The multiple roles of life stress in metabolic disorders

Mika Kivimäki[1,2] ORCID 0000-0002-4699-5627

Alessandro Bartolomucci[3,4] ORCID 0000-0001-6439-8829

Ichiro Kawachi[5] ORCID 0000-0001-8488-1420

Author affiliations:

1 Department of Old Age Mental Health, Faculty of Brain Sciences, University College London, W1T 7NF London, UK

2 Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland

3 Department of Integrative Biology and Physiology, University of Minnesota, Minneapolis, MN 55455, US

4 Department of Medicine, University of Parma, Parma 43100, Italy

5 Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, Massachusetts 02115, US

Emails: m.kivimaki@ucl.ac.uk; abartolo@umn.edu; ikawachi@hsph.harvard.edu

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Abstract

The stress response is evolutionarily conserved across vertebrates to maintain homeostasis, but in excess can be damaging for body functions. We review the most recent research from basic sciences and epidemiology linking stress to the development and progression of metabolic disorders across the life course. Findings from rodents demonstrate that stress can affect features of metabolic dysfunction, such as insulin resistance, glucose and lipid homeostasis, as well as fundamental ageing processes such as cellular senescence and telomere length shortening. In human studies, stressors in the home, workplace and neighbourhood are associated with accelerated biological ageing and metabolic and immune alterations, both directly as well as indirectly via behavioural risks, including low physical activity, sleep disturbances, and alcohol abuse. The likelihood of developing clinical conditions, such as diabetes and fatty liver disease is increased in individuals with adverse childhood experiences or long-term stress at work or in private life – often as part of disease trajectories associated with other stress-related disorders, such as mental health problems, cardiovascular disease and increased susceptibility to infections. Among people with a metabolic disorder, stress may worsen disease prognosis. As favourable modifications in stressors are associated with reductions in incidence of metabolic disorders, the therapeutic value of targeting stress in personalised medicine merits further investigation.

Key points

- Both animal and human research suggests that stress and related changes in sympathetic-parasympathetic balance as well as hypothalamic-pituitary-adrenal axis can accelerate biological ageing, including unfavourable changes in metabolism and immune function.

- Childhood appears to be a sensitive period to stress exposure. The adverse impact on metabolic disease risk in adults with a history of childhood adversity is potentiated by mental disorders and behavioural risks and can be over 2-fold compared to those without childhood adversity.

- In relation to stress in adulthood, the excess risk of obesity, diabetes and liver disease is 1.1 to 1.4-fold. The excess risk of mental disorders, such as depression, and cardiovascular disease among individuals with stress in adulthood is slightly higher.

- Life stress is also a prognostic factor in patients, accelerating the transition of metabolic diseases towards multimorbidity, frailty and death.

The age-standardised burden of chronic diseases has declined world-wide over the past 30 years, but this has not been the case for metabolic disorders[1,2]. Between 1990 and 2019, obesity increased by 13% in women and 27% in men[3], while diabetes increased by 24%[1]. A similar trend has been observed for non-alcoholic fatty liver disease (NAFLD), which is strongly associated with obesity[2]. These trends combined with the fact that hyperglycaemia and obesity now rank as the third and fifth leading risk factors for the global burden of disease, respectively, underscore the need to refine our understanding of metabolic physiology and to identify additional targets for prevention of metabolic disorders[1,2].

One emerging risk factor for metabolic disorders is life stress, the topic of this Review. The physiological and behavioural responses to everyday challenges are evolutionarily conserved across mammals, birds, fish, reptiles, and amphibians. Most of the physiological responses activated to maintain homeostasis are short-lasting and adaptive with no harmful impact on body functions[4,5]. However, chronic or very intensive stressors characterised by uncontrollability and unpredictability can be damaging for body functions increasing disease susceptibility, particularly in vulnerable individuals[5]. Such stressors can also modify the course of disease among those already living with a disease.

In this Review, we evaluate the evidence on life stress as a risk and prognostic factor for metabolic disorders. Our focus is on a broad spectrum of stressors, ranging from adverse childhood experiences and major life events to chronic adulthood stressors and disadvantage. Our overview is organised according to the disease process. We begin with stress-related changes in metabolic traits and the phenomenon of accelerated ageing. Following these preclinical impacts, we evaluate the significance of life stress as a risk factor for clinical endpoints, with particular focus on obesity, type 2 diabetes and liver disease. To describe the role of stress in disease progression, we review clinical studies on patients with pre-existing

metabolic disease. We conclude the Review with a discussion of the implications of managing stress for prevention and treatment of metabolic diseases.

Stress measurement in human and animal studies

Rather than being a monolithic concept, "life stress" is considered a process that involves interactions between individual and environmental factors, current and past events, allostatic states, and psychological and physiological reactivity[4-6]. Accordingly, different approaches to measure stress and quantify the stress response and putative biomarkers have been developed. Measurement of stress has focused on one or more of 3 components: the conditions that elicit stress (i.e., stressors); stress appraisal; and the stress response (**table 1**).

Stressors. In animal models, several different stressors (i.e. agents causing a stress response) have been studied, including physical (e.g. foot shock), psychological (e.g. immobilisation) and psychosocial (social defeat, social subordination) factors. Among those stressors, social defeat in an aggressive encounter and subordinate status within a group or dyads have been studied extensively[5,7,8].

In human stress research, tasks which involve a social-evaluative threat (in which task performance could be negatively judged by others) have been found to elicit a measurable neuroendocrine stress response. One of the most widely used standardised stress induction protocols of this type is the Trier Social Stress Test in which subjects undergo a public speaking task followed by mental arithmetic[9].

Real-life stressors in human studies include adverse childhood experiences (e.g. family financial problems, psychological/physical abuse, death of parent), low socioeconomic status (e.g., low occupational position, living in socioeconomically disadvantaged neighbourhoods), major life events (e.g. divorce, job loss), natural catastrophes (war, earthquake, terrorist attack) and chronic adversity (e.g., daily hassles, work stress, caregiver stress, racial micro-aggressions

and social isolation)[10,11]. Several of these real-life stressors have been reproduced in animal studies as well[7].

Assessment of stress perception. A variety of individual factors are thought to affect stress perception (or stress appraisal), including personality, cognitive style, earlier stress exposure, behaviours, concurrent physiological responses and genetic vulnerability[10]. Stress appraisal is assumed to occur when an individual perceives that environmental demands tax or exceed their regulatory homeostatic range or adaptive capacity[4-6]. Thus, the same exposure can be viewed as stressful or not, depending on individual appraisal[12].

While stress appraisal (also referred to as cognitive stress response[10]) and stress-related emotions and behaviours (i.e., affective and behavioural stress responses) are typically assessed using self-administered questionnaires, more recent approaches have used eDiaries, health applications on mobile telephones, and wearable devices. These technologies allow for momentary assessment of how stressors are being perceived and enable these perceptions to be linked to physiologic changes using real time biometric data collection. This is a promising approach for integrated multidimensional data collection, although to date few large-scale studies have been completed[13].

Physiological stress response. The purpose of the homeostatic systems is to maintain optimal physiological functions under conditions of objective or perceived challenge[4]. In terms of health, a favourable profile consists of low basal stress-related hormone levels, acute activation in the presence of stressors, followed by rapid recovery. This physiological response is common to most daily responses to a variety of challenges, including mild stressors. In contrast, maladaptive processes potentially leading to clinical disorders, particularly when experienced during periods of rapid brain development, can result from intensive, repeated and frequent stressors, lack of adaptation, or inadequate responses that lead to compensatory hyperactivity of other physiological mediators[4,14,15].

The physiological stress response involves changes in brain neurocircuitry (e.g. the limbic forebrain, the hypothalamus and the brainstem[16]), which affect vigilance to sensory stimuli, produce emotional responses of fear and avoidance and can be imaged using functional MRI (fMRI) or ^{18}F-fluoro deoxyglucose PET/CT[17]. It has been shown that limbic regions intersect with circuits that are responsible for memory and reward, providing a means to tailor the stress response with respect to prior experience and anticipated outcomes[16].

The acute physiological stress response is well characterized and consists of the activation of several neuroendocrine circuits, including the hypothalamus–pituitary–adrenal (HPA) axis, the sympatho-medullary axis (SAM), the autonomic nervous system and other systems (**Figure 1;** for reviews of the neuroendocrine systems implicated in the stress response, see e.g.[14-16]).

Activation of the HPA axis results in secretion of adrenal glucocorticoid cortisol which is one of the most widely assessed stress effector and is also often used as a stress biomarker[11]. Cortisol can be measured in saliva, urine and blood samples, but due to large diurnal variation, repeat measures are necessary for meaningful assessment[18]. Cortisol is easy to measure repeatedly from saliva allowing determination of morning levels, the cortisol awakening response, and the slope in cortisol decline across the day. However, collection of data over months and years required to observe transitions from a healthy stage to the development and progression of stress-related morbidity may be difficult at scale. Hair samples provide a summary cortisol measure over a longer exposure period (months), but they miss potential stress-related disturbances in the diurnal regulation of cortisol.

Other major systems activated during stress include the SAM resulting in secretion of catecholamine adrenaline (and other factors) from the adrenal medulla and the sympathetic nervous system (SNS) resulting in noradrenaline (and other factors) secretion from nerve terminals and spillover to the general circulation[14-16]. These stress hormones are secreted very

rapidly (within fractions of a second after stress exposure) and are tightly controlled via synaptic reuptake or plasma clearance. Thus, to be useful as biomarkers, the blood collection needs to be carefully controlled and biofluids, including the urine, need to be preserved or frozen immediately after collection. For this reason, the secretion of catecholamines is often not measured directly, but rather determined indirectly via measures of heart rate variability, skin conductance or rarely direct nerve activation (activation of the SNS leads to increased heart rate, blood pressure, pulse pressure, and systemic vascular resistance). Activation of another branch of the autonomic nervous system, the parasympathetic nervous system (PNS, e.g. vagal tone) generally opposes SNS mediated effects and facilitates recovery from stress. Consistently, withdrawal of the PNS activity contributes to physiological stress reactions (e.g. reduced heart rate variability) and adversely affects the immune system[19].

Challenges in interpreting the evidence. Studies in laboratory animals complement research on humans as their shorter lives allow observation of the development of metabolic disorders across the entire lifespan[20]. Animal studies also allow for experimental manipulation and randomization of conditions which trigger stress (such as position in a status hierarchy), which would be either unethical or infeasible in human studies[21].

However, generalisation of findings from animals to humans can be challenging since there are differences in stress responsiveness across species. While the general pattern of neuroendocrine response to stressors is conserved in rodents and humans, including responsiveness of the autonomic nervous system and other neuroendocrine mediators, rodents have a more reactive HPA axis than humans. In the Trier Social Stress test (one of the most stressful acute experimental protocols[9]), the elevation of cortisol is on average only moderate and due to adaptation, repeating this test in the same subjects may lead to no clear HPA axis activation. Furthermore, while a sustained increase in HPA axis activation is commonly

observed in various social and non-social stress models in rodents[5,16], in humans several highly stressful conditions results in reduced (rather than normal) HPA activation and cortisol[14,15].

Another challenge involves extrapolations of the findings from neuroendocrine diseases (Cushing's syndrome or pheocromocytoma) or post-traumatic stress disorder (PSTD) to the general stress response. Cushing's syndrome (a condition characterised by excessive production of ACTH caused e.g. by a pituitary cancer, resulting in high cortisol) has been used as a model to study the possible long-term consequences of chronic hormone activation on function and health[22,23]. However, the excessive cortisol levels caused by Cushing's disease occur in the absence of stressors or activation of hypothalamic corticotropin-releasing hormone (CRH). Likewise, pheochromocytoma (a rare, usually noncancerous tumour in adrenal gland) and PTSD (a condition that develops in some people who have experienced a shocking, frightening, or dangerous event) have been used as proxy to understand the mediators of the stress response. Pheocromocytoma manifests itself with chronically increased plasma catecholamine levels which in some studies have also been found to be associated with elevated cortisol levels[24]. PSTD is associated with high catecholamine levels (sympathetic nervous system overactivation), but, unlike Cushing`s disease, low cortisol levels. Overall, these three conditions do not have a shared biology or pathophysiology, hence they can be only informative about specific mechanisms subserving the physiological stress response[25,26].

In observational studies, the technique of Mendelian randomization leverages randomly assigned genetic variation at conception as an instrument to examine the causal effect on disease onset[27]. The low levels of cortisol observed in PTSD and people with stressful life events[14,28,29] and null findings in Mendelian randomization analyses[27] suggest it is an oversimplification to treat high cortisol levels as a sole marker for harmful stress. Animal models confirm that HPA-axis activation per se is not a unique biomarker of chronic stress by demonstrating that high glucocorticoids exist in response to both stressful and pleasurable

stimuli[5]. Indeed, both high and blunted physiological stress response may characterise harmful conditions in humans, with the latter pattern suggested to be indicative of "burnout" as a result of extended exposure to stressors[4,30].

In terms of stress-related pathophysiology, disturbances in the 24-hour rhythm of circulating glucocorticoids (in addition to the levels of concentration) also play an important role[31]. Among all circulating factors showing a dynamic pattern of secretion, the circadian rhythm of plasma glucocorticoids is one of the largest (with values being generally highest in the mornings and lowest at night)[31]. In addition to a well-recognized circadian rhythm of cortisol secretion, significant knowledge is now available on ultradian rhythms and pulsatile cortisol secretion and their upstream mechanism (reviewed in[15,18]). When stress becomes chronic and cortisol levels stay elevated, the 24-hour glucocorticoid rhythm can be disrupted and part of the beneficial actions of cortisol are lost, particularly at the time of the usual nadir.

Because the physiological neuroendocrine stress response is variable and complex including many mediators, it is reductive to mechanistically explain the effect of stress only focusing on or measuring HPA axis activation[31-33].

Stress-related mechanisms and preclinical changes

Research has linked life stress exposure with indicators of adverse glycaemic and anthropometric changes, deterioration of immune function, and accelerated biological ageing[20,34-41] (**figure 1**). Many findings have been confirmed in studies which used different measurement methods or different stressors. Such verification of results across disparate lines of evidence — a technique called triangulation – strengthens validity, yet it does not necessarily prove causality. Studies have also highlighted that the associations between life stress and adverse biological changes may be partially attributable to (or even potentiated by) the higher prevalence of unhealthy behaviours and mental health problems among stressed individuals.

Changes in glucose and insulin metabolism. In cells, actions of glucocorticoids are mediated by the glucocorticoid receptors (expressed throughout the body) and mineralocorticoid receptors (expressed e.g. in the kidney, heart, colon, and specific brain nuclei[42]). Glucocorticoids are essential for the regulation of glycaemia and lipid metabolism, but they also regulate immunity, inflammation, growth, reproduction, and cardiovascular function[43]. Metabolic processes regulated by glucocorticoid receptors include lipolysis, hepatic gluconeogenesis, amino acid mobilization, and reduced skeletal muscle glucose uptake. It has been observed that in certain chronic stress conditions, hypothalamic activation of the pituitary changes from a predominant CRH-dominant to arginine vasopressin (AVP)-dominant regulation, and cortisol levels may remain raised due to decreased cortisol metabolism (in addition HPA-axis dysregulation)[15]. These changes contribute to higher glucose levels and insulin resistance. States of excess secretion of stress-related hormones, such as Cushing syndrome and pheochromocytoma, and systemic administration of glucocorticoids also induce insulin resistance[44,45]. In insulin resistance, metabolic tissues that are sensitive to insulin (e.g. skeletal muscle, liver, and white adipose tissue) become less sensitive to insulin increasing the risk of diabetes and fatty liver disease[46]. This may be one of the major pathways linking stress to metabolic disorders.

Epidemiological evidence supports this concept. An observational cohort study of 3,000 human participants aged 6–18 years at baseline and followed up for over 30 years via eight repeated biomedical examinations provides population-level evidence measured life stress using indicators of disadvantaged residential neighbourhoods[47] (**figure 2a**). While groups with high vs low life stress did not differ in metabolic traits at baseline, by early adulthood the high-stress group was characterised by increased blood lipid levels, decreased insulin sensitivity, and compensatory increases in insulin which, however, were insufficient to prevent elevated circulating glucose concentrations. By midlife, individuals consistently exposed to high stress

were more likely to be obese, hypertensive, and have a fatty liver and diabetes compared with those who were consistently exposed to low stress. In a randomised trial for patients with type 2 diabetes, stress management training was associated with a small but significant improvement in long-term glycaemic control[48].

Immune dysfunction and inflammation. There is a complex interaction between the physiological stress response and immune system activation[8,32,49,50]. One hypothesis is that exposure to chronic stress may induce glucocorticoid receptor resistance, a condition of reduced sensitivity of immune cells to glucocorticoids that normally terminate the inflammatory response[50]. According to this view, what matters is the way target tissue responds to stress hormones rather than the levels of the hormone per se. Glucocorticoid receptor resistance leads to increased duration and/or intensity of the inflammatory response contributing to the development and progression of insulin resistance, type 2 diabetes and cardiovascular disease. Experimental studies based on viral-challenge paradigm for groups with and without stressors, such as adverse life events, loneliness and severe disease of a child or spouse, support this hypothesis although assessment of glucocorticoid receptor resistance has relied on indirect data[50].

PNS activation leads to release of neurotransmitter acetylcholine to target tissues. Acetylcholine has an anti-inflammatory function as it binds to macrophage surface receptors blocking release of inflammatory cytokines including IL-1, -2, and -6, and tumour necrosis factor alpha (TNF-α). Conversely, activation of the SNS-mediated release of norepinephrine tends to increase the secretion of those molecules. Thus, stressful conditions associated with sustained SNS activity or withdrawal of the PNS may elevate the levels of these proinflammatory proteins contributing to chronic inflammation[19]. There is also a bidirectional communication between the immune systems and stress neuroendocrine axes, as certain cytokines can trigger the

223 activation of the HPA axis and the SNS. These include TNF-α, IL-1, and IL-6 produced at
224 inflammatory sites and elsewhere in response to inflammation[32].

225 Observational evidence from real-life settings supports associations between long-term
226 stress, altered immune function and metabolic changes. Prospective life course studies, for
227 example, have linked exposure to stressors at individual and community levels and stress
228 appraisal with increased systemic inflammation (circulating C-reactive protein and glycoprotein
229 acetyls) as well as worse glycaemic traits, high blood pressure and composite measures of
230 adverse metabolic profile (allostatic load)[39,47,51-56]. In the 1958 British Birth Cohort study,
231 psychological distress was more strongly associated with a composite metabolic index (C-
232 reactive protein, glycosylated haemoglobin, fibrinogen, triglycerides, total cholesterol, high-
233 density-lipoprotein cholesterol (reversed scored), blood pressure, resting heart rate) in
234 childhood than adulthood[51]. Supporting a dose-response pattern, psychological distress across
235 childhood and adulthood was more strongly associated with this metabolic index than
236 psychological distress in either childhood or adulthood but not in both[51] (**figure 2b**).

237 Evidence from clinical disorders is also converging (but see limitation to extrapolate
238 these results to the general population discussed above). Cushing's syndrome is associated with
239 proinflammatory state (increased circulating cytokines) and immune suppression (e.g. reduced
240 B- and T-cell count)[23,57,58] and other metabolic alterations (hyperglycaemia, hypertension,
241 dyslipidaemia). PSTD is also associated with alterations of inflammatory-immune activity (e.g.
242 elevated levels of the proinflammatory cytokines interleukin 1β, interleukin 6, and interferon
243 γ[59,60]) and elevated blood pressure[25,61], although little research suggests dyslipidaemia as an
244 important clinical feature of PTSD[25,62]. Furthermore, chronic catecholamine excess in
245 pheochromocytoma is accompanied by an increase in inflammation markers which is reversed
246 by the tumour removal[63].

Finally, epidemiological evidence also confirms the link between life stress and declining immune function at older ages. In the Health and Retirement Study, adulthood socioeconomic adversity and unhealthy behaviours was associated with age-related metabolic and immune biomarkers (included albumin, creatinine, glucose, C-reactive protein, lymphocyte percent, mean cell volume, red cell distribution width, alkaline phosphatase, and white blood cell count)[64].

Stress induced acceleration of biological ageing. Similar to stress, ageing is associated with impaired metabolic function including increased insulin resistance, impaired unrestrained hepatic gluconeogenesis and adipose lipogenesis, and increasingly defective glycogen synthesis and glucose uptake in skeletal muscle[65]. Many components of the immune system also change with age, including a rise in circulating inflammatory mediators, such as proinflammatory cytokines (which interfere with insulin action) and the overall down-regulation of immune responsiveness[66,67]. Parallels in the effects of stress and ageing are in agreement with the stress-induced accelerated ageing hypothesis. This hypothesis relies on the assumption that ageing is characterised by a gradual accumulation of damage to cells and tissues, and that this effect can be affected by external factors such as environmental exposures, lifestyle, diet, and diseases. According to the stress-acceleration of ageing hypothesis, life stress is one of the factors that accelerate biological ageing[68,69].

Supporting this notion, research suggests that stressors in childhood and adulthood stressors and chronically elevated stress biomarkers are not only linked to metabolic and immune dysfunction, but also other hallmarks of biological ageing[70], such as telomere erosion[69] and accumulation of senescent cells. The molecular mechanisms linking stress to senescence mechanisms are being actively investigated but this field is still in its infancy[38,71]. It has been observed that stress-induced glucocorticoid secretion generates reactive oxidative stress (ROS) via increased mitochondrial activity, potentially damaging telomeres and inhibiting telomerase

activity, both contributing to cellular senescence[72]. Cellular senescence appears to accumulate under stress conditions in animal models and humans[20,38], resulting in pro-oxidant, pro-inflammatory "senescence associated secretory phenotype" (SASP) which reinforces stress-induced systemic inflammation and cellular ageing[72]. A recent meta-analysis of nine human studies found an association between early life threat and biomarkers of cellular ageing, such as telomere length shortening in immune cells[73], although there was heterogeneity in study-specific estimates which also included some null findings. Positive findings were reported at least for caregiver stress[74]. Another meta-analysis based on a different set of studies concluded that there is a link between exposure to childhood trauma, lifetime PTSD severity and accelerated ageing as indicated by accelerated DNA methylation ageing[75]. Findings from the Environmental Risk (E-Risk) Longitudinal Twin Study found that children raised in more socioeconomically disadvantaged neighbourhoods may enter young adulthood epigenetically distinct from their less disadvantaged peers[76]. A recent review of studies on socioeconomic disadvantage in childhood and adulthood confirmed an association with accelerated epigenetic ageing[77]. Lastly, the Northern Finland Birth Cohort 1966 Study suggested that working long hours may contribute to age acceleration, although such an association was not observed for other work-related stressors, such as job strain and effort-reward imbalance[78].

Childhood could be a more sensitive period for adverse stress effects on biological ageing than adulthood. A systematic review including 13 animal and 27 human studies published since 2004 found consistent support for associations between early-life adversity and accelerated cellular ageing (89% of studies reported positive findings) whereas the evidence for parental stress and other adulthood psychosocial stressors was somewhat less consistent (67-70% positive findings)[79]. In the E-Risk study, there was a graded relationship between a higher number of childhood victimisations and more advanced biological ageing score at age 18

296 (**figure 2c**)[39]. In agreement with this observation, a meta-analysis suggested that early-life
297 adversity characterized by threat is associated with accelerated pubertal development[73].

298 **Impact of stress on body composition**. Obesity is a major driver of metabolic
299 diseases[80,81]. Computational tomography studies in humans and research on aged rodents
300 show that subcutaneous fat decreases, whereas visceral fat (the sum of fat depots inside the
301 abdominal cavity) increases with age[65,82]. Body weight tends to increase up to ~70 years of age
302 in humans and ~22 month of age in laboratory mice, while values decline at older ages in both
303 species with the weight loss being more pronounced in mice[20,82]. Osteoporosis and skeletal
304 muscle loss (sarcopenia) represent further age-related changes, increasing the risk of frailty at
305 older ages.

306 Fat tissue, skeletal muscle and bones are organs that respond to efferent signals from
307 hormone systems and the central nervous system and are therefore plausibly affected by life
308 stress. Supporting the hypothesis of stress-acceleration of ageing in humans, some studies
309 suggest chronic stress and stress hormone hypersecretion are associated with increased fat
310 mass, cellular dehydration, osteo-sarcopenia, and frailty[83]. In the Prospective Urban and Rural
311 Epidemiological (PURE) study of 120,000 people, those with higher composite indicator of life
312 stress (stress at work and home, major life events, and financial stress) had higher prevalence
313 of abdominal obesity compared to participants with low life stress[84]. Similarly, long-term
314 socioeconomic adversity has been related to small birth weight (a risk factor for diabetes) but
315 subsequent weight gain and obesity in a number of birth cohort studies (e.g. British Birth
316 Cohort 1958, UK, Dunedin cohort, New Zealand, the Southwest Finland Birth Cohort and the
317 Young Finns Study, Finland, the Dutch perinatal registry study, the Netherlands)[47,51-55,85,86].
318 Stress-induced hyperphagia has been demonstrated in humans and some animal models of
319 psychosocial stress[87].

However, not all the studies of stress and weight change have been consistent[88]. There may be stable individual differences in response to stress such that stress appraisal and stressors contribute to upward BMI trajectories for some people, downward trajectories for others and no weight change in still others[87,89]. This is likely to be mediated by dietary behaviour. Some people eat more in response to stress (hyperphagic), craving foods with high fat-salt/sugar content[89]. Others become hypophagic and eat less[89]. Differences in response to stress are supported by longitudinal studies[90] and a large cross-sectional individual-participant meta-analysis (IPD Work consortium) which reported increased prevalence of both obese and underweight individuals among those reporting work stress[91]. In animal models, physical and psychological stressors have been linked to negative energy balance, while psychosocial stressors appear to contribute to positive energy balance[87,92].

Behavioural pathways. Life stress can affect metabolic health directly through autonomic, neuroendocrine and immune responses, but also indirectly, through changes in health-related behaviours and mental health. Psychosocial stressors at work and in private life and PSTD have been linked to unhealthy behaviours which may partially mediate the stress-metabolic disease association. Large-scale cohort studies, such as PURE, and a meta-analysis of 61 cohorts found stressors at work stress and in private life to be associated with greater alcohol consumption[84,93], a finding consistent with the observation of higher alanine transaminase and gamma-glutamyl transferase levels in stressed men in another large study[94]. Longitudinal analyses of IPD-Work suggest a link between stress and lower physical activity[95] and PURE found greater smoking prevalence among participants with work stress[84]. Stress-related behavioural effects are also supported by research showing reduced physical activity and increased smoking in patients with PSTD[96,97].

In addition, sleep disturbances and short sleep are common under stress contributing to dysregulated homeostasis[97,98]. Population studies have shown exposure to stressful events

(such as major life events and daily hassles) may impair normal sleep function resulting in difficulty falling and staying asleep[99]. A review of major life events, life trauma and perceived chronic stress concluded that stress may be associated with impaired sleep[100]. A meta-analysis of 31 studies with polysomnography measurements found PTSD patients to have decreased total sleep time, slow wave sleep and sleep efficiency, and increased wake time after sleep onset compared with healthy controls[97].

The mediating role of disturbed sleep in the associations between life stress and metabolic disorders is biologically plausible as disturbances in the circadian regulation of stress hormones, cortisol in particular, are considered to contribute to pathophysiologies[31,101]. Critically, abnormal glucocorticoid rhythm, sleep disturbances and sleep loss are risk factors for insulin resistance, chronic inflammation, high glucose and cardiometabolic disorders, such as type 2 diabetes and cardiovascular disease[31,102-105].

Psychological mediators. Indirect effects through changes in mental health are also likely. In the Twins Early Development Study, adverse childhood experiences assessed between 3 and 11 years of age were associated with elevated depressive symptoms at age 21[106]. Meta-analyses of prospective cohort studies have reported increased risk of depressive symptoms and disorders in individuals with personal or neighbourhood socioeconomic adversity and work-related stress[107-109]. Furthermore, Cushing's syndrome is a risk factor for psychiatric disorders[57] and anxiety is a common symptom in patients with pheochromocytoma[110].

Similar findings have been reported from natural catastrophes. In a study from Iran, increased prevalence rates for anxiety and depressive symptoms, ranging between 40% and 65% were observed among individuals who were exposed to high-intensity warfare and chemical weapons in the 1980-1988 Iran-Iraq war[111]. The corresponding rates were lower, 6-18% among those exposed to low-intensity warfare. The prevalence of depression and PTSD increased among survivors in the aftermath of the 2011 Great East Japan Earthquake and

Tsunami[112]. Disaster-related trauma was also associated with marked increases in obesity, as well as elevated blood pressure and lipids, based on linkage to individual medical records before and after the disaster. Cardiometabolic risk was also correlated with the extent of housing damage (e.g., minor damage versus total destruction) caused by the tsunami[112].

Plausible biological pathways underlying the association between mental health problems and obesity include alterations in systems involved in HPA axis, immuno-inflammatory activation, neuroendocrine regulators of energy metabolism and brain circuitries integrating homeostatic and mood regulatory responses[113,114]. In a population-based register study of 5.9 million Danish people, those with mood or neurotic disorder, such as depression or anxiety, had approximately 1.5-fold increased risk of developing type 2 diabetes, liver disease or kidney disorders[115]. Other studies have identified a bi-directional association for type 2 diabetes and NAFLD, such that having these metabolic disorders also increase the risk of developing mental health problems[113,116-119].

Stress and risk of clinical disease

In light of the above-reviewed evidence on cardiometabolic and immune dysfunction and stress-acceleration of ageing amplified by unhealthy behaviours and mental health problems, an association of life stress with a broad set of clinical conditions is expected. Supporting this hypothesis, life stress has been linked to metabolic disorders, such as diabetes[7,22,25,120], fatty liver[23,121,122], and composite morbidity indices[123] in separate prospective studies across multiple stressors. This evidence is strengthened by the dose-response pattern observed between stress and risks of diabetes and liver disease across the life course: higher exposure to early life stress seems to increase adulthood disease risk in a graded fashion[7].

Outcome-wide studies. Outcome-wide studies allow an evaluation of the relative importance of stress in the aetiology of metabolic diseases compared to other health

conditions[91,109,124-133]. As shown in **table 2**, individuals exposed to stressors at work and private life and at community level have increased risk of mental disorders and cardiometabolic disease. Stressors across the life course are associated with about 1.1 to 1.4-fold increased risk of diabetes[124-129,131,132]. In people with childhood adverse experiences, the risk of adulthood cardiovascular, liver and digestive diseases, sexually transmitted infections, illicit drug use and mental disorders is particularly marked, 2- to 6-fold compared to those with no such experiences[124].

Cushing's syndrome presents with partially similar metabolic comorbidities and complications as seen in stress-related disorders, implicating ACTH and glucocorticoids in the sequalae of stress-induced metabolic changes. This notion is consistent with findings from studies on glucocorticoid receptor agonists, such as prednisone and cortisone, which are commonly used in the treatment of inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis) due their anti-inflammatory, immunosuppressive action. In line with findings for chronic stress, long-term use of oral glucocorticoids is associated with serious side effects, such as metabolic disease and increased risk of cardiovascular and inflammatory disease, and osteoporosis. However, caution should be taken because chronic steroid treatment leads to a blunted HPA axis activation, unlike chronic physiological stress. Additionally, the potency of oral glucocorticoids drugs is much higher than that observed for endogenous cortisol[134].

The scale of the problem (a horizontal comparison). Findings from large-scale studies and meta-analyses on various stressors in relation to obesity, type 2 diabetes and liver disease are summarised in **table 3**[23,96,124,125,131,132,135-150]. The relative risk estimates have varied between 1.1 and 1.5 for markers of stress, such as PSTD, workplace bullying, psychological distress, job strain, long working hours, effort-reward imbalance and stressful life events. Relative risk of liver disease associated with adverse childhood experiences was higher, almost

3-fold. As expected, the strongest link involves a primary neuroendocrine disease, Cushing's syndrome.

A horizontal comparison of these estimates to those from other metabolic risk factors suggests that life stress represents a moderate-size risk factor. Life stress is obviously associated with more modest excess risk of metabolic disease than major risk factors, such as obesity and intermediate hyperglycaemia (i.e. prediabetes). The relative risk of diabetes is approximately 7-fold for obesity and about 3-fold for overweight compared to normal weight[151]. The relative risk of type 2 diabetes for low versus high physical activity and for high vs normal triglycerides is ≈1.5-fold and thus of a similar or slightly higher order of magnitude than life stress[152,153].

Support for causality. While strong experimental evidence exists on mechanisms in cells and tissues activated by stress-mediators, these data may not fully inform processes that underlie the pathological effects of life stress. The physiological stress response is complex and includes both adaptive mechanisms to maintain homeostasis in a changing environment, and pathophysiological alterations that compromise health in relation to chronic and intensive stressors[4-6]. Many physiological stress mediators affect metabolic functions in different, sometimes opposite directions[87]. Additionally, the laboratory paradigm in humans does not allow extended time windows to explore chronic stress and randomization of people to different degree of real-life stressors is not possible or ethically acceptable. Given these limitations, the causal role of life stress in the development of clinical disease, such as metabolic disorders, cannot be proven by current evidence, although causality seems likely in light of the converging findings from multiple lines of research.

Stress and disease progression

It is important to evaluate evidence on risk of disease incidence separately from disease prognosis because the same exposure can increase the likelihood of developing a specific disease only marginally but affect progression of this disease substantially (or vice versa). While the same stress-related pathophysiological mechanisms that contribute to the development of metabolic disease may also worsen the outcome of the disease, additional effects of stress might also come into the play. For example, life stress is related to reduced self-care, both directly and via mental health problems, thereby posing a potential barrier for treatment adherence. Studies suggest that people with overweight and life stress benefit less from weight loss interventions than those without stress[100] and that financial strain among older adults is associated with lower medication adherence[154].

Adverse stress effects may be more pronounced among people with disease than healthy controls, exacerbating the development of complications and comorbidities. In an experimental study of 140 diabetic and 280 matched nondiabetic participants, for example, those with diabetes showed impaired post-stress recovery in systolic and diastolic blood pressure, heart rate and cholesterol and inadequate responses in other mediating pathways after a stress exposure (modified Stroop colour-word interference task and a mirror drawing task)[155]. Stress-induced elevation in cortisol and IL6 concentrations measured over the day were particularly marked in the diabetes group.

Disease complications and outcomes. Findings from real-life settings support the notion that stress may accelerate the progression of disease. In IPD-Work, work-related stress was not associated with total mortality among healthy employees, but a 1.6-fold increased risk of death was observed among stressed men with cardiometabolic disease (diabetes, myocardial infarction or stroke), with the contribution of stress being clinically significant and independent of conventional risk factors and their treatment[156]. A similar interaction was observed in another large-scale study of over 485,000 adults who participated in the National

Health Interview Survey[157]. During 8-year follow-up, severe psychological distress was associated with a 2-fold increased risk of death in individuals with diabetes but only 1.5-fold increased risk in non-diabetic people, while the corresponding relative risks were 2.0- and 1.4-fold for cardiovascular deaths. In other studies, psychological distress was associated with 1.4 to 1.8 times higher cardiovascular disease risk, all-cause mortality,[158] and liver disease mortality[144]. These findings in humans are paralleled by observations in randomised mouse models in which subordination stress (a model of low socioeconomic status) induced an earlier onset of lesions in multiple organs, resulting in significantly shortened lifespan when compared to mice high in social rank[20].

Disease cascades and multimorbidity. At least one outcome-wide study has examined the temporal sequence of the onset of multiple diseases during adulthood[125] (**figure 5a**). This multicohort study from Finland and the UK used linked electronic health records for disease ascertainment. The findings highlighted the importance of mental health and behavioural problems in setting in motion the development of a range of stress-related physical illnesses, such as liver and kidney diseases, ischaemic heart disease, cerebral infarction, and dementia among people with socioeconomic disadvantage. In contrast, the association of socioeconomic disadvantage with diabetes was largely independent of preceding mental health problems[125].

Diabetes, liver and kidney diseases in the socioeconomically disadvantaged group were strongly linked to subsequent cardiovascular diseases, suggesting that life stress may increase the risk of complications and multimorbidity among those with metabolic disease[125]. While liver diseases were additionally associated with increased risk of dementia, this was not seen for diabetes in the study population which included a relatively low number of elderly people[125]. Nonetheless, the majority of research evidence suggests that type 2 diabetes increases the risk of dementia[159] and also observational cohort studies have linked chronic work stress with increased risk of developing dementia in old age[160].

Mortality. Cumulative early life adversity and low social rank predict longevity in animal studies including mice, wild rabbits, meerkats, baboons, rhesus macaques, and long-tailed (cynomolgus) macaques baboons[7,20,161]. In humans, a range of stressors, including adverse childhood experiences[162], socioeconomic adversity[163], stressful life events (e.g. bereavement)[164,165], work stress[156], financial strain[166] and perceived stress or distress[167,168], particularly among those living with disease or multimorbidity, present risks for premature mortality[169] (**figure 5b**). According to results from the Whitehall II study, socioeconomic disadvantage affects disease progression from the development of first cardiometabolic disease to multimorbidity, frailty (a state of impaired function across multiple physiologic systems compromising the ability to cope with stressors) and death[170,171].

Impact of stress prevention

In the following section, we evaluate benefits and harms of selected interventions altering life stress in terms of metabolic health (**table 2**). In addition, we describe recommendations regarding stress reduction in current clinical guidelines for metabolic disease prevention.

Policies and interventions to reduce life stress. Societal interventions to reduce the amount of stress in people's lives lie outside the realm of health care at present. Examples of such structural interventions include the provision of income security through government safety nets, assuring access to the basic necessities of life (such as health care, housing, safe neighbourhoods, secure jobs), and improving the conditions of work (e.g. regulating over-time and work schedules, provision of paid sick leave and parental leave). Unfortunately, randomized trials evaluating the impact of social policies on population health remain sparse due to feasibility and cost, and the existing studies were under-powered to detect improvements in health outcomes[172]. Individual studies, such as the Moving to Opportunity (MTO) experiment in the United States provide some clue about the expected magnitude of

519 health improvement as a result of improving people's social circumstances. In the MTO, adults
520 living in disadvantaged areas in five US cities were randomly given the opportunity to move to a
521 less disadvantaged area[173]. Follow-up 10-15 years later showed that people who moved to a
522 less disadvantaged area had lower prevalence of extreme obesity and diabetes than did
523 members of the control group who were not given this opportunity. The incidence of having
524 BMI≥35 at follow-up was 31.1% in the experimental group and 35.5% in controls, the
525 corresponding incidence for BMI≥40 (morbid obesity) being 14.4% versus 17.7%.

526 In a large observational study from Finland (N=114,000), changes in health were
527 observed among people who experienced improvements in residential neighbourhood
528 conditions[174]. The risk of diabetes was 15% lower among residents of neighbourhoods where
529 unemployment dropped from high to low compared to those whose neighbourhood
530 unemployment rate remained high[174]. A further 'natural experiment' followed up 61,000
531 refugees who arrived in Sweden and were assigned to one of 4,833 neighbourhoods[175]. Being
532 assigned to an area deemed low deprivation versus high deprivation was associated with a 18%
533 lower relative risk of diabetes. Neighbourhood effects grew over time such that 5 years of
534 additional exposure to lower deprivation neighbourhoods was associated with a 9% lower
535 diabetes risk.

536 In summary, structural interventions hold the promise of addressing the root causes of
537 life stress but they have proved difficult to evaluate due to feasibility and cost. Meantime, in
538 the realm of health care, interventions have targeted individuals with the aim of reducing
539 health disparities.

540 **Individual level interventions and clinical guidelines**. Health care utilizes the high-risk
541 individual approach in which individuals at high risk of disease are targeted for treatment.
542 Stress management interventions to reduce stress perception and symptoms have shown
543 relatively little effect on risk or prognosis of metabolic diseases. A Cochrane review of

randomized controlled trials concluded that due to low quality of evidence from psychological interventions it remains unclear whether they can improve self-efficacy and glycaemic control, although psychological interventions added to usual care probably did not result in significant harm[176]. A subsequent systematic review and meta-analysis suggested minimal, if any, clinical benefit for psychological interventions in improving glycaemic control[177]. This result contrasts with findings on policy interventions, suggesting that psychological interventions to relieve stress are not addressing the root causes of stress-induced metabolic diseases.

Except for alcohol-associated liver diseases[178], there are only vague recommendations regarding stress reduction in clinical guidelines for metabolic disease prevention. This is appropriate given the current state of evidence, viz., modest findings from psychological interventions. The International Diabetes Federation (IDF), for example, recommends the following: “Be alert to signs of cognitive, emotional, behavioural and/or social problems which may negatively impact quality of life and complicate self-care, particularly where diabetes outcomes are sub-optimal” and that “Screening for depression with a validated tool should be encouraged in primary care diabetes clinics”. The recommendation by the American Diabetes Association is to follow a standardised diabetes prevention programme. The 16-session core curriculum includes sections on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviours, and psychological, social, and motivational challenges[179]. In the real world, however, patient adherence to treatment advice remains a significant hurdle in achieving health-care targets. According to personalised medicine, this should be addressed with more tailored management of patients, including, as necessary, psychological support as an adjunct to treatment[180], but to date, development of these approaches is still in progress.

Further approaches. A further suggested approach to mitigating the harmful effects of stress is through strengthening resilience. Benefits of building stress resilience by strengthening

social relations are supported by animal and human evidence. Research on wild macaques suggests that responses to social and environmental stress are attenuated by strong male bonds[181]. In chimpanzees, consolation has been shown to reduce behavioural measures of stress in recipients of aggression[182]. Even in rats, the adverse behavioural and physiological consequences of an aggressive interaction are more severe if the subject is subsequently housed in isolation rather than returned to its sibling group[183]. In humans, neighbourhood social capital and social cohesion have been associated with reduced risk of obesity, although the findings vary depending on the measures and covariates used[184,185].

Conclusions

Life stress is linked to a broad range of stressors in the home, workplace, and neighbourhood and studies have discussed life stress in terms of a general "predisposing risk factor", a source of "accumulated wear and tear", and a disturbed physiological state. In this narrative review of animal models, epidemiological research, and experimental and genetic studies, converging findings from many lines of investigation supported three general conclusions:

First, observational evidence suggests that life stress is an important prognostic factor for metabolic diseases, adversely affecting the course of disease. Long-term follow-ups highlight the importance of metabolic diseases as part of stress-related disease cascades during the lifecourse in which behavioural and mental health problems set in motion the development of a range of physical illnesses. These studies show that life stress does not only increase the risk of first metabolic disease, but also contributes to subsequent multimorbidity.

Second, several large-scale studies show that people with life stress are at increased risk of clinical metabolic disorders, including obesity, type 2 diabetes and fatty liver disease. The excess disease risk is not specific to metabolic pathologies but is also related to other non-communicable diseases and severe infections, with the link between life stress and

cardiovascular and mental disorders being slightly stronger than that with diabetes. In terms of effect size, horizontal comparisons suggest life stress represents a moderate size risk factor for metabolic diseases.

Third, there is evidence to suggest that life stress results in cumulative acceleration of biological age and senescence, including unfavourable changes in metabolism and immune function and exacerbation of genetic disease. In addition to these direct pathophysiological alterations, life stress may contribute to increased risk of metabolic disorders indirectly via mental health problems and unhealthy behaviours. Childhood appears to be a sensitive period during which long-term trajectories of adverse stress effects are likely to become established.

Further translational research is needed because population trends in metabolic disorders suggest that national prevention programmes, lifestyle interventions (weight reduction, increased physical activity, healthy diet, smoking cessation, moderation of alcohol consumption) and preventive medications (blood pressure-, lipid- and glucose-lowering therapies) have not been sufficient in reversing the continual growth in the burden of metabolic disease. Emerging evidence from structural interventions suggests that policies that reduce sources of life stress (e.g., via improving socioeconomic circumstances or strengthening social safety nets with the aim of reducing uncertainty in people's lives and increasing controllability of the social and physical environment) might complement individually-targeted approaches to metabolic disease prevention. Once metabolic disorder has developed, patient adherence to lifestyle and treatment advice poses a major barrier in achieving treatment targets and may be further complicated by the presence of daily stress. Additional evaluation in the context of personalised medicine is warranted to determine whether more individualised treatment regimes that take into account the patient's life situation could provide improved, cost-effective treatment options.

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Author contributions

All authors researched the literature for the article, provided substantial contributions to discussions of its content, wrote the article, and undertook review and editing of the manuscript before submission.

Competing interests statement

The authors declare no competing interests.

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Table 1**. Assessment methods of life stress by measurement focus, indicators and mode**

Focus	Indicator	Measurement mode*
Exposure to stressors	**Community level**	
	Neighbourhood socioeconomic disadvantage	S or M
	Catastrophical events (e.g. earth quake, 9/11 terror attack)	M
	Individual level	
	Trier Social Stress Test	E
	Adverse childhood experiences	S
	Major life events	S or M
	Socioeconomic disadvantage	S or M
	Work stress, parental stress, caregiver stress	S
	Loneliness, social isolation, lack of social contacts	S
	Animals in naturalistic settings	
	Subordinate status in stable social hierarchies	M + B
	Overall social rank instability	M + B
	Social conflict, aggression	M + B
	Animal models in laboratory	
	Chronic subordination stress	E
	Social instability stress	E
	Single prolonged stress (e.g. restraint)	E
Stress response	**Acute stress**	
	Blood/saliva/faecal/urine stress hormones (glucocorticoids, catecholamines)	B
	Implantable cardioverter–defibrillator recording + eDiary	M + S
	Chronic or repeated stress	
	Hair cortisol, allostatic load index	B
	Genetic variants of stress chemistry (Mendelian randomisation)	B
	Stress reactivity trait	E + B
	Post-traumatic stress disorder	D
	Cushing's syndrome (a stress hormone disorder)	D, B
Stress appraisal	**Retrospective and online reporting**	
	Psychological distress, symptom check lists	S
	Perceived stress, daily hassles	S
	Mobile monitoring (smart phone applications)	S

*Abbreviations: B, measurement of stress biomarkers (e.g. cortisol); E, external manipulation (e.g. Trier Social Stress Test); D, diagnosed condition; M, measurement of stressor (e.g. record of widowhood, death of child or neighbourhood disadvantage from national registries); S, self-report (e.g. questionnaire, interview, eDiary)

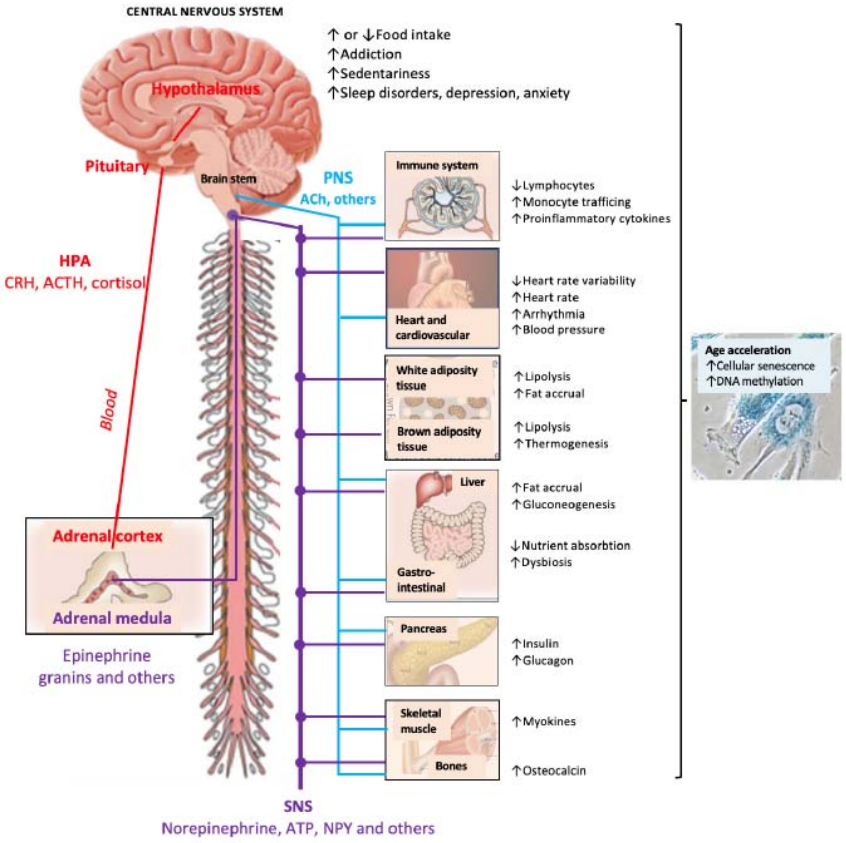

Figure 1. **Mechanisms of stress-induced metabolic changes.** The figure summarizes major neuroendocrine pathways and behavioural disorders implicated in chronic stress, affecting (either directly or indirectly) metabolic functions, risk of metabolic disease and the pace of biological ageing. Major stress-related pathways include: The Hypothalamus Pituitary Adrenocortical (HPA) axis secreted hormones, such as corticotrophin releasing factor (CRH), adrenocorticotrophin hormone (ACTH) and cortisol; the Sympatho-Adreno-Medullary axis secreted catecholamines (epinephrine>>norepinephrine), granins and other hormones and neuropeptides[34]; the Sympathetic Nervous System (SNS) secreted neurotransmitters, including norepinephrine, ATP, Neuropetide Y (NPY) and other factors[35,36]; and the Parasympathetic Nervous System (PNS) secreted neurotransmitters, such as acetylcholine (ACh) and other factors. SNS activation and PNS withdrawal contribute to stress reactions whereas PNS activation facilitates recovery[11,19]. In addition to classical stress-associated metabolic regulators (such as insulin), glucagon and several cytokines, myokines and osteocalcin[37] have been recently identified as regulators of the stress response. In addition, growing evidence suggest that stress can induce markers of immune senescence, DNA methylation and accumulation of senescent cells in multiple metabolic organs, including the liver, adipose and the brain[20,38-41,74].

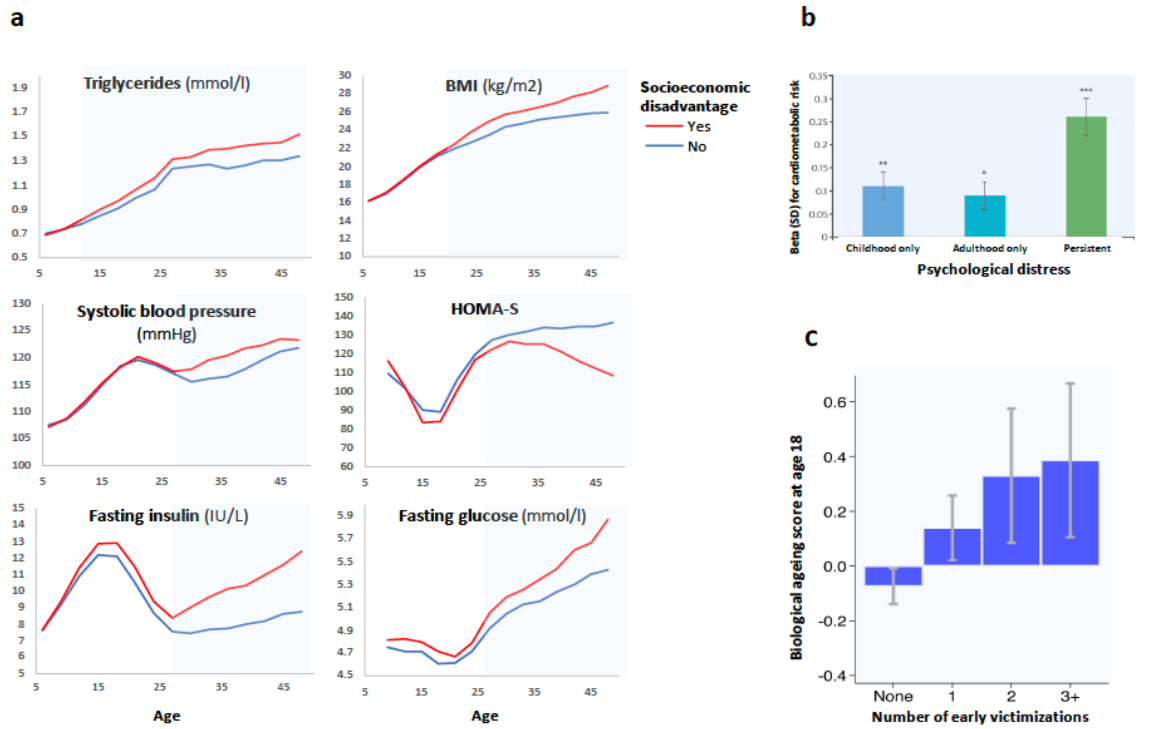

Figure 2**. Preclinical metabolic changes from childhood to adulthood in individuals exposed to stressors at individual level and in community and with stress appraisal. a** Repeated measurements from childhood to adulthood in the Young Finns cohort show no difference in metabolic traits between groups with vs without socioeconomic disadvantage at age 6 but gradually increasing differences in trajectories of triglycerides, glycaemic traits and BMI between these groups until age 48. **b** In the 1958 British Birth Cohort study, the association between psychological distress and a composite cardiometabolic index incorporating inflammatory markers is significant in both childhood and adulthood. Supporting a dose-response pattern, persistent psychological distress across both childhood and adulthood is more strongly associated with the cardiometabolic index than psychological distress in just childhood or adulthood but not both. **c** In the E-Risk study, there is a graded relationship between a higher number of childhood victimisations (domestic violence, peer bullying, physical and sexual harm by an adult, and neglect) and accelerated biological ageing score at age 18. Figures have been adapted from references [39,47,51].

Table 2**. Relative risk of health outcomes for life stressors (exposed vs non-exposed) in selected large outcome-wide meta-analyses and outcome-wide cohort studies**

Relative risk for a disease (descending effect)*	Stressor in private life		Stressor at work	
	Adverse childhood experiences	**Neighbourhood socioeconomic disadvantage**	**Long working hours**	**Job strain**
2.00 or higher (strong effect)	Sexually transmitted infections Illicit drug use Depression, anxiety Respiratory disease Liver or digestive disease Cancer, all sites Cardiovascular disease			
1.50 to 1.99		Stroke (intracerebral haemorrhage) Obesity requiring hospital treatment Self-harm COPD	Early cardiovascular death	
1.20 to 1.49	Overweight & obesity Diabetes	Lung cancer Substance abuse Mood disorders Viral infections Stroke (cerebral infarction) Liver disease Ischaemic heart disease	Atrial fibrillation Haemorrhagic stroke Obesity requiring hospital treatment Self-harm	Obesity (class II or III) Depressive disorder Coronary heart disease
1.10 to 1.19		Osteoarthritis Bacterial infections	COPD Lung cancer Substance abuse Heart failure	Stroke (ischaemic) Lung cancer Diabetes COPD

<1.10 or no effect	Colorectal cancer	Mood disorders	Asthma
	Breast cancer	Viral infections	Stroke (haemorrhagic)
	Prostate cancer	Diabetes	Any cancer

*Relative risks refer to hazard ratios for associations between life stressors (exposed vs non-exposed) and health outcomes from references[91,109,124-133]. The strongest links are between adverse childhood experiences and clinical diseases suggesting that childhood is a sensitive period, particularly in terms of risk of poor mental health. Moderate excess risk of metabolic diseases (obesity, diabetes, liver disease) is observed in individuals with adverse childhood experiences, neighbourhood socioeconomic disadvantage and job strain. Risk of cardiovascular diseases and infections is also elevated among those exposed to stressors.

Table 3**. Strength of association between indicators of stress and risk of three metabolic diseases from large epidemiologic and clinical studies**

	Obesity/overweight	Diabetes	Liver disease
Cushing's syndrome	2.00	9.40	4.30
Adverse childhood experiences	1.39	1.52	2.76
Low occupational position	1.82	1.31	1.21
PSTD	1.31	1.49	–
Workplace bullying	1.24	1.46	–
Psychological distress	1.26	1.33	1.40
Job strain	1.30	1.16	–
Long working hours	1.13	1.18	1.22
Effort-reward imbalance	1.09	1.24	–
Stressful life events	1.07	1.18	–

*Numbers are hazard ratios for being exposed (versus not being exposed) to various stressors, stress appraisal and proxy measures of the stress response from references[23,96,124,125,131,132,135-150]. The strongest associations with obesity, diabetes and liver disease are observed for Cushing's syndrome (a disease with high cortisol secretion), adverse childhood experiences, and low occupational position.

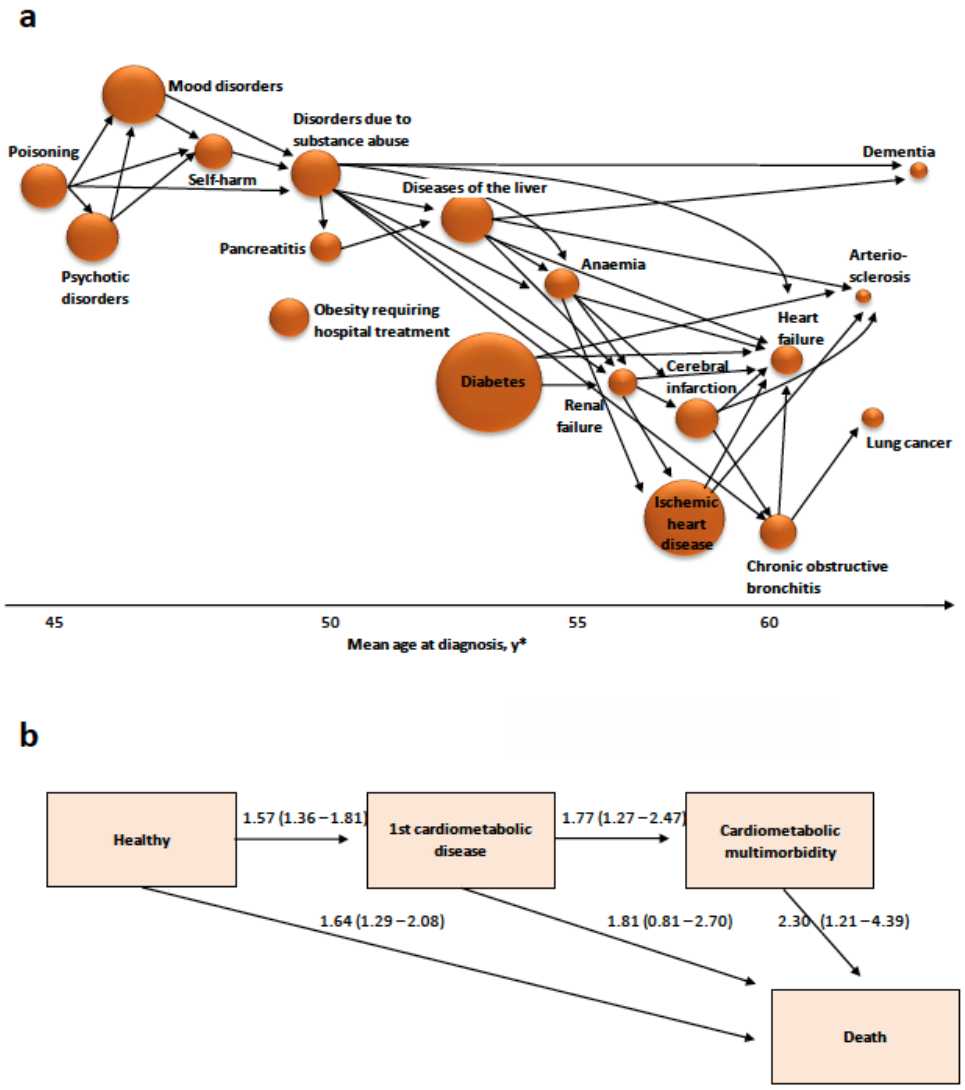

Figure 3**. Disease trajectories, multimorbidity and death in individuals exposed to socioeconomic stressors at individual and community levels. a** Associations between diseases in participants with neighbourhood socioeconomic adversity, pooled data from the Health and Social Support study and the Finnish Public Sector study (reference[125]). Arrows link only pairs of diseases with hazard ratios greater than 3. Diseases along the x-axis are in order of increasing mean age at diagnosis or hospitalisation. The size of plots is proportional to the incidence of disease. **b** Numbers are hazard ratios (95% confidence intervals) from the British Whitehall II study for low vs high occupational position. They show increased risk of developing cardiometabolic disease (diabetes, coronary heart disease or stroke), multimorbidity and dying (reference[170]).

Table 4. **Approaches to reduce life stress and prevent metabolic disease**

Intervention	Description	Evidence
Structural interventions	Improvements in government safety nets, socioeconomic circumstances and the conditions of work reduce a wide range of stressors.	Reduced risk of obesity and diabetes demonstrated in real-life randomised and natural experiments and longitudinal observational studies on change in neighbourhoods.
Increase in resilience	Higher social capital and social cohesion in community may relate to better emotional and instrumental social support.	Animal models show attenuated responses to social and environmental stress. Comparisons of human communities suggest social capital and social cohesion may be associated with reduced risk of obesity.
Psychological interventions	Stress management training, meditation and other interventions to alter stress perception and relieve symptoms	Randomized controlled trials suggest that psychological interventions alone have little benefit in terms of metabolic disease prevention or treatment.
Precision medicine	Aims to develop tailored treatments centred on the patient's needs and circumstances, including as necessary stress management	Limited evidence on effectiveness