

Articles – Titles, References, and Abstracts about <Mind on Infections>

These articles (abstracts)s are the basis for an AURELIS blog, ‘Mind on Infections.’

Contents

1. Longo D, Koehn K. Psychosocial factors and recurrent genital herpes: a review of prediction and psychiatric treatment studies. *Int J Psychiatry Med.* 1993;23(2):99-117. doi: 10.2190/L5MH-0TCW-1PKD-5BM0. PMID: 8360003. 6
2. Katz J, McDermott MP, Cooper EM, Walther RR, Sweeney EW, Dworkin RH. Psychosocial risk factors for postherpetic neuralgia: a prospective study of patients with herpes zoster. *J Pain.* 2005 Dec;6(12):782-90. doi: 10.1016/j.jpain.2005.07.006. PMID: 16326366 7
3. Fiedler N, Ohman-Strickland P, Shen JD, Black K, Horton DB, Panettieri R Jr, Blaser MJ, Carson J, Bendinskas K, Cheng H, Barrett ES. Age and Hair Cortisol Levels as Predictors of SARS-CoV-2 Infection. *Int J Environ Res Public Health.* 2024 Sep 2;21(9):116. doi: 10.3390/ijerph21091166. PMID: 39338049; PMCID: PMC11430878. 7
4. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med.* 1991 Aug 29;325(9):606-12. doi: 10.1056/NEJM199108293250903. PMID: 1713648. 8
5. Stoner MCD, Kelly NK, Gomez-Olive FX, Mall S, Wagner D, Aiello AE, Bhushan N, Kahn K, Pettifor AE. Elevated stress-responsive biomarkers are associated with HIV acquisition in young women in rural South Africa. *AIDS.* 2024 Nov 1;38(13):1866-1873. doi: 10.097/QAD.0000000000003981. Epub 2024 Jul 17. PMID: 39022994; PMCID: PMC11427142..... 9
6. Leserman J, Petitto JM, Gu H, Gaynes BN, Barroso J, Golden RN, Perkins DO, Folds JD, Evans DL. Progression to AIDS, a clinical AIDS condition and mortality: psychosocial and physiological predictors. *Psychol Med.* 2002 Aug;32(6):1059-73. doi: 10.1017/s003291702005949. PMID: 12214787..... 10
7. Pereira DB, Antoni MH, Danielson A, Simon T, Efantis-Potter J, Carver CS, Durán RE, Ironson G, Klimas N, Fletcher MA, O'Sullivan MJ. Stress as a predictor of symptomatic genital herpes virus recurrence in women with human

immunodeficiency virus. *J Psychoom Res.* 2003 Mar;54(3):237-44. doi: 10.1016/s0022-3999(02)00494-4. PMID: 12614833..... 11

8. Leserman J. Role of depression, stress, and trauma in HIV disease progression. *Psychosom Med.* 2008 Jun;70(5):539-45. doi: 10.1097/PSY.0b013e3181777a5f. Epub 2008 Jun 2. PMID: 18519880..... 12

9. Ironson G, O'Cleirigh C, Kumar M, Kaplan L, Balbin E, Kelsch CB, Fletcher MA, Schneiderman N. Psychosocial and Neurohormonal Predictors of HIV Disease Progression (CD4 Cells and Viral Load): A 4 Year Prospective Study. *AIDS Behav.* 2015 Aug;19(8):1388-97. doi: 10.1007/s10461-014-0877-x. PMID: 25234251; PMCID: PMC4465405. 12

10. Weinstein TL, Li X. The relationship between stress and clinical outcomes for persons living with HIV/AIDS: a systematic review of the global literature. *AIDS Care.* 2016;28(2):160-9. doi: 10.1080/09540121.2015.1090532. Epub 2015 Nov 13. PMID: 26565754..... 13

11. Aiello AE, Simanek AM, Galea S. Population levels of psychological stress, herpesvirus reactivation and HIV. *AIDS Behav.* 2010 Apr;14(2):308-17. doi: 10.1007/s10461-008-9358-4. Epub 2008 Feb 9. PMID: 18264753; PMCID: PMC4156100. 14

12. Pedersen AF, Zachariae R, Bovbjerg DH. Psychological stress and antibody response to influenza vaccination: a meta-analysis. *Brain Behav Immun.* 2009 May;23(4):427-33. doi: 10.1016/j.bbi.2009.01.004. Epub 2009 Jan 14. PMID: 19486657..... 14

13. Ballesio A, Zagaria A, Violani C, Lombardo C. Psychosocial and behavioural predictors of immune response to influenza vaccination: a systematic review and meta-analysis. *Health Psychol Rev.* 2024 Jun;18(2):255-284. doi: 10.1080/17437199.2023.2208652. Epub2023 May 9. PMID: 37106577. 15

14. Prösch S, Wendt CE, Reinke P, Priemer C, Oppert M, Krüger DH, Volk HD, Döcke WD. A novel link between stress and human cytomegalovirus (HCMV) infection: sympathetic hyperactivity stimulates HCMV activation. *Virology.* 2000 Jul 5;272(2):357-65. doi: 10.1006/viro.2000.0367. PMID: 10873779..... 16

15. Rector JL, Dowd JB, Loerbroks A, Burns VE, Moss PA, Jarczok MN, Stalder T, Hoffman K, Fischer JE, Bosch JA. Consistent associations between measures of psychological stress and CMV antibody levels in a large occupational sample. *Brain Behav Immun.* 2014 My;38:133-41. doi: 10.1016/j.bbi.2014.01.012. Epub 2014 Jan 26. PMID: 24472683..... 16

16. Kelly NK, Gómez-Olivé FX, Wagner LD, Aiello AE, Kahn K, Pettifor A, Stoner MCD. Intimate partner violence is associated with cytomegalovirus among young women in rural South Africa: An HPTN 068 analysis. *Glob Public Health.* 2023

Jan;18(1):2258962. doi: 1.1080/17441692.2023.2258962. PMID: 37715682; PMCID: PMC10580295..... 17

17. Jang YS, Lam P, Chiang J. Low early life socioeconomic status and susceptibility to the common cold in adulthood: The moderating role of negative affective reactivity. *Health Psychol.* 2024 Apr;43(4):247-258. doi: 10.1037/hea0001337. Epub 2023 Dec 7. PMID 38059931. 18

18. Cohen S. Psychosocial Vulnerabilities to Upper Respiratory Infectious Illness: Implications for Susceptibility to Coronavirus Disease 2019 (COVID-19). *Perspect Psychol Sci.* 2021 Jan;16(1):161-174. doi: 10.1177/1745691620942516. Epub 2020 Jul 8. PMID: 32640177; PMCID: PMC7345443..... 19

19. Cobb JM, Steptoe A. Psychosocial stress and susceptibility to upper respiratory tract illness in an adult population sample. *Psychosom Med.* 1996 Sep-Oct;58(5):404-12. doi: 10.1097/00006842-199609000-00003. PMID: 8902892. 20

20. Turner Cobb JM, Steptoe A. Psychosocial influences on upper respiratory infectious illness in children. *J Psychosom Res.* 1998 Oct;45(4):319-30. doi: 10.1016/s0022-3999(97)00311-5. PMID: 9794278..... 20

21. Falagas ME, Karamanidou C, Kastoris AC, Karlis G, Rafailidis PI. Psychosocial factors and susceptibility to or outcome of acute respiratory tract infections. *Int J Tuberc Lung Dis.* 2010 Feb;14(2):141-8. PMID: 20074403..... 21

22. Silverman MN, Pearce BD, Biron CA, Miller AH. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunol.* 2005;18(1):41-78. doi: 10.1089/vim.2005.18.41. PMID: 15802953; PMCID: PMC1224723. 22

23. Cohen S, Doyle WJ, Skoner DP. Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosom Med.* 1999 Mar-Apr;61(2):175-80. doi: 10.1097/00006842-199903000-00009. PMID: 10204970. 22

24. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM Jr. Social ties and susceptibility to the common cold. *JAMA.* 1997 Jun 25;277(24):1940-4. PMID: 9200634. 23

25. Cohen S, Alper CM, Doyle WJ, Treanor JJ, Turner RB. Positive emotional style predicts resistance to illness after experimental exposure to rhinovirus or influenza a virus. *Psychosom Med.* 2006 Nov-Dec;68(6):809-15. doi: 10.1097/01.psy.0000245867.92364.3c.Epub 2006 Nov 13. PMID: 17101814. 24

26. Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM Jr. Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol.* 1998 May;17(3):214-23. doi: 10.1037//0278-6133.17.3.214. PMID: 9619470.

27. Cohen S, Janicki-Deverts D, Turner RB, Doyle WJ. Does hugging provide stress-buffering social support? A study of susceptibility to upper respiratory infection and illness. *Psychol Sci.* 2015 Feb;26(2):135-47. doi: 10.1177/0956797614559284. Epub 2014 Dec 9. PMID: 25526910; PMCID: PMC4323947. 25
28. Campisi J, Bynog P, McGehee H, Oakland JC, Quirk S, Taga C, Taylor M. Facebook, stress, and incidence of upper respiratory infection in undergraduate college students. *Cyberpsychol Behav Soc Netw.* 2012 Dec;15(12):675-81. doi: 10.1089/cyber.2012.0156. Epub 2012 Sep 28. PMID: 23020744. 26
29. Stover CM. Mechanisms of Stress-Mediated Modulation of Upper and Lower Respiratory Tract Infections. *Adv Exp Med Biol.* 2016;874:215-23. doi: 10.1007/978-3-319-20215-0_10. PMID: 26589221. 27
30. Drummond PD, Hewson-Bower B. Increased psychosocial stress and decreased mucosal immunity in children with recurrent upper respiratory tract infections. *J Psychosom Res.* 1997 Sep;43(3):271-8. doi: 10.1016/s0022-3999(97)00002-0. PMID: 9304553. 27
31. Fondell E, Lagerros YT, Sundberg CJ, Lekander M, Bälter O, Rothman KJ, Bälter K. Physical activity, stress, and self-reported upper respiratory tract infection. *Med Sci Sports Exerc.* 2011 Feb;43(2):272-9. doi: 10.1249/MSS.0b013e3181edf108. PMID: 20581713..... 28
32. Pedersen A, Zachariae R, Bovbjerg DH. Influence of psychological stress on upper respiratory infection--a meta-analysis of prospective studies. *Psychosom Med.* 2010 Oct;72(8):823-32. doi: 10.1097/PSY.0b013e3181f1d003. Epub 2010 Aug 17. PMID: 20716708. 29
33. Graham NM, Douglas RM, Ryan P. Stress and acute respiratory infection. *Am J Epidemiol.* 1986 Sep;124(3):389-401. doi: 10.1093/oxfordjournals.aje.a114409. PMID: 3740039..... 29
34. Clover RD, Abell T, Becker LA, Crawford S, Ramsey CN Jr. Family functioning and stress as predictors of influenza B infection. *J Fam Pract.* 1989 May;28(5):535-9. PMID: 2715769..... 30
35. Stone AA, Bovbjerg DH, Neale JM, Napoli A, Valdimarsdottir H, Cox D, Hayden FG, Gwaltney JM Jr. Development of common cold symptoms following experimental rhinovirus infection is related to prior stressful life events. *Behav Med.* 1992 Fall;18(3):115-20. doi: 10.1080/08964289.1992.9936961. PMID: 1330102..... 31
36. Mohren DC, Swaen GM, Kant I, van Schayck CP, Galama JM. Fatigue and job stress as predictors for sickness absence during common infections. *Int J Behav Med.* 2005;12(1):11-20. doi: 10.1207/s15327558ijbm1201_2. PMID: 15743731. 31
37. Mohren DC, Swaen GM, Borm PJ, Bast A, Galama JM. Psychological job demands as a risk factor for common cold in a Dutch working population. *J*

Psychosom Res. 2001 Jan;50(1):21-7. doi: 10.1016/s0022-3999(00)00212-9. PMID: 11259797.....	32
38. Biondi M, Zannino LG. Psychological stress, neuroimmunomodulation, and susceptibility to infectious diseases in animals and man: a review. <i>Psychother Psychosom.</i> 1997;66(1):3-26. doi: 10.1159/000289101. PMID: 8996711.	33
39. Cohen S, Hamrick N, Rodriguez MS, Feldman PJ, Rabin BS, Manuck SB. Reactivity and vulnerability to stress-associated risk for upper respiratory illness. <i>Psychosom Med.</i> 2002 Mar-Apr;64(2):302-10. doi: 10.1097/00006842-200203000-00014. PMID: 11914447.	33
40. Takkouche B, Ragueira C, Gestal-Otero JJ. A cohort study of stress and the common cold. <i>Epidemiology.</i> 2001 May;12(3):345-9. doi: 10.1097/00001648-200105000-00015. PMID: 11338315.	35
41. Evans PD, Edgerton N. Life-events and mood as predictors of the common cold. <i>Br J Med Psychol.</i> 1991 Mar;64 (Pt 1):35-44. doi: 10.1111/j.2044-8341.1991.tb01640.x. PMID: 2043504.	35
42. Smolderen KG, Vingerhoets AJ, Croon MA, Denollet J. Personality, psychological stress, and self-reported influenza symptomatology. <i>BMC Public Health.</i> 2007 Nov 23;7:339. doi: 10.1186/1471-2458-7-339. PMID: 18036207; PMCID: PMC2241613.	36
43. Deinzer R, Schüller N. Dynamics of stress-related decrease of salivary immunoglobulin A (sIgA): relationship to symptoms of the common cold and studying behavior. <i>Behav Med.</i> 1998 Winter;23(4):161-9. doi: 10.1080/08964289809596372. Erratum in: <i>Behav Med</i> 198 Spring;24(1):27. PMID: 9494693.	37
44. Miller GE, Cohen S, Pressman S, Barkin A, Rabin BS, Treanor JJ. Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? <i>Psychosom Med.</i> 2004 Mar-Apr;66(2):215-23. do: 10.1097/01.psy.0000116718.54414.9e. PMID: 15039506.	37
45. Cohen S. Social status and susceptibility to respiratory infections. <i>Ann N Y Acad Sci.</i> 1999;896:246-53. doi: 10.1111/j.1749-6632.1999.tb08119.x. PMID: 10681901.....	38
46. Cohen S. Keynote Presentation at the Eight International Congress of Behavioral Medicine: the Pittsburgh common cold studies: psychosocial predictors of susceptibility to respiratory infectious illness. <i>Int J Behav Med.</i> 2005;12(3):123-31. doi: 10.1207/s1327558ijbm1203_1. PMID: 16083315; PMCID: PMC7091093.	39
47. Peters EMJ, Schedlowski M, Watzl C, Gimsa U. To stress or not to stress: Brain-behavior-immune interaction may weaken or promote the immune response to SARS-CoV-2. <i>Neurobiol Stress.</i> 2021 May;14:100296. doi: 10.1016/j.ynstr.2021.100296. Epub 2021 Jan 27. PMID: 33527083; PMCID: PMC7839386.	39

48. Cohen S, Murphy MLM, Prather AA. Ten Surprising Facts About Stressful Life Events and Disease Risk. *Annu Rev Psychol.* 2019 Jan 4;70:577-597. doi: 10.1146/annurev-psych-010418-102857. Epub 2018 Jun 27. PMID: 29949726; PMCID: PMC6996482. 40
49. Ewin DM. Treatment of HPV with hypnosis--psychodynamic considerations of psychoneuroimmunology: a brief communication. *Int J Clin Exp Hypn.* 2011 Oct-Dec;59(4):392-8. doi: 10.1080/00207144.2011.594664. PMID: 21867375. 41
50. Bailey M, Engler H, Hunzeker J, Sheridan JF. The hypothalamic-pituitary-adrenal axis and viral infection. *Viral Immunol.* 2003;16(2):141-57. doi: 10.1089/088282403322017884. PMID: 12828866. 41
51. Robinson FP, Mathews HL, Witek-Janusek L. Stress reduction and HIV disease: a review of intervention studies using a psychoneuroimmunology framework. *J Assoc Nurses AIDS Care.* 2000 Mar-Apr;11(2):87-96. doi: 10.1016/S1055-3290(06)60289-6. PMID: 10752051. 41

1. Longo D, Koehn K. Psychosocial factors and recurrent genital herpes: a review of prediction and psychiatric treatment studies. *Int J Psychiatry Med.* 1993;23(2):99-117. doi: 10.2190/L5MH-OTCW-1PKD-5BM0. PMID: 8360003.

Objective: The purpose of this review was to evaluate the evidence which supports the association between psychosocial factors and genital herpes simplex virus recurrences (HSV), as well as to examine the biological and psychological treatments for disease.

Method: Forty-five studies were reviewed from the years 1928 to 1991. Studies were identified via computerized biographic literature search of Psychological Abstracts and Medline. Additional studies were located by inspection of key article reference sections. Studies were included in the review if the sample consisted of recurrent genital herpes sufferers and the design was either correlational or experimental. Cases studies were reviewed if they described HSV psychiatric treatment and provided outcome information.

Results: Psychosocial variables are important elements in the prediction, maintenance, and management of recurrent genital herpes. Furthermore, the effectiveness of psychological treatment regimes may be explained via psychoimmunological theory.

Conclusions: Psychosocial treatment should be considered as adjunctive therapy for biological treatment of recurrent HSV infections. Future research should address primary prevention of genital herpes and other sexually transmitted diseases, including HIV infections.

2. Katz J, McDermott MP, Cooper EM, Walther RR, Sweeney EW, Dworkin RH. Psychosocial risk factors for postherpetic neuralgia: a prospective study of patients with herpes zoster. *J Pain*. 2005 Dec;6(12):782-90. doi: 10.1016/j.jpain.2005.07.006. PMID: 16326366.

The results of previous studies using retrospective methods or small samples have suggested that there may be psychosocial risk factors for postherpetic neuralgia (PHN). We conducted a prospective study in which 110 patients with herpes zoster were assessed within the first month after rash onset with measures of acute pain and five broad domains of psychosocial functioning-physical, role, social, and emotional functioning, and stress and social support. Twenty of the 102 patients with follow-up data were diagnosed with PHN, defined as pain that had persisted for 4 months after rash onset. Measures of role functioning, personality disorder symptoms, and disease conviction during herpes zoster each made independent contributions to predicting either presence or intensity of PHN in logistic and linear regression analyses that controlled for relevant demographic and clinical variables, including age and acute pain intensity. These findings indicate that psychosocial variables are risk factors for the development of PHN.

Perspective: The results of this prospective study of patients with herpes zoster suggest that future research on the mechanisms and prevention of PHN should consider psychosocial as well as neurobiologic processes.

3. Fiedler N, Ohman-Strickland P, Shen JD, Black K, Horton DB, Panettieri R Jr, Blaser MJ, Carson J, Bendinskas K, Cheng H, Barrett ES. Age and Hair Cortisol Levels as Predictors of SARS-CoV-2 Infection. *Int J Environ Res Public Health*. 2024 Sep 2;21(9):1166. doi: 10.3390/ijerph21091166. PMID: 39338049; PMCID: PMC11430878.

Chronic psychosocial stress is known to adversely impact immune function. During the SARS-CoV-2 pandemic, occupational stress among workers in healthcare was at an unprecedented level due to risks of infection and work demands. We performed a

nested case-control study to investigate the associations between chronic stress and the risks of contracting SARS-CoV-2. We collected 3 cm of hair from employees at an academic medical center who tested positive for SARS-CoV-2 (N = 49) and controls who tested negative (N = 49), matched for age, race, and sex. The diagnosis of SARS-CoV-2 was based on polymerase chain reaction or antibody tests. As a proxy for chronic stress, we segmented hair into 1 cm sections each representing one month and measured cortisol levels using a cortisol enzyme-linked immunosorbent assay. For cases, we used cortisol concentrations measured in hair segments from the month prior to a positive SARS-CoV-2 test, and for controls, we used time-matched hair segments. We fitted conditional logistic regression models adjusted for sex, age, race, body mass index, and healthcare worker status, and stratified models by older vs. younger age (cutoff = 41 years). African Americans had higher hair cortisol levels relative to participants of other races and ethnicities. In adjusted models, higher hair cortisol concentrations were associated with an increased odds of infection with SARS-CoV-2 (OR = 1.84; CI: 1.10-3.07) among older, but not younger, participants. The results suggest that psychosocial stress may be a risk factor for SARS-CoV-2 infection; stress management may be an important part of a comprehensive approach to protect against SARS-CoV-2 infection.

4. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med.* 1991 Aug 29;325(9):606-12. doi: 10.1056/NEJM199108293250903. PMID: 1713648.

Background: It is not known whether psychological stress suppresses host resistance to infection. To investigate this issue, we prospectively studied the relation between psychological stress and the frequency of documented clinical colds among subjects intentionally exposed to respiratory viruses.

Methods: After completing questionnaires assessing degrees of psychological stress, 394 healthy subjects were given nasal drops containing one of five respiratory viruses (rhinovirus type 2, 9, or 14, respiratory syncytial virus, or coronavirus type 229E), and an additional 26 were given saline nasal drops. The subjects were then quarantined and monitored for the development of evidence of infection and symptoms. Clinical colds were defined as clinical symptoms in the presence of an infection verified by the isolation of virus or by an increase in the virus-specific antibody titer.

Results: The rates of both respiratory infection (P less than 0.005) and clinical colds (P less than 0.02) increased in a dose-response manner with increases in the degree

of psychological stress. Infection rates ranged from approximately 74 percent to approximately 90 percent, according to levels of psychological stress, and the incidence of clinical colds ranged from approximately 27 percent to 47 percent. These effects were not altered when we controlled for age, sex, education, allergic status, weight, the season, the number of subjects housed together, the infectious status of subjects sharing the same housing, and virus-specific antibody status at base line (before challenge). Moreover, the associations observed were similar for all five challenge viruses. Several potential stress-illness mediators, including smoking, alcohol consumption, exercise, diet, quality of sleep, white-cell counts, and total immunoglobulin levels, did not explain the association between stress and illness. Similarly, controls for personality variables (self-esteem, personal control, and introversion-extraversion) failed to alter our findings.

Conclusions: Psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness, and this risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection.

5. Stoner MCD, Kelly NK, Gomez-Olive FX, Mall S, Wagner D, Aiello AE, Bhushan N, Kahn K, Pettifor AE. Elevated stress-responsive biomarkers are associated with HIV acquisition in young women in rural South Africa. *AIDS*. 2024 Nov 1;38(13):1866-1873. doi: 10.1097/QAD.0000000000003981. Epub 2024 Jul 17. PMID: 39022994; PMCID: PMC11427142.

Objective: Biological markers of stress have been associated with HIV progression and pathogenesis but not with HIV incidence. We sought to determine if elevated stress-responsive biomarkers would be associated with incident HIV among adolescent girls and young women (AGYW).

Design: We conducted a case-cohort study within the HIV Prevention Trials Network (HPTN) 068 study among 949 AGYW in South Africa. Cases were AGYW who tested HIV-positive during the eight-year follow-up. Unmatched controls were randomly selected from the HIV-negative population at enrollment.

Methods: Dried blood spots from cases and controls were tested from enrollment (2011-2012) for C-reactive protein (CRP), herpes simplex virus type-1 (HSV-1) antibody titers, and cytomegalovirus (CMV) antibody titers. Cox proportional hazards models estimated the association between each biomarker and time to incident HIV.

Results: Compared to AGYW with the lowest CRP levels, those with medium and high CRP levels had a higher hazard ratio (HR) of incident HIV [HR: 1.45, 95% confidence interval (CI): 0.95, 2.21; HR: 1.50, 95% CI: 0.98, 2.30, respectively], although not statistically significant. The relative hazard of incident HIV was also higher among AGYW who were CMV seropositive vs. seronegative (low antibodies HR: 2.18, 95% CI: 1.2, 3.87; medium HR: 2.25, 95% CI: 1.28, 3.95; high HR: 1.78, 95% CI: 0.99, 3.21). Those with the highest HSV-1 antibody levels experienced an increased hazard of HIV compared to those who were HSV-1 seronegative (HR: 1.58, 95% CI: 1.03, 2.44).

Conclusions: Biological stress may increase AGYW's susceptibility to HIV acquisition through changes in immune function, viral infection, and increased biological vulnerability to disease.

6. Leserman J, Petitto JM, Gu H, Gaynes BN, Barroso J, Golden RN, Perkins DO, Folds JD, Evans DL. Progression to AIDS, a clinical AIDS condition and mortality: psychosocial and physiological predictors. *Psychol Med.* 2002 Aug;32(6):1059-73. doi: 10.1017/s0033291702005949. PMID: 12214787.

Background: The primary aim of this study is to examine prospectively the association of stressful life events, social support, depressive symptoms, anger, serum cortisol and lymphocyte subsets with changes in multiple measures of human immunodeficiency virus (HIV) disease progression.

Methods: Ninety-six HIV-infected gay men without symptoms or anti-retroviral medication use at baseline were studied every 6 months for up to 9 years. Disease progression was defined in three ways using the Centers for Disease Control (CDC) classifications (e.g. AIDS, clinical AIDS condition and mortality). Cox regression models with time-dependent covariates were used, adjusting for control variables (e.g. race, age, baseline, CD4 T cells and viral load, number of anti-retroviral medications).

Results: Higher cumulative average stressful life events and lower cumulative average social support predicted faster progression to both the CDC AIDS classification and a clinical AIDS condition. Higher anger scores and CD8 T cells were associated with faster progression to AIDS, and depressive symptoms were associated with faster development of an AIDS clinical condition. Higher levels of serum cortisol predicted all three measures of disease progression.

Conclusions: These results suggest that stressful life events, dysphoric mood and limited social support are associated with more rapid clinical progression in HIV

infection, with serum cortisol also exerting an independent effect on disease progression.

7. Pereira DB, Antoni MH, Danielson A, Simon T, Efantis-Potter J, Carver CS, Durán RE, Ironson G, Klimas N, Fletcher MA, O'Sullivan MJ. Stress as a predictor of symptomatic genital herpes virus recurrence in women with human immunodeficiency virus. *J Psychosom Res.* 2003 Mar;54(3):237-44. doi: 10.1016/s0022-3999(02)00494-4. PMID: 12614833.

Objective: Genital herpes (Herpes Simplex Virus Type 2, HSV-2) is a significant public health problem for HIV+ women, who have high rates of HSV-2 seropositivity and elevated risk for HSV-2 associated morbidity and mortality. Life stress has been identified as a co-factor in genital herpes recurrence. However, no research has evaluated the relationship between stress and genital herpes recurrences in HIV+ women. The purpose of this study was to determine whether stress was associated with symptomatic genital herpes recurrences in women seropositive for HIV and HSV-2.

Methods: Thirty-four HIV-infected African-American and Caribbean-American women underwent a psychosocial interview, blood draw and gynecologic examination to assess gynecologic symptoms (including genital herpes) at study entry. Life stress was measured using a 10-item modified version of the Life Experiences Survey (LES). Genital herpes recurrence over 1-year follow-up was abstracted using medical chart review.

Results: Using hierarchical linear regression analysis, life stress at study entry was significantly associated with number of genital herpes recurrences during 1-year follow-up ($\beta=.38$, $P=.03$) after controlling for HIV disease variables and relevant behavioral factors. Recent life stress, in particular, was highly predictive of genital herpes recurrence during follow-up ($\beta=.57$, $P=.002$). The relationship between life stress and genital herpes recurrence persisted after controlling for HSV-2 viral reactivation (i.e., HSV-2 IgG titers) at study entry.

Conclusion: These findings suggest that stress may be a significant predictor of genital herpes recurrence in women with HIV and HSV-2. Stress management interventions may buffer HSV-related morbidity and mortality in women with HIV.

8. Leserman J. Role of depression, stress, and trauma in HIV disease progression. *Psychosom Med.* 2008 Jun;70(5):539-45. doi: 10.1097/PSY.0b013e3181777a5f. Epub 2008 Jun 2. PMID: 18519880.

Despite advances in HIV treatment, there continues to be great variability in the progression of this disease. This paper reviews the evidence that depression, stressful life events, and trauma account for some of the variation in HIV disease course. Longitudinal studies both before and after the advent of highly active antiretroviral therapies (HAART) are reviewed. To ensure a complete review, PubMed was searched for all English language articles from January 1990 to July 2007. We found substantial and consistent evidence that chronic depression, stressful events, and trauma may negatively affect HIV disease progression in terms of decreases in CD4 T lymphocytes, increases in viral load, and greater risk for clinical decline and mortality. More research is warranted to investigate biological and behavioral mediators of these psychoimmune relationships, and the types of interventions that might mitigate the negative health impact of chronic depression and trauma. Given the high rates of depression and past trauma in persons living with HIV/AIDS, it is important for healthcare providers to address these problems as part of standard HIV care.

9. Ironson G, O'Cleirigh C, Kumar M, Kaplan L, Balbin E, Kelsch CB, Fletcher MA, Schneiderman N. Psychosocial and Neurohormonal Predictors of HIV Disease Progression (CD4 Cells and Viral Load): A 4 Year Prospective Study. *AIDS Behav.* 2015 Aug;19(8):1388-97. doi: 10.1007/s10461-014-0877-x. PMID: 25234251; PMCID: PMC4465405.

Most studies of psychosocial predictors of disease progression in HIV have not considered norepinephrine (NE), a neurohormone related to emotion and stress, even though NE has been related to accelerated viral replication in vitro and impaired response to antiretroviral therapy (ART). We therefore examined NE, cortisol, depression, hopelessness, coping, and life event stress as predictors of HIV progression in a diverse sample. Participants (n = 177) completed psychological assessment, blood draws [CD4, viral load (VL)], and a 15 h urine sample (NE, cortisol) every 6 months over 4 years. Hierarchical linear modeling (HLM) was used to model slope in CD4 and VL controlling for ART at every time point, gender, age, race, SES, and initial disease status. NE (as well as depression, hopelessness, and avoidant coping) significantly predicted a greater rate of decrease in CD4 and increase in VL.

Cortisol was not significantly related to CD4, but predicted VL increase. To our knowledge, this is the first study relating NE, in vivo, to accelerated disease progression over an extended time. It also extends our previous 2 year study by relating depressed mood and coping to accelerated disease progression over 4 years.

10. Weinstein TL, Li X. The relationship between stress and clinical outcomes for persons living with HIV/AIDS: a systematic review of the global literature. *AIDS Care*. 2016;28(2):160-9. doi: 10.1080/09540121.2015.1090532. Epub 2015 Nov 13. PMID: 26565754.

For persons living with HIV/AIDS, the relationship between stress and clinical outcomes has received little attention in current research, yet represents an important area for future research and intervention. Chronic illness has been theorized to place additional demands on a person that may exceed their ability to cope with daily life, leading to long-term stress, which then increases the risk for negative health outcomes in persons already at risk. This paper reviews the existing global literature to answer two main questions: (1) how is stress conceptualized in research with persons living with HIV/AIDS? and (2) what are the current findings linking stress to clinical outcomes? Twenty-three articles are included in the final review. Findings reveal that researchers conceptualize stress in multiple ways for persons living with HIV/AIDS, including depressive symptomology, post-traumatic stress, life events, emotions linked to stress, and biological markers (such as cortisol levels and autonomic nervous system activity). Further, findings related to the link between stress and clinical outcomes are mixed; however, stress was shown to be related to lower CD4 cell counts, higher viral load, and disease progression. Several studies also showed a link between stress and poorer treatment adherence. Implications and directions for future research are discussed, including further thought into how we conceptualize stress for persons living with HIV, future research that is necessary to elucidate current mixed findings on the link between stress and clinical outcomes, and preliminary suggestions for intervention to prevent and alleviate stress in this population.

11. Aiello AE, Simanek AM, Galea S. Population levels of psychological stress, herpesvirus reactivation and HIV. *AIDS Behav.* 2010 Apr;14(2):308-17. doi: 10.1007/s10461-008-9358-4. Epub 2008 Feb 9. PMID: 18264753; PMCID: PMC4156100.

Nearly 40,000 Americans are newly infected with Human Immunodeficiency Virus (HIV) each year. Recently, studies have demonstrated associations between group-level characteristics and the prevalence and incidence of HIV/Acquired Immune Deficiency Syndrome (AIDS) and other sexually transmitted diseases. Two mechanisms previously posited to explain these associations are neighborhood effects on risk behaviors and social or institutional policies. In this paper, we hypothesize that adversity at the population level, such as neighborhood poverty, also influences HIV risk through stress-mediated aberrations in immunological susceptibility by reviewing existing data examining each of these pathways. In particular, we review the evidence showing that: (1) Neighborhood ecologic stressors influence neighborhood- and individual-levels of mental health, psychosocial stress, and HIV/AIDS risk, (2) Individual-level psychosocial stressors influence progression from HIV to AIDS through stress-related hormonal changes, and (3) Individual-level psychosocial stressors influence HIV acquisition via stress-related reactivation of latent herpesviruses, specifically EBV and HSV-2. Our review indicates that further studies are needed to examine the joint pathways linking neighborhood-level sources of psychosocial stress, stress-related reactivation of HSV-2 and EBV, and increased acquisition rates of HIV. We suggest using a multi-level framework for targeting HIV prevention efforts that address not only behavioral risk factors, but structural, political, and institutional factors associated with neighborhood disadvantage, levels of psychosocial stress, and prevention or treatment of HSV-2 and EBV.

12. Pedersen AF, Zachariae R, Bovbjerg DH. Psychological stress and antibody response to influenza vaccination: a meta-analysis. *Brain Behav Immun.* 2009 May;23(4):427-33. doi: 10.1016/j.bbi.2009.01.004. Epub 2009 Jan 14. PMID: 19486657.

Vaccination is an important public health strategy for reducing the risk of influenza at the societal level. However, at the individual level, not everyone is protected by vaccination, and increases in antibody titers may fail to reach protective levels. Several recent studies suggest that psychological stress may contribute to these

individual differences. Exploring this hypothesis, we conducted a meta-analysis of 13 studies examining the influence of psychological stress on antibody responses following influenza vaccination. The studies were identified through systematic searches in MEDLINE and PsychINFO and included a total of 1158 men and women. In five studies, the increased antibody levels of caregivers following vaccination were compared to those of non-caregivers. The remaining studies focused on associations between self-reported stressful life events or perceived stress and increased antibody titers following vaccination. The meta-analysis revealed a significant negative association between psychological stress and antibody responses to influenza vaccination. While effect sizes were similar across different indicators of stress, antibody responses to the A/H1N1 and B-influenza types appeared to be more sensitive to stress than the A/H3N2 type. It was investigated whether the association between stress and antibody response differed between young and elderly, and the results revealed significant negative associations between stress and peak antibody titers in both age groups. These findings suggest the importance of additional research to explore responsible mechanisms and possible contributions of stress to the public health problem of inadequate responses to vaccination.

13. **Ballesio A, Zagaria A, Violani C, Lombardo C. Psychosocial and behavioural predictors of immune response to influenza vaccination: a systematic review and meta-analysis. Health Psychol Rev. 2024 Jun;18(2):255-284. doi: 10.1080/17437199.2023.2208652. Epub 2023 May 9. PMID: 37106577.**

High variability of influenza vaccine efficacy requires the identification of modulators of immunisation that may be targeted as adjuvants in health psychology interventions. Psychosocial and behavioural variables such as psychological stress, greater negative and lower positive affectivity, poor sleep, loneliness, and lack of social support, have been associated with abnormal immune and inflammatory responses and negative health outcomes, yet their effects in modulating vaccine efficacy are yet to be fully understood. We conducted an updated systematic review of longitudinal and experimental studies examining the effects of such variables in predicting immune response to influenza vaccine. PubMed, Medline, PsycINFO, CINAHL and Scopus were searched up to November 2022. Twenty-five studies met the inclusion criteria for qualitative synthesis and 16 provided data for meta-analysis. Low positive and high negative affect were associated with low antibodies and weak

cell-mediated immunity following vaccination in qualitative synthesis. Literature on sleep disturbance, loneliness and social support was limited and yielded inconsistent results. Psychological stress was associated with poorer antibody response in meta-analysis. In conclusion, findings from this review suggest a need for further longitudinal and experimental studies on these factors to support their inclusion as target variables in vaccine adjuvant interventions.

14. Prösch S, Wendt CE, Reinke P, Priemer C, Oppert M, Krüger DH, Volk HD, Döcke WD. A novel link between stress and human cytomegalovirus (HCMV) infection: sympathetic hyperactivity stimulates HCMV activation. *Virology*. 2000 Jul 5;272(2):357-65. doi: 10.1006/viro.2000.0367. PMID: 10873779.

Recently, inflammatory mediators such as TNF α were identified as triggering active human cytomegalovirus (HCMV) infection. Here, we demonstrate that a highly stressful event in the absence of systemic inflammation, as observed in patients with acute myocardial infarction, leads to the development of an active HCMV infection in latently infected patients. Elucidating the molecular mechanism of virus activation, we could show that catecholamines directly stimulate the HCMV immediate-early (IE) enhancer/promoter in monocytic cells via beta-2 adrenergic receptors. Subsequent activation of the cAMP/PK-A-signaling pathway results in enhanced synthesis and binding of the transcription factor CREB-1/ATF-1 to the cAMP-responsive elements within the IE enhancer. Epinephrine also enhanced HCMV gene expression in infected THP-1 cells by about 50% in three of four experiments. These data suggest that HCMV, like HSV-1 and VZV, can be (re)activated under stress conditions.

15. Rector JL, Dowd JB, Loerbroks A, Burns VE, Moss PA, Jarczok MN, Stalder T, Hoffman K, Fischer JE, Bosch JA. Consistent associations between measures of psychological stress and CMV antibody levels in a large occupational sample. *Brain Behav Immun*. 2014 May;38:133-41. doi: 10.1016/j.bbi.2014.01.012. Epub 2014 Jan 26. PMID: 24472683.

Cytomegalovirus (CMV) is a herpes virus that has been implicated in biological aging and impaired health. Evidence, largely accrued from small-scale studies involving select populations, suggests that stress may promote non-clinical reactivation of this virus. However, absent is evidence from larger studies, which allow better statistical

adjustment for confounding and mediating factors, in more representative samples. The present study involved a large occupational cohort (N=887, mean age=44, 88% male). Questionnaires assessed psychological (i.e., depression, anxiety, vital exhaustion, SF-12 mental health), demographic, socioeconomic (SES), and lifestyle variables. Plasma samples were analyzed for both the presence and level of CMV-specific IgG antibodies (CMV-IgG), used as markers for infection status and viral reactivation, respectively. Also assessed were potential biological mediators of stress-induced reactivation, such as inflammation (C-reactive protein) and HPA function (awakening and diurnal cortisol). Predictors of CMV infection and CMV-IgG among the infected individuals were analyzed using logistic and linear regression analyses, respectively. Confirming prior reports, lower SES (education and job status) was positively associated with infection status. Among those infected (N=329), higher CMV-IgG were associated with increased anxiety ($\beta=.14$, $p<.05$), depression ($\beta=.11$, $p=.06$), vital exhaustion ($\beta=.14$, $p<.05$), and decreased SF-12 mental health ($\beta=-.14$, $p<.05$), adjusting for a range of potential confounders. Exploratory analyses showed that these associations were generally stronger in low SES individuals. We found no evidence that elevated inflammation or HPA-function mediated any of the associations. In the largest study to date, we established associations between CMV-IgG levels and multiple indicators of psychological stress. These results demonstrate the robustness of prior findings, and extend these to a general working population. We propose that stress-induced CMV replication warrants further research as a psychobiological mechanism linking stress, aging and health.

16. Kelly NK, Gómez-Olivé FX, Wagner LD, Aiello AE, Kahn K, Pettifor A, Stoner MCD. Intimate partner violence is associated with cytomegalovirus among young women in rural South Africa: An HPTN 068 analysis. *Glob Public Health*. 2023 Jan;18(1):2258962. doi: 10.1080/17441692.2023.2258962. PMID: 37715682; PMCID: PMC10580295.

Stressful life circumstances (e.g. violence and poverty) have been associated with elevated biomarkers, including C-reactive protein (CRP), cytomegalovirus (CMV), and herpes simplex virus type-1 (HSV-1), among older adults in high-income settings. Yet, it remains unknown whether these relationships exist among younger populations in resource-limited settings. We therefore utilised a cohort of 1,279 adolescent girls and young women (AGYW) from the HIV Prevention Trials Network 068 study in rural South Africa to examine the associations between 6 hypothesized stressors (intimate

partner violence (IPV), food insecurity, depression, socioeconomic status (SES), HIV, childhood violence) and 3 biomarkers that were measured using dried blood spots (CRP, CMV, and HSV-1). Ordinal logistic regression estimated the lagged and cross-sectional associations between each stressor and each biomarker. IPV was cross-sectionally associated with elevated CMV (OR = 2.45, 95% CI = 1.05,5.72), while low SES was cross-sectionally associated with reduced CMV (OR = 0.73, 95% CI = 0.58,0.93). AGYW with HIV had elevated biomarkers cross-sectionally (CRP: OR = 1.51, 95% CI = 1.08,2.09; CMV: OR = 1.86, 95% CI = 1.31,2.63; HSV-1: OR = 1.68, 95% CI = 1.17,2.41) and in a lagged analysis. The association between violence and CMV could help explain how violence results in stress and subsequently worse health among AGYW; however, additional research is needed to disentangle the longitudinal nature of IPV and stress.

17. Jang YS, Lam P, Chiang J. Low early life socioeconomic status and susceptibility to the common cold in adulthood: The moderating role of negative affective reactivity. *Health Psychol.* 2024 Apr;43(4):247-258. doi: 10.1037/hea0001337. Epub 2023 Dec 7. PMID: 38059931.

Objective: Socioeconomic disadvantage during childhood and adolescence is associated with higher risk for many physical health problems, including infectious disease, throughout the lifespan. Greater negative affective (NA) reactivity has shown similar links to greater risk for physical health conditions and altered patterns of biological functioning associated with acute respiratory infection as socioeconomic disadvantage; yet their interactive effects on physical health outcomes have not been examined. Thus, the present study examined whether NA reactivity accentuated the link between early socioeconomic disadvantage and susceptibility to the common cold.

Method: Participants were 212 adults (42% female, 18-55 years old) who completed measures of childhood socioeconomic status (SES; parental home ownership) and were subsequently exposed to a virus that causes the common cold. Participants then remained quarantined for 5 days, during which multiple indicators of viral infection and clinical illness were assessed. Before and after quarantine, participants completed a laboratory stress task to assess NA reactivity.

Results: NA reactivity moderated the relationship between parental home ownership and clinical cold diagnosis in adulthood ($b = -0.11, p = .018$), such that fewer years of parental home ownership was associated with increased odds for developing a cold

only among adults who had greater NA reactivity ($OR = 0.89$, 95% confidence interval, $CI [0.82, 0.96]$), but not among those who had lower NA reactivity ($OR = 1.01$, 95% $CI [0.94, 1.09]$).

Conclusions: These findings suggest that how individuals negatively react to psychosocial stressors in adulthood may exacerbate the impact of childhood SES on acute infection susceptibility. (PsycInfo Database Record (c) 2024 APA, all rights reserved).

18. Cohen S. Psychosocial Vulnerabilities to Upper Respiratory Infectious Illness: Implications for Susceptibility to Coronavirus Disease 2019 (COVID-19). *Perspect Psychol Sci.* 2021 Jan;16(1):161-174. doi: 10.1177/1745691620942516. Epub 2020 Jul 8. PMID: 32640177; PMCID: PMC7345443.

For 35 years, our laboratory has been involved in identifying psychosocial factors that predict who becomes ill when they are exposed to a virus affecting the upper respiratory tract. To pursue this question, we used a unique viral-challenge design in which we assessed behavioral, social, and psychological factors in healthy adults. We subsequently exposed these adults to a cold or influenza virus and then monitored them in quarantine for 5 to 6 days for onset of respiratory illness. Factors we found to be associated with greater risk of respiratory illnesses after virus exposure included smoking, ingesting an inadequate level of vitamin C, and chronic psychological stress. Those associated with decreased risk included social integration, social support, physical activity, adequate and efficient sleep, and moderate alcohol intake. We cautiously suggest that our findings could have implications for identifying who becomes ill when exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19). This argument is based on evidence that the associations we report are replicable across multiple respiratory viruses and that the pathways found to link psychosocial factors to colds and influenza may play similar roles in COVID-19.

19. Cobb JM, Steptoe A. Psychosocial stress and susceptibility to upper respiratory tract illness in an adult population sample. *Psychosom Med.* 1996 Sep-Oct;58(5):404-12. doi: 10.1097/00006842-199609000-00003. PMID: 8902892.

Objective: To assess the influence of life event stress and hassles, and the moderating effects of psychological coping style, social support, and family environment, on susceptibility to upper respiratory tract infectious illness.

Method: One hundred seven adults aged 18 to 65 years took part in a 15-week study. Measures of life event stress were obtained for the 12 months preceding the study and for the study period itself, and social support, information seeking and avoidant coping styles, and family environment were assessed. Hassles and perceived stress were measured weekly, whereas dysphoric mood and changes in personal health practices (smoking, alcohol consumption, exercise, and sleep patterns) were assessed at three weekly intervals. Episodes of upper respiratory tract infectious illness were verified by clinical examination.

Results: During the study period, 29 individuals experienced at least one clinically verified episode of upper respiratory tract illness. There were no differences in cigarette smoking, sleep habits, or exercise between those who did and did not become ill but alcohol consumption was lower among those who experienced verified episodes. Risk of infectious illness was greater in those who experienced high life event stress both before and during the study period, but the impact of life events was buffered by an avoidant coping style. Strict family organization was associated with illness risk. The three weeks preceding illness onset were characterised by high levels of perceived stress, but also by a decrease in the number of hassles reported.

Conclusions: Results suggest that under naturalistic conditions, the influence of stressful experience on risk of infectious illness is moderated by psychosocial resources. Variations in personal health practices do not seem to be responsible.

20. Turner Cobb JM, Steptoe A. Psychosocial influences on upper respiratory infectious illness in children. *J Psychosom Res.* 1998 Oct;45(4):319-30. doi: 10.1016/s0022-3999(97)00311-5. PMID: 9794278.

Fifty-five boys and 61 girls, aged 5-16 years, took part in a 15-week longitudinal study of stress and upper respiratory infectious illness. Life events, social support, and psychological coping were measured, and hassles and mood were assessed

repeatedly throughout the study period. Upper respiratory symptoms were recorded daily, and episodes of upper respiratory infection were verified by clinical examination. Forty-eight verified episodes of infection were recorded from 41 participants (35.3% of the total sample). Life events and social support interacted in predicting the occurrence of infection, whereas hassles interacted with avoidant psychological coping, independently of age, gender, family composition, social class, negative affect, parental perceived stress, parental smoking, or alcohol consumption. The duration of symptomatic episodes was negatively associated with problem-focused coping, and positively related to avoidant coping. Hassle levels were elevated 3 weeks prior to symptom onset. These results indicate that the impact of life stress on vulnerability to infectious illness in children is moderated by psychological coping and social resources, and that different psychosocial factors influence the occurrence and duration of infections.

21. Falagas ME, Karamanidou C, Kastoris AC, Karlis G, Rafailidis PI. Psychosocial factors and susceptibility to or outcome of acute respiratory tract infections. *Int J Tuberc Lung Dis.* 2010 Feb;14(2):141-8. PMID: 20074403.

Objective: To perform a systematic review of the literature to assess the possible effect that psychosocial variables may have on the susceptibility and/or outcome of acute respiratory tract infections (ARTIs).

Methods: We performed searches for relevant studies on PubMed, Scopus and PsychInfo.

Results: We identified 44 studies published between 1986 and 2008, examining the role of psychosocial variables and the onset or progression of ARTI. Of these 44 studies, 41 (93.1%) showed at least one statistically significant association between psychosocial variables and susceptibility to ARTI; 20 (45.5%) revealed at least one statistically significant association between psychosocial variables and outcome of ARTI. Variables associated with susceptibility to and outcome of infection were higher levels of perceived stress, negative affect, anxiety and depression. Negative life events were associated with susceptibility to infection.

Conclusion: Most of the relevant studies show a significant relationship between psychosocial factors and the onset or progression of acute respiratory tract illness. However, the psychosocial variables were not consistently evaluated across the included studies, and different methodological approaches were used to examine the association between psychosocial factors and acute respiratory tract illness.

22. Silverman MN, Pearce BD, Biron CA, Miller AH. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunol.* 2005;18(1):41-78. doi: 10.1089/vim.2005.18.41. PMID: 15802953; PMCID: PMC1224723.

Compelling data has been amassed indicating that soluble factors, or cytokines, emanating from the immune system can have profound effects on the neuroendocrine system, in particular the hypothalamic-pituitary-adrenal (HPA) axis. HPA activation by cytokines (via the release of glucocorticoids), in turn, has been found to play a critical role in restraining and shaping immune responses. Thus, cytokine-HPA interactions represent a fundamental consideration regarding the maintenance of homeostasis and the development of disease during viral infection. Although reviews exist that focus on the bi-directional communication between the immune system and the HPA axis during viral infection (188,235), others have focused on the immunomodulatory effects of glucocorticoids during viral infection (14,225). This review, however, concentrates on the other side of the bi-directional loop of neuroendocrine-immune interactions, namely, the characterization of HPA axis activity during viral infection and the mechanisms employed by cytokines to stimulate glucocorticoid release.

23. Cohen S, Doyle WJ, Skoner DP. Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosom Med.* 1999 Mar-Apr;61(2):175-80. doi: 10.1097/00006842-199903000-00009. PMID: 10204970.

Objective: The purpose of this study is to assess the role of psychological stress in the expression of illness among infected subjects and to test the plausibility of local proinflammatory cytokine production as a pathway linking stress to illness.

Methods: After completing a measure of psychological stress, 55 subjects were experimentally infected with an influenza A virus. Subjects were monitored in quarantine daily for upper respiratory symptoms, mucus production, and nasal lavage levels of interleukin (IL)-6.

Results: Higher psychological stress assessed before the viral challenge was associated with greater symptom scores, greater mucus weights, and higher IL-6 lavage concentrations in response to infection. The IL-6 response was temporally

related to the two markers of illness severity, and mediation analyses indicated that these data were consistent with IL-6 acting as a major pathway through which stress was associated with increased symptoms of illness. However, this pattern of data is also consistent with increases in IL-6 occurring in response to tissue damage associated with illness symptoms.

Conclusions: Psychological stress predicts a greater expression of illness and an increased production of IL-6 in response to an upper respiratory infection.

24. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM Jr.
Social ties and susceptibility to the common cold. *JAMA*. 1997
Jun 25;277(24):1940-4. PMID: 9200634.

Objective: To examine the hypothesis that diverse ties to friends, family, work, and community are associated with increased host resistance to infection.

Design: After reporting the extent of participation in 12 types of social ties (eg, spouse, parent, friend, workmate, member of social group), subjects were given nasal drops containing 1 of 2 rhinoviruses and monitored for the development of a common cold.

Setting: Quarantine.

Participants: A total of 276 healthy volunteers, aged 18 to 55 years, neither seropositive for human immunodeficiency virus nor pregnant.

Outcome measures: Colds (illness in the presence of a verified infection), mucus production, mucociliary clearance function, and amount of viral replication.

Results: In response to both viruses, those with more types of social ties were less susceptible to common colds, produced less mucus, were more effective in ciliary clearance of their nasal passages, and shed less virus. These relationships were unaltered by statistical controls for prechallenge virus-specific antibody, virus type, age, sex, season, body mass index, education, and race. Susceptibility to colds decreased in a dose-response manner with increased diversity of the social network. There was an adjusted relative risk of 4.2 comparing persons with fewest (1 to 3) to those with most (6 or more) types of social ties. Although smoking, poor sleep quality, alcohol abstinence, low dietary intake of vitamin C, elevated catecholamine levels, and being introverted were all associated with greater susceptibility to colds, they could only partially account for the relation between social network diversity and incidence of colds.

Conclusions: More diverse social networks were associated with greater resistance to upper respiratory illness.

25. Cohen S, Alper CM, Doyle WJ, Treanor JJ, Turner RB.
Positive emotional style predicts resistance to illness after
experimental exposure to rhinovirus or influenza a virus.
Psychosom Med. 2006 Nov-Dec;68(6):809-15. doi:
10.1097/01.psy.0000245867.92364.3c. Epub 2006 Nov 13.
PMID: 17101814.

Objective: In an earlier study, positive emotional style (PES) was associated with resistance to the common cold and a bias to underreport (relative to objective disease markers) symptom severity. This work did not control for social and cognitive factors closely associated with PES. We replicate the original study using a different virus and controls for these alternative explanations.

Methods: One hundred ninety-three healthy volunteers ages 21 to 55 years were assessed for a PES characterized by being happy, lively, and calm; a negative emotional style (NES) characterized by being anxious, hostile, and depressed; other cognitive and social dispositions; and self-reported health. Subsequently, they were exposed by nasal drops to a rhinovirus or influenza virus and monitored in quarantine for objective signs of illness and self-reported symptoms.

Results: For both viruses, increased PES was associated with lower risk of developing an upper respiratory illness as defined by objective criteria (adjusted odds ratio comparing lowest with highest tertile = 2.9) and with reporting fewer symptoms than expected from concurrent objective markers of illness. These associations were independent of prechallenge virus-specific antibody, virus type, age, sex, education, race, body mass, season, and NES. They were also independent of optimism, extraversion, mastery, self-esteem, purpose, and self-reported health.

Conclusions: We replicated the prospective association of PES and colds and PES and biased symptom reporting, extended those results to infection with an influenza virus, and "ruled out" alternative hypotheses. These results indicate that PES may play a more important role in health than previously thought.

26. Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM Jr. Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychol.* 1998 May;17(3):214-23. doi: 10.1037//0278-6133.17.3.214. PMID: 9619470.

Two-hundred seventy-six volunteers completed a life stressor interview and psychological questionnaires and provided blood and urine samples. They were then inoculated with common cold viruses and monitored for the onset of disease. Although severe acute stressful life events (less than 1 month long) were not associated with developing colds, severe chronic stressors (1 month or longer) were associated with a substantial increase in risk of disease. This relation was attributable primarily to under- or unemployment and to enduring interpersonal difficulties with family or friends. The association between chronic stressors and susceptibility to colds could not be fully explained by differences among stressed and nonstressed persons in social network characteristics, personality, health practices, or prechallenge endocrine or immune measures.

27. Cohen S, Janicki-Deverts D, Turner RB, Doyle WJ. Does hugging provide stress-buffering social support? A study of susceptibility to upper respiratory infection and illness. *Psychol Sci.* 2015 Feb;26(2):135-47. doi: 10.1177/0956797614559284. Epub 2014 Dec 19. PMID: 25526910; PMCID: PMC4323947.

Perceived social support has been hypothesized to protect against the pathogenic effects of stress. How such protection might be conferred, however, is not well understood. Using a sample of 404 healthy adults, we examined the roles of perceived social support and received hugs in buffering against interpersonal stress-induced susceptibility to infectious disease. Perceived support was assessed by questionnaire, and daily interpersonal conflict and receipt of hugs were assessed by telephone interviews on 14 consecutive evenings. Subsequently, participants were exposed to a virus that causes a common cold and were monitored in quarantine to assess infection and illness signs. Perceived support protected against the rise in infection risk associated with increasing frequency of conflict. A similar stress-buffering effect emerged for hugging, which explained 32% of the attenuating effect of support. Among infected participants, greater perceived support and more-

frequent hugs each predicted less-severe illness signs. These data suggest that hugging may effectively convey social support.

28. Campisi J, Bynog P, McGehee H, Oakland JC, Quirk S, Taga C, Taylor M. Facebook, stress, and incidence of upper respiratory infection in undergraduate college students. *Cyberpsychol Behav Soc Netw.* 2012 Dec;15(12):675-81. doi: 10.1089/cyber.2012.0156. Epub 2012 Sep 28. PMID: 23020744.

Having a large social network is generally beneficial to health. However, it is unclear how Internet-based social networks might influence health. Chronic stress can have negative health consequences, and some data suggest that Facebook could be a new source of psychological stress. Thus, we examined undergraduate college student perceptions of Facebook use and incidence of upper respiratory infections (URIs). We hypothesized that subjects with more diverse networks (i.e., more friends on Facebook) would have fewer URIs than their less diverse counterparts; that subjects reporting Facebook-induced stress would be more susceptible to URIs; and that subjects with more diverse networks who report Facebook-induced stress would be less susceptible to URIs than subjects with less diverse social networks who reported Facebook-induced stress. In this prospective study, healthy college students completed online questionnaires that assessed use and perceptions of Facebook and technology, and then were interviewed weekly for 10 weeks to track incidence of URI. URI episodes were defined by a symptom-based criterion. The social network size was significantly related to the rate of URI, such that, the larger the social network, the greater the incidence rate of URI. Most (85.7 percent) respondents experienced some degree of Facebook-induced stress. The effects of Facebook-induced stress on incidence of URI varied across the social network size, such that, the impact of stress on the URI incidence rate increased with the size of the social network. These results are largely in contrast to our hypotheses, but clearly suggest an association between Facebook use, psychological stress, and health.

29. Stover CM. Mechanisms of Stress-Mediated Modulation of Upper and Lower Respiratory Tract Infections. *Adv Exp Med Biol.* 2016;874:215-23. doi: 10.1007/978-3-319-20215-0_10. PMID: 26589221.

Stress is an external factor known to be a potent exacerbator of respiratory infections. Most explanations of how stress affects susceptibility to airway infections focus on the immune system. However, evidence is increasing that respiratory pathogens are equally responsive to the hormonal output of stress. This chapter considers the bacterial and mucosal determinants of respiratory tract infections and their interrelationship during stressful conditions.

30. Drummond PD, Hewson-Bower B. Increased psychosocial stress and decreased mucosal immunity in children with recurrent upper respiratory tract infections. *J Psychosom Res.* 1997 Sep;43(3):271-8. doi: 10.1016/s0022-3999(97)00002-0. PMID: 9304553.

The association between psychosocial stress and susceptibility to upper respiratory tract infection was investigated in 45 children with a history of recurrent colds and flu, and in 45 healthy children of similar age and distribution. In addition, mucosal immune protection against upper respiratory tract infections was assessed by measuring the concentration of secretory immunoglobulin A (sIgA) and its ratio to albumin in saliva. Several dimensions of psychosocial stress, including exposure to stressful experiences, stress-prone personality traits, and signs of emotional disturbance were elevated in children with a history of recurrent colds and flu. Furthermore, lower sIgA/albumin ratios in these children indicated a deficiency in local mucosal immunity. Thus, the findings are consistent with the view that psychosocial stress depletes local immune protection against viral invasion or bacterial colonization of the upper respiratory tract; this depletion may increase susceptibility to colds and flu. Alternatively, psychological disturbances could develop in response to frequent illness.

31. Fondell E, Lagerros YT, Sundberg CJ, Lekander M, Bälter O, Rothman KJ, Bälter K. Physical activity, stress, and self-reported upper respiratory tract infection. *Med Sci Sports Exerc.* 2011 Feb;43(2):272-9. doi: 10.1249/MSS.0b013e3181edf108. PMID: 20581713.

Purpose: upper respiratory tract infection (URTI) is the most common reason for seeking primary care in many countries. Still, little is known about potential strategies to reduce susceptibility. We investigated the relationships between physical activity level, perceived stress, and incidence of self-reported URTI.

Methods: we conducted a population-based prospective cohort study of 1509 Swedish men and women aged 20-60 yr with a follow-up period of 4 months. We used a Web-based questionnaire to assess disease status and lifestyle factors at the start of the study. We assessed physical activity and inactivity as total MET-hours (MET task) per day and perceived stress by the 14-item Perceived Stress Scale. Participants were contacted every 3 wk via e-mail to assess incidence of URTI. They reported a total of 1181 occurrences of URTI. We used Poisson regression models to control for age, sex, and other potential confounding factors.

Results: we found that high levels of physical activity (≥ 55 MET·h·d) were associated with an 18% reduced risk (incidence rate ratio (IRR) = 0.82, 95% confidence interval (CI) = 0.69-0.98) of self-reporting URTI compared with low levels of physical activity (<45 MET·h·d). This association was stronger among those reporting high levels of stress (IRR = 0.58, 95% CI = 0.43-0.78), especially among men (IRR = 0.37, 95% CI = 0.24-0.59), but absent in the group with low levels of stress.

Conclusions: we found that high physical activity was associated with a lower risk of contracting URTI for both men and women. In addition, we found that highly stressed people, particularly men, appear to benefit more from physical activity than those with lower stress levels.

32. Pedersen A, Zachariae R, Bovbjerg DH. Influence of psychological stress on upper respiratory infection--a meta-analysis of prospective studies. *Psychosom Med*. 2010 Oct;72(8):823-32. doi: 10.1097/PSY.0b013e3181f1d003. Epub 2010 Aug 17. PMID: 20716708.

Objective: To quantify the available evidence for the hypothesis that reduced resistance caused by psychological stress may influence the development of clinical disease in those exposed to an infectious agent.

Methods: We conducted a systematic review and meta-analysis of 27 prospective studies examining the association between psychological stress and subsequent upper respiratory infection (URI).

Results: The results revealed a significant overall main effect of psychological stress on the risk of developing URI (effect size correlation coefficient, 0.21; 95% confidence interval, 0.15-0.27). Further analyses showed that effect sizes for the association did not vary according to type of stress, how URI was assessed, or whether the studies had controlled for preexposure.

Conclusions: The meta-analytical findings confirmed the hypothesis that psychological stress is associated with increased susceptibility to URI, lending support to an emerging appreciation of the potential importance of psychological factors in infectious disease.

33. Graham NM, Douglas RM, Ryan P. Stress and acute respiratory infection. *Am J Epidemiol*. 1986 Sep;124(3):389-401. doi: 10.1093/oxfordjournals.aje.a114409. PMID: 3740039.

To examine the relationship between stress and upper respiratory tract infection, 235 adults aged 14-57 years, from 94 families affiliated with three suburban family physicians in Adelaide, South Australia, participated in a six-month prospective study. High and low stress groups were identified by median splits of data collected from the Life Events Inventory, the Daily Hassles Scale, and the General Health Questionnaire, which were administered both before and during the six months of respiratory diary data collection. Using intra-study stress data, the high stress group experienced significantly more episodes (mean of 2.71 vs. 1.56, p less than 0.0005) and symptom days (mean of 29.43 vs. 15.42, $p = 0.005$) of respiratory illness. The two groups were almost identical with respect to age, sex, occupational status, smoking,

passive smoking, exposure to air pollution, family size, and proneness to acute respiratory infection in childhood. In a multivariate model with total respiratory episodes as the dependent variable, 21% of the variance was explained, and two stress variables accounted for 9% of the explained variance. Significant, but less strong relationships were also identified between intra-study stress variables and clinically "definite" episodes and symptom days in both clinically definite and total respiratory episodes. Pre-study measures of stress emphasized chronic stresses and were less strongly related to measures of respiratory illness than those collected during the study. However, significantly more episodes (mean of 2.50 vs. 1.75, p less than 0.02) and symptom days (mean of 28.00 vs. 17.06, p less than 0.03) were experienced in the high stress group. In the multivariate analyses, pre-study stress remained significantly associated with total respiratory episodes and symptom days in total and "definite" respiratory episodes. In all of the multivariate analyses performed, sex (female) and age also appeared as important correlates of respiratory illness.

34. Clover RD, Abell T, Becker LA, Crawford S, Ramsey CN Jr. Family functioning and stress as predictors of influenza B infection. *J Fam Pract.* 1989 May;28(5):535-9. PMID: 2715769.

A prospective cohort study was designed to study the effects of family functioning and stress on the incidence of influenza infection. Families from the clinic roster, containing two adults and at least one child between the ages of 1 and 18 years, were asked to participate. Baseline (pre-influenza) data included a serum determination for influenza A and B antibodies, family functioning as measured by the Family Adaptability and Cohesion Evaluation Scales (FACES) II and the Family APGAR, and parental stress as measured by the social readjustment rating scale (SRRS). During the study all family members of patients with upper respiratory tract infection symptoms or fever were seen, and throat swabs were obtained for viral culture. Approximately 2 weeks after the influenza epidemic ended (March 1984), sera for antibodies were again collected on all family members. Chi-square analysis showed that infection (defined as a fourfold titer rise or a positive viral throat culture) was significantly associated with both cohesion and adaptability as measured by FACES II. Neither the Family APGAR nor the SRRS was associated with influenza B infection. It was concluded that family functioning affects the frequency of influenza B infection within families. This finding raises the possibility that family dysfunction may lead to altered immune responses, which increases susceptibility to infection

35. Stone AA, Bovbjerg DH, Neale JM, Napoli A, Valdimarsdottir H, Cox D, Hayden FG, Gwaltney JM Jr. Development of common cold symptoms following experimental rhinovirus infection is related to prior stressful life events. *Behav Med.* 1992 Fall;18(3):115-20. doi: 10.1080/08964289.1992.9936961. PMID: 1330102.

Previous studies of rhinovirus infection indicate that about one third of the persons with confirmed viral infection do not show evidence of cold symptoms. Factors that determine which infected individuals will develop colds are not known. Using a rhinovirus inoculation protocol, the authors explored the possible role of recent life events, current mood, and perceived stress in the development of symptoms in individuals known to be infected. As part of a larger study, 17 subjects were exposed to a rhinovirus and were individually isolated for 5 consecutive days; cold symptoms, mucus weights, and tissue use were monitored on a daily basis during this period. Although all 17 subjects had confirmed rhinovirus infection, only 12 subjects developed clinical colds, as indicated by self-reported symptoms and by objective symptom indices. The average number of reported major life events for the previous year was significantly higher for those who developed colds than for those who did not ($p < .05$). Measures of affect and perceived stress before the inoculation were not different for those who did and did not develop colds. Complementing recent research demonstrating psychosocial influences on experimental infection rates, these results provide evidence that the development of cold symptomatology in experimentally infected individuals is related to prior life events.

36. Mohren DC, Swaen GM, Kant I, van Schayck CP, Galama JM. Fatigue and job stress as predictors for sickness absence during common infections. *Int J Behav Med.* 2005;12(1):11-20. doi: 10.1207/s15327558ijbm1201_2. PMID: 15743731.

The objective of this study was to investigate the effect of health and work-related factors as predictors of subsequent sickness absence when experiencing common infections (common cold, flu-like illness, and gastroenteritis). Self-administered questionnaire data were used (baseline $n = 12,140$). To perform the analysis, employees reporting common infections in the final questionnaire were selected. Employees reporting sickness absence due to common infections were compared with a group who stayed at work during an infection. Multivariate survival analysis

revealed no significant effects of job demands, decision latitude, or job strain on absence in workers experiencing common infections. Low levels of commitment (risk [RR] 1.22; confidence interval [CI] 1.03-1.44) and low job satisfaction (RR 1.36; CI 1.13-1.164) increased the chance of being absent during a common cold. Also, having a long-standing disease (RR 1.22; CI 1.05-1.41) and fatigue (RR 1.20; CI 1.05-1.37) increased the chance of being absent during a common infection. Having an executive function decreased the chance of being absent. We conclude that absence during a common cold is partly influenced by motivational factors in work, in contrast to more severe common infections which are more health related. Insight in factors related to absenteeism are important as a start for preventive measures to reduce sickness absence.

37. Mohren DC, Swaen GM, Borm PJ, Bast A, Galama JM. Psychological job demands as a risk factor for common cold in a Dutch working population. *J Psychosom Res.* 2001 Jan;50(1):21-7. doi: 10.1016/s0022-3999(00)00212-9. PMID: 11259797.

Objective: We investigated the effect of Psychological Job Demands (PJD) on the occurrence of the clinical symptoms of common cold.

Methods: Subjects, participating in a large prospective cohort study on psychological determinants of fatigue at work, were asked to fill in a questionnaire on the occurrence of common cold during the previous four months. High PJD were considered as a potential risk factor. Other factors such as age, gender, and having young children were considered as potential confounders.

Results: In logistic regression analysis, the adjusted odds ratio (OR) for having a recent cold in subjects reporting high PJD vs. those reporting low PJD was 1.20 (95% confidence interval (CI), 1.08-1.33). A higher risk emerged among those with young children (OR, 1.70; 95% CI, 1.47-1.96), those having a history of asthma (OR, 1.69; 95% CI, 1.28-2.22), or being under the age of 40 (OR, 1.28; 95% CI, 1.14-1.43) and among smokers (OR, 1.23; 95% CI, 1.09-1.38).

Conclusion: The results support an association between PJD and common cold. In spite of the almost inevitable shortcoming of a large cohort study using questionnaires, this study gave us the opportunity to study the relationship between common cold and work-related factors in a nonexperimental setting with participants observed in a natural environment with all the normal everyday hassles.

38. Biondi M, Zannino LG. Psychological stress, neuroimmunomodulation, and susceptibility to infectious diseases in animals and man: a review. *Psychother Psychosom.* 1997;66(1):3-26. doi: 10.1159/000289101. PMID: 8996711.

This article reviews research on the role of psychological stress, personality, social support and other psychosocial factors in bacterial, viral and parasitic infections. After 100 years of research on man and animals, psychological stress is considered as a potential cofactor in the pathogenesis of infectious disease. Psychological stress seems able to alter the susceptibility of animals and man to infectious agents, influencing the onset, course and outcome of certain infectious pathologies. Many experiments have identified in neuroimmunomodulation the principal mediator of the alterations associated with conditions of stress. The development of psychoneuroimmunology has fostered in-depth study of the complex relationship between psychosocial factors, the central nervous system, the immune system and infectious disease. Although antimicrobial drugs have certainly remained the basis of all anti-infective therapy, this type of study has already led some authors to propose and experiment protocols of psychological intervention or psychoimmunotherapy in pathologies such as tuberculosis, or herpes simplex virus or human immunodeficiency virus infections. The psychoneuroimmunological approach to infectious diseases will probably grow in importance in the future not only in the setting of research in psychosomatic medicine but also in that of clinical microbiology.

39. Cohen S, Hamrick N, Rodriguez MS, Feldman PJ, Rabin BS, Manuck SB. Reactivity and vulnerability to stress-associated risk for upper respiratory illness. *Psychosom Med.* 2002 Mar-Apr;64(2):302-10. doi: 10.1097/00006842-200203000-00014. PMID: 11914447.

Objective: We tested the hypothesis that the greater a person's laboratory stress-elicited elevation in cortisol, the greater the life stress-related risk for upper respiratory infection (URI). We also tested the prediction that the greater the laboratory stress-elicited rise in natural killer cell (NK) cytotoxicity, the smaller the life stress-related URI risk. Finally, we explored whether sympathetic nervous system (SNS) and enumerative immune reactivities to laboratory stress moderate the relation between life stress and URI.

Methods: At baseline, 115 healthy subjects were administered a negative stressful life events checklist and were tested to assess their SNS (blood pressure, heart rate, and catecholamines), HPA (cortisol), and immune (NK cell cytotoxicity and lymphocyte subsets) reactivities to laboratory speech tasks administered 2 weeks apart. Responses were averaged across the two laboratory assessments to create reactivity scores. After these assessments were completed, participants were followed weekly for 12 consecutive weeks. At each follow-up they completed a measure of perceived stress experienced over the last week. They were also instructed to contact the study coordinator if they had a cold or flu at any time during follow-up. A health care worker verified reported illnesses.

Results: In a traditional prospective analysis, high cortisol reactors with high levels of life events had a greater incidence of verified URI than did high reactors with low levels of life events and low reactors irrespective of their life event scores. Using hierarchical linear modeling, CD8(+) number, Natural Killer (NK) cell number, and NK cell cytotoxicity, each interacted with weekly perceived stress levels in predicting concurrent occurrences of self-reported URIs. For these outcomes, low immune reactors were more likely to experience an URI during high stress than low stress weeks. High immune reactors did not exhibit differences in weekly URIs as a function of weekly stress level. The SNS reactivity markers did not moderate the association of stress and URI incidence in either analysis.

Conclusions: Acute HPA and immune responses to laboratory stressors are markers of how vulnerable people are to the increased risk for URI associated with stressors in the natural environment.

Hamrick N, Cohen S, Rodriguez MS. Being popular can be healthy or unhealthy: stress, social network diversity, and incidence of upper respiratory infection. *Health Psychol.* 2002 May;21(3):294-8. PMID: 12027036.

Diverse social contacts are generally associated with better health. However, diverse contacts can increase exposure to infectious agents. This should increase risk for disease, particularly among those whose host resistance is otherwise compromised (e.g., stressed individuals). In this prospective study, healthy college students who completed questionnaires assessing social network diversity and stressful life events were subsequently interviewed weekly for 12 weeks to track incidence of upper respiratory infections (URIs). URI episodes were defined by a symptom criterion and by clinically verified self-reported illness. Stress and diversity of social contacts interacted; diversity was associated with more illnesses among those with more stressful life events and slightly fewer illnesses among those with fewer stressful life events. Associations remained after controlling for neuroticism.

40. Takkouche B, Regueira C, Gestal-Otero JJ. A cohort study of stress and the common cold. *Epidemiology*. 2001 May;12(3):345-9. doi: 10.1097/00001648-200105000-00015. PMID: 11338315.

The common cold is one of the major causes of work absenteeism. Former studies, based on artificial inoculation of rhinovirus, implicated psychological stress in the occurrence of this syndrome, either by increasing susceptibility to the virus or by causing the subject to overrate the perception of the symptoms. Nevertheless, few studies on the effect of stress on the naturally acquired common cold have been conducted. We carried out a 1-year prospective cohort study among the faculty and staff of a Spanish university (N = 1,149). By means of standardized questionnaires, validated in a random sample of the population, we assessed the relation between the occurrence of common cold episodes and exposure to four dimensions of stress: stressful life events, negative affect, positive affect, and perceived stress. All four aspects of stress were related to the occurrence of the common cold. Subjects with a high (fourth quartile) index of negative affect showed an incidence rate ratio of 3.7 (95% confidence interval = 2.2-6.2). The incidence rate ratios for the fourth quartile were 2.5 (95% confidence interval = 1.5-4.1) and 1.9 (95% confidence interval = 1.1-3.2) for perceived stress and stressful events, respectively. A high index of positive affect was associated with an incidence rate ratio of 0.6 (95% confidence interval = 0.3-1.0). These findings suggest that psychological stress is a risk factor for the common cold.

41. Evans PD, Edgerton N. Life-events and mood as predictors of the common cold. *Br J Med Psychol*. 1991 Mar;64 (Pt 1):35-44. doi: 10.1111/j.2044-8341.1991.tb01640.x. PMID: 2043504.

One hundred subjects volunteered to take part in a 'diary-type' study in which they were to check, at the end of each day, a variety of items dealing with events, mood states and health. A subsample was selected who had both provided several weeks of data and had, during that time, suffered at least one common cold episode. A lagged relationship between events and the onset of cold episodes was found. Desirable events ('uplifts') were found to decrease significantly in frequency during a period commencing four days prior to cold onset. There was a less significant tendency for the number of undesirable events ('hassles') to rise during this same period. Subjects' ratings also indicated that they had been feeling more angry, tense and sceptical

during this period. It is argued that the lagged relationship, the use of subjects as their own controls, and the partly replicatory nature of the study, give strong support to psycho-immunological hypotheses concerning links between life-events and illness. Individual item analysis suggests that fluctuations in perceived intimacy, social support and self-esteem may be important mediators of the effects.

42. Smolderen KG, Vingerhoets AJ, Croon MA, Denollet J. Personality, psychological stress, and self-reported influenza symptomatology. *BMC Public Health*. 2007 Nov 23;7:339. doi: 10.1186/1471-2458-7-339. PMID: 18036207; PMCID: PMC2241613.

Background: Psychological stress and negative mood have been related to increased vulnerability to influenza-like illness (ILI). This prospective study re-evaluated the predictive value of perceived stress for self-reported ILI. We additionally explored the role of the negative affectivity and social inhibition traits.

Methods: In this study, 5,404 respondents from the general population were assessed in terms of perceived stress, personality, and control variables (vaccination, vitamin use, exercise, etc.). ILI were registered weekly using self-report measures during a follow-up period of four weeks.

Results: Multivariable logistic regression analysis on ILI was performed to test the predictive power of stress and personality. In this model, negative affectivity (OR = 1.05, $p = 0.009$), social inhibition (OR = 0.97, $p = 0.011$), and perceived stress (OR = 1.03, $p = 0.048$) predicted ILI reporting. Having a history of asthma (OR = 2.33, $p < 0.0001$) was also associated with ILI reporting. Older age was associated with less self-reported ILI (OR = 0.98, $P = 0.017$).

Conclusion: Elderly and socially inhibited persons tend to report less ILI as compared to their younger and less socially inhibited counterparts. In contrast, asthma, trait negative affectivity, and perceived stress were associated with higher self-report of ILI. Our results demonstrate the importance of including trait markers in future studies examining the relation between stress and self-report symptom measures.

43. Deinzer R, Schüller N. Dynamics of stress-related decrease of salivary immunoglobulin A (sIgA): relationship to symptoms of the common cold and studying behavior. *Behav Med*. 1998 Winter;23(4):161-9. doi: 10.1080/08964289809596372. Erratum in: *Behav Med* 1998 Spring;24(1):27. PMID: 9494693.

The dynamics of stress-related decrease of salivary Immunoglobulin A (sIgA) were examined with respect to whether an increase of upper respiratory tract (URT) symptoms can be observed concurrently with or subsequent to sIgA alterations and whether one can use students' studying behavior during academic examinations to predict changes in sIgA. From a 2-part medical examination of 42 students, daily measures of sIgA were obtained, and symptoms of URT infections and studying behavior were determined by means of questionnaires. Assessment periods began 7 days before each part of the academic examination began and lasted until the 6th day afterward. A control group of 24 medical students who were not undergoing examinations also responded to all questionnaires. A progressive suppression of sIgA, outlasting the examination period by more than 6 days, was observed. Time spent studying explained a significant proportion in sIgA variation. However, no relationship between sIgA and URT symptoms was observed, nor did students who took academic examinations differ from untested controls in symptom rates.

44. Miller GE, Cohen S, Pressman S, Barkin A, Rabin BS, Treanor JJ. Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? *Psychosom Med*. 2004 Mar-Apr;66(2):215-23. doi: 10.1097/01.psy.0000116718.54414.9e. PMID: 15039506.

Objectives: This study attempted to determine whether stress of moderate intensity could modulate the antibody response to an influenza vaccination in healthy young adults, identify critical periods during which stress could influence antibody response, and delineate behavioral and biological pathways that might explain relations between stress and antibody.

Methods: A cohort of 83 healthy young adults underwent 13 days of ambulatory monitoring before, during, and after vaccination. Four times daily, subjects reported

the extent to which they felt stressed and overwhelmed and collected a saliva sample that was later used to measure cortisol. A battery of health practices (cigarette smoking, alcohol use, physical activity, sleep hygiene) was assessed daily. Antibody titers to the vaccine components were measured at baseline and at 1-month and 4-month follow-up assessments.

Results and conclusions: To the extent that they reported higher levels of stress across the monitoring period, subjects exhibited poorer antibody responses to the New Caledonia strain of the vaccine. Stress ratings on the 2 days before the vaccine and the day it was given were not associated with antibody response. However, the 10 days afterward appeared to be a window of opportunity during which stress could shape the long-term antibody response to varying degrees. With respect to potential mediating pathways, little evidence emerged in favor of cortisol secretion, alcohol consumption, physical activity, or cigarette smoking. However, analyses were consistent with a pattern in which feelings of stress and loss of sleep become locked into a feed-forward circuit that ultimately diminishes the humoral immune response. These findings may shed light on the mechanisms through which stress increase vulnerability to infectious disease.

45. Cohen S. Social status and susceptibility to respiratory infections. *Ann N Y Acad Sci.* 1999;896:246-53. doi: 10.1111/j.1749-6632.1999.tb08119.x. PMID: 10681901.

Adults and children of lower socioeconomic status (SES) are at higher risk for a wide range of communicable infectious diseases, especially respiratory infections. Greater risk for infectious illness among people with lower SES is thought to be attributable to increased exposure to infectious agents and decreased host resistance to infection. We summarize three studies that examine the prospective association of several markers of social status (unemployment, perceived and observed social status) with host resistance to upper respiratory infections. Unemployment was associated with increased susceptibility to infection in adult humans. Lower social status in male monkeys was also associated with increased susceptibility, as was lower perceived social status in humans. The association of social status and susceptibility was accounted for primarily by increased risk in the lowest social status groups. However, further increases in social status were associated with further decreases in susceptibility in both monkeys and humans.

46. Cohen S. Keynote Presentation at the Eight International Congress of Behavioral Medicine: the Pittsburgh common cold studies: psychosocial predictors of susceptibility to respiratory infectious illness. *Int J Behav Med.* 2005;12(3):123-31. doi: 10.1207/s15327558ijbm1203_1. PMID: 16083315; PMCID: PMC7091093.

This article provides a selected overview of 20 years of research on the role of psychosocial factors in susceptibility to upper respiratory infections. We present evidence from our laboratory that psychological stress is associated with increased risk for developing respiratory illness for persons intentionally exposed to a common cold virus, that the longer the duration of the stressor the greater the risk, and that stress association with susceptibility may be mediated by stress-induced disruption of the regulation of proinflammatory cytokines. We further provide evidence that social relationships (social integration and social support) are also associated with risk for respiratory illness: Social integration is associated with reduced risk irrespective of stress level and social support protects persons from the pathogenic influences of stress. Finally, we report recent evidence that lower levels of early childhood socioeconomic status (SES) are associated with greater risk of viral-induced illness during adulthood, independent of adult SES.

47. Peters EMJ, Schedlowski M, Watzl C, Gimsa U. To stress or not to stress: Brain-behavior-immune interaction may weaken or promote the immune response to SARS-CoV-2. *Neurobiol Stress.* 2021 May;14:100296. doi: 10.1016/j.ynstr.2021.100296. Epub 2021 Jan 27. PMID: 33527083; PMCID: PMC7839386.

The COVID-19 pandemic continues to strongly affect people with health disadvantages, creating a heavy burden on medical systems and societies worldwide. Research is growing rapidly and recently revealed that stress-related factors such as socio-economic status, may also play a pivotal role. However, stress research investigating the underlying psychoneuroimmune interactions is missing. Here we address the question whether stress-associated neuroendocrine-immune mechanisms can possibly contribute to an increase in SARS-CoV-2 infections and influence the course of COVID-19 disease. Additionally, we discuss that not all forms of stress (e.g. acute versus chronic) are detrimental and that some types of stress could attenuate infection-risk and -progression. The overall aim of this review is to

motivate future research efforts to clarify whether psychosocial interventions have the potential to optimize neuroendocrine-immune responses against respiratory viral infections during and beyond the COVID-19 pandemic. The current state of research on different types of stress is summarized in a comprehensive narrative review to promote a psychoneuroimmune understanding of how stress and its mediators cortisol, (nor)adrenaline, neuropeptides and neurotrophins can shape the immune defense against viral diseases. Based on this understanding, we describe how people with high psychosocial stress can be identified, which behaviors and psychosocial interventions may contribute to optimal stress management, and how psychoneuroimmune knowledge can be used to improve adequate care for COVID-19 and other patients with viral infections.

48. Cohen S, Murphy MLM, Prather AA. Ten Surprising Facts About Stressful Life Events and Disease Risk. *Annu Rev Psychol.* 2019 Jan 4;70:577-597. doi: 10.1146/annurev-psych-010418-102857. Epub 2018 Jun 27. PMID: 29949726; PMCID: PMC6996482.

After over 70 years of research on the association between stressful life events and health, it is generally accepted that we have a good understanding of the role of stressors in disease risk. In this review, we highlight that knowledge but also emphasize misunderstandings and weaknesses in this literature with the hope of triggering further theoretical and empirical development. We organize this review in a somewhat provocative manner, with each section focusing on an important issue in the literature where we feel that there has been some misunderstanding of the evidence and its implications. Issues that we address include the definition of a stressful event, characteristics of diseases that are impacted by events, differences in the effects of chronic and acute events, the cumulative effects of events, differences in events across the life course, differences in events for men and women, resilience to events, and methodological challenges in the literature.

49. Ewin DM. Treatment of HPV with hypnosis--
psychodynamic considerations of psychoneuroimmunology: a
brief communication. *Int J Clin Exp Hypn*. 2011 Oct-
Dec;59(4):392-8. doi: 10.1080/00207144.2011.594664. PMID:
21867375.

There is increasing evidence that the hypnotic cure of warts (infection by the human papilloma virus or HPV) results from activation of an immune response, but whether this is cellular or systemic is unknown. The hypnosis can be by direct suggestion or analytical hypnotherapy when indicated. The evidence is reviewed, and 4 clinical cases suggesting cellular immune response are presented.

50. Bailey M, Engler H, Hunzeker J, Sheridan JF. The
hypothalamic-pituitary-adrenal axis and viral infection. *Viral
Immunol*. 2003;16(2):141-57. doi:
10.1089/088282403322017884. PMID: 12828866.

The hypothalamic-pituitary-adrenal (HPA) axis plays an important immunomodulatory role during viral infection. Activation of the HPA axis ultimately leads to elevated plasma levels of glucocorticoid (GC) hormones with the ability to mediate adaptive behavioral, metabolic, cardiovascular and immune system effects. In this review, we focus on the modulation of anti-viral immunity and viral pathogenesis by the HPA axis.

51. Robinson FP, Mathews HL, Witek-Janusek L. Stress
reduction and HIV disease: a review of intervention studies using
a psychoneuroimmunology framework. *J Assoc Nurses AIDS
Care*. 2000 Mar-Apr;11(2):87-96. doi: 10.1016/S1055-
3290(06)60289-6. PMID: 10752051.

The field of psychoneuroimmunology (PNI) posits that relationships exist between stress, immunological impairment, and health outcomes. Accumulating evidence suggests that stress may hasten HIV disease progression by increasing viral replication, suppressing immune response, and inducing deleterious health-related behaviors. Interventions that attenuate the effects of stress are postulated to operate by altering cognitive perception and/or modulating neuroendocrine and sympathetic reactivity. A review of HIV/PNI intervention studies is presented as a guide for the

inclusion of stress reduction interventions in comprehensive plans of care for HIV-infected individuals. Although effect and sample sizes are small, the results of these studies provide support for a positive effect of various interventions on immunological and health-related indices in HIV-infected individuals.