

Review

Where psychology meets physiology: chronic stress and premature mortality—the Central-Eastern European health paradox

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Abstract

A substantial and still growing body of research tries to link different psychological models and chronic diseases, with special emphasis on cardiovascular disease. These efforts have established several conceptual bridges that connect psychological alterations and psychosocial factors to the risks, onset and prognosis of cardiovascular disease. However, several different models have been suggested. Depression and learned helplessness are two central psychological models that have been shown to have major explanatory power in the development of chronic diseases. In this respect the so called Central-Eastern European health paradox, that is the morbidity and mortality crisis in these transforming societies can be regarded as a special experimental model.

In this review chronic stress is proposed as an integrating theory that can be applied to different psychological models. Chronic stress and allostatic load has been shown to lead to typical pathogenetic results in animal experiments. Chronic stress theory is applicable to the explanation of the suddenly changing patterns of premature mortality rates in transforming societies. Literature and the different models in the field of psychology, behavioural sciences, and epidemiology are reviewed in terms of the chronic stress theory. The applicability of these results are investigated for further research, clinical and policy implications.

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1. Introduction: parallel findings in behavioural sciences and physiology

Depending on the field of observation there are several parallel concepts, which analyse similar phenomena. These are the different stress theories in physiology, learned helplessness and control theory in psychology, depression research in psychiatry, research of psychosocial factors in sociology.

Interestingly stress models in physiology are mostly based on acute or relatively short term experiments. If we return to the original concept of the General Adaptation Theory of János Selye [131,132], the three phases of stress are alarm reaction, resistance phase and, the third, physiologically most harmful phase, exhaustion [26]. Among all of the existing hypotheses chronic stress theory could be the most fruitful explanation, which incorporates—the learned helplessness model, the psychosocial and psychiatric models of depression, the control theory of stress and health

[46,141,142,162], and the concept of vital exhaustion as a cardiovascular risk factor [2,3,17,30,63].

Furthermore, such a unified stress model could best explain the morbidity and mortality crisis in the middle aged male population in Central and Eastern Europe in the last decades [19,41,57,61,62,71–74,76,86,87,152,155].

The temporal factor in existing stress models is often neglected. Laboratory investigations frequently focus on the short term physiological effects of acute stressors, while chronic stress shows different patterns [78].

Although the enduring negative emotional evaluation of a life situation depends primarily on the given situation, however, the vulnerability of the person is similarly important. The subjective appraisal, interpretation of the situation depends to a great extent on the early environmental influences on development, both in respect to the development of the brain structures and psychological coping abilities. One type of the animal “social stress model” of depression can be characterised with an early life chronic stress situation [90]. It is the result of the disruption of mother–infant or peer bonding, which seems to resemble human depression or vulnerability to depression. Initially, the infant displays

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so-called “protest” behaviour (acute and resistance phases of stress). This is generally followed by a second phase, which is characterised by locomotor inactivity and a disinterest in motivationally salient external stimuli. This state is characterised by “despair”. The third phase is called “detachment”. This process seems to be “hardwired” in the brain of many social mammals and results in high vulnerability [90]. In the last decades attachment theory has become the organising framework of studies related to physiological, psychological and developmental importance of the early childhood affective mother–child bond and the negative consequences of the disruption of this relationship [12]. According to follow up studies, insecure attachment predicts later emotional instability and health deterioration [33]. Maltreatment at an early age can have enduring negative effects on a child’s brain development and function, and on his or her vulnerability to stress [146].

1.1. Chronic stress, learned helplessness, control and depression

In several types of animal depression models, for example in the “behavioural despair model” or the “chronic mild unpredictable stress models” the altered affective state of the animals reflect the “hopelessness” state. This model can also be interpreted as the “learned helplessness” model, which seems to be the best animal model of depression [90].

Learned helplessness means a condition of loss of control created by subjecting animals or humans to an unavoidable, emotionally negative life situation (such as unavoidable shocks, relative deprivation, role conflict, etc). Being unable to avoid or escape (flight or fight) an aversive situation for a long period of time produces a feeling of helplessness that generalises to subsequent situations [129,130]. Learned helplessness is a typical chronic stress situation, when a persistent deadlock, feeling of total lack of control makes the avoidance of an emotionally negative situation impossible. An animal exposed to inescapable, uncontrollable stress shows subsequent deficits in learning how to terminate the noxious stimulus, even when it is escapable or controllable. In such a state, the hippocampus appears to become primarily affected by the long-lasting elevations of circulating corticosteroids resulting from uncontrollable stress. Severe stress for a prolonged period causes damage in hippocampal pyramidal neurons, especially in the CA3 and CA4 region and reductions in the length and arborization of their dendrites [45]. In connection with the physiological consequences of chronic stress the feeling of lack of control has central importance.

Stephens [142] has summarised the adverse effects of uncontrollable stress in comparison with matched controllable aversive stimulation. These effects are: decreased food, water consumption, greater weight loss, higher plasma corticosteron, increased gastric lesions, reduced production of specific antibodies, reduced lymphocyte reactivity, decreased cytotoxic activity of natural killer cells, de-

creased tumour rejection, increased susceptibility to malignancy.

Sense of control is an individual belief pattern that also has developmental and social determinants. Animal studies indicate that monkeys, provided with experiences of controllable (contingent) events early in life, are subsequently less reactive to stressful events in adulthood. The experience of a major uncontrollable event in childhood, such as the death of one’s mother, is associated with increased likelihood of depression following negative life events in adult life [142].

The unique conceptual review of Huether [45] makes an attempt to combine data from biological and psychosocial stress literature. According to his evolutionary model stress responses act as triggers for the adaptive modification of the structure and the function of the brain. Stress responses serve to adjust in the physical, emotional and personality development in a self-optimising manner, in accordance with the ever-changing requirements of the external world. The repertoire of emotional, cognitive and behavioural coping strategies might partly be due to hereditary factors governing the expression of certain genes for specific hormones, receptors or enzymes. The magnitude and duration of aversive experiences, the critical timing of the events, the actual genetic vulnerability of an individual determine the possibility for adaptive modifications of the functions and structure of the neuronal circuits and associative networks involved in the regulation of the behavioural and endocrine responses of an individual to aversive stressful experiences.

According to animal studies, males appear to be more vulnerable to long-lasting, stress-induced hippocampal damage than females [147], as the decline of circulating testosterone levels resulting from uncontrollable stress seem to play an additional role [98,147]. It is an interesting parallel finding, that depression seems to influence cardiovascular risk more among men than among women according to follow up studies [35,102,106]. Despite similar free cortisol responses of men and women (studied in the luteal phase) to psychosocial stress, gender may exert differential effects on the immune system by modulating glucocorticoid sensitivity of proinflammatory cytokine production [116].

Petty et al. [107] and Ronan et al. [117] analysed the brain mechanisms which might protect the animals from learned helplessness after exposure to inescapable stress. Petty et al. [107] found that rats which did not become helpless after exposure to uncontrollable shock had increased basal hippocampal norepinephrine levels, as well as higher stress-induced hippocampal norepinephrine, compared with control nonshocked rats and with rats with learned helplessness. These results indicate that the hippocampal norepinephrine system plays a role in the attention processes involved in interpreting external stressful events and in developing a behavioural response. Other transmitters have also been implicated in learned helplessness, including GABA, serotonin, and dopamin. According to Ronan et al. [117], increased serotonin metabolism in the lateral septum may protect animals from adverse behavioural conse-

quences in inescapable stress. Pyridoxine nutritional status has a significant and selective modulatory impact on the central production of both serotonin and GABA. Thus, high dose pyridoxine, by amplifying tissue levels of pyridoxal phosphate, may be expected to have a favourable impact on dysphoric mental states, while diminishing sympathetic output and acting peripherally to blunt the physiological impact of corticosteroids [93]. According to the experimental results of Minor et al. [97], a compromised brain energy metabolism might contribute to deficits in escape performance following inescapable shock. Pharmacological blockage of centrally located adenosine receptors is both necessary and sufficient to reverse the behavioural impairment induced by metabolic stress and pre-treatment with inescapable shock. Escape deficits can be completely reversed by peripheral and intracranial administration of the adenosine receptor antagonist caffeine. According to these results the behavioural impairments in helplessness might follow inescapable shock as a consequence of an excessive and prolonged fear reaction and its subsequent effects on neural excitability and energy homeostasis [97]. According to Schurr [127], glucose induced glucocorticoid release plays a significant role in preventing the quick collapse of energy metabolism in the brain and consequently, the better recovery from cerebral ischemia.

Recent data suggest that chronic stress results in slowly developing neurochemical changes, possibly via changes in gene expression [39]. Heller et al. [39] examined the interaction between chronic social stress and the resulting depressive behaviours in noradrenaline transporter knockout (NET-KO) mice. In these animals the situation specific behavioural depression was similar to NET mice, but this reaction was not generalised to subsequent situations, which might mean relative protection against learned helplessness in the NET-KO animals.

Learned helplessness might be called a behavioural depression [108] resulting from exposure to inescapable stress. Learned helplessness might be conceptualised as a limbic system dysregulation, with different brain regions involved as medial prefrontal cortex, hippocampus, septum, hypothalamus, amygdala and nucleus accumbens.

Seligman et al. [129,130] asserted that learned helplessness appears very much like human depression. Seligman hypothesised that both learned helplessness and reactive depression result from the expectancy that responses and outcomes are uncontrollable and might result in only emotionally negative consequences. In humans, learned helplessness also refers to the motivational, cognitive and emotional components of the interpretation of the environmental stimuli. In humans, defensive mechanisms also operate at mental level through putative ego defences, the psychological function of which is to preserve self-esteem by hindering the access of disturbing emotional material into awareness [24].

Human psychological stress reactions depend on the subject's interpretation of the changes perceived from their outside world and on the optimisation principles of

the person. The ability to deal successfully with stressors strengthens the self-esteem, self-efficacy and the problem solving, coping skills of the person [45]. The experience of the controllability of stress situations is the driving force of the so-called learned resourcefulness, which is the opposite of learned helplessness.

A special feature of human stress is when an imaginary scenario is constructed. The scenario may never occur, but it is still regarded as a real and constant risk by the person [45]. Therefore the cognitive, mental interpretation of the situations has a central importance in human stress research.

2. Findings in psychiatric and cardiological epidemiology: depression, hopelessness and vital exhaustion: what is the evidence that psychosocial factors influence cardiovascular risk?

Hemingway and Marmot [43] reviewed systematically the prospective cohort studies testing special psychosocial hypotheses in connection with aetiological factors in coronary heart disease (CHD). Each of the 11 follow-up studies showed that depression and anxiety are risk factors in cardiovascular morbidity and mortality. The prospective cohort studies prove strong evidence that depression is independent aetiological and prognostic risk factor for coronary heart disease [106].

In their review Kubzansky and Kawachi [78] tried to reach the "heart of the matter" and discussed the question "Do negative emotions cause coronary heart disease?" They summarised the epidemiological evidence for an association between negative emotions and coronary heart disease (CHD) and discussed briefly the mechanisms by which emotions may be linked to CHD in the light of mainstream psychological research on emotions. According to their conclusion growing evidence indicates that negative emotions may influence the development of CHD.

Musselman et al. [102] and Glassman and Shapiro [35] reviewed the relation between depression and cardiovascular disorders, chiefly morbidity and mortality in myocardial infarction. After controlling the results for smoking and other known risk factors for cardiovascular diseases (gender, weight, activity, blood pressure, and cholesterol), the apparently healthy individuals who had elevated depression ratings were more likely both to develop and die of ischemic heart disease. That is depressive symptomatology is an independent risk factor, especially among men. The results of five long-term studies with follow-ups show that people with depression, but no cardiovascular disorders at the beginning of the study, were 2–4 times more likely to die in myocardial infarction in case of serious depression, if their data were standardised by other risk factors [99,110]. Consequently, the actual risk is substantially higher, since depression increases the probability of other known risk factors, such as smoking, excessive alcohol consumption, stress related eating problems. Another important conclusion can

be drawn from the prospective studies, that is not only diagnosed depression, but also depressive symptoms checked by suitable clinical scales mean increased risk in subjects with and without cardiac disease at baseline [95,106,110].

The latest results of the 10-year long follow up results of the National Health and Nutrition Examination Survey (NHANESI) and the Normative Aging Study [31,133] supported the above findings. While controlling for the possible confounding factors, depression was associated with increased risk of CHD incidence in both men and women, as well as CHD mortality in men [31]. Symptoms of depression are also predictive of stroke in all strata, among white and black men and women [48]. Depression seems to be an independent risk factor after myocardial infarction as well [34,91].

Not only depression but also hopelessness alone seems to be an independent cardiovascular and overall risk factor. According to the series of studies by Barefoot et al. [6], negative affect and hopelessness predicted mortality in a 19.4-year follow-up study after controlling the data according to the other confounding factors.

Everson et al. [27] in a six-year follow-up study of 2500 middle-aged Finnish men proved that mortality due to myocardial infarction showed close connection to hopelessness recorded six years earlier, given that the data were standardised by the known risk factors. Moderately and highly hopeless men have significantly increased risk of all-cause and cause specific mortality compared to men with low hopelessness scores. High hopelessness predicted higher incident of myocardial infarct. In this study independently from depression and the traditional risk factors hopelessness was a strong predictor of adverse health outcomes. Men, reporting high levels of hopelessness at baseline, had a faster progression of carotid atherosclerosis, assessed by four measures of intima-media thickening than men reporting low to moderate levels of hopelessness [27]. Traditional coronary risk factors and use of cholesterol lowering and antihypertensive medication did not account for much variance in this observed relationship. These findings indicate that hopelessness contributes to accelerated progression of carotid atherosclerosis, particularly among men with early evidence of atherosclerosis, and chronically high levels of hopelessness [28,29,154]. Incidence of hypertension is also predicted by high levels of hopelessness. After adjusting the data according to age, body mass index, baseline resting blood pressure, physical activity, smoking, alcohol consumption, education, parental history of hypertension and self-reported depressive symptoms, men reporting high levels of hopelessness at baseline were three times more likely to become hypertensive (systolic blood pressure above 165 mmHg and/or diastolic blood pressure above 95 mmHg) or confirmed use of antihypertensive medication [28,29].

The summary published by the National Heart, Lung and Blood Institute [103] considers vital exhaustion a separate cardiovascular risk factor besides depression [2,3,30,64]. According to Cole et al. [17] a sense of exhaustion was as-

sociated with twofold increase in coronary heart disease after adjusting the data according to age, body mass index, smoking, history of diabetes and hypertension, sleep duration, insomnia, depression, alcohol intake, and physical activity. Wirtz et al. [158] found that in highly exhausted individuals, glucocorticoids exert less suppressive action on monocyte IL-6 release than in nonexhausted subjects. This finding points to altered regulation of monocyte cytokine production as one possible pathway linking exhaustion with atherosclerosis.

According to the data of 2731 complete twin pairs [126], 64% of the variance of heart disease was common with depression symptoms and hypertension. Men who reported cardiovascular disease were significantly more likely to have depression symptoms. The lifetime co-occurrence of these phenotypes is partly explained by common genetic risk [126].

The results of randomised trials of treating depression after myocardial infarction are controversial [75]. According to the final results of the multicenter ENRICHD randomised trial, the intervention did not increase the event free survival [7], although depression and social isolation decreased. According to the comprehensive review of Rozansky et al. [118] the psychosocial intervention trials yielded both positive and negative evidences for the efficacy of these interventions on cardiovascular morbidity and mortality. According to Linden et al. [83] depending on the way of intervention the addition of psychosocial treatments to standard cardiac rehabilitation regiments might reduce mortality, morbidity, psychological distress, and some biological risk factors [83]. Those psychosocial intervention trials, which have yielded positive results on cardiac morbidity and mortality, have provided encouraging data [38,104,105]. However, the negative results highlight the fact that several uncertainties exist in terms of the most appropriate and effective intervention methods, and the practical questions about how these should be administered in particular groups of patients [118].

There are more than 19 million adults in the US suffering from depression, and only one out of three receives treatment [159]. Major depression is a common disorder, associated with substantial role impairment, reduced performance at work and a low quality of life [55,119,143]. Therefore there is a need for improving the quality of treatment, which might be based on integrated bio-psycho-social approaches [113,159,160]. Depression causes 12% of all disability in the civilised world and in the 15–44 years old population mental disorders are the most important components of the global burden of diseases [101].

Depression and enduring negative emotions can make the course of other disorders, such as cancer, diabetes, immunological abnormalities, osteoporosis and the ageing process more serious [16,23,27,44,56]. The connection between bone mineral content and depression can be considered proven, that is to say the threat of osteoporosis increases in cases of depression [85,96,128].

3. Physiological mechanisms

The paper of Sklar and Anisman [135] was among the first which described, that in a chronic stress situation which can be characterised by permanent loss of control the tumour growth increased considerably among the experimental animals.

There are excellent reviews on the physiological pathways of negative emotion, chronic stress and depression on CHD [36,44,57,78,102]. The review of Kubzansky and Kawachi [78] describes the biological, social and behavioural pathways as well.

The main biological pathways are:

- Dysregulation of the hypothalamus–hypophysis–adrenocortical (HPA) axis and the sympathetic–adrenal–medullary system (SAM) resulting in elevations in serum catecholamin and cortisol levels. Sympathoadrenal hyperactivity contributes to the development of CVD through effects of catecholamines upon the heart, blood vessels and platelets. Sympathoadrenal activation modifies the function of circulating platelets through direct effects, catecholamin induced changes of hemodynamic factors, circulating lipids. Prostaglandins contribute to diverse circulatory and hemostatic functions including inhibition of platelet aggregation and vascular contractility and permeability.
- Alterations in autonomic nervous system activity, as demonstrated by reduced heart rate variability (HRV), is a sensitive measure of the dysregulation of the functioning of the rapidly reacting sympathetic, parasympathetic and renin-angiotensin system. Reduced high-frequency heart rate variability has been observed in depressed patients in comparison with non-depressed groups [102].
- Alterations in platelet receptors and reactivity.

The adverse effects of depression on CVD might be mediated via platelet mechanisms. Platelets play a central role in hemostasis, thrombosis, development of atherosclerosis and acute coronary syndromes, through interactions with subendothelial components of damaged vessel walls and plasma coagulation factors, primarily thrombin. Human platelets contain adrenergic, serotonergic and dopoaminergic receptors. Platelets also contribute to vascular damage by stimulating lipoproteine uptake by macrophages and mediating vasoconstriction. Serotonin mediated platelet activation can contribute to the development of atherosclerosis, thrombosis and vasoconstriction in depressed persons [102]. Camacho and Dimsdale [14] and Von Kanel et al. [150] reviewed recently the literature on the effects of stress on hemostasis which might be the most plausible biobehavioural link between negative emotions, chronic stress and coronary artery diseases.

A recent history of major depressive episodes revealed a strong association with elevated C-reactive protein in middle aged men. In this group, the low grade systemic inflamma-

tion could also represent a mechanism linking depression to cardiovascular risk [21].

Gold and Chrousos [36] described in detail the endocrinology of melancholic and atypical depression in relation to neurocircuitry and somatic consequences. The stress-responsive neuroendocrine systems have been the prime focus on endocrine studies on depression. Melancholia resembles a state of chronic stress and often is accompanied by sustained hypercortisolism. In melancholia, hypercortisolism does not adequately restrain the production of corticotropin releasing hormone (CRH) in the hypothalamus. Long-term glucocorticoid excess downregulates hippocampal glucocorticoid receptors and it may be detrimental to hippocampal neurons containing glucocorticoid receptors with reduced hippocampal volumes in patients with depression. Repeated, long-lasting, i.e. chronic stress downregulates hypothalamic glucocorticoid receptors as well. Sustained hypercortisolism can initiate a vicious circle of progressive hypercortisolism and also diminishes dopamine release in the nucleus accumbens, an important component of the mesolimbic reward system. This effect plays an important role in anhedonia in depression [144].

The integrity of hippocampus is essential for memory functions. Chronic stress can permanently downregulate hippocampal cell receptors, and produce chronic hippocampal inflammation (astroglial) killing the cells. Hippocampal damage could be associated with some degree of impairment of learning and memory [142].

The abnormal activity of the HPA axis, changes on mood and central neurotransmission in depression may result from over-production of pro-inflammatory cytokines [145]. The action of antidepressants in *in vitro* studies may help to explain the suppressive effects of anti-depressants on pro-inflammatory cytokine production on immune functions in depression [139]. Cytokines have effects on the central nervous system and modulate the HPA axis acting at all three levels. They activate cerebral norepinephrine metabolism [25,148,149]. In the laboratory of Vizi and Elenkov [25,149] convincing evidence has been obtained that noradrenaline released nonsynaptically from sympathetic axon terminals and enhanced in concentration in the close proximity of immune cells is able to influence cytokine production under stressful conditions. Attention has been focused recently on alpha and beta receptor mediated modulation by endogenous noradrenaline of pro- and anti-inflammatory cytokine production [25,148,149]. In understanding the complexity of stress processes it is fundamental to concentrate more on the cross-talk between the body's integrative systems, both the nervous system and the immune system [25,148,149].

Hypersecretion of paraventricular CRH, acting via intrahypothalamic connections and at pituitary ACTH secreting cells, suppresses the reproductive growth hormone and immune axes at multiple levels. That is hypercortisolism, diminished growth hormone secretion, hypothalamic hypogonadism, and catecholamine-induced enhancement of lokal interleukin-6 release are the long term conse-

quences of chronic stress in relation to melancholia. The depression-related susceptibility to coronary artery disease involves a number of factors similar to those seen in metabolic syndrome X, including visceral obesity, insulin resistance, hypertension, and dyslipidemia [8]. Visceral fat can increase even when weight is lost during melancholic depression. Melancholic depression can lead to these components of metabolic syndrome X as well as to excessive clotting, deficient fibrinolysis, and enhanced endothelial inflammation [36].

The HPA axis, along with the sympathetic nervous system dominates the stress response. Perceived stressors cause hypothalamic release of cortisol releasing factor (CRF) which triggers pituitary release of ACTH. CRF is the principal but not the sole releaser of ACTH, various ACTH “secretagogues”, such as vasopressin, oxytocin, and catecholamines stimulate ACTH release and/or augment CRF action [94]. This processes cause adrenal secretion of glucocorticoids. The steroids are vital for surviving physical stressors, they mobilize energy, increase cardiovascular tone, and suppress unessential anabolism such as growth, reproduction and inflammation. However, glucocorticoid excess can cause steroid diabetes, myopathy, hypertension, and reproductive as well as immune suppression [123,124,144]. Glucocorticoid pathology occurs when the natural recovery phase to noxious stimuli is prevented from occurring and prolonged glucocorticoid elevation is maintained [125].

Horrobin and Bennett [44] postulate that impaired phospholipid metabolism and impaired fatty acid-related signal transduction processes may explain the interactions between depression and other diseases.

In chronic stress the HPA dysregulation might result in hypocortisolism as well. Reduced reactivity of the HPA axis in chronic stress and depression has been attributed to negative feedback inhibition due to increased levels of circulating corticosteroids [42].

Depression as defined by the DSM-IV-TR [32], can present itself with widely varying psychological and physiological features, it is still unclear whether it represents groups of separate illnesses with overlapping features or a single pathophysiological process. One of the most common features in depression is an obsessional preoccupation with personal inadequacy and the inevitability of loss. The behavioural and psychologic changes that occur during chronic stress are strikingly similar to the chronic changes in melancholic depression [13,36,37]. The common features include enhanced arousal and focus, increased anxiety and vigilance, inhibited eating and sexual behaviour, immune suppression, and activated pituitary-adrenal and sympathetic function. These similarities appear to be the result of similar, if not identical, effectors (e.g., corticotropin releasing hormone and locus coeruleus-norepinephrine systems). These similarities suggest that melancholic depression arises from a generalized stress response that has escaped the usual counter regulatory restraint [36,37,125].

The hopeless, long-lasting negative emotional state is one of the central features of depression, but not in each form of it and not always in the same amount. It is an important task of future studies to differentiate the physiological consequences of hopelessness from the effects of other components of depression. There are attempts to differentiate the hopeless subtype of depression [1]. These features are most pronounced in dysthymia and in melancholic subtype of depression.

4. The behavioural model of adaptation to environmental influences: the importance of psychosocial factors in transforming societies?

While in modern societies our living conditions have improved in many respects, other aspects have been fundamentally damaged. Important factors of personality development, for instance mother child relationship, social models of the extended family, and in what order values are passed on are challenged. The accelerated pace of life, unpredictable environmental changes are added to the above factors, for this reasons it is understandable that in all developed countries the number of adults and children suffering from anxiety and depression symptoms has increased [101,159–161]. Compared to other countries, in this respect more dramatic changes could be experienced in the suddenly changing Central-Eastern European and Eastern European countries. For example, in Hungary the prevalence of severe depressive symptomatology increased between 1988 and 1995 from 2.9 to 7.1% [69,71,73].

From an evolutionary perspective [20,140] the development of modern medical practice depreciated natural selection by its achievements to reduce prenatal and infant mortality leading to a rise of phenotypically silent mutations from generation to generation. As a consequence we carry more and more chaperone-buffered, silent mutations. These phenotypically exposed mutations contribute to a more abundant manifestation of multigene diseases, such as atherosclerosis, cancer, diabetes, hypertension and several psychiatric illnesses [20].

Over the last two centuries, although technology and civilization have achieved unbelievable successes, little attention has been given to what effect these absolutely new historical “experiments” have had on people.

The individual can be considered as one of the players, in a game theory model, where the other player is the natural and social environment [60,62,66,68]. The environment tries to impose its own demands and conditions on the individual, while the individual is an active being who shapes his surroundings and tries to achieve his aims and values.

For the human being attitudes, values, perceived self-efficacy and self-esteem which were developed during socialisation dominate in controlling the actual behaviour with the same or greater force as conservation of the physiological balance.

The cognitive evaluation, appraisal of the situation means that we compare our perceived capabilities that are available to solve the situation with the perceived environmental expectations, and decide on the basis of our previous experiences whether we are capable of solving the problem [4,5].

The basic connecting point of psychological and physiological phenomena is that mechanism to which the above mentioned examples point, since the environmental effects can cause physiological symptoms only through cognitive appraisal. If we interpret a situation as dangerous, if we react with an alarm reaction—independent of the degree of danger present in a situation—the first phase of stress reaction occurs and a sequence of vegetative reactions develops [58,67].

Our image of our actual self is formed continuously by the influence of environmental feedback, and we classify ourselves according to this feedback. During socialisation, the complex learning process forms what we would like to become, what our self-ideal is, what values we accept and which values we identify ourselves with.

In each life situation, we compare it with our ideal self and question whether we can come up to the expectations demanded of us. If somebody makes unrealistic demands of himself, then he can find himself facing unaccomplishable tasks and hence always classifies himself negatively. If somebody expects some kind of ideal behaviour from his environment the reality rarely matches these expectations.

The experience and demand for successful and purposeful behaviour and the ability to control our own situations is called self-efficacy or competence—this is the most generally formulated basic optimization principle, towards which man is striving with his behavioural decisions.

Fig. 1 shows that both the behavioural patterns and the cognitive feedback are characteristic of the person's conflict solving ability, the so-called coping strategy [22,82,114]. It is obvious from the model that the non-adaptive conflict solving strategies play an important role in resulting chronic stress situation and causing and maintaining physical symptoms and illnesses of psychological origin. During sudden cultural and socioeconomic transition there is a need for change in attitudes, ways of coping, therefore in such a situation only people with flexible coping resources can adapt successfully.

4.1. Pathogenesis during the chronic stress process

If we consider the ability to control our situation as the basic optimisation principle of behavioural regulation, it is evident that lasting conditions of loss of control or anxiety are the basic determinants of negative consequences of stress situations [58,59,62,67]. Modern ways of life create innumerable situations of loss of control. In such a situation the cardiovascular and metabolic responses might dissociate, as Cannon [15] had already described: "The organism prepares for action and, should the increased preparedness

endure without the development of activity, this can be followed by catastrophic consequences" [64,65].

In case of humans perceived control has a central importance [141,142]. Perceived control has two elements, the first is the perception that the situation is potentially controllable, and the second is that the individual has sufficient information to take a correct action. People vary in the extent to which they believe that important outcomes are determined by their own internal abilities and activities or by external factors. Both extremes mean higher psychological vulnerability, because in the case of too high internal locus of control people blame themselves very often and in the case of external locus of control they depend too much on their environment [142]. One important aspect of human control is the perceived control in work. According to Siegrist [134] low control and high effort at work predict increased mortality from ischemic heart disease.

4.2. Psychological responses

In every life situation we compare our perceived abilities and the perceived environmental expectations to our self-ideal. The behavioural decisions depend on this balance. From this situation two kinds of basic non-adaptive behavioural patterns can arise. Firstly, if we set a standard too high for ourselves or for our environment then there is a very high probability that we will judge the situation as failing to meet our expectations. If we classify our situation, environment and future negatively then, if repeated (Fig. 1), this condition can lead to anxiety, and in the end the chronic stress can lead to learned helplessness, that is to a depressive state.

According to Fig. 1, if a standard is set too high by the self-ideal this can also cause another kind of non-adaptive behaviour pattern. The essence of this is that by sacrificing the physiological balance of the organism for a long time, we create a psychological balance by consuming our own physiological adaptation reserves [68].

One such non-adaptive possibility is using drugs or alcohol to re-establish the cognitive balance. Since earliest times humans have used a wide spectrum of drugs to influence the central nervous system, the most common of which is alcohol. In this way drinking alcohol can become fixed as a conditioned reaction for avoiding anxious situations. The wide range of drugs may work in the same way.

Negative emotional states, the avoidance of anxiety and the feeling of control over our situation are very powerful motivational factors. All those responses which intensify this condition, or the feeling of control over our situation, can remain and get permanently fixed as conditioned responses. Fig. 1 shows that solving a problem temporarily with alcohol or other drugs can have an effect on the abilities of the person and it can seriously and lastingly damage the organism's condition and the relationship formed with the environment.

Other non-adaptive active behavioural reactions are those which assure the person's cognitive evaluation balance with

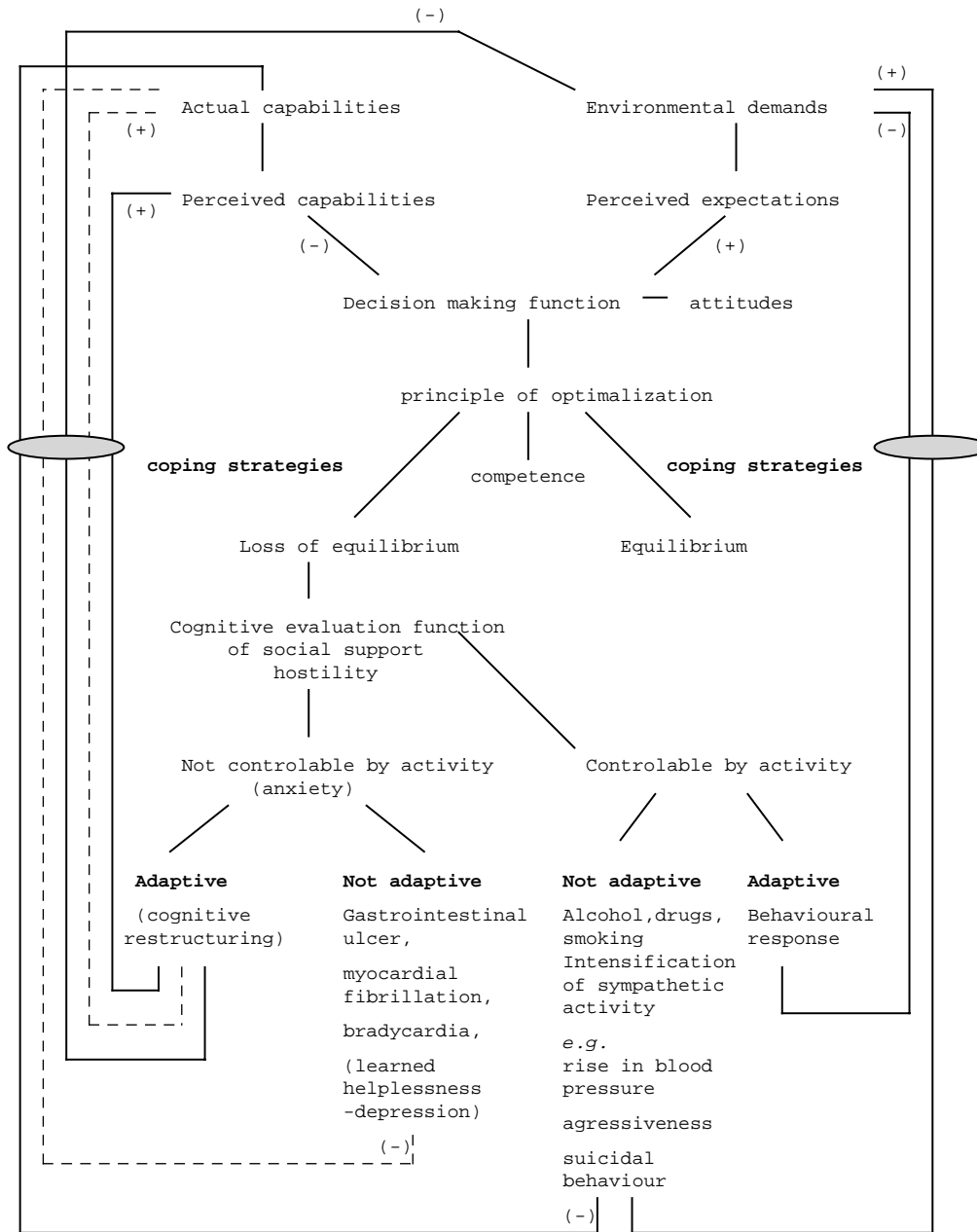


Fig. 1. Model of regulation of human behavior in the man–environment system.

an abnormal increase of sympathetic activity. In this case the psychological expectations of ourselves, as an inner compulsion, assert themselves with greater efficacy in determining our way of life than does maintaining the physiological balance.

4.3. Chronic stress as psychosocial risk and socio-economic differences in chronic diseases

In humans uncontrollable stress is experienced particularly by individuals who failed to develop a broad spectrum of behavioural strategies for the control of psychosocial conflicts. This might explain, why depressive symptomatology

shows a strong socioeconomic gradient [100,151], especially in suddenly changing societies [71,73,76,77,115].

One social stress model observable in hierarchy systems of primates is very relevant in connection with this type of stress. After falling in rank, monkeys can exhibit prolonged withdrawal from social interactions and produce depression like symptoms and increased cardiovascular risk [122–125]. There are several social competition hypotheses of depression, which analyse the depressive symptom formation from evolutionary adaptationist perspectives and in the framework of stress theory [111,112].

In the last decade possibly the most important observation in “new public health” is that relative socio-economic dis-

advantage constitutes a basic health risk in society. If morbidity and mortality data are corrected with the traditional risk factors, such as smoking, obesity, lack of exercise, then relative social disadvantage has a far greater effect than the other factors [138,153,155–157]. In practice this means that an English unskilled worker dies several years earlier than a person with higher education, even if he does not drink or smoke more. The surveys of Marmot [87], Marmot and Wilkinson [86], and Marmot et al. [88,89] conducted among English civil servants showed that their level of employment is in close and inverse relation with their mortality rates, just as with the occurrence of cardiovascular diseases and chronic, nonspecific respiratory disorders. Adverse social circumstances in childhood are strongly and independently associated with increased risk of insulin resistance and other metabolic risk factors [81]. Lehelma and Vakonen [79] compared the international research results of social inequality and health status to Finnish data, and found that both morbidity rates and self-rated health status [47] are in the closest relation with social inequalities. These differences can be observed within certain countries, but not among different countries. Since modern Western European societies grant adequate nutrition conditions, housing and medical care for the whole society, the question arises: why is a relatively disadvantageous socio-economic situation the most significant risk factor?

While health status in developing countries improves proportionally with national income, in developed (OECD) countries the greater income and social differences in the country itself bring about higher mortality rates [156].

Kaplan et al. [49,50] arrived at the same conclusions concerning the United States. The higher the differences between rich and poor are within a state, the higher the morbidity and mortality rates, that is to say not the absolute degree of wealth, but social differences, inequalities of the society are the main predictors for health status. Inequality within states can be characterised not only by health status but also with unemployment, homicide, crime, disability, higher number of infants born with low weight, lower percentage of people having higher education, as well as lower financial support of education. Kawachi et al. [51–53] found similar differences among the states in the US in relation to socio-economic differences.

5. Central-Eastern European health paradox

Up to the end of the 1970s mortality rates in Hungary had been actually lower than in Britain or Austria. Subsequently, mortality rates continued to decline in Western Europe, whereas in Hungary and in other Central-East European (CEE) countries this tendency reversed, especially among middle-aged men [9–11,86,155,156]. In the late 1980s, the mortality rates among 45–64-year-old men in Hungary rose to higher levels than they were in the 1930s, while the mortality rates in the older age groups were comparable to

the worst in Western Europe [20,41,61,71,72,74,136,137]. Cardiovascular mortality accounts for the majority of this excess mortality in these countries [152] (Fig. 2).

What is the explanation for the vulnerability of middle aged men during this period of rapid economic change? This deterioration cannot be ascribed to deficiencies in health care, because during these years there was a significant decrease in infant and old age mortality and improvements in other dimensions of health care [71,136]. Furthermore, between 1960 and 1989 there was a constant increase in the gross domestic product in Hungary. Thus, the worsening health status of the Hungarian male population cannot be explained by a worsening material situation [71,136].

A growing polarisation of the socio-economic situation occurred in the CEE countries, especially in Hungary between 1960 and 1990. The vast majority of the population lived at similarly low level in 1960, with practically no income inequality, and there were no mortality differences between socio-economic strata. Since that time increasing disparities in socio-economic conditions have been accompanied by a widening socio-economic gradient in mortality, especially among men [9,53].

The theory of relative deprivation hypothesises that chronic stress can arise out of situations in which there is rapid improvement in living standards for some but not for others. As summarised by Coleman [18], “as long as there is no visible change in objective conditions, all persons feel that they are “in the same boat”. However, when there is rapid improvement in conditions, those of some improve more rapidly than those of others. Those for whom conditions are not improving very rapidly see other, perhaps no more qualified people, doing much better than they are. It is from this perspective that they perceive a widening gap, which leads them to feel frustration” ([18], pp. 475–476). Relative deprivation may be deleterious to both psychological and physical health, mediated by through stress-related coping responses (e.g., more smoking, heavier drinking) as well as invidious social comparisons. Conversely, social cohesion may help to counterbalance the widening gap in material circumstances [137].

One of the most interesting features of the so-called “Central-Eastern-European health paradox” is the gender difference in worsening mortality, in spite of the fact that men and women share the same socio-economic and political circumstances [19]. In Hungary the male/female differences in life expectancy in 2001 was 8.3 years, which is considerably higher than the average difference found in countries of Western Europe, for example 5, 8 years in the neighboring Austria, 4.8 years in Denmark and Great Britain [137]. The mortality ratio comparing the lowest to highest educational stratum is 1.8 for Hungarian males, while 1.2 for females [84] (Fig. 3). There are also marked morbidity and mortality differences according to the Hungarian counties and sub-regions.

Based on the data of our national representative surveys conducted in the Hungarian population (Hungary study

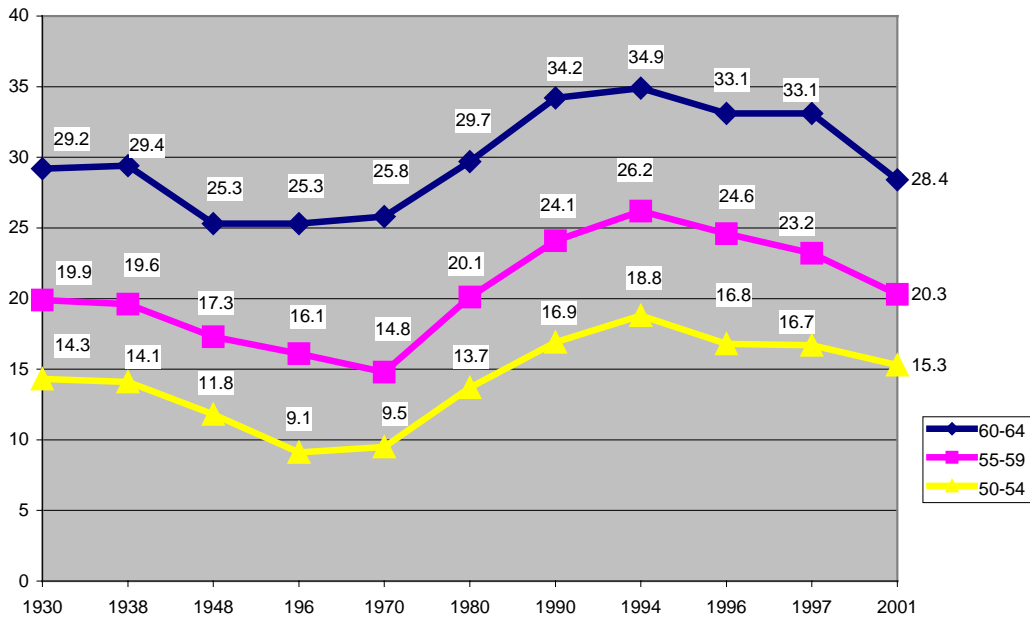


Fig. 2. Mortality rate in 1000 men in corresponding age groups in the Hungarian population (Demographic Yearbook, 2001).

1983, 1988, 1995, 2002) [68–71,74,136], we found that a worse socioeconomic situation is linked to higher morbidity and mortality rates in Hungary as well [70,71,137]. According to multi-variate analyses, however, higher morbidity rates are connected to relatively poor socioeconomic situations mainly through the mediation of depressive symptoms (Fig. 4). Fig. 4 shows, that in 1988, according to our national representative study in the Hungarian population, depression mediated between low income and self-rated morbidity among men, while among women low income was not significantly connected either to depression, or with self reported morbidity. In 1995 this picture had changed, low income became directly connected to morbidity both in men and women, but the mediating effect of depression between low income and morbidity remained more important among men than among women. The thickness

of connecting line is proportional to the strength of the direct connection [71,73]. Consequently, not only the difficult social situation in itself, but the subjective experience of relative disadvantage, the prolonged negative emotional state, that is chronic stress proves to be the most important health risk factor [69,70,73,74].

Presumably a self-destructive circle develops from the enduring relatively disadvantageous socioeconomic situation and depressive symptoms. This circle resulting in chronic stress, plays a significant role in the increase of morbidity and mortality rates in the lower socioeconomic groups of the population. Until the 1970s with the uniformly low living standards, Hungarian health statistics showed more favourable data, than in several Western countries, such as in Great Britain or in Austria. During rapid socioeconomic changes the disadvantaged continuously blame themselves

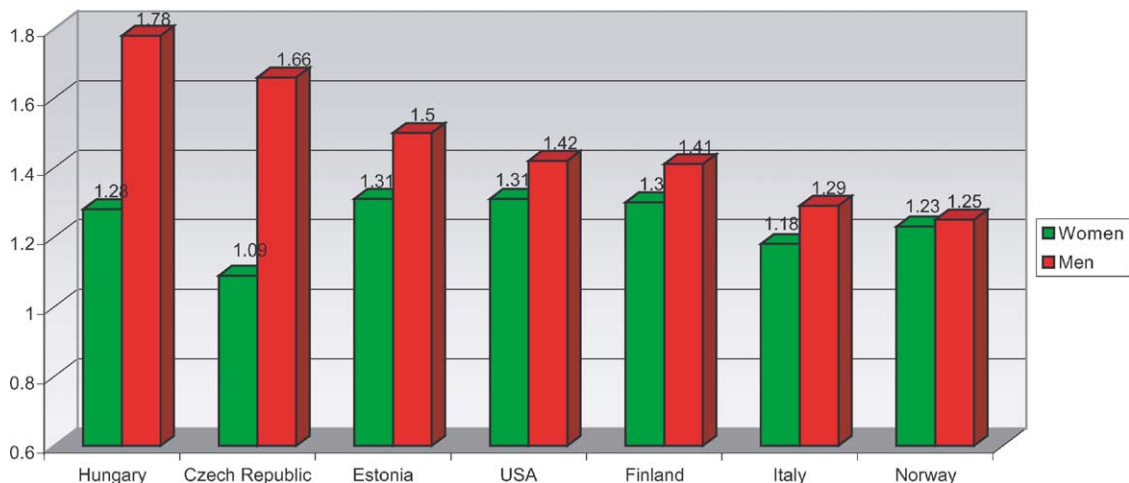


Fig. 3. Mortality differences according to low (undergraduate) versus high education in different countries. All Causes mortality.

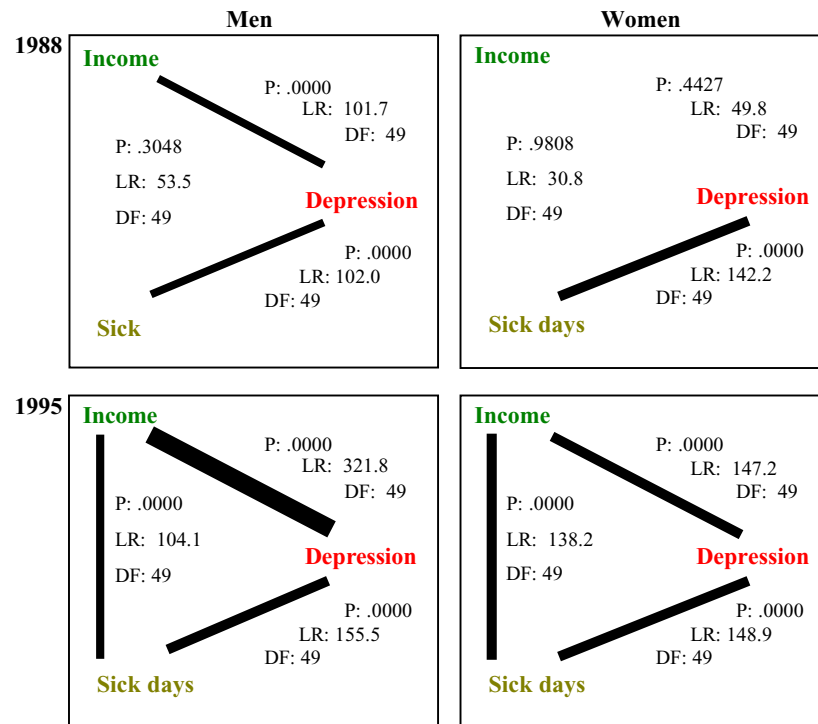


Fig. 4. Relationship between personal income, number of self-reported sick days and severity of Beck depression by gender in 1988 and 1995 in Hungary controlled by age.

or their environment, consider their future hopeless, experience permanent loss of control and helplessness, because they cannot afford a car, better living conditions, higher income, while others around them are able to achieve these. They constantly rate their own situation negatively, feel helplessness, and a loss of control. This experience becomes widespread when society becomes rapidly polarised and social cohesion, trust, reciprocity and social support decrease dramatically [62,69,109,136,137].

Though the relationship is true in general, the significance of the different factors varies according to periods and to environmental processes. In relatively stable societies, existing without great social shocks, the social factors and the psychological coping with these factors have less significance. In a region like Hungary and the other Central and Eastern European countries, dramatic changes have occurred in the last decades. During this time period depression and premature cardiovascular and overall mortality increased in parallel, primarily among men [54,61,71,84,109,136,152,155,161].

Men were found to be more susceptible to the effects of relative income inequality and GDP deprivation, but the pathway of this relationship is yet to be explained. Two possible explanations can be hypothesised. One is that the income inequality is much higher among men. In Hungary, in 1988 the main income of working women was 31% lower than that of working men, with a standard deviation 26% lower, while in 1995 the average personal income of women was 24% lower with 37% lower standard deviation, that is

the income inequalities among men were and remained more substantial [71].

The other possible explanation might be, that men are more susceptible to loss of status than women. Animal experiments have shown males to be more sensitive than females to loss of dominance position, that is loss of position in hierarchy [40,92,122–125]. Most animal studies on social rank examine males, where social rank is the best predictor of quality of life and health [40,92,122–124]. The relationship between social inequality and health applies to women as well as to men in several respects according to several studies [80], although the income and occupation of women are not as powerful predictors of mortality as they are for men [86,88,89]. Especially in a suddenly changing society, such as Hungary, the social inequalities in mortality rates are much more pronounced among men [9,84,152,155]. In such a situation, in a more traditional society, the relative income deprivation might be a more important risk factor for men than for women. There are significant gender differences in ways of coping during the sudden changes of the political-economic system, male morbidity seems to be more affected by the socio-economic changes [57,76,119–121,152]. During the modernisation process of society the female patterns of inequity, risk factors and health might approach male patterns as it could also be experienced in several Western countries [71].

In comparison to women among men socio-economic factors are nearly four times more important predictors of

middle-aged mortality differences among regions. Social distrust and the rival attitude are important predictors of middle aged mortality differences among men [136,137]. This indicates that in a suddenly changing socio-economic situation relative economic deprivation, rival attitude and social distrust are all more important risk factors for men while the strong collective efficacy could be a protective factor, even in the case of men. Rival attitude was in highly significant negative association with participation in civic organisations, consequently the protective effect of participation in civic associations might influence health through a lower rival, competitive attitude in members of civic networks among men.

The existing and broad socio-economic differences among the Hungarian regions are less important regarding the middle aged female mortality differences. Neighbourhood cohesion, religious involvement, trust and reciprocity were not so much influenced by sudden socio-economic changes in the last decades, therefore, the protective network of women remained relatively unchanged.

The results of a Swedish and Lithuanian research, the so-called LiViCordia study are very similar to our results [76,77]. In the seventies the cardiovascular mortality rate of Lithuanian men was not worse than that of Swedish men, but in 1994 the incidence of CHD mortality for middle aged men was fourfold higher in Lithuania compared to Sweden. In this study a thorough medical and psychological examination was conducted among a representative sample of the male population of Linköping and Vilnius. They found that the traditional risk factors of cardiovascular diseases were not worse in Vilnius than in Linköping, the Lithuanians did not smoke more, the serum-cholesterol level of Swedish men was even higher. However, they found significant differences in psychological features, more men from Vilnius suffered from depression, more of them felt that in difficult situations they could not depend on the help of others, and the occurrence of chronic stress or the so-called vital exhaustion was far more frequent among them. Their physiological reaction patterns differed as well, the patterns of Vilnius men showed the signs typical of chronic stress. The men from Vilnius had an attenuated cortisone response to stress. Several studies showed an attenuated cortisone response to stress among groups exposed to chronic stress [76]. Similar psychosocial differences were found in a Swedish and Estonian comparative study [57].

A stress situation in itself does not affect health harmfully when it is accompanied by the feeling that one is able to overcome difficulties successfully, which is actually the basis of physical and mental development. Challenges, new situations lead to deterioration if one does not know the solutions, if one is faced with too long lasting, too many and seemingly unsolvable situations, if society seems unpredictable, chaotic and uncontrollable. Maintaining homeostasis is the capacity to respond to meeting new demands. This dynamic capacity—allostasis—is lost in the state of chronic stress [76].

6. Conclusion

This paper gives a broad overview of the latest psychological, physiological and clinical studies on the mechanisms by which psychological and psychosocial factors might result in health deterioration, especially cardiovascular risk. Depending on the field of research there are several parallel concepts, which analyse practically the same phenomena. These are the stress theories in physiology, learned helplessness and control theory in psychology, depression research in psychiatry, the concept of vital exhaustion and the psychosocial risk research in sociology. The temporal factor in existing stress models is often neglected. In this review chronic stress is proposed as an integrating theory that can be applied to different psychological models. Because chronic stress results in adverse health effects through biological, social and behavioural pathways, this theory might also have the best explanatory power to understand the premature male morbidity and mortality crisis in Central and Eastern Europe in the last decades.

Animal studies indicate that monkeys provided with experiences of controllable (contingent) events early in life are subsequently less reactive to stressful events in adulthood. The experience of a major uncontrollable event in childhood is associated with increased likelihood of depression following life events in adult life. Learned helplessness might be called behavioural depression resulting from exposure to inescapable stresses and might be conceptualised as a limbic system dysregulation, with different brain regions also involved. According to animal studies, males appear to be more vulnerable to long-lasting stress-induced hippocampal damage than females, the decline of circulating testosterone levels resulting from uncontrollable stress seems to play a role. Despite similar free cortisol responses of men and women to psychosocial stress gender may exert differential effects on the immune system by modulating glucocorticoid sensitivity of proinflammatory cytokine production.

Both learned helplessness and reactive depression stems from the expectancy that responses and outcomes are uncontrollable and might result in only emotionally negative consequences. In humans learned helplessness also refers to the motivational, cognitive and emotional components in the interpretation of the environmental stimuli. Defensive mechanisms also operate at the mental level through putative ego defences, the psychological function of which is to preserve self-esteem by hindering the access of disturbing emotional material into awareness. Human psychological stress reactions depend on the subjects interpretation of the changes perceived from their outside world and on the optimalization principles of the person. Uncontrollable stress is experienced particularly by individuals who failed to develop a broad spectrum of behavioural strategies for the controlling of psychosocial conflicts. This might explain, that depressive symptomatology shows a strong socioeconomic gradient, especially in suddenly changing societies. There is a so-

cial stress model which is very relevant in connection with this type of stress. After falling in rank, monkeys can exhibit prolonged withdrawal from social interactions and produce depression like symptoms and increased cardiovascular risk.

The prospective cohort studies provide strong evidence that depression is independent aetiological and prognostic risk factor for coronary heart disease. After controlling the results for smoking and other known risk factors for cardiovascular diseases the apparently healthy individuals who had elevated depression ratings were more likely both to develop and die of ischemic heart disease. Prevalence of depression is significantly higher among women, but according to follow up studies depression seems to influence cardiovascular risk more among men, than among women.

In the last decade one of the most important observations in “new public health” is that in society relative socioeconomic disadvantage constitutes an independent health risk. When morbidity and mortality data are corrected with the traditional risk factors then relative social disadvantage has a far greater effect than the other factors. Based on the data of national representative surveys of the Hungarian population, worse socioeconomic situation is linked to higher morbidity rates. According to multi-variate analyses, however, higher morbidity rates are connected to relatively poor socioeconomic situations mainly through the mediation of depressive symptoms. Consequently, not so much the difficult social situation in itself, rather the subjective experience of relative disadvantage is the most important health risk factor.

According to several studies, men were found to be more susceptible to the health deteriorating effects of relative income inequality and economic deprivation. One possible explanation might be, that men are more susceptible to loss of status than women. Animal experiments have shown males to be more sensitive to loss of dominance position, that is a loss of position in hierarchy, than females. Most animal studies on social rank examine males, where social rank is the best predictor of quality of life and health. The relationship between social inequality and health applies to women in several respects, although the income and occupation of women are not as powerful predictors of mortality as they are for men. Especially in a society in rapid socio-economic transformation, such as in Hungary, the social inequalities in morbidity and mortality rates are more pronounced among men.

These paradoxical features of premature mortality and morbidity in Central-Eastern European countries might be regarded as a special experimental model to understand better the human consequences of chronic stress and those processes where psychology meets physiology.

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