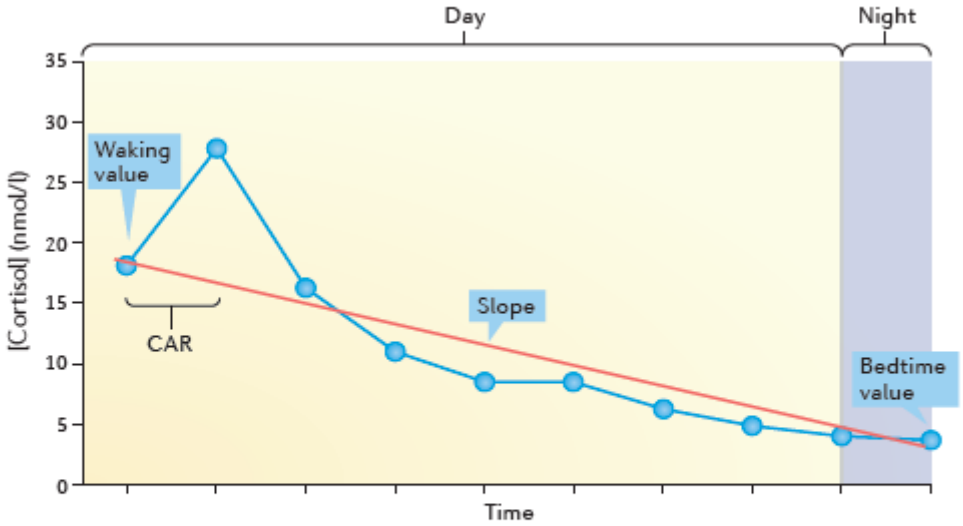

Figure 3 | **The diurnal pattern of cortisol output.** An overview of the daily pattern of cortisol release is shown. Cortisol is highest in the morning, reaching a peak 30–45 min after waking (termed the cortisol awakening response (CAR)). Following this peak, it declines gently over the course of the day (cortisol slope), reaching a low point at night time.