Alcohol consumption and the risk of Tuberculosis: A systematic review and Meta-analysis

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SUMMARY

OBJECTIVE: To perform a systematic review and meta-analysis of the association between alcohol consumption and tuberculosis risk.

METHODS: Medline, EMBASE and Web of Science were searched for observational studies from 2005 to April 2018. Reference lists of included studies were screened.

RESULTS: Forty nine studies were included. Compared to people with low or no alcohol intake, the risk of tuberculosis in people with high or any alcohol consumption was increased by a relative odds of 1.90 (95%CI: 1.63-2.23). Substantial levels of heterogeneity were seen ($I^2=82\%$), but there was no evidence of publication bias ($P=0.54$). Sensitivity analysis restricted to studies using no alcohol drinking as a reference group found a slightly lower but still increased risk (Odds Ratio= 1.59, 95%CI: 1.38-1.84). Subgroup analyses found no significant differences in relation to study design and quality, geographic location, publication year, and adjustment for confounders. A pooled analysis of a further four studies reporting hazard ratios, found nearly a tripling increase in risk of TB in relation to alcohol consumption during follow-up (HR=2.81, 95%CI: 2.12-3.74). An exposure-response analysis showed that for every 10-20 grams daily alcohol intake, there was 12% increase in TB risk.

CONCLUSION: Alcohol consumption is an important risk factor for the development of TB.

Keywords: alcohol; tuberculosis; meta-analysis

INTRODUCTION

51 Tuberculosis (TB) is a major global health problem with high morbidity and mortality. In
52 2015, TB was the 10th leading global cause of death, according to WHO, accounting for an
53 estimated annual 1.4 million deaths each year. The global incidence of tuberculosis is about
54 10.4 million new cases, of which 5.9, 3.5 and 1.0 million occur respectively among men,
55 women and children. This burden of disease falls particularly on low and middle income
56 countries ^{1, 2}

57 *Mycobacterium tuberculosis* is the causal agent of TB and known risk factors include HIV
58 infection, smoking, socio-economic deprivation, undernutrition, diabetes, indoor air
59 pollution and alcohol consumption ³⁻⁵.

60 Alcohol consumption is also a potential risk factor for TB, because alcohol can impair the
61 immune system ^{6, 7} and increase susceptibility to both primary infection and reactivation of
62 disease⁸; and is associated with a higher risk of malnutrition and liver disease both of which
63 impair immunity⁹. Alcohol consumption may further increase TB risk as a result of poor
64 uptake of medical services among heavy alcohol consumers ¹⁰. High alcohol consumption
65 may also be associated with TB either through causal pathways involving, or confounding by
66 homelessness, imprisonment and illicit drug use, all of which also increase the risk of
67 tuberculosis ^{11, 12}.

68 A systematic review published almost 10 years ago identified that alcohol is associated with
69 TB¹³, and was updated in a new systematic review and meta-analysis published in 2017¹⁴.

70 However both of these reviews limited their searches to two databases, and may thus have
71 missed important studies, while the most recent review¹⁴ included studies only up to June
72 2016, since when several relevant studies have been published. Another review assessed

the effects of alcohol on the risk of active TB, but used only self-reported symptoms of productive cough and haemoptysis to ascertain disease status¹⁵.

We have therefore performed a comprehensive systematic review and meta-analysis to provide a more valid estimate of the magnitude and exposure-response characteristics of the association between alcohol intake and tuberculosis risk.

METHODS

Our review uses the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)¹⁶ and Meta-analysis of Observational Studies in Epidemiology (MOOSE)¹⁷ methods. The protocol was published in PROSPERO under the registration number: CRD42015029910

The review included studies which met the following inclusion criteria: (1) comparative observational study designs (cohort/ longitudinal, case control, cross sectional); (2) adults aged 18+ years; (3) alcohol consumption reported as an exposure; (4) comparative/reference group of either no alcohol consumption or the lowest exposed category; and (5) tuberculosis reported as an outcome. Studies which provided only the abstract or reported as conference articles were also included. We excluded studies related to latent tuberculosis, multidrug resistant TB, TB prevention, treatment compliance and hospital acquired TB.

Search strategy

A search of Medline (Ovid), EMBASE (Ovid) and Web of Science was performed from January 2005 to April 2018. We also reviewed the reference lists of the included studies and previous systematic reviews to identify further potential eligible studies. Specific search

filters ¹⁸ (SIGN) for observational study designs were used and search terms for both alcohol and TB created using relevant Cochrane Review groups ¹⁹. No language restriction was imposed and where necessary papers were translated into English. The database search strategies are provided as Supplementary material. Two reviewers (ES, JL-B) independently screened the titles/ abstract in the first stage and the full text of the eligible ones in the second stage of the review process. Discrepancies were resolved with help of a third reviewer (JB). Where duplicate publications were found, the most comprehensive paper or the most recent paper was included.

Data extraction

Two reviewers (ES, JLB) independently extracted the data. Variables of interest included: author, year of study, study design, definitions and diagnostic criteria for exposure (alcohol) and outcome (TB), geographic location, reference population, demographic of study population setting, and adjustment for confounders.

Quality assessment

The Newcastle-Ottawa Quality Scale was used for the assessment of methodological quality of the included studies ²⁰. A study having a score of ≥ 6 or was deemed to be high quality. Two researchers (ES, JLB) independently assessed the quality of the studies. Discrepancies were resolved through discussion. Where the studies were only published in abstract form we didn't further conduct a quality assessment due to the required information not being adequate.

Statistical analysis

Results were expressed as odds ratio (OR), risk ratios (RR) or hazard ratios (HR) with 95% confidence intervals (95% CI). Where available, we used measures of risk adjusted for smoking and socioeconomic status, in preference to unadjusted estimates reported or derived from the raw data. Where we used raw data from the included studies, we estimated ORs for case control studies and RRs for longitudinal, cohort and cross sectional studies. We pooled ORs and RRs together to estimate pooled ORs in cases of a rare outcome; however HRs were pooled as a separate analysis.

We used a random effects (DerSimonian and Laird) meta-analysis, taking into account the heterogeneity/ variation of the included studies (τ^2), using the generic inverse variance method. We used the I^2 statistic for the quantification of heterogeneity²¹. Funnel plots were used to assess publication bias; and where data for at least 10 studies were available we used Egger's asymmetry tests to formally assess the evidence of publication bias.

When high levels of heterogeneity were identified ($I^2 > 50\%$), we carried out subgroup analyses to explore potential reasons for heterogeneity based on study design, study quality, year of publication, adjustment for confounders and geographic location. We also conducted sensitivity analyses to explore the robustness of our findings, through restricting our analysis to studies which reported the reference groups as those with no alcohol drinking, studies which assessed the effects of alcoholism or alcohol abuse, studies that recruited from HIV populations and studies that adjusted for smoking as a confounder.

A dose response analysis was performed using a random-effects dose response meta-regression model, assuming a linear dose response relation^{22, 23}. Studies included in the analysis were required to have at least three different exposure categories, and the midpoints of categories used to quantify exposure. Where the highest category was open-

ended; the midpoint value was estimated as the lower bound plus 1.2 times the lower boundary. Grams per day were used as a standard measure for our analysis. Dose categories relating to quantities of alcohol were created to equate to 10-20 grams of pure alcohol per day (approximately one drink per day). Where individual studies reported categories which contained the same dose ranges we collapsed these into a single dose category, estimating a pooled effect estimates based on a fixed effect meta- analysis model. All statistical analyses were performed using Stata (14.0) and Review Manager (5.3) software. A p-value <0.05 was used to represent a statistically significant level.

RESULTS

The electronic searches yielded a total of 1739 articles, and a further 14 were identified from reference list searches. After removal of 400 duplicates, 1353 articles were screened for title/ abstract eligibility and 121 found to justify full text screening.

Of these, 72 were excluded due to the ineligibility of the outcome or the exposure (n=12) or the exposure (n=2); or insufficient data on alcohol consumption (n=4); no comparison group for the outcome (n=52); or outcome information was incorporated with other diseases (n=2). Thus, 49 studies met our inclusion criteria and were included in the review.

Overview of the studies

The study characteristics of the included studies in this review are presented in Table 1. The studies included a total of 560.598 participants, and the mean ages of people with TB within the sixteen studies reported this was ranged from: 33.6-61.2 years.

Twenty eight studies were conducted in Asia; 10 in Africa; 7 in America and 4 in Europe.

Thirty three were case control studies; ten were cross sectional and six were cohort studies.

Forty four of the studies reported ORs or RRs ²⁴⁻⁶⁷ ; 4 reported HRs ⁶⁸⁻⁷¹ and one did not provide sufficient information ⁷². Thirty four studies provided adjusted effect estimates and thirteen of these had also adjusted for smoking ^{24, 28-30, 34, 36, 42, 44, 49, 52, 55, 64, 71}.

The majority of studies (45 studies) assessed alcohol use through self-report via a questionnaire or an interview. Of the rest, two studies assessed alcohol using the AUDIT (Alcohol Use Disorders Identification Test), one study used ICD codes ³³, and one used medical records ³⁴.

The reference group for 27 studies comprised people who never consumed alcohol, while in three studies the comparison was between consumption defined as abuse or non-abuse ^{33, 35, 53}, and five studies compared alcoholism to no alcoholism ^{32, 36, 47, 62, 69}. The reference group for the remaining fourteen studies comprised people who consumed the lowest quantity of alcohol.

For the diagnosis of TB, the majority of studies used bacteriological confirmation with sputum smear and/ or culture and chest x-ray characteristics. Others used ICD codes ^{33, 52, 70, 71}; medical records ⁴⁶; questionnaire ²⁷; record linkage ⁶⁷, clinic database data ³⁵; Revised National Tuberculosis Control Programme definition ⁴⁹. In three studies the method of TB ascertainment was not provided ^{30, 48, 63}.

The quality assessment scores indicated that 24 studies were of high quality. However, 23 studies found to have a low quality score, with the main reason for this was either the lack of adjustment for confounders; the information bias as a result of the lack of provided information description in outcome or exposure assessment; or due to a low response rate. No quality assessment was conducted for two studies for which only an abstract was

available. In total the quality assessment indicated a median score of 6 with a range of: 2-8 (Table 2).

Meta-analysis findings

Forty eight of the forty nine studies were included in the meta-analysis. One study could not be included in the meta-analysis, as data were reported in insufficient detail ⁷²; briefly in this study both the TB cases and controls were non- consumers of alcohol. Forty four of the 48 included studies provided data from which pooled odds ratios could be estimated. A meta-analysis of these studies showed a 90% increase in the odds of TB among people who consumed alcohol at all, or in higher amounts, than in those who consumed no, or lower amounts of alcohol respectively (pooled OR= 1.90, 95% CI 1.63 to 2.23, I²= 82%, Figure 2). No evidence of publication bias was detected either visually via a funnel plot or statistically via Egger's asymmetry test (P = 0.54).

Subgroup analyses exploring the possible reasons for the identified heterogeneity in the meta-analysis are presented (see Table 2 in the online data supplement). However, the high level of heterogeneity was not explained by study design (case control, longitudinal/cohort; p for subgroup differences=0.24), methodological quality (high versus low; p=0.31), adjustment for confounders (adjusted versus unadjusted; p=0.32), country of study (America, Asia, Europe, Australia; p=0.25) or year of publication (2005-2010 versus 2011 - 2017; p= 0.28).

Sensitivity analyses were conducted restricting the meta-analysis to studies with *a priori* defined criteria. Studies which reported the reference group as no drinking produced a pooled effect estimate lower than the unrestricted meta-analysis, with an OR of 1.59

(95%CI: 1.38-1.84, $I^2=63\%$, 25 studies)^{24-26, 28, 30, 34, 37, 39-42, 44, 45, 49-51, 55, 57, 60, 61, 63-67}. Analysis limited to studies categorizing alcohol intake as alcohol abuse/alcoholism found a similar magnitude of increased risk compared to the unrestricted meta-analysis (pooled OR=1.81, 95%CI: 1.28-2.57, $I^2=66\%$, 8 studies)^{32, 33, 35, 36, 47, 53, 59, 62}. Restricting the meta-analysis to TB patients with HIV co-infection showed similar results to the main meta-analysis (OR=2.02, 95%CI: 1.22-3.36, $I^2=55\%$, 6 studies)^{24, 29, 42, 46, 51, 60}. Also restricting the meta-analysis to studies reporting smoking adjusted estimates showed that alcohol consumption was also associated with increased risk for TB (pooled OR=1.73, 95%CI: 1.18-2.53, $I^2=91\%$, 12 studies)^{24, 28-30, 34, 36, 42, 44, 49, 52, 55, 64}.

Four of the 48 included studies presented effect estimates as hazard ratios⁶⁸⁻⁷¹. A separate pooled analysis of these studies found a higher hazard ratio of 2.81 for TB in relation to alcohol consumption (95% CI: 2.12-3.74, $I^2=9\%$, Figure 3).

Dose response effect

Three of the included studies provided data which enabled a dose-response effect meta-analysis^{42, 44, 52}. The pooled dose-response analysis identified a significant increase in TB risk in relation to quantity of alcohol consumed, by 12% for every additional 10-20 grams daily intake (pooled RR= 1.12, 95% CI 1.10 to 1.13; $p<0.0001$; Figure 6).

DISCUSSION

Summary of the findings

In this systematic review and meta-analysis we provide contemporary estimates of the effect of alcohol consumption on the risk of TB among adults. Our pooled analysis demonstrates a 90% higher odd of TB risk in relation to alcohol consumption, and that the

magnitude of this effect appears robust to differences in alcohol reference group definition and to be consistent in subgroup analyses. The effect is also exposure-related.

Strengths and limitations

Our study constitutes a comprehensive review using specific search strategy and with no language restriction. A large number of studies were identified and included in our meta-analysis. Also, our results are likely to be generalizable, as our review includes global evidence of many different countries. There was also no evidence of publication bias. However, we found a high level of between study heterogeneity. Almost all of the studies ascertained alcohol intake by self-report methods, raising the possibility of reporting bias, but the potential for misclassification arising from inclusion of non-drinkers in the lowest exposure category in some studies does not seem to have influenced our findings, since the estimated effect of alcohol was similar; if slightly lower, in those studies involving a zero-intake reference group. Residual confounding or recall bias arising from retrospective designs may also have influenced our results.

Comparison with other studies

A meta-analysis by Lönnroth et al ¹³, published ten years ago, showed that there is a three-fold increased risk only in people with an average daily alcohol consumption of more than 40 grams or have an alcohol use disorder. This estimate is higher than that arising from our dose response analysis, which indicated that a daily alcohol consumption of 40-50 grams would lead to a 48% increased risk for TB. A possible explanation for this difference is the inclusion of alcohol use disorder in the analysis of Lönnroth study¹³.

Recently a meta-analysis of alcohol effects on TB incidence published in 2017 by Imitiaz et al¹⁴, which was an update of the previous published systematic review of Lönnroth¹³ estimated a 35% increase in risk among those who consume alcohol relative to those who do not, and the risk was marginally greater (RR=1.50) when drinkers were also included in the reference category. They also performed a dose response analysis indicating an increasing risk of TB with increasing amounts of alcohol consumed, but when they performed categorical dose-response meta-analyses non-significant results were found for the ≤ 24 and >24 to ≤ 60 alcohol categories. In contrast to the previous systematic review by Imitiaz¹⁴, our more comprehensive searches and meta-analysis found that drinkers are 1.59 times more likely to have TB compared to non-drinkers. Similarly higher odds of TB (OR=1.90) were also found when in our analysis people who consumed low alcohol were included in the reference group. We further found that consuming drinks that contain 10-20 grams of alcohol everyday was linked to a 12% increased risk of TB, but we did not performed a categorical dose response meta-analysis as Imitiaz et al did¹⁴. However the Imitiaz study was restricted to searches of only two databases which, as acknowledged by the authors, will miss eligible studies, therefore making their findings misleading. This concern is borne out by our finding of 33 eligible studies that were missed from the Imitiaz et al review,¹⁴ making our estimates more likely to be valid.

Another meta-analysis in 14 high Tuberculosis burden countries assessed the effect of alcohol, diabetes, low body mass index on the risk of self-reported symptoms of active tuberculosis was conducted in 2014 by Patra et al¹⁵. They found that ever drinking was associated with a 26% increased risk of TB symptoms in men and with a 50% increased risk in women when adjusted for age and education. However adjustment for further

confounders showed a non-significant association. However Patra study¹⁵ relied on self-reported productive cough and haemoptysis to ascertain active TB, which while a pragmatic approach is likely to be less valid than the clinical diagnoses used in our meta-analysis.

Conclusions

In conclusion, our review confirms that alcohol drinking is associated with an increased risk of tuberculosis. Also, in the dose–response analysis, the increase in tuberculosis risk associated with every 10-20 grams linear increment in daily alcohol intake. Therefore our findings suggest that measures that reduce alcohol consumption are likely to lead to a reduced risk of TB in the general population.

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Table 1.Characteristics of included studies

Study& Year	Study design	Geographical location	Population	Characteristics of people with TB	Number of included subjects	Alcohol ascertainment	Alcohol definition	Tuberculosis ascertainment	Adjustment/ matching
Alemu, 2015 ²⁴	Case-control	Africa	HIV population	Male: 46% Mean age: -	446	Questionnaire interview	Alcohol consumption Yes vs no	Sputum microscopy, X-ray, histopathology, culture or molecular	Adjusted for: HAART, CPT, IPT, smoking, khat, TB family patient
Bhat, 2017 ⁶⁴	Case-control	India/Asia	District population	Male: 79% Mean age: -	1602	Questionnaire	Alcohol consumption Yes vs no	Sputum smear and culture examinations	Adjusted for: age, sex, occupation, BMI, family income, history of asthma, chewing tobacco, smoking tobacco, blood sugar
Bhana, 2017 ⁶³	Cross-sectional	Africa	Hospital population	Male: 24.8% Mean age:46.8	1332	AUDIT Questionnaire	Alcohol consumption Yes vs no	-	No adjustment/ matching performed
Boccia, 2011 ⁵³	Case-control	Africa	General population	Male:53.9% Mean age:36	370	Questionnaire/ interview	Alcohol abuse >3 drinks per occasion	Sputum sample culture positive	Adjusted for sex, age group, area of residence, household socioeconomic position
Bym, 2014 ⁵⁰	Case-control	Indonesia/Asia	General population	-	152	Self-report	Alcohol consumption yes vs no	Sputum positive test	Matched for: sex, age and ethnic
Chelleng 2014 ²⁵	Case-control	Asia	Occupational population	-	873	Questionnaire	Alcohol consumption yes vs no	sputum smear and culture positive	Adjusted for: age and sex, BMI, income, literacy
Chen, 2015 ²⁶	Case-control	China/Asia	General population	Male: 74.4% Mean age: -	1156	Self-report Questionnaire	Alcohol drinking (yes vs no)	Bacteriological results	Matched for: gender and age
Cois, 2013 ²⁷	Cross-sectional	South Africa/ Africa	Research database data	-	8115	CAGE Questionnaire	Problem drinking vs moderate/ abstainers	Questionnaire Has a doctor or nurse or health worker at	Matched for: gender and age

								a clinic or hospital told you that you have or have had TB	
Coker 2006 ⁵⁴	Case-control	Russia/ Europe	General population	-	668	Questionnaire	Heavy drinking at least once/month in past year	Culture positive	Adjusted for: age, sex, diabetes
Davis, 2016 ²⁸	Case-control	Kazakhstan/Asia	General population	Male:55% Mean age:35.4	1600	Questionnaire	Ever drank alcohol vs never alcohol	Culture methods	Adjusted for: age, sex, ethnicity, education level, incarceration, marital status, smoking, drug use, HIV, diabetes
de Lima, 2016 ⁵⁵	Case-control	Brazil/ South America	Outpatient population	Male:61.4% Mean age:36	622	Questionnaire	Alcohol yes (Women: >=120 ml & Men: >= 150 ml At the same time within the last 30 days) vs no	Sputum smear and culture positive	Adjusted for: sex, smoking
Fox, 2015 ²⁹	Case-control	Canada/North America	HIV population	-	65	Self-report Questionnaire/ Interview	Recent alcohol use	Culture positive	Adjusted for: age stratum, sex, living with a person with smear-positive tuberculosis, visiting a gathering house, room occupancy, and low vegetable intake, smoking, cannabis use
Gajalakshmi, 2009 ³⁰	Case-control	India/Asia	Rural general population	-	2912	Interview	Ever vs never drinkers	-	Adjusted for: age, education, smoking
Gambhir, 2010 ⁵⁶	Case-control	Asia	Hospital population	Male:78.9% Mean age: 43.2	287	Questionnaire	Regular alcohol use >= 200 ml of 40%–60% alcohol for four days or more in a week for the last five years or more.	Sputum smear positive	Matched for: age and sex
Gninafon, 2010 ³¹	Case-control	Africa	General population	Male: 69.5% Mean age: 35.2	600	Questionnaire	Daily alcohol use yes vs no	Smear positive	Matched: age and sex
Gyawali, 2012 ³²	Cross-sectional	Asia	General population	Male:40.9% Mean age: -	986	Self-report Questionnaire	Alcoholic (yes vs no)	Sputum smear	No adjustment/ matching performed
Hill 2006 ⁵⁷	Case-control	Africa	Outpatient population	Male: 65% Mean age: 33.6	300	Questionnaire	current/past vs never consumers	Sputum smear and culture positive	Matched for: age and sex

Hochberg, 2017 ⁶⁵	Case control	India/Asia	General population	Male: 75.1% Mean age: 45	409	AUDIT questionnaire	Alcohol consumption Yes vs no	Smear positive	No adjustment/ matching performed
Hong, 2017 ⁶⁶	Case-control	Korea/ Asia	Two research databases data	Mean age: 61.2 Mean age: 58.1	2459	Self-report Questionnaire	Current vs non-drinkers	sputum smear and culture positive	No adjustment/ matching performed
Hsu, 2014 ³³	Case-control	Taiwan/Asia	Research database data	Male:65.4% Mean age:57.7	71951	ICD 9 codes	Alcohol abuse	ICD 9 codes	Matched for: age, sex, year/month of index visit
Inghammar, 2011 ⁶⁸	Cohort	Sweden/Europe	General population	-	28.907	Questionnaire	Problematic drinking yes vs no	Confirmed bacteriology or diagnosed by a clinician	No adjustment/ matching performed
Jung, 2015 ³⁴	Cohort	Asia	Gastric cancer population	Male: 87.5% Mean age: -	1776	Medical records	Alcohol history yes vs no	Culture	Adjusted for: sex, age, BMI, smoking, previous TB infection, surgery gastrectomy
Kan, 2011 ⁵⁹	Case-control	Asia	Outpatient population	Male:72.8% Median age:63	624	Questionnaire	Daily alcohol use Frequency & amount of alcoholic beverages	Sputum smear positive	Matched for: age, sex
Kibret, 2013 ⁶⁰	Case-control	Africa	HIV population	Male:56.6% Mean age:36.7	613	Questionnaire/ interview	alcohol drinking yes vs no	Sputum smear positive	No adjustment/ matching performed
Kim, 2005 ³⁵	Case-control	USA /North America	Clinic database data	Male: - Mean age: 37.7	919	Questionnaire	Alcohol abuser	TB database clinic data	Adjusted for: ethnicity, married, homeless, drug user, HIV positive, type of crime, length of stay in jail
Kolappan, 2007 ³⁶	Cross-sectional	India/Asia	General population	-	93.945	Self-report Questionnaire	Alcoholism vs non-alcoholism	Sputum smear/ culture examination	Adjusted for: age, sex, smoking
Kolappan, 2009 ³⁷	Case-control	India/Asia	Rural and urban units	Male:87% Mean age: -	1530	Self-report Questionnaire/ interview	Alcohol user vs non drinkers Ever had consumed alcoholic liquor before interview	Sputum smear or culture examination	Adjusted for: age and sex, biomass fuel
Ladefoged, 2011 ³⁸	Case-control	Greenland/ North America	Hospital population	Male: 58% Median age:37	730	Questionnaire	Alcohol often(at least once/week)	X ray/positive histology/culture positive	Adjusted for: age, sex, ethnicity, town, immunosuppressive treatment, occupation

							vs seldom (less than once a week)		
Lakshmi, 2010 ⁷²	Case-control	Asia	General population	-	378	Questionnaire	Alcohol intake yes vs no	Sputum smear positive	Matched for: age and residence area
Lienhardt, 2005 ³⁹	Case-control	West Africa/ Africa	General population	Male: 69% Mean age: -	2325 controls	Questionnaire	Alcohol intake Current/past vs never	Smear positive	Matched for: age
Lin, 2015 ⁴⁰	Cross-sectional	Taiwan/Asia	Hospital and public health centre population	-	2.979	Self-report Questionnaire	Alcohol consumption (yes vs no)	Sputum culture	No adjustment/ matching performed
Marak, 2015 ⁴¹	Cross-sectional	India/Asia	Outpatient patients	Male:63.6% Mean age: -	210	Self-report Questionnaire	Current alcohol consumer >=1 drinks in the year preceding the survey vs never	Confirmed bacteriology or diagnosed by a clinician	No adjustment/ matching performed
Mendoza, 2010 ⁶⁹	Cohort	Canada/North America	Clinic database data	Male:57% Mean age: -	33.146	Questionnaire	Alcoholism yes vs no	Sputum smear and culture positive	Adjusted for: immunosuppressive condition, age, LBTI treatment, Closeness of contact, drug use, ethnicity, socioeconomic status, sex, country with high tuberculosis prevalence
Murrison, 2016 ⁴²	Case-control	Africa	HIV hospital and outpatient populations	Male: - Median age: 38	279	Questionnaire	Drinks/week >=15 drinks vs 0 drinks	Sputum smear microscopy or sputum culture	Adjusted for: smoking, age, education, employment status, household income, CD4, History of previous TB, Duration of HIV
Nielsen, 2010 ⁴³	Case-control	Greenland/ North America	Hospital population	-	754	Questionnaire	Frequent (every day or 1-6 times/week) vs (non- frequent <1/ week)	Culture/x-ray	Matched for: sex, age and district, 25(OH)D and ethnicity
Pednekar, 2012 ⁷¹	Cohort	India/Asia	General population	-	35.102	Questionnaire	Drinkers vs never drinkers	ICD codes	Adjusted for age, education, and tobacco use.
Pokhrel 2010 ⁶¹	Case-control	Asia	Hospital population	Male: - Mean age: 35	375	Questionnaire	Alcohol consumption yes vs no	Chest x ray and positive active sputum smear	Matched for: age

Prasad, 2009 ⁶²	Case-control	Asia	Hospital population		444	Questionnaire/ interview	Alcoholism yes vs no	Sputum smear positive +interview	Matched for: age, sex
Rao, 2011 ⁴⁵	Cross-sectional	India/Asia	General population	-	9.538	Questionnaire	Alcohol consumption (yes vs no)	Sputum samples smear microscopy and solid media culture methods	No adjustment/ matching performed
Rao, 2014 ⁴⁴	Cross-sectional	India/Asia	General population	-	95.071	Questionnaire	Alcohol/day Heavy alcohol (>500 ml/day for >20 years) Vs Non-alcohol consumers	Sputum smear specimen	Adjusted for: sex, age, smoking, social class
Rodriguez, 2015 ⁴⁶	Cross-sectional	Africa	HIV population	Male:33% Mean age:38.2	300	Questionnaire/ Interview	Heavy/moderate drinker vs light/non-drinker	Medical records	Adjusted for: age, marital status, outdoor environment
Sacchi, 2012 ⁴⁷	Case-control	Brazil/ South America	Indigenous general population	Male:57.1% Mean age: -	189	Questionnaire/ interview	Alcoholism yes vs no	X-ray, thorax CT (computed tomography) and/or positive sputum smear or culture.	Matched for: age, geographic location
Savicevic, 2013 ⁵⁸	Case-control	Europe	General population	-	600	Questionnaire	Current vs never consumer Daily alcohol last 12 months Vs Less than once a week, last 12 months	Culture positive pulmonary TB	Matched for: age, sex, country of residence
Schluger, 2013 ⁴⁸	Case-control	Asia	General population	Male:50% Mean age: -	173	Self-report Questionnaire	Regular alcohol users	-	No adjustment/ matching performed
Shetty, 2006 ⁴⁹	Case-control	India/Asia	Outpatient population	-	378	Questionnaire	Alcohol use Current (at least 6 months)	Revised National Tuberculosis Control Programme	Adjusted for: age, sex, marital status, religion, household income, persons per room,

							vs never	(RNTCP) case definition	cooking fuel, smoking
Soh, 2017 ⁶⁷	Cohort	Asia	Research database data	Male:73.5% Mean age:59.1	57471	Questionnaire	Alcohol consumption Yes vs no	Record linkage	No adjustment/ matching performed
Verma, 2012 ⁵¹	Cross-sectional	Asia	HIV population	-	184	Self-report Questionnaire/ interview	Alcohol habit yes vs no	Culture /smear	No adjustment/ matching performed
Yen, 2017 ⁷⁰	Cohort	Asia	General population	Male:41.9% Mean age:43.2	46.196	Self-report Questionnaire interview	Heavy alcohol consumption: intoxication at least once/week vs never drinking	ICD 9 codes	Adjusted for: age, sex, marital status, educational level
Zaridze, 2009 ⁵²	Case-control	Russia/Europe	General population	-	48.557	Questionnaire	Weekly intake (>=3 bottles of vodka vs <0.5 bottles of vodka)	ICD codes	Adjusted for: age, city, and smoking

Table 2. Critical appraisal of included studies using Newcastle Ottawa Scale

Study, year	Stars number		
	Selection†	Comparability‡	Exposure§
Alemu, 2015 ²⁴	3	2	2
Bhat, 2017 ⁶⁴	3	2	2
Bhana, 2017 ⁶³	0	0	2
Boccia, 2011 ⁵³	4	1	1
Bym, 2014* ⁵⁰	-	-	-
Chelleng 2014 ²⁵	3	1	1
Chen, 2015 ²⁶	3	1	1
Cois, 2013 ²⁷	1	1	3
Coker 2006 ⁵⁴	4	1	1
Davis, 2016 ²⁸	4	2	2
de Lima, 2016 ⁵⁵	3	2	1
Fox, 2015 ²⁹	3	2	1
Gajalakshmi, 2009 ³⁰	3	2	2
Gambhir, 2010 ⁵⁶	3	1	2
Gninafon, 2010 ³¹	4	2	1
Gyawali, 2012 ³²	2	0	1
Hill 2006 ⁵⁷	3	1	2
Hochberg, 2017 ⁶⁵	2	0	3
Hong, 2017 ⁶⁶	4	0	1
Hsu, 2014 ³³	3	0	1
Inghammar 2011 ⁶⁸	2	0	2
Jung, 2015 ³⁴	2	2	2
Kan, 2011 ⁵⁹	4	1	1
Kibret KT, 2013 ⁶⁰	3	0	2
Kim, 2005 ³⁵	3	2	1
Kolappan, 2007 ³⁶	2	2	1
Kolappan, 2009 ³⁷	4	1	2
Ladefoged, 2011 ³⁸	3	1	3
Lakshmi, 2010 ⁷²	2	1	2
Lienhardt, 2005 ³⁹	4	0	1
Lin, 2015 ⁴⁰	1	0	1
Marak, 2015 ⁴¹	1	0	2
Mendoza, 2010 ⁶⁹	2	1	3
Murrison, 2016 ⁴²	2	2	1
Nielsen, 2010 ⁴³	3	1	1
Pednekar, 2012 ⁷¹	2	2	3
Pokhrel 2010 ⁶¹	2	1	2
Prasad, 2009 ⁶²	3	1	1
Rao, 2010 ⁴⁵	1	0	1
Rao, 2014 ⁴⁴	2	2	2
Rodriguez, 2015 ⁴⁶	2	1	1
Sacchi, 2012 ⁴⁷	3	1	2
Savicevic, 2013 ⁵⁸	4	1	2
Schluger, 2013* ⁴⁸	-	-	-
Shetty, 2006 ⁴⁹	2	2	1
Soh, 2017 ⁶⁷	3	0	3
Verma, 2012 ⁵¹	2	0	1
Yen, 2017 ⁷⁰	2	2	3
Zaridze, 2009 ⁵²	4	2	2

*Abstract only available-not quality assessment

† Maximum 4 stars

‡ Maximum 2 stars

§ Maximum 3 stars

Figure 1. PRISMA Flow Diagram

Figure 2. Forest plot of the association between any alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of TB

Figure 3. Forest plot of the association between any alcohol versus no alcohol consumption and the risk of TB

Figure 4. Forest plot of the association between alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of TB (data presented as hazard ratios)

Figure 5. Linear dose response meta-analysis for the association between categories of alcohol intake(grams/day) and the risk of TB

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