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Current Perspectives in Stress Research and Cardiometabolic Risk

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Abstract

The most important objective of this research was to analyze and discuss the current relationship between the level of stress perception and the consequences on cardiometabolic risk in population. The study was based on a literature review, including books, published articles and internet information, as well as on the author's own experience in this field, regarding the most important concepts about stress, the mediators and systems involved, methods of assessment and evidences about the influences of stress on cardiac, endocrine and metabolic system. Stress and coping with stress have been identified as important variables affecting health, now recognized to be involved in pathogenesis of many diseases: cardiometabolic, respiratory and digestive pathologies, cancer, neuroendocrine and psychiatric disorders. Glucocorticoids, catecholamines, pro- and antiinflammatory cytokines and the parasympathetic nervous system are involved in the adaptation to stressors. The overload of these allostatic systems is characterized by persistent high levels of stress mediators and damaging effects on human

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health. The stress assessment combine the rating scales for self-evaluation and the laboratory tests. From the medical point of view, the most important step forward in the stress research was made by using salivary stress markers. Measuring cortisol, alpha-amylase, or dehydroepiandrosterone in saliva became a reliable method of investigating stress in human because avoid venipuncture and offer the possibility of self-collection at home or at work, several times per day. Stress markers were significantly increased in metabolic syndrome, hypertension, stroke, ischemic heart disease and heart failure.

Keywords: stress; coping; cardiometabolic risk; cortisol; autonomic nervous system.

Introduction

Stress, a booming concept in modern society, is used both in everyday vocabulary to describe certain incidents considered disruptive to the individual and his life experience ("In that moment, I was really stressed out") and in social or medical terminology, related to disease risk and protection of health (Lyon, 2012). Since the late 1950s, stress and coping with stress have been identified as important variables affecting health. Different disciplines (sociology, psychology, medicine, nursing) recognized the importance of stress in pathogenesis and onset of many diseases: cardiovascular pathologies (Benschop *et al*., 1998; Ikeda, Iso, Kawachi, Yamagishi, Inoue, & Tsugane, 2008; Ornish, Scherwitz, & Doody, 1983; Vrijkotte, van Doornen, & de Geus, 2000), obesity, metabolic syndrome and diabetes mellitus (Chandola, Brunner, & Marmot, 2006; Fowler-Brown, Bennett, Goodman, Wee, Corbie-Smith, & James, 2009; Hjemdahl, 2002; Kumari, Head, & Marmot, 2004), cancer (Antonova & Mueller, 2008; Cohen & Rabin, 1998), and other respiratory (McCormick, Nezu, Sherman, Davey, & Collins, 2014), digestive (Dancey, Taghavi, & Fox, 1998), endocrine (Helmreich *et al*., 2012), neurological and psychiatric (Giubilei *et al*., 2001) diseases.

The brain is the organ that closes the vicious circle between potential and actual stressors and behavioral or endocrine adaptative response. Glucocorticoids and catecholamines are the two defining stress hormone response, regulated by the central nervous system, but there are many other mediators, such as pro- and antiinflammatory cytokines and the parasympathetic nervous system, that are also involved in the adaptation to stressors (McEwen, 2008). The effect of the social environment load stress is acting mainly on three important body systems: endocrine, immune and autonomic nervous system, which are known as being first attacked by the chronic stress and an unhealthy lifestyle.

Hans Selye (1907 – 1983) had described in 1936 "the general adaptation syndrome" in response to stressors and had anticipated the most important paradox, revealed during the unfolding of rapid and tardive adaptation to stress. The adrenocortical and the autonomic nervous system are important protectors of the body during the baseline reaction and become harmful and dangerous for health if are activated recurrently for long time. Bruce McEwen, neuroendocrinologist, another scientist dedicated to the "stress" field, has recognized and described this effect of stress, acting in 2 stages; he used the term "allostasis" describing the adaptive processes that maintain homeostasis in stress condition, by synthesis and releasing of mediators such as adrenalin and cortisol and explained that a long period stimulation of these systems will determine the phenomenon of "allostatic overload", characterized by persistent high levels of stress mediators and damaging effects on human health (McEwen, 2005). The author explain that chronic stress („bad stress" or „stressed out") affects negatively physical and psychosocial condition of the person expressing chronic fatigue, frustration and inability to cope.

On the other hand, stress has myriad effects on behavior and social ability of a person. Recent articles have shown that adaptive stress response includes metabolic and behavioral changes in the same time: stress – released vasopressin influence thirst behavior and increase water retention in the kidney; epinephrine improves attentional processes and, in the same time, influence heart rate and vascular tone. Recent observations go further and discuss the influence of stress on decision making and risk taking at the individual level. The influence is complex and could rest with age and gender of the person involved or the type of decision taken (Buchanan & Preston, 2014; Starcke & Brand, 2012). Influences on health and behavior are part of a complex transactional model of coping with stress, based on influences in work and social living (social functioning), quality of life (life satisfaction) and somatic health (illness and physical functioning) (Lyon, 2012).

Cardiometabolic diseases remain one of the most threatening public health problems, in close relationship with unhealthy lifestyle changes and increased incidence of atherosclerotic vascular disease. The metabolic syndrome (introduced first by Reaven, in 1988, as "syndrome X" or "insulin resistance syndrome") was revealed as a cluster of proatherogenic risk factors, centered on insulin resistance: abdominal obesity, impaired glucose tolerance or diabetes mellitus, atherogenic dyslipidemia (high triglyceride, apolipoprotein B and small dense LDL particles and a reduced concentration of HDL-cholesterol), systemic hypertension, inflammatory and prothrombotic state. Despite numerous clinical and experimental studies, the question if insulin resistance or abdominal and visceral obesity is the key point of initiation of clinical syndrome, is still under debate. The presence of the metabolic syndrome was associated with an approximately 2-fold increase in cardiovascular disease risk (Després *et al*., 2008; Galassi, Reynolds, & He, 2006).

Incidence of the metabolic syndrome is constantly growing in last decade, congruently with profound lifestyle changes in modern society: diets are becoming less healthy and obesity has epidemic proportions, more people are sedentary and chronic stress is frequent. Stress is involved in the pathophysiology of cardiovascular and metabolic disease, by activating sympathoadrenal system and the hypothalamic-pituitary-adrenocortical (HPA) axis. The degree of the activation of the sympathetic nervous system may produce only an increase in heart rate, blood pressure and free fatty acids in patients with uncomplicated forms of the disease, or can precipitate angina, myocardial infarction, ventricular arrhythmia and acute heart failure, in patients with significant coronary lesions (Dimsdale, 1991). By elevating sympathetic activity, chronic stress could contribute to rapid evolution of the atherosclerosis, acting in combination with inflammatory pathway, elevated cortisol levels, unhealthy lifestyle and other components of the metabolic syndrome.

Methods

The main objectives of this research were selection, synthesis, discussion and presentation of the current relationship between stress definition or investigation methods and the coexistence of high cardiometabolic risk in population, as an important component of health status in different countries. The study was based on a literature review, including books, published articles and internet resources, as well as on the author's own experience in this field. The information have included the evolution of stress definition in the last century, the principal methods of investigation from the medical and the social point of view, emphasizing on self-perception stress tests and non-invasive methods for studying the salivary biomarkers of neuroendocrine activation in saliva. The authors present and discuss the relevant clinical studies reporting the impact of psychosocial stress on the principal components of the cardiovascular system and disease risk.

Results and discussion

Evolution of the "stress" concept

Incidentally, the concept has some ancient origins, because Seneca, a Roman stoic philosopher, preceptor of the emperor Nero, noted in one of his wise quotes that "A man who suffers or stresses before it is necessary, suffers more than necessary." In biomedical regard, Charles Darwin, famous British naturalist, the originator of the biological theory of evolution, has been emphasized the relationship between neuroendocrine and cardiovascular system: "We know that the

vasomotor system, which regulates the capillary circulation, is much influenced by the mind" (Darwin, 1872). From these beginnings, it was far to the results of large-scale studies supporting evidence-based data about stress impact on cardiovascular health; citing large scale research results contained in INTERHEART Study evaluating cardiovascular risk factors in 29 972 people from 52 countries predicting risk of first myocardial infarction, Richard Milani and Carl Lavie emphasized in an editorial commentary, published in 2007, that psychosocial risk factors, increased the odds of first myocardial infarction by 3-fold, a magnitude similar to standard risk factors, such as smoking, diabetes, and hypertension (Milani & Lavie, 2007; Rosengren *et al*., 2004).

In the scientific literature, the term began to be used frequently after 1930, but did not become popular until the late 1970s and early 1980s. Largely, the term is attributed to Hans Selye, who explained stress as a "nonspecific response of the body to noxious stimuli" (Selye, 1956) and developed the first pertinent theory regarding stress from a physiological and medical point of view. He described the pattern of physiological response to stress, aimed to maintain the homeostasis of the internal medium of the body (glucose and lipids levels, temperature, blood pressure and heart rate) known as general adaptation syndrome. He accepted the possible polarization of the phenomenon including both negatively and positively facets (negative and positive stress – "eustress"). Failure of the adaptation to chronic stress was called exhaustion, raising the issue of an increased risk for particular illness (hypertension and diabetes mellitus, arthritis and cancer) (Lyon, 2012).

Starting from the theory proposed by Selye, the following research has been developed towards a neuoroendocrine and socioeconomic perspective. Bruce McEwen described the activation of the autonomic nervous system and the HPA axis in acute and chronic stress and proposed the terms "allostasis" and "allostatic load". Allostasis is referring to the rapid release of stress hormones, especially norepinephrine and cortisol, for restoring homeostasis in the first stage (McEwen, 1998; Sterling & Eyer, 1988). Allostatic load comprise the negative consequences result from the over-exposure to stress hormones resulting in the various types of pathophysiology, high cardiometabolic risk, an earlier decline of both physical and mental functioning and more depression (McEwen, 2000).

Theories presented by H. Selye and B. McEwen have focused on the response to stress and contain a well-documented medical component. On the other hand, the socio-psychological vision of the stress concept was described better by the authors as T. Holmes, R. Lazarus and S. Folkman, who imagine a stimulus-based or a transaction-based theory of stress. The stimulus-based approach was useful because the authors generated many standardized scales for stress assessment and the transactional theory of stress was important because R. Lazarus introduced, in the same time, the notion of stress "coping", explained that stress perception is variable and subjective and stress is only a "result of a transaction between a

person and his environment"; in his vision, coping is defined as "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceed-ing the resources of the person", reinterpreting the automatic adaptive reactions to an active, conscious attempt for managing the stressful situation (Holmes & Rahe, 1967; Lazarus & Folkman, 1984; Lyon, 2012).

This way of assessing and interpreting the state of stress is related to notions of individuality and identity, that may explain differences in response to stress. In this view, an individuality could have some different identities related to the main activities and facets of life, like family and obligations of being parents, the improvement of study level and job activities, health concerns and lifestyle changes. At the intersection of these identities, when certain facets of existence are more demanding, a person could experience a higher level of stress and more stressful situations. Especially for women, in some period of life, the combination of employment, marriage and parenthood, could be an important source of stressful events. On the other hand, the level of tension of the situation, depend with the individual's stress perception (Burke, 1991). The most important stress theories (Lyon, 2012) described in medical and sociological field, with characteristic terminology and concepts, are synthesized in *Table 1.*

Table 1. *Characteristics of principal stress theories*

Promoters authors, year	**Terminology**	**Concepts**	**Sociological and health outcomes**
Selye, 1956	Negative and positive stress (eustress), general adaptation syndrome	Response-based theory about stress	Physiological response to stress will maintain the homeostasis of the internal medium
Holmes & Rahe, 1967	Stress as stimulus	Stimulus-based theory about stress	Importance of stress quantification by utilization of specific scales
Lazarus & Folkman, 1984	Stress, coping, transaction with stress	Transaction-based theory about stress	Active and conscious response to a stressful event, using coping strategies
McEwen, 1998, 2000	Allostasis and allostatic load, stress hormones	Acute and chronic stress concept	Neuroendocrine activation realize adaptation to stress, but chronic stress, in stage of allostatic load has negative consequences on health

Neuroendocrine activation and stress mediators

With the new methods of research, the concept of stress has evolved from the original theory proposed by Hans Selye. The activation of stress systems and releasing of stress mediators were the most studied in the last years. Glucocorticoids are produced by the adrenal cortex and norepinephrine are released by the activation of the sympathetic nervous system. Both, glucocorticoids and cathecolamines plays an important regulatory role in production of pro-inflammatory cytokines: usually, glucocorticoids inhibit this production whereas catecholamines can increase pro-inflammatory cytokine level. The parasympathetic nervous system is the main opponent of the neuroendocrine activation, slows the heart and has anti-inflammatory effects (Borovikova, 2000; McEwen, 2008).

The brain is the organ capable to coordinate the other systems, to decide what is stressful, and to promote behavioral and physiological reactions, sometimes prolonged and health-damaging. The excessive stress may cause changes in lifestyle, habits and psychological profile: anxiety, depression, and isolation, disorders of eating and sleeping, smoking and drinking alcohol. Short and long-term consequences of excessive stress ("stressed out") are more evident on metabolic, endocrine, cardiovascular and immune system. Lifestyle modification is interconnected with endocrine, metabolic and cardiovascular disorders and determine long-term complications.

Sleep deprivation, which is a frequent consequence of being "stressed out", will disrupt other homeostatic systems:

- reduced parasympathetic activity increase the risk for hypertension, tachycardia and cardiac rhythm troubles;
- activation of the renin-angiotensin system;
- circadian profile of cortisol is inverted, decreasing in the morning and increasing in the evening;
- release some gut hormone, as ghrelin, which influence feeding behavior and increase appetite;
- increased caloric intake and hyperinsulinism prone to obesity, metabolic syndrome and diabetes mellitus (McEwen, 2008).

Recent experimental studies showed that during the stress period, in different brain areas (cortex, nucleus striatum, hippocampus) are released increased amounts of excitatory aminoacid glutamate to the extracellular space in combination with inflammatory markers. In many cases, HPA axis itself could be activated by inflammatory state, which act as a stress stimulus. Hippocampal region is the most vulnerable to the stress effects and explain the cognitive impairment and memory gaps found after a period of chronic evolution. High cortisol levels were good predictors of memory deficits, especially for women (García-Bueno, 2008; McEwen, 1998). Involving stress in cardiovascular disease

has been demonstrated initially in animal experiments (Henry & Grim, 1990). In human, epidemiological studies have shown associations between psychosocial factors, neuroendocrine activation and risk for metabolic syndrome and cardiovascular disease (Hemingway & Marmot, 1999; Hjemdahl, 2002). Chronic stress initiates an inflammatory response in adipose tissue, resulting in perturbation of glucose metabolism and a procoagulant state (decline in insulin sensitivity, prothrombotic reactions and increased plasma monocyte chemoattractant protein-1: MCP-1) (Uchida *et al*., 2012).

Stress assessment and cardiometabolic complications

Complex evaluation of stress effects on human health are based on self-assessment of strained states and medical quantification of stress hormones or it's repercussions on physiological parameters. Over the years, the work of the researchers resulted in the development of different rating scales, created for assessment of exposure and self-perception of the state of stress, from which we selected:

- *Social Readjustment Rating Scale* (SRRS) and Schedule of Recent Experiences were based on the model that too many life changes could increase the level of stress; the SRRS consisted of 42 life events (like marriage, loss of a loved one, pregnancy, vacation, divorce, retire-ment, change in residence and other) and the evaluation of stress and adaptation required by this states (Holmes & Rahe, 1967);
- *Life Experiences Survey* (LES), a 57-item self-report measuring life events impact on health, widely used in stress studies (Sarason, Johnson, & Siegel, 1979);
- *Internal-External Locus of Control Scale*, the Alienation Test, and the Achievement Scale of the Personality Research Form, introduced by S. Kobasa, who used the term of hardiness, as a moderator factor between the personality and the environment (Kobasa, 1979);
- *Hassles Scale* consisting of 117 items and the Uplifts Scale containing 135 items, evaluating daily experiences versus major life events (Kanner, Coyne, Schaefer, & Lazarus, 1981).

Some of these scales could be combined with neuroendocrine laboratory determinations, in order to create standard reproducible tests, useful in clinical trials. Thus was standardized the "Trier Social Stress Test" (TSST), at the University of Trier, Germany, for the experimental induction of moderate psychological stress. Subjects are tested according to the following protocol: after 45 minutes of resting phase (the neuroendocrine system return to baseline and are taken the first samples of blood and saliva), subjects are invited to perform a speech or some arithmetic calculations in front of a panel, and thereafter additional

multiple saliva and blood samples will be collected, heart rate and blood pressure being permanently recorded. In the same time with saliva and blood collection the subjects will fill out specific questionnaires assessing the stress perception. This test was very important for the evolution of stress research because it combine the social and medical facet of stress assessment in human (Kirschbaum, Pirke, & Hellhammer, 1993).

From the medical point of view, the most important step forward in the stress research was made by using salivary stress markers. Investigating the physiology of stress has shown that rapid effects appear in 20-30 seconds by releasing epinephrine and norepinephrine from sympathetic nervous system and prolonged or mixed effects (from minutes to weeks) depend on activation of HPA and other hormonal axis. Measuring some of this hormones (cortisol, alpha-amylase, dehydroepiandrosterone) in saliva became a reliable method of investigating stress in human because avoid venipuncture and offer the possibility of self-collection at home or at work, many times of the day, using a disposable sample device called salivette. In saliva could be measured only free cortisol, but studies showed that the levels correlate very well with the amount of free cortisol in blood. In basal condition, salivary cortisol peak about 30 minutes after awakening and at lunch time and decrease during afternoon and evening hours (Ghiciuc, Dima-Cozma, Pasquali, Renzi, Lupușoru, & Patacchioli, 2011; Hellhammer, Wüst, & Kudielka, 2009). Salivary cortisol responses to challenge are dependent from some variables like age, gender and sex steroids, pregnancy and lactation, food, nicotine, coffee, alcohol and dietary energy supplies (Kudielka, Hellhammer, & Wüst, 2009). In many papers, of special interest was the aime of obtaining cortisol values repeatedly before and after exposure to acute stress or pathological diurnal fluctuations accompanying work stress, anxiety, depression, pain and sleep disturbancies (Fries, Dettenborn, & Kirschbaum, 2009).

The last component of the evaluation is the detection of the long-term negative consequences of stress on the body, in the allostatic load period, a very important link with cardiometabolic pathologies. Cardiovascular activity could be fallow by repeated measurements of systolic and diastolic blood pressure, heart rate and 24-hour continuous monitoring of these parameters and detecting heart rate variability, using holter systems. Metabolic consequences are evaluated by nutrition state, lipid profile and glucose metabolism (glycosylated hemoglobin). The parameters to be monitored are synthesized in *Table 2,* after T. Seeman and B. McEwen (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997; McEwen, 2000).

Table 2. *Cardiometabolic evaluation in chronic stress*

Organs and systems	**Measurement of allostatic load**
Cardiovascular system	Systolic and diastolic blood pressure, ambulatory blood pressure monitoring, heart rate, heart rate variability
Endocrine system	Activation of HPA axis (salivary cortisol, over-night urinary cortisol excretion) A functional HPA axis antagonist (serum and salivary dehydroepiandrosterone) Activation of sympathetic nervous system (salivary alpha-amylase, serum norepinephrine, overnight urinary noradrenalin and adrenalin excretion)
Metabolism	Nutrition state (body mass index, abdominal circumference) Lipid profile (total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) Glucose metabolism (fasting and postprandial glycemia, glycosylated hemoglobin)

Using stress tests and cardiometabolic parameters mentioned above, major epidemiological studies have demonstrated the significant relationship between different forms of stress and major cardiovascular disease. Evidences from the EPIC-Norfolk Prospective Cohort Study, supervising a total number of 20 629 participants, aged 41 to 80 years, showed that stress adaptive capacity is a potentially important candidate risk factor for stroke (Surtees *et al.*, 2007). Hypertension itself, an important risk factor for stroke and ischemic heart disease, has been proven to be in relationship with work stress, who mediates an increase in systolic blood pressure and heart rate reactivity and a decrease in vagal tone (Vrijkotte, van Doornen, & de Geus, 2000). In patients with diagnosed coronary artery disease and exercise-induced ischemia, the associated mental stress was a predictor for subsequent death (Sheps *et al.*, 2002). Inflammation and insulin resistance are also amplified by stress and in Whitehall II cohort lower social position was associated with metabolic syndrome (Hjemdahl, 2002). These evidences argue the possible utility of the mind-body therapeutic interventions in stress management: biofeedback methods, meditation techniques, and relaxation therapies.

Conclusions

As can be seen from the publications and evidences discussed in this review, stress it is an important component of psychosocial risk factors (by the side of social isolation, personality factors, anxiety and depression) and determine a neuroendocrine activation, origin of significant increase in cardiometabolic risk. The new noninvasive methods for testing cortisol and alpha-amylase in saliva

will permit an active search of dangerous levels of stress in target risk population. Understanding and avoiding stress in future will represent a novel social and medical tool for cardiovascular and metabolic prevention.

References

Antonova, L., & Mueller, C. R. (2008). Hydrocortisone down-regulates the tumor suppressor gene BRAC1 in mammary cells: A possible molecular link between stress and breast cancer. *Genes, Chromosomes & Cancer*, *47*(4), 341–352.

Benschop, R. J., Greenen, R., Mills, P. J., Naliboff, B. D., Kiecolt-Glaser, J. K., Herbert, T. B., Cacioppo, J. T. (1998). Cardiovascular and immune responses to acute psychological stress in young and old women: A meta-analysis. *Psychosomatic Medicine*, *60* (3), 290–296.

Borovikova, L.V., Ivanova, S., Zhang, M., Yang, H., Botchkina, G.I., Watkins, L.R., Tracey, K.J. (2000). Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*, *405*, 458–462.

Buchanan, T. W., & Preston, S. D. (2014). Stress leads to prosocial action in immediate need situations. *Frontiers in Behavioral Neuroscience*, 8 (5), 1-6. doi: 10.3389/fnbeh.2014.00005

Burke, P. J. (1991). Identity processes and social stress. *American Sociological Review*, *56*(6), 836-849.

Cohen, S., & Rabin, B. S. (1998). Psychologic stress, immunity, and cancer. *Journal of the National Cancer Institute*, *90*, 30-36.

Chandola, T., Brunner, E., & Marmot, M. (2006). Chronic stress at work and the metabolic syndrome: prospective study. *British Medical Journal*, *332*, 521-525.

Dancey, J. C. P., Taghavi, M., & Fox, R. J. (1998). The relationship between daily stress and symptoms of irritable bowel: A time-series approach. *Journal of Psychosomatic Research*, *44* (5), 537–545.

Darwin, C. (1872). *The expression of the emotions in man and animals*. London: John Murray, Albemarle Street, 1st edition.

Després, J. P., Lemieux, I., Bergeron, J., Pibarot, P., Mathieu, P., Larose, E., Poirier, P. (2008). Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arteriosclerosis, Thrombosis, and Vascular Biology, 28*, 1039-1049.

Dimsdale, J. E. (1991). A new mechanism linking stress to coronary pathophysiology? *Circulation*, *84*, 2201-2202.

Emani, S., & Binkley, P. F. (2010). Mind-Body medicine in chronic heart failure: a translational science challenge. *Circulation: Heart Failure, 3*, 715-725.

Fowler-Brown, A. G., Bennett, G. G., Goodman, M. S., Wee, C. C., Corbie-Smith, G. M., & James, S. A. (2009). Psychosocial stress and 13-year BMI change among blacks: The Pitt County Study. *Obesity*, *17*, 2106-2109.

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR): facts and future directions. *International Journal of Psychophysiology, 72*, 67-73.

Galassi, A., Reynolds, K., & He, J. (2006). Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *American Journal of Medicine*, *119*, 812-819.

García-Bueno, B., Madrigal, L. M., Pérez-Nievas, B. G., & Leza, J. C. (2008). Stress mediators regulate brain prostaglandin synthesis and peroxisome proliferator-activated receptor-d activation after stress in rats. *Endocrinology*, *149* (4), 1969-1978.

Ghiciuc, C. M., Dima-Cozma, L. C., Pasquali, V., Renzi, P., Lupușoru, C. E., & Patacchioli, F. R. (2011). Awakening responses and diurnal fluctuations of salivary cortisol, DHEA-S and alpha-amylase in healthy male subjects. *Neuroendocrinology Letters*, *32*(4), 475-480.

Giubilei, F., Patacchioli, F. R., Antonini, G., Sepe Monti, M., Tisei, P., Bastianello, S., Angelucci, L. (2001). Altered circadian cortisol secretion in Alzheimer's disease: clinical and neuroradiological aspects. *Journal of Neuroscience Research, 66*, 262-265.

Hellhammer, D. H., Wüst, S., & Kudielka, B. M. (2009). Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology*, *34*, 163-171.

Helmreich, D. L., Tylee, D., Christianson, J. P., Kubala, K. H., Govindarajan, T. S., O'Neill, W. E., Maier, S. F. (2012). Active behavioral coping alters the behavioral but not the endocrine response to stress. *Psychoneuroendocrinology*, *37* (12), 1941-1948.

Hemingway, H., & Marmot, M. (1999). Psychosocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. *British Medical Journal*, *318*, 1460-1467.

Henry, J. P., & Grim, C. E. (1990). Psychosocial mechanisms of primary hypertension. *Journal of Hypertension*, *8*(9), 783-793.

Hjemdahl, P. (2002). Stress and the metabolic syndrome: an interesting but enigmatic association. *Circulation*, *106*, 2634-2636.

Holmes, T., & Rahe, R. (1967). The social readjustment rating scale. *Journal of Psychosomatic Research*, *12*, 213-233.

Ikeda, A., Iso, H., Kawachi, I., Yamagishi, K., Inoue, M., & Tsugane, S. (2008). Social support and stroke and coronary heart disease: The JPHC Study Cohorts II. *Stroke*, 39, 768-775.

Kanner, A. D., Coyne, J. C., Schaefer, J. C., & Lazarus, R. S. (1981). Comparison of two modes of stress measurement: Daily hassles and uplifts versus major life events. *Journal of Behavioral Medicine*, *4*, 1-39.

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test' - A tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, *28*(1-2), 76-81.

Kobasa, S. C. (1979). Stressful life events, personality, and health: An inquiry into hardiness. *Journal of Personality and Social Psychology*, *37*, 1-11.

Kudielka, B. M., Hellhammer, D. H., & Wüst, S. (2009). Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. *Psychoneuroendocrinology*, *34*, 2-18.

Kumari, M., Head, J., & Marmot, M. (2004). Prospective study of social and other risk factors for incidence of type 2 diabetes in the Whitehall II study. *Archives of Internal Medicine*, *164*, 1873-1880.

Lazarus, R. S., & Folkman, S. (1984). *Psychological stress and the coping process.* New York, NY: Springer.

Lyon, B. L. (2012). Stress, Coping, and Health. In: V. H. Rice (Ed.), *Handbook of Stress, Coping, and Health. Implications for nursing research, theory and practice*, Second edition (pp. 2-20). SAGE Publications, Detroit.

McCormick, S. P., Nezu, C. M., Nezu, A. M., Sherman, M., Davey, A., & Collins, B. N. (2014). Coping and social problem solving correlates of asthma control and quality of life. *Chronic Respiratory Disease*, *11*(1), 15-21.

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, *338*, 171-179.

McEwen, B. S. (2000). Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology*, *22*, 108-124.

McEwen, B. S. (2005). Stressed or stressed out: What is the difference? *Journal of Psychiatry & Neuroscience*, *30*(5), 315-318.

McEwen, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology, 583*, 174-185.

Milani, R. V., & Lavie, C. L. (2007). Stopping stress at its origins. *Hypertension*, *49*, 268-269.

Ornish, D. M., Scherwitz, L. W., & Doody, S. Jr. (1983). Effects of stress management training and dietary changes in treating ischemic heart disease. *Journal of the American Medical Association*, *249*, 54-59.

Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A., Yusuf, S. (2004). Association of psychosocial risk factors with risk of acute myocardial inf arction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*, *364*, 953-962.

Sarason, I. G., Johnson, J. H., & Siegel, J. M. (1979). Development of the life experiences survey. In I. G. Sarason & C. D. Spielberger (Eds.), *Stress and anxiety*, Volume 6 (pp. 131–149). New York, NY: John Wiley.

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation—allostatic load and its health consequences: MacArthur studies of successful aging. *Archives of Internal Medicine*, *157*, 2259-2268.

Selye, H. (1956). *The stress of life*. New York, NY: McGraw-Hill.

Sheps, D. S., McMahon, R. P., Becker, L., Carney, R. M., Freedland, K. E., Cohen, J., Kaufmann, P. G. (2002). Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease: results from the psychophysiological investigations of myocardial ischemia study. *Circulation, 105*, 1780-1784.

Starcke, K., & Brand, M. (2012). Decision making under stress: a selective review. *Neuroscience & Biobehavioral Reviews, 36*, 1228-1248.

Sterling, P., Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In S. Fisher, & J. Reason (Eds.), *Handbook of Life Stress, Cognition and Health* (pp. 629-649). New York: John Wiley & Sons.

Surtees, P. G., Wainwright, N., Luben, R., Wareham, N., Bingham, S., & Khaw, K. (2007). Adaptation to social adversity is associated with stroke incidence: evidence from the EPIC-Norfolk Prospective Cohort Study. *Stroke, 38*, 1447-1453.

Uchida, Y., Takeshita, K., Yamamoto, K., Kikuchi, R., Nakayama, T., Nomura, M., Murohara, T. (2012). Stress augments insulin resistance and prothrombotic state. *Diabetes*, *61*, 1552-1561.

Vrijkotte, T., van Doornen, L., & de Geus, E. (2000). Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability. *Hypertension*, *35*, 880-886.