

# **"The Relationship Between Stress, Depression, Positive Emotions and Happiness with Psycho-Neuro-Immune Disorders: A comprehensive Review"**

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## **ABSTRACT**

Stress is common phenomenon faced by most of the people in our everyday life whereas depression represents a vast constellations of mental disorders of multifarious etiology. It has been seen that stressful condition and depression alter functioning of immune responses. Psychoneuroimmunology is study of interrelationships among psychological , neuroendocrine and immunology and is concerned with how these relationships may affect individual's health. Number of studies have demonstrated that stress increase risk of many diseases like cancer, viral infections, etc. Stress and depression can depress our immune system whereas reduction in stress and depression enhance our immune responses. While on the other Positive Emotions like happiness, optimism or resilience etc has been proven to be major "Good" Prognostic factor for disorders. As it is the time of COVID19 Pandemic and is already proven that it is the immunity of the individual which can be the best prevention and prognostic criterion to fight with it. An understanding of Psycho-Neuro-Immune Disorders and its relation with 'Good' and 'Bad' emotional state more specifically Stress and Depression or happiness and feeling Well being will provide an understanding of the interplay of these elements. Thus having said this much present study is aiming at reviewing 30+ research papers to analyze the role play and impact of these factors in the Risk, Prognosis and Prevention of Psycho-Neuro- Immune Disorders.

**Key Words:** Psycho-Neuro-Immune Disorders, Stress, Depression, Positive Emotions and Happiness

## **INTRODUCTION**

Psychoneuroimmune (PNI) disorders such as HIV, Cancer , Diabetes, Hormonal Dysfunctions, Skin Diseases and other Autoimmune and Infectious diseases are increasing worldwide with alarming pace. This trend has stretched researcher's attention on this issue. Same time ample of researches indicate towards its link with psychological factors. Thus researcher has taken four psychological state found to be linked with PNI disorders. Out of which two that is Stress and Depression play role in advancement while state of Well Being and Happiness serve in

prevention, intervention and treatment of the PNI disorders. To serve this purpose more than 50 papers were reviewed out of which 21 are mentioned in the present paper.

Psycho-neuro-immunology is the "discipline that studies the modalities of interactions between the immune system and the central nervous system and their functional outcomes. Clinical and pre clinical studies in this field have confirmed the sensitivity of the immune system to psychosocial stressors and deciphered the pathways of communication from the brain to the immune system, including innervations of the lymphoid organs. However, it has soon become apparent that influences of the brain on the immune system are part of a regulatory pathway that enables the whole organism to cope with infectious agents" (1) Available from Walter Cannon, a professor of physiology at Harvard University coined the term 'homeostasis' in his book 'The wisdom of body' in 1932. In his work with animals Cannon noticed that any kind of change in the emotional state, such as anxiety, distress, or anger was associated with total cessation of stomach movement. These studies focused on the relationship between the effects of emotions and perception on Autonomic Nervous System, and the response that resulting in to freezing, flight and fight response.

In 1964 G. Solomon coined the term 'psychoimmunology'. In 1975 Robert Ader and Nicholas Cohen demonstrated "classical conditioning of immune function and coined the term 'psychoneuroimmunology'." Classical conditioning experiment on immune response by Cohen showed that conditioned rats exposed to conditioned stimulus were immune suppressed. This demonstrated that nervous system can affect immune system.

In 1981 David Felten then working at Indiana University of medicine discovered network of nerves leading to blood vessels as well as cells of immune system. The researchers also found nerves in thymus and spleen ending near cluster of lymphocytes, Macrophages and mast cells, control immune function. This led to discovery of how neurological -immunological interactions occur.

Examples of PSHYCONEUROIMMUNE (PNI) disorders:

**PSORIASIS** : It is the best example of PNI. It perfectly explain how our CNS, stress, immune system are linked. Chronic condition of psoriasis led to rapid growth of skin cells. Our body usually shed extra skin but in psoriasis, these extra skin keeps on building on our skin which result in intense itching and pain. Due to chronic stress when cortisol level increases which led to releases of pro-inflammatory cytokine which causes over growth of our skin cells. People with psoriasis often complain of depression and stress and suicidal thoughts .

**CANCER**: women with genetic risk factors for developing cancer showed abnormalities in immune system in response to stress.

**CORONARY ARTERY DISEASE** : increase in pro-inflammatory cytokine due to stress result in increase in heartrate and blood pressure. Increase in cytokine promote feeling of sickness and fatigue. Long term stress may result in cardiac disease.

**IRRITABLE BOWEL SYNDROME** : It has been established that there is strong association between sustained Stressful events and onset of symptoms in functional gastrointestinal disorders.

**HIV:** Elevated level of stress and diminished social support accelerates progression of HIV infection.

**WOUND HEALING :** Speed at which surgical patient has been linked to psychological factors. For instance, increased levels of fear or distress before surgery have been associated with worse outcomes, including longer stays in the hospital, more postoperative complications and higher rates of re-hospitalization. Depression and anxiety showed significantly delayed healing.

**Other Disorders** includes Diabetes and other Autoimmune and Infectious disorders.

**Stress:** "In a medical or biological context **stress** is a physical, mental, or emotional factor that causes bodily or mental tension. Stresses can be external (from the environment, psychological, or social situations) or internal (illness, or from a medical procedure)." (3)

**Depression:** It is the state of persistent and pervasive sadness throughout all the day and disinterest in almost all the activities.

**Positive Emotions:** According to Oxford Handbook of Positive Psychology "*pleasant or desirable situational responses... distinct from pleasurable sensation and undifferentiated positive affect*" (Cohn & Fredrickson, 2009) It is the state when a person perceives him/her self physically and psychologically healthy and has sense of self control.

**Happiness:** " The field of positive psychology often defines a happy person as someone who experiences frequent positive emotions, such as joy, interest, and pride, and infrequent (though not absent) negative emotions, such as sadness, anxiety, and anger" (Lyubomirsky et al., 2005). (4)

**Table 1.0**

**Indicates Title of the paper, Name of the Author/s, Journal/ Source Information and Findings**

S. No	TITLE OF PAPER	NAME OF AUTHOR	NAME OF JOURNAL	FINDINGS
1	Stress and Immunity in Humans: A Meta-Analytic Review	Herbert and Cohen	<i>Psychosomatic Medicine</i> 55:364-379 (1993)	they examined 38 studies of stressful event and immune function in adults. They reported consistent stress increases white blood cells, decreases helper T cells, suppressor T cells and cytotoxic T cells, B

				cells, natural killer cells as well.
2.	The Relationship of Depression and Stressors to Immunological Assays: A Meta-Analytic Review	Eric P. Zorrilla, Lester Luborsky, James R. McKay, Robert Rosenthal, Arlene Houldin, Anne Tax, Ruth McCorkle, David A. Seligman, and Kelly Schmidt 2001	<i>Brain, Behavior, and Immunity</i> 15, 199–226 (2001) doi:10.1006/brbi.2000.0597, available online at <a href="http://www.idealibrary.com">http://www.idealibrary.com</a>	They analyzed studies of stressor and human immunity. They reported naturalistic stressors are associated with increase in number of circulating neutrophils, decrease in number and percentage of total T cells and helper T cells, decrease in percentage of natural killer cells and cytotoxic T Cells lymphocytes.
3.	Psychoneuroimmunology: Psychological influences on immune function and health.	<u>Kiecolt-Glaser, Janice</u> <u>K. McGuire,</u> <u>Lynanne Robles,</u> <u>Theodore F. Glaser,</u> <u>Ronald</u>	<i>Journal of Consulting and Clinical Psychology</i> , 70(3), 537–547. <a href="https://doi.org/10.1037/0022-006X.70.3.537">https://doi.org/10.1037/0022-006X.70.3.537</a>	The research goals were to show the effects of psychological coping, and social support on the ability of the immune system to respond to a hepatitis B vaccine .In a study conducted on the immune responses to hepatitis B vaccinations, 48 second year medical students on the last day of a three day examination were chosen to determine the effect of academic stress on the abilities of immune response (Glaser, et al., 1992). It was interesting that results showed that those students who felt they had social support reported less stress, and had greater activation of immune functioning

4.	Psychoneuroimmune Phenomena (1)	Robert Dantzer , Keith W. Kelley (2012)	<i>Springer Science+Business Media, LLC( Copy Right Holders)</i>	Findings Indicated that Stress, Helplessness, emotional suppression and other neurotic personality factors lead to PNI disorders while Positive emotions like resilience and other psychosocial factors protect against Cancer, HIV and other PNI disorders.
5.	A PSYCHONEUROIMMUNE MODEL OF POSTPARTUM DEPRESSION (Conference Paper) (2)	<u>Elizabeth J Corwin</u> ; Kathleen Pajer (April ,2010)	<i>Conference: 2011 Western Institute of Nursing Annual Communicating Nursing Research Conference</i>	Authors found that Post Partum Depression is linked with physiological changes occur after delivery and psychological factors like social and family support etc which leads to PNI disorders.
6.	Somatization: A psychoneuroimmune perspective	Robert Dantzer (November 2005)	<i>Psychoneuroendocrinology 30(10):947-52</i> <i>DOI: <a href="https://doi.org/10.1016/j.psycneuen.2005.03.011">10.1016/j.psycneuen.2005.03.011</a></i> <i>Source :PubMed</i>	Findings of this research indicates Interaction between CNS and Immune system can be represented in the form of depression and Somatization and Somatoform Disorders.
7.	Are Perceived Stress and Cytokine Genotypes Clinically Feasible as Predictors of Psychoneuroimmune Symptoms in Advanced Cancer?	Stephanie Gilbertson, White Ariana Shahnazi, Catherine H Cherwin ( December 2018)	<i>The Permanente journal 23</i> <i>DOI: <a href="https://doi.org/10.7812/TPP/18-120">10.7812/TPP/18-120</a></i>	According to this research Genetic factors and Stress are main predictors of developing PNI symptoms in cancer patients
8.	Psychoneuroimmunology of HIV Infection	Margaret E. Kemeny Ph D	<i>Psychiatric Clinics of North America Volume 17, Issue 1, March 1994, Pages 55-68</i>	This article indicates towards psychosocial cofactors in progression of the disease (HIV). Three potential

				biologic pathways through which psychosocial factors could act on HIV progression are described: the neuroendocrine system, the autonomic nervous system, and the reactivation of latent viruses
9.	Psychoneuroimmunology: stress effects on pathogenesis and immunity during infection.	J F Sheridan, C Dobbs, D Brown, B Zwilling (1994)	<i>CLINICAL MICROBIOLOGY REVIEWS</i> , Apr. 1994, p. 200-212 Vol. 7, No. 2 0893-8512/94 ©) 1994, American Society for Microbiology	Out of Stress response CNS and hypothalamic-pituitary-adrenal axis release some soluble products. Cell interacts with hormones and Neurotransmitters which has great effects on immune system and other infectious disorders in mammals.
10	Psychoneuroimmunology: Can psychological interventions modulate immunity?	By Kiecolt-Glaser, Janice K., Glaser, Ronald	<i>Journal of Consulting and Clinical Psychology</i> , Vol 60(4), Aug 1992, 569-575	This article talks about positive correlation between stressors and progression of PNI disorders. Thus Researchers have used a number of diverse strategies to modulate immune function, including relaxation, hypnosis, exercise, classical conditioning, self-disclosure, exposure to a phobic stressor to enhance perceived coping self-efficacy, and cognitive-behavioral interventions, and these interventions have generally produced positive changes
11	Psychological influences on surgical	Kiecolt-Glaser, J. K., Page, G.	<i>Psychological influences on</i>	This paper suggests a number of routes

	recovery: Perspectives from psychoneuroimmunology.	G., Marucha, P. T., MacCallum, R. C., & Glaser, R. (1998)	<i>surgical recovery: Perspectives from psychoneuroimmunology</i> . American Psychologist, 53(11), 1209–1218. <a href="https://doi.org/10.1037/0003-066X.53.11.1209">https://doi.org/10.1037/0003-066X.53.11.1209</a>	through which psychological and behavioral responses can influence surgery and postsurgical outcomes. (Stress delays wound healing)
12	Psychological intervention in cancer patients (December 2005)	<u>Carmen Yélamos</u> ; <u>B. Fernández Sánchez</u>	<i>Revisiones en Cancer</i> 20(1):14-21	This paper suggests that Cancer is associated with multiple emotional reactions that produce personal distress. Anxiety and depression are the most frequent signs. The present paper is a review on the psychological intervention most frequently used in cancer patients.
13	Psychological intervention in cancer patients: A randomized study	<u>Lea Baider</u> , <u>Tami Peretz</u> , <u>Pnina Ever Hadani</u> , <u>Uwe Koch</u>	<i>General Hospital Psychiatry</i> 23(5):27 2-7 (August 2001)  DOI: <a href="https://doi.org/10.1016/S0163-8343(01)00158-X">10.1016/S0163-8343(01)00158-X</a>	Study had been conducted on 116 Cancer patients, divided in two groups (Experimental and Control Group) Experimental group has been given psychological intervention for one month (Relaxation etc. to minimize stress and increase sense of internal control). finding indicates positive impact on experimental group.
14	Biobehavioral outcomes following psychological interventions for cancer patients	<u>Barbara Lee Andersen</u> (June 2002)	<i>Journal of Consulting and Clinical Psychology</i> 70(3):59 0-610 DOI: <a href="https://doi.org/10.1037/0022-006X.70.3.590">10.1037/0022-006X.70.3.590</a>	Psychological approach to deal with adult cancer patients was mainly aimed at minimizing stress and improving quality of life. Researcher, here

			<i>Source:PubMed Project: <u>Stress and immunity breast cancer project clinical trial</u></i>	has been further focused on bio-behavioral outcomes--health behaviors, compliance, biologic responses, and disease outcomes.
15	Evaluating the Effectiveness of Psychological Interventions in Patients with Psoriasis: A Review	<u>Anh N. Tran;</u> <u>John Y. Koo</u> (February 2014)	<i>DOI: <u>10.1177/247553031420a00103</u></i>	Psoriasis is a common condition, often found associated with psychological morbidity. Stress is frequently preceded in the onset or worsening of psoriasis, gives rise to the preferred use of psychotherapeutic techniques in treatment. Current article reviewed the literature discussing about the cases and trials of psychotherapeutic interventions (i.e., hypnosis biofeedback, , psychotherapy, meditation, and emotional disclosure) in the treatment of patients with psoriasis. All the six case reports demonstrated desirable outcomes. Among the 7 trials out of 11, found significant physical improvement and 4 out of 7 found significant psychological benefit
16	Subjective Well-Being and Physical Health: A Narrative Literature Review with Suggestions for Future Research	<u>Alex Zautra, Ann Hempel</u>	<i>The International Journal of Aging and Human Development Volume: 19 issue: 2, page(s): 95-110 Issue published: Septembe</i>	In this article the authors review the findings of eighty-one studies that have tested the relationship between health status and subjective well-being. Support was

			<i>r 1, 1984</i>	found for an association between health and well-being.
17	Psychological interventions for children with asthma (Cochrane review)	<u>Janelle Yorke,</u> <u>Sharon Fleming,</u> <u>Caroline Shuldham</u> (Jan 2005)	<i>Cochrane database of systematic reviews (Online)</i>  <i>DOI: <a href="https://doi.org/10.1002/14651858.CD003272.pub2">10.1002/14651858.CD003272.pub2</a></i>	It is thought that psychological factors may play an important part in asthma. But only one out of 12 has shown improvement.
18	The Effects of Psychological Intervention on Atopic Dermatitis	<u>Yoichi Chida,</u> <u>Andrew Steptoe,</u>  <u>Noriaki Hirakawa,</u>  <u>Nobuyuki Sudo,</u>  <u>Chiharu Kubo</u> (2007)	<i>International Archives of Allergy and Immunology 144(1): 1-9</i>  <i>DOI: <a href="https://doi.org/10.1159/000101940">10.1159/000101940</a></i>	Between 1986 to 2006, 8 journal articles were published. Eight types of intervention were tested: cognitive-behavioral therapy, habit reversal behavioral therapy, autogenic training, aromatherapy, psychotherapy, brief dynamic, dermatological education and, , a stress management program, and structured educational programs. Effect sizes were computed as correlation coefficient ( $r$ ), and random effects models were used in the analysis. The present meta-analysis revealed that psychological interventions had a significant effect on eczema severity, itching intensity and scratching in atopic

				dermatitis patients
19	The Psychoneuroimmunological Data Base for Psychological Interventions in HIV Infection	<u>Peter Todd</u> (2008)	<i>Author/Gay &amp; Lesbian Issues &amp; Psychology Interest Group of the Australian Psychological Society, ISSN 1833-4512 © 2008</i>	, the field of psychoneuroimmunology (PNI) has provided a vast empirical data base of psychosocial determinants of immunity, illness progression and mortality in HIV infection data have demonstrated that psychosocial factors are highly significant predictors of behaviour known to enhance risk of exposure to HIV and therefore need to be considered as a vital foundation of primary prevention programs aiming to minimize new infection rates.
20	The effectiveness of psychological interventions among tinnitus sufferers: A review	<u>Wan suhailah wan husain,</u> <u>Mohd Normani Zakaria,</u> <u>Nik Adilah Nik Othman,</u> <u>Azizah Othman,</u> <u>Cheu Lih Aw,</u> <u>Nor Zainal</u> (May 2015)	<i>The Medical journal of Malaysia 70(3):188-97 (May 2015)</i>  <i>Source :PubMed</i>	The aim of this article was to review the types of psychological interventions for patients with tinnitus, professionals involved in giving the intervention, the effectiveness of each method of interventions and comparisons with non-psychological approaches in treating tinnitus. PubMed database searched. Twenty one articles that employed randomized controlled trials design were included. Cognitive behavioural therapy (CBT) was the most common intervention conducted

				by the researchers. Clinical psychologists and trainee psychologists were the most professionals involved in the therapy. The length of therapy ranged from six weeks to three months. Psychological interventions were more effective in reducing psychological impacts of tinnitus than non-psychological interventions such as the use of tinnitus maskers
21	Long-term immune-endocrine effects of bereavement: relationships with anxiety levels and mood	GilbertoGerra; <sup>a</sup> DanielaMonti <sup>b</sup> ; Alberto E.Panerai <sup>c</sup> PaolaSacerdote <sup>c</sup> RobertaAnderlini <sup>b</sup> PaolaAvanzini <sup>a</sup> AmirZaimovic <sup>a</sup> FrancescaBrambilla <sup>c</sup> ClaudioFranceschi <sup>b</sup>	<i>Psychiatry Research</i> <i>Volume 121, Issue</i> <i>2, 1 December 2003,</i> <i>Pages 145-158</i>	In the present paper researchers conducted a study in which Psychological, endocrine and immune parameters were measured over a 6-month period in 14 healthy subjects who underwent an unpredictable acute emotional stress compared with 14 controls who did not. Controls showed no changes in <u>psychometric</u> , endocrine and immune measures during the 6-month study while experimental group have significant changes on above parameters.

Result and Discussion: Above table indicates the links between PNI disorders and various psychosocial factors. Findings of the present paper is given below:

1. In the present paper researcher reviewed more than 50 papers out of which 21 papers were mentioned in above table. Out of which most of the papers are those which are direct intervention / assessment of the PNI patients or the papers which have reviewed significant amount of research papers.
2. Except one research paper (Janelle Yorke, Sharon Fleming, Caroline Shuldham, 2005) almost every research paper indicates that psychological factors play very important role either in advancement, vulnerability or intervention of the PNI disorders.
3. Stress, Depression, Bereavement and other negative emotions bring about negative changes in blood composition.
4. Negative emotions can make a person vulnerable for one or other kind of PNI disorders/ Diseases.
5. Negative emotions serve as one of the very significant factors responsible advancement of PNI disorders/ Diseases.
6. Negative emotions hinders the prognosis of PNI disorders/ Diseases.
7. Happiness, Feeling of well being, Feeling of internal sense of control and other positive emotions have proven to be very effective factor for prevention, intervention and treatment of PNI disorders/ Diseases.
8. Various therapies like CBT, Hypnotherapy , Neurobiofeedback and other psychotherapies are evident in the successful treatment of PNI disorders/ Diseases.

As it is evident that psychological factors have immense impact on 'CNS-Endocrine-Immune system' mechanism. Psychological factors can either Initiate/ Advance or Prevent/ Treat PNI disorders. It is said "pain and diseases are the language through which your body communicates something, which needs immediate attention" and most of the times these messages are psychological in natures. This is actually evident in above reviews, where psychosocial factors are found to be one of the main predictors of various PNI disorders. Not only this these factors have been successfully utilized in the treatment of PNI disorders. The significance of the present study increases in the current scenario. As the COVID19 has created havoc worldwide and as per the medical suggestions its patients'/ individuals' immune system which can prevent or can serve as good/ bad prognostic factor. Thus having said this much researchers would like to conclude that our physiological problems are somehow rooted in our psyche. Thus just by handling our psychological activities in healthier way we can prevent ourselves against so many infections and other PNI disorders. lastly as we all know the importance of IMMUNITY in

'Combating' COVID19 is unquestionable, this paper will serve the purpose of promoting overall well being among the readers, in the current situation.

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