



Review Article

A systematic review of the impact of psychosocial factors on immunity: Implications for enhancing BCG response against tuberculosis

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ABSTRACT

Background: Tuberculosis (TB) remains an urgent global public health priority, causing 1.5 million deaths worldwide in 2018. There is evidence that psychosocial factors modulate immune function; however, how this may influence TB risk or BCG vaccine response, and whether this pathway can be modified through social protection, has not been investigated. This paper aims to: a) systematically review evidence of how psychosocial factors influence the expression of biomarkers of immunity, and b) apply this general evidence to propose plausible TB-specific pathways for future study.

Methods: Papers reporting on the impact of psychosocial stressors on immune biomarkers in relation to infectious disease risk were identified through a search of the databases MEDLINE, PsycINFO, Global Health and PsycEXTRA alongside reference list and citation searching of key papers. Data extraction and critical appraisal were carried out using a standardised form. The findings were tabulated and synthesised narratively by infectious disease category, and used to propose plausible mechanisms for how psychosocial exposures might influence immune outcomes relevant to TB and BCG response.

Results: 27,026 citations were identified, of which 51 met the inclusion criteria. The literature provides evidence of a relationship between psychosocial factors and immune biomarkers. While the direction and strength of associations is heterogenous, some overarching patterns emerged: adverse psychosocial factors (e.g. stress) were generally associated with compromised vaccine response and higher antibody titres to herpesviruses, and vice versa for positive psychosocial factors (e.g. social support).

Conclusions: The evidence identifies pathways linking psychosocial factors and immune response: co-viral infection and immune suppression, both of which are potentially relevant to TB and BCG response. However, the heterogeneity in the strength and nature of the impact of psychosocial factors on immune function, and lack of research on the implications of this relationship for TB, underscore the need for TB-specific research.

1. Introduction

1.1. A bio-social approach to TB research

With an estimated 1.5 million deaths worldwide in 2018, tuberculosis (TB) remains the leading cause of death from a single infectious agent (World Health Organization, 2019).

Biomedical advances, including diagnostics, antibiotic treatment and

the Bacille Calmette-Guérin (BCG) vaccine, are important contributors to the reduction in TB mortality and morbidity. However, it is widely acknowledged that TB is closely associated with social determinants, and is considered a sensitive marker of impoverished and unequal societies (Oxlade & Murray, 2012). As such, human development remains the biggest driver of TB incidence decline worldwide (Hargreaves et al., 2011).

Despite the pervasive role of social determinants in the epidemiology

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and control of TB, research developments that explore biomedical and social lines of enquiry have proceeded largely independently, and examples of unified conceptual models linking biological and social determinants of TB are rare. These theoretical models can inform a more holistic approach to tackling TB based on better integration of social development strategies and biomedical interventions (Dowd, Fletcher, & Boccia, 2018).

1.2. VALIDATE project

The VALIDATE project ‘*Enhancing BCG Efficacy: the Social Technology Lab Initiative*’ has attempted to bridge biomedical and social models by advocating for an environ-vaccinology approach to the research and development of vaccines against diseases of poverty like TB (Dowd et al., 2018). According to this framework, social determinants can influence immunity and contribute to the differential efficacy of vaccines and susceptibility to disease often observed across populations of different socioeconomic status (Dowd et al., 2018). From this it follows that the

response to existing or new immunisation tools can be enhanced by combining their administration with poverty-reduction strategies in order to boost the immunity of populations living in severely deprived conditions.

This can be achieved through social protection interventions, a set of risk management measures that aim to prevent, manage, and overcome situations that adversely affect people’s wellbeing, which are widely implemented in low- and middle-income countries (LMICs) (Schmitt & De, 2013). Social protection encompasses social security and safety net measures with the aim of raising people out of extreme poverty and protecting them from the risks and consequences of livelihood shocks (Adato, 2008). This includes social protection programmes implemented to improve resilience to natural disasters, which – like other social protection programmes – can lead to poverty-reduction and associated improvements in mental and physical health and wellbeing (Pelham, Clay, & Braunholz, 2011). Such social protection interventions may reduce the burden of infectious diseases like TB through a number of mechanisms, including improving socio-economic factors contributing to transmission of disease

Box 1

Background literature supporting the postulated conceptual framework.

The biological and epidemiological plausibility of the postulated conceptual framework shown in Fig. 1 is supported by a variable quantity and quality of literature. The framework should therefore be interpreted as a visual representation of potential mechanisms, which will require future testing to confirm which putative causal pathways are supported. Below we discuss the evidence that is available for some of the main pathways in the conceptual framework.

Social protection, poverty and TB.

There is strong and consistent evidence that social protection interventions such as cash transfers and microfinance can reduce poverty and inequalities (Goldberg, 2005; Hagen-Zanker et al., 2016). There is also more limited evidence that they can influence risk factors relevant for TB, and very little evidence that they can directly impact TB outcomes, due to a paucity of studies of social protection interventions that specifically address TB (Boccia et al., 2011). However, a country’s social protection level has been shown to be inversely associated with TB prevalence, incidence and mortality, adjusting for various confounders (Siroka, Ponce, & Lonroth, 2016).

Social protection and psychosocial factors.

Social protection interventions may affect psychological stress by acting on underlying drivers of stress such as poverty (i.e. inability to meet basic needs or needs that are deemed important to satisfy individual wellbeing or the wellbeing of family members) and severe socioeconomic inequalities. The effect of social protection on these two social determinants is well documented (Bastagli et al., 2016; World Bank, 2015). Additionally, by acting on poverty and inequalities, social protection not only improves material living conditions, but indirectly mitigates the sense of exclusion and injustice often reported by people living in poverty or exposed to inequalities, with associated improvements in psychosocial stressors and mental health (Kilburn, Handa, Angeles, Tsoka, & Mvula, 2018; Natali, Handa, Peterman, Seidenfeld, & Tembo, 2018; Ozer, Fernald, Weber, Flynn, & VanderWeele, 2011; Powell-Jackson et al., 2016).

Impacts of poverty on TB: material, psychosocial and behavioural.

Poverty may influence health by multiple pathways, including material living conditions, psychosocial factors and health-related behaviours (Bartley, 2017). In the context of TB, the impact of material (e.g. overcrowding, malnutrition) and behavioural (e.g. smoking, diabetes) factors have been discussed extensively (Bothamley, 2005; Cegielski & McMurray, 2004; Dubos & Dubos, 1996; Harries et al., 2016). However, evidence on the influence of psychosocial factors on TB outcomes is lacking.

Psychosocial factors/mental health and TB.

Given the association between TB and poverty (Lönroth, Jaramillo, & Williams, 2009), and between poverty and chronic psychosocial stressors (Jani, 2013) and mental disorders (Lund et al., 2010), many TB patients are likely to have been exposed to various psychosocial factors prior to TB infection or the development of active disease. Indeed, TB patients are known to have a high prevalence of psychosocial factors such as stress and anxiety; for example, a study in South Africa found high levels of distress among TB patients, associated with underlying stressors such as poverty (Peltzer et al., 2012).

In the 1950s Thomas Holmes, a physician at a Seattle sanatorium, found that individuals who had experienced stressors such as divorce, being widowed, or unemployment were more likely to contract TB and less likely to recover (Lerner, 1996). While the relationships between TB and psychosocial factors/mental health are complex and bidirectional (Sweetland et al., 2017), several cohort studies indicate that depression often precedes and is therefore possibly a risk factor for TB (Cheng, Liao, Lin, & Lai, 2017; Oh, Choi, Kim, Kim, & Cho, 2017). Further prospective studies are required to fully disentangle the complex causal pathways involved.

Psychosocial factors/mental health and immunity.

Psychosocial stressors are known to modulate the immune response. For example, those experiencing chronic stress have been shown to have reductions in the numbers of B-cells (Futterman, Wellisch, Zigelboim, Luna-Raines, & Weiner, 1996; Kiecolt-Glaser et al., 1987a, 1987b), T-cells (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989), and salivary IgA secretion (Deinzer, Kleinedam, Stiller-Winkler, Idel, & Bachg, 2000; Jemmott et al., 1983; Jemmott & Magloire, 1988) compared with controls. Such associations occur via interactions between the central

nervous system (CNS), endocrine and immune systems. Stressors can activate the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes, provoking the release of hormones including catecholamines (e.g. adrenaline) and glucocorticoids (e.g. cortisol), which can in turn modulate immune function. This may occur directly, by the hormone binding to immune cell-surface receptors, or indirectly, for example by inducing the dysregulation of cytokines such as IFN γ and interleukins (Glaser & Kiecolt-Glaser, 2005; Padgett & Glaser, 2003; Webster, Tonelli, & Sternberg, 2002).

It is possible that mental health may mediate the relationship between psychosocial factors and immune response. While there is no existing evidence that directly tests this pathway in entirety, we postulate this as a plausible mechanism given evidence of the links between psychosocial factors and mental health and between mental health and immunity. For example, stressful life events can precipitate depressive episodes in vulnerable persons (Kendler, Karkowski, & Prescott, 1999), and childhood abuse or neglect increases risk of depression in adulthood (Pechtel & Pizzagalli, 2011). Additionally, evidence links mental health to immune function. A meta-analysis found that depression is associated with various immunological assays, including impairments in T-cell mediated activities and reduced NK cell counts and cytotoxicity (Zorrilla et al., 2001).

Psychosocial factors, immunity and TB outcomes.

There are several biological pathways by which psychosocial factors could influence immune response to TB:

- a) There is evidence that psychosocial stressors can partially suppress certain aspects of immune function (Glaser & Kiecolt-Glaser, 2005). Given that protective immunity against *M.tb* depends on various innate and adaptive immune mechanisms, there are various pathways that could be disrupted by immune suppression. For example, the T-cell mediated immune response is vital in host control of *M.tb* infection. In particular, the capacity of CD4⁺ T-cells to produce IFN γ , which stimulates phagocytes to contain intracellular *M.tb*, is crucial. This is supported by studies of host genetic susceptibility showing that individuals with deficiencies in signalling pathways for the cytokines IFN γ and interleukin-12 (IL-12) have increased susceptibility to mycobacterial infection (Altare et al., 1998). Additionally, CD4⁺ T-cell decline in HIV-infected individuals is associated with increased susceptibility to TB disease (Lawn, Myer, Edwards, Bekker, & Wood, 2009). Given this, if psychosocial stress could suppress CD4⁺ T-cell proliferation and/or IFN γ secretion, this would likely reduce host ability to contain *M.tb* infection. A potential association between psychosocial stress and impaired T-cell immunity is supported by evidence in animal models. For example, rats exposed to repeated stress show significant decreases in mononuclear cell count, especially CD8⁺ T cells, and reduced IL-2 production (Batuman, Sajewski, Ottenweller, Pitman, & Natelson, 1990), and mice exposed to experimental stressors show suppressed production of IFN γ (Curtin, Boyle, Mills, & Connor, 2009; Zhang, Okutsu, Kanemi, Gametchu, & Nagatomi, 2005). It is also supported by evidence in humans. In medical students, stress due to examinations is associated with reduced overall numbers of T cells, as well as a reduction in helper T cell and suppressor T cell counts compared with 6 weeks earlier (Glaser et al., 1985; Kiecolt-Glaser et al., 1984). In addition, caregivers of dementia patients show poor HSV-1 specific memory T cell proliferation compared with controls (Glaser & Kiecolt-Glaser, 1997). It is also possible that immune suppression could interfere with BCG response, perhaps through limiting the BCG-associated expansion of CD4⁺ and CD8⁺ T-cells (Godfrey, Uldrich, McCluskey, Rossjohn, & Moody, 2015) and release of IFN γ (Fletcher et al., 2016).
- b) There is evidence of an association between psychosocial stressors and herpesvirus infection and reactivation (Jenkins & Baum, 1995), and also between certain herpesviruses and TB (Cobelens, Nagelkerke, & Fletcher, 2018), suggesting a further plausible pathway. TB patients are more likely to be cytomegalovirus (CMV) seropositive (Olaleye, Omilabu, & Baba, 1990) and have higher titres of anti-CMV antibodies (Amran et al., 2016) (reflecting increased CMV exposure) compared with controls. This was demonstrated recently in a Ugandan cohort, in which increased CMV-specific immunoglobulin G levels were associated with active pulmonary TB (Stockdale et al., 2018). Similarly, the CMV-specific IFN γ response has been associated with a greater than twofold increased TB disease risk in infants (Muller et al., 2019). Indeed, active CMV infection could be involved in progression from latent TB infection to active disease, a proposal supported by the similarity in the two infections' age-sex distributions (Cobelens et al., 2018). It is likely that the relationship between CMV and TB is bi-directional, and some of the observed association may be accounted for by their shared epidemiology and risk factors, especially poverty. However, in a prospective study in rural Uganda, CMV IgG was associated with increased risk of active TB disease up to 10 years before TB diagnosis (p=0.006), suggesting that CMV may indeed be a risk factor for TB disease (Stockdale et al., 2019). Beyond CMV, fewer studies have investigated the link between other herpesviruses and TB. However, a study in Finland showed that EBV antibody levels were higher in patients with pulmonary TB than in controls (Nikoskelainen, Hannuksela, & Palva, 1974), and a study in Taiwan showed that TB patients have a higher rate of seropositivity (p=0.01) and higher antibody titres (p=0.006) for HHV-8 than matched controls (Su et al., 2015). In a study in Georgia, prevalence of HHV-2 prevalence was 92% in TB patients and 29% in controls; for CMV prevalence was 68.5% in TB patients 5.8% in healthy controls (Karalian, 2008).

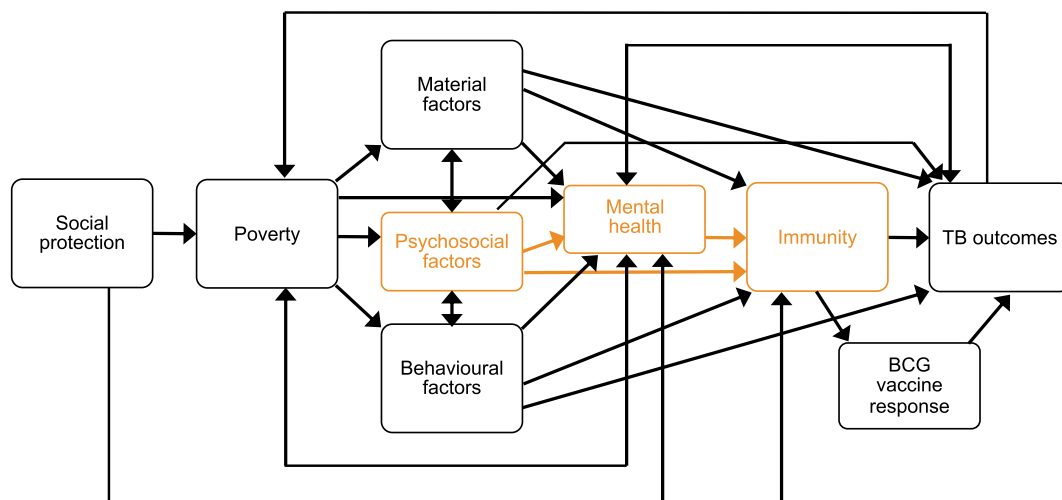


Fig. 1. Conceptual framework. This conceptual framework depicts several pathways through which social protection interventions may affect TB outcomes. ‘TB outcomes’ here includes TB exposure, infection, disease, and adverse outcomes. In this paper we focus on the pathway linking psychosocial factors with biomarkers of immunity (orange boxes in the figure) and apply the findings to the context of TB. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(e.g. living conditions, hygiene and sanitation, access to healthcare), reducing psychosocial stress, and supporting immune function (see [Box 1](#)).

The currently available vaccine against TB, *Mycobacterium bovis* BCG, represents a key proof-of-concept for the environ-vaccinology model. BCG is notoriously only partially effective; while it reliably protects against disseminated forms of TB including meningitis and miliary disease in infants, efficacy in protecting against pulmonary TB is highly variable across geographic populations, especially in adults ([World Health Organization, 2018a](#)). While there are several new TB candidate vaccines in development, some of which are in advanced stages of clinical trials, none of these are likely to become widely available in the near future ([World Health Organization, 2018a](#)). In the meantime, mathematical modelling studies suggest that combining existing biomedical tools against TB with social protection interventions would accelerate the global decline in TB incidence; for example, one model demonstrates that increasing social protection coverage – defined by the proportion of people covered by labour market protections, social assistance, and social insurance – to 100% (as set for one of the Sustainable Development Goal 1 targets) could lead to a 76% reduction of TB incidence by 2035 ([Carter et al., 2018](#)).

However, the mechanisms by which social protection might influence BCG response and TB risk are not understood. In particular, there has been little research on the potential role for social factors in the immune response to TB and BCG. This is despite evidence that improved BCG efficacy is associated with higher latitudes, an observation that may be partially accounted for by the variation in socio-economic conditions seen across latitudes ([Wilson, Fineberg, & Colditz, 1995](#)). For example, BCG response as measured by increase in interferon- γ (IFN- γ) production to *Mycobacterium tuberculosis* purified protein derivative (*M.tb* PPD) is much larger in adolescents in the UK than in Malawian adolescents ([Lalor et al., 2009](#)).

1.3. Conceptual framework

The conceptual model in [Fig. 1](#) illustrates several pathways by which social protection interventions could alter immune function, via material, psychosocial or behavioural pathways. In turn, modulated immune

function may lead to better resilience against TB infection and disease or improved BCG response.

The biological and epidemiological plausibility of this conceptual framework is supported by a variable quantity and quality of literature ([Box 1](#)). In particular, evidence on the effect of psychosocial factors on immunity remains inconclusive. Psychosocial theory postulates that vulnerability to disease is linked to psychological stress, in particular arising from perceptions and experiences of adverse living conditions and social inequalities compounded by a perceived lack of agency and control ([Marmot & Wilkinson, 2001](#)).

A growing body of research in the field of psychoneuroimmunology explores how psychosocial stressors modulate the immune system, influencing infectious disease risk/outcomes ([Kemeny & Schedlowski, 2007](#)) and vaccination response ([Burns, Carroll, Ring, & Drayson, 2003b](#)). For example, in healthy volunteers inoculated with a respiratory virus, severity of infection and symptoms increased in a dose-response relationship with psychosocial stress index score ([Cohen, Tyrrell, & Smith, 1991](#)). However, while psychosocial influences on immune biomarkers have been investigated (see [Box 1](#)), and applied for example to human immunodeficiency virus (HIV) ([Kemeny, 2003](#)), the application of this knowledge to TB is lacking.

1.4. Aims and objectives

This paper seeks to address this research gap, reviewing existing literature on how psychosocial factors influence immunity, and applying this evidence to the context of TB. We focus on the relationship between psychosocial factors and immunity in relation to TB with the aim of drawing attention to this specific and understudied pathway *vis a vis* material and behavioural pathways between poverty and TB/immune function, which have been studied more extensively. This research will increase understandings of potential mechanisms underlying TB risk, and through its application within the VALIDATE project will contribute to the development of a more creative, interdisciplinary response to tackling TB, combining social protection interventions with existing biomedical tools.

Firstly, to understand how psychosocial factors influence biomarkers

Table 1
Inclusion criteria.

Population	- Any age group in any geographic location - Exclude HIV-infected populations
Exposure	- Psychosocial factors - Defined by psychosocial exposure or perception thereof, rather than solely the physiological response - Precedes onset of infectious disease (although include cross-sectional studies where directionality is unclear) - Exclude 'extreme' stressors
Control	- Level of psychosocial factor (e.g. stress level), or no psychosocial factor (e.g. no childhood abuse)
Outcome	- Biomarkers of immunity - Restrict to studies relating to infectious disease - Include vaccine response
Study design	- Original epidemiological studies - Exclude protocols, case reports (sample size must be >2), abstracts and conferences - Exclude commentaries and reviews - Exclude laboratory and animal studies

of immunity, a systematic literature review will be undertaken. This literature has not been systematically examined since 1993 (Van Rood, Bogaards, Goulmy, & Van Houwelingen, 1993). It is anticipated that no or very little existing literature will explore psychosocial influences on the immune response to TB specifically. Therefore, the scope of this review encompasses knowledge relating to any infectious disease. Secondly, these general findings will be used to make inferences about plausible mechanisms by which psychosocial factors could influence the expression of biomarkers of immunity in ways relevant to TB.

While these proposed mechanisms are putative and will require further research to confirm or refute, the extrapolation of general findings to TB is a valid exercise given that many markers of immune response are overlapping and not pathogen-specific. Various immune correlates have been shown to be significantly associated with increased risk of TB disease in case-control studies which control for non-specific immune activation in the host environment (Fletcher et al., 2016; Zak et al., 2016). While not diagnostic of TB disease, such markers are significantly associated with increased risk of developing TB disease and are therefore relevant to our conceptual framework.

This paper has two aims, which are reflected in the structure of the paper:

1. To systematically review research into psychosocial influences on immune function (reported in 3. Results)
2. To use the existing general evidence to propose plausible TB-specific pathways for future study (reported in 4.2. Implications for TB and BCG response)

2. Methods

2.1. Inclusion criteria

This systematic review sought to identify primary epidemiological research investigating the impact of psychosocial factors on the expression of biomarkers of immunity relevant to infectious diseases including TB (see Table 1). Included papers therefore assessed psychosocial factors as exposures and immune biomarkers as outcomes. Studies that examine the impact of psychosocial stress on epidemiological or clinical evidence of infection, without assessment of immunological correlates, were excluded, given the review's aims of understanding the biological pathways between psychosocial factors and infectious disease and applying the findings to TB.

Following existing literature (Brunner, 2017), psychosocial factors of interest include stress, anxiety, stigma, isolation/exclusion,

discrimination, control, demands, autonomy, lack of self-esteem and social support. However, most of the literature focuses on stress/anxiety and social support/isolation. Despite significant evidence that such factors are associated with various health outcomes (Martikainen, Bartley, & Lahelma, 2002), their definition and measurement varies widely and is often unclear (Epel et al., 2018). The term 'stress' is used to refer to stressful exposures/life events (both acute (short-term) and chronic (long-term)), the perception of such exposures, and associated physiological responses. Here, we included papers that defined psychosocial factors by the factor itself (e.g. stressful life events) or perception thereof (e.g. anxiety), rather than by the physiological response (e.g. cortisol). These are usually measured using questionnaire tools, such as the Perceived Stress Scale (PSS), which assesses how often individuals have felt stressed during the past month based on several questions on a scale of 0 (never) to 4 (very often) (Cohen, Kamarck, & Mermelstein, 1983). We included papers with mental health as a mediator, but those looking solely at the impact of mental health on immunity without reference to underlying psychosocial causes were excluded. Since the findings had to be relevant to infections including TB, we only included papers presenting any changes in immune biomarkers in relation to infectious disease risk.

The review aimed to understand pathways relating commonly-experienced psychosocial stresses that are potentially amenable to modification by social protection to immune functioning in the general population. Therefore, studies of 'extreme' stressors, defined as situations involving intensely stressful experiences (either acute or chronic) not experienced by the general population, either because of their abrupt onset or catastrophic consequences (e.g. natural disasters, military stressors, caregiving), are excluded, as these are distinct from the widespread poverty-related stressors commonly experienced in TB-affected communities. Moreover, studies in HIV-infected populations are excluded, as the immunosuppression acquired immunodeficiency syndrome (AIDS) entails is considered a strong effect modifier which could obscure the pattern of how psychosocial factors influence immune functioning in the general population. Similarly, laboratory and animal studies are excluded, as this review focuses on pathways between psychosocial factors and immunity that operate in situ.

2.2. Search strategy

MEDLINE (1946–2018), PsycINFO (1806–2018) and Global Health (1910–2018) were searched from inception to 11/05/2018, combining free text terms and subject headings for psychosocial factors, immunity, and infectious disease including TB (shown in Appendix A). The search was restricted to papers in English and relating to humans. For grey literature, PsycEXTRA (1908–2018) was searched from inception to 15/07/2018 using the same search strategy. Key reviews (Burns et al., 2003b; Glaser & Kiecolt-Glaser, 2005; Kemeny & Schedlowski, 2007) had their reference lists examined and citation searching carried out using the Web of Science citation search tool. All references were imported into EndNote, and duplicates deleted, followed by title, abstract, and full-text screening to assess eligibility. Finally, bibliographic screening of the included papers was undertaken.

2.3. Data extraction

Data were extracted using the form in Appendix B. This is adapted from the Cochrane EPOC group's data collection form (Cochrane Effective Practice and Organisation of Care (EPOC), 2017). The extracted data were tabulated, detailing participants, methods and results of included studies.

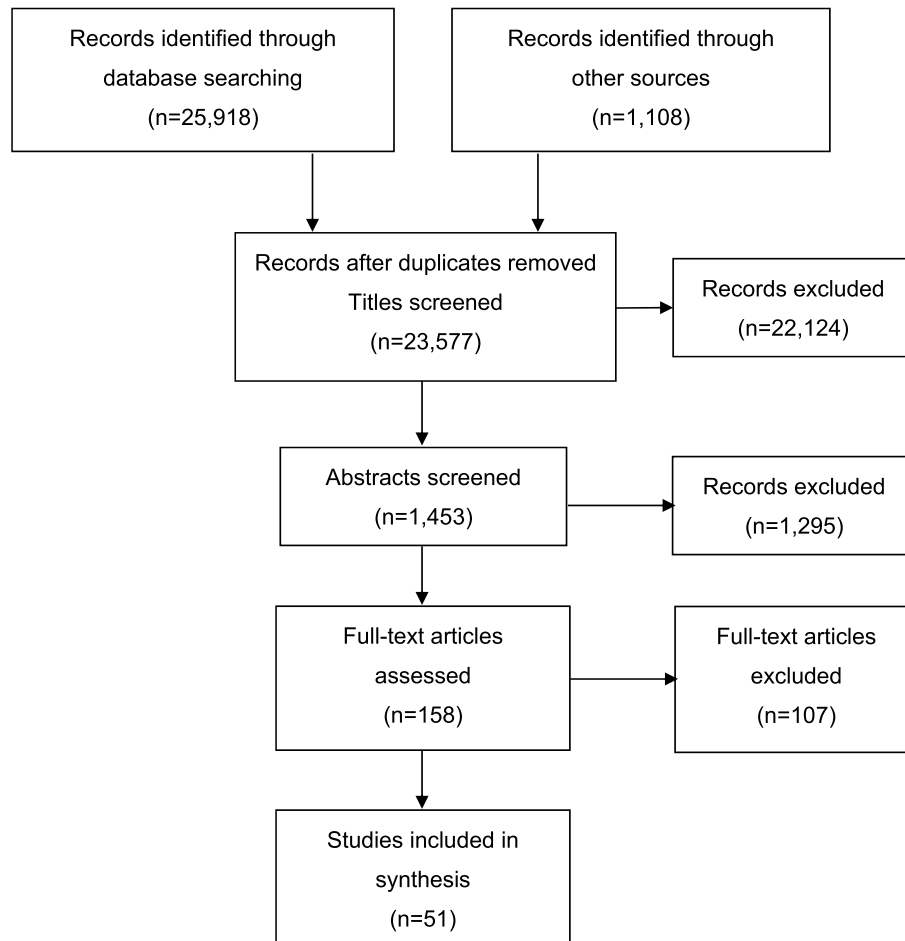


Fig. 2. Flow chart of literature search. Adapted from PRISMA 2009 Flow Diagram (Moher, Liberati, Tetzlaff, Altman, & The Prisma Group, 2009). 107 articles were excluded following full-text screening because they did not meet the inclusion criteria. The most common reasons for exclusion at this stage were: HIV-infected population, 'extreme' stressor, onset of infection precedes psychosocial stressor, and not relating to infectious disease.

2.4. Critical appraisal

The quality of all included studies was assessed by commenting on the methods' suitability for answering the review question at each relevant stage of the data extraction form. Comments were made following questions on the CASP checklists for cohort (Critical Appraisal Skills Programme, 2018b) and case-control (Critical Appraisal Skills Programme, 2018a) studies, and the AXIS tool for cross-sectional studies (EpiNet). This critical appraisal process informed a judgement on overall study quality: high, moderate or low.

2.5. Synthesis

The eligible studies identified through the systematic review of the literature were categorised into three thematic areas:

1. Impact of psychosocial factors on immune response to vaccination. This was considered especially pertinent given our interest in understanding how social protection interventions could influence BCG vaccine response.
2. Impact of psychosocial factors on immune response to herpesviruses. This was considered particularly relevant given the increasing evidence indicating an association between herpesviruses and TB, discussed in Box 1.
3. Impact of psychosocial factors on immunity to other infectious diseases. This was considered relevant given the communicable nature of TB.

Studies within each category often measured the same type of biomarkers of immunity, although there remained significant heterogeneity even within categories. Nevertheless, the categorisation facilitated direct comparisons among studies where appropriate and allowed a more coherent synthesis of the study findings.

Given the variety of study designs, psychosocial factors and immune biomarkers measured, and metrics for reporting findings, meta-analysis was deemed inappropriate. A narrative synthesis was therefore completed, separately by thematic area, using the tabulated data to draw out relevant findings and salient points regarding study design and methods. Within each study group, the findings were reviewed to identify whether direction and strength of association varied according to the psychosocial factors and immune biomarkers measured, or by study design and quality. Additionally, any mediation was reported. The collective evidence was assessed as to whether and how psychosocial factors influence biomarkers of immunity, and the extent to which the findings could be extrapolated to the case of TB.

3. Results

51 articles met the inclusion criteria (Fig. 2). Included studies fall into three broad thematic areas regarding their infectious disease application: vaccine response (18 studies), herpesviruses (19 studies) and other infections (14 studies). The vaccine response studies are primarily longitudinal, whereas the herpesvirus and other infection studies are mostly cross-sectional. The median number of participants is 95 overall: 78.5 for the vaccine response studies, 121 for the herpesvirus studies, and 109.5 for other infection studies. Study quality is highest for the vaccine response studies and lowest for the studies of other infections.

3.1. Vaccine response studies

18 papers out of 51 investigated the relationship between psychosocial factors and vaccination response (Burns, Carroll, Drayson,

Whitham, & Ring, 2003a; Burns, Carroll, Ring, Harrison, & Drayson, 2002a; Burns, Drayson, Ring, & Carroll, 2002b; Gallagher, Phillips, Ferraro, Drayson, & Carroll, 2008a, 2008b; Hayney et al., 2003; Jabaajj et al., 1993; Jabaajj et al., 1996; Kohut, Cooper, Nickolaus, Russell, & Cunnick, 2002; Miller et al., 2004; Moynihan et al., 2004; O'Connor et al., 2013; Petry, Weems, & Livingstone, 1991; Phillips, Burns, Carroll, Ring, & Drayson, 2005; Phillips et al., 2006; Pressman et al., 2005; Segerstrom, Hardy, Evans, & Greenberg, 2012; Wu, Zimmerman, & Lin, 2017). Findings are summarised in Fig. 3 and detailed in Appendix C.

Most (16/18) vaccination studies were longitudinal (Fig. 3a), assessing psychosocial factors and administering vaccines at baseline, and following up participants to assess their response. The two cross-sectional studies (Burns et al., 2002a, 2002b) assessed psychosocial factors and vaccine response in previously-vaccinated participants. The most common infection vaccinated against was influenza (8 studies), with others including hepatitis A and B, meningitis A and C, pneumococcal infections and human papillomavirus (HPV) (Fig. 3b). Various psychosocial factors were assessed, broadly relating to stress and social interactions (Fig. 3c). The most common biomarker of immunity measured was antibody titre, in 17 studies, although four additionally or instead measure cytokine levels in response to vaccination (Fig. 3d). Most studies are moderate- or high-quality, with only one low-quality study (Hayney et al., 2003) (Fig. 3e).

The findings were varied. 14/18 studies gave mixed results, with significant associations only uncovered for some of the psychosocial factors and immune biomarkers measured. A further two studies showed a weak association, and two others no association (Fig. 3f).

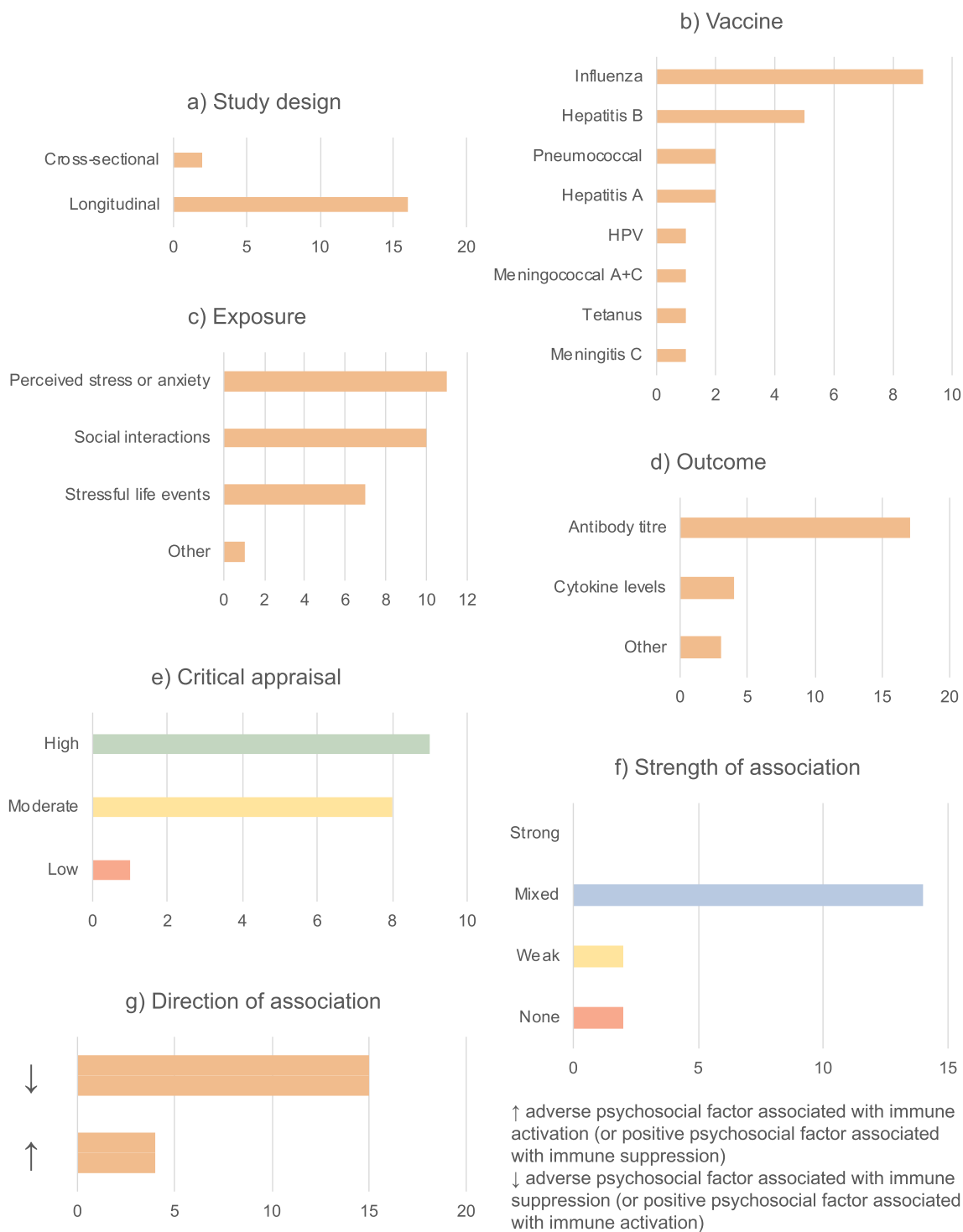
In general, where associations were observed, adverse psychosocial exposures (e.g. stress) were associated with compromised vaccine response, whereas positive psychosocial factors (e.g. social support) were associated with improved response (Fig. 3g). There were, however, some exceptions. For example, one study found that higher life event exposure and perceived stress were associated with protective antibody titres at five weeks, with the reverse true at five months (Burns et al., 2003a).

Four papers investigated mediation. In one, coping strategy mediated the association between stressful life events and antibody titre: acceptance coping was protective whereas coping by substance use increased risk of having an inadequate antibody titre (Burns et al., 2002a). In other studies, sleep quantity mediated the relationship between stress and antibody response (Miller et al., 2004), and stress mediated the association between loneliness and antibody titre (Pressman et al., 2005). No other significant mediation effects were found.

There was no apparent overall trend between study quality and association strength. However, the amount of time between psychosocial assessment/vaccination and assessment of immune biomarkers seems to influence the findings, with studies with the longest follow-up showing the weakest associations (Jabaajj et al., 1996; Segerstrom et al., 2012; Wu et al., 2017). This variation is also seen within longitudinal studies, with some finding significant associations at early timepoints but not later during follow-up (Phillips et al., 2005, 2006; Wu et al., 2017). However, the relationship is not entirely straightforward, and varies according to the psychosocial factor and vaccine response assessed (Gallagher, Phillips, Ferraro, Drayson, & Carroll, 2008a).

3.2. Herpesvirus studies

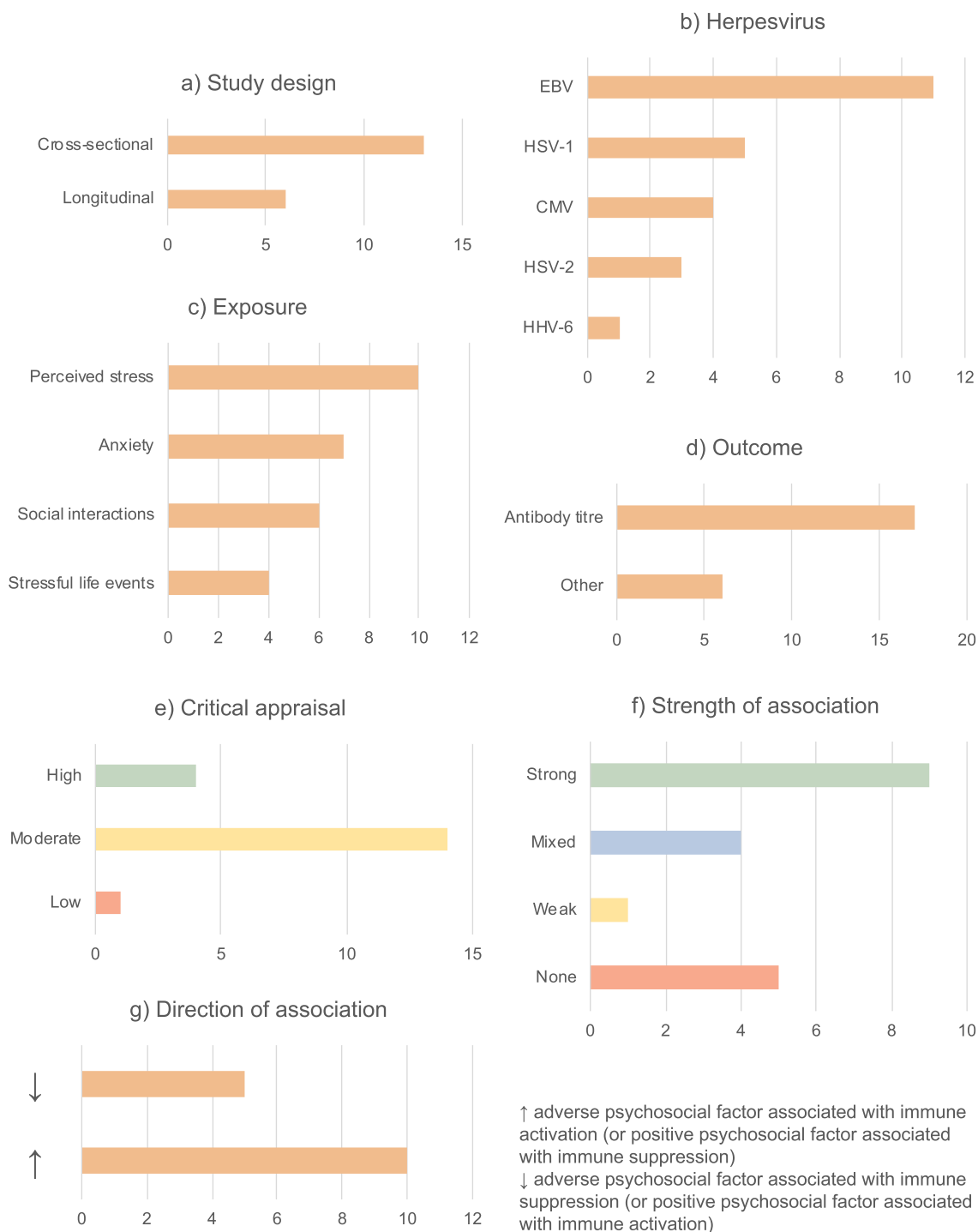
19 studies explored the relationship between psychosocial factors and immune response to herpesviruses (Benschop, Jabaajj, Oostveen, Vingerhoets, & Ballieux, 1998; Brook, Christian, Hade, & Ruffin, 2017; Christian, Iams, Porter, & Glaser, 2012; Dowd, Palermo, Chyu, Adam, & McDade, 2014; Esterling, Antoni, Kumar, & Schneiderman, 1993; Floyd, Hesse, Boren, & Veksler, 2014; Garcia-Linares, Sanchez-Lorente, Coe, &



- a) study design distribution in the included studies
- b) vaccine responses reported on across the included studies
- c) types of psychosocial stressors reported across the included studies
- d) biomarkers of immunity reported across the included studies
- e) quality of included studies
- f) strength of association between exposure to psychosocial stressors and biomarkers of vaccine response across the included studies
- g) direction of association identified across the included studies

Please note that some studies appear more than once in each section of the figure, e.g. a study that investigates response to multiple vaccines will appear multiple times in section b).

Fig. 3. Summary of vaccine response studies.

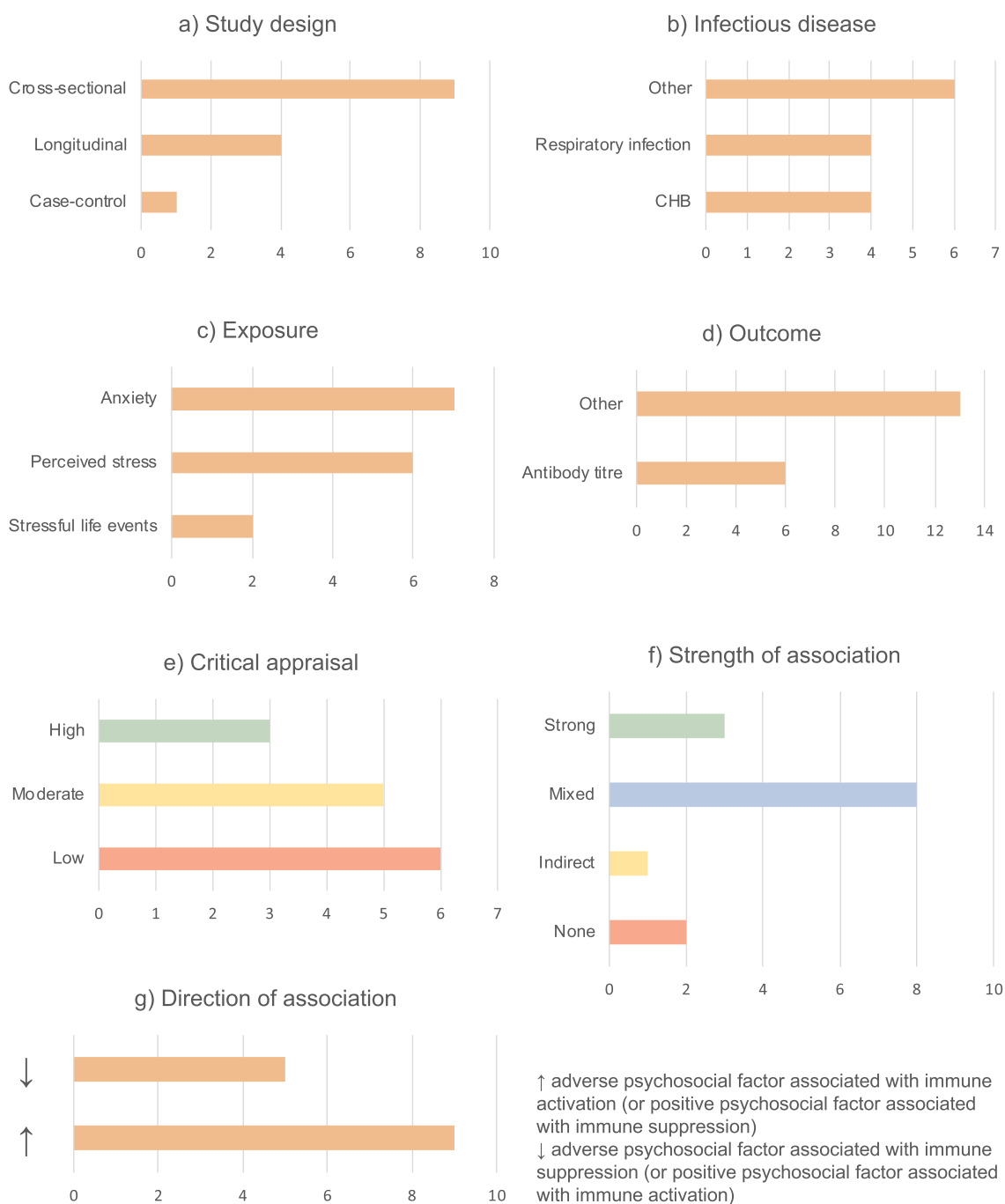


- a) study design distribution in the included studies
- b) herpesviruses reported on across the included studies
- c) types of psychosocial stressors reported across the included studies
- d) biomarkers of immunity reported across the included studies
- e) quality of included studies
- f) strength of association between exposure to psychosocial stressors and biomarkers of herpesvirus response across the included studies
- g) direction of association identified across the included studies

↑ adverse psychosocial factor associated with immune activation (or positive psychosocial factor associated with immune suppression)
 ↓ adverse psychosocial factor associated with immune suppression (or positive psychosocial factor associated with immune activation)

Please note that some studies appear more than once in each section of the figure, e.g. a study that investigates response to multiple vaccines will appear multiple times in section b).

Fig. 4. Summary of herpesviruses studies.



- a) study design distribution in the included studies
- b) infectious diseases reported on across the included studies
- c) types of psychosocial stressors reported across the included studies
- d) biomarkers of immunity reported across the included studies
- e) quality of included studies
- f) strength of association between exposure to psychosocial stressors and biomarkers of immunity across the included studies
- g) direction of association identified across the included studies

Please note that some studies appear more than once in each section of the figure, e.g. a study that investigates response to multiple vaccines will appear multiple times in section b).

Fig. 5. Summary of other infectious disease studies.

Martinez, 2004; Horn, Turkheimer, & Strachan, 2015; Hsu et al., 2016; Janicki-Deverts, Cohen, Doyle, Marsland, & Bosch, 2014; Kemeny, Cohen, Zegans, & Conant, 1989; Kiecolt-Glaser et al., 1987a; Panter-Brick, Eggerman, Mojadidi, & McDade, 2008; Phillips, Carroll, Khan, & Moss, 2008; Rector et al., 2014; Sanchez-Lorente, Blasco-Ros, Coe, & Martinez, 2010; Shirtcliff, Coe, & Pollak, 2009; Slopen, McLaughlin, Dunn, & Koenen, 2013). Findings are summarised in Fig. 4 and detailed in Appendix D.

13/19 studies were cross-sectional (Fig. 4a), assessing psychosocial exposures and immune outcomes at a single timepoint. The remaining six were longitudinal, either measuring psychosocial factors at baseline and immune response at follow-up, or involving repeated measures of both psychosocial and immunological factors. The herpesvirus most commonly investigated was Epstein-Barr virus (EBV, in 11 studies), although herpes simplex viruses (HSV-1 and HSV-2) and cytomegalovirus (CMV) were also common (Fig. 4b). Various psychosocial factors were investigated, mostly relating to stress and social support (Fig. 4c). In most studies, the biomarker of immunity measured was antibody titre to a herpesvirus (Fig. 4d). Study quality was moderate in 14 studies, high in 4, and low in 1 (Fig. 4e).

Results were extremely diverse, with nine studies showing strong results, five no evidence of associations between psychosocial factors and immunity, and the remaining five mixed or weak results (Fig. 4f). Notably, only one study was carried out in a low-income country (LIC) (Panter-Brick et al., 2008). Herpesviruses are much more common in LICs than high-income countries (HICs); in LICs where data is available, over 90% of the population are seropositive for CMV, compared with ~40–70% in HICs (Manicklal, Emery, Lazzarotto, Boppana, & Gupta, 2013). It is therefore difficult to extrapolate the findings from HICs to LICs, where TB is more common. However, given that antibody response studies are typically undertaken among the seropositive, the immune responses observed in this group in HICs can be used to infer likely responses among the seropositive in LICs.

With only one exception, where associations were observed, adverse psychosocial exposures were associated with higher antibody titres to herpesviruses, whereas positive psychosocial factors were associated with lower antibody titres (Fig. 4g). High herpesvirus-specific antibody titres reflect greater herpesvirus exposure, and greater risk of immune exhaustion resulting in impaired immunity to other infections. There was no consistent relationship between the type of psychosocial factor or herpesvirus studied and the direction or strength of associations. However, given relatively few papers considered herpesviruses other than EBV (only five studies investigate HSV-1, and fewer for other herpesviruses), this cannot be concluded with certainty. Finally, there were no clear correlations between type of immune biomarker and strength of findings, because all studies measured antibody titre. In the three studies that measured total antibody concentrations, no associations were found between psychosocial factors and this biomarker, indicating that any significant associations were due to herpesvirus-specific antibodies rather than overall immune system changes (Garcia-Linares et al., 2004; Sanchez-Lorente et al., 2010; Shirtcliff et al., 2009). Moreover, in studies that measured any biomarker of immunity other than antibody titre or herpesvirus neutralising capacity, adverse psychosocial factors were associated with immune suppression rather than activation (Horn et al., 2015; Kemeny et al., 1989; Kiecolt-Glaser et al., 1987a).

Six papers undertook mediation analysis. Potential mediators investigated included lifestyle and behavioural factors, mental health, inflammation and cortisol. However, only one study found evidence of mediation: the follow-up intimate partner violence (IPV) study found that evolution and cessation of IPV mediated the recovery of HSV-1 neutralisation (defined as the ability of saliva to inhibit the formation

of virus-induced cytopathologic effects in cell cultures incubated with HSV-1) between baseline and follow-up in physically-abused women (Sanchez-Lorente et al., 2010).

No overall pattern appeared between study quality and strength of findings. Cross-sectional studies more often gave strong findings, with 53.8% of cross-sectional studies uncovering strong associations compared with 33.3% of longitudinal studies. This suggests that associations found in cross-sectional studies could be partially attributable to relationships in the other direction, with immune response to herpesviruses somehow influencing psychosocial factors (e.g. if poor immune response increases risk of herpesvirus infection or reactivation, or worsens symptoms, this may be a cause of stress or stigmatisation) or, perhaps more likely, to common causes of both.

3.3. Studies of other infectious diseases

14 studies investigated the relationship between psychosocial factors and immunity in the context of infectious diseases other than vaccine response or herpesviruses. This includes four studies in chronic hepatitis B (CHB) patients (Aliabad et al., 2016; Bahramabadi et al., 2017; He, Gao, Li, & Zhao, 2014; Liu, Zhang, & Jiang, 2011), four relating to respiratory infections (Boyce et al., 1995; Drummond & Hewson-Bower, 1997; Koh, Yong, Ng, & Chia, 2002; Schaubroeck, Jones, & Xie, 2001; Yang et al., 2002), and six relating to other infectious diseases (Caserta et al., 2008; Clays et al., 2005; Darwin, Murni, & Nurdin, 2017; Groër et al., 2011; Levy et al., 1991; Wouters et al., 2016). Findings are summarised in Fig. 5 and detailed in Appendix E.

Study design and quality were highly variable, something unsurprising given the variety of infectious diseases and biomarkers of immunity investigated. The results were also extremely heterogeneous. More studies found that adverse psychosocial factors have a suppressive effect on immune function (nine studies) than have an enhancing effect (five studies). However, the relatively small number of studies and their diverse nature makes identifying any overarching trend difficult.

Among CHB patients, anxiety was associated with reduced CD4⁺ T-cells and CD4⁺/CD8⁺ ratio (Liu et al., 2011), and an increased percentage of CD36-positive monocytes (Aliabad et al., 2016), and both stress and anxiety were correlated with increased interleukin 10 (IL-10) level and IFN γ :IL-10 ratio (He et al., 2014). Psychosocial factors therefore appear to suppress some aspects of immunity while enhancing others in CHB patients. The respiratory infection and other infectious disease studies similarly indicate that psychosocial stressors can both suppress and enhance different aspects of immune function.

The strength of the findings was also variable: three studies showed strong associations, eight were mixed, one was indirect, and two showed no association. Neither direction nor strength of findings seemed to vary by infectious disease investigated or immune biomarker measured. However, it is hard to detect patterns given the paucity of studies relating to each disease/biomarker. Similarly, no clear overall pattern exists between study quality and strength of findings.

4. Discussion

4.1. Summary of findings

Overall, most studies (42/51) found some relationship between psychosocial factors and biomarkers of immunity. However, associations were generally only uncovered for some of the psychosocial factors and biomarkers investigated. Moreover, the direction and strength of associations were mixed and not dependent on the type of biomarker or psychosocial factor investigated. Some overarching patterns can be

cautiously identified: adverse psychosocial factors were often associated with compromised vaccine response and higher antibody titres to herpesviruses, with the reverse true for positive psychosocial factors. However, there were exceptions to both trends.

Such inconsistency is perhaps unsurprising, given the breadth of psychosocial factors, immune biomarkers, and infectious diseases investigated. A possible explanation may also lie in the nature of the psychosocial stressors and their measurement, in particular whether they were acute or chronic stressors. Both evolutionary theory (McEwen, 1998) and studies in mice exposed to brief stressors (Glaser & Kiecolt-Glaser, 2005) suggest that acute stressors might enhance aspects of immune function, whereas chronic stressors are usually immunosuppressive. However, this cannot be demonstrated in our review since most of the studies included (whether cross-sectional or longitudinal) only measured psychosocial factors at a single timepoint, rendering it impossible to differentiate between chronic and acute stressors.

A further interesting finding of the vaccine response studies is that the time between measurement of psychosocial factors and immune outcomes seems to matter for the strength and nature of findings, but in a complex manner. This is an important limitation of all the cross-sectional studies included: since immune system functioning is constantly fluctuating, immune activation measured at a given timepoint following a stressor may be followed by a period of immune suppression, and vice versa. More longitudinal studies are therefore required, measuring psychosocial exposures and immune outcomes at multiple timepoints.

4.2. Implications for TB and BCG response

Although the relationship between psychosocial factors and biomarkers of immunity was investigated for various infectious diseases, no study examined this in relation to TB risk, progression from latent to active disease, or BCG response. This makes it impossible to draw direct conclusions for TB, meaning that future TB-specific research in this area is essential. However, inferences for TB can be made based on the general evidence. In particular, this review has found evidence supporting two mechanisms through which psychosocial factors affect immune response, both of which are potentially relevant to the immunological processes involved in TB and BCG response:

4.2.1. Co-viral infection

The studies in this review found that adverse psychosocial circumstances are generally associated with an increase in antibody titres to herpesviruses, suggesting that psychosocial factors could precipitate herpesvirus infection, reinfection or reactivation. This is consistent with evidence that individuals of low socio-economic position (something commonly associated with adverse psychosocial factors (Jani, 2013)) are more likely to be seropositive for CMV (Dowd, Aiello, & Alley, 2009) and have higher CMV-specific circulating antibody levels across the life-course (Dowd & Aiello, 2009). An increase in the CMV-specific IFN γ response (which, like increased antibody titre, indicates CMV exposure) has been associated with increased TB disease risk among infants (Muller et al., 2017) and a lower BCG antigen-specific T-cell response following vaccination (Fletcher et al., 2016). A plausible mechanism underlying such associations could be that herpesvirus-associated chronic immune activation of the T-cell response (Bekker et al., 2005; Elwenspoek et al., 2017; Fülöp, Larbi, & Pawelec, 2013; Slyker et al., 2012) ultimately leads to immune exhaustion and senescence, reducing the host's ability to respond to TB infection. For example, primary CMV infection is characterised by expansion of CMV-specific CD4 $^{+}$ and CD8 $^{+}$ T-cells and natural killer (NK) cells, both of which are important for

defence against TB (Fletcher et al., 2016; Muller et al., 2019). This herpesvirus-specific expansion can ultimately result in immune exhaustion, with CMV-specific NK cells showing reduced IFN γ secretion in response to other pathogens such as TB (Cobelens et al., 2018). Moreover, expansion of CMV-specific T-cells, a phenomenon known as memory inflation (something associated with immune senescence), may displace naïve T-cells that could otherwise respond to *M.tb* antigens (White, Beard, & Barton, 2012). While CMV is used as an example here, it is not the only chronic viral infection known to be associated with TB (see Box 1), meaning that the proposed mechanisms are potentially more widely applicable.

4.2.2. Immune suppression

The studies in this review found that adverse psychosocial factors are generally associated with compromised immune response to vaccination, including influenza, hepatitis A and B, meningitis C and pneumococcal vaccines. BCG is absent from this list, meaning that firm conclusions cannot be drawn about whether a similar effect would be seen of psychosocial factors on BCG response. However, it is a plausible future research avenue. Adverse psychosocial factors were generally associated with compromised vaccine response evidenced by reduced antibody titres, something relevant to TB given increasing evidence for the antibody response's role in host defence against *M.tb* (Lu et al., 2016). However, a few studies also investigated vaccine response by cytokine levels; for example psychosocial factors were associated with both antigen-specific IFN γ levels (Hayney et al., 2003) and antigen-specific IFN γ -producing cell frequencies (O'Connor et al., 2013). This is particularly relevant to TB, given that IFN γ production by CD4 $^{+}$ T-cells is central to the immune response to BCG vaccination (Fletcher et al., 2016). An additional tentative pathway may be suggested based on two studies in which stress and anxiety correlate with a reduced proportion of CD4 $^{+}$ and CD8 $^{+}$ T-cells among patients with chronic recurrent HSV (Kemeny et al., 1989) and CHB (Liu et al., 2011). These findings suggest a direct pathway by which adverse psychosocial factors could provoke immune suppression manifested as a lower proportion of CD4 $^{+}$ and CD8 $^{+}$ T-cells. More indirectly, they could be a result of the pathway outlined above in which chronic immune activation due to persistent viral infection leads to T-cell exhaustion, precipitating reduced T-cell proliferation and cytokine production. A lower number and compromised cytokine-producing ability of CD4 $^{+}$ and CD8 $^{+}$ T-cells would likely lead to reduced IFN γ secretion and thus increased risk of TB disease. Evidence supports this; in infants, BCG-specific T-cells secreting IFN γ associate with reduced risk of TB (Fletcher et al., 2016).

4.3. Strengths and limitations

This study represents the first attempt to systematically assess the association between a wide range of psychosocial factors and biomarkers of immunity and apply this knowledge to strengthen our understanding of the impact of psychosocial factors on BCG response. However, the lack of TB-specific evidence means that our review can only produce provisional hypotheses in this respect. Other limitations impose caution in drawing conclusions: while synthesis across disparate studies has allowed the evidence to be brought together and analysed holistically, this diversity makes drawing direct comparisons between studies difficult, and meta-analysis inappropriate. Moreover, there remain gaps in the evidence base. Most studies are based in HICs, making it difficult to infer whether the findings hold for populations in LICs.

An important limitation to take into consideration is that it is beyond the scope of the included studies to fully account for the upstream social

environment that underlies the stressors measured. While some studies adjust for education, income and/or occupation as underlying causes, this is not the case in all studies. Upward bias in the estimates of stressors is thus possible, since psychosocial stress is associated with socioeconomic deprivation (Jani, 2013). For example, poverty may influence immunity via material or behavioural pathways in addition to psychosocial mechanisms (see Fig. 1), thus lack of adjustment for socioeconomic factors or other pathways may overestimate the effect of stress. Given the complexity of the causal pathways involved, it is difficult to draw conclusions with certainty. However, that an effect of psychosocial stress on immunity is seen in longitudinal studies and across different population groups, and that the findings are consistent with experimental evidence in animals (Batuman et al., 1990; Curtin et al., 2009; Zhang et al., 2005), suggests that the possibility of a real effect of psychosocial factors on immunity should not be discounted.

In all systematic reviews, publication bias is a risk, since studies with no or weak findings are less likely to be published. However, a robust approach was used to systematically identify relevant published literature. The large number of titles screened – 23,577 after de-duplication – the use of additional strategies beyond database searching including bibliographic screening and citation searching, and critical appraisal of included papers ensured a comprehensive examination of existing evidence in this field. Whilst the review did not include non-English language papers, ‘extreme’ stressors, HIV-infected populations, or laboratory studies, future reviews could focus on these categories.

5. Conclusions

This is the first study to our knowledge to systematically examine psychosocial influences on immunity since 1993 (Van Rood et al., 1993), and the first to apply the findings to TB and BCG response. Firstly, the reviewed evidence suggests that psychosocial factors can influence immune response to infectious diseases and immunisation, but in a highly heterogeneous manner. This renders the current lack of TB-specific studies an important gap in the evidence base. Secondly, this review provides evidence to support the plausibility of the hypothesised conceptual framework linking social protection interventions and BCG

Appendix A. Search strategies

MEDLINE search strategy:

1. (Psychosocial or anxiety* or depression* or stress*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2. Psychosocial deprivation/
3. exp Anxiety/
4. exp Anxiety Disorders/
5. exp Depression/
6. exp Stress, psychological/
7. 1 or 2 or 3 or 4 or 5 or 6
8. (Immune OR Immunity OR Immunosuppress* OR Immunosenescence OR Immunology OR Immunological OR Psychoimmunology OR Psychoneuroimmunology OR Inflammation OR Inflammatory).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. exp Immune system phenomena/
10. exp Immune system/
11. 8 or 9 or 10
12. (Infect* or communicable or epidemic or bacteri* or virus or viral).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. exp Infection/

response, underscoring the need for further research to confirm or refute whether a psychosocial framework can describe the nature of the hypothesised relationship between social determinants and BCG vaccine response. Specifically, this review can postulate two pathways linking psychosocial factors to immune biomarkers relevant to TB: co-viral infection and suppressed immune response. Future research must confirm whether these mechanisms indeed hold true in the case of TB and BCG response.

From a broader perspective, we postulate that better integration between social protection and BCG immunisation may improve vaccine response among severely deprived populations. To our knowledge, there is no evidence as yet about the influence of social protection and social policies in general on biomarkers of immunity. In particular, there is a significant paucity of data about the influence of social adversities on the immune response to TB. In addition, very little is known on how and the extent to which any alteration to these processes could be modified or recovered through interventions, like social protection, able to tackle adverse living conditions. Understanding the pathways between social determinants, psychosocial exposures, and immune response to TB and BCG, and whether these can be modulated by social protection policies, is therefore an important agenda for further research.

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Declaration of competing interest

None.

14. exp Bacterial infections/
15. exp Virus diseases/
16. exp Parasitic diseases/
17. (Tuberculosis or TB).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
18. exp Tuberculosis/
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 7 and 11 and 19
21. Limit 20 to (English language and humans)

PsycINFO/PsycEXTRA search strategy:

1. (Psychosocial or anxi* or depress* or stress*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2. exp Psychosocial factors/
3. exp Anxiety/
4. exp Anxiety disorders/
5. exp Recurrent depression/
6. exp "Depression (emotion)"/
7. exp Major depression/
8. exp Stress/
9. exp Social stress/
10. exp Psychological stress/
11. exp Chronic stress/
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. (Immune OR Immunity OR Immunosuppress* OR Immunosenescence OR Immunology OR Immunological OR Psychoimmunology OR Psychoneuroimmunology OR Inflammation OR Inflammatory).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
14. exp Immune system/
15. exp Immunology/
16. exp Inflammation
17. 13 or 14 or 15 or 16
18. (Infect* or communicable or epidemic or bacteri* or virus or viral).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
19. exp Infectious disorders/
20. (Tuberculosis or TB).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
21. exp Tuberculosis/
22. 18 or 19 or 20 or 21
23. 12 and 17 and 22
24. Limit 20 to (English language and human)

Global Health search strategy:

1. (Psychosocial or anxi* or depress* or stress*).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
2. exp Psychosocial aspects/
3. exp Anxiety/
4. exp Depression/
5. exp Stress/
6. 1 or 2 or 3 or 4 or 5
7. (Immune OR Immunity OR Immunosuppress* OR Immunosenescence OR Immunology OR Immunological OR Psychoimmunology OR Psychoneuroimmunology OR Inflammation OR Inflammatory).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
8. exp Immune response/
9. exp Immune system/
10. exp Immunity/
11. 7 or 8 or 9 or 10
12. (Infect* or communicable or epidemic or bacteri* or virus or viral).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
13. exp Infection/
14. exp Infectious diseases/
15. exp Bacterial diseases/

16. exp Viral diseases/
17. (Tuberculosis or TB).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes]
18. exp Tuberculosis/
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 6 and 11 and 19
21. Limit 20 to English language

Appendix B. Data extraction/critical appraisal form

	Data Extraction	Critical Appraisal
General Information		
First author		
Year		
Title		
Participants		
Population		
Setting		
Sampling method		
Inclusion/exclusion criteria		
Sample size		
Response rate		
Sample characteristics		
Methods		
Aim of study		
Study design		
Description of methods		
Duration of follow-up (if relevant)		
Loss to follow-up (if relevant)		
Statistical methods used		
Variables		
Exposure variables (psychosocial factors)		
Measurement of exposure		
Outcome variables (biomarkers of immunity)		
Measurement of outcome		
Mediator variables		
Measurement of mediators		
Confounder variables		
Measurement of confounders		
Application to infectious disease		
Findings		
Strength of findings (none, weak, mixed, strong)		
Key findings		
Key conclusions of authors		
Notes		
Study quality overall judgement: high/moderate/low		
Other comments		

Appendix C. Vaccine response studies

1 st author, year of publication	Study design (follow-up)	Population	Sample size	Vaccine	Exposure	Outcome	Critical appraisal	Results	
								Strength, direction	Summary point estimates
<i>Cross-sectional studies</i>									
Burns 2002a	Cross-sectional	UK university students	259	Hepatitis B	Stressful life events	Antibody titre	High	Mixed ↓	In earlier vaccination cohort, high life events exposure associated with increased risk of having an inadequate antibody titre (adjusted OR=2.15, 95% CI=1.02-4.53, p=0.04), but no effect in recently vaccinated cohort
Burns 2002b	Cross-sectional	UK university students	60	Meningitis C	Stress, stressful life events, anxiety/insomnia, social support	Antibody titre	High	Mixed ↓	Life events stress and social support not significantly associated with antibody status; high perceived stress associated with low antibody titre (OR=4.75, 95% CI=1.58-14.25, p=0.005); high anxiety/insomnia associated with low antibody titre (OR=4.03, 95% CI=1.37-11.84, p=0.01)
<i>Longitudinal studies</i>									
Petry 1991	Longitudinal (9 months)	US university students	82	Hepatitis B	Stress, anxiety	Antibody titre	Moderate	Mixed ↑	Negatively perceived stress during induction phase of immunisation (at final dose) associated with higher peak antibody titres (r=0.19, p=0.044); anxiety during induction phase of immunisation (at final dose) associated with higher peak antibody titres (r=0.23, p=0.02); no significant associations at booster phase (3 months after final dose)
Jabaaij 1993	Longitudinal (7 months)	Dutch university students	95	Low-dose hepatitis B	Stress, social isolation	Antibody titre	Moderate	Mixed ↓	Among subjects with protective antibody levels, stress was associated with reduced anti-hepatitis B antibody titres at 6 (β=-0.23, p=0.06) and 7 months (β=-0.29, p<0.05); social isolation did not influence antibody response when adjusting for stress; no significant associations among subjects with inadequate antibody levels
Jabaaij 1996	Longitudinal (7 months)	Dutch university students	68	Hepatitis B	Stress	Antibody titre	Moderate	None	No relationship found between stress and antibody levels at months 2, 6 or 7 after controlling for confounders
Kohut 2002	Longitudinal (2 weeks)	Elderly US individuals	56	Influenza	Stress, social activities	Antibody titre, cytokine levels (IL-2, IFN γ , IL-10), PBMC proliferation	High	Mixed ↓	High stress was a significant predictor of reduced anti-influenza IgG and influenza-specific IL-2 (p=0.042); greater social activity was associated with greater IL-10 production; no reported effect on other immune outcomes
Burns 2003	Longitudinal (5 months)	UK university students	31	Influenza	Stress, stressful life events	Antibody titre	Moderate	Mixed ↑↓	Higher life event exposure (F(1,29)=3.87, p=0.06) and higher perceived stress (F(1,29)=3.97, p=0.06) in individuals protected against A/Panama strain at 5 weeks; higher life event exposure (F(1,29)=6.66, p=0.02) (p=0.02) and higher perceived stress (F(1,29)=3.26, p=0.08) in individuals without overall protection at 5 months
Hayney 2003	Longitudinal (28 days)	US adults	18	Influenza, hepatitis A	Psychological wellbeing, relationship quality	Cytokine levels (IFN γ , IL-10)	Low	Mixed ↓	Some significant positive correlations were made between psychological wellbeing and quality relationships and IFN γ and IL-10 production to influenza and hepatitis A prior to immunisation and on day 28 (Pearson correlations: 0.6-0.7, p<0.05)
Miller 2004	Longitudinal (4 months)	US university students	83	Influenza	Stress	Antibody titre	High	Mixed ↓	Higher stress was associated with impaired antibody response to the New Caledonia strain (F(2,76)=4.12, p<0.03); stress was not associated with antibody response to the Panama (p=0.97), Victoria (p=0.40), or Yamanashi (p=0.12) strains
Moynihan 2004	Longitudinal (3 weeks)	Elderly US nursing home residents	37	Influenza	Stress, social support	Antibody titre	Moderate	Mixed ↑↓	Social support positively associated with pre-vaccination titres to the New Caledonia (r=0.35, p<0.05) and Hong Kong (r=0.32, p=0.057) strains and negatively associated with pre- (r=-0.39, p<0.05) and post- (r=-0.49, p<0.05) titres to the Pan strain; perceived stress negatively associated with pre-vaccination antibody titres to the New Caledonia (r=-0.36, p<0.05) and Hong Kong (r=-0.38, p<0.05) strains, but not with the Pan strain
Phillips 2005	Longitudinal (5 months)	UK university students	57	Influenza, meningococcal A + C	Stressful life events, social support	Antibody titre	High	Mixed ↓	Stressful life events score associated with lower antibody titres for B/Shangdong influenza strain at 5 weeks (β=-0.02, p=0.003) and 5 months (β=-0.28, p=0.01); number of stressful life events associated with lower meningococcal C antibody titre at 5 weeks (β=-0.24, p=0.05); higher social support associated with higher antibody titre to A/Panama influenza strain at 5 weeks (β=0.29, p=0.04) but not at 5 months

1st author, year of publication	Study design (follow-up)	Population	Sample size	Vaccine	Exposure	Outcome	Critical appraisal	Results	
								Strength, direction	Summary point estimates
Pressman 2005	Longitudinal (4 months)	US university students	83	Influenza	Loneliness, social network size	Antibody titre	High	Mixed ↓	Smaller social networks and higher levels of total loneliness associated with lower antibody production at both 1 month (F(2,71)=4.91, p<0.05; F(1,72)=4.79, p<0.05) and 4 months (F(2,70)=5.35, p<0.01; F(1,71)=5.04, p<0.05) in response to the A/New Caledonia virus but not to the A/Panama or the B viruses; loneliness at baseline not related to antibody response; stress significantly associated with response to A/New Caledonia at 1 month (F(1,72)=4.83, p<0.05) and 4 months (F(1,71)=4.91, p<0.05); negative affect (including anxiety) not significantly associated with antibody response
Phillips 2006	Longitudinal (12 months)	Elderly UK individuals	136	Influenza	Stressful life events, social support, marital satisfaction	Antibody titre	High	Mixed ↓	Overall stressful life events not associated with antibody titres at 1 month, but bereavement in the year prior to vaccination was negatively associated with the antibody response at 1 month to A/Panama ($\beta=-0.15$, p=0.02) and B/Shangdong ($\beta=-0.21$, p=0.001); no association between social support and antibody titre, for married/cohabiting individuals, marital satisfaction was positively associated with antibody titre to A/Panama at 1 month ($\beta=0.20$, p=0.03)
Gallagher 2008a	Longitudinal (18 weeks)	UK university students	75	Hepatitis A, pneumococcal	Stressful life events, social support	Antibody titre	High	Mixed ↓	Stressful life events associated with reduced antibody responses to hepatitis A vaccine at 18 weeks ($\beta=-0.22$, p=0.04) but not 4 weeks; stressful life events not associated with antibody response to pneumococcal vaccine; social support not associated with antibody response to hepatitis A vaccine; number of friends associated with increased antibody response to pneumococcal vaccine at 4 weeks ($\beta=0.19$, p=0.03) but not 18 weeks
Gallagher 2008b	Longitudinal (~5 days)	UK university students	74	Pneumococcal	Stressful life events, social support	Antibody titre	High	Weak ↓	Life event stress not associated with antibody response; aggregate functional support associated with increased antibody response to pneumococcal serotypes 3 ($\beta=0.018$, p=0.03) and 23 ($\beta=0.10$, p=0.10) only
Segerstrom 2012	Longitudinal (8 years)	Elderly US individuals	134	Influenza	Distress (stress, depression)	Antibody titre, IL-6 levels, β -2 microglobulin	Moderate	None	No overall effect of trait or state distress on biomarkers of immunity
O'Connor 2013	Longitudinal (~11 months)	US pregnant women and their infants	142	Hepatitis B, tetanus	Maternal anxiety	Infant antibody titre, cytokine-producing cell frequencies, cytokine levels (IL-2, IL-4, IL-12)	Moderate	Mixed ↓	No association between maternal prenatal anxiety and infant hepatitis B antibody response or cytokine-producing cell frequencies at 2 months; among infants who had not received the full 3-dose hepatitis B vaccination series at 6 months, maternal prenatal anxiety was negatively associated with antibody titre (r=-0.35, p<0.05), but not among those who had received the full dose; at 6 months, prenatal maternal anxiety was significantly associated with decreased IFN γ -producing cell frequencies to hepatitis B surface antigen (r=-0.29, p<0.05) and increased IL-4 responder cell frequencies in response to tetanus antigen (r=0.28, p<0.05); modest negative association between prenatal anxiety and IL-12 concentration at 2 months (r=-0.34, p=0.065) but not at 6 months
Wu 2017	Longitudinal (~6 or 12 months)	Young US men	204	HPV	Stress	Antibody titre	Moderate	Weak ↑↓	Overall stress not associated with antibody titre; however, antibody titres appeared to follow a U-shaped pattern with the highest titres in the lowest and highest stress quartiles for all HPV strains in the 6-month group and HPV-18 in the 12-month group; significant correlations between stress and antibody titre for HPV-6 (r=0.35, p<0.01), HPV-16 (r=0.29, p<0.03), and HPV-18 (r=0.36, <0.01) but not for HPV-11 in the 6-month group, and no correlations in the 12-month group

↑ adverse psychosocial factor associated with immune activation (or positive psychosocial factor associated with immune suppression)

↓ adverse psychosocial factor associated with immune suppression (or positive psychosocial factor associated with immune activation)

↑↓ psychosocial factor associated with both immune activation and suppression

A critical appraisal form (Appendix B) was used to assess high, moderate and low study quality; completed forms for each study can be made available upon request.

Abbreviations: HPV=human papillomavirus, IFN γ =interferon-gamma, IgG=immunoglobulin G, IL=interleukin, PBMC=peripheral blood mononuclear cell

Appendix D. Herpesvirus studies

1st author, year of publication	Study design (follow-up)	Population	Sample size	Exposure	Outcome	Critical appraisal	Results	
							Strength, direction	Summary point estimates
Cross-sectional studies								
Kiecolt-Glaser 1987	Cross-sectional	US women	76	Marital quality, attachment	Antibody titre to EBV-VCA, NK and T cells, blastogenesis with Con A and PHA	Moderate	Mixed ↑↓	Marital quality negatively associated with EBV-VCA antibody titres ($\beta=-0.52$, $p<0.05$); high marital quality group shows a stronger lymphocyte response to PHA stimulation ($F(1,32)=4.15$, $p<0.05$); attachment associated with lower percentage of helper T cells ($\beta=-0.33$, $p<0.05$) and helper-suppressor ratio ($\beta=-0.37$, $p<0.01$); high attachment to (ex)spouse associated with significantly weaker lymphocyte response to Con A stimulation ($F(1,26)=4.47$, $p<0.05$)
Esterling 1993	Cross-sectional	US students	54	Anxiety	Antibody titre to EBV-VCA and EBV-EA, Forssman antibody (marker of polyclonal B cell activation)	Moderate	Strong ↑	Anxiety associated with higher EBV-VCA antibody titre ($F(2,45)=5.04$, $p<0.01$), but not with Forssman antibody
Benschop 1998 (study a)	Cross-sectional	Dutch students	121	Stress, social isolation	Antibody titre to EBV-VCA	Moderate	None	No statistically significant associations
Benschop 1998 (study b)	Cross-sectional	Dutch students	95	Stress	Antibody titre to EBV-VCA, EBV-specific cytotoxic activity	Moderate	None	No statistically significant associations
Garcia-Linares 2004	Cross-sectional	Spanish women	111	IPV	Antibody titre to HSV-1, total IgA antibody levels, HSV-1 neutralising capacity	Moderate	Strong ↓	25.5% of physically abused women, 63.0% of psychologically abused women and 83.8% non-abused women showed some virus neutralisation ($\chi^2=28.7$, $p<0.001$); HSV-1-sIgA differed between groups, with lowest in physically abused women ($F(2,110)=3.7$, $p<0.03$); no significant differences between groups in total IgA
Panter-Brick 2008	Cross-sectional	Afghan students	161	Stress, social aspirations	Antibody titre to EBV-VCA	Moderate	Weak ↑	No overall associations in healthy EBV seropositive sample; for healthy women, high EBV antibody titre associated with family stressors (χ^2 , $p=0.038$) and strong disagreement with decisions made at home (t -test, $p=0.023$)
Phillips 2008	Cross-sectional	Elderly UK individuals	137	Anxiety	Antibody titre to CMV	High	Strong ↑	Anxiety not associated with CMV serostatus; among CMV positive individuals, high anxiety associated with high CMV-specific antibody titres (OR=1.17, 95% CI 1.05-1.31, $p=0.005$)
Shirtcliff 2009	Cross-sectional	US adolescents	155	Early/current adversity	Antibody titre to HSV-1 and total IgA concentration	High	Strong ↑	Early/current adversity not associated with HSV serostatus; post-institutionalised and physically abused adolescents had elevated HSV-1 antibody titres compared with controls ($F(2,109)=5.57$, $p<0.005$); physically abused adolescents had higher antibodies than controls ($p<0.009$) and post-institutionalised adolescents had higher antibodies than physically abused adolescents ($p=0.015$)
Floyd 2014	Cross-sectional	US university staff and students	52	Trait expressed affection	Antibody titre to EBV-VCA	Moderate	Strong ↓	High expressed affection associated with increased antibody titre ($\rho=0.24$, $p<0.05$)
Janicki-Deverts 2014	Cross-sectional	US adults	140	Childhood family interpersonal environment, adult stress and emotional stability	Antibody titre to CMV	Moderate	Mixed ↑	No factors associated with CMV serostatus; among CMV positive individuals, greater family warmth ($\beta=0.246$, $p=0.002$), greater family harmony ($\beta=-0.012$, $p=0.035$), lower family dysfunction ($\beta=0.010$, $p=0.052$) and better parental bonding ($\beta=-0.025$, $p=0.014$) associated with lower antibody levels; neither perceived stress nor emotional stability related to antibody levels among seropositive persons
Rector 2014	Cross-sectional	German employees	887	Anxiety	Antibody titre to CMV	High	Strong ↑	Anxiety not associated with CMV serostatus; among CMV positive individuals, high anxiety associated with high CMV-specific antibody titres ($\beta=0.137$, $p<0.01$)
Hsu 2016	Cross-sectional	US pregnant women	247	Stress, anxiety	Antibody titre to HSV-1, HSV-2, HHV-6, CMV, EBV-VCA	Moderate	None	No statistically significant associations
Brook 2017	Cross-sectional	US young women	169	Stress, social support	Antibody titre to EBV-VCA	Moderate	Strong ↑	Stress associated with increased EBV antibody titre ($\beta=0.02$, $p<0.05$); social support associated with decreased EBV antibody titre ($\beta=-0.01$, $p<0.05$)
Longitudinal studies								
Kemeny 1989	Longitudinal (6 months)	US patients with chronic recurrent HSV	19	Stress, anxiety	Proportion of CD4+ and CD8+ T cells	Low	Strong ↓	Stress associated with a lower proportion of CD4+ ($r=-0.47$, $p=0.02$) and CD8+ ($r=-0.41$, $p=0.04$) T cells; anxiety associated with a lower proportion of CD8+ T cells ($r=-0.47$, $p<0.05$)
Sanchez-Lorente 2010	Longitudinal (3 years) Follow-up from Garcia-Linares 2004	Spanish women	60	IPV	Antibody titre to HSV-1, total IgA antibody levels, HSV-1 neutralising capacity	Moderate	None	No longer any marked differences between groups in virus neutralisation or HSV-1-sIgA titre; physically abused women had shown a statistically significant increase in virus neutralisation ($t=-6.3$, $p<0.001$) and HSV-1-sIgA ($t=-3.3$, $p=0.004$), with no significant change in the other groups; no significant differences between groups in total IgA; variables contributing to the recovery of HSV-1 neutralisation for the physically abused women were evolution of IPV ($F(5,40)=2.4$, $p=0.54$) and cessation of physical IPV ($\beta=-0.5$, $p=0.013$)

1 st author, year of publication	Study design (follow-up)	Population	Sample size	Exposure	Outcome	Critical appraisal	Results	
							Strength, direction	Summary point estimates
Christian 2012	Longitudinal (up to 11 months)	Pregnant US women	56	Stress, prenatal distress, anxiety, discrimination	Antibody titre to EBV-VCA	Moderate	Mixed ↑	No overall association in sample as a whole; among African American women, those reporting high discrimination showed higher EBV-VCA antibody titres than those reporting low discrimination during the 1 st (p=0.03), 2 nd (p=0.04) and 3 rd (p=0.12) trimesters of pregnancy and at postpartum (p=0.06)
Slopen 2013	Longitudinal (~15 years)	US adolescents	13,162	Childhood physical and sexual abuse	Antibody titre to EBV-VCA	Moderate	Mixed ↑	Exposure to any childhood physical or sexual abuse not associated with EBV antibodies; sexual abuse occurring more than 10 times associated with elevated EBV antibodies (β=0.13, p=0.03); physical abuse that began during preschool had a greater association with EBV antibodies relative to those that were never abused (β=0.17, p=0.04) or physical abuse that began during adolescence (β=0.15, p=0.004)
Dowd 2014	Longitudinal (14-15 years)	US adolescents	11,050	Stress, stressful life events	Antibody titre to EBV-VCA	High	None	No statistically significant associations
Horn 2015	Longitudinal (10 weeks)	US women	19	Stress, anxiety	Viral shedding (i.e. presence of HSV-2 on swabs of genital mucosa)	Moderate	Strong ↓	High anxiety (η ² =0.003, SE=0.001) and stress (η ² =0.003, SE=0.001) and poor ability to regulate anxiety (η ² =0.011, SE=0.001) and stress (η ² =0.012, SE=0.001) levels associated with faster viral shedding cycling

↑ adverse psychosocial factor associated with immune activation (or positive psychosocial factor associated with immune suppression)

↓ adverse psychosocial factor associated with immune suppression (or positive psychosocial factor associated with immune activation)

↑↓ psychosocial factor associated with both immune activation and suppression

A critical appraisal form (Appendix B) was used to assess high, moderate and low study quality; completed forms for each study can be made available upon request.

Abbreviations: CMV=cytomegalovirus, Con A=concanavalin A, EBV-EA= Epstein-Barr virus early antigen, EBV-VCA=Epstein-Barr virus viral capsid antigen,

HHV=human herpes virus, HSV=herpes simplex virus, IgA=immunoglobulin A, IPV=intimate partner violence, NK=natural killer, PHA=phytohemagglutinin

Appendix E. Other infectious disease studies

1st author, year of publication	Study design (follow-up)	Population	Sample size	Exposure	Outcome	Infectious disease application	Critical appraisal	Results	
								Strength, direction	Summary point estimates
<i>Chronic hepatitis B</i>									
Liu 2011	Cross-sectional	Chinese CHB patients	120	Anxiety	CD4+/CD8+ ratio	CHB patients	Low	Strong ↓	Anxiety associated with reduced CD4+ T cells (χ^2 , $p<0.01$) and CD4+/CD8+ ratio (χ^2 , $p<0.05$)
He 2014	Cross-sectional	Chinese CHB patients	80	Stress, anxiety	T cell count, ALT, viral load, IL-10 and IFN γ levels	CHB patients	Low	Mixed ↑↓	Stress ($t=-4.308$, $p=0.000$), state anxiety ($t=-3.085$, $p=0.003$) and trait anxiety ($t=-4.925$, $p=0.000$) associated with reduced ALT (a surrogate marker of hepatocyte injury, which is mainly a consequence of immune response); state ($t=5.821$, $p=0.000$) and trait ($t=6.238$, $p=0.000$) anxiety associated with increased IL-10 level; major stress associated with increased IL-10 level compared with minor stress ($t=6.538$, $p=0.000$); stress and anxiety associated with increased IFN γ but not significantly; stress ($t=4.606$, $p=0.000$), state anxiety ($t=5.126$, $p=0.000$) and trait anxiety ($t=4.670$, $p=0.000$) associated with higher IFN γ :IL-10 ratio; no significant effect on other immune outcomes
Aliabad 2016	Cross-sectional	Iranian CHB patients	60	Anxiety	Expression of CD9, CD36 and CD68 on peripheral blood monocytes	CHB patients	Low	Mixed ↑	Patients with moderate anxiety had an increased percentage of CD36-positive monocytes versus those with no anxiety ($p=0.026$) Neither percentages of CD9- and CD68-positive monocytes nor the expression of CD9, CD36 and CD68 significantly different among patients with no, mild, moderate and severe anxiety
Bahramabadi 2017	Cross-sectional	Iranian CHB patients	60	Anxiety	IL-6, IL-8, TNF- α , TGF- β	CHB patients	Low	None	No statistically significant associations
<i>Respiratory infections</i>									
Schaubroeck 2001	Cross-sectional	US employees	217	Job stress (control, demands, self-efficacy)	IgA antibody titre	Subjects report recent and chronic symptoms of URTIs	Moderate	Mixed ↑↓	3-way interaction between job control, demands and self-efficacy did not predict IgA; 3-way interaction between job control, demands and explanatory style significantly predicted IgA; in those with low job control, job demands were associated with slightly increased IgA; in those with high job control, job complexity was associated with reduced IgA; in those with a low self-blaming explanatory style, job demands were associated with reduced IgA
Yang 2002 Koh 2002	Cross-sectional	Singaporean nurses	132	Job stress	IgA and lysozyme secretion rates	Subjects report URTIs in the past 6 months	Moderate	Strong ↓	Job stress associated with reduced log salivary IgA secretion rate ($r=-0.28$, $p=0.001$) and reduced log salivary lysozyme secretion rate ($r=-0.28$, $p=0.001$)
Boyce 1995	Longitudinal (2 weeks)	US 5-year-old children at kindergarten entry	99	Stressful family life events, family conflict	CD4+ (helper/inducer), CD8+ (suppressor/cytotoxic) and CD19+ (B lymphocyte) cells, PWM stimulation, antibody titre to pneumococcal vaccine	Respiratory illnesses monitored over 12 weeks	Moderate	Mixed ↑↓	Stressful life events predicted respiratory illness incidence by CD19+ cell change score ($\beta=0.51$, $p<0.05$) and PWM stimulation change score ($\beta=0.45$, $p<0.10$); no other significant findings

1 st author, year of publication	Study design (follow-up)	Population	Sample size	Exposure	Outcome	Infectious disease application	Critical appraisal	Results	
								Strength, direction	Summary point estimates
Drummond 1997	Case-control	Australian children	90	Stressful life events, anxiety	slgA antibody titre, slgA/albumin ratio	Children with recurrent URTIs and healthy controls	Moderate	Indirect ↓	Children with recurrent URTIs reported more stressful life events in the past year than healthy controls (t=4.21, p<0.001); children with recurrent URTIs reported more anxiety than healthy controls (t=2.56, p<0.05); children with recurrent URTIs had a lower slgA/albumin ratio than controls (F(1,84)=10.42, p<0.01); association between psychosocial factors and biomarkers of immunity not investigated explicitly
<i>Other</i>									
Clays 2005	Cross-sectional	Belgian employees	892	Job stress (control, demands, support)	Inflammation (fibrinogen, high-sensitivity CRP, serum amyloid A), antibody titres to C. pneumoniae, CMV and H. pylori	C. pneumoniae, CMV and H. pylori	High	Mixed ↓	Job control associated with reduced plasma fibrinogen concentration (ANOVA, p=0.04); high social support at work associated with increased plasma fibrinogen concentration (ANOVA, p=0.05); high social support associated with CMV positivity (OR=0.62, 95% CI 0.42-0.90, p<0.05); no other significant findings
Groër 2011	Cross-sectional	US pregnant women	414	Anxiety	IgG antibody titre to T. gondii, cytokines, TPO autoantibody status	T. gondii	High	Mixed ↑	Anxiety not associated with T. gondii positivity; among the T. gondii-positive group, anxiety associated with increased IgG antibody titre to T. gondii (r=0.31, p<0.04); anxiety associated with TPO-positivity (t=2.28, p<0.02)
Darwin 2017	Cross-sectional	Indonesian patients with dyspepsia	40	Stress	IL-6 expression	H. pylori activity	Low	Strong ↓	Stress associated with reduced IL-6 expression (8.25% in stress group vs. 7.25% in non-stress group, χ^2 , p=0.00) and increased H. pylori activity
Levy 1991	Longitudinal (6 months)	US adults	81	Stress	NK cell activity	Subjects record any symptoms of acute infectious illness	Low	None	In a 3-factor path model, including age, stress, and B-endorphin values, stress did not emerge as a predictor of illness acting via NK activity
Caserta 2008	Longitudinal (3 years)	UK children	169	Parental psychosocial factors	NK cell function, percentage of CD4 and CD8 cells associated with CMV, HHV-6 viral load	Subjects record any symptoms of illness	High	Mixed ↑↓	Parental psychiatric symptoms associated with enhanced NK cell function (adjusted mean difference 0.15, 95% CI 0.05-0.26, p<0.01) and increased percentages of CD8+CD28-CD57+ cells in CMV-positive children (adjusted mean difference 2.57, 95% CI 0.36-4.79, p=0.02); family conflict associated with compromised NK cell function (adjusted mean difference -0.01, 95% CI -0.03, 0.00 p<0.01); no other significant findings
Wouters 2016	Longitudinal (1 year)	Belgian adults exposed to contaminated drinking water	968	Anxiety	PBMC immune phenotyping, cytokine analysis, expression of inflammatory genes in rectal biopsies	Infectious gastroenteritis (IGE) and post-infectious irritable bowel syndrome (IBS)	Moderate	Mixed ↓	At baseline, anxiety associated with reduced number of CD4+CD8-IL-2+ T cells, a cell type critical in maintaining regulatory T cells (r=0.6, p=0.01); no other significant findings

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 ↓ adverse psychosocial factor associated with immune suppression (or positive psychosocial factor associated with immune activation)

↑↓ psychosocial factor associated with both immune activation and suppression
 Detailed data extraction tables can be made available upon request.

A critical appraisal form (Appendix B) was used to assess high, moderate and low study quality; completed forms for each study can be made available upon request.
 Abbreviations: ALT=alanine aminotransferase, CHB=chronic hepatitis B, CRP=C-reactive protein, CMV=cytomegalovirus, C. pneumoniae=Chlamydia pneumoniae, HHV=human herpesvirus, H. pylori=Helicobacter pylori, IFN γ =interferon-gamma, IgA=immunoglobulin A, IBS= irritable bowel syndrome, IGE=infectious gastroenteritis, IL=interleukin, NK=natural killer, PBMC=peripheral blood mononuclear cell, PWM=pokeweed mitogen, slgA=serum immunoglobulin A, TGF- β =transforming growth factor beta, TNF- α =tumour necrosis factor alpha, TPO=thyroid peroxidase, T. gondii=Toxoplasma gondii, URTI=upper respiratory tract infection

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