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REVIEW

Association between tobacco smoking and drug-resistant tuberculosis

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Background: Tobacco smoking is a risk factor for tuberculosis but little is known about the relationship between tobacco smoking and drug-resistant tuberculosis (DR-TB). We undertook a systematic review and meta-analysis to quantitatively assess the association between DR-TB and tobacco smoking.

Methods: We searched for relevant studies in the Ovid MEDLINE, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, WANFANG, and WEIPU databases from inception to September 1, 2017. Results were expressed as odds ratios (ORs) with accompanying 95% CIs, and subgroup analyses were performed by study design, smoking type, DR-TB type, and multivariate analysis.

Results: Thirty-three studies related to tobacco smoking and DR-TB were included. We found substantial evidence that tobacco smoking is associated with an increased risk of DR-TB (OR 1.57, 95% CI 1.33–1.86). Associations were also found in subgroup analyses: for multidrug-resistant tuberculosis (OR 1.49, 95% CI 1.19–1.86) and for any DR-TB (OR 1.70, 95% CI 1.3–2.23); the pooled OR was 1.45 (95% CI 1.11–1.90) for current smoking, 2.25 (95% CI 1.46–3.47) for past smoking, and 1.56 (95% CI 1.22–1.98) for smoking history; and similar ORs were also observed in study design and multivariate analysis subgroup analysis.

Conclusion: This study demonstrated that tobacco smoking is an independent risk factor for DR-TB.

Keywords: tobacco smoking, drug-resistant tuberculosis, multidrug-resistant tuberculosis, MDR-TB, meta-analysis

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB) and remains one of the leading causes of death worldwide, despite the availability of effective anti-TB drugs.[1] Globally, there were an estimated 10.4 million new TB cases and 2.0 million deaths due to the disease in 2016.[2] The number of new cases increased from 9 million in 2013 to 10.4 million in 2016.[2,3]

Antimicrobial resistance has become an important health concern for countries worldwide and the emergence of drug-resistant tuberculosis (DR-TB) is a great challenge for the elimination of TB.[4] According to a global surveillance project from 1999 to 2002, resistance to any drug in new cases of TB was 10.2% and this number has been gradually increasing.[5,6] Multidrug-resistant tuberculosis (MDR-TB), which is defined as drug resistance at least to both isoniazid and rifampicin, has spread globally since 2000.[2,5,6] Extensively drug-resistant tuberculosis (XDR-TB) is defined

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as MDR-TB plus resistance to at least one drug in both of the two most important classes of medicines in an MDR-TB regimen: fluoroquinolones and second-line injectable agents (amikacin, capreomycin, or kanamycin).[2] The World Health Organization (WHO) estimates that 4% of new cases and 19% of previously treated TB cases were MDR-TB or rifampicin-resistant tuberculosis (RR-TB) in 2016, and almost half (47%) of these cases were in India, China, and the Russian Federation.[2] Globally, nearly 20% of MDR-TB/RR-TB cases have resistance to any fluoroquinolone, while 6% of MDR-TB cases are XDR-TB.[2] Unlike the majority of TB patients worldwide who can be cured with a 6 month effective first-line drug treatment,[7] cases of DR-TB such as isoniazid-resistant TB, RR-TB, and MDR-TB require long-term treatment and the therapy is less effective. The treatment of MDR-TB is extremely challenging owing to the complexity of chemotherapy regimens, the toxicity of alternative drugs, and the high cost of these drugs. Therefore, it is particularly important to identify the risk factors associated with DR-TB.

Several risk factors have been considered for DR-TB.[8–11] Previous treatment ranks as the strongest and most frequent determinant of DR-TB,[8,10] and diabetes mellitus is also considered as an independent risk factor, especially for primary MDR-TB.[9] Other factors include HIV infection, younger age, and being foreign born.[8,11–13]

The Global Adult Tobacco Survey (GATS) found that in 2015 there were 879 million current tobacco users, including 721 million men and 158 million women among GATS countries.[14] There is substantial evidence to suggest that tobacco smoking is associated with TB infection and disease:[15–18] smokers have two-fold increased risk of TB infection and active TB.[16,17] Maurya et al[19] found that active smoking increases the risk of extrapulmonary TB. Cigarette smoking was not only strongly associated with an increased risk of TB, but also associated with the recurrence and severity of pulmonary TB.[18,20,21]

Since both tobacco smoking and DR-TB are global problems, the association between tobacco smoking and DR-TB has attracted much attention from researchers. However, previous studies on the association between tobacco smoking and DR-TB were varied in regard to geographic region, ethnicity, and study design. Moreover, epidemiological data on this association have not been systematically reviewed. Therefore, we conducted a meta-analysis to determine whether tobacco smoking was an independent risk factor for DR-TB, and our results may help to guide health interventions.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategies

We searched the Ovid MEDLINE, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, WANFANG, and WEIPU databases to identify all published articles that evaluated the association between tobacco smoking and the risk of DR-TB, from their inception until September 16, 2017. The search terms were used as follows: "smok*" or "smoking" or "cigarette" or "tobacco" in combination with "drug-resistant tuberculosis" or "multidrug resistant tuberculosis" or "extensively drug resistant tuberculosis." The following criteria were used for selecting studies in the meta-analysis: 1) the study included patients with a diagnosis of TB; 2) the study evaluated the association between tobacco smoking and DR-TB; 3) the study design was cross-sectional, case–control, or cohort; and 4) adjusted odds ratios (ORs) or crude ORs and 95% CIs were reported or could be calculated. In addition, the following exclusion criteria were used: 1) abstracts or reviews; 2) studies on children aged <15 years; 3) studies conducted on animal models or not reporting the exposures/outcomes of interest; 4) repeated or overlapping publications; and 5) studies not in English or Chinese. For duplicate or overlapping publications, the study with the largest sample size or the latest to be published was included.

Data extraction and definitions

Two independent authors (Ming-Gui Wang and Yun-Xia Zhang) checked all potentially relevant studies and tried to reach a consensus on all items. Any disagreement was assessed by a third author (Miao-Miao Zhang). The following data were extracted from each study: first author, year of publication, location of the study population, age, study design, type of DR-TB (any DR-TB, M/XDR-TB), adjusted OR (or crude OR), and 95% CI. Any DR-TB was defined as MTB strains that show resistance to at least one of the anti-TB drugs, including monoresistant TB, polyresistant TB (resistant to two or more antibiotics), and M/XDR-TB. MDR-TB was defined as MTB strains that show resistance at least to rifampicin and isoniazid. MDR-TB with additional resistance to any fluoroquinolone and at least one of the three injectable second-line drugs was classified as XDR-TB.

Quality assessment

All selected studies in the meta-analysis were scored for methodological quality using the Newcastle–Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). This scale uses a "star system" in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the exposure for case–control or cross-sectional studies, or the outcome for cohort studies. The maximum score was 9 points. A score of <5 was considered low quality, 5–7 was considered medium quality, and >7 was considered high quality.

Statistical analysis

Since the included studies were conducted with different study designs and populations, the pooled ORs and 95% CIs were calculated using random effects models. Subgroup analyses were performed by study design (cross-sectional, case–control, and cohort), smoking type (past smoking, current smoking, and smoking history), DR-TB type (any DR-TB and M/XDR-TB), and multivariate analysis (Yes or No). We assessed the heterogeneity among the studies by computing values for chi-square (Q), p-values ($p<0.10$ was considered statistically significant), and I^2 (values of 25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively).[22] Sensitivity analysis was also performed to explore the sources of heterogeneity. The Begg rank correlation and Egger weighted regression test methods were also used to statistically assess publication bias ($p< 0.05$ was considered as indicative of statistically significant publication bias). STATA version 12.0 software (STATA Corporation, College Station, TX, USA) was utilized for all statistical analyses.

Results

Characteristics of studies included in the review

A total of 726 studies were identified after the initial search (Figure 1). Of these, 663 were excluded after screening by titles and abstracts. The excluded studies were those that were duplicated papers, case reports, reviews, or unrelated studies. Of the remaining 63 articles, 12 studies were excluded

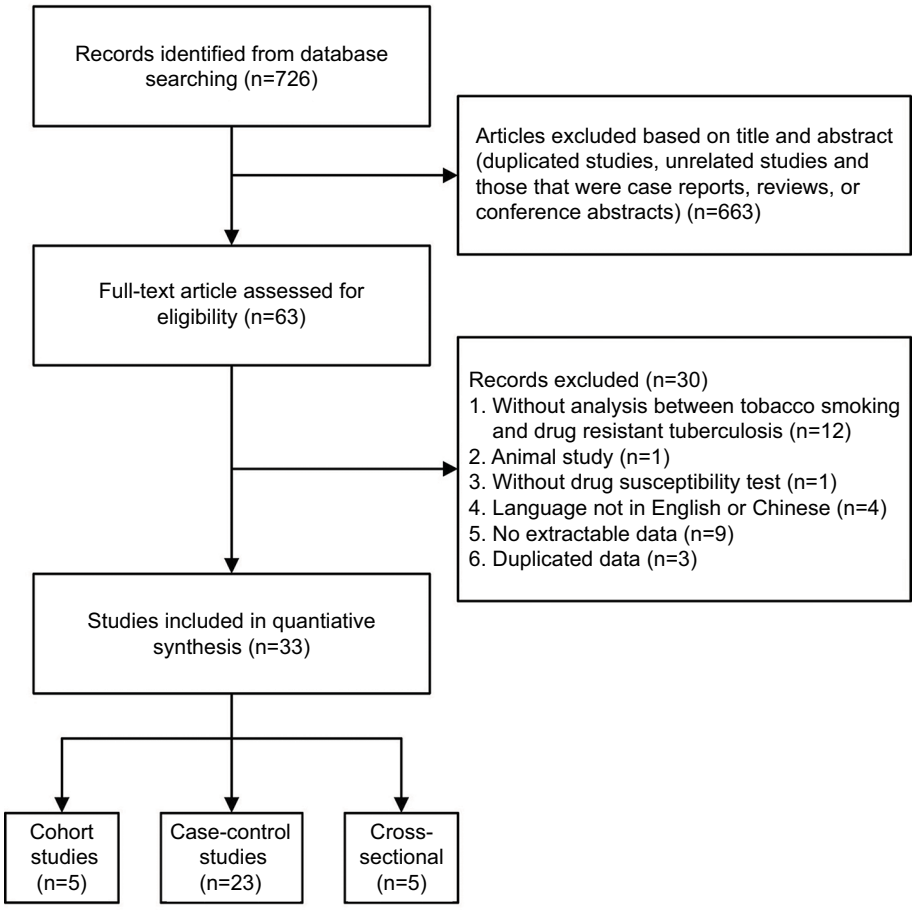

Figure 1 Flow diagram of included studies.

owing to a lack of analysis of smoking and drug resistance, nine studies were excluded as they contained no extractable data, one study was conducted on animals, four studies were excluded as they were not in English or Chinese, three studies duplicated data, and one study did not include a drug susceptibility test. Finally, 33 articles were included in the systematic review and the meta-analysis.[10,13,23–53] Of the 33 eligible studies, 23 were designed as case–control studies, five were cohort studies, and five were cross-sectional studies. The characteristics of all included studies are presented in Table 1. The methodological quality was mixed as the NOS ranged from 5 to 8, as shown in Table 1; seven articles were awarded 8 stars, 19 studies were awarded 7 stars, six articles were awarded 6 stars, and one article was awarded 5 stars.

The association of smoking and drug-resistant tuberculosis

The overall pooling result of all included studies is shown in Figure 2, and there was a significant association between DR-TB and tobacco smoking (OR 1.57, 95% CI 1.33–1.86). We assessed heterogeneity using the I^2 statistic, and there was statistically significant heterogeneity observed among studies ($p<0.001$, $I^2=67.7\%$). Given the heterogeneity of the effect estimates, we conducted sensitivity analyses in which we compared pooled effect estimates for subgroups stratified on important study characteristics (Table 2). No evidence for substantial publication bias was found by either Begg's test ($p=0.809$) or Egger's test ($p=0.099$). The Begg's funnel plot is shown in Figure 3.

Subgroup analyses were performed by study design, DR-TB type, smoking type, and whether multivariate analysis had been performed (in each analysis data were available from at least three studies for each subgroup) (Figures S1–S4), and the results are summarized in Table 2. Stratification of the data by study design showed that the OR was 1.63 (95% CI 1.17–2.29) for cohort studies, 1.45 (95% CI 1.19–1.77) for case–control studies, and 2.44 (95% CI 1.32–4.49) for cross-sectional studies. Two subgroups were used for the type of DR-TB: any DR-TB (OR 1.70, 95% CI 1.3–2.23) and M/XDR-TB (OR 1.49, 95% CI 1.19–1.86). Significant associations were also observed in smoking type and multivariate analysis subgroup analysis (Table 2). Heterogeneity was reduced in the cohort study group ($p=0.265$, $I^2=20.70\%$) compared with the overall pooled analysis.

Discussion

This systematic review and meta-analysis addressed the association of tobacco smoking and DR-TB using 33 selected studies. The results demonstrated that tobacco smoking was a significant independent risk factor for DR-TB regardless of study design, smoking status, and type of DR-TB. The subgroup analysis further showed that those exposed to tobacco smoking were found to have higher risks of M/XDR-TB than those who were not exposed.

To the best of our knowledge, this is the first meta-analysis to evaluate the association between tobacco smoking and DR-TB. Previous reviews had examined the association of tobacco smoking and TB, and the overall pooled summary data indicate that tobacco smoking is associated with an increased risk of TB infection and TB disease.[15,17,18] Active smoking was considered as a risk factor for TB recurrence and increased mortality due to TB.[16,17] Smokers were also found to be at higher risk of extrapulmonary TB than non-smokers.[19] However, whether tobacco smoking is associated with DR-TB had not been systematically reviewed previously.

TB patients who had a history of smoking exposure (regardless of whether they were current smokers or past smokers) were 1.57 times more likely to develop DR-TB compared with non-smoker TB cases. Our subgroup analyses indicated that current smokers had a 1.45-fold and past smokers had a 2.25-fold increased risk of DR-TB. Previous studies indicated that TB patients who are smokers are less likely to complete anti-TB treatment,[54,55] which may lead to poor treatment outcome. It has been reported that 16.7% of unsuccessful treatment outcomes in Chinese patients were attributable to smoking.[56] Improving the treatment compliance of patients with TB is an effective way to reduce DR-TB and increase the cure rate.[56–58] Measures to promote smoking cessation may be an effective way to reduce DR-TB, TB relapse, and secondary transmission.[56,59]

Another important finding of our study is the association between M/XDR-TB and tobacco smoking. The pooled risk of MDR-TB was 1.45 times higher in smokers than in non-smokers. Previous treatment, HIV infection, diabetes mellitus, low education, low income, and alcohol abuse have previously been associated with MDR-TB.[8,9,11,58] The WHO has estimated that only 54% of patients with MDR/RR-TB and 30% of those with XDR-TB had a successful treatment outcome.[2] Owing to the poor outcome of M/XDR-TB treatment, it is important to reduce the occurrence of M/XDR-TB. Our findings suggest that, in addition to the usual benefits of smoking cessation, TB patients may benefit by reducing their risk of developing M/XDR-TB.

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Country	Design	Sample size	Mean age (years)	Male n (%)	DR type	OR or AOR (95% CI)	Multivariate analysis	NOS score
Fox et al[23]	2011	Israel	Case–control	590	NA	337 (57)	HDR-TB and MDR-TB	OR 1.11 (0.62–2.01)	No	7
Zhang et al[24]	2016	China	Case–control	578	NA	431 (75)	MDR-TB	AOR 2.93 (1.98–4.36)	Yes	7
Rifat et al[25]	2014	Bangladesh	Case–control	1000	NA	609 (61)	MDR-TB	AOR 0.04 (0.005–0.29) for current smokers; 1.58 (0.99–2.50) for past smokers	Yes	7
Gómez-Gómez et al[26]	2015	Mexico	Case–control	175	NA	124 (71)	MDR-TB	AOR 2.10 (0.86–5.16)	Yes	7
Salindri et al[27]	2016	Georgia	Cohort	267	NA	NA	Any (except M/XDR) and M/XDR-TB	Any: AOR 4.56 (1.49–14.02) for current smokers; 3.94 (1.25–12.47) for past smokers; M/XDR-TB: AOR 1.52 (0.50–4.59) for current smokers; 1.52 (0.48–4.76) for past smokers	Yes	8
Toungoussova et al[28]	2002	Russia	Case–control	119	38.9	89 (75)	Any and MDR-TB	Any: AOR 0.90 (0.30–2.20); MDR-TB: AOR 0.50 (0.20–1.30)	Yes	7
Meriki et al[29]	2013	Cameroon	Cross-sectional	256	NA	NA	Any	OR 1.15 (0.64–2.05)	No	7
Lee et al[30]	2009	South Korea	Case–control	146	21	146 (100)	MDR-TB	AOR 1.12 (0.30–4.12)	Yes	7
Skrahina et al[10]	2013	Belarus	Case–control	1344	46	NA	M/XDR-TB	AOR 1.50 (1.10–2.00)	Yes	8
Sahebi et al[31]	2016	Iran	Cross-sectional	280	52.0	152 (54)	Any	AOR 1.16 (0.08–16.68)	Yes	8
El Mahalli et al[32]	2015	Saudi Arabia	Case–control	181	NA	138 (76)	Any	AOR 4.61 (1.86–11.38)	Yes	7
Otu et al[33]	2014	Nigeria	Cohort	100	32.9	53 (53)	Any	AOR 1.57 (0.47–5.27)	Yes	8
Dalton et al[34]	2012	Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea, and Thailand	Cohort	214	NA	96 (45)	XDR	AOR 1.19 (0.74–1.91)	Yes	7
Hang et al[35]	2013	Vietnam	Cohort	488	NA	385 (79)	Any	AOR 1.87 (0.99–3.49)	Yes	8
Ruddy et al[13]	2005	Russia	Cross-sectional	309	NA	NA	HDR-TB	AOR 3.30 (1.20–9.20)	Yes	7
Ignatyeva et al[36]	2015	Baltic countries	Case–control	1041	NA	787 (76)	M/XDR-TB	AOR 0.91 (0.60–1.39)	Yes	7
Marahatta et al[39]	2010	Nepal	Case–control	110	NA	77 (70)	MDR-TB	OR 2.35 (1.071–5.16)	No	7
Prakash et al[40]	2016	India	Cross-sectional	185 89	38.3 39.7	140 (76) 72 (81)	MDR-TB MDR-TB	OR 4.46 (1.44–13.84) for Sahariya tribe OR 1.46 (0.154–13.81) for non–tribal	No No	7
Blanquer et al[37]	2015	Spain	Cohort	476	NA	NA	HDR-TB	OR 1.01 (0.47–2.17)	No	6
Fregona et al[38]	2017	Brazil	Cross-sectional	609	NA	NA	MDR-TB	AOR 3.93 (1.98–7.79)	Yes	7
Fan et al[41]	2013	China	Case–control	671	NA	463 (60)	Any	OR 1.62 (1.21–2.09)	No	6

(*Continued*)

Table 1 (*Continued*)

Author	Year	Country	Design	Sample size	Mean age (years)	Male n (%)	DR type	OR or AOR (95% CI)	Multivariate analysis	NOS score
Yu et al[42]	2016	China	Case–control	181	NA	123 (68)	MDR-TB	AOR 3.17 (1.21–4.23)	Yes	6
Li et al[45]	2012	China	Case–control	344	NA	251 (73)	Any	AOR 3.49 (0.82–39.37)	Yes	6
Yang et al[43]	2014	China	Case–control	445	NA	323 (73)	Any	AOR 1.76 (1.07–3.37)	Yes	8
Deng et al[44]	2017	China	Case–control	172	NA	94 (55)	MDR-TB	OR 1.11 (0.98–1.27)	No	7
Zhou et al[46]	2016	China	Case–control	180	NA	100 (56)	Any	OR 4.51 (2.30–8.85)	No	5
Liu et al[47]	2015	China	Case–control	269	NA	151 (56)	MDR-TB	OR 2.37 (1.06–5.29)	No	7
Liu et al[48]	2016	China	Case–control	319	NA	214 (67)	Any	AOR 0.61 (0.27–1.40)	Yes	6
Zhu et al[49]	2015	China	Case–control	230	NA	NA	MDR-TB	AOR 1.48 (1.13–1.76)	Yes	8
Chen et al[50]	2017	China	Case–control	201	NA	140 (70)	Any	OR 1.08 (0.49–2.34)	No	7
Wei et al[51]	2007	China	Case–control	292	NA	NA	Any	OR 1.34 (0.76–2.36)	No	7
Gao et al[52]	2016	China	Case–control	823	NA	614 (75)	MDR-TB	OR 1.14 (0.67–1.93)	No	7
Liu et al[53]	2015	China	Case–control	276	NA	197 (71)	MDR-TB	OR 0.66 (0.39–1.13)	No	6

Abbreviations: HDR-TB, isoniazid resistant tuberculosis; M/XDR-TB, multidrug-/extensively drug-resistant tuberculosis; AOR, adjusted odds ratio; NA, data not available in article; NOS, Newcastle–Ottawa Scale.

Heterogeneity analysis

The test for heterogeneity was statistically significant (I^2=67.7%, p<0.001), indicating that there was considerable heterogeneity between studies. Unfortunately, we did not find any specific study that contributed a large portion of the heterogeneity in sensitivity analyses. Subgroup analyses showed that there was a significantly increased risk of DR-TB among smokers regardless of outcome definition (M/XDR-TB versus any DR-TB), type of study, smoking status, or type of analysis. As shown in Table 2, the heterogeneity is mainly from study design and smoking type. Heterogeneity was low in the cohort studies (I^2=20.70%, p=0.265) but high in case–control studies (I^2=73.80%, p<0.001), most likely attributable to the quality of study design. When pooled estimates of studies grouped by the smoking type were compared, the heterogeneity was highest in the smoking history group (I^2=70.10%, p<0.001), which did not distinguish between current smoking and past smoking. Although stratification by these study-specific variables did not fully explain the heterogeneity in the study, we consistently found a higher risk of DR-TB in TB patients with a smoking habit.

Limitations of the study

It is necessary to point out that although most of our included studies scored as high quality using the NOS, there are several potential limitations to this study. First, in this meta-analysis we only included studies published in English or Chinese, which may have resulted in a lack of data for four studies published in other languages, (Russian, Spanish, and Japanese). Although we failed to read the full text of these studies, associations between smoking and drug resistance could be discerned from the abstract of a study published in Russian,[60] and another in Spanish.[61] Second, we included data from different study designs, which may have led to the heterogeneity of the results. However, the similar positive association detected between smoking and DR-TB in cohort study subgroups, which are more liable to prove a cause-and-effect relationship than case–control and cross-sectional studies, reinforces our conclusion. Third, the assessment of tobacco smoking relied on self-reported behavior, which may not have been accurate because of recall error among TB patients. Furthermore, some studies did not distinguish between current smokers and past smokers, which may have led to inaccurate conclusions and contributed to the heterogeneity of the results. Fourth, studies employing both univariate and multivariate analysis were included. Univariate analysis may be influenced by other factors such as alcohol use, previous treatment of TB, primary or secondary DR, and diabetes. However, our results found

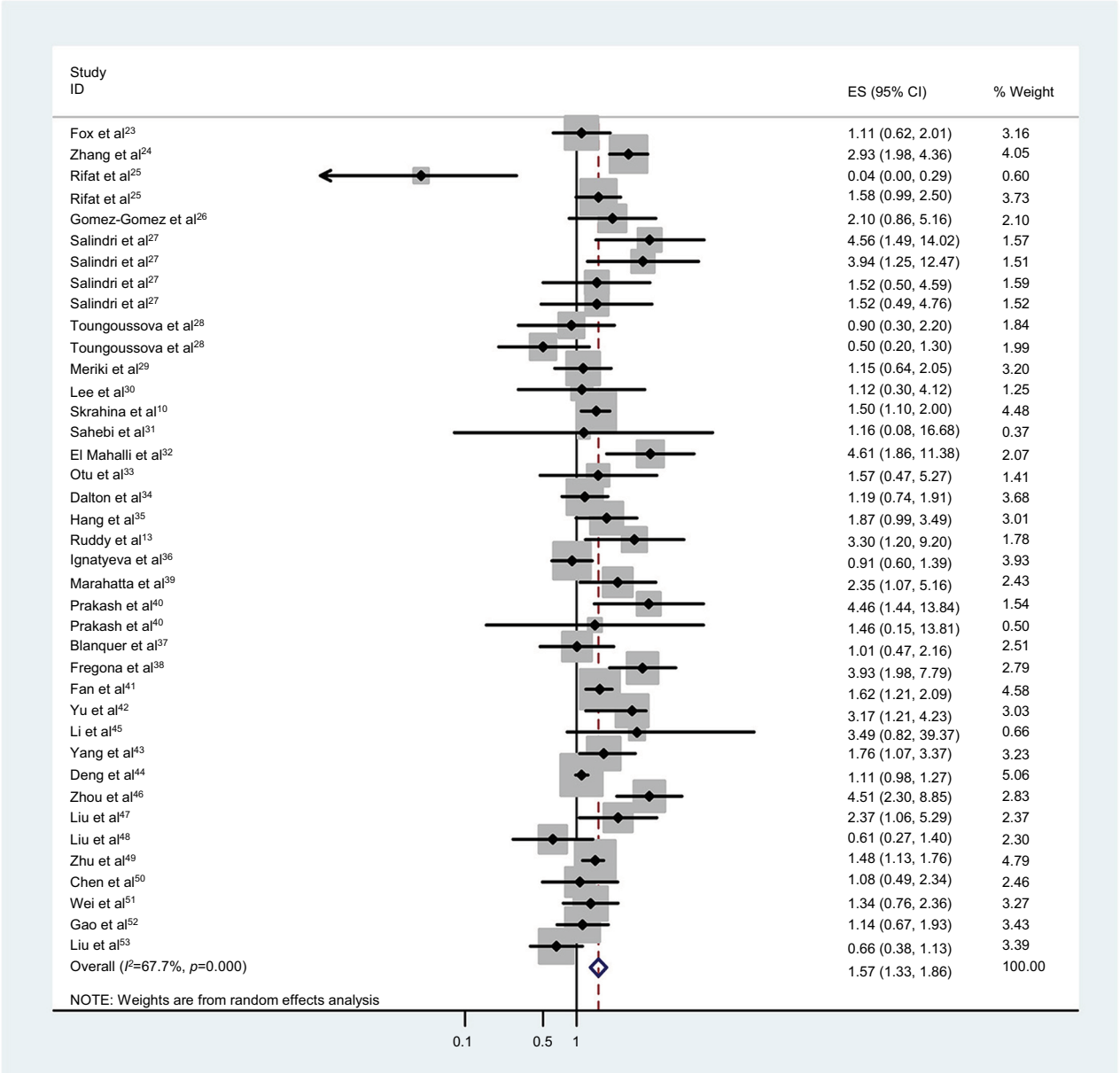

Figure 2 Forest plot of ORs assessing the association between tobacco smoking and drug-resistant tuberculosis.
Abbreviations: ES, effect size; OR, odds ratio.

Table 2 Subgroup analyses

Measure or outcome	Study characteristics (number of studies)	Pooled OR	95% CI	I^2 (%)
Type of study	Cohort studies (5)	1.63	1.17–2.29	20.70
	Case–control studies (25)	1.45	1.19–1.77	73.80
	Cross-sectional (5)	2.44	1.32–4.49	49.40
Type of DR-TB	Any DR-TB (15)	1.70	1.30–2.23	52.40
	M/XDR-TB (18)	1.49	1.19–1.86	58.25
Type of smoking	Smoking history (14)	1.56	1.22–1.98	70.10
	Current smoking (18)	1.45	1.11–1.90	63.30
	Past smoking (3)	2.25	1.46–3.47	43.50
Multivariate analysis	Yes (20)	1.68	1.33–2.12	65.20
	No (13)	1.41	1.11–1.80	64.60

Abbreviations: DR-TB, drug resistant tuberculosis; M/XDR-TB, multidrug- or extensively drug-resistant tuberculosis; OR, odds ratio.

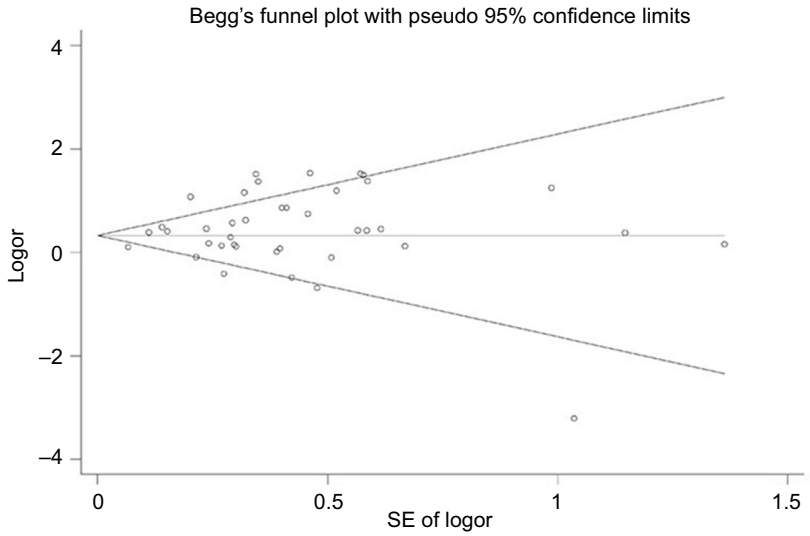

Figure 3 Funnel plot for publication bias.
Abbreviation: logor, natural log of odds ratio.

similar ORs and heterogeneity between the univariate and multivariate analysis groups, which strengthens the reliability of our conclusion. Finally, the laboratory conditions and technical proficiency of medical staff vary in different areas, and these factors may limit the accuracy of DR testing.

Conclusion

Our meta-analysis indicates that tobacco smoking was positively and significantly associated with DR-TB. Subgroup analysis also showed that tobacco smoking was an independent risk factor for M/XDR-TB. These findings suggest that DR-TB control might benefit from interventions aimed at reducing tobacco use. In other words, additional efforts should be made to encourage TB patients to quit smoking once they are diagnosed.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

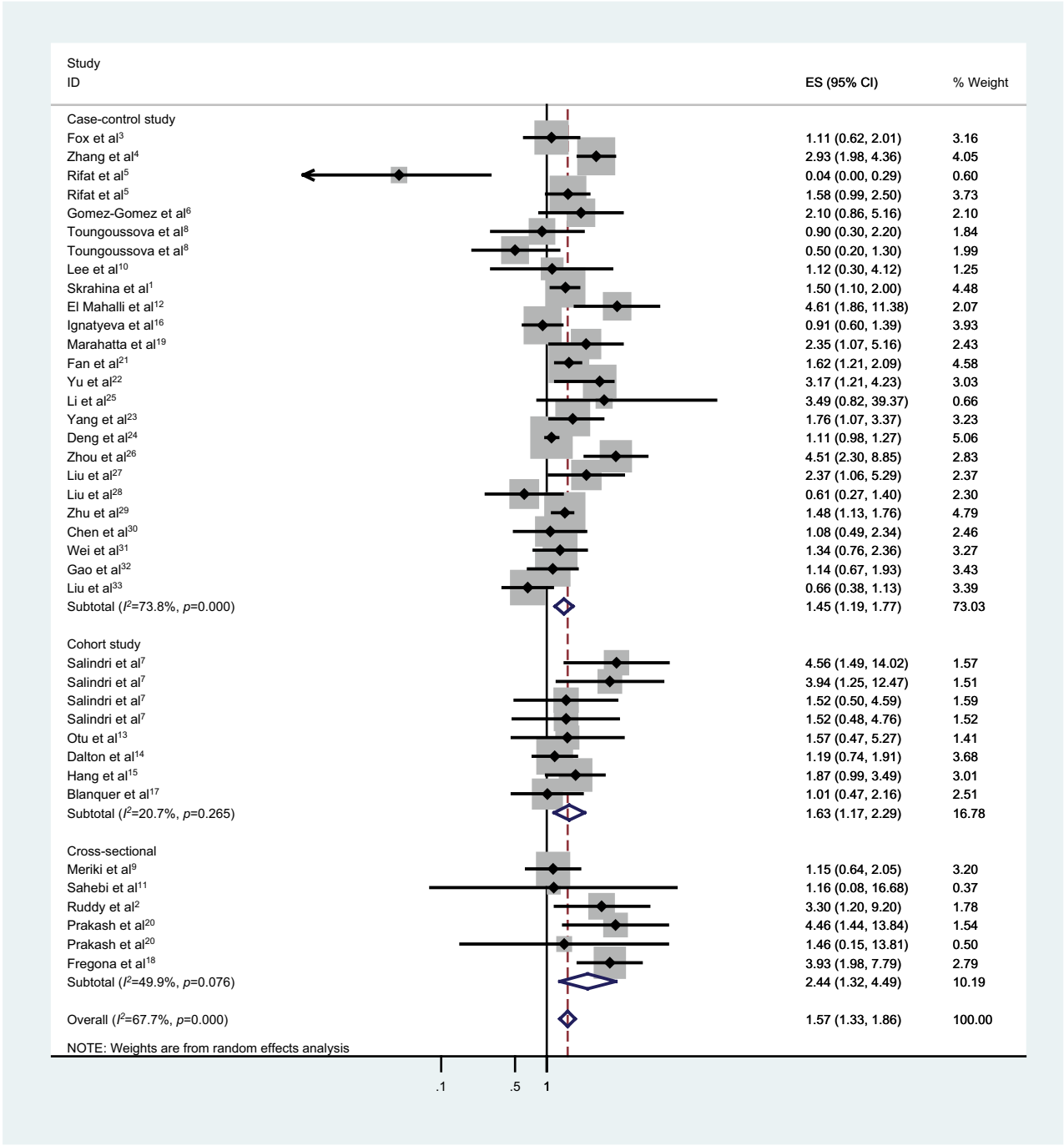

Figure S1 Subgroup analysis of study design.
Abbreviation: ES, effect size.

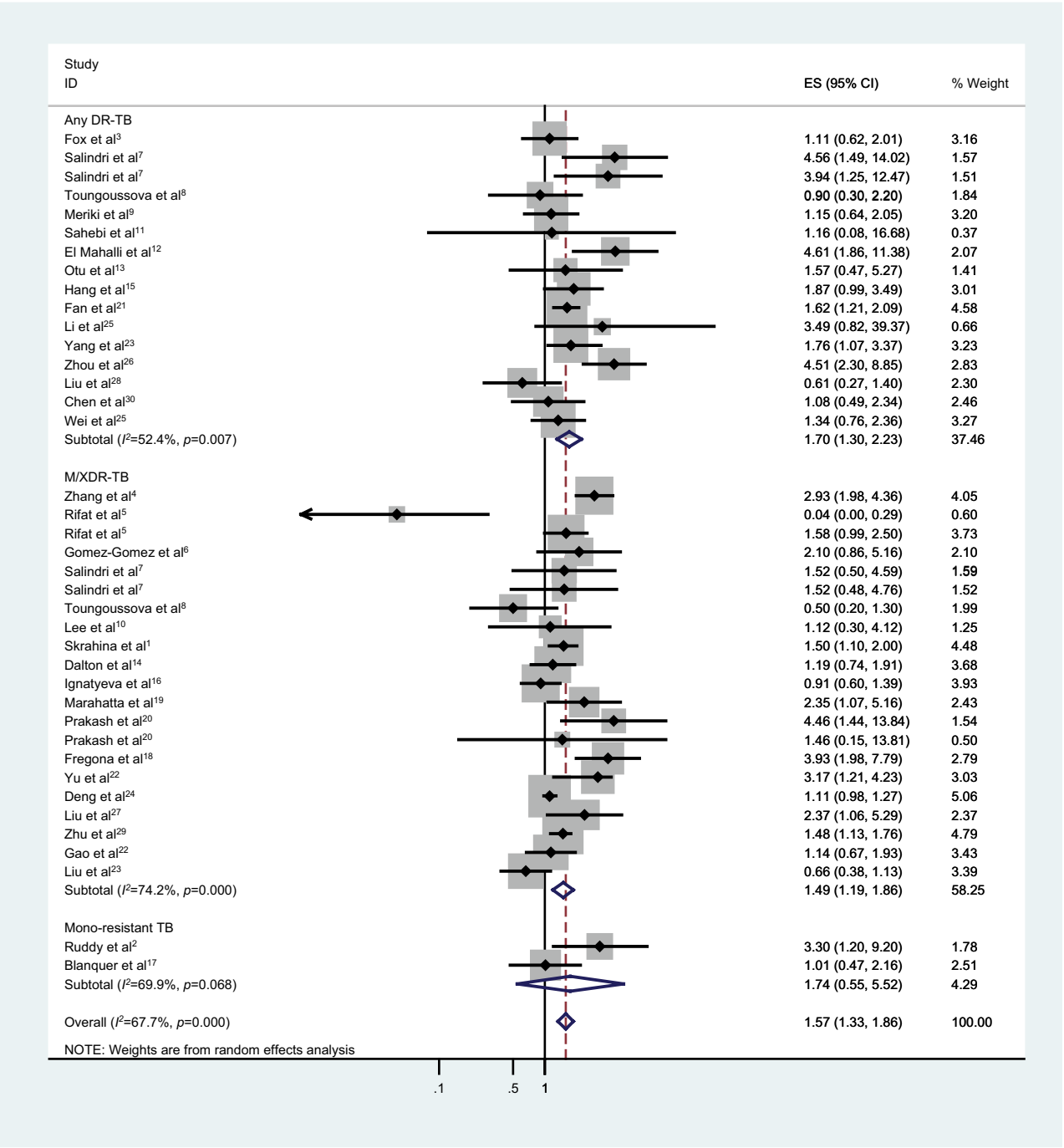

Figure S2 Subgroup analysis of DR-TB type.
Abbreviations: DR-TB, drug-resistant tuberculosis; ES, effect size; M/XDR-TB, multidrug-resistant tuberculosis.

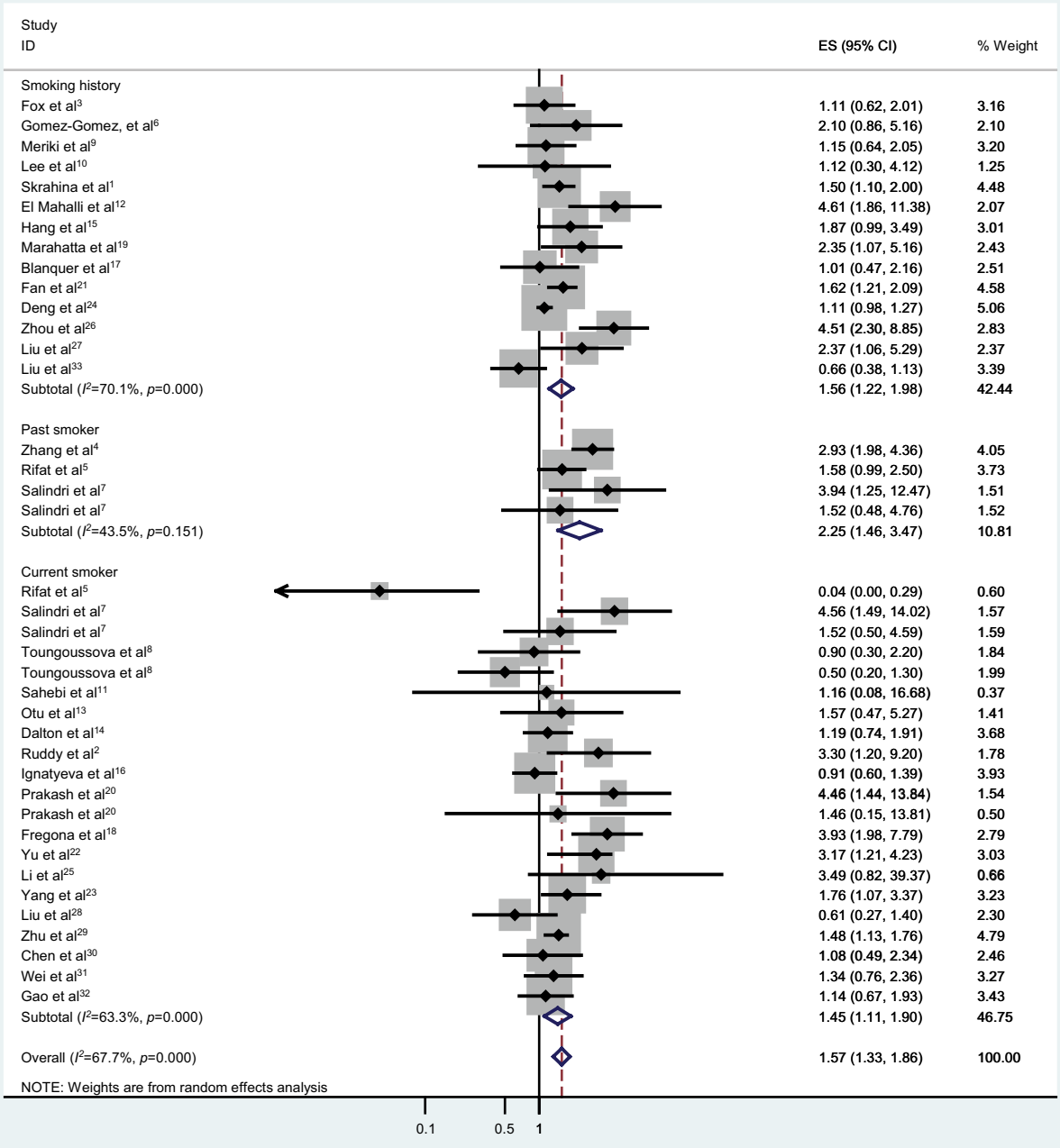

Figure S3 Subgroup analysis of smoking type.
Abbreviation: ES, effect size.

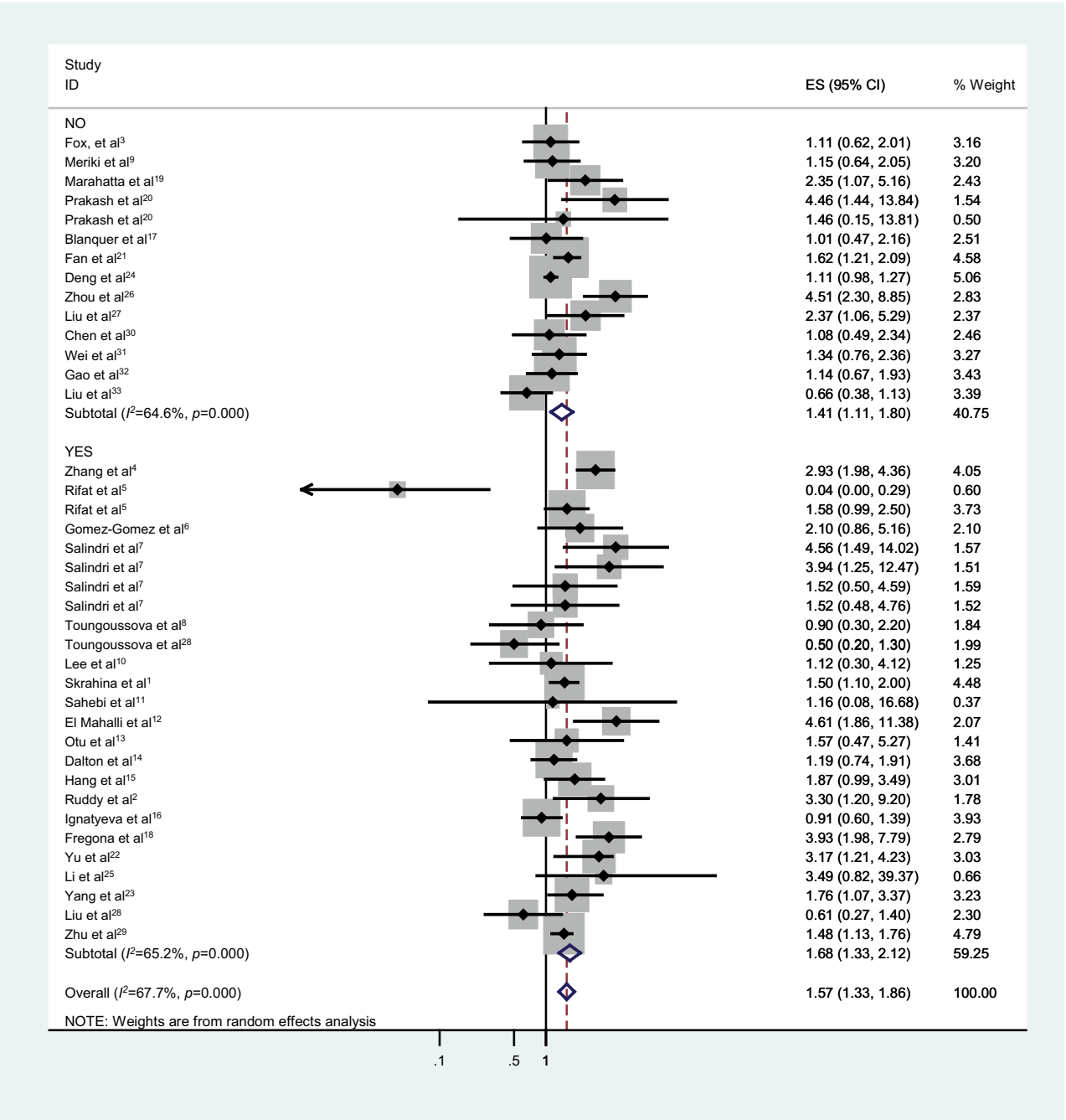

Figure S4 Subgroup analysis of OR type (YES: adjusted OR; NO: crude OR).
Abbreviations: ES, effect size; OR, odds ratio.

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