Determinants of non-adherence to anti-TB treatment in high income, low TB incidence settings: a scoping review

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ABSTRACT

Background

Improving adherence to anti-tuberculosis (TB) treatment is a public health priority in high income, low incidence (HILI) regions. We conducted a scoping review to identify reported determinants of non-adherence in HILI settings.

Methods

Key terms related to tuberculosis, treatment, and adherence were used to search MEDLINE, EMBASE, Web of Science, PsycINFO, and CINAHL in June 2019. Quantitative studies examining determinants (demographic, clinical, health systems, or psychosocial) of non-adherence to anti-TB treatment in HILI settings were included.

Results

From 10,801 results, we identified 24 relevant studies from 10 countries. Definitions and methods of assessing adherence were highly variable, as were documented levels of non-adherence (0.9%–89%). Demographic factors were assessed in all studies and clinical factors frequently assessed (23/24). Determinants commonly associated with non-adherence were homelessness, imprisonment, and alcohol or drug misuse. Health system (8/24) and psychosocial factors (6/24) were less commonly evaluated.

Conclusion

Our review identified some key factors associated with non-adherence to anti-TB treatment in HILI settings. Modifiable determinants such as psychosocial factors are under-evidenced and should be further explored as these may be better targeted by adherence support. There is an urgent need to standardise definitions and measurement of adherence to more accurately identify the strongest determinants.

INTRODUCTION

Despite the availability of effective, low-cost medication, tuberculosis (TB) remains a global health concern [1]. One reason for this is non-adherence to anti-TB treatment, which increases morbidity and mortality [2,3], transmission, the development of drug resistance, and health disparity [4–6].

We have yet to identify the best adherence support for anti-TB treatment. Directly-observed therapy (DOT) has been recommended by the World Health Organization (WHO) since the 1990s [7], but research does not consistently find DOT superior to self-administered therapy (SAT) in reducing adverse treatment outcomes such as loss to follow-up [8,9]. Furthermore, improved outcomes from DOT dissipate when patients receiving SAT have increased contact with healthcare services [8], suggesting the benefit of DOT may result from the "encounter" rather than the "observation". This is important as DOT is resource-intensive, and can be perceived negatively by patients [10–12].

Interventions to support adherence are more likely to be effective if they address the specific causes of non-adherence relevant to the individual patient [13,14]. Identifying specific, and potentially modifiable, determinants of adherence to anti-TB treatment is therefore critical in developing more targeted and effective support [15].

Improving anti-TB treatment adherence is a priority for high income, low TB incidence (HILI) countries progressing toward TB elimination [16]. To date, determinants have mostly been examined in high incidence regions [17–19]. Determinants in high and low incidence regions may differ, based on differences in populations with TB and resources for care [20–22]. Therefore, as formative research for an intervention to promote adherence to anti-TB treatment in the UK [23], we undertook a scoping review to explore determinants of non-adherence to anti-TB treatment within HILI settings, and identify evidence gaps relevant to patients and healthcare providers to be addressed by future research.

METHODS

We selected a scoping review methodology to provide a broad overview and highlight key evidence gaps [24], given expectations of study heterogeneity [25,26] and diverse definitions and measurements of TB treatment adherence [27]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension Checklist for Scoping Reviews (PRISMA-ScR) was used [25].

Literature search

Five databases (MEDLINE, EMBASE, Web of Science, PsycINFO, and CINAHL) were searched in June 2019. Researchers developed and refined search terms related to TB, treatment, and adherence, with support from an experienced librarian (Supplementary Material 1).

Search terms were mapped to the Population-Concept-Context framework recommended for scoping reviews [28] (Table 1). Identified studies were imported into Endnote [29] and duplicates were removed. Two authors independently screened titles and abstracts using the website Rayyan, designed for article screening in reviews [30]. Any discrepancies were resolved through discussion. Reference lists of included studies were hand-searched to identify additional relevant studies.

Eligibility criteria are listed in Table 1. Included studies were peer-reviewed, English language studies, whose aim was to report primary, observational, quantitative data on determinants of non-adherence to anti-TB treatment, in countries classified as high income [31] with low TB incidence rates (<40 per 100,000 people), when the study was conducted. We included outcomes of both discontinuation (early cessation of treatment, including loss to follow-up) and suboptimal implementation (missing doses during treatment) [32–34]. We excluded qualitative research, as our research group has reviewed this separately [35].

Data extraction and synthesis

Two authors independently extracted data (cross-checking 50% of studies). Determinants were included if studied as primary exposures of interest or potentially confounding factors. Determinants were labelled as demographic, clinical, health systems-related, or psychosocial.

Categorises were used to reflect the strength of evidence for each determinant. A proxy measure was created for this, based on the size and direction of the effect size (ES) estimate and statistical certainty. Evidence was classified from strongest to weakest using the following categories:

- Category 1: ***Strongest:*** ES (ratio) ≥1.5, p-value ≤0.05;
- Category 2: ES (ratio) ≥1.5, p-value >0.05, small sample size (n <154) i.e. study likely to be under-powered;
- Category 3: ES (ratio) >1.0 to <1.5, p-value ≤0.05;
- Category 4: ***Weakest:*** ES (ratio) >1.0, p-value >0.05.

The equivalent categories were used to classify determinants observed to have a protective effect. In order to provide a standardised classification for category 2, a sample size calculation was required. It was calculated that a minimum of 154 participants would indicate an adequately powered sample size, using 90% power and 5% significance level, statistically conservatively assuming that 50% of individuals had the outcome among the unexposed, and assuming a one-to-one ratio of exposed to unexposed or cases to controls. Although this threshold did not perfectly reflect the analyses in all studies, it provided a framework for weighting the evidence of each determinant. It did not indicate judgement on the quality of included studies. Where possible, determinants were classified based on ES in multivariable, not univariable, analyses.

Ethics

Ethics approval was not required as this was a scoping review.

RESULTS

Description of included studies

The initial search found 10,801 studies. After removing duplicates, 9,932 remained for title and abstract screening, and 25 met the inclusion criteria (Figure 1, Supplementary Material 2). Data on determinants were extracted for 24 studies, as one [36] reported no ES.

Included studies were published 1986-2019, from 10 different countries, including the UK and Ireland (n=7) [37–43], USA (n=6) [36,44–48], and Spain (n=5) [49–53]. The most

common study design was retrospective cohort (n=12) [37,40,46,48,49,53–59]. Sample sizes ranged from 62 to 73,591 (median= 1009; interquartile range (IQR)= 184-2576). The mean/median participant age ranged from 28.0 to 52.1 years. The median percentage of males was 64.4% (IQR= 56.0-71.0%).

Most studies (n=20) included all patients starting treatment in a given setting [36–45,47,48,50–52,54–58]. Three studies sampled specific high-risk groups, of people experiencing homelessness or unstable living arrangements [60], individuals with multidrug-resistant TB (MDR-TB) [59], or HIV/TB co-infection [53]. Two studies compared outcomes between groups within a cohort, such as immigrants versus individuals born within a country [46,49].

Non-adherence: definitions and assessment

Supplementary Material 2 demonstrates the considerable variability in definitions of adherence. Most study outcomes (n=15) related to treatment discontinuation (stopping treatment early) [38,40,44–47,49,50,53–56,58–60]. Fewer study outcomes (n=7) appeared to record suboptimal implementation (missed doses during treatment) [36,37,39,41,43,48,57]. One study included both a discontinuation and suboptimal implementation outcome [42]. Two studies used a single outcome encapsulating both discontinuation and suboptimal implementation [51,52].

Discontinuation outcomes were often measured using state or national registries/surveillance databases [40,44–47,53–55,58,59], hospital/lab records [44,45,47,49,59], or medical notes [38,60].

Sub-optimal implementation was assessed using various methods, including adherence scale scores [36], medical records [57], physician impression from interviews/assessments [39,41], patient self-report [39], health visitor reports (including pill counts) [41], urine samples (to detect rifampicin) [39,43], attendance at appointments [41,48,57], and prescription requests [48,57].

Overall, retrospective studies most often used surveillance/registry data to determine adherence [37,40,45–47,53–55,58,59], whereas prospective studies used more varied

methods (Supplementary Material 2). Reported non-adherence ranged from 0.9% to 89% across studies (median= 7.0%; IQR= 5.2-16.3%). Two studies did not report levels of non-adherence [36,60].

Determinants of non-adherence

Demographic determinants

Demographic determinants were assessed by all 24 studies (Supplementary Material 2). Specifically, the most studied determinant groups were place of residence and age (Supplementary Material 3). The variable with the greatest strength of evidence for a large effect on non-adherence (Categories 1 or 2- large effect sizes with p-value≤0.05 or a small sample size, see Methods; Supplementary Material 2) was place of residence (Figure 2). Within that variable, homelessness [37,42,44,46–48,50,53,57,60] and living in an institution or prison (e.g. a "confined institution", a residence hall, or mental hospital) [37,42,46,47,51,52,55,58] had the strongest evidence, weighted overall, towards non-adherence (Supplementary Material 2).

Age, sex, ethnicity, and nationality also showed mixed evidence of effects, as within each variable just as many or more studies found a weak effect with non-adherence as a large effect (Figure 2). Ethnicity and nationality determinants appeared very context-specific, demonstrated by the variation in baseline comparators within these categories. Overall, few demographic determinants were classified in categories 2 (i.e. large ES, p-value>0.05, but small sample size) or 3 (small ES, p-value≤0.05) in terms of strength of evidence. The grouping variables most commonly found to have a weak effect on adherence (category 4, small ES, p-value>0.05) were age, nationality/origin, and ethnicity. No variable had a consistently large effect with non-adherence.

Clinical determinants

Clinical determinants were the second most studied category (23/24 studies Supplementary Material 2). The substance use/misuse grouping variable was the most frequently assessed and had the most evidence weighted towards a large effect (Supplementary Material 3 and Figure 2). Specifically, illicit drug misuse/addiction had the strongest evidence for this [48,50–52,55] (Supplementary Material 2). The evidence for clinical determinants was also mixed, in terms of both

strength of evidence and direction. For example, in the HIV grouping variable, HIV positive status was a risk factor for non-adherence [50,51,55], yet a diagnosis of AIDS was protective against non-adherence [44,46] (Supplementary Material 4). Again, few determinants fell into categories 2 and 3 in terms of strength of evidence, and the grouping variables which most commonly showed a weak effect with adherence were smear and sputum result, substance use/misuse, and HIV infection.

Health systems determinants

Health systems determinants were less frequently investigated (8/24 studies). Within this category, route to care was the most studied grouping variable (Supplementary Material 3). Healthcare professionals' perception of patient understanding (e.g. lack of awareness of TB severity, understanding of treatment instructions, language barriers) had a consistently large effect with non-adherence, though this determinant was minimally studied. The grouping variables most often found to have a weak effect with adherence were route to care, and those classified as "other".

Psychosocial determinants

Psychosocial determinants were the least studied (6/46 studies), where only mental health and having close relationships were assessed (Supplementary Material 3, Figure 2). Of these, having a mental health problem was both a risk for [42] and protective against non-adherence [47] (Supplementary Material 2). Strength of evidence for mental health problems was also mixed, with as many studies finding strong and weak effects on adherence.

DISCUSSION

In our scoping review investigating the determinants of non-adherence to anti-TB treatment within HILI settings, homelessness, imprisonment, and alcohol or drug misuse were commonly associated factors. Health systems and psychosocial determinants were under-explored. Considerable heterogeneity in measurements and definitions of non-adherence was present across studies, hindering the conclusions that can be drawn.

When synthesising the literature on determinants, we found that demographic and clinical factors were most studied. This may reflect the relative ease of capturing this

data through TB surveillance in HILI settings, such as the UK [61]. However, the context required to understand mixed findings for these determinants was largely missing from studies, which may result from utilising these data sources. Without context, these findings are unhelpful for explaining non-adherence. For example, a recent systematic review found that despite assumptions, non-adherence was as likely to occur in both migrants and non-migrants [62]. Such findings highlight the importance of contextualising demographic and clinical determinants, if researchers are to utilise this data in intervention design.

In addition, demographic and clinical determinants are largely non-modifiable (e.g. history of imprisonment) or difficult to change (such as homelessness, illicit drug use/addiction) within a feasible, scalable healthcare intervention [63]. Improving adherence to anti-TB treatment requires identifying potentially modifiable determinants that can be targeted within a pragmatic, person-centred healthcare intervention.

Determinants more amenable to change, such as health systems issues, have rarely been quantitatively assessed in HILI settings. Health systems barriers in high incidence regions, such as distance to treatment facilities and transport costs [17–19], may be less apparent in HILI countries with better-resourced health services. Nonetheless, they may affect subgroups of patients, given that TB disproportionately affects people with lower socioeconomic status in high income settings [20]. In addition, health systems determinants may interact with other factors (such as fear of stigma making an individual seek care at a more distant hospital), reinforcing the need to better understand their influence in HILI settings.

Psychosocial determinants are also under-researched in quantitative literature on TB adherence. This oversight is significant given the known relationship between TB, stigma, and adherence, even in low incidence settings [64]. Understanding the social context of TB treatment is significant for reaching TB control goals, given the well-established links between social determinants of health and inequality [65], even within regions of low TB incidence [66].

Theory in behavioural medicine suggests adherence is best viewed as a modifiable behaviour and not a trait [67], as adherence patterns can change within an individual over time [32,68], and also differ between people with shared demographic characteristics. Theory and evidence suggest that amendable, cognitive and affective factors, such as beliefs about illness and treatment, influence subsequent coping strategies, including treatment adherence [69–71]. Understanding psychosocial determinants may enable us, therefore, to provide better adherence support.

Evidence from this review has important clinical implications for intervention development in TB. Interventions should: 1) accurately assess known risk factors for non-adherence to anti-TB treatment in HILI settings; and 2) mitigate the influence of these on perceptual and practical barriers to adherence [70]. For example, interventions should be tailored to both target a patient's beliefs about TB and treatment, and provide practical support to overcome personal barriers to treatment.

Our scoping review followed PRISMA-ScR guidelines to systematically search the available literature. We may have been limited by including only English language studies. We may have missed secondary data reported (e.g. in intervention studies) by only including studies whose primary aim was to examine determinants of non-adherence. In addition, as this was a scoping review, the quality of included studies was not assessed.

Our understanding of non-adherence to anti-TB treatment within HILI settings is severely limited by the heterogeneity of included studies. Clearer and consistent definitions of which type of non-adherence is being assessed in studies [33], and data presented beyond simple binary summary measures, are urgently needed [72].

By including all data on reported determinants, whether measured as primary exposures of interest or potential confounding factors, some estimates may be subject to bias. Of note, few (n=2) studies assessed all four categories of determinants and therefore adjusted for confounders appropriately. This considerably impairs our ability to understand the interaction between determinants and their relationship to non-adherence, and may explain the inconsistency of the included evidence.

In conclusion, this scoping review identifes determinants with the best supportive evidence, and highlights a gap in our understanding of adherence to anti-TB treatment in HILI settings. Understanding how demographic and clinical determinants are associated with adherence to anti-TB treatment is necessary to inform intervention development. Qualitative work could extend current understanding by examining how health systems and psychosocial factors influence anti-TB treatment in HILI settings [23]. Stakeholders in TB policy and service implementation should also consider how factors influencing patient adherence are currently evaluated and understood. Existing care practices, such as risk assessments, should ensure the range of complex factors involved in adherence are comprehensively addressed.

We also identified a need for greater consistency in definitions and measurement of adherence within the TB literature. Without this, it will remain difficult to effectively synthesise data, and understand reported patterns of adherence behaviour.

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AJ, NB, RH, HRS, FBW and MCIL conceived of and designed the work. All authors acquired, analysed, or interpreted the data. AJ drafted the paper. All authors revised it critically for important intellectual content. All authors give final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity are appropriately investigated and resolved.

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608 Table 1. Patient-Concept-Context (PCC) elements and inclusion/exclusion criteria.

PCC element	Definition in scoping review	Inclusion criteria	Exclusion criteria
Population	Patients taking anti-tuberculosis treatment	Studies reporting data on non-adherence to treatment for pulmonary tuberculosis.	• Studies with a non-human sample. • Studies with patients taking prophylactic TB treatment or treatment for latent TB. • Studies where the majority of patients (>50%) had extra-pulmonary disease. • Studies with a co-morbid sample (excluding HIV).
Concept	Determinants of non-adherence to treatment	Peer-reviewed studies reporting primary, observational, data on determinants of non-adherence to treatment.	• Studies reporting interventions (including studies where DOT/VOT were standard treatment, or more than 50% of the sample was receiving DOT/VOT). • Qualitative studies. • Studies that were not primary research articles (e.g. reviews, commentaries, or letters). • Studies that did not measure determinants of non-adherence. • Studies where treatment completion was the outcome (as this is conflated with successful treatment outcome and is not a measure of patient adherence).
Context	HILI TB settings	Countries classified as high income and low TB incidence at time of study.	• Studies in settings defined as low and middle income, or with high TB incidence.

609 Note. DOT= directly-observed therapy; HILI= high income, low (TB) incidence; TB=
610 tuberculosis; VOT= video-observed therapy.
611

List of Figures

Figure 1.

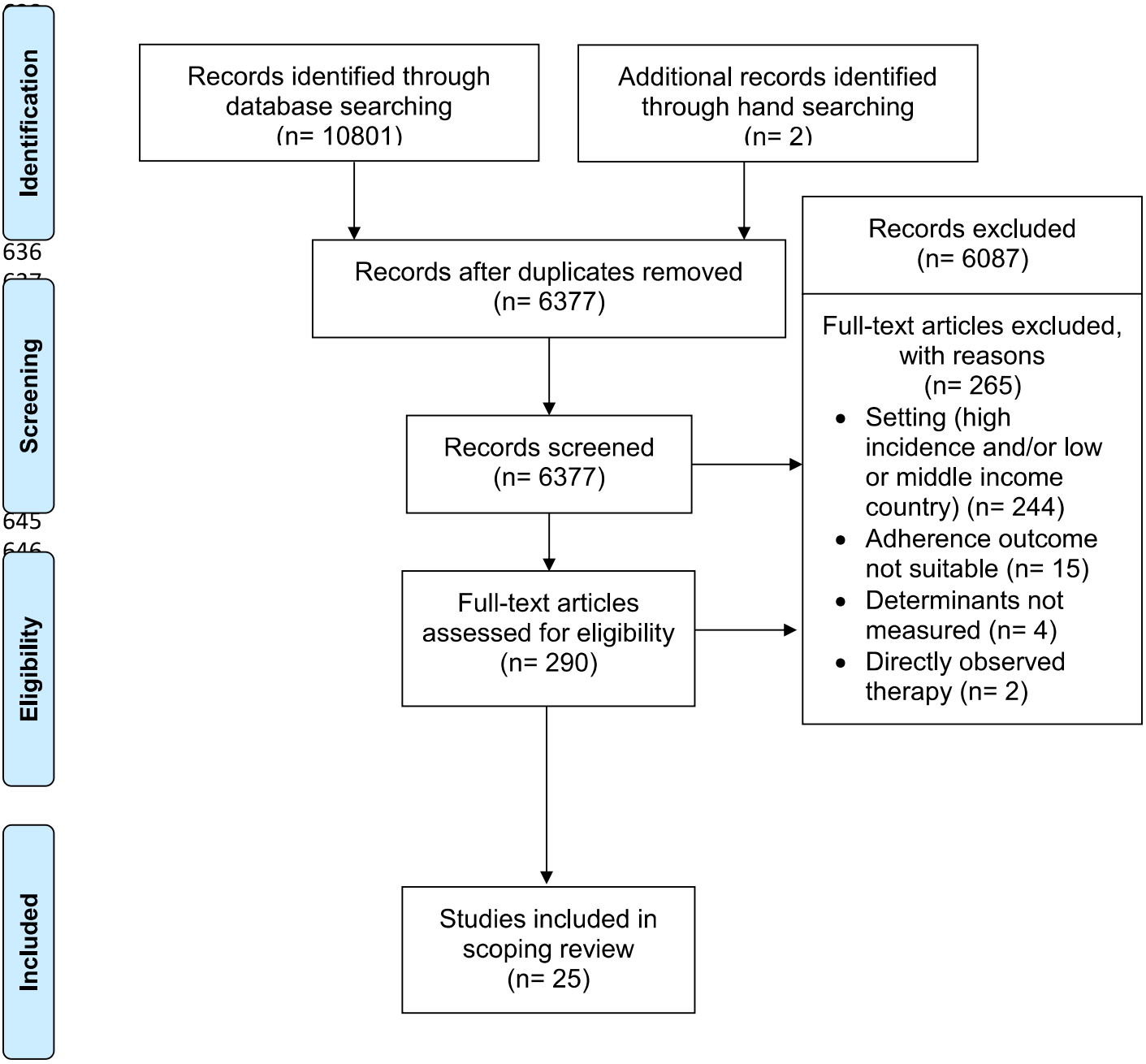
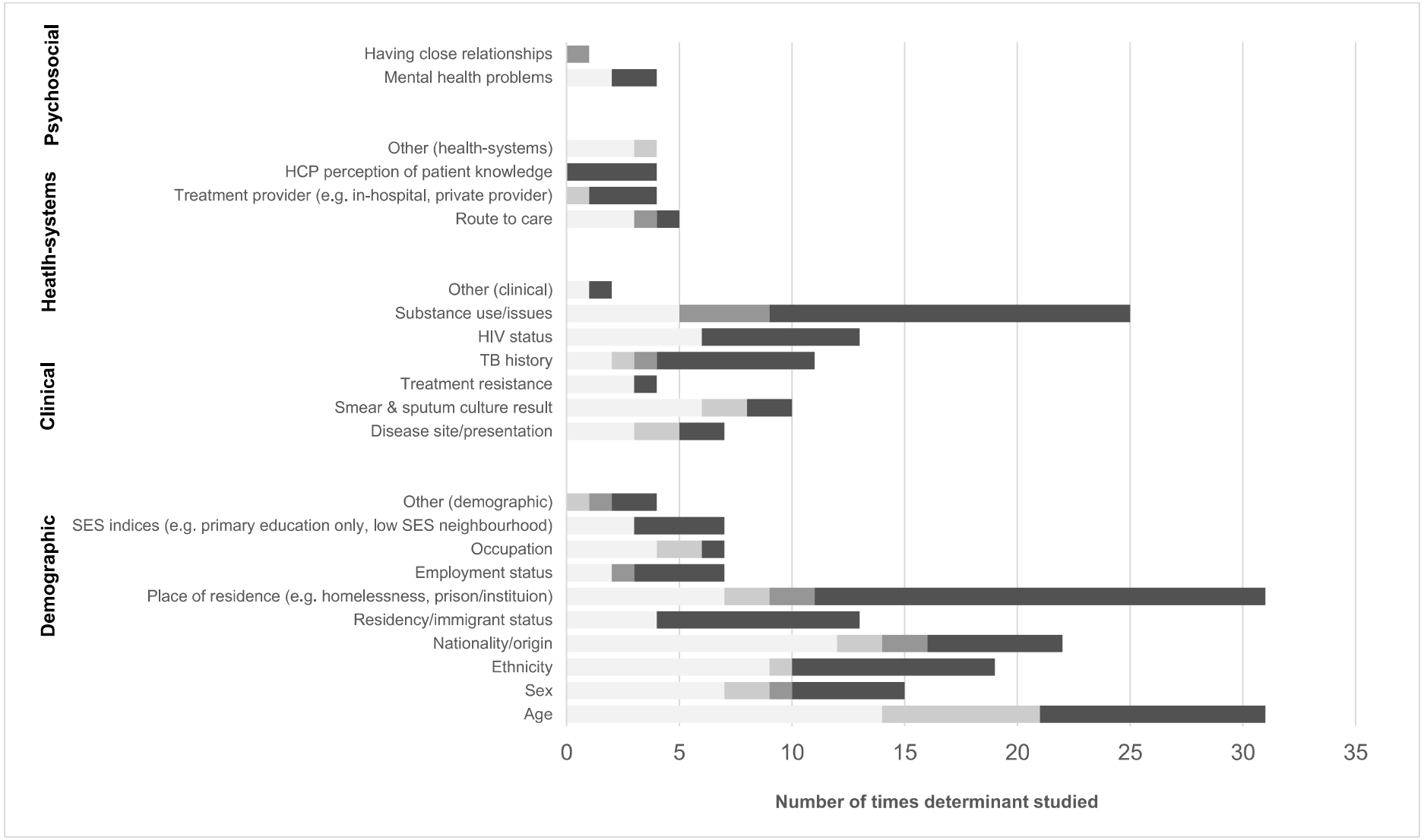

Identification
Screening
Eligibility
Included
Records identified through database searching (n= 10801)
Additional records identified through hand searching (n= 2)
Records after duplicates removed (n= 6377)
Records excluded (n= 6087)
Records screened (n= 6377)
Full-text articles excluded, with reasons (n= 265)
Setting (high incidence and/or low or middle income country) (n= 244)
Adherence outcome not suitable (n= 15)
Determinants not measured (n= 4)
Directly observed therapy (n= 2)
Full-text articles assessed for eligibility (n= 290)
Studies included in scoping review (n= 25)

Figure 2


Psychosocial
Having close relationships
Mental health problems
Heatlh-systems
Other (health-systems)
HCP perception of patient knowledge
Treatment provider (e.g. in-hospital, private provider)
Route to care
Clinical
Other (clinical)
Substance use/issues
HIV status
TB history
Treatment resistance
Smear & sputum culture result
Disease site/presentation
Demographic
Other (demographic)
SES indices (e.g. primary education only, low SES neighbourhood)
Occupation
Employment status
Place of residence (e.g. homelessness, prison/instituion)
Residency/immigrant status
Nationality/origin
Ethnicity
Sex
Age
0
5
10
15
20
25
30
35
Number of times determinant studied

Determinants of non-adherence to anti-tuberculosis treatment in high income, low incidence, settings: A scoping review

Annie S. K. Jones, Natalie Bidad, Rob Horne Helen R. Stagg, Fatima B. Wurie, Karina Kielmann, Aaron S. Karat, Heinke Kunst, Colin N. J. Campbell, Marcia Darvell, and Marc Lipman, on behalf of the IMPACT study group (NIHR 16/88/06)

Online Supplement

Supplementary material 1

Scoping review search example strategy from MEDLINE

1. Tuberculosis/
2. (TB or tuberculo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. Drug Therapy/
5. (medication* or medicine* or treatment* or therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. 4 or 5
7. 3 and 6
8. Antitubercular Agents/
9. 7 or 8
10. Medication Adherence/ or "Treatment Adherence and Compliance"/
11. (adheren* or complian* or non-adheren* or non-complian* or nonadheren* or concordan* or non-concordan*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. (LTFU or “los* to follow-up” or “los* to follow up” or LFU or default).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. Lost to Follow-Up/
14. 10 or 11 or 12 or 13
15. 9 and 14
16. limit 15 to (english language and humans)

Supplementary material 2. Bibliometric data from included studies (n=25).

Year(s) of study	Sample size (N)	Country	Study population	Study design	Categories of determinants assessed	Adherence measure	Non-adherence definition	% Non-adherent	Citation information
Prospective designs									
Not given	90	Ireland	Patients being treated for pulmonary TB and discharged from a Dublin hospital.	Prospective cohort	Demographic Clinical	Urine sample, self-report or physician's impression from interview	Non-compliance: based on interview evidence and ≥1 negative urine sample(s).	23.3	Corcoran [39]
Not given	113	UK	Patients being treated at Leeds Chest Clinic receiving a rifampicin-containing regimen.	Prospective cohort	Demographic Clinical	Urine sample	Non-compliance: negative urine sample.	7.0	Wardman et al. [43]
1988-1989	224	USA	Patients being treated in Harlem Hospital Center, New York.	Prospective cohort	Demographic Clinical	State TB registry data and hospital records	Noncompliance: no follow-up treatment or LTFU.	89.0	Brudney & Dobkin [44]
1995–1996	62	USA	Patients being treated and residing within Georgia.	Prospective cohort	Psychosocial	Tuberculosis General Adherence Scale (TBGAS)	Lower scores on TBGAS scale	Not given (mean TBGAS score= 92.6%)	McDonnell et al. [36*]
1999–2000	1515	Spain	Patients being treated by a member of the Tuberculosis and Respiratory Infections Group of the Sociedad Española de Neumología y Cirugía Torácica (SEPAR).	Prospective cohort	Demographic Clinical Health systems	Epidemiological questionnaire completed by staff, including assessments of "appointment attendance, physician estimation, and patient confirmation" (data source not specified)	Default: no treatment received for >1 month or missed appointments.	4.0	Cayla et al. [50]

Year(s) of study	Sample size (N)	Country	Study population	Study design	Categories of determinants assessed	Adherence measure	Non-adherence definition	% Non-adherent	Citation information
1998–2003	119	Japan	Homeless patients or those in fragile living situations who received treatment in a Tokyo hospital (excluded patients with HIV/TB co-infection).	Prospective cohort	Demographic Clinical Health systems Psychosocial	Medical notes	Treatment interruption during outpatient care: no treatment for ≥2 consecutive months.	Not given (19.33 worked out from results)	Kizuki et al. [60]
2000–2003	575	UK	Patients being treated in the East of England.	Prospective cohort	Demographic Clinical	Patient notes (extracted by TB staff)	LTFU	7.8	Anyama et al. [38]
2003	1941	UK	Patients in Greater London who were or should have been on treatment.	Prospective cohort	Demographic Clinical Psychosocial	Self-report, pill counts, urine tests, medical records, case-manager "knowledge" of patient	Poor adherence: self-reported, inconsistent pill counts, negative urine test, or patients switched to DOT or hospitalised for poor adherence. LTFU: being out of contact with services for at ≥2 months without medication during first 6 months of treatment.	Poor adherence: 46.0 LTFU: 15.0	Story et al. [42]
2006–2007	1490	Spain	Patients being treated by a member of the Tuberculosis and Respiratory Infections Group of the Sociedad Española de Neumología y Cirugía Torácica (SEPAR) (excluded patients with known drug resistance or those not initiating standard treatment).	Prospective cohort	Demographic Clinical Health systems	Electronic diary completed by staff (no details regarding from where data obtained)	Poor adherence: including default (treatment interruption for >2 months, non-completion by 9-months on standard regimen, or <80% prescribed doses taken) and LFTU.	6.2	Cayla et al. [51]

Year(s) of study	Sample size (N)	Country	Study population	Study design	Categories of determinants assessed	Adherence measure	Non-adherence definition	% Non-adherent	Citation information
2006–2009	1490	Spain	Patients being treated with culture-positive or smear-positive disease, extrapulmonary TB with caseating granuloma, identification by histology, or clinical, radiological, epidemiological or laboratory suspicion of TB (excluded patients with known drug-resistance or those with a contraindication to start standard treatment).	Prospective cohort	Demographic Clinical Health systems	Not specified	LFTU: treatment interruption (any reason) for ≥2 months, non-completion of treatment within 9 months for standard therapy, or taking <80% of prescribed dose.	6.48	Rodrigo et al. [52]
Retrospective designs									
1988–1992	103	Switzerland	Patients with bacteriologically confirmed pulmonary TB being treated in Vaud County.	Retrospective cohort	Demographic Clinical Psychosocial	Questionnaire completed by practitioners (using medical records)	Not adherent: not specified (adherence considered satisfactory if patient attended scheduled visits and requested prescriptions).	18.4	Zellweger & Coulon [57]
1993	2576	USA	Compared patients being treated in California who did and did not move during treatment to another health jurisdiction.	Retrospective cohort	Demographic Clinical Psychosocial	National TB surveillance data	Default: patients who refused treatment or were LTFU.	5.5	Cummings et al. [46]
1991–1994	184	USA	Patients with a first time, positive-culture being treated in New York City.	Retrospective cohort	Demographic Clinical	Contacting providers for clinic attendance and prescription information	Noncompliance: not attending clinic appointments for ≥2 months, or ≥3 months during 1 year.	48.0	Pablos-Mendez et al. [48]
1993–1994	3520	USA	Patients with culture-confirmed, rifampin- susceptible TB, starting a rifampin-containing regimen of at least 60 days, being treated in New York City.	Retrospective case-control	Demographic Clinical Health systems	State TB registry data and hospital records	Inappropriate treatment discontinuation: discontinuing rifampicin without experiencing serious adverse effects related to use.	0.9	Cook et al. [45]

Year(s) of study	Sample size (N)	Country	Study population	Study design	Categories of determinants assessed	Adherence measure	Non-adherence definition	% Non-adherent	Citation information
1987–1996	1354	Spain	Patients with HIV/TB co-infection, detected by the Active Epidemiological Surveillance System of the Barcelona Tuberculosis Prevention and Control Programme, being treated in Barcelona.	Retrospective cohort	Demographic Clinical	National TB surveillance data	Treatment abandonment: LTFU or failed medical controls and not found by public health surveillance nursing team.	13.1	Galdós Tangüis et al. [53]
1993–1997	7529	The Netherlands	Patients being treated in the Netherlands.	Retrospective cohort	Demographic Clinical Health systems	National TB registry data	LTFU (excludes patients reportedly continuing treatment elsewhere)	8	Borgdorff et al. [58]
1998–2002	328	USA	Patients who were culture-positive being treated in New York City (excluded patients with MDR-TB).	Retrospective case-control	Demographic Clinical Health systems Psychosocial	State TB registry data, patient interview forms, hospital records (including case manager notes)	Default (treatment interrupted for ≥60 days) with return to therapy Default without return to therapy (including LTFU or treatment refusal)	4.2	Driver et al. [47]
2001–2007	41,120	UK	Patients being treated in England, Wales and Northern Ireland reported to the Enhanced Tuberculosis Surveillance (ETS) system.	Retrospective cohort	Demographic Clinical	National TB surveillance data	LTFU (before treatment completion, including patients who moved overseas)	5.9	Millet et al. [40]
2000–2011	503	Spain	Compares immigrant and native patients being treated in Catalonia.	Retrospective cohort	Demographic Clinical Psychosocial	Hospital records	Treatment abandonment: treatment interrupted for ≥2 months (without medical advice), or LTFU with no information available.	1.8	Ballesteros et al. [49]
2009–2012	12,908	UK	Patients being treated in London, England.	Retrospective cohort	Demographic Clinical	National TB surveillance and laboratory data (matched with national outreach data - "find and treat" registry)	Non-adherence (not specified)	5.6	Anderson et al. [37]

Year(s) of study	Sample size (N)	Country	Study population	Study design	Categories of determinants assessed	Adherence measure	Non-adherence definition	% Non-adherent	Citation information
2000–2013	27,894	Portugal	Patients with pulmonary TB being treated in continental Portugal, as identified through the national TB surveillance database (SVIG-TB).	Retrospective cohort	Demographic Clinical	National TB surveillance data	Default: treatment interrupted for >8 weeks after completing ≥1 month of treatment)	4.9	Nunes et al. [55]
1995–2014	68	Norway	Patients with MDR-TB being treated in Norway.	Retrospective cohort	Demographic Clinical	Hospital and laboratory records, TB registry data	LTFU: WHO 2013 definition (no treatment initiation, or treatment interrupted for ≥2 consecutive months).	17.6	Jensenius et al. [59]
2006–2015	73,591	Japan	Patients with pulmonary TB being treated in Japan.	Retrospective cohort	Demographic Clinical Health systems	National TB surveillance data	LTFU: definition from Japanese TB surveillance system (treatment interrupted for ≥2 consecutive months, or treatment duration <6 months).	7.8	Kawatsu et al. [54]
1997–2017	190	France	Patients diagnosed at Dron Hospital in Tourcoing (excluding those with MDR-TB or XDR-TB).	Retrospective cohort	Demographic Clinical	Not specified (appears to be medical and laboratory records)	LTFU: no treatment initiation or treatment interrupted for ≥2 consecutive months.	15.0	Tetart et al. [56]
Mixed designs									
1978–1987	1009	UK	Patients being treated in Blackburn, England.	Retrospective and prospective cohort	Demographic	Physician assessment, monthly health visitor reports (including pill counts) and clinic attendance	Poor compliance: ≥3 missed appointments or unfavourable assessments.	3.0	Ormerod & Prescott [41]

Note. *determinants not extracted for this study. TB= Tuberculosis; LTFU= Loss to follow-up; MDR-TB= Multidrug-resistant tuberculosis; WHO = World Health Organization; XDR-TB= Extensively drug-resistant tuberculosis.

Supplementary material 3. Frequency of determinants assessed by included studies.

Determinant category	Determinant grouping variable	Studies assessing determinant grouping variable:
Demographic	Age	n= 14 37 38 40 41 42 46 47 49 50 51 53 58 59 55
	Sex	n= 14 38 40 42 43 44 48 50 51 53 57 58 59 54 55
	Ethnicity	n= 5 40 42 45 46 48
	Nationality/origin	n= 7 37 38 43 48 58 59 54
	Residency/Immigration status	n= 9 40 49 50 51 52 56 57 58 55
	Place of residence (e.g. homelessness, history of living in an institution or prison)	n= 16 37 42 44 46 47 48 49 50 51 52 53 57 58 54 55 60
	Employment status	n= 4 51 56 54 60
	Occupation	n= 2 46 54

Determinant category	Determinant grouping variable	Studies assessing determinant grouping variable:
	SES indices (e.g. primary education only, living in low SES neighbourhood)	n= 5 38 39 43 53 54
	Other (e.g. relationship status, receiving leave for appointments, place of residency, travelling behaviour, moved health jurisdiction during treatment)	n= 4 39 40 46 59
Clinical	Disease site/presentation	n= 6 37 38 40 48 56 54
	Smear & sputum culture result	n= 6 38 47 48 57 58 54
	Treatment resistance	n= 3 46 48 60
	TB history	n= 9 37 38 40 43 45 52 53 56 60
	HIV status	n= 9 44 46 48 49 50 51 53 56 55
	Substance use/issues	n= 17 37 39 42 44 45 46 47 48 50 51 52 53 56 57 59 55 60
	Other (e.g. relapse (unspecified, diabetes co-morbidity)	n= 2 57 60

Determinant category	Determinant grouping variable	Studies assessing determinant grouping variable:
Health systems	Route to care	n= 3 [51 58 60]
	Treatment provider (e.g. treated at referral hospital, treated by private health provider)	n= 2 [45 54]
	HCP perceptions of patient knowledge	n=3 [47 51 52]
	Other (e.g. hospitalisation, health insurance status, time from culture confirmation to presentation)	n= 3 [47 50 54]
Psychosocial factors	Mental health problems	n= 3 [42 47 57]
	Having close relationships	n= 1 [60]

Note. HCP= health care professional, SES= socioeconomic status, TB= tuberculosis

Supplementary material 4

Strength of evidence for demographic, clinical, health-systems and psychosocial factors associated with adherence to TB treatment

Grouping variable	Potential risk factor	Strength of evidence				Potential protective factor	Strength of evidence			
		1	2	3	4		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05		OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
Demographic Factors										
Age	Under 30 y/o	37 *[16-24]* 51* *[>50]* 59 *[≥40]* 41* *[30-44, 45-59, >60]*			42§,‖ *[30-59]*					
	25-34 y/o				38* *[0-24]* 58 *[<25]*					
	30-65 y/o			58¶ *[<25]*	51* *[>50]* 53* *[15-29]* 58** *[<25]*	30-65 y/o			40 *[15-44]* 55 *[15-34]*	37 *[16-24]* 38* *[0-24]*
	Over or equal 65 y/o				42§,‖ *[30-59]*	Over or equal 65 y/o	37 *[16-24]* 50* *[≤17]*		40 *[15-44]* 55 *[15-34]*	38* *[0-24]*
	Other (e.g. unspecified, broad range)	59 *[≥40]* 49 *[<40]*		50* *[≤17]*	53* *[15-29]* 58‖‖	Other (e.g. unspecified, broad range)			47¶¶ *[NS]*	38* *[0-24]* 47***

Grouping variable	Potential risk factor	Strength of evidence				Potential protective factor	Strength of evidence			
		1	2	3	4		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05		OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
		46††,‡‡ *[>45]* 58§§ *[<25]*			*[<25]*					*[NS]*
Sex	Male *[Female]*	50* 51* 55* 42§,‖ 57*	59*	40 58	44 48* 53* 38*	Male *[Female]*				44 43* 54
Ethnicity	Hispanic	45* *[non-Hispanic Black]* 46††,‡‡ *[Asian]*			48* *[White]*					
	Asian *[White]*	40*,†††		40*,‡‡‡	48* 42‖	Asian *[White]*				40*,§§§ 42§
	Black African/ Caribbean/Black British/non-Hispanic black	46††,‡‡ *[Asian]* 48* *[White]* 40* *[White]*			42§, ‖ *[White]*					
	Non-Hispanic White	45* *[non-Hispanic Black]*								
	Ethnicity category non-specific (e.g. White, Asian, or Hispanic) *[NS]*	45								
	Other *[White]*	40*			42‖	Other *[White]*				42§
						Black Caribbean *[White]*				42‖
Nationality/ origin‡	Europe	37‖‖‖‖‖‖ *[South Asia]* 58 *[Dutch]*		37¶¶¶ *[South Asia]*	37**** *[South Asia]*					

Grouping variable	Potential risk factor	Strength of evidence			
		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05
	Asia		43* *[British]*		37 *[South Asia]* 58 *[Dutch]*
	North America and Oceania *[Abroad]*				48*
	Africa	58†††† *[Dutch]*	59 *[NS]*		37 *[South Asia]* 58‡‡‡‡ *[Dutch]*
	East Mediterranean *[Dutch]*	58			
	Foreign-born *[UK born]*	38*			
	Other/country of birth unknown *[Dutch]*	58			
	Latin, South, Central America or Caribbean				37 *[South Asia]* 58 *[Dutch]*
Residency/ immigration status	Immigrant or migrant *[native]*	49 50 51 55 52 57*			
	Recent migrant (under 4 years)	40* *[UK born}*			58 *[other]*
	Migrant 5+ years *[UK born]*				40*
	Illegal immigrant *[not in category]*	58			
	Asylum seeker *[not in category]*				58
	Time in resident country unknown *[UK born]*	40*			

Potential protective factor	Strength of evidence			
	1	2	3	4
	OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
North America and Oceania *[South Asia]*				37
East Mediterranean *[South Asia]*				37
Foreign-born *[Japan born]*				54
Other/Country of birth unknown *[Japan born]*			54	
North Africa *[South Asia]*				37
Immigrant or migrant *[native]*				56*

Grouping variable	Potential risk factor	Strength of evidence				Potential protective factor	Strength of evidence			
		1	2	3	4		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05		OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
Place of residence	Living alone	51 *[with family]* 52 *[NS]*								
	Homelessness/no fixed abode *[has fixed abode]*	37 44 50* 46††,‡‡ 47¶¶,*** 60§§§§ 48 53 42§,‖	60‖‖‖‖‖‖‖ 57*		58 49	Homelessness/no fixed abode [has fixed abode]			55	54
	History/living in institution or prison	52 *[NS]* 58 *[no history]* 55* *[no history]* 47¶¶ *[not incarcerated]* 42§ *[no imprisonment during current treatment]* 37 *[NS* 51 *[with family]*		53* *[no history]*	50* *[NS]* 46†† *[not in category]*					

Grouping variable	Potential risk factor	Strength of evidence			
		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05
		46‡‡ *[not in category]*			
	Shared accommodation *[with family]*				51
	Living in a county jail at diagnosis	46††,‡‡ *[not in category]*			51 *[with family]*
Employment status	Active occupational status *[retired]*	51*			
	Unemployed	51* *[retired]*	60* *[employed]*		
	Disabled occupational status *[retired]*	51*			
Occupation	HCP *[Full/part- time employed]*			54¶¶¶¶	54*****
	Housemaker *[Full/part- time employed]*				54
	Job/employment unknown *[Full/part- time employed]*			54	
	Migrant agricultural work *[NS]*	46††,‡‡			
SES indices	Receiving social welfare benefit *[not in category]*				54
	Low SES level neighbourhood *[any other SES level neighbourhood]*	53			
	Townsend score high deprivation *[Townsend score least deprivation]*				38*

Potential protective factor	Strength of evidence			
	1	2	3	4
	OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
Unemployed *[Full/part- time employed]*				54
Temporary/self employed	56* *[NS]*			54 *[Full/part- time employed]*
HCP *[Full/part- time employed]*				54†††††
Student *[Full/part- time employed]*				54

Grouping variable	Potential risk factor	Strength of evidence				Potential protective factor	Strength of evidence			
		1	2	3	4		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05		OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
	Primary education only *[2nd/3rd level education only]*	39*								
	SES Level 4/5 (high deprivation) *[SES Level 1,2, or 3]*	43*								
	Having medical card *[no medical card]*	39*								
						Townsend score between low and high deprivation *[Townsend score least deprivation]*				38*
Other	Living outside of London *[living in London]*			40*						
	Living in Oslo *[NS]*		59							
	Single/separated or widowed *[married]*	39*								
	Moved health jurisdiction within state during T_x *[not moving during Tx]*	46*								
Clinical Factors										
Disease site/ presentation	Pulmonary *[extra-pulmonary]*	37 56*		40		Pulmonary *[extra-pulmonary]*				38*
	Extra-pulmonary *[not in category]*				48*					
						With cavity			54 *[no cavity]*	48* *[no cavitary disease]*
Smear & sputum culture	Smear +ve and/or culture +ve				38* *[-ve]*	Smear +ve and/or culture +ve	47*** *[not +ve in first 30 days of initial sputum collection]*		54 *[-ve]*	

Grouping variable	Potential risk factor	Strength of evidence			
		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05
					47¶¶ *[not +ve in first 30 days of initial sputum collection]*
					57* *[NS]*
	Culture/smear unknown/not done			54‡‡‡‡‡ *[-ve]*	48* *[+ve]*
					54§§§§§ *[-ve]*
T_x resistance	MDR	46††,‡‡ *[NS]*			48* *[No resistance]*
	Other resistance *[no resistance]*				48*
TB history	Previous TB	37 *[NS]*	60* *[no history]*		40 *[no history]*
	Previous TB T_x *[no previous Tx]*	45			
		52			
		53			
		43*			
	Unknown previous TB status *[no history]*			40	
	Previous TB T_x default *[no previous default]*	43*			
HIV status	HIV infection *[HIV negative]*	50*			48*
		51*			
		55			
	HIV status known/missing *[HIV negative]*				51*
					48*
	HIV negative *[NS]*	56			
	AIDS *[HIV negative]*				48*

Potential protective factor	Strength of evidence			
	1	2	3	4
	OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
	58 *[no bacteriological confirmation]*			
Smear -ve and/or culture –ve *[+ve]*				48*
Other resistance *[no resistance]*				60*
Previous TB *[no history]*				38*
First episode of TB *[NS]*	56			
HIV infection *[HIV negative]*				49*
	44			

Grouping variable	Potential risk factor	Strength of evidence				Potential protective factor	Strength of evidence			
		1	2	3	4		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05		OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
						AIDS (or AIDS related complex) *[NS]*	46††			46‡‡
	HIV infection via IDU transmission *[sexual transmission]*	53*								
Substance use/misuse	Alcohol use *[NS]*	37								
	Alcohol misuse/addiction	44 *[NS]*	39* *[0 drinks per week]*		48* *[no history of alcoholism]*					
		55 *[not in category]*	57* *[NS]*		53* *[No alcoholism]*					
		56* *[NS]*								
	Illicit drug use	37 *[NS]*	57* *[NS]*		48* *[No cocaine use]*	Illicit drug use *[NS]*				47***
		42‖ *[NS]*			47¶¶ *[NS]*					
		59 *[NS]*								
	Illicit drug misuse/addiction	51 *[No IDU]*								
		55 *[NS]*								
		48 *[no IDU]*								
		52 *[NS]*								
		50 *[not drug addict]*								
	Drug use unknown	51 *[No IDU]*								
		52 *[NS]*								

Grouping variable	Potential risk factor	Strength of evidence				Potential protective factor	Strength of evidence			
		1	2	3	4		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05		OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
	Any substance misuse (including IDU, non-IDU, and alcohol) *[NS]*	46††,‡‡								
	Being treated with methadone *[NS]*	45								
	Alcohol problems in hospital *[Not in category]*		60*							
Other	Relapse (unspecified) *[NS]*	57*								
						Diabetes co-morbidity *[not in category]*				60*
Health-Systems Factors										
Route to care	Source – emergencies *[primary care]*	51*								
	Source – specialist *[primary care]*				51*					
	Source – other *[primary care]*				51*					
	Collapsing on street *[other reason]*		60*							
	Detection of TB by screening *[other detection]*				58					
T_x provider	T_x started in OP department *[initial hospitalisation]*			54						
	Private health provider *[provider was DOH]*	45*								
	Private health provider with low volume of patients *[private health provider with high volume]*	45*								
	T_x by low volume provider *[NS]*	45								
HCP perception of	Had previous T_x comprehension† *[no previous Tx comprehension]*	51								

Grouping variable	Potential risk factor	Strength of evidence				Potential protective factor	Strength of evidence			
		1	2	3	4		1	2	3	4
		OR/RR≥ 1.5, P≤ 0.05	OR/RR≥ 1.5, P> 0.05, n< 154	OR/RR> 1.0 to <1.5, P≤ 0.05	OR/RR< 1.5, P> 0.05		OR/RR≤ 0.5, P≤ 0.05	OR/RR≤ 0.5, P> 0.05, n< 154	OR/RR> 0.5 to <1.0, P≤ 0.05	OR/RR> 0.5, P> 0.05
patient's knowledge	Had difficulty with previous T_x comprehension† *[easy previous Tx comprehension]*	[51]								
	Poor understanding *[NS]*	[52]								
	Lack of awareness of TB severity *[NS]*	[47]¶¶,***								
Other	Hospitalised (includes IP care) *[not hospitalised]*				[50]*					
	Months from +ve culture to DOH interview† *[NS]*			[47]¶¶		Months from +ve culture to DOH interview *[NS]*				[47]***
	No health insurance *[has health insurance]*				[54]					
Psychosocial Factors										
Mental health issues	Mental health problems *[NS]*	[42]§,‖				Mental health problems *[NS]*	[47]***			[47]¶¶
										[57]*
Having close relationships						Having close relationships *[no close relationships]*		[60]*		

Note. Where variable levels are non-binary, baseline comparator is given italicised in square brackets, either next to variable level or individual study reference where this differs between studies. No data was extracted from [36]. Some variables could not be extracted from [58] (urban residence, previous default from TB Tx, homelessness, alcohol addiction, drug addiction, occupation, travel to endemic areas, disease site, HIV co-infection), [57] (age), [43] (age, nationality (other)), [60] (sex, age, disease site, cavitary disease, sputum smear result), and [39] (drinking (moderate drinking)). +ve= positive, -ve= negative, DOH= Department of Health, HCP= healthcare professional, IDU= intravenous drug use, IP= inpatient, MDR= multidrug-resistant, NS=not specified, OP= outpatient, SES= socioeconomic status, TB= tuberculosis, T_x= Treatment *=univariate/ bivariate analysis. †=Determinants were not further defined. ‡=nationality: studies [37], [48], and [38] comparator is not the study country, for studies [58], [59], [43] and [54], comparator is study country. §=outcome: outcome: non-adherent in first 2 months, ‖= outcome: loss to follow-up within 6 months, ¶= age: 35-44, **= age: 55-64, ††= outcome: excludes patients who moved during study, ‡‡= outcome: includes patients who moved during study, §§= age: 75, ‖‖= age: 45-54, ¶¶= outcome: default with return to therapy, ***= outcome: default without return to therapy, †††= ethnicity: Indian, ‡‡‡= ethnicity: Pakistani, §§§= ethnicity: Bangladeshi, ‖‖‖= nationality/origin: born in Central Europe, ¶¶¶= nationality/origin: born in West Europe, ****= nationality/origin: born in East Europe, ††††= nationality/origin: Somalian and other