Supplement. Examples of adverse outcomes of stress and anxiety on respiratory infections, lung function and immune status in children and adults, and its effect on vaccination efficiency.

Compilation of published studies based on ad-hoc literature searches, as to allow evaluation of the impact of stress and anxiety, on immune response/respiratory infections in adults and children. Draft/narrative listing of findings in the individual studies or conclusions from relevant reviews. No systematic review.
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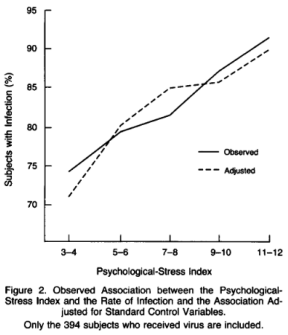
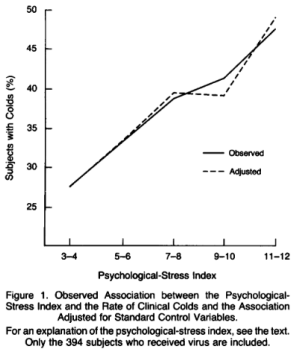
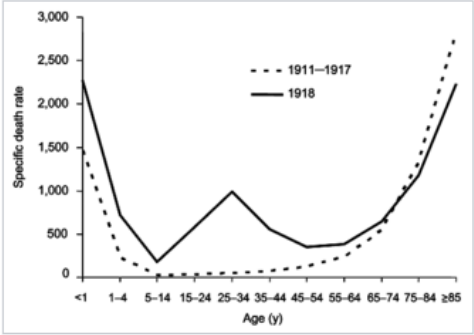
Effects of stress on respiratory infections, lung function & immunity	
General	Stress appears to damage the normal cellular and humoral immune responses, particularly involving T (helper) cells and cytokine response: these processes are affected psychological stress, while have been associated with enhanced contraction of viral infections (Hou 2012, https://onlinelibrary.wiley.com/doi/pdf/10.1002/hup.1259 ; Glaser and Kiecolt-Glaser 2005; Seiler 2020). to illustrate the effect of stress on viral infection, here a listing of examples implicating the role of stress on viral infections
Interactions of stress & loneliness with upper respiratory infections, health and mortality	• Psychological stress suppresses the host resistance to infection and increases susceptibility to the common cold / rates of upper respiratory infection/ after a standardized nasal challenge with upper respiratory infectious/common cold viruses(Cohen et al. 1991 - 1996).  Figure 2. Observed Association between the Psychological-Stress Index and the Rate of Infection and the Association Adjusted for Standard Control Variables. Only the 394 subjects who received virus are included.  Figure 1. Observed Association between the Psychological-Stress Index and the Rate of Clinical Colds and the Association Adjusted for Standard Control Variables. For an explanation of the psychological-stress index, see the text. Only the 394 subjects who received virus are included. https://www.nejm.org/doi/pdf/10.1056/nejm199108293250903 Cohen S et al. 1992. Psychological stress and susceptibility to the common cold. The New England J Medicine 1991; 325:606-612. • It was s further shown that all four aspects of stress (stressful life events, negative affect, positive affect, and perceived stress) impacted the contraction rate of common colds. • Loneliness is another well-established risk factor for poor physical health and enhanced mortality. Loneliness apparently predicts self-reported cold symptoms after a viral challenge, suggesting that cold symptoms are more severe among those who feel lonely (LeRoy et al. 2017; Beller 2016 & 2018; Holt-Lunstad 2015). Loneliness and social isolation act synergistically on mortality (Beller 2016) • Panic has been found to decrease the blastogenic response, the immunological response that develops following an infectious challenge and which is needed to fight a viral infection (Schleifer et al. 2002, Takkouche at al. 2001)
Direct/acute effects on lung function:	Everyone knows the direct effect of psychological stress on toothaches. Or feeling palpitations and shortness of breath when stressed. Stress also directly affects our lung function, even unconsciously (review Ritz 2012, Khan 1977): • Our airways respond to all kinds of triggers, such as physical exertion, allergens and medicines - Stress can influence those reactions. • For example, if one gives a medicine that opens the airways for better breathing, but at the same time you tell that the medicine constricts the lungs, the medicine will only work half as well in improving the tidal volume. • Conversely, when giving a placebo in persons with asthma, saying it will work, the

	available lung volume will increase by up to 25%. But if an inhaler is used with the placebo, the increase will only be 10% [the idea of an inhaler therefore unconsciously causes stress and a spontaneous decrease in lung volume.] • The lungs also function less well if one evokes a stressful life experience during the assessment, e.g. also by letting watching a negative film, or when one shows a surgical operation on the film screen; the latter even caused severe bronchoconstriction (contraction of the airways) in a number of test subjects. • Severe anxiety decreases lung volume by 20% or more in 39% of patients; it happens even when the fear is provoked under hypnosis. These phenomena explain why introducing oral and nasal saline rinses as an early hygienic measure in COVID-19 may already help in relieving breathlessness in a number of COVID-19 patients, currently sent to the hospital.
Effects on inflammatory markers, lung inflammation and death	• Psychosocial stress enhances the incidence of upper respiratory infection and IL-6 response after a standardized nasal challenge with upper respiratory viruses (Cohen 1999). 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. • In experimental studies of pneumonia, it has been shown that enhanced stress drives up mortality: social disruption stress induced lung inflammation and enhanced the susceptibility to endotoxic shock following application of bacterial endotoxin (Quan 2001, Curry 2010).
Effects of stress and isolation in animal studies	• Some examples of the effects of stress on immunity in animal studies: ○ A higher anxiety state in old rats after social isolation is associated with an impairment of the immune response (Cruces 2014); inducing "behavioral despair" of individually housed rats is accompanied by higher levels of ACTH and TNF-α but also of IL-4 and IL-10 (Krügel 2014). ○ Social isolation suppressed wound healing in male and female rats. https://www.apa.org/monitor/nov06/isolated.html ○ Reducing stress by promoting the well-being of pigs in their pigsty lowered the rate of infections (Dixhoorn 2016). ○ Effects are also long-term: For instance, post-Weaning Social Isolation of Rats led to Long-term Disruption of the Gut Microbiota-Immune-Brain Axis (Doherty 2017)
Effects on CD8+ T Cell and cytokines in human	• Slota 2015 investigated the effect of stress hormone in vitro and the effect of stress on family caregivers of stem cell transplant recipients: she found complex interactions between stress and the response of memory CD8 T-cell and cytokines, calling for more efforts in exploring the exact mechanisms behind these stress-related changes (https://repository.upenn.edu/cgi/viewcontent.cgi?article=2948&context=edissertations). • Psychological stress was also found to compromises the CD8+ T Cell control of latent herpes simplex virus type 1 infections. This and other stress related responses in the immune response have bene associated with the higher contraction rate of viral herpes infections in stressed people. (Freeman et al. 2007 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2367250/ ; Sainz et al. 2001 https://www.ncbi.nlm.nih.gov/pubmed/11359358)
Stress and latent immunity	• Stress also interferes with latent immunity. As reviewed by Seiler 2020, this has been shown for herpes viruses, including herpes simplex virus (HSV) I and II, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), not only in animal studies, but also a body of literature in humans confirming that psychosocial stressors such as self-reported health, depression, perceived stress, attachment anxiety, bereavement or divorce and even exam stress, predict reactivation of latent viruses. • Together, the evidence supports that stress can modulate the steady-state expression of latent herpesviruses, downregulating specific T-cell responses to the virus to an extent that is sufficient to result in viral activation. • There is also a substantial body of evidence pointing at a relationship between stressful life events, depression, hopelessness, avoidant coping or chronic stress, *and* the rate of HIV disease progression, impact on the viral load and CD4 cell count, and/or inflammatory markers.
Children & Mothers	

Anxiety has adverse outcome on pneumonia in children	• In pediatric patients hospitalized for pneumonia, a comorbid mood or anxiety disorder is associated with increased odds of complications and longer hospital stay. • 5- 12 years: 29.4% with anxiety **hospitalized** versus 19% without (p<0.001) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5802356/
	• Tachycardia may be due to multiple factors including pain, anxiety/fear, fever, dehydration, and underlying disease processes https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6454831/
Psychological Stress in Children May Alter the Immune Response	• Children from families with high psychological stress showed a low spontaneous immune activity (IL-5, IL-10, IL-13, IL-17, CCL2, CCL3, and CXCL10; $p < 0.01$) but an increased immune response to tetanus toxoid, β-lactoglobulin, and the autoantigens glutamic acid decarboxylase 65, heat shock protein 60, and tyrosine phosphatase (IL-5, IL-6, IL-10, IL-13, IL-17, IFN-γ, TNF-α, CCL2, CCL3, and CXCL10; $p < 0.05$). • Children within the high-stress group showed high level of cortisol, but low level of C-peptide, compared with the control group ($p < 0.05$). • This supports the hypothesis that psychological stress may contribute to an imbalance in the immune response but also to a pathological effect on the insulin-producing β cells. https://www.diva-portal.org/smash/record.jsf?pid=diva2%3A704225&dswid=-2276
Responses to Stress in Allergic Children: Interaction with the Immune Response	• Impact of stress on the manifestation and exacerbation of allergy has been demonstrated • A growing number of studies have suggested an altered hypothalamus-pituitary-adrenal (HPA) axis function to stress in allergic children. • It is speculated that a dysfunctional HPA axis in response to stress may facilitate and/or consolidate immunological aberrations and thus, may increase the risk for allergic sensitization and exacerbation especially under stressful conditions. Both a *hypo*responsive as well as a *hyper*responsive HPA axis may contribute to the onset and chronification of childhood allergy. • Potential factors that may contribute to the development of an aberrant HPA axis responsiveness in allergy are discussed. https://www.karger.com/Article/Abstract/216190
Parents pass anxiety to kids	There is evidence that children of anxious parents are more likely to exhibit anxiety themselves, a probable combination of genetic risk factors and learned behaviors. - Parent anxiety disorders increase the risk for similar problems in children (e.g., Beidel and Turner 1997; Biederman et al. 2006; Merikangas et al. 1999; Merikangas et al. 1998) https://childmind.org/article/how-to-avoid-passing-anxiety-on-to-your-kids/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3362924/ • parent anxiety confers poorer treatment outcomes for childhood anxiety disorders https://pediatrics.aappublications.org/content/118/2/651.short • Anxious children have postoperatively a higher incidence of emergence delirium compared with the children who were not anxious (9.7% vs 1.5%) and had a higher incidence of postoperative anxiety and sleep problems. https://pediatrics.aappublications.org/content/118/2/651.short
Heart rate and QT variability in children with anxiety disorders	• More sudden death [A preliminary report]. The findings suggest a relative increase in sympathetic activity and a relative decrease in cardiac vagal activity in children with anxiety disorders, and are discussed in the context of the effects of tricyclics on cardiac autonomic function in children, and the rare occurrence of sudden death during tricyclic antidepressant treatment https://onlinelibrary.wiley.com/doi/abs/10.1002/da.1019
Lactating mothers	Even the immunological quality of breast milk decreases with psychological stress (Moirasgenti 2019)
Adults: cardiac effects of anxiety are thought to be due to an exaggerated sensitivity to exogenous stress, which itself has been shown to have profound effects on the heart	• a compelling 2.5-fold increase in risk for ischemic complications resulting from anxiety following MI, while a substudy from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial[45] suggested that patients with acute MI and a high level of in-hospital anxiety (assessed via the Brief Symptom Inventory[51]) had an almost 5-fold increase in risk for recurrent ischemia, reinfarction, or death compared with patients with MI without high levels of anxiety • several psychosocial risk factors contribute to the development of cardiovascular disease and influence the course of those who have it. These risk factors included anger,6-8 hostility,7 social isolation,9,10 stress,11-13 anxiety,14-18 and depression.19-23 • Experimentally, stress (acute, subacute, or chronic) has been shown to provoke

	myocardial ischemia via numerous mechanisms in patients with CAD • patients with anxiety and CAD often exhibit an exaggerated systemic response to stress, characterized by an abnormally increased production of catecholamines, which can result in increased myocardial oxygen demand due to elevations in heart rate, blood pressure, and the rate of ventricular contraction • abnormalities of thrombosis and hemostasis, including increases in platelet aggregability,62 and alterations in the fibrinolytic system (possibly as a consequence of elevated plasminogen activator inhibitor 1 levels)63 have been noted in patients subjected to chronic stress. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/485397 • Vice versa, decrease in anxiety score during behavioral therapy could be associated with improved blastogenic response in humans (Koh 2004).
Population & Gender effect	• Anxiety disorders significantly increased mortality risk.(natural mortality rate ratio (MRR) = 1.39, 95% CI 1.28–1.51; unnatural MRR = 2.46, 95% CI 2.20–2.73) – Non corrected for age…: 2.49-6 47 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5082973/
General effects on immune system	• Dhabhar (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2790771/) reviewed in 2009 the effect of stress on the immune system, and its interaction with the short-term fight-or-flight stress response (via the HPA-axis), which is one of nature's fundamental defense mechanisms that enables the cardiovascular and musculoskeletal systems to promote survival. To cite his abstract: • Acute or short-term stress experienced at the time of immune activation can enhance innate and adaptive immune responses. • Chronic or long-term stress can suppress immunity by decreasing immune cell numbers and function and/or increasing active immunosuppressive mechanisms (e.g. regulatory T cells). • Chronic stress can also dysregulate immune function by promoting proinflammatory and type-2 cytokine-driven responses." Dhabhar 2009 further evoked various pathways and goes into the underlying mechanistic observations, concluding that tackling these maladaptive ramifications of acute stress response may help to sculpt the survival mechanism. Also other investigators have found relationships between stress/anxiety disorders and the immune response, and although the findings are not always straight-forward consistent, it is increasingly shown that (chronic) stress and elevated inflammation results in serious health consequences in cardiovascular disease, diabetes/metabolic disease, and (lung) cancer and that chronic stress during early development of diseases could have lasting effects on the responsiveness of the nervous system and immune system (Godbout 2006, Segerstrom 2004, Graham 2006; Seiler 2020 https://link.springer.com/chapter/10.1007/978-3-030-16996-1_6).
Effects of stress on vaccination (efficiency)	Based on epidemiologic and vaccination surveys, the following eggects of strees • Psychological stress has been associated with reduced antibody responses following vaccination, and this not only against viral germs, such as the flue (influenza), hepatitis B, rubella, but also against bacterial infections such as pneumococci or against meningitis (Jabaaij et al. 1996; Glaser et al. 2000; Morag et al. 1999; Burns et al. 2002, Vedhara et al. 1999; Vedhara et al. 2002; Miller et al., 2004 https://www.ncbi.nlm.nih.gov/pubmed/15039506). • The negative effect of stress on the flue vaccination was observed in older subjects, while not so in younger in one study. A meta-analysis of 13 studies concluded that the effect of stress on antibody responses to influenza virus vaccination corresponded to adequate antibody responses among 41% of stressed individuals versus 59% of less-stressed individuals with a reducing effects of stress both among older and younger adults (Pedersen et al. 2009). Yet, as pointed to in the review by Seiler 2020, "psychological distress and biobehavioral vulnerabilities, which arise from being older or sedentary, have independently been found to alter immune responses to influenza vaccination (Segerstrom et al. 2012); in adults and adolescence has been confirmed that negative emotions, including anxiety and depression, can modulate the antibody and T-cell responses to antiviral vaccinations, resulting in suppressed immune responses (O'Connor et al. 2014; Coughlin 2012). • Interestingly, a 4-week massage intervention in students embarking on academic

	examinations was associated with reduced distress and enhanced antibody responses after a hepatitis B vaccine (Loft et al. 2012). • Positive effects of other mind-body therapies, including Tai Chi, Qi Gong, meditation, and Yoga, on the immune system and virus-specific antibody responses to vaccines have also been documented in a meta-analysis of 34 studies (Morgan et al. 2014)." •
Role of HPA-axis? Gender effect	Our response to stress normally proceeds through the hypothalamic-pituitary-adrenal (HPA) axis. How relevant is this in view of the stressing media releases & social measures in COVID-19? • The relationship between immunomodulation and anxiety states is very complex and has been discussed in multiple reference works, as mentioned above. • But some animal models are staggering: if the animals are disrupted in their social behaviour ('social disruption stress'), they die more quickly from shock in response to a heavy microbial trigger, which is accompanied by resistance to the stress hormones (glucocorticoids) and an increased production of proteins/inflammatory cytokines (Quan et al. 2001). • Extrapolating this to COVID-19, spreading panic or social disruption may thus increase the risk of contributing to an inflammatory cascade. The stress axis is very sensitive to the effects of gender and age, and even if you are overweight: • This axis is activated more in men than in women under psychological stress – this has been proposed as one of the reason why men have a higher risk for cardiovascular diseases than women (Uhart 2006, Traustadottir 2009). Women, especially at age, have a significantly more resilient stress response of the body to various stressors and can also maintain this response longer than men (Pasquali et al. 2012; Seeman 1995; Veldhuis 2014). • Age is also thought to play a role in the release of the stress hormones, which may possibly explain in part why there is increased mortality in especially cardiovascular-compromised men compared to women as age increases in COVID-19 infection. • Also interaction with BMI is to be expected. If the HPA balance is disturbed as in severely obese individuals (Akalesou et al. 2020; Pasquali et al. 2012), the adaptive response to a stressor is apparently absent. It is proposed as reason that the circulating glucocorticoids are secreted in an increased way by the adrenal glands, but also are immediately metabolized away; combined with gender effects, a severely obese man is therefore less likely to respond well to stress than an obese woman (Akalesou et al. 2020; Pasquali et al. 2012). • To enhance the complexity of interactions, the stress-axis is further affected by Angiotensin II interaction, as suggested by animal research. For instance, Angiotensin II Inhibition Reduces Stress Sensitivity of Hypothalamo-Pituitary-Adrenal Axis in Spontaneously Hypertensive Rats. https://academic.oup.com/endo/article/147/7/3539/2501303
Conclusions	• In summary, stress can not only increase susceptibility to viral illness in the community upon exposure to infectious agents but also can inhibit or interfere with antibody and virus-specific (latent) T cell responses such as to vaccines or involved in reactivation or progression of latent viruses. Aging itself has been associated in general with a decreased immunological response to infection and vaccination. Together, the above interactions support that evoking stress and anxiety will further weaken the immune response, so this may add up to the weaker or failing immune response due to aging in elderly, as well as amplify chronic stress which is already enhanced in patients compromised by co-morbidity, so that these are even become more prone to dysregulation of the immune response (Dhabhar 2008 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2790771/). • The adverse effects of creating continuous stress and the expected benefits of decreasing the psycho-social burden by stopping negative news and attitude to disease deserves to be weighed against the impact than can be gained from testing, solation, and mongering fear to make people adhere to hygienic measures (part of

	the success of Africa in combatting COVID-19??) • To note: the highest death rate among 15-45 years during the Spanish flue was among the soldiers: the above analysis indicated that not just close living of soldiers, but possibly also the extreme stress of going to/being in war may have played a role, explaining the weird age-dependent death rate.  The difference between the influenza mortality age-distributions of the 1918 epidemic and normal epidemics – deaths per 100,000 persons in each age group, United States, for the interpandemic years 1911–1917 (dashed line) and the pandemic year 1918 (solid line)[43]