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 over time.

Glucocorticosteroids

Blood pressure:

Stress-induced sympathetic activation of the auto- nomic 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 mellitus4

Polygenetic scores and diabetes:

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 mellitus44. Studies investigating variants in the genes that encode CRP and IL-1 have not detected statistically significant associations with T2DM45. This area of research has not yet been widely investigated, and thus future studies might detect associations45.

Recommended future research:

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 systems22. 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 risk57; however, another investigation of 53 individuals failed to detect an association58.

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.

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 medication13. 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 men61. 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 exercise62.

More research investigating the complex relationships between psychological stress, health behaviours and onset of diabetes T2 is needed.

Predictor:

* Cumulative time-varying discrimination
* Other stressors (psychological stress: job-related etc)

Mechanism:

* Blood pressure
* Saliva cortisol
* Polygenetic scores for diabetes
* Inflammatory markers (are they included in the HRS and ELSA)
* Actigraph data

Outcome:

* Onset of diabetes T2

44. Swerdlow, D. I. *et al.* The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* **379**, 1214–1224 (2012).

45. Swerdlow, D. I. Mendelian randomization and type 2 diabetes. *Cardiovasc. Drugs Ther.* **30**, 51–57 (2016).