Impact of mental disorders on active tuberculosis treatment outcomes: a systematic review and meta-analysis

Ga Eun Lee, MScPH[*,1], **James Scuffell, MBChB MSc**[*,2], **Jerome T. Galea, PhD MSW**[3,4], **Sanghyuk S. Shin, PhD**[5], **Elizabeth Magill, BA**[6], **Ernesto Jaramillo, MD PhD**[7], **Annika C. Sweetland, DrPH MSW**[6]

[1]Independent researcher [2]King's College London, London [3]School of Social Work, College of Behavioral and Community Sciences, University of South Florida, Tampa, Florida [4]College of Public Health, University of South Florida [5]Sue & Bill Gross School of Nursing, University of California at Irvine, Irvine, California [6]Department of Psychiatry, Columbia Vagelos College of Physicians and Surgeons, New York State Psychiatric Institute, New York, New York [7]Global Tuberculosis Programme, WHO, Geneva, Switzerland

Abstract

Background: Comorbid mental disorders in patients with tuberculosis (TB) may exacerbate TB treatment outcomes. We systematically reviewed current evidence on the association between mental disorders and TB outcomes.

Methods: We searched eight databases for studies published from 1990-2018 that compared TB treatment outcomes among patients with and without mental disorders. We excluded studies that did not systematically assess mental disorders and studies limited to substance use. We extracted study and patient characteristics and effect measures and performed a meta-analysis using random-effects models to calculate summary odds ratios (OR) with 95% confidence intervals (CI).

Findings: Of 7,687 studies identified, ten were included in the systematic review and nine in the meta-analysis. Measurement of mental disorders and TB outcomes were heterogeneous across studies. The pooled association between mental disorders and any poor outcome, loss to follow-up, and non-adherence were OR 2.13 (95% CI: 0.85-5.37), 1.90 (0.33-10.91), and 1.60 (0.81-3.02), respectively. High statistical heterogeneity was present.

Interpretation: Our review suggests that mental disorders in TB patients increase the risk of poor TB outcomes, but pooled estimates were imprecise due to small number of eligible studies. Integration of psychological and TB services might improve TB outcomes and progress towards TB elimination.

Keywords

Infectious Disease; Lost to Follow-up; Psychiatry; Treatment Adherence and Compliance; Treatment Failure

Correspondence to: Dr. James Scuffell, King's College London, London SE1 9RT, UK. Electronic address: james.scuffell@kcl.ac.uk.
*These authors contributed equally to the manuscript.

INTRODUCTION

To eliminate tuberculosis (TB) by 2030, the World Health Organization's End TB Strategy calls for integrated, patient-centered care and prevention.[1] This strategic pillar underscores the management of co-morbidities, including mental disorders, which have been identified in up to 70% of TB patients.[2] TB and mental disorders share common risk factors including homelessness, substance use, and HIV infection which may affect health-related behaviours and treatment outcomes.[2]

A large body of work suggests an association between mental disorders and poor TB treatment outcomes,[2-9] yet many studies were not primarily designed to answer this research question.[3-6] Not all studies assess mental disorders systematically across all participants,[8,9] making results difficult to interpret.[10] This gap in evidence greatly impedes progress to formulate an evidence-based strategy to address mental health in TB patients.

The purpose of this study was to systematically review evidence on the impact of mental disorders on TB treatment outcomes. We only included studies that assessed mental disorders systematically for all TB patients. Our primary objective was to determine whether TB patients with concurrent mental disorders have poorer treatment outcomes than patients without mental disorders. We also examined evidence on delayed treatment initiation and medication adherence.

METHODS

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines and the protocol was registered in the PROSPERO database (CRD42019122382). Ethical approval was not required for this study.

Search strategy

We searched PubMed, Embase Classic, PsycINFO, Global Health, CINAHL, LILACS, Scopus, and Web of Science Core Collection databases for terms related to TB, mental disorder, and TB treatment outcomes. We used both free-text and subject heading (MeSH) terms adapted for use in each database. The MeSH terms search was: "Tuberculosis AND Mental disorders AND (Mortality OR Morbidity OR Death OR Prognosis OR Disease-Free Survival OR Treatment Outcome OR Drug Resistance OR Disease transmission, infectious OR Patient Acceptance of Health Care OR Treatment Failure OR Patient Compliance OR Lost to Follow-Up OR Patient Dropouts OR Treatment Refusal OR Health behavior OR Help-seeking Behavior OR recurrence)". The full search strategy for PubMed is available in Table 1.

Database searches were conducted during October 2018. We included articles published between January 1, 1990 - towards the beginning of the Directly Observed Therapy, Short Course (DOTS) strategy[11] - and October 29, 2018. At full-text screening, we reviewed articles published in languages familiar to the co-authors (English, French, Spanish, Portuguese, Korean). We also screened relevant citations in included articles and searched for subsequent publication of study protocols.

Eligibility criteria

Study type and participants—Study types included cross-sectional, case-control, and retrospective and prospective cohort studies, as well as randomized controlled trials. We excluded qualitative studies, case reports and series, theses, literature reviews, meta-analyses, commentaries, editorials, conference abstracts, and latent TB studies. Studies included patients initiating or undergoing treatment for active TB in any setting, with or without multidrug-resistance (MDR).

Exposures and outcomes of interest—We defined mental disorders as mood disorders including depression, anxiety disorders, post-traumatic stress disorder and psychotic disorders. The comparison group was no mental disorders. We only included studies that assessed mental disorders in all TB patients based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD), or using a validated psychiatric screening instrument. We excluded substance use disorders.

Our primary outcome of interest was TB treatment outcomes as defined by the World Health Organization (WHO): successful (cured, treatment completion) and poor (default or loss to follow-up, failure, death).[12] Secondary outcomes were diagnostic delay, defined by time from symptom onset to TB diagnosis or treatment initiation; and medication non-adherence measured by self-report, missed visits, pill count, or physiological tests.

Data analysis

Records found in database searching were uploaded and de-duplicated in EndNote using the Bramer method.[13] In duplicate, two reviewers (GL, JS) independently screened abstracts and reviewed the full texts of relevant studies for inclusion. We used Rayyan for screening.[14]

Data from all studies were extracted independently and duplicated by three authors (GL, JS, EM) using a form based on the Cochrane Data Extraction and Assessment template.[15] Data included study characteristics (year, country, study design, sample size) and patient characteristics (type of TB patient, mental health assessment and prevalence, treatment for mental disorder, TB treatment outcomes). Adjusted and unadjusted effect measures (odds, risk, prevalence and hazard ratios) were extracted or calculated for the association between mental disorders and each outcome.

Quality of each study was assessed independently and duplicated among five assessors (GL, JS, EM, JG, AS) using the Risk Of Bias In Non-Randomized Studies of Interventions tool (ROBINS-I).[16] Based on the literature, we specified age, sex, and socioeconomic status as key *a priori* confounders. If studies adjusted for all three confounders, the best bias judgement attributed for the confounding domain was moderate, according to the ROBINS-I tool.[16] Disagreements arising in the data extraction and quality assessment process were resolved by consensus.

Statistical analysis

We calculated odds ratios (OR) and 95% confidence intervals (CI) for the association between mental disorders and treatment outcomes. When direct calculation was not possible, we calculated ORs from risk, hazard and prevalence ratios.[17,18] Poor outcomes were considered the inverse of successful outcomes. We estimated pooled odds ratios based on the following TB treatment outcomes: any poor outcome (combinations of failure, loss to follow-up, or death), loss to follow-up, and "non-adherence", which included all definitions of non-adherence across studies. Random-effects models were used, given the clinical heterogeneity of study populations and mental disorders assessed across studies. Heterogeneity was measured using I^2 statistics.[19] Analysis was done in R (Vienna, Austria).

RESULTS

We considered 5,086 studies for inclusion in the review (Figure 1). Abstract screening eliminated 4,931 articles, leaving 155 for full-text screening. An additional 41 articles were screened from citations within included studies. The most common reasons for exclusion were: lack of relevant exposure or outcome (46.2%), outcome not stratified by exposure (28.5%), or mental illness not systematically assessed (7.0%). In total, ten studies met our inclusion criteria, and nine were included in meta-analysis (Figure 1). We found no studies on TB treatment delay.

Characteristics of included studies

The ten included studies reported data on patients beginning TB treatment between 1999 and 2016 (Table 2). They were conducted in sub-Saharan Africa (South Africa, Ethiopia, Zimbabwe, Zambia, and Tanzania) (n=6),[20-25] Peru (n=3);[26-28] and China (n=1).[29] Six studies were cohort studies,[20,21,25-28] three were cross-sectional studies,[23,24,29] and one was a case-control study.[22] The total sample size was 12,868 (range: 49-4,900). Two studies included MDR-TB patients only.[27,28]

Mental disorder was measured at baseline either by psychiatric assessment[22,27,28] or self-reported screening tools.[20,21,23-26,29] (Table 2) The prevalence of mental disorders among TB patients ranged from 18.9%[28] to 67.6%.[21] Four studies measured depression,[20,22,26,29] three psychological distress,[21,24,25] and one post-traumatic stress disorder.[23] Two studies reported mental disorder as a composite variable.[27,28] Only two studies indicated that mental health support was provided to patients outside of usual care.[26,28]

Primary outcomes

Association between mental disorders and poor TB treatment outcomes—Four studies estimated the association between mental disorders and poor TB treatment outcomes as a composite measure combining some or all of: treatment failure, loss to follow-up, death (Table 3, Figure 2).[20,21,26,27] Overall, mental disorders were associated with increased odds of poor TB treatment outcomes (pooled OR 2.13, 95% CI 0.85-5.37, Figure 2). Heterogeneity was high across studies (I^2 82%).

Association between mental disorders and TB treatment loss to follow-up—
Two studies focused on the association between mental disorders and loss to follow-up, but used different definitions (Table 3, Figure 2).[20,28] One study defined loss to follow-up as a patient on treatment for at least four weeks and whose treatment was interrupted for eight or more consecutive weeks.[20] The other study was defined loss to follow-up as any patient missing 30 or more consecutive days of treatment.[26] In the meta-analysis (Figure 2), mental disorder was associated with nearly double the odds of loss to follow-up compared with no mental disorder (pooled OR 1.90, 95% CI 0.33-10.91). There was high heterogeneity (I^2 78%).

Association between mental disorders and death—Two studies reported an association between mental disorders and death (Table 3).[20,25] In one study, depression was associated with 2.99 times the risk of death (95% CI 1.54-5.78).[20] Another study revealed that for each point increase of psychological distress score, odds of death increased by 6% (95% CI 4-8%).[25] Meta-analysis was not conducted for this outcome.

Secondary outcomes

Association between mental disorders and non-adherence to TB treatment—
TB treatment non-adherence was examined in five studies, but definitions varied (Table 3, Figure 3). Three studies used self-reported non-adherence,[23,24,29] one used "discontinuation of treatment beyond the intensive phase of therapy,"[22] and the fifth defined it as "missing a scheduled DOTS visit".[25] One study had insufficient information to calculate an effect estimate and was excluded from the meta-analysis.[22] Summarizing the effect estimates, there was a trend towards increased odds of non-adherence (OR 1.60, 95% CI 0.84-3.02), with high statistical heterogeneity (I^2 86%) (Figure 3).

Risk of bias assessment

All included studies were observational studies, putting them at risk of bias according to ROBINS-I (Table 4). Half of the studies showed moderate risk of bias related to confounders by adjusting results for age, sex and socioeconomic status,[20,24-26,29] while the other half displayed serious risk of bias by not accounting for these confounders.[21-23,27,28] Five studies had low risk of bias in selection of participants,[20,25-28] but the other five studies were at serious risk of bias with study inclusion being related to mental health status and TB treatment outcome.[21-24,29] The most serious methodological concern was risk of classification of exposure. Six studies were at serious risk of bias for this domain, either because mental health was determined at the same time as the outcome or because the definition of mental disorder was not clear.[21-25,29] The other four studies had low risk of bias because they used locally validated tools or psychiatric interviews.[20,26-28] Two studies reported the provision of psychiatric treatment outside of usual care and were classified as serious risk of bias for deviations from intended exposure.[26,28] The other studies were either at low risk of bias or had insufficient information.[20-25,27,29] For missing data one study was at serious risk of bias,[22] seven were at low risk of bias,[20,21,24,25,27-29] and two had no information.[23,26] Four studies used self-reported measures and were classified as serious risk of bias due to measurement of outcomes.[22-24,29] All except one study[24] presented a low risk of bias in selection of reported results.

DISCUSSION

Our systematic review and meta-analysis found TB patients with mental disorders may have double the risk of loss to follow-up and three times the risk of death compared with patients without mental disorders. Mental disorders were also associated with twice the risk of treatment non-adherence. Still, few studies met criteria for inclusion, resulting in decreased precision of effect estimates, and most included studies had serious risk of bias.

These results are similar to but weaker than associations reported in another recent systematic review focused only on depression.[30] This difference may be partially due to variations in outcome definitions and statistical approaches between studies. The strong link between mental disorders and non-adherence to TB treatment is consistent with studies examining medication adherence in patients with mental disorders comorbid with HIV and non-communicable diseases.[31-33]

We found highly heterogeneous definitions of mental disorders across studies. Of the ten included studies, only three captured mental disorders using ICD or DSM criteria.[22,27,28] The remaining seven used screening tools with various cut-off scores.[20,21,23-26,29] Given the overlap between some symptoms of TB and mental disorders (e.g. disturbances in appetite, energy, and sleep), screening tools may not be as effective at distinguishing etiology.[34] Although half of the studies using screening tools described validation in local populations, none described specific validation among TB patients. This validation is imperative to better evaluate mental health in this population.[35]

There was also variation in definitions of TB outcomes. The WHO defines loss to follow-up as "a TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more."[12] However, only one study used this definition;[19] the other defined loss to follow-up as one month of treatment interruption.[28] The five studies evaluating TB treatment adherence[22-25,29] had even more disparate definitions: yes or no,[22] taking less than 90% of medication,[23,24] missing a scheduled DOTS visit,[25] and a score qualifying low, medium, or high adherence.[29] Variations in outcome definitions may partially explain differences in magnitude and precision of these results.

All included studies except one[20] had serious risk of bias using the ROBINS-I tool,[18] which limits the interpretation of current evidence. Half of the included studies did not adjust for important confounders of age, sex, and socioeconomic status,[34] and we could not account for these in meta-analysis. Residual confounding is likely present since none of the studies measured and adjusted for malnutrition, substance, alcohol or tobacco use.[36-39] There are also likely variations in quality and expectations of TB care between studies.

Only one study specifically described mental health intervention provided.[28] MDR-TB patients in Peru received group therapy and psychiatric medications to facilitate adherence, which may explain why the association between mental disorders and loss to follow-up was not significant in the study.[28] Interventions that aim to directly support TB patients (e.g. psychological therapies and anti-depressant treatment) have been shown to be acceptable[40,41] and improve TB outcomes.[42] Individual psychotherapy, peer-led "TB clubs", and psychotropic medications have been shown to improve adherence to TB treatment and

TB.[10,43] Patient-centered approaches like these either address mental health directly or address TB-related stigma, but are not widely adopted.

Strengths and limitations of study

Our meta-analysis was limited by the small number of studies that met inclusion criteria. For example, 13 studies from retrospective chart review or registry data were excluded because it was unclear if mental disorders were assessed for all patients. To mitigate the small number of studies, we combined all types of mental disorders and both TB and MDR-TB together in the meta-analyses, resulting in high levels of heterogeneity and wide confidence intervals in our pooled estimates. For example, compared to drug-sensitive TB, psychosocial stressors associated with MDR-TB are significantly more complicated;[35,44] treatment regimens often include medicines with psychiatric side effects, and treatment duration is much longer.[45] As a result, we were unable to form conclusions for specific mental disorders, although different mental disorders may have different impacts on TB outcomes.

CONCLUSIONS

This review emphasizes the scarcity of high quality studies that investigate the impact of mental disorders on TB treatment outcomes. A strong evidence base is essential to close the treatment gap in mental health care and accelerate progress towards achieving the targets of the WHO's End-TB Strategy. Future studies should systematically assess mental disorders in TB patients using locally validated screening tools or psychiatric evaluations, use standard outcome definitions, and measure and control for confounders. Improving the quality of future studies will showcase the magnitude of associations between mental disorders and TB treatment outcomes.

ACKNOWLEDGEMENTS

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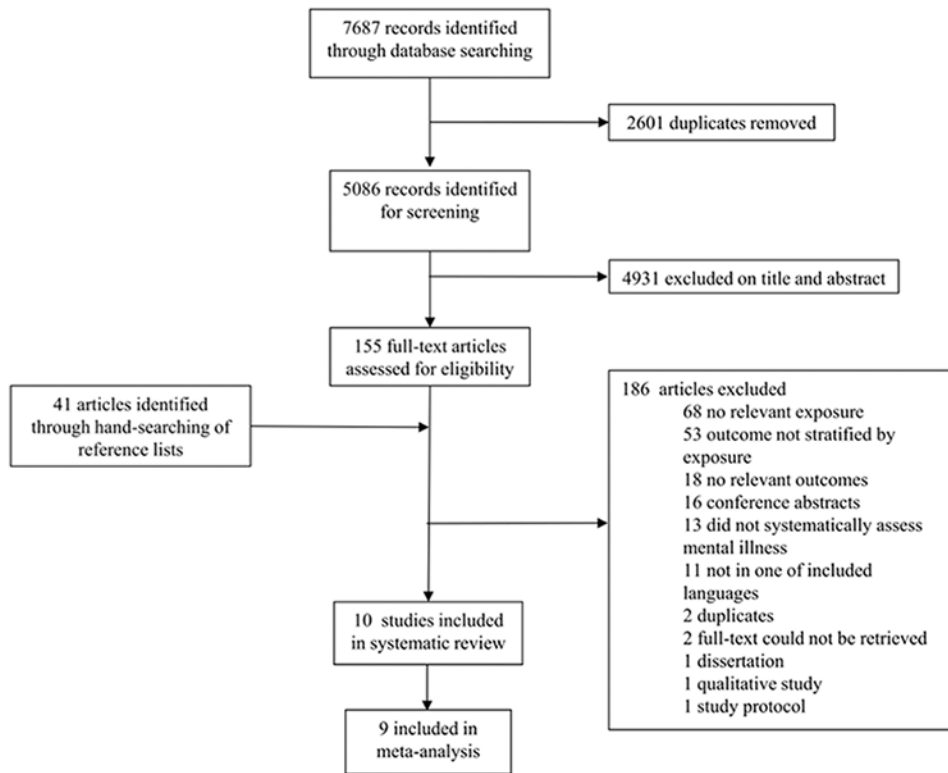
Figure 1.
Identification, screening, eligibility, and inclusion of studies, reported using the PRISMA guidelines
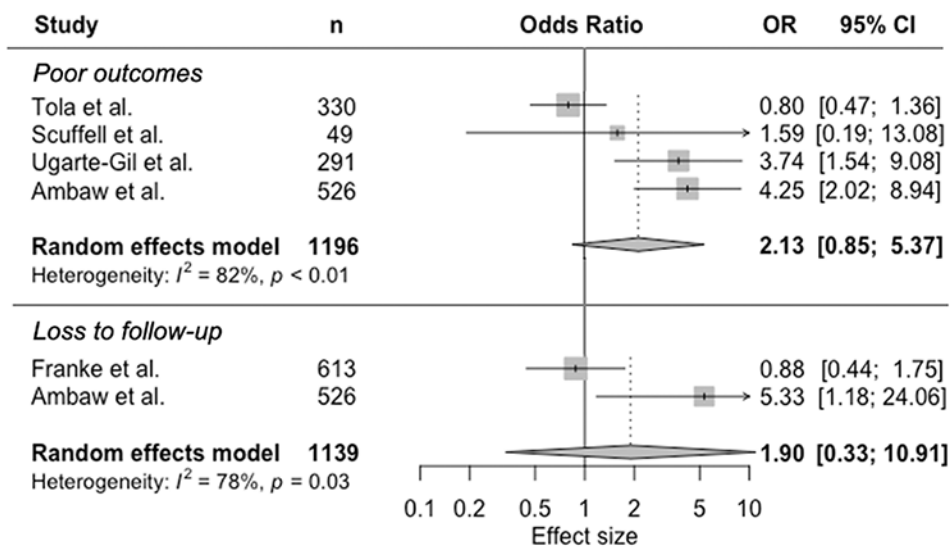
Figure 2.
Random-effects meta-analysis of observational studies on mental disorders and tuberculosis treatment outcomes

Study	n	Odds Ratio	OR	95% CI
Non-adherence				
Naidoo et al.	3107		0.94	[0.73; 1.22]
Peltzer et al.	4900		1.05	[0.91; 1.22]
Theron et al.	1502		2.29	[1.03; 5.10]
Yan et al.	1342		3.67	[2.04; 6.61]
Random effects model	**10851**		**1.60**	**[0.84; 3.02]**
Heterogeneity: $I^2 = 86\%$, $p < 0.01$				

0.1 0.2   0.5 1   2   5   10
Effect size

Figure 3.
Random-effects meta-analysis of observational studies on mental disorders and tuberculosis treatment non-adherence

Table 1
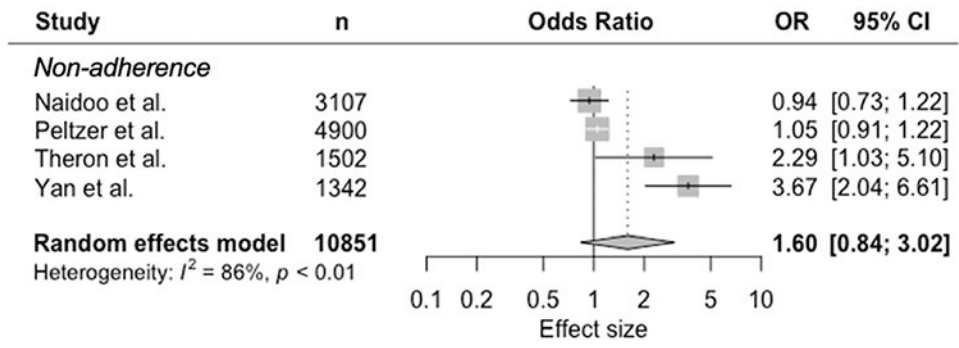
Search strategy for Pubmed

Search Number	Query
1	Tuberculosis [mh]
2	"tuberculosis"
3	#1 OR #2
4	Mental disorders [mh] mental disorder* OR mental illness* OR mental disease* OR mental health
5	condition*
6	psychiatric disorder* OR psychiatric illness* OR psychiatric disease* anxiety disorder* OR mood disorder* OR depression OR "depressive disorder" OR "depressive disorders" OR depressive episode* OR affective disorder* OR
7	psychotic disorder* OR "psychosis" OR "psychoses"
8	#5 OR #6 OR #7
9	#4 OR #8 Mortality [mh] OR Morbidity [mh] OR Death [mh] OR Prognosis [mh:noexp] OR
10	Disease-Free Survival [mh] OR Treatment Outcome [mh:noexp]
11	Drug Resistance [mh] OR Disease transmission, infectious [mh] Patient Acceptance of Health Care [mh:noexp] OR Treatment Failure [mh] OR Patient Compliance [mh] OR Lost to Follow-Up [mh] OR Patient Dropouts [mh] OR Treatment Refusal [mh] OR Health behavior [mh:noexp] OR Help-seeking
12	Behavior [mh] OR recurrence [mh]
13	#10 OR #11 OR #12 "Mortality" OR "death" OR "deaths" OR "died" OR "cause of death" OR "morbidity" OR fatal OR fatality OR fatal outcome* OR "prognosis" OR
14	"prognoses" cure OR cures OR cured OR "disease clearance" OR "pathogen clearance" OR "microbe clearance" OR "microbial clearance" OR "bacteria clearance" OR "bacterial clearance" OR "infection clearance" OR "organism clearance" OR
15	"disease-free survival" OR "disease-free interval" treatment dropout* OR dropout patient* OR patient dropout* OR no-show
16	patient* "patient compliance" OR "patient noncompliance" OR "patient adherence" OR "patient nonadherence" OR "treatment compliance" OR "treatment
17	noncompliance" OR "treatment adherence" OR "treatment nonadherence" "medication adherence" OR "medication nonadherence" OR "medication
18	compliance" OR "medication noncompliance" "lost to follow-up" OR lost to follow up* OR loss to follow up* OR "loss to follow-up" OR "default" OR "defaults" OR "defaulter" OR "defaulters" OR "defaulting"
19	OR treatment abandon* treatment outcome* OR treatment success* OR treatment fail* OR treatment complet* OR "completion of treatment" OR "success" OR "successes" OR "succeed" OR "succeeds" OR "succeeded" OR "successful" OR "successfully"
20	OR favorabl* OR favourabl* OR unfavorabl* OR unfavourabl*
21	treatment delay* OR treatment refus*
22	help-seeking behavi* OR treatment seeking behavi* OR health behavi* drug resistan* OR multiple drug resistan* OR multi drug resistan* OR multi-drug resistan* OR multidrug resistant* OR polydrug resistan* OR extensive* drug resistan* OR antibiotic resistan* OR antimicrobial resistan* OR disease transmission* OR resistance amplif* OR "amplification of resistance" OR "relapse" OR "relapses" OR "relapsed" OR "relapser" OR "relapsers" OR
23	"relapsing" OR "recurrent" OR "recurrence" OR "recurrences"
24	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25	#13 OR #24
26	#3 AND #9 AND #25

Table 2

Characteristics of included studies reporting an association between mental disorders and tuberculosis treatment outcomes.

Study	Years	Country	Study design	Sample size	Type of TB patient	Mental health assessment	Mental disorder (prevalence)	Treatment for mental disorder	TB treatment outcomes
Ambaw	2014–2016	Ethiopia	Prospective cohort	575	Adults starting sensitive TB treatment	Locally validated Patient Health Questionnaire 9 score of 10 or above at baseline	Depression (53.9%)	Patients responding positively to questionnaire item of suicidal ideation referred to health workers at facilities trained in mental health care as part of WHO's mhGAP[a].	Success Failure Loss to follow-up Death
Franke	1999–2002	Peru	Retrospective cohort	613	Patients starting MDR-TB[b] treatment	Clinically diagnosed at baseline	Mental disorder (18.9%), predominantly depression	Psychiatric consults and group therapy were offered to patients to address mental health needs, including depression, and increase social support. Patients received psychiatric medications when indicated.	Loss to follow-up Death after loss to follow-up
Scuffell	2010–2012	Peru	Retrospective cohort	49	Adults starting XDR-TB[c] treatment	Psychiatric evaluations per ICD-10 criteria at baseline	Mental disorder (22.4%), sum of depression, anxiety, mixed anxiety-depressive disorder, psychosis	NI[d]	Poor (failure, loss to follow-up, death)
Tola	2014	Ethiopia	Prospective cohort	330	Adults starting diagnosed with all types of TB on treatment for 1-2 months	Locally validated Kessler K-10 score 16 or above, at baseline	Psychological distress (67.6%)	NI[d]	Success (cure, completion) Poor (loss to follow-up, failure, death)
Ugarte-Gil	2010–2011	Peru	Prospective cohort	291	Adults newly diagnosed with TB starting treatment	Locally validated 5-item Center for Epidemiologic Studies Depression Scale score 6 or above at baseline	Depression (37.5%)	Patients who had scores compatible with depression were referred to the treating physician of the Peruvian National TB Program.	Poor (death, loss to follow-up)
Theron	2011–2012	South Africa, Zimbabwe, Zambia, Tanzania	Prospective cohort within randomized controlled trial	1,502	Adults with TB symptoms	Kessler K-10 scale as a continuous exposure at baseline	Psychological distress (22% with score greater or equal to 30)	NI[d]	Death Non-adherence

Study	Years	Country	Study design	Sample size	Type of TB patient	Mental health assessment	Mental disorder (prevalence)	Treatment for mental disorder	TB treatment outcomes
Govender	NI[d]	South Africa	Case-control	159	Newly registered patients starting TB treatment	ICD-10 criteria at baseline, considered as a depression score	Depression (prevalence not recorded)	NI[d]	Non-adherence
Naidoo	2011	South Africa	Cross-sectional	3,107	Adult new TB and new retreatment patients within one month of anti-TB treatment	Kessler K-10 scale score 30 or above	Psychological distress (25.0%)	NI[d]	Non-adherence
Peltzer	2011	South Africa	Cross-sectional	4,900	Adults starting new treatment or retreatment within 1 month of treatment	4 item Primary Care PTSD Screen score of 2 or above	Post-traumatic stress disorder (29.6%)	NI[d]	Non-adherence
Yan	2013-2014	China	Cross-sectional	1,342	Patients with a diagnosis of TB, without a diagnosis of psychosis	Locally validated 20-item Center for Epidemiologic Studies Depression Scale score 16 or above. Mild depressive symptoms (16-25), severe depressive symptoms (26)	Depression (prevalence not reported)	NI[d]	Non-adherence

[a] mhGAP = Mental Health Gap Action Programme

[b] MDR-TB = Multi drug resistant tuberculosis

[c] XDR-TB = Extensively drug resistant tuberculosis

[d] NI = No information

Table 3

Findings of included studies reporting an association between mental disorders and tuberculosis treatment outcomes

Study	Mental disorder	TB treatment outcome	Definition of TB treatment outcome	Time of outcome assessment	Adjustment for confounders[a]	Findings
Ambaw	Depression	Success	Cure or treatment course completion	6 months	Age, Sex, SES	Adjusted RR 0.95 (0.91-1.00)
Tola	Psychological distress	Success	Cure or treatment course completion	6 months	Age, Sex, SES	Adjusted OR 2.87 (1.05-7.81)
Scuffell	Mental disorder	Poor	Failure, loss to follow-up, or death	Not applicable	None	Unadjusted OR 1.59 (0.26-17.6)
Ugarte-Gil	Depression	Poor	Death or loss to follow-up	6 months	Age, Sex, SES	Adjusted HR 3.46 (1.48-8.08)
Ambaw	Depression	Loss to follow-up	Patient on treatment for at least four weeks and whose treatment was interrupted for eight or more consecutive weeks	6 months	Age, Sex, SES	Adjusted RR 9.09 (6.72-12.30)
Franke	Mental disorder	Loss to follow-up	Patient missed ≥30 consecutive days of treatment, prior to physician-approved treatment completion or a physician suspended medications for a patient who was repeatedly nonadherent even after having undergone adherence counseling.	Not applicable	Age, Sex, SES	Unadjusted HR 0.96 (0.50-1.83)
Ambaw	Depression	Death	Death of patient (due to any cause) within six months of starting treatment	6 months	Age, Sex, SES	Adjusted RR 2.99 (1.54-5.78)
Theron	Psychological distress	Death	Not specified	6 months	Not reported	Unadjusted OR for continuous exposure 1.056 (1.035-1.082)
Theron	Psychological distress	Non-adherence	Patients who were noted to have missed at a scheduled DOTS visit as recorded on the patient's DOTS clinic card	2 months	Not specified. Adjusted for site-baseline morbidity, and other clinical and socioeconomic differences.	Adjusted OR 2.29 (1.03-5.10)
Govender	Depression	Non-adherence	Patients still taking their anti-TB treatment at the end of the intensive phase.	End of intensive phase	None	Reported mean depression score of 7.14 (6.28-8.00) non-adherence versus 2.55 (1.88-3.22) adherence
Naidoo	Psychological distress	Non-adherence	Adherence assessed with the following question: "In your tuberculosis treatment in the past 3-4 weeks how many percent of your anti-tuberculosis medication did you take?" Adherence defined as having taken less than 90% of the anti-TB drugs.	During intensive phase of DOTS programme	Age, Sex, SES	Adjusted OR 0.94 (0.73-1.22)
Peltzer	Post-traumatic stress disorder	Non-adherence	Visual Analogue Scale to answer "In past 3-4 weeks how many percent were you taking your anti-tuberculosis	Within 1 month of treatment	None	Unadjusted OR 1.00 (0.86-1.17)

Study	Mental disorder	TB treatment outcome	Definition of TB treatment outcome	Time of outcome assessment	Adjustment for confounders[a]	Findings
Yan	Severe depressive symptoms	Non-adherence	8-item Morisky Medication Adherence Scale score less than 6 being low adherence, 6 to less than 8 being medium adherence, and 8 and higher being high adherence	No information	Age, Sex, SES	Compared to high adherence, adjusted OR 3.67 (2.04–6.61) for low TB treatment adherence

medication?". Non-adherence defined as having taken less than 90% of their anti-TB medication.

[a]SES = socioeconomic status

Table 4

Risk of bias assessment of observational studies on mental disorder and TB treatment outcomes and non-adherence, according to ROBINS-I criteria

Study	Risk of bias							
	Due to confounding	Selection of participants into the study	Classification of exposure	Deviations from intended exposure	Missing data	Measurement of outcomes	Selection of the reported result	Overall bias judgement
Ambaw	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Franke	Serious	Low	Low	Serious	Low	Low	Low	Serious
Govender	Serious	Serious	Serious	?	Serious	Serious	Low	Serious
Naidoo	Moderate	Serious	Serious	?	Low	Serious	Serious	Serious
Peltzer	Serious	Serious	Serious	Low	?	Serious	Low	Serious
Scuffell	Serious	Low	Low	?	Low	Low	Low	Serious
Theron	Moderate	Low	Serious	?	Low	Low	Low	Serious
Tola	Serious	Serious	Serious	?	Low	Low	Low	Serious
Ugarte-Gil	Moderate	Low	Low	Serious	?	Low	Low	Serious
Yan	Moderate	Serious	Serious	Low	Low	Serious	Low	Serious

? = no information on which to base a judgement about risk of bias for this domain

Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)

Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial)

Serious risk of bias (the study has some important problems)

Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)