

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

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

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26 **Keywords**

27 Physiologic stress response, socioeconomic status, health inequalities, prospective studies

28 **Abstract (150 words right now)**

29

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

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

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

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

43

44 **Table of Contents**

45

46	Keywords.....	2
47	Abstract (150 words right now)	2
48	Table of Contents.....	3
49	Introduction	4
50	Stress terminology	5
51	The stress mechanism hypothesis	5
52	Methodology.....	7
53	The nature of the review and classification process for the literature	7
54	Results.....	8
55	Longitudinal studies of subjective and objective exposure to stressors	8
56	Mental health and the development of T2D	10
57	Aggressive behaviour and conflict with others.....	12
58	Effects of position in the social status hierarchy	13
59	Discussion.....	16
60	A new model of the stress-related causation of T2D	Error! Bookmark not defined.
61	Future research and policy implications.....	Error! Bookmark not defined.
62	Conclusion.....	Error! Bookmark not defined.
63	Acknowledgements	18
64	Table 1 – Summary of the longitudinal studies included in this review	19
65	Literature cited.....	26
66	Acronyms	26

67

68

69

71 **Introduction**

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

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

87 T2D, like cardiovascular disease (CVD), has a prevalence that increases substantially with
88 decreasing social position. And, in the case of CVD, a solid body of research evidence
89 indicates that neither genetic factors nor lifestyle can fully explain socioeconomic status
90 (SES) gradients or ethnic disparities in the disease prevalence within a country (e.g.(2, 3),) or
91 explain differences in CVD rates between countries (e.g.,(4, 5)). And, it should be recognised
92 that while CVD and T2D share many common risk factors, only for CVD is there much
93 research on the role that stress-related exposure plays in the development of the disease. For
94 example, the mechanisms by which living in more difficult circumstances (for which low
95 SES is an indicator) might impact health are debated, but the most prominent theories
96 propose mechanisms such as cumulative exposure to stressors (allostatic load) (6), perceived
97 lack of control (7), and stress-related consequences arising from unfavourable social
98 comparisons (8). Much of the research describes the mechanism as ‘stress’ related, but the
99 terminology is inconsistent (9).

100 This paper will review the evidence concerning psychosocial factors and the development of
101 T2D, outlines possible mechanisms and make recommendations for future research and
102 policy directions. It begins with a clarification regarding the terminology of stress as this will
103 play an important role throughout.

104 **Stress terminology**

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

117 **The stress mechanism hypothesis**

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

124 One could plausibly argue that stress-related risk factors act via behavioural risk factors and,
125 indeed, most of the literature reviewed here does use this explanation. But, as will be seen
126 later, most of the studies in this review controlled the statistical analyses for many/most of the
127 behavioural risk factors and still found an effect from stress-related factors. For example,
128 some of the studies highlighted in this review have shown that risk is considerably greater for
129 those of low socioeconomic (16) or racial minority status (17) suggesting pathways above
130 and beyond the behavioural.

131 The immediate PSR is not thought to be the problem affecting health; rather chronic
132 activation of the PSR is thought to be the key. The role of the PSR is to maintain physiologic
133 homeostasis; it consists of an inter-related response from the sympathetic adrenomedullary
134 system (SAM) and the hypothalamic pituitary adrenal axis (HPA). Initially the SAM releases
135 epinephrine and norepinephrine but if the stressor is sustained the HPA comes into play. The
136 development of abdominal obesity, an important risk factor for diabetes, is a key step in the
137 development of the condition.

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

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

153 Cross-sectional studies have shown that people with T2D, compared with those who do not
154 have T2D, have poorer mental health (26), are more likely to be depressed (27, 28), to be
155 alcohol dependent (29), and to have post-traumatic stress disorder (PTSD) (30). Type 2
156 diabetics report more chronic stressors (31), greater work distress (26) and exposure to a
157 greater number of stressful life events (26). There is a socioeconomic gradient in T2D such
158 that the lower the socioeconomic status (SES), the greater the prevalence of T2D (e.g., (32).
159 Above and beyond the SES-effect, disadvantaged minority populations are generally at
160 greater risk of developing T2D (e.g., (33, 34)). The majority of these cross-sectional analyses
161 controlled for the behavioural risk factors for T2D such as obesity, family history, poor diet
162 and lack of physical activity. But cross sectional studies cannot be used to determine the

163 direction of causality or temporal sequence. It might be that coping with T2D could make
164 people depressed and less likely to maintain the necessary health behaviours such as adhering
165 to their diet. They may also tend to view the world negatively, and be more affected by, and
166 likely to report, stressors. Thus, where possible, the remainder of this review focuses on
167 longitudinal studies in which people begin free from T2D, but are exposed to stressors or
168 reporting distress, and are followed to assess their risk of developing T2D.

169

170 **Methodology**

171 **The nature of the review and classification process for the literature**

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

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

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

191 The papers were reviewed in detail and the following factors abstracted: cohort name,
192 country, size of study population, percent female, genders combined or split in analysis,

193 length of follow-up, how the diabetic status was determined, and other factors included in the
194 analysis.

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

198

199 **Results**

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

210

211 **Subjective and objective exposure to stressors**

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

216 Two longitudinal studies have examined the relationship between T2D and self-
217 reported “mental stress” (distress) level. One, following only women, found no relationship
218 after controlling for general mental health (39), while the other found an association only in
219 males (42). As people’s ability to accurately describe their personal stress burden has been
220 questioned (43) some researchers prefer to rely on more objective measures such as
221 inventories of life events that are generally acknowledged as traumatic or life-altering.
222 Finnish researchers followed people who were child evacuees during World War II (44) and

223 found an increased risk for developing T2D in midlife even after controlling for age, gender
224 and SES. The United Kingdom (UK) Whitehall II Study asked participants about life events
225 such as death of a friend or relative, marital problems or accidents over the previous 12
226 months and found a non-significantly increased risk of T2D in multivariate models that
227 included other stressors and risk factors for T2D (36). Moderate and severe childhood abuse
228 has been shown to increase the risk for T2D in a dose-response fashion even after controlling
229 for the conventional risk factors (45). The US National Comorbidity Study has also
230 demonstrated a relationship between childhood neglect and mid-life diabetes (46) after
231 controlling for age, gender, ethnicity and SES.

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

247 This echoes one of the key features of the impact of occupational stressors in the
248 development of CVD; the different responses in men and women, sometimes with
249 associations operating in opposite directions (e.g. (12)). Much of the gender differences have
250 been attributed to differences in social support at work. For example, in Sweden, T2D
251 research using a nested case-control study design found that low emotional support increased
252 the impact of job strain (a commonly used measure of work stress) on T2D development in
253 women but not men (50) even though men and women reported similar levels of emotional
254 support.

255 A recent neuroscience review concluded that stressful life events that involve social
 256 rejection are more likely to precipitate depression with downstream PSR (51). And effects of
 257 traumatic live events can be long lasting. A Danish database linkage study found that parents
 258 who experienced the death of a child were at increased risk of developing diabetes for up to
 259 18 years after the bereavement (52).

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

264 **Mental health and the development of T2D**

265 We posit that severe, rather than minor, mental health problems are a chronic stressor and it is
 266 well established that depression and T2D are co-morbid conditions with a **bidirectional**
 267 relationship between them (53). Three systematic reviews (28, 54, 55) have found an overall
 268 small, but statistically significant, increased risk for the development of T2D in people with
 269 depression, with the latest reporting an overall risk estimate of 1.17 (confidence interval: 1.05,
 270 1.29). It is because we think the mental health condition has to be severe enough to activate
 271 the PSR that we re-examined the nature of the mental health measure within this literature.

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

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

Study Population (ref)	MH measure	findings	controlled for conventional 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

283 sig - statistically significant; ns = not statistically significant; ↑ = increasing score associated
284 with increasing risk of diabetes; M = males; F = females
285 * created by factor analysing the GHQ

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

292 “Vital exhaustion” and “burnout” are two conditions which share many features with
293 depression. ‘Vital Exhaustion’ (VE) (or burnout syndrome) is characterised by: 1) feelings of
294 excessive fatigue and lack of energy; 2) increased irritability; 3) feelings of demoralisation
295 (67). American researchers found a significantly increased risk of T2D in the top, as
296 compared to the bottom, quartile of the VE scale (63) and Israeli workers, who met the
297 criteria for burnout, were at increased risk for developing diabetes over the subsequent three
298 to five years (64).

299 Do mild non-specific mental health problems (everyday strains) increase the risk of
300 diabetes or is it only severe problems? The research findings are mixed. Of three studies that
301 have prospectively examined whether poor scores on general mental health scales (SF-36 and
302 GHQ) predict an increase in the development of T2D, two report a non-significant increase
303 (36, 66) and one reports a statistically significant increase (39). These studies were large and
304 the analyses included many of the conventional medical risk factors for T2D and should have
305 been able to identify an association if one were present.

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

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

318

319 **Aggressive behaviour and conflict with others**

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

325 Using a retrospective review of primary care medical records, McDermott et al.,
326 identified psychiatrist- or psychologist-diagnosed schizophrenia or affective psychoses and
327 examined their subsequent co-morbid physical health conditions (72). They found a non-
328 significant increase in T2D for schizophrenics and a statistically significant increase in
329 patients diagnosed with affective psychoses after controlling for age, race, gender, smoking,

330 obesity, hypertension and depression. The authors noted that the affective psychoses patients
331 were more likely to develop T2D earlier.

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

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

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

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

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

359 It has repeatedly been demonstrated, in cross-sectional studies, that T2D rates increase
360 with decreasing socioeconomic position (e.g., (32, 79)); but it has been argued, without clear

361 evidence, that having T2D affects a person's ability to maintain a high social standing. There
362 is a need for longitudinal studies demonstrating that having T2D changes a person's SES to
363 support this view.

364 Most of the longitudinal studies in this review included SES, but generally as an adjustment
365 variable without reporting the relationship with T2D. A recently published systematic review
366 of 23 longitudinal studies (80) examined the relationship between SES and T2D incidence. It
367 found that the risk was significantly greater in the lowest compared to the highest SES group,
368 although the risk varied somewhat depending upon the specific measure of SES: RR
369 (95%CI); occupational prestige 1.31 (1.09, 1.57); education level 1.41 (1.28, 1.55); income
370 1.40 (1.04, 1.88). Subgroup analysis found higher risks in women than men, and when
371 medical records were used to determine diabetic status risk, it was greater than when self-
372 reports were used. The overall SES of an area has also been demonstrated to have an
373 additional impact on the risk of T2D with Scottish researchers finding an increased risk with
374 increasing area deprivation (81).

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

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

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

393 alcohol consumption, diet, and physical activity and; 4) adult SES in the development of T2D.
394 In multivariate analysis only poor-quality parenting associated with neglect and early
395 childhood adversity was significantly associated with the development of T2D (85).

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

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

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

412 As a result of this review, we propose a new model of how exposure to chronic stressors
413 increases the risk of developing T2D (Figure 1).

414

415 **Discussion** this review paper has explored the association between T2D and PSF
416 focusing on prospective studies of the risk for developing diabetes/T2D. It has identified
417 a wide array of stress-related circumstances were associated with T2D in longitudinal
418 studies. Even after controlling for conventional risk factors an increased risk for T2D is
419 seen in people: exposed to stressful working conditions or traumatic life events; with
420 depression; with personality traits or mental health problems that put them in conflict
421 with others (such as those with Type A personality or schizophrenia); of low SES either
422 currently or in childhood; and in minority populations independent of current SES.
423 The amount of research available to support this hypothesis varies considerably with
424 the most literature for mental health conditions and SES, and the least for aggressive
425 behaviour and stressor exposure. And the most significant finding is the lack of attention
426 paid to recognise a direct pathway in addition to a behavioural pathway.
427 The hypothesised PSR mechanism is supported in the literature. Inflammatory marker levels
428 (an indicator of PSR) have also been demonstrated to increase with decreasing SES (93) and to
429 be greater in minority populations (94) suggesting a common mechanism for all these social
430 hierarchy stressors.

431 Our hypothesis that severe mental health problems are a chronic stressor, is supported by the
432 finding that inflammatory markers are increased in major depressive disorder (57) and social
433 rejection, social isolation and interpersonal stress have all been shown to activate the PSR
434 (55). Only two of the studies in this review measured inflammatory factor levels {Carnethon,
435 2007 #20}{Golden, 2008 #15} and neither reported the individual effect of inflammatory
436 factor levels on the risk of diabetes as both studies were concerned with the effect of
437 depression on the development of diabetes. Published reviews have suggested a PSR model
438 to explain the link but the reviewers report that there is little research to support this model
439 (77) and the role of antipsychotic medication on glucose metabolism is also unclear (78). We
440 also note that mental health patients might be more clinically scrutinised and more likely to
441 have diabetes diagnosed earlier.

442

443 While, for the most part, these studies have been conducted with large study populations and
444 most analyses adjusted for other risk factors for T2D, many did rely on self-reports of both
445 T2D and the stress-related measure. Self-reports are considered less reliable measures than
446 'objective' measures. As such, biochemical confirmation of diabetic status and robust
447 measures of depression, rather than depressive symptoms would present a stronger argument.
448 Still, one would have to argue that both the T2D and stress-related measure were consistently
449 misreported in the same direction for this to bias the results in any one particular direction.

450 More likely, misreporting reduces the possibility of finding an association when one actually
451 exists by increasing the overall error in all components.

452 If we accept this working hypothesis then the results of much of the research reported
453 here would be reported differently and would attribute risks beyond the individual. For
454 example, Blacks et als' explanation for very high rates of T2D in minority populations is an
455 example of the new way of thinking about the aetiology of T2D. The authors concluded that
456 “a significant relationship between internalized racism and glucose intolerance might be
457 mediated through abdominal fat” (23). By combining pathways prescribed by the traditional
458 behavioural model with activation of the PSR by stress-related factors, Black et al made a
459 plausible conjecture that is increasingly supported by empirical evidence from other research.
460 That is (see figure 1),

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

465

466 **Future research and policy implications**

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

478 The incorporation of stress-related factors also needs to become a priority area of diabetes
479 research and support charities. Current policy around T2D interventions to try and reduce
480 incidence and prevalence (e.g., <http://www.idf.org/node/2137>) still largely invokes a
481 behavioural model (e.g., http://www.diabetes.org.uk/About_us/What-we-say/). If diabetes

482 organisations understood the effect of stress-related factors they could join in with the social
483 determinants of health agenda and lobby governments to change the social and economic
484 conditions which lead to avoidable health inequities. Given the number of people with T2D
485 there is the possibility of a powerful lobby for change.

486 **Conclusion**

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

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499

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

Study population	public ation 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 adrenomedullary system

HPA - hypothalamic pituitary adrenal axis

PTSD – post traumatic stress disorder

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