Disentangling the impacts of anxiety, stress and depression on immunity: a cross-cultural comparison

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Abstract

While immunity and psychological distress are strongly associated, studies seldom consider how different types of distress relate to immune functioning. The literature tends to emphasis the impact of stress on immunity. The present study estimated the unique contributions of stress, depression and anxiety on immune function in culturally diverse samples of adults from Italy, New Zealand and India. The participants were Italian (n = 1061), New Zealand (n = 1037), and Indian (n = 384) volunteers. Stepwise multiple linear regression and dominance analysis were used to analyse differences in immunity uniquely explained by anxiety, depression, and stress, with immune functioning defined by physical symptoms. While samples from the three countries differed significantly, anxiety consistently explained the greatest proportion of differences in immunity. After accounting for the effect of anxiety, stress and depression explained only small portion of variation in immune functioning, differing between countries. The association of anxiety with immune functioning was consistent across three different countries and the unique impact was further confirmed by the results of dominance analysis. These findings suggest a clear link between anxiety and immunity, when disentangling between distress types. This challenges the prevailing stress-disease model and calls for further research into the impact of anxiety on immunity. If future research supports a causal link where anxiety precedes immunity deficiency, interventions to reduce anxiety may improve immune functioning and health outcomes in the general population.

***Keywords*:** Stress, anxiety, depression, immunity, cross-cultural

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Chapter 1: Introduction

Stress, affective disorders and immune functioning are intertwined; with numerous studies over the past half century examining the impact of specific psychological conditions on immune dysfunction (Furman et al., 2019; Momen et al., 2020; Netea et al., 2020). Consequently, there has been great interest in gaining a more nuanced understanding of the relationship of psychological disturbances and immune functioning, with an ultimate view to the impact on health and wellbeing (Cohen & McKay, 2020). Despite broad evidence that distress contributes to immune dysregulation, there is a paucity of research which focuses on the degree to which the specific types of distress facets impact immune functioning (Lasselin et al., 2016). This work aims to examine the degree to which stress, depression and anxiety influence immune functioning, detangling the unique impact of this distinct distress types on immunity.

Evidence that distress leads to increased vulnerability to diseases through impaired immune functioning has led to a proliferation of research highlighting the impact of various psychological disturbances on the immune system, through the hypothalamic-pituitary adrenal axis, autonomic nervous systems and chronic low level inflammation (Cohen & McKay, 2020; Lamers et al., 2020; Marsland et al., 2002; O'Connor et al., 2021; Vinkers., 2021). More recent work has drawn attention to the impaired blood-brain barrier (Welcome, 2020) and altered gut microbiome in those experiencing distress (Cruz-Pereira et al., 2020). Low level chronic inflammation of various specific biomarkers has proved of particular interest. Various psychological disturbances, whether they be clinical or non-clinical, are also associated with inflammation and immune dysfunction, with some suggesting that the effects of distress on immunity and poorer health outcomes may be reified through chronic low-level inflammation (Miller & Raison, 2016; O'Connor et al.,2021). This relationship has been dubbed the *systemic inflammation hypothesis*, and the hypothesis assumes interactions

between endocrinal and nervous systems through inflammatory proteins and cytokines (Furman et al., 2019). A considerable body of evidence has developed around the myriad of effects of low-level inflammation on immune functioning. Specific inflammatory markers, the expression of which also correlate with psychological disturbances, have proved predictive of poorer medical outcomes later in life (Momen et al., 2020; O'Toole et al., 2018; Russ et al., 2012; Scott et al., 2016; Song et al., 2018; Turner et al., 2020).

However, biomarkers associated with immune dysfunction do not reliably distinguish between individuals who are frequently ill, and those who rarely get sick (Liu et al., 2021). Only the actual incidence of symptoms of illness is a reliable indicator of overall immune functioning (Zhou et al., 2014). There is no low-level inflammatory biomarker which maps to clear clinical threshold of immune functioning in the absence of disease symptoms. As such, isolated biomarkers and physiological measures are not used for the diagnoses of illness (Liu et al., 2021). Medical assessments are only undertaken after a patient self-refers. Biomarkers and physiological measures may inform a prognosis, in addition to the adjacent presence of physical symptoms and many other disease indices, identifying phenotypes responsive to specific drugs (Zhou et al., 2014). However, even in the presence of self-report and physical symptoms of disease, such as those used for diagnosis by general practitioners and health professionals, establishing a diagnostic link with inflammatory biomarkers and assigning clinically relevant threshold levels has proved a fraught exercise (Kananen et al., 2021; Liu et al., 2021; Torres et al., 2020).

Illustrating this complexity, inflammation biomarkers show a dynamic, rather than static response, and may act as pro-inflammatory or anti-inflammatory depending on the circumstances (Netea et al., 2020). A patient may experience both chronic inflammation, yet also show temporal variation in blood or plasma borne levels, with biomarkers acting in an immuno-protective or immuno-dysfunctional manner at various points in time. This variation

limits the ability to make claims from static time point measurements (Virtanen, et al, 2015). Moreover, in their detailed review, Del Giudice and Gangestad (2018) note that some studies of inflammation, distress and immunity have omitted to name the specific protein isoform, leading to other meta-reviews inappropriately grouping together different protein isoforms from the same gene family for analysis. This is concerning, as the biochemical function of the protein involved is known to vary with topography, misclassification which can only cloud any correlational inferences (Del Giudice & Gangestad, 2018).

Furthermore, a consequence of low-level chronic inflammation is that most studies carried out in this area show effect sizes which are small, with limited explained variance (Vinkers et al., 2021). In examining the link between 150 biomarkers, disease and immunity, Kananen et al. (2021) found 57 significant correlations of biomarkers with self-reported immunity alongside those with disease symptom, with largely weak correlations. These complexities, along with the lack of consilience of biomarkers and physiological measures produced by those with an active immune system responding to diseases, underscore the ecological validity of actual physical illness and symptoms as best indices of immune functioning. Self-report and directly observable symptoms remain the basis of clinical disease classification, and global immune functioning (Zhou et al., 2014)

Distress is a term which may be used to describe broad negative emotional affect, with cognitive, emotional, behavioural, spiritual and social elements (Adeyemi et al., 2021). Alternatively, it can be used as a narrower term encompassing various specific internalising negative disorders and emotional stressors, such as hostility and stress (Osman et al., 2012; Yarrington et al., 2022). Herein, the term distress will be used as a collective for the combination of three components: depression, anxiety and stress. Depression, anxiety and stress are prevalent forms of psychological distress. These negative affectivity facets contributes to changes in immune functioning, both directly and indirectly. The indirect

efforts of increased emotional tension may occur through altered behaviours, such as increased smoking or sleep disturbances (Lasselin, 2021). Alternatively, beliefs and behaviours could be explained by the Health Belief Model (Jones et al., 2014). The Health belief model encapsulates risk to ratio benefits for the individual, along with motivational and accessibility issues, in deciding to take action, such as seeing a general practioner or undergoing a diet change. Most studies examining the direct effects of emotional distress on immune mechanisms have focussed on specific distress types and their impact on a focussed combination of biological measures (Lamers et al., 2020; Miller & Raison, 2016; O'Connor et al., 2021, Vinkers et al., 2021).

Stress is a feature of life, and can be adaptive or pathological. Stress is marked by physiological arousal, which is common in response to stimuli including features of challenges and novelty, and also common amongst affective disorders (Crosswell et al., 2022; Lovibond & Lovibond, 1991; Epel, 2020). For example, the prospect of being a defendant in a court case, or driving on a motorway in an unfamiliar area, may contribute to a sense of feeling of being on edge, or even overwhelmed. Stress in this sense is an emergency state, with heightened feelings of arousal in response a current or perceived threat, which may lead to avoidance or defensive behaviours, or the seeking of support (Goette et al., 2015). Stress responses may include muscle tension, due to physiological responses, or altered breathing or heart rate (Daviu et al., 2019).

Conversely, stress can also be experienced in a positive way, during public performances or recreational experiences of sky diving, and these brief experiences with stress can show positive physiological and psychological outcomes (Epel, 2020). The degree to which a novel, and potentially stressful, challenge is experienced as a negative stressor is influenced by other factors, such as positive affect (Blevins et al., 2017). Some individuals show overconfidence in the face of stressor (Goette et al., 2015). The event of realising a

successful outcome in the face of a stressor may lead to improvements in beliefs around self-efficacy, influencing behavioural approaches in the future (Aschbacher et al., 2013). An acute stress response may boost vigilance and appears to help an individual fight off disease through immune activation (O'Connor et al., 2021), thus serving adaptive functions (Daviu et al., 2019; Marsland et al., 2002).

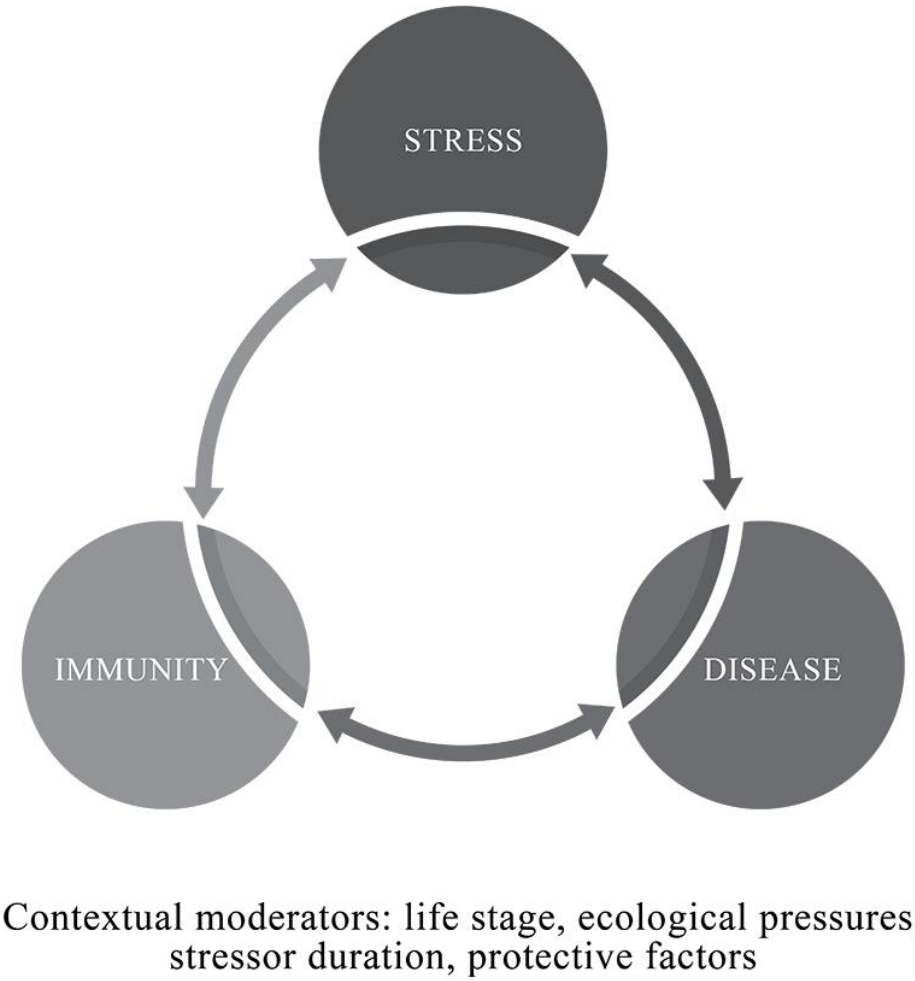
However, while short-term stress responses may provide benefits, chronic stress is strongly associated with poorer immune outcomes, induced through inappropriate immune activation and inhibition (Epel, 2020; Dang et al., 2019; O'Connor et al., 2021; Turner et al., 2020). The impacts of stress may be cumulative, increasing the total allostatic load of stress with each subsequent stressor (Daviu et al., 2019). The adverse impacts of chronic stress have long-standing recognition through both physiological and molecular responses, and experiences of stress may contribute to the development of anxiety and depression (McEwen, 2017; Miller & Raison, 2016; Morey et al., 2015). Chronically elevated stress levels, saliently those mediated through cortisol and the hypothalamic-pituitary axis, are associated with damaging increases in pro-inflammatory markers and dysregulation of other inflammatory indices (Aschbacher et al., 2013). Chronic stress may further sensitise those subject to pressure to disproportionate subsequent responses to stressors of a lesser magnitude (Charney & Manji, 2004). This is of concerns, as rapid physiological reactivity to a perceived threat, shown through swift increases in blood pressure, decreased heart rate variability, and relative cortisol increases are predictors for poorer health outcomes later in life (McEwen, 2017; Turner et al., 2020).

Stress was one of the first components of distress that was demonstrated to adversely impact immunity (Cohen et al., 1991). This was formally reflected in the model of Morey et al. (2015), linking stress with disease and immunity outcomes (O'Connor et al., 2021; Turner et al., 2020). However, there may be semantic and diagnostic limits to the use of the term

stress, which conflict with the model as depicted (Crosswell et al., 2022). Various negative adverse life events and experiences, such trauma and bereavement, are sometimes included under the mantle of stress, without necessarily being defined by a stress-focussed dimensional measure. Proponents of this unifying, lumping approach note that the broader use of the term *stress* can be a useful heuristic for conveying important findings (Morey et al., 2015; O'Connor et al., 2021; Song et al., 2018). Some detractors of this view note that while many negative life events may feature stress, this approach limits the ability to tease the impacts of stress out from other commonly covarying features, such as trauma, adjustment disorder or anxiety (Crosswell et al., 2022; Pai et al., 2017). Those arguing for greater precision in the definition of the term stress, calling to separate and name the different types of stress within studies, contend that further delineation of specific stress subtypes provides greater precision, which will enhance quality of comparisons of results between independent studies (Epel, 2020; Marsland et al., 2017; Song et al., 2019). The distinction between broader and narrower uses of the term *stress* can prove a significant one for interpretation of studies within the area of stress, immunity and disease. The attempts to analyse the impacts of stress on immunity may be impacted by the high comorbidity of stress alongside other forms of negative affectivity, unless specific measures are taken to control for this comorbidity (Charney & Manj, 2004; O'Connor et al., 2021).

Figure 1

Traditional Stress-Disease diagram based on Morey et al. (2015).



From the 1990s onwards, a considerable body of literature has been published outlining the association between depression, immune malfunction and early mortality (Dantzer et al., 2008; Miller & Raison, 2016). Like those affected by stress, those afflicted with depression show automatic, endocrinal and inflammatory disturbances, along with evidence of an impaired blood-brain barrier (Marsland et al., 2002; Lamers et al., 2020; Welcome, 2020). Depression is marked by various behaviours, cognitions and emotions, such

as sleep disturbances, low mood and rumination (Dantzer et al., 2008). Beck et al. (1979) developed what has become a prominent model relating depression to a triad of negative cognitive beliefs regarding the self, the world and the future. Of the emotional disturbances, depression shows the strongest, and clearest link with immunity, if immunity is defined by measures using inflammatory markers (Milaneschi et al., 2021).

It is striking that some of the behaviours that define depression, such as disturbances of appetite, sleep, and reduced motivation, are also behaviours associated with illness, and it possible that these shared symptoms partially mediate the strength of the relationship seen between depression and immunity (Andreason et al., 2018; Lasselin, 2021). For example, it has been demonstrated that a temporary depression-like response to endotoxins can be explained through an immune-mediated sickness response (Andreason et al., 2018; Lasselin, 2021). However, even within depressive disorders, there are a range of subtypes. Research in this area had categorised depression types between the melancholic subtype, marked with feelings of anhedonia and depressed mood and or the atypical, energy related depression subtype, more closely linked with fatigue and sleep disturbances. When relating these depression subtypes to biological stress systems, Lamer et al. (2021) found the symptoms of fatigue, shifts in appetite and weight changes were most strongly associated with inflammation biomarkers (Lamer et al., 2020). In contrast, the melancholic subtype of depression was not significantly related to inflammation. The Lamers et al. (2021) study highlights limitations of the use of inflammatory biomarkers to make inferences around immunity, since the relationship between apparent sickness induced symptoms of depression and inflammation may mask the relationship between depression and immunity.

The relationship between anxiety and immunity has been less well characterised, despite long-standing recognition of an association between anxiety and poorer health outcomes (Costello et al., 2019; Culpepper, 2009; Kariuki-Nyuthe & Stein, 2015; Otto-Meyer

et al., 2019). This is also despite the close association between stress and anxiety, as both share features of high arousal or muscle tension (Patriquin & Mathew, 2017). Anxiety has been characterised as a generalisation of the fear response, independent from acute challenges (Patriquin & Mathew, 2017). It is the element of anticipation of the fear, or the maladaptive repeated worries about various latent and looming threats which separates stress from anxiety (Daviu et al., 2019). While a person may be stressed by exposure to reckless driving, the emotions and cognitions differ for someone who is anxious and worries repeatedly that there are dangerous individuals, whether they be driving or not, with whom they may come into contact. Those with greater levels of anxiety are biased towards negative or fearful interpretations of neutral stimuli. For example, those high in anxiety interpret surprised faces to evince negative emotional states (Park et al., 2016).

Anxiety involves cognitive, emotional and behavioural elements (Behar et al., 2009). While anxiety is defined by a generalised fear, anxiety transdiagnostic elements such as intolerance of uncertainty and anxiety sensitivity (Dennis et al., 2021). Intolerance of uncertainty is the incapacity to tolerate the aversive response generated by the absence of desired specific information (Dennis et al., 2021). Anxiety sensitivity consists of three facets. The first facet involves cognitive thoughts that the worries will led to an undesirable outcome, such as loss of public composure or a mental breakdown. Moreover, anxiety sensitivity involves social concerns, such preoccupation that others may notice one hyperventilating or sweating. Lastly, anxiety sensitivity involves increased physiological vigilance with the physical symptoms of anxiety. An instance of this would be interpretating a racing heart as in indication of possible cardiac event, or vulnerability. This intolerance of the physical symptoms shares features of disorders related to other anxiety disorders with an emphasis on somatic symptoms, such as health anxiety (Jungmann and Witthoft, 2020).

A systematic review and meta-analysis found that anxiety was significantly associated with increased expression of inflammatory cytokines and proteins, and that this relationship was not moderated by depression (Renna et al., 2018). Conversely, Lamers et al. (2020) observed that high anxious-distress symptoms had a significant, inverse relationship with indices of inappropriate immune inhibition. This inconsistency in outcomes contributes to ambiguities in findings, when examining immunity defined by low level inflammation. Namli et al. (2022) observed an inverse relationship between anxiety and systemic immune inflammation, though anxiety was correlated with increases in immunological cell proliferation indexes, in a study using cross-sectional analysis. Other research has also found the relationship between immunity and anxiety to be inconsistent (Baldwin et al., 2018; Milaneschi et al., 2021). Until recently, these interactions have seldom been the subject of sustained scrutiny, and there is a paucity of research investigating the impact of anxiety on immunity(Costello et al., 2019; Furtado & Katzman, 2015; Hou et al., 2017; Lasselin et al., 2016).

While studies have shown stress often precedes anxiety and depression, anxiety and depression also show high comorbidity at time points, as well as high life-course prevalence (Charney & Manji, 2004; Kelly & Mezuk, 2017; Kessler et al., 2015; Lamers et al., 2011; Plana-Ripoll et al., 2019). Furthermore, these types of distress show increased prevalence amongst those facing impaired immune functioning and are associated with a poorer prognosis (Ko et al., 2022; Otto-Meyers et al., 2019; Scott et al., 2016; Zamani et al., 2019). However, research in this area has rarely considered the co-occurrence of depression, anxiety, and stress as they impact immunity, even though these internalising negative mood states and symptoms share commonalities (Kessler et al., 2015; Spinhoven et al., 2018; Yarrington et al., 2022). The comorbidity is so pronounced that subclinical depression, anxiety and stress may present within studies irrespective of whether they are measured, accounted, or

controlled for (Medvedev et al., 2018). The comorbidity is notable for the frequent co-occurrence of certain symptoms across these disorders in adults. For example, all three distress types may exhibit common physical symptoms such as restlessness and muscle tension.

These distress types share etiological pathways, and are often preluded by higher negative affect, traumatic life events and biased cognitive processes (Caspi & Moffitt, 2018). Anxiety and stress share features of dynamic fear (Patriquin & Mathew, 2017) and also what has been varyingly referred to as stress-tension, or anxious arousal which involves physiological outcomes (Osman et al., 2012; Yarrington et al., 2021). Depression shares the characteristic of repeated intrusive, negative thoughts with anxiety (Taylor & Snyder, 2021), as well as increased sensitivity to perceived slights, contributing to stress resulting from a negative self-image, and a resulting stressful sense of foreboding regard the self, the world and the future (Beck et al., 1979; Dondaville et al., 2023). For example, a disease diagnosis could be a source of significant, repeated negative cognitions, psychological arousal, along with elements of anxiety in the form of worry. Depression, anxiety and stress show some shared negative affect features (Yarrington et al., 2021).

Despite these commonalities, each distress type shows distinct patterns in the emotional and cognitive domains and are not considered overlapping emotional states (Eysenck & Fajkowska, 2018). Differences between them may be due to their heterogeneous nature, adaptive function, and relations with regulatory processes, positive affect, and motivation or other complex cognitive processes. Anxiety tends to be characterised physiological arousal and by excessive, repetitive, negative thinking focussed on potential risks, often referred to as worry (Patriquin & Mathew, 2017). The recurrently feared potential events which are the source of this angst may be purely conjectural (Patriquin & Mathew, 2017; Taylor & Snyder, 2021). Furthermore, anxiety often involves increased anxiety

sensitivity, where reactive individuals show an intolerance for the physical symptoms of anxiety (Taylor et al., 2007). By comparison, depression lacks arousal, though it is associated with repetitive negative thinking, although this may encompass both the self, future and world, and is often referred to as rumination, with themes of depreciation, anhedonia and negative evaluations (Eysenck & Fajkowska, 2018; Spinhoven et al., 2018; Taylor & Snyder, 2021). In addition to these physiological and cognitive differences, meta-reviews note that within non-clinical and clinical populations, the more depressed participants show attentional biases, where positive stimuli are avoided (Winer & Salem, 2016). However, those prone to anxiety show no such attentional bias (Armstrong & Olatunji, 2012).

Various researchers have suggested that stress, anxiety and depression exist as sequential threat responses. For example, Miller and Raison (2016) argued that stress or hyper-arousal typically precedes anxiety, which then contributes to the development of depression. Each emotion can be viewed as a functional response, in relation to problem solving potential threats. Stress first provides the energy to respond, anxiety provides vigilance towards dangers, and depression may lead to retreat, recovery and reorientation towards more suitable motivational goals (Danzter et al., 2008; Lasselin, 2021). Alternatively, Clark and Watson's (1991) classic tripartite model sought to explain the association between depression and anxiety through shared negative affect and common distress symptoms. Within the tripartite model, depression was characterised by anhedonia, while anxiety was discernible through arousal, despite the conditions possessing shared features. The third factor, stress, sometimes referred to as *hyperarousal* or *stress-tension*, captures physiological arousal less closely associated with anxiety or depression (Clark & Watson, 1991; Lovibond & Lovibond, 1993). Given the acceptance that depression, stress, and anxiety are distinct conditions, consideration of these different constructs against robust

self-reported immunity measures is a worthwhile project to separate the influence of each strand (Lasselin et al., 2016; Osman et al., 2012).

Subjective reports of health or disease symptoms, such as fever, headache, cough and joint pain, are important indices for measuring immune functioning used by general practitioners and are primary indicators to suspect viral or bacterial infections such as flu or COVID-19 (Alghamdi et al., 2021; Laracy, et al., 2023). Immune or illness questionnaires capture information about experiences that may or may not lead to contact with public health systems, whether to visit a medical professional or to begin behavioural changes, such as sleep or exercise modifications to mitigate risk. Such patient -centred questionnaires capture environmental validity that specific biomarkers may miss and have been found to be expedient and cost-effective. They may be more accurate predictors than clinical measures (Adeyemi et al., 2021; Ganna & Ingelsson, 2015; Schnittker & Bacak, 2014).

Few previous questionnaires focus on *quantifying* immunity. There is a pronounced trend for health or illness questionnaires, such as the Sickness Questionnaire, Illness Perceptions Questionnaire and the General Health Questionnaire to conflate *sickness symptoms* and *psychological outcomes* related to illness (Andreasson et al., 2018; Goldberg & Hillier, 1979; Ware et al., 1996; Weinman et al., 1996). While the tendency for these surveys to incorporate negative physical symptoms and distress domains underscores their close relationship, they would not enable comparisons to immunity. Others have used self-rated health instead of immunity scores (Adeyemi et al., 2021), and indeed, self-rated health has been found to predict mortality (Adeyemi et al., 2021; Ganna & Ingelsson, 2015; Schnittker & Bacak, 2014). However, while poor immunity is associated with poorer health, health is a broader construct than immunity, involving more than the absence of physical disease symptoms. For example, constructs of health may specifically incorporate elements of energy or vitality (Megari, 2013; Folker et al., 2019; Verster et al., 2023).

Focussing on immunity, the researchers Donners et al. (2015) used reduced immunity as a binary category, allowing participants to indicate whether they were experiencing perceived normal health status or reduced immunity at the moment of questioning. Others have expanded this approach to assess immune fitness using a Likert scale (Merlo et al., 2021; Verster et al., 2023). The use of such scales may still be limited, as the participants may consider overall health more broadly, in the absence of specific symptoms that are linked to immunity to guide those using this measure. The Immune System Assessment Questionnaire focuses on disease diagnostics rather than immune fitness and activity (Wilod Versprille et al., 2019). This questionnaire, from which later immunity measures were refined, correlates with health and physician visits; however, it lacks relevant common health-referral items such as incidence of muscle pain and the common cold (Romano et al., 2017).

The Immune Status Questionnaire (ISQ) developed by the Wilod Versprille research group assesses the most relevant symptoms linked to immune function and currently appears to be the sole scale of this nature developed to measure immunity. While there are other illness scales, none are designed to quantify immunity over the period of the past year (Wilod Versprille et al., 2019). If the relationship between immunity and distress is to be explored, then it is important that the immune scale be quantifiable and specific to immune functioning (Husquin et al., 2018; Nédélec et al., 2016; Quintana-Murci & Barreiro et al., 2010). A small, exploratory randomised controlled study with placebo sought to map biological responses against ISQ scores (Khadhke et al., 2023). ISQ scores did positively correlate with significant increases in immunological cell populations, shifts cytokines to an anti-inflammatory state and the reduction in measures of oxidative stress (Khadhke et al. 2023). While this could be considered encouraging, the study was limited by small sample sizes, with shifts in measures which were very modest, as is typical in this area (Kananen et al., 2021; Vinkers et al., 2021).

Physical symptoms of disease remain the primary indices of immune activity (Zhou et al., 2014).

Whether different emotional disturbances may be observed in immunological outcomes across different populations is unclear. Others have noted that different cultures may show differences in mental health stigma, which may affect self-reports of psychological disturbances, due to social desirability effect (Krendl & Pescosolido, 2020). Furthermore, different cultural groups may adopt different affective responses and coping mechanisms, expressing distress through shared culturally specific forms (Khambaty & Parikh, 2022). For example, different groups may vary in the degree of social integration and thus social support, perhaps based around interdependent or independent self-construal, which could be posited to be a protective feature, possibly boosting immunity through increasing resilience by buffering stress (Cohen & Mckay, 2020; De Vaus et al., 2018).

Furthermore, there are also likely to be complex environmental variations between populations and cultures due to a variety of features, including genetics, varying environmental conditions and diet (Martin et al., 2020). For example, the Mediterranean or the Blue Zone Diet, which has historically been common to certain geographic regions, seems to confer positive benefits on health and longevity, and could be considered to incorporate immune boosting elements (Liu et al., 2020; Suardi et al., 2021). There may also be genetic differences between geographically distinct populations, relating to features such as ethnicity (Sirugo et al., 2019). The selective pressure for genes linked with immunity is considered to be very powerful (Martin et al., 2020; Sirugo et al., 2019). Overall, the combination of the effects of cultural and environmental effects on immunity is unclear.

For the purposes of this study, a comparison between Italy, India, and New Zealand (NZ) was undertaken, as it is possible that there are cultural, environmental or genetic distinctions between impacts of the types of distress on immunity. This comparison of three

different countries has the advantage of including distinctive multicultural populations, with ethnicities, customs and traditions that diverge significantly. Italy and India contain a range of different ethnic and religious groups. Likewise, NZ also possesses people who identify with multiple different ethnic groups, in addition to an Indigenous population with a unique culture. This grouping produces a heterogenous sample and enables some comparisons across countries.

Evidence indicates that psychological distress types can impact immunity detrimentally, and various studies have investigated the impact of specific psychological disorders on immunity. However, there is a lack of research disentangling the impacts of depression, anxiety, and stress, in order to assess their individual unique contributions to immune functioning, as defined by physical symptoms. The present study examines the unique contributions of depression, anxiety and stress on immune status in a cross-country, non-clinical sample, using stepwise multiple linear regression and dominance analysis. Stepwise multiple linear regression first identifies and extracts the first predictor, which explains most of the variance using mathematical criteria (Roemer et al., 2021). Subsequent predictors, which explain the unique variance not explained by the preceding predictors, are extracted in descending order, and appear according to the proportion of the total variance they explain. Subsequently, dominance analysis was undertaken to determine and rank the impact of the distress facets on immunity by apportioning the variance between possible models (Van Iddekinge & Ployhart, 2008). Since this study was undertaken to investigate the relative importance of three distress components to immunity, dominance analysis is a useful addition to regression analysis (Tonidandel & LeBreton, 2011). This further analysis permits identification of the most relevant distress predictors, comparing their impact on immunity while controlling for immune-related variance shared between the various distress predictors. The aim of the study is to identify the distress facet with the strongest impact on immunity.

Chapter 2: Method

Participants

The total sample (n = 2482) was composed of Italian university students and from the general Italian population (n = 1061), NZ general population (n = 1037) and Indian university students (n = 384) above the age of 18. The Italian sample was composed of 97.64% of people who identified as European, Asiatic (0.26%), African (0.56%), American (0.56%) with the remainder (0.94%) made up of other ethnicities not specified. The NZ sample was composed of the general population of NZ European (64.6%), Māori (14.8), Pacific nations (3.9%), Asian (12.6%) and (4.1%) of other ethnicities not specified. All India student participants identified as Indian. The age distribution of the sample (M = 42.88, SD = 19.17) was mildly platykurtic. When age was viewed by country, the average NZ sample age (M = 49.00, SD = 17.63) showed greater variation. The Italian (M = 29.99, SD = 13.85) and Indian sample (M = 23.67, SD = 7.68) were relatively more youthful. A chi-square test of independence examined distribution of sex by country, and noted significant differences in two of the countries, with the Italian sample being weighted towards disproportionately more females (n = 834; 78.61%) to males, $p < .01$) with the Indian sample ($p < .01$) likewise possessing significantly more females (n = 251; 67%) to males ($p < .01$), compared to the sex balanced NZ sample with females (n = 534; 51%) commensurate to males (n = 505; 49%). Under 4% of values in the data set were missing. Preliminary checks suggested stochastic patterns, and due to the minimal size of missing data points relative to the large and heterogenous data-set, these values were not included in the analyses.

Procedure

The study was approved by the authors' institutional ethics committee, which follows internationally recognised ethical standards in accordance with APA 7 guideline editions. The current study is one facets of a broader research project, funded by the University of Waikato.

Written informed consent was obtained from all participants prior to completing the questionnaire. Participation was anonymous, and the participants gave their consent after reading information about the study. Data collection took place through an online survey and no time limit was imposed. Participants were recruited by a combination of techniques. The Italian students and general citizens were recruited through a convenient sample technique. Further participants were recruited through outreach by snowballing techniques. All Italian participants accessed the survey through the university based Qualtrics website, during October 2022. Dynata distributed the NZ survey online through their network, and participants obtained compensation up to the value of $5 for completing the form. Further NZ participants were recruited through outreach by snowballing techniques, during January to February 2022. The Indian students were recruited through a convenient sample technique. The link of the study was shared with teachers in different universities and shared with the associated classes. Moreover, the link of the study was also shared with different students' group, taking place during March to May 2022. No compensation was provided to the Italian or Indian participants for taking part in the study. While the survey was not subject to a time limit for submission, data was excluded from those who completed the survey in less than ten minutes, to protect the validity of the data, based on estimated likely completion times.

Measures

Depression, Anxiety and Stress Scales (DASS-21)

The DASS-21 is the widely used abbreviated variant of the original self-report 42-item measure (Lovibond & Lovibond, 1993; Sinclair et al., 2021). The measure requires participants to rank their agreement for each of the 21 items on a four-point Likert scale based on participant perception of emotions over the past week. Possible responses range from zero (did not apply to me at all – never); to three, (applied to me very much, or most of the time – almost always) indicating greater distress. In addition to the benefits of brevity, the

DASS-21 retains the three, seven-item subscales of depression, anxiety, and stress (Osman et al., 2012). These broadly used scales show strong internal reliability, with an overall McDonald's Omega of .94; with McDonald's Omega of .91, .85 and .85 for depression, anxiety, and stress respectively. The DASS-21 is a robust and well-characterised scale (Lightburn, et al., 2023).

Immune Status Questionnaire (ISQ)

The ISQ is a recently developed and validated self-report seven-item measure of immune functioning or immunity (Wilod Versprille et al., 2019). The participants are asked to rank the frequency of experiencing common disease symptoms including fever, diarrhoea, headache, skin problems, muscle, and joint pain, common cold and cough over the past twelve months on 5-point Likert scale. Items range in severity from one (never) to five ('almost' always), with higher score indicating poorer immune functioning. In the current study, McDonald's Omega was .72, highlighting the research reliability of this measure of distinct physical symptoms.

MacArthur scale of Subjective Social Status (SSS)

The SSS is a self-report measure which asks the participants to assess and indicate where they currently stand in their community on a 10-point scale, ranging from one (worst off) to 10 (best off; Adler et al., 1994). The scale is widely used across industrial cultures and is thought to capture subtleties of socio-economic status outcomes that more objective measures may miss. The scale strongly correlates with objective measures (Oswald & Wu, 2010).

Data Analyses

Data analyses were undertaken using IBM statistical package for the Social Sciences (SPSS) Version 27.0 software (IBM Corp.). The required sample size was estimated using G*Power software 3.1.9.4, and indicated that with the maximum number of predictors limited to 10 to detect a small effect size (.01), under the α=.05 with a certainty of 95% (1-β=.95), the required sample size would be ≥254 participants. The dataset exceeded this figure, reflecting strong statistical power. The data met the assumptions for multiple linear regression with variables being normally distributed and with skewness and kurtosis falling within the acceptable range between +2 and –2 (West et al., 1995). There was no multicollinearity among predictor variables, according to the criterion of Variance Inflating Factors (VIF) below 5 (Podsakoff et al., 2021; Roemer et al., 2021). Pearson correlation coefficients were calculated between age, SSS, the ISQ and the subscales of depression, anxiety, and stress.

Stepwise multiple linear regression was used to examine the relationships between the three facets of distress and the ISQ outcome variable (immunity). The analysis, combined forward and backward entry to ensure robustness (Babyak, 2004). Demographic variables including sex, age and SSS were controlled for and entered together in the first block. Following this, depression, anxiety, and stress were entered together using combined forward and backward stepwise entry. The predictor, which explains the greatest amount of the total variance, (known as the strongest predictor) was then identified. After accounting for, and deducting, the variance of the predictors already extracted, the process was then continued reiteratively to successively identify less important predictors, which progressively explain less of the variance. This continued until no more significant predictors remained (Roemer et al., 2021). The threshold for significant predictor inclusion was $p < .05$ and for removal was $p \geq .10$. These analyses were conducted individually for the Italian, Indian and NZ samples,

both due to marked difference in sociodemographic factors, and also to uncover any possible further distinctions between countries.

Dominance analysis was undertaken to determine the direct comparison of measures impacting the outcome of immunity (Van Iddekinge & Ployhart, 2008). The utility of dominance analysis is the way in which the analysis permits direct comparisons of measures within a model (Tonidandel & LeBreton, 2011). When scales are highly correlated, such as distress facets, the interdependence may impact the outcomes of unique predictor combinations in regression analysis, with a significant shift in one predictor altering another predictor (Budescu, 1993; Tonidandel & LeBreton, 2011). Dominance analysis reduces potential distortions through multicollinearity and enables direct comparisons of predictors within a model (that is, *X* is twice as important as *Y*).

Dominance analysis depicts and examines all possible combinations of the model in a pairwise fashion, in this instance a 3-predictor model. Each predictor contribution of R^2 is compared with one other predictor, and then with both other predictors. The general dominance is produced by averaging all ΔR^2 values. Rescaled dominance is generated by dividing the general dominance of a specific predictor by the sum of R^2 for the total number of predictors. To conduct dominance analysis in the present study, which has three predictors, seven regression analyses were run using SPSS, containing all possible combinations of predictors. Following these analyses, the ΔR^2 values were averaged and compared to identify the variable with the highest mean incremental contribution to variance explained, using Excel (Tonidandel & LeBreton, 2011). The percentage value of relative importance of predictors is derived by dividing the overall average incremental R^2 by the contribution of average predictors to the model (Azen & Budescu, 2003).

Chapter 3: Results

Demographic characteristics such as means and confidence intervals for all study variables split by country are represented in Table . Skewness and kurtosis values were given for the overall sample. The subscales of depression, stress and anxiety all showed a slight positive skew, indicative of the non-clinical origin of the sample. In comparing sociodemographic, affective and immunity subscales scores, independent *t*-tests paired between countries indicated substantive differences between the countries across domains of age, immunity, and affective subscales. The Indian and Italian participants were significantly younger, and their indices of average distress levels, saliently stress, were significantly higher compared to the NZ sample. Immunity measures were lowest for the Italians. The NZ sample reported lower perceived SSS, yet also produced lower average distress levels.

Table 1

Means (M), 95% confidence intervals (CI) of the samples by country and combined, also including skewness and kurtosis data for the total sample.

	Italian sample (*n* = 1061)		Indian students (*n* = 384)		NZ sample (*n* = 1037)		Total sample (*n* = 2482)			
Variable	*M*	*CI*	*M*	*CI*	*M*	*CI*	*M*	*CI*	Skewness	Kurtosis
Age	29.99	[29.16, 30.83]	23.67	[22.84, 24.50]	49.00	[47.92, 50.07]	42.88	[41.87, 43.90]	0.778	-0.609
SSS	6.56	[6.45, 6.66]	6.52	[6.29, 6.75]	5.60	[5.49, 5.72]	5.83	[5.72, 5.93]	-0.357	0.040
Immunity	5.86	[5.70, 6.03]	6.41	[6.10, 6.72]	6.92	[6.77, 7.08]	6.80	[6.66, 6.94]	-0.659	-0.342
Depression	6.81	[6.51, 7.12]	6.99	[6.45, 7.53]	5.70	[5.36, 6.03]	6.01	[5.72, 6.30]	0.805	-0.071
Stress	9.12	[8.84, 9.40]	7.36	[6.92, 7.80]	6.01	[5.73, 6.30]	6.34	[6.09, 6.58]	0.478	-0.275
Anxiety	5.95	[5.66, 6.23]	6.81	[6.31, 7.30]	4.36	[4.09, 4.63]	4.95	[4.70, 5.19]	0.889	0.193

Note. *n* = sample.

Pearson's correlations were computed between age, SSS and distress subscales, and the results can be seen in Table 2. The distress subscales of depression, stress, and anxiety were strongly and significantly positively correlated with each other, with correlation coefficients ranging from .72 to .76. Immunity was significantly inversely correlated with all negative affectivity subscales, with the strongest inverse relationship observed with anxiety (r = -.49, p < .01), closely followed by stress (r = -.45, p < .01). Age had an inverse relationship with the distress scores, yet within the study age showed a modest positive association with immunity (r = .26, p < .01). Immunity also showed a modest yet significant positive correlation with SSS (r = .13, p < .01).

Table 2

Pearson correlation matrix between age, SSS, negative affectivity subscales and immunity for the full sample (n = 2484)

Variables	Age	SSS	Depression	Anxiety	Stress
SSS	-.075**				
Depression	-.256**	-.271**			
Stress	-.332**	-.148**	.724**		
Anxiety	-.366**	-.142**	.755**	.740**	
Immunity	.264**	.126**	-.403**	-.485**	-.453**

Note. **p<.01.

Table 3 presents the results of stepwise multiple linear regression predicting immunity as the dependent variable within the Italian, Indian and NZ samples. Within the Italian sample, sociodemographic features accounts for 11% of the variance, with age showing the strongest impact (β = .27, p < .01) on immunity. Anxiety was the strongest affective influence on immunity (β = .4, p = .015), accounting for the further 14% of the variance.

Depression also appeared to explain a further 1.1% of the variance. Stress was not observed to be a significant predictor within the Italian sample.

The NZ socio-demographic characteristics of sex, SSS and age accounted for 9.3% of the variation with SSS ($\beta = .19$, $p < .01$) and age ($\beta = .17$, $p < .01$), showing a significant association with immunity. When the socio-demographics were controlled for, anxiety was the variable with the strongest association with immune outcomes compared with the other variables ($\beta = -.48$, $p < .001$), accounting for 20% of the variation in immunity scores, a medium effect size according to Cohen's standards (Cohen, 1992). After this, stress was identified as accounting for a further 0.5% of the variance. Depression was not observed to influence immune outcomes of the Indian or NZ samples.

Table 3

Summary of multiple linear stepwise regression analyses predicting immunity and the impact of affective subscales from the Italian sample (n =1061), Indian sample (n = 384) and NZ sample (n = 1039)

Outcome	Step	Block and Predictors		R^2	R^2 change	Standardized β	*p*
Italian sample	Control			.106	.106		
		1	Age			.266	$p < .01$
		2	SSS			.122	$p < .01$
		3	Sex			-.080	.007**
	Affective subscales	1		.249	.143		
			Anxiety			-.400	$p < .01$
		2		.257	.011		
			Depression			-.162	$p < .01$
Indian sample	Control			.036	.036		
		1	Age			.099	.072
		2	SSS			.135	.013*
		3	Sex			-.048	.382
	Affective subscales	1		.186	.151		
			Anxiety			-.405	$p < .01$
		2		.197	.011		
			Stress			-.142	.036*
NZ sample	Control			.093	.093		
		1	Age			.166	$p < .01$
		2	SSS			.193	$p < .01$
		3	Sex			-.107	$p < .01$
	Affective subscales	1		.293	.200		
			Anxiety			-.480	$p < .01$
		2		.298	.005		
			Stress			-.117	.007**

Note. $^{**}p < .01$; $^{*}p < .05$

Table 4 shows results summarised results of the dominance analysis; full results can be viewed in the appendix. Values in the table show the average ΔR^2 of the focal predictor when added to regression analysis with different combinations of the distress predictors. Table 4 shows that anxiety consistently has the greatest dominance value for samples from different countries, showing general dominance over the other distress facets (Budescu, 1993). Anxiety accounts for between 42% to 50% of variance explained, indicating that anxiety is the most import contributor to differences in immune functioning in the model. Stress was the second most important contributor for the NZ and Indian samples, while depression was the most important second contributor for the Italian sample (Azen & Budescu, 2003).

Table 4

Dominance analysis: average R^2, general dominance and rescaled dominance across distress facets and countries

Outcome	Numbers of predictors in the model	Depression	Anxiety	Stress
Italy	0	0.181	0.212	0.172
	1	0.022	0.050	0.016
	2	0.006	0.032	0.003
	General dominance	0.070	0.098	0.064
	Rescaled dominance %	30.09	42.42	27.49
India	0	0.100	0.169	0.132
	1	0.005	0.058	0.023
	2	0.000	0.036	0.003
	General dominance	0.035	0.088	0.053
	Rescaled dominance %	20.00	50.00	30.00
NZ	0	0.156	0.268	0.215
	1	0.003	0.087	0.036
	2	0.000	0.057	0.007
	General dominance	0.053	0.137	0.086
	Rescaled dominance %	19.14	49.76	31.10

Chapter 4: Discussion

This study focused on investigating the unique contributions of depression, anxiety and stress to immune functioning within a large sample with participants drawn from Italy, India and NZ. The study has shown that when considering the unique impacts, anxiety consistently demonstrated the strongest negative association with immune functioning. After accounting for the effects of anxiety, stress was found to exert a minor effect on immunity, in the Indian and NZ samples and finally, depression was found to have an equally negligible impact on immunity solely in the Italian sample. These results showed that contributions from the three distress constructs were indeed found to vary between countries, however the strength and consistency of the close association of anxiety with immunity was the most salient feature of the study. In contrast to expectations, this study did not find a strong, unique association between stress and immunity as proposed by the Morey stress-immune model, shown in Figure 1 (Morey et al., 2015). Furthermore, the results did not indicate a strong relationship between immunity and depression (Lamers et al., 2020). As the body of literature investigating psychological disorders impacting immunity has emphasised the relationship of stress and depression to immune dysfunction, this finding was unexpected (Lamers et al., 2020; Lasselin et al., 2016). However, there is currently a relative rarity of research into the effects of anxiety on immune functioning. Research differentiating between the unique contributions of mental health disorders and their relationship to immune functioning is scarcer still.

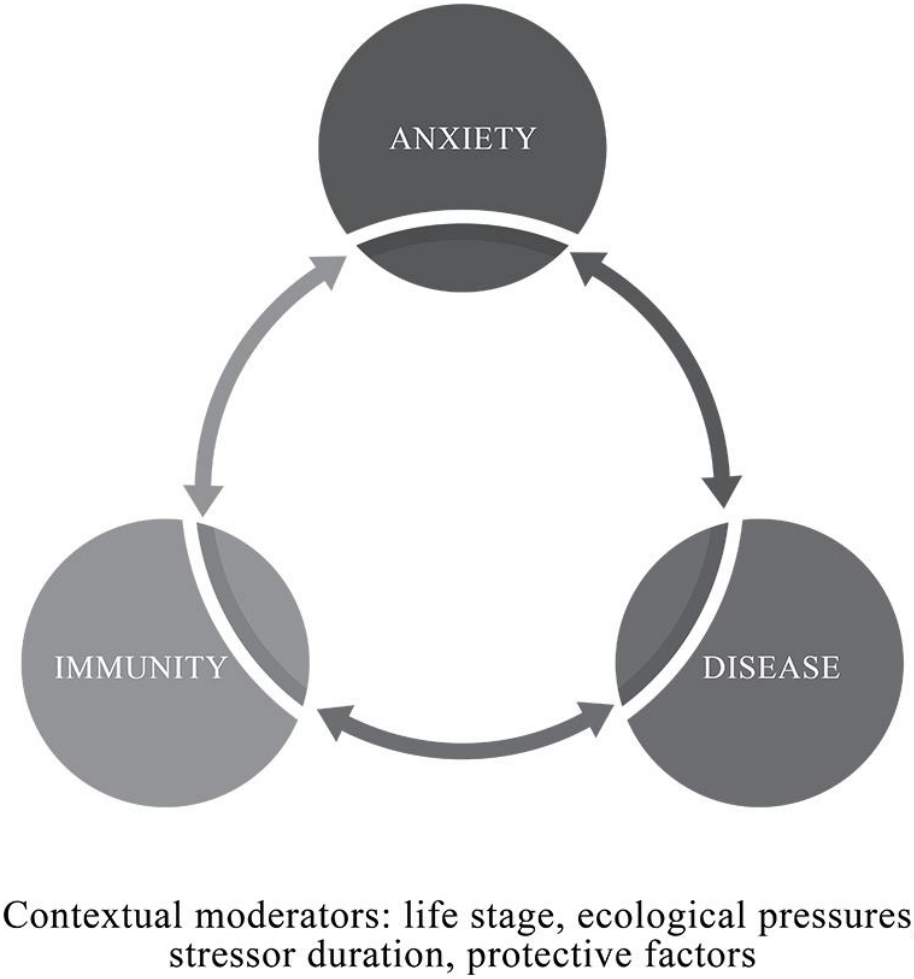
The present findings indicate that the associations of immunity between stress and depression in previous studies may be partially explained by unmeasured anxiety, which tends to be strongly associated and frequently comorbid with depression and stress (Lasselin et al., 2016; Medvedev et al., 2018). This strong association with anxiety becomes apparent when the unique variance associated with each disorder is controlled for (Barlow et al., 2014;

Budescu, 1993). The associations found within the study did not support a strong, unique relationship between stress, immunity, and disease (Morey et al., 2015). In view of this, an anxiety-disease model, such as that outlined in Figure 2, may convey the impacts of negative affectivity, immunity, and adverse health outcomes, in a manner more consistent with the evidence from the large, cross-country sample within this study.

While to date, relatively scant attention has been given to the association of anxiety and immunity, the results from this study suggest that anxiety is the strongest emotional state contributing to differences in immune functioning. This divergence from the established literature, which has focused on the impact of stress and depression on immune dysfunction suggests avenues for future studies to explore possible protective mechanisms or other moderating biomarkers, given the discrepancy seen in results from immunity considered by self-report of physical symptoms, contrasted with immunity considered using various biomarkers and physiological parameters fg(Lasselin et al., 2016; Renna et al., 2018). Future work could make use of methodologies which control for covarying affective conditions, when examining the impacts of types of distress or psychological disorders on immunity.

Figure 2

Proposed Anxiety-Disease model.



There are similarities between this study's findings and those of a recent cross-sectional study in Saudi Arabia (Alghamdi et al., 2021). Participants in that study reported distress impacting immunity, and they also differentiated between depression, anxiety and stress, with data collection undertaken one month after severe movement restrictions had been imposed to minimise the spread of COVID-19. Using stepwise binary logistic regression, those reporting mild to moderate anxiety were between two and four times more

likely to report reduced immune status, measured using DASS21 and ISQ (Alghamdi et al., 2021). As in the current study, anxiety and immunity also showed the strongest relationship. More severe anxiety was associated with much poorer immune functioning, in a manner which is suggestive of a dose-dependent relationship (Alghamdi et al., 2021).

That study also found strong and significant associations between stress and immunity (Alghamdi et al., 2021). However, the variance explained by anxiety, while estimating the contribution of stress, was not controlled for. Consequently, the Alghamdi et al. (2021) findings of associations of immune functioning with stress might be due to shared variance between anxiety and stress. In the current study, we controlled for anxiety and found only very weak remaining associations between stress and immune functioning within the Indian and NZ samples. This difference in results between the studies highlights the influence of the methodology which, in this case, allowed the identification of the unique effects of specific predictors, such as anxiety. The capacity to disentangle distress types was limited in the Saudi Arabian study by methodology that dichotomized continuous variables, namely immune functioning, which inevitably leads to a loss of information and consequently, reduced accuracy of estimates. These factors may have reduced the power of their analysis and contributed to the differences in association found in outcomes between Alghamdi et al. (2021) and the associations found in this study (Roemer et al., 2021). However, it is striking that anxiety exhibited the strongest relationship to immunity in both Alghamdi et al. (2021) and the present study.

Anxiety was the strongest factor impacting immunity *between* countries. This persisted despite differences in culture, age and slight differences in time of data collection, and this consistency is striking. Comparisons of types of distress relationships tend to show differences between countries (De Vaus et al., 2018; Long et al., 2022). When controlling for the variance shared between distress types, the analysis of the Italian sample showed a

negligible association between immunity and depression, despite the very high levels of depression and stress seen in the Italians (Caldirola et al., 2022; Fioravanti et al., 2022). Stress levels were detected, albeit were negligible, in the NZ citizens and Indian students. It is unclear from this work, though interesting to speculate, as to what degree this may be a culturally mediated effect. There are certainly Eastern cultural traditions that increase mind and body awareness, together with a more interdependent, collectivist outlook (De Vaus et al., 2018; Khambaty and Parikh, 2022).

However, it is also possible that the difficulties faced by the Indian students, around exams and financial strain, are experienced as short-term difficulties, which contribute to arousal, which the students learn to adapt to. NZ citizens, with lower SSS scores suggestive of economic strain may likewise experience arousal, but navigate challenges faced, using other resources, such as coping skills developed with increased age. Alternatively, the faint associations may simply reflect recent localised geopolitical events and conditions. For example, markedly increased stress and depression within Italy around the period of data collection may be due to the relative economic strain and high levels of unemployment that the country faced, and this may be partially reflected in the slight differences in emotional associations with immunity (Fioravanti et al., 2022; Caldirola et al., 2022; Pompili et al., 2022).

It is curious that, unlike the New Zealand population or the younger Indian students, the Italian sample was characterised by high levels of stress and depression, relatively high self-perceived socioeconomic status, yet good immune status (Fioravanti et al., 2022). This grouping is partially accounted for and explained by age and socio-economic differences between the different populations in this study, which was controlled for (Melku et al., 2019). However, it may also be a culturally mediated effect reflecting features of diet, or social integration (Liu et al., 2020; Suardi et al., 2021). On the other hand, both the NZ and Italian

samples, with the latter simply identifying as ‘European’ encompass a diverse range of cultures, so the diversity inherent to each sample could be used challenge any specific claim. The strength of the relationship of anxiety to immunity, once socio-demographic features were controlled for, remains the most distinctive feature of the study.

Despite the literature emphasising the close association between depression and inflammation markers (Milaneschi et al., 2021; Miller & Raison, 2016) our regression results did not show a strong impact of depression on immune symptoms. Since depression shares common variance with both anxiety and stress, there are limitations for studies connecting immunity with depression, as analysis may not control for other commonly comorbid types of distress, such as non-clinical or clinical anxiety and stress (Medvedev et al., 2018; Roemer et al., 2021; West et al., 1995). There are suggestions that the relationship between depression and the immune system is partially mediated through fatigue and sleep disturbances, as part of sickness behaviour in correlational studies (Andersson et al., 2018; Milaneschi et al., 2021; Vinkers et al., 2021). Unlike self-rated health, neither the DASS-21 nor ISQ includes self-report of prompted symptoms such as self-perceived fatigue or vitality (Lovibond & Lovibond, 1993; Verster et al., 2023; Wilod Versprille et al., 2019). Once the portion of those whose depression most clearly aligns with the atypical energy, fatigue sub-group, the link between depression and inflammation greatly weakens (Milaneschi et al., 2021; Vinkers et al., 2021).

This study has shown a weak association between stress and immune functioning. The term ‘stress’ has been used in research to cover a range of conditions, which may include various features covarying with stress, such as trauma and socioeconomic deprivation (Dieleman et al., 2015), which remain buried but blur the ability to separate out the specified components of distress, and consequently effect the descriptive accuracy of relationships observed. This is partially captured in the historic use of the term trauma, which has seen the

diagnosis classed under stress related disorders, until later research separated these disorders into distinct conditions (Pai et al., 2017). Whilst research using stress within the broad sense of the term conveys important information, such usage could be considered to come at a cost of precision in terminology for a myriad of specific details which may covary with the broader use of the term stress (Crosswell et al., 2022; Epel, 2020). Again, this highlights the significance methodological decisions have in affecting the outcome of the analyses. In this case, our use of stepwise multiple linear regression followed by dominance analysis appeared to assist our examination of the unique contributions of distress symptoms on immunity, since the effects of stress and depression are forced away when analysed simultaneously (Babyak, 2004; Budescu, 1993).

The lack of association between stress and immune functioning, after accounting for the effect of anxiety, was salient, given the high statistical power of this experimental design. There are a couple of possible explanations. Firstly, the method of stepwise multiple linear regression deducts the variance of predictors already explained by the model, and as noted, anxiety explained most of the variance (Roemer et al., 2021; Budescu,1993). Secondly, as well as negative effects, acute stress-response hormesis can have some beneficial effects on both immunity and distress levels (Dang et al., 2019; O'Connor et al., 2020). Such processes could weaken the broad association of stress and immunity found within this study, since the current study's measurement, and the measurements used in many studies considering stress (Aschbacher et al., 2013; Lasselin et al., 2016) does not distinguish acute from chronic stress. Other types of acute stress, such as public speaking, the illusion of imminent danger from theme parks and various risky recreational activities such as skydiving, skiing or swimming with sharks may all produce stress, but the type of stress generated by such activities may have positive, generative affects, conveying various benefits such as coping skills, improved emotional regulation and health benefits (Epel, 2020). By contrast anxiety, with features of

intrusive, repetitive worries and negative appraisals of coping capacity possesses pronounced features of negative affect, and is less compatible with mood stability (Spinhoven et al., 2018; Taylor & Snyder, 2021).

Strengths, Limitations and Directions of Future Research

As has been discussed, the strengths of this study lie in its statistical power, cross-country participation encompassing significant cultural diversity and participant heterogeneity. The statistical power arises from the use of appropriate statistical techniques used to undertake preliminary analysis, and the large sample size. The central limitation of the study is the cross-sectional nature, which means it is not possible to make causal inferences, so the associations found cannot be deemed deterministic (Roemer et al., 2021). For example, psychological disorders and immune dysfunction may share other commonalities which fall outside of the scope of this study, such as adverse experiences early in life (Caspi & Moffitt, 2018; Dieleman et al., 2015). Alternatively, experiences of a disease with physical symptoms may sensitise individuals towards greater anxiety, and cross-sectional analysis cannot indicate the factor which operated as an antecedent (Dennis et al., 2021). Temporal investigations could be more suitably explored through longitudinal analysis. The Environmental Risk Longitudinal Twin Study could examine and compare adverse early life events, or the effects of anxiety and depression on inflammation and health outcomes of the cohort during varying life stages, while controlling for socioeconomic factors and genetics (Baldwin et al., 2018).

Psychological distress from participants who were members of the general population was generally skewed towards being subclinical, and consequently the study may benefit from the inclusion of a broader psychiatric range (Antony et al., 1998). Continuing on this theme, the addition of participants encompassing greater heterogeneity in self-reported immunity, such as patients in primary medical health care, may have strengthened the study.

The involvement of those in primary healthcare could reduce potential criticisms around possible recall biases, through third party confirmation of disease symptoms and impaired immunity (Kananen et al., 2021). Research in this arena would also benefit from further exploration by examination using alternative psychological assessments. Different subtypes of emotional disorders may display different relationships to immunity. Only three types of distress disorders were examined within this study; future research may wish to investigate further conditions associated with distress in a broader sense, such as negative effect or trauma, which also appear to impact immunity (Renna et al., 2018; Schnurr et al., 2007; Shattuck & Muehlenbein, 2015).

With a focus on anxiety, future research could explore the relationship towards state and trait anxiety, or anxiety sensitivity (Lasselin et al., 2017; Taylor et al, 2007). It is possible that anxiety sensitivity, or undue interest in the physical effects of anxiety on the body influences research into disease symptoms and consequently, recall of immune symptoms (Jungmann & Witthoft, 2020). This association leads people more impacted by anxiety to conclude that they have poorer health, though influences around health research and health risk perception (Jones et al., 2014; Jungmann & Witthoft, 2020). In the same manner that fatigue may blur the relationship between inflammation and depression (Vinkers et al., 2021), some symptoms of anxiety, such as muscle and joint pain or skin problems may be related to physiological or behavioural elements of immunity symptoms, such muscle tension and dermatitis (Pluess et al., 2009; Sun et al., 2021). For example, dermatitis could have a relationship between immunity and anxiety sensitivity, namely intrusive, repetitive negative thinking catastrophising the social consequences of dermatitis, magnifying perception of the skin damage (Dennis et al., 2021). Future work could look to examine various specific ISQ symptoms and their relationship with negative affect, to examine whether muscle or joint pain or more experiences of fever more clearly emphasise distress. Alternatively, work could

look to break down the impact of cognitive, behavioural and physiological symptoms of negative affect on ISQ scores, to investigation the variance that distress symptoms explain. However, dimensional measures of emotional disturbances used in this study are robust and very well established (Lightburn et al., 2023; Osman et al., 2012).

It would be interesting to observe whether greater levels of anxiety impacted known immunological responses, in a dose dependent pattern, as was suggested in the cross-sectional Alghamdi et al. (2021) study. For example, evidence whether higher anxiety levels correspond to reduced immune responses when volunteers are injected with endotoxins known to stimulate immune responses could support or falsify any causal relationship, if depression and stress were controlled for (Lasselin, 2021). Alternatively, the immune responses of non-clinical participants to standard immunisation compared with placebo in randomised controlled trials could be measured against anxiety levels. Such work could demonstrate proof of concept, and the effectiveness of interventions, such as vaccinations, are based on the assumptions of typical immune functioning (Ballesio et al., 2023). Further insights about features that may impact the success of vaccines would be useful for those looking to enhance responses (Schakel et al., 2019).

The study is also limited by common method bias; multiple constructs being assessed using common methods (that is, multiple-item scales presented within the same survey) may lead to spurious effects due to the assessment instruments, rather than to the constructs themselves (Podsakoff et al., 2012). For example, participants are asked to report their subjective perceptions or impressions on two or more constructs within the same survey. This includes similar items such as *I felt that I had nothing to look forward to* and *I was worried about situations in which I might panic and make a fool of myself*. The close sequence of certain questions is likely to produce some spurious correlations among the items measuring these constructs owing to response styles, social desirability, and priming effects. These

issues may create some distortions, which may be affect the true associations between the constructs that the study intended to measure (Podsakoff et al., 2012). A similar cause for concern arises because participants are required to consider different assessments over different time periods: the DASS-21 refers to the past week, the ISQ refers to the past year, and the SSS refers to the participants current point in life (Adler et al., 1994; Lovibond & Lovibond, 1993; Wilod Versprille et al., 2019). While a set temporal reference point reflects common practice to capture health and affective variability, the window ranges being considered could be critiqued as inviting multiple recall biases associated with the varying time periods.

The DASS-21 and SSS used for mood and socioeconomic measures are both highly validated and robust measures (Antony et al., 1998; Lightburn et al., 2023; Oswald & Wu, 2010). In contrast, the recently developed ISQ, while increasingly globally used, including in other English, Indian and Italian studies, has been subject to less scrutiny (Nesari et al., 2022; Tarantino et al., 2021; Verster et al., 2023). While physical symptoms have the advantages of environmental validity, there are limits to the strengths of associations between different immunity symptoms. The symptoms for certain immune conditions, such as headaches and rashes, are not necessarily closely related, nor are expected to correlate highly with one another, although both have ramifications for overall immune system functioning (Wilod Versprille et al., 2019). Analysing the outcomes using Rasch transformed measures would improve the precision of the study, as analysis of immunity and distress relationships was undertaken using raw scores, and there is no particular reason to assume that the outcomes would be linear. Rasch transformed scores do exist for the DASS-21(Medvedev et al., 2020)., yet do not yet appear to have been created for the ISQ. Examination with Rasch transformed measures would improve the accuracy of the model

Within this comparison across countries, there were marked differences in age, sex, and distress levels between members of the general public and university students. The participants were youthful, and the sex ratio was disproportionately weighted towards females, which may partially account for the high rates of distress, given prevalent mental unwellness in females (Kessler et al., 2015; Long et al., 2022). Relative to the general public, students are generally higher on distress indices, which echoes research highlighting enhanced psychological distress in females and students (Cvetkovski et al., 2019; Kessler et al., 2015; Spence et al., 1987). While the increased distress did recommend inclusion for the purposes of the current study, results specific to university students may not be readily generalised to the broader population. It has been noted that student populations possess some unique features associated with improved reported parenting and psychological resilience when matched with non-university attending age-related peers (Cvetkovski et al., 2019). Future studies could use a make use of clinical, general citizen participants to strengthen the comparison.

Conclusions

Although there is keen interest in the relationship of psychological distress and immune functioning, most studies have investigated and emphasised the relationship of stress and depression to immune functioning (Dantzer et al., 2008; Marsland et al., 2017). The impact of anxiety on immunity has remained relatively neglected (Costello et al., 2019). Within the present study, which uses physical immunity symptoms and dimensional affective measures, anxiety consistently explained the greatest proportion of differences, when investigating the unique contributions of common psychological distress types on immune status. After accounting for effects of anxiety, other distress symptoms explained only negligible variation in immune function. While preliminary, these cross-country results highlight a close relationship between anxiety and immunity, and strongly encourage greater

examination into the impact of anxiety on immune functioning, with a view to fortifying immune functioning and disease outcomes.

References

Adeyemi, O. J., Gill, T. L., Paul, R., & Huber, L. B. (2021). Evaluating the association of self-reported psychological distress and self-rated health on survival times among women with breast cancer in the U.S. *PloS One, 16*(12), e0260481–e0260481. https://doi.org/10.1371/journal.pone.0260481

Adler, N. E., Boyce, T., Chesney, M. A., Cohen, S., Folkman, S., Kah, R. L., & Syme, S. L. (1994). Socioeconomic status and health: The challenge of the gradient. American Psychologist, 49(1), 15-24. https://doi.org/10.1037/0003-066x.49.1.15

Alghamdi, B. S., Alatawi, Y., Alshehri, F. S., Tayeb, H. O., & Tarazi, F. I. (2021). Relationship between public mental health and immune status during the COVID-19 pandemic: cross-sectional data from Saudi Arabia. *Risk Management and Healthcare Policy, 14*, 1439 - 1447. https://doi.org/10.2147/RMHP.S302144

Andreasson, A., Wicksell, R. K., Lodin, K., Karshikoff, B., Axelsson, J., & Lekander, M. (2018). A global measure of sickness behaviour: Development of the Sickness Questionnaire. *Journal of Health Psychology, 23(*11), 1452–1463. https://doi.org/10.1177/1359105316659917

Antony, M. M., Bieling, P. J., Cox, B. J., Enns, M. W., & Swinson, R. P. (1998). Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. *Psychological Assessment, 10*(2), 176-181. https://doi.org/10.1037/1040-3590.10.2.176

Armstrong, T., & Olatunji, B. (2012). Eye tracking of attention in the affective disorders: A meta-analytic review and synthesis. *Clinical Psychology Review, 32*, 704–723. https://doi.org/10.1016/j.cpr. 2012.09.004Sh

Aschbacher, K., O'Donovan, A., Wolkowitz, O. M., Dhabhar, F. S., Su, Y., & Epel, E. (2013). Good stress, bad stress and oxidative stress: Insights from anticipatory cortisol

reactivity. *Psychoneuroendocrinology*, *38*(9), 1698-1708. https://doi.org/10.1016/j.psyneuen.2013.02.004

Atabani, S., Landucci, G., Steward, M. W., Whittle, H., Tilles, J. G., & Forthal, D. N. (2000). Sex-associated differences in the antibody-dependent cellular cytotoxicity antibody response to measles vaccines. *Clinical and Diagnostic Laboratory Immunology*, *7*(1), 111–113. https://doi.org/10.1128/cdli.7.1.111-113.2000

Azen, R., & Budescu, D. V. (2003). The dominance analysis approach for comparing predictors in multiple regression. *Psychological Methods*, *8*(2), 129–148. https://doi.org/10.1037/1082-989X.8.2.129

Babyak, M. A. (2004). What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosomatic Medicine*, *66*(3), 411-421.

Baldwin, J. R., Arseneault, L., Caspi, A., Fisher, H. L., Moffitt, T. E., Odgers, C. L., Pariante, C., Ambler, A., Dove, R., Kepa, A., Matthews, T., Menard, A., Sugden, K., Williams, B., & Danese, A. (2018). Childhood victimization and inflammation in young adulthood: A genetically sensitive cohort study. *Brain, Behavior, and Immunity*, *67*, 211–217. https://doi.org/10.1016/j.bbi.2017.08.025

Ballesio, A., Zagaria, A., Violani, C., & Lombardo, C. (2023). Psychosocial and behavioural predictors of immune response to influenza vaccination: a systematic review and meta-analysis. *Health Psychology Review*, *ahead-of-print(ahead-of-print)*, 1–30. https://doi.org/10.1080/17437199.2023.2208652

Barbon, A., & Magri, C. (2020). RNA editing and modifications in Mood Disorders. *Genes*, *11*(8), 872. https://doi.org/10.3390/genes11080872

Barlow, Sauer-Zavala, S., Carl, J. R., Bullis, J. R., & Ellard, K. K. (2014). The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clinical Psychological Science, 2*(3), 344–365. https://doi.org/10.1177/2167702613505532

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive therapy of depression.* Guilford Press.

Behar, E., DiMarco, I. D., Hekler, E. B., Mohlman, J., & Staples, A. M. (2009). Current theoretical models of generalized anxiety disorder (GAD): Conceptual review and treatment implications. *Journal of Anxiety Disorders,23(*8), 1011-1023. https://doi.org/10.1016/j.janxdis.2009.07.006

Bennett, F. C., & Molofsky, A. V. (2019). The immune system and psychiatric disease: A basic science perspective. *Clinical and Experimental Immunology, 197*(3), 294–307. https://doi.org/10.1111/cei.13334

Binder, E., & Nemeroff, C. (2010). The CRF system, stress, depression and anxiety: Insights from human genetic studies. *Molecular Psychiatry, 15(*6), 574-588. https://doi.org/doi.org/10.1038/mp.2009.141

Blevins, C. L., Sagui, S. J., & Bennett, J. M. (2017). Inflammation and positive affect: Examining the stress-buffering hypothesis with data from the National Longitudinal Study of Adolescent to Adult Health. Brain, Behavior, and Immunity, 61, 21-26. https://doi.org/10.1016/j.bbi.2016.07.149

Budescu, D. V. (1993). Dominance analysis: A new approach to the problem of relative importance of predictors in multiple regression. *Psychological Bulletin, 114*(3), 542–551. https://doi.org/10.1037/0033-2909.114.3.542

Caldirola, D., Daccò, S., Cuniberti, F., Grassi, M., Alciati, A., Torti, T., & Perna, G. (2022). First-onset major depression during the COVID-19 pandemic: A predictive machine

learning model. *Journal of Affective Disorders*, *310*, 75–86. https://doi.org/10.1016/j.jad.2022.04.145

Caspi, A., & Moffitt, T. E. (2018). All for one and one for all: Mental disorders in one dimension. *American Journal of Psychiatry, 175*(9), 831-844. https://doi.org/10.1176/appi.ajp.2018.17121383

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology, 100*(3), 316 - 336. https://doi.org/10.1037/0021-843X.100.3.316

Cohen, J. (1992). Quantitative methods in psychology: A power primer. In *Psychological bulletin*.

Cohen, S., Alper, C. M., Doyle, W. J., Adler, N., Treanor, J. J., & Turner, R. B. (2008). Objective and subjective socioeconomic status and susceptibility to the common cold. *Health Psychology*, *27*(2), 268–274. https://doi.org/10.1037/0278-6133.27.2.268

Cohen, S., & McKay, G. (2020). Social support, stress and the buffering hypothesis: A theoretical analysis. In S. E. Taylor, J. E. Singer, & A. Baum (Eds.), *Handbook of Psychology and Health (Volume IV*, pp. 253-267). Routledge. https://doi.org/10.4324/9781003044307-10

Cohen, S., Tyrrell, D. A., & Smith, A. P. (1991). Psychological stress and susceptibility to the common cold. *New England Journal of Medicine, 325*(9), 606-612. https://doi.org/10.1056/NEJM199108293250903

Costello, H., Gould, R. L., Abrol, E., & Howard, R. (2019). Systematic review and meta-analysis of the association between peripheral inflammatory cytokines and generalised anxiety disorder. *BMJ Open*, *9*(7), e027925–e027925. https://doi.org/10.1136/bmjopen-2018-027925

Crosswell, A. D., Epel, E. S., Mendes, W. B., & Prather, A. A. (2022). Improving the language specificity of stress in psychological and population health science. *Psychosomatic Medicine, 84*(5), 643-644. http://doi.org/10.1097/PSY.0000000000001090

Cruz-Pereira, J. S., Rea, K., Nolan, Y. M., O'Leary, O. F., Dinan, T. G., & Cryan, J. F. (2020). Depression's unholy trinity: Dysregulated stress, immunity, and the microbiome. *Annual Review of Psychology, 71*(1), 49–78. https://doi.org/10.1146/annurev-psych-122216-011613

Culpepper, L. (2009). Generalized anxiety disorder and medical illness. *Journal of Clinical Psychiatry, 70*(2), 20-24. https://doi.org/10.4088/JCP.s.7002.04

Cvetkovski, S., Jorm, A. F., & Mackinnon, A. J. (2019). An analysis of the mental health trajectories of university students compared to their community peers using a national longitudinal survey. *Studies in Higher Education, 44*(1), 185-200. https://doi.org/10.1080/03075079.2017.1356281

Dang, R., Guo, Y.-Y., Zhang, K., Jiang, P., & Zhao, M.-G. (2019). Predictable chronic mild stress promotes recovery from LPS-induced depression. *Molecular Brain, 12*(1), 42–42. https://doi.org/10.1186/s13041-019-0463-2

Dantzer, R., Cohen, S., Russo, S. J., & Dinan, T. G. (2018). Resilience and immunity. *Brain, Behavior, and Immunity, 74*, 28–42. https://doi.org/10.1016/j.bbi.2018.08.010

Dantzer, R., O'connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience, 9*(1), 46-56. https://doi.org/10.1038/nrn2297

Daviu, N., Bruchas, M. R., Moghaddam, B., Sandi, C., & Beyeler, A. (2019). Neurobiological links between stress and anxiety. *Neurobiology of Stress,11,* 100191. https://doi.org/10.1016/j.ynstr.2019.100191

Dennis, D., Radnitz, C., & Wheaton, M. G. (2021). A perfect storm? Health anxiety, contamination fears, and COVID-19: Lessons learned from past pandemics and current challenges. *International Journal of Cognitive Therapy, 14*(3), 497-513. https://doi.org/10.1007/s41811-021-00109-7

Del Giudice, M., & Gangestad, S. W. (2018). Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain, Behavior, and Immunity*, *70*, 61–75. https://doi.org/10.1016/j.bbi.2018.02.013

De Vaus, J., Hornsey, M. J., Kuppens, P., & Bastian, B. (2018). Exploring the East-West divide in prevalence of affective disorder: A case for cultural differences in coping with negative emotion. *Personality and Social Psychology Review*, *22*(3), 285-304. https://doi.org/10.1177/1088868317736222

Dieleman, G. C., Huizink, A. C., Tulen, J. H., Utens, E. M., Creemers, H. E., van der Ende, J., & Verhulst, F. C. (2015). Alterations in HPA-axis and autonomic nervous system functioning in childhood anxiety disorders point to a chronic stress hypothesis. *Psychoneuroendocrinology*, *51*, 135-150. https://doi.org/10.1016/j.psyneuen.2014.09.002

Dondanville, A. A., Pössel, P., & Fernandez-Botran, G. R. (2023). Relation between the negative cognitive triad, perceived everyday discrimination, depressive symptoms, and TNF-α in adolescents. *Child Psychiatry and Human Development.* 1-12. https://doi.org/10.1007/s10578-023-01530-z

Donners, A. A. M. T., Tromp, M. D. P., Garssen, J., Roth, T., & Verster, J. C. (2015). Perceived immune status and sleep: A survey among Dutch students. *Sleep Disorders, 2015*, 721607–721612. https://doi.org/10.1155/2015/721607

Epel, E. S. (2020). The geroscience agenda: Toxic stress, hormetic stress, and the rate of aging. *Ageing Research Reviews, 63,* 101167–101167. https://doi.org/10.1016/j.arr.2020.101167

Eysenck, M. W., & Fajkowska, M. (2018). Anxiety and depression: toward overlapping and distinctive features. *Cognition and Emotion, 32*(7), 1391-1400. https://doi.org/10.1080/02699931.2017.1330255

Fioravanti, G., Benucci, S. B., Prostamo, A., Banchi, V., & Casale, S. (2022). Effects of the COVID-19 pandemic on psychological health in a sample of Italian adults: A three-wave longitudinal study. *Psychiatry Research, 315,* 114705. https://doi.org/10.1016/j.psychres.2022.114705

Folker, A. P., Hegelund, E. R., Mortensen, E. L., Wimmelmann, C. L., & Flensborg-Madsen, T. (2019). The association between life satisfaction, vitality, self-rated health, and risk of cancer. *Quality of Life Research, 28,* 947-954. https://doi.org/10.1007/s11136-018-2083-1

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D. W., Fasano, A., Miller, G. W., Miller, A. H., Mantovani, A., Weyand, C. M., Barzilai, N., Goronzy, J. J., Rando, T. A., Effros, R. B., Lucia, A., Kleinstreuer, N., & Slavich, G. M. (2019). Chronic inflammation in the etiology of disease across the life span. *Nature Medicine, 25*(12), 1822–1832. https://doi.org/10.1038/s41591-019-0675-0

Furtado, M., & Katzman, M. (2015). Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive-compulsive disorders. *Psychiatry Research, 229*(1), 37–48. https://doi.org/10.1016/j.psychres.2015.05.036

Ganna, A., & Ingelsson, E. (2015). 5 year mortality predictors in 498 103 UK Biobank participants: a prospective population-based study. *The Lancet (British Edition)*, *386*(9993), 533–540. https://doi.org/10.1016/S0140-6736(15)60175-1

Goette, L., Bendahan, S., Thoresen, J., Hollis, F., & Sandi, C. (2015). Stress pulls us apart: Anxiety leads to differences in competitive confidence under stress. *Psychoneuroendocrinology, 54,* 115-123. https://doi.org/10.1016/j.psyneuen.2015.01.019

Hou, R., Garner, M., Holmes, C., Osmond, C., Teeling, J., Lau, L., & Baldwin, D. S. (2017). Peripheral inflammatory cytokines and immune balance in Generalised Anxiety Disorder: Case-controlled study. *Brain, Behavior, and Immunity, 62,* 212–218. https://doi.org/10.1016/j.bbi.2017.01.021

Hou, R., Ye, G., Liu, Y., Chen, X., Pan, M., Zhu, F., ... & Tang, Z. (2019). Effects of SSRIs on peripheral inflammatory cytokines in patients with Generalized Anxiety Disorder. *Brain, Behavior, and Immunity, 81,* 105-110. https://doi.org/10.1016/j.bbi.2019.06.001

Huang, Q. Q., Ritchie, S. C., Brozynska, M., & Inouye, M. (2018). Power, false discovery rate and Winner's Curse in eQTL studies. *Nucleic Acids Research, 46*(22), e133-e133. https://doi.org/10.1093/nar/gky780

Husquin, L. T., Rotival, M., Fagny, M., Quach, H., Zidane, N., McEwen, L. M., MacIsaac, J. L., Kobor, M. S., Aschard, H., Patin, E., & Quintana-Murci, L. (2018). Exploring the genetic basis of human population differences in DNA methylation and their causal impact on immune gene regulation. *Genome Biology, 19*(1), 222–222. https://doi.org/10.1186/s13059-018-1601-3

Jansen, R., Penninx, B. W. J. H., Madar, V., Xia, K., Milaneschi, Y., Hottenga, J. J., ... & Sullivan, P. F. (2016). Gene expression in major depressive disorder. *Molecular Psychiatry, 21*(3), 339-347. https://doi.org/10.1038/mp.2015.57

Jones, C. J., Smith, H., & Llewellyn, C. (2014). Evaluating the effectiveness of health belief model interventions in improving adherence: a systematic review. *Health Psychology Review, 8*(3), 253-269. https://doi.org/10.1080/17437199.2013.802623

Jungmann, S. M., & Witthöft, M. (2020). Health anxiety, cyberchondria, and coping in the current COVID-19 pandemic: Which factors are related to coronavirus anxiety?. *Journal of Anxiety Disorders, 73,* 102239. https://doi.org/10.1016/j.janxdis.2020.102239

Kananen, L., Enroth, L., Raitanen, J., Jylhävä, J., Bürkle, A., Moreno-Villanueva, M., Bernhardt, J., Toussaint, O., Grubeck-Loebenstein, B., Malavolta, M., Basso, A., Piacenza, F., Collino, S., Gonos, E. S., Sikora, E., Gradinaru, D., Jansen, E. H. J. M., Dollé, M. E. T., Salmon, M., … Jylhä, M. (2021). Self-rated health in individuals with and without disease is associated with multiple biomarkers representing multiple biological domains. *Scientific Reports, 11*(1), 6139–14. https://doi.org/10.1038/s41598-021-85668-7

Kariuki-Nyuthe, C., & Stein, D. J. (2015). Anxiety and Related Disorders and Physical Illness. In N. Sartorius, R. I. G. Holt, & M. Maj (Eds.), *Comorbidity of Mental and Physical Disorders* (pp. 81–87). S. Karger AG. https://doi.org/10.1159/000365538

Kelly, K. M., & Mezuk, B. (2017). Predictors of remission from generalized anxiety disorder and major depressive disorder. *Journal of Affective Disorders, 208,* 467-474. https://doi.org/10.1016/j.jad.2016.10.042

Kessler, R. C., Sampson, N. A., Berglund, P., Gruber, M. J., Al-Hamzawi, A., Andrade, L., ... & Wilcox, M. A. (2015). Anxious and non-anxious major depressive disorder in the

World Health Organization World Mental Health surveys. *Epidemiology and Psychiatric Sciences, 24*(3), 210-226. https://doi.org/10.1017/S2045796015000189

Khadke, S., Gupte, P., Mourya, A., Yadav, A., Mane, S., Joshi, A., ... & Bhalerao, S. (2023). Immunomodulatory effect of a proprietary polyherbal formulation on healthy participants: A single-blind, randomized, placebo-controlled, exploratory clinical study. *Perspectives in Clinical Research, 14*(3), 130-138. https://DO 10.4103/picr.picr_100_22

Khodarahimi, S., Mirderikvand, F., & Amraei, K. (2023). Negative affectivity, sensory processing hypersensitivity, sleep quality and dreams: A conceptual model for generalised anxiety disorder in adults. *Current Psychology, 42*(1), 368–377. https://doi.org/10.1007/s12144-021-01428-w

Ko, M. S. M., Poh, P.-F., Heng, K. Y. C., Sultana, R., Murphy, B., Ng, R. W. L., & Lee, J. H. (2022). Assessment of long-term psychological outcomes after pediatric intensive care unit addmission: A systematic review and meta-analysis. *Archives of Pediatrics & Adolescent Medicine, 176*(3), e215767–e215767. https://doi.org/10.1001/jamapediatrics.2021.5767

Khambaty, M., & Parikh, R. M. (2022). Cultural aspects of anxiety disorders in India. *Dialogues in Clinical Neuroscience. 19(2),* 117–126. https://doi.org/10.31887/DCNS.2017.19.2/rparikh

Khandaker, G. M., Cousins, L., Deakin, J., Lennox, B. R., Yolken, R., & Jones, P. B. (2015). Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. The Lancet Psychiatry, 2(3), 258-270. https://doi.org/10.1016/S2215-0366(14)00122-9

Krendl, A. C., & Pescosolido, B. A. (2020). Countries and cultural differences in the stigma of mental illness: The East–West divide. *Journal of Cross-Cultural Psychology, 51*(2), 149–167. https://doi.org/10.1177/0022022119901297

Kuhnt, S., Brähler, E., Faller, H., Härter, M., Keller, M., Schulz, H., Wegscheider, K., Weis, J., Boehncke, A., Hund, B., Reuter, K., Richard, M., Sehner, S., Wittchen, H.-U., Koch, U., & Mehnert, A. (2016). Twelve-Month and Lifetime Prevalence of Mental Disorders in Cancer Patients. *Psychotherapy and Psychosomatics, 85*(5), 289–296. https://doi.org/10.1159/000446991

Lamers, F., van Oppen, P., Comijs, H. C., Smit, J. H., Spinhoven, P., van Balkom, A. J., ... & Penninx, B. W. (2011). Comorbidity patterns of anxiety and depressive disorders in a large cohort study: The Netherlands Study of Depression and Anxiety (NESDA). The *Journal of Clinical Psychiatry, 72*(3), 3397. https://doi.org/10.4088/JCP.10m06176blu

Laracy, J. C., Robilotti, E. V., Yan, J., Lucca, A., Aslam, A., Babady, N. E., & Kamboj, M. (2023). Comparison of coronavirus disease 2019 (COVID-19) symptoms at diagnosis among healthcare personnel before and after the emergence of the omicron variant. *Infection Control and Hospital Epidemiology, 44*(5), 821–823. https://doi.org/10.1017/ice.2022.105

Lasselin, J. (2021). Back to the future of psychoneuroimmunology: Studying inflammation-induced sickness behavior. *Brain, Behavior, & Immunity-Health, 18*, 100379 - 100379. https://doi.org/10.1016/j.bbih.2021.100379

Lasselin, J., Elsenbruch, S., Lekander, M., Axelsson, J., Karshikoff, B., Grigoleit, J.-S., Engler, H., Schedlowski, M., & Benson, S. (2016). Mood disturbance during experimental endotoxemia: Predictors of state anxiety as a psychological component

of sickness behavior. *Brain, Behavior, and Immunity, 57*, 30–37. https://doi.org/10.1016/j.bbi.2016.01.003

Libet, B. (2004). *Mind time the temporal factor in consciousness.* Harvard University Press. https://doi.org/10.4159/9780674040168

Lightburn, S. J., Pratscher, S. D., Bettencourt, B. A., Hartstone, J. M., & Medvedev, O. N. (2023). Evaluating depression anxiety and stress assessment before and during the COVID-19 pandemic using generalisability theory. *International Journal of Psychology*. https://doi.org/:10.1002/ijop.12907

Llibre, A., & Duffy, D. (2018). Immune response biomarkers in human and veterinary research. *Comparative Immunology, Microbiology and Infectious Diseases, 59*, 57-62. http://doi.org/ 10.1016/j.cimid.2018.09.008

Liu, C., Chu, D., Kalantar-Zadeh, K., George, J., Young, H. A., & Liu, G. (2021). Cytokines: from clinical significance to quantification. *Advanced Science, 8*(15), 2004433.

Liu, T., Gatto, N. M., Chen, Z., Qiu, H., Lee, G., Duerksen-Hughes, P., Fraser, G., & Wang, C. (2020). Vegetarian diets, circulating miRNA expression and healthspan in subjects living in the Blue Zone. *Precision Clinical Medicine, 3(*4), 245–259. https://doi.org/10.1093/PCMEDI/PBAA037

Lodin, K., Lekander, M., Syk, J., Alving, K., & Andreasson, A. (2017). Associations between self-rated health, sickness behaviour and inflammatory markers in primary care patients with allergic asthma: a longitudinal study. *NPJ Primary Care Respiratory Medicine*, *27*(1), 67–6. https://doi.org/10.1038/s41533-017-0068-0

Long, D., Bonsel, G. J., Lubetkin, E. I., Janssen, M. F., & Haagsma, J. A. (2022). Anxiety, depression, and social connectedness among the general population of eight countries during the COVID-19 pandemic. *Archives of Public Health = Archives Belges de Santé Publique, 80*(1), 237–237. https://doi.org/10.1186/s13690-022-00990-4

Lovibond, S. H., & Lovibond, P. F. (1993). *Manual for the Depression, Anxiety, Stress Scales (DASS).* Psychology Foundation Monograph, University of New South Wales.

Luca M., Luca A. (2019) Oxidative stress-related endothelial damage in vascular depression and vascular cognitive impairment: beneficial effects of aerobic physical exercise. Oxid Med Cell Longev 2019:8067045. https://doi.org/10.1155/2019/8067045

Merlo, A., Hendriksen, P. A., Severeijns, N. R., Garssen, J., Bruce, G., & Verster, J. C. (2021). Alcohol consumption patterns during COVID-19 lockdown and their relationship with perceived immune fitness and reported COVID-19 symptoms. *Healthcare (Basel), 9*(8), 1039–. https://doi.org/10.3390/healthcare9081039

Mariani, N., Cattane, N., Pariante, C., & Cattaneo, A. (2021). Gene expression studies in depression development and treatment: An overview of the underlying molecular mechanisms and biological processes to identify biomarkers. *Translational Psychiatry, 11*(1), 1-23. https://doi.org/10.1038/s41398-021-01469-6

Marsland, A. L., Bachen, E. A., Cohen, S., Rabin, B., & Manuck, S. B. (2002). Stress, immune reactivity and susceptibility to infectious disease. *Physiology & Behavior, 77*(4-5), 711-716. https://doi.org/10.1016/S0031-9384(02)00923-X

Martin, A. R., Gignoux, C. R., Walters, R. K., Wojcik, G. L., Neale, B. M., Gravel, S., Daly, M. J., Bustamante, C. D., & Kenny, E. E. (2020). Human demographic history impacts genetic risk prediction across diverse populations. *American Journal of Human Genetics*, *107*(4), 788–789. https://doi.org/10.1016/j.ajhg.2020.08.020

Marsland, A. L., Walsh, C., Lockwood, K., & John-Henderson, N. A. (2017). The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis. *Brain, Behavior, and Immunity, 64,* 208–219. https://doi.org/10.1016/j.bbi.2017.01.011

Mazza, M. G., De Lorenzo, R., Conte, C., Poletti, S., Vai, B., Bollettini, I., Melloni, E. M. T., Furlan, R., Ciceri, F., Rovere-Querini, P., & Benedetti, F. (2020). Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain, Behavior, and Immunity, 89*, 594–600. https://doi.org/10.1016/j.bbi.2020.07.037

McEwen, B. S. (2017). Neurobiological and systemic effects of chronic stress. *Chronic Stress, 1*, 2470547017692328. https://doi.org/10.1177/2470547017692328

McInnes, I. B., & Gravallese, E. M. (2021). Immune-mediated inflammatory disease therapeutics: past, Present and future. *Nature Reviews. Immunology, 21*(10), 680–686. https://doi.org/10.1038/s41577-021-00603-1

Melaku, Y. A., Gill, T. K., Appleton, S. L., Hill, C., Boyd, M. A., & Adams, R. J. (2019). Sociodemographic, lifestyle and metabolic predictors of all-cause mortality in a cohort of community-dwelling population: An 18-year follow-up of the North West Adelaide Health Study. *BMJ open, 9*(8), e030079. https://doi:10.1136/bmjopen-2019-030079

Medvedev, O. N., Norden, P. A., Krägeloh, C. U., & Siegert, R. J. (2018). Investigating unique contributions of dispositional mindfulness facets to depression, anxiety, and stress in general and student populations. *Mindfulness, 9*(6), 1757–1767. https://doi.org/10.1007/s12671-018-0917-0

Medvedev, O. N., Krägeloh, C. U., Titkova, E. A., & Siegert, R. J. (2020). Rasch analysis and ordinal-to-interval conversion tables for the Depression, Anxiety and Stress Scale. *Journal of Health Psychology, 25*(10-11), 1374-1383. https://doi.org/10.1177/1359105318755261

Milaneschi, Y., Kappelmann, N., Ye, Z., Lamers, F., Moser, S., Jones, P. B., Burgess, S., Penninx, B. W. J. ., & Khandaker, G. M. (2021). Association of inflammation with

depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts. *Molecular Psychiatry, 26*(12), 7393–7402. https://doi.org/10.1038/s41380-021-01188-w

Miller, & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews. Immunology, 16*(1), 22–34. https://doi.org/10.1038/nri.2015.5

Momen, N. C., Plana-Ripoll, O., Agerbo, E., Benros, M. E., Børglum, A. D., Christensen, M. K., ... McGrath, J. J. (2020). Association between mental disorders and subsequent medical conditions. *New England Journal of Medicine, 382*(18), 1721–1731. https://doi.org/10.1056/NEJMoa1915784.

Morey, J., Boggero, I., Scott, A., & Segerstrom, S. (2015). Current directions in stress and human immune function. *Current Opinion in Psychology*, *5*, 13–17. https://doi.org/10.1016/j.copsyc.2015.03.007

Namli, M. N., Gokcay, H., Tas, B., Balcioglu, Y. H., Sagaltici, E., & Belli, H. (2022). Association of clinical features and systemic immune-inflammation index with psychological distress in acne vulgaris. *Dusunen Adam*, *35*(3), 174-180. http://doi.org/10.14744/DAJPNS.2022.00190

Nédélec, Y., Sanz, J., Baharian, G., Szpiech, Z. A., Pacis, A., Dumaine, A., Grenier, J.-C., Freiman, A., Sams, A. J., Hebert, S., Pagé Sabourin, A., Luca, F., Blekhman, R., Hernandez, R. D., Pique-Regi, R., Tung, J., Yotova, V., & Barreiro, L. B. (2016). Genetic ancestry and natural selection drive population differences in immune responses to pathogens. *Cell, 167*(3), 657–669.e21. https://doi.org/10.1016/j.cell.2016.09.025

Netea, M. G., Domínguez-Anés, J., Barreiro, L. B., Chavakis, T., Divangahi, M., Fuchs, E., Joosten, L. A. B., van der Meer, J. W. M., Mhlanga, M. M., Mulder, W. J. M., Riksen,

N. P., Schlitzer, A., Schultze, J. L., Stabell Benn, C., Sun, J. C., Xavier, R. J., & Latz, E. (2020). Defining trained immunity and its role in health and disease. *Nature Reviews. Immunology, 20*(6), 375–388. https://doi.org/10.1038/s41577-020-0285-6

Nesari, T., Kadam, S., Vyas, M., Huddar, V. G., Prajapati, P. K., Rajagopala, M., More, A., Rajagopala, S. K., Bhatted, S. K., Yadav, R. K., Mahanta, V., Mandal, S. K., Mahto, R. R., Kajaria, D., Sherkhane, R., Bavalatti, N., Kundal, P., Dharmarajan, P., Bhojani, M., … Tripathi, R. (2022). AYURAKSHA, a prophylactic ayurvedic immunity boosting kit reducing positivity percentage of IgG COVID-19 among frontline Indian Delhi police personnel: A non-randomized controlled intervention trial. *Frontiers in Public Health, 10*, 920126–920126. https://doi.org/10.3389/fpubh.2022.920126

Nicoletti, I., Migliorati, G., Pagliacci, M. C., Grignani, F., & Riccardi, C. (1991). A rapid and simple method for measuring thymocyte apoptosis by propidium iodide staining and flow cytometry. *Journal of Immunological Methods, 139*(2), 271-279. https://doi.org/10.1016/0022-1759(91)90198-O

O'Connor, D. B., Thayer, J. F., & Vedhara, K. (2021). Stress and health: A review of psychobiological processes. *Annual Review of Psychology, 72,* 663-688. https://doi.org/10.1146/annurev-psych-062520-122331

O'Toole, M. S., Bovbjerg, D. H., Renna, M. E., Lekander, M., Mennin, D. S., & Zachariae, R. (2018). Effects of psychological interventions on systemic levels of inflammatory biomarkers in humans: A systematic review and meta-analysis. *Brain, Behavior, and Immunity, 74*, 68–78. https://doi.org/10.1016/j.bbi.2018.04.005

Otto-Meyer, S., Lumibao, J., Kim, E., Ladomersky, E., Zhai, L., Lauing, K. L., Scholtens, D. M., Penedo, F., Amidei, C., Lukas, R. V., & Wainwright, D. A. (2019). The interplay among psychological distress, the immune system, and brain tumor patient outcomes.

Current Opinion in Behavioral Sciences, 28, 44–50. https://doi.org/10.1016/j.cobeha.2019.01.009

Osman, A., Wong, J. L., Bagge, C. L., Freedenthal, S., Gutierrez, P. M., & Lozano, G. (2012). The depression anxiety stress Scales—21 (DASS-21): further examination of dimensions, scale reliability, and correlates. *Journal of Clinical Psychology*, *68*(12), 1322–1338. https://doi.org/10.1002/jclp.21908

Oswald, A. J., & Wu, S. (2010). Objective confirmation of subjective measures of human well-being: Evidence from the U.S.A. *Science*, *327*(5965), 576–579. https://doi .org/10.1126/science.1180606

Pai, A., Suris, A. M., & North, C. S. (2017). Posttraumatic stress disorder in the DSM-5: Controversy, change, and conceptual considerations. *Behavioral Sciences, 7*(1), 7. https://doi.org/10.3390/bs7010007

Patriquin, M. A., & Mathew, S. J. (2017). The neurobiological mechanisms of generalized anxiety disorder and chronic stress. *Chronic Stress, 1*, 2470547017703993.

Park, J., & Moghaddam, B. (2017). Impact of anxiety on prefrontal cortex encoding of cognitive flexibility. *Neuroscience, 345*, 193-202. https://doi.org/10.1016/j.neuroscience.2016.06.013

Plana-Ripoll, O., Pedersen, C. B., Holtz, Y., Benros, M. E., Dalsgaard, S., De Jonge, P., ... & McGrath, J. J. (2019). Exploring comorbidity within mental disorders among a Danish national population. *JAMA Psychiatry, 76*(3), 259-270. https://doi.org/ 10.1001/jamapsychiatry.2018.3658

Pluess, M., Conrad, A., & Wilhelm, F. H. (2009). Muscle tension in generalized anxiety disorder: a critical review of the literature. *Journal of Anxiety Disorders, 23(*1), 1-11. https://doi.org/10.1016/j.janxdis.2008.03.016

Podsakoff, P. M., MacKenzie, S. B., & Podsakoff, N. P. (2012). Sources of method bias in social science research and recommendations on how to control it. *Annual Review of Psychology,63*(1), 539-569. https://doi.org/10.1146/annurev-psych-120710-100452

Pompili, M., Innamorati, M., Sampogna, G., Albert, U., Carmassi, C., Carrà, G., ... & Fiorillo, A. (2022). The impact of Covid-19 on unemployment across Italy: Consequences for those affected by psychiatric conditions. *Journal of Affective Disorders, 296*, 59-66. https://doi.org/10.1016/j.jad.2021.09.035

Quintana-Murci, L., & Barreiro, L. B. (2010). From evolutionary genetics to human immunology: how selection shapes host defence genes. *Nature Reviews. Genetics, 11*(1), 17–30. https://doi.org/10.1038/nrg2698

Raison, C. L., Rutherford, R. E., Woolwine, B. J., Shuo, C., Schettler, P., Drake, D. F., ... & Miller, A. H. (2013). A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry, 70(1),* 31-41. https://doi.org/10.1001/2013.jamapsychiatry.4

Renna, M., O'Toole, M. S., Spaeth, P. E., Lekander, M., & Mennin, D. S. (2018). The association between anxiety, traumatic stress, and obsessive–compulsive disorders and chronic inflammation: A systematic review and meta-analysis. *Depression and Anxiety, 35(*11), 1081–1094. https://doi.org/10.1002/da.22790

Roemer, A., Sutton, A., Grimm, C., & Medvedev, O. N. (2021). Differential contribution of the five facets of mindfulness to well-being and psychological distress. *Mindfulness, 12*(3), 693–700. https://doi.org/10.1007/s12671-020-01535-y

Rois, R., Ray, M., Rahman, A., & Roy, S. K. (2021). Prevalence and predicting factors of perceived stress among Bangladeshi university students using machine learning

algorithms. *Journal of Health, Population and Nutrition, 40*(1), 50–50. https://doi.org/10.1186/s41043-021-00276-5

Rogers, K., & Kelloway, E. K. (1997). Violence at work: Personal and organizational outcomes. *Journal of Occupational Health Psychology*, *2*(1), 63–71. https://doi.org/10.1037/1076-8998.2.1.63

Romano, M., Roaro, A., Re, F., Osborne, L. A., Truzoli, R., & Reed, P. (2017). Problematic internet users' skin conductance and anxiety increase after exposure to the internet. *Addictive Behaviors*, *75*, 70–74. https://doi.org/10.1016/j.addbeh.2017.07.003

Schakel, L., Veldhuijzen, D. S., Crompvoets, P. I., Bosch, J. A., Cohen, S., van Middendorp, H., ... & Evers, A. W. (2019). Effectiveness of stress-reducing interventions on the response to challenges to the immune system: a meta-analytic review. *Psychotherapy and Psychosomatics*, *88*(5), 274-286.

Schnittker, J., & Bacak, V. (2014). The increasing predictive validity of self-rated health. *PloS One*, *9*(1), e84933–e84933. https://doi.org/10.1371/journal.pone.008493

Schnurr, P. P., Green, B. L., & Kaltman, S. (2007). Trauma exposure and physical health. In M. J. Friedman, T. M. Keane, & P. A. Resick (Eds.), *Handbook of PTSD: Science and practice* (pp. 406–424). New York, NY: Guilford Press.

Scott, K. M., Lim, C., Al-Hamzawi, A., Alonso, J., Bruffaerts, R., Caldas-de-Almeida, J. M., ... & Kessler, R. C. (2016). Association of mental disorders with subsequent chronic physical conditions: World mental health surveys from 17 countries. *JAMA Psychiatry, 73*(2), 150-158. http://doi.org/ 10.1001/jamapsychiatry.2015.2688

Sirugo, G., Williams, S. M., & Tishkoff, S. A. (2019). The missing diversity in human genetic studies. *Cell, 177*(4), 1080–1080. https://doi.org/10.1016/j.cell.2019.04.032

Sinclair, S. J., Siefert, C. J., Slavin-Mulford, J. M., Stein, M. B., Renna, M., & Blais, M. A. (2012). Psychometric evaluation and normative data for the depression, anxiety, and

stress scales-21 (DASS-21) in a nonclinical sample of US adults. *Evaluation & the Health Professions, 35*(3), 259–279. https://doi.org/10.1177/0163278711424282

Shattuck, E. C., & Muehlenbein, M. P. (2015). Human sickness behavior: Ultimate and proximate explanations. *American Journal of Physical Anthropology, 157*(1), 1–18. https://doi.org/10.1002/ajpa.22698

Song, H., Fang, F., Tomasson, G., Arnberg, F. K., Mataix-Cols, D., de la Cruz, L. F., ... & Valdimarsdóttir, U. A. (2018). Association of stress-related disorders with subsequent autoimmune disease. *JAMA*, *319*(23), 2388-2400. https://doi.org/10.1001/jama.2018.7028

Spence, J., Helmreich, R., & Pred, R. (1987). Impatience versus achievement strivings in the Type A Pattern: Differential effects on students' health and academic achievement. *Journal of Applied Psychology*, *72*(4), 522–528. https://doi.org/10.1037/0021-9010.72.4.522

Spinhoven, P., van Hemert, A. M., & Penninx, B. W. (2018). Repetitive negative thinking as a predictor of depression and anxiety: A longitudinal cohort study. *Journal of Affective Disorders, 241*, 216–225. https://doi.org/10.1016/j.jad.2018.08.037

Suardi, C., Cazzaniga, E., Graci, S., Dongo, D., & Palestini, P. (2021). Link between viral infections, immune System, inflammation and diet. *International Journal of Environmental Research and Public Health, 18*(5), 2455–. https://doi.org/10.3390/ijerph18052455

Sun, C., Ren, Y., & Zhang, W. (2023). Association between skin disease and anxiety: a logistic analysis and prediction. *Annals of Translational Medicine, 11(*2). https://dx.doi.org/10.21037/atm-22-6511

Tayab, M. A., Islam, M. N., Chowdhury, K. A. A., & Tasnim, F. M. (2022). Targeting neuroinflammation by polyphenols: A promising therapeutic approach against

inflammation-associated depression. *Biomedicine & Pharmacotherapy, 147*, 112668. https://doi.org/10.1016/j.biopha.2022.112668

Tarantino, V., Tasca, I., Giannetto, N., Mangano, G. R., Turriziani, P., & Oliveri, M. (2021). Impact of Perceived Stress and Immune Status on Decision-Making Abilities during COVID-19 Pandemic Lockdown. *Behavioral Sciences*, *11*(12), 167–. https://doi.org/10.3390/bs11120167

Taylor, M. M., & Snyder, H. R. (2021). Repetitive negative thinking shared across rumination and worry predicts symptoms of depression and anxiety. *Journal of Psychopathology and Behavioral Assessment, 43*, 904–915. https://doi.org/10.1007/s10862-021-09898-9

Taylor, S., Zvolensky, M. J., Cox, B. J., Deacon, B., Heimberg, R. G., Ledley, D. R., Abramowitz, J. S., Holaway, R. M., Sandin, B., Stewart, S. H., Coles, M., Eng, W., Daly, E. S., Arrindell, W. A., Bouvard, M., & Cardenas, S. J. (2007). Robust dimensions of anxiety sensitivity: Development and initial validation of the Anxiety Sensitivity Index-3. *Psychological Assessment, 19*(2), 176–188. https://doi.org/10.1037/1040-3590.19.2.176

Thom, R. P., Keary, C. J., Palumbo, M. L., Ravichandran, C. T., Mullett, J. E., Hazen, E. P., ... & McDougle, C. J. (2019). Beyond the brain: a multi-system inflammatory subtype of autism spectrum disorder. *Psychopharmacology, 236,* 3045-3061. https://doi.org/10.1007/s00213-019-05280-6

Tonidandel, S., & LeBreton, J. M. (2011). Relative importance analysis: A useful supplement to regression analysis. *Journal of Business and Psychology, 26*(1), 1–9. https://doi.org/10.1007/s10869-010-9204-3

Torres, J., Petralia, F., Sato, T., Wang, P., Telesco, S. E., Strauss, R., ... & Colombel, J. F. (2020). Serum biomarkers identify patients who will develop inflammatory bowel

diseases up to 5 years before diagnosis. *Gastroenterology, 159*(1), 96-104. https://doi.org/10.1053/j.gastro.2020.03.007

Turner, A. I., Smyth, N., Hall, S. J., Torres, S. J., Hussein, M., Jayasinghe, S. U., ... & Clow, A. J. (2020). Psychological stress reactivity and future health and disease outcomes: A systematic review of prospective evidence. *Psychoneuroendocrinology, 114*, 104599. https://doi.org/10.1016/j.psyneuen.2020.104599

Van Iddekinge, C. H. & Ployhart, R. E. (2008). Developments in the criterion-related validation of selection procedures: A critical review and recommendations for practice. *Personnel Psychology, 61*(4), 871–925. https://doi.org/10.1111/j.1744-6570.2008.00133.x

Virtanen, M., Shipley, M. J., Batty, G. D., Hamer, M., Allan, C. L., Lowe, G. D., ... & Kivimäki, M. (2015). Interleukin-6 as a predictor of symptom resolution in psychological distress: a cohort study. *Psychological Medicine, 45*(10), 2137-2144. https://doi.org/10.1017/S0033291715000070

Verster, J. C., Kraneveld, A. D., & Garssen, J. (2022). The assessment of immune fitness. *Journal of Clinical Medicine*, *12*(1), 22–. https://doi.org/10.3390/jcm12010022

Welcome MO (2020) Cellular mechanisms and molecular signaling pathways in stress-induced anxiety, depression, and blood–brain barrier inflammation and leakage. *Inflammopharmacology 28*(3):643–665 https://doi.org/10.1007/s10787-020-00712-8

West, S. G., Finch, J. F., & Curran, P. J. (1995). Structural equation models with nonnormal variables: Problems and remedies. In R. H. Hoyle (Ed.), *Structural equation modeling: Concepts, issues, and applications* (pp. 56–75). Sage Publications, Inc.

Wilod Versprille, L. J., van de Loo, A. J., Mackus, M., Arnoldy, L., Sulzer, T. A., Vermeulen, S. A., ... & Verster, J. C. (2019). Development and validation of the

immune status questionnaire (ISQ). *International Journal of Environmental Research and Public Health*, *16*(23), 4743. https://doi.org/10.3390/ijerph16234743

Winer, E. S., & Salem, T. (2016). Reward devaluation: Dot-probe meta-analytic evidence of avoidance of positive information in depressed persons. *Psychological Bulletin*, *142*(1), 18–78. https://doi.org/10.1037/bul0000022

Zamani, M., Alizadeh-Tabari, S., & Zamani, V. (2019). Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*, *50*(2), 132–143. https://doi.org/10.1111/apt.15325

Zuccarella-Hackl, C., Princip, M., Auschra, B., Meister-Langraf, R. E., Barth, J., & von Känel, R. (2023). Association of positive psychological well-being with circulating inflammatory markers: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *150*, 105186–105186. https://doi.org/10.1016/j.neubiorev.2023.105186

Zou, W., Feng, R., & Yang, Y. (2018). Changes in the serum levels of inflammatory cytokines in antidepressant drug-naïve patients with major depression. *PloS one*, *13*(6), e0197267. https://doi.org/10.1371/journal.pone.0197267

Zhou, X., Menche, J., Barabási, A.-L., & Sharma, A. (2014). Human symptoms-disease network. *Nature Communications*, *5*(1), 4212–4212. https://doi.org/10.1038/ncomms5212

Appendices

Appendix A – Publications Co-authored from this work

Journal of Affective Disorders Reports 15 (2024) 100699

Contents lists ScienceDir

Journal of Affective Disorders Reports

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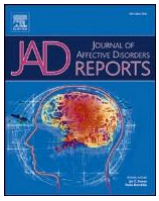

Research Paper

Unique contributions of anxiety, stress and depression to immunity: A cross-cultural investigation

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ARTICLEINFO

Keywords: While immunity and psychological distress are strongly associated, studies seldom consider how different types Anxiety of distress relate to immune functioning. The literature tends to emphasis the impact of stress on immunity. The Stress present cross-sectional study estimated the unique contributions of depression, anxiety, and stress on immune

Depression Immunity Stress-disease model

ABSTRACT

function in culturally diverse samples of adults from Italy, New Zealand and India. Participants were Italian (1061), New Zealand (n = 1037), and Indian (n = 384) volunteers. Stepwise multiple linear regression and n =

Dominance analysis dominance analysis were used to analyse differences in immunity uniquely explained by anxiety, depression, and stress. While samples from the three countries differed significantly, anxiety consistently explained the greatest proportion of differences in immunity. After accounting for the effect of anxiety, stress and depression explained only negligible variation in immune functioning. This association of anxiety with immune functioning was consistent across three different countries and this unique impact was further confirmed by the results of dominance analysis. These findings suggest a clear link between anxiety and immunity, which advances the prevailing stress-disease model and foster further experimental and longitudinal research into the impact of anxiety on immunity.

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Introduction

The relationship between affective conditions and immune dysfunction has garnered significant attention in recent studies, especially considering the adverse health outcomes resulting from immune system disruptions due to stress (Andreasson et al., 2018; Momen et al., 2020; Lasselin, 2021; Seiler et al., 2020). While the general impact of negative affect on immune imbalances is understood, there remains a paucity of research focusing on specific negative affect facets, such as depression and anxiety, and their unique roles on immune functioning.

Subjective reports of infectious symptoms, such as fever and cough, serve as pivotal indices in immune functioning and play a crucial role in the preliminary diagnosis of infections like flu or COVID-19 (Alghamdi et al., 2021; Libet, 2004). These patient-centred reports, though cost-effective, sometimes yield inconsistent results when mapped with inflammatory biomarkers, stressing the complexity of the immune system and the challenges of having clear clinical thresholds for these biomarkers (O'Connor et al., 2021; Lodin et al., 2017). Depression, anxiety, and stress, while often coexisting, manifest distinct patterns and impacts on immune function (Barlow et al., 2014; Eysenck and Fajkowska, 2018; Mariani et al., 2021; Momen et al., 2020). While depression's association with immune deregulation is well-documented, the nuances of anxiety's relationship with immunity require more comprehensive research (Dantzer et al., 2008; Culpepper, 2009; Renna et al., 2018). The comorbidity of depression, anxiety, and stress is evident, with shared symptoms like repetitive negative thinking. However, their unique emotional and cognitive domains highlight the need to understand them as separate entities (Spinhoven et al., 2018; Eysenck and Fajkowska, 2018). Various models, such as Clark and Watson's tripartite model, have sought to explain their interrelationships, emphasizing their distinct conditions and the importance of analyzing their individual impacts on immune functioning (Clark and Watson, 1991; Lasselin, 2021).

Given the variability of affective responses across populations and the cultural nuances in expressing negative affect, this study undertakes a comparison among Italy, India, and New Zealand (NZ), leveraging their diverse cultural backgrounds to

provide richer insights. In response to the existing literature, our research seeks to delineate the unique contributions of depression, anxiety, and stress to immune status by examining a cross-country non-clinical sample from these three countries.

Method

Participants

The total sample (n = 2482) was composed of Italian university students and general population, NZ general population and Indian university students above the age of 18. The Italian sample was composed of 97.64 % of people who identified as European, Asiatic (0.26 %), African (0.56 %), American (0.56 %), with the remainder (0.94 %) made up of other ethnicities not specified. The NZ sample was composed of NZ European (64.6 %), Maori (14.8), Pacific nations (3.9 ¯ %), Asian (12.6 %) and (4.1 %) of other ethnicities not specified. All India student participants identified as Indian.

Procedure

The study was approved by the ALPSS Divisional Human Research Ethics Committee of the University of Waikato (FS2021−58), New Zealand, which is following the internationally recognised ethical standards consistent with APA 7 edition. Written informed consent was obtained from all participants prior to completing the questionnaire. Participation was anonymous, and participants gave their consent after reading information about the study. Data collection took place through an online survey and no time limit was imposed. Participants were recruited by a combination of techniques. The Italian students were recruited in October 2022 through a convenient sample technique. Further participants were recruited through outreach by snowballing techniques. All Italian participants accessed the survey through the university based Qualtrics website. Dynata distributed the NZ survey online through their network in January-February 2022, and participants obtained compensation up to the value of $5 for completing the form. Further NZ participants were recruited through outreach by snowballing techniques. The Indian students were recruited in March-May 2022, through a convenient sample technique. The link of the study was shared with teachers in different universities and shared with associated classes. Moreover, the link of the study was also shared with different students' group. No compensation was provided to the Italian or

Indian participants for taking part in the study because these data collection methods did not involve monetary compensation, unlike Dynata in New Zealand. To ensure the reliability and integrity of our data, we implemented specific quality control measures. Although participants were not confined to a strict time limit for survey completion, we recognized the potential risk of hastily filled-out or random responses. Using the Qualtrics software, we estimated the expected completion time for our survey to be between 10 and 30 min. Based on this estimation, we made the decision to exclude any data from participants who completed the survey in less than 10 min. This approach was adopted to filter out potential responses from participants who might have skimmed through questions or selected options without genuine contemplation, thereby ensuring the validity of the collected data.

Measures

Depression, anxiety and stress scales (DASS-21)

The DASS-21 is an abbreviated 21-item version of the original self- report measure that captures perceptions of emotions over the past week with strong reliability (Lovibond and Lovibond, 1993). It consists of three subscales: depression, anxiety, and stress, with reliability indices ranging from 0.83 to 0.94 across scales and countries (Lightburn et al., 2023). In our study, the scores from these subscales were used as continuous variables.

Immune status questionnaire (ISQ)

The ISQ is a seven-item self-report tool that gauges the frequency of infectious symptoms experienced over the past twelve months and overall health perceptions (Wilod Versprille et al., 2019). Its reliability metrics in our study were between 0.70 to 0.76 across countries, showcasing its consistent research reliability.

MacArthur scale of subjective social status (SSS)

The SSS is a self-assessment measure where participants indicate their perceived social standing within their community on a 10-point scale (Adler et al., 1994). It offers insights into socio-economic status nuances and has been shown to correlate well with objective measures in industrial cultures (Oswald and Wu, 2010).

Data analyses

Data analyses were undertaken using IBM SPSS Statistics (Version 27). The required sample size was estimated using G*Power software 3.1 (Faul et al., 2009) and indicated that with the maximum number of predictors limited to 10 to detect a small

effect size (0.01) under the α=0.05 with a certainty of 95 % (1-β=0.95), the required sample size would be ≥254 participants. The dataset exceeded this figure, reflecting strong statistical power. During data preparation, we noted that less than 4 % of our dataset values were missing. Despite its low rate, we carefully evaluated methods for handling missing data, including multiple imputations, mean imputation, and model-based methods. Ultimately, we chose to exclude missing values for several reasons: the missingness was minimal and unlikely to affect our analysis's power or generalizability given our sample's size and diversity; our preliminary checks indicated the data was missing completely at random (MCAR), ensuring no systematic bias; and this direct exclusion approach provided simplicity, transparency, and ease of interpretation or replication by peers. This approach underpins the integrity and clarity of our results.

The data met the assumptions for multiple linear regression. with variables being normally distributed and with skewness and kurtosis falling within the acceptable range between +2 and – 2 (West et al., 1995). There was no multicollinearity among predictor variables, according to the criterion of Variance Inflating Factors (VIF) below 5 (Roemer et al., 2021; Podsakoff et al., 2021). For linearity, we visually inspected scatter plots of the observed versus predicted values. Additionally, we used the Partial Regression Plots for individual predictors to ensure that the relationship was linear with the outcome variable. Homoscedasticity, or the assumption of equal variance of the errors, was assessed using the residuals-versus-fits plot. We looked for any evident patterns in these plots; a random distribution of points suggested that the assumption was met. Pearson correlation coefficients were calculated between age, SSS, the ISQ and the subscales of depression, anxiety, and stress.

Stepwise multiple linear regression on the outcome variable the ISQ (immunity), combining forward and backward entry to ensure robustness was used to examine the unique contributions of depression, anxiety, and stress on immune status (Babyak, 2004). Stepwise multiple linear regression extracts and lists the strongest predictor which explains most of the variance first, using mathematical criteria (Roemer et al., 2021).

Demographic variables including sex, age and SSS were controlled for and entered together in the first block. Analysis was undertaken by country, as although socio-demographic differences were controlled for, cross-country variation was to be explored. Following this, depression, anxiety, and stress were entered using combined forward and backward stepwise entry, by country. In this method, the strongest significant predictor that explains the greatest amount of the variance is extracted first based on mathematical criteria. Subsequent predictors, which explain the unique variance not explained by the first predictor, appear in order of their unique predictability and were extracted sequentially, while reiteratively accounting for and deducting the variance of predictors which were already extracted, until no more significant predictors remained (Roemer et al., 2021). The threshold for inclusion was $p < .05$ and for removal was $p \geq .10$. These analyses were conducted individually for the Italian, Indian and NZ samples due to significant differences between samples demographics for the countries.

To determine the unique variance explained by each of the predictors, dominance analysis was conducted (Budescu, 1993). In dominance analysis, all subsets of predictors are examined in relation to the dependent variable and the unique contribution of each predictor is estimated. Dominance analysis reduces potential distortions through multicollinearity and enables direct comparisons of predictors within a model. To conduct dominance analysis in the present study, that included three predictors, seven regression analyses were run using SPSS, containing all possible combinations of predictors. Following these analyses, the ΔR^2 values were averaged and compared to identify the variable with the highest mean incremental contribution to variance explained, using Excel (Tonidandel and LeBreton, 2011). The percentage value of relative importance of predictors is derived by dividing the overall average incremental R^2 by the contribution of average predictors to the model.

Results

Demographic characteristics of the sample are shown in Table 1. When age was viewed by country, the average NZ sample age showed greater variation relative to the more youthful Italian and Indian sample. A chi-square test of independence examined distribution of sex by country, and noted

significant differences in two of the countries, with the Italian and Indian sample being weighted towards significantly more females compared to males ($p < .01$). Descriptive statistics are represented in Table 2, with skewness and kurtosis values being in the acceptable range. The Indian and Italian participants were significantly younger, and their indices of negative affect levels, notably stress, were significantly higher compared to the NZ sample. The NZ sample reported lower perceived SSS and lower average negative affect levels.

Table 3 presents the results of stepwise multiple linear regression predicting immunity in each sample. Within the Italian sample, sociodemographic features accounted for 11 % of the variance, with age showing the strongest impact on immunity. After accounting for the effect of demographics, anxiety was significantly associated with immunity and the strongest affective predictor and accounted for a further 14 % of the variance.

In the Indian sample, sociodemographic characteristics accounted for 3.6 % of the variation with SSS being the only significant predictor. After controlling for demographics anxiety was significantly associated with immunity and the strongest affective predictor and accounted for a further 15 % of the variance.

In the NZ sample, sociodemographic characteristics accounted for 9.3 % of the variation with SSS and age being a significant predictors. After accounting for demographics, anxiety was significantly associated with immunity and the strongest affective predictor and accounted for a further 20 % of the variance.

Table 4 shows the results of the dominance analyses; full results are available by request from the first author. Anxiety had the greatest dominance value in all samples, showing general dominance over the other affect facets and accounting for between 42 % to 50 % of the total variance explained. Stress was the second most important contributor in the NZ and Indian samples, while depression was the second most important second contributor for the Italian sample.

Discussion

This study focused on investigating the unique contributions of depression, anxiety and stress to immune functioning within a large sample drawing participants from Italy, India and NZ. When disentangling the three constructs, anxiety

consistently demonstrated the strongest negative impact associated with immune functioning. After accounting for the effects of anxiety, stress had only negligible association with immunity in the Indian and NZ samples. Depression had a modest impact on the Italian sample, indicating variation between countries. While this study found an association between stress and immunity as proposed by the stress immune model (O'Connor et al., 2021; McEwen, 2017; Morey et al., 2015), the association was notably stronger for anxiety and immunity. The present findings indicate that associations between stress, depression and immunity in previous studies may have been partially explained by unmeasured anxiety, which tends to be strongly associated and frequently comorbid with depression and stress (Patriquin and Mathew, 2017; Renna et al., 2018). This is irrespective of whether negative affect types are differentiated between, or whether disorders are controlled for (Barlow et al., 2014; Budescu, 1993). The results suggest that when the frequently comorbid and co-varying constructs of stress and depression are controlled for, anxiety is shown to have the greatest impact on immunity. As such, an anxiety-disease model, as outlined in Fig. 1, would appear to outline the relationship more accurately between types of negative affect, immunity, and adverse health outcomes, which is supported by this study. While relatively scant attention is provided to the association of anxiety and immunity, these results suggest that anxiety is the strongest affective condition contributing to differences in immune deregulation across different countries (Culpepper, 2009; Renna et al., 2018). There are similarities in this study's findings to those of a recent cross-sectional study in Saudi Arabia (Alghamdi et al., 2021). Those reporting mild to moderate anxiety were two to four times more likely to report reduced immune status. Anxiety and immunity also showed the strongest relationship, with a trend for severe anxiety to be associated with poorer immune functioning, in a dose dependent manner (Alghamdi et al., 2021).

The study also found significant associations with stress and immu-

Country	*n*	Sample	Age *M* (*SD*)	% Females
NZ	1037	General Population	49.00 (17.63)	51.0

Italy	1061	University Students & General Population	29.99 (13.85)	78.6
India	384	University Students	23.67 (7.68)	67.0

Table 1
Demographic Characteristics of Participants.

nity (Alghamdi et al., 2021). However, the variance explained by anxiety while estimating contribution of stress was not controlled for. Therefore, the association with stress might be due to shared variance between anxiety and stress. In the current study, we controlled for anxiety and only found weak associations between stress and immune functioning within the Indian and NZ samples. This highlights the importance of using appropriate methodology that allows identification of the unique effects of specific predictors, such as anxiety. The limitation of the Saudi Arabian study is related to using methodology that involved dichotomization of continuous variables, namely immune

Table 2
Means (M), 95 % confidence intervals (CI) of the samples by country and combined, also including skewness and kurtosis data for the total sample.

	Italian (*n* = 1061)		Indian (*n* = 384)		New Zealand (*n* = 1037)		Total sample (*n* = 2482)			
Variable	*M*	Confidence intervals	*M*	Confidence intervals	*M*	Confidence intervals	*M*	Confidence intervals	Skewness	Kurtosis
Age	29.99	[29.16, 30.83]	23.67	[22.84, 24.50]	49.00	[47.92, 50.07]	42.88	[41.87, 43.90]	0.778	− 0.609
SSS	6.56	[6.45, 6.66]	6.52	[6.29, 6.75]	5.60	[5.49, 5.72]	5.83	[5.72, 5.93]	− 0.357	0.040
Immunity	5.86	[5.70, 6.03]	6.41	[6.10, 6.72]	6.92	[6.77, 7.08]	6.80	[6.66, 6.94]	− 0.659	− 0.342
Depression	6.81	[6.51, 7.12]	6.99	[6.45, 7.53]	5.70	[5.36, 6.03]	6.01	[5.72, 6.30]	0.805	− 0.071
Stress	9.12	[8.84, 9.40]	7.36	[6.92, 7.80]	6.01	[5.73, 6.30]	6.34	[6.09, 6.58]	0.478	− 0.275
Anxiety	5.95	[5.66, 6.23]	6.81	[6.31, 7.30]	4.36	[4.09, 4.63]	4.95	[4.70, 5.19]	0.889	0.193

Note. *n* = sample size, *M* = mean.

Table 3
Summary of multiple linear stepwise regression (*n* = 384) and NZ sample (*n* = 1039).

	analyses predicting immunity a		nd the im pact of affective subsc		ıles from	he Italian sample (*n* = 1061)	ian sample
Outcome	Step	Block and Predictors	R_2	R^2 change		Standardized *β*	*p*
Italian sample	Demographics		.106	.106			
		1 Age				.266[.205, 0.321]	< 0.001
		2 SSS				.122[.064, 0.180]	< 0.001
		3 Sex				− 0.080[− 0.138,− 0.022]	.007
	Affective scales	1 Anxiety	.249	.143		− 0.400[− 0.455,− 0.345]	< 0.001
		2 Depression	.257	.011		− 0.162[− 0.243,− 0.083]	< 0.001
Indian sample	Demographics		.036	.036			
		1 Age				.099[− 0.008, 0.206]	.072
		2 SSS				.135[.029, 0.242]	.013
		3 Sex				− 0.048[− 0.156, 0.060]	.382
	Affective scales	1 Anxiety	.186	.151		− 0.405[− 0.507,− 0.303]	< 0.001

		2	Stress	.197	.011	− 0.142[− 0.274,− 0.010]	.036
NZ sample	Demographics			.093	.093		
		1	Sex			− 0.107[− 0.047, − 0.0167]	< 0.001
		2	SSS			.193[.135, 0.251]	< 0.001
		3	Age			.166[.111, 228]	< 0.001
	Affective scales	1	Anxiety	.293	.200	− 0.480[− 0.535,− 0.425]	< 0.001
		2	Stress	.298	.005	− 0.117[− 0.202,− 0.031]	.007

Table 4

Dominance analysis: average R^2, general dominance and rescaled dominance across negative affect facets and countries.

Outcome	Numbers of predictors in the model	Depression	Anxiety	Stress
Italy	1	0.181	0.212	0.172
	2	0.022	0.050	0.016
	3	0.006	0.032	0.003
	General dominance	0.070	0.098	0.064
	Rescaled dominance%	30.09	42.42	27.49
India	1	0.100	0.169	0.132
	2	0.005	0.058	0.023
	3	0.000	0.036	0.003
	General dominance	0.035	0.088	0.053
	Rescaled dominance%	20.00	50.00	30.00
NZ	1	0.156	0.268	0.215
	2	0.003	0.087	0.036
	3	0.000	0.057	0.007
	General dominance	0.053	0.137	0.086
	Rescaled dominance%	19.14	49.76	31.10

dysfunction, which inevitably leads to losing information and consequently, accuracy of estimates. This may have reduced the power of the analysis and contributed to differences compared with our findings (Roemer et al., 2021). However, it is striking that anxiety exhibited the strongest relationship to immunity in both studies.

Anxiety was the strongest factor associated with immunity across countries. This persisted despite discrepancies in culture, age and other demographic factors, and this consistency is salient. Comparisons of types of affective relationships do show some differences between countries (De Vaus et al., 2018; Long et al., 2022). Stress levels were detected in the Indian students and NZ citizens. Depression was found to be the second most important feature for the Italians. Again, despite the

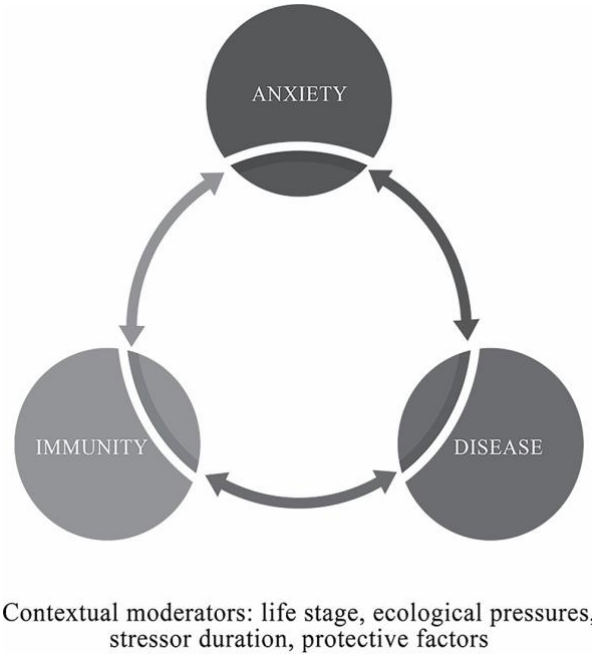

Fig. 1. Anxiety-disease model.

high recent prevalence of depression and anxiety in Italy, the methodology showed a negligible association between immunity and depression (Caldirola et al., 2022; Fioravanti et al., 2022). It is unclear though interesting to speculate to what degree this may be a culturally mediated effect. There are Eastern cultural traditions that increase mind and body awareness, in addition to other features (De Vaus et al., 2018; Khambaty and Parikh, 2022; Long et al., 2022). Alternatively, it may simply reflect recent geopolitical events and conditions, which may have contributed to a relative increase in mood languor within Italy (Caldirola et al., 2022; Fioravanti et al., 2022).

The regression results indicated that after accounting for the effect of anxiety, stress and depression did not appear to have a strong association with immunity. This is despite the literature emphasising the close association between depression, stress, immunity and sickness (Andreasson et al., 2018; Binder and Nemeroff, 2010). Since depression shares common variance with both anxiety and stress, studies on stress and depression may not be able to control for effects of anxiety and stress when measuring solely depression (Medvedev et al., 2018; Roemer et al., 2021; West et al., 1995). It does highlight the advantages of using appropriate methodology including stepwise multiple linear regression and dominance analysis when examining unique contributions of psychological symptoms on immunity, since the effects of stress and depression are forced away when analysed simultaneously (Babyak, 2004; Budescu, 1993).

The lack of association between stress and immune functioning after accounting for the effect of anxiety was salient given the high statistical power of this sample. There are a couple of possible explanations. Firstly, the method of stepwise multiple linear regression deducts the variance of predictors already explained by the model, and as noted, anxiety accounted for most of the variance (Budescu,1993; Roemer et al., 2021). Secondly, acute stress-response hormesis can have some beneficial effects on immunity, which may weaken the broader association of stress and immunity within this study, since the measurement used may not distinguish acute from chronic stress, as is true of many studies considering stress (Aschbacher et al., 2013); Lovibond and Lovibond, 1993). For example, theme parks may induce stress levels through illusions of imminent danger, but the acute stress response from the fear produced may not necessarily lead to illness, as this type of stress is still compatible with positive affect (Aschbacher et al., 2013). Anxiety, with features of incessant worry and the negative appraisals of one's ability to cope with looming potential threats possesses clearer features of negative affect, and is less compatible with mood stability (Spinhoven et al., 2018; Taylor and Snyder, 2021).

Our study emphasizes the intricate relationships between psychological constructs, such as depression, anxiety, and stress, and immune functioning across populations from Italy, India, and New Zealand. Most strikingly, anxiety was identified as having a consistent negative link with immune functioning. On the other hand, depression demonstrates a robust connection with immune deregulation, with some immunological reactions differing from those elicited by stress (Dantzer et al., 2008; Lasselin, 2021; Mariani et al., 2021; Miller and Raison, 2016). Our results supported a modest link between depression and immune functioning in the Italian sample.

Contrastingly, the relationship between stress and immunity in our study was weaker than suggested by the stress-immune model. This deviation from established literature, which often underscores a robust connection between stress and immune response, invites speculation on potential protective biological mechanisms or other moderating biomarkers. Such factors might be influenced by genetic, environmental, or lifestyle differences inherent to the populations studied. In sum, delving deeper into the biological mechanisms, such as hormonal, genetic, and inflammatory pathways, could elucidate our findings and account for the observed inter-country variations.

Strengths, limitations and directions of future research

Naturally, this study has strengths and limitations. The strengths lie in the size of the study, statistical power, cross-country participants which encompasses great cultural diversity and participant heterogeneity, the use of appropriate statistical techniques to undertake preliminary analysis. However, some of the common limitations are related to the cross-sectional nature of the study, which does not permit causal inferences, so the association found across countries cannot be deemed deterministic. Psychological disorders and immune dysfunction may share other commonalities, such as adverse experiences early in life (Dieleman et al., 2015). Also, temporal snapshots lack the ability to detect time related nuances. For example, the impact of negative affect on immunity may vary during time-sensitive windows, which could be further explored through longitudinal analysis, such as the Environmental Risk Longitudinal Twin Study (Baldwin et al., 2018). Considering that psychological symptoms from participants who were members of the general population was generally skewed toward being subclinical, the study may benefit from the inclusion of a broader psychiatric range (Antony et al.,

1998). Further research which encompasses and targets certain features, such as patients in primary medical health care, would augment the study. The study would also benefit from further refinement by examination with other assessments, such as anxiety sensitivity (Lasselin et al., 2016; Taylor et al., 2007).

From biological perspective, it would be interesting to observe whether greater levels of anxiety impacted known immunological responses, in a dose dependent pattern. For example, whether higher anxiety levels correspond to reduced immune responses to deliberate viral exposure challenges could support or falsify these findings. Alternatively, the immune responses of non-clinical participants to standard immunisation can be compared with placebo in randomised controlled trials while accounting for anxiety levels. This research may prove very useful, as the effectiveness of interventions, such as vaccinations, are based on the assumptions of typical immune functioning.

The study results may also be affected by common method bias (Podsakoff et al., 2012). The fact that multiple constructs are measured using common methods (e.g., multiple-item scales presented within the same survey) leads to spurious effects due to the assessment instruments rather than to the constructs being measured. For example, the fact that subjects are asked to report their own perceptions or impressions on two or more constructs in the same survey is likely to produce spurious correlations among the items measuring these constructs owing to response styles, social desirability, and priming effects, which may be independent from the true correlations among the constructs being measured.

In addition, there was no consistency time periods indicated in the measures for participants to consider, with the DASS referring to the past week, the ISQ referring to the past year, and the SSS

referring to the participants' current point in life (Adler et al., 1994; Lovibond and Lovibond, 1993; Wilod Versprille et al., 2019). While common, such discrepancy could be criticised due to recall bias, and variation. However, the DASS subscales were well validated as a trait measures while changes in the SSS are very unlikely withing a short period of time (Antony et al., 1998; Lightburn et al., 2023). The ISQ, while increasingly globally used, including in English, Indian and Italian studies has been validated to the lesser extent (Nesari et al., 2022; Tarantino et al., 2021; Verster et al., 2022).

Given the highly comorbid nature of depression, stress and anxiety, it is not possible to conclude that individual conditions of anxiety, depression and stress in isolation are contributing to immunity, because shared factors between the conditions may drive this association. While the DASS-21 has been employed as a reliable instrument to assess the severity of these conditions, it is inherent to the tool's design to measure domains that have shared variance. Our analyses sought to discern unique contributions of each domain. However, we recognize the challenge posed by their interrelatedness. It's conceivable that shared factors among depression, anxiety, and stress might influence the observed associations with immunity. Thus, while our findings shed light on the differential contributions of these psychological states, the potential for underlying shared factors to drive these associations remains. In the context of our study, it's essential to interpret the results with an understanding of this overlap and the limitations of any single tool, including the DASS-21, in fully isolating the unique effects of intertwined psychological domains. Future research employing a multi- faceted assessment approach, perhaps incorporating multiple tools and methodologies, could provide additional clarity on this matter.

Among the limitations of our study, a significant concern relates to the sampling

strategy employed. While drawing comparisons across countries, we noted marked differences in factors such as age, sex, and negative affect levels between members of the general public and university students. The participants were predominantly youthful with a disproportionate representation of females. This skewness towards younger females could partially explain the elevated rates of negative affect observed, considering the heightened mental unwellness typically associated with this demographic (Medvedev et al., 2018; Spence et al., 1987). Moreover, the student participants tended to score higher on negative affect indices, underscoring the prevalent negative affect challenges faced by females and students (Spence et al., 1987). However, it's essential to highlight that findings specific to university students might not generalize to the broader population, as student cohorts often exhibit unique attributes like enhanced reported parenting and psychological resilience compared to their non-university attending peers (Cvetkovski et al., 2019). Furthermore, we acknowledge the potential for volunteer bias, which may influence our results. Individuals more inclined to participate in such studies might possess particular characteristics or be more motivated by specific factors, potentially skewing our sample. Our recruitment strategies varied across countries, and only participants from New Zealand were compensated for their time. Such variations in recruitment and compensation might have led to differential participation motivations and could introduce biases in the sample composition. The lack of compensation in other regions, compared to New Zealand, might affect the motivation and the demographic mix of the participants, possibly influencing their responses. Future research would benefit from more standardized recruitment strategies and broader, more representative participant

populations to bolster cross-country comparisons.

Conclusions

Studies which have examined the relationship between immunity and affective conditions have greatly emphasised stress and depression. The impact of anxiety on immunity has remained relatively neglected. Within the present study, anxiety consistently explained the greatest proportion (between 14 % and 20 %) of differences, when investigating the unique contributions of affective symptoms on immune status. After accounting for effects of anxiety, other affective symptoms explained only negligible variation in immune function. While preliminary, these cross-country results highlight a relationship between anxiety and immunity, and strongly encourage greater examination of the impact of anxiety on immune functioning, with a view to improving health outcomes.

Statement of Ethics

The study was approved by the ALPSS Divisional Human Research Ethics Committee of the University of Waikato, New Zealand, which is following the internationally recognised ethical standards consistent with APA 7 edition.

Informed Consent

All participants provided their informed consent before participating in the study.

Use of Artificial Intelligence

Artificial intelligence was not used in the creation of this manuscript.

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Data availability

The data are deposited in the OSF and accessible through the following link https://osf.io/k6su3/?view_only=6722b87d0032444 6ae3cb128bc9b197a

CRediT authorship contribution statement

Catherine Breeze: Conceptualization, Formal analysis, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Oleg N. Medvedev:** Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Writing – review & editing. **Matti Cervin:** Conceptualization, Methodology, Writing – review & editing. **Anna Sutton:** Funding acquisition, Project administration, Writing – review & editing. **Barbara Barcaccia:** Data curation, Project administration, Writing – review & editing, Conceptualization. **Alessandro Couyoumdjian:** . **Susanna Pallini:** Conceptualization, Data curation, Project administration, Writing – review & editing. **Moana Billot:** Data curation, Project administration, Writing – review & editing. **Rebecca Chalmers:** Data curation, Project administration, Writing – review & editing. **Naved Iqbal:** Data curation, Project administration, Writing – review & editing. **Vincent Reid:** Conceptualization, Funding acquisition, Project administration, Resources, Writing – review & editing. **Nirbhay N. Singh:** Conceptualization, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest in regards of this manuscript.

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References

Adler, N.E., Boyce, T., Chesney, M.A., Cohen, S., Folkman, S., Kahn, R.L., Syme, S.L., 1994. Socioeconomic status and health: the challenge of the gradient. Am. Psychol. 49 (1), 15–24. https://doi.org/10.1037//0003-066x.49.1.15.

Alghamdi, B.S., Alatawi, Y., Alshehri, F.S., Tayeb, H.O., Tarazi, F.I., 2021. Relationship between public mental health and immune status during the COVID-19 pandemic:
cross-sectional data from Saudi Arabia. Risk Manage. Healthc. Policy 14, 1439–1447. https://doi.org/10.2147/RMHP.S302144.

Andreasson, A., Wicksell, R.K., Lodin, K., Karshikoff, B., Axelsson, J., Lekander, M., 2018. A global measure of sickness behaviour: development of the sickness questionnaire.
J. Health Psychol. 23 (11), 1452–1463. https://doi.org/10.1177/1359105316659917.

Antony, M.M., Bieling, P.J., Cox, B.J., Enns, M.W., Swinson, R.P., 1998. Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. Psychol. Assess. 10 (2), 176–181. https://doi.org/10.1037/1040-3590.10.2.176.

Aschbacher, K., O'Donovan, A., Wolkowitz, O.M., Dhabhar, F.S., Su, Y., Epel, E., 2013. Good stress, bad stress and oxidative stress: insights from anticipatory cortisol reactivity. Psychoneuroendocrinology 38 (9), 1698–1708. https://doi.org/10.1016/ j.psyneuen.2013.02.004.

Babyak, M.A., 2004. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom. Med. 66 (3), 411–421.

Baldwin, J.R., Arseneault, L., Caspi, A., Fisher, H.L., Moffitt, T.E., Odgers, C.L., Pariante, C., Ambler, A., Dove, R., Kepa, A., Matthews, T., Menard, A., Sugden, K., Williams, B., Danese, A., 2018. Childhood victimization and inflammation in young adulthood: a genetically sensitive cohort study. Brain Behav. Immun. 67, 211–217. https://doi.org/10.1016/j.bbi.2017.08.025.

Barlow, Sauer-Zavala, S., Carl, J.R., Bullis, J.R., Ellard, K.K, 2014. The nature, diagnosis, and treatment of neuroticism: back to the future. Clin. Psychol. Sci. 2 (3), 344–365. https://doi.org/10.1177/2167702613505532.

Binder, E., Nemeroff, C., 2010. The CRF system, stress, depression and anxiety: insights from human genetic studies. Mol. Psychiatry 15 (6), 574–588. https://doi.org/ 10.1038/mp.2009.141.

Budescu, D.V., 1993. Dominance analysis: a new approach to the problem of relative importance of predictors in multiple regression. Psychol. Bull. 114 (3), 542–551. https://doi.org/10.1037/0033-2909.114.3.542.

Caldirola, D., Dacco, S., Cuniberti, F., Grassi, M., Alciati, A., Torti, T., Perna, G., 2022. ` First-onset major depression during the COVID-19 pandemic: a predictive machine learning model. J. Affect. Disord. 310, 75–86. https://doi.org/10.1016/j. jad.2022.04.145.

Clark, L.A., Watson, D., 1991. Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. J. Abnorm. Psychol. 100 (3), 316–336. https://doi.org/10.1037/0021-843X.100.3.316.

Culpepper, L., 2009. Generalized anxiety disorder and medical illness. J. Clin. Psychiatry 70 (2), 20–24. https://doi.org/10.4088/JCP.s.7002.04.

Cvetkovski, S., Jorm, A.F., Mackinnon, A.J., 2019. An analysis of the mental health trajectories of university students compared to their community peers using a national longitudinal survey. Stud. Higher Edu. 44 (1), 185–200. https://doi.org/ 10.1080/03075079.2017.1356281.

Dantzer, R., O'connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9 (1), 46–56. https://doi.org/10.1038/nrn2297.

De Vaus, J., Hornsey, M.J., Kuppens, P., Bastian, B., 2018. Exploring the East-West divide in prevalence of affective disorder: a case for cultural differences in coping with negative emotion. Personality Soc. Psychol. Rev. 22 (3), 285–304. https://doi.org/ 10.1177/1088868317736222.

Dieleman, G.C., Huizink, A.C., Tulen, J.H., Utens, E.M., Creemers, H.E., van der Ende, J., Verhulst, F.C., 2015. Alterations in HPA-axis and autonomic nervous system functioning in childhood anxiety disorders point to a chronic stress hypothesis. Psychoneuroendocrinology 51, 135–150. https://doi.org/10.1016/j. psyneuen.2014.09.002.

Eysenck, M.W., Fajkowska, M., 2018. Anxiety and depression: toward overlapping and distinctive features. Cognit. Emotion 32 (7), 1391–1400. https://doi.org/10.1080/ 02699931.2017.1330255.

Faul, F., Erdfelder, E., Buchner, A., Lang, A.-G., 2009. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav. Res. Methods 41, 1149–1160.

Fioravanti, G., Benucci, S.B., Prostamo, A., Banchi, V., Casale, S., 2022. Effects of the COVID-19 pandemic on psychological health in a sample of Italian adults: a three- wave longitudinal study. Psychiatry Res. 315, 114705 https://doi.org/10.1016/j. psychres.2022.114705.

Khambaty, M., Parikh, R.M., 2022. Cultural aspects of anxiety disorders in India. Dialogues Clin. Neurosci. 19 (2), 117–126. https://doi.org/10.31887/ DCNS.2017.19.2/rparikh.

Lasselin, J., 2021. Back to the future of psychoneuroimmunology: studying inflammation-induced sickness behavior. Brain, Behav. Immun.-Health 18 (18), 100379. https://doi.org/10.1016/j.bbih.2021.100379.

Lasselin, J., Elsenbruch, S., Lekander, M., Axelsson, J., Karshikoff, B., Grigoleit, J.-S., Engler, H., Schedlowski, M., Benson, S., 2016. Mood disturbance during experimental endotoxemia: predictors of state anxiety as a psychological component of sickness behavior. Brain Behav. Immun. 57, 30–37. https://doi.org/10.1016/j. bbi.2016.01.003.

Libet, B., 2004. Mind Time the Temporal Factor in Consciousness. Harvard University Press. https://doi.org/10.4159/9780674040168.

Lightburn, S.J., Pratscher, S.D., Bettencourt, B.A., Hartstone, J.M., Medvedev, O.N., 2023. Evaluating depression anxiety and stress assessment before and during the COVID-19 pandemic using generalisability theory. Int. J. Psychol. https://doi.org/ 10.1002/ijop.12907.

Lodin, K., Lekander, M., Syk, J., Alving, K., Andreasson, A., 2017. Associations between self-rated health, sickness behaviour and inflammatory markers in primary care patients with allergic asthma: a longitudinal study. NPJ Prim. Care Respir. Med. 27 (1), 67. https://doi.org/10.1038/s41533-017-0068-0.

Long, D., Bonsel, G.J., Lubetkin, E.I., Janssen, M.F., & Haagsma, J.A. (2022). Anxiety, depression, and social connectedness among the general population of eight countries during the COVID-19 pandemic. *archives of public health = archives belges de sant´e publique,* 80(1), 237–237. https://doi.org/10.1186/s13690-022-00990-4.

Lovibond, S.H., Lovibond, P.F., 1993. Manual For the Depression, Anxiety, Stress Scales (DASS). University of New South Wales. Psychology Foundation Monograph.

Mariani, N., Cattane, N., Pariante, C., Cattaneo, A., 2021. Gene expression studies in depression development and treatment: an overview of the underlying molecular mechanisms and biological processes to identify biomarkers. Trans. Psychiatry 11 (1), 1–23. https://doi.org/10.1038/s41398-021-01469-6.

McEwen, B.S., 2017. Neurobiological and systemic effects of chronic stress. Chronic. Stress 1, 2470547017692328. https://doi.org/10.1177/2470547017692328.

Medvedev, O.N., Norden, P.A., Krageloh, C.U., Siegert, R.J., 2018. Investigating unique ¨ contributions of dispositional mindfulness facets to depression, anxiety, and stress in general and student populations. Mindfulness 9 (6), 1757–1767. https://doi.org/ 10.1007/s12671-018-0917-0.

Miller, Raison, C.L, 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16 (1), 22–34. https:// doi.org/10.1038/nri.2015.5.

Momen, N.C., Plana-Ripoll, O., Agerbo, E., Benros, M.E., Børglum, A.D., Christensen, M. K., McGrath, J.J., 2020. Association between mental disorders and subsequent medical conditions. N Engl. J. Med. 382 (18), 1721–1731. https://doi.org/10.1056/ NEJMoa1915784.

Morey, J., Boggero, I., Scott, A., Segerstrom, S., 2015. Current directions in stress and human immune function. Curr. Opin. Psychol. 5, 13–17. https://doi.org/10.1016/j. copsyc.2015.03.007.

Nesari, T., Kadam, S., Vyas, M., Huddar, V.G., Prajapati, P.K., Rajagopala, M., More, A., Rajagopala, S.K., Bhatted, S.K., Yadav, R.K., Mahanta, V., Mandal, S.K., Mahto, R.R., Kajaria, D., Sherkhane, R., Bavalatti, N., Kundal, P., Dharmarajan, P., Bhojani, M., Tripathi, R., 2022. AYURAKSHA, a prophylactic ayurvedic immunity boosting kit reducing positivity percentage of IgG COVID-19 among frontline Indian Delhi police personnel: a non-randomized controlled intervention trial. Front. Public Health 10, 920126. https://doi.org/10.3389/fpubh.2022.920126.

O'Connor, D.B., Thayer, J.F., Vedhara, K., 2021. Stress and health: a review of psychobiological processes. Annu. Rev. Psychol. 72, 663–688. https://doi.org/ 10.1146/annurev-psych-062520-122331.

Oswald, A.J., Wu, S., 2010. Objective confirmation of subjective measures of human well-being: evidence from the U.S.A. Science 327 (5965), 576–579. https://doi.org/ 10.1126/science.1180606.

Patriquin, M.A., Mathew, S.J., 2017. The neurobiological mechanisms of generalized anxiety disorder and chronic stress. Chronic. Stress 1, 2470547017703993.

Podsakoff, P.M., MacKenzie, S.B., Podsakoff, N.P., 2012. Sources of method bias in social science research and recommendations on how to control it. Annu. Rev. Psychol. 63 (1), 539–569. https://doi.org/10.1146/annurev-psych-120710-100452.

Renna, M., O'Toole, M.S., Spaeth, P.E., Lekander, M., Mennin, D.S., 2018. The association between anxiety, traumatic stress, and obsessive–compulsive disorders and chronic inflammation: a systematic review and meta-analysis. Depress. Anxiety 35 (11), 1081–1094. https://doi.org/10.1002/da.22790.

Roemer, A., Sutton, A., Grimm, C., Medvedev, O.N., 2021. Differential contribution of the five facets of mindfulness to well-being and psychological distress. Mindfulness 12 (3), 693–700. https://doi.org/10.1007/s12671-020-01535-y.

Seiler, A., Fagundes, C.P., Christian, L.M., 2020. The Impact of Everyday Stressors on the Immune System and Health. In: Chouk`er, A. (Ed.), Stress Challenges and Immunity in space: From mechanisms to Monitoring and Preventive Strategies. Springer. https://doi.org/10.1007/978-3-030-16996-1_6.

Spence, J., Helmreich, R., Pred, R., 1987. Impatience versus achievement strivings in the Type A Pattern: differential effects on students' health and academic achievement. J. Appl. Psychol. 72 (4), 522–528. https://doi.org/10.1037/0021-9010.72.4.522.

Spinhoven, P., van Hemert, A.M., Penninx, B.W., 2018. Repetitive negative thinking as a predictor of depression and anxiety: a longitudinal cohort study. J. Affect. Disord. 241, 216–225. https://doi.org/10.1016/j.jad.2018.08.037.

Tarantino, V., Tasca, I., Giannetto, N., Mangano, G.R., Turriziani, P., Oliveri, M., 2021. Impact of perceived stress and immune status on decision-making abilities during COVID-19 pandemic lockdown. Behav. Sci. 11 (12), 167. https://doi.org/10.3390/ bs11120167.

Taylor, M.M., Snyder, H.R., 2021. Repetitive negative thinking shared across rumination and worry predicts symptoms of depression and anxiety. J Psychopathol. Behav. Assess. 43, 904–915. https://doi.org/10.1007/s10862-021-09898-9.

Taylor, S., Zvolensky, M.J., Cox, B.J., Deacon, B., Heimberg, R.G., Ledley, D.R., Abramowitz, J.S., Holaway, R.M., Sandin, B., Stewart, S.H., Coles, M., Eng, W., Daly, E.S., Arrindell, W.A., Bouvard, M., Cardenas, S.J., 2007. Robust dimensions of anxiety sensitivity: development and initial validation of the anxiety sensitivity Index-3. Psychol. Assess. 19 (2), 176–188. https://doi.org/10.1037/1040- 3590.19.2.176.

Tonidandel, S., LeBreton, J.M., 2011. Relative importance analysis: a useful supplement to regression analysis. J. Bus. Psychol. 26 (1), 1–9. https://doi.org/10.1007/s10869- 010-9204-3.

Verster, J.C., Kraneveld, A.D., Garssen, J., 2022. The assessment of immune fitness. J. Clin. Med. 12 (1), 22. https://doi.org/10.3390/jcm12010022. –.

West, S.G., Finch, J.F., Curran, P.J., 1995. Structural equation models with nonnormal variables: problems and remedies. In: Hoyle, R.H. (Ed.), Structural Equation modeling: Concepts, issues, and Applications. Sage Publications, Inc, pp. 56–75. Wilod Versprille, L.J., van de Loo, A.J., Mackus, M., Arnoldy, L., Sulzer, T.A., Vermeulen, S.A., Verster, J.C, 2019. Development and validation of the immune status questionnaire (ISQ). Int. J. Environ. Res. Public Health 16 (23), 4743. https:// doi.org/10.3390/ijerph16234743.

Appendix B General recruitment poster for participants (general population)

Picture by Pixabay: https://pixabay.com/de/vectors/rahmen-bl%C3%A4tter-aquarell-hintergrund-4822807/

Appendix C Recruitment email – general participants

Tēnā koe [name of recipient],

My name is Oleg Medvedev and I'm a Senior Lecturer at the University of Waikato.

You recently indicated interest in participating in my research.

You are invited to take part in the project, which will explore protective and risk factors of immune function. Your input will help to investigate psychological protective and risk factors predicting human immune resilience in a survey study. The project will contribute to knowledge and understanding of interactive network mechanisms involved in immune function and inform development of interventions to enhance immune resilience in humans.

The results of the study may feature in academic articles and presented at national and international conferences.

Please note that this research study is not connected to any type of commercial interest.

The (fully-anonymised) data from this study may be used for educational purposes.

The research project has received ethical approval from the Division of Arts, Law, Psychology & Social Sciences Human Research Ethics Committee at the University of Waikato. Any questions about the ethical conduct of this research may be sent to the Secretary of the Committee, email alpss-ethics@waikato.ac.nz, postal address, Division of Arts, Law, Psychology and Social Sciences, University of Waikato, Te Whare Wananga o Waikato, Private Bag 3105, Hamilton 3240

The questionnaire asks for personal responses and should take around 25 minutes to complete.

If you agree to participate in the questionnaires, all information and responses you provide will be kept private and treated in a strictly confidential manner.

Through completing the questionnaire, you demonstrate consent to participate in the survey. You can withdraw from the study at any time by simply closing the browser window without finishing the questionnaire.

If you would like further information on this research study, please contact me by email:

oleg.medvedev@waikato.ac.nz

Ngā mihi nui

Oleg Medvedev

Appendix D: Research project information and informed consent

Research project information and informed consent

Tēnā koe,

You are invited to take part in the project, which will explore protective and risk factors of immune function. Your input will help to investigate psychological protective and risk factors predicting human immune resilience in a survey study. The project will contribute to knowledge and understanding of interactive network mechanisms involved in immune function and inform development of interventions to enhance immune resilience in humans.

This study is being conducted by Oleg Medvedev, a Senior Lecturer at the School of Psychology, University of Waikato.

The results of the study may feature in academic articles and presented at national and international conferences.

The research project is not connected to any type of commercial interest.

The research project has received ethical approval from the Division of Arts, Law, Psychology & Social Sciences Human Research Ethics Committee at the University of Waikato. Any questions about the ethical conduct of this research may be sent to the Secretary of the Committee, email alpss-ethics@waikato.ac.nz, postal address, Division of Arts, Law, Psychology and Social Sciences, University of Waikato, Te Whare Wananga o Waikato, Private Bag 3105, Hamilton 3240The following questionnaire asks for personal responses.

All information and responses you provide will be kept private and treated in a strictly confidential manner.

The data from this study will be fully-anonymised before the facilitation of statistical analyses that may be conducted for both research and teaching purposes.

The questionnaire asks for personal responses and should take around 25 minutes to complete.

Through completing the questionnaire, you give your informed consent to participate in this study and agree that your fully-anonymised data will be used for research and teaching purposes.

You can withdraw from the study at any time by simply closing the browser window without finishing the questionnaire.

If you have any questions regarding this research project before beginning the questionnaire, please contact me (Oleg Medvedev) at oleg.medvedev@waikato.ac.nz.

Thank you so much for participating – ng*ā* mihi nui ki a koe! Your input will help in the advancement of our understanding of mindfulness, contemplation, and their relationship with mental health.

Appendix E Ethics Approval

The study was approved by the University ethics committee, which follows internationally recognised ethical standards. Studies undertaken in Italy and India followed similar internationally recognised ethical standards.

Te Wānanga o Ngā Kete | ***Division of Arts, Law, Psychology & Social Sciences***

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THE UNIVERSITY OF WAIKATO
Te Whare Wānanga o Waikato

Dr Oleg Medvedev

School of Psychology

26 October 2021

Dear Oleg

Re: **FS2021-58: Investigating Protective and Risk Factors of Immune Function: A Network Analysis**

Thank you for submitting your revised application to the ALPSS Human Research Ethics Committee. We have reviewed the final electronic version of your application and the Committee is now pleased to offer formal approval for the research activities detailed therein.

Please contact the Committee should other issues arise during your data collection, or should you wish to add further research activities or make changes to your project as it unfolds. All the best with your research. Thank you for engaging with the process of ethical review.

Kind regards

Nathan Cooper, Chair
Division of Arts, Law, Psychology & Social Sciences Human Research Ethics Committee

Appendix F The DASS21

This scale consists of a number of words that describe different feelings and emotions. Read each item and then indicate the appropriate answer. Indicate to what extent you felt this way over the past week.

1. I found it hard to wind down.

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

2. I was aware of dryness of my mouth

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

3. I couldn't seem to experience any positive feeling at all

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

4. I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion)

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

5. I found it difficult to work up the initiative to do things

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

6. I tended to over-react to situations

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

7. I experienced trembling (e.g., in the hands)

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

8. I felt that I was using a lot of nervous energy

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

9. I was worried about situations in which I might panic and make a fool of myself

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

10. I felt that I had nothing to look forward to

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

11. I found myself getting agitated

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

12. I found it difficult to relax

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

13. I felt down-hearted and blue

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

14. I was intolerant of anything that kept me from getting on with what I was doing

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

15. I felt I was close to panic

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

16. I was unable to become enthusiastic about anything

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

17. I felt I wasn't worth much as a person

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

18. I felt that I was rather touchy

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

19. I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat)

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

20. I felt scared without any good reason

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

21. I felt that life was meaningless

___ Did not apply to me at all

___ Applied to me to some degree, or some of the time

___ Applied to me to a considerable degree, or a good part of time

___ Applied to me very much, or most of the time

Appendix G ISQ

Please indicate how often you have had the following complains in the past 12 months:

Never Sometimes Regularly Often Almost always

1. Sudden high fever
2.Diarrhea
3. Skin problems
(e.g. acne & eczema)
4. Muscle & joint pain
5. Common Cold
6. Coughing
7. Headache

How you feel at this moment?

1s.High fever Yes/No

2s. Diarrhea Yes/No

3s. Skin problems (e.g. acne & eczema) Yes/No

4s. Muscle & joint pain Yes/No

5s. Common Cold Yes/No

6s. Coughing Yes/No

7s. Headache

A. I score my general health the following grade (from 0=very bad to 10=very good):

B. I score my immune functioning the following grade (from 0=very bad to 10=very good):

C. Do you have reduced immune functioning at the moment Yes/No

D. Do you have a chronic disease Yes/No

If Yes, please specify……..

Appendix H – SSS - Demographic Information

Demographic information

1. What is your sex?
   ☐ Male ☐ Female

2. What is your age?
   ____ years.

3. Which ethnic group(s) do you identify with?
   ☐ European/P*ā*kehā

   ☐ M*ā*ori

   ☐ Pasifika

   ☐ Asian

- Other (please specify): _____

4. Which religion do you identify with? or Which religion do you belong to?
   1. Hindu

   2. Muslim

   3. Sikh

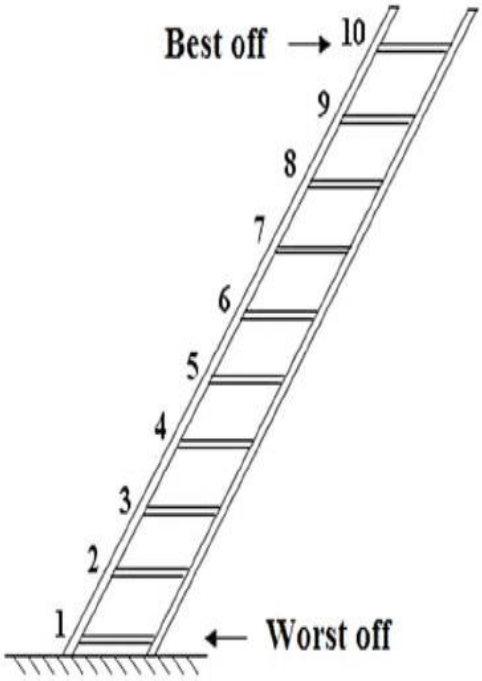
   4. Christian

   5. Buddhist

   6. Other (please specify)

5. Think of this ladder as representing where people stand in their communities. People define community in different ways; please define it in whatever way is most meaningful to you. At the top of the ladder are people who have the highest standing in their community. At the bottom are the people who have the lowest standing in their community.

At this time in your life, where would you place yourself on this ladder relative to other people in your community? Please write the corresponding number in the space below.



Appendix I Dominance analysis

Model for Dominance Analysis for the three predictors (depression, anxiety and stress) on the outcome of immunity.

Dominance Analysis for 3 Predictors

ImmuneStatus

Y= final

X1= Depression

X2= Anxiety

X3= Stress

Table Five

Predictors in the Model	Model R-Square	X1 Depression	X2 Anxiety	X3 Stress
--		0.1560	0.2680	0.2150
X1	0.156		0.1130	0.0630
X2	0.268	0.0010		0.0080
X3	0.215	0.0040	0.0610	
X1,X2	0.269			0.0070
X1,X3	0.219		0.0570	
X2,X3	0.276	0.0000		
X1,X2,X3	0.276			

Table Six Computing R-Squared averages to view dominance

Average R-Square Across Subsets			
	X1	X2	X3
k	Depression	Anxiety	Stress
0	0.1560	0.2680	0.2150
1	0.0025	0.0870	0.0355
2	0.0000	0.0570	0.0070
General Dominance	0.0528	0.1373	0.0858
Rescaled Dominance	19.1425	49.7585	31.0990

R-squared 0.2760