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The impact of alcohol use on tuberculosis treatment outcomes: a systematic review and meta-analysis

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SUMMARY

Alcohol use is associated with increased risk of developing tuberculosis (TB) disease, yet the impact of alcohol use on TB treatment outcomes has not been summarized. We aimed to quantitatively review evidence of the relationship between alcohol use and poor TB treatment outcomes. We conducted a systematic review of PubMed, EMBASE, and Web of Science (January 1980–May 2018). We categorized studies as having a high- or low-quality alcohol use definition and examined poor treatment outcomes individually and as two aggregated definitions (i.e., including or excluding loss to follow-up [LTFU]). We analyzed drug-susceptible (DS-) and multidrug-resistant (MDR-) TB studies separately. Our systematic review yielded 111 studies reporting alcohol use as a predictor of DS- and MDR-TB treatment outcomes. Alcohol use was associated with increased odds of poor treatment outcomes (i.e., death, treatment failure, and LTFU) in DS (OR 1.99, 95% CI 1.57–2.51) and MDR-TB studies (OR 2.00, 95% CI 1.73–2.32). This association persisted for aggregated poor treatment outcomes excluding LTFU, each individual poor outcome, and across sub-group and sensitivity analyses. Only 19% of studies used high-quality alcohol definitions. Alcohol use significantly increased the risk of poor treatment outcomes in both DS- and MDR-TB patients. This study highlights the need for improved assessment of alcohol use in TB outcomes research and potentially modified treatment guidelines for TB patients who consume alcohol.

KEY WORDS: alcohol use disorder; multidrug-resistant TB; drug-susceptible TB; risk factors

IN 2017, AN ESTIMATED 10 MILLION individuals developed tuberculosis (TB) disease, with 1.6 million resultant deaths, more than from disease caused by any other pathogen.[1] Alcohol use has been identified as a major risk factor for both developing TB disease and having worse outcomes;[1–4] 10–20% of all TB deaths worldwide have been attributed to alcohol use.[2,5] The 2017 World Health Organization (WHO) Sustainable Development Goals (SDG) for TB highlight the prevention and treatment of alcohol use disorders (AUDs), defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as including alcohol abuse and dependence,[6] as key to decreasing global TB incidence and deaths.[1] Neither the magnitude of the impact of alcohol use on TB treatment response nor the drivers of the association have been systematically quantified, a critical first step in informing novel approaches to improving TB outcomes.

Heavy alcohol use or AUD prevalence among TB patients worldwide ranges from 15% to 70%.[7–11] Those who use alcohol may have worse TB treatment outcomes due to behavioral mechanisms, including worse medication adherence and greater loss to follow-up (LTFU),[12–14] or biologic mechanisms, including the impact of alcohol on innate and adaptive immune responses,[15] lung function and barrier protection,[16] hepatotoxicity,[17] and TB and human immunodeficiency virus (HIV) drug absorption and metabolism.[18]

In this systematic review and meta-analysis, we aimed to quantify the strength of the association between alcohol use and drug-susceptible TB (DS-TB) and multidrug-resistant TB (MDR-TB) treatment outcomes, including whether the association persists beyond LTFU, and to identify gaps in knowledge. DS- and MDR-TB studies were analyzed separately, given

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their distinctly different treatment regimens and risk factors for poor outcomes.

METHODS

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary Table S1).[19] Ethical approval was not required for the study.

Data sources and searches

We searched PubMed, EMBASE, and Web of Science from January 1980 to May 2018 for articles and abstracts evaluating risk factors for TB treatment outcomes (Supplementary Table S2). We also searched references of identified review articles for studies meeting our criteria.

Study review and selection

Studies written in English, Spanish, French, Portuguese, Russian, Mandarin, Italian, Dutch, and Korean were included. We resolved discrepancies by discussion and consensus, and third party arbitration if needed. Two individuals independently reviewed titles and abstracts of articles for inclusion. Articles were included if they were peer-reviewed, reported participants receiving standard treatment regimens for TB disease, and described factors associated with TB treatment outcomes comparable to WHO definitions (Supplementary Table S3). Studies were excluded if they reported three or fewer patients, were reviews or commentaries, reported an exclusively pediatric population (<16 years of age), or reported treatment prior to 1980. For our analyses, the alcohol exposure group was considered the highest level of exposure reported by the authors (e.g., the highest volume of consumption or highest AUD risk), while the reference group was the lowest level of exposure (which mostly referred to no alcohol consumption, but could also include low levels of consumption). If a study reported more than two alcohol exposure levels, participants from the intermediate levels were excluded. Due to between-study variations in how alcohol use was assessed, we refer to exposure as 'alcohol use,' recognizing that severity varies.

For studies identified through title and abstract review, two reviewers conducted a full-text review of all articles that mentioned alcohol terms. Reviewers documented on a coding sheet the primary reason for exclusion using the criteria listed above, with additional exclusion of studies that did not stratify treatment outcome by alcohol use or did not report either count data or effect measure estimates.

Data extraction

For each included study, two investigators independently extracted variables of interest (Supplementary Table S4). For papers presenting data on more than one distinct cohort, we treated each cohort as a distinct "study," adding 'a' or 'b' to the assigned study ID.

Data analysis

MDR-TB was defined as resistance to at least isoniazid and rifampin. If >20% of participants had MDR-TB, we classified it as an MDR-TB study. Separate analyses were performed for each of the following outcomes: 1) poor outcome A (i.e., death, treatment failure, and LTFU) compared to cure and treatment completion; 2) poor outcome B (i.e., death or treatment failure) compared to cure and treatment completion; 3) death compared to treatment failure, LTFU, cure, and treatment completion; 4) treatment failure compared to death, LTFU, cure and treatment completion; and, 5) LTFU compared to death, treatment failure, cure and treatment completion. We excluded participants who transferred out. We performed sensitivity analyses where LTFU was added to the reference group of poor outcome B and the other poor outcomes were compared only to cure and treatment completion.

The study sample was the number of individuals with alcohol use information reported in the authors' final analysis. We used study counts to calculate unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) for each outcome. For studies that reported adjusted effect measures or did not provide counts, we used the authors' reported effect measure estimates and 95% CIs. We considered adjusted effect measures adequate if the model included age and sex. Overall study quality was assessed by looking at the case, exposure, and outcome definitions. All included studies used standard definitions for TB disease and treatment outcomes. We also assessed study strategy for documenting alcohol use. Assessment of alcohol use was determined to be higher-quality if a validated screening instrument was used, or alcohol use was well categorized by quantity and/or frequency of drinking.

We assessed heterogeneity of effect estimates using the Cochran *Q* test for heterogeneity and calculating the I^2 statistic.[20,21] We computed summary estimates for both the unadjusted and adjusted effect estimates using the random-effects model and weighting method according to the maximum likelihood method described by Normand.[22] Studies that were highly influential or contributed greatly to the estimate of heterogeneity were identified using Baujat et al.'s graphical method.[23] We conducted sensitivity analyses by recalculating combined effect sizes after removing these studies. We assessed publication bias using the Egger test,[24] and visually reviewed funnel plots of the effect estimate logarithms against the standard errors for asymmetry.[24]

We conducted sub-group and meta-regression analyses to identify additional sources of heterogene-

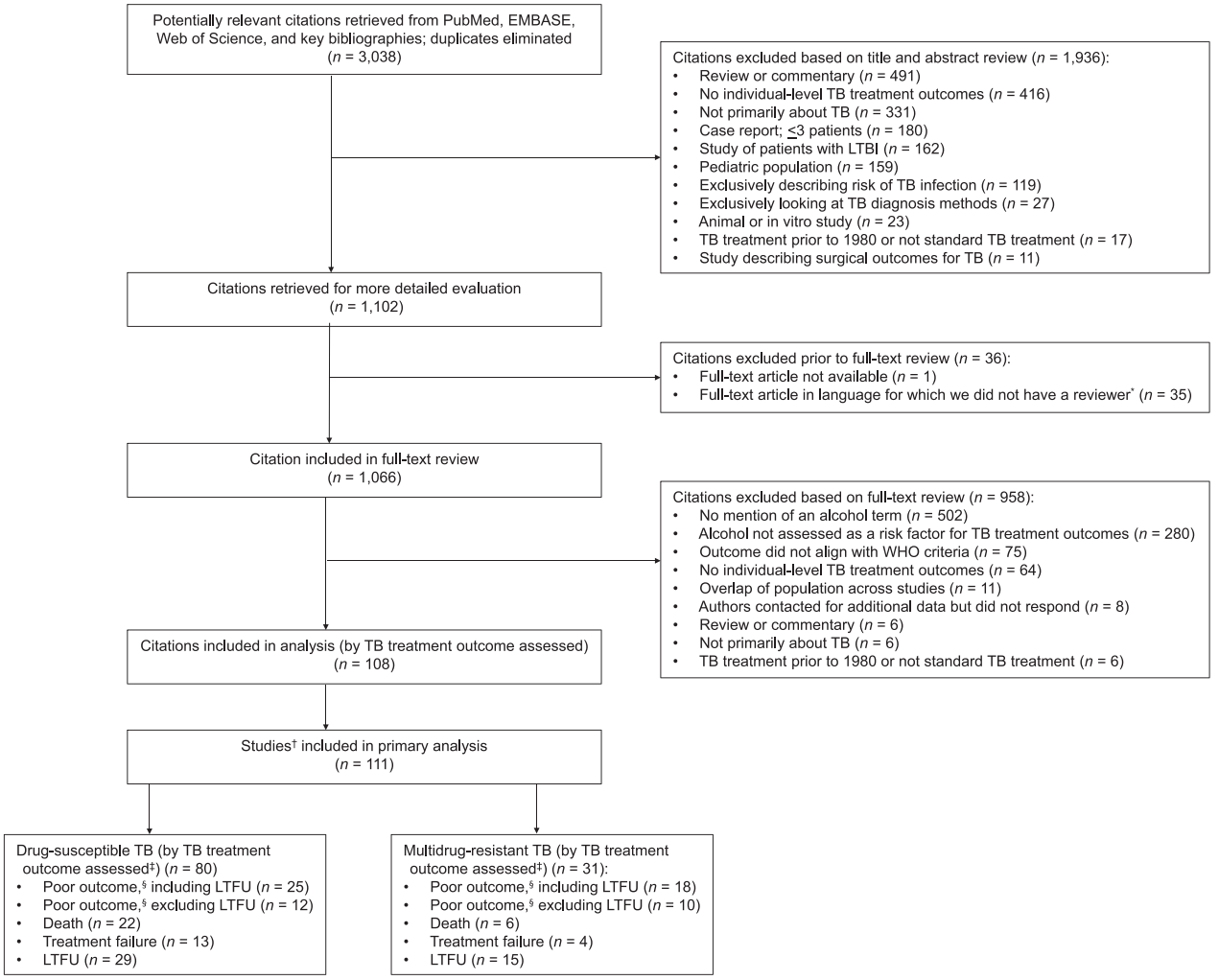

Figure 1 PRISMA flow chart of studies included in the meta-analysis. * Japanese ($n = 21$), German ($n = 8$), Polish ($n = 5$), and Hungarian ($n = 1$). † Three citations were split due to reporting on two unique cohorts, therefore were treated as two studies each. ‡ List not mutually exclusive as many studies report more than one outcome. § Death or treatment failure. TB = tuberculosis; LTBI = latent tuberculosis infection; WHO = World Health Organization; LTFU = loss to follow-up; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

ity, assess the impact of study quality on the summary estimates, and look for effect modification. We performed individual random-effects meta-regression analyses, restricting analyses to sub-groups with a minimum of five studies. Background TB incidence was determined by WHO classifications of high-burden (HBC) or not high-burden countries (not HBC), differentiated by overall TB and MDR-TB burden.[1] Country income was based on the World Bank's 2019 fiscal year classifications.[25]

Statistical procedures were performed using SAS v9.4 (SAS Institute, Cary, NC, USA) and R v3.5.1 (R Computing, Vienna, Austria).

RESULTS

We identified 3038 citations for title and abstract review; 1102 met criteria for full review (Figure 1). We excluded 35 citations in languages for which we lacked fluent reviewers and one whose full text was not available. Nine hundred and fifty-eight papers were excluded upon full-text review. We contacted the authors of 10 studies and obtained clarification from three. We ultimately included 80 studies on DS-TB and 31 studies on MDR-TB (Figure 1; Supplementary Data I). The included studies were in English ($n = 105$), Spanish ($n = 3$), French ($n = 2$), and Portuguese ($n = 1$). The studies included 81 cohort, 29 case-control, and one randomized controlled trial.

Quality of alcohol measurement

Off the 111 studies included, four used a validated screening method for alcohol exposure (i.e., CAGE Alcohol Questionnaire. One study used DSM-5 definitions, two reported the volume consumed, and 12 reported consumption frequency (Supplementary Tables S5 and S6). The remaining ($n = 90$, 81%) used

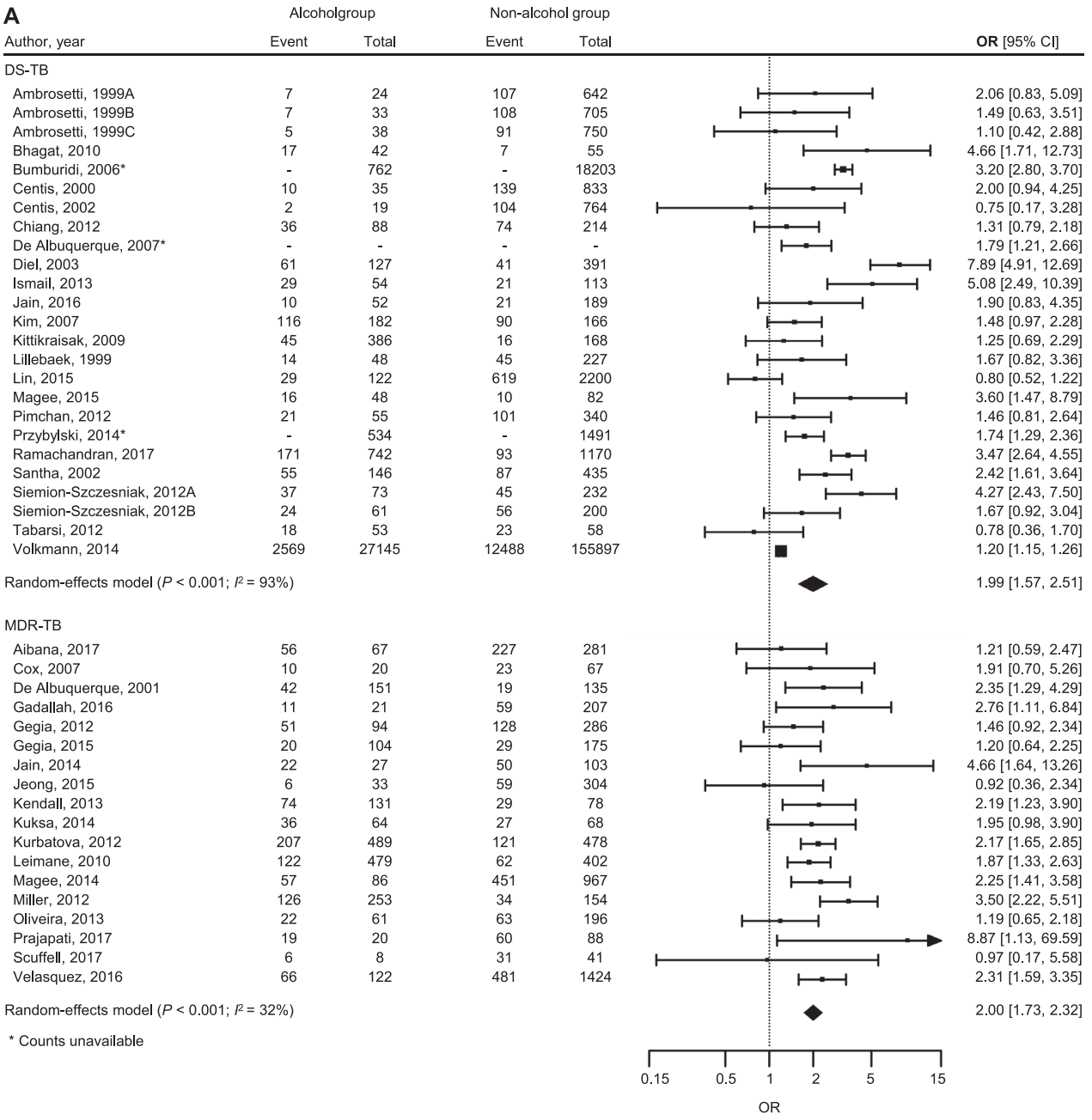

Figure 2 **A)** Forest plots of the association between alcohol use and Poor Outcome A (i.e., death, failure, and LTFU) for both DS-TB and MDR-TB studies and the breakdown of participants with poor outcome by exposure group. **B)** Forest plots of the association between alcohol use and Poor Outcome B (i.e., death and failure) for both DS-TB and MDR-TB studies and the breakdown of participants with poor outcome by exposure group. Squares indicate ORs from individual studies; square size reflects the statistical weight of the study. Horizontal lines indicate 95% CIs. Diamonds represent the combined ORs and 95% CIs. The vertical solid line shows no effect (OR = 1). The *P* values are from tests that the combined ORs equal 1. OR = odds ratio; CI = confidence interval; DS-TB = drug-susceptible tuberculosis; MDR-TB = multidrug-resistant TB; LTFU = loss to follow-up.

a lower-quality alcohol exposure variable: 58 (52%) relied on medical chart extraction, 28 (25%) on questionnaire/interview self-report, and 21 (19%) lacked detail on how alcohol use was assessed.

Poor outcome A (including loss to follow-up)

Among DS-TB studies, patients who consumed alcohol had significantly higher odds of poor outcome A (i.e., death, treatment failure, and LTFU) than the reference alcohol group (i.e., no or low alcohol use) ($n = 25$; OR 1.99, 95% CI 1.57–2.51; Figure 2A, Table 1). The finding was similar for MDR-TB studies ($n = 18$; OR 2.00, 95% CI 1.73–2.32; Figure 2A, Table 1). Sub-group analyses among DS-TB studies that used a high-quality definition for alcohol use revealed an increase in the association between alcohol use and poor outcome A ($n = 4$; OR 3.05, 95% CI 1.58–5.89). All sub-group analyses for

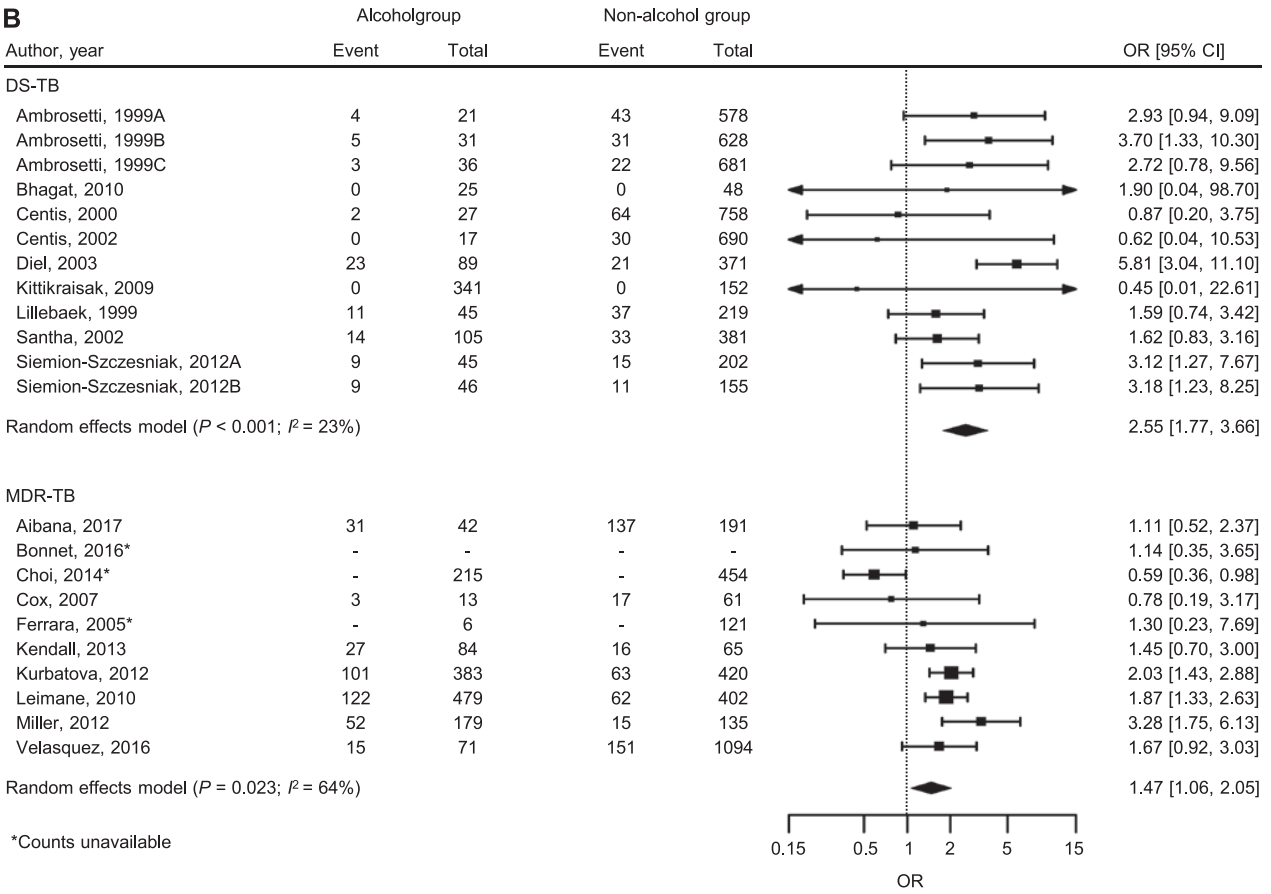

Figure 2 (*continued*)

poor outcome A among both DS-TB and MDR-TB studies retained a significant association with alcohol use, except DS-TB studies of pulmonary TB patients ($n = 3$; OR 2.02; 95% CI 0.92–4.45) and MDR-TB studies reporting an adjusted measure of association ($n = 5$; OR 1.48, 95% CI 0.84–2.61), both of which contained a small number of studies in each analysis (Table 2).

Poor outcome B (excluding loss to follow-up)

Among DS-TB studies, patients who consumed alcohol had significantly higher odds of poor outcome B (i.e., death and treatment failure) than the reference alcohol group ($n = 12$; OR 2.55, 95% CI 1.77–3.66; Figure 2B, Table 1). This relationship was also observed in MDR-TB studies ($n = 10$; OR 1.47, 95% CI 1.06–2.05; Figure 2B, Table 1). Sub-group

Table 1 **A)** Meta-analysis results for poor treatment outcomes, studies on drug-susceptible TB

Treatment outcome	Studies *n*	Summary effect estimate	95% CI	I^2 %	*P* value heterogeneity
Poor outcome A*	25	1.99	1.57–2.51	93	<0.001
Poor outcome B†	12	2.55	1.77–3.66	23	0.222
Death	22	1.58	1.24–2.00	73	<0.001
Treatment failure	13	3.12	1.83–5.33	52	0.014
LTFU	29	2.25	1.74–2.91	79	<0.001

B) Meta-analysis results for poor treatment outcomes, studies on multidrug-resistant TB

Treatment outcome	Studies *n*	Summary effect estimate	95% CI	I^2 %	*P* value heterogeneity
Poor outcome A*	18	2.00	1.73–2.32	32	0.098
Poor outcome B†	10	1.47	1.06–2.05	64	0.003
Death	6	1.38	1.04–1.83	0	0.551
Treatment failure	4	1.54	1.09–2.17	45	0.143
LTFU	15	1.87	1.56–2.24	51	0.013

* Death, treatment failure, and LTFU.
† Death and treatment failure.
TB = tuberculosis; CI = confidence interval; LTFU = loss to follow-up.

Table 2 **A)** Meta-analysis results of sub-group analyses for treatment outcomes for drug-susceptible TB studies

Treatment outcome	Variable	Study characteristics	Studies *n*	Summary effect estimate	95% CI	I^2 %	*P* value heterogeneity
Poor outcome A*	Country TB burden	High burden	7	2.18	1.62–2.93	67	<0.001
		Not high burden	18	1.92	1.42–2.59	94	<0.001
	Country income	HIC	14	1.75	1.26–2.42	86	<0.001
		LMIC	12	2.05	1.43–2.95	84	<0.001
	Type of TB	Pulmonary	3	2.02	0.92–4.45	95	<0.001
		Pulmonary and extrapulmonary	18	2.00	1.52–2.65	89	<0.001
	High-quality alcohol definition	Yes	4	3.05	1.58–5.89	88	<0.001
	Adjusted effect measure	Yes	7	2.03	1.54–2.69	88	<0.001
	Minimally adjusted effect measure	Yes	3	1.63	1.21–2.18	92	<0.001
Poor outcome B†	Country TB burden	High burden	3	1.57	0.82–3.01	0	0.814
		Not high burden	9	2.86	1.94–4.21	26	0.214
	Country income	HIC	9	2.86	1.94–4.21	26	0.214
		LMIC	3	1.57	0.82–3.01	0	0.814
	Type of TB	Pulmonary	0	NA	NA	NA	NA
		Pulmonary and extrapulmonary	10	2.37	1.52–3.70	35	0.129
	High-quality alcohol definition	Yes	2	3.15	1.29–7.69	84	0.011
	Adjusted effect measure	Yes	1	1.80	0.42–7.69	NA	NA
	Minimally adjusted effect measure	Yes	1	1.80	0.42–7.69	NA	NA
Death	Country TB burden	High burden	3	1.85	0.88–3.89	79	0.009
		Not high burden	19	1.46	1.18–1.81	49	0.009
	Country income	HIC	15	1.20	1.15–1.26	38	0.065
		LMIC	6	2.15	1.58–2.93	54	0.053
	Type of TB	Pulmonary	2	1.02	0.67–1.55	66	0.088
		Pulmonary and extrapulmonary	15	1.49	1.20–1.85	50	0.014
	High-quality alcohol definition	Yes	4	1.49	0.96–2.31	29	0.240
	Adjusted effect measure	Yes	4	2.26	1.80–2.83	31	0.228
	Minimally adjusted effect measure	Yes	3	2.35	1.89–2.93	8	0.337
Treatment failure	Country TB burden	High burden	2	1.70	0.86–3.39	47	0.168
		Not high burden	11	3.90	2.06–7.39	54	0.016
	Country income	HIC	9	5.27	2.68–10.36	21	0.255
		LMIC	4	1.84	1.04–3.23	59	0.064
	Type of TB	Pulmonary	1	2.63	1.04–6.60	NA	NA
		Pulmonary and extrapulmonary	10	3.99	1.85–8.63	64	0.003
	High-quality alcohol definition	Yes	2	12.15	3.63–40.71	0	0.447
	Adjusted effect measure	Yes	2	1.85	0.80–4.27	0	0.427
	Minimally adjusted effect measure	Yes	1	1.09	0.23–5.11	NA	NA
Loss to follow-up	Country TB burden	High burden	14	2.36	1.95–2.87	65	<0.001
		Not high burden	15	1.92	1.20–3.08	85	<0.001
	Country income	HIC	11	1.92	1.13–3.24	73	<0.001
		LMIC	18	2.37	1.77–3.17	82	<0.001
	Type of TB	Pulmonary	5	2.20	0.93–5.20	94	<0.001
		Pulmonary and extrapulmonary	18	2.10	1.68–2.62	61	<0.001
	High-quality alcohol definition	Yes	6	3.20	1.86–5.50	85	<0.001
	Adjusted effect measure	Yes	8	2.12	1.58–2.84	72	0.001
	Minimally adjusted effect measure	Yes	4	1.71	1.53–1.92	79	0.003

B) Meta-analysis results for treatment outcomes, sub-group analyses for MDR-TB

Treatment outcome	Group	Study characteristics	Studies *n*	Summary effect estimate	95% CI	I^2 %	*P* value heterogeneity
Poor outcome A*	Country TB burden	High burden	6	2.52	2.05–3.11	20	0.284
		Not high burden	11	1.73	1.46–2.06	11	0.341
	Country MDR-TB burden	High burden	9	2.33	1.95–2.77	28	0.197
		Not high burden	8	1.72	1.43–2.08	17	0.292
	Country income	HIC	4	1.64	1.26–2.13	12	0.335
		LMIC	13	2.13	1.73–2.63	34	0.110
	Type of TB	Pulmonary	3	1.81	1.15–2.84	28	0.252
		Pulmonary and extrapulmonary	8	2.06	1.77–2.40	0	0.712
	High-quality alcohol definition	Yes	2	1.87	1.26–2.78	68	0.079
	Adjusted effect measure	Yes	5	1.48	0.84–2.61	63	0.029
	Minimally adjusted effect measure	Yes	2	0.85	0.43–1.69	0	0.628

Table 2 B) (*continued*)

Treatment outcome	Variable	Study characteristics	Studies *n*	Summary effect estimate	95% CI	I^2 %	*P* value heterogeneity
Poor outcome B[†]	Country TB burden	High burden	4	2.05	1.56–2.70	25	0.263
		Not high burden	6	1.18	0.77–1.82	67	0.009
	Country MDR-TB burden	High burden	7	1.83	1.45–2.31	24	0.249
		Not high burden	3	1.11	0.55–2.24	86	0.001
	Country income	HIC	3	1.11	0.55–2.24	86	0.001
		LMIC	5	1.69	1.14–2.49	41	0.147
	Type of TB	Pulmonary	1	0.78	0.19–3.17	NA	NA
		Pulmonary and extrapulmonary	5	1.85	1.49–2.29	0	0.915
	High-quality alcohol definition	Yes	3	0.99	0.55–1.8	72	0.030
	Adjusted effect measure	Yes	1	1.10	0.56–2.19	NA	NA
	Minimally adjusted effect measure	Yes	1	1.10	0.56–2.19	NA	NA
Death	Country TB burden	High burden	4	1.63	1.10–2.41	0	0.463
		Not high burden	2	1.15	0.76–1.74	0	0.992
	Country MDR-TB burden	High burden	5	1.38	1.04–1.85	0	0.409
		Not high burden	1	1.26	0.27–5.83	NA	NA
	Country income	HIC	0	NA	NA	NA	NA
		LMIC	5	1.35	0.95–1.93	0	0.411
	Type of TB	Pulmonary	0	NA	NA	NA	NA
		Pulmonary and extrapulmonary	2	1.32	0.90–1.93	0	0.598
	High-quality alcohol definition	Yes	1	1.15	0.62–2.15	NA	NA
	Adjusted effect measure	Yes	0	NA	NA	NA	NA
	Minimally adjusted effect measure	Yes	0	NA	NA	NA	NA
Treatment failure	Country TB burden	High burden	2	1.82	1.25–2.66	0	0.933
		Not high burden	2	0.73	0.33–1.63	28	0.240
	Country MDR-TB burden	High burden	4	1.54	1.09–2.17	45	0.143
		Not high burden	0	NA	NA	NA	NA
	Country income	HIC	0	NA	NA	NA	NA
		LMIC	3	1.15	0.61–2.17	51	0.131
	Type of TB	Pulmonary	0	NA	NA	NA	NA
		Pulmonary and extrapulmonary	2	1.75	1.15–2.68	0	0.562
	High-quality alcohol definition	Yes	1	1.26	0.38–4.20	NA	NA
	Adjusted effect measure	Yes	0	NA	NA	NA	NA
	Minimally adjusted effect measure	Yes	0	NA	NA	NA	NA
Loss to follow-up	Country TB burden	High burden	7	1.82	1.47–2.25	38	0.140
		Not high burden	7	2.14	1.53–2.99	50	0.061
	Country MDR-TB burden	High burden	11	1.83	1.53–2.19	42	0.067
		Not high burden	3	3.11	2.00–4.81	0	0.790
	Country income	HIC	2	3.15	1.96–5.07	0	0.505
		LMIC	11	1.83	1.50–2.22	45	0.052
	Type of TB	Pulmonary	3	2.76	1.94–3.92	35	0.213
		Pulmonary and extrapulmonary	8	1.72	1.39–2.13	45	0.078
	High-quality alcohol definition	Yes	2	2.68	1.99–3.60	0	0.334
	Adjusted effect measure	Yes	4	2.59	1.91–3.53	0	0.670
	Minimally adjusted effect measure	Yes	1	2.10	1.10–4.00	NA	NA

* Death, treatment failure, and LTFU.
[†] Death and treatment failure.
TB = tuberculosis; CI = confidence interval; HIC = high-income country; LMIC = low- to middle-income country; NA = not applicable or available; MDR-TB = multidrug-resistant TB; LTFU = loss to follow-up.

analyses did not reveal a noticeable difference in effect measure for poor outcome B (Table 2). When LTFU was included in the reference outcome group, along with cure and treatment completion, alcohol use remained significantly associated with poor outcome B for both DS-TB ($n = 12$; OR 2.16, 95% CI 1.55–3.01) and MDR-TB ($n = 7$; OR 1.44, 95% CI 1.12–1.86 (Supplementary Table S7).

Death

Among DS-TB studies, alcohol use was associated with significantly higher odds of death ($n = 22$; OR 1.58, 95% CI 1.24–2.00; Table 1; Supplementary Figure S1A). The same relationship was observed among MDR-TB studies ($n = 6$; OR 1.38, 95% CI 1.04–1.83; Table 1; Supplementary Figure S1A). Subgroup analyses among DS-TB studies conducted in low and middle-income countries showed an increase in the association between alcohol use and death ($n = 6$; OR 2.15, 95% CI 1.58–2.93; Table 2). When compared only to cure and treatment completion, alcohol use remained significantly associated with death in both DS-TB and MDR-TB patients (DS-TB: $n = 16$; OR 1.53, 95% CI 1.16–2.01; MDR-TB: $n = 5$;

OR 1.86; 95% CI, 1.34–2.60; Supplementary Table S7).

Treatment failure

Among DS-TB studies, alcohol use was associated with higher odds of treatment failure ($n = 13$; OR 3.12, 95% CI 1.83–5.33) (Table 1; Supplementary Figure S1B). The same was observed among MDR-TB studies ($n = 4$; OR 1.54, 95% CI 1.09–2.17; Table 1; Supplementary Figure S1B). Sub-group analyses showed an increase in the association between alcohol use and treatment failure among DS-TB studies conducted in countries not considered high TB burden ($n = 11$; OR 3.90, 95% CI 2.06–7.39) and high-income countries ($n = 9$; OR 5.27, 95% CI 2.68–10.36) (Table 2). The relationship between alcohol use and treatment failure for both DS- and MDR-TB remained significant when only cure and treatment completion were used as the reference outcome group (DS-TB: $n = 14$; OR 3.23, 95% CI 1.75–5.96; MDR-TB: $n = 4$; OR 2.05, 95% CI 1.44–2.92; Supplementary Table S7).

Loss to follow-up

Alcohol use was associated with an increased odds of LTFU in both DS-TB ($n = 29$; OR 2.25, 95% CI 1.74–2.91; Table 1; Supplementary Figure S1C) and MDR-TB studies ($n = 15$; OR 1.87, 95% CI 1.56–2.24; Table 1; Supplementary Figure S1C). Sub-group analyses showed an increase in the association between alcohol use and LTFU in DS-TB studies that reported a higher-quality definition of alcohol use ($n = 6$; OR 3.20, 95% CI 1.86–5.50; Table 2). Alcohol use remained significantly associated with LTFU when cure and treatment completion were used as the reference outcome for both DS-TB ($n = 30$; OR 2.71, 95% CI 2.07–3.55) and MDR-TB studies ($n = 9$; OR 2.18, 95% CI 1.64–2.90; Supplementary Table S7).

Heterogeneity, publication bias, and meta-regression

Considerable heterogeneity was present in many of the main and sub-group analyses, even when outliers were removed (Tables 1 and 2; Supplementary Table S7). Egger's test for publication bias was significant for the DS-TB analyses of poor outcome A ($P = 0.03$) and treatment failure ($P = 0.03$). Visual inspection of funnel plots showed no compelling evidence of publication bias for poor outcome A, but was suggestive of bias for treatment failure due to a lack of small studies with odds ratios below the combined value (Supplementary Figure S2). In meta-regression, the proportions of patients with diabetes mellitus (DM), patients who were smear-positive at diagnosis, illicit drug users, and the WHO region each significantly modified the associations between alcohol use and at least one outcome (Supplementary Table S8). No covariate had a consistently significant impact across all outcomes or TB susceptibility types.

DISCUSSION

In this systematic review and meta-analysis, alcohol use was associated with a 1.5–2-fold increased odds of poor DS-TB and MDR-TB treatment outcomes, relative to minimal or no alcohol exposure. Alcohol use was a risk factor for poor TB outcomes in aggregate, in addition to each poor treatment outcome (treatment failure, death, LTFU) individually. While much of the literature has pointed to poor adherence and retention in care as primary drivers of this association,[26–28] our finding that those who consumed alcohol had increased risk of treatment failure and death, independent of LTFU, suggests that the negative impact of alcohol may have biologic drivers as well. Our review reveals that most TB studies that capture alcohol use reported only dichotomous use (i.e., yes/no), relying heavily on medical record documentation or patient self-report. An increased body of TB literature with validated measures of alcohol use may ultimately reveal that the strong associations we highlight in this review are conservative.

With the large number of identified studies, we were able to look at the impact of alcohol on DS- and MDR-TB separately, which had not been done in previous reviews on alcohol use and TB.[3,4,29,30] MDR-TB patients globally have a more than two-fold higher rate of poor outcomes than DS-TB patients.[1] This indicates a potentially greater number of competing risks for poor outcomes that may diminish the observed effect of alcohol. Even so, our findings indicate that alcohol use contributes to poor outcomes for both forms of TB.

Our sub-group and meta-regression analyses indicated potential for effect modification, but ultimately did not explain the high heterogeneity observed. Sub-group analyses of studies reporting a high-quality alcohol measurement indicated a strengthened relationship between alcohol use and poor treatment outcomes for DS-TB and LTFU for MDR-TB. Sub-group analyses of country income showed a stronger alcohol use effect on treatment failure and death in higher-income countries. Country wealth is positively associated with the number of individuals with problem alcohol use.[5] High TB burden countries experiencing economic growth, such as India or South Africa, may become locations where the epidemics of alcohol use and TB co-occur, with potential for explosive impact, similar to that predicted for DM and TB. This analysis was limited because lower-income and high TB burden countries were largely under-represented. Findings from our meta-regression analyses were ultimately mixed, but highlight the importance of collecting high-quality

information on covariates associated with poor treatment outcomes that may have an additive effect with alcohol, namely DM, smear status, and illicit drug use.

Strong associations between alcohol use and poor TB outcomes were observed in this review despite several limitations of the summarized literature. First, misclassification was likely for both treatment outcomes and exposure to alcohol. LTFU was a frequent event in the studies we reviewed, ranging from 4% to 57% in DS-TB and from 0% to 33% in MDR-TB cohort studies, but is a TB outcome for which the appropriate reference group remains unclear. Although primarily considered a poor outcome, LTFU is intermediary, as a patient LTFU may ultimately have a favorable or a poor outcome had they continued treatment. Similarly, treatment failure and death may be a result of poor adherence or borderline LTFU. To account for this, we used two aggregate poor outcome definitions, including and excluding LTFU, and performed sensitivity analyses where each individual poor outcome was compared only to successful outcomes. Inclusion or exclusion of LTFU in the reference group did not meaningfully alter the observed effect. With respect to exposure, very few studies used a higher-quality alcohol use measure. Given that alcohol use is often under-reported,[31] misclassification would likely diminish the observed effect and render our findings conservative. This is supported by the observed strengthened effect on all poor outcomes except death in subgroup analyses of DS-TB studies collecting a high-quality alcohol use variable (poor outcome A, OR 3.05; poor outcome B, OR 3.15; failure, OR 12.15; LTFU, OR 3.20; Table 2).

Second, a common methodological issue among the reviewed studies was that few reported hazard ratios (HRs). As highlighted by Huangfu et al., logistic regression is the most commonly used analysis for treatment outcome studies, but survival analysis is often the more appropriate method to account for competing risk and avoid outcome misclassification.[32] We attempted to reduce misclassification by including only studies that reported standardized definitions and aggregating outcomes in various combinations. Third, few studies reported adjusted effect measures which may have led to within-study confounding. Finally, we found high heterogeneity in many of our analyses which was not fully explained by secondary analyses or meta-regression, potentially driven by differences in the patient populations (e.g., geography, burden, comorbidities) and alcohol use definitions.

The findings of our meta-analysis indicate a clear, quantifiable relationship between alcohol use and poor TB treatment outcomes, and highlight the need for interventions for TB patients in treatment who consume alcohol. All TB outcome studies should include rigorous alcohol measurements, as a larger body of studies reporting high-quality measures may better illuminate causal mechanisms, a dose-response relationship, and a differential impact of chronic vs. acute problem drinking.[33] Numerous validated instruments (e.g., Alcohol Use Disorder Identification Test [AUDIT] or CAGE) can be incorporated easily into data collection for both observational and interventional studies.[34,35] Recent treatment guidelines from the WHO, American Thoracic Society (ATS), and the US Centers for Disease Control and Prevention (CDC) lack guidance on how to integrate alcohol use interventions into treatment for active TB.[36–38] Our findings suggest that guidelines for treating TB, integrated with interventions that address the impact of alcohol use via both biologic and behavioral mechanisms, are warranted, similar to what has been developed or proposed for integrating TB treatment with HIV and DM care.[39–41]

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References

1 World Health Organization. Global tuberculosis report, 2018. WHO/CDS/TB/2018.20. Geneva, Switzerland: WHO, 2018.
2 Kyu H H, Maddison E R, Henry N J, et al. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. Lancet Infect Dis 2018; 18(3): 261–284.
3 Imtiaz S, Shield K D, Roerecke M, Samokhvalov A V, Lönnroth K, Rehm J. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J 2017; 50: 1700216.
4 Simou E, Britton J, Leonardi-Bee J. Alcohol consumption and risk of tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis 2018; 22(11): 1277–1285.
5 World Health Organization. Global status report on alcohol and health, 2018. Geneva, Switzerland: WHO, 2018.
6 American Psychiatric Association. Diagnostic and statistical manual of mental disorders: Fifth Edition. Arlington, VA, USA: APA, 2013.
7 Shin S S, Mathew T A, Yanova G V, et al. Alcohol consumption among men and women with tuberculosis in Tomsk, Russia. Cent Eur J Public Health 2010; 18(3): 132.
8 Veerakumar A M, Sahu S K, Sarkar S, Kattimani S, Govindarajan S. Alcohol use disorders among pulmonary

tuberculosis patients under RNTCP in urban Pondicherry, India. Indian J Tuberc 2015; 62(3): 171–177.
9 Laprawat S, Peltzer K, Pansila W, Tansakul C. Alcohol use disorder and tuberculosis treatment: A longitudinal mixed method study in Thailand. S Afr J Psychiatry 2017; 23(1): 1074.
10 Peltzer K, Louw J, McHunu G, Naidoo P, Matseke G, Tutshana B. Hazardous and harmful alcohol use and associated factors in tuberculosis public primary care patients in South Africa. Int J Environ Res Public Health 2012; 9(9): 3245–3257.
11 Volkmann T, Moonan P K, Miramontes R, Oeltmann J E. Tuberculosis and excess alcohol use in the United States, 1997–2012. Int J Tuberc Lung Dis 2014; 19(1): 111–119.
12 de Albuquerque M d F M, Ximenes R A d A, Lucena-Silva N, et al. Factors associated with treatment failure, dropout, and death in a cohort of tuberculosis patients in Recife, Pernambuco State, Brazil. Cad Saude Publica 2007; 23(7): 1573–1582.
13 Kurbatova E V, Taylor A, Gammino V M, et al. Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. Tuberculosis 2012; 92(5): 397–403.
14 Miller A C, Gelmanova I Y, Keshavjee S, et al. Alcohol use and the management of multidrug-resistant tuberculosis in Tomsk, Russian Federation. Int J Tuberc Lung Dis 2012; 16(7): 891–896.
15 Molina P E, Happel K I, Zhang P, Kolls J K, Nelson S. Focus on: alcohol and the immune system. Alcohol Res Health 2010; 33(1–2): 97–108.
16 Quintero D, Guidot D M. Focus on the lung. Alcohol Res Health 2010; 33(3): 219.
17 Saukkonen J J, Cohn D L, Jasmer R M, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174(8): 935–952.
18 Koriakin V, Sokolova G, Grinchar N, Iurchenko L. Pharmacokinetics of isoniazid in patients with pulmonary tuberculosis and alcoholism. Probl Tuberk 1986; 12: 43–46.
19 Moher D, Liberati A, Tetzlaff J, Altman D; The PRISMA Group. Preferred reporting items for systematic review and meta-analysis: the PRISMA statement. Open Med. 2009; 3(3): e123–e130.
20 Cochran W. The combination of estimates from different experiments. Biometrics 1954; 10: 101–129.
21 Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21(11): 1539–1558.
22 Normand S-L. Formulating, evaluating, combining and reporting. Stat Med 1999; 18: 321–359.
23 Baujat B, Mahé C, Pignon J-P, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Stat Med 2002; 21(18): 2641–2652.
24 Egger M, Davey-Smith G, Altman D. Systematic reviews in health care: meta-analysis in context. 2nd ed. London, UK: BMJ Books, 2001.
25 The World Bank. World Bank country and lending groups. Washington DC, USA: World Bank, 2018.
26 Garrido M D, Penna M L, Perez-Porcuna T M, et al. Factors associated with tuberculosis treatment default in an endemic area of the Brazilian Amazon: a case control-study. PLoS One 2012; 7(6): 7.
27 Gelmanova I Y, Keshavjee S, Golubchikova V T, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. Bull World Heal Organ 2007; 85(9): 703–711.
28 Jakubowiak W M, Bogorodskaya E M, Borisov E S, Danilova D I, Kourbatova E K. Risk factors associated with default among new pulmonary TB patients and social support in six Russian regions. Int J Tuberc Lung Dis 2007; 11(1): 46–53.
29 Rehm J J, Samokhvalov A V, Neuman M G M, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health 2009; 9(1): 450.
30 Lönnroth K, Williams B G, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis: a systematic review. BMC Public Health 2008; 8: 289.
31 Bajunirwe F, Haberer J E, Boum Y, et al. Comparison of self-reported alcohol consumption to phosphatidylethanol measurement among HIV-infected patients initiating antiretroviral treatment in southwestern Uganda. PLoS One 2014; 9(12): e113152.
32 Huangfu P, Pearson F, Ugarte-Gil C, Critchley J. Diabetes and poor tuberculosis treatment outcomes: issues and implications in data interpretation and analysis. Int J Tuberc Lung Dis 2017; 21(12): 1214–1219.
33 Myers B, Bouton T C, Ragan E J, et al. Impact of alcohol consumption on tuberculosis treatment outcomes: a prospective longitudinal cohort study protocol. BMC Infect Dis 2018; 18(1): 488.
34 Saunders J B, Aasland O G, Babor T F, de la Fuente J R, Grant M. Development of the Alcohol Use Disorders Screening Test (AUDIT). WHO collaborative project on early detection of persons with harmful alcohol consumption. Addiction 1993; 88: 791–804.
35 Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. Am J Psychiatry 1974; 131(10): 1121–1123.
36 Nahid P, Dorman S E, Alipanah N, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016; 63(7): 853–867.
37 World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis. WHO/HTM/TB/2016.04. Geneva, Switzerland: WHO, 2016. http://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf?sequence=1 Accessed November 2019.
38 World Health Organization. Guidelines of treatment for drug-susceptible tuberculosis and patient care. WHO/HTM/TB/2017.05. Geneva, Switzerland: WHO, 2017. http://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf;jsessionid=CBE386EEEBC3D48EE5F02A6BA68FDB34?sequence=1 Accessed November 2019.
39 Riza A L, Pearson F, Ugarte-Gil C, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrinol 2014; 2(9): 740–753.
40 Khan F A, Minion J, Al-Motairi A, Benedetti A, Harries A D, Menzies D. An updated systematic review and meta-analysis on the treatment of active tuberculosis in patients with HIV infection. Clin Infect Dis 2012; 55(8): 1154–1163.
41 Onyebujoh P C, Ribeiro I, Whalen C C. Treatment options for HIV-associated tuberculosis. J Infect Dis 2007; 196 (Suppl 1): S35–S45.

RÉSUMÉ

La consommation d'alcool est associée à un risque accru de développer une tuberculose (TB), mais l'impact de la consommation d'alcool sur le résultat du traitement de la TB n'a pas été synthétisé. Nous avons revu quantitativement les éléments en faveur de la relation entre consommation d'alcool et résultats médiocres du traitement de la TB. Nous avons réalisé une revue systématique sur PubMed, EMBASE et Web of Science (janvier 1980–mai 2018). Nous avons catégorisé les études en fonction de la qualité élevée ou faible de la définition de la consommation l'alcool et examiné les résultats du traitement au niveau individuel et sous forme de deux définitions cumulées (c'est-à-dire incluant ou excluant les pertes de vue [LTFU]). Nous avons analysé les études consacrées à la TB pharmacosensible (DS-) et multirésistante (MDR-) séparément. Notre revue a abouti à 111 études rapportant la consommation d'alcool comme facteur de prédiction du résultat du traitement de la DS-TB et de la MDR-TB. La consommation d'alcool a été associée à un risque accru de mauvais résultat du traitement (c'est-à-dire décès, échec du traitement et LTFU) parmi les études relatives à la DS-TB (OR 1,99 ; IC 95% 1,57–2,51) et à la MDR-TB (OR 2,00 ; IC 95% 1,73–2,32]. Cette association a persisté pour les mauvais résultats des traitements combinés excluant les LTFU, pour chaque mauvais résultat individuel et dans les sous-groupes et les analyses de sensibilité. Seulement 19% des études ont utilisé des définitions de bonne qualité de la consommation d'alcool. Celle-ci a significativement accru le risque de mauvais résultat du traitement à la fois pour la DS-TB et la MDR-TB. Cette étude met en lumière le besoin d'améliorer l'évaluation de la consommation d'alcool dans le cadre de la recherche en matière de résultats de traitement de TB et peut-être de modifier les directives de traitement destinées aux patients TB qui consomment de l'alcool.

RESUMEN

El consumo de alcohol se asocia con un mayor riesgo de aparición de la tuberculosis (TB); sin embargo, no se ha hecho una síntesis de la repercusión del consumo de alcohol en los desenlaces del tratamiento antituberculoso. En el presente estudio se realizó una revisión cuantitativa de la evidencia sobre la correlación entre el consumo de alcohol y los desenlaces desfavorables del tratamiento de la TB. La revisión sistemática incluyó las bases datos PubMed, EMBASE y Web of Science (de enero de 1980 a mayo del 2018). Los estudios se categorizaron en artículos con una definición de calidad alta o baja de consumo de alcohol y se examinaron los desenlaces terapéuticos desfavorables de manera individual o como dos definiciones agregadas (es decir, que incluían o excluían la pérdida durante el seguimiento). Se analizaron separadamente los estudios de TB normosensible (DS-TB) y TB multirresistente (MDR-TB). En la revisión sistemática se encontraron 111 estudios que comunicaban el consumo de alcohol como un factor pronóstico del desenlace terapéutico de la DS- y la MDR-TB. El consumo de alcohol se asoció con una mayor posibilidad de desenlaces desfavorables (es decir, muerte, fracaso y pérdida durante el seguimiento) en los estudios de DS-TB (OR 1,99; IC 95% 1,57–2,51) y de MDR-TB (OR 2,00; IC 95% 1,73–2,32). Esta asociación persistió cuando los desenlaces desfavorables agregados excluían la pérdida durante el seguimiento y en los análisis de sensibilidad de cada desenlace desfavorable y de todos los subgrupos. Solo 19% de los estudios aplicaban definiciones de gran calidad del consumo de alcohol. El consumo de alcohol aumentó de manera significativa el riesgo de desenlaces desfavorables tanto en los casos de DS-TB como de MDR-TB. Los resultados del presente estudio ponen de manifiesto la necesidad de mejorar la evaluación del consumo de alcohol en la investigación sobre los desenlaces de la TB y eventualmente modificar las directrices del tratamiento de los pacientes que consumen alcohol.