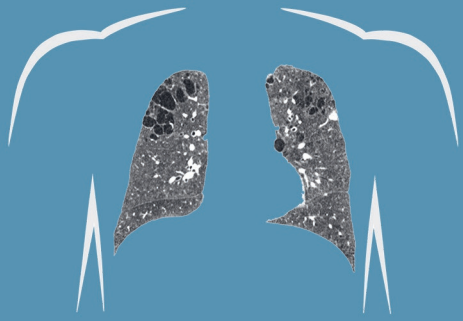

Chapter 4

Association between Chest CT defined Emphysema and Lung Cancer: A Systematic Review and Meta-Analysis

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Abstract

***Background*:** Given the different methods of assessing emphysema, controversy exists as to whether it is associated with lung cancer. anaaysis

Purpose: To perform a systematic review and meta-analysis of the association between emphysema found on chest CT with the presence of lung cancer.

***Materials and Methods*:** The PubMed, EMBASE, and Cochrane databases were searched up to July 15, 2021 to identify studies on the association between emphysema assessed visually or quantitatively by CT and lung cancer. Associations were determined by emphysema severity (trace, mild, and moderate-severe; assessed visually and quantitatively) and subtype (centrilobular and paraseptal assessed visually). Overall and stratified pooled odds ratios (ORs) with their 95% confidence intervals were obtained.

Results: Of the 3343 screened studies, 21 studies (107,082 participants) with 26 subsets were included. The overall pooled ORs for lung cancer given the presence of emphysema were 2.3 (95% CI: 2.0, 2.6; I^2 = 35%; 19 subsets) and 1.02 (95% CI, 1.01, 1.02; 6 subsets) per 1% increase in low attenuation area. Studies with visual (pooled OR, 2.3; 95% CI: 1.9, 2.6; I^2 = 48.4%; 12 subsets) and quantitative (pooled OR, 2.2; 95% CI, 1.8, 2.8; I^2 = 3.7%; eight subsets) assessments yielded comparable results for the dichotomous assessment. Based on six studies (1716 participants), the pooled ORs for lung cancer increased with emphysema severity and were higher for visual assessment (2.5, 3.7, and 4.5 for trace, mild, and moderate-severe, respectively) than for quantitative assessment (1.9, 2.2 and 2.5) based on point estimates. Compared with no emphysema, only centrilobular emphysema (three studies) was associated with lung cancer (pooled OR, 2.2; 95% CI: 1.5, 3.2; P <.001).

Conclusion: Both visual and quantitative CT assessments of emphysema were associated with a higher odds of lung cancer, and this odds increased with emphysema severity. Regarding subtype, only centrilobular emphysema was significantly associated with lung

cancer.

Clinical trial registration no. CRD42021262163

Summary

Both visual and quantitative emphysema assessed at chest CT were associated with a higher odds ratio of lung cancer, and this association increased with emphysema severity.

Key Results

- Systematic review of 21 studies (107,082 participants) comparing the association of chest-CT-defined emphysema with lung cancer showed an overall pooled odds ratio (OR) of 2.3 (P<.001)
- ORs for lung cancer increased with emphysema severity and were higher for visual assessment (OR: 2.5, 3.7, and 4.5 for trace, mild, and moderate to severe emphysema, respectively) compared with quantitative assessment (OR: 1.9, 2.2, and 2.5, respectively).

Abbreviations

HR = hazard ratio

HU = hounsfield unit

LAA = low attenuation area

OR = odds ratio

Introduction

Lung cancer is the primary cause of cancer-related death worldwide (1), with more than 1 million attributable deaths each year since 2000 (2). However, lung cancer risk can be reduced by identifying treatable risk factors, such as chronic lung inflammation (3), together with smoking, genetics, diet, and occupational exposure (3). Emphysema is characterized pathologically by the presence of diffuse chronic inflammation of the lung parenchyma, oxidative stress, and lung destruction (4). Thus, lung cancer and emphysema are linked by common predisposing risk factors and multiple molecular inflammatory processes (5).

Emphysema can be assessed by chest CT, radiography, or pulmonary function tests, though chest CT has the highest sensitivity (6, 7) and is considered the reference standard for non-invasive assessment (8). Numerous studies have explored the association between the chest CT assessment of emphysema and lung cancer, but these have yielded inconsistent results (9-12). Associations have been shown between emphysema and lung cancer on chest CTs for qualitative visual assessment by radiologists (12, 13) but not for automated quantitative assessment (9, 10). These data were subsequently confirmed by comparing the two methods directly (14), indicating that the method used to assess emphysema may have affected previous outcomes. Consistent with this, a meta-analysis in 2012 showed that visual assessment of emphysema on chest CT was independently associated with lung cancer (15), but no such association was present for quantitative assessment. However, that conclusion was based on data from only two studies. Although systematic reviews in 2020 and 2016 concluded that emphysema assessed with chest CT was associated with an increased risk of lung cancer (16, 17), these did not provide pooled risk estimates or stratify data by how emphysema was assessed, which may have affected their results. Other studies exploring the association of emphysema severity or subtype on CT with lung cancer have produced mixed results (9, 18-21). To the best of our knowledge, a pooled analysis about these associations has not been performed.

There is a need to update and synthesize data from existing and new studies, especially those using quantitative emphysema assessment. Our purpose was to perform a systematic review and meta-analysis of the association between emphysema found on chest CT with the presence of lung cancer.

Materials and Methods

Search Strategy and Study Selection

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis reporting guidelines (22) and registered in the international prospective register of systematic reviews (PROSPERO[CRD42021262163]). The published studies were retrieved and screened from the PubMed, EMBASE, and Cochrane databases from inception to the 15th of July 2021(Table E1).

We included studies investigating the association between emphysema and lung cancer if they were original research and published in English, with lung cancer diagnosed by histopathology (independent of histologic subtype) and emphysema diagnosed by CT. The exclusion criteria of studies were specifically described in Figure 1. For multiple articles concerning the same cohort, we selected the study from which most data could be extracted.

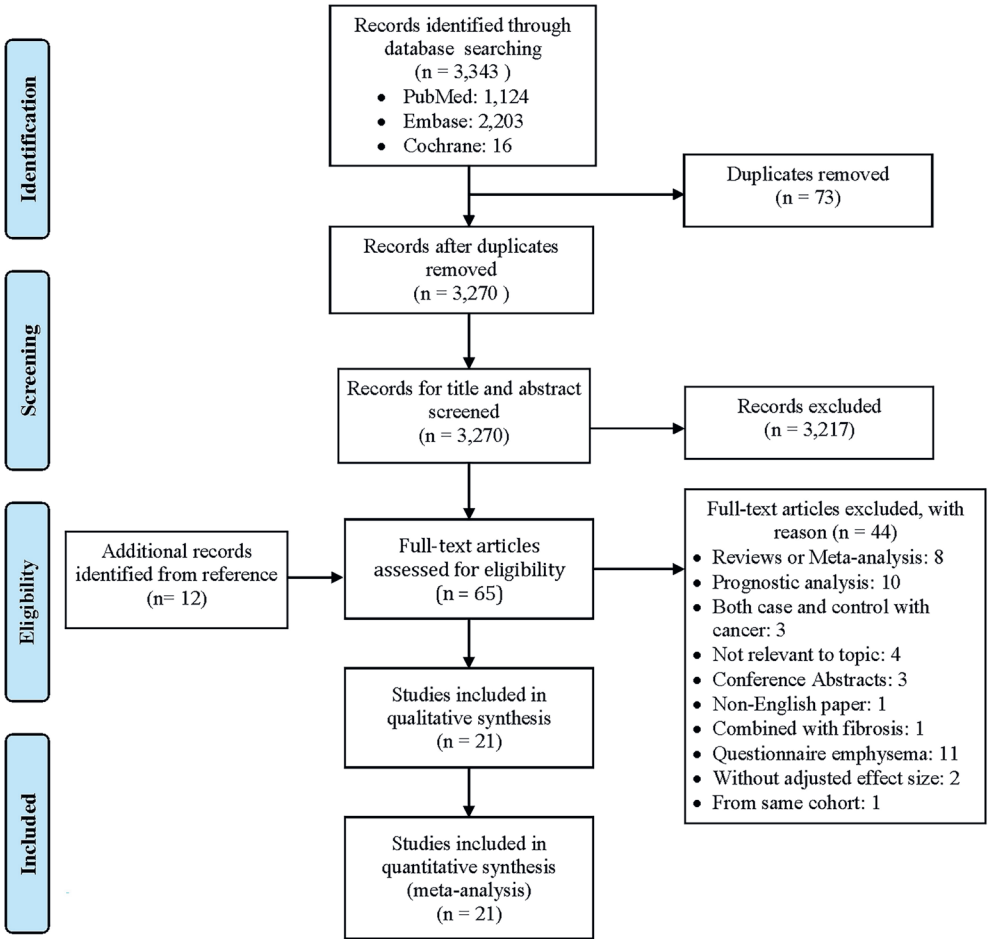

Figure 1: Flowchart of study selection.

Definitions of Emphysema and Lung Cancer

Visual emphysema was defined as disrupted lung vasculature and parenchyma with low attenuation occupy in any lung zone (at least trace) on chest CT, as evaluated by radiologists using the National Emphysema Treatment Trial (NETT) or Fleischner Society (23, 24) guidelines or comparable (See table E2). Quantitative emphysema was defined by the percentage of total lung volume below a given Hounsfield unit (HU) threshold (−950 HU at full inspiration), reported as the low attenuation area percentage (LAA%). A specific

LAA% threshold was defined "emphysema present." When grading emphysema severity (trace, mild, moderate, and severe), specific percentages of visual (Fleischner society or NETT) or quantitation were used to assess emphysematous lung tissue destruction on CT (e.g. mild: 0-25%, moderate: 26-50%, and severe: ≥ 51%). The main emphysema subtypes were paraseptal and centrilobular, which could only be assessed visually on CT. Paraseptal emphysema was defined as the presence of a few well-demarcated, round, juxta-pleural lucencies; while, centrilobular emphysema was defined as centrilobular distribution of lucencies. Finally, eligible cases of lung cancer were confirmed pathologically from surgical, biopsy, or cytological samples, without specifying the subtype.

Data Collection and Quality Assessment

Two researchers (X.F. with 5 years of experience in radiology. H.J.W. with 3 years of experience in radiology) independently performed all data collection and assessments. Study eligibility was determined by title and abstract screening, followed by full-text evaluation. Disagreements were settled by consensus or referral to a third reviewer (M.D.D., with over 10 years of experience in radiology), and agreement was quantified by kappa statistics. A standardized table was used to extract data, including first author name; publication year; country; study design; participant source, age, and sex; assessment method; emphysema definition, subtype, and severity; CT scanner, scanning mode, slice thickness, reconstruction algorithm, HU threshold, and LAA%; effect sizes, including odds ratios (ORs), risk ratios, and hazard ratios (HRs), with 95% CIs; and adjusted or matched factors.

The Newcastle–Ottawa scale was used to assess cohort and case-control study quality by group selection, comparability, and exposure/outcome reliability, with a star-based scale ranging from 0 to 9 stars (25). We awarded stars for comparability if there was adjustment for age and sex and additional adjustment for smoking. Studies were considered to be

low, medium, or high quality if they had ≤5, 6–7, or 8–9 stars, respectively (26). Any discrepancies were resolved by consensus.

Statistical Analysis

We stratified studies by visual or quantitative assessment and set confirmed lung cancer as the main outcome. The adjusted OR given the presence of emphysema was the main outcome, with risk ratios and HRs interpreted as ORs due to the low incidence of lung cancer (27, 28). When a study reported stratified ORs, an overall OR was estimated by applying a random-effect model. For studies that stratified ORs by severity, we pooled data for moderate and severe emphysema. To estimate the odds of developing lung cancer among participants with and without emphysema, we pooled data under the assumption of homogeneity by applying a random-effect model. Forest plots were presented to illustrate the pooled results and related heterogeneity. Pooled ORs and 95% CIs were provided for dichotomous or continuous measurements of emphysema. Analyses were repeated for emphysema severity and subtype (visual assessment).

Heterogeneity was estimated by the I^2 statistic and quantified as low (0%–25%), moderate (26%–50%), substantial (51%–75%), or considerable (76%–100%) (29, 30). Potential sources of heterogeneity were explored by stratified analysis based on participant sources, study design, effect size study quality, CT slice thickness (normal ≥ 5 mm vs thin 0.5-1.25 mm), and HU cut-off value. Funnel plots were presented to evaluate publication bias. Asymmetry which is an indication for publication bias was evaluated visually and by Egger's test. As a next step, the trim-and-fill method was applied to evaluate the stability of our results by correcting for publication bias. The robustness of estimates was evaluated by leave-one-out sensitivity analysis, removing each study sequentially and recalculating the OR.

Statistical analysis was conducted with Stata Standard Edition, version 15.1 (StataCorp); *P*

< .05 was considered indicative of statistically significant difference.

Results

Study Selection and Quality

As shown in Figure 1, 3,217 of 3,270 studies were excluded after screening abstract and title. Full-text screening resulted in 21 articles that met all criteria for inclusion in the meta-analysis. The kappa values of the two screening stages were 0.80 (title and abstract) and 0.62 (full text), respectively. Of the included studies, 2 featured both visual and quantitative assessment (31, 32), 20 reported emphysema as a dichotomous variable only (visual and quantitative assessment), 2 as a continuous variable only (33, 34), and 4 as both variables (9, 10, 19, 31). This resulted in 26 study subsets for inclusion in the final meta-analysis. Regarding study quality, 15, six and none were considered high, medium and low quality, respectively (Table E3).

Study Characteristics

Overall, the 21 studies included 3,907 participants with lung cancer and 103,175 controls (Table 1, 2), with sample sizes ranging from 120 to 62,124. By study design, cohort studies (52%, 11 of 21) contributed 1,868 cases of lung cancer from 101,679 participants and case-control studies (48%, 10 of 21) contributed 2,039 cases of lung cancer from 5,403 participants. In total, 74% of the 107,082 participants came from North America (78,874 [11 studies]), 26% from Europe (27,392 of 107,082, eight studies), and 0.8% from Asia (816 of 107,082, two studies).

Table 1: Characteristics of included studies that assessed emphysema visually on chest CT

Study	Country	With/Without Lung Cancer	Age (Mean ± SD)	Source	Study Design	Effect Size (95% CI)
de Torres 2007 (13)	Spain	23/1,166	Case: 54 ± 8 Control: 54 ± 8	PB	Cohort; Prospective study	RR: 2.5 (1.0, 6.2)
Wilson 2008 (12)	U.S.	99/3,539	NS	PB	Cohort; Prospective study	OR: 3.1 (1.9, 5.2)
Li 2011 (35)	U.S.	565/450	Case: 67 ± 8 Control: 66 ± 6	HB	Case-control; Retrospective study	OR: 2.8 (2.1, –3.8)
Maisonneuve 2011 (36)	Italy	85/4,511	NS	PB	Cohort; Retrospective study	HR: 1.8 (1.2, 2.6)
Henschke 2015 (37)	U.S.	668/61,456	NS	PB	Cohort; Prospective study	OR: 2.0 (1.4, 2.9)
Sanchez-Salcedo 2015 (38)	Spain	53/2,936	Case: 60 (55–65) [#] Control: 55 (49–62) [#]	HB	Cohort; Prospective study	HR: 3.3 (1.8, 5.9)
de Torres 2015 (39)	U.S.	134/1,419	Overall: 61 ± 7	PB	Cohort; Prospective study	HR: 2.7 (1.7, 4.3)
Liu 2018 (40)	U.S.	73/157	Case: 64 (55–74) [#] Control: 63 (55–74) [#]	PB	Case-control; Prospective study	OR: 1.8 (1.4, 1.9)
Gonzalez 2019 (21)	Spain	72/215	Case: 64 ± 9 Control: 64 ± 9	PB	Case-control; Prospective study	OR: 5.4 (2.6, 11.4)
Yong 2019 (41)	Norway	367/16,257	Case: 62 ± 6 Control: 61 ± 5	PB	Cohort; Retrospective study	HR: 2.0 (1.6, 2.6)

Note.— See Table E4 for full detail. HB = hospital-based, HR = hazard ratio, NS = not specified, OR = odds ratio, PB = population-based, RR = risk ratio, SD = standard deviation. All the effect sizes adjusted for smoking, except for study Henschke 2015; For specific adjusted factors, see Tables E2. [#]Numbers are medians, with ranges in parentheses.

Table 2: Characteristics of included studies that assessed emphysema quantitatively on chest CT

Study	Country	With/Without Lung Cancer[#]	Age (Mean ± SD)	Source	Study Design	Effect Size (95% CI)
Kishi 2002 (10)	U.S.	24/96	Case: 64 ± 7 Control: 63 ± 6	HB	Case-control; Retrospective study	OR:1.1 (0.5, 2.4) *OR: 1.1(0.6, 1.9)
Maldonado 2010 (9, 42)	U.S.	64/377	Case: 63 ± 7 Control: 62 ±6	PB	Case-control; Prospective study	OR: 1.9 (1.1, 3.3) *OR:1.04 (0.8, 1.3)
Gierada 2011 (11)	U.S.	279/279	Case: 63 ± 5 Control: 61 ± 5	PB	Case-control; Retrospective study	OR:2.0 (1.0–3.8)
Aamli Gagnat 2017 (19)	Norway	34/741	Overall: 59 ± 10	PB	Cohort; Prospective study	HR: 2.4 (0.9, 6.2) *HR: 1.03(0.7, 1.5)
Chubachi 2017 (18)	Japan	21/219	Case: 73 ± 7 Control: 73 ± 8	HB	Cohort; Prospective study	OR: 4.2 (1.0–29.0)
Mouronte-Roibas 2018 (20)	Spain	169/74	Case: 69 ± 9 Control: 65 ± 10	HB	Case-control; Retrospective study	OR: 2.2 (1.1, 4.3)
Nishio 2019 (34)	Japan	283/293	Case: 69 ± 10 Control: 65 ± 14	HB	Case-control; Retrospective study	*OR: 1.01 (1.00–1.02)
Husebø 2019 (43)	Norway	31/681	Case: 64 ± 7 Overall: 58 ±10	HB	Cohort; Prospective study	HR: 4.4 (1.7, 10.8)
Labaki 2021 (33)	U.S.	353/6,909	Overall: 62 ± 5	PB	Cohort; Prospective study	*HR: 1.02 (1.01–1.03)
Schwartz 2016 (32)	U.S.	341/752	Case: 64 ± 10 Control: 62 ± 9	PB	Case-control; Retrospective study	OR (visual): 1.8 (1.4, 2.4) OR (quantitative): 2.7 (1.8, 4.0)
Carr 2018 (31)	U.S.	169/671	Case: 66 ± 8 Control: 64 ± 8	PB	Case-control; Prospective study	OR (visual)*: 2.3 (1.4, 3.8) *OR (quantitative): 1.03 (0.6, 1.8)

Note.— See Table E5 for full detail. HB = hospital-based, HR = hazard ratio, OR = odds ratio, PB = population-based, SD = standard deviation. [#] Data are numbers of patients * Effect size when emphysema was assessed as a continuous variable. All the effect sizes adjusted for smoking; For specific adjusted factors, see Tables E2.

Visual assessment was used in 12 study subsets with 95,062 participants, while quantitative dichotomous assessment was used in 8 study subsets with 4,758 participants, identifying emphysema in 25% (23,742 of 95,062) and 27% (1,079 of 4,046), respectively. Moreover, quantitative continuous assessment (i.e., LAA%) was used in 6 subsets with 10,014 participants. The definitions of emphysema used for visual and quantitative assessment varied across studies (Table E2). The HU threshold for LAA in quantitative assessments varied from -880 to -950 HU, while LAA% cut-offs for the presence of emphysema varied from 1% to 25%. This contributed to a wide variation in the incidence of emphysema from 8% (44 of 558 participants) to 80% (195 of 243 participants). Moreover, uniformity was lacking for both HU thresholds and LAA% cut-offs for emphysema severity.

All studies confirmed lung cancer by histological examination. A total of six studies (three visual, three quantitative; 459 lung cancers among 6,242 participants) explored the relationship between emphysema severity and lung cancer, whereas 3 studies (all visual; 380 lung cancers among 1,716 participants) explored the association between emphysema subtype and lung cancer. Participant sources, were hospital-based (33%, [seven of 21 studies]), or population-based (67% [14 of 21]).

Data Synthesis and Meta-Analysis

The overall pooled estimate for the association between emphysema and lung cancer was 2.3 (95% CI: 2.0, 2.6) (Figure 2), which was robust in the leave-one-out sensitivity analysis (Figure E1). The pooled OR for every 1% increase in the LAA% was 1.02 (95% CI: 1.01, 1.02) (Figure E2). Moderate heterogeneity was observed among studies (I^2 = 34.6%; P = .07), reasonable symmetry was identified at the visual inspection of funnel plot (Figure E3), and Egger's test identified evidence of potential publication bias (P =.04) favoring the existence of unpublished studies. Thus, the trim-and-fill correction for potential publication bias did not alter the association (pooled OR, 2.0; 95% CI: 1.7, 2.3; Figure E4).

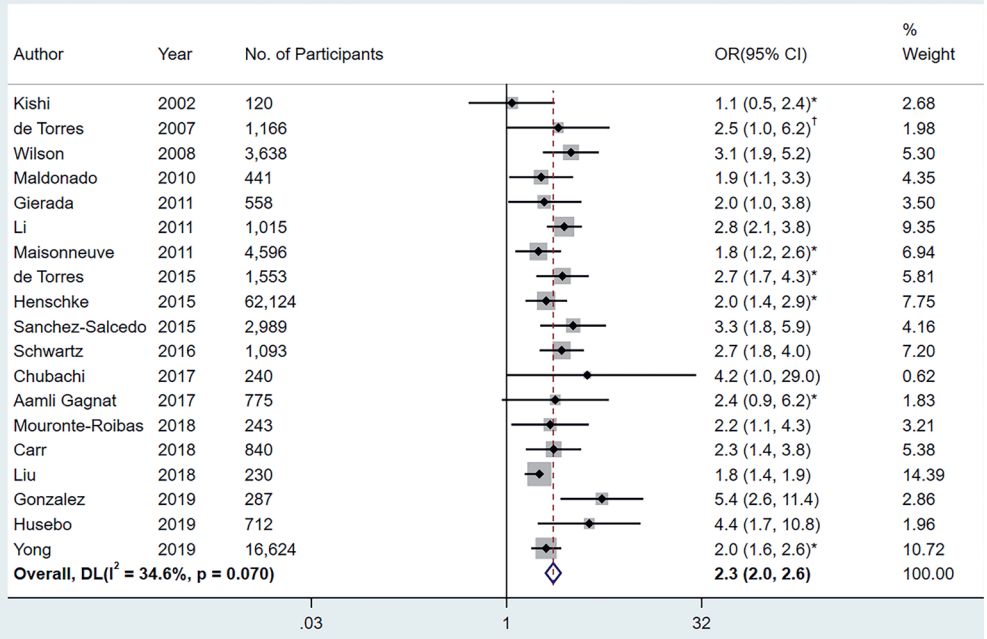

Figure 2. Forest plot of the random-effects meta-analysis for the association between emphysema (dichotomous variable) assessed visually and or quantitatively by CT and lung cancer within 19 studies. The overall pooled OR of emphysema for lung cancer was 2.3 (95% CI: 2.0, 2.6; [$P < .001$]). For the studies which assessed emphysema by two methods, only the ORs assessed by the main method were pooled in the overall estimates. Squares and horizontal lines represent the estimate and 95% CI, respectively, for each study part. Diamond indicates pooled effect sizes and 95% CIs. DL = DerSimonian & Laird. * = Study reported hazard ratios. † = Study reported risk ratios.

Association between Emphysema and Lung Cancer

The pooled OR for lung cancer given emphysema was 2.3 (95% CI: 1.9, 2.6) in studies using visual assessment and 2.2 (95% CI: 1.8, 2.8) in studies using quantitative dichotomous assessment (Figure 3). Low heterogeneity (I^2 = 3.7%; P = .40) was observed in studies using quantitative assessment and moderate heterogeneity (I^2 = 48.4%; P = .03) was observed in studies using visual assessment (Table 3).

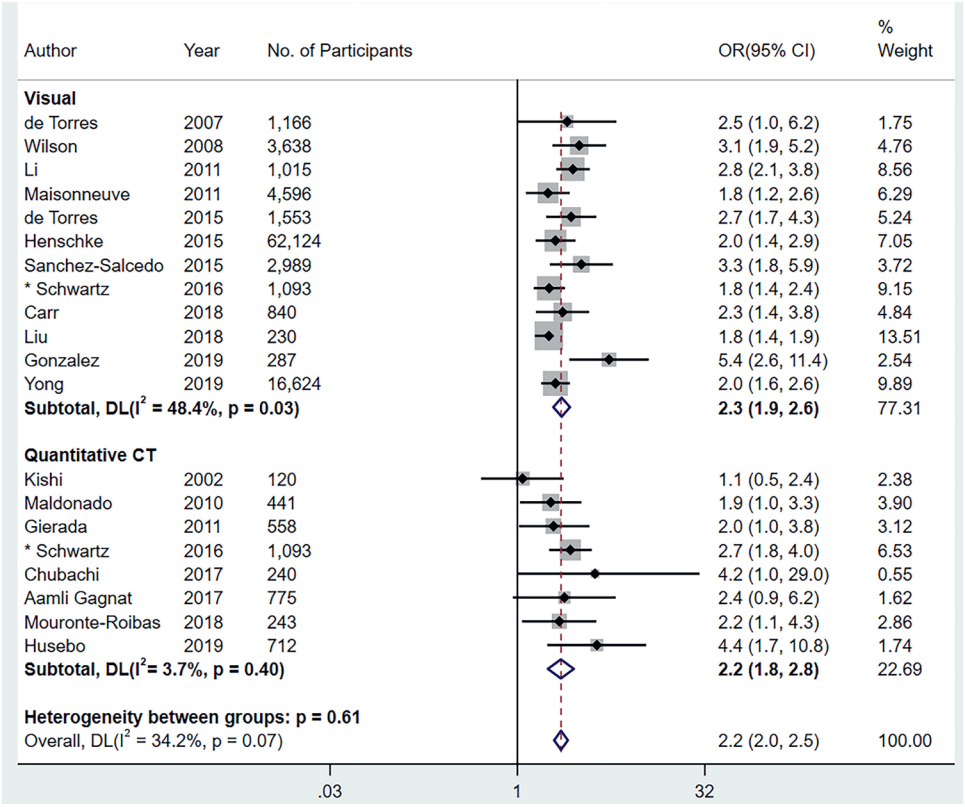

Figure 3: Forest plot of the random-effects meta-analysis for the association between emphysema and lung cancer, stratified by the emphysema assessment method. The pooled odds ratios (ORs) for lung cancer given visual and quantitative dichotomous emphysema assessment were 2.3 (95% CI: 1.9, 2.6 [$P < .001$]) and 2.2 (95% CI: 1.8, 2.8 [$P < .001$]), respectively. Squares and horizontal lines represent estimates and 95% CIs, respectively, for each study part. Diamonds indicate pooled effect sizes with 95% CIs. * = Study assessed emphysema both visually and quantitatively. DL = DerSimonian and Laird.

Table 3: Association Between Emphysema and Lung Cancer Stratified by Emphysema Assessment Method

Assessment method	No. of Studies	No. of Participants	No. of Lung cancers	Pooled Odds Ratio	95% CI	I^2(%)	P Value for heterogeneity	P Value for Method
Visual	12	95,561	2,330	2.3	1.9, 2.6	48.4%	.03	.61
Quantitative	8	5,531	1,616	2.2	1.8, 2.8	3.7%	.40	

Note.—Unless otherwise specified, analysis was based on emphysema when measured as a dichotomous variable.

Association between Emphysema Severity and Lung Cancer

Independent associations existed between different emphysema severities and lung cancer (Figure 4), with the overall pooled ORs for lung cancer gradually increasing (2.2, 3.2, and 3.6) as the emphysema severity increased (trace, mild, and moderate-to-severe, respectively; Table 4). Substantial heterogeneity was observed for studies that reported moderate-to-severe emphysema (I^2 = 52.6%) compared with trace (I^2 = 0%) and mild (I^2 = 20.7%) emphysema. The three studies that used visual assessment gave pooled ORs of 2.5, 3.7, and 4.5 for trace, mild, and moderate-to-severe emphysema, respectively; by contrast, the three studies that used quantitative assessment produced corresponding pooled ORs of 1.9, 2.2, and 2.5.

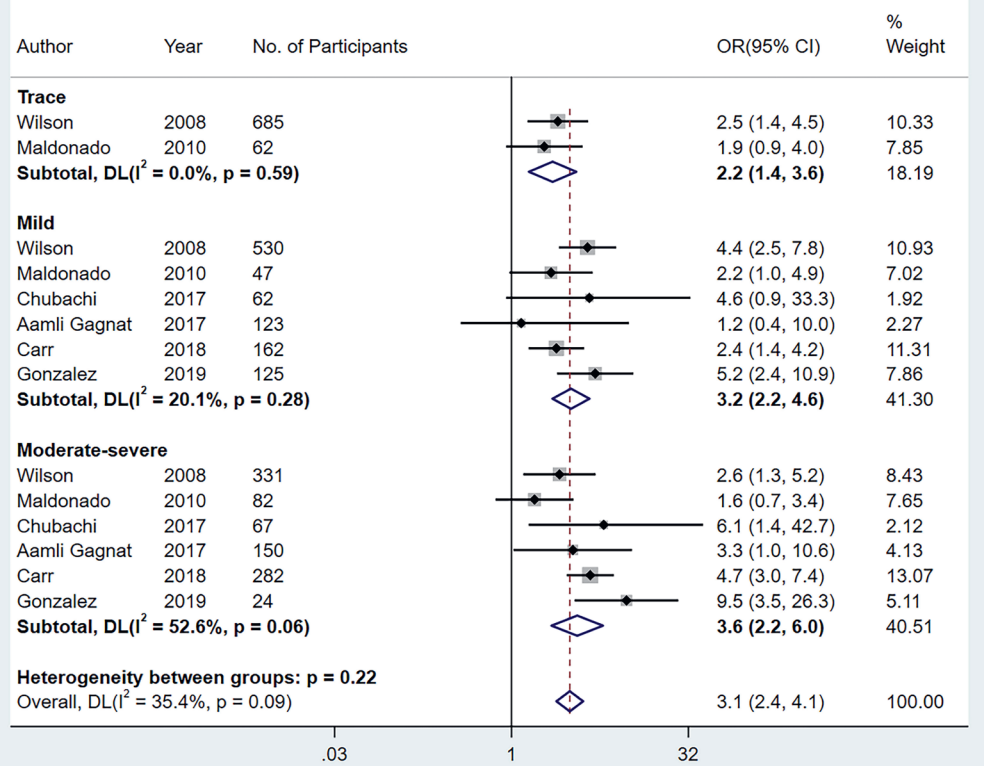

Figure 4: Forest plot of the random-effects meta-analysis for the association between emphysema severity (assessed visually and/or quantitatively) and lung cancer. The overall pooled odds ratios (ORs) of trace, mild, and moderate to severe emphysema for lung cancer were 2.2 (95% CI: 1.4, 3.6 [P = .001]), 3.2 (95% CI: 2.2, 4.6 [P < .001]) and 3.6 (95% CI: 2.2, 6.0 [P < .001]), respectively. Adjusted factors in these mixed-effects models varied, as shown in Table E2. Squares and horizontal lines represent estimates and 95% CIs, respectively, for each study part. Diamonds indicate pooled effect sizes with 95% CIs. DL = DerSimonian and Laird.

Table 4: Association Between Emphysema Severity and Lung Cancer

Emphysema severity	No. of Studies	No. of Participants	No. of Lung Cancers	Pooled Odds Ratio	95%CI	I^2(%)	P Value for heterogeneity	P Value for Severity
Overall								.22
Trace	3	747	34	2.2	1.4, 3.6	0	.59	
Mild	6	1049	140	3.2	2.2, 4.6	20.1	.28	
Moderate-severe	6	936	168	3.6	2.2, 6.0	52.6	.06	
Visual								.27
Trace	1	685	22	2.5	1.4, 4.5	–	–	
Mild	3	817	118	3.7	2.3, 5.8	42.9	.17	
Moderate-severe	3	637	124	4.5	2.5, 8.3	55.9	.10	
Quantitative*								.94
Trace	1	62	12	1.9	0.9, 4.0	–	–	
Mild	3	232	22	2.2	1.1, 4.3	0	.56	
Moderate-severe	3	299	44	2.5	1.2, 5.1	23.0	.27	

* Cut-off value for emphysema severity varied among 6 studies.

Table 5: Association Between Emphysema Subtype (Visual Assessment) and Lung Cancer

Emphysema subtype	No. of Studies	No. of Participants	No. of Lung Cancers	Pooled Odds Ratio	95% CI	I^2 (%)	P Value for heterogeneity	P Value for subtype
Centrilobular emphysema	3	660	258	2.2	1.5, 3.2	0	.37	.003
Paraseptal emphysema	3	471	153	1.1	0.6, 2.0	65.6	.06	

Association between Visual Emphysema Subtypes and Lung Cancer

The pooled OR for lung cancer odds in the presence of centrilobular emphysema was 2.2 (95% CI: 1.5, 3.2), with no heterogeneity observed across the three relevant studies (I^2 = 0%). However, we found no evidence of an association between paraseptal emphysema and lung cancer (pooled OR, 1.1; 95% CI: 0.6, 2.0; Table 4) and there was high heterogeneity (I^2 = 65.6%; Figure 5) in this subset.

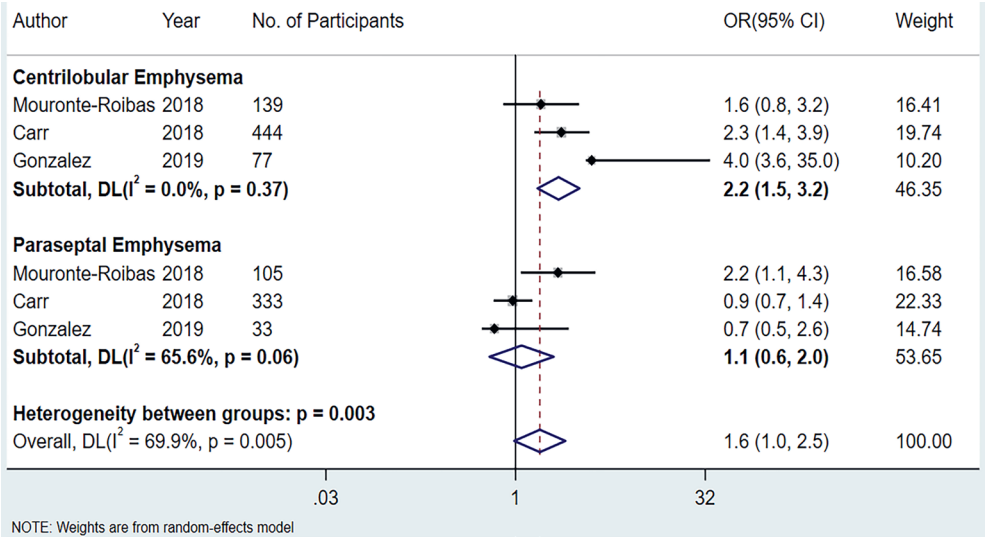

Figure 5: Forest plot of the random-effects meta-analysis for the association between emphysema subtype (assessed visually only) and lung cancer. The pooled odds ratios (ORs) for lung cancer odds in the presence of centrilobular and paraseptal emphysema were 2.2 (95% CI: 1.5, 3.2 [P < .001]) and 1.1 (95% CI: 0.6, 2.0 [P = .71]). Adjusted factors in these mixed-effects models varied, as shown in Table E2. Squares and horizontal lines represent estimates and 95% CIs, respectively, for each study part. Diamonds indicate effect sizes with 95% CIs. DL = DerSimonian and Laird.

Sources of Heterogeneity

In the additional stratified analyses the potential reasons for heterogeneity were explored (Table E6), but we could not find any explanation. The pooled ORs were comparable

between case-control (2.2; 95% CI: 1.8, 2.8; I^2 = 55.0%) and cohort (2.3; 95% CI: 2.0–2.7; I^2 = 0%) studies (P = .46). Population-based studies, which had moderate heterogeneity (I^2 = 27.0%), had a comparable pooled ORs (2.2; 95% CI: 1.9, 2.5) to those of hospital-based studies (2.6; 95% CI, 1.9, 3.6; I^2 = 32.7%) [P = .06]). The variation in study characteristics and study quality did not affect our results (Table E6). The pooled effect sizes were comparable between studies that reported HR (2.3; 95% CI: 1.9, 2.9; I^2 = 19.3%) and studies that reported OR (2.3; 95% CI: 1.9, 2.8; I^2 = 47.6%) [P = .64]). Emphysema assessed quantitatively based on thin CT slices was associated with lung cancer (pooled OR, 2.2; 95%CI: 1.3, 3.7; P = .002), while this was not the case for the assessment based on normal slice thickness. Similarly for LAA HU thresholds, an association with lung cancer was found based on cut-off -950 HU (pooled OR, 2.6; 95% CI: 2.0, 3.4; P < .001), but not for -900 HU.

Discussion

In this systematic review and meta-analysis comparing the association of emphysema on chest CT with presence of lung cancer, we found that both the visual and quantitative CT assessments of emphysema were associated with a higher risk of lung cancer (pooled OR, 2.3; 95% CI: 1.9, 2.6, P < .001), and the odds increased with emphysema severity. Regarding subtype, only centrilobular emphysema was associated with lung cancer (pooled OR, 2.2; 95% CI: 1.5, 3.2, P < .001).

Our study showed that emphysema on CT was associated with a 2.3-fold increased odds of lung cancer, comparable to that reported by Brenner et al. (44) and Zhang et al. (45). However, Smith et al. (15) only found this association for visually diagnosed emphysema, whereas our study demonstrated it for both visual and quantitative methods, irrespective of whether emphysema was analysed as a dichotomous or continuous variable. An explanation for this difference may be that Smith et al. only included two quantitative CT studies in

2012 (1,549 participants), while in our study ten studies were included (12,841 participants).

There was no evidence showing that source of population and study design influenced the overall association between emphysema and lung cancer. Besides, in our study we found comparable pooled ORs for visual and quantitative assessment, implying no difference between them. Nonetheless, each method of emphysema assessment has its own limitations. Visual assessment is time-consuming, subjective, experience-dependent, and suffers high inter-and intra-observer variability despite well-established and standardized criteria (24, 27). In contrast, although quantitative assessment is objective, quick, and highly reproducible when using similar devices and protocols, it is hampered by inconsistencies in factors like the slice thickness, HU threshold (-900 HU or -950 HU), and LAA% cut-offs (1%–25%). To illustrate this, we found no evidence of an association (P = .09) between emphysema and lung cancer when emphysema was quantitatively assessed on thick slice chest CT using a cut-off value -900 HU. Therefore, it is recommended that a thin slice (≤ 1.5mm) thickness and -950 HU cut-off value are used for quantitative emphysema assessment. Given that each of these factors may affect emphysema detection by the quantitative method (14), standardization is needed to ensure the precision, reliability, and robustness needed for widespread use (46-48).

The presence of emphysema, irrespective of its severity, was related to the presence of lung cancer. The odds of lung cancer increased with increasing levels of emphysema severity. We identified several studies that reported inconsistent results regarding the association between increasing emphysema severity and increasing lung cancer odds, with some suggesting that this trend existed (18, 21) and others suggesting the opposite (9, 31). It may be that the limited sample sizes for severe emphysema in the studies resulted in showing no trend (82 and 135 participants). The analysis stratified by assessment method showed that ORs for lung cancer increased with increasing emphysema severity and that this association was higher for visual assessment. This is not surprising given that visual

assessment relies on subjective estimation of emphysema severity and not a prespecified HU threshold. Validated or cross-calibrated quantitative and visual assessments of severity has not previously been well established in the literature. Our cut-off values for categorizing emphysema severity were generally higher for the visual (mild, 25%; moderate, >25%) than for the quantitative (mild, 10%; moderate, >10%) assessments (9, 12).

Centrilobular emphysema, but not paraseptal emphysema, was independently associated with an increased odds of lung cancer. Although these results should be interpreted cautiously due to their reliance on only three studies, the large sample of 1,370 participants should increase the reliability (48% centrilobular, 34% paraseptal, 15% controls) (20, 21, 31). If paraseptal emphysema truly has no association with lung cancer, its presence may also explain existing discrepancies.

This study has limitations. First, airflow obstruction is an independent risk factor for lung cancer (49), yet some included studies did not adjust for its presence (62%, 13 of 21). This confounder could have affected the pooled OR for lung cancer. Second, only six studies reported the effect of emphysema severity on lung cancer, and only two reported the association for trace emphysema. Third, based on the included data in this meta-analysis, it was not possible to determine whether the presence of CT defined emphysema leads to incremental and independent prognostic value over that of already known (shared) risk factors of emphysema and lung cancer. Finally, the cut-off value for the presence of emphysema and its severity varied among the studies, and this may likely have affected the pooled ORs.

In conclusion, chest CT diagnosed emphysema was independently associated with a higher odds of developing lung cancer, regardless of whether assessed visually or quantitatively. Moreover, this risk increased as emphysema severity increased. Concerning visual assessment by subtype, only centrilobular emphysema was significantly associated with lung cancer. To benefit from the potential value of visual and quantitative CT assessments

in early emphysema detection and lung cancer screening, research must now establish uniform guidelines for scanning protocols and evaluation.

Appendices

Disclosures of conflicts of interest

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Data Sharing

All data generated or analyzed during the study are included in the published paper.

Supplemental material

Supplemental tables

Table E1: Search Strategy by Database*

Database	Search strategy
PubMed	(“Pulmonary Emphysema”[Mesh] OR pulmonary emphysema*[tiab]) AND (“Lung Neoplasms”[Mesh] OR “Solitary Pulmonary Nodule”[Mesh] OR lung nodule*[tiab] OR pulmonary nodule*[tiab] OR lung neoplasm*[tiab] OR lung cancer*[tiab] OR lung tumor*[tiab] OR lung tumour*[tiab] OR lung malignanc*[tiab]) NOT (“animals”[MeSH] NOT “humans”[MeSH])
Embase	(“Lung Emphysema”/exp OR ‘lung emphysema*‘:ti,ab) AND (‘Lung cancer’/exp OR ‘lung nodule’/exp OR ‘lung nodule*’:ab,ti OR ‘pulmonary nodule*’:ab,ti OR ‘lung neoplasm*’:ti,ab OR ‘lung tumor*’:ti,ab OR ‘ lung tumour*’:ti,ab OR ‘lung cancer*’:ab,ti OR ‘lung malignanc*’:ab,ti) NOT (‘animal’/exp NOT ‘human’/exp)
Cochrane	“pulmonary emphysema*” AND (“lung nodule*” OR “pulmonary nodule*” OR “lung neoplasm*” OR “lung cancer*” OR “lung tumor*” OR “lung tumour*” OR “lung malignanc*”)

* The search strategy was optimized by a medical information specialist for terms that specified exposure and outcome. We also checked the references of included articles to identify any that were missed in the initial searches.

Table E2: Definition of Visual and Quantitative Emphysema and CT Scan Parameters Across the Included Studies

Study	CT scan parameters	Definition of emphysema	Definition of severity of emphysema	Matched or adjusted factors
Individual studies assessed emphysema by visual				
de Torres 2007 (13)	CT scanner: Siemens (single-slice helical scanner, Somatom Volume Zoom); Scanning mode: Low-dose CT Slice thickness: 1.25 mm; Reconstruction algorithm: High spatial frequency	Definition: ≥ 1 score where areas of vascular, lung disruption and low attenuation value occupy up to 25% of any 3 apical-to-basal lung zones	NA	Adjusted: age, gender, pack-years, airflow obstruction
Wilson 2008 (12)	CT scanner: GE (multidetector) Scanning mode: Low-dose CT; Slice thickness: Not specified; Reconstruction algorithm: High spatial frequency	Definition: ≥ 1 score where areas of vascular, lung disruption and low attenuation value occupy up to 10% of any 3 apical-to-basal lung zones	Five-level semiquantitative scale, based on modified NETT. Trace: low trace attenuation value occupy 0-10%; mild:11%-25%; moderate:26%-50%; severe emphysema: >50%	Adjusted: sex, age, years of smoking, smoking dose intensity, airflow obstruction
Li 2011 (35)	CT scanner: Not specified; Scanning mode: Standard-dose CT; Slice thickness: 5.0 mm; Reconstruction algorithm: High spatial frequency	Definition: Estimate of the percentage of lung tissue destroyed by emphysema is more than 0%	NA	Matched: age, gender, race, area, smoking status Adjusted: pack-years, Airflow obstruction, family history of lung cancer
Maisonneuve 2011 (36)	CT scanner: GE (8-slice or 16-slice multidetector, High-Speed Advantage); Scanning mode: Low-dose CT; Reconstructed slice thickness: 1.2 mm; Reconstruction algorithm: Not specified	Definition: presence of subtle areas of low attenuation and loss of parenchymal structures that contrast with the surrounding lung parenchyma with normal attenuation	NA	Adjusted: age, gender, asbestos exposure, largest nodule size, nodule type, cigarettes per day, duration of smoking, and quitting

Table E2 (Continued)

Study	CT scan parameters	Definition of emphysema	Definition of severity of emphysema	Matched or adjusted factors
Henschke 2015 (37)	CT scanner: Not specified; Scanning mode: Low-dose CT; Slice thickness: 1.25 mm; Reconstruction algorithm: Not specified	Definition: discrete areas of decreased attenuation could be identified anywhere in the lung parenchyma	NA	Adjusted: age, female gender, ethnicity
Sanchez-Salcedo 2015 (38)	CT scanner: Siemens (single-slice helical scanner, Somatom Volume Zoom) Scanning mode: Low-dose CT; Slice thickness: 1.25 mm; Reconstruction algorithm: Not specified	Definition: ≥ 1 score where areas of vascular, lung disruption and low attenuation value occupy up to 25% of any 3 apical-to-basal lung zones	NA	Adjusted: age, sex, pack-years, airflow obstruction
de Torres 2015 (39)	CT scanner: GE Systems scanner; Scanning mode: Low-dose CT; Slice thickness: Not specified; Reconstruction algorithm: High spatial frequency	Definition:≥ 1 score where areas of vascular, lung disruption and low attenuation value occupy up to 10% of any 3 apical-to-basal lung zones	NA	Adjusted: Age, BMI, pack-years
Liu 2018 (40)	CT scanner: Not specified; Scanning mode: Low-dose CT; Reconstruction algorithm: Soft tissue or thin section; Slice thickness: 1.0--3.2 mm	Definition: percentage of low attenuation and vascular disruption area in 3 levels (top of aortic arch, tracheal carina, and 2 cm above highest hemidiaphragm) is more than 0%	NA	Matched: age, sex, race, smoking status Adjusted: age, sex, race, smoking status, pack-years, family history of lung cancer
Gonzalez 2019 (21)	CT scanner: Siemens (64 detectors Somatom Plus 4) or Siemens Healthcare (Somatom Sensation 64, Somatom Definition) Scanning mode: Low-dose CT; Slice thickness: 1.0 mm; Reconstruction algorithm Kernel: B60	Definition: centrilobular emphysema (estimate of the percentage of centrilobular lucencies is more than 0% of lung zone); Paraseptal emphysema: presence of a few well-demarcated rounded juxtapleural lucencies	Based on criteria of NETT: Mild: low attenuation value occupy 0%–25%; moderate:26%-50%; severe emphysema: >50%	Matched: sex, age, smoking status, pack years Adjusted: smoking status, airflow obstruction

Table E2 (Continued)

Study	CT scan parameters	Definition of emphysema	Definition of severity of emphysema	Matched or adjusted factors
Carr 2018 (31)	CT scanner: Not specified; Scanning mode: Not specified; Slice thickness: 0.75 mm; Reconstruction algorithm: B35 F	Definition: centrilobular emphysema (Estimate of the percentage of centrilobular lucencies is more than 0% of lung zone); Paraseptal emphysema: presence of a few well-demarcated rounded juxtapleural lucencies	Based on criteria of Fleischner Society: Mild: scattered centrilobular lucencies, usually separated by large regions of normal lung, involving an estimated 0.5-5% of a lung zone; Moderate: many well-defined centrilobular lucencies, occupying > 5% of any lung zone; Confluent: coalescent centrilobular or lobular lucencies, including multiple regions of lucencies that span several secondary pulmonary lobules; Advanced destructive emphysema: panlobular lucencies with hyper expansion and distortion of pulmonary architecture.	Matched: age, race, sex, and smoking history Adjusted: age, sex, race, smoking status, pack-years, years since quitting, and airflow obstruction
Yong 2019 (41)	CT scanner: Not specified; Scanning mode: Low-dose CT; Slice thickness: 1.0 mm; Reconstruction algorithm: Soft tissue	Definition: no specific diagnostic criteria	NA	Adjusted: age, gender, smoking duration, family history of lung cancer, personal history of cancer, history of pneumonia, asbestos exposure

Table E2 (Continued)

Study	CT scan parameters	Definition of emphysema	Definition of severity of emphysema	Matched or adjusted factors
Individual studies assessed emphysema by quantitative CT				
Kishi 2002 (10)	CT scanner: GE (High Speed Advantage); Scanning mode: Low-dose CT; slice thickness: 5 mm; reconstruction algorithm: Edge-enhancing	Definition: % LAA -900 HU > 5% (dichotomous and continuous)	NA	Matched: sex, age, pack-years Adjusted: pack-years
Maldonado 2010 (9, 42)	CT scanner: GE (High-Speed Advantage) Scanning mode: Low-dose CT; Slice thickness: 5 mm; Reconstruction algorithm: standard	Definition: % LAA -900 HU > 5% (dichotomous and continuous)	%LAA trace: 5%-9% Mild: 10%-14%; Moderate:>15%	Matched: sex, age, smoking history
Gierada 2011 (11)	CT scanner: Toshiba (16 slice Aquilion 16), GE (4 slice, HiSpeed Qxi/i) and Siemens (16 slice, Sensation 16); Scanning mode: Low-dose CT; Slice thickness: 1.0-2.5 mm; Reconstruction algorithm: FC 51, B50f; standard, C and B30f	Definition: % upper lung LAA -950 HU ≥ 25% (dichotomous)	NA	Matched: sex, age, and smoking history Adjusted: age, sex, pack-years, BMI, history of asthma
Schwartz 2016 (32)	CT scanner: Not specified Scanning mode: low-dose CT; Slice thickness: Not specified; Reconstruction algorithm: Not specified	Definition: % LAA -950 HU > 4.8% (dichotomous)	NA	Adjusted: age, race, gender, pack-years; total lung volume
Aamli Gagnat 2017 (19)	CT scanner: GE (8 slice, LightSpeed Ultra) Scanning mode: Standard-dose CT; Slice thickness: 1 mm; Reconstruction algorithm: Not specified	Definition: % LAA -950 HU ≥ 3% (dichotomous and continuous)	Mild: % LAA 3%–10% Moderate/severe: % LAA% ≥ 10%	Adjusted: age, sex, smoking status, pack-years, age of smoking, airflow obstruction

Table E2 (Continued)

Study	CT scan parameters	Definition of emphysema	Definition of severity of emphysema	Matched or adjusted factors
Chubachi 2017 (18)	CT scanner: GE (64 detectors), LightSpeed VCT, and Discovery CT 750 HD; Toshiba (64 detectors, Aquilion 64), GE (256 detectors, Revolution CT) or Toshiba (320 detectors, Aquilion One Genesis); Scanning mode: Standard-dose CT; Slice thickness: 1.0-1.25 mm; Reconstruction algorithm: Chest and FC 50	Definition: % LAA -950 HU ≥ 10% (dichotomous)	Mild: 10% ≤%LAA < 20% Moderate/severe:%LAA ≥ 20%	Adjusted: gender, age, and pack-years, and interstitial lung abnormality
Mouronte-Roibas 2018 (20)	CT scanner: GE (64 detectors), Lightspeed VCT, or Siemens (6 detectors, Somatom Emotion); Scanning mode: Not specified; Slice thickness: Not specified; Reconstruction algorithm: Not specified	Definition: % LAA -950 HU ≥ 1% (dichotomous)	NA	Adjusted: sex, age, BMI, pack-years
Nishio 2019 (34)	CT scanner: Toshiba (320 or 64 detectors, Aquilion ONE or Aquilion 64); Scanning mode: Standard-dose CT; slice thickness: 0.5 or 1.0 mm; Reconstruction algorithm: Not specified	Definition: % LAA −880 HU (continuous)	NA	Adjusted: sex, age, smoking history (Brinkman Index)
Husebø 2019 (43)	CT scanner: Not specified; Scanning mode: Not specified; Slice thickness: Not specified; Reconstruction algorithm: Not specified	Definition: % LAA -950 HU > 10% (dichotomous)	NA	Adjusted: age, sex, smoking status, pack-years, BMI, use of inhaled steroids

Table E2 (Continued)

Study	CT scan parameters	Definition of emphysema	Definition of severity of emphysema	Matched or adjusted factors
Labaki 2021(33)	CT scanner: Not specified; Scanning mode: Low-dose CT; Reconstruction algorithm: Soft tissue or thin section; Slice thickness: 1.0–3.2 mm	Definition: % LAA -950 HU (continuous)	NA	Adjusted: age, BMI, race, education level, smoking intensity, and duration, time since smoking cessation, self-reported COPD, and a personal and family history of lung cancer

Note.—NA = not appliable; NETT = National Emphysema Treatment Trial, LAA = low attenuation area.

Table E3: Quality Assessment of Studies Included in the Meta-Analysis

Author-Year	Selection (4 stars)	Comparability (2 stars)	Exposure/ outcome (3 stars)	Total (9 stars) / Degree
Case-control study				
Kishi-2002	4	2	3	9 (High)
Maldonado-2010	3	2	3	8 (High)
Gierada-2011	4	2	3	9 (High)
Li-2011	3	2	3	8 (High)
Schwartz-2016	4	2	2	8 (High)
Mouronte-Roibas-2018	2	2	2	6 (Medium)
Carr-2018	4	2	2	8 (High)
Liu-2018	4	2	2	8 (High)
Gonzalez -2019	4	2	3	9 (High)
Nishio-2019	3	2	2	7 (Medium)
Cohort study				
de Torres-2007	4	2	2	8 (High)
Wilson-2008	4	2	2	8 (High)
Maisonneuve-2011	4	2	2	8 (High)
Henschke-2015	3	2	1	6 (Medium)
deTorres-2015	4	1	2	7 (Medium)
Sanchez-Salcedo-2015	4	2	2	8 (High)
Aamli Gagnat -2017	4	2	3	9 (High)
Chubachi-2017	4	2	1	7 (Medium)
Husebø-2019	4	2	3	9 (High)
Yong-2019	4	2	2	8 (High)
Labaki-2021	4	1	2	7 (Medium)

Note.—Scoring was with the Newcastle–Ottawa Scale (NOS), with one star awarded if the item was met.

Table E4: Characteristics of included studies that assessed emphysema visually on chest CT

Study	Country	With/Without Lung Cancer	Lung Cancer Histologic Type	Age (Mean ± SD)	Source	Study Design	Feature of Evaluation	Effect Size (95% CI)
de Torres 2007 (13)	Spain	23/1,166	13 (57%) Adenocarcinoma; 5 (22%) Squamous cell carcinoma; 4 (17%) Small cell carcinoma; 1 (4%) Large cell carcinoma;	Case: 54 ± 8 Control: 54 ± 8	PB	Cohort; Prospective study	Chest Radiologist; Guideline: NETT	RR: 2.5 (1.0, 6.2)
Wilson 2008 (12)	USA	99/3,539	86 (87%) Non–small cell carcinoma (NSCLC); 13 (13%) Small cell carcinoma;	NS	PB	Cohort; Prospective study	Pulmonologist, general radiologist, chest radiologist. Guideline: NETT	OR: 3.1 (1.9, 5.2)
Li 2011 (35)	USA	565/450	259 (46%) Adenocarcinoma; 159 (28%) Squamous cell carcinoma; 13 (2%) Large cell; 63 (11%) Other NSCLC; 71 (13%) Small cell carcinoma;	Case: 67 ± 8 Control: 66 ± 6	HB	Case-control; Retrospective study	Chest radiologist. Guideline: NS	OR: 2.8 (2.1, 3.8)
Maisonneuve 2011 (36)	Italy	85/4,511	NS	NS	PB	Cohort; Retrospective study	Radiologist. Guideline: NS	HR: 1.8 (1.2, 2.6)
Henschke 2015 (37)	USA	668/61,456	NS	NS	PB	Cohort; Prospective study	Radiologist. Guideline: NS	OR: 2.0 (1.4, 2.9)
Sanchez-Salcedo 2015 (38)	Spain	53/2,936	53 Participants (60 Lesions): 33 (55%) Adenocarcinoma; 13 (22%) Squamous carcinoma; 7 (12%) Large cell carcinoma; 5 (8%) Small cell carcinoma; 2 (3%) Others;	Case: 60 (55–65) [#] Control: 55 (49–62) [#]	HB	Cohort; Prospective study	Chest radiologist. Guideline: NS	HR: 3.3 (1.8, 5.9)

Table E 4 (Continued)

Study	Country	With/Without Lung Cancer	Lung Cancer Histologic Type	Age (Mean ± SD)	Source	Study Design	Feature of Evaluation	Effect Size (95% CI)
de Torres 2015 (39)	USA	134/1,419	NS	Overall: 61 ± 7	PB	Cohort; Prospective study	Pulmonologist, general radiologist, chest radiologist. Guideline: NETT	HR: 2.7 (1.7, 4.3)
Liu 2018 (40)	USA	73/157	33 (45%) Adenocarcinoma; 21 (29%) Squamous cell carcinoma; 3 (4%) Small cell carcinoma; 16 (22%) Other and not otherwise specified NSCLC;	Case: 64 (55–74)[#] Control: 63 (55–74)[#]	PB	Case-control; Prospective study	Clinical radiologist. Guideline: Modified NETT	OR: 1.8 (1.4, 1.9)
Gonzalez 2019 (21)	Spain	72/215	36 (50%) Adenocarcinoma; 15 (21%) Squamous cell carcinoma; 5 (7%) Small cell carcinoma; 7 (10%) Large cell carcinoma; 7 (10%) Others; 2 (3%) Unknown;	Case: 64 ± 9 Control: 64 ± 9	PB	Case-control; Prospective study	Pulmonologist; Guideline: Fleischner Society	OR: 5.4 (2.6, 11.4)
Yong 2019 (41)	Norway	367/16,257	NS	Case: 62 ± 6 Control: 61 ± 5	PB	Cohort; Retrospective study	Radiologist. Guideline: NS	HR: 2.0 (1.6, 2.6)

Note.— HB = hospital-based, HR = hazard ratio, NETT = National Emphysema Treatment Trial, NS = not specified, OR = odds ratio, PB = population-based, RR = risk ratio, SD = standard deviation. All the effect sizes adjusted for smoking, except for study Henschke 2015; For specific adjusted factors, see Tables E3. [#] Numbers are medians, with ranges in parentheses.

Table E5: Characteristics of included studies that assessed emphysema quantitatively on chest CT

Study	Country	With/Without Lung Cancer	Lung Cancer Histologic Type	Age (Mean ± SD)	Source	Study Design	Feature of Evaluation	Effect Size (95% CI)
Kishi 2002 (10)	USA	24/96	14 (58%) Adenocarcinoma; 6 (25%) Squamous cell carcinoma; 3 (13%) Small cell carcinoma; 1 (4%) Large cell carcinoma;	Case: 64 ± 7 Control: 63 ± 6	HB	Case-control; Retrospective study	% LAA -900 HU ≥ 5% (dichotomous and continuous)	OR: 1.1 (0.5, 2.4) *OR: 1.1(0.6, 1.9)
Maldonado 2010 (9, 42)	USA	64/377	34 (53%); Adenocarcinomas; 14 (22%) Small cell carcinoma; 5 (8%) NSCLC without specified; 2 (3%) Large cell neuroendocrine mixed large and small cell carcinomas; 1(2%) Unknown;	Case: 63 ± 7 Control: 62 ±6	PB	Case-control; Prospective study	% LAA -900 HU > 5% (dichotomous and continuous)	OR: 1.9 (1.1, 3.3) *OR: 1.04 (0.8, 1.3)
Gierada 2011 (11)	USA	279/279	NS	Case: 63 ± 5 Control: 61 ± 5	PB	Case-control; Retrospective study	% Upper lung -950 HU ≥ 25% (dichotomous) Semiautomatic assessment	OR: 2.0 (1.03, 3.8)
Aamli Gagnat 2017 (19)	Norway	34/741	NS	Overall: 59 ± 10	PB	Cohort; Prospective study	% LAA -950 HU ≥ 3% (dichotomous and continuous)	HR: 2.4 (0.9, 6.2) *HR: 1.03(0.7, 1.5)
Chubachi 2017 (18)	Japan	21/219	9 (43%) Adenocarcinoma; 4 (19%) Squamous cell carcinoma; 3 (14%) Small cell carcinoma; 5 (24%) Unknown;	Case: 73 ± 7 Control: 73 ± 8	HB	Cohort; Prospective study	% LAA -950 HU > 10% (dichotomous)	OR: 4.2 (1.0, 29.0)
Mouronte-Roibas 2018 (20)	Spain	139/56	70 (41%) Adenocarcinoma; 58 (35%) Squamous cell carcinoma; 28 (16%) Small cell carcinoma; 13 (8%) Unknown;	Case: 69 ± 9 Control: 65 ± 10	HB	Case-control; Retrospective study	% LAA -950 HU > 1% (dichotomous)	OR: 2.2 (1.1, 4.3)

Table E5 (Continued)

Study	Country	With/Without Lung Cancer	Lung Cancer Histologic Type	Age (Mean ± SD)	Source	Study Design	Feature of Evaluation	Effect Size (95% CI)
Nishio 2019 (34)	Japan	283/293	NS	Case: 69 ± 10 Control: 65 ± 14	HB	Case-control; Retrospective study	% LAA-880 HU (continuous)	*OR: 1.01 (1.00, 1.02)
Husebø 2019 (43)	Norway	31/681	11 (36%) Adenocarcinoma; 9 (29%) Unspecified NSCLC; 5 (16%) Squamous cell carcinoma; 5 (16%) Unspecified cancer; 1 (3%) Small-cell carcinoma;	Case: 64 ± 7 Overall: 58 ±10	HB	Cohort; Prospective study	% LAA -950 HU > 10% (dichotomous)	HR: 4.4 (1.7, 10.8)
Labaki 2021 (33)	USA	353/6,909	NS	Overall: 62 ± 5	PB	Cohort; Prospective study	% LAA -950 HU (continuous) Automatic assessment	*HR: 1.02 (1.01, 1.03)
Individual studies assessed emphysema by visual and quantitative CT								
Schwartz 2016 (32)	USA	341/752	183 (54%) Adenocarcinoma; 91 (27%) Squamous cell carcinoma; 30 (9%) Small cell carcinoma; 14 (4.5%) Other NSCLC; 21 (6%) Other;	Case: 64 ± 10 Control: 62 ± 9	PB	Case-control; Retrospective study	Radiologist read And % LAA -950 HU > 4.8% (dichotomous)	OR (visual): 1.8 (1.5, 2.6) OR (quantitative): 2.7 (1.8, 4.0)
Carr 2018 (31)	USA	169/671	61 (36%) Adenocarcinoma; 17 (10%) Squamous cell carcinoma; 68 (40%) Unknown; 18 (11%) Small cell carcinoma; 3 (2%) Large cell carcinoma; 2 (1%) Others;	Case: 66 ± 8 Contorl: 64 ± 8	PB	Case-control; Prospective study	Radiologist based on Fleischner society guideline And % LAA-950 HU per 1% increase	OR (visual)*: 2.3 (1.4, 3.8) *OR (quantitative): 1.03 (0.6, 1.8)

Note.— HB = hospital-based, HR = hazard ratio, LAA = low attenuation area, NS = not specified, OR = odds ratio, PB = population-based, RR = risk ratio, SD = standard deviation.* Effect size when emphysema was assessed as a continuous variable. All the effect sizes adjusted for smoking; For specific adjusted factors, see Tables E2

Table E6: Overall and Stratified Pooled Odds Ratios for Lung Cancer Given Emphysema

Stratifications	Studies (n)	Pooled OR	95% CI	I^2	$P_{(heterogeneity)}$	$P_{(groups)}$
Overall (dichotomous)	19	2.3	2.0, 2.6	34.6%	.07	–
Overall (continuous)	6	1.02	1.01, 1.02	0	0.9	–
Study design #						.33
Cohort	10	2.3	2.0, 2.7	0%	.46	
Case-control	9	2.2	1.8, 2.8	55.%	.02	
Retrospective	8	2.2	1.8, 2.6	25.0%	.24	.83
Prospective	11	2.5	2.0, 3.1	43.5%	.053	
Population source #						.06
Population-based	13	2.2	1.9, 2.5	27.0%	.17	
Hospital-based	6	2.6	1.9, 3.6	32.7%	.19	
Study quality #						.30
Low quality	0	–	–	–	–	
Medium quality	5	2.4	1.9, 3.0	0%	.76	
High quality	14	2.3	1.9, 2.7	47.1%	.03	
Effect sizes #						.64
HR	6	2.3	1.9, 2.9	19.3%	.29	
OR	12	2.3	1.9, 2.8	47.5%	.03	
Slice thickness (mm) *						.30
Normal (≥ 5)	2	1.5	0.9, 2.5	12.9%	.28	
Thin (0.5-1.25)	3	2.2	1.3, 3.7	0%	.70	
Cut-off value (HU) *						.06
-900	2	1.5	0.9, 2.5	12.9%	.28	
-950	6	2.6	2.0, 3.4	0%	.76	

Note.— HR = hazard ratio, OR = odds ratio. * Only within studies assessed emphysema quantitatively. # Within studies assessed emphysema visually or quantitatively.

Supplemental figures

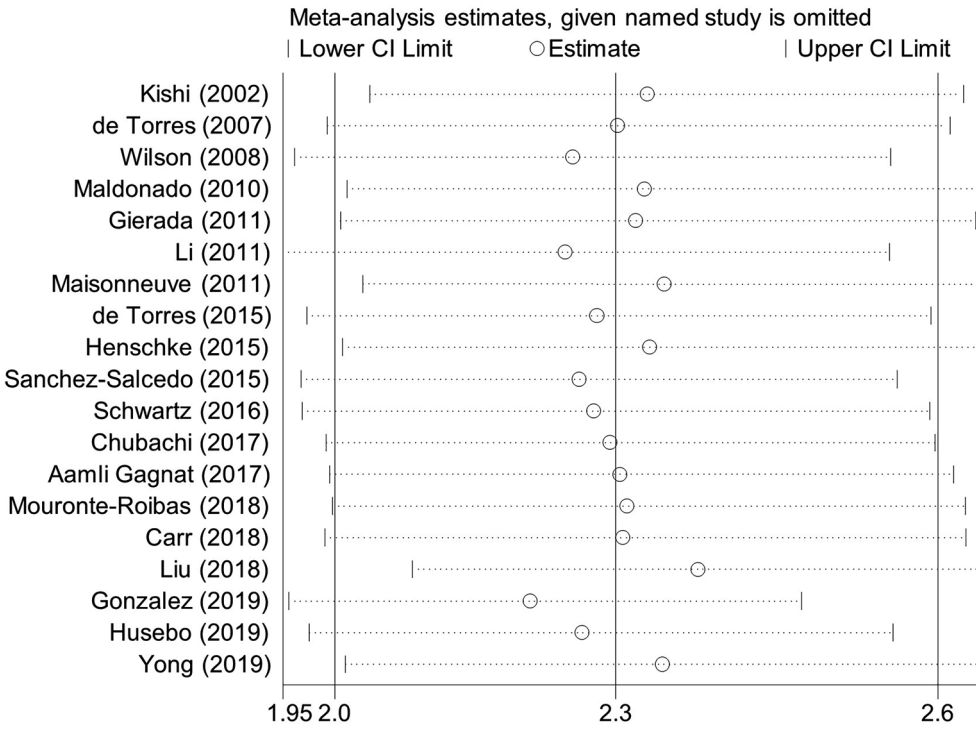

Figure E1: Sensitivity analysis for the overall association between emphysema (dichotomous variable, assessed visually and or quantitatively) and lung cancer within 19 studies. Adjusted factors in these mixed effects models varied, as shown in Table E3. Circles and horizontal lines represent the estimates and 95% CIs, respectively, for each study part.

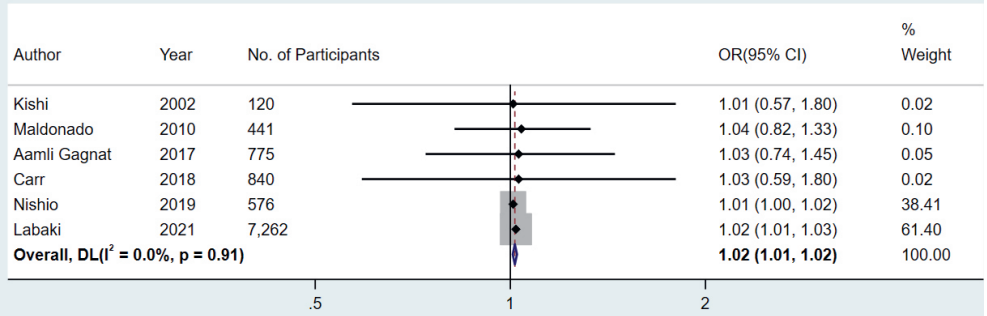

Figure E2: Forest plot of random-effects meta-analysis for the association between emphysema (continuous variable, assessed quantitatively only) and lung cancer. The pooled OR was 1.02 (95% CI: 1.01,1.02; P < .001) per 1% increase in LAA. Adjusted factors in these mixed effects models varied, as shown in Table E3. Squares and horizontal lines represent the estimates and 95% CIs, respectively, for each study part. Diamond indicates effect size and 95% CI. DL = DerSimonian & Laird, LAA = low attenuation area, OR = odds ratio.

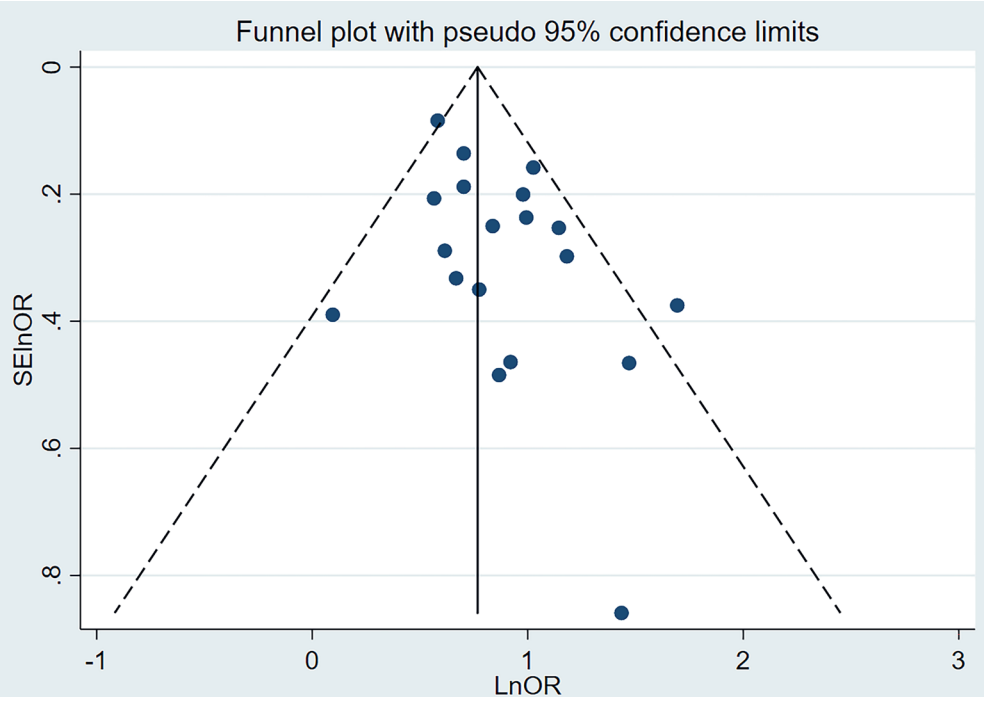

Figure E3: Funnel plot to evaluate publication bias for the association between emphysema (assessed visually and or quantitatively) and lung cancer. The Y-axis shows the precision of the study (the

inverse standard error), and the x-axis shows the emphysema effect. Studies with high precision will be near the average, and studies with low precision will spread evenly on both sides of average. Deviation from funnel-shaped indicates publication bias. ln = natural logarithm, OR = odds ratio, SE = standard error.

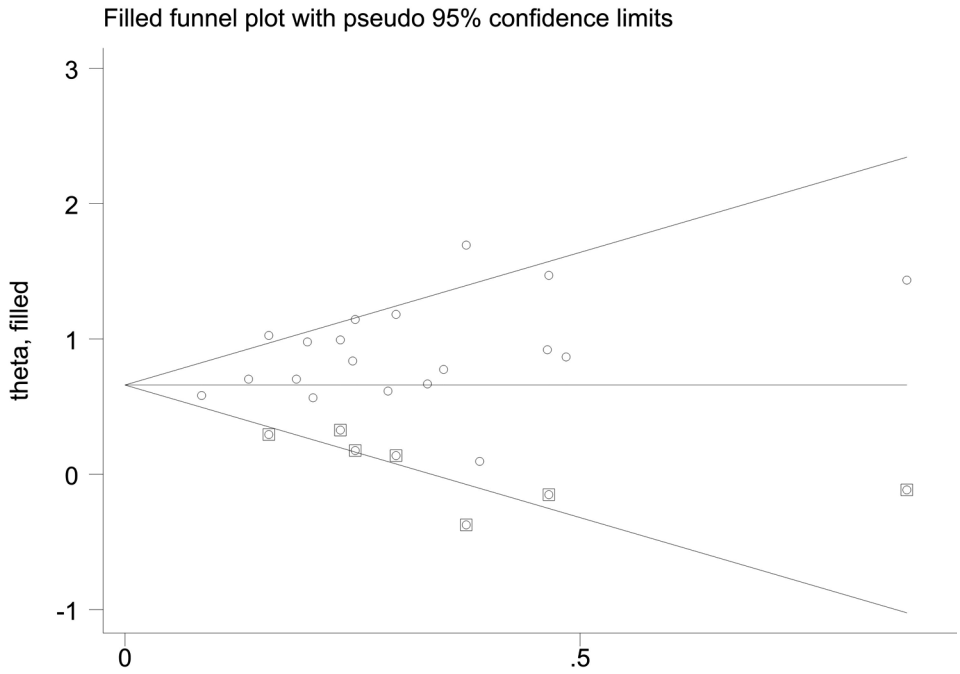

Figure E4: Trim and fill analysis for correction of overall publication bias in studies that evaluated the association between emphysema (assessed visually and or quantitatively) and lung cancer. Theta indicates true overall effect size. ln = natural logarithm, OR = odds ratio, s.e. = standard error.

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