The Interplay Between Psychological Stress and Tuberculosis: Assessing Infection Vulnerability.

Are Individuals Experiencing Psychosocial Stressors More Likely to Contract Tuberculosis?

Abstract

Objective: This literature review focuses on the intersections of psychosocial stressors, infection vulnerability, immunology, and Tuberculosis (TB) to identify at-risk groups and biomarkers related to immunosuppression and TB contraction.

Method: The goals of this paper are to demonstrate that individuals who experience psychosocial stressors, including chronic stress and depression, have a higher risk of developing TB due to immunological alterations related to disease vulnerability. This paper will be a literature review utilizing two Google Scholar searches. Articles related to psychosocial stress, mental illness and tuberculosis will be analyzed for trends in biomarkers and at-risk groups.

Results: Psychosocial stressors, specifically depression, cause dysregulations in the pro-inflammatory cytokine macrophage migration inhibitory factor, IL-6, IL-2, and IL-1β, as well as T-cell functions and CD4/CD8 ratios, which place individuals in immunocompromised states. Biological markers are part of intersectional structures that frequently put specific individuals at risk. These groups include people experiencing homelessness, migrants, individuals with depression, anxiety, mental illness, or who are experiencing grief, financial hardship and substance abuse issues.

Conclusion: Psychosocial factors, specifically depression, create biological changes and immunosuppression that place individuals at a heightened risk of developing Tuberculosis.

Introduction

Tuberculosis (TB) is a contagious chronic inflammatory disease which frequently impacts the lungs as pulmonary tuberculosis (Liu et al., 2022). TB is transmissible by respiratory droplets with a nucleus of 1-5 μm in diameter and remain in the air for several hours, and is impacted by a variety of factors, including strength of the infectious source, infectiousness of TB bacilli and immunology of the host (Richeldi, 2006). The intracellular pathogen *Mycobacterium tuberculosis* (M.tb) was discovered as the causative agent of TB by Robert Koch in 1882. TB typically develops in only 10% of the humans exposed to *Mycobacterium tuberculosis,* and of

those, 5% develop within 1-2 years of infection (Richeldi, 2006). Tuberculosis is a leading cause of disease burden, with approximately 90 million cases and 30 million deaths from 1990-1999 (Biondi et al., 1997). This trend has continued, with 1.93 billion active and latent cases in 2017, 10 million cases and 1.45 million deaths in 2018 (Van Der Walt & Keddy, 2021), and 1.25 million deaths in 2023. Disease burden is typically highest in Southeast Asia, with most cases occurring in Banglesash, China, India and Pakistan (Van Der Walt & Keddy, 2021; Cheng et al., 2017). Depression is often cited as a contributor to infection rates, as the prevalence of depression among people who develop active TB is more significant than with other medical conditions (Cheng et al., 2017). Lifetime depressive disorders affect 120 million people globally, and from 1990-2007, an increase in depression prevalence rose by 33.4%, with the majority of cases impacting South Asia, Africa, and the Middle East (Van Der Walt & Keddy, 2021). This consistency between incidence areas for tuberculosis infection and depression prevalence may hold biological significance.

A psychosocial stressor is an event or situation that places individuals at heightened or chronic stress levels (Kogler et al., 2015). These events typically involve psychological characteristics or social experiences that can impact a person's health, well-being, or behaviour and can include divorce, grief, mental illness, homelessness, drug and alcohol abuse and poverty (Kogler., 2015). The goals of this paper are to demonstrate that psychosocial stressors impair immunological functions necessary for maintaining immunity and resistance against illness and disease and demonstrate that this compromised immunological resistance places individuals at a higher risk of contracting TB, ultimately proving that individuals who experience psychological stress and psychosocial stressors are at a higher risk of developing tuberculosis.

Background

HPA axis and Stressors

The central nervous system (CNS) regulates the immune system response and is a network of axes connecting the nervous, endocrine, and immune systems (Glaser & Kiecolt-Glaser, 2005). The hypothalamic-pituitary-adrenal (HPA) axis is a communication system between the hypothalamus, pituitary glands, and adrenal glands, in which corticotrophin-releasing hormones are released from the hypothalamus into the hypophyseal portal blood supply which stimulates the release of adrenocorticotropic hormone (ACTH) and subsequent release of glucocorticoid (GC) hormones (Padgett & Glaser, 2023; Glaser & Kiecolt-Glaser, 2005). Through the activation of the HPA axis, the adrenal medulla activates catecholamine production, which includes adrenaline and noradrenaline, ACTH, cortisol, growth hormone and prolactin (Padgett & Glaser, 2023; Glaser & Kiecolt-Glaser, 2005). As the immune system and CNS relationship are bidirectional, stressors that increase corticotropin-releasing hormones (CRH) dysregulate the HPA axis through increased stress hormone levels (Glaser & Kiecolt-Glaser, 2005). Immunological alterations may occur through the biding of the hormone to the surface of the cognate receptor cell or by stimulating the dysregulated production of cytokines like interferon-γ (IFN-γ), interleukin-1 (IL-1), IL-2, IL-6 and tumour-necrosis factor (TNF) (Glaser & Kiecolt-Glaser, 2005). If chronically activated, the HPA axis can harm immunological resistance. Immunocompetence can modify hosts' resistance to infectious agents and suppress the antiviral immune response, specifically through increased corticosteroids, catecholamines, and plasmatic glucocorticoid levels (Biondi et al., 1997). Constant stressors may increase the risks of developing diseases and prolong infection periods. Factors like alcohol and

drug abuse can alter the bidirectional relationship between immune system response and the CNS (Biondi et al., 1997).

Depression-Tuberculosis Syndemic

Depression and tuberculosis are both significant health conditions responsible for high global morbidity and mortality rates, as tuberculosis is a comorbidity of depression. Approximately 39%–70% of pulmonary TB cases involved anxiety or depression, insinuating that they share a bidirectional relationship (Birmaher et al., 1994). The tuberculosis-depression syndemic asserts that increased vulnerability to TB contraction stems from the immunological compromisation after depression (Birmaher et al., 1994). Chronic depressive episodes can increase the frequency of cortisol production and alter the production of IL-6. These alterations would compromise the ability to challenge antigens and reduce inflammatory responses to a bacterium (Glaser & Kiecolt-Glaser, 2005) or contribute to the activation of latent TB (Hayward et al., 2019). The relationships between depression, immunological alterations and psychosocial stressors explore the negative dysregulation of immunity necessary to combat infection. However, these stressors are common risk factors in at-risk groups like people experiencing homelessness and alcohol and substance dependence (Van Der Walt & Keddy, 2021; Hernández Sarmiento et al., 2013).

Original Research

Psychoneuroimmunology emphasizes the interactions between the nervous, endocrine, and immune systems. This interdisciplinary field often intersects with psychology, neuroscience, and immunology (Padgett & Glaser, 2023; Glaser & Kiecolt-Glaser, 2005). The field was initially pioneered by Japanese scientist Dr. T. Ishigami, who studied the relationship between immune system alterations and stress conditions, specifically in leukocyte alterations during

psychological stress (Biondi et al., 1997). This work asserted that immunodepression increased the probability of vulnerability to TB, paving the way for further research by Holmes. Thomas Holmes was a physician at a Seattle tuberculosis sanatorium from 1949 to 1961, who wanted to study the relationship between emotions, social environments and health (Lerner et al., 2022). His work discovered that sanatorium patients had experienced stressful life events between 2-5 years before tuberculosis infection and hospitalization (Biondi et al., 1997; Lerner et al., 2022). These life events included spousal death, divorce, irregular sleep patterns, financial hardship, alcohol and drug use and job dissatisfaction, with 71% experiencing financial hardship, 52% job dissatisfaction, and 31% meeting the criteria for alcoholism (Lerner et al., 2022). Holmes discovered a correlation between low 17-ketosteroid levels and TB contraction among these individuals. These individuals were usually depressed, with more advanced TB levels, and deteriorated more rapidly than their infected counterparts (Lerner et al., 2022). This original work by Holmes and Isigmai prompted the discussion of the interconnectedness between host-pathogen interactions and psychosocial stressors.

Materials and Methods

The articles included in this literature review were chosen through two Google Scholar searches, the first being "Psychological Stress and Tuberculosis." This produced 293,000 results, in which the first ten pages were screened for keywords such as Depression-Tuberculosis syndemic, depression, psychosocial factors, and bidirectional relationship. The second search was for articles relating to "Mental Health and Tuberculosis," which produced 702,000 results. Similarly, the first ten pages were screened for words such as stressors, tuberculosis, interplay, depression, and syndemic. Further criteria were established to determine the article utilized in this review. The population groups could include any demographic of any geographic region,

except for papers based on animal testing and papers written in languages other than English. The group involved had to have experienced some psychosocial stressors before Tuberculosis infection, and this group had to be contrasted with a control group not experiencing psychosocial stressors or tuberculosis infection. The outcome of the articles used had to be a perceived increase in vulnerability to tuberculosis, no connection between psychosocial stressors and tuberculosis, or unclear results. The search results for "Psychological Stress and Tuberculosis" yielded ten articles that fit the criteria (Figure 2), and the search for "Mental Illness and Tuberculosis" yielded twenty-two relevant articles (Figure 1). The articles were then used in one of two sections of this paper: the negative impact of psychosocial factors on immunological systems, which functioned as background research and the effect of psychosocial factors on the contraction of Tuberculosis, which were the results of this literature review. The "Psychological Stress and Tuberculosis" search produced many results that did not meet my criteria as they referenced the impact of psychosocial stressors on the quality of care of tuberculosis patients and the impact of psychological stress on treatment outcomes. For example, the article *Cognitive-behavioral therapy on psychological stress and quality of life in subjects with pulmonary tuberculosis: a community-based cluster randomized controlled trial* (Zuo et al., 2022) was rejected on this basis. Other articles were excluded based on the inclusion of animal trials like *Psychological stress creates an immune suppressive environment in the lung that increases the susceptibility of aged mice to Mycobacterium tuberculosis infection* (Lafuse et al., 2022). The articles included were analyzed for indications that infected cohorts of participants had experienced psychosocial stressors, placing them in immunologically compromised conditions before contraction. The literature was reviewed to compile specific immunological changes such as Pro-inflammatory protein Mϕ migration inhibitory factors (MIF), interleukin-1

(IL-1), IL-2, IL-6 and tumour-necrosis factors (TNF), and CD4/CD8 ratios, which may indicate susceptibility to contraction of tuberculosis.

Results (Figure 5)

Pro-inflammatory protein Mϕ Migration Inhibitory Factor (MIF)

Macrophage migration inhibitory factor (MIF) is a naturally occurring cytokine secreted from Mϕs and T cells. It acts as a mitigator for inflammation and controls infection (Das et al.,1956; Zhang et al., 2019). Macrophages deficient in MIF demonstrate reduced cytokine production and impaired innate immune response, which can increase the risk of TB disease (Das et al., 1956; Zhang et al.,2019). Chronic depression can specifically dysregulate the MIF responses, and studies have shown that reduced MIF can exacerbate depression symptoms and reduce the production of cytokines TNF-α, IL-10, and T-cells (Birmaher et al., 1994; Das et al., 1956). As *M.tb* typically enters the lungs via phagocytosis through Mϕs, lipolytic enzymes can increase the host's immune status through lipid accumulation (Birmaher et al., 1994). The metabolism also plays a key role in depressive patients in that depression can disturb metabolism, which increases inflammation (Birmaher et al., 1994). MIF is a critical mediator in the response to *Mtb* infection and is explicitly expressed in patients with depression, placing them at a higher risk of contracting TB through the dysregulation of normal inflammatory responses.

CD4/CD8 ratios

Lymphocytes are typically categorized into two phenotypes: CD4 helper/inducer cells and CD8 cytotoxic/suppressor cells. Both are found in lymph nodes but display different surface markers (Obeagu et al., 2023). The typical ‘normal’ range for a CD4/CD8 ratio is between 1.5 and 2.5; however, normal levels are subjective based on sex, age, ethnicity, and genetics (Obeagu

et al., 2023). When CD4/CD8 ratios are inverted, meaning more CD8 cells than CD4 cells, it can be considered an immune risk phenotype (Obeagu et al., 2023; Hayward et al., 2019). TB studies have concluded that counts of CD3, CD4 and CD8 are all decreased in patients with TB and who also experience depressive symptoms, which can prompt immune system suppression (Hayward et al., 2019; Liu et al., 2022; Zhang et al.,2019). Reduced lymphocyte counts are considered to encourage immunosuppression, which would increase susceptibility to TB and is a quality recognized in individuals with anxiety and depression.

Cytokine Dysregulation

Cytokines are small proteins critical in signalling and comprise various substances, the most notable being interleukin and interferon. Interleukin 6 (IL-6) is a pro-inflammatory cytokine and an anti-inflammatory myokine typically expressed by antigen-presenting cells (APCs) in response to external stimuli (Dienz & Rincon, 2009). It is a vital mediator of immune responses, protecting CD4 T-cells from activation-induced cell death (AICD) (Dienz & Rincon, 2009). Interleukin 2 (IL-2) is a cytokine signalling molecule in the immune system responsible for producing and expanding CD4 T-cells to promote antigen response (Malek, 2003). Interleukin-1 beta (IL-1β) is a cytokine that modulates autoimmune inflammation (Ben-Sasson et al., 2013). IL-1β can enhance the expansion of CD4 and CD8 cells, specifically in the liver and lungs (Ben-Sasson et al., 2013). Interleukin-12 (IL-12) is a cytokine produced by white blood cells which plays a role in defending against infection and autoimmune diseases. The ability of IFNγ to contain intracellular *M.tb* relies on phagocyte stimulation, meaning reduced IFNγ levels can increase susceptibility to mycobacterial infection (Hayward et al., 2019). IL-12 is essential for enhancing protective immunity against less pathogenic bacterium and would, therefore, also aid in suppressing increasingly virulent bacterium (Hayward et al., 2019). IL-2 and IL-6 both

work to monitor and regulate the HPA axis and the nerve–endocrine–immune network, increasing the CD4 cell counts necessary to promote immune responses (Zhang et al.,2019). IL-2 and IL-6 are also biomarkers for inflammation in patients with depression, while increased levels of IL-1β due to depression can increase inflammation and reduce immune system responses to TB (Zhang et al.,2019).

T-Cell Availability

T-cells are white blood cells necessary to help the body's immune response against infection and disease. They are typically grouped into cytotoxic T-cells/ killer T-cells, which destroy infected cells through apoptosis, and helper T-cells, which work to force B-cells to create antibodies. The availability of T-cells will impact the effectiveness of disease prevention and immunity, and they are considered responsible for the immune activation of depression and TB (Birmaher et al., 1994). If depression is constant, T-cells and B-cells may continuously multiply to combat pathogens until this production becomes pathogenic and influences the body's ability to effectively defend itself from pathogens (Birmaher et al., 1994; Zhang et al.,2019). Depression has been recorded explicitly to impair T-cell counts necessary for innate and adaptive immune mechanisms to fight *M.tb* (Hernández Sarmiento et al., 2013; Birmaher et al., 1994; Hayward et al., 2019).

Discussion

Psychosocial factors such as depression, anxiety, adverse housing, financial hardship, migration and grief can create immunological change, which act as risk factors and biological markers of tuberculosis susceptibility. The pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) is necessary to control inflammation and infection; those macrophages exhibiting reduced MIF can contribute to a weakened innate immune system response. Chronic

depression can also mediate the effects of MIF, which impairs the functions of cytokines like T-cell activation and IL-12. The dysregulation of IL-6, IL-2, and IL-1β would impact the ability of the body to complete immune signalling and produce accurate inflammatory responses effectively. IL-6 and IL-2 also support CD4 t-cell functions, which are tied to innate and adaptive immunity and work to regulate the HPA axis. Consistent depressive states or chronic stress can cause consistent HPA axis activation, which increases T-cell levels and impairs the ability to respond to *M.tb* infection. This is expressed when CD4 and CD8 ratios are inverted, and lymphocyte counts are reduced, acting as an immune risk phenotype.

Trends

These markers are considered biological markers for increased susceptibility to tuberculosis, and trends were observed in the literature reviewed regarding the increased prevalence of biomarkers in specific at-risk groups. Individuals who experienced depression or mental illness were commonly cited as reflecting the biomarkers for TB contraction. A nationwide database search in Korea asserted that patients with depression were at a 2.63-fold higher risk of contracting TB, and a similar study in Taiwan concluded a 1.16-fold higher risk for depressive patients (Birmaher et al., 1994). Studies in Ethiopia have concluded that individuals with depression are 5 times more likely to develop TB than the general public (Temesgen et al., 2021). At the same time, research in Denmark places individuals with depression seven times more likely to develop TB (Nordholm et al., 2023a). This is due to the reduced immunity necessary to control the *M.tb* bacterium and heightened inflammatory responses, but it is also correlated to environmental situations that place individuals at a higher risk of developing latent TB. These environmental risk factors include homelessness or living in congregate housing (McQuinstion et al.,1997; Hernández Sarmiento et al., 2013), alcohol and drug abuse and

migration (McQuinstion et al.,1997; Nordholm et al., 2023a; Goel et al., 2023). Explaining TB prevalence among those who experience depression and mental illness cannot be separated from the adverse conditions which contribute to a complex interplay between depression, poverty, substance abuse, behaviour and immunosuppression. While the articles utilized in this study represent a wide variety of global infection and tuberculosis research, a variety of articles highlight the connection between individuals of a lower socio-economic position, regardless of geography, are at-risk groups due to the interconnected nature of poverty and psychosocial factors which would influence immunosuppression (Hayward et al., 2019) A key trend observed throughout the literature involved in this review is the continuing impact of sanatorium hospitalization on TB infection. Tuberculosis is consistently contracted at higher rates among hospitalized mental health patients than their prospective public populations (Wassersug & McLaughlin, 1951; Katz et al., 1954). Social risk factors for contraction can include substance abuse, unstable socioeconomic status, and close living environments; however, the current research is not substantial enough to provide definitive answers for the increased cases of TB. This trend, however, is crucial due to its persistent identification of sanatorium patients as an at-risk group over 30-70 years of research (Wassersug & McLaughlin, 1951; Katz et al., 1954).

Future Research

This paper aims to analyze and bridge gaps in the research on the tuberculosis depression syndemic by analyzing qualities like psychosocial factors, immunity, and vulnerability to disease. By examining the comorbidities and psychosocial stressors associated with TB contraction, preventative structures and resources can be allocated to at-risk groups experiencing the majority of TB cases and reduce social structures which perpetuate the contraction of TB. Future directions in research should focus on highlighting at-risk groups and creating

preventative frameworks to reduce the global impact of tuberculosis. Conceptual frameworks should focus on all aspects of social intervention and include psychosocial theory, which argues that vulnerability to TB includes aspects like psychological stress, depression, adverse living conditions and inequality. Following a biosocial model similar to the proposed model by Maciel et al. (2015) is beneficial in highlighting all axes that impact disease contraction. The model should include an individual vulnerability axis, focusing on aspects like age, education status, ethnicity, mental illness, and alcoholism; a programmatic vulnerability axis, which highlights institutional vulnerability through testing or occupational hazards; and a social vulnerability axis, which references aspects like institutionalization, and geography (Maciel et al., 2015).

This review aimed to demonstrate that psychosocial stressors impair immunological functions necessary for maintaining immunity and resistance against illness and disease and that this immunocompromisation places these individuals at a heightened risk of developing tuberculosis. Of the articles utilized that referenced a relationship between a psychosocial stressor and tuberculosis,

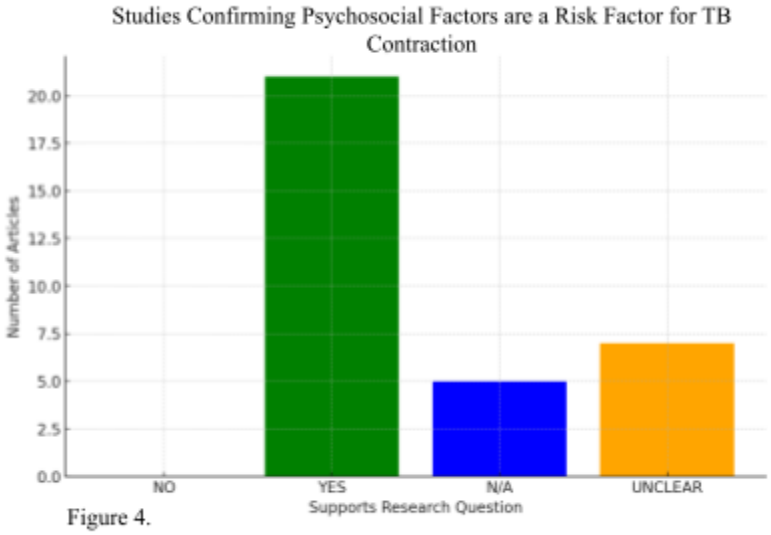

Figure 4.

21/33 (63.6%) stated that there was a connection between psychosocial stressors and TB contraction, 0/33 (0%) said there was no connection, and 7/33 (21.2%) stated the connection was unclear (Figure 4). Of the articles unable to prove a positive correlation, the majority took an

unclear status to advocate for further research before making conclusions. For example, Zhang et al. (2019) produce findings on reduced T-cell counts, dysregulated interleukin function and CD4/CD8 ratios that align with a majority of the articles arguing causation between psychosocial factors and tuberculosis contraction but highlight in their conclusions, “Although reports have indicated the possibility of a bidirectional association between depression and TB infection, whether and how depression increases the risk of TB remains unclear” (Zhang et al., 2019) Simmilarily Araújo et al., (2014) states “further epidemiological studies are required to increase our understanding of the possible biological and social mechanisms responsible” (Araújo et al., 2014). While the study by Zhang et al. (2019) presented sufficient methodology, the study by Araújo et al. (2014) relied heavily on self-assessments, which may have impacted the reliability of the results. Birmaher et al. conducted a study on the stress levels of adolescents with depression and the subsequent biological markers (Birmaher et al., 1994). The study concluded that there were no significant differences between cellular immune measurements in the depression and control groups (Birmaher et al., 1994). However, the sample result was only 17 individuals in each group, meaning the sample may not reflect larger populations. As TB is an infectious disease driven by *Mycobacterium tuberculosis,* biological factors, including exposure immunity and genetics, will play a role that is arguably more crucial than social stressors. However, as psychosocial stressors have also been proven to influence biological determinants of health, the connection between psychosocial stress and infection susceptibility is not surprising. The combined connection between biological and environmental stressors influencing tuberculosis development aligns with previous correlation expectations.

Limitations

As a literature review attempting to decipher a definitive connection between psychosocial stressors and tuberculosis, this paper is limited to the individual limitations of each article utilized. Missed TB diagnoses within the clinical studies reviewed may shift results regarding the over-exaggeration or underspecification of at-risk groups. As TB is a disease which shares various comorbidities that often cause immunosuppression through similar biological mechanisms, it may have been difficult for researchers to determine whether behavioural variables were the primary or secondary psychosocial symptoms prompting TB contraction. For example, according to Hernández Sarmiento et al. (2015), psychosocial factors among the homeless population in Columbia influence higher TB rates; however, the primary factor may be adverse living conditions, mental health or alcohol and drug usage. Biondi (1997) highlights the importance of noting limitations in studies that utilize self-reported stress measures. These factors are often subjective to various participants (Biondi et al., 1997). Due to the chosen methodology, this literature review relies on an abundance of research from the 1950s, including work by Holmes (1957), Ishigami (1919), and Wassersug (1951), which, although it supports the paper thesis may not reflect methodology standard of modern research. Additionally, the search method often produced multiple articles from the same author, meaning the statistics that demonstrate 63.6% of articles utilized in this paper support the thesis, including various articles from the same author and duplicate articles that appeared in both Google Scholar searches. This means that 63.6% may not accurately reflect the academic opinion on the connection between psychosocial stressors and tuberculosis.

Conclusion

Individuals who experience psychological stress and psychosocial stressors are at a higher risk of developing tuberculosis. Biological markers such as reduced T-cell availability, dysregulated cytokine and interleukin function, and over-activation of the HPA axis cause pathogenic alterations to immune functions, placing individuals at heightened TB vulnerability. Completing further research regarding the comorbidity of psychosocial stressors and tuberculosis will help bridge existing research gaps to fully understand the dynamics between social structures, mental health, immunity, vulnerability and tuberculosis. By determining at-risk groups and the related biomarkers associated with TB susceptibility, social structures which perpetuate heightened contraction within specific groups can be effectively addressed to reduce the global burden of Tuberculosis.

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Goel, N., Goyal, V., Girdhar, R., Goel, S., & Kumar, V. (2023). Association of common mental disorders with pulmonary tuberculosis: A cross-sectional study. *The Journal of Association of Chest Physicians, 11*(2), 77–80.
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Liu, X., Bai, X., Ren, R., Tan, L., Zhang, Y., Lan, H., ... & Tang, X. (2022). Association between depression or anxiety symptoms and immune-inflammatory characteristics in in-patients with tuberculosis: A cross-sectional study. *Frontiers in Psychiatry, 13*, 985823.
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McQuistion, H. L., Colson, P., Yankowitz, R., & Susser, E. (1997). Tuberculosis infection among people with severe mental illness. *Psychiatric Services, 48*(6), 833–835.
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Nordholm, A. C., Andersen, A. B., Wejse, C., Norman, A., Ekstrøm, C. T., Andersen, P. H., ... & Lillebaek, T. (2023). Mental illness, substance abuse, and tuberculosis risk. *International Journal of Infectious Diseases*.
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Temesgen, E., Belete, Y., Haile, K., & Ali, S. (2021). Prevalence of active tuberculosis and associated factors among people with chronic psychotic disorders at St. Amanuel Mental Specialized Hospital and Gergesenon Mental Rehabilitation Center, Addis Ababa, Ethiopia. *BMC Infectious Diseases, 21*, 1–9.
Van Der Walt, M., & Keddy, K. H. (2021). The tuberculosis-depression syndemic and evolution of pharmaceutical therapeutics: From ancient times to the future. *Frontiers in Psychiatry, 12*, 617751.
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Zmak, L., Obrovac, M., Lovric, Z., Makek, M. J., & Jankovic, V. K. (2017). Neglected disease in mentally ill patients: Major tuberculosis outbreak in a psychiatric hospital. *American Journal of Infection Control, 45*(4), 456–457.

Figure 1. Articles utilized from the "Mental Illness and Tuberculosis" search.

Citations
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Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews Immunology, 5*(3), 243–251.
Hayward, S. E., Dowd, J. B., Fletcher, H., Nellums, L. B., Wurie, F., & Boccia, D. (2019). A systematic review of the impact of psychosocial factors on immunity: Implications for enhancing BCG response against tuberculosis. *SSM - Population Health, 10*, 100522.
Holmes, T. H., Hawkins, N. G., Bowerman, C. E., Clarke Jr., E. R., & Joffe, J. R. (1957). Psychosocial and psychophysiologic studies of tuberculosis. *Psychosomatic Medicine, 19*(2), 134–143.
Lerner, B. H. (1996). Can stress cause disease? Revisiting the tuberculosis research of Thomas Holmes, 1949–1961. *Annals of Internal Medicine, 124*(7), 673–680.
Padgett, D. A., & Glaser, R. (2003). How stress influences the immune response. *Trends in Immunology, 24*(8), 444–448.
Sparer, P. J. (1956). Personality, stress, and tuberculosis. *International Universities Press*.
Sweetland, A. C., Kritski, A., Oquendo, M. A., Sublette, M. E., Norcini Pala, A., Silva, L. R., ... & Wainberg, M. L. (2017). Addressing the tuberculosis–depression syndemic to end the tuberculosis epidemic. *The International Journal of Tuberculosis and Lung Disease, 21*(8), 852–861.
Zhang, K., Wang, X., Tu, J., Rong, H., Werz, O., & Chen, X. (2019). The interplay between depression and tuberculosis. Journal of leukocyte biology, 106(3), 749-757.

Figure 2. Articles utilized from the "Psychological stress and Tuberculosis." search

Figure 5. Thirty-three included studies from search results for “Psychological Stress and Tuberculosis” and “Mental Illness and Tuberculosis,” screened for relevant participant groups, psychosocial stressors, the biological results of the studies, and whether they can be used to support this thesis.

Citation	Study Participants	Psychosocial Factors	Biological Results	Support Thesis
Altshuler, S. S., & Bailey, L. J. (1941). Control of tuberculosis in an institution for the mentally ill. *American Review of Tuberculosis, 44*(3), 335–345.	Patients Hospitalized in Eloise Hospital for mental health	Chronic stress, depression anxiety	N/A	Yes
Araújo, G. S. D., Pereira, S. M., Santos, D. N. D., Marinho, J. M., Rodrigues, L. C., & Barreto, M. L. (2014). Common mental disorders associated with tuberculosis: A matched case-control study. *PLoS One, 9*(6), e99551.	Salvador, Brazil, 1,434 individuals	Depressive, anxiety or Somatoform symptoms, Including irritability, Insomnia, nervousness fatigue, and feelings of uselessness	Possible increased vulnerability	Unclear
Birmaher, B., Rabin, B. S., Garcia, M. R., Jain, U., Whiteside, T. L., Williamson, D. E., ... & Ryan, N. D. (1994). Cellular immunity in depressed, conduct disorder, and normal adolescents: Role of adverse life events. *Journal of the American Academy of Child & Adolescent Psychiatry, 33*(5), 671–678.	Twenty adolescent subjects with major depressive disorder	Depression	Reduced natural T-cell activity	Unclear
Cheng, K. C., Liao, K. F., Lin, C. L., & Lai, S. W. (2017). Increased risk of pulmonary tuberculosis in patients with depression: A cohort study in Taiwan. *Frontiers in Psychiatry, 8*, 235.	Taiwan National Health Insurance Program, depression and non-depression groups	Depression	Higher proportion of asbestosis, CKD, HIV infection, gastrectomy, pneumoconiosis and splenectomy	Yes
Collins, G. H. (1956). Physique, mental illness, and pulmonary tuberculosis. *British Medical Journal, 1*(4978), 1298.	700 male patients in a mental hospital	Depressive states, epilepsy, chronic mania, senile confusional state, mental deficiency, chronic alcoholism	Possible increased vulnerability	Unclear
Doherty, A. M., Kelly, J., McDonald, C., O’Dywer, A. M., Keane, J., & Cooney, J. (2013). A review of the interplay between tuberculosis and mental health. *General Hospital Psychiatry, 35*(4), 398–406	Literature review	Depression, anxiety, mental illness	Increased vulnerability to contracting TB	Yes
Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews Immunology, 5*(3), 243–251.	Literature review	Depression	Activation of HPA axis, CNS and SNS, release of ACTH, augment production of IL-6	N/A
Goel, N., Goyal, V., Girdhar, R., Goel, S., & Kumar, V. (2023). Association of common mental disorders with pulmonary tuberculosis: A cross-sectional study. *The Journal of Association of Chest Physicians, 11*(2), 77–80.	Patients at a tertiary care center	Depression and Stress	Decreased immunity	Yes

Hayward, S. E., Dowd, J. B., Fletcher, H., Nellums, L. B., Wurie, F., & Boccia, D. (2019). A systematic review of the impact of psychosocial factors on immunity: Implications for enhancing BCG response against tuberculosis. *SSM - Population Health, 10*, 100522	Literature review	Depression	Impairments in CD4+ T-cell mediated activities, reduced NK cell counts, cytotoxicity	Yes
Hayward, S. E., Deal, A., Rustage, K., Nellums, L. B., Sweetland, A. C., Boccia, D., ... & Friedland, J. S. (2022). The relationship between mental health and risk of active tuberculosis: A systematic review. *BMJ Open, 12*(1), e048945.	Literature review	Mental illness, neuropsychiatric disorders, depression, homelessness, anxiety	Heightened relative risk of TB incidence contraction	Yes
Hernández Sarmiento, J. M., Correa, N., Correa, M., Franco, J. G., Alvarez, M., Ramírez, C., ... & Robledo, J. (2013). Tuberculosis among homeless population from Medellín, Colombia: Associated mental disorders and sociodemographic characteristics. *Journal of Immigrant and Minority Health, 15*, 693–699.	426 homeless people in Columbia	Homelessness, depression, mental illness, drug and alcohol dependency	Heightened relative risk of TB incidence contraction	Yes
Holmes, T. H., Hawkins, N. G., Bowerman, C. E., Clarke Jr., E. R., & Joffe, J. R. (1957). Psychosocial and psychophysiologic studies of tuberculosis. *Psychosomatic Medicine, 19*(2), 134–143	200 patients with tuberculosis	Death, divorce, or separation of parents, financial worry, unemployment, depression	Reduced 17-ketosteroid output	YEs
Katz, J., Kunofsky, S., & Locke, B. Z. (1954). Tuberculosis morbidity and mortality among mental patients as compared with the general population. *American Review of Tuberculosis, 70*(1), 32–48.	Mental Patients	Depression, anxiety, mental illness	Possible increased vulnerability to contracting TB	Unclear
Katz, J., Plunkett, R. E., & Thompson, M. E. (1945). Prevalence of pulmonary tuberculosis in New York State institutions for the mentally ill. *American Review of Tuberculosis*.	73,658 patients in Brooklyn State Hospital and Kings Park State Hospital	Mental illness	Possible increased vulnerability to contracting TB	Unclear
Lerner, B. H. (1996). Can stress cause disease? Revisiting the tuberculosis research of Thomas Holmes, 1949–1961. *Annals of Internal Medicine, 124*(7), 673–680.	Literature review	Stress, marital break, divorce, death, irregular sleep, financial hardship, alcoholism, drug dependency, depression	Possible increased vulnerability to contracting TB	Unclear
Liu, X., Bai, X., Ren, R., Tan, L., Zhang, Y., Lan, H., ... & Tang, X. (2022). Association between depression or anxiety symptoms and immune-inflammatory characteristics in in-patients with tuberculosis: A	338 in- patients with TB from 3 hospitals in China using the nine-item Patient Health Questionnaire (PHQ-9)	Depression, anxiety	Lower CD3, CD4, CD8, and lymphocytes drug resistance	Yes

cross-sectional study. *Frontiers in Psychiatry, 13*, 985823.				
Maciel, E. L., & Reis-Santos, B. (2015). Determinants of tuberculosis in Brazil: From conceptual framework to practical application. *Revista Panamericana de Salud Pública, 38*, 28–34.	N/A	N/A	N/A	N/A
McQuistion, H. L., Colson, P., Yankowitz, R., & Susser, E. (1997). Tuberculosis infection among people with severe mental illness. *Psychiatric Services, 48*(6), 833–835.	New York City Teaching Hospital, 75 participants	Depression, anxiety, homelessness, alcohol and drug dependency, HIV positive, mental illness	PPD Positive Testing	Yes
Nordholm, A. C., Andersen, A. B., Wejse, C., Norman, A., Ekstrøm, C. T., Andersen, P. H., ... & Koch, A. (2023). Mortality, risk factors, and causes of death among people with tuberculosis in Denmark, 1990–2018. *International Journal of Infectious Diseases, 130*, 76–82.	Nationwide case-control study in Denmark spanning three decades	Low socioeconomic status, mental illness, substance abuse	Increased vulnerability to contracting TB	Yes
Nordholm, A. C., Andersen, A. B., Wejse, C., Norman, A., Ekstrøm, C. T., Andersen, P. H., ... & Lillebaek, T. (2023). Mental illness, substance abuse, and tuberculosis risk. *International Journal of Infectious Diseases*.	Nationwide case-control study in Denmark spanning three decades	Mental illness, substance abuse (MISA)	Increased vulnerability to contracting TB	YEs
Padgett, D. A., & Glaser, R. (2003). How stress influences the immune response. *Trends in Immunology, 24*(8), 444–448.	N/A	N/A	N/A	N/A
Qader, G., Seddiq, M. K., Rashidi, K. M., Hamim, A., Akhgar, M. H., Ahmad, B., ... & Suarez, P. G. (2019). Prevalence of tuberculosis among mentally ill patients in conflict-stricken Afghanistan: A cross-sectional study. *International Journal of Infectious Diseases, 89*, 45–50.	Population. based study led by the CDC in Afghanistan	Widowed. mental illness, depression	Increased vulnerability to contracting TB	Yes
Sparer, P. J. (1956). Personality, stress, and tuberculosis. *International Universities Press*.	N/A	N/A	N/A	N/A
Sweetland, A., Oquendo, M., Wickramaratne, P., Weissman, M., & Wainberg, M. (2014). Depression: A silent driver of the global tuberculosis epidemic. *World Psychiatry, 13*(3), 325.	Literature review	Depression	Increased vulnerability to contracting TB	Yes
Sweetland, A. C., Kritski, A., Oquendo, M. A., Sublette, M. E., Norcini Pala, A., Silva, L.	Literature review	Depression	Increased vulnerability to contracting TB	Yes

R., ... & Wainberg, M. L. (2017). Addressing the tuberculosis–depression syndemic to end the tuberculosis epidemic. *The International Journal of Tuberculosis and Lung Disease, 21*(8), 852–861.				
Temesgen, E., Belete, Y., Haile, K., & Ali, S. (2021). Prevalence of active tuberculosis and associated factors among people with chronic psychotic disorders at St. Amanuel Mental Specialized Hospital and Gergesenon Mental Rehabilitation Center, Addis Ababa, Ethiopia. *BMC Infectious Diseases, 21*, 1–9.	A cross-sectional study Mental Specialized Hospital and Gergensenon Mental rehabilitation canter 2070	Chronic psychotic disorders	Increased vulnerability to contracting TB	Yes
Van Der Walt, M., & Keddy, K. H. (2021). The tuberculosis-depression syndemic and evolution of pharmaceutical therapeutics: From ancient times to the future. *Frontiers in Psychiatry, 12*, 617751.	Literature review	Homelessness, co-infection, alcohol and Substance dependacy	Increased vulnerability to contracting TB	Yes
Wassersug, J. D., & McLaughlin, W. F. (1951). Tuberculosis in mental hospitals. *The Journal of Nervous and Mental Disease, 113*(2), 115–126.	Literature review	Mental Illness	Increased vulnerability to contracting TB	Yes
Zhang, K., Wang, X., Tu, J., Rong, H., Werz, O., & Chen, X. (2019). The interplay between depression and tuberculosis. Journal of leukocyte biology, 106(3), 749-757.	Nationwide database search conducted in Korea	Depression	Decreasing circulating levels of IL-6, MIF	Unclear
Zmak, L., Obrovac, M., Lovric, Z., Makek, M. J., & Jankovic, V. K. (2017). Neglected disease in mentally ill patients: Major tuberculosis outbreak in a psychiatric hospital. *American Journal of Infection Control, 45*(4), 456–457.	Mental Hospital Patients	Mental Illness	Increased vulnerability to contracting TB	Yes
Zorrilla, E. P., Luborsky, L., McKay, J. R., Rosenthal, R., Houldin, A., Tax, A., ... & Schmidt, K. (2001). The relationship of depression and stressors to immunological assays: A meta-analytic review. *Brain, Behavior, and Immunity, 15*(3), 199–226	Literature review	Depression	Decreases in- and NK-cell function. increases in CD4/CD8 ratios leukocytosis	Yes