The impact of parasitic infection on mental health and illness in humans in Africa: A systematic review


1Institute of Immunology & Infection Research, University of Edinburgh, Ashworth Laboratories, King's Buildings, Charlotte Auerbach Road, Edinburgh EH9 3FL; 2NIHR Global Health Research Unit Tackling Infections to Benefit Africa (TIBA), University of Edinburgh, Ashworth Laboratories, King's Buildings, Charlotte Auerbach Road, Edinburgh, EH9 3FL.

Current Addresses

+Imperial College London, St Mary's Campus, Praed Street, London W2 1NY
++The University of Cambridge, The Old Schools, Trinity Lane, Cambridge, CB2 1TN

Author for correspondence: Alexandra Lampard-Scotford,
E-mail: Alexandra.LampardScotford@ed.ac.uk
Molecular adaptations
(I) Loss of neurotrophic support
(II) Alterations in intracellular signalling
(III) Alterations in synaptic proteins

Cellular and tissue changes
(I) Decreased neural network activity
(II) Cell atrophy and decreased neurogenesis
(III) Decreased structure volume

Social and environmental factors
(I) High stigmatisation conducive to developing mental illness and worsening pre-existing conditions
(II) Chronically low self-esteem and low worth, lack of self-regulation
(III) Dissociation, intense and ongoing emotional turbulence, regression

Psychological Illness
• Depression and mood disorders
• Anxiety, OCD and PTSD
• Schizophrenia and other delusionary disorders

Immune-inflammatory response system
• Activation of the HPA pathway
• Release of IL-6 and TNF-α
• Cytokines passing through the blood brain barrier
• Activation of the vagus nerve, resulting in central cytokine signalling
• Production, activation and trafficking of neurotoxic metabolites of the tryptophan cascade in both the brain and the liver

Psychological stress

Physiological stress

Systemic/physical illness
• Parasite infections
• Immune disorders
• Gastrointestinal disorders

Social and psychological influences
• Stigmatisation
• Exposure to trauma and social inequities
• Social deprivation

Brain, CNS and behavioural adaptations

Psychological Illness

Parasite infections
Immune disorders
Gastrointestinal disorders

Systemic/physical illness

Psychological stress

Physiological stress

Immune-inflammatory response system

Social and psychological influences

Brain, CNS and behavioural adaptations

Psychological Illness

Parasite infections
Immune disorders
Gastrointestinal disorders
Abstract

A growing body of research implicates inflammation as a potential pathway in the aetiology and pathophysiology of some mental illnesses. A systematic review was conducted to determine the association between parasitic infection and mental illnesses in humans in Africa and reviewed the state of the evidence available. The search focused on publications from Africa documenting the relationship between parasites from two parasite groups, helminths and protozoans, and four classifications of mental illness: mood affective disorders, neurotic and stress related disorders, schizotypal disorders and unspecified mental illnesses. In the 26 reviewed papers, the prevalence of mental illness was significantly higher in people with parasitic infection compared to those without infection, i.e., 58.2% vs 41.8% (p<0.001). An overall odds ratio found that the association of having a mental illness when testing positive for a parasitic infection was four times that of people without infection. Whilst the study showed significant associations between parasite infection and mental illness, it also highlights gaps in present literature on the pathophysiology of mental illness in people exposed to parasite infection. This study highlighted the importance of an integrated intervention for parasitic infection and mental illness.

Key words:
Parasitology, immunology, psychopathology, psychology, parasite infection, helminth infection, protozoa infection, mental illness, Africa
Key findings

- Across protozoan and helminth parasite types and all mental illness, the prevalence of mental illness was significantly higher in people with parasitic infection compared to those without infection.
- Evidence of greater prevalence between helminth and protozoan infection types and mental illness was limited; overall, results did not observe strong significant differences between the two parasite infection types.
- The relationship between inflammation and mental illnesses is an interplay between immunological, environmental and social factors that can be associated with a parasitic infection.

Introduction

The burden of mental illness is a growing problem globally, with approximately 80% of people in low to middle income countries (LMIC) likely to experience a mental disorder within their lifetime (Wilson, 2016). Psychiatric disorders (also referred to as mental illnesses) are psychological and behavioural patterns or syndromes that cause significant distress, impairment of personal functioning, involving abnormal emotions, thoughts, and behaviours (Parekh, 2018). Psychiatric disorders make up 30% of the global disease burden; however only 3% of global health investment is directed towards them, which drops to 1% in Africa (Vigo, Thornicroft, & Atun, 2016). Half of individuals living with a mental illness in high income countries receive insufficient care, and this figure rises to nearly 90% in low income countries (W. WHO & DO, 2017). The standard of care for mental illnesses in low-income countries has declined further during the global COVID-19 pandemic due to breakdown or health services provision as well as the socioeconomic impacts of COVID-19 mitigation strategies such as lockdown (Sodi et al., 2021).
The aetiology and therefore treatment of mental illness is complex. Various systemic infections can lead to a syndrome known as sickness behaviour, which is a behavioural complex induced by infections and immune trauma, mediated by pro-inflammatory cytokines (Kelley & Kent, 2020). The term ‘sickness behaviour’ is theorised to be, in part, orchestrated by inflammatory responses, which can trigger changes including increased hypervigilance and decreased motivation. The hypothesis postulates that these behaviours are thought to be evolutionarily advantageous in aiding survival by allocating more energy to the healing process (A. H. Miller & Raison, 2016).

Humans are host to nearly 300 species of parasitic worms and over 70 species of protozoa, with over a billion people affected by helminth infections, causing chronic inflammation (WHO, 2020). Many socioeconomic, emotional and psychological factors have long been associated with contributing to and facilitating depression. However, recent empirical work has found that biological factors, such as higher baseline inflammation due to high pathogen environments, as being potential contributors to the development of depression (Stieglitz et al., 2015); (Lee & Giuliani, 2019); (Zunszain, Hepgul, & Pariante, 2012); (Felger, 2019). A higher prevalence of psychiatric disorders in countries where parasite infections are more prevalent suggests that parasitic infections may play a role in psychiatric disorders. An increased parasitic load is associated with changes in mental health status; and the notion that treating psychiatric patients for chronic inflammation, caused by pathogens such as parasites, can improve mental health outcomes has gained momentum (C. M. Pariante, 2016); (Fond et al., 2014); (Na, Lee, Lee, Cho, & Jung, 2014). It has been proposed that in addition to suppressing the immune system, pathogens also induce the release of neuromodulators that regulate mental states (Adamo, 2002), some of which appear to be induced by endogenous opiates (Kavaliers, Colwell, & Choleris, 1999). For example, the parasite \textit{Schistosoma mansoni} produces opioid peptides, which are thought to suppress the
immune system (Pryor & Elizee, 2000). However, whether parasite-produced opioids have a
direct effect on the CNS and behaviour is unknown. It has been theorised that as opioids are
both immune and neuromodulators, the parasite could potentially use the same compound to
suppress the host’s immune system and alter neural function (Salzet, 2000). Or, through more
indirect means, the parasite could manipulate immune-neural connections in the host to alter
neural functions and change behaviour (Thompson & Kavaliers, 1994); (Kavaliers et al.,
1999). Genes coding for an increased anti-pathogen immune response have been selected for
as they were beneficial to host survival, leading to the ‘inflammation bias’ in the human
genome (A. H. Miller & Raison, 2016). Whilst this inflammatory bias has aided mankind
well, in protecting against pathogens and ensuring the survival and propagation of humans as
a species, it is important to recognise that successful defence against pathogens is reliant on
both immunologic and behavioural responses. Considering the intimate relationship existing
between the brain and the immune system, it has been suggested that a consequence of the
inflammatory bias is a susceptibility to behavioural and mental disorders, including reduced
exploratory behaviour manifesting in the form of depression and hypervigilance in the form
of anxiety (Charles L Raison & Miller, 2013). Supporting this notion is empirical work
suggesting that depression risk alleles are regularly associated with immune responses to
infection that were likely to enhance survival in ancestral environments (Charles L Raison &
Miller, 2013; Charles L. Raison et al., 2013).

Depressive symptoms are consistently associated with inflammation in both human
and animal models (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008); (van den
Biggelaar et al., 2007). Risk alleles for depression are high in the general population and they
are thought to have been retained to promote defence against pathogen through a range of
immunological and behavioural responses (Charles L. Raison & Miller, 2017). The genes
involved with such responses to pathogens have been shown to be altered in schizophrenic
(Sainz et al., 2013) and anxiety disorders (Luciano et al., 2010). Furthermore, it has been observed in empirical work that inflammation in otherwise healthy individuals, can work as a potential predictor of future development of psychopathology over the subsequent months or years (Valkanova, Ebmeier, & Allan, 2013). In addition, reducing inflammation therapeutically improves conditions such as depression in some patients (Charles L. Raison et al., 2013). Whilst such work does provide support to the hypothesis that a causational pathway exists between inflammation and some mental illnesses, more evidence is required to determine the exact nature of this association.

There are now concerted efforts to understand the mechanisms underlying the aetiology of mental illness. Nonetheless, these efforts are slow in relation to the increase of the burden of mental illness and the contribution of pathogens remains poorly understood as there are many other contributing and potentially confounding proximal pathways that blur the lines of pathogenic and inflammatory contributions to the development of mental illness. Over one billion people are affected by helminth infections and most of these are chronic infections causing chronic inflammation (WHO, 2020). During chronic inflammation, physiological processes become compromised through prolonged cytokine release. This can cause alterations to metabolism and homeostatic set points. Inflammatory mediators such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL6) and prostaglandins are involved in hypothalamic–pituitary–adrenal (HPA) regulation. The HPA axis dysfunction is implicated in psychiatric conditions such as bipolar disorder and schizophrenia (Tsigos & Chrousos, 1994); (Carmine M Pariante & Lightman, 2008).

Africa carries the highest burden of infectious diseases, with a particularly large burden of helminth and protozoan infections (Orish, 2015). To date there has been no analysis of the association parasitic infection and mental illness in Africa. This knowledge would inform prioritisation and integrated health interventions within health systems often
working with limited budgets. In this systematic review the primary aim was to investigate the prevalence of mental illness associated with parasitic infections in human populations in Africa. We further investigated if individuals infected with protozoan or helminth infection were more likely than uninfected individuals to present with a mental illness.

Materials and methods

Search methods

This study approach was a systematic review of published literature. A PRISMA (Page et al., 2021) compliant systematic search of published data was performed in Embase, Global Health, Medline, PsycInfo, Pubmed and Web of Science (see appendix Figure 1). The search was conducted by four independent reviewers and includes studies published from the years 2000-2020. The search terms were as inclusive as possible and included those indicated in appendix Figure 2.

Selection criteria

Abstracts were screened for selection if they included data on both parasite infections and mental illnesses in human populations. Data extracted included participants of any ethnicity, sex, and age; educational attainment or sociodemographic factors were not controlled for as not all publications gave this information. The studies included are all based in African countries. Following the primary exclusion criteria (see appendix figure 2) 63 selected papers were saved to a bibliography in EndNote and were then reviewed using the secondary inclusion and exclusion criteria (see appendix figure 2), leaving 26 papers for final analysis. Only papers published in English were considered. There were eight study types included in this review: cross-sectional, case controls, case series, case studies, systematic reviews,
qualitative, observational/exploratory and pilot studies. This information was included in the
169 data extracted.
170
The International Classification of Diseases 10 of Mental and Behavioural Disorders
171 for researchers (ICD-10) (WHO, 1993) was used to classify the mental illnesses included in
172 this review. Mood affective disorders (MAD) (ICD-10 codes F30-39) including all types of
depression (mild, moderate, severe, recurrent and major depressive disorder) and bipolar
175 disorder were included. Neurotic, stress related disorders (NSRD) (ICD-10 codes F40-48),
176 including anxiety (mild, moderate, severe, general and social), obsessive compulsive disorder
177 and post-traumatic stress disorder were included. Schizotypal disorders (SD) (ICD-10 codes
178 F20-29) including schizophrenia, delusions, hallucinations, and psychosis were also included.
179 Unspecified mental illnesses (UMI), including stigmatisation, low self-esteem, low quality of
180 life (QoL) and health Related QoL were included, as most papers list such illnesses as
181 afflicting the sample populations. All other types of mental illness were excluded. As the
182 focus of this review was on mental illness, neurological disorders were excluded. Suicidal
183 ideation was included under mood affective disorders, but suicide mortality was excluded.
184
The following protozoa parasite infections were considered: leishmaniasis caused by
185 Leishmania donovani, L. infantum, or L. major, human African trypanosomiasis caused by
186 Trypanosoma brucei gambiense and T. brucei rhodesiense, malaria caused by Plasmodium
187 falciparum, P. malariae, P. vivax, P. ovale or P. knowlesi, toxoplasmosis caused by
188 Toxoplasma gondii, and Chagas disease caused by Trypanosoma cruzi.
189
The following helminth parasite infection types were considered: helminthiasis
189 caused by Ascaris lumbricoides, Trichuris trichiura, Ancylostoma duodenale or Necator
189 americanus, schistosomiasis caused by Schistosoma mansoni or S. haematobium, lymphatic
189 filariasis caused by Wuchereria bancrofti, Brugia malayi and B. timori, toxocariasis caused
by Toxocara, nodding syndrome caused Onchocerca volvulus, dracontiasis caused by Dracunculus medinensis, onchocerciasis caused by Onchocerca volvulus and cysticercosis caused by Taenia solium.

Data extraction

Data was extracted from all papers meeting the inclusion criteria and inputted into an Excel MS table. This process was repeated by the independent reviewers and the final datasheets compared and merged before analysis (see Appendix Table 5). The columns were organised as follows: Reference title; Reference number; Country and continent; Year of publication; Study design; Sex; Sample size; Type of parasitic infection; Percentage of participants with parasite infection; ICD-10 mental illness classification code; Percentage of participants with mental illness; Percentage of participants that have both a mental illness and parasitic infection; Number of participants with a parasitic infection and mental illness; Number of participants with a parasite infection but no mental illness; Odds ratio.

The type of parasite infection and mental illness of each study was inputted into the data extraction table. The number and percentage of association of those with both a parasite infection and mental illness was calculated for each study, giving one output detailing the overall prevalence of mental illness and parasite infection in each reviewed study.

Grading of studies (GRADE)

Papers presenting incidence or prevalence of any parasite infection and associated mental illness were evaluated using an adapted GRADE score (Guyatt et al., 2008) (see appendix Table 1) based on the following features: the type of diagnostic tool of parasite infection used, the type of diagnostic tool of mental illness used, sample size, year of study, type of publication (i.e. research paper, review paper or case study), methodology and the presence/absence of control group. Laboratory, clinical and/or imaging diagnostic tools score
the highest as they are the gold standard and most reliable tool with the greatest assurance of validity in the results. Furthermore, studies that were published in the last five years score higher than those which were published in the last twenty plus years, as results can differ with time, through changes to cultural/societal any of attitudes and diagnostic advances. Papers/ studies with a GRADE score of >7 out of a total of 16 were deemed to meet the minimal quality of information presented and were included in the analysis. Papers with a score of <7 were excluded. See appendix Table 2 for the Modified GRADE score table for all studies included in this review.

Data synthesis

Descriptive analysis on the extracted data was performed on IBM SPSS v.24 and GraphPad Prism v.8.0. Descriptive statistics summarised the prevalence of parasite infection and any type of mental illness. Chi-Square and Fishers Exact tests were utilized to determine if the frequency of mental illness differed significantly between people co-infected with a parasite and those free of parasitic infection across all papers. Odds ratios for each paper were calculated to ascertain the risk of developing a mental illness when testing positive for a parasite infection.

Non-parametric tests were utilized in the analysis of the data. The Kruskal-Wallis and the Mann Whitney-U tests were performed to compare the differences in the prevalence of association for mental illness and parasite infection. This was conducted both for all parasites and all mental illnesses combined and then broken down by parasite infection type (protozoan and helminth) and by mental illness.

For papers not suitable for inclusion in statistical data analysis, Textual Narrative Synthesis Barnett-Page et al., 2009) (TNS) was utilised. TNS results were presented as a table summarising the study characteristics, study design, methods, the diagnostic tools
utilised to assess the presence of both parasite infection and mental illness, the prevalence of parasite infection and mental illness, the prevalence with association of parasite infection and mental illness, the prevalence of association of parasite infection and no mental illness and the overall perceptions, understanding and expectations of mental illnesses associated with parasite infections and the main findings of the papers. These findings are reported to identify commonalities, themes and differences reported across the papers (Appendix Table 4).

Results

Systematic Review

A total of 139 full text papers were selected for full review of which 63 passed the inclusion and exclusion criteria. Following the secondary inclusion and exclusion process, the 37 excluded papers were omitted due to little or no relevance to the aims of the review, no access to the papers due to language barriers, no results had been yielded from the paper as of yet, because the study was not based in Africa or due to a low GRADE score (Wise et al., 2012; Goldner-Vukov et al., 2014), leaving 26 papers for final analysis. Figure 2 depicts the review process. The papers that met the inclusion criteria are detailed in Appendix Table 4. Full reference list is given in the bibliography in the appendix.

The total population of persons included in all papers examined in this review was 14,856. The types of study included were cross-sectional (15), case-control (1), case-series (1), systematic review (4), qualitative (2), observational/ exploratory (1) and pilot studies (2) (see appendix figure 3a). The sample sizes ranged from 22 (Idro et al., 2013) to 3927 individuals (Lasebikan et al., 2017) (see appendix figure 3c). The mean age was 29.55 (SD±16.19). The majority of papers investigated populations with both sexes; but three papers looked at male only populations (Dienye et al., 2011; Gyapong et al., 2000; Okoye et
and three papers looked at female only populations (Downs et al., 2011; Chahed et al., 2019; Nwoke et al., 2005).

Comparison of mental illness prevalence

The \( \chi^2 \) test showed that the prevalence of mental illness among parasite infected individuals, 58.2%, was significantly higher than those without parasitic infection 41.8%, \( \chi^2 (1) = 684.1, \) \( P<0.001 \) (one-tailed). The odds of individuals with a parasite infection subsequently developing a mental illness were found to have a likelihood of 4.11 (95% CI [1.916-4.406]).

Looking at specific mental illness, neurotic stress related disorder (Median = 44.90%, CI 95% [19.23-65.85], n=9) was the most prevalent disorder among individuals carrying a parasite infection, followed jointly by mood affective disorder (Median = 44.64%, CI 95% [16.74-70.00], n=16) and schizotypal disorder (Median = 44.64% (CI 95% [12.44-100], n=6), then unspecified mental illness (Median = 39.45% (CI 95% [18.60-53.30], n = 18).

Nonetheless, there was no significant association between specific mental illnesses classifications and the presence of parasite infection (H (3) = 0.615, P= 0.96, see appendix figure 4).

From the papers that could not be analysed through statistical data analyses, using the Textual Narrative Synthesis (TNS), mental illness was found to be highly associated with parasite infection in those afflicted. TNS observed high levels of stigmatisation across the synthesised papers, which worked to aggravate the pre-existing mental illnesses and isolate persons afflicted with parasite infections. The key themes and commonalities relating to the stigmatisation of parasite infection across the analysed papers were found to be fear of contagion, physical appearance, becoming a burden to family, becoming ostracised or shunned, loss of employment and inability to fulfil particular gender roles due to illness. A clear overlap in consequences related to parasite infections was also seen, in terms of social,
economic, health-related and emotional concerns. Furthermore, lower quality of life and health related quality of life related to socioeconomic and emotional consequences of parasite infection, was often reported across the synthesised papers, as not only perpetuating the development of mental illness in the afflicted, but also increasing the global health burden of parasite infections overall (Appendix Table 4).

Comparison of mental illness prevalence of specific parasite infections with specific mental illnesses

There was no significant association observed from the Kruskal-Wallis test between specific parasite infection classes and presence of any mental illness ($H(3) = 3.42, P=0.33$, see appendix figure 5a). Nor was there a significant result yielded from the Kruskal-Wallis test examining specific parasitic infection type and specific mental illness classification ($H(7) = 7.62, P=0.367$, see appendix figure 5e). There was insufficient data to compare the protozoa and schizotypal disorder (n=1) and helminth and schizotypal disorder (n=4). Conversely, there were no significant differences in association between specific parasite infections and specific mental illnesses. However, there was a greater prevalence of unspecified mental illnesses in individuals with protozoal infections compared to helminth infections ($U=12, P<0.05$, see appendix figure 5b), although the small sample size of the protozoa group must be noted.

Discussion

The primary purpose of this meta-analysis was to determine if the prevalence of mental illness was higher in people presenting with a parasite infection. From a systematic literature search, the 26 included studies revealed evidence of associations between parasitic infections and mental illness. Among people with parasitic infection, 58.2% had a mental illness
compared to 41.8% of uninfected people with mental illnesses and the risk of an individual
developing a mental illness was found to increase 4-fold when presenting with a parasitic
infection. Helminth parasite infection types were separated from protozoan infection types as
their mode of infection, physiology, niches and pathophysiology are different. These
differences can potentially lead to different mechanistic pathways affecting the host’s mental
health. While protozoans are neurotropic, this is not a common phenomenon in helminths
(with the exception of tapeworms causing cysticercosis). There are also secondary effects
resulting from these biological differences between protozoa and helminths. For example, it
has been previously shown that schistosome infections impact on the host’s gut microbiome
(Osakunor et al., 2020) and there have been studies relating the gut microbiome structure to
mental health via the gut-brain axis (Clapp et al., 2017);(Järbrink-Sehgal & Andreasson,
2020).

The present findings are consistent with research showing direct and indirect
associations between parasitic infection and mental illness. For example, *T. gondii* has been
shown to play a role in several psychiatric disorders such as schizophrenia, bipolar disorder
and mood affective disorders (Arling et al., 2009); (Webster, Lamberton, Donnelly, &
Torrey, 2006);(de Barros et al., 2017).

Mechanistic pathways include the involvement of the host’s immune response to the
parasitic infections, particularly inflammatory responses in the potential development of
psychiatric illnesses (Borsini, Zunszain, Thuret, & Pariante, 2015); Miller & Raison, 2016;
(Maizels & McSorley, 2016); (Charles L. Raison, Capuron, & Miller, 2006); (G. E. Miller &
Cohen, 2001). Peripheral inflammation can affect the CNS via three mechanisms (Miller &
Raison 2016). Firstly, the humoral pathway where cytokines in the blood pass through
permeable regions such as the circumventricular of the blood brain barrier. Secondly, direct
activation of the vagus nerve activates ascending catecholamine pathways in the brain, resulting in central cytokine signaling. A third pathway involving the production and trafficking of neurotoxic metabolites of the tryptophan cascade, activated in both the brain and the liver has been identified from post-mortem studies (Torres-Platas, Cruceanu, Chen, Turecki, & Mechawar, 2014); (Dantzer et al., 2008). Such alterations to the immune system caused by parasitic infection and the loss of key immune cells such as T lymphocytes have been documented as having a negative impact on emotional well-being and cognition (Pariante, 2016).

Host genetics plays an important role in susceptibility to both parasitic infection (Alcaïs, Abel, & Casanova, 2009) and in the prediction and regulation of depression (Bull et al., 2009). Parasite infections are well-known to cause increased immune activation, in which certain gene variants are associated with an increased risk of psychopathology; with immune genes being observed to have greater effects on behavioural outcomes than so called ‘psychiatry genes’ (Bufalino, Hepgul, Aguglia, & Pariante, 2013). This makes it difficult to determine the specific links between parasitic infection and mental illness for therapeutic intervention. As such, there is a need for more mechanistic studies in wider populations. It has been hypothesized and to an extent tested, that by treating disorders of the immune system, it is also possible to treat comorbid psychiatric disorders (Pariante, 2016; Baumeister et al., 2016b; (Capuron & Miller, 2004); (Harrison et al., 2009). Adding anti-inflammatory medications alongside anti-depressants or anti-psychotics in patients with a psychiatric disorder, increases the efficacy of these medications (Fond et al., 2014); (Na et al., 2014).

Regardless of the paucity of mechanistic studies, our review did highlight the public health and individual health impact of the comorbidity between parasitic infection and mental illness. The social and health consequences of stigma related to parasite infections were
strongly evidenced throughout the reviewed papers as contributing factors to the development of psychological disorders, primarily anxiety and depression. The studies reviewed and analysed in this meta-analysis indicated various factors that affect and predispose to both parasitic infections and mental health disorders. While increased immune activation and risk of developing a psychiatric disorder can be caused by genetic predispositions; environmental influences such as exposure to trauma, social inequities, stigmatisation, urbanicity, deprivation and poor nutrition also play a key role in the development of psychopathologies, all of which tend to be highly prevalent in parasite endemic nations (Pariante, 2016). Exposure to trauma early in life is one of the most prolific causes of developing a psychiatric disorder, and it has been evidenced that early life trauma activates the immune system in young adults, even in the absence of psychopathology (Danese, Pariante, Caspi, Taylor, & Poulton, 2007). Individuals with increased immune activation and exposure to personal maltreatment, socioeconomic disadvantage, isolation and other forms of chronic stress have an increased likelihood of developing a psychiatric disorder in the future (G. E. Miller et al., 2009; G. E. Miller et al., 2008); (Danese et al., 2009); (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Baumeister, Ciufolini, & Mondelli, 2016). Results from this review and that of empirical work suggest that there is a causational relationship between genetics/social factors and mental illnesses through immune-related mechanisms; that the relationship between inflammation caused by infection and mental illnesses is a blend of biological and environmental factors.

Across all studies included in this review, the stigma and general lack of understanding and acceptance of parasite infections was highly prevalent and reported across nearly all of the papers reviewed. The stigmatisation of afflicted persons was seen to be a direct contributor of the development of psychological disorders, namely anxiety and depression (Hofstraat & Brakel, 2016). Perhaps unsurprisingly, studies looking at parasite
infections with highly visible characteristics, such as leishmaniosis scarring, leprosy, lymphatic filariasis and onchocerciasis, reported extremely high levels of stigma among their populations, with the reported effects of stigma being severe to the sufferer’s mental well-being, with fears of social and familial rejection and socioeconomic strain exacerbating the toll of mental illness (Bennis et al., 2017; Eneanya et al., 2019; Obindo et al., 2017; Martindale et al., 2014; van’t Noordende et al., 2020; Mbanefo et al., 2010; Bailey et al., 2019; Pires et al., 2019).

There were also some gender differences in the reporting of stigma across the reviewed papers. The majority of the studies included both genders, but those that examined men or women only yielded interesting results with regards to the differences and similarities faced by either gender when afflicted with a parasitic infection. Both men and women affected by parasite infection, were found to be less likely to marry or had higher rates of divorce. Mental illness, particularly depression, was found to be particularly prevalent across both men and women, often reported as a result of the severe stigmatisation afflicted men and women experienced due to the physical manifestations of the parasite infection (e.g., hydrocele in men, and leishmaniosis in women). However, differences were also observed between men and women, with women reporting to experience higher levels of rejection and avoidance of stress and were less likely than men to promptly seek treatment (Chahed et al., 2016; Al-Kamel, 2017).

The papers focusing on male only populations were focused on the psychological and social effects of hydrocele (Gyapong et al., 2000; Dienye et al., 2011; Okoye et al., 2007) which revealed similar results, in that stigmatisation of men with certain parasite infections was often debilitating and resulted in the development of depression. Furthermore, such men were less likely to wed and those already with a spouse were often divorced shortly thereafter. Overall, rates of depression were much more prevalent in men with conditions
such as hydrocele and onchocerciasis compared to non-afflicted persons, with shame, low self-esteem, embarrassment and isolation as a result of their condition, being frequently reported. Such fears combined with perceived and actuated consequences of parasitic infection, are not only stigmatising but are also conducive to developing a mental illness.

Similarly, studies examining the psychological and social effects of parasite infections on women only, reported similar effects (Chahed et al., 2016; Downs et al., 2011). The scarring often caused by leishmaniasis has a particularly derogatory effect on young girls and women, who similarly to men, if they are unwed are much less likely to ever marry due to stigma (Pires et al., 2019; Yanik, Gurel, Simsek, & Kati, 2004), rejection and shunning from their community. The stigma experienced due to the dermatological aspects of leishmaniasis can hinder health seeking behaviours in the afflicted, further exacerbating public health consequences (Al-Kamel, 2017). Rates of depression tended to be very high in women afflicted by both leishmaniasis, as well as female urogenital schistosomiasis, with depression and any other psychological disorders experienced, often being accredited to the stigma anticipated and experienced by such women (Grifferty et al., 2021). However, the psychological effects of leishmaniasis were reported to reduce as women got older, with the greatest psychosocial burden seen to be on younger women reporting to experience stigma more frequently than older women (Bennis et al., 2017; Chahed et al., 2016). Furthermore, the more educated an individual is on their disease, the greater their cognitive (perception of consequences) and emotional (emotional representation) sensitivity is (Pires et al., 2019), thus reducing the effects of stigma on depression and anxiety for afflicted women due to improved education and understanding.

Limitations

The studies included in the analysis were heterogeneous in terms of study design, parasite types and mental illness and the sample size meant these factors and potential confounders
could not be allowed for in the analyses. Similarly small sample sizes for some of the mental illnesses and parasites reduced the statistical power to detect any significant differences. As many studies as possible were included through Textual Narrative Synthesis.

**Conclusions/Future directions**

The results from this review suggest that there is a significantly increased risk of developing a mental illness when testing positive for a parasitic infection, however little evidence was found to imply that specific parasitic infections have a greater likelihood of leading to the development of specific mental illnesses. Taking together the results of this review and that of empirical work, it can be inferred that there is a potentially causational relationship between parasite infection and mental illness, through a blend of biological and environmental factors borne of an interplay between genetic, immunological, environmental and social influences. Whilst inflammation poses as a potential contributor and offers a prospective explanation for the development of mental illness, mental illnesses are complex conditions which ultimately do not have one single cause, aetiology or treatment. Questions remain to be answered in future investigations, and further research is required to ascertain the exact nature of the association between parasitic infection and mental illness with greater clarification on the proportion of mental illnesses that can be attributed to inflammation caused by parasite infection. The study highlights the public health importance of addressing both health challenges simultaneously for improved human health.

**Supplementary Materials**

The GRADE classification system and the PRISMA checklist and flow diagrams were used to improve the reporting of this systematic review to ensure validity in data extraction and
analyses. The International Classifications of Diseases 10 of Mental and Behavioural Disorders for researchers was used to classify the mental disorders included in this review.

Data

All raw data is included in the appendices. See Table 1 for the GRADE scoring system, Table 2 for the reviewed papers GRADE scores, Table 3 for the data table used for the Chi-Square test and PAF, Table 4 for the Textual Narrative Synthesis results and Table 5 for the final data extraction table. See Figure 6 for the PRISMA chart conducted by JK and RI and Figure 7 for the studies excluded from final analysis based on secondary exclusion criteria.

Acknowledgements

We thank the Parasite Immunoepidemiology Group at the University of Edinburgh and their feedback on early drafts of the manuscript.

Author Contribution

ALS - conducted the literature review, data extraction, data analysis and prepared the first draft of the manuscript.

JK, RI, AM all conducted independent literature reviews, data extraction and preliminary data analyses.

FM conceived of the idea, supervised the work and co-wrote the first draft of the manuscript.

All co-authors read and approved the final manuscript before submission.

Financial Support

This research was commissioned by the National Institute for Health Research (NIHR) Global Health Research programme (16/136/33) using UK aid from the UK Government.
The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Conflicts of Interest

The authors declare no conflict of interest.

Ethical Standards

Not applicable

doi:10.1159/000067790


doi:10.4236/oalib.1102138


doi:https://doi.org/10.1111/j.1365-2230.2004.01605.x


Bibliography of reviewed papers


Psychosocial impact of scars due to cutaneous leishmaniasis on high school students in Errachidia province, Morocco. *Infectious Diseases of Poverty*, 6(1), 46. doi:10.1186/s40249-017-0267-5


and Health Development, 10(2), 87-93.


of Life of Children in Schistosoma haematobium-endemic Communities in Kenya: A
Cross-sectional Study. *PLOS Neglected Tropical Diseases*, 7(3), e2106.
doi:10.1371/journal.pntd.0002106

van ‘t Noordende, A. T., Aycheh, M. W., & Schippers, A. (2020). The impact of leprosy,
podoconiosis and lymphatic filariasis on family quality of life: A qualitative study in
doi:10.1371/journal.pntd.0008173

community in Nigeria. *The journal of the Royal Society for the Promotion of Health*,
124(3), 134-136.
Table 1: Scoring system for modified GRADE criteria

<table>
<thead>
<tr>
<th>Diagnostic of Parasitic Infection</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory + clinical + imaging</td>
<td>2</td>
</tr>
<tr>
<td>Culture, smear, histology, interviews, presence of scarring from PI</td>
<td>1</td>
</tr>
<tr>
<td>Clinical suspicion only/self-report</td>
<td>0</td>
</tr>
</tbody>
</table>

**Diagnostic of Mental Illness**

<table>
<thead>
<tr>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>Ascertained by interview and/or FGD</td>
</tr>
<tr>
<td>Self-report/ suspicion of</td>
</tr>
</tbody>
</table>

**Patient sample size**

<table>
<thead>
<tr>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30</td>
</tr>
<tr>
<td>≥20</td>
</tr>
<tr>
<td>&lt;20</td>
</tr>
</tbody>
</table>

**Year of study**

<table>
<thead>
<tr>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
</tr>
<tr>
<td>5-10 years</td>
</tr>
<tr>
<td>10-20 years</td>
</tr>
<tr>
<td>&gt;20 years</td>
</tr>
</tbody>
</table>

**Presence/Absence of Control Group**

<table>
<thead>
<tr>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equal and matched controls</td>
</tr>
<tr>
<td>Presence of any controls (not equal/matched)</td>
</tr>
<tr>
<td>No established control group (e.g., in group of participants there is those who test positive for MI/PI and those who test negative)</td>
</tr>
<tr>
<td>No controls</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td><strong>Methodology (well designed)</strong></td>
</tr>
<tr>
<td>Well-designed</td>
</tr>
<tr>
<td>Adequately designed (passable but flawed)</td>
</tr>
<tr>
<td>Poorly designed</td>
</tr>
<tr>
<td><strong>Type of publication</strong></td>
</tr>
<tr>
<td>Research paper</td>
</tr>
<tr>
<td>Review paper (SR/ meta-analyses)</td>
</tr>
<tr>
<td>Case study/ report</td>
</tr>
<tr>
<td><strong>Possible total score</strong></td>
</tr>
</tbody>
</table>
Table 2: Modified GRADE score for the papers in SR
<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic accuracy(PI)</th>
<th>Diagnostic accuracy(MI)</th>
<th>Patient sample size</th>
<th>Year of Study</th>
<th>Type of publication</th>
<th>Methodology</th>
<th>Presence/absence of control group</th>
<th>Overall score</th>
<th>Ref no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennis</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Dienye</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Eneanya</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Lasebikan</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Martindale</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Musuva</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Nyundo</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Obindo</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Abdulmalik</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Downs</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Richard</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Semrau</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Akogun</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Chahed</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Gyapong</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Idro</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Okoye</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Name</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Terer</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Wagbatsoma</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Bailey</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Dare</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Hofstraat</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>13</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Pires</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Goldner-Vukov</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Wise</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Vant Noordende</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Srivastava</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Mbanefo</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Person</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Nwoke</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Data table for Chi-Square and Fishers Exact Test.

<table>
<thead>
<tr>
<th></th>
<th>Number with Mental Illness</th>
<th>Number without Mental Illness</th>
<th>Row Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number With Parasitic Infection</td>
<td>4478</td>
<td>3217</td>
<td>7695</td>
</tr>
<tr>
<td>Number Without Parasitic Infection</td>
<td>1812</td>
<td>5349</td>
<td>7161</td>
</tr>
<tr>
<td>Column Total</td>
<td>6290</td>
<td>8566</td>
<td>14,856</td>
</tr>
</tbody>
</table>
Table 4: Textual Narrative Synthesis Table

<table>
<thead>
<tr>
<th>Reference</th>
<th>Continent</th>
<th>Study Characteristics</th>
<th>Diagnostic tools used to identify parasite infection</th>
<th>Diagnostic tools used to identify mental illness</th>
<th>Prevalence of mental illness</th>
<th>Prevalence of association between mental illness and parasite infection</th>
<th>Prevalence of parasite infection</th>
<th>Perceptions, understanding and expectations of mental illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey et al., 2019</td>
<td>Africa, Asia, South America</td>
<td>A systematic review of 29 studies examining the psychosocial impact of active (aCL) and inactive cutaneous leishmaniasis (iCL). Major depressive disorder (MDD) associated with chronic NTDs has been identified as a significant and overlooked contributor of overall disease burden. Upon the inclusion of co-morbid MDD alone in both aCL and iCL, the disability adjusted life years (DALY) burden was 7 times higher than previously estimated. Modified DALY Model was used to calculate the burden of co-morbid conditions; where the prevalence of aCL and iCL was prevalent in all papers reviewed.</td>
<td>The diagnostic tools vary with each of the papers included; however, the tools used across the papers were laboratory and clinical diagnosis, histology, interviews and self-report.</td>
<td>The diagnostic tools vary with each of the papers included; however, the tools used across the papers were clinical diagnosis, self-report and interviews.</td>
<td>Across all papers approximately 70% of individuals report high co-morbidity with CL and psychosocial issues.</td>
<td>CL was prevalent in all papers reviewed.</td>
<td>In countries where CL is more stigmatised, MDD and depression has higher association in CL patients. CL and co-morbid MDD has substantial weight in the global health burden. iCL also has significant impact on Quality of Life (QoL) and has high co-morbidity with MDD; increasing the global health burden of CL overall.</td>
<td></td>
</tr>
</tbody>
</table>
was multiplied with co-morbid MDD by the disability weight for MDD at 3 levels (mild, moderate, severe).

| Dare et al., 2019 | Africa, Asia, South America | 18 papers included in this systematic review and meta-analyses: including 16 analytical studies and 2 prevalence studies. 1:1 female to male ratio with mean age of 43.9 years. High prevalence of mental illness amongst parasite afflicted individuals, with some causational associations made between parasite infections and specific mental illnesses. | The diagnostic tools vary with each of the papers included; however, the tools used across the papers were laboratory and clinical diagnosis, histology, interviews and self-report. | The diagnostic tools vary with each of the papers included; however, the tools used across the papers were clinical diagnosis, self-report and interviews. | All included studies reported mental illness. The percentage varies between 40-60% prevalence of mental illness. | All studies reported an association between mental illness and parasite infection. The meta-analysis yielded an odds ratio of 2.1 with 95% CI (1.7-3.4). The review conservatively estimated that approximately 50% of individuals with a parasite infection also had a mental illness. There was an especially high prevalence of schizophrenia and bipolar disorder and patients presenting with toxoplasmosis, with strong Parasite infections prevalent in all 18 papers reviewed. | The general perception of mental illness was highly stigmatising; with individuals with parasite infections often being shunned and isolated, with a lower QoL and HRQoL reported. |
Hofstraat et al., 2016  |  Africa, Asia, North/South America, Europe  |  A systematic review of 52 papers on a multitude of NTDs, primarily parasites, but other non-parasitic diseases were included also. Relationship between individuals with NTDs and the levels of stigma they experience was examined. The results found that similarities predominated in the stigma related to NTDs and only minimal differences between stigma reasons and measures were found.  
Diagnostic tools vary with each paper, however the tools utilised across the paper were interviews, signs of scarring, smear tests and laboratory/clinical tests.  
Diagnostic tools vary with each paper, however the tools utilised across the paper are clinical diagnosis, interviews, focus group discussion (FGD) and self-reporting measures.  
75.75% of the 63% (25/33 papers on parasite infection) of parasite papers report psychological consequences.  
25 out of the 33 papers on parasite infection report a notable comorbidity between parasite infection and mental illness.  
63% (33/52 papers) of the papers included were on parasite infections.  
This SR found evidence for stigma attached to NTDs (including parasite infections). For NTDs with physical manifestations (e.g. scars, ulcers etc.), stigmatisation was greater anticipated, as opposed to NTDs with less physically obvious manifestations, stigma was less anticipated. However, despite the expectations of stigma being high, it was also indicated in several studies, that there was a strong community support and acceptance for the affected persons.

Pires et al., 2019  |  Africa, Asia, South America  |  Systematic review of 14 studies on the impact of leishmaniasis on mental health and psychosocial  
Clinical diagnosis, histology and all included studies reported an association between leishmaniasis and self-reporting measures.  
All 14 studies reported an association between leishmaniasis and mental illness.  
Scarring from leishmaniasis was found to have an association with social and family rejection, with high prevalence’s of stigma.
wellbeing. Cross-sectional cohort, case control, qualitative papers and other systematic reviews were examined. Narrative synthesis was carried out as data was too heterogeneous for meta-analysis. Results found evidence that leishmaniasis has significant impact on the mental health and QoL of sufferers and their families.

Interviews used to ascertain leishmaniasis diagnosis were reported used mental illness and lower QoL consequences mental illness and psychosocial consequences reported across all papers. Decreased QoL, isolation and shunning were also widely reported, with this often and consequentially leading onto afflicted persons developing a mental illness. Scarring from leishmaniasis was also associated with a decreased chance of ever marrying, which was especially prevalent in girls and women. Leishmaniasis was also associated with a negative impact on sufferers’ social and economic livelihoods.
<table>
<thead>
<tr>
<th>Reference Title</th>
<th>Country</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Sex</th>
<th>Sample size</th>
<th>Type of Parasite Infection</th>
<th>Prevalence of P.I. (%)</th>
<th>Type of Mental Illness Classification</th>
<th>Prevalence of MI (%)</th>
<th>Percentage with association</th>
<th>Number with association</th>
<th>Number with PI but no MI</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennis et al., 2017</td>
<td>Morocco</td>
<td>2017</td>
<td>1</td>
<td>3</td>
<td>448</td>
<td>1</td>
<td>20%</td>
<td>F30-39</td>
<td>86%</td>
<td>16.74</td>
<td>75</td>
<td>14</td>
<td>0.88 (0.13-0.20)</td>
</tr>
<tr>
<td>Dienye et al., 2011</td>
<td>Nigeria</td>
<td>2011</td>
<td>1</td>
<td>1</td>
<td>52</td>
<td>8</td>
<td>50%</td>
<td>F30-39</td>
<td>61.54%</td>
<td>30.76</td>
<td>16</td>
<td>10</td>
<td>8.99 (0.47-0.74)</td>
</tr>
<tr>
<td>Enejma et al., 2019</td>
<td>Nigeria</td>
<td>2019</td>
<td>1</td>
<td>3</td>
<td>104</td>
<td>8</td>
<td>50%</td>
<td>F40-48; UMI</td>
<td>40%</td>
<td>19.23</td>
<td>20</td>
<td>32</td>
<td>2.33 (0.12-0.28)</td>
</tr>
<tr>
<td>Laselikan et al., 2017</td>
<td>Nigeria</td>
<td>2017</td>
<td>8</td>
<td>3</td>
<td>3927</td>
<td>7.11.3</td>
<td>75%</td>
<td>F30-39; F20-29</td>
<td>64.17%</td>
<td>44.38</td>
<td>1743</td>
<td>732</td>
<td>1.57 (0.42-0.45)</td>
</tr>
<tr>
<td>Motorndale et al., 2014</td>
<td>Malawi</td>
<td>2014</td>
<td>1</td>
<td>3</td>
<td>69</td>
<td>8</td>
<td>100%</td>
<td>F30-39; F40-48</td>
<td>45%</td>
<td>44.93</td>
<td>31</td>
<td>38</td>
<td>0.82 (0.32-0.57)</td>
</tr>
<tr>
<td>Musuva et al., 2017</td>
<td>Kenya</td>
<td>2017</td>
<td>8</td>
<td>3</td>
<td>36</td>
<td>7</td>
<td>50%</td>
<td>F30-39; F40-48</td>
<td>65%</td>
<td>33.33</td>
<td>12</td>
<td>6</td>
<td>4 (0.18-0.50)</td>
</tr>
<tr>
<td>Nyondo et al (2017)</td>
<td>Tanzania</td>
<td>2017</td>
<td>1</td>
<td>3</td>
<td>233</td>
<td>6</td>
<td>12.45%</td>
<td>F30-39; F40-48; F20-25; UMI</td>
<td>100%</td>
<td>12.44</td>
<td>29</td>
<td>0</td>
<td>0.14 (0.08-0.17)</td>
</tr>
<tr>
<td>Obondo et al (2017)</td>
<td>Nigeria</td>
<td>2017</td>
<td>1</td>
<td>3</td>
<td>94</td>
<td>8</td>
<td>100%</td>
<td>F30-39</td>
<td>93.29%</td>
<td>92.55</td>
<td>87</td>
<td>7</td>
<td>0.20 (0.85-0.96)</td>
</tr>
<tr>
<td>Abdulmalki et al (2018)</td>
<td>Nigeria</td>
<td>2018</td>
<td>6</td>
<td>3</td>
<td>69</td>
<td>8</td>
<td>100%</td>
<td>F30-39</td>
<td>81%</td>
<td>81.16</td>
<td>56</td>
<td>13</td>
<td>4.31 (0.69-0.89)</td>
</tr>
<tr>
<td>Downs et al., 2011</td>
<td>Tanzania</td>
<td>2011</td>
<td>1</td>
<td>2</td>
<td>457</td>
<td>9</td>
<td>5%</td>
<td>F30-39</td>
<td>77%</td>
<td>3.72</td>
<td>17</td>
<td>6</td>
<td>0.85 (0.72-0.80)</td>
</tr>
<tr>
<td>Richard et al., 2007</td>
<td>Togo</td>
<td>2007</td>
<td>1</td>
<td>3</td>
<td>188</td>
<td>8</td>
<td>100%</td>
<td>F30-39; F40-48</td>
<td>70%</td>
<td>70.21</td>
<td>132</td>
<td>56</td>
<td>2.36 (0.62-0.76)</td>
</tr>
<tr>
<td>Semrau et al., 2013</td>
<td>Cameroon</td>
<td>2013</td>
<td>1</td>
<td>3</td>
<td>83</td>
<td>8</td>
<td>37%</td>
<td>F40-39</td>
<td>41.93%</td>
<td>15.66</td>
<td>31</td>
<td>18</td>
<td>1.26 (0.26-0.48)</td>
</tr>
<tr>
<td>Akogun et al., 2011</td>
<td>Nigeria</td>
<td>2011</td>
<td>6</td>
<td>3</td>
<td>182</td>
<td>8</td>
<td>100%</td>
<td>UMI</td>
<td>53.80%</td>
<td>53.3</td>
<td>97</td>
<td>84</td>
<td>1.67 (0.45-0.60)</td>
</tr>
<tr>
<td>Chahed et al., 2019</td>
<td>Tunisia</td>
<td>2019</td>
<td>7</td>
<td>2</td>
<td>41</td>
<td>1</td>
<td>100%</td>
<td>F40-48; UMI</td>
<td>73%</td>
<td>65.85</td>
<td>27</td>
<td>14</td>
<td>1.93 (0.54)</td>
</tr>
<tr>
<td>Gyapong et al 2000</td>
<td>Ghana</td>
<td>2000</td>
<td>1.6</td>
<td>1</td>
<td>41</td>
<td>8</td>
<td>100%</td>
<td>UMI</td>
<td>50%</td>
<td>24.39</td>
<td>10</td>
<td>10</td>
<td>0.05 (0.12-0.40)</td>
</tr>
<tr>
<td>Idro et al., 2013</td>
<td>Uganda</td>
<td>2013</td>
<td>3</td>
<td>3</td>
<td>22</td>
<td>10</td>
<td>100%</td>
<td>F30-39; UMI</td>
<td>50%</td>
<td>50</td>
<td>11</td>
<td>11</td>
<td>0.28-0.71</td>
</tr>
<tr>
<td>Okoye et al., 2007</td>
<td>Nigeria</td>
<td>2007</td>
<td>1</td>
<td>1</td>
<td>1479</td>
<td>12</td>
<td>62.80%</td>
<td>UMI</td>
<td>54.00%</td>
<td>33.87</td>
<td>501</td>
<td>427</td>
<td>1.17 (0.60-0.65)</td>
</tr>
<tr>
<td>Terer et al., 2013</td>
<td>Kenya</td>
<td>2013</td>
<td>1</td>
<td>3</td>
<td>1580</td>
<td>7</td>
<td>42.20%</td>
<td>UMI</td>
<td>4%</td>
<td>1.71</td>
<td>27</td>
<td>639</td>
<td>0.01 (0.01-0.02)</td>
</tr>
<tr>
<td>Wagbatsoma et al., 2004</td>
<td>Nigeria</td>
<td>2004</td>
<td>1</td>
<td>3</td>
<td>385</td>
<td>12</td>
<td>3.37%</td>
<td>UMI</td>
<td>33%</td>
<td>11.17</td>
<td>127</td>
<td>88</td>
<td>0.49 (0.28-0.37)</td>
</tr>
<tr>
<td>Bailey et al., 2019</td>
<td>Eastern Mediterranean &amp; the Americas</td>
<td>2019</td>
<td>5</td>
<td>3</td>
<td>29 studies</td>
<td>1</td>
<td>100%</td>
<td>F30-39</td>
<td>70%</td>
<td>70</td>
<td>70%</td>
<td>30%</td>
<td>N/A</td>
</tr>
<tr>
<td>Dare et al., 2019</td>
<td>Africa, Asia, America</td>
<td>2019</td>
<td>5</td>
<td>3</td>
<td>18 studies</td>
<td>3,13,4,2,5,1</td>
<td>100%</td>
<td>F30-39; F40-48; F20-29; UMI</td>
<td>44.90%</td>
<td>44.9</td>
<td>18</td>
<td>1776</td>
<td>2.1 (1.7-3.4)</td>
</tr>
<tr>
<td>Hofstraat et al., 2016</td>
<td>Africa, Asia, North America, South America, Europe</td>
<td>2016</td>
<td>5</td>
<td>3</td>
<td>52 studies</td>
<td>8,12,7,4,3,5,6</td>
<td>63%</td>
<td>UMI</td>
<td>46%</td>
<td>46</td>
<td>25</td>
<td>8</td>
<td>N/A</td>
</tr>
<tr>
<td>Pires et al., 2019</td>
<td>Africa, Asia, South America, Middle East</td>
<td>2019</td>
<td>5</td>
<td>3</td>
<td>14 studies</td>
<td>1</td>
<td>100%</td>
<td>F30-39; F40-48; UMI</td>
<td>50%</td>
<td>50</td>
<td>7</td>
<td>7</td>
<td>N/A</td>
</tr>
<tr>
<td>Vant Noordende et al, 2013</td>
<td>Ethiopia</td>
<td>2020</td>
<td>1</td>
<td>86</td>
<td>8</td>
<td>29%</td>
<td>UMI</td>
<td>18.60%</td>
<td>18.6</td>
<td>16</td>
<td>9</td>
<td>1.91 (0.10-0.27)</td>
<td></td>
</tr>
<tr>
<td>Mbanefo et al., 2010</td>
<td>Nigeria</td>
<td>2010</td>
<td>1</td>
<td>894</td>
<td>12</td>
<td>20.80%</td>
<td>UMI</td>
<td>34.30%</td>
<td>7.16</td>
<td>64</td>
<td>122</td>
<td>0.52 (0.69-0.82)</td>
<td></td>
</tr>
<tr>
<td>Nwoke et al., 2005</td>
<td>Nigeria</td>
<td>2005</td>
<td>1</td>
<td>2</td>
<td>420</td>
<td>12</td>
<td>100.00%</td>
<td>UMI</td>
<td>69.00%</td>
<td>69</td>
<td>290</td>
<td>130</td>
<td>2.23 (0.64-0.73)</td>
</tr>
</tbody>
</table>

777  | **Table 5**: Final Data Extraction Table by ALS |
**Figures**

**Figure 1:** Search terms used to find papers on parasite infection and mental illness

| Parasite, Parasitic, Parasite disease, Parasitation, Parasitism, Parasites, Parasitic infestation, Helminthiasis, Helminth, Helminthic, Helminthic infection, Parasitology, Mental, Health, Illness, Mental health, Mentally ill, Mental illness, Mental illnesses, Disorder, Disorders, Mental disorder, Mental disorders, Psychiatric, Disease, Psychiatric diseases, Psychiatric disease, Psychiatric illness, Psychiatric illnesses, Psychiatric diagnosis, Psychiatric diagnoses, Psychiatric disorder, Psychiatric disorders, Behaviour, Behavior, Behaviour disorder, Behavior disorder, Behaviour disorders, Behavior disorders, Severe, Severe mental disorder, Severe mental illness, Severe psychiatric illness, Anxiety disorder, Anxiety disorders, Anxiety, Bipolar and related disorders, Bipolar, Schizophrenia, Schizophrenias, Schizophrenic, Schizophrenic disorder, Schizophrenic disorders, Schizophrenic illness, Schizoaffective, Schizoaffective disorder, Mood disorder, Mania, Affective disorder, Mood (affective) disorder, mood disorders, Affective disorders, Bipolar disorder, Bipolar affective disorder, Bipolar disorders, Bipolar affective disorders, Psychosis, Depressive, Depressive episode, Depression, Depressions, Recurrent depressive disorder, Recurrent depressive disorders, Anxiety, Anxiety disorder, Anxiety disorders, Anxiety neuroses, Phobic anxiety disorder, Phobic anxiety disorders |
Figure 2: PRISMA chart for inclusion and exclusion criteria on studies on parasite infection and mental illness.
Figure 3: Descriptive statistics of included studies

3A) Number of publications as per study design

3B) Number of publications per year

3C) Spread of sample sizes of the reviewed papers
**Figure 4:** Comparison of association between mental illness prevalence and parasite infection.

4A) Mood affective disorders vs neurotic stress related disorders

4B) Mood affective disorders vs schizotypal disorders

4C) Mood affective disorders vs unspecified mental illnesses

4D) Neurotic stress related disorders vs unspecified mental illnesses

4E) Schizotypal disorders vs unspecified mental illnesses

4G) Specific mental illness prevalence of association with any parasite infection.

Error bars represent 95% Confidence Intervals. Each data point represents the prevalence of parasitic infection in that mental illness group. Significance levels as displayed on graphs are abbreviated; abbreviations are as follows: ‘ns’ for not significant; for $P$ levels ($* P < 0.05$).
Figure 5: Comparison of association between specific parasite infection and mental illness.

5A) Comparison of association specific parasite infection classification and any mental illness.

5B) Protozoa and unspecified mental illness vs Helminth and unspecified mental illness

5C) Protozoa and mood affective disorders vs Helminth and mood affective disorders

5D) Protozoa and neurotic stress related disorder vs Helminth and neurotic stress related disorder

5E) Comparison of association between specific parasite infection class and specific mental illness classifications.

Error bars represent 95% Confidence Intervals. Each data point represents the prevalence of the specific parasitic infection and mental illness. Significance levels as displayed on graphs are abbreviated; abbreviations are as follows: ‘ns’ for not significant; for $P$ levels (* $P<0.05$).
**Figure 6:** Studies excluded from final analysis based on secondary exclusion criteria.

<table>
<thead>
<tr>
<th>No results yielded from the study as of yet (1):</th>
</tr>
</thead>
<tbody>
<tr>
<td>ØErber (2018)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Little/no relevance to the research question and aims (23):</th>
</tr>
</thead>
<tbody>
<tr>
<td>ØWatts (1989)</td>
</tr>
<tr>
<td>ØStillwaggon (2018)</td>
</tr>
<tr>
<td>ØMusisi (2013)</td>
</tr>
<tr>
<td>ØTchounkeu (2012)</td>
</tr>
<tr>
<td>ØStocks (2015)</td>
</tr>
<tr>
<td>ØO’Neill (2019)</td>
</tr>
<tr>
<td>ØHotterbeekx (2019)</td>
</tr>
<tr>
<td>ØNau (2018)</td>
</tr>
<tr>
<td>ØBrut (1999) [qualitative paper]</td>
</tr>
<tr>
<td>ØWinkler (1994) [qualitative paper]</td>
</tr>
<tr>
<td>ØSan Juano Orta (2009)</td>
</tr>
<tr>
<td>ØLelo (1994)</td>
</tr>
<tr>
<td>ØHotez (2014)</td>
</tr>
<tr>
<td>ØKim (2014)</td>
</tr>
<tr>
<td>ØOvuga (1995)</td>
</tr>
<tr>
<td>ØTapsoba (2019)</td>
</tr>
<tr>
<td>ØPollach (2014)</td>
</tr>
<tr>
<td>ØMackenzie (2009) [qualitative paper]</td>
</tr>
<tr>
<td>ØBast (2015) [qualitative paper]</td>
</tr>
<tr>
<td>ØDzikoweil (2017) [qualitative paper]</td>
</tr>
<tr>
<td>ØMas Coma (2014) [qualitative paper]</td>
</tr>
<tr>
<td>ØPicado (2019) [qualitative paper]</td>
</tr>
<tr>
<td>ØKelly Hope (2017)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Language barrier (1):</th>
</tr>
</thead>
<tbody>
<tr>
<td>ØKirschbaum (1931) [qualitative paper]</td>
</tr>
<tr>
<td>ØHart (2004)ØSan Juano Orta</td>
</tr>
</tbody>
</table>