Associations of mental disorders and neurotropic parasitic diseases: a meta-analysis in developing and emerging countries

CURRENT STATUS: ACCEPTED

Labanté Outcha Daré
Universite de Limoges
outcha_dare1986@yahoo.com
Corresponding Author
ORCiD: https://orcid.org/0000-0003-0075-9271

Pierre-Emile Bruand
Sanofi

Daniel Gérard
Sanofi

Benoît Marin
Universite de Limoges

Valérie Lameyre
Sanofi

Farid Boumédiène
Universite de Limoges

Pierre-Marie Preux
Universite de Limoges

DOI:
10.21203/rs.2.13886/v4

SUBJECT AREAS
Health Economics & Outcomes Research  Health Policy

KEYWORDS
Meta-analysis, association, co-morbidities, mental disorders, neurotropic parasitic diseases.
Abstract
Although they are declining worldwide, neurotropic parasitic diseases are still common in developing and emerging countries. The aim of this study was to estimate the pooled prevalence and pooled association measures of comorbidities between mental disorders (anxiety, depression, bipolar disorder, and schizophrenia) and neurotropic parasitic diseases (malaria, cysticercosis, toxoplasmosis, human African trypanosomiasis, Chagas disease, and human toxocariasis) in developing and emerging countries.

As the first meta-analysis on this topic, this study was performed in accordance with PRISMA guidelines. The protocol was registered in PROSPERO (N°CRD42017056521). The Medline, Embase, Lilacs, and Institute of Epidemiology and Tropical Neurology databases were used to search for articles without any restriction in language or date. We evaluated the quality of studies independently by two investigators using the Downs and Black assessment grid and pooled estimates using the random-effects method from CMA (Comprehensive Meta Analysis) Version 3.0.

In total, 18 studies published between 1997 and 2016 met our inclusion criteria. We found that the prevalence of anxiety and depression in people suffering from Chagas disease and/or neurocysticercosis was 44.9% (95% CI, 34.4 – 55.9). In 16 pooled studies that included 1,782 people with mental disorders and 1,776 controls, toxoplasmosis and/or toxocariasis were associated with increased risk of schizophrenia and/or bipolar disorders (odds ratio = 2.3; 95% CI, 1.7 – 3.2). Finally, toxocariasis and/or toxoplasmosis were associated with an increased risk of the onset of schizophrenia (odds ratio = 2.4; 95% CI, 1.7 – 3.4).

Our pooled estimates show that the associations between diseases studied are relatively high in developing and emerging countries. This meta-analysis supports the hypothesis that toxoplasmosis could be the cause of schizophrenia. These findings could prove useful to researchers who want to further explore and understand the associations studied.

Keywords: Meta-analysis, association, co-morbidities, mental disorders, neurotropic parasitic diseases.

Background
Although parasitic diseases are declining, they are still common in developing and emerging countries. Among the public health issues typically faced by developing and emerging countries (all non high income countries according to World Bank rankings) [1], neurotropic parasitic diseases are very common [2]. Neurotropic parasitic diseases such as malaria, cysticercosis, toxoplasmosis, human African trypanosomiasis (HAT), Chagas disease, and human toxocariasis have a predilection for infesting the central nervous system, which can lead to neurological disorders. Similarly, mental disorders are frequent with pooled 12-month period prevalence estimates of 17.6% (15.5% – 20.0%) in low and middle-income countries [3]. However, there are few studies regarding the association of mental disorders with neurological parasitoses in these countries.

To date, epidemiological studies have identified several risk factors for the different disease groups studied [4-9]. The table below (Table 1) provides a summary of the main risk factors of interest diseases in this meta-analysis. We have focused our attention on parasitic diseases due to the ever-present burden of these diseases in developing and emerging countries, and we selected the diseases according to their overall burden [10-13]. Mental disorders rank third among the foremost frequent diseases in the world after cancer and cardiovascular diseases [14].

In line with surveys conducted in developing and emerging countries, over 25% of individuals develop one or more mental or behavioural disorders throughout their lifetime [15]. Among the general population, severe depression affects 3% of people, generalised anxiety disorder affect 2%, and schizophrenia affects nearly 1% [16]. Parasitic diseases remain a major burden to developing and emerging countries, although this type of disease has declined globally. In 2015, out of 95 countries and territories in the world where malaria transmission remains high, it is estimated that the number of malaria cases was 214 million (95% CI, 149 - 303) and that malaria is responsible for 438,000 deaths per year (95% CI, 236 000 - 635 000) mainly in Africa (88%) [17]. In 2012, eight million individuals were already infected with Trypanosoma cruzi, the parasite that causes Chagas disease, in endemic areas of 21 Latin American countries. In addition, the chronic infection caused by this parasite is incurable, can be disabling, and causes more than 10,000 deaths per year [18]. The seroprevalence of toxocariasis varies from 2.4% to 30.0% in Europe [19], but in tropical countries,
higher prevalences have been reported: 7.5% to 92.8% in Africa [20, 21], 6.4% to 52.0% in South America [22, 23], and 5.0% to 84.6% in Asia [24, 25]. Human African trypanosomiasis (HAT) affects 60 million inhabitants mainly living in rural areas of 36 endemic sub-Saharan countries in East, West and Central Africa [26]. Toxoplasmosis remains frequent in these countries and even in developed countries [27]. Finally, the agent responsible for cysticercosis, *Taenia solium*, is found mainly in Latin America, Asia, sub-Saharan Africa, and the Indian Ocean region. According to the World Health Organization (WHO), cysticercosis is responsible for 50,000 deaths per year with 2.5 to 5 million adult worm carriers and 50 million cysticercal larvae carriers [28, 29]. Neurocysticercosis, a type of brain damage resulting from cysticercosis, is thought to be a factor responsible for more than 50% of late onset epileptic seizures in developing countries [28].

In recent years, there has been an increasing number of studies on co-morbidities between mental disorders and parasitic diseases, particularly those with neurological tropism such as toxoplasmosis [9], human toxocariasis [30, 31], and cysticercosis [32-35]. However, these have produced heterogenous data and to date, no meta-analysis has been published on the association of mental disorders and parasitic diseases in developing and emerging countries; hence the reason why we decided to perform this study.

**PURPOSE OF THE STUDY**

The purpose of this study was to estimate the pooled prevalence and pooled association measures of comorbidities between mental disorders and neurotropic parasitic diseases in developing and emerging countries.

**Methods**

**Implementation procedure**

To perform this meta-analysis, the diseases of interest are neutropic parasitic diseases: malaria, cysticercosis, toxoplasmosis, HAT, Chagas disease, and human toxocariasis [9, 13]. These are forms of parasitoses that have a predilection for infesting the central nervous system and which can result in neurological disorders. Mental disorders of interest included: anxiety, depression, bipolar disorder, and schizophrenia [10, 11]. Mental disorders are outlined as medical conditions that interfere with
thinking, feeling, mood, communication, and daily functioning, which typically lead to a reduced ability to address routine daily activities, such as working or raising a family [36].

Since this meta-analysis is the continuation of a previously published study on the association of mental disorders and chronic physical diseases in developing and emerging countries, its shares the same methods and research strategy [37]. Its protocol was recorded in PROSPERO, accessible via the following link: http://www.crd.york.ac.uk/PROSPERO and registered under CRD42017056521. It follows the recommended methodology for the meta-analysis of observational studies [38] and was performed in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [39].

**Research strategy**

The search for articles was conducted through four databases: Medline, Embase, Lilacs, and IENT (database of the Institute of Epidemiology and Tropical Neurology of the University of Limoges in France: http://www-ient.unilim.fr/). LOD, the principal investigator, conducted article searches on these databases from February to May 2017 without linguistic or date restrictions, using the same research equation built on Medline [37].

\[
\text{("Depressive Disorder"[Mesh] OR "Depression" [Mesh] OR "Anxiety Disorders"[Mesh] OR "Anxiety" [Mesh] OR "Bipolar Disorder"[Mesh] OR "Schizophrenia"[Mesh]) AND ("Diabetes metillus"[Mesh] OR "Obesity"[Mesh] OR "Neoplasms"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Malaria"[Mesh] OR "Cysticercosis"[Mesh] OR "Toxoplasmosis"[Mesh] OR "Toxocariasis"[Mesh] OR "Trypanosomiasis"[Mesh] OR "Chagas Disease"[Mesh]) AND ("Name of a country"[Mesh]).}
\]

This equation, initially built for both studies, allowed us to search articles on: associations of mental disorders and chronic physical diseases, which have been published in another meta-analysis; and associations of mental disorders and neurotropic parasitic diseases, that we discuss in this article.

In Lilacs and Embase, the keywords employed to build the research equation were identical. In total, 139 different equations corresponding to the 139 developing and emerging countries studied were used to search for articles on three databases (Medline, Embase, and Lilacs). When searching on the
IEN'T database, articles were searched using the additional terms “comorbidity” or “comorbidity in mental health.” This methodology was adopted for the latter database because it is specifically dedicated to research on neurotropic parasitoses in developing and emerging countries. Finally, the registration and selection of articles throughout this work was done through the Zotéro bibliographical management software package.

**Inclusion criteria and selection of articles**

Every article included in this meta-analysis had to be: an article with full text available; a cross-sectional or analytical study; conducted among adults, male and female, of all ages (age ≥ fifteen years); and a study involving either only hospitalised subjects or only non-hospitalised subjects (but not hospitalised subjects and non-hospitalised subjects at the same time). Every article also had to specify the method used to diagnose the diseases. In this study, by non-hospitalised, we mean patients who reside in the community or who attended a health centre (clinic or hospital) for care but did not remain at the health centre for one or more nights. On the other hand, hospitalised patients are those who have stayed in a health care centre for one or more nights. The cross-sectional studies included in this meta-analysis had to each present the prevalence, or the data from which it might be calculated. Analytical studies had to offer the association measures, or the data from which they might be calculated.

**Data extraction and assessment of article quality**

The data were extracted from each article by LOD (the principal investigator). This included: reference, title, country and continent, the study type and study population, the original disease, the associated disease searched for and its method of diagnosis, the prevalence or measures of association of the disease searched for (or the data needed to calculate them), as well as the sample size, sex ratio, and mean subjects age.

The assessment of the studies quality was performed independently by two investigators (LOD and PEB) using the revised Downs and Black assessment grid. Every article was assigned a score by each investigator [40, 41] and, therefore, the final score was set by mutual agreement after examination of the ratings. In the event of a disagreement, the expert opinion of a third investigator (PMP) was
requested, without this investigator knowing the scores given by the first two investigators. The final score was given by mutual agreement between the three investigators.

**Statistical analyses**

The software system Comprehensive Meta-Analysis (CMA) Version 3.0 [42] was used for the analyses. The heterogeneity of the selected studies was assessed using Q and \( I^2 \) statistical tests [43, 44]. The value of \( I^2 \) was considered such that \( I^2 = 0 \) showed a lack of heterogeneity, \( I^2 < 0.25 \) showed low heterogeneity, \( I^2 \) between 0.25 and 0.5 showed moderate heterogeneity, and \( I^2 > 0.5 \) showed significant heterogeneity. Pooled estimates were then calculated using the DerSimonian-Laird random-effects technique [45], with the results obtained displayed on a forest plot [46] with a significance threshold of 5%. Afterwards, the investigation for publication bias was performed by constructing a funnel plot, a Duval and Tweedie trim and fill test check [45], and an Egger’s regression [47]. To assess the robustness of the principal results of our meta-analysis, we carried out a sensitivity analysis by removing the study with the greatest weighting as well as the studies of lower quality within the pooled studies. The study variables “original disease,” “associated disease,” “subjects type,” and “continent” were used to perform subgroup analyses.

**Results**

**General results**

Through the built research equation, we identified 2,604 articles in several languages (English, French, Spanish, Portuguese, Chinese, and Russian). Among the articles meeting our inclusion criteria, there were 18 co-morbidity studies on mental disorders and neurotropic parasitic diseases [48-65] (Figure 1) with two of those being prevalence studies in individuals with neurotropic parasitic diseases who were screened for mental disorders, and sixteen analytical studies in individuals with mental disorders who were screened for neurotropic parasitic diseases (Table 2 and Table 3). These studies were conducted between 1997 and 2016.

In the prevalence studies examined in this meta-analysis, the female to male sex ratio was 1.1 and the mean age was 43.9 ± 7.5 years. In the analytical case-control studies, the female to male sex ratio was 0.7, while the mean age was 36.0 ± 11.0 years for cases, and 37.6 ± 10.5 years for
controls. In the 18 analytical studies conducted, 11 were hospitalised patients. Non-hospitalised patients were studied in two prevalence studies and in the 7 remaining analytical studies. With the Downs and Black assessment grid, the mean quality score for the prevalence studies was found to be $18.5 \pm 2$ (maximum score of 22), while the mean for the case-control studies was found to be $16.4 \pm 3.1$ (maximum score of 25) (Table S1 and Table S2).

**Main findings**

In the prevalence studies, the diseases found were anxiety and/or depression for mental disorders, and Chagas disease and neurocysticercosis for neurotropic parasitic diseases. There were 16,610 subjects enrolled in these studies. The prevalence of depression in the 148 individuals with Chagas disease and neurocysticercosis was 44.9% (95% CI, 34.4 – 55.9) (Figure 2). With regard to neurotropic parasitic diseases, toxoplasmosis and toxocariasis were found. In the 16 pooled studies that included 1,782 people with schizophrenia and/or bipolar disorders, and 1,776 controls, mental disorders (schizophrenia and/or bipolar disorders) were associated with an increased risk of toxoplasmosis and/or toxocariasis (odds ratio = 2.3; 95% CI, 1.7 – 3.2) (Figure 3). The distribution of the pooled studies was illustrated using a funnel plot. Based on Duval and Tweedie's "trim and fill" visual method, we found that 2 analytical studies were missing (Figures 4). Afterwards, we found that the intercept result obtained by the Egger test was 2.4 (95% CI, -0.5 - 5.3 / p = 0.09), which confirms the existence of publication bias.

From the included analytical studies, we found that the pooled odds ratio of the association of schizophrenia and/or bipolar disorders and toxoplasmosis and/or toxocariasis in cases (people with mental disorders) versus controls after sensitivity analyses did not change. It varied from 2.3 (95% CI, 1.7 – 3.2) to 2.3 (95% CI, 1.7 – 3.3) when the study with the greatest weight, Esshili et al. [54], was withdrawn. And it became 2.2 (95% CI, 1.6 – 3.1) when Cetinkaya et al. [51] and Hamidinejat et al. [56], the studies with the lowest quality scores, were withdrawn.

Analysis of the selected subgroups by type of disease investigated, type of associated disease, type of subjects included, and continent allowed us to show the following findings: the odds ratio of the association between schizophrenia and toxocariasis was 2.7 (95% CI, 1.1 – 7.0) in people with
schizophrenia compared to the control group. And the association between mental disorders (schizophrenia and/or bipolar disorders) with toxoplasmosis was 2.3 (95% CI, 1.7 – 3.2) in people with schizophrenia and/or bipolar disorders compared to the control group. For the association between schizophrenia and neurotropic parasitic diseases (toxocariasis and/or toxoplasmosis) the odd ratio was 2.4 (95% CI, 1.7 – 3.4). Co-morbidities between mental disorders (schizophrenia and/or bipolar disorders) and neurotropic parasitic diseases (toxoplasmosis and/or toxocariasis) had closely similar odds ratios in both hospitalised and non-hospitalised people. The odds ratio was 2.3 (95% CI, 1.5 – 3.3) for the association between mental disorders (schizophrenia and/or bipolar disorders) and neurotropic parasitic diseases (toxoplasmosis and/or toxocariasis) when comparing cases with schizophrenia and/or bipolar disorders and controls. It was 2.5 (95% CI, 1.4 – 4.4) for the association between mental disorders (schizophrenia and/or bipolar disorders) and toxoplasmosis when comparing cases with schizophrenia and/or bipolar disorders and controls (Figure 5). Finally, the subgroup analysis by continent showed that in Asia, the odds ratio of co-morbidities between mental disorders (schizophrenia and/or bipolar disorders) and neurotropic parasitic diseases (toxoplasmosis and/or toxocariasis) was 2.3 (95% CI, 1.6 – 3.3).

Discussion

We focused on developing and emerging countries studied due to their high burden in the selected diseases. For mental disorders, these were anxiety, depression, bipolar disorder, and schizophrenia [10, 11] and for parasitic diseases with neurological tropism, these were malaria, cysticercosis, toxoplasmosis, HAT, Chagas disease, and human toxocariasis [9, 13].

In general, the diagnosis of diseases in the studies selected in this meta-analysis was performed using acceptable diagnostic techniques. Indeed, the quality of diagnostic techniques used to screen for mental disorders has been developed in accordance with DSM-5 and ICD-10 [66]. Nevertheless, it has been shown, as in the study of Kirkil et al., that the questionnaire used can also influence the results in terms of diagnosis [67]. The variety of questionnaires used in the studies included in this meta-analysis can be explained by the need to adapt the questionnaire to the population studied [68-76], as is usually recommended. Regarding laboratory diagnostic techniques, it is recommended to use
two complementary diagnostic tests (one very sensitive and therefore very specific) and to have the samples handed by two different technicians who do not know the clinical condition of the subject [77]. However, most of the studies included in this meta-analysis generally use only one fairly sensitive and specific diagnostic method at a time, which is not the best practice. This can be partly explained by financial constraints related to the cost of diagnostic tests, which are often quite expensive in low-income countries, and by the nature of the sample size, which increases the burden of work. This may be acceptable for this type of disease, since parasitic diseases are very commonly found in these countries.

The quality scores of the studies included in this meta-analysis are in line with those found by other authors [78]. There was publication bias and great heterogeneity in our estimates. In both the prevalence studies and the analytical studies, the quality scores were all largely above the average score (i.e. above half the maximum score: 11 for prevalence studies and 12.5 for case-control studies). But since our estimates did not change after we performed the sensitivity analysis. In our pooled estimates after withdrawing the study with the highest weight on the one hand, and the study with the lowest quality score on the other, using the two recommended methods, the sensitivity test had almost no impact on our results and the results remained robust. However, the different levels of heterogeneity found in the pooled estimates after analysis of the selected subgroups (type of original disease, type of associated disease, type of subjects included, and continent) implied that there were other covariates in play and that the latter could be the source of these heterogeneities.

This meta-analysis revealed that, despite the small number of studies included, the prevalence of anxiety and/or depression was almost 50% in people with Chagas disease and/or neurocysticercosis. "In addition, toxocariasis and/or toxoplasmosis was associated with an increased risk of schizophrenia and/or bipolar disorders (odds ratio = 2.3). More specifically, through subgroup analysis, we were able to show that toxocariasis (odds ratio = 2.7) and toxocariasis and/or toxoplasmosis (odds ratio = 2.4) were associated with increased risk of schizophrenia. In hospitalised subjects, the results of the subgroup analysis showed that in the presence toxocariasis and/or toxoplasmosis, the increased risk of mental disorders (schizophrenia and/or bipolar disorders) was 130%, and, in non-hospitalised
subjects the increased risk of mental disorders (schizophrenia and/or bipolar disorders) in presence of toxoplasmosis was 150%. This similarity of results in the two types of subjects might reflect the difficulties of access to mental and neurological health care in developing and emerging countries, with mental and neurological diseases being grossly under-diagnosed, and suffering both from a low ranking in terms of public health priority.

Due to the well-known neurotropic characteristics of *Toxoplasma gondii*, it is commonly accepted that many psychiatric symptoms, like mental retardation, may be due to *Toxoplasma gondii* infections [79]. Much interest exists in determining a causative relationship between this parasite and some mental disorders, in particular schizophrenia [80] and bipolar disorders [81]. Our investigation into the presence of IgG antibodies in people with mental disorders produced results that are similar to those obtained by other authors. People living with schizophrenia were found to have a risk ratio of 1.43 to 2.73 for toxoplasmosis and/or toxocariasis [80, 82], while people with bipolar disorders were found to have a risk ratio of 1.26 to 1.52 [81, 82].

The analytical studies on the association of mental disorders with neurotropic parasitic diseases (mostly conducted in Asia) didn’t allow statistical analyses, such as subgroup analysis. Only Asia, which accounted for most of the studies, made it possible to estimate that there was a 130% increased risk of toxoplasmosis and/or toxocariasis for a person living with schizophrenia and/or bipolar disorders. This lack of data on mental disorders in some developing and emerging countries may well be explained by the dearth of medical consultations for individuals with mental disorders and, additionally, by the rather limited number of health centres which, when they exist, do not seem to be accessible or to have healthcare providers trained to manage mental disorders. Additionally, faith and religion can have a significant impact on the diagnosis of mental disorders and neurotropic parasitic diseases in developing and emerging countries. Often wrongly attributing mental illness to a spiritual effect, 80% of people with mental disorders and their families prefer to consult religious leaders, healers, or exorcist-priests [83], and between 76% and 85% of people with severe mental disorders receive no treatment for their disorder in these countries [84]. Poverty and the lack of national and international funding for mental health often further exacerbate the situation. The
results from this meta-analysis would suggest that further studies on comorbidities of mental disorders and neurotropic parasitic diseases in developing and emerging countries might be required. Despite efforts made to reduce bias in this study, it still had some limitations. These limitations primarily involve: the size of the various samples, which were often relatively small; the identification of mental disorders which were not confirmed by a specialist in some studies; and the focus on Asia, which may well be an obstacle towards generalizing the results to other continents. Additionally, some estimates could not be determined due to the lack of studies meeting our inclusion criteria. Nonetheless, our meta-analysis on the co-morbidities between mental disorders and neurotropic parasitic diseases is the first to involve primarily developing and emerging countries. It has been performed following the PRISMA 2015 guidelines and the protocol was registered in the PROSPERO database. Finally, we performed our sensitivity tests by withdrawing the studies with the greatest weight and the studies with the lowest quality as it is it is recommended.

Conclusion
In this meta-analysis, the results show that the pooled estimates of co-morbidities between mental disorders and neurotropic parasitic diseases in developing and emerging countries are relatively high. Most of the included studies were conducted in Asia. In conclusion, our findings support the hypothesis that toxoplasmosis could be the cause of schizophrenia and/or bipolar disorders. We hope that this meta-analysis, the first of its kind to focus on developing and emerging countries, can provide some guidance to researchers to further explore and understand the associations between mental disorders and neurotropic parasitic diseases in developing and emerging countries.

Abbreviations
BDI: Beck Depression Inventory
CMA: Comprehensive Meta Analysis
DSM-5: Diagnostic and Statistical Manual of Mental Disorders
EIA: Enzyme Immuno Assay Enzyme Immuno Assay
ELISA: Immunosorbant Enzyme-Linked Assay
GHQ: General Health Questionnaire
HAT: Human African Trypanosomiasis
ICD-10: International Classification of Diseases
IENT: Institute of Epidemiology and Tropical Neurology
IFA: Immunofluorescent Assay
MMSE: Mini Mental State Examination
MSE: Mental Status Examination
PCR: Polymerase Chain Reaction
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PSE: Present State Examination
qPCR: quantitive Polymerase Chain Reaction
SADS-L: Schedule for Affective Disorders and Schizophrenia-Lifetime

Declarations

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All information generated or analyzed during this meta-analysis is available in the additional data provided by the first author.

**Competing interests**

VL and PEB are Sanofi employees and own Sanofi stocks. DG is a former employee of Sanofi. All other authors declare that there is no conflict of interest related to the writing and publication of this article.

**Funding**

The first author (LOB) was an intern at SANOFI for 6 months during which he received a grant. SANOFI has also provided access to its electronic databases.

**Authors' contributions**

PMP contributed to writing funding applications, the design of the research protocol, the validation of
the studies’ quality scores, the interpretation of the data, and the preparation of the manuscript. BM and FB contributed to finalizing the research protocol, data analysis, and preparation of the manuscript. VL contributed to finalizing the research protocol and preparation of the manuscript. PEB contributed to finalizing the research protocol, the evaluation of the studies’ quality scores, the interpretation of the data, and the preparation of the manuscript. DG contributed to finalizing the research protocol and the preparation of the manuscript. He also contributed to writing funding applications. Finally, LOD contributed to the drafting of the research protocol, its registration in PROSPERO, the selection of articles, the evaluation of the studies’ quality scores, the data analysis, the interpretation of the data, and the preparation of the manuscript.

This manuscript has been read and approved by all authors.

Acknowledgements

Not applicable.

References

1. World Bank : Country and Lending Groups. http://data.worldbank.org/income-level/low-and-middle-income (2016). Accessed 18 sep 2016.

2. Mallewa M, Wilmshurst JM: Overview of the Effect and Epidemiology of Parasitic Central Nervous System Infections in African Children. Seminars in Pediatric Neurology 2014, 21(1):19-25.

3. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, Silove D: The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. International Journal of Epidemiology 2014, 43(2):476-493.

4. Centers for Disease Control and prevention - National Center for Chronic Diseases Prevention and Health Promotion: Mental Health and Chronic Diseases. National Healthy Worksites (NHW).

https://www.cdc.gov/workplacehealthpromotion/tools-resources/pdfs/issue-brief-no-2-mental-health-and-chronic-disease.pdf (2012). Accessed 18 Sep 2016.
5. Aillon J-L, Ndetei DM, Khasakhala L, Ngari WN, Achola HO, Akinyi S, Ribero S: Prevalence, types and comorbidity of mental disorders in a Kenyan primary health centre. *Social Psychiatry and Psychiatric Epidemiology* 2014, **49**:1257-1268.

6. Zoller T, Fèvre EM, Welburn SC, Odiit M, Coleman PG: Analysis of risk factors for T. brucei rhodesiense sleeping sickness within villages in south-east Uganda. *BMC Infectious Diseases* 2008, **8**:88.

7. Okia M, Mbulamberi DB, De Muynck A: Risk factors assessment for T. b. rhodesiense sleeping sickness acquisition in S.E. Uganda. A case-control study. *Annales De La Societe Belge De Medecine Tropicale* 1994, **74**:105-112.

8. Rostami A, Seyyedtabaei SJ, Aghamolaie S, Behniafar H, Lasjerdi Z, Abdolrasouli A, Mehravar S, Alvarado-Esquivel C: Seroprevalence and risk factors associated with toxoplasma gondii infection among rural communities in northern Iran. *Revista Do Instituto De Medicina Tropical De Sao Paulo* 2016, **58**:70.

9. Nourollahpour Shiadeh M, Rostami A, Pearce BD, Gholipourmalekabadi M, Newport DJ, Danesh M, Mehravar S, Seyyedtabaei SJ: The correlation between Toxoplasma gondii infection and prenatal depression in pregnant women. *European Journal of Clinical Microbiology & Infectious Diseases: Official Publication of the European Society of Clinical Microbiology* 2016, **35**:1829-1835.

10. Vigo D, Thornicroft G, Atun R: Estimating the true global burden of mental illness. *The Lancet Psychiatry* 2016, **3**:171-178.

11. Aillon J-L, Ndetei DM, Khasakhala L, Ngari WN, Achola HO, Akinyi S, Ribero S: Prevalence, types and comorbidity of mental disorders in a Kenyan primary health centre. *Social Psychiatry and Psychiatric Epidemiology* 2014, **49**:1257-1268.

12. Blakemore A, Dickens C, Guthrie E, Bower P, Kontopantelis E, Afzal C, Coventry PA: Depression and anxiety predict health-related quality of life in chronic
obstructive pulmonary disease: systematic review and meta-analysis.
International Journal of Chronic Obstructive Pulmonary Disease 2014, 9:501-512.

13. Elsheikha HM, Büsselberg D, Zhu X-Q: The known and missing links between Toxoplasma gondii and schizophrenia. Metabolic Brain Disease 2016, 31:749-759.

14. World Health Organization: World Health Report 2001 - Mental Health: New Design, New Hope. WHO. Geneva: WHO library; 172p. 2001.
http://www.who.int/whr/2001/media_centre/press_release/fr/. Accessed 13 sept 2017.

15. World Health Organization: Chapter 2: Impact of mental and behavioural disorders. http://www.who.int/whr/2001/chapter2/fr/index5.html. Accessed 24 apr 2017.

16. Haute Autorité de Santé: Guidance Note. Multi-annual programme on psychiatry and mental health. 2013. http://www.has-sante.fr/portail/upload/docs/application/pdf/2014-01/2013_10_08_programme_sante_mentale_college.pdf. Accessed 24 apr 2017.

17. World Health Organization: World Malaria Report 2015. Geneva; WHO library; 280p. 2015. http://www.who.int/malaria/publications/world-malaria-report-2015/report/en/. Accessed 13 Mar 2019.

18. Institut Pasteur: Chagas disease. Institut Pasteur. 2015.
https://www.pasteur.fr/fr/centre-medical/fiches-maladies/maladie-chagas. Accessed 23 Apr 2017.

19. Nicoletti A: Chapter 16 - Toxocariasis. In: Handbook of Clinical Neurology. Volume 114, edn. Edited by Hector H. Garcia HBTaOHDB: Elsevier; 2013: 217-228.

20. Magnaval JF, Glickman LT, Dorchies P, Morassin B: Highlights of human toxocariasis. Korean Journal of Parasitology 2001, 39:1-11.
21. Kenny JV, MacCabe RJ, Smith HV, Holland C: **Serological evidence for the presence of toxocariasis in the Turkana District of Kenya.** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1995, **89**:377-378.

22. Chieffi PP, Ueda M, Camargo ED, de S, Guedes ML, Gerbi LJ, Spir M, Moreira AS: **Visceral larva migrans: a seroepidemiological survey in five municipalities of São Paulo state, Brazil.** *Revista do Instituto de Medicina Tropical de Sao Paulo* 1990, **32**:204-210.

23. Damian MM, Martins M, Sardinha JF, De S, Chaves A, Tavares ADM: **Frequency of the antibody anti-Toxocara canis in a community along the Uatumã River, State of Amazonas.** *Revista da Sociedade Brasileira de Medicina Tropical* 2007, **40**:661-664.

24. Park HY, Lee SU, Huh S, Kong Y, Magnaval JF: **A seroepidemiological survey for toxocariasis in apparently healthy residents in Gangwon-do, Korea.** *Korean Journal of Parasitology* 2002, **40**:113-117.

25. Hayashi E, Tuda J, Imada M, Akao N, Fujita K: **The high prevalence of asymptomatic Toxocara infection among schoolchildren in Manado, Indonesia.** *Southeast Asian Journal of Tropical Medicine and Public Health* 2005, **36**:1399-1406.

26. SANOFI. **Sanofi's commitment to the fight against sleeping sickness.** In: *Le Hub*. 2017. https://lehub.sanofi.com/fr/acces-aux-soins/maladie-du-sommeil/.

   Accessed 24 apr 2017.

27. Flegr J: **Predictors of Toxoplasma gondii infection in Czech and Slovak populations: the possible role of cat-related injuries and risky sexual behavior in the parasite transmission.** *Epidemiology and Infection* 2017, **145**:1351-1362.
28. Bouteille B: *Epidemiology of cysticercosis and neurocysticercosis*. *Medecine Et Sante Tropicales* 2014, **24**:367-374.

29. World Health Organization: *Working to overcome the global impact of neglected tropical diseases: first WHO report on neglected tropical diseases*. Geneva: Department of Reproductive health and Research, World Health Organization; 2010.

30. Alvarado-Esquivel C: *Toxocara Infection in Psychiatric Inpatients: A Case Control Seroprevalence Study*. *PLOS ONE* 2013, **8**:e62606.

31. Cong W, Zhang X-X, Zhou N, Yu C-Z, Chen J, Wang X-Y, Li B, Qian A-D, Zhu X-Q: *Toxocara Seroprevalence among Clinically Healthy Individuals, Pregnant Women and Psychiatric Patients and Associated Risk Factors in Shandong Province, Eastern China*. *PLoS Neglected Tropical Diseases* 2014, **8**.

32. Abdoli A, Dalimi A, Arbabi M, Ghaffarifar F: *Neuropsychiatric manifestations of latent toxoplasmosis on mothers and their offspring*. *Journal of Maternal-Fetal and Neonatal Medicine* 2014, **27**:1368-1374.

33. Forlenza OV, Vieira Filho AH, Machado LR, Nóbrega JP, de Barros NG: *Depressive disorders associated with neurocysticercosis: prevalence and clinical correlations*. *Arquivos de neuro-psiiquiatria* 1998, **56**:45-52.

34. Ramírez-Bermudez J, Corona T: *Neuropsiquiatic manifestation in cerebral cysticercosis*. *Archivos de Neurociencias* 2005, **10**:92-94.

35. Wiwanitkit V: *Dementia and neurocysticercosis*. *Acta Neurologica Taiwanica* 2014, **23**:1-3.

36. Centers for Disease Control and prevention - National Center for Chronic Diseases Prevention and Health Promotion: *Mental Health and Chronic Diseases*. National Healthy Worksites (NHW). https://www.cdc.gov/workplacehealthpromotion/tools-resources/pdfs/issue-brief-no-2-mental-health-and-chronic-disease.pdf (2012).
37. Daré LO, Bruand P-E, Gérard D, Marin B, Lameyre V, Boumédiène F, Preux P-M: Comorbidities of mental disorders and chronic physical diseases in developing and emerging countries: a meta-analysis. BMC Public Health 2019, 19(1):304.

38. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000, 283:2008-2012.

39. Moher D., Shamseer L., Gherzi D., Liberati A., Petticrew M., Shekelle P., et al. PRISMA for systematic review protocols (PRISMA-P). http://prisma-statement.org/Extensions/Protocols.aspx. Accessed 30 oct 2016.

40. National Collaborating Centre for Methods and Tools: Quality Checklist for Health Care Intervention Studies. Hamilton, On : McMaster University : Meta-analysis in medical research. (2008). http://www.nccmt.ca/resources/search/9. Accessed 23 mar 2017.

41. Downs SH, Black N: The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology and Community Health 1998, 52:377-384.

42. CMA Manuals : Comprehensive Meta-Analysis Software. (2017). https://www.meta-analysis.com/pages/cma_manual.php. Accessed 31 mar 2017.

43. Borenstein M, Larry V. H, Julian P. T. H, Hannah R. R: Introduction to Meta-Analysis -. Oxford: Wiley; 2009.

44. Boyle MH: Guidelines for evaluating prevalence studies. Evidence-Based Mental Health 1998, 1:37-39.
45. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR: A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods 2010, 1:97-111.

46. Borenstein M, Larry V. H, Julian P. T. H, Hannah R. R. Introduction to forest plots. Oxford: Wiley, 2009.

44. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ: British Medical Journal 1997, 315:629-634.

47. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ: British Medical Journal 1997, 315:629-634.

48. Alipour A, Shojaae S, Mohebali M, Tehranidoost M, Abdi Masoleh F, Keshavarz H: Toxoplasma infection in schizophrenia patients: A comparative study with control group. Iranian Journal of Parasitology 2011, 6:31-37.

49. Alvarado-Esquivel C, Hernández-Tinoco J, Sánchez-Anguiano LF, Cisneros-Martínez JA: Low seroprevalence of Toxocara infection in schizophrenic inpatients in Durango, Mexico: A case control study. International Journal of Biomedical Science 2014, 10:269-271.

50. Alvarado-Esquivel C, Urbina-Álvarez JD, Estrada-Martínez S, Torres-Castorena A, Molotla-de-León G, Liesenfeld O, Dubey JP: Toxoplasma gondii infection and schizophrenia: a case control study in a low Toxoplasma seroprevalence Mexican population. Parasitology International 2011, 60:151-155.

51. Cetinkaya Z, Yazar S, Gecici O, Namli MN: Anti-Toxoplasma gondii antibodies in patients with schizophrenia--preliminary findings in a Turkish sample. Schizophrenia Bulletin 2007, 33:789-791.

52. Daryani A, Sharif M, Hosseini SH, Karimi SA, Gholami S: Serological survey of Toxoplasma gondii in schizophrenia patients referred to Psychiatric
Hospital, Sari City, Iran. Tropical Biomedicine 2010, 27:476-482.

53. Emelia O, Amal RN, Ruzanna ZZ, Shahida H, Azzubair Z, Tan KS, Noor Aadila S, Siti NaM, Aisah MY: Seroprevalence of anti-Toxoplasma gondii IgG antibody in patients with schizophrenia. Tropical Biomedicine 2012, 29:151-159.

54. Esshili A, Thabet S, Jemli A, Trifa F, Mechri A, Zaafrane F, Gaha L, Juckel G, Babba H, Bel Hadj Jrad B: Toxoplasma gondii infection in schizophrenia and associated clinical features. Psychiatry Research 2016, 245:327-332.

55. Forlenza OV, Filho AH, Nobrega JP, dos Ramos Machado L, de Barros NG, de Camargo CH, da Silva MF: Psychiatric manifestations of neurocysticercosis: a study of 38 patients from a neurology clinic in Brazil. Journal of Neurology, Neurosurgery, and Psychiatry 1997, 62:612-616.

56. Hamidinejat H, Ghorbanpoor M, Hosseini H, Alavi SM, Nabavi L, Jalali MHR, Borojeni MP, Jafari H, Mohammadaligol S: Toxoplasma gondii infection in first-episode and inpatient individuals with schizophrenia. International Journal of Infectious Diseases 2010, 14:e978-e981.

57. Juanah LY, Jalaludin J, Osman M, Osman ZJ: Seroprevalence of Toxoplasma Gondii among schizophrenics at Hospital Kajang. American Journal of Infectious Diseases 2013, 9:11-16.

58. Kaplan M, Kalkan A, Kuk S, Demirdag K, Ozden M, Kilic SS: Toxocara seroprevalence in schizophrenic patients in Turkey. Yonsei Medical Journal 2008, 49:224-229.

59. Karabulut N, Bilgiç S, Gürok MG, Karaboğa F: Is there any role of latent toxoplasmosis in schizophrenia disease? Journal of the Chinese Medical Association 2015, 78:533-537.

60. Khademvatan S, Khajeddin N, Izadi S, Saki J: Study of Toxoplasma gondii
infection in patients with bipolar disorder. *Journal of Medical Sciences (Faisalabad)* 2013, 13:215-220.

61. Khademvatan S, Saki J, Khajeddin N, Izadi-Mazidi M, Beladi R, Shafiee B, Salehi Z: *Toxoplasma gondii exposure and the risk of schizophrenia*. *Jundishapur Journal of Microbiology* 2014, 7.

62. Kheirandish F, Nazari H, Mahmoudvand H, Yaseri Y, Tarahi MJ, Fallahi S, Ezatpour B: *Possible link between toxoplasma gondii infection and mood disorders in Lorestan province, Western Iran*. *Archives of Clinical Infectious Diseases* 2016, 11.

63. Omar A, Bakar OC, Adam NF, Osman H, Osman A, Suleiman AH, Manaf MRA, Selamat MI: *Seropositivity and serointensity of Toxoplasma gondii antibodies and DNA among patients with schizophrenia*. *The Korean Journal of Parasitology* 2015, 53:29-34.

64. Ozaki Y, Guariento ME, de Almeida EA: *Quality of life and depressive symptoms in Chagas disease patients*. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation* 2011, 20:133-138.

65. Tamer GS, Dundar D, Yalug I, Caliskan S, Yazar S, Aker A: *The schizophrenia and Toxoplasma gondii connection: infectious, immune or both?* *Advances in therapy* 2008, 25:703-709.

66. Stolic RV, Trajkovic GZ, Mihailovic B, Sipic MV, Celic DB, Lazic SF, Nikolic GR, Sovtic SR, Stolic DZ: *Characteristics of depression in obese people living in an insecure environment*. *Indian Journal of Medical Sciences* 2010, 64:307-314.

67. Kirkil G, Deveci F, Deveci SE, Atmaca M: *Anxiety and depression symptoms in patients with chronic obstructive pulmonary disease (copd)*. *Klinik Psikofarmakoloji Bulteni* 2015, 25:151-161.
68. Aghanwa HS, Erhabor GE: *Specific psychiatric morbidity among patients with chronic obstructive pulmonary disease in a Nigerian general hospital*. Journal of Psychosomatic Research 2001, *50*:179-183.

69. Fanger PC, Azevedo RCSd, Mauro MLF, Lima DD, Gaspar KC, Silva VFd, Nascimento WTJd, Botega NJ: [Depression and suicidal behavior of cancer inpatients: prevalence and associated factors]. Revista Da Associacao Medica Brasileira (1992) 2010, *56*:173-178.

70. Hong JS, Tian J: *Prevalence of anxiety and depression and their risk factors in Chinese cancer patients*. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer 2014, *22*:453-459.

71. Huang Y, Chen J, Yang J, Song K, Wang X, Cheng X, Qu S: *Evaluation of depressive symptoms in obese patients with or without acanthosis nigricans*. Hormones (Athens, Greece) 2015, *14*:417-424.

72. Islam SMS, Ferrari U, Seissler J, Niessen L, Lechner A: *Association between depression and diabetes amongst adults in Bangladesh: a hospital based case-control study*. Journal of Global Health 2015, *5*:020406.

73. Mollaoglu H, Ucok K, Kaplan A, Genc A, Mayda H, Guzel HI, Sener U, Uygur E, Ozbulut O: *Association analyses of depression, anxiety, and physical fitness parameters in Turkish obese adults*. Journal of Back and Musculoskeletal Rehabilitation 2012, *25*:253-260.

74. Negi H, Sarkar M, Raval AD, Pandey K, Das P: *Presence of depression & its risk factors in patients with chronic obstructive pulmonary disease*. The Indian Journal of Medical Research 2014, *139*:402-408.

75. Yildirim A, Hacihasanoğlu Aşilar R, Bakar N, Demir N: *Effect of anxiety and depression on self-care agency and quality of life in hospitalized patients*
with chronic obstructive pulmonary disease: A questionnaire survey. International Journal of Nursing Practice 2013, 19:14-22.

76. Zhao L, Li X, Zhang Z, Song C, Guo C, Zhang Y, Zhang Y, Li L, Lu G, Zheng G et al: Prevalence, correlates and recognition of depression in Chinese inpatients with cancer. General Hospital Psychiatry 2014, 36:477-482.

77. World Health Organization: Good Laboratory Practice : Quality Practices for Regulated Non-clinical Research and Development. Geneva: WHO library; 232p. 2010.

78. Amerio A, Stubbs B, Odone A, Tonna M, Marchesi C, Nassir Ghaemi S: Bipolar I and II Disorders; A Systematic Review and Meta-Analysis on Differences in Comorbid Obsessive-Compulsive Disorder. Iranian Journal of Psychiatry and Behavioral Sciences 2016, 10.

79. Zhu S, Guo M-F, Feng Q-C, Fan J-M, Zhang L-X: Epidemiological evidences from China assume that psychiatric-related diseases may be associated with Toxoplasma gondii infection. Neuroendocrinology Letters 2007, 28:115-120.

80. Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, Gutierrez B, Gutierrez J: Infectious agents associated with schizophrenia: a meta-analysis. Schizophrenia Research 2012, 136:128-136.

81. de Barros JLVM, Barbosa IG, Salem H, Rocha NP, Kummer A, Okusaga OO, Soares JC, Teixeira AL: Is there any association between Toxoplasma gondii infection and bipolar disorder? A systematic review and meta-analysis. Journal of Affective Disorders 2017, 209:59-65.

82. Sutterland AL, Fond G, Kuin A, Koeter MWJ, Lutter R, van Gool T, Yolken R, Szoke A, Leboyer M, de Haan L: Beyond the association. Toxoplasma gondii in schizophrenia, bipolar disorder, and addiction: systematic review and meta-
83. Toftegaard KL, Gustafsson LN, Uwakwe R, Andersen UA, Becker T, Bickel GG, Bork B, Cordes J, Frasch K, Jacobsen BA et al: Where are patients who have co-occurring mental and physical diseases located? *The International Journal of Social Psychiatry* 2015, 61:456-464.

84. World Health Organization: *Mental Health Action Plan 2013-2020*. Geneva: WHO. Library Cataloguing-in-Publication Data; 50p. 2013.

Tables
Table 1: Risk factors of interest diseases
| Disease                                      | Risk factor                                                                 |
|----------------------------------------------|-----------------------------------------------------------------------------|
| Mental disorders                             | ◦ Family history                                                            |
|                                              | ◦ Stressful living conditions                                                |
|                                              | ◦ Existence of a chronic disease                                             |
|                                              | ◦ Traumatisms                                                                |
|                                              | ◦ Drug use                                                                   |
|                                              | ◦ Child abuse or neglect and/or lack of social support [4, 5]                 |
| Neurotropic parasitic diseases                | ◦ Family history of HAT, living near a wetland [6]                            |
| Human African Trypanosomiasis (HAT) Chagas   | ◦ Economic, cultural, and human behaviour [7]                                |
| disease                                      |                                                                            |
| Cysticercosis                                |                                                                            |
| Toxoplasmosis                                |                                                                            |
| Human Toxocariasis                           |                                                                            |
|                                              | ◦ Age, home, consumption of undercooked meat, and unwashed fruit or raw      |
|                                              |     vegetables [8]                                                           |
|                                              | ◦ Bare hand contact with the ground or injury to animals, consumption of     |
|                                              |     poorly washed vegetables [27]                                            |

Table 2: Characteristics of prevalence studies of associations of mental disorders and neurotropic parasitic diseases
| Reference                        | Continent | Subjects type       | Original disease   | Associated disease     |
|----------------------------------|-----------|---------------------|--------------------|------------------------|
| Ozaki et al. [64]                | Asia      | Non-hospitalised    | Chagas disease     | Anxiety and Depression |
| Qual Life Res, 2011              |           |                     |                    |                        |
| Forlenza et al. [55]             | America   | Non-hospitalised    | Neurocysticercosis | Depression             |
| J Neurol Neurosurg Psychiatry, 1997 |           |                     |                    |                        |

Description of data:
BDI: Beck Depression Inventory, PSE: Present State Examination, MMSE: Mini Mental State Examination, SADS-L: Schedule for Affective Disorders and Schizophrenia-Lifetime, MSE: Mental Status Examination, F: Female, M: male, Age in years.

Table 3: Characteristics of analytical studies of associations of mental disorders and neurotropic parasitic diseases
| Reference                          | Continent   | Subjects type | Original disease      | Associated disease               | Positive (n) |
|-----------------------------------|-------------|---------------|-----------------------|----------------------------------|--------------|
| Daryani et al. [52] Trop Biomed, 2010 | Asia        | Non-hospitalised | Schizophrenia          | *T. gondii* infection             | 28 and 25   |
| Alipour et al. [48] Iran J Parasitol, 2011 | Asia        | Hospitalised  | Schizophrenia          | *T. gondii* infection             | 42 and 23   |
| Karabulut et al. [59] J Chin Med Assoc, 2015 | Asia        | Hospitalised  | Schizophrenia          | *T. gondii* infection             | -            |
| Khademvat et al. [61] Jundishapur J Microbiol, 2014 | Asia        | Non-hospitalised | Schizophrenia          | *T. gondii* infection             | 34 and 53   |
| Hamidinejat et al. [56] Int J Infect Dis, 2010 | Asia        | Hospitalised  | Schizophrenia          | *T. gondii* infection             | -            |
| Tamer et al. [65] Adv Ther, 2008 | Asia        | Hospitalised  | Schizophrenia          | *T. gondii* infection             | 16 and 5    |
| Alvarado-Esquivel et al. [50] Parasitol Int, 2011 | America     | Hospitalised  | Schizophrenia          | *T. gondii* infection             | -            |
| Cetinkaya et al. [51] Schizophr Bull, 2007 | Asia        | Non-hospitalised | Schizophrenia          | *T. gondii* infection             | 66 and 33   |
| Omar et al. [63] Korean J Parasitol, 2015 | Asia        | Non-hospitalised | Schizophrenia          | *T. gondii* infection             | 52 and 10   |
| Eshhili et al. [54] Psychiatry Res, 2016 | Africa      | Non-hospitalised | Schizophrenia          | *T. gondii* infection             | -            |
| Juanah et al. [57] Am J Infect Dis, 2013 | Asia        | Hospitalised  | Schizophrenia          | *T. gondii* infection             | -            |
| Kheirandish et al. [62] Arch Clin Infect Dis, 2016 | Asia        | Hospitalised  | Schizophrenia          | Toxoplasmosis and bipolar disorders | 49 and 54 and 65 and 65 |
| Emelia et al. [53] Trop Biomed, 2012 | Asia        | Hospitalised  | Schizophrenia          | Toxocariasis                      | 54 and 49   |
| Alvarado-Esquivel et al. [49] Int Int J Biomed Sci, 2014 | America     | Hospitalised  | Schizophrenia          | Toxocariasis                      | 50 and 100  |
| Reference                           | Continent | Subjects type | Origin disease | Associated disease | Positive (n) | Total (N) | O R | Diagnostic method                         | F/M | Age (case / control) |
|------------------------------------|-----------|---------------|----------------|--------------------|--------------|-----------|-----|------------------------------------------|-----|----------------------|
| Kaplan et al. [58] Yonsei Yonsei Med J, 2008 | Asia      | Hospitalised  | Schizophrenia   | Toxocariasis       | 45           | 98        | 2   | ELISA kit “IgG & M” (Germany) ELISA microtiter plate reader | 95/10 | 38 ± 11               |
| Yonsei Med J, 2008                 |           |               |                |                    | 2            | 10        | 0   |                                          | 3   | 35 ± 8                |
| Khademvatan et al. [60] J Med Sci Faisalabad, 2013 | Asia      | Hospitalised  | Bipolar disorders (I) | Toxoplasma | 11           | 0         | 7   | ELISA “IgG & M” (USA)                        | 16  | 33.93 ±11.8           |
|                                   |           |               |                |                    | 20           | 7         | 0   |                                          | 55  | 33.88 ±11.4           |

Description of data:
Kheirandish et al., 2016: Cases = 49 patients with schizophrenia and 54 patients with bipolar disorders, Controls = 85 for schizophrenia cases and 85 for bipolar disorder cases.
T. gondii: Toxoplasma gondii, GHQ: General Health Questionnaire, ELISA: Immunosorbant Enzyme-Linked Assay, IFA: Immunofluorescent Assay, EIA: Enzyme Immuno Assay Enzyme Immuno Assay, PCR: Polymerase Chain Reaction, qPCR: quantitative Polymerase Chain Reaction, F: Female, M: male, Age in years.

Additional Files

**Table S1:** Characteristics of quality scores of prevalence studies

**Description of data:** Global quality (Items: 1-2-3-5-6-7-9-10); External validity (Items:11-12-13);
Results bias (Items: 15-16-18-20); Confusion and selection bias (Item: 25); Power (Item: 27) and S: Quality score.

**Additional file 2**

**Table S2:** Characteristics of quality scores of analytical studies

**Description of data:** Global quality (Items: 1-2-3-5-6-7-9-10); External validity (Items:11-12-13);
Results bias (Items: 15-16-18-20); Confusion and selection bias (Item: 25); Power (Item: 27) and S: Quality score.

Figures
Electronic databases research = 2,604 articles
(Medline = 1,207; Embase = 1,164;
Lilacs=147; and IENT = 86)
Manual research = 0 articles

Articles retained after duplicates elimination = 1,917
Excluded for:
Animal study = 23
Letter to editor = 12
Other comorbidity = 986
Other subject = 502
Articles retained by Title = 394
Excluded for abstract irrelevance = 275
Articles retained by Abstract = 120
Excluded for:
Absence of full text = 16
Absence of results = 03
Not meeting criteria = 43
Articles from list of references = 1
Articles included in the Meta-Analysis = 18
Prevalence studies = 2
Analytical studies = 16

Figure 1
Research strategy flow chart for the meta-analysis of associations of mental disorders and neurotropic parasitic diseases in developing and emerging countries
Figure 2

Forest plot of the pooled prevalence of anxiety and/or depression in people with Chagas disease and/or neurocysticercosis. Legend: Heterogeneity: $Q = 1.56$, df = 1, $p = 0.21$, I$^2 = 36.03$. 

| Study name       | Outcome | Statistics for each study | Event rate | Lower limit | Upper limit | Relative weight |
|------------------|---------|----------------------------|------------|-------------|-------------|-----------------|
| Forlenza et al., 1997 | Depression | Event rate | 0.526 | 0.370 | 0.677 | 34.82 |
| Ozaki et al., 2011 | Depression | Event rate | 0.409 | 0.321 | 0.503 | 65.18 |
|                   |         | Event rate | 0.449 | 0.344 | 0.559 |                  |
**Figure 3**

Forest plot of the pooled odds ratio of toxoplasmosis and/or toxocariasis in people with schizophrenia and/or bipolar disorders Legend: Heterogeneity: $Q = 62.67$, df = 16, $p < 0.0001$, $I^2 = 74.47$ Kheirandish et al., 2016*: Schizophrenia Kheirandish et al., 2016**: Bipolar disorders
Figure 4

Funnel plot showing found and missing analytical studies of associations of mental disorders and neurotropic parasitic diseases.
### Figure 5

Forest plot of the pooled odds ratio of associations of mental disorders and neurotropic parasitic diseases by type of subjects (hospitalised and non-hospitalised). Legend:

Heterogeneity: $Q = 62.67$, $df = 16$, $p < 0.0001$, $I^2 = 74.47$ Kheirandish et al., 2016*:

Schizophrenia** Kheirandish et al., 2016**: Bipolar disorders

#### Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additional file 2.pdf
- PRISMA 2009 checklist.doc
- Additional file 1.pdf