Stress and type 2 diabetes: a review of how stress contribute to the development of type 2 diabetes

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Stress and type 2 diabetes: A review of how stress contribute to the development of T2D

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Abstract (150 words right now)

Current policy and research around Type 2 diabetes (T2D) interventions largely invokes a behavioural model. We suggest that chronic activation of the physiologic stress response from chronic exposure to stressors, low socioeconomic status, severe mental health problems, or aggressive behaviour increases the risk of T2D.

The project is a comprehensive review of the literature on the link between T2D and PSF focusing on prospective studies of the risk for developing diabetes.

The review found an increased risk for T2D in people: exposed to stressful working conditions or traumatic events; with depression; with personality traits or mental health problems that put them in conflict with others; of low SES either currently or in childhood; and in minority populations independent of current SES.

T2D prevention would be more effective if 1) PSF (especially social disparities) were recognised and 2) intervention programmes targeted the reduction in social disparities as part of a comprehensive approach.
**Introduction**

Type 2 diabetes (T2D) is a group of conditions characterised by a background of insulin insensitivity with a failure of pancreatic insulin secretion to compensate for this and is diagnosed clinically by elevated plasma glucose levels frequently in association with obesity and other metabolic abnormalities such as dyslipidemia as well as endothelial and cardiovascular dysfunction. The causes of T2D are attributed to lifestyle or genetics, both of which have been invoked, also to varying degrees, to explain ethnic disparities in disease prevalence and outcomes (e.g., (1)).

There is a solid body of literature showing the importance of conventional (non-psychosocial) risk factors for T2D. However, in spite of interventions based on these conventional risk factors, the incidence of diabetes continues to rise. We propose that chronic activation of the physiologic stress response (PSR) increases the risk of developing T2D but the amount of literature examining the relationship remains limited and, conceptually, the link remains largely unrecognized. This is surprising when one considers the large amount of stress-related literature in diabetes management. Hence, ignoring the role of chronic stress factors in the development of T2D potentially deprives researchers and clinicians of valuable insights.

T2D, like cardiovascular disease (CVD), has a prevalence that increases substantially with decreasing social position. And, in the case of CVD, a solid body of research evidence indicates that neither genetic factors nor lifestyle can fully explain socioeconomic status (SES) gradients or ethnic disparities in the disease prevalence within a country (e.g., (2, 3)) or explain differences in CVD rates between countries (e.g., (4, 5)). And, it should be recognised that while CVD and T2D share many common risk factors, only for CVD is there much research on the role that stress-related exposure plays in the development of the disease. For example, the mechanisms by which living in more difficult circumstances (for which low SES is an indicator) might impact health are debated, but the most prominent theories propose mechanisms such as cumulative exposure to stressors (allostatic load) (6), perceived lack of control (7), and stress-related consequences arising from unfavourable social comparisons (8). Much of the research describes the mechanism as ‘stress’ related, but the terminology is inconsistent (9).
This paper will review the evidence concerning psychosocial factors and the development of T2D, outlines possible mechanisms and make recommendations for future research and policy directions. It begins with a clarification regarding the terminology of stress as this will play an important role throughout.

**Stress terminology**

Stress is widely regarded (10) as an important cause of ill-health and it is frequently cited as an important contributor to socioeconomic gradients in health (11, 12). A central problem is the terminology as, even in research, the term 'stress' has been used to describe "the stimuli that produce a certain state, the subjective feelings of discomfort in this state and the responses that occur in an organisms in this state" (13). Or as Cohen and colleagues describe it 'stress may have environmental, psychological and biological roles in the development of ill-health' (14). To clearly indicate which meaning we are referring to in this paper the term “stressor” refers to objective events or circumstances which are generally agreed to be stressful (e.g., traumatic life events); “distress” refers to subjective feelings of discomfort; and PSR refers to the physiological responses that occur within an organism that is exposed to stressors. In this paper we are particularly focused on the PSR and whether it provides a testable hypothesis to link psychosocial risk factors with the development of T2D.

**The stress mechanism hypothesis**

As with CVD, the original models for the development of T2D were largely behavioural and posited that, in particular, poor diet and lack of physical activity were primarily responsible. The development of CVD, however, has been shown to be independently associated with a variety of stress-related factors including control, hostility and life events (e.g., (4, 15)). Such stress-related factors, which have been demonstrated to be important for the development of CVD may also be important for the development of T2D.

One could plausibly argue that stress-related risk factors act via behavioural risk factors and, indeed, most of the literature reviewed here does use this explanation. But, as will be seen later, most of the studies in this review controlled the statistical analyses for many/most of the behavioural risk factors and still found an effect from stress-related factors. For example, some of the studies highlighted in this review have shown that risk is considerably greater for those of low socioeconomic (16) or racial minority status (17) suggesting pathways above and beyond the behavioural.
The immediate PSR is not thought to be the problem affecting health; rather chronic activation of the PSR is thought to be the key. The role of the PSR is to maintain physiologic homeostasis; it consists of an inter-related response from the sympathetic adrenomedularly system (SAM) and the hypothalamic pituitary adrenal axis (HPA). Initially the SAM releases epinephrine and norepinephrine but if the stressor is sustained the HPA comes into play. The development of abdominal obesity, an important risk factor for diabetes, is a key step in the development of the condition.

In the early 1990’s Bjorntorp and Rosmond proposed that “neuroendocrine responses to stress-related pressures” might increase the accumulation of abdominal fat (18). Their final model proposed that the HPA-axis is reprogrammed with chronic stress exposure (19, 20). The key is that the stressor exposure must be of sufficient magnitude or duration to reprogram the HPA-axis.

With the current recognition that T2D is an inflammatory disease, the hypothesized mechanism can shift from a behavioural model to a model of repeated episodes of acute or chronic PSR which induces a chronic inflammatory process which produces inflammatory diseases (21, 22). Animal models have shown that stressor exposure precedes the development of chronic subclinical inflammation. The animals develop central obesity, insulin resistance, dyslipidemia, hypertension, and depression. They go on to develop T2D, Metabolic Syndrome, and coronary artery disease (21). In humans prospective work has shown that increased levels of inflammatory markers predicts the development of T2D ((23), (24)) and even subclinical elevations have been shown to predict the development of T2D in the ARIC cohort (23, 25), particularly in the first 3 years (25).

Cross-sectional studies have shown that people with T2D, compared with those who do not have T2D, have poorer mental health (26), are more likely to be depressed (27, 28), to be alcohol dependent (29), and to have post-traumatic stress disorder (PTSD) (30). Type 2 diabetics report more chronic stressors (31), greater work distress (26) and exposure to a greater number of stressful life events (26). There is a socioeconomic gradient in T2D such that the lower the socioeconomic status (SES), the greater the prevalence of T2D (e.g., (32).

Above and beyond the SES-effect, disadvantaged minority populations are generally at greater risk of developing T2D (e.g., (33, 34)). The majority of these cross-sectional analyses controlled for the behavioural risk factors for T2D such as obesity, family history, poor diet and lack of physical activity. But cross sectional studies cannot be used to determine the
direction of causality or temporal sequence. It might be that coping with T2D could make people depressed and less likely to maintain the necessary health behaviours such as adhering to their diet. They may also tend to view the world negatively, and be more affected by, and likely to report, stressors. Thus, where possible, the remainder of this review focuses on longitudinal studies in which people begin free from T2D, but are exposed to stressors or reporting distress, and are followed to assess their risk of developing T2D.

Methodology

The nature of the review and classification process for the literature

A search in Medline of “stress” and “T2D” produces more than 1000 results, most of which are concerned with diabetes management. As our interest was in prospective studies we initiated the search process by focusing on identifying longitudinal studies. A search of “longitudinal” or “prospective” and “diabetes” was the starting point. This highlighted another issue – diabetes was rarely mentioned in either the title or abstract but was one of many health conditions listed in tables within the document. An additional strategy was to create a list of stress-related risk factors from the CVD literature to use in a further series of literature review.

An extensive review, covering the entire time period of the databases, was conducted in Ovid Medline, EbscoPsycArticles, Ebsco Psychology & Behavioral Sciences Collection, EbscoPsycINFO, Proquest Social Sciences Journals, Proquest Psychology Journals, and Sociological Abstracts from Cambridge Scientific Abstracts. We combined T2D with: depression, schizophrenia, Type A behaviour, psychosis, life events, stress(or), work/occupational stress, burnout, anger, distress, anxiety, education, income, occupation, poverty and mental health.

The initial database searchers produced 930 titles of which 39 papers (covering 32 cohorts) were relevant. The major reasons for exclusion were duplicates, not a longitudinal design, or because the papers were about following people who already had diabetes. With the exception of research on depression, which had published systematic reviews.,

The papers were reviewed in detail and the following factors abstracted: cohort name, country, size of study population, percent female, genders combined or split in analysis,
length of follow-up, how the diabetic status was determined, and other factors included in the
analysis.

The stress-related factors were classified into four broad categories for this review: 1) subjective and objective exposure to stressors, 2) mental health, 3) aggressive behaviour and conflict, and 4) living at the bottom of the social status hierarchy.

Results
Length of follow-up varied from 1 to 60 years and the majority of the studies had very large sample sizes (see Table 2). The majority of cohorts were developed for a purpose other than predicting the development of T2D. When the information was available, depending upon the data source, the analyses included the known clinical and behavioural risk factors in the final statistical models (see Table 3). Most of the behavioural risk factors were included as control variables and the relationships not reported. But in the few studies where they were reported the findings are similar to those seen in cross-sectional studies; i.e., an increasing risk for the development of T2D is associated with increasing age (35), body mass index (BMI) (36), waist girth (37), and is greater in people with hypertension (38), limited physical activity (39), and those who are smokers (40).

Subjective and objective exposure to stressors
Self-reported feelings of stress and/or exposure to stressful life events or circumstances are often cited as a significant factor in precipitating health problems (e.g., (41)). Using the terminology we described earlier, the literature examining the role of ‘stress’ in the development of T2D is divided into ‘distress’ and ‘stressors’.

Two longitudinal studies have examined the relationship between T2D and self-reported “mental stress” (distress) level. One, following only women, found no relationship after controlling for general mental health (39), while the other found an association only in males (42). As people’s ability to accurately describe their personal stress burden has been questioned (43) some researchers prefer to rely on more objective measures such as inventories of life events that are generally acknowledged as traumatic or life-altering. Finnish researchers followed people who were child evacuees during World War II (44) and
found an increased risk for developing T2D in midlife even after controlling for age, gender
and SES. The United Kingdom (UK) Whitehall II Study asked participants about life events
such as death of a friend or relative, marital problems or accidents over the previous 12
months and found a non-significantly increased risk of T2D in multivariate models that
included other stressors and risk factors for T2D (36). Moderate and severe childhood abuse
has been shown to increase the risk for T2D in a dose-response fashion even after controlling
for the conventional risk factors (45). The US National Comorbidity Study has also
demonstrated a relationship between childhood neglect and mid-life diabetes (46) after
controlling for age, gender, ethnicity and SES.

Objectively-determined stressful work conditions from questions that ask about specific
stressful characteristics of work have been linked to an increased risk of subsequent CVD,
but there have been few attempts to extend this work to T2D. The Japanese have used their
system of annual medical check-ups in large occupational cohorts to look at several aspects
of work that are presumed to be stressful (35, 40, 47, 48). For example, this routinely
collected data have shown an elevated risk for the development of T2D in those who work
extensive overtime (35), and those who found the introduction of new technology stressful
(47). In both studies the associations remained after controlling for an extensive list of
behavioural risk factors for T2D (47). In the overtime study the researchers also found a non-
significant increased risk of T2D in shift workers compared with white collar (non-shift)
workers (35) which may be due to either shift work or social position within the occupational
social hierarchy. Alternating shift work was associated with a greater the risk of T2D along
with age, BMI, liver enzymes, and lack of exercise in another Japanese occupational cohort
(48). A study of the British Civil Service (49) found a doubling of the risk for diabetes in
women, but not men exposed to job strain (a measure of work stress).

This echoes one of the key features of the impact of occupational stressors in the
development of CVD; the different responses in men and women, sometimes with
associations operating in opposite directions (e.g. (12)). Much of the gender differences have
been attributed to differences in social support at work. For example, in Sweden, T2D
research using a nested case-control study design found that low emotional support increased
the impact of job strain (a commonly used measure of work stress) on T2D development in
women but not men (50) even though men and women reported similar levels of emotional
support.
A recent neuroscience review concluded that stressful life events that involve social rejection are more likely to precipitate depression with downstream PSR (51). And effects of traumatic live events can be long lasting. A Danish database linkage study found that parents who experienced the death of a child were at increased risk of developing diabetes for up to 18 years after the bereavement (52).

Overall, objective measures of stressor exposure are associated with a greater risk of developing T2D but gender differences may occur. The limited amount of research into distress (perceived stress) does not suggest a greater risk for those perceiving their lives as more stressful.

**Mental health and the development of T2D**

We posit that severe, rather than minor, mental health problems are a chronic stressor and it is well established that depression and T2D are co-morbid conditions with a bidirectional relationship between them (53). Three systematic reviews (28, 54, 55) have found an overall small, but statistically significant, increased risk for the development of T2D in people with depression, with the latest reporting an overall risk estimate of 1.17 (confidence interval: 1.05, 1.29). It is because we think the mental health condition has to be severe enough to activate the PSR that we re-examined the nature of the mental health measure within this literature.

It is interesting to note that while the quality of the T2D diagnosis was evaluated in one of these reviews (28), the quality of the depression diagnosis was not. Examining the papers cited in the reviews, and others published since then, we noted that the more clinically robust the instrument used to classify the depression, the more likely the study was to find a significant association between T2D and a previous diagnosis of depression (56, 57) or depressive symptoms (37, 38, 40, 58). Those studies defining depression by utilizing depressive symptoms collected within a general mental health scale were less likely to find a statistically significantly elevated risk (36, 59) although some did (60, 61). These findings need to be reproduced in a full systematic review.

**Table 1 Associations between mental health measures (ranked from most to least robust) and risk of developing T2D**

<table>
<thead>
<tr>
<th>Study Population (ref)</th>
<th>MH measure</th>
<th>findings</th>
<th>controlled for conventional factors?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baltimore Epidemiologic Catchment</td>
<td>Diagnostic Interview</td>
<td>sig ↑</td>
<td>yes</td>
</tr>
<tr>
<td>Medical Practice Database (57)</td>
<td>Schedule</td>
<td>Sig ↑ only in M &lt;50</td>
<td>Some</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>------</td>
</tr>
<tr>
<td>Study of Women's Health Across the Nation (37)</td>
<td>CES-D</td>
<td>Sig ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Multiethnic Study of Atherosclerosis (58)</td>
<td>CES-D</td>
<td>Sig ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Massachusetts Male Aging Study (38)</td>
<td>CES-D</td>
<td>Sig ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Occupational Health Cohort (40)</td>
<td>Zung self-rating depression scale</td>
<td>Sig ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Healthy Women Study (62)</td>
<td>Beck Depression Inventory</td>
<td>Sig ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Atherosclerosis Risk in Communities (63)</td>
<td>Vital exhaustion</td>
<td>Sig ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiovascular Health Study (65)</td>
<td>Depressive symptoms</td>
<td>Sig ↑ in least educated only</td>
<td>Yes</td>
</tr>
<tr>
<td>Whitehall II (36)</td>
<td>GHQ + depression subscale*</td>
<td>Ns</td>
<td>Yes</td>
</tr>
<tr>
<td>Nurses' Health Study (59)</td>
<td>Depressive symptoms from SF-36</td>
<td>Ns ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Stockholm Diabetes Prevention Programme (61)</td>
<td>Psychological distress</td>
<td>F ns; male sig ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Australian Women's Health Survey (39)</td>
<td>SF-36 mental health</td>
<td>Sig ↑</td>
<td>Yes</td>
</tr>
<tr>
<td>English Longitudinal Study of Aging (66)</td>
<td>SF-36 mental health</td>
<td>Ns</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Sig - statistically significant; Ns = not statistically significant; ↑ = increasing score associated with increasing risk of diabetes; M = males; F = females

* Created by factor analysing the GHQ

Interactions with socioeconomic status (SES) and gender were noted in these studies of depression. Two studies found an interaction with education (56, 60) such that individuals with low education and depression are at greater risk for the development of T2D than those with more education and depression and those with neither risk factor. Again, gender differences are seen with two studies also found an association of T2D with depression in males but not in females (57, 61).

“Vital exhaustion” and “burnout” are two conditions which share many features with depression. Vital Exhaustion’ (VE) (or burnout syndrome) is characterised by: 1) feelings of excessive fatigue and lack of energy; 2) increased irritability; 3) feelings of demoralisation (67). American researchers found a significantly increased risk of T2D in the top, as compared to the bottom, quartile of the VE scale (63) and Israeli workers, who met the criteria for burnout, were at increased risk for developing diabetes over the subsequent three to five years (64).
Do mild non-specific mental health problems (everyday strains) increase the risk of diabetes or is it only severe problems? The research findings are mixed. Of three studies that have prospectively examined whether poor scores on general mental health scales (SF-36 and GHQ) predict an increase in the development of T2D, two report a non-significant increase (36, 66) and one reports a statistically significant increase (39). These studies were large and the analyses included many of the conventional medical risk factors for T2D and should have been able to identify an association if one were present.

There is very little longitudinal research prospectively examining the role of positive mental health and disease, possibly because there are considerably fewer measures of positive mental health. A high sense of coherence (SOC) which is a measure of a positive orientation towards life (68) has been associated with lower mortality from all causes, CVD and cancer (69). A low SOC score (poorer mental health) has also been associated with an increased incidence of T2D in Finnish men over the subsequent 17 years (70).

In summary, there is sufficient evidence from prospective studies to conclude that depression leads to T2D with only a small risk of the reverse (T2D increasing the risk for depression) (58). In addition, our review suggests that mild mental health problems are less likely to be associated with an increase in T2D risk than more severe mental health problems. The relationship between positive mental health measures and T2D development needs more investigation.

**Aggressive behaviour and conflict with others**

Aggressive behaviour and higher levels of anger in experiences of conflict are positively correlated with the development of CVD (71). Research on a similar relationship for T2D, with a few exceptions, has not been recognised. We take the perspective that angry and aggressive behaviour puts people in conflict with others and is likely to chronically activate the PSR.

Using a retrospective review of primary care medical records, McDermott et al., identified psychiatrist- or psychologist-diagnosed schizophrenia or affective psychoses and examined their subsequent co-morbid physical health conditions (72). They found a non-significant increase in T2D for schizophrenics and a statistically significant increase in patients diagnosed with affective psychoses after controlling for age, race, gender, smoking,
obesity, hypertension and depression. The authors noted that the affective psychoses patients were more likely to develop T2D earlier.

The type A behaviour pattern is hypothesized to activate the PSR and a person with this personality is dominating, hostile, aggressive and impatient which often puts them in conflict with other people. Japanese researchers found that the risk of T2D increased with increasing level of type A behaviour in women but not men (42). Similarly, in a group of aging middle-aged and older men, the Massachusetts Male Aging Study failed to find a relationship between the subsequent development of T2D and dominance (from a subscale of the Jackson Personality Research Form E) (38). The Atherosclerosis Risk in Communities Study found no overall relationship between trait anger measured with the Spielberger Trait Anger Scale and the onset of T2D but those in the top tertile of scores were 34% more likely to develop T2D than those in the lowest tertile (73).

In summary, the hypothesis that these conditions and personality traits put people in conflict with others and are thus stressful is not widely recognized, there is little research and the theory needs a systematic research agenda to confirm it.

**Effects of position in the social status hierarchy**

It well established that living in poor economic circumstances affect people’s health but it is only within the last few decades that we have come to recognize that there is a social gradient in health such that even middle-class people have more disease and shorter life expectancy than people just a step higher in the social hierarchy (74). Socioeconomic status (SES) is the most studied measure of social position and in developed countries it is typically measured as education, income and/or occupational prestige.

While it has been shown that the prevalence of health-adverse behaviours increases with decreasing social position (26, 75, 76) it has also been shown that there is increasing exposure to stressors such as poor social circumstances and psychological challenges (74). For example, Canadian data has shown that self-reported chronic stressors ranging from marital, neighbourhood, job, financial and life stressor were all more common as income decreased (77), and Monden et.al., demonstrated that people with lower education reported significantly more stressful work factors (78).

It has repeatedly been demonstrated, in cross-sectional studies, that T2D rates increase with decreasing socioeconomic position (e.g., (32, 79)); but it has been argued, without clear
evidence, that having T2D affects a person’s ability to maintain a high social standing. There
is a need for longitudinal studies demonstrating that having T2D changes a person’s SES to
support this view.

Most of the longitudinal studies in this review included SES, but generally as an adjustment
variable without reporting the relationship with T2D. A recently published systematic review
of 23 longitudinal studies (80) examined the relationship between SES and T2D incidence. It
found that the risk was significantly greater in the lowest compared to the highest SES group,
although the risk varied somewhat depending upon the specific measure of SES: RR
(95%CI); occupational prestige 1.31 (1.09, 1.57); education level 1.41 (1.28, 1.55); income
1.40 (1.04, 1.88). Subgroup analysis found higher risks in women than men, and when
medical records were used to determine diabetic status risk, it was greater than when self-
reports were used. The overall SES of an area has also been demonstrated to have an
additional impact on the risk of T2D with Scottish researchers finding an increased risk with
increasing area deprivation (81).

The higher T2D prevalence in minority populations is usually attributed to a poorer
lifestyle (e.g., (33)) and lower SES. But some studies have reported greater risk for minorities
that have higher education and income (e.g., (82)) and there has been a call to focus more on
the stress-related risks of minorities rather than just on health behaviours (34).

The thrifty-gene hypothesis suggests that some ethnic groups with a history of famine
have developed a ‘thrifty gene’ that increases their risk of diabetes in a non-famine
environment. This hypothesised gene would allow them to fatten more quickly in times of
food abundance, but in modern society it prepares them for a food scarcity which no longer
occurs. This hypothesis continues to be invoked to explain high rates of T2D in minority
populations (e.g., (83)) in spite of other researchers finding that low SES explains most of the
relationship in some populations (34) and the fact that many of the populations at risk have
no history of famine or starvation (e.g. Pacific Islanders).

Socioeconomic status in childhood has also been linked to the development of T2D in
midlife. A recent systematic review of the effects of early childhood concluded that there is
evidence that childhood neglect, trauma or deprivation increase the future risk of T2D (84).
For example, using data from the 1958 Birth Cohort, researchers sought to distinguish the
effect on T2D risk among: 1) stressful emotional or neglectful childhood adversities; 2) other
childhood factors, such as material disadvantage; 3) adult health behaviours (smoking,
alcohol consumption, diet, and physical activity and; 4) adult SES in the development of T2D.

In multivariate analysis only poor-quality parenting associated with neglect and early childhood adversity was significantly associated with the development of T2D (85).

As has been seen in other sections, gender differences exist and it may be that there is an interaction between birth and current SES that is more important in one gender than the other. For example, the Alameda County Study found childhood SES was a risk factor for adult T2D in women, but not men after adjusting for a wide array of behavioural risk factors (86), and the Nurses’ Health Study found an increased risk of T2D only for women whose father was “blue or lower white collar”.

Relevant to this hypothesis was the finding, in two US Studies, of an interaction between depression and low social status (56, 60) which found the increased risk of developing T2D only in those with both depression and low social status after controlling for behavioural risk factors.

The fact that SES has been shown to interact with depression and differ in relevance by gender suggests that the inclusion of SES in analyses needs to be more carefully considered and not merely an adjustment variable in analysis. Each measure of SES (education, income and occupational prestige) could provide different pathways/mechanisms to connect stressful conditions with the development of T2D and measures of SES should be included in any analysis of risk factors for the development of T2D.

As a result of this review, we propose a new model of how exposure to chronic stressors increases the risk of developing T2D (Figure 1).
Discussion this review paper has explored the association between T2D and PSF focusing on prospective studies of the risk for developing diabetes/T2D. It has identified a wide array of stress-related circumstances were associated with T2D in longitudinal studies. Even after controlling for conventional risk factors an increased risk for T2D is seen in people: exposed to stressful working conditions or traumatic life events; with depression; with personality traits or mental health problems that put them in conflict with others (such as those with Type A personality or schizophrenia); of low SES either currently or in childhood; and in minority populations independent of current SES. The amount of research available to support this hypothesis varies considerably with the most literature for mental health conditions and SES, and the least for aggressive behaviour and stress exposure. And the most significant finding is the lack of attention paid to recognise a direct pathway in addition to a behavioural pathway.

The hypothesised PSR mechanism is supported in the literature. Inflammatory marker levels (an indicator of PSR) have also been demonstrated to increase with decreasing SES (93) and to be greater in minority populations (94) suggesting a common mechanism for all these social hierarchy stressors.

Our hypothesis that severe mental health problems are a chronic stressor, is supported by the finding that inflammatory markers are increased in major depressive disorder (57) and social rejection, social isolation and interpersonal stress have all been shown to activate the PSR (55). Only two of the studies in this review measured inflammatory factor levels {Carnethon, 2007 #20} {Golden, 2008 #15} and neither reported the individual effect of inflammatory factor levels on the risk of diabetes as both studies were concerned with the effect of depression on the development of diabetes. Published reviews have suggested a PSR model to explain the link but the reviewers report that there is little research to support this model (77) and the role of antipsychotic medication on glucose metabolism is also unclear (78). We also note that mental health patients might be more clinically scrutinised and more likely to have diabetes diagnosed earlier.

While, for the most part, these studies have been conducted with large study populations and most analyses adjusted for other risk factors for T2D, many did rely on self-reports of both T2D and the stress-related measure. Self-reports are considered less reliable measures than ‘objective’ measures. As such, biochemical confirmation of diabetic status and robust measures of depression, rather than depressive symptoms would present a stronger argument. Still, one would have to argue that both the T2D and stress-related measure were consistently misreported in the same direction for this to bias the results in any one particular direction.
More likely, misreporting reduces the possibility of finding an association when one actually exists by increasing the overall error in all components.

If we accept this working hypothesis then the results of much of the research reported here would be reported differently and would attribute risks beyond the individual. For example, Blacks et al's explanation for very high rates of T2D in minority populations is an example of the new way of thinking about the aetiology of T2D. The authors concluded that “a significant relationship between internalized racism and glucose intolerance might be mediated through abdominal fat” (23). By combining pathways prescribed by the traditional behavioural model with activation of the PSR by stress-related factors, Black et al made a plausible conjecture that is increasingly supported by empirical evidence from other research.

That is (see figure 1),

1. Stress-related factors influence PSR activation, which is highly correlated with increased abdominal adiposity.
2. Visceral fat is highly correlated with inflammation and glucose intolerance, both of which are correlates of T2D.

**Future research and policy implications**

This review indicate the relative lack of attention paid to the role that stress-related factors may play in the development of T2D. We feel that a research model that integrates the behavioural model with stress-related factors needs to become the standard. But rather than considering any 'stress' as a risk factor we note that the review has also highlighted the fact that exposure to negative stress-related factors need to sustained and intensive for an effect to be seen. For example, mild distress was less likely to be identified as a risk factor for T2D than major depressive disorder. The health and research communities need to recognise that chronic stressor exposure (such as living in poverty) has a health impact that is more than just people behaving badly. This is entirely consistent with the WHO priority area “Tackling Social Determinants of Health” which forms part of their general programme of work 2014 – 2019.

The incorporation of stress-related factors also needs to become a priority area of diabetes research and support charities. Current policy around T2D interventions to try and reduce incidence and prevalence (e.g., [http://www.idf.org/node/2137](http://www.idf.org/node/2137)) still largely invokes a behavioural model (e.g., [http://www.diabetes.org.uk/About_us/What-we-say/](http://www.diabetes.org.uk/About_us/What-we-say/)). If diabetes...
organisations understood the effect of stress-related factors they could join in with the social
determinants of health agenda and lobby governments to change the social and economic
conditions which lead to avoidable health inequities. Given the number of people with T2D
there is the possibility of a powerful lobby for change.

**Conclusion**

This review provides consistent case to support the hypothesis that stress-related factors are a
cause of T2D independent of behavioural factors. The case would be substantially improved
if the hypothesis was accepted broadly and incorporated into future research on the risk
factors for the development of diabetes. This may be via reframing the research questions for
existing datasets or designing new longitudinal studies.

**Acknowledgements**

We would like to thank Peter Allmark for reviewing and proofreading this paper. The first
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Daniel, Matt Harren, Anne Taylor, Gary Wittert, Peter Lekkas, Leonie Segal, Karen Collins,
and Deb Jack. Apologies if anyone has been inadvertently missed.
Table 2 – Summary of the longitudinal studies included in this review

<table>
<thead>
<tr>
<th>Study population</th>
<th>publication year</th>
<th>country</th>
<th>N</th>
<th>follow-up time</th>
<th>T2D #</th>
<th>Chronic Stressors</th>
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<td></td>
<td></td>
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<td></td>
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<td>Age</td>
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<td>Follow-Up (years)</td>
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<td>5827 M</td>
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<td>Sweden</td>
<td>3100 F 2127 M</td>
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<td>2662 F</td>
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**Source of T2D information:** Clinical = diagnosis from laboratory measures and/or on diabetes medication.; medical records = from hospital/medical records,
<table>
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<th>Study population</th>
<th>Chronic Stress</th>
<th>demographic &amp; socioeconomic</th>
<th>medical &amp; physical measures</th>
<th>Behavioural</th>
<th>Other</th>
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<td>gender, education, childhood SES</td>
<td>BMI, waist girth, family history T2D, diabetes medication</td>
<td>alcohol, smoking, physical activity</td>
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<tr>
<td>Alameda County (95)</td>
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<td>age, ethnicity, marital status, type of health insurance</td>
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<td>BMI, waist girth/WHR, hypertension, lipids</td>
<td>diet, smoking, physical activity</td>
<td>geographic location</td>
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<td>gender, age</td>
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<td>geographic location</td>
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<td>BMI, CRP</td>
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<td>Outcome measures</td>
<td>Covariates</td>
<td>Location</td>
<td></td>
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<td>Danish Database Linkage Study (52)</td>
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<td>age, education</td>
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<td>hypertension, lipids, BMI, waist girth</td>
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<td>age</td>
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<td>age</td>
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<td>age</td>
<td>BMI, hypertension, family history T2D</td>
<td>alcohol, smoking, physical activity, coffee, sleep</td>
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<td>BMI, hypertension, family history T2D, menopausal status/HRT</td>
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<td>Confounders</td>
<td>Other Variables</td>
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<td>cohort (35)</td>
<td>Work conditions</td>
<td>age</td>
<td>hypertension, BMI, lipids</td>
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<td>occupational health cohort (48)</td>
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<td>alcohol, smoking, physical activity</td>
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<td>Still Working Study (70)</td>
<td>sense of coherence</td>
<td>age, marital status, education</td>
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<td>Stockholm Diabetes Prevention Programme (61)</td>
<td>Depression/distress/anxiety</td>
<td>age occupational prestige</td>
<td>BMI, family history T2D</td>
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<td>Study of Women's Health Across the Nation (37)</td>
<td>Depression/distress/anxiety</td>
<td>age, ethnicity, education</td>
<td>BMI, waist girth, glucose &amp; insulin, antidepressant use</td>
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<td>Vasterbotten Intervention Programme (50)</td>
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<td>gender, age, ethnicity, marital</td>
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<td>General mental health, work social support, Depression, work stress, life events, occupational prestige, material limitations</td>
<td>age, ethnicity</td>
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<td>age, gender, occupational prestige</td>
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<td>Anger trait</td>
<td>gender, age, ethnicity, education</td>
<td>BMI, WHR, hypertension, insulin, glucose, lipids, hypertension</td>
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BMI = body mass index; CRP = C-reactive protein
Literature cited

Acronyms
T2D – type 2 diabetes
SES – socioeconomic status
CVD – cardiovascular disease
UK – United Kingdom
PSR – physiologic stress response
SAM - sympathetic adrenomedular system
HPA - hypothalamic pituitary adrenal axis
PTSD – post traumatic stress disorder