Pulmonary Tuberculosis and Risk of Lung Cancer

Subjects: Infectious Diseases | Public, Environmental & Occupational Health | Respiratory System

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Lung cancer accounts for approximately 18.4% of the total cancer-related deaths, the highest of all cancer types. The prognosis of lung cancer is relatively unfavorable compared to that of other malignancies, and as a prognosis largely depends on the stage of onset, thus, the early diagnosis of lung cancer is very important. Pulmonary tuberculosis (TB) is a known risk factor for lung cancer.

pulmonary tuberculosis lung cancer

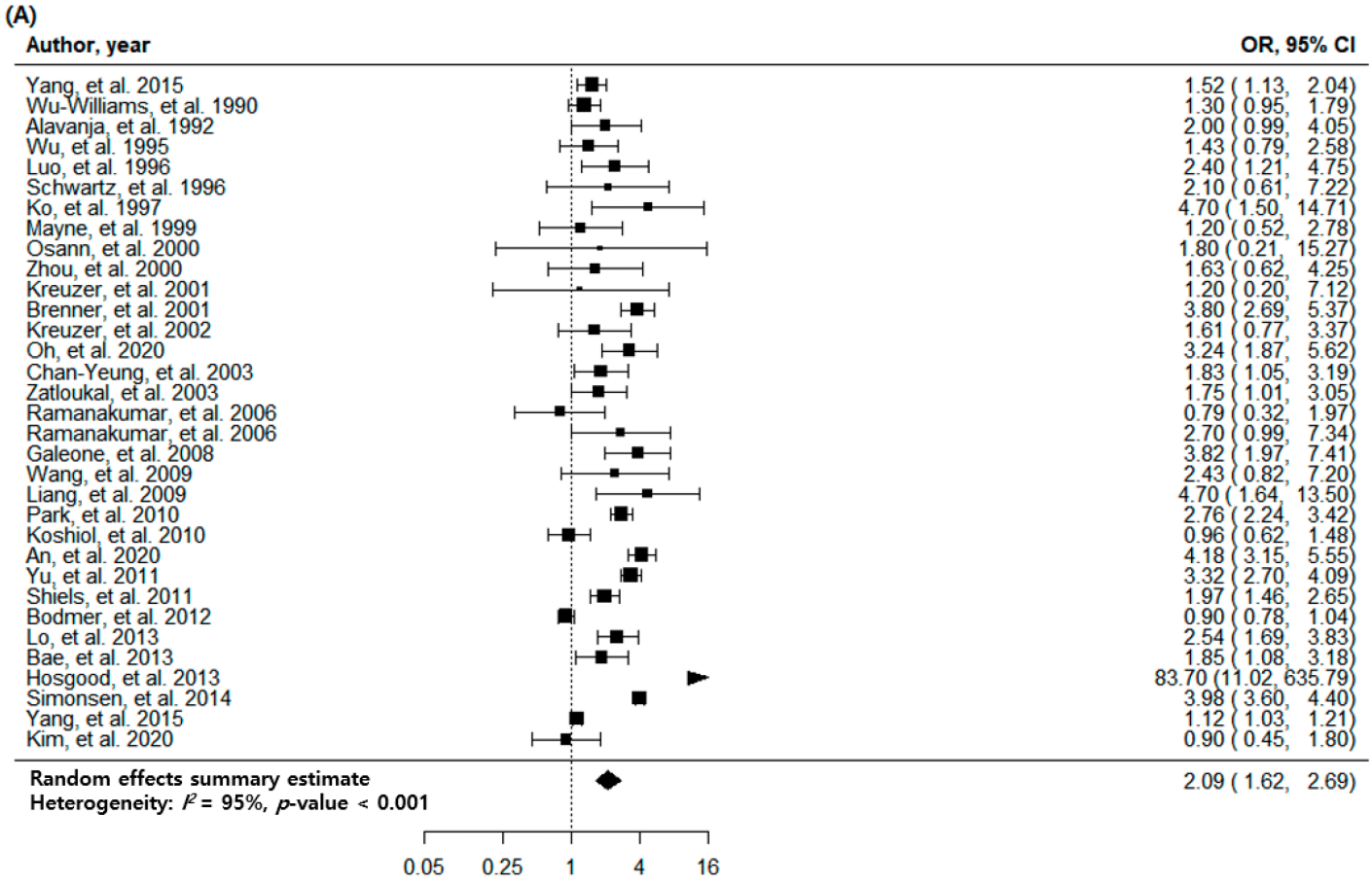
1. Introduction

Chronic inflammation resulting in pathological changes is a major risk factor in carcinogenesis. Inflammation is known to play a key role in carcinogenesis, such as infection with hepatitis B and C viruses in hepatocellular carcinoma, *Helicobacter pylori* in gastric cancer, and human papilloma virus in gynecological cancers [1]. Several meta-analyses have shown that previous inflammatory diseases in the lungs, such as pneumonia, chronic bronchitis, and pulmonary tuberculosis (TB), may increase the risk of lung cancer (relative risk ratio 1.36–1.90), independent of cigarette smoking [2][3]. According to forty-nine studies, pulmonary and extra-pulmonary TB infections increase the risk of 10 cancer types, including head and neck cancer, leukemia, lymphoma, gastrointestinal cancer, kidney cancer, bladder cancer, and lung cancer [4]. Thus, TB infection may influence the pathogenesis of lung cancer with or without cigarette smoking. To prevent the emergence of airborne transmittable TB and its progression to cancer, the control and prevention of TB is very important.

2. Pulmonary TB and Risk of Lung Cancer with All Eligible Studies

The overall association between a previous history of pulmonary TB and newly diagnosed lung cancer was statistically significant (odds ratio (OR): 2.09; 95% confidence interval (CI): 1.62–2.69, $p < 0.001$). There was high heterogeneity ($I^2 = 95\%$), no evidence of publication bias, the egger p-value was 0.447, and no visual asymmetry in the funnel plot (**Figure 1**A and **Figure 2**A). In the subgroup analysis by TB burden, the high-burden countries showed higher OR (2.57, 95% CI: 1.68–3.93, $p < 0.001$) than the medium-burden (OR: 2.48, 95% CI: 1.71–3.58, $p < 0.001$) and low-burden countries (OR: 1.77, 95% CI: 1.22–2.56, $p = 0.003$). Geographically, East Asia and the Pacific region showed a prominent risk (OR: 2.49, 95% CI: 1.83–3.39, $p < 0.001$) compared to the Europe and Central Asia (OR: 1.60, 95% CI: 0.80–3.22, $p = 0.185$) or North America (OR: 1.53, 95% CI: 1.11–2.12, $p = 0.010$)

regions. The economic income statuses of the countries also reflected the characteristics of patients with TB, and the countries with upper-middle incomes (OR: 2.57, 95% CI: 1.68–3.93, $p < 0.001$) demonstrated a higher risk of lung cancer than high-income status countries (OR: 1.91, 95% CI: 1.41–2.59, $p < 0.001$). The association between pulmonary TB and newly developed lung cancer was statistically significant regardless of the adjustment for age, sex, smoking status, and cohort type or study design. The magnitude of association was similar regardless of whether pulmonary TB was diagnosed based on medical records (OR: 2.26, 95% CI: 1.29–3.94, $p = 0.004$), imaging (OR: 2.13, 95% CI: 1.16–3.92, $p = 0.015$), or self-report/physical examination (OR: 1.96, 95% CI: 1.56–2.47, $p < 0.001$). The heterogeneity within subgroups remained at a high level in a majority of the subgroup analyses (**Table 1**).



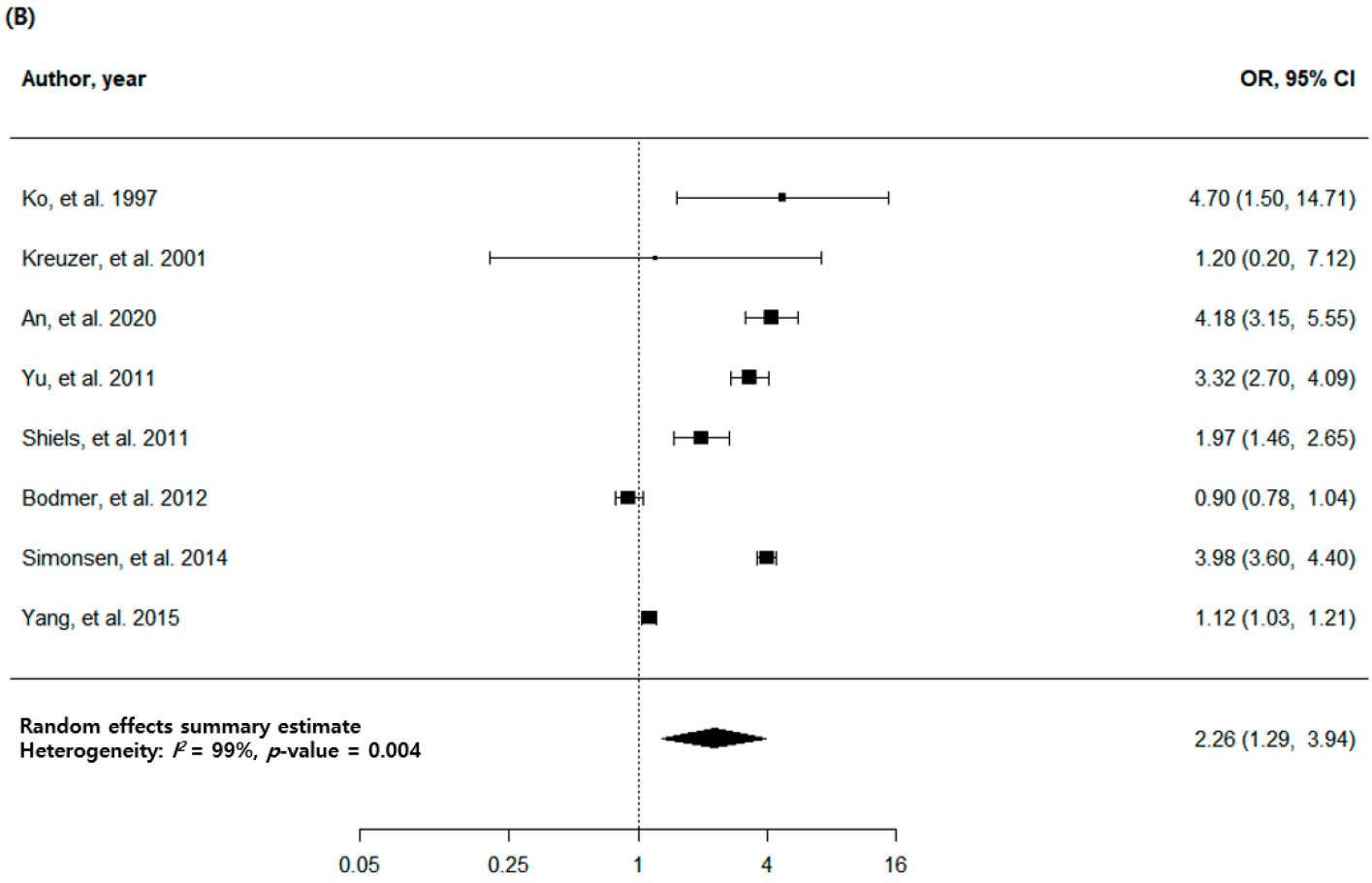


Figure 1. Forest plots of risk estimates for the association between tuberculosis and lung cancer. (**A**) Meta-analysis of all eligible studies. (**B**) Meta-analysis of high-quality studies.

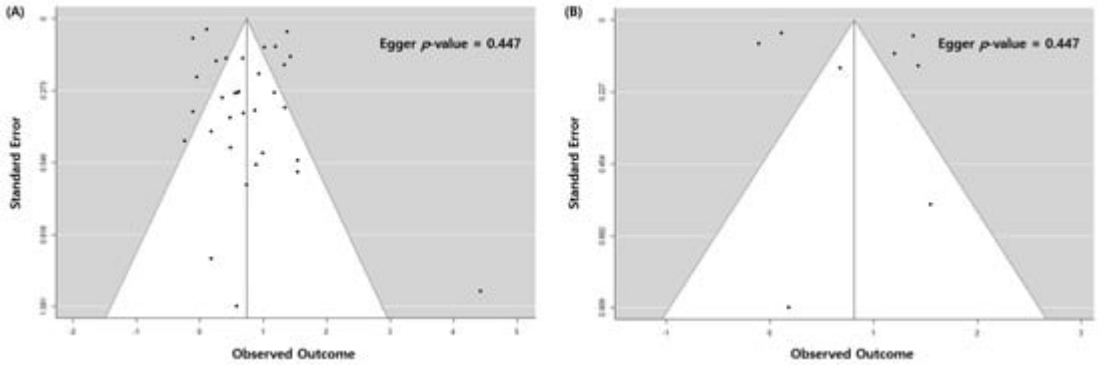


Figure 2. Funnel plot of the study estimates. (**A**) All eligible studies. (**B**) High-quality studies.

Table 1. Meta-analysis of 33 eligible cohorts to assess the association between pulmonary tuberculosis and lung cancer.

Subgroup	No. of Cohorts *	OR (95% CI)	*p*-Value	I^2 Value (%)	I^2 between Subgroups (%)
All cohorts	33	2.09 (1.62–2.69)	<0.001	95	

Subgroup	No. of Cohorts *	OR (95% CI)	*p*-Value	I^2 Value (%)	I^2 between Subgroups (%)
TB burden of country					
Low	18	1.77 (1.22–2.56)	0.003	97	12
Medium	6	2.48 (1.71–3.58)	<0.001	75	
High	9	2.57 (1.68–3.93)	<0.001	81	
Region of country					
East Asia and Pacific	19	2.49 (1.83–3.39)	<0.001	93	58
Europe and Central Asia	7	1.60 (0.80–3.22)	0.185	98	
North America	7	1.53 (1.11–2.12)	0.010	0	
Economic status of country					
High-income	24	1.91 (1.41–2.59)	<0.001	96	20
Upper-middle-income	9	2.57 (1.68–3.93)	<0.001	81	
Age					
Adjusted	29	2.00 (1.54–2.61)	<0.001	95	14
Not adjusted	4	3.84 (1.21–12.15)	0.022	82	
Sex					
Adjusted	22	2.23 (1.60–3.11)	<0.001	96	0
Not adjusted	11	1.90 (1.47–2.46)	<0.001	61	
Smoking					
Adjusted	22	2.03 (1.51–2.73)	<0.001	90	0
Not adjusted	11	2.19 (1.34–3.59)	0.002	98	
Hypertension					
Adjusted	2	1.92 (0.66–5.57)	0.230	99	0
Not adjusted	31	2.10 (1.62–2.73)	<0.001	92	

Subgroup	No. of Cohorts *	OR (95% CI)	*p*-Value	I^2 Value (%)	I^2 between Subgroups (%)
Diabetes					
Adjusted	2	1.72 (0.48–6.20)	0.404	99	0
Not adjusted	31	2.13 (1.63–2.77)	<0.001	94	
Respiratory comorbidities					
Adjusted	8	1.32 (0.93–1.86)	0.121	94	90
Not adjusted	25	2.51 (2.04–3.08)	<0.001	78	
Cohort of the study					
Population-based	23	1.95 (1.41–2.68)	<0.001	96	0
Hospital-based	10	2.36 (1.85–3.01)	<0.001	49	
Study design					
Prospective cohort study	4	1.96 (1.22–3.15)	0.005	84	94
Retrospective cohort study	2	3.95 (3.58–4.36)	<0.001	0	
Case-control study	27	1.99 (1.56–2.53)	<0.001	89	
Diagnostic method of pulmonary TB					
Medical record	8	2.26 (1.29–3.94)	0.004	99	0
Imaging	3	2.13 (1.16–3.92)	0.015	80	
Self-report or physical examination	22	1.96 (1.56–2.47)	<0.001	66	

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gger p = 0.621, and no visual asymmetry in the funnel plot (**Figure 1**B and **Figure 2**B). Of the eight articles, seven had cohorts from countries with a low TB burden, and only one had a cohort from a country with a medium TB burden. In the subgroup analysis with a TB burden, the medium-burden countries showed higher OR (4.18, 95% CI: 3.15–5.55, $p < 0.001$) than the low-burden countries (OR: 2.04, 95% CI: 1.12–3.73, $p = 0.020$). Geographically, the East Asia and the Pacific region showed a more prominent risk (OR: 2.79, 95% CI: 1.21–6.39, $p = 0.016$) compared to the Europe and Central Asia regions (OR: 1.79, 95% CI: 0.67–4.77, $p = 0.244$) (**Table 2**).

Table 2. Meta-analysis of high-quality studies to assess the association between TB and lung cancer.

Subgroup	No. of Studies	OR (95% CI)	*p*-Value	I^2 Value (%)	I^2 between Subgroups (%)
All studies	8	2.26 (1.29–3.94)	0.004	99	
Country of TB burden					
Low	7	2.04 (1.12–3.73)	0.020	99	78
Medium	1	4.18 (3.15–5.55)	<0.001	-	
High	0	-	-	-	
Region of country					
East Asia and Pacific	4	2.79 (1.21–6.39)	0.016	98	0
Europe and Central Asia	4	1.79 (0.67–4.77)	0.244	99	
North America	0	-	-	-	

Abbreviations: CI, confidence interval; No, Number; OR, odds ratio; TB, tuberculosis.

4. Stratified and Sensitivity Analysis

The quality of the 33 included articles was evaluated using the NOS. The quality assessment of 27 case–control studies is shown in **Table 3** and that of six retrospective cohort studies is demonstrated in **Table 4**. Meta-regression analyses were performed with continuous variables, such as the mean age at diagnosis of pulmonary TB, baseline characteristics including comorbidity, and pathological cell type of lung cancer. Of these, patients with a low mean age at diagnosis of pulmonary TB showed a significant association between pulmonary TB and lung cancer. The primary analysis with all 32 articles estimated a regression coefficient of 0.949 ($p < 0.001$). The secondary analysis with eight high-quality studies with stringent TB diagnostic methods showed similar results (regression coefficient = 0.945, $p < 0.001$) (**Figure 3**).

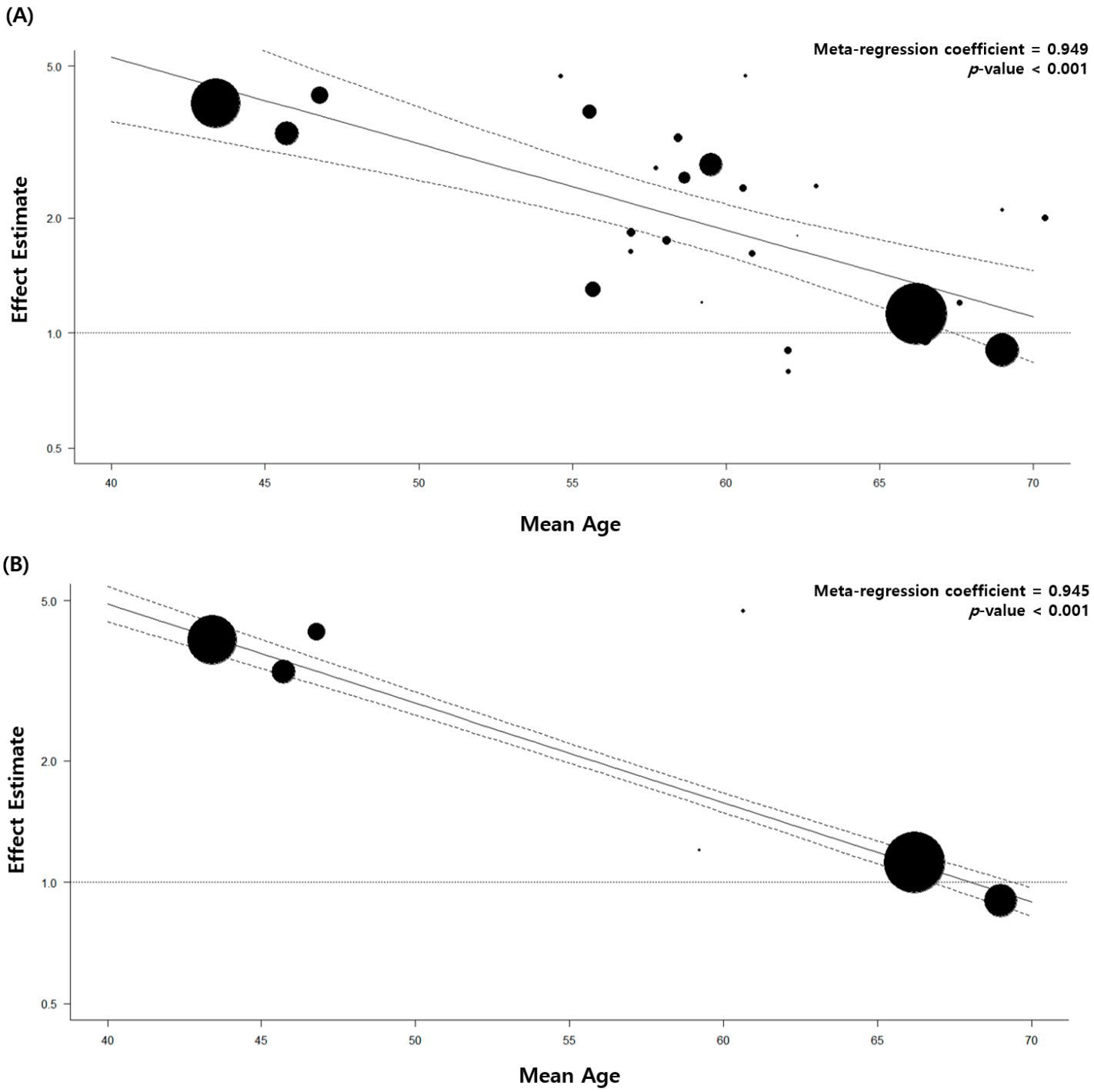

Figure 3. Meta-regression analysis of the mean patient age and association between tuberculosis and lung cancer. (**A**) All eligible studies. (**B**) High-quality studies.

Table 3. Quality assessment of the included case–control studies using the Newcastle–Ottawa Scale.

Study	Selection				Comparability	Outcome			Quality Score
	Adequacy of Case Definition	Degree of Representation of Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of Design or Analysis	Confirmation of Exposure	Same Method of Confirmation for Cases and Controls	Non-Response Rate	
An et al. 2020 [5]	*	*	*	*	**	*	*	*	9
Yang et al. 2015 [6]	*	*	*	*	**		*	*	8
Yang et al. 2015 [7]	*	*	*	*	*	*	*	*	8
Hosgood et al. 2013 [8]	*	*	*	*	*		*	*	7
Lo et al. 2013 [9]	*	*	*	*	**		*	*	8
Bodmer et al. 2012 [10]	*	*	*	*	**	*	*	*	9
Koshiol et al. 2010 [11]	*	*	*	*	**		*	*	8
Park et al. 2010 [12]	*	*	*	*	**		*		7
Liang et al. 2009 [13]	*	*	*	*	**		*	*	8
Wang et al. 2009 [14]	*	*	*	*	*		*	*	7
Galeone et al. 2008 [15]	*	*	*	*	**		*	*	8
Ramanakumar et al. 2006 [16] a	*	*	*	*	**		*	*	8
Ramanakumar et al. 2006 [16] b	*	*	*	*	**		*	*	8
Zatloukal et al. 2003 [17]	*	*	*	*	**		*	*	8

Study	Selection			Comparability		Outcome			Quality Score
	Adequacy of Case Definition	Degree of Representation of Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of Design or Analysis	Confirmation of Exposure	Same Method of Confirmation for Cases and Controls	Non-Response Rate	
Chan-Yeung et al. 2003 [18]	*	*	*	*	*		*	*	7
Kreuzer et al. 2002 [19]	*	*	*	*	*		*	*	7
Brenner et al. 2001 [20]	*	*	*	*	**		*	*	8
Kreuzer et al. 2001 [21]	*	*	*	*	*	*	*	*	8
Zhou et al. 2000 [22]	*	*	*	*	*		*	*	7
Osann et al. 2000 [23]	*	*	*	*	**		*	*	8
Mayne et al. 1999 [24]	*	*	*	*	*		*	*	7
Ko et al. 1997 [25]	*	*	*	*		*	*	*	7
Schwartz et al. 1996 [26]	*	*	*	*	**		*	*	8
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Study	Selection			Comparability		Outcome			Quality Score
	Degree of Representation of the Exposed Cohort	Selection of the Non-Exposed Cohort	Confirmation of Exposure	Demonstration That the Current Outcome of Interest Is Absent at the Start of the Study	Comparability of Cohorts Based on Design or Analysis	Assessment of Outcome	Sufficiency of Follow-Up to Detect Outcomes	Adequacy of Follow-Up of Cohorts	
Kim et al. 2020 [31]	*	*		*	**	*	*		7
Oh et al. 2020 [32]	*	*		*	**	*	*	*	8
Simonsen et al. 2014 [33]	*	*	*	*	*	*	*	*	8
Bae et al. 2013 [34]	*	*		*	**	*	*		7
Shiels et al. 2011	*	*	*	*	**	*	*	*	9

	Selection				Comparability	Outcome			
Study	Degree of Representation of the Exposed Cohort	Selection of the Non-Exposed Cohort	Confirmation of Exposure	Demonstration That the Current Outcome of Interest Is Absent at the Start of the Study	Comparability of Cohorts Based on Design or Analysis	Assessment of Outcome	Sufficiency of Follow-Up to Detect Outcomes	Adequacy of Follow-Up of Cohorts	Quality Score
[35]									
Yu et al. 2011 [36]	*	*	*	*	*	*	*		7

It can be awarded a maximum of one star for each item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

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