IJMPR 2024, 8(9), 86-95

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Revive Article
SJIF Impact Factor: 6.669

INFECTIOUS DISEASES BROUGHT ON BY STRESS AND ARTIFICIAL INTELLIGENCE'S POTENTIAL TO COMBAT THEM

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Article Received on: 20/07/2024
Article Revised on: 10/08/2024
Article Accepted on: 30/08/2024

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ABSTRACT
Research has indicated that individuals who experience higher amounts of ongoing stress are more vulnerable to some infectious diseases. But it's crucial to remember that everyone has a different level of stress because everyone is different in terms of their emotional and physical characteristics. As a result, a circumstance that greatly stresses one individual may or may not have the same impact on another. Stressful life experiences reduce the host's ability to fight off infection is widely accepted. Multiple factors influence the result of stress, which can be either distress (illness) or recovered homeostasis. Previous research has shown a direct correlation between psychological stress and an increased incidence of confirmed acute infectious respiratory infection. An elevated risk of contracting an infectious disease has been linked to psychological stress. Artificial intelligence role in detecting and treating infectious disease is crucial. In this review we focused on stress related infectious disease, various stressors, mechanism of stress induced infection susceptibility, prenatal and neonatal psychosocial stress and the role of Artificial intelligence in fighting against infectious diseases.

KEYWORDS: Infectious disease, Stress, Psychosocial, Infections, bacteria.

INTRODUCTION

The term "stress" has its roots in the work of Empedocles, who lived in the fifth century B.C. Hans Selye, however, coined the term "stress" as we know it today in the late 1930s.[1,2] The definition of stress given by Webster's Medical Dictionary ("a state of bodily or mental tension resulting from factors that tend to alter an existent equilibrium"[3]) is compatible with how researchers in this field currently use the term,[2] despite the fact that it is intrinsically difficult to define (in fact, many experts refuse to do so).

It is difficult to define stress succinctly enough to encompass all of its implications because it is such a vast term. Hippocrates, the Greek philosopher, may have been the first to attempt to explain stress in terms of "disharmony," which was thought to show as illness when disturbed, and "balance," which was seen to be a necessary state of health.[2] Hans Seyle developed the general adaption syndrome at the beginning of the 20th century, offering the first thorough biological explanation of stress.[5] This was recognised in the veterinary field as an unusual or drastic adaptation made by the animal's physiology to deal with unfavourable changes in its surroundings and care.[32] Hippocrates' description of internal balance is known as homeostasis in the perspective of current biology.

Stressors are any number of physiological, psychological, and environmental stimuli that interfere with equilibrium, or the regular regulation cycles (homeostasis). Multiple factors influence the result of stress, which can be either distress (illness) or recovered homeostasis.

Stress is defined as a psychologically upsetting state brought on by unfavourable outside factors that have the potential to have an impact on one's physical health. Among the major psychological stressors are transportation, fear (fright and flight response), crowding, and weaning through social reorganisation. Because stress is common, recurrent in nature, and harmful to health, it is a serious worry.

Numerous studies have shown that a range of psychological stressors, such as academic pressure, loss of self-worth, and bereavement, can cause immunologic impairment to be seen in the laboratory; the neuroendocrine pathways and anatomic structures within the nervous system that mediate these effects have been clarified.[4–9] Numerous stress-responsive neuropeptides and neurotransmitters, including corticotropin-releasing factor, adrenocorticotropin, glucocorticoids, Beta-endorphin, prolactin, somatotropin, arginine, vasopressin, norepinephrine, epinephrine, enkephalin, and substance P, have been demonstrated to interact with immune cells in vitro.[10] These molecules have been proposed as mediators of stress-induced immunosuppression. Intestinal vasoactive peptide. It has also been demonstrated that a few of these peptides, along with other neurohormones like melatonin,[11] have immune-augmenting or antistress properties. Conversely,

it has been demonstrated that the immune system and the brain communicate through an expanding repertoire of "immune-transmitters," such as interleukin-6, interleukin-1, tumour necrosis factor-a, and interferons,[4] additionally, several neuroendocrine hormones generated by the immune cells themselves may be involved.[12]

The field of infectious disease prevention and control has entered a revolutionary era marked by the growth of Artificial Intelligence (AI) technologies in recent years. These days, artificial intelligence (AI) is driving fast forward, increasing the search for anti-infective drugs, improving our knowledge of infection biology, and hastening the creation of novel diagnostics. In this review, highlighting the advancements made possible by AI in each infectious disease scenario.

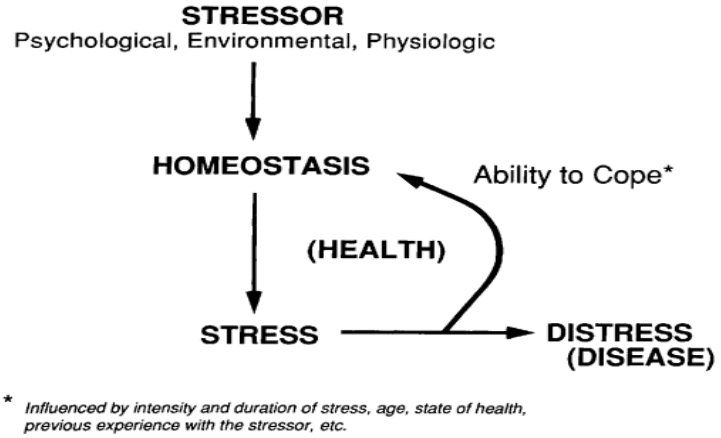


Figure 1: A physiological, psychological, or environmental stressor can cause a condition of disrupted homeostasis, which is known as stress.

Stressful life experiences reduce the host's ability to fight off infection is widely accepted. Events that place more demands on a person than they can handle can cause a psychological stress reaction, which is characterised by unfavourable cognitive and emotional states.[13] In turn, it is believed that psychological stress affects immune function via altering immune cells through hormone-mediated processes or by innervating lymphoid tissue through autonomic nerves.[14-16] Adoption of coping mechanisms such increased alcohol and tobacco use and smoking might also affect immunological responses.[17]

Early-life exposure to adversity, such as stress or maternal deprivation, can shape or reprogram persistent neuroendocrine, behavioural, and metabolic changes (Maccari et al., 2014).[18] These programming effects may be viewed as adaptive, allowing an organism to adapt to unfavourable conditions, but new research indicates that over time, this programming may be largely maladaptive, increasing an individual's susceptibility to adulthood pathways, such as metabolic syndrome, cardiovascular disease, respiratory and chronic lung diseases, allergies, and mood disorders (Maccari et al., 2014; Merlot et al., 2008).[18,19] There is significant proof linking stressful life experiences and stress perception to immune system alterations.[20-22] While psychological stress is frequently associated with immune response suppression, the consequences of immunological alterations brought on by stress for disease vulnerability remain unclear.[23,24] Previous research has shown a direct correlation between psychological stress and an increased incidence of confirmed acute infectious respiratory infection.[25-27]

A growing body of research indicates that psychological stress experienced throughout early childhood may impact the immune system's development, which in turn may change an individual's capacity to handle viral challenges. Aversive or demanding circumstances that exhaust an organism's behavioural resources are known as psychosocial stressors (Lazarus, 1966).[28] A cognitive assessment of "what is at stake" and "what can be done about it" leads to psychosocial stress, which involves dangers to one's social standing, social self-esteem, respect, or acceptance within a group.

Stress and Disease

Psychological stress has been demonstrated for many years to markedly enhance the vulnerability to disease.[33,34] Twenty years ago, studies on infectious diseases were overlooked by researchers looking into the psychological aspects of human disease, and they mostly focused on cancer and coronary heart disease.[35] However, as evidence indicating psychological variables affected immune function was published, interest in this field began to change.[36] In addition, there was a growing recognition that stress and other psychological variables contributed to the development of acquired immunodeficiency syndrome (AIDS).[37]

These findings sparked interest in the impact of stressors in other diseases by demonstrating the substantial role that psychological stressors play in lowering immunity. Understanding the genesis and severity of respiratory disorders as a result of psychological stress has received a lot of attention.[38]

Interaction of Virus and Bacteria

Numerous species have shown an increased risk of dying from bacterial respiratory infections that follow a first viral infection. Viral-bacterial synergy is a phenomena that was first identified in the aftermath of human influenza epidemics, when a range of secondary bacterial respiratory illnesses were linked to higher fatality rates.[39] Research has also connected a range of psychological stressors to higher rates and more severe respiratory illnesses in both humans and animals.[40-43] It is well established that respiratory illnesses have a significant financial impact on the food sector, animal welfare, and human health.[44,45]

Relationship between stress and Viral & bacterial infection

There have been reports that demonstrate a clear correlation between immune system function and stress.[22] Similarly, other studies have shown that social stressors could also increase the risk for upper respiratory infection.[25] The most convincing proof of a connection between stress and cold susceptibility comes from a viral challenge research.[23] Other studies have extended these results by considering a wider range of psychosocial factors.[46] A variety of psychological elements frequently function as mediators between stress and its consequences on health. Cohen and colleagues found that social support enhanced mucociliary clearance of infection and decreased the pace at which viruses replicate, indicating that social support frequently functions as a buffer against the negative consequences of stress.[38,40]

In a different report, they looked at how social support and stress affected upper respiratory tract infections in a typical study.[47] When stress levels were low, social support was linked to a lower risk of infection; but, when stress levels were high, social support had no effect. The relationships between psychosocial variables (stress, social support, mood swings) and viral exacerbations of asthma were investigated in a different study. The study kept many significant aspects of Cohen and colleagues' methodology, but it employed naturally occurring illnesses instead of infections created through experimentation.[23]

In a study conducted by Isolde Gina Rojas et al 2002,[48] psychological stress hinders immunological and inflammatory responses necessary for the removal of microorganisms from the body and delays the healing of wounds. Three days before cutaneous wounds were placed, female SKH-1 mice were placed under restraint stress (RST) to see if stress enhances the susceptibility to wound infection.

Stress response

The body's initial line of defence against infectious pathogens (such bacteria and viruses) is the innate immune response, which gives an instantaneous and generalised reaction. Soon after, body starts to produce an adaptive immune response, in which white blood cells selectively target and destroy infections.

Acute stress response

An instant reaction to a stressful occurrence is known as the acute stress response. Stress hormones, which aid the body in producing energy, are released by the body as soon as possible. Muscle and brain tissues get this energy, and some immune system cells may become more active. In order to search for pathogenic bacteria, researchers have discovered that during times of severe stress, innate immune system cells become more active and circulate more widely throughout the body.[49,50]

Chronic stress response

When an individual consistently experiences acute stress reactions, chronic stress results. Long-term physiological changes brought on by chronic stress include elevated blood pressure, which can eventually lead to artery damage and heart disease. The persistent elevation of stress hormones may also lead to the depletion of white blood cells in the immune system, hence raising the risk of infections. High amounts of stress hormones impair the adaptive immune system during times of chronic stress. As a result, body may be less able to manufacture antibodies, heal more slowly, and be more vulnerable to infections.[49,50]

Research has connected long-term stress to infections such as shingles, TB, herpes simplex virus reactivation, ulcers (produced by the Helicobacter pylori bacteria), and other infectious disorders.

Certain research on immunisations have indicated a decline in efficacy in people who experience high levels of ongoing stress. It's unclear, though, how much of an impact stress actually has on the likelihood of infection.[49]

HIV infection causes AIDS, a disease marked by profound immunodeficiency. Although stress does not directly cause HIV infection, it can hasten the progression of HIV infection into AIDS in those who already have it.

According to a 2000 UNC-Chapel Hill study, males with HIV developed AIDS more quickly if they experienced ongoing stress throughout their lives. The chance of AIDS progression increasing with each stressful incident doubled.[51]

Mechanism of stress-induced infection susceptibility

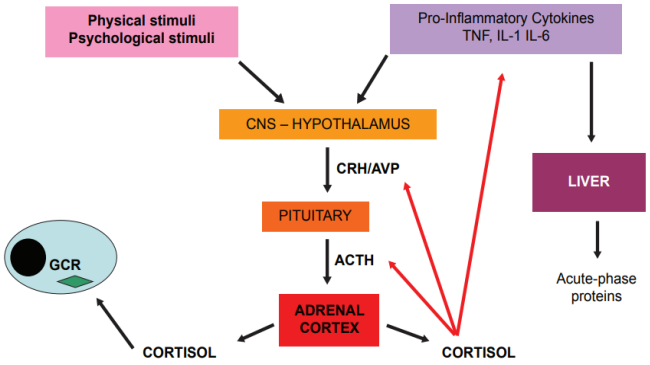
The association between depression and psychological (psychogenic) and physical (neurogenic) stressors has long been recognised, there is evidence to suggest that systemic stressors, such as immune system modifications, may also have a stimulating effect.[52] Communication takes place among the autonomic, endocrine, central neurological, and immune systems,[53] such that psychological occurrences influencing central

neurochemical processes might influence immune function. On the other hand, immunological stimulation may impact central neurotransmitter activity and hormonal functions. Immune activation may therefore influence behavioural outcomes and may even be connected to behavioural pathology like depressive illness due to the neurochemical effects it imparts.[54]

The idea that different stressors could lead to varied immune activation developed over time. Hans Seyles' GAS, which was developed through observation and testing on lab animals, provided the original theory. Seyle defined a common nonspecific stress response pathway using a range of stressors, including as pain, severe temperatures, and famine.[55] The animal initiates a fight-or-flight response or emergency alert upon first sensing a stressor. Both overall metabolism and cardiovascular function are raised as a result of this catecholamine-driven response.

The resistance phase, also known as the "conservation withdrawal reaction," is the body's physiological response to the increasing demands of preserving homeostasis, and it begins if the stressor continues. Prolonged stress triggers the fatigue phase and has the potential to cause pathology. Seyle's idea offered a similar reaction pathway to all the different stressors encountered, which helped to unify the stress phenomena.

This system, known as the HPA axis, is involved in perception in the brain and causes the anterior pituitary to secrete ACTH by stimulating the production of vasopressin and hypothalamic corticotropin-releasing factor (CRF).



Glucocorticoids (GC) are produced by the adrenal cortex in response to ACTH circulating.

In order to convert fat into glucose for the central nervous system (CNS) and other purposes, glucocorticoids induce gluconeogenesis. As a result, GAS made it possible to identify stressors and, presumably, the animal's state of wellbeing through the measurement of GC levels. Since measuring GC levels was relatively simple, the notion appeared appealing.[5]

Tragically, it has been shown that the GAS idea is overly simplistic. Mason's studies on Rhesus monkeys subjected to various stressors showed that distinct stressors elicited varied neuroendocrine reactions.[55] For example, monkeys under emotional stress showed higher serum GC levels, but those under a heat-stress regimen did not exhibit higher serum GC levels. Certain stimuli elicited the typical production of neuroendocrine mediators in addition to GC.38 There are at least four possible pathways for neuroendocrine responses, according on newly available data on stressor response. These include the HPA axis, neuropeptides, neurotransmitters, and neuro-immunological peptides and receptors. They also involve the autonomic nervous system.[5]

Prenatal psychosocial stress

Pregnancy-related maternal psychosocial stress is linked to adverse outcomes for the foetus. Research utilising an extensive array of diverse methodologies and demographics substantiate a connection between adverse life experiences experienced during pregnancy and modifications in the maturation of critical bodily systems, reduced foetal growth, heightened likelihood of preterm birth, and a higher prevalence of low birth weight (Field, 2011; Field et al., 2004).[29,30] Further research, bolstered by animal trials, has revealed alterations in the behaviour and physiology of offspring, suggesting that adverse events during pregnancy could have enduring consequences for health and welfare (Field, 2011; Glover et al., 2010).[29,31] According to other research, prenatal psychological traumas may also affect the host's immunological response, which may have a significant impact on the host's later propensity to contract infectious diseases.

Human research has shown a link between prenatal psychosocial stressors and a higher chance of developing a number of diseases in both adults and children. The majority of research used reports from mothers or their offspring to assess the incidence of significant stressful life events that occurred during or shortly before gestation. Major stressors like divorce, the death of a close relative, or financial troubles have been the subject

of many studies. For example, a sizable population-based cohort study assessed the correlation between mother exposure to spousal death, older child mortality, or maternal divorce during pregnancy and the rate of hospitalisation for infectious diseases in children ages 0–14 years. The findings demonstrated a noteworthy rise in the likelihood of hospitalisation due to severe infectious illnesses for offspring whose mothers experienced these big stressful life events while pregnant. (Nielsen et al., 2011).[56]

Another large-scale population-based study y (Khashan et al., 2012) looked at the health of the offspring after the mother experienced the death of a spouse or child while she was pregnant or up to six months before she gave birth. The findings indicated that there was a greater risk of hospitalisation for asthma in children with any prenatal exposure to mourning during the exposure period; the risk was larger when the exposure period was limited to pregnancy alone.[57]

The relationship between mother stress during pregnancy and the risk of childhood eczema was investigated in a second prospective cohort research. This study did not allow for a clear separation of the impact of psychosocial components because maternal stress was characterised as the cumulative effect of physical stressors such early pregnancy haemorrhage and social events like parental divorce. The findings, however, are consistent with earlier research showing that a mother's exposure to significant stress during pregnancy was linked to an increased risk of eczema in the first two years of the child's life (Sausenthaler et al., 2009).[58]

Neonatal psychosocial Stress and Infectious disease

The early environment has an impact on an individual's development, particularly in the newborn stage. Numerous studies have shown that early-life stress results in long-term alterations to the brain's structure and neurotransmitter systems; these neurobiological changes may be the cause of later-life greater sensitivity (Kaufman et al., 2000).[59] Adverse experiences during infancy are linked to alterations in the stress reaction and brain structure in later life, and are connected to severe depression and further mental disorders (McEwen, 2008).[60]

Studies show a correlation between early adverse life experiences and elevated C-reactive protein levels, increased TNF-a and IL-6 secretion, elevated sICAM-1 and E-selectin production, and increased nuclear factor-kB activity. (Danese et al., 2007; Taylor et al., 2006; Kiecolt-Glaser et al., 2011; Pace et al., 2012; Slopen et al., 2010).[61-65]

There is a correlation between higher rates of rheumatoid arthritis, cardiovascular illness, diabetes, and chronic lung diseases with child abuse and neglect (Danese et al., 2007; Spitzer et al., 2013).[61,66] Furthermore, greater CMV and Epstein-Barr virus antibody titers are linked to childhood traumas, and salivary herpes simplex virus-specific antibody titers are higher in adolescents who experienced physical abuse as children (Shirtcliff et al., 2009, Fagundes et al., 2013).[67,68]

Artificial intelligence and infectious disease

Artificial intelligence (AI) has been recognised as the most potent and promising analytical instrument now available to humanity. According to recent findings, machine learning adds value to image processing in situations where traditional methods are unable to detect early illness indications (Chen and Asch, 2017).[70] This is especially true for cancer, whose detection and treatment are frequently aided by AI techniques (Boon et al., 2018).[71] This is relevant even in developing nations when it is not possible to provide the best care due to a lack of resources, the expense of healthcare, and other issues. Recent research by Im et al. (2018)[72] suggests that a low-cost point of care for lymphoma diagnosis based on deep learning and basic imaging may be possible. According to Xu et al. (2016),[73] a number of studies recommended using Bayesian networks (BN) to describe statistical interdependence. According to Belle et al. (2013),[74] a BN is a graph-based model of joint multivariate probability distributions that represents the characteristics of conditional independence between variables.

Artificial intelligence in the diagnosis of Infectious disease

Authorities have established procedures to identify people who are at risk due to their concern over the spread of infectious diseases. As a result, temperature checks are routinely carried out in Singapore airport terminals using a thermal camera to identify people who have excessive temperatures. This basic check is just one of several actions being taken to prevent the spread of illnesses. Recent methods that make use of mathematical modelling are making this kind of surveillance better. Sun et al. (2015)[75] developed a comparable approach that uses vital sign categorisation to identify infected patients. In increasingly complex situations, machine learning techniques can be applied. To better separate gene sequences from bacteria than previous approaches like high-resolution melt (HRM), for example, a combination of Matlab, the leave one out cross-validation (LOOCV) method, the support vector machine (SVM) learning algorithm, and nested one-versus-one (OVO) SVM was utilised. SVM and HRM together could identify isolated bacteria with a high degree of accuracy (100%) (Fraley et al., 2016).[76]

The accuracy was impacted when using blood samples from patients in real life, which highlights the drawbacks of creating tools based solely on data produced in a laboratory setting. It is unknown if this resulted from the biological samples' poor quality or from the interactions of the bacteria in an unaltered environment. Nevertheless, this demonstrates that some practical considerations, such sample quality or lab procedure

duration, should be taken into account while developing mathematical tools. This was addressed in relation to the diagnosis of tuberculosis, which is the second most common cause of infection-related death worldwide (Saybani et al., 2015).[77]

There are methods in place for diagnosing different diseases, such as the artificial immune recognition system (AIRS). AIRS was created utilising a characteristic of the immune system. The immune system's job is to identify dangers and remember them. Probably the most significant aspect of immunity is immunological memory, which makes it possible for humans to react more effectively the next time the infectious agent (danger) presents itself. According to Cuevas et al. (2012),[79] the supervised machine learning techniques used by the AIRS (Watkins and Boggess, 2002)[78] have demonstrated good accuracy. Diagnosing malaria takes time and sometimes involves multiple health providers. Using very cheap digital in-line holographic microscopy data, machine learning algorithms were created to identify malaria-infected red blood cells (RBCs) (Go et al., 2018).[80]

Autoregressive integrated moving average (ARIMA) is a tool that has been used by several teams from the United States (Kane et al., 2014),[81] China, New Zealand (Zhang et al., 2014),[82] and South Africa (Adeboye et al., 2016)[83] to predict infectious diseases. Although the ARIMA model was initially created for economic uses, it has been applied to other fields as well, such as illnesses that repeat or cycle. Because time series models like ARIMA remove high-frequency noise from data and identify local trends based on linear dependence in series observations, they are used to forecast future outbreaks. Dynamic relationships can be integrated into the ARIMA model, which can then be updated in response to current events.

As a result, ARIMA models have been extensively utilised for forecasting epidemic time series, such as those involving tuberculosis, dengue disease, and hemorrhagic fever. Seasonality is a significant factor in the later and other infectious diseases (Mohammed et al., 2018).[84] Incidence and seasonality of tuberculosis in South Africa were examined using seasonal ARIMA (SARIMA) and neural network auto-regression (SARIMA-NNAR). This machine learning method showed that peak festival times are risk factors for HIV transmission and that coinfection issues, in particular, need to be addressed.

Treatment and antimicrobial drug resistance

Antibacterial and antiparasitic medication resistance is a serious issue, even with current diagnostic methods for malaria being rather good and likely to improve in the near future (Blasco et al., 2017).[85] The advent of Plasmodium falciparum malaria parasites that are less susceptible to artemisinin-based combination therapies is posing a challenge to the 20-year-old practice of adopting artemisinin-based combination therapies. It was expected by mathematical modelling based on intrahost parasite stage-specific pharmacokinetic-pharmacodynamic connections that drug action-resistant ring stages would lead to ART resistance (Saralamba et al., 2011).[86] The presence of databases that reflect the problem of antibiotic resistance can aid in combating it more effectively (Jia et al., 2017).[87]

Additionally, recent research has demonstrated the effectiveness of machine learning in determining a candidate compound's potential antibacterial activity (Wang et al., 2016).[88] To predict mice's reaction to tuberculosis infection, Ekins et al. employed a number of machine learning techniques in a more methodical manner (Ekins et al., 2016).[89]

Testing for HIV RNA in the blood is one method of tracking the virus's progression in the HIV case. Although this is a very effective way to modify therapy, it is rarely feasible in settings with limited resources. Antiretroviral therapy plays a critical role in the evolution of HIV infectivity (Petersen et al., 2008).[90] Therefore, it is imperative to ensure that therapy is administered effectively and that treatment adherence prevents viral load reduction.

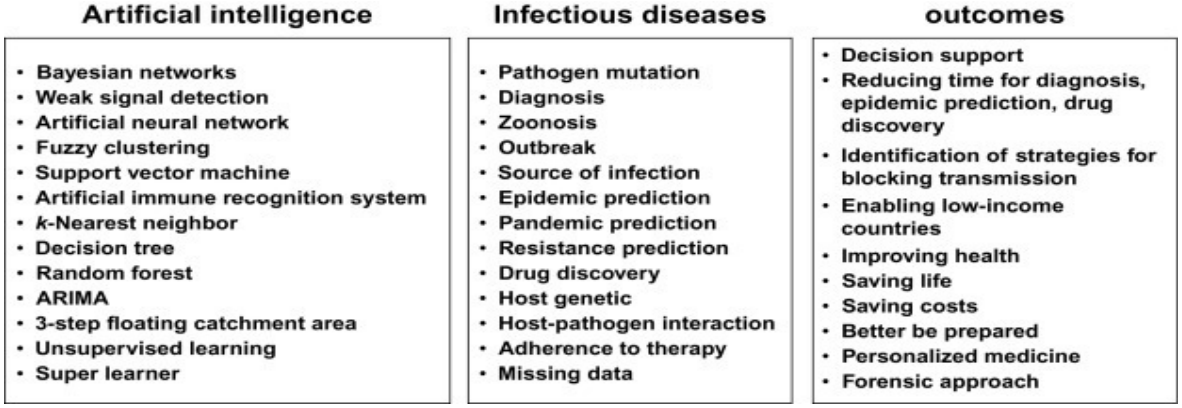


Figure: AI tools and their potential outcomes.
(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7153335/)

CONCLUSION

The significance of psychological stress and its impact on susceptibility to infectious diseases, particularly respiratory infections, were established by the current review. We conclude that there is an unexplained mechanism underlying psychological stress and infectious diseases, as evidenced by many literatures. To fully comprehend the physiological distinctions between acute and chronic stress, as well as the compounding effects of multiple stressors, more research is required. It is increasingly clear that stress can both increase an individual's risk of contracting an illness and increase the severity of an existing one. Prenatal and neonatal psychosocial stress are more prone to infectious diseases. Fighting infectious diseases is made possible in large part by artificial intelligence. AI also aids in the early detection and prevention of infectious diseases.

REFERENCES

1. Mason Jw. A historical view of the stress field. J Human Stress, 1975; 1: 6-12.
2. Chrousos GP, Loriaux DL, Gold PW. Introduction: The concept of stress and its historical development. InMechanisms of physical and emotional stress, 1988; 3-7. Boston, MA: Springer US.
3. Webster's medical desk dictionary. Springfield, MA: Merriam-Webster, 1986.
4. Dantzer R, Kelley KW. Stress and immunity: an integrated view of relationships between the brain and the immune system. Life Sci, 1989; 44: 1995-2008.
5. Griffin JF. Stress and immunity: a unifying concept. Veterinary immunology and immunopathology, 1989; 1, 20(3): 263-312.
6. Rabin BS, Cohen S, Ganguli R, Lysle DT, Cunnick JE. Bidirectional interaction between the central nervous system and the immune system. CRC Crit Rev Immunol, 1989; 9: 279-312.
7. Brown SL, BlalockJE. Neuroendocrine immune interactions. In: Oppenheim JJ, Shevach EM, eds. Immunophysiology: the role of cells and cytokines in immunity and inflammation. New York: Oxford University Press, 1990; 306-19.
8. Bonneau RH, Kiecolt-Glaser JK, Glaser R. Stress-induced modulation of the immune response. Ann N Y Acad Sci, 1990; 594: 253-69.
9. Khansari DN, Murgo AI, Faith RE. Effects of stress on the immune system. Immunol Today, 1990; 11: 170-5.
10. Peterson PK, Chao CC, Molitor T, Murtaugh M, Strgar F, Sharp BM. Stress and pathogenesis of infectious disease. Reviews of infectious diseases, 1991; 1, 13(4): 710-20.
11. Maestroni GJM, Conti A. Beta-endorphin and dynorphin mimic the circadian immunoenhancing and anti-stress effects of melatonin. Int J Immunopharmacol, 1989; 11: 333-40.
12. Brown SL, BlalockJE. Neuroendocrine immune interactions. In: Oppenheim JJ, Shevach EM, eds. Immunophysiology: the role of cells and cytokines in immunity and inflammation. New York: Oxford University Press, 1990; 306-19.
13. Lazarus RS, Folkman S. Stress, appraisal, and coping. Springer publishing company, 1984; 15.
14. Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S. Noradrenergic and peptidergic innervation of lymphoid tissue. Journal of Immunology (Baltimore, Md.: 1950), 1985; 1, 135(2): 755s-65s.
15. Felten SY, Olschowka J. Noradrenergic sympathetic innervation of the spleen: II. Tyrosine hydroxylase (TH)-positive nerve terminals form synapticlike contacts on lymphocytes in the splenic white pulp. Journal of neuroscience research, 1987; 18(1): 37-48.
16. Shavit Y, Lewis JW, Terman GW, Gale RP, Liebeskind JC. Opioid peptides mediate the suppressive effect of stress on natural killer cell cytotoxicity. Science, 1984; 13, 223(4632): 188-90.
17. Kiecolt-Glaser JK, Glaser R. Methodological issues in behavioral immunology research with humans. Brain, behavior, and immunity, 1988; 1, 2(1): 67-78.
18. Maccari S, Krugers HJ, Morley-Fletcher S, Szyf M, Brunton PJ. The consequences of early life adversity: neurobiological, behavioural and epigenetic adaptations. J Neuroendocrinol, 2014; 26(10): 707–23.
19. Merlot E, Couret D, Otten W. Prenatal stress, fetal imprinting and immunity. Brain Behav Immun, 2008; 22(1): 42–51.
20. Ader R, ed. Psychoneuroimmunology. New York: Academic Press, 1981.
21. Calabrese JR, Kling MA, Gold PW. Alterations in immunocompetence during stress, bereavement, and depression: focus on neuroendocrine regulation. The American journal of psychiatry, 1987; 1, 144(9): 1123-34.
22. Kiecolt-Glaser JK, Glaser R. Psychosocial factors, stress, disease, and immunity. In: Ader R, Feiten DL, Cohen N, eds. Psychoneuroimmunology. New York: Academic Press, 1991; 849–67.
23. Cohen S, Williamson GM. Stress and infectious disease in humans. Psychological bulletin, 1991; 109(1): 5.
24. Laudenslager ML. Psychosocial stress and susceptibility to infectious disease. InViruses, immunity, and mental disorders, 1987; 391-402. Boston, MA: Springer US.
25. Graham NM, Douglas RM, Ryan P. Stress and acute respiratory infection. American Journal of Epidemiology, 1986; 1, 124(3): 389-401.
26. Boyce WT, Jensen EW, Cassel JC, Collier AM, Smith AH, Ramey CT. Influence of life events and family routines on childhood respiratory tract illness. Pediatrics, 1977; 1, 60(4): 609-15.
27. Meyer RJ, Haggerty RJ. Streptococcal infections in families: Factors altering individual susceptibility. Pediatrics, 1962; 1, 29(4): 539-49.
28. Lazarus R. Psychological stress and the coping process. New York: McGraw-Hill, 1966.

29. Field T. Prenatal depression effects on early development: a review. Infant Behav Dev, 2011; 34(1): 1–14.
30. Field T, Diego M, Hernandez-Reif M, Vera Y, Gil K, Schanberg S, Kuhn C, Gonzalez-Garcia A. Prenatal maternal biochemistry predicts neonatal biochemistry. Int J Neurosci, 2004; 114(8): 933–45.
31. Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis. Neurosci Biobehav Rev, 2010; 35(1): 17–22.
32. Fraser D, Fraser AF, Ritchie JS. The term "stress" in a veterinary context. British Veterinary Journal, 1975; 1, 131(6): 653-62.
33. Marsland AL, Bachen EA, Cohen S, Rabin B, Manuck SB. Stress, immune reactivity and susceptibility to infectious disease. Physiology & behaviour, 2002; 1, 77(4-5): 711-6.
34. Yang EV, Glaser R. Stress-induced immunomodulation and the implications for health. International immunopharmacology, 2002; 1, 2(2-3): 315-24.
35. Matarazzo JD. Behavioral health: A handbook of health enhancement and disease prevention. (No Title), 1984.
36. Jemmott JB, Locke SE. Psychosocial factors, immunologic mediation, and human susceptibility to infectious diseases: How much do we know?. Psychological bulletin, 1984; 95(1): 78.
37. Krantz DS, Grunberg NE, Baum A. Health psychology. Annual review of psychology, 1985; 1, 36(1): 349-83.
38. Cohen S, Line S, Manuck SB, Rabin BS, Heise ER, Kaplan JR. Chronic social stress, social status, and susceptibility to upper respiratory infections in nonhuman primates. Psychosomatic medicine, 1997; 1, 59(3): 213-21.
39. Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. The Journal of infectious diseases, 2000; 1, 181(3): 831-7.
40. Cohen S, Doyle WJ, Skoner DP. Psychological stress, cytokine production, and severity of upper respiratory illness. Psychosomatic medicine, 1999; 1, 61(2): 175-80.
41. Clover RD, Abell T, Becker LA, Crawford S, Ramsey CN. Family functioning and stress as predictors of influenza B infection. J Fam Pract, 1989; 1, 28(5): 535-9.
42. Hermann G, Tovar CA, Beck FM, Allen C, Sheridan JF. Restraint stress differentially affects the pathogenesis of an experimental influenza viral infection in three inbred strains of mice. Journal of neuroimmunology, 1993; 1, 47(1): 83-93.
43. Sheridan JF, Feng N, Bonneau RH, Allen CM, Huneycutt BS, Glaser R. Restraint stress differentially affects anti-viral cellular and humoral immune responses in mice. Journal of neuroimmunology, 1991; 1, 31(3): 245-55.
44. Deshpande SA, Northern V. The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. Archives of disease in childhood, 2003; 1, 88(12): 1065-9.
45. Ganguin HG. Respiratory tract diseases, their health-political importance and trends. Zeitschrift fur die Gesamte Innere Medizin und Ihre Grenzgebiete, 1979; 1, 34(4): 18-20.
46. Cohen S. Psychological stress and susceptibility to upper respiratory infections. American journal of respiratory and critical care medicine, 1995; 1, 152(4): S53.
47. Cobb JM, Steptoe A. Psychosocial stress and susceptibility to upper respiratory tract illness in an adult population sample. Psychosomatic medicine, 1996; 1, 58(5): 404-12.
48. Rojas IG, Padgett DA, Sheridan JF, Marucha PT. Stress-induced susceptibility to bacterial infection during cutaneous wound healing. Brain, behavior, and immunity, 2002; 1, 16(1): 74-84.
49. Schneiderman N, Ironson G, Siegel SD. Stress and health: psychological, behavioral, and biological determinants. Annu. Rev. Clin. Psychol, 2005; 27, 1(1): 607-28.
50. Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, Turner RB. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proceedings of the National Academy of Sciences, 2012; 17, 109(16): 5995-9.
51. Leserman J, Petitto JM, Golden RN, Gaynes BN, Gu H, Perkins DO, Silva SG, Folds JD, Evans DL. Impact of stressful life events, depression, social support, coping, and cortisol on progression to AIDS. American Journal of Psychiatry, 2000; 1, 157(8): 1221-8.
52. Maes M. Major depression and activation of the inflammatory response system. Cytokines, stress, and depression, 1999; 25-46.
53. Rothwell NJ, Hopkins SJ. Cytokines and the nervous system II: actions and mechanisms of action. Trends in neurosciences, 1995; 1, 18(3): 130-6.
54. Licinio J, Wong ML. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Molecular psychiatry, 1999; 4(4): 317-27.
55. Goldberg JM, Moberg GP. Autonomic control of heart rate in the neonatal rhesus monkey. Journal of medical primatology, 1985; 14(1): 19-27.
56. Nielsen NM, Hansen AV, Simonsen J, Hviid A. Prenatal stress and risk of infectious diseases in offspring. American journal of epidemiology, 2011; 1, 173(9): 990-7.
57. Khashan AS, Wicks S, Dalman C, Henriksen TB, Li J, Mortensen PB, Kenny LC. Prenatal stress and risk of asthma hospitalization in the offspring: a Swedish population-based study. Psychosomatic medicine, 2012; 1, 74(6): 635-41.

58. Sausenthaler S, Rzehak P, Chen CM, Arck P, Bockelbrink A, Schäfer T, Schaaf B, Borte M, Herbarth O, Krämer U, Von Berg A. 9 Stress-Related Maternal Factors During Pregnancy in Relation to Childhood Eczema: Results From the LISA Study. Journal of investigational allergology & clinical immunology, 2009; 1, 19(6): 481.
59. Kaufman J, Plotsky PM, Nemeroff CB, Charney DS. Effects of early adverse experiences on brain structure and function: clinical implications. Biological psychiatry, 2000; 15, 48(8): 778-90.
60. McEwen BS. Understanding the potency of stressful early life experiences on brain and body function. Metabolism, 2008; 1, 57: S11-5.
61. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proceedings of the National Academy of Sciences, 2007; 23, 104(4): 1319-24.
62. Taylor SE, Lehman BJ, Kiefe CI, Seeman TE. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. Biological psychiatry, 2006; 15, 60(8): 819-24.
63. Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, Glaser R. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosomatic medicine, 2011; 1, 73(1): 16-22.
64. Pace TW, Wingenfeld K, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim CM. Increased peripheral NF-κB pathway activity in women with childhood abuse-related posttraumatic stress disorder. Brain, behavior, and immunity, 2012; 1, 26(1): 13-7.
65. Slopen N, Lewis TT, Gruenewald TL, Mujahid MS, Ryff CD, Albert MA, Williams DR. Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey. Psychosomatic medicine, 2010; 1, 72(7): 694-701.
66. Spitzer C, Wegert S, Wollenhaupt J, Wingenfeld K, Barnow S, Grabe HJ. Gender-specific association between childhood trauma and rheumatoid arthritis: A case–control study. Journal of psychosomatic research, 2013; 1, 74(4): 296-300.
67. Shirtcliff EA, Coe CL, Pollak SD. Early childhood stress is associated with elevated antibody levels to herpes simplex virus type 1. Proceedings of the National Academy of Sciences, 2009; 24, 106(8): 2963-7.
68. Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan. Brain, behavior, and immunity, 2013; 1, 27: 8-12.
69. Silver D, Schrittwieser J, Simonyan K, Antonoglou I, Huang A, Guez A, Hubert T, Baker L, Lai M, Bolton A, Chen Y. Mastering the game of go without human knowledge. Nature, 2017; 550(7676): 354-9.
70. Chen JH, Asch SM. Machine learning and prediction in medicine—beyond the peak of inflated expectations. The New England journal of medicine, 2017; 6, 376(26): 2507.
71. Boon IS, Au Yong TP, Boon CS. Assessing the role of artificial intelligence (AI) in clinical oncology: utility of machine learning in radiotherapy target volume delineation. Medicines, 2018; 11, 5(4): 131.
72. Im H, Pathania D, McFarland PJ, Sohani AR, Degani I, Allen M, Coble B, Kilcoyne A, Hong S, Rohrer L, Abramson JS. Design and clinical validation of a point-of-care device for the diagnosis of lymphoma via contrast-enhanced microholography and machine learning. Nature biomedical engineering, 2018; 2(9): 666-74.
73. Xu J, Wickramarathne TL, Chawla NV. Representing higher-order dependencies in networks. Science advances, 2016; 20, 2(5): e1600028.
74. Belle A, Kon MA, Najarian K. Biomedical Informatics for Computer-Aided Decision Support Systems: A Survey. The Scientific World Journal, 2013; 2013(1): 769639.
75. Sun G, Matsui T, Hakozaki Y, Abe S. An infectious disease/fever screening radar system which stratifies higher-risk patients within ten seconds using a neural network and the fuzzy grouping method. Journal of Infection, 2015; 1, 70(3): 230-6.
76. Fraley SI, Athamanolap P, Masek BJ, Hardick J, Carroll KC, Hsieh YH, Rothman RE, Gaydos CA, Wang TH, Yang S. Nested machine learning facilitates increased sequence content for large-scale automated high resolution melt genotyping. Scientific reports, 2016; 18, 6(1): 19218.
77. Saybani MR, Shamshirband S, Hormozi SG, Wah TY, Aghabozorgi S, Pourhoseingholi MA, Olariu T. Diagnosing tuberculosis with a novel support vector machine-based artificial immune recognition system. Iranian Red Crescent Medical Journal, 2015; 17(4).
78. Watkins A, Boggess L. A new classifier based on resource limited artificial immune systems. InProceedings of the 2002 Congress on Evolutionary Computation. CEC'02 (Cat. No. 02TH8600), 2002; 12: (2, 1546-1551). IEEE.
79. Cuevas E, Osuna-Enciso V, Zaldivar D, Perez-Cisneros M, Sossa H. Multithreshold segmentation based on artificial immune systems. Mathematical Problems in Engineering, 2012; 2012(1): 874761.
80. Go T, Kim JH, Byeon H, Lee SJ. Machine learning-based in-line holographic sensing of unstained malaria-infected red blood cells. Journal of biophotonics, 2018; 11(9): e201800101.
81. Kane MJ, Price N, Scotch M, Rabinowitz P. Comparison of ARIMA and Random Forest time series models for prediction of avian influenza H5N1 outbreaks. BMC bioinformatics, 2014; 15: 1-9.
82. Zhang X, Zhang T, Young AA, Li X. Applications and comparisons of four time series models in epidemiological surveillance data. Plos one, 2014; 5, 9(2): e88075.

83. Azeez A, Obaromi D, Odeyemi A, Ndege J, Muntabayi R. Seasonality and trend forecasting of tuberculosis prevalence data in Eastern Cape, South Africa, using a hybrid model. International journal of environmental research and public health, 2016; 13(8): 757.
84. Mohammed SH, Ahmed MM, Al-Mousawi AM, Azeez A. Seasonal behavior and forecasting trends of tuberculosis incidence in Holy Kerbala, Iraq. The International Journal of Mycobacteriology, 2018; 1, 7(4): 361-7.
85. Blasco B, Leroy D, Fidock DA. Antimalarial drug resistance: linking Plasmodium falciparum parasite biology to the clinic. Nature medicine, 2017; 1, 23(8): 917-28.
86. Saralamba S, Pan-Ngum W, Maude RJ, Lee SJ, Tarning J, Lindegårdh N, Chotivanich K, Nosten F, Day NP, Socheat D, White NJ. Intrahost modeling of artemisinin resistance in Plasmodium falciparum. Proceedings of the national academy of sciences, 2011; 4, 108(1): 397-402.
87. Jia B, Raphenya AR, Alcock B, Waglechner N, Guo P, Tsang KK, Lago BA, Dave BM, Pereira S, Sharma AN, Doshi S. CARD 2017: expansion and model-centric curation of the comprehensive antibiotic resistance database. Nucleic acids research, 2016; 25: 1004.
88. Wang Y, Yang YJ, Chen YN, Zhao HY, Zhang S. Computer-aided design, structural dynamics analysis, and in vitro susceptibility test of antibacterial peptides incorporating unnatural amino acids against microbial infections. Computer Methods and Programs in Biomedicine, 2016; 1, 134: 215-23.
89. Ekins S, Perryman AL, Clark AM, Reynolds RC, Freundlich JS. Machine learning model analysis and data visualization with small molecules tested in a mouse model of Mycobacterium tuberculosis infection (2014–2015). Journal of chemical information and modelling, 2016; 25, 56(7): 1332-43.
90. Petersen ML, Van Der Laan MJ, Napravnik S, Eron JJ, Moore RD, Deeks SG. Long-term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification. Aids, 2008; 18, 22(16): 2097-106.