



Review

Stress habituation, body shape and cardiovascular mortality

Achim Peters^{a,*}, Bruce S. McEwen^b^a Medical Clinic 1, University of Luebeck, Luebeck, Germany^b Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY, USA

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This article is dedicated to the memory of
 Per Björntorp (1931–2003).

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ABSTRACT

High cardiovascular mortality is well documented in lean phenotypes exhibiting visceral fat accumulation. In contrast, corpulent phenotypes with predominantly subcutaneous fat accumulation display a surprisingly low mortality. The term ‘obesity paradox’ reflects the difficulty in understanding the biological mechanisms underlying these clinical observations. The allostatic load model of chronic stress focuses on glucocorticoid dysregulation as part of a ‘network of allostasis’ involving autonomic, endocrine, metabolic, and immune mediators. Here, we expand upon the energetic demands of the brain and show that ‘habitutors’ and ‘non-habitutors’ develop divergent patterns of fat distribution. Central to this process is the recurrent rise in the cerebral energy need (arousal) that non-habitutors experience during chronic stress. These neuroenergetic alterations promote visceral fat accumulation, subcutaneous fat loss, and atherogenesis with subsequent cardiovascular events. Habitutors are more or less protected against such cardiovascular complications, but there is a metabolic trade-off that we shall discuss in the present paper.

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* Corresponding author. Tel.: +49 4515003546; fax: +49 4515004807.
 E-mail address: achim.peters@uksh.de (A. Peters).

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1. Introduction

Ten years ago, the American nephrologist Kamyar Kalantar-Zadeh called attention to a series of surprising observations (Kalantar-Zadeh and Kopple, 2006). In patients with chronic kidney disease undergoing maintenance hemodialysis a high body mass was incrementally associated with better survival (Kalantar-Zadeh et al., 2005; Kopple et al., 1999). These counterintuitive findings prompted a long-lasting debate labeled the 'obesity paradox'. In line with these reports, better survival rates have also been documented in obese patients who had suffered from stroke, intracerebral hemorrhage, myocardial infarction, heart failure, sepsis or type-2-diabetes when they were compared with those of lean patients with the same disease (Garroute-Orgeas et al., 2004; Buettner et al., 2007; Hallin et al., 2007; Fitzgibbons et al., 2009; Kim et al., 2011; Vemmos et al., 2011; Carnethon et al., 2012). Note-worthy, the earlier studies did make use of one anthropometric measure only: the body mass index (BMI).

In the 1980s, the Swedish endocrinologist Per Björntorp emphasized the role of visceral fat (Björntorp, 2001). First, he found that visceral fat mass was associated with hypercortisolemic states (Rebuffe-Scrive et al., 1988). Björntorp liked to recount his problems in publishing data that clearly demonstrated that women displaying visceral fat accumulation were more likely to carry psychosocial burdens. They were more often unemployed, had gone through a divorce, had spent time in prison, or had financial problems. For Björntorp this was a clinical and socioeconomic way to describe stress eventually leading to the accumulation of visceral fat. Initially nobody was willing to publish these data, because they seemed too unlikely. However, Per Björntorp systematically built up a plausible sequence proposing that chronic stress, affecting the hypothalamus–pituitary–adrenal (HPA) axis, would eventually lead to visceral fat accumulation. Second, Björntorp was among the first investigators who reported that visceral fat accumulation was associated with a high cardiovascular mortality risk (Larsson et al., 1984).

Per Björntorp's findings add an important aspect to the 'obesity paradox' debate. The earlier studies – lacking data on visceral fat – showed the often-mentioned U-shaped BMI-mortality curves (Whitlock et al., 2009). In contrast, recent epidemiological studies made combined use of two anthropometric measures: waist circumference (as an estimate of visceral fat) and the BMI (as an estimate of subcutaneous fat). By using mutual statistical adjustment for both of these measures, several large population-based cohort studies from the United States, the United Kingdom, Denmark, Norway, and Mauritius could show a more differentiated picture (Cameron et al., 2012; Berentzen et al., 2010; Petursson et al., 2011; Krakauer and Krakauer, 2012, 2014): First, they showed no U-shaped mortality curves. Second, each of these studies confirmed what Björntorp had described as the risk effects of waist circumference on mortality, and also what Kalantar-Zadeh had reported as the protective effects of high BMI on mortality. In line with these findings, the Whitehall Study and the Aerobics Center Longitudinal Study (ACLS) provided evidence that lean subjects who displayed high waist circumference (or another metabolic abnormality) had the highest mortality risk, while subjects with a high body mass who lacked high waist circumference (or other metabolic abnormalities) had the lowest mortality risk (Hamer and Stamatakis, 2012; Ortega et al., 2013). In all, there is

mounting evidence that waist circumference and BMI indicate divergent mortality risks.

Unfortunately, the obesity-paradox debate refers almost exclusively to correlational studies, and the only existing randomized controlled trial in the field does not even support a direct causal relationship between body mass and mortality (Look AHEAD Research Group, 2013). Nevertheless, the opponents in this debate do more and more agree upon 'body shape' as being essential for assessing the cardiovascular mortality risk in general populations: Visceral fat appears to identify the high risk phenotype, while subcutaneous fat doesn't. Although the clinical picture has become much clearer today (Peters and McEwen, 2012), it remains still poorly understood what biological mechanisms underlie the 'obesity paradox' phenomenon. Here we look at its pathophysiology from a neuroendocrine and neuroenergetic perspective and bring together concepts and lines of investigation that highlight the role of toxic stress and the inability to handle daily stressors as fundamental determinants.

2. Allostatic load

In the 21st century, a number of randomized controlled trials concerning chronic stress provided causal evidence for Björntorp's original ideas. First, chronic psychosocial stress has been shown to increase visceral fat mass in non-human primates (Kaufman et al., 2007). Second, cognitive-behavioral and resource-activating stress management programs have been shown to reduce cortisol stress responses during a standardized psychosocial challenge (Storch et al., 2007; Hammerfald et al., 2006; Gaab et al., 2003). 'Stress reduction' programs in turn have been shown to improve cardiovascular survival (Orth-Gomer et al., 2009; Gulliksson et al., 2011). In detail, two large-scale trials from Sweden have studied patients who had suffered from their first myocardial infarction. The stress reduction program consisted of five key components with specific goals – education, self-monitoring, skills training, cognitive restructuring and spiritual development – and was focused on stress management, coping with stress, and reducing experience of daily stress, time urgency, and hostility. Both studies showed that those in the intervention group had a lower rate of second or third myocardial infarction and a lower rate of cardiovascular mortality as compared to the control group. Thus, chronic psychosocial stress – as Björntorp has predicted – can cause both visceral fat accumulation and cardiovascular death.

Here we refer to the conceptual frameworks of 'allostasis and allostatic load' (McEwen and Stellar, 1993) and the 'Selfish Brain' theory (Peters et al., 2004) to address the question how genetic endowments and life experience interact to differentially affect visceral fat, subcutaneous fat, and mortality. According to the concept of 'allostasis', allostatic regulation occurs when a subject is exposed to a changing environment and engages in behaviors and physiological responses that promote adaptation and increased chances for survival, at least in the short run. As part of allostatic regulation the brain is supplied with extra energy, which in turn can be used to cover the increased brain energy needs arising from enhanced cerebral functioning (e.g. increased vigilance, updating the probability distributions of expected outcomes). Yet, the metabolic and regulatory events occurring during an acute challenge differ from those occurring under chronic inhospitable conditions. According to the concept of 'allostatic load' the mediators of neuroendocrine,

autonomic, metabolic and immune systems become chronically activated so that turbulent blood flow, hypertension, macrophage tissue infiltration, oxidative stress, atherosclerosis, impaired memory and deteriorated mood accelerate disease progression. All the long-term effects of chronically activated stress responses – which lead to the wear and tear of the organism – are referred to as allostatic load (McEwen, 1998). Once, serious pathophysiology has occurred the effects are denoted as ‘allostatic overload’ (McEwen and Wingfield, 2003).

In the current paper, we define ‘stress’ as a ‘state of increased cerebral energy need’ that occurs when a person is uncertain of how to safeguard his/her future physical, mental and social well-being. Such a state of increased individual uncertainty can lead to three results: first, ‘good’ stress processes indicate a satisfying result, in which certainty can be regained and the individual experiences a sense of mastery and good self-esteem (McEwen and Gianaros, 2010). Second, tolerable stress processes indicate a result, in which the uncertainty could not be resolved but nevertheless the individual may stabilize through buffering mechanisms such as habituation, coping strategies or supportive relationships. Third, ‘toxic stress’ processes indicate the result in which the buffering mechanisms fail, and the individual is at high risk for physical and mental morbidity and excess cardiovascular mortality (McEwen, 2012).

3. Brain energy ‘supply and demand’

So far, the field of neuroenergetics has received little attention among the obesity paradox disputants. The Selfish Brain theory – founded in 1998 by one of the authors (A. P.) – integrated cerebral and peripheral energy metabolism (Peters et al., 2004). Its central idea is that the brain occupies a special hierarchical position in the human organism. The theory was based on experimental evidence from more than 12,000 publications. Among other things, the list of evaluated publications included the groundbreaking work of Luc Pellerin and Pierre Magistretti on the ‘astrocyte-neuron-energy-on-demand’ principle (Pellerin and Magistretti, 1994). Key to the Selfish Brain theory is the brain-pull hypothesis (Peters and Langemann, 2009). ‘Brain-pull’ is referred to as the force with which the brain actively demands energy from the body. It contrasts with the conventional nutritionist’s and obesity-expert’s view (the null hypothesis), which states that the brain is supplied in a passive manner, e.g. by diffusion or passive transport driven by a concentration gradient. According to the conventional view no brain-pull function is required. The brain-pull hypothesis, however, stated that the brain is supplied in an active manner with the help of specific brain-pull mechanisms.

After the Selfish Brain theory has been explicated in 2004, unexpected evidence emerged. Published in 1921, then missing for almost a century before surfacing in 2007, the work of Marie Krieger provided a unique opportunity for comparing the two above-mentioned competing hypotheses (Krieger, 1921). Just prior to the appearance of Krieger’s data, logistic-supply-chain analyses have been made that predicted opposing metabolic outcomes in the scenario of food deprivation (Peters and Langemann, 2009): If the conventional view (null hypothesis) were true, substantial mass loss was predicted to occur in both body and brain. If the brain-pull hypothesis were true, mass loss was predicted to occur only in the body—but not in the brain.

In fact, Krieger had reported that in the state of inanition all organs like the heart, liver and kidney lost approximately 40% of their mass, whereas the brain mass hardly changed (less than 2%) (Krieger, 1921). Thus, updating the probabilities of the competing hypothesis with the help of Krieger’s data gave a huge boost to the brain-pull hypothesis. Adding further evidence from

experiments using state-of-the-art technology, including magnet resonance imaging and spectroscopy (Peters et al., 2011; Kubera et al., 2013; Oltmanns et al., 2008; Goodman et al., 1984; Muhlau et al., 2007) and positron-emission-tomography (Kuzawa et al., 2014), more and more increased the likelihood of the brain-pull hypothesis being true.

Now, that the conventional view advocating the null hypothesis has become increasingly unlikely, it seems promising to look at the ‘obesity paradox’ observations in the light of brain-pull mechanisms. Acute stress belongs to the conditions when the brain enters a hypervigilant state; the additional cerebral energy needs arising from this transition are covered by brain-pull mechanisms (Hitze et al., 2010; Madsen et al., 1995; Kubera et al., 2012). One of these mechanisms is called ‘cerebral insulin suppression’. Cerebral activation of the sympathetic-nervous system (SNS) and the HPA axis vigorously suppresses insulin secretion from pancreatic β cells (Hitze et al., 2010; Ahren, 2000; Billaudel and Sutter, 1982; Woods and Porte, 1974). Concomitant lowering of the vagal tone also contributes to the suppression of insulin secretion (Woods and Porte, 1974). As a consequence, the insulin-dependent glucose uptake via glucose transporter GLUT4 into the body periphery (muscle, subcutaneous and visceral fat) becomes limited. At this point, glucose is available via insulin-independent GLUT1 transport across the blood brain barrier (Hasselbalch et al., 1999; Seaquist et al., 2001). **Important Conclusion:** *GLUT1 glucose uptake safeguards basal energy supply of vital organs, like brain and immune cells (Deng et al., 2014), while GLUT4 allows the storage of surplus energy in muscle and fat cells (Shepherd and Kahn, 1999). Thus, ‘cerebral insulin suppression’ allocates energy to the brain in order to maintain cerebral energy concentrations.*

Chronic stress belongs to the conditions when repeated rises in cerebral need (arousal) and brain-pull activity occur, inhibiting peripheral GLUT4-mediated glucose uptake in the long run, thereby promoting the loss of subcutaneous adipose tissue. In visceral fat, however, chronic stress exerts opposite effects. This is so because visceral adipocytes are particularly sensitive to glucocorticoids (Lee et al., 2014). Here, chronic stress leads to an increase in adipocyte GLUT1-gene expression (Zini et al., 2009) and a decrease in adipocyte GLUT4-gene expression (Waller et al., 2011; Lefebvre et al., 1998). These changes in transporter profiles are triggered by chronic activation of SNS and the HPA-axis (Kuo et al., 2007). Thereupon, macrophages invade into the visceral fat tissue where they release tumor necrosis factor (TNF α). TNF α in turn alters the gene expression of the respective glucose transporters (Lumeng et al., 2007; Cornelius et al., 1990; Battelino et al., 1999). Enhanced GLUT1-mediated glucose uptake into abdominal adipocytes favors visceral fat accumulation (Lundgren et al., 2004). In all, repeated activation of brain-pull mechanisms during chronic stress leads to loss of subcutaneous fat – but to accumulation of visceral fat.

Epel et al. (2000) brought Björntorp’s first idea “*chronic stress makes visceral fat grow*” a decisive step further. When the researchers studied lean people with visceral fat accumulation and compared them with those showing other body shapes, they made a spectacular discovery. This was precisely the kind of phenotype that was ‘non-habituator’. Thus, non-habitulators, but not habituators, react to chronic stress by developing the above-described ‘lean-but-wide-waisted’ phenotype. ‘Stress habituation’ is an essential form of plasticity that reduces glucocorticoid mobilization in response to stressors that have been previously experienced, but not to novel stressors (Fig. 1). In this way, habituation avoids needless glucocorticoid secretion but maintains the ability to mount a hormonal response. The metabolic consequences of chronic stress in habituators are completely different from those seen in non-habitulators. These consequences essentially concern the ‘body-pull’ (Box 1), i.e. appetite and ingestive behavior, and will be discussed further below.

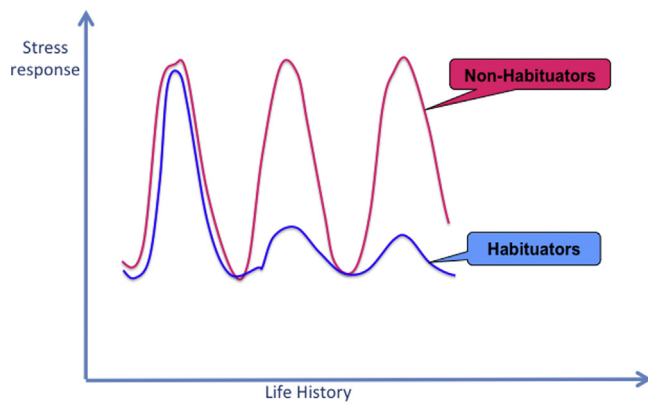


Fig. 1. Differential modifications of stress reactivity. We define 'habitulators' as those who show repetition-induced response attenuation (neuroendocrine, cardiovascular, neuroenergetic, and emotional), when being chronically exposed to an unsafe environment. Over time, they develop a low 'stress reactivity'. In contrast, we define 'non-habitulators' as those who do not show such a modification of responses. They uphold their high stress reactivity, when continuously being exposed to an unsafe environment. With repeated experimental stress challenges (TSST), subjects have been shown to either habituate or not habituate in their cortisol response (Kirschbaum et al., 1995).

Box 1: Glossary

Allostasis The process whereby an organism maintains physiological stability (homeostasis) through changing parameters of its internal milieu by matching them appropriately to the environment.

Allostatic load The biological 'wear and tear' that allostatic mechanisms exert on organs and tissues under chronic stress that cumulatively predisposes to the development of disease.

Allostatic overload An extreme form of allostatic load in which dysregulation of allostatic responses, often in response to chronic stressors, lead to disease. Both allostatic load and allostatic overload occur in nature.

Selfish Brain theory Conceptual framework that describes the characteristic of the brain to cover its own energy requirements with the highest priority. In the competition between organs, the brain appears to behave in a 'selfish' manner. The theory has been founded and formulated mathematically between 1998 and 2004. Meanwhile, interdisciplinary work has provided experimental evidence for the validity of its axioms.

Brain-pull The force with which the brain actively demands energy from the body. The most important brain-pull mechanism is referred to as 'cerebral insulin suppression'.

Cerebral insulin suppression A fall in amygdala or hypothalamic neuronal adenosine triphosphate (ATP) concentrations stimulates the sympathetic nervous system and the hypothalamus–pituitary–adrenal axis. Both systems suppress insulin secretion from the pancreatic β cells, and in so doing limit the *insulin-dependent* glucose uptake into the body periphery (muscle, fat tissue). As a consequence, glucose is available via the *insulin-independent* transport across the blood-brain barrier.

Body-pull The force with which the body actively demands energy from the environment. Appetite and total energy intake depend on the energy status of the blood (glucose), the brain (ATP) and the body (indicated by leptin, ghrelin, etc.).

4. Non-habitators' trade-offs

4.1. Hypervigilance

Once the environment changes and becomes unsafe, individuals may find themselves confronted with the question: "Can one of my options safeguard my future physical, mental and social wellbeing?" 'Stress' occurs in those individuals who are uncertain about the answer. During acute stress, the brain enters a hypervigilant state in order to reduce the occurring uncertainty as soon as possible. To obtain the necessary information, additional cerebral energy is required. In principle, getting any information costs energy (Brillouin, 1953). Redundant brain-pull mechanisms have been discovered that are able to immediately procure the brain with such extra energy from the body.

The anterior cingulate cortex (ACC) plays a key role in processing the subjective estimation as to whether future outcomes are uncertain (Sarinopoulos et al., 2010; Karlsson et al., 2012; Behrens et al., 2007; Liljeholm et al., 2013; Paulus et al., 2002; Feinstein et al., 2006). The amygdala, on the other hand, has a key function for assessing threat to wellbeing (McEwen, 2007). Subjects who feel uncertain about their future wellbeing typically display interactions between ACC and amygdala (Sarinopoulos et al., 2010). The ACC-amygdala complex can activate two descending pathways: first, projections to the locus coeruleus norepinephrine (LC-NE) system, (thereby inducing a hypervigilant state (Valentino and Van Bockstaele, 2008; Reyes et al., 2011), which has been found associated with an increased cerebral energy need, Hitze et al., 2010; Kubera et al., 2012); and second, projections to the ventromedial hypothalamus and the paraventricular nucleus (thereby activating the SNS and HPA-axis, which in turn procure the brain with the extra energy needed) (Hitze et al., 2010; Kubera et al., 2012).

During chronic stress, non-habitators have to find a neuroenergetic solution that allows them to activate their energy-costly hypervigilant state. The three following solutions are feasible

- enhancing cerebral blood flow,
- enhancing cerebral glucose supply and
- enhancing cerebral ketone supply, but these strategies are afflicted with the trade-offs
- high-flow-speed arterial turbulences,
- subcutaneous fat loss and
- visceral fat accumulation, respectively.

4.2. High-flow-speed arterial turbulences

During psychosocial stress, SNS-activation raises cardiac output mainly by accelerating heart rate (Jones et al., 2011). High cardiac output in turn mounts cerebral energy supply. However, the increase in blood flow velocity has a trade-off of great consequence: turbulences. Experimentally induced adrenoreceptor activation increased heart rate, blood flow velocity, and caused turbulences in the arterial system (Falsetti et al., 1983; Hanai et al., 1991). Since turbulent flow is irregular, it turns out to be highly uneconomical with respect to energy transport. From a physical point of view, turbulences greatly increase friction and for the same discharge a higher blood pressure must be applied than in the laminar case. Therefore it appears of primary importance to maintain laminar (regular) blood flow in order to fuel the brain in the most economical manner. The problem is that toxic stress can cause turbulent blood flow that starts a vicious cycle, which can lead to atherosclerosis.

4.2.1. The laminar-turbulent transition

The transition to turbulence in fluid flow is an everyday experience. As a faucet slowly opens, the initial laminar flow of water

changes into an irregular flow. Modern physical experiments presented in detail how high flow speed increases the risk of turbulences (Hof et al., 2004; Darbyshire and Mullin, 1995).

The transition to turbulent flow also depends on the geometry of the pipes. In the human vascular system bifurcations, branching points and the inner aspect of curvatures are predilection sites, where disruption of laminar flow is often observed (Malek et al., 1999). Areas with reversed flow (i.e., flow separation, recirculation) or circumferential swirling are characteristic of disturbed laminar flow. In turbulent flow the velocity at any given point varies continuously over time, even though the overall flow is steady. The outer edges of vessel bifurcations are particular susceptible areas where turbulences occur.

4.2.2. Adaptive vascular remodeling

The arterial branch of circulation is a biological system displaying a high degree of plasticity (Chatzizisis et al., 2007). If the vasculature is burdened by increased flow speed, e.g. during tolerable stress, it may react upon the flow changes by modifying its diameter or its local shape. Remodeling of the local shape occurs particularly at the outer edges of blood vessel bifurcations.

The luminal surface of the blood vessel and its endothelial surface are constantly exposed to hemodynamic shear stress. Endothelial shear stress is the tangential component of the frictional force exerted in the endothelial layer by the flowing blood. Endothelial shear stress plays a key role in flow-speed control and in wall remodeling (Caro et al., 1971; Kamiya and Togawa, 1980; Girerd et al., 1996; Langille and O'Donnell, 1986). Shear forces are detected by specific mechanosensors, which are located in the tight junctions between neighboring endothelial cells and directly transmit mechanical force in chemical signaling (Tzima et al., 2005).

These mechanoreceptors help to either prevent or eliminate turbulences. If the risk of a laminar-turbulent transition rises with increasing flow speed, endothelial shear stress increases at the same time; then these mechanoreceptors upturn endothelial nitric oxide synthase (eNOS), thereby increasing the bioavailability of nitric oxide (NO), and in so doing they induce vasodilatation, which finally slows down flow speed (Kwak et al., 2014; Chatzizisis et al., 2007). In this way, mechanoreceptor-induced regulatory mechanisms help to normalize flow speed and minimize the risk of a laminar-turbulent transition.

If the turbulences are already present, these mechanoreceptors detect such flow irregularities (e.g. recirculation) by assessing low endothelial shear stress (Kwak et al., 2014; Chatzizisis et al., 2007). Thereupon they promote the uptake of circulating low-density lipoprotein cholesterol (LDL) particles into the endothelial cells (Chatzizisis et al., 2007). When LDL particles are engulfed in the endothelial layer they are associated with intimal proteoglycans, become entrapped, and undergo oxidative modification (Nakashima et al., 2007; Libby, 2002). Oxidation of LDL results in recruitment of circulating monocytes, T-lymphocytes, mast cells into the intima. These cells sustain dynamic matrix remodeling. Over time, vascular smooth muscle cells along with fibroblasts create a fibrous cap around the lipid core.

The fibrous cap along with the lipid core constitutes the so called 'fibrous cap atheroma' (Chatzizisis et al., 2007). Such a fibrous cap atheroma may mechanically function as a filling element, a sort of 'fat pad', which can expand into the vessel lumen. The protrusion might help to fill out and quiet down the area of turbulent flow. Thus, the fibrous cap atheroma can be regarded as the final product of a regulatory process that aims at reestablishing laminar blood flow. In all, the arterial branch of circulation is able to adapt to the burden of tolerable stress by undergoing plastic modification,

thereby safeguarding laminar blood flow particularly at susceptible vessel sites.

4.2.3. Persistent turbulences and atherosclerosis

During toxic stress, recurrent or persistent high cardiac output overstrains the capacity of 'adaptive vascular remodeling' to reestablish laminar blood flow. At this point, allostatic load manifests in an increased risk of turbulences at predilection sites, thereby causing atheroma progression and complications. This situation is aggravated by the fact that high sympathetic activity coincides with low parasympathetic activity. Impaired parasympathetic activity and lack of 'vagal brake' would allow sympathetic reaction to ordinary events and have greater impact on blood vessels (Sloan et al., 2007a,b). At the same time, sympathetic activity increases inflammation (Bierhaus et al., 2003; Djuric et al., 2012), and impaired parasympathetic activity leads to a lack of anti-inflammatory processes (Rosas-Ballina and Tracey, 2009; Sloan et al., 2007a). In the presence of a persistently high cardiac output and an unfavorable sympathetic/parasympathetic balance, turbulences will promote either 'excessive expansive modeling' or 'constrictive modeling' of the local vascular wall.

With excessive expansive remodeling both vessel and lumen become actually larger than the neighboring noninvolved areas. A self-perpetuating pathological interaction is established among local low endothelial shear stress, excessive expansive remodeling and plaque inflammation transforming the fibrous cap atheroma into a thin cap fibroatheromas (Koskinas et al., 2010). Thin cap fibroatheromas have a high risk of plaque rupture, which may lead to occlusive thrombosis and subsequent acute coronary syndrome or stroke.

With constrictive remodeling, persistent low endothelial shear stress leads to further fibroproliferation, expansion of the atheroma into the vessel lumen, stenotic plaque development and lumen narrowing (Stone et al., 2012). As complications of constrictive remodeling stable angina, arterial fibrillation, or transient ischemic attacks may occur. In all, repeated rises in brain energy demand during chronic stress may increase the risk of turbulent blood flow, thereby promoting the progression of atherosclerosis and its complications.

4.2.4. Stress reactivity and cardiovascular mortality

Epidemiological evidence showed that in stress-burdened people, stress reactivity was positively associated with the risk of atherosclerosis and mortality (Seldenrijk et al., 2012; Hamer et al., 2010, 2012; Lynch et al., 1998; Everson et al., 1997). Cardiovascular reactivity to acute mental stress has also been shown to be positively associated with 16-year cardiovascular mortality (Carroll et al., 2012). When compared to women, men displayed higher cortisol reactivity to a psychosocial challenge (Kudielka et al., 2009), experienced different environmental strains (e.g. in relations with family) (Block et al., 2009), and showed earlier first manifestation of cardiovascular disease (Lloyd-Jones et al., 1999; Leening et al., 2014). When studying a population of men and women, the gender gap in cardiovascular disease was found partly explained by differences in cortisol reactivity and partly by other gender-related differences (Hamer et al., 2010, 2012), e.g. level of social support (Weidner, 2000). A neuroimaging study demonstrated that carotid intima-media thickness was positively associated with amygdala reactivity and a higher functional connectivity between the ACC and the amygdala (Gianaros et al., 2009). Thus, the 'allostatic overload', which manifests at heart and brain vessels in a detrimental manner, depends on both the presence of an adverse environment and the individual's stress reactivity. In this way, Björntorp's second

idea “chronic stress causes cardiovascular mortality” found considerable support from latest studies.

4.3. Subcutaneous fat loss

During psychosocial stress, SNS-activation releases free fatty acids from subcutaneous fat depots into the venous system, which coalesces into the two major veins, the superior and inferior vena cava. From here, free fatty acids are transported into the coronary arteries, where they supply cardiac muscles, and into the systemic circulation, where they mainly supply skeletal muscles. The heart uses free fatty acids as its principle fuel (>70%), but it also uses glucose as a supplementary fuel, particularly during increased workload (via GLUT4) and myocardial ischemia (via GLUT1) (Abel, 2004; Young et al., 1999; Brosius et al., 1997). The skeletal muscles also use free fatty acids and glucose. The more the energetic needs of cardiac and skeletal muscles are covered by free fatty acids (instead of the means of glucose), the more mounts the share of glucose that is available for the brain. During psychosocial challenges, this here-described brain-pull mechanism operates in combination with the above-mentioned brain-pull mechanism ‘cerebral insulin suppression’. The latter mechanism prevents glucose uptake by skeletal muscle and subcutaneous fat, thereby additionally mounting the share of glucose for the brain. So far, so good—but enhancing cerebral glucose supply has a trade-off. As recurrent brain-pull activations blunt adipocyte energy influx and heighten its energy efflux, they cause long-term losses of subcutaneous fat mass and thus shape a lean phenotype.

4.4. Visceral fat accumulation

During psychosocial stress, SNS-activation releases free fatty acids from visceral fat depots into the hepatic portal vein. In the liver, free fatty acids are converted into ketone bodies (e.g. β -hydroxybutyrate). From there, ketones are transported via the systemic circulation toward the brain, where they enhance cerebral energy supply. In fact, experimentally-induced psychosocial stress increased concentrations of serum β -hydroxybutyrate by more than 400% (Kubera et al., 2014).

Frequent demands for free fatty acids from visceral fat may induce phenotypic changes, which may be regarded as a long-term adaptation: visceral fat accumulation. Psychosocial stress leads to the release of neuropeptide Y (NPY) from sympathetic nerves, which in turn up regulates NPY and its receptors in a glucocorticoid-dependent manner in the visceral fat (Kuo et al., 2007). This NPY response leads to angiogenesis in visceral fat tissue, local macrophage infiltration and the proliferation in differentiation of new adipocytes resulting in an increase in visceral fat mass. As mentioned above, TNF α from visceral-fat-resident macrophages favors basal glucose uptake via GLUT1 into visceral adipocytes (Lumeng et al., 2007; Cornelius et al., 1990; Battelino et al., 1999). The shift in adipocyte glucose transporter profile makes these cells more similar to the endothelial cells at the blood-brain barrier, which are exclusively equipped with GLUT1. Thus, with chronic stress both the brain and the visceral fat depot are supplied by basal GLUT1-mediated glucose uptake. Given these parallel transport features of brain and visceral fat tissue, it appears that during chronic stress the visceral fat grows in order to supply the brain with extra fuel from an extra-cerebrally located energy depot. Nevertheless, Per Björntorp’s original idea that chronic stress leads to visceral fat accumulation has here received convincing experimental support. As we will see in more detail below, habituators and non-habituators differ in their fat distribution patterns: habituators do not develop such large visceral depots.

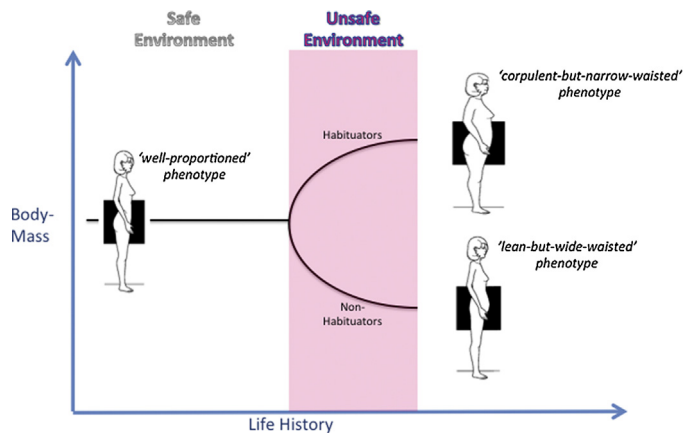


Fig. 2. The bifurcation in life history. Different phenotypic traits may develop when people live in unsafe environments. If ‘non-habituators’ are exposed to an unsafe environment, they develop a ‘lean-but-wide-waisted’ phenotype; they display a high cardiovascular mortality risk. In contrast, ‘habitua-tors’ exposed to an unsafe environment develop a ‘corpulent-but-narrow-waisted’ phenotype; they display a lower cardiovascular mortality risk. Of course, there are also transitional or mixed phenotypes.

5. Habitua-tors’ trade-offs

5.1. Blunted hypervigilance

Stress reactivity can be viewed as a trait that may change during the life course. Once exposed to a volatile environment (e.g. low control at work, unhappy relationship, poverty) people have been shown to react in two distinct genetically predisposed patterns (Figs. 1 and 2). As non-habitua-tors are characterized by their maintenance of a high reactivity to recurrent stress episodes, habitua-tors – who initially responded to stress in a high reactive manner – reduce their response by time, and from now on exhibit low neuroendocrine, cardiovascular, neuroenergetic, and emotional reactivity to stress. Noteworthy, habitua-tion is selective—allowing better discrimination of what is not versus what may be threaten-ing.

Kirschbaum et al. (1995) performed a ‘classical habitua-tion experiment’ where they repeatedly exposed participants to the same ‘homotypic’ stressor (Trier Social Stress Test; ‘TSST’). Strikingly, participants showed ‘all-or-none’ reactions: two third of them habituated, while one third did not. As habitua-tors become low reactive to stress, they may avoid futile hypervigilance, save brain energy, and thereby prevent high-flow-speed arterial turbulences (McEwen, 2012). In this way, habitua-tors can reduce their allostatic load by attenuating their stress responses, despite of being exposed to an inhospitable environment. However, becoming low reactive to stress limits one of people’s most vital abilities: being able to demand sufficient brain energy from the body. When trapped in an unsafe environment, habitua-tors are faced with the difficulty of having low brain-pull reactivity. Now, their organisms strive to find a neuroenergetic solution that allows them to preserve cerebral functioning and cerebral energy concentrations. As we will see further below, one solution is feasible for dealing with a limited brain-pull function, i.e.

- compensatory enhancement of the body-pull (appetite and ingestive behavior), but this strategy is afflicted with a trade-off:
- body mass gain (Peters and Langemann, 2009).

Stress habitua-tion is governed by the medial prefrontal cortex (mPFC) (Hill and Tasker, 2012). If an individual has habituated to a homotypic stressor, the mPFC disrupts stressor-induced amygdala

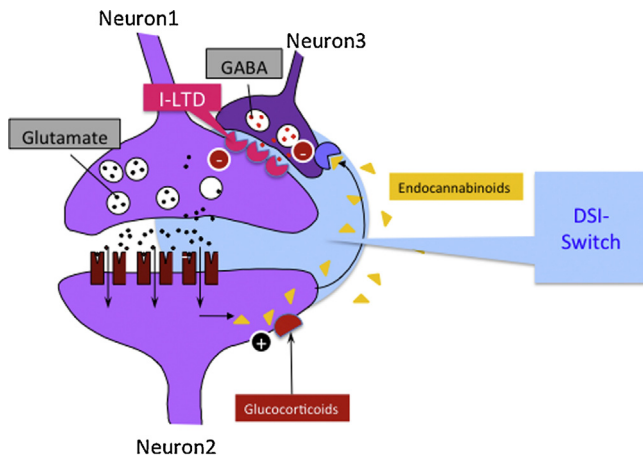


Fig. 3. Simplified model integrating molecular mechanisms underlying stress habituation in the mPFC. DSI denotes 'Depolarization-induced Suppression of Inhibition'. A homotypic stressor stimulates neuron1 to release glutamate, thereby activating neuron2. If the stimulus is strong enough, neuron2 releases large amounts of endocannabinoids, which in turn – via neuron3 – disinhibit neuron1. In this way, only strong stimuli can turn the DSI switches into the ON position, thereby reinforcing neuron1-to-neuron2 transmission. During chronic stress, elevated glucocorticoid concentrations enhance endocannabinoid production in neuron2. At those mPFC synapses that are exposed to high glucocorticoid concentrations and that are simultaneously stimulated by a homotypic stressor, the DSI switches are most likely to be turned into the ON position. Tagged in this way, these synapses are prone to undergo plastic changes through the induction of inhibitory long-term depression (I-LTD) on neuron1 (Hill et al., 2011b). In such a case of synaptic plasticity at PFC neuron1, the principal neurons2 may effectively disrupt stressor-induced amygdala signaling to the upper brain stem. Such DSI-mediated processes may lead to 'all-or-none' reactions resulting either in stress habituation or not.

signaling to the LC-NE system, thereby preventing the transition into the hypervigilant state. The endocannabinoid system in the prefrontal cortex plays an important role in that process (Hill et al., 2010, 2011b). The endocannabinoids act in a bisynaptic process (Hill et al., 2011b) that is referred to as 'depolarization-induced suppression of inhibition' (DSI) (Pitler and Alger, 1992). DSI functions as a synaptic switch, and this is reason enough why we observe 'all-or-none' reactions in stress habituation (Fig. 3) (Angeli et al., 2004).

The mechanistic elements involved in the DSI-switch are promising candidates, which might allow discriminating habituators from non-habituators. Among these candidates are the glucocorticoid receptors (Malcher-Lopes et al., 2008; McKlveen et al., 2013), the cannabinoid receptors (Fride et al., 2005; Hill et al., 2011a), and the endocannabinoid degrading enzyme fatty acid amide hydrolase (Hill et al., 2013). Interestingly, polymorphisms in the glucocorticoid and endocannabinoid receptor gene and in the fatty acid amide hydrolase gene have been found associated with several differences in body shape and body mass (Benzinou et al., 2008; van Rossum and Lamberts, 2004; Harismendy et al., 2010; Frost et al., 2010).

5.2. Cardiovascular protection

In case of habituation to a homotypic stressor, the mPFC disrupts the stressor-induced amygdala signaling not only to the LC-NE system, but also to the hypothalamus. Here, particularly the ventromedial hypothalamus and the paraventricular nucleus are affected, which results in blunted SNS and HPA axis responses. Without rise in SNS and HPA axis activity, the occurrence of high-flow-speed arterial turbulences becomes less likely (Falsetti et al., 1983; Hanai et al., 1991). As already mentioned, evidence from cohort studies shows that in people suffering from chronic stress, high stress reactivity is positively associated with atherogenesis and cardiovascular mortality (Seldenrijk et al., 2012; Hamer et al., 2012; Lynch

et al., 1998; Everson et al., 1997; Carroll et al., 2012). The other way round, people who are low reactive to stress have a low risk of cardiovascular mortality, even if they live in an unsafe environment. In this way, habituators can turn off their network of allostasis when being confronted with homotypic stressors. As a consequence of alleviated allostatic load, habituators do not only accumulate less visceral fat (Epel et al., 2000; Steptoe and Wardle, 2005; Goldbacher et al., 2005), but are also protected against cardio- and cerebrovascular disease (Seldenrijk et al., 2012; Hamer et al., 2012; Lynch et al., 1998; Everson et al., 1997; Carroll et al., 2012).

5.3. Body mass gain

Blunted SNS and HPA-axis responses, however, put the individual into a metabolic dilemma. Proper functioning of SNS and HPA-axis is indispensable for maintaining cerebral functioning and cerebral energy concentrations when food availability is low (Klement et al., 2010; Peters and Langemann, 2009). When food availability is high, however, a limited SNS and HPA axis effectiveness can be compensated for by an increased body-pull (Klement et al., 2010; Peters and Langemann, 2009). In detail: With blunted brain-pull reactivity, the 'percentage-of-glucose-allocated-to-the brain' decreases. Without taking countermeasures, the brain is at risk of being undersupplied. Significant for the context examined here is the following simple relationship. The 'percentage-of-glucose-allocated-to-the brain' multiplied by the 'total energy intake' determines the 'cerebral energy supply'. Thus, given a decreased 'percentage-of-glucose-allocated-to-the brain', compensatory enhancement of the 'total energy intake' enables the brain to supply itself in an adequate manner. In such a situation, subjects who restrain from ingesting the required extra energy would suffer from two serious problems: firstly, 'cerebral energy sparing' leading to neuroglycopenic states and low cognitive performance (Brunstrom et al., 2005; Green et al., 2000; Kemps et al., 2005; Kemps and Tiggenmann, 2005) or, secondly, a 'too high load on the cerebral energy demand' (indicated by high cortisol concentrations) (Rutters et al., 2009; Anderson et al., 2002; Rideout et al., 2006; Tomiyama et al., 2010; Langfort et al., 1996; Edelstein et al., 1983; Prouteau et al., 2006) leading to a reduction in bone mass (Villareal et al., 2006; Vescovi et al., 2008) and menstrual irregularities (Vescovi et al., 2008). Thus, habituators may benefit from eating extra calories, namely from those that are needed in the brain.

Again, there is a trade-off. As has been shown analytically, an important property is inherent to the cerebral supply chain: The 'percentage-of-glucose-allocated-to-the body' increases in inverse proportion to the 'brain-pull reactivity' (Peters and Langemann, 2009). Thus, in case of low brain-pull reactivity, the surplus of the ingested energy is preferentially allocated to the body periphery (Peters and Langemann, 2009). As the power of 'cerebral insulin suppression' subsides, a particularly large amount of energy enters the subcutaneous fat stores—thereby leading to body mass gain in the long term.

Hence, habituators may also experience the complications of high body mass, which mainly include poor mobility and osteoarthritis in knees and hips (Lohmander et al., 2009; Mork et al., 2012; Wills et al., 2012). It should not be forgotten that people with high body mass also suffer from weight stigmatization that is quite common in our society (Puhl and Heuer, 2009; Sikorski et al., 2012). But, on the other hand, habituators are unlikely to build up visceral fat depots, because their cortisol concentrations are rather low (Epel et al., 2000; Steptoe and Wardle, 2005; Goldbacher et al., 2005). In this way, habituators who live in uncertainty are likely sooner or later to develop a corpulent phenotype with predominant accumulation of subcutaneous fat (the 'corpulent-but-narrow-waisted' phenotype).

Several lines of evidence support the hypothesis that low stress reactivity is strongly linked to body mass gain. Epidemiological evidence demonstrates that individuals with low stress reactivity are at risk of gaining body mass over the next decades (Flaa et al., 2008; Phillips et al., 2012; Carroll et al., 2008). Experimental evidence shows that corpulent subjects react to a mental and psychosocial stress test in a low reactive manner (Jones et al., 2012; Kubera et al., 2012). When compared to lean subjects, the subjects with a high body mass displayed low cortisol reactivity to both an acute mental challenge and to a subsequent meal, displayed smaller changes in the vigilant state, less pronounced post-stress-neuroglycopenic states, less pronounced rises in serum ketone concentrations, and showed less 'cerebral insulin suppression' during a meal (Jones et al., 2012; Kubera et al., 2012, 2014). Moreover, the corpulent subjects showed less anxiety, less uneasiness, less physical malaise and less sadness during the psychosocial challenge (Peters et al., 2013). Thus, individuals with a high body mass demonstrated low neuroendocrine, cardiovascular, neuroenergetic, and emotional reactivity to stress. There is further experimental evidence showing that people with a high stress exposure, who were low reactive to a psychosocial challenge, consumed more calories regardless whether they were stressed or not (Tryon et al., 2013). Here we find exactly determined what Dallman et al. (2003) has pointed out more than 10 years ago: namely, reduced activity in the chronic stress-response network and eating 'comfort food' go together. In all, body mass gain can be regarded as an adverse effect of habituators' neuroenergetic strategy that safeguards cerebral functioning and cerebral energy concentrations.

6. Non-homogeneous populations

When analyzing data from non-homogeneous populations, scientists often run into problems (Patterson et al., 2006). An example should illustrate this: A drug is tested in a placebo-controlled trial. In the study sample, half of the subjects have a genetic factor that is absent in the other half. The drug is effective only in combination with the genetic factor—otherwise it is harmful. At this point, statistical analysis fails to reveal significant differences between the drug- and the placebo-group. The pitfall of analyzing such a non-homogeneous population is that the drug is classified as totally ineffective, although it actually has beneficial effects in about half of the cases.

With respect to body mass gain and loss, another thought provoking set of paradoxical findings emerged. We consider it closely related to the 'obesity paradox'. First-year students at the University College of London reported an effect of perceived stress on their eating behavior and body mass: in particular, 42% reported decreased food intake, whereas 38% reported increased food intake (Oliver and Wardle, 1999). Later investigations of this university student population revealed reported body mass gain in 55%, body mass loss in 12% of the students, and stable body mass over the one-year period in 33% (Serlachius et al., 2007). Confirmation came from larger cohort studies showing that some stressed individuals gained body mass while others lost it (Kivimaki et al., 2006; Block et al., 2009; Lopez-Jimenez et al., 2008). Given the evidence from the above-mentioned 'classical habituation experiment' showing that two third of participants were habituators while one third were non-habituators (Kirschbaum et al., 1995), it is likely that the London first-year students also belong to a non-homogeneous study population. To avoid false conclusions when analyzing studies on body mass and body shape we should be aware of eventually dealing with non-homogeneous study populations.

Complex environments acting on non-homogeneous populations produce a particularly high degree of phenotypic diversity. With habituation to a 'homotypic' stressor, the capability to

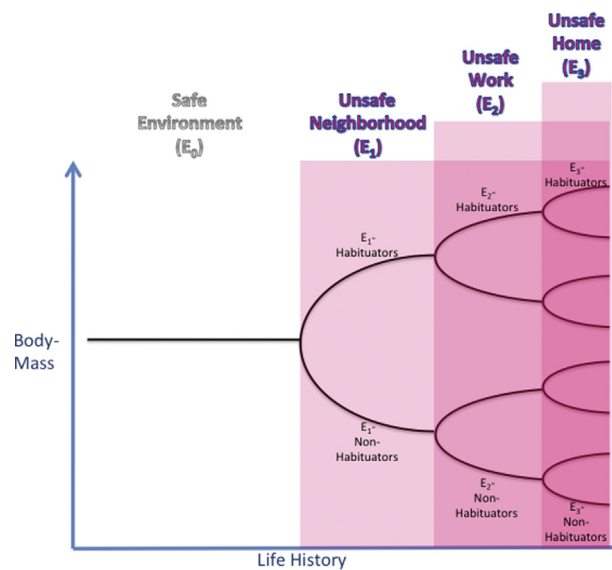


Fig. 4. Phenotypic diversity originating from heterotypic stressors prevailing in different stressful environments. Different phenotypic traits may develop when living in stressful environments like the neighborhood, work, and home. Whether habituation does occur or not depends on whether the situation-specific stress-induced cortisol surge stimulates endocannabinoid production strongly enough to exceed the critical threshold for the all-or-none habituation process.

respond to a novel 'heterotypic' stressor is still preserved. Thus, habituation is likely related to recognizing that the same threat is tolerable, but does not mean lack of vigilance to novel threats—an important distinction, because habituation also means greater discrimination and more precise responses, rather than a general reaction to many stimuli, which is characteristic of an anxiety disorder such as post-traumatic stress disorder and generalized anxiety disorder. With heterotypic stressors originating from different stressful environments (e.g. work, home, or neighborhood) diversity in phenotypes can develop (Fig. 4). It could be that a person, who habituated to the homotypic stressors at work, did not habituate to heterotypic stressors prevailing at home, because the response to the latter stressor does not exceed a certain threshold. In this way, mixed phenotypes may develop that exhibit both subcutaneous and visceral fat accumulation. In all, non-homogeneous populations living in complex environments may generate a remarkable diversity of phenotypes.

Evolutionary biology has extensively studied adaptations to environmental changes. When environments within the range of a species differ, it is unlikely that any single phenotype will confer high fitness in all situations. In such a case, a change in the phenotype (e.g., habituation, body shape) that depends on the environment can provide increased environmental tolerance (Via and Lande, 1985; Via et al., 1995; Agrawal, 2001).

7. Conclusions

For us as authors, it is the historical merit of Per Björntorp to have laid the foundations for understanding how stress mediators damage the cardiovascular system, how habituation protects the vasculature, and why, in that context, the different fat distribution patterns – visceral vs. subcutaneous fat accumulation – display diverging prognostic values.

When people live in unsafe environments their phenotype may change during the life course. Broadly speaking, we encounter three human phenotypes (apart from mixed types): First, the phenotype of people who do experience 'good' stress only. They live in favorable socioeconomic environments and favorable emotional family

environments. They experience challenge and reward, a sense of mastery and good self-esteem. Their body waist, hip and height measurements stay well proportioned, and their cardiovascular mortality risk remains low (Pulkki-Raback et al., 2015). Second, the phenotype of people who experience tolerable stress. Their cardiovascular mortality risk remains low, too (Seldenrijk et al., 2012; Hamer et al., 2012; Lynch et al., 1998; Everson et al., 1997; Carroll et al., 2012; Hamer and Stamatakis, 2012; Cameron et al., 2012; Berentzen et al., 2010; Petursson et al., 2011). They may habituate and in so doing become able to tolerate aversive circumstances by buffering the allostatic load. Their main trade-off is that they often become corpulent (Flaa et al., 2008; Phillips et al., 2012; Carroll et al., 2008) (thereby suffering mainly from osteoarthritis and poor mobility), but they do not accumulate much visceral fat (Epel et al., 2000; Steptoe and Wardle, 2005; Goldbacher et al., 2005). Third, the phenotype of people who experience the unbuffered allostatic overload of toxic stress. They belong to the non-habituated and display compromised recovery. They become lean, but in spite of that they acquire large visceral fat depots (Epel et al., 2000; Steptoe and Wardle, 2005; Goldbacher et al., 2005). When compared with habituated, they view themselves as having less self-esteem, and being more often in a depressed mood (Kirschbaum et al., 1995). Their life-long risk for physical and mental disorders is increased (Xu et al., 2015). From among all of these phenotypes, they carry the highest cardiovascular mortality risk (Seldenrijk et al., 2012; Hamer et al., 2012; Lynch et al., 1998; Everson et al., 1997; Carroll et al., 2012; Hamer and Stamatakis, 2012; Cameron et al., 2012; Berentzen et al., 2010; Petursson et al., 2011).

Based on the lessons learned from the modern population-based studies, which made combined use of waist circumference and body mass index, a simple and practical tool had been proposed to assess the mortality hazard. It is called 'Body Shape Index' (ABSI) and describes the risk associated with visceral fat accumulation as indicated by a wide waist relative to body mass index and height (Krakauer and Krakauer, 2012, 2014). It predicted quite precisely the mortality risks in the United States National Health and Nutrition Examination Survey and in the British Health and Lifestyle Survey. ABSI values are low in the 'well-proportioned' phenotype, comparably low in the 'corpulent-but-narrow-waisted' phenotype, and high in the 'lean-but-wide-waisted' phenotype. With the help of the 'body shape index' we can identify those lean high-risk people that have escaped medical attention for so long.

Based on evidence from randomized controlled trials, we here recommend paying more attention to this high-risk 'lean-but-wide-waisted' phenotype and intervene against cardiovascular disease and visceral fat accumulation by targeting their common fundamental cause (Kaufman et al., 2007; Orth-Gomer et al., 2009; Gulliksson et al., 2011). Such a more in-depth approach would involve improving people's psychosocial skills to cope with an inhospitable environment (Storch et al., 2007; Hammerfald et al., 2006; Gaab et al., 2003; Orth-Gomer et al., 2009; Gulliksson et al., 2011) or, better still, improving people's environment and providing them with more certainty (Ludwig et al., 2011, 2012).

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