NIGERIAN JOURNAL OF PSYCHOLOGY

Volume 22, No.1, 2022 ISSN 0331-0574 (Print), 2635-3806 (Online)

Published by the Nigerian Psychological Association

NPA JOURNALS - www.npa-journals.org

Effect of Stress on Human Immune System

Chinwe Onyemaechi[1]
Nwagbo Chikelue Abumchukwu[2]
Moses Tingir[3]

ARTICLE INFO

Article history:
Received: 12th June, 2022
Revised: 10th July, 2022
Accepted: 18th July, 2022

Authors' Affiliation:
[1]*Department of Psychology, Chukwuemeka Odumegwu University, Igbariam Campuis*
ifeachoc@gmail.com

[2]*Department of Psychology Chukwuemeka Odumegwu Ojukwu University*
nwagbochike@gmail.com

[3]*Excellence Community Education Welfare Scheme (ECEWS), Uyo, Akwa Ibom State.*
moses@ecews.orgt

Keywords:
Cancer, Vascular disease,

Stress, Vaccination, Well-being.

ABSTRACT

The effects of psychological stress on clinically important human immune system outcomes, such as inflammatory processes, wound healing, responses to infectious agents, and other immunological challenges, have been conclusively demonstrated by research over the last three to four decades (e.g., vaccinations, autoimmunity, cancer). Individuals differ in their capacity to handle stressful life events, as well as in how they perceive stress and how they feel. The degree to which stressors have a negative impact on immune function can be altered by depressive symptoms, unfavorable life events, and stressors. Key research connecting common stressors to immune function and health is summarized in this presentation. Additionally, a complex plausible mechanism that explains how persistent stress and high levels of inflammation might have detrimental effects on people's health, including cancer, diabetes, and cardiovascular disease is outlined. Understanding the impacts of more extreme stressors, such as those faced during space travel, a complex environmental, physiological, and psychological challenge with numerous negative effects on human health, depends heavily on research analyzing stresses in daily life.

Introduction

Human immune system is a large network of organs, white blood cells, proteins (antibodies) and chemicals. This system works together to protect the human from foreign invaders (bacteria, viruses, parasites, and fungi) that cause infection, illness and disease. When the immune system of the human body is working properly, it can tell which substances are foreign to the body. It activates, mobilizes, attacks and kills foreign invader germs that can cause harm. Human immune system learns about germs after it has been exposed to them too. The body develops antibodies to protect you from those specific germs. When the human immune system can't mount a winning attack against an invader, a problem, such as an infection, develops. Also, sometimes the immune system mounts an attack when there is no invader or doesn't stop an attack after the invader has been killed. These activities result in such problems as autoimmune diseases and allergic reactions. Stress is the major cause of changes in the immune responses in the human body and are defined as a state of disharmony or threatened homeostasis.

Complex systems that interact with one another include the immune system, endocrine system, and central nervous system (CNS). Stressful life experiences and the negative emotions they cause can disrupt the delicate interaction between these systems, which in turn can dysregulate the immunological response. (Glaser and Kiecolt-Glaser 2005). Psychoneuroimmunology (PNI) is a field of investigation concerned with the interactions of psychological factors with the neuroendocrine and immune system and consequences for higher brain function and human behavior (Dantzer 2010). According to Lazarus and Folkman (1984), a stressor is an incident that surpasses a person's perceived capacity for coping and can lead to an allostatic load and overload. The degree to which humans mount a physiological stress response varies from person to person. The brain, which is essential for appreciating stresses and regulating immune system reactivity to physical and social dangers, is one factor that contributes to individual variances in stress physiology (Slavich and Irwin 2014). The intensity, severity, controllability, and predictability of the stressor are other aspects of a circumstance that are linked to stronger stress reactions. Even after exposure to the same stressor repeatedly, physiological responsiveness to it is frequently seen (Dhabhar 2014). Two important stress-signaling pathways that contribute to immunological dysregulation are the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis (Glaser and Kiecolt-Glaser 2005). Experiencing a stressful situation, as perceived by the brain, activates the HPA axis and the sympathetic-adrenal medullary axis (SAM), which provokes the release of hormones which modulate immune function including adrenocorticotropic hormone (ACTH), cortisol, growth hormone, prolactin, epinephrine, and norepinephrine (Glaser and Kiecolt-Glaser 2005).

Immunity is the natural or acquired resistance of an organism to bacterial or viral invaders, diseases, or infections, while having adequate tolerance to avoid allergy, and autoimmune diseases. Lymphocytes, including T and B cells are the main type of cells of the immune system. T cells orchestrate the immune response via the production of cytokines and stimulate B cells to produce antibodies and signal killer cells to destroy the antigen-displaying cell (Sompayrac 2016). Chronic stress can affect the balance of cytokines and inhibit or dysregulate innate and adaptive immune responses, leading to low-grade inflammation and the deactivation of immunological-protective cells (Dhabhar 2014). Understanding the connection between stress and inflammatory reactions has been a major focus of the science of psychoneuroimmunology. Long-term stress has been directly connected with risk for a wide range of illnesses, including infectious diseases, cardiovascular disease, diabetes, several malignancies, and autoimmune disease, as well as general frailty and mortality. Chronic inflammation is a result of chronic stress (Glaser and Kiecolt-Glaser 2005; Dhabhar 2014; Padro and Sanders 2014; Webster Marketon and Glaser 2008). Long-term stressors can lead to glucocorticoid receptor resistance, which in turn can lead to dysregulated hypothalamic-pituitary-adrenal (HPA) axis function and interfere with the proper regulation of inflammation. This is one theory for the mechanism

connecting chronic stress and inflammation in the onset of a wide range of diseases (Cohen et al. 2012).

Many investigators have studied pathways between major life events and inflammation. Caring for a loved one with a chronic medical condition, such as a spouse with dementia, is commonly characterized by significant life changes and social isolation (Holmes and Rahe 1967). The chronic stress of caregiving has been linked with exacerbation of typical age-related increases in serum levels of IL-6 and CRP (Gouin et al. 2012), providing a plausible physiological pathway via which chronic stress may lead to poor health. Analogously, the loss of a spouse is considered one of the most stressful life events one may encounter (Holmes and Rahe 1967). There is growing evidence that inflammation plays a role in the relationship between adult trauma exposure and increased risks for psychiatric illness and poor health outcomes (Flory and Yehuda 2015). Trauma exposure and posttraumatic stress disorder (PTSD) have been linked to increased risks of both depression (Dunn et al. 2017) and cardiovascular disorders (Edmondson and von Kanel 2017). Early adversity confers risk for physical and mental illness in adulthood (Ziol-Guest et al. 2012; Ehrlich et al. 2016) with more robust effects amongst those experiencing multiple adversities (Hughes et al. 2017).

Stress and Body Healing

When recovering from an injury or surgery, healing is a crucial process. Poor healing is linked to a higher risk of wound infections and other complications, discomfort for the patient, extended hospital stays, and a delay in returning to regular activities (Tevis and Kennedy 2013). Converging data from observational, experimental, and interventional studies suggests that stress and other behavioral factors can impair immune function through a variety of physiological mechanisms and slow the healing of wounds (Kiecolt-Glaser et al. 1998; Gouin et al. 2008; Ebrecht et al. 2004; Pinto et al. 2016; Walburn et al. 2009). Body healing progresses through several sequential and overlapping phases, including inflammation, proliferation, and regeneration. Cellular immunity plays an important role in the regulation of wound healing through the production of proinflammatory cytokines and chemokines which mediate many of the complex interactions involved in wound healing. Inflammation is a prerequisite to healing. Proinflammatory cytokines help to protect against infection and prepare injured tissue for repair by enhancing the recruitment and activation of phagocytes. Sadly, stress interferes with the generation of proinflammatory cytokines, which are crucial for wound healing and, when misregulated, cause a significant delay in wound healing (Gouin & Kiecolt-Glaser 2011).

Numerous studies have shown the therapeutic applicability of the link between stress and poor wound healing. In one study, people who healed more slowly had greater levels of stress and cortisol when they awoke. This suggests that raised cortisol levels have a significant role in the healing of cutaneous wounds (Ebrecht et al. 2004). These results were supported by a meta-analysis (Walburn et al. 2009), which synthesized 17 publications that showed how stress is significantly linked to slowed healing and dysregulation of vital biomarkers for wound healing. In summary, acute and chronic stressors can negatively impact the wound healing process, by interrupting the inflammatory cascade that is fundamental for wound repair.

Stress and Cardiovascular Disease

Cardiovascular disease (CVD) is a major cause of morbidity and mortality. Chronic low-grade inflammation is implicated in the link between stress and CVD via contributions to the early emergence, progression, and thrombotic complications of atherosclerosis (Liu et al. 2017). IL-6 and CRP, two important biomarkers of inflammation, are thought to be indicative and potentially predictive of atherosclerosis (Nadrowski et al. 2016). Clinically significant is the fact that unhealthy behaviors including poor diet, insufficient exercise, tobacco use, and non-adherence to medicine can exacerbate the physiologic effects of stress (Lagraauw et al. 2015).

Epidemiological research over the years has conclusively linked chronic stress and other psychosocial factors to the increased incidence of

coronary artery disease (von Kanel 2012). People who experience work-related stressors like shift work, workplace conflict, and jobs characterized by high demands and little control, for example, are at an increased risk of developing CVD and having elevated serum levels of CRP and IL-6 (Kivimaki and Kawachi, 2015). Additionally, research suggests that trauma experienced throughout childhood, particularly severe physical and sexual abuse, increases the risk of cardiovascular events, especially in women (Garad et al. 2017). Similarly, raised risk for depressive symptoms, higher blood CRP, decreased methylation of the IL-6 promoter, and higher serum IL-6 have been seen in adults who had more adversity or stress during childhood (Janusek et al. 2017). These findings illuminate potential epigenetic pathways that can connect childhood adversity to disproportionately higher adult risks of inflammatory diseases.

Stress and Metabolic Disease

Type-2 diabetes mellitus (T2DM) is a chronic metabolic disorder that results from defects in insulin secretion and insulin action (Hackett and Steptoe 2017). A growing body of research indicates that stress may contribute to the genesis of T2DM, both as a predictor of newly developing T2DM and as a prognostic factor for people who already have the condition (Hackett and Steptoe 2017). Stress-related biological pathways, including chronic activation of the HPA axis, which can lead to dysregulated cortisol output and neuroendocrine dysfunction, have been conjectured to contribute to the pathogenesis of T2DM (Hackett and Steptoe 2017). For instance, insulin resistance frequently develops during acute or chronic stress (Tsuneki et al. 2013).

Results from meta-analyses suggest that depression further contributes to an increased risk of diabetes mellitus (Bădescu et al. 2016; Yu et al. 2015). Stress exposure during childhood has also been found to constitute a risk factor for obesity and diabetes. A child's risk of developing type 1 diabetes as a child rises as a result of negative childhood experiences (Nygren et al. 2015). The impacts of neglect and sexual abuse were most pronounced, and a review of the literature found a substantial correlation between childhood adversity and an elevated risk of T2DM in adulthood (Huffhines et al. 2016; Hughes et al. 2017; Huang et al. 2015).

Stress and Cancer

Research over the past 30 years in the field of psychoneuroimmunology has contributed to considerable understanding of the effect of stress on cancer biology, and has identified psychosocial factors including stress, depression, and the lack of social support as risk factors for tumor progression (Moreno-Smith et al. 2010). Stress hormones (e.g., glucocorticoids, norepinephrine, epinephrine) have multiple effects on human tumor biology. Studies on both humans and animals have repeatedly shown that a β2-adrenergic receptor antagonist (such as propranolol) can reverse the detrimental effects of stress on tumor cell dissemination, supporting the use of β-blockers to control cancer metastasis (Sloan et al. 2010; Shaashua et al. 2017).

Statement of the problem

Some factors such as stress have been found to cause a deficient immune system because of the nature of the body's response in dealing with stress. The strength of the immune system are diminished after frequent activation of the autonomic nervous system, especially in the case of chronic stresses. The question, how could stress “get inside the body” to affect the immune response? Has been relevant in study of psychoneuroimmunology.

There has been a continuous debate that when we’re stressed, the immune system’s ability to fight off antigens is reduced. That is why we are more susceptible to infections. This has raised the question of how stress affects the human immune system. Despite widespread public belief that psychological stress leads to disease, the biomedical community remains skeptical of this conclusion. The quest to find solutions to various health challenges has raised more concern among health professionals to investigate how stress affects health directly or indirectly.

Objectives of the research

The objectives of this research can thus be summarized as follows:

1) To review empirical studies on the effect of psychological stress on immune system.
2) To point out certain health challenges that can be attributed to chronic psychological stress
3) To point out remedies to psychological stress

Research Questions

1) Could stress suppress the effectiveness of the immune system?
2) What are the health challenges that can be attributed to chronic stress?
3) What are the remedies for the management and treatment of stress?

METHOD

Instrument

This review aimed to include publications that address, directly or indirectly, the effect of stress on immune system. The following broad keywords were used in the literature search to maximize the scope of the search: stress, psychological stress, stress and immune system, psychoneuroimmunology, stress and diseases. A total of eight popular databases, including EBSCOhost, Cochrane Library, PubMed, PsychOnline, PsychLit, Social Science Citation Index, Jama Network, and African Journals On-line, were searched. Additional papers were found by consulting the reference lists of the featured articles.

Procedure

The review only covered peer-reviewed works that were written in English. In order to be as inclusive as possible, no starting period was given. The current review included quantitative and qualitative studies which provided insight into the effect of stress on the immune system.

Design

The design has analytical design. The analytical design is a non-empirical design in which facts and information already available are used to analyse and make critical evaluation of a phenomenon. Analytical design, especially when considered with another design(s) allows a researcher to achieve creative thinking that gives insight into performance dynamics of event (Coral & Bokelmann 2017). It involves the in-depth study and evaluation of available information in an attempt to explain complex social issues like the negative effect of stress on the immune system which is the focus of the current study.

FINDINGS

The following findings are presented according to the research questions;

Could stress suppress the effectiveness of the immune system? According to Glaser and Kiecolt-Glaser (2005), Stressful life events and the negative emotions they generate can dyregulate the immune response by disturbing the sensitive interplay among the human immune systems. Acute stress according to Marsland et al., (2017) tends to enhance inflammatory potential while chronic stress suppresses inflammatory potential; acute stressors boost endogenous and LPS-stimulated cytokine production to protect the body from infection. But chronic psychosocial stress is associated with a diminished initial response to bacterial challenge and a slower recovery (Dhabhar, 2014).

What are the health challenges that can be attributed to chronic stress? Delayed wound healing can be attributed to chronic stress. A reduction in the levels of inflammatory cytokines and enzymes involved in tissue repair will inhibit the regeneration of endothelial cells, resulting in delayed wound healing (Coutts, Woo & Bourque, 2008). Furthermore, prolonged immune suppression might progressively decrease, giving way to the opposite effect: an excessive immune response in which the immune system attacks its own body, which could potentially result in further damage to the healing process (Melzack, 1996). stress is associated with slower or delayed wound healing in stressed older adults, adults with leg wounds and surgical patients.

Stress is associated with slower or delayed wound healing in stressed older adults, adults with leg wounds and surgical patients (Finestone, Alfeeli & Fisher, 2008). A study by Kiecolt-Glaser et al (2005) looked at the impact of hostile marital interactions on pro-inflammatory cytokine production and the healing of experimentally induced blister wounds. It was found that couples categorised as high-hostile

experienced slower wound healing compared to low-hostile couples.

Cardiovascular Disease (i.e, heart disease, high blood pressure, abnormal hearth rhythms, heart attacks and strokes) has been linked to chronic stress in different studies. Epidemiological research over the years has conclusively linked chronic stress and other psychosocial factors to the increased incidence of coronary artery disease (Von Kanel 2012). People who experience work-related stressors like shift work, workplace conflict, and jobs characterized by high demands and little control, for example, are at an increased risk of developing cardiovascular disease and having elevated serum levels of CRP and IL-6 (Kivimaki and Kawachi 2015). Additionally, research suggests that trauma experienced throughout childhood, particularly severe physical and sexual abuse, which can be characterized as a past stressful event can increases the risk of cardiovascular events, especially in women (Garad et al. 2017).

Mental Health problems such as depression has also been linked to chronic stress, as Janusek et al, (2007), found that raised risk for depressive symptoms have been seen in adults who had more adversity or stress during childhood.

Metabolic disease such as Diabetes has also been associated to chronic stress. A growing body of research indicates that stress may contribute to the genesis of Type-2 diabetes mellitus (T2DM), both as a predictor of newly developing T2DM and as a prognostic factor for people who already have the condition (Hackett and Steptoe 2017). Stress-related biological pathways, including chronic activation of the HPA axis, which can lead to dysregulated cortisol output and neuroendocrine dysfunction, have been conjectured to contribute to the pathogenesis of T2DM (Hackett and Steptoe, 2017). According to Tsuneki et al, (2013), insulin resistance frequently develops during acute or chronic stress. Stress exposure during childhood has also been found to constitute a risk factor for obesity and diabetes (Nygren et al. 2015).

What are the remedies for the management and treatment of stress? Managing stress calls for addressing the mind as well as the body, since both the brain and body contribute to symptoms. Integrative treatments can help reduce stress and related problems.Some researched based treatments includes; Psychotherapy (i.e., Cognitive behavioral therapy and mindfulness-based stress reduction (MBSR), Medication and Coping strategies (i.e. Regular exercise, Medition and Mindfulness).

Discussion

In psychological sciences, stress is a feeling of mental tension. Reduced stress level is useful and healthy. Positive stress can improve biopsychosocial health and facilitate performance. However, high levels of stress could result in biological, psychological, and social problems and even serious harms to people (Tucker, et al, 2008). Life is mixed up with stress in all its aspects (Shahsavarani, Arshayeri, Lotfian & Satarri, 2013; Lynch, Kaplan & Shema, 2012). According to Amir, Esfandiar and Maryam (2015), Stress may be either external with environmental source, or caused by internal perceptions of the individual. External factors are not in their essence stressful and/or threatening; rather the individual perceives it as such. Stress triggering factors, such as sudden and horrible events, or observing specific types of objects that resemble acute incidents for individuals, may be interpreted as strains. Human experience stress whenever she/he cannot believe to have adequate resources to cope with such obstacles (stimuli, people, situations, etc.) (Lucas, Scammel & Hagelskamp, 2005). Although stress is considered as a routine characteristic of the modern life, if stress become continuous and increasing, most of the individuals show problematic signs and symptoms which may endanger their heath and even their surrounding people's and society's (Edwards, Webster, Vanlaar & Eastoln, 2008).

Interventions addressing stress from a psychosocial, physical, nutritional/dietary, and pharmaceutical standpoint are of clinical importance given the obvious detrimental effects of stress on immune function and health. Comprehensive and multidisciplinary approaches, including psychopharmacological treatment, education, cognitive behavioral therapy, mindfulness-based approaches, and relaxation techniques should be made available early on, especially in the case of physically ill patients, in

order to manage stress appropriately in both healthy and ill individuals.

A variety of stress-reduction techniques have demonstrated beneficial effects for reducing stress and improving mental health and quality of life, including cognitive behavioral therapy (Antoni et al. 2009), mindfulness-based stress reduction interventions (Gallegos et al. 2015), meditation (Rosenkranz et al. 2016), and yoga (Kiecolt-Glaser et al. 2010). Moreover, psychological interventions including cognitive behavioral stress management (Antoni et al. 2009; Gallegos et al. 2015), meditation (Rosenkranz et al. 2016), and yoga (Kiecolt-Glaser et al. 2010) have been demonstrated to improve immune function in diverse populations, including healthy individuals, women exposed to trauma, and cancer patients. These stress-reduction interventions seem to result in a healthy balance between sympathetic and parasympathetic arousal (Chaoul et al. 2014).

Exercise presents a promising intervention to counteract the deleterious effects of chronic stress. A body of research has already examined the ability of physical/aerobic exercise to enhance immune responses when performed regularly and in moderation (Simpson et al. 2015). Exercise and lifestyle changes have been shown to have positive impacts on stress reduction, inflammation, and general well-being in healthy working adults (Kettunen et al. 2015), older people (Emery et al. 2005), T2DM patients (Chen et al. 2015), and cancer patients (Zhu et al. 2016).

Conclusion

The review synthesized above highlight the complex interactions that underlie the relationships among stress, immunity, and health outcomes. Numerous clinically significant immunological parameters, such as wound healing, antibody responses to vaccinations, susceptibility to infectious diseases, the immune system's capacity to suppress latent viruses, and numerous inflammatory processes are all impacted by chronic stress and its correlates. These effects, in turn, can increase risk for a variety of physical and mental disorders, including cardiovascular disease, diabetes, certain cancers, and autoimmune disease, as well as general frailty and mortality. The findings on this review provide a robust pathway through which chronic stress and immune dysregulation may contribute to serious adverse health outcomes.

Reference

Antoni, M. H., Lechner, S., Diaz, A., Vargas, S., Holley, H., Phillips, K., McGregor, B., Carver, C. S., and Blomberg, B. (2009). Cognitive behavioral stress management effects on psychosocial and physiological adaptation in women undergoing treatment for breast cancer. *Brain Behaviour Immunity, 23,* 580–591.

Bădescu, S.V., Tătaru, C., Kobylinska, L., Georgescu, E.L., Zahiu, D.M., Zăgrean, A.M., and Zăgrean, L. (2016). The association between diabetes mellitus and depression. *The Journal of Medicine and Life, 9*, 120–125.

Chaoul, A., Milbury, K., Sood, A.K., Prinsloo, S., and Cohen, L. (2014). Mind-body practices in cancer care. *Current Oncology Reports*, *16*, 417.

Chen, L., Pei, J.H., Kuang, J., Chen, H.M., Chen, Z., Li, Z.W., and Yang, H.Z. (2015). Effect of lifestyle intervention in patients with type 2 diabetes: a meta-analysis. *Metabolism: Clinical and Experimental, 64,*338–347.

Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., and Turner, R.B. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 5995–5999.

Coutts, P., Woo, K.Y., Bourque, S. (2008). Treating patients with painful chronic wounds. *Nursing Standard, 23(10)*, 42-46.

Dantzer, R. (2010). *Psychoneuroendocrinology of stress*. Encyclopedia of behavioral neuroscience. Academic, Oxford, 126–131.

Dunn, E.C., Nishimi, K., Powers, A., and Bradley, B. (2017). Is developmental timing of trauma exposure associated with depressive and post-traumatic stress disorder symptoms in adulthood? *Journal of Psychiatry Research*, *84*, 119–127.

Dhabhar, F.S. (2014). Effects of stress on immune function: the good, the bad, and the beautiful. *Immunological Research*. *58*, 193–210.

Ebrecht, M., Hextall, J., Kirtley, L.G., Taylor, A., Dyson, M., and Weinman, J. (2004).

Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. *Psychoneuroendocrinology*, *29*, 798–809.

Edmondson, D., von-Kanel, R. (2017). Post-traumatic stress disorder and cardiovascular disease. *Lancet Psychiatry*, *4*, 320–329.

Edwards, J.A., Webster, S., VanLaar, D., and Eastoln, S. (2008). Psychometric analysis of the UK Health and Safety Executive's Management Standards work-related stress Indicator Tool. *Work Stress*, *22*, 96-107.

Emery, C.F., Kiecolt-Glaser, J.K., Glaser, R., Malarkey, W.B., and Frid, D.J. (2005). Exercise accelerates wound healing among healthy older adults: a preliminary investigation. *Journal of Gerontology, Series A: Bioliogical Sciences. 60*, 1432–1436.

Ehrlich, K.B., Miller, G.E., Chen, E. (2016). *Childhood adversity and adult physical health. Developmental psychopathology*. John Wiley & Sons, Inc.

Finestone, H.M., Alfeeli, A., and Fisher, W.A. (2008). Stress-induced physiologic changes as a basis for the biopsychosocial model of chronic musculoskeletal pain: a new theory? *Clinical Journal of Pain*, *24*(9), 767-775.

Flory, J.D., and Yehuda, R. (2015). Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues in Clinical Neuroscience*, *17*, 141–150.

Gallegos, A.M., Lytle, M.C., Moynihan, J.A., and Talbot, N.L. (2015). Mindfulness-based stress reduction to enhance psychological functioning and improve inflammatory biomarkers in trauma-exposed women: a pilot study. *Psychological Trauma, 7*, 525–532.

Garad, Y., Maximova, K., MacKinnon, N., McGrath, J.J., Kozyrskyj, A.L, and Colman, I. (2017). Sex-specific differences in the association between childhood adversity and cardiovascular disease in adulthood: evidence from a national cohort study. *Canadian Journal of Cardiology*, *33*, 1013–1019.

Glaser, R., and Kiecolt-Glaser, J.K. (2005). Stress-induced immune dysfunction: implications for health. *Nature Reviews Immunology*, *5*, 243–251.

Gouin, J.P., Glaser, R., Malarkey, W.B., Beversdorf, D., and Kiecolt-Glaser, J. (2012). Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychology journal, 31*, 264–268.

Gouin, J.P., and Kiecolt-Glaser, J.K. (2011). The impact of psychological stress on wound healing: methods and mechanisms. *Immunology and Allergy Clinics in North America*, *31*, 81–93.

Gouin, J.P., Hantsoo, L., and Kiecolt-Glaser, J.K. (2008). Immune dysregulation and chronic stress among older adults: a review. *Neuroimmunomodulation. 15*, 251–259.

Hackett R.A., and Steptoe, A. (2017). Type 2 diabetes mellitus and psychological stress; a modifiable risk factor. *National Review of Endocrinology*, *13*, 547–560.

Holmes, T.H., and Rahe, R.H. (1967). The social readjustment rating scale. *Journal of Psychosomatic Research*, *11*, 213–218.

Huang, H., Yan, P., Shan, Z., Chen, S., Li, M., Luo, C., Gao, H., Hao, L., and Liu, L. (2015). Adverse childhood experiences and risk of type 2 diabetes: a systematic review and meta-analysis. *Metabolism-Clinical and Experimental*, *64*,1408–1418.

Huffhines, L., Noser, A., and Patton, S.R. (2016). The link between adverse childhood experiences and diabetes. *Current Diabetes Report*, *16*, 54.

Hughes, K., Bellis, M.A., Hardcastle, K.A., Sethi, D., Butchart, A., Mikton, C., Jones, L., and Dunne, M.P. (2017). The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health*, *2*, 356–366.

Kiecolt-Glaser, J.K., Page, G.G., Marucha, P.T., MacCallum, R.C., and Glaser, R. (1998). Psychological influences on surgical recovery. Perspectives from psychoneuroimmunology. *American Psychologist journal*, *53*,1209–1218.

Kiecolt-Glaser, J.K., Christian, L., Preston, H., Houts, C.R., Malarkey, W.B., Emery, C.F., and Glaser, R. (2010). Stress, inflammation, and yoga practice. *Psychosomatic Medicine, 72*, 113–121.

Janusek, L.W., Tell, D., Gaylord-Harden, N., Mathews, H.L. (2017). Relationship of childhood adversity and neighborhood violence to a proinflammatory phenotype in emerging adult African American men: an epigenetic link. *Brain Behavior and Immunity*, *60*, 126–135.

Kettunen, O., Vuorimaa, T., Vasankari, T. (2015). A 12-month exercise intervention decreased

stress symptoms and increased mental resources among working adults – results perceived after a 12-month follow-up. *International Journal of Occupational Medicine and Environmental Health, 28,*157–168.

Kiecolt-Glaser, J.K., Loving, T.J., Stowell, J.R. (2005). Hostile marital interactions, proinflammatory cytokine production and wound healing. Archives of General Psychiatry, *62*, 1377-1384.

Kivimaki, M., and Kawachi, I. (2015). Work stress as a risk factor for cardiovascular disease. *Current Cardiology Report*, *17*, 630.

Lagraauw, H.M., Kuiper, J., and Bot, I. (2015). Acute and chronic psychological stress as risk factors for cardiovascular disease: insights gained from epidemiological, clinical and experimental studies. *Brain Behavour and Immunity*, *50*, 18–30.

Lazarus, R.S., and Folkman, S. (1984). *Stress, appraisal, and coping*. Springer.

Liu, Y.Z., Wang, Y.X., and Jiang, C.L. (2017). Inflammation: the common pathway of stress-related diseases. *Frontiers in Human Neuroscience*. *11*, 316.

Lucas, H., Scammell, A., and Hagelskamp, C. (2005). How do G.P registrars feel about dealing with mental health issues in the primary care setting? *A qualitative investigation, Primary Health Care Research and Developmen,. 6,* 60–71.

Lynch, J.W., Kaplan, G.A., Shema, M.S. (2012). Cumulative impact of sustained economic hardship on physical, cognitive, psychological, and social functioning. *New England Journal of Medicine. 398*, 1889-1895.

Melzack, R., Wall, P. (1996). The Challenge of Pain. Penguin.

Moreno-Smith, M., Lutgendorf, S.K., and Sood, A.K. (2010). Impact of stress on cancer metastasis. *Future Oncology (London)*, 6, 1863–1881.

Nygren, M., Carstensen, J., Koch, F., Ludvigsson, J., Frostell, A. (2015). Experience of a serious life event increases the risk for childhood type 1 diabetes: the ABIS population-based prospective cohort study. *Diabetologia*. *58*, 1188–1197.

Nadrowski, P., Chudek, J., Skrzypek, M., Puzianowska-Kuznicka, M., Mossakowska, M., Wiecek, A., Zdrojewski, T., Grodzicki, T., and Kozakiewicz, K. (2016). Associations between cardiovascular disease risk factors and IL-6 and hsCRP levels in the elderly. *Experimental Gerontology*, *85*, 112–117.

Padro, C.J., Sanders, V.M. (2014). Neuroendocrine regulation of inflammation. *Seminars in Immunology*. *26*, 357–368.

Pinto, A., Faiz, O., Davis, R., Almoudaris, A., and Vincent, C. (2016). Surgical complications and their impact on patients' psychosocial well-being: a systematic review and meta-analysis. *BMJ Open*, *6*, 224.

Rosenkranz, M.A., Lutz, A., Perlman, D.M., Bachhuber, D.R., Schuyler, B.S., MacCoon, D.G., and Davidson, R.J. (2016). Reduced stress and inflammatory responsiveness in experienced meditators compared to a matched healthy control group. *Psychoneuroendocrinology, 68*, 117–125.

Shaashua, L., Shabat-Simon, M., Haldar, R., Matzner, P., Zmora, O., Shabtai, M., Sharon, E., Allweis, T., Barshack, I., Hayman, L., Arevalo, J.M.G., Ma, J., Horowitz, M., Cole, S.W., and Ben-Eliyahu, S. (2017). Perioperative COX-2 and β-adrenergic blockade improves metastatic biomarkers in breast cancer patients in a phase-II randomized trial. *Clinical Cancer Resources*, *23(16)*, 4651–4661.

Shahsavarani, A.M., Ashayeri, H., Lotfian, M., and Sattari, K. (2013). The effects of Stress on Visual Selective Attention: The Moderating Role of Personality Factors. *Journal of American Science. 9(6s),*1-16.

Simpson, R.J., Kunz, H., Agha, N., and Graff, R. (2015). Exercise and the regulation of immune functions. *Progress in Molecular Bioliogy and Translational Science, 135,* 355–380.

Slavich, G.M., and Irwin, M.R. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological Bulletin*, *140*, 774–815.

Sloan, E.K., Priceman, S.J., Cox, B.F., Yu, S., Pimentel, M.A., Tangkanangnukul, V., Arevalo, J.M., Morizono, K., Karanikolas, B.D., Wu, L., Sood, A.K, and Cole, S.W. (2010). The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Resources*, *70*, 7042–7052.

Sompayrac, L. (2016). How the immune system works (5th ed). Wiley Blackwell.

Tevis, S.E., and Kennedy, G.D. (2013). Postoperative complications and

implications on patient-centered outcomes. *Journal of Surgical Research*, *181*, 106–113.

Tsuneki, H., Tokai, E., Sugawara, C., Wada, T., Sakurai, T., and Sasaoka, T. (2013). Hypothalamic orexin prevents hepatic insulin resistance induced by social defeat stress in mice. *Neuropeptides. 47*, 213–219.

Tucker, J., Sinclair, R., Mohr, C., Adler, A., Thomas, J., and Salvi, A. (2008). A temporal investigation of the direct, interactive, and reverse relations between demand and control and affective strain, *Work & Stress, 22*, 81-95.

Von Kanel, R. (2012). Psychosocial stress and cardiovascular risk: current opinion. *Swiss Medical Weekly, 142*, 13502.

von Kanel, R., Bellingrath, S., and Kudielka, B.M. (2008). Association between burnout and circulating levels of pro- and anti-inflammatory cytokines in schoolteachers. *Journal of Psychosomatic Research*, *65*, 51–59.

Walburn, J., Vedhara, K., Hankins, M., Rixon, L., and Weinman, J. (2009). Psychological stress and wound healing in humans: a systematic review and meta-analysis. *Journal of Psychosomatic Research*, *67*, 253–271.

Webster Marketon, J.I., and Glaser, R. (2008). Stress hormones and immune function. *Cell Immunology*, *252*, 16–26.

Yu, M., Zhang, X., Lu, F., and Fang, L. (2015). Depression and risk for diabetes: a meta-analysis. *Canadian Journal of Diabetes. 39*, 266–272.

Zhu, G., Zhang, X., Wang, Y., Xiong, H., Zhao, Y., and Sun, F. (2016). Effects of exercise intervention in breast cancer survivors: a meta-analysis of 33 randomized controlled trails. *OncoTargets and Therapy, 9,* 2153–2168.

Ziol-Guest, K.M., Duncan, G.J., Kalil, A., and Boyce, W.T. (2012). Early childhood poverty, immune-mediated disease processes, and adult productivity. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(2), 17289–17293.