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

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14   ES, JB and JLB have no competing interest

15   **Author contributions**: ES, JB and JL-B designed the study and wrote the protocol. ES wrote

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17   manuscript. ES and JLB undertook study screening, data extraction, and quality assessment.

18   ES undertook all data analysis, supervised by JL-B. All authors contributed to the

19   interpretation of the findings. JB and JLB provided critical revisions to the article, and all

20   authors approved the final version of the article to be published. ES acts as guarantor of the

21   manuscript.

30   **Running head:** Alcohol and tuberculosis risk

31   **SUMMARY**

32   **OBJECTIVE:** To perform a systematic review and meta-analysis of the association between

33   alcohol consumption and tuberculosis risk.

34   **METHODS:** Medline, EMBASE and Web of Science were searched for observational studies

35   from 2005 to April 2018. Reference lists of included studies were screened.

36   **RESULTS:** Forty nine studies were included. Compared to people with low or no alcohol

37   intake, the risk of tuberculosis in people with high or any alcohol consumption was

38   increased by a relative odds of 1.90 (95%CI: 1.63-2.23). Substantial levels of heterogeneity

39   were seen (I^2=82%), but there was no evidence of publication bias (P=0.54). Sensitivity

40   analysis restricted to studies using no alcohol drinking as a reference group found a slightly

41   lower but still increased risk (Odds Ratio= 1.59, 95%CI: 1.38-1.84). Subgroup analyses found

42   no significant differences in relation to study design and quality, geographic location,

43   publication year, and adjustment for confounders. A pooled analysis of a further four

44   studies reporting hazard ratios, found nearly a tripling increase in risk of TB in relation to

45   alcohol consumption during follow-up (HR=2.81, 95%CI: 2.12-3.74). An exposure-response

46   analysis showed that for every 10-20 grams daily alcohol intake, there was 12% increase in

47   TB risk.

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

49   **Keywords:** alcohol; tuberculosis; meta-analysis

50   **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   disease[8]; and is associated with a higher risk of malnutrition and liver disease both of which

63   impair immunity[9]. 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   TB[13], and was updated in a new systematic review and meta-analysis published in 2017[14].

70   However both of these reviews limited their searches to two databases, and may thus have

71   missed important studies, while the most recent review[14] included studies only up to June

72   2016, since when several relevant studies have been published. Another review assessed

73   the effects of alcohol on the risk of active TB, but used only self-reported symptoms of

74   productive cough and haemoptysis to ascertain disease status[15].

75   We have therefore performed a comprehensive systematic review and meta-analysis to

76   provide a more valid estimate of the magnitude and exposure-response characteristics of

77   the association between alcohol intake and tuberculosis risk.

78   **METHODS**

79   Our review uses the Preferred Reporting Items for Systematic Reviews and Meta-Analysis

80   (PRISMA) [16] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [17]

81   methods. The protocol was published in PROSPERO under the registration number:

82   CRD42015029910

83   The review included studies which met the following inclusion criteria: (1) comparative

84   observational study designs (cohort/ longitudinal, case control, cross sectional); (2) adults

85   aged 18+ years; (3) alcohol consumption reported as an exposure; (4)

86   comparative/reference group of either no alcohol consumption or the lowest exposed

87   category; and (5) tuberculosis reported as an outcome. Studies which provided only the

88   abstract or reported as conference articles were also included. We excluded studies related

89   to latent tuberculosis, multidrug resistant TB, TB prevention, treatment compliance and

90   hospital acquired TB.

91   **Search strategy**

92   A search of Medline (Ovid), EMBASE (Ovid) and Web of Science was performed from

93   January 2005 to April 2018. We also reviewed the reference lists of the included studies and

94   previous systematic reviews to identify further potential eligible studies. Specific search

95   filters [18] (SIGN) for observational study designs were used and search terms for both alcohol

96   and TB created using relevant Cochrane Review groups [19]. No language restriction was

97   imposed and where necessary papers were translated into English. The database search

98   strategies are provided as Supplementary material. Two reviewers (ES, JL-B) independently

99   screened the titles/ abstract in the first stage and the full text of the eligible ones in the

100   second stage of the review process. Discrepancies were resolved with help of a third

101   reviewer (JB). Where duplicate publications were found, the most comprehensive paper or

102   the most recent paper was included.

103   **Data extraction**

104   Two reviewers (ES, JLB) independently extracted the data. Variables of interest included:

105   author, year of study, study design, definitions and diagnostic criteria for exposure (alcohol)

106   and outcome (TB), geographic location, reference population, demographic of study

107   population setting, and adjustment for confounders.

108   **Quality assessment**

109   The Newcastle-Ottawa Quality Scale was used for the assessment of methodological quality

110   of the included studies [20]. A study having a score of >= 6 or was deemed to be high quality.

111   Two researchers (ES, JLB) independently assessed the quality of the studies. Discrepancies

112   were resolved through discussion. Where the studies were only published in abstract form

113   we didn't further conduct a quality assessment due to the required information not being

114   adequate.

115   **Statistical analysis**

116   Results were expressed as odds ratio (OR), risk ratios (RR) or hazard ratios (HR) with 95%

117   confidence intervals (95% CI). Where available, we used measures of risk adjusted for

118   smoking and socioeconomic status, in preference to unadjusted estimates reported or

119   derived from the raw data. Where we used raw data from the included studies, we

120   estimated ORs for case control studies and RRs for longitudinal, cohort and cross sectional

121   studies. We pooled ORs and RRs together to estimate pooled ORs in cases of a rare

122   outcome; however HRs were pooled as a separate analysis.

123   We used a random effects (DerSimonian and Laird) meta-analysis, taking into account the

124   heterogeneity/ variation of the included studies (τ^2), using the generic inverse variance

125   method. We used the I^2 statistic for the quantification of heterogeneity[21]. Funnel plots were

126   used to assess publication bias; and where data for at least 10 studies were available we

127   used Egger's asymmetry tests to formally assess the evidence of publication bias.

128   When high levels of heterogeneity were identified (I^2>50%), we carried out subgroup

129   analyses to explore potential reasons for heterogeneity based on study design, study

130   quality, year of publication, adjustment for confounders and geographic location. We also

131   conducted sensitivity analyses to explore the robustness of our findings, through restricting

132   our analysis to studies which reported the reference groups as those with no alcohol

133   drinking, studies which assessed the effects of alcoholism or alcohol abuse, studies that

134   recruited from HIV populations and studies that adjusted for smoking as a confounder.

135   A dose response analysis was performed using a random- effects dose response meta-

136   regression model, assuming a linear dose response relation [22, 23]. Studies included in the

137   analysis were required to have at least three different exposure categories, and the

138   midpoints of categories used to quantify exposure. Where the highest category was open-

139 ended; the midpoint value was estimated as the lower bound plus 1.2 times the lower

140 boundary. Grams per day were used as a standard measure for our analysis. Dose categories

141 relating to quantities of alcohol were created to equate to 10-20 grams of pure alcohol per

142 day (approximately one drink per day). Where individual studies reported categories which

143 contained the same dose ranges we collapsed these into a single dose category, estimating

144 a pooled effect estimates based on a fixed effect meta- analysis model. All statistical

145 analyses were performed using Stata (14.0) and Review Manager (5.3) software. A p-value

146 <0.05 was used to represent a statistically significant level.

147 **RESULTS**

148 The electronic searches yielded a total of 1739 articles, and a further 14 were identified

149 from reference list searches. After removal of 400 duplicates, 1353 articles were screened

150 for title/ abstract eligibility and 121 found to justify full text screening.

151 Of these, 72 were excluded due to the ineligibility of the outcome or the exposure (n=12) or

152 the exposure (n=2); or insufficient data on alcohol consumption (n=4); no comparison group

153 for the outcome (n=52); or outcome information was incorporated with other diseases

154 (n=2). Thus, 49 studies met our inclusion criteria and were included in the review.

155 **Overview of the studies**

156 The study characteristics of the included studies in this review are presented in Table 1. The

157 studies included a total of 560.598 participants, and the mean ages of people with TB within

158 the sixteen studies reported this was ranged from: 33.6-61.2 years**.**

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

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

161 Forty four of the studies reported ORs or RRs [24-67] ; 4 reported HRs [68-71] and one did not

162 provide sufficient information [72].Thirty four studies provided adjusted effect estimates and

163 thirteen of these had also adjusted for smoking [24, 28-30, 34, 36, 42, 44, 49, 52, 55, 64, 71].

164 The majority of studies (45 studies) assessed alcohol use through self-report via a

165 questionnaire or an interview. Of the rest, two studies assessed alcohol using the AUDIT

166 (Alcohol Use Disorders Identification Test), one study used ICD codes [33], and one used

167 medical records [34].

168 The reference group for 27studies comprised people who never consumed alcohol, while in

169 three studies the comparison was between consumption defined as abuse or non-abuse [33,

170 [35, 53], and five studies compared alcoholism to no alcoholism [32, 36, 47, 62, 69]. The reference

171 group for the remaining fourteen studies comprised people who consumed the lowest

172 quantity of alcohol.

173 For the diagnosis of TB, the majority of studies used bacteriological confirmation with

174 sputum smear and/ or culture and chest x-ray characteristics. Others used ICD codes [33, 52, 70,

175 [71]; medical records [46]; questionnaire [27]; record linkage[67], clinic database data [35]; Revised

176 National Tuberculosis Control Programme definition [49]. In three studies the method of TB

177 ascertainment was not provided [30, 48, 63].

178 The quality assessment scores indicated that 24 studies were of high quality. However, 23

179 studies found to have a low quality score, with the main reason for this was either the lack

180 of adjustment for confounders; the information bias as a result of the lack of provided

181 information description in outcome or exposure assessment; or due to a low response rate.

182 No quality assessment was conducted for two studies for which only an abstract was

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

184 (Table 2).

185 **Meta-analysis findings**

186 Forty eight of the forty nine studies were included in the meta-analysis. One study could not

187 be included in the meta-analysis, as data were reported in insufficient detail [72]; briefly in this

188 study both the TB cases and controls were non- consumers of alcohol. Forty four of the 48

189 included studies provided data from which pooled odds ratios could be estimated. A meta-

190 analysis of these studies showed a 90% increase in the odds of TB among people who

191 consumed alcohol at all, or in higher amounts, than in those who consumed no, or lower

192 amounts of alcohol respectively (pooled OR= 1.90, 95% CI 1.63 to 2.23, I^2= 82%, Figure 2).

193 No evidence of publication bias was detected either visually via a funnel plot or statistically

194 via Egger's asymmetry test (P = 0.54).

195 Subgroup analyses exploring the possible reasons for the identified heterogeneity in the

196 meta-analysis are presented (see Table 2 in the online data supplement). However, the high

197 level of heterogeneity was not explained by study design (case control, longitudinal/cohort;

198 p for subgroup differences=0.24), methodological quality (high versus low; p=0.31),

199 adjustment for confounders (adjusted versus unadjusted; p=0.32), country of study

200 (America, Asia, Europe, Australia; p=0.25) or year of publication (2005-2010 versus 2011 -

201 2017; p= 0.28).

202 Sensitivity analyses were conducted restricting the meta-analysis to studies with *a priori*

203 defined criteria. Studies which reported the reference group as no drinking produced a

204 pooled effect estimate lower than the unrestricted meta-analysis, with an OR of 1.59

205 (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

206 limited to studies categorizing alcohol intake as alcohol abuse/alcoholism found a similar

207 magnitude of increased risk compared to the unrestricted meta-analysis (pooled OR=1.81,

208 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

209 patients with HIV co-infection showed similar results to the main meta-analysis (OR=2.02,

210 95%CI: 1.22-3.36, I^2= 55%, 6 studies) [24, 29, 42, 46, 51, 60]. Also restricting the meta-analysis to

211 studies reporting smoking adjusted estimates showed that alcohol consumption was also

212 associated with increased risk for TB (pooled OR=1.73, 95%CI: 1.18-2.53, I^2= 91%, 12 studies)

213 [24, 28-30, 34, 36, 42, 44, 49, 52, 55, 64].

214 Four of the 48 included studies presented effect estimates as hazard ratios [68-71]. A separate

215 pooled analysis of these studies found a higher hazard ratio of 2.81 for TB in relation to

216 alcohol consumption (95% CI: 2.12-3.74, I^2= 9%, Figure 3).

217 **Dose response effect**

218 Three of the included studies provided data which enabled a dose-response effect meta-

219 analysis [42, 44, 52]. The pooled dose-response analysis identified a significant increase in TB risk

220 in relation to quantity of alcohol consumed, by 12% for every additional 10-20 grams daily

221 intake (pooled RR= 1.12, 95% CI 1.10 to 1.13; p<0.0001; Figure 6).

222 **DISCUSSION**

223 **Summary of the findings**

224 In this systematic review and meta-analysis we provide contemporary estimates of the

225 effect of alcohol consumption on the risk of TB among adults. Our pooled analysis

226 demonstrates a 90% higher odd of TB risk in relation to alcohol consumption, and that the

227   magnitude of this effect appears robust to differences in alcohol reference group definition

228   and to be consistent in subgroup analyses. The effect is also exposure-related.

Strengths and limitations

230   Our study constitutes a comprehensive review using specific search strategy and with no

231   language restriction. A large number of studies were identified and included in our meta-

232   analysis. Also, our results are likely to be generalizable, as our review includes global

233   evidence of many different countries. There was also no evidence of publication bias.

234   However, we found a high level of between study heterogeneity. Almost all of the studies

235   ascertained alcohol intake by self-report methods, raising the possibility of reporting bias,

236   but the potential for misclassification arising from inclusion of non-drinkers in the lowest

237   exposure category in some studies does not seem to have influenced our findings, since the

238   estimated effect of alcohol was similar; if slightly lower, in those studies involving a zero-

239   intake reference group. Residual confounding or recall bias arising from retrospective

240   designs may also have influenced our results.

Comparison with other studies

242   A meta-analysis by Lönnroth et al [13], published ten years ago, showed that there is a three-

243   fold increased risk only in people with an average daily alcohol consumption of more than

244   40 grams or have an alcohol use disorder. This estimate is higher than that arising from our

245   dose response analysis, which indicated that a daily alcohol consumption of 40-50 grams

246   would lead to a 48% increased risk for TB. A possible explanation for this difference is the

247   inclusion of alcohol use disorder in the analysis of Lönnroth study[13].

248   Recently a meta-analysis of alcohol effects on TB incidence published in 2017 by Imitiaz et al

249   [14], which was an update of the previous published systematic review of Lönnroth[13]estimated

250   a 35% increase in risk among those who consume alcohol relative to those who do not, and

251   the risk was marginally greater (RR=1.50) when drinkers were also included in the reference

252   category. They also performed a dose response analysis indicating an increasing risk of TB

253   with increasing amounts of alcohol consumed, but when they performed categorical dose-

254   response meta-analyses non-significant results were found for the ≤ 24 and >24 to ≤ 60

255   alcohol categories. In contrast to the previous systematic review by Imitiaz[14], our more

256   comprehensive searches and meta-analysis found that drinkers are 1.59 times more likely to

257   have TB compared to non-drinkers. Similarly higher odds of TB (OR=1.90) were also found

258   when in our analysis people who consumed low alcohol were included in the reference

259   group. We further found that consuming drinks that contain 10-20 grams of alcohol

260   everyday was linked to a 12% increased risk of TB, but we did not performed a categorical

261   dose response meta-analysis as Imitiaz et al did[14]. However the Imitiaz study was restricted

262   to searches of only two databases which, as acknowledged by the authors, will miss eligible

263   studies, therefore making their findings misleading. This concern is borne out by our finding

264   of 33 eligible studies that were missed from the Imitiaz et al review, [14] making our

265   estimates more likely to be valid.

266   Another meta-analysis in 14 high Tuberculosis burden countries assessed the effect of

267   alcohol, diabetes, low body mass index on the risk of self-reported symptoms of active

268   tuberculosis was conducted in 2014 by Patra et al [15]. They found that ever drinking was

269   associated with a 26% increased risk of TB symptoms in men and with a 50% increased risk

270   in women when adjusted for age and education. However adjustment for further

271 confounders showed a non-significant association. However Patra study[15] relied on self-

272 reported productive cough and haemoptysis to ascertain active TB, which while a pragmatic

273 approach is likely to be less valid than the clinical diagnoses used in our meta-analysis.

Conclusions

275 In conclusion, our review confirms that alcohol drinking is associated with an increased risk

276 of tuberculosis. Also, in the dose–response analysis, the increase in tuberculosis risk

277 associated with every 10-20 grams linear increment in daily alcohol intake. Therefore our

278 findings suggest that measures that reduce alcohol consumption are likely to lead to a

279 reduced risk of TB in the general population.

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461

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,

								(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

Identification

Screening

Eligibility

Included

Records identified through database searching (n = 1739)	Additional records identified through other sources (n =14)

Records after duplicates removed (n =1353)

Records screened (n = 1353)	Records excluded (n =1232)

Full-text articles assessed for eligibility (n = 121)	Full-text articles excluded, with reasons (n = 72) • no comparison group for outcome, n=52 • outcome/ not eligible, n=12 • exposure/ not eligible, n=2 • no information for alcohol, n=4 • incorporated outcome with other disease, n=2

Studies included in qualitative synthesis (n =49)

Studies included in quantitative synthesis (meta-analysis) (n = 48)

Figure 1.PRISMA Flow Diagram

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Alemu, 2015	0.9123	0.3349	2.1%	2.49 [1.29, 4.80]	
Bhana 2017	0.174	0.1147	3.1%	1.19 [0.95, 1.49]	
Bhat 2017	-0.1625	0.1844	2.8%	0.85 [0.59, 1.22]	
Boccia, 2011	0.47	0.3375	2.1%	1.60 [0.83, 3.10]	
Bym, 2014	-0.3857	1.18	0.4%	0.68 [0.07, 6.87]	
Chelleng 2014	0.392	0.2315	2.6%	1.48 [0.94, 2.33]	
Chen, 2015	0.1596	0.1613	2.9%	1.17 [0.86, 1.61]	
Cois, 2013	0.8109	0.1797	2.9%	2.25 [1.58, 3.20]	
Coker 2006	0.8879	0.3526	2.0%	2.43 [1.22, 4.85]	
Davis, 2017	0.3436	0.1602	3.0%	1.41 [1.03, 1.93]	
de Lima 2016	1.4633	0.4628	1.6%	4.32 [1.74, 10.70]	
Fox, 2015	-0.3567	0.6695	1.0%	0.70 [0.19, 2.60]	
Gajalakshmi1, 2009	0.4055	0.1206	3.1%	1.50 [1.18, 1.90]	
Gajalakshmi2, 2009	0.1823	0.2855	2.3%	1.20 [0.69, 2.10]	
Gambhir,2013	0.4574	0.2715	2.4%	1.58 [0.93, 2.69]	
Gninafon, 2010	0.5306	0.4237	1.7%	1.70 [0.74, 3.90]	
Gyawali, 2012	2.1078	0.5665	1.2%	8.23 [2.71, 24.98]	
Hill 2006	0.7178	0.4866	1.5%	2.05 [0.79, 5.32]	
Hochberg men 2017	2.0541	0.3404	2.1%	7.80 [4.00, 15.20]	
Hochberg women 2017	1.0647	1.5023	0.3%	2.90 [0.15, 55.10]	
Hong 2017	0.3436	0.0952	3.2%	1.41 [1.17, 1.70]	
Hsu, 2014	1.3913	0.3193	2.2%	4.02 [2.15, 7.52]	
Jung, 2016	0.1989	0.4147	1.8%	1.22 [0.54, 2.75]	
Kan, 2011	-0.1054	0.3154	2.2%	0.90 [0.49, 1.67]	
Kibret, 2013	0.8713	0.1975	2.8%	2.39 [1.62, 3.52]	
Kim, 2005	0.4637	0.18	2.9%	1.59 [1.12, 2.26]	
Kolappan 2007	0.4055	0.1468	3.0%	1.50 [1.12, 2.00]	
Kolappan, 2009	0.2624	0.166	2.9%	1.30 [0.94, 1.80]	
Ladefoged, 2011	1.1184	0.5349	1.3%	3.06 [1.07, 8.73]	
Lienhardt, 2005	0.6098	0.188	2.8%	1.84 [1.27, 2.66]	
Lin, 2015	0.7309	0.6687	1.0%	2.08 [0.56, 7.70]	
Marak, 2015	0.3542	0.1425	3.0%	1.43 [1.08, 1.88]	
Murrison, 2016	-0.9163	0.7073	0.9%	0.40 [0.10, 1.60]	
Nielsen, 2010	1.361	0.5382	1.3%	3.90 [1.36, 11.20]	
Pokhrel 2006	1.3002	0.4008	1.8%	3.67 [1.67, 8.05]	
Prasad, 2009	0.5306	0.3384	2.1%	1.70 [0.88, 3.30]	
Rao, 2011	0.5306	0.2168	2.7%	1.70 [1.11, 2.60]	
Rao, 2014	0.131	0.6075	1.1%	1.14 [0.35, 3.75]	
Rodriguez, 2015	1.2413	0.4075	1.8%	3.46 [1.56, 7.69]	
Sacchi, 2013	0.0953	0.5905	1.2%	1.10 [0.35, 3.50]	
Savicevic, 2013	0.3221	0.2019	2.8%	1.38 [0.93, 2.05]	
Schluger, 2013	1.5705	0.3441	2.1%	4.81 [2.45, 9.44]	
Shetty, 2006	0.8629	0.4679	1.6%	2.37 [0.95, 5.93]	
Soh 2017	0.4612	0.0762	3.2%	1.59 [1.37, 1.84]	
Verma, 2012	1.3354	0.6064	1.1%	3.80 [1.16, 12.48]	
Zaridze men, 2009	1.4207	0.0943	3.2%	4.14 [3.44, 4.98]	
Zaridze women, 2009	1.6715	0.1853	2.8%	5.32 [3.70, 7.65]	
Total (95% CI)			100.0%	1.90 [1.63, 2.23]	

Heterogeneity: Tau² = 0.19; Chi² = 250.22, df = 46 (P < 0.00001); I² = 82%
Test for overall effect: Z = 8.09 (P < 0.00001)

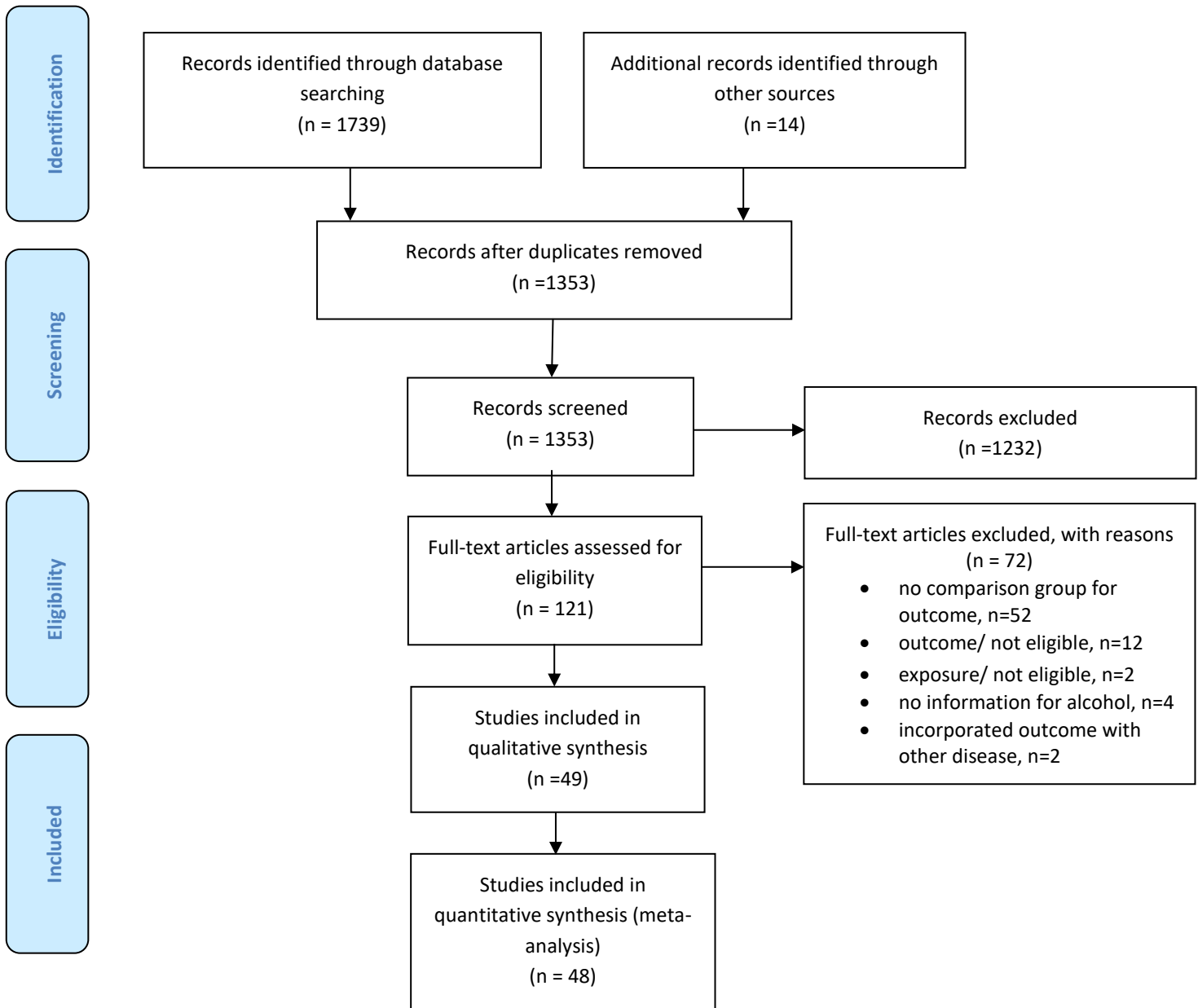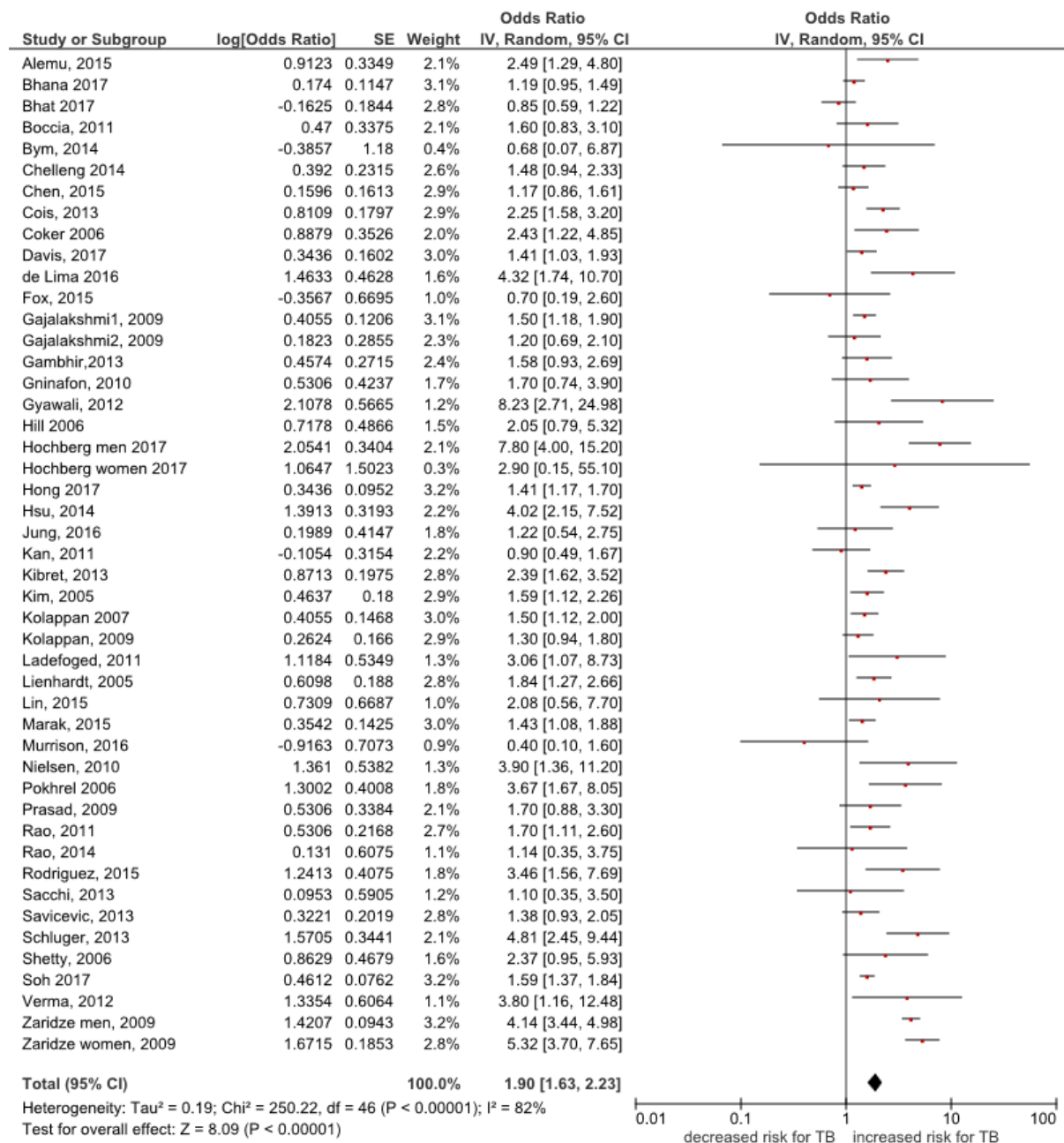**Figure 2. Forest plot of the association between any alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of TB**
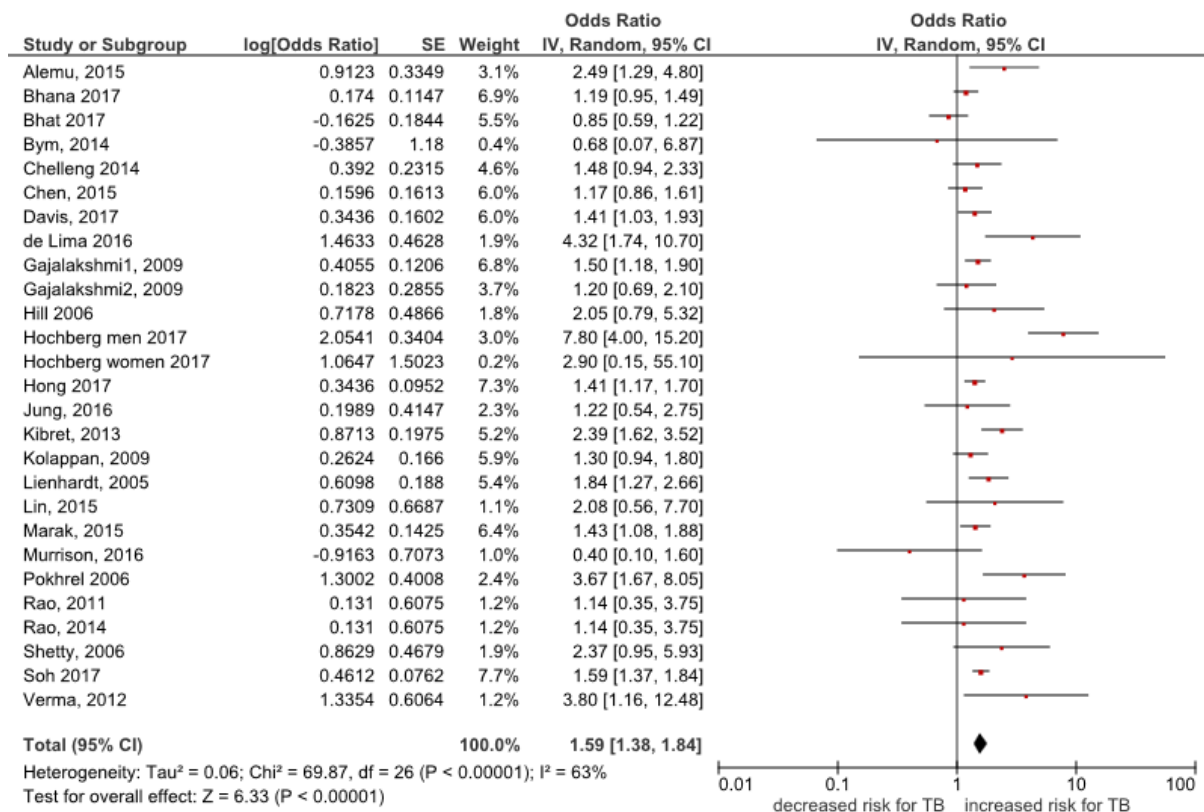
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Alemu, 2015	0.9123	0.3349	3.1%	2.49 [1.29, 4.80]
Bhana 2017	0.174	0.1147	6.9%	1.19 [0.95, 1.49]
Bhat 2017	-0.1625	0.1844	5.5%	0.85 [0.59, 1.22]
Bym, 2014	-0.3857	1.18	0.4%	0.68 [0.07, 6.87]
Chelleng 2014	0.392	0.2315	4.6%	1.48 [0.94, 2.33]
Chen, 2015	0.1596	0.1613	6.0%	1.17 [0.86, 1.61]
Davis, 2017	0.3436	0.1602	6.0%	1.41 [1.03, 1.93]
de Lima 2016	1.4633	0.4628	1.9%	4.32 [1.74, 10.70]
Gajalakshmi1, 2009	0.4055	0.1206	6.8%	1.50 [1.18, 1.90]
Gajalakshmi2, 2009	0.1823	0.2855	3.7%	1.20 [0.69, 2.10]
Hill 2006	0.7178	0.4866	1.8%	2.05 [0.79, 5.32]
Hochberg men 2017	2.0541	0.3404	3.0%	7.80 [4.00, 15.20]
Hochberg women 2017	1.0647	1.5023	0.2%	2.90 [0.15, 55.10]
Hong 2017	0.3436	0.0952	7.3%	1.41 [1.17, 1.70]
Jung, 2016	0.1989	0.4147	2.3%	1.22 [0.54, 2.75]
Kibret, 2013	0.8713	0.1975	5.2%	2.39 [1.62, 3.52]
Kolappan, 2009	0.2624	0.166	5.9%	1.30 [0.94, 1.80]
Lienhardt, 2005	0.6098	0.188	5.4%	1.84 [1.27, 2.66]
Lin, 2015	0.7309	0.6687	1.1%	2.08 [0.56, 7.70]
Marak, 2015	0.3542	0.1425	6.4%	1.43 [1.08, 1.88]
Murrison, 2016	-0.9163	0.7073	1.0%	0.40 [0.10, 1.60]
Pokhrel 2006	1.3002	0.4008	2.4%	3.67 [1.67, 8.05]
Rao, 2011	0.131	0.6075	1.2%	1.14 [0.35, 3.75]
Rao, 2014	0.131	0.6075	1.2%	1.14 [0.35, 3.75]
Shetty, 2006	0.8629	0.4679	1.9%	2.37 [0.95, 5.93]
Soh 2017	0.4612	0.0762	7.7%	1.59 [1.37, 1.84]
Verma, 2012	1.3354	0.6064	1.2%	3.80 [1.16, 12.48]
Total (95% CI)			100.0%	1.59 [1.38, 1.84]

Heterogeneity: Tau² = 0.06; Chi² = 69.87, df = 26 (P < 0.00001); I² = 63%
Test for overall effect: Z = 6.33 (P < 0.00001)

decreased risk for TB   increased risk for TB

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

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Inghammar 2011	0.9203	0.4446	10.1%	2.51 [1.05, 6.00]
Pednekar, 2012	0.9282	0.1508	64.5%	2.53 [1.88, 3.40]
Mendoza 2010	0.9858	0.4121	11.7%	2.68 [1.19, 6.01]
Yen 2017	1.662	0.3796	13.7%	5.27 [2.50, 11.09]
Total (95% CI)			100.0%	2.81 [2.12, 3.74]

Heterogeneity: Tau² = 0.01; Chi² = 3.29, df = 3 (P = 0.35); I² = 9%
Test for overall effect: Z = 7.13 (P < 0.00001)

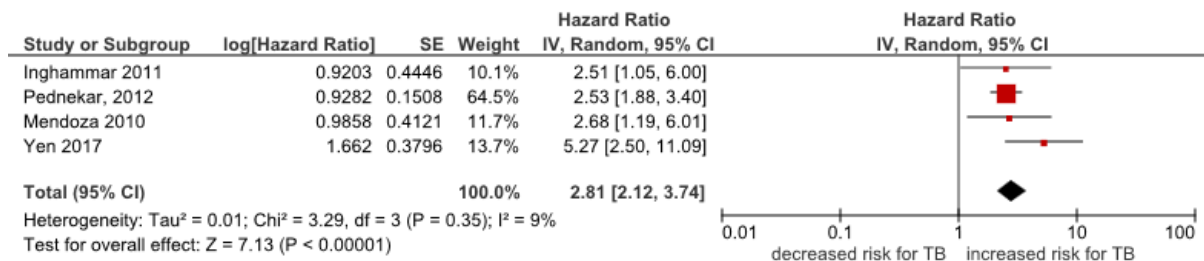decreased risk for TB   increased risk for TB

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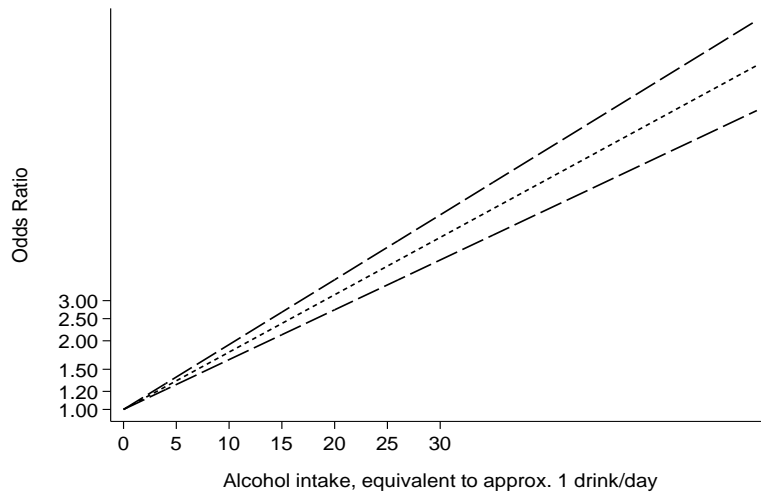
Figure 5.Linear dose response meta-analysis for the association between categories of alcohol intake(grams/day) and the risk of TB

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