Posttraumatic stress disorder

Prevalence, stress hormones and metabolism

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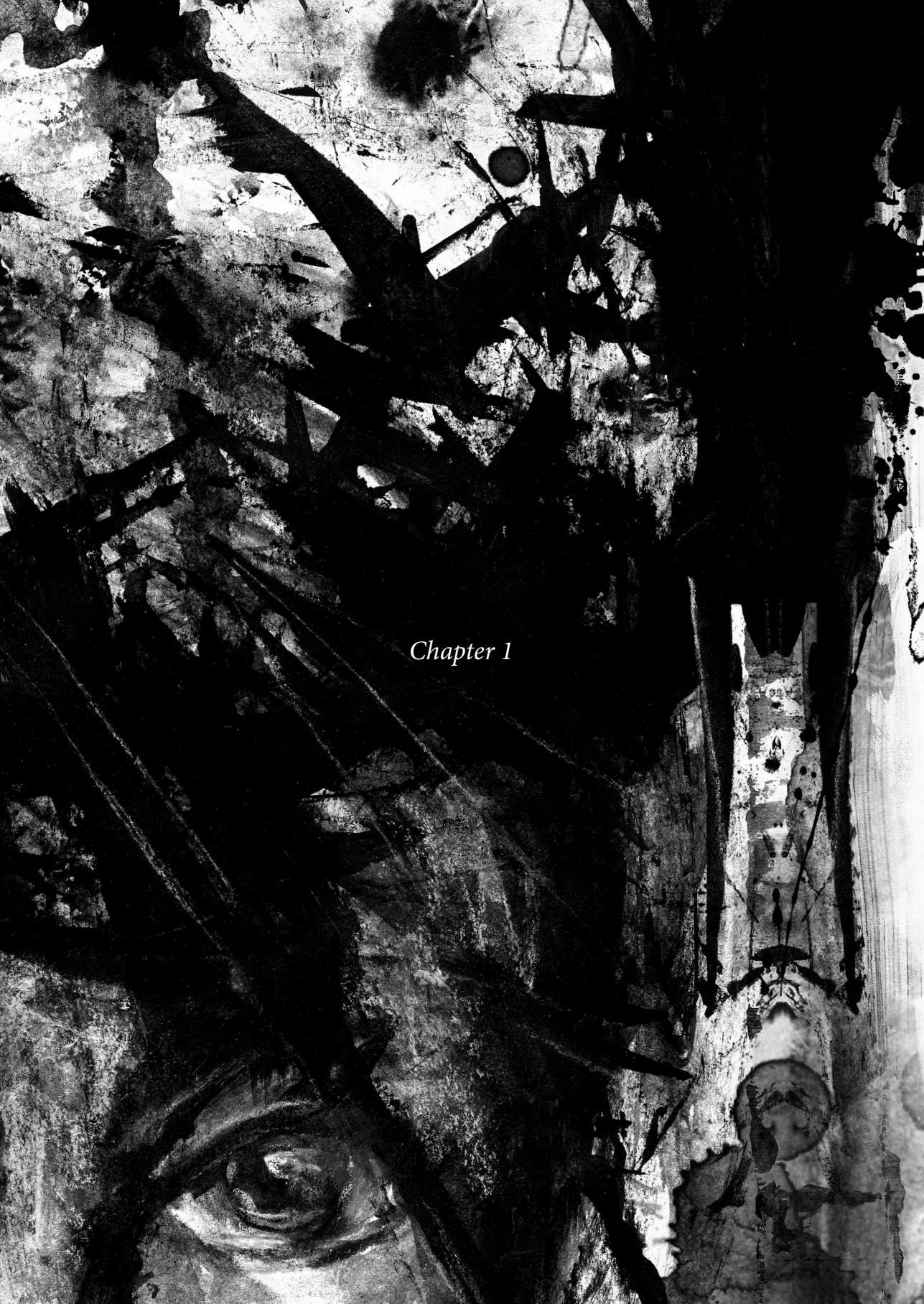

Chapter 1

Introduction

We are built for survival and to thrive in complex, demanding and potentially dangerous environments. We are continuously challenged to accommodate to daily hassles and sometimes even pushed to our limits to handle extreme conditions such as situations of life or death. In response to any challenges, our body constantly attempts to regulates bodily functions and the underlying biochemical processes of breaking down and building up of molecules in order to meet current energetic demands and simultaneously to maintain physiological integrity. Stress is a state where this condition of balance or homeostasis is disturbed as a consequence of provoking, or in anticipation of, stressors of physical, physiological, psychological or socioenvironmental origin and where adaptive processes are required to regain homeostasis again (1-5).

Extreme or overwhelming stress

Stress may be overwhelming when people are exposed to situations of extreme or traumatic stressors; events that involve actual or threatened death, serious injury or violation of one's physical integrity (*i.e.* car accidents, natural disaster, starvation, physical assault or sexual abuse) (6). Exposure to such terrifying ordeals involves intense fear responses and often feelings of impotence, horror or helplessness. Fortunately, the majority of exposed individuals will recover from the initial and considered adaptive stress response, and regains normal functioning (7). A smaller part of the people, however, will develop ongoing mental health problems in the aftermath of the traumatic experience with corresponding impairment in personal, social and occupational functioning (8).

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a mental health condition which is etiologically connected with exposure to traumatic events. The syndrome includes having repeating uncontrollable and intrusive recollections about the traumatic event(s) (*i.e.,* flashbacks, nightmares), avoidance of stimuli evoking the traumatic memories, persistent negative shifts in mood and cognition, and a state of hypervigilance, reactivity and feeling chronically aroused (6). A formal diagnosis of PTSD can be determined if PTSD symptoms are present for the period of a month, and result in impairment in personal, social, occupational or other important domains of functioning (6).

The term PTSD was introduced in 1980 with the release of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in the aftermath of the Vietnam War, but terms used in earlier conflicts such as soldier's heart, shell shock and war neurosis describe quite a similar clinical picture, indicating that this mental condition existed long before the formal description (9). Currently both DSM-5 and ICD-11 are in use. The DSM-5 definition differs from the previous DSM-IV version as it now consists of four symptoms clusters and has updated items.

This great personal suffering in PTSD-patients comes with the loss of both mental and physical health related quality of life (10, 11), with considerable somatic morbidity (12), and increases the risk for suicidal behaviour and premature death through suicide (13). PTSD has also great impact on society as a whole, since it is responsible for an invalidating disease burden worldwide (14-16), has considerable economic impact (17), and is associated with increased health care utilization (18).

Contribution of traumatic stress to broad development of psychopathology

Not every individual responds to stressors in the same manner. Traumatic events are associated with broader mental health problems and contribute to the development of psychopathology in general (19-21). Some people, for instance, exposed to traumatic events will develop symptoms classified as a major depressive disorder (MDD). They suffer from depressed mood and anhedonia with accompanying problems as fatigue, difficulty sleeping and concentration, and loss of appetite and weight. It is generally accepted that exposure to chronic and traumatic stressors is also an important risk factor in the development of MDD (22, 23). Comorbidity of depression in PTSD-patients is high, with up to 85% of the patients affected (24).

Neuroendocrine response to stress

There now exists ample evidence that one of the key features of PTSD is the altered regulation of stress hormones by both the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system (25-28). In line with this, stress can also be defined as "a stimulus, either internal or external, that activates the HPA and the sympathetic nervous system (SNS), resulting in a physiological change or adaptation so that the organism can deal with the threat" (4).

After a stressor has been encountered, the physiological stress response is promptly initiated in order to help regulate responses to these new environmental stimuli, to mobilize energy resources and to restore homeostasis (29). The key brain areas involved in forming the experience of stress and in the initiating of a stress response, are the amygdala, involved in fear responses and arousal, the hippocampus, engaged in learning and memory, and the medial prefrontal cortex, involved in cognition and fear extinction (30). These interconnected brain areas are not only related to the cognitive and affective experience to stress, but also provide for the modulation of the endocrine system as projections to the brain stem and hypothalamus mediate the activation of the two main hormone-sensitive effector systems, the SAM system and HPA-axis (30).

The SAM system is activated only a few seconds after a stressor is detected. Excitation of the SNS causes the release of noradrenaline, inducing an increase in blood pressure, heart and breathing rate, and stimulates adrenomedullary adrenaline release, preparing

the body for 'fight, flight or freeze' in response to the threat (31). Adrenaline is secreted predominantly by the adrenal glands, while noradrenaline is manufactured at a number of sites throughout the body and brain.

The HPA-axis response is seen long after the 'fight, flight or freeze' response. Chemical mediators, including noradrenaline, serotonin and acetylcholine, stimulate neurons in the paraventricular nucleus of the hypothalamus to release corticotropin-releasing hormone (CRH). CRH then acts on the anterior pituitary to produce proopiomelanocortin, which is transformed into adrenocorticotropic hormone (ACTH) (32). ACTH subsequently stimulates the adrenal cortex to secrete cortisol, a glucocorticoid, the end product and main effector of the HPA-axis. The more stress experienced, the more catecholamines and cortisol are released (33).

Cortisol is released in a circadian pattern from the adrenal gland in pulsations, following an ultradian release pattern that is maintained in the face of acute or chronic stress, with its frequency dictating the overall magnitude of both baseline activity and the stress response (34). The rhythmicity of cortisol release is essential for maintaining cellular responsiveness (35). Primarily bounded to the transport protein cortisol-binding globulin (CBG), cortisol then travels via the blood stream throughout the body, employing its various effects in almost every organ of the body.

The availability of cortisol depends on the activity of the 11β-hydroxysteroid dehydrogenase (11β-HSD) enzyme, because inactive cortisone is converted into cortisol by its 11β-HSD1 isoform and cortisol is transformed back into cortisone by the 11β-HSD2 isoform (25). Delivered at the various target sites, cortisol binds to the glucocorticoid receptor, which is a transcription factor, and ultimately stimulates a cascade of gene transcription changes that greatly impact metabolism (25).

The androgen dehydroepiandrosterone (DHEA) and its sulfate ester DHEA-sulfate (DHEA-S), together called DHEA(S), are secreted together with cortisol from the adrenal cortex in response to CRH and ACTH, somewhat later than the release of cortisol but with its peak preceding that of cortisol levels (36-38). DHEA(S) are positively associated with the scale of the ACTH and cortisol response (38). DHEA-S is the primary steroid hormone of the adrenal gland and most abundantly available in the human body (39). Unlike cortisol, the secretion of DHEA(S) has been shown to be maintained after repeated or chronic stress (36). DHEA(S) is known to have anti-glucocorticoid effects and although precise mechanisms remain unclear, it may affect glucocorticoid metabolism through its effects on both 11β-HSD1 and 11β-HSD2 (39).

Metabolism: anabolism and catabolism

One of the major goals of metabolism is to maintain a tightly balanced and constant glucose level in the blood. When the body is in an absorptive and resting or anabolic state, the focus of metabolism is on the conversion of food into smaller molecules along the

digestive tract and on using them as a source of energy or building blocks. Glucose, fatty acids (FAs) and amino acids are transported from the intestines into the blood. Some of these digested molecules are called essential as they can only be derived from diet and cannot be synthesized from other molecules. The omega-3 and –6 polyunsaturated FAs alpha-linolenic acid and linoleic acid, for instance, are known to be essential for humans and to form an important factor in several psychiatric disorders (40).

Insulin is secreted from the pancreas under the influence of the abundant availability of glucose in this stage and stimulates the conservation of energy through the formation of large chains of glycogen from glucose (glycogenesis) in the liver and muscle cell to be used for later energy needs. It also stimulates the conversion of glucose into pyruvate (glycolysis), which is an essential molecule in Krebb cycle and cellular respiration. The synthetization of FAs is promoted as a result of this process. Furthermore, insulin affects amino acids and protein metabolism by motivating protein synthesis, promoting the build-up of proteins in muscle tissue, and inhibiting the degradation of proteins. Moreover, insulin promotes the formation of triglycerides by binding a glycerol molecule to three FAs synthesized out of glucose or amino acids in the liver (lipogenesis) or directly from FAs obtained from diet in adipose tissue. At the same time, it inhibits the breakdown of triglycerides in adipocytes. The triglycerides formed in the liver are transported to adipose tissue through the use of lipoproteins, which enable the transportation of the hydrophobic triglycerides through the water-based blood circulation.

Non-essential FAs are synthesized using the intermediates acetyl-CoA and nicotinamide adenine dinucleotide (NAD^+), formed in the glycolytic pathway through the action of FA synthases. Phospholipids can be synthesized by binding a glycerol molecule to two FAs and a phosphorylated molecule, such as phosphatidylcholine. Phospholipids are the main constituent of the lipid bilayers that form the basis for cell membranes.

Anabolism also motivates the constructing of other macromolecules such as proteins, RNA and DNA during the formation of cells and tissues. Other hormones that stimulate anabolism are: sex steroids (*i.e.* DHEA(S) and testosterone), thyroxine, prolactin and growth hormone.

However, in a post-absorptive or catabolic state the focus of metabolism is on making energy available again. When blood-glucose levels begin to fall and insulin secretion is decreased in consequence, glucogon secretion by the pancreas is increased. Glucogon stimulates the liver to regain glucose from glycogen in liver and muscle cells (glycogenolysis), from certain non-carbohydrate carbon substrates such as triglycerides and proteins (gluconeogenesis) after the breakdown of triglycerides into glycerol and free FAs (lipolysis), and from the breakdown of proteins into amino acids (proteolysis).

Glucogon also inhibits glycolysis and FA synthesis. Previously stored FAs are now released by adipocytes. Liver and muscle cells switch from glucose to the usage of FAs as their main energy source.

Cortisol stimulates gluconeogenesis, proteolysis and lipolysis at several sites including muscle, adipose and lymphoid tissue. Cortisol has to be co-present to permit glucagon its calorigenic action. Catecholamines also stimulate lipolysis in white and brown adipocytes and enhance thermogenesis (41), but only when combined with cortisol. Cortisol affects the production, utilization, and degradation of FAs as it influences the functioning of enzymes and increases oxidative stress (40). Besides cortisol, adrenaline and glucagon, other hormones such as thyroxine and growth hormone also stimulate catabolism.

Although we present metabolism here as largely divided into the two metabolic pathways of anabolism and catabolism, it has become increasingly clear that metabolism operates more as a highly integrated network (42).

Acute stress response to trauma and metabolism

In the face of extreme stress, the acute stress response is vastly prompted after which metabolism sharply shifts to a state of mobilizing energy resources and protein substrates to protect tissue damage repair and critical organ functions (29) in order to execute 'fight, flight or freeze' responses. The body responds with a powerful increase in temperature, heart and breathing rate, and oxygen usage. The SNS and the release of catecholamines are largely responsible for this initial sharp increase in energy consumption.

Glucose output through gluconeogenesis by the liver rapidly increases. Initially, the energy needed to increase gluconeogenesis is delivered from lactate and amino acids in the liver, after which the liver turns to fat oxidation as its primary energy source. Not only is the output of glucose increased, at the same time the uptake of glucose in muscle and adipose tissue is reduced as well, consequently leading to a sharp increase in blood glucose levels. Additionally, inflammatory mediators induce peripheral insulin resistance. Together this results in large amounts of glucose in the blood, which is considered to be adaptive and increasing chances of survival (43).

The released glucose is mainly used by tissues that do not depend on insulin, including the brain and other parts of the nervous system. For the major part of the body, however, free FAs form the main source of energy after extreme stress, severe injury and critical illness (44). Through lipolysis FA and glycerol levels increase, with the increased free FAs to inhibit glycolysis (45, 46). While at the same time FA synthesis is inhibited by an increase in glucagon and increasing intracellular FAs (45, 46). The acute stress response also leads to diminished protein synthesis and elevated protein degradation, resulting in a negative protein turnover and nitrogen balance (45, 47).

With the increase in metabolic activities, the production of reactive oxygen species (ROS) intensifies in cells. While oxygenated radicals and oxidizing agents are normally generated at low frequency in the mitochondrion and are neutralized by antioxidant defenses, the presence of extreme stressors may overwhelm these natural defenses leading to potential cell damage including modification to cellular proteins, lipids and DNA (48). Folate metabolism, also known as the one-carbon metabolism is a set of important biochemical pathways involved in this imbalance, often referred to as oxidative stress. One-carbon metabolism is a universal metabolic process largely executed in mitochondria that serves to activate and transfer single carbon units for various essential processes such as biosynthesis, amino acid homeostasis, epigenetic processes, and protection against ROS (49).

Need for termination of the acute stress and catabolic response

The acute response is of immediate benefit and increases chances of survival in the short-term, but is potentially damaging if prolonged. Intensive catabolic reactions may be harmful as tissues got damaged and energy storage is depleted (44). And excess glucocorticoid exposure can lead to pathological outcomes (*e.g.* 32). Therefore a feedback mechanism is needed to limit the duration of neural responses and hormone secretion. Once the acute stressor is no longer detected by the amygdala, cortisol initiates a negative feedback inhibitory response (50, 51) on the hypothalamus, pituitary, amygdala and hippocampus, each of which contains high concentrations of glucocorticoid receptors (52-54). The body then shifts back to the anabolic phase to start recovery from the stressful event.

Needless to say, the actual biology of the HPA-axis and stress response is more nuanced than presented here. For example, cytokines can cause an increase in cortisol in the absence of an increase in ACTH (55) and FAs stimulate cortisol secretion through their effects on CRH-secretion, while increasing inhibitory feedback through glucocorticoid receptor-sensitivity at the same time (40). A comprehensive and more detailed clarification of the regulation of the stress response can be found elsewhere (55).

Prolonged exposure to trauma and PTSD

Prolonged exposure to stress stimulates long-term adaptation processes, including changes in gene regulation and neuronal structure, to cope with new environmental demands and adversity (*e.g.* 56, 57). For instance, HPA-axis habituation is probably the results of such adaptive processes (56). However, extensive pressure on neuronal and metabolic systems can also lead to increased and inflated sensitivity to new challenges, thereby putting the stress systems in a new equilibrium of hyper- or hypo-responsiveness with an increased risk for the development of respectively PTSD and depression as a result (58, 59). Chronic activation of the stress-responsive systems, with its mediators

constantly put in motion to achieve homeostasis according to new demands, causes some degree of wear of underlying physiological systems (*i.e.* 'allostatic load' (60, 61)), and therefore may contribute to long-term consequences of stress in the form of physical and mental health conditions. Because age, sex, genetic predisposition and environmental context all have their influence on the neuroendocrine stress response, they all add to the great individual variation in stress sensitivity and resilience (62).

Adverse physical conditions are associated with PTSD

A myriad of adverse psychical conditions has been observed to be commonly prevalent in PTSD-patients. Studies have shown an association between PTSD and the metabolic syndrome (63-68), a cluster of risk factors for the development of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) incorporating insulin resistance, abdominal obesity, high triglyceride level, low high-density lipoprotein cholesterol, and high blood pressure (69).

Furthermore, there is ample evidence that the diagnosis of PTSD is associated with an increased risk for a wide range of physical conditions such as hypertension (70-72), cardiac disease (70, 71, 73-75), stroke (70, 74, 76), and T2DM (70, 72, 77, 78). In prospective studies, PTSD has been found to contribute to the development of CVD (79-81). This association of PTSD with CVD has been consistently found separately from both depression and adjustment for comorbidity with other mental disorders (82).

Due to these comorbid physical conditions PTSD-patients have a considerable lower life expectancy than non-affected individuals (75, 83-85). A large prospective study examining early-age heart disease in male veterans using survival analysis found that veterans having the lifetime PTSD diagnosis may die at over twice the rate at any given year as those without the diagnosis, irrespective of lifetime depression, and that PTSD severity considerably increased mortality risk (84). Aggregating the results of several mortality studies indicated a 29% increased risk for mortality at any given point in time in those with PTSD compared to the comparison subjects (86). A review of studies investigating senescence in PTSD by comparing leukocyte telomere length between patients and non-patients found that the PTSD group had shorter telomeres compared to non-PTSD subjects (medium to large effect size), and together with evidence from the effect of PTSD on comorbid physical conditions the authors concluded that PTSD may be associated with accelerated aging (86). Furthermore, having PTSD may affect the course and outcome of physical conditions. For instance, PTSD may adversely impact cardiovascular outcome after surviving myocardial infarction (87). Medical illness burden is larger in patients with PTSD (88). Comorbid PTSD increases the non-fatal burden of injury for patients presented at the emergency unit or those being hospitalized by more than 50% from 116,000 to 178,000 DALYs (89).

Understanding the link between PTSD and physical conditions

Although huge progress is made in the past decades or so in the theorization and understanding of the link between PTSD and physical diseases, mechanistic evidence still remains relatively limited. Complicating the investigation of the link between PTSD and physical diseases is the co-existence of PTSD with other psychiatric conditions (*e.g.,* MDD, panic disorder) and that it often goes along with adverse lifestyle factors such as smoking, alcohol or substance abuse, poor diet and lack of physical exercise (90, 91). Moreover, the physiological effects of PTSD are wide-spread, affecting multiple organ systems with intertwined health consequences (92). A direct cause and effect relationship is therefore hard to be found.

This means that we are limited to finding statistical associations suggesting that the PTSD diagnosis is assumed of being associated with the causal effect, *i.e.* risk factors. A risk factor is a biological condition or behavior that has an association with but has not been proven to cause an event or disease. Already at the start of our investigation back in 2004, a number of studies had shown biological alterations in the neuro-endocrine and metabolic response to stress that statistically discriminated PTSD-patients from non-PTSD controls, considered risk factors for PTSD. Such biological deviations may be loosely regarded as biomarkers. Biomarkers are used to describe the risks, exposures, intermediate effects of treatment and biological mechanisms, and are used to predict health outcomes (93). But even as biomarkers can reflect the influence of an intervention, changes in their levels may not necessarily be indicative of changes in risk. In the past few decades, scientists have tried to better understand PTSD from a biological perspective. Finding biological markers for PTSD may support the understanding of the ways PTSD and physical conditions are linked, and may help to prevent the large and growing burden of especially cardiovascular morbidity and mortality in PTSD-patients.

Scope and general outline of the thesis

In sum, the prevalence of trauma and PTSD is high worldwide and the majority of the cases persist for over a year (8). The stressful continuous exposure to intrusive and spontaneous recollections of the once experienced horrifying ordeals is accompanied with an increased risk for a myriad of physical conditions, especially CVD. CVD is the main driver of the observed decrease in life expectancy. Improving our understanding of the disease hopefully leads to the prevention of the development of PTSD, new or augmented treatment options for PTSD, and the prevention or reduction of comorbid CVD. In an attempt to understand PTSD and the association of PTSD with cardiovascular disease in particular, we investigated:

- the disease burden or prevalence rate of (potential) traumatic events and PTSD;

- the neurobiology of the (endocrinological) stress response and the effect of treatment;
- the impact of PTSD on metabolism, particularly its impact on one-carbon metabolism, fatty acids metabolism, lipoproteins and body weight.

We will present the results in the following chapters. In **chapter 2** we focused on establishing estimates of lifetime prevalence rates of exposure to potentially traumatic events and PTSD in the general Dutch population in order to provide information for policy makers on the size of its impact or burden on society. In **chapter 3 and 4** we show results from our investigations of the neuroendocrine stress response in PTSD. In **chapter 3** we investigated the HPA-axis functioning by determining whether PTSD-patients differed in basal cortisol levels. The study also evaluated other hormones, including DHEA(S), prolactin, thyroid-stimulating hormone (TSH) and free thyroid levels, because they are all components of or related to HPA-axis functioning. We further determined the association of PTSD symptom severity with these hormones. We describe our study investigating whether recovery from PTSD following trauma focused treatment for PTSD (using Brief Eclectic Psychotherapy for PTSD, BEPP) was associated with changes in basal neuroendocrine levels in **chapter 4**. In **chapter 5** we demonstrate findings from our study evaluating some key components of the one-carbon metabolism (homocysteine, folate, vitamin B_6 and B_{12}). We also investigated the interplay of the HPA-axis (see chapter 3) with the one-carbon metabolism. In **chapter 6** we investigated whether PTSD-patients differ from healthy controls in concentrations of the FAs: docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), arachidonic acid (AA) and nervonic acid (NA) in erythrocytes. We also assessed overall FA-profiles and compared patients and controls on a number of indices related to oxidative stress. Finally, we exploratively compared concentrations of other FA's of all FA-subclasses (*e.g.* omega–3, omega–9) between patients and controls. We close our study on biomarkers in PTSD with **chapter 7**, which describes our investigation of the role of lipoproteins in PTSD. We assessed whether plasma concentrations of total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides differed between PTSD-patients and healthy controls. We especially focused on the presumed sex differences in lipid profiles. We also related plasma concentrations of the measured stress hormones in chapter 3 to the measured lipoproteins. In **chapter 8** we investigated whether an exposure-dosage-like relationship exists between body weight measured as body mass index (BMI) and PTSD symptom severity for the DSM-IV PTSD symptom clusters (intrusions, avoidance and hyperarousal) using data from the Collaborative Psychiatric Epidemiology Surveys. We additionally studied whether length of exposure to PTSD and the period of recovery from PTSD were associated with BMI. Finally, **chapter 9** will provide an overall summary and discussion of the findings presented in this thesis in the light of related work of others.

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