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 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 forT2D 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.

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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 he 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

Study Population (ref)	MH measure	findings	controlled for conventonal factors?
Baltimore Epidemiologic Catchment	Diagnostic Interview	sig ↑	yes

Area Study (56)	Schedule		
medical practice database (57)	from medical records	sig ↑ only in M <50	some
Study of Women's Health Across the Nation (37)	CES-D	sig ↑	yes
Multiethnic Study of Atherosclerosis (58)	CES-D	sig ↑	yes
Massachusetts Male Aging Study (38)	CES-D	sig ↑	yes
occupational health cohort (40)	Zung self-rating depression scale	sig ↑	yes
Healthy Women Study (62)	Beck Depression Inventory	sig ↑	yes
Atherosclerosis Risk in Communities (63)	vital exhaustion	sig ↑	yes
occupational health cohort (64)	burnout	sig ↑	yes
Cardiovascular Health Study (65)	depressive symptoms	sig ↑ in least educated only	yes
Whitehall II (36)	GHQ + depression subscale*	ns	yes
Nurses' Health Study (59)	depressive symptoms from SF-36	ns ↑	yes
Stockholm Diabetes Prevention Programme (61)	psychological distress	F ns; male sig ↑	yes
Australian Women's Health Survey (39)	SF-36 mental health	sig ↑	yes
English Longitudinal Study of Aging (66)	SF-36 mental health	ns	yes

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 then 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 stessor 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 be 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 als' 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) still largely invokes a behavioural model (e.g., 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.

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Table 2 – Summary of the longitudinal studies included in this review

Study population	publication year	country	N	follow-up time	T2D #	Chronic Stressors
1958 Birth Cohort (94)	2007	UK	7518	45	Clinical or self report	Childhood SES
1958 Birth Cohort (85)	2008	UK	7784	45	Clinical or self report	Poor parenting
Alameda County (95)	2005	USA	3293 F 2854 M	34	self report	Education, income, occupational prestige
Alameda County (86)	2008	USA	3157 F 2756 M	34	self report	Education, income, occupational prestige, childhood SES
Atherosclerosis Risk in Communities (63)	2004	USA	15,972	6	Clinical	Vital exhaustion
AusDiab - Australian Diabetes, Obesity & Lifestyle Study (76)	2010	Australia	4405	5	Clinical	education, income, occupational prestige
Australian Women's Health Survey (39)	2006	Australia	8896 F	3	self report	General mental health, perceived stress, life events, poor social networks, education
Baltimore Epidemiologic Catchment Area Study (56)	2008	USA	1070	23	self report	clinically defined depression
Cardiovascular Health Study (65)	2007	USA	4681	10	Clinical	depression
Danish Database Linkage Study (52)	2005	Denmark	314,807 F 314,807 M	18	medical records	life events
English Longitudinal Study of Aging (66)	2006	UK	919	4	Clinical or self report	General mental health

English Longitudinal Study of Aging (96)	2012	UK	8578 F 8578 M	4	self report	income
Finnish Diabetes Prevention Study (97)]	2011	Finland	1593 F 789 M	1	Clinical	education, income, occupational prestige
Gifu Prefectural Centre for Health Check & Health Promotion (98)	2006	Japan	5130 M	8.4	Clinical	work stress
Gifu Prefectural Centre for Health Check & Health Promotion (98)	2006	Japan	13,537 M	7.4	Clinical	occupational prestige
Healthy Women Study (62)	2007	USA	432 F	15	metabolic syndrome	depressive symptoms, trait anger, trait anxiety, Framingham tension score, perceived stress, life events
Helsinki Birth Cohort (44)	2009	Finland	2003	37-50	Clinical	Early traumatic life experience
Japan Public Health Centre-based Prospective Study (42)	2009	Japan	55,826 F	10	self report	Type A personality, perceived stress
Massachusetts Male Aging Study (38)	2000	USA	1095 M	8	self report	Depression/distress/anxiety, other mental health cond
medical practice database (57)	2004	Netherlands	34,818 F 33,186 M	25	Clinical	Depression/distress/anxiety
medical practice database (72)	2005	USA	357	8	Clinical	Schizophrenia
Multiethnic Study of Atherosclerosis (58)	2008	USA	5201	5	Clinical	depression
National Comorbidity Survey (46)	2004	USA	4251 F 3847 M	retro-spective	self report	childhood abuse
NHEFS - NHANES I death followup (60)	2003	USA	6190	M=15.6	medical records or self report	Depression/distress/anxiety, education
NHEFS - NHANES I death followup (99)	2005	USA	6825 F 4244 M	M=10	Clinical	SES

Nurses' Health Study (59)	2004	USA	72,178 F	4	Clinical	depression
Nurses' Health Study (16)	2007	USA	100,330 F	16	Clinical	Childhood, partner and lifecourse SES
Nurses' Health Study (45)	2010	USA	67,853 F	16	Clinical	Lifetime abuse
occupational health cohort (64)	2006	Israel	677	3.6	self report	burnout
occupational health cohort (40)	1999	Japan	2764 M	8	Clinical	Depression/distress/anxiety
occupational health cohort (47)	1999	Japan	2194 M	8	Clinical	Work stress & conditions, education
occupational health cohort (35)	2005	Japan	3106 M	8	Clinical	Work conditions
occupational health cohort (48)	2006	Japan	5629 M	10	Clinical	Work conditions
Still Working Study (70)	2008	Finland	5827 M	18	Clinical	sense of coherence
Stockholm Diabetes Prevention Programme (61)	2008	Sweden	3100 F 2127 M	8-10	Clinical	Depression/distress/anxiety
Study of Women's Health Across the Nation (37)	2004	USA	2662 F	3	Clinical	Depression/distress/anxiety
Vasterbotten Intervention Programme (50)	2007	Sweden	1070	23	self report	Depression/distress/anxiety, education
Whitehall II (36)	2004	UK	2680 F 5950 M	M=10.5	Clinical	General mental health, Depression/distress/anxiety, work stress, life events, occupational prestige, material limitations
Whitehall II (49)	2009	UK	5895 F	11.6	Clinical	work stress
Whitehall II (100)	2012	UK	7237	14.2	Clinical	occupational prestige
Women's Health Study (73)	2006	USA	11,615	6	Clinical	Anger trait

 # Source of T2D information: Clinical = diagnosis from laboratory measures and/or on diabetes medication,; medical records = from hospital/medical records,

Table 3 Summary of the stress and other factors included in the longitudinal studies in this review

Study population	Chronic Stessor	demographic & socioeconomic	medical & physical measures	Behavioural	Other
1958 Birth Cohort (94)	Childhood SES	gender	BMI, waist girth, family history T2D, birthweight, other neonatal		
1958 Birth Cohort (85)	Poor parenting	gender , education, childhood SES	BMI, waist girth, family history T2D, diabetes medication	alcohol, smoking, physical activity	
Alameda County (95)	Education, income, occupational prestige	age, ethnicity, marital status, type of health insurance	BMI, waist girth, hypertension, regular access to MD	alcohol, smoking, physical activity	depression
Alameda County (86)	Education, income, occupational prestige, childhood SES	age, ethnicity, marital status, type of health insurance	BMI, height, waist girth, hypertension, regular access to MD	alcohol, smoking, physical activity	depression
Atherosclerosis Risk in Communities (63),	Vital exhaustion	gender, age, ethnicity, education	BMI, waist girth/WHR, hypertension, lipids	diet, smoking, physical activity	geographic location
AusDiab - Australian Diabetes, Obesity & Lifestyle Study (76)	education, income, occupational prestige	gender, age	waist girth/WHR, hypertension, lipids	smoking, physical activity	
Australian Women's Health Survey (39)	General mental health, perceived stress, life events, poor social networks, education	marital status	BMI, hypertension, menopausal status/hrt, physician visits	diet, alcohol, physical activity	geographic location
Baltimore Epidemiologic Catchment Area Study (56)	depression education	gender, age, ethnicity	BMI, family history T2D, regular access to MD, antidepressant use	diet, alcohol, smoking, physical activity	poor social networks
Cardiovascular Health Study (65)	depression	gender, age, ethnicity, marital status, education	BMI, CRP	alcohol, smoking, physical activity	

Danish Database Linkage Study (52)	life events	age, education			geographic location
English Longitudinal Study of Aging (66)	General mental health	gender, age, income	BMI, hypertension, glucose & insulin levels		geographic location
English Longitudinal Study of Aging (96)	income	age, ethnicity, marital status, education, occupational prestige, material limitations	BMI	alcohol, smoking, physical activity	
Finnish Diabetes Prevention Study (97)	education, occupational prestige	age	hypertension, lipids, BMI, waist girth		
Gifu Prefectural Centre for Health Check & Health Promotion (98)	work stress	age, education	BMI	alcohol, smoking, physical activity	
Gifu Prefectural Centre for Health Check & Health Promotion (98)	occupational prestige	age, education	BMI	alcohol, smoking	
Healthy Women Study (62)	depressive symptoms, trait anger, trait anxiety, Framingham tension score, perceived stress, life events	age, education	menopausal status/HRT	physical activity, alcohol, smoking	
Helsinki Birth Cohort (44)	Early traumatic life experience	age, gender, education, childhood SES			
Japan Public Health Centre-based Prospective Study (42)	Type A personality, perceived stress	age	BMI, hypertension, family history T2D	alcohol, smoking, physical activity, coffee, sleep	
Massachusetts Male Aging Study (38)	Depressive symptoms, other mental health cond	age	BMI, hypertension, sex hormone levels	alcohol, physical activity	
medical practice database	Depression	age, education, type of			

(57)		insurance			
medical practice database (72)	Schizophrenia, affective psychosis	gender, age, ethnicity	other chronic health conditions	smoking	
Multiethnic Study of Atherosclerosis (58)	depression	gender, age, ethnicity, education, income	BMI, lipids, insulin, inflammatory markers, hypertension,	diet, alcohol, smoking, physical activity	geographic location
National Comorbidity Survey (46)	childhood abuse	age, ethnicity, marital status, education, income			depression or anxiety disorder
NHEFS - NHANES I death follow-up (60)	depressive symptoms, education	gender, age, ethnicity	BMI	alcohol, smoking, physical activity	
NHEFS - NHANES I death followup (99)	education, occupational prestige, poverty index	age, ethnicity	BMI	diet, alcohol, smoking, physical activity	
Nurses' Health Study (59)	depression	age	BMI, hypertension, family history T2D, menopausal status/HRT	alcohol, smoking, physical activity	
Nurses' Health Study (16)	Childhood, partner and life course SES	age, ethnicity	BMI, hypertension, family history T2D, menopausal status/HRT, birthweight, breastfed	diet, alcohol, smoking, physical activity	
Nurses' Health Study (45)	Lifetime abuse	age, ethnicity, parents education	BMI, age 5 somatotype, family history T2D	smoking, alcohol	
occupational health cohort (64)	burnout	gender ,age, education	BMI, hypertension	alcohol, smoking, physical activity	
occupational health cohort (40)	Depressive symptoms	age	BMI, family history of T2D, other chronic health problem	alcohol, smoking, physical activity	
occupational health cohort (47)	Work stress & working conditions	age, education occupational prestige	BMI, family history of T2D	alcohol, smoking, physical activity	
occupational health	Work conditions	age	BMI, family history of T2D	alcohol, smoking,	

cohort (35)				physical activity	
occupational health cohort (48)	Work conditions	age	hypertension, BMI, lipids	alcohol, smoking, physical activity	
Still Working Study (70)	sense of coherence	age, marital status, education		alcohol, smoking, physical activity	self-reported health, distress
Stockholm Diabetes Prevention Programme (61)	Depression/distress/anxiety	age occupational prestige	BMI, family history T2D	smoking, physical activity	
Study of Women's Health Across the Nation (37)	Depression/distress/anxiety	age, ethnicity, education	BMI, waist girth, glucose & insulin, antidepressant use	physical activity	
Vasterbotten Intervention Programme (50)	work stress, education, social support	gender, age, ethnicity, marital	BMI		
Whitehall II (36)	General mental health, work social support, Depression, work stress, life events, occupational prestige, material limitations	age, ethnicity	BMI, height, hypertension, family history T2D	smoking, physical activity	
Whitehall II (49)	work stress	age, gender, occupational prestige	BMI, height, hypertension, lipids, CRP, family history T2D	diet, alcohol, smoking, physical activity	traumatic life events
Whitehall II (100)	occupational prestige	gender, age, ethnicity	BMI, hypertension, lipids	diet, alcohol, smoking, physical activity	
Women's Health Study (73)	Anger trait	gender, age, ethnicity, education	BMI, WHR, hypertension, insulin, glucose, lipids, hypertension	diet, smoking, physical activity	geographic location

BMI = body mass index; CRP = C-reactive protein

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Acronyms

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

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