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REVIEW

Lung Cancer Risk in US Adults with COPD: A Systematic Review and Meta-Analysis

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Background: Chronic obstructive pulmonary disease (COPD) is an important risk factor for the development of, and death from, lung cancer.

Methods: We conducted a systematic review and meta-analysis assessing the risk of lung cancer incidence and mortality among adults with a COPD diagnosis in the United States (US) and exploring differences by subgroups. We searched MEDLINE, Embase, and PubMed from inception to July 2024 for observational studies that investigated the association between COPD and lung cancer incidence and mortality risk. We conducted a meta-analysis for overall risk and COPD assessment methods, and a systematic review for analyses within sex, race/ethnicity, smoking status.

Results: Twenty observational studies (n=638,610) were included in the systematic review and meta-analysis. US adults with COPD were found to have higher odds of developing (OR, 1.76; [1.53 to 1.99]) and higher hazards of dying (HR, 1.48; [1.06 to 1.89]) from lung cancer compared to those without COPD. Mixed results were observed when stratifying the impact of COPD on lung cancer risk by subgroups (ie, sex, race and ethnicity and smoking status). Generally, the same trend was observed where people in each subgroup with COPD were at higher risk of lung cancer incidence and mortality compared to those in the same subgroups without the disease. Individuals assessed by self-reported COPD and spirometry showed greater incidence risk but not mortality risk.

Conclusion: US adults with COPD, including those with a smoking history, are at an increased risk for lung cancer incidence and mortality compared to those without COPD regardless of sex and race and ethnicity.

Keywords: chronic obstructive pulmonary diseases, systematic review, United States, incidence, mortality, smoking

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive, but preventive and treatable, lung disease characterized by an obstruction of airflow. It is an umbrella term which includes chronic bronchitis, emphysema, or a combination of both conditions,[1] and continues to be among the leading causes of global mortality.[2] In 2020, the age-adjusted prevalence of COPD within the United States (US), was 5.6%[3] – affecting more than 15 million Americans.[4] The estimated total economic burden of COPD in the US is approximately $50 billion each year[5] and mortality rates from COPD continue to increase.[6]

COPD has been associated with an increased risk of mortality from several chronic conditions such as chronic lower respiratory diseases,[7] cardiovascular diseases,[8] cerebrovascular diseases,[7] and lung cancer.[9] In the US, lung cancer is the third most common cancer diagnosis and the leading cause of cancer deaths with an estimated 300,000 incident cases[10] in 2020 and 14.3 deaths per 100,000 in the standard population.[11] Estimates of the prevalence of COPD in people diagnosed with lung cancer range from 40% to 70%, dependent on diagnostic criteria and population.[12–14]

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There is a reciprocal association between COPD and lung cancer: lung cancer may occur as a comorbidity of COPD[15] and COPD is a risk factor for lung cancer.[16,17] Both diseases share the etiology of tobacco exposure – whether from active smoking or second-hand smoke.[9,18,19] Additionally, a pathogenic relationship exists between the two conditions as characteristics of COPD – such as pulmonary inflammation[20] and lung matrix remodelling[21] – are precursors to lung cancer. It has been observed that the progression of COPD and the COPD-lung cancer risk relationship are also highly influenced by biopsychosocial determinants such as sex[22] and race and ethnicity,[23] due in part to interactions between social, structural, environmental, and genetic[24] risk factors.

Assessing the differential effects of COPD on the risk of lung cancer incidence and mortality in the US population, as well as the differential effects on subgroups of the population, provides critical information on US-specific health outcomes and health inequalities. As lung cancer is the leading cause of cancer-related deaths in the United States, and COPD is one of the main causes of morbidity,[25] it is important to gain an understanding of how specific characteristics differentially impact the US population.

Although individual studies have assessed the effects of COPD on lung cancer incidence and mortality, there exists a relative gap in terms of precisely estimating the sizes of these effects particularly in the US. Moreover, there is not much evidence on how differences in sex, race and ethnicity, and/or smoking status differentially impact these estimates. This review seeks to fill in the gap by pooling available summary data. This systematic review and meta-analysis assess the risk of lung cancer incidence and mortality in the US overall adult population with COPD diagnosis and explores differences in risk by sex, race and ethnicity, smoking status, and COPD assessment methods.

Methods

Study Protocol

This systematic review and meta-analysis examine the association of COPD with the risk of developing lung cancer as found in peer-reviewed studies. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Table 1)[26] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist (Supplementary Table 2).[27] The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022349594).

Search Strategy and Search Terms

We searched OVID MEDLINE, OVID EMBASE, and PubMed to identify articles published through July 2024 that reported on the impact of COPD on lung cancer risk incidence and mortality risk among adults within the United States. Search terms were developed with a scientific librarian. A detailed description of the search is in Supplementary Table 3.

Inclusion and Exclusion Criteria

We included observational studies that examined the incidence and mortality risk of lung cancer associated with COPD overall and across subgroups (sex, race and ethnicity, smoking status, and COPD assessment methods) in the US general adult population. We excluded studies that 1) lacked data on the outcomes of interest: mortality risk, incidence risk, or the association between lung cancer and COPD (defined as COPD, chronic bronchitis, and/or emphysema); 2) was the incorrect population: not specific to the US or had co-occurring conditions (eg, HIV, chronic kidney disease, etc).; 3) only presented results by COPD severity stage; and 4) were clinical trials, post-surgical studies, in-hospital mortality studies, basic science studies, conference procedures, abstracts, or study protocols (Supplementary Table 3).

Study Selection

Two independent reviewers (LMS-R and MEV-F) conducted the literature search. Duplicates were deleted first by using two reference manager software: EndNote[28] and Zotero[29] followed by the systematic reviewing software Rayyan.[30] Three reviewers (PO-N, LMS-R, and MEV-F) independently screened the titles and abstracts to assess eligibility and two reviewers (PO-N and MEV-F) independently conducted full text screening. Any discrepancies were resolved through discussion and consensus.

Data Extraction and Analysis

We developed a template for data abstraction in Google Sheets. One reviewer (PO-N) conducted data extraction. Extracted data included: study location, years of data collection, study design, outcomes, COPD definition (COPD, chronic bronchitis, and/or emphysema), COPD assessment/diagnosis method (self-reported, medical records, spirometry, etc), sociodemographic characteristics, lung cancer histology, values of measures of association, and adjusted covariates.

Results from included studies were extracted in the form of adjusted odds ratios (OR), hazard ratios (HR), incidence ratios (IR), and incidence rate ratios (IRR), along with 95% confidence intervals (95% CIs). Unadjusted outcomes were extracted when adjusted results were not available. Authors occasionally reported results for multiple outcomes of interest. This led to the extraction of a varying number of findings (ie, observations) from each study.

Studies were categorized by the two main outcomes – lung cancer incidence and lung cancer mortality – with further stratification by COPD type (COPD, chronic bronchitis, and/or emphysema). The collected outcomes examined findings across the overall population and subgroups: 1) *Sex*: male and female; 2) *Race and Ethnicity*: non-Hispanic Black or non-Hispanic White; 3) *Smoking Status*: current, former, and never; and 4) *COPD Assessment Methods*: self-reported, physician diagnosis only, spirometry only, medical records only, and combination; the latter group was used when studies employed more than one method of assessing COPD (eg, spirometry and CT scanner self-reported and medical records). Details about the subgroup categories (comparator and reference) from each study are provided in Supplementary Table 4.

Statistical Analyses

We conducted a random-effects meta-analysis to assess overall risk of lung cancer incidence and mortality among US adults diagnosed with COPD and for COPD assessment method. Meta-analysis was conducted when two or more eligible studies were identified based on similarities in their design, methods, definitions, populations, and/or outcomes.[31] Because of the variability in the definitions and methods of the studies that reported outcomes for sex, race and ethnicity, and smoking status subgroups, we conducted only descriptive analyses –as part of the systematic review.

We reported the inconsistency index (I^2) to quantify the percentage of variability in results due to heterogeneity. Based on Cochrane's recommendation, heterogeneity can be interpreted as: 0–40% might not important, 30–60% moderate, 50–90% substantial, and 75–100% considerable.[32] I^2 values greater than 75% were considered statistically significant.[33,34] Additionally, the point estimate with 95% CI were used to assess effect size and statistical significance. All statistical analyses were performed using Stata/BE 17.0.[35]

Risk of Bias Assessment

The risk of bias of each study was independently assessed by two researchers (PO-N and MEV-F) using the Risk of Bias In Non-randomized Studies – of Exposure (ROBINS-E) tool (Supplementary Table 5).[36] The assessment comprised seven domains that analyzed the risk of bias due to confounding, exposure measurements, participant selection/analysis, post-exposure interventions, missing data, outcome measurements, and selection of reported data. The total score for each study was assessed on a scale of 1 to 5 – with 1 representing low and 5 representing very high risk of bias. The total score – in conjunction with the scores of the domains and sub-domains – were assessed to evaluate if the risk of bias was sufficiently high to threaten conclusions about the association between COPD and the outcomes of interest. We reproduce the meta-analyses for the primary outcomes with only studies at low risk of bias to assess the potential impact of bias in the included studies. Additionally, a common-effect model with the inverse-variance method funnel plot was created for studies with a low risk of bias (RoB=1).

Sensitivity Analysis

Studies often reported results for overall COPD (COPD, chronic bronchitis and emphysema) and/or for individual diseases (chronic bronchitis or emphysema) and defined the disease based on different assessment methods. Including all the available data in the evidence synthesis allows for more generalizable results. However, it can lead to population overlap (double counting) that could introduce bias in the analysis.[37–39] To address this issue, we conducted a sensitivity analysis for incidence and mortality risk meta-analysis. We included only one observation per study, prioritizing results for studies defining COPD as either a standalone diagnosis or an umbrella term. This approach was chosen because

comorbidity of emphysema and chronic bronchitis is common, and studies suggest less misclassification among participants reporting both conditions compared to those reporting only one.[40] Furthermore, we prioritized objective assessment methods over self-reported diagnoses due to their established reliability.[40] Similarly, we selected outcomes from fully adjusted models to strengthen the validity of our findings compared to unadjusted modes.[41]

Results

Study Characteristics

Our initial search identified 10,435 articles, of which 59 were selected for full text review. Twenty studies were included (Figure 1). The 20 studies reported 119 relevant observations, of which 88 measured lung cancer incidence (17 studies)

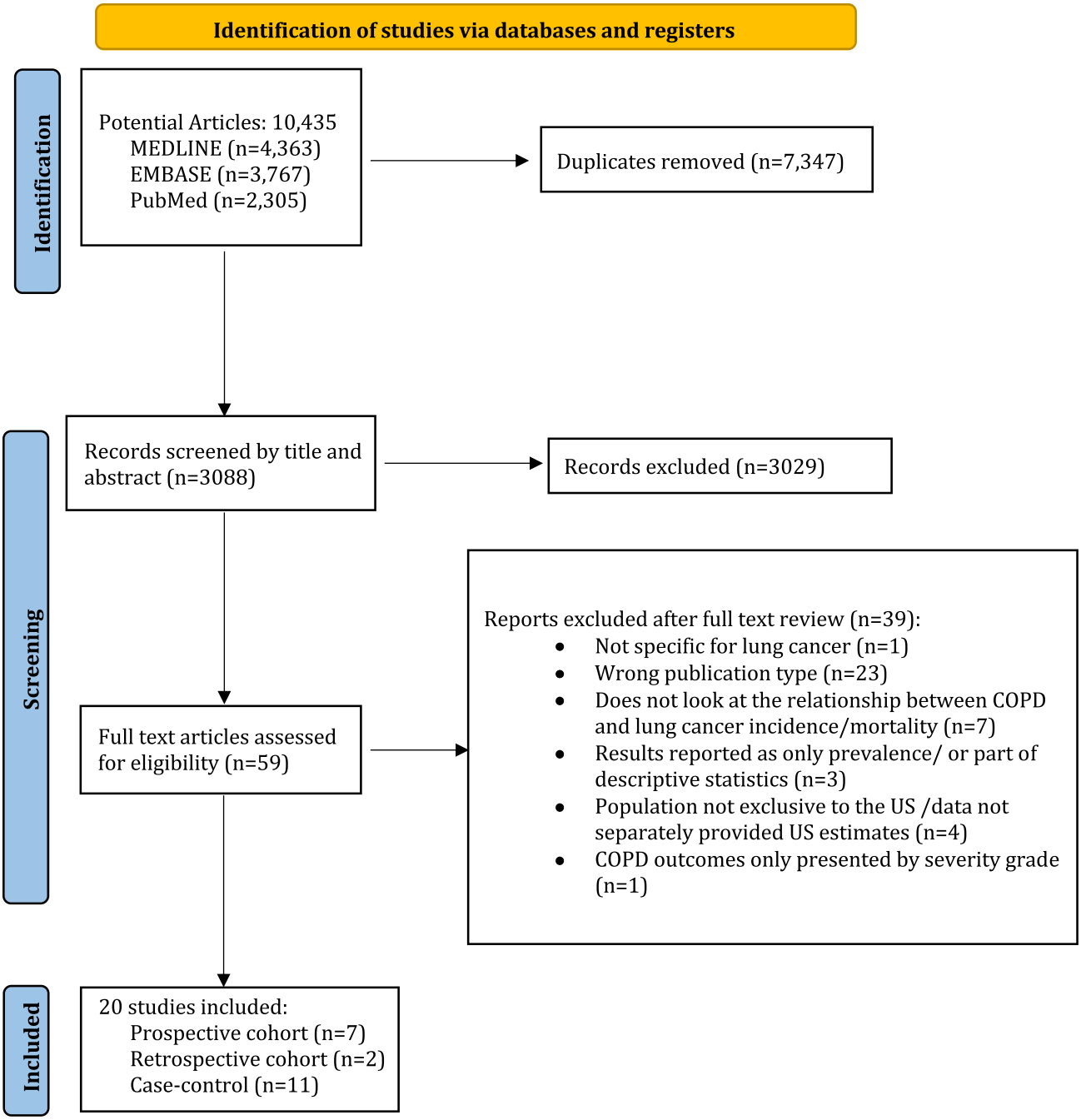

Figure 1 PRISMA flow diagram of the selection.[62]* *The reasons for full-text exclusion can be seen in Supplementary Material B.

and 31 measured lung cancer mortality (three studies). Our sample includes four studies conducted at the national level and 16 conducted at a city or state level. Eleven included studies were case-control and nine were cohort studies (seven prospective and two retrospective). Table 1 contains characteristics of the included studies. Supplementary Material B described the reasons for exclusion of articles retrieved.

The 20 studies included in the review used different definitions of COPD. Seven studies[47,53,54,57,58,61,63] employed the umbrella definition of COPD (ie, COPD, chronic bronchitis, and/or emphysema) only, one study[51] reported emphysema only, and two studies[56,59] reported airflow limitation only. The remaining ten studies[42–46,48–50,52,55] employed two or more definitions of COPD, emphysema, chronic bronchitis, or airflow limitation, with individual point estimates provided for each definition.

Meta-Analysis

Lung Cancer Incidence Risk

Results from the meta-analysis assessing the risk of lung cancer incidence are presented in Figure 2.[42,45,46,50,53,55,56,59,61] Across the 17 studies assessed, there was variability in the statistical measures. Studies reported odds ratios (ORs) (n=12), hazard ratios (HRs) (n=2), incidence ratios (IRs) (n=1), and incidence rate ratios (IRRs) (n=2); Hopkins et al[56] presented both IRs and IRRs. For this meta-analysis, we only included the studies which provided ORs and IRRs and assumed that IRRs were similar to ORs.[64] The studies by Littman et al[47] and Nagasaka et al[58] were excluded from this meta-analysis since the results were presented as HRs and the manuscript did not provide sufficient data for transformation; they were however included in the systematic review. Zhai et al[63] was also removed from the meta-analysis since it only provided outcomes by smoking status. Li et al[51] had the widest confidence interval, likely due to variability in the sample since the sample size was reasonably large.[65]

The pooled results indicated that US adults with COPD had 76% greater odds of developing lung cancer compared to adults without the disease (OR, 1.76; 95% CI=1.53 to 1.99; I^2 =58.9%). Across the fourteen included studies, eight studies[49,50,53,55–57,59,61] reported estimates for the umbrella definition of COPD and indicate that COPD diagnosis increased the odds of lung cancer incidence (OR, 1.81; 95% CI=1.54 to 2.07; I^2=42.4%). Higher odds of lung cancer incidence were observed for individuals with emphysema[42–46,49–51,55] (OR, 2.20; 95% CI=1.65 to 2.75; I^2=48.8%), but individuals with chronic bronchitis[42–46,50] had the lowest odds (OR, 1.41; 95% CI=1.10 to 1.73; I^2=45.0%). Across all analyses, a moderate level of statistical heterogeneity was noted.

Lung Cancer Mortality Risk

Results from the meta-analysis assessing the risk of lung cancer mortality are presented in Figure 3. All three studies[48,52,54] measured the outcome using hazard ratios (HRs) and assessed COPD as an umbrella definition (ie, COPD, chronic bronchitis, and/or emphysema). Mina et al[52] also reported estimates for emphysema while Turner et al[48] reported separate estimates for both chronic bronchitis and emphysema.

The pooled results indicate that individuals with COPD had a 48% higher risk of lung cancer mortality than those without the disease (HR, 1.48; 95% CI=1.06 to 1.89; I^2=79.1%). A significant risk was also found when using the umbrella COPD definition (HR, 1.70; 95% CI=1.13 to 2.27; I^2 =77.8%).[66] The pooled analyses for emphysema and chronic bronchitis alone were not statistically significant. Across all analyses, there was a high level of heterogeneity.

Risk of Bias (RoB) Assessment

Overall, the quality of the 20 included articles was high, with RoB scores between 1 and 3. The remaining eight studies presented some concerns for RoB (score 3); in these studies, the potential bias of the studies the bias was determined not to threaten their conclusions regarding the impact of the exposure on the outcome. Potential bias was not estimated for Hopkins et al[56] since that study only provided unadjusted results and did not provide analyses to demonstrate the degree of uncontrolled confounding nor the effect on the conclusions. No articles were determined to have high or very high RoB (Supplementary Table 5).

The meta-analyses conducted after removal of studies at moderate or high risk of bias (RoB ≥2) had little impact on estimates of the incidence (HR 1.74; 95% CI=1.36 to 2.11. I^2=52.3%). However, pooled mortality risk was no longer

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Table 1 Characteristics of the Included Studies

Author, Publication Year	Data Collection Years (Study Name)	Data Collection Location(s)	Population Description	Study Design (n)	COPD Definition (Assessment Method)	Outcome	Point Estimate (95% CI)	Adjustments	Referent Group
Alavanja et al 1992[42]	1 June 1986–1 April 1991	Missouri	Non-Hispanic white non-smoking women between 30–84 years; mean age: 71.5 years (cases) and 69.9 years (controls); both direct interviews and next-of-kin interviews	Case-control (n_{cases}=618, $n_{controls}$=1402)	Chronic bronchitis (Self-reported)	Incidence	OR=0.9 (0.6 to 1.3)	Age and smoking history	No previous lung diseases
					Emphysema (Self-reported)	Incidence	OR=2.6 (1.5 to 4.7)	Age and smoking history	No previous lung diseases
Wu et al 1995[43]	1985-1990	Atlanta, Georgia; Houston, Texas; New Orleans, Louisiana; and the San Francisco Bay Area and Los Angeles County, California	Women aged 20–79 years who were never smokers	Case-control (n_{cases}=397, $n_{controls}$=1236)	Chronic bronchitis (Self-reported)	Incidence	OR=1.34 (0.9 to 2.0)	Asthma, chronic bronchitis, pneumonia, tuberculosis, pleurisy, emphysema, other lung diseases, age, area, ethnicity, and education	No chronic bronchitis
					Emphysema (Self-reported)	Incidence	OR=2.14 (0.8–5.6)	Asthma, chronic bronchitis, pneumonia, tuberculosis, pleurisy, emphysema, other lung diseases, age, area, ethnicity, and education	No emphysema
Mayne et al 1999[44]	1982-1984	New York	Never or former smokers (aged 20–80 years)	Case-control (n_{cases}=434, $n_{controls}$=436)	Emphysema (Self-reported)	Incidence	OR=1.48 (0.77 to 2.84)	Smoking-related variables, dietary variables, and educational level (<15 years vs >15 years)	No emphysema
					Chronic bronchitis (Self-reported)	Incidence	OR=1.30 (0.79 to 2.14)	Smoking-related variables, dietary variables, and educational level (<15 years vs >15 years)	No chronic bronchitis
Brownson and Alavanja, 2000[45]	1 January 1993–31 January 1994	Missouri	Women aged 30–84 years; mean age: 66.2 years (cases) and 66.4 years (controls); all subjects	Case-control (n_{cases}=676, $n_{controls}$=700)	Chronic bronchitis (Self-reported)	Incidence	OR=1.7 (1.2 to 2.3)[a]	Pack-years of smoking	No previous lung diseases
					Emphysema (Self-reported)	Incidence	OR=2.7 (1.8 to 4.2)[a]	Pack-years of smoking	No previous lung diseases
Brownson and Alavanja, 2000[45]	1 January 1993–31 January 1994	Missouri	Only subjects directly interviewed	Case-control (n_{cases}=172, $n_{controls}$=149)	Chronic bronchitis (Self-reported)	Incidence	OR=1.8 (1.2 to 2.5)[b]	Pack-years of smoking	No previous lung diseases
					Emphysema (Self-reported)	Incidence	OR=2.5 (1.6 to 4.1)[b]	Pack-years of smoking	No previous lung diseases

Osann et al 2000[46]	1 July 1990–30 June 1993	California	Non-Hispanic white women; mean age: 61.7 years (cases) and 62.6 years (controls)	Case-control (n_{cases}=98, $n_{controls}$=204)	Chronic bronchitis (Self-reported)	Incidence	OR=1.9 (0.8 to 4.7)	Age, education, and smoking	No chronic bronchitis
					Emphysema (Self-reported)	Incidence	OR=1.1 (0.4 to 3.5)	Age, education, and smoking	No emphysema
Littman et al 2004[47]	CARET ran from 1985-January 1996; this study used participants from CARET with follow-up /censoring through 1 June 2002	Baltimore, MD; New Haven, CT; Portland, OR; San Francisco, CA; Seattle, WA; and Irvine, CA	Male and female participants in the heavy smoker cohort of the Carotene and Retinol Efficacy Trial (CARET); median age: 58 years	Prospective cohort (n=17698; median follow-up of 9.1 years with a maximum of 16 years)	Chronic bronchitis or emphysema; grouped (Self-reported)	Incidence	HR=1.29 (1.09 to 1.53)	Sex and exposure cohort, study arm, education, BMI, years smoked and years smoked squared, average number of cigarettes smoked per day, average number of cigarettes smoked per day squared, and all other lung diseases, and stratified by former or current smoking status	No diagnosis of chronic bronchitis or emphysema
Turner et al 2007[48]	1982-2002	All 50 states as well as the District of Columbia and Puerto Rico	Male and female participants in the Cancer Prevention Study II (CPS-II) cohort	Prospective cohort (n=448,600) 20-year follow-up period)	Chronic bronchitis (Self-reported)	Mortality	HR=0.96 (0.72 to 1.28)	Stratified by age, sex, and race; adjusted for education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, vegetable/fruit/fiber intake, fat intake, and passive smoking	No chronic bronchitis
					Emphysema (Self-reported)	Mortality	HR=1.66 (1.06 to 2.59)	Stratified by age, sex, and race; adjusted for education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, vegetable/fruit/fiber intake, fat intake, and passive smoking	No emphysema
					Chronic bronchitis and emphysema (Self-reported)	Mortality	HR=2.44 (1.22 to 4.90)	Stratified by age, sex, and race; adjusted for education, marital status, BMI, occupational exposures, beer, wine, and liquor consumption, vegetable/fruit/fiber intake, fat intake, and passive smoking	No chronic bronchitis and emphysema
Wilson et al 2008[49]	2002-2006 (The Pittsburgh Lung Screening Study)	Pennsylvania	Current or former smokers aged 50–79 years with at least one-half pack of cigarettes per day for at least 25 years, and if no longer smoking, had quit smoking for no more than 10 years	Prospective cohort (n=3638; total follow-up of over 13,000 person-years with an average of 3.7 years per subject)	Airflow obstruction (Spirometry)	Incidence	OR=1.41 (0.87 to 2.29)	Sex, age, years of cigarette smoking, smoking dose intensity (four categories), and radiographic emphysema (four categories) or airflow obstruction (four categories), as appropriate.	No airflow obstruction
					Emphysema (CT)	Incidence	OR=3.14 (1.91 to 5.15)	Sex, age, years of cigarette smoking, smoking dose intensity (four categories), and radiographic emphysema (four categories) or airflow obstruction (four categories), as appropriate.	No emphysema

(*Continued*)

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Table 1 (Continued).

Author, Publication Year	Data Collection Years (Study Name)	Data Collection Location(s)	Population Description	Study Design (n)	COPD Definition (Assessment Method)	Outcome	Point Estimate (95% CI)	Adjustments	Referent Group
Schwartz et al 2009[50]	November 2001 to October 2005	Metropolitan Detroit	Female residents between the ages of 18–74; mean age: 60.1 ± 9.2 years (cases) and 59.4 ± 9.4 (controls)	Case-control (n_{cases}=562, $n_{controls}$=564)	Chronic bronchitis (Self-reported)	Incidence	OR=1.71 (1.13 to 2.59)	Age at diagnosis/interview, race, pack years, family history of lung cancer, education, current BMI, and adult aspirin use	No chronic bronchitis
					Emphysema (Self-reported)	Incidence	OR=3.21 (1.60 to 6.45)	Age at diagnosis/interview, race, pack years, family history of lung cancer, education, current BMI, and adult aspirin use	No emphysema
					Chronic obstructive lung disease; includes chronic bronchitis, emphysema, or COPD (Self-reported)	Incidence	OR=1.67 (1.15 to 2.41)	Age at diagnosis/interview, race, pack years, family history of lung cancer, education, current BMI, and adult aspirin use	No chronic obstructive lung disease
Li et al 2011[51]	1997-2004	Minnesota	Cigarette smokers who had smoked at least 20 pack-years	Case-control (n_{cases}=565, $n_{controls}$=450)	Emphysema (Medical Records)	Incidence	OR=13.37 (8.29 to 21.56)	Age, pack-years, other lung disease (including chronic bronchitis and unspecified COPD), and family history of lung cancer	No emphysema
Mina et al 2012[52]	1 September 1999 and 3 June 2010	Detroit, Michigan	Non-Hispanic Black people with a lung cancer diagnosis	Retrospective cohort (n=114; median follow-up time of 42.5 months; range 17–100 months)	Emphysema (CT)	Mortality	HR=0.74 (0.40 to 1.33)[c]	Age, sex, and stage	Not diagnosed with emphysema by CT
					COPD (Medical Records)	Mortality	HR=1.22 (0.70 to 2.08)[c]	Age, sex, and stage	Not clinical history
					COPD (Spirometry and/or CT)	Mortality	HR=0.76 (0.40 to 1.47)[c]	Age, sex, and stage	Not diagnosed with COPD (spirometry and/or CT)
McHugh et al 2013[53]	1991-2010	Houston, Texas	Self-reported Mexican Americans; mean age: 63.5 ± 10.8 years (cases) and 60.9 ± 13.8 (controls)	Case-control (n_{cases}=204, $n_{controls}$=325)	COPD (Self-reported)	Incidence	OR=2.0 (1.2 to 3.3)	Age, sex, self-reported pesticide exposure, and smoking intensity (number of smoking years/number of cigarettes per day)	No COPD

Aldrich et al 2015[54]	March 2002 to September 2009 (Southern Community Cohort Study)	12-state area of the Southeast (AL, AK, FL, GA, KY, LA, MS, NC, SC, TN, VA, and WV)	Low-income adults (aged 40–79) from medically underserved populations	Prospective Cohort (n=26927; median follow-up of over 6 years)	Chronic bronchitis or Emphysema (Self-reported only)	Mortality	HR=1.09 (0.65 to 1.83)	Coverage time on Medicare or Medicaid, sex, race, income, education, BMI, smoking, CESD-10 score and comorbidity count	No COPD diagnosis
					Chronic bronchitis or Emphysema (Medical records)	Mortality	HR=2.28 (1.77 to 2.95)	Coverage time on Medicare or Medicaid, sex, race, income, education, BMI, smoking, CESD-10 score and comorbidity count	No COPD diagnosis
					Chronic bronchitis or Emphysema (Medical records only)	Mortality	HR=2.12 (1.59 to 2.82)	Coverage time on Medicare or Medicaid, sex, race, income, education, BMI, smoking, CESD-10 score and comorbidity count	No COPD diagnosis
					Chronic bronchitis or Emphysema (Self report and medical records)	Mortality	HR=2.66 (1.88 to 3.76)	Coverage time on Medicare or Medicaid, sex, race, income, education, BMI, smoking, CESD-10 score and comorbidity count	No COPD diagnosis
Schwartz et al 2016[55]	May 2012-July 2014 (INHALE)	Detroit	Non-Hispanic Black and Non-Hispanic white adults aged 21–89; mean age: 63.7 ± 9.8 years (cases) and 61.5 ± 9.3 (controls)	Case-control (n_{cases}=341, $n_{controls}$=752)	Emphysema (Self-reported)	Incidence	OR=1.87 (1.25 to 2.79)	Age, race, gender, and pack years	No emphysema
					Emphysema (CT)	Incidence	OR=1.80 (1.35 to 2.41)	Age, race, gender, and pack years	No emphysema
					COPD (Self-reported)	Incidence	OR=1.43 (1.05 to 1.94)	Age, race, gender, and pack years	No COPD
					COPD (Spirometry)	Incidence	OR=1.98 (1.50 to 2.61)	Age, race, gender, and pack years	No COPD
Hopkins et al 2017[56]	April 2004-December 2009[79] (American College of Radiology, Imaging Network cohort of the National Lung Screening Trial)	United States of America	Older heavy smokers from the American College of Radiology Imaging Network (ACRIN) subcohort of the National Lung Screening Trial; mean age: 61.6 ± 5.0 years	Prospective cohort (n=18466; mean follow-up, 6.4 years)	Airflow limitation (Spirometry)	Incidence	IR= 8.11 (7.34 to 8.94)	N/A	No airflow limitation
					Airflow limitation (Spirometry)	Incidence	IRR=2.14 (1.85 to 2.48)	N/A	No airflow limitation

(*Continued*)

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Table 1 (Continued).

Author, Publication Year	Data Collection Years (Study Name)	Data Collection Location(s)	Population Description	Study Design (n)	COPD Definition (Assessment Method)	Outcome	Point Estimate (95% CI)	Adjustments	Referent Group
Gardner et al 2018[57]	1998-2015 (Maryland Lung Cancer Study)	Maryland	Black and white adults; mean age: 65.6 ± 0.26 years (cases) and 65.9 ± 0.19 (controls)	Case-control (n_{cases}=1660, $n_{controls}$=1959)	COPD (Self-reported)	Incidence	OR=2.19 (1.76 to 2.72)	Year of interview, year steroid stopped as exclusion, age at interview, smoking status (never, former, and current) and pack-years, marital status, environmental tobacco smoke exposure in adulthood and at work, family history of lung cancer, sex and race (for the overall model), or either sex or race for the stratified ones	No COPD
Nagasaka et al 2020[58]	Enrollment: January 1, 1993 - December 31, 1998 (Women's Health Initiative Observational Study)	United States of America	Women aged 50–79 years old who were postmenopausal at the time of enrollment	Prospective cohort (n=92798; follow up through December 31, 2015)	COPD (Self-reported)	Incidence	HR=1.64 (1.43 to 1.89)	Combined smoking status and intensity, ethnicity, education, body mass index, and income	No COPD
Charokopos et al 2021[59]	April 2004-December 2009[60] (American College of Radiology, Imaging Network cohort of the National Lung Screening Trial)	United States of America	Sub-cohort of NLST participants enrolled by Lung Screening Study network or ACRIN centers who underwent prebronchodilator spirometry; all participants have COPD; median age: 62 (IQR: 58–67) years	Prospective cohort (n=13939; no follow-up time given)	Airway obstruction (Spirometry)	Incidence	IRR= 1.21 (0.69 to 2.12)	Randomization group, age, sex, race/ethnicity, marital status, education, lung cancer family history, history of asbestos exposure, body mass index, current versus former smoker status, and pack-years smoked.	Asthma–COPD overlap
Singh et al 2021[61]	1 March 2015–31 December 2019	Boston, MA	Patients at an urban safety-net hospital aged 55–74 years, who were asymptomatic, had at least a 30 pack-year smoking history and were current smokers or had quit smoking in the past 15 years; median age: 62 (IQR: 9) years	Retrospective cohort (n=2847; no follow-up time given)	COPD (Medical records)	Incidence	OR=2.14 (1.22 to 4.28)	N/A	No COPD

Notes: [a]Calculated for all subjects (n=1376). [b]Calculated for subjects with direct interviews only. [c]The Mina et al study observations were inverted since results in the study were presented for people who did not have a clinical diagnosis of COPD, people who were not diagnosed with COPD (by spirometry and/or CT), and for people who were not diagnosed with emphysema (by CT).
Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio; IR, Incidence Ratio; IRR, Incidence Rate Ratio; BMI, body mass index (kg/m^2).

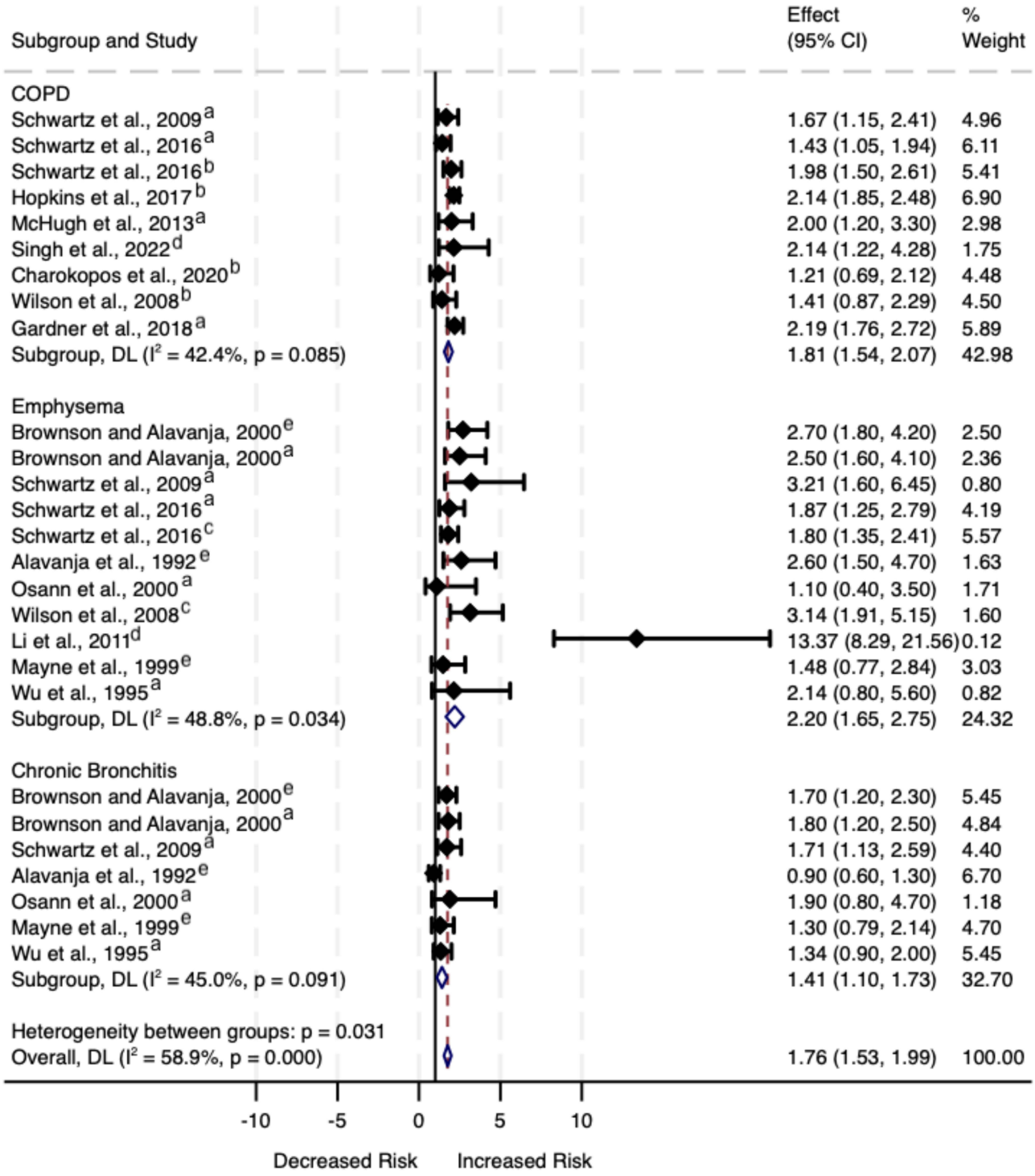

Figure 2 Association between Chronic Obstructive Pulmonary Disease (COPD) and Lung. Cancer Incidence Risk. [a]Direct interviews. [b]Assessed with spirometry. [c]Assessed with CT. [d]Assessed with medical records. [e]Direct and proxy interviews.

statistically significant (HR 1.51; 95% CI=0.95 to 2.07. I^2=82.9%) (Figures 4 and 5). Additionally, the funnel plot produced after removal of studies at moderate or high risk of bias (RoB=1) was symmetric, further indicating no publication bias (Supplementary Figure 1).

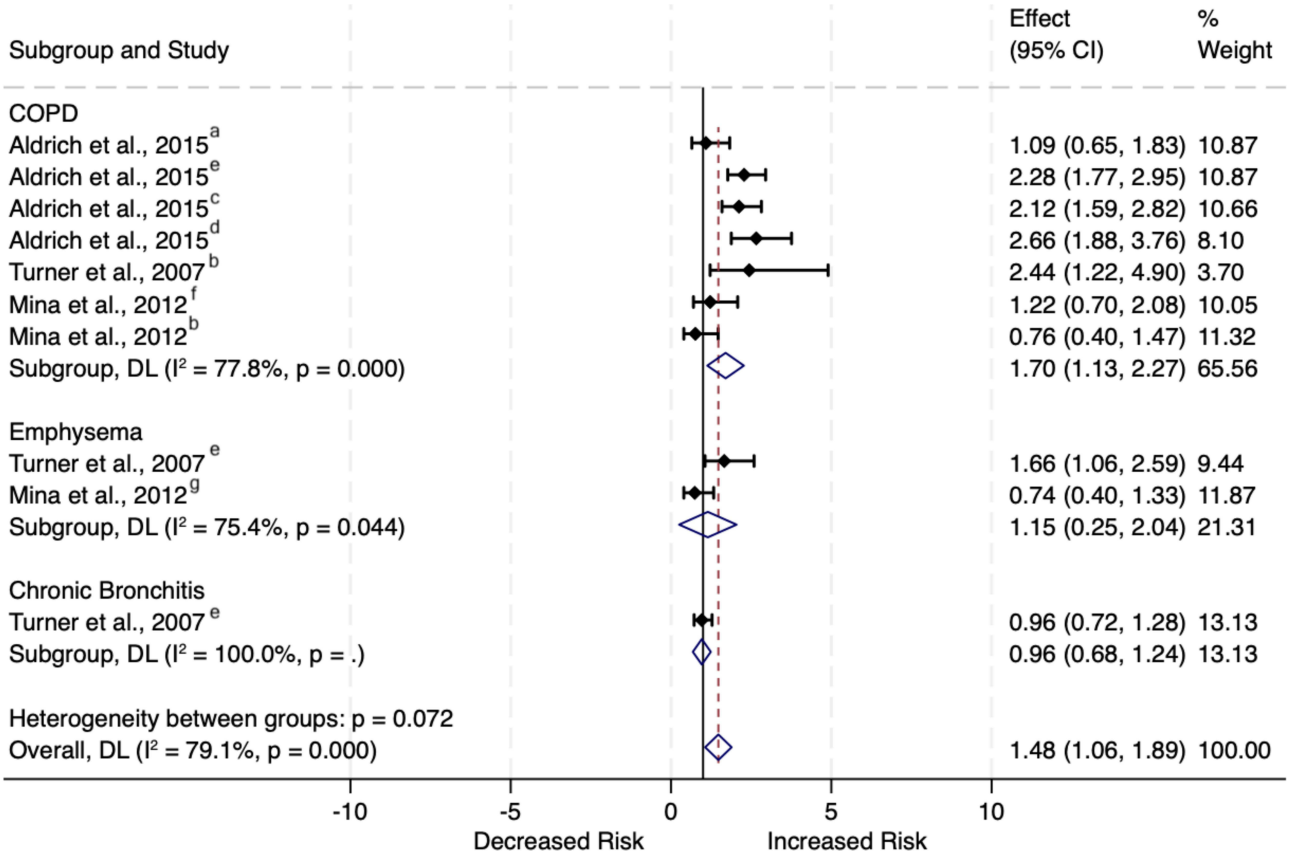

Figure 3 Assessing the Association between Chronic Obstructive Pulmonary Disease. (COPD) and Lung Cancer Mortality Risk. [a]Direct interviews. [b]Assessed with medical records. [c]Assessed with direct interviews and medical records. [d]Assessed with medical records (combined medical records (b) and direct interviews and medical records (c)). [e]Assessed with self-administered questionnaire. [f]Assessed with spirometry and/or CT. [g]Assessed with CT.

Outcomes in Population Subgroups

Only five studies examined the primary outcomes by sex[44,47,48,54,57] or race/ethnicity.[50,54,55,57,58] Seven studies examined outcomes by smoking status with variability on the smoking definition used across studies[42,44,47,50,54,56,63] (Table 1).

Sex

Of the fifteen observations (5 studies)[47,48,54] that examined lung cancer risk by sex, eight observations from three studies (Mayne et al[44] Littman et al[47] and Gardner et al[57]) assessed incidence and seven observations from two studies (Aldrich et al[54] and Turner et al[48]) assessed mortality (Supplementary Table 6).

Incidence by Sex

Mayne et al[44] (four observations), in a population of non-smokers (ie, never and former), found that males with chronic bronchitis (OR, 2.08; 95% CI=1.05 to 4.15) and females with emphysema (OR, 4.00; 95% CI=1.13 to 14.18) had higher odds of lung cancer incidence compared to controls without lung cancer. Littman et al[47] (two observations) found that ever smokers (current and former) males (HR, 1.52; 95% CI=1.19 to 1.94) but not females (HR, 1.14; 95% CI=0.85 to 1.52) with COPD – defined as chronic bronchitis or emphysema – had higher risk of lung cancer incidence compared to those without COPD. However, Gardner et al[57] (two observations) assessed the odds of lung cancer in people with a history of COPD compared to those without and found that both females (OR, 2.10; 95% CI=1.54 to 2.86) and males (OR, 2.28; 95% CI=1.67 to 3.10) with COPD had a higher odds of lung cancer incidence compared to those without COPD.

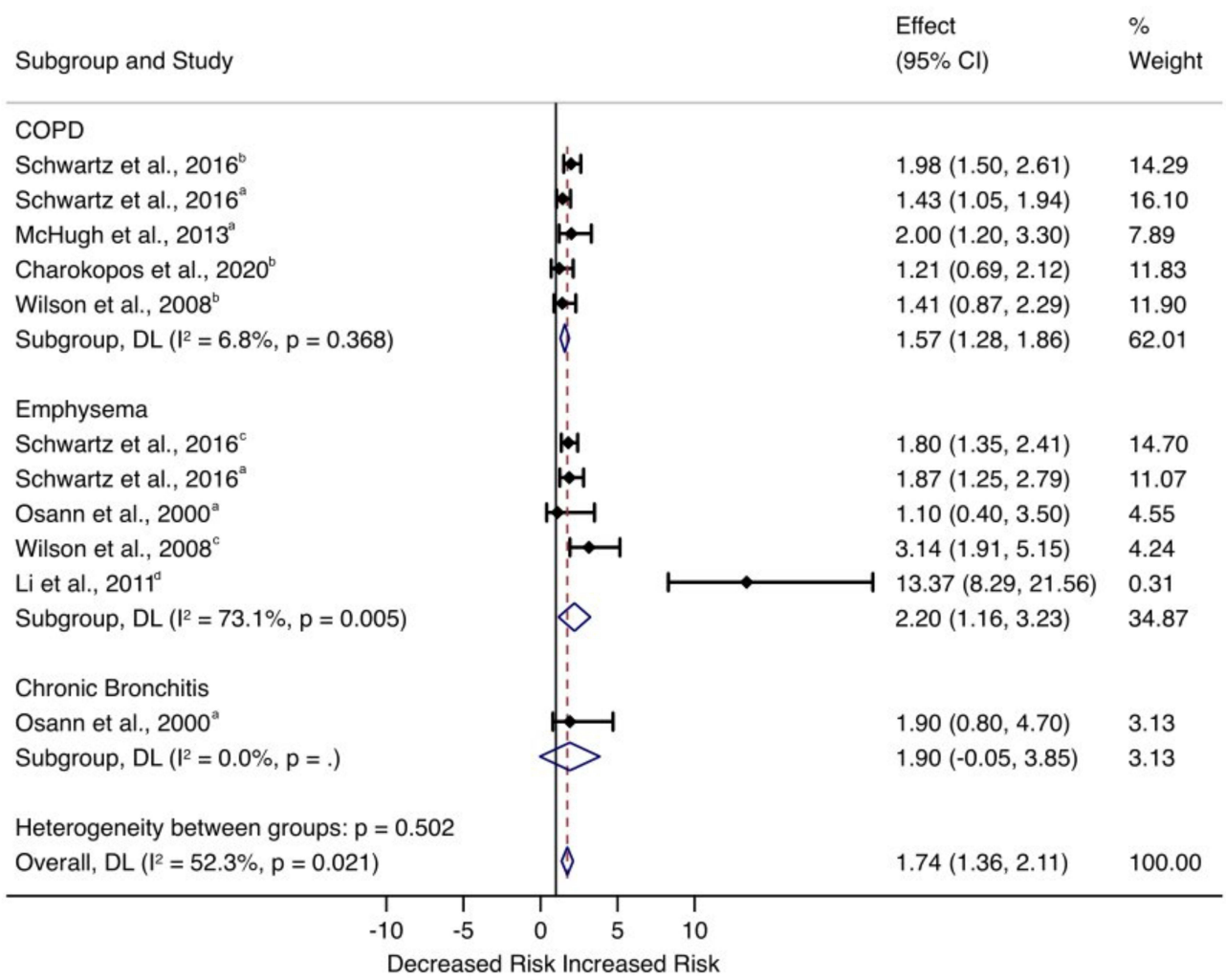

Figure 4 Sensitivity Analysis of Lung Cancer Incidence Risk among Studies with Low Risk of Bias (RoB=1). [a]Direct interviews. [b]Assessed with spirometry. [c]Assessed with CT.

Mortality by Sex

Aldrich et al[54] was the only study that reported lung cancer mortality risk comparing males and females with COPD, and found no difference in lung cancer mortality risk between the sexes (HR, 1.26; 95% CI=0.87 to 1.82). Turner et al[48] (six observations) conducted separate analyses comparing each sex with and without chronic bronchitis, emphysema and COPD, and lung cancer mortality. The study found greater risk of lung cancer mortality among males with COPD (HR, 3.60; 95% CI=1.34 to 9.73) but not females (HR, 1.82; 95% CI=0.68 to 4.87). Higher mortality risk was observed among females with emphysema (HR, 1.82; 95% CI=1.03 to 3.21) but not among males (HR, 1.42; 95% CI=0.70 to 2.88). Nonstatistical significance between chronic bronchitis and lung cancer risk was observed among males (HR, 1.59 95% CI: 0.95, 2.66) or females (HR, 0.82 95% CI=0.58, 1.16).

Race and Ethnicity

Five studies reported risks by race and ethnicity,[50,54,55] with results primarily reported for Black/non-Hispanic Black (NHB) and White/non-Hispanic White (NHW) populations. Nagasaka et al[58] was the only study to provide an observation for the heterogenous category of "Other". The five studies resulted in 19 observations – one reporting mortality and 18 incidence outcomes (Supplementary Table 7).

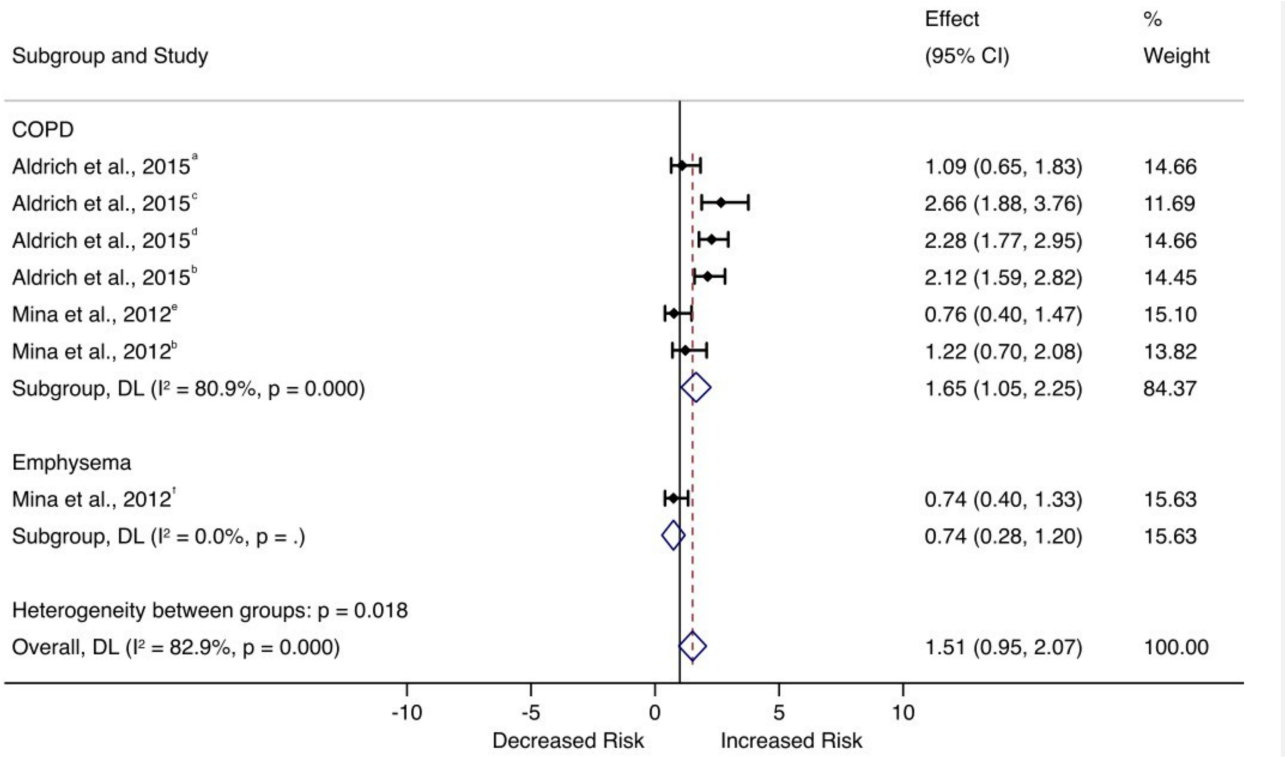

Figure 5 Sensitivity Analysis of Lung Cancer Mortality Risk among Studies with Low Risk of Bias (RoB=1). [a]Direct interviews. [b]Assessed with medical records. [c]Assessed with direct interviews and medical records. [d]Assessed with medical records (combined medical records (b) and direct interviews and medical records (c)). [e]Assessed with spirometry and/or CT. [f]Assessed with CT.

Incidence by Race and Ethnicity

Nagasaka et al[58] (2 observations) reported no risk difference in lung cancer incidence and COPD for Black (OR, 1.22 95% CI=0.97, 1.52) or "Other" (OR 0.97, 95% CI=0.74, 1.26) participants compared to White participants. Gardner et al[57] (2 observations) found that White participants with COPD were at higher risk for lung cancer incidence (OR, 2.04; 95% CI=1.57 to 2.67) compared to those without COPD. Similar findings were reported for Black participants (OR, 2.83; 95% CI=1.92 to 4.16). A total of 14 observations were extracted from two studies by Schwartz et al 2009[50] (6 observations) and 2016[55](8 observations). Five observations showed statistically significant greater odds of lung cancer incidence among non-Hispanic White (NHW) participants with COPD (2 observations) (defined as chronic bronchitis, emphysema, or COPD or spirometry) and emphysema alone (2 observations),[50,55] or chronic bronchitis alone (1 observation)[50] – compared to NHW participants without COPD (range from OR, 1.82; 95% CI=1.13 to 2.92 to OR, 3.75; 95% CI=1.69 to 8.32). Only Schwartz et al 2016[55] observed that non-Hispanic Black (NHB) participants (four of the eight observations) with COPD – defined as the umbrella term and emphysema alone – had statistically significant greater odds of lung cancer incidence than NHB participants without COPD (range from OR, 1.97; 95% CI=1.31 to 2.95 to OR, 2.40; 95% CI=1.55 to 3.72). The remaining five observations across Schwartz et al 2009[50] and 2016[55] found no differences in incidence risk.

Mortality by Race and Ethnicity

Aldrich et al[54] was the only study to examine the association between lung cancer mortality and COPD stratified by race and ethnicity and found no difference in risk between NHW and NHB participants with COPD (HR, 1.17; 95% CI=0.81 to 1.69) using NHB participants as reference.

Smoking Status

The definition of smoking status varied across the studies but generally fell into the categories of never smokers, current smokers, and former smokers. Of the included 26 observations (seven studies), six observations (three studies)[42,44,50]

assessed the relationship between COPD and lung cancer among never smokers, ten observations (six studies)[42,44,47,50,54,63] among former smokers, five observations (three studies)[47,50,63] among current smokers, and one observation (one study)[56] evaluated "healthy smokers" (ie, heavy smokers without COPD). Additionally, 25 of the 26 observations included looked at incidence and one looked at mortality. Four separate observations from Zhai et al[63] reported incidence risk by sex and smoking status (Supplementary Table 8).

Incidence by Smoking Status

Studies found no difference in lung cancer risk among never smokers with vs without chronic lung diseases but reported an increased risk for current and former smokers. Alavanja et al[42] found no difference in the risk of lung cancer in never smokers with chronic bronchitis (OR, 1.4; 95% CI=0.70 to 2.50) or emphysema (OR, 0.7; 95% CI=0.1 to 5.5) compared to those without the disease. Mayne et al[44] in a sample of non-smokers (never and former), also found no increased incidence risk in individuals with chronic bronchitis (OR, 3.01; 95% CI=0.6 to14.86) or emphysema (OR, 1.57; 95% CI=0.80 to 2.72) compared to non-smokers without the disease.

Among current smokers with COPD (defined as chronic bronchitis or emphysema), Littman et al[47] and Schwartz et al[50] found an increased risk (HR, 1.25; 95% CI=1.04 to 1.51 and OR, 1.93; 95% CI=1.06 to 3.49, respectively) compared to those without COPD. Schwartz et al 2009[50] also found that current smokers with chronic bronchitis had greater odds of incidence than those without chronic bronchitis (OR, 3.08; 95% CI=1.47 to 6.43). Hopkins et al[56] found increased incidence of lung cancer for heavy smokers with COPD compared to "healthy smokers" (ie, heavy smokers without COPD) (unadjusted IR, 3.04, 95% CI=2.65 to 3.48).

Regarding former smokers, Mayne et al[44] found that former smokers with chronic bronchitis had greater odds of lung cancer incidence compared to those without (OR, 1.88; 95% CI=1.02 to 3.44). Schwartz et al 2009[50] found that former smokers with COPD – defined as the umbrella term and as emphysema – had greater odds of lung cancer incidence compared to those without COPD (range from OR, 2.03; 95% CI=1.11 to 3.71 to OR, 5.33; 95% CI=1.65 to 17.20).

Studies that compared smoking status in individuals with COPD reported higher incidence risk in smokers vs non-smokers. Zhai et al[63] found increased odds of lung cancer incidence for current smokers with COPD compared to never smokers with COPD (OR, 7.92; 95% CI=5.43 to 11.57). This study also observed that male (OR, 6.43; 95% CI=3.47 to 11.89) and female (OR, 8.95; 95% CI=5.55 to 14.47) current smokers had a higher risk compared to never smokers. Zhai et al[63] also found an increased odds for former smokers with COPD compared to never smokers with COPD (OR, 4.69; 95% CI=3.22 to 6.81), and when stratifying by sex (OR, 3.95; 95% CI=2.16 to 7.24 for male and OR, 5.06; 95% CI=3.14 to 8.15 for female former smokers vs never smokers).

Mortality by Smoking Status

Aldrich et al[54,56] was the only study to evaluate mortality risk by smoking status. They found higher risk of COPD and lung cancer mortality among former smokers compared to never smokers (HR, 4.67; 95% CI=1.66 to 13.17).

COPD Assessment Method

The method of assessing COPD varied across studies. The majority (twelve studies) classified COPD through self-reported physician diagnoses of COPD, emphysema, and/or chronic bronchitis only.[42–48,50,53,57,58,63] Two studies[56,59] used spirometry only, two studies[51,61] used medical records only, and four studies[49,52,54,55] used a combination of assessment methods, including CT.

Our stratified meta-analysis results indicate that COPD defined by self-report (n=9) (OR, 1.68; 95% CI=1.43 to 1.93; I^2=46.9%) and by spirometry only (n=4) showed greater odds (OR, 1.84; 95% CI=1.49 to 2.19; I^2=50.3%) of lung cancer incidence (Figure 6). Assessment of COPD using medical records only, reported no significant differences for lung cancer incidence (n=2) but significant for lung cancer mortality (n=2) (HR, 1.89; 95% CI=1.28 to 2.51; I^2=65.4%). However, pooled results of studies with COPD diagnosed by self-reported, spirometry, and combined assessment methods reported no higher risk of lung cancer mortality (Figure 7), and the individual assessment methods 95% CIs overlapped for all subgroups indicating a potentially statistically insignificant difference in risk between assessment methods.

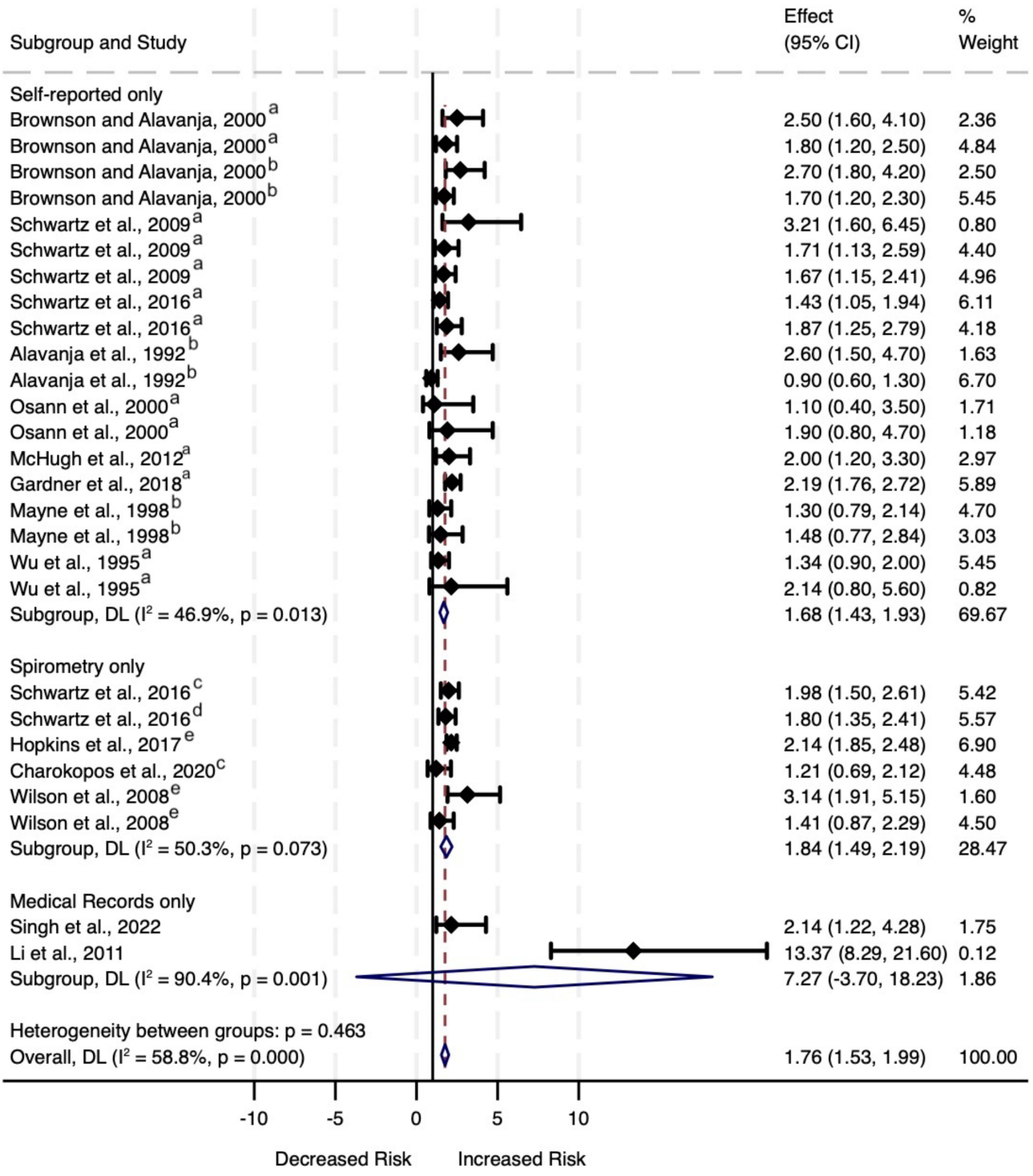

Figure 6 Meta-Analysis of the Effect of COPD Assessment Method on Lung Cancer. Incidence Risk. [a]Direct interviews. [b]Direct and proxy interviews c FEV1/FVC < 0.70. [d]GOLD I–IV. [e]Assessed with CT.

Sensitivity Analyses

To address the issue of potential double counting, we conducted a sensitivity analysis using only one observation from included studies. Details on the methods used for study selection can be found in Supplementary Material A.

From the 14 studies (37 observations) included in the main meta-analyses for incidence and mortality, this analysis was conducted for a total of 14 observations, one for each included study. The pooled results from the sensitivity analysis

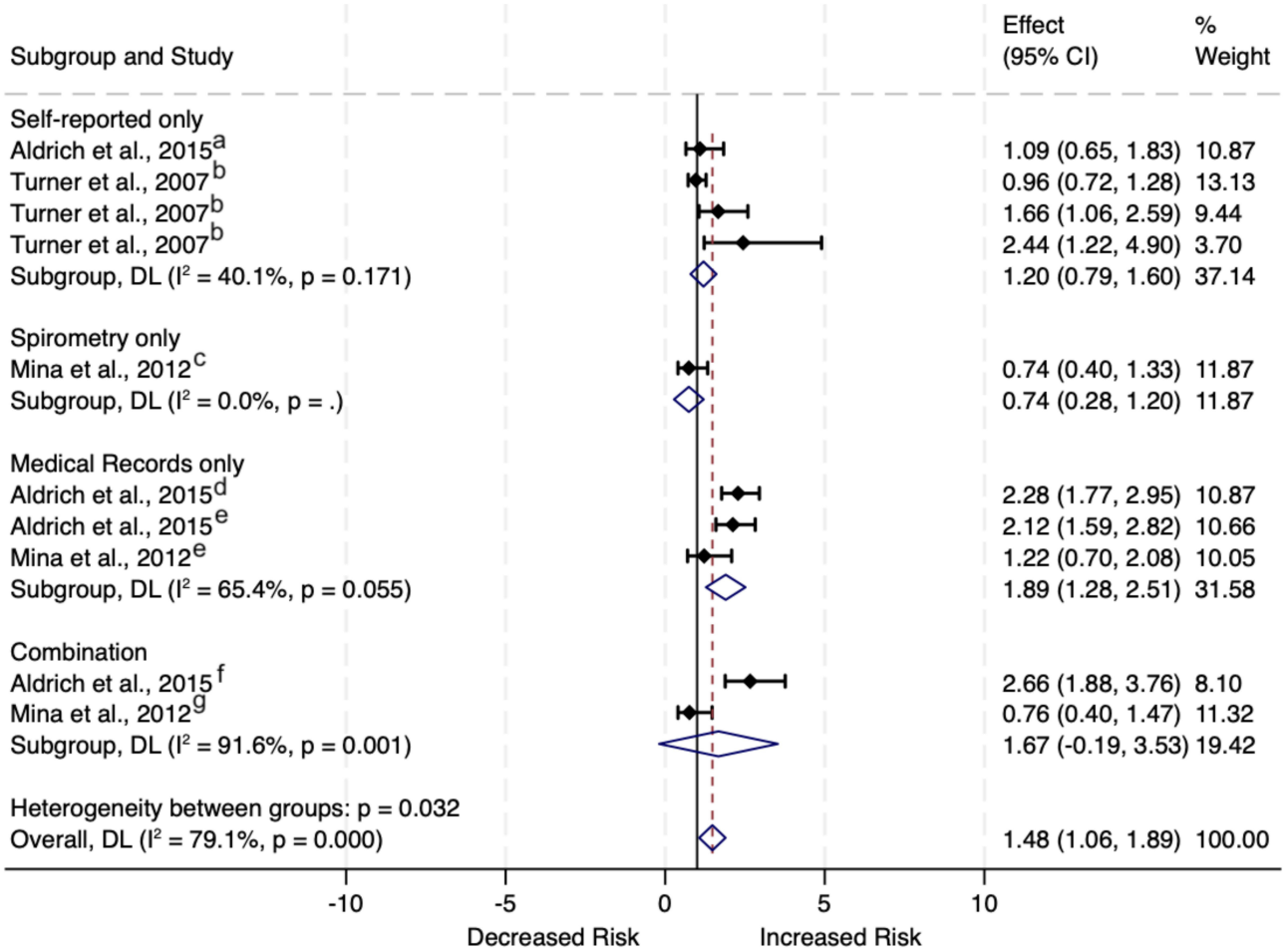

Figure 7 Meta-Analysis of the Effect of COPD Assessment Method on Lung Cancer. Mortality Risk. [a]Direct interviews. [b]Assessed with self-administered questionnaire. [c]Assessed with CT. [d]Assessed with medical records (combined medical records (e) and direct interviews and medical records (f)). [e]Assessed with medical records. [f]Assessed with direct interviews and medical records. [g]Assessed with spirometry and/or CT.

indicated that US adults with COPD had 83% greater odds of developing lung cancer compared to adults without the disease (OR, 1.83; 95% CI=1.50 to 2.17; I^2=55.9%). This result aligns with the main analysis (HR, 1.76; 95% CI=1.53 to 1.99) (Supplementary Figure 2). The mortality analysis was conducted only on three studies that used the COPD umbrella definition. The pooled results indicate a non-significant difference in lung cancer mortality risk between individuals with COPD and those without the disease (HR, 1.22; 95% CI=0.78 to 1.65; I^2=0.0%). This differed from the main analysis which showed a higher mortality risk in those with COPD vs without (HR, 1.48; 95% CI=1.06 to 1.89) (Supplementary Figure 3).

Discussion

We conducted a systematic review and meta-analysis of the risk of lung cancer incidence and mortality among US adults with a diagnosis of COPD, within the overall general population and across subgroups. The overall pooled summary estimates (PSE) indicate that adults with COPD – inclusive of all definitions – have a 76% higher risk of developing lung cancer and 48% greater risk of lung cancer mortality compared to those without the COPD. The observed difference between incidence and mortality risk may be partially explained by early intervention strategies. Smoking cessation and timely COPD treatment improve overall respiratory health and may slow disease progression,[67,68] while lung cancer screening facilitates earlier detection and treatment.[69] These combined strategies enhance lung cancer survival. Additionally, individuals with COPD frequently face competing comorbidities that may lead to non-cancer associated mortality, attenuating the observed lung cancer mortality risk.[6,70]

When categorized by the different COPD definitions, the odds of lung cancer incidence increased by 41% for chronic bronchitis, 120% for emphysema, and 81% by the umbrella definition of COPD for those with the diseases compared to those without. Lung cancer mortality risk results indicate that the umbrella definition of COPD conferred a 70% increase in lung cancer mortality risk. However, the results did not show statistically significant differences when defined separately as chronic bronchitis or emphysema. Mixed results were observed in our systematic review when stratifying the impact of COPD on lung cancer risk by sex, race and ethnicity, and smoking status.

Our findings are largely consistent with previous systematic reviews and meta-analyses inclusive of populations within and outside the US. Ang et al[71] conducted a meta-analysis using 71 studies across various countries – including the US – which combined methods of association and reported that having emphysema (PSE: 2.21; 95% CI=2.04 to 2.40) and COPD (PSE: 2.51; 95% CI=1.71 to 3.68) conferred about two times the risk of developing lung cancer. Similarly, a significant but lower risk, was associated with history of chronic bronchitis (PSE: 1.49; 95% CI=1.32 to 1.69). Likewise, Zhang et al[72] conducted a meta-analysis using US and international studies and they reported an increased risk of developing lung cancer for individuals with COPD (summary relative risk (SRR), 2.06; 95% CI=1.50 to 2.85) and emphysema (SRR, 2.33; 95% CI=1.56 to 3.49) but not for those with chronic bronchitis (SRR, 1.17; 95% CI=0.79 to 1.73). Another review by Brenner et al[73] – conducted using US and international studies – found that having COPD (relative risks (RR), 2.22; 95% CI=1.66 to 2.97), chronic bronchitis (RR, 1.52; 95% CI=1.25 to 1.84), or emphysema (RR, 2.04; 95% CI=1.72 to 2.41) increased lung cancer incidence risk. Our results – from only US populations – showed an increased risk of mortality and incidence with COPD that was consistent with Zhang et al,[72] and Brenner et al[73] albeit with slightly lower PSEs than Zhang et al. The discrepancy in PSE may reflect the inclusion of international studies, the grouping of mortality and incidence estimates, and the scarcity of studies that reported risk for lung cancer mortality with chronic bronchitis or emphysema separately.

Our results, and prior meta-analysis, report a substantial increased risk of lung cancer among individuals with COPD and emphysema. These findings highlight the importance of targeted surveillance in this population. COPD and lung cancer are highly prevalent in older individuals who currently or formerly smoked. Therefore, individuals with COPD are more likely to undergo lung cancer screening (LCS) with low-dose computed tomography (LDCT). LCS offers dual clinical benefits for survival. Beyond detecting early-stage lung cancer, which reduces lung cancer-specific mortality,[74,75] LDCT frequently reveals the presence of emphysema, allowing for timely intervention and potential reduction in lung cancer incidence.[76–78]

In our review, subgroup analyses are similar to those from other systematic reviews and meta-analyses. Only one study in our systematic review compared mortality risk between males and females; this study found no differences in lung cancer mortality risk by sex.[54] All other assessments by sex compared males or females with COPD to males or females without COPD and generally found higher risk of lung cancer mortality[48] and lung cancer incidence[47] among those with COPD compared to those without. Our results are in accordance with the meta-analysis conducted by Zhang et al[72] which found increased risk of lung cancer in both males (SRR, 2.04; 95% CI=1.11 to 3.74) and females (SRR, 2.67; 95% CI=1.27 to 5.59) with COPD and no differences in risk by sex.

We also found an increased risk of lung cancer mortality[48] and lung cancer incidence[63] among people with smoking history (ie, former or current smokers) compared to never smokers. Individuals with a history of smoking and COPD were at increased risk of lung cancer incidence compared to those without COPD.[50] Zhang et al[72] also found that current smokers were at higher risk for lung cancer incidence (SRR, 1.63; 95% CI=1.11 to 2.39). However, their meta-analysis did not find increased risk for former smokers (SRR, 1.32; 95% CI=0.65 to 2.68). This difference may be due to Zhang et al[72] restricting their analysis to prospective cohort studies or including populations from different countries outside the US.

Lung cancer risk varies by sex, race and ethnicity, and smoking status[60] – which in turn propagates health inequalities through disparities in incidence,[79] stage at diagnosis, treatment,[80] mortality, and survival. Results stratified by sex or smoking status were more commonly found in the included studies while studies that reported results by race and ethnicity were limited and Black participants were often underrepresented. Schwartz et al 2009[50] found increased odds of lung cancer incidence in White populations. However, for this study, the population was comprised of approximately 76% White and 24% Black participants – compared to the 2016 study[55] which was approximately 53% White and 47% Black. Because of the differences in population size, it is difficult to determine the reliability of the data and brings up

a question of whether the results among the Black participants in the 2009 study population are due to underreporting, underdiagnosis, or lower risk of COPD.

Additionally, the studies included in the race and ethnicity analysis commonly classified populations that were not non-Hispanic Black or non-Hispanic-White as "Other". This practice results in an incomplete understanding of the differential effects by race and ethnicity since a distinct focus is provided to two racial/ethnic subgroups, relegating other racial and ethnic identities to a nonspecific category. Studies conducted using National Health and Nutritional Examination Surveys (NHANES) data show that belonging to an underrepresented group, specifically Black or Mexican American, increases the odds of undiagnosed COPD.[81] The sparseness of the literature restricted a comprehensive analysis of the differential impacts of race and ethnicity on COPD associated lung cancer disease burden. Further understanding of racial/ethnic diversity is needed where each identity confers its own characteristic risk because of unique interactions with health systems.

During the review process, we observed that authors defined COPD diagnosis using various assessment method. This variability, likely influence both the magnitude and direction of the observed associations. We conducted a meta-analysis examining the impact of the different COPD diagnosis assessment methods on lung cancer risk (Figures 6 and 7). Our results showed that COPD diagnosed by self-report or spirometry conferred greater odds of lung cancer incidence while COPD diagnosed with medical records conferred greater risk of lung cancer mortality. These findings are consistent with existing evidence that assessment method may influence disease categorization and consequently prevalence estimates of the disease.[82] Ho et al[83] in their review found that within the US, COPD prevalence ranged from 10% to 21% with pre and post-spirometry data. Studies have also shown that underdiagnosis rates with spirometry-assessed COPD range from 12% to 72%[83,84] while overdiagnosis with medical records is approximately 42.5%.[85]

The moderate to high levels of heterogeneity in our review results may be due to differences in how each study defined and assessed COPD. Moderate levels of heterogeneity were observed in the analyses of lung cancer incidence, which is likely driven by the magnitude of the association, while high levels of heterogeneity were observed in the analyses of lung cancer mortality likely driven by the direction of the effect as well as the magnitude of association. Because COPD is an umbrella term encompassing chronic bronchitis, emphysema, or combinations of both, these differences likely had a relevant effect on the observed results. Heterogeneity may also be due to study design. Our included studies were a mix of case-control and cohort studies. Differences in study population may also impact heterogeneity; some studies only included women[42,45,46,50] or were restricted to specific racial/ethnic backgrounds such as Mexican Americans[53] or Black participants.[52] Similarly, there was little consistency in the studies' definitions of smoking status (eg, former smokers were defined as those who quit smoking for 2 years or quit for 15 years or more or quit 12+ months) and only one study evaluated mortality risk, which limited our comparability of the studies. Finally, in our analyses, we included unadjusted outcomes from studies which did not provide adjusted outcomes[56] or relied on bootstrapping,[61] which raises the possibility of confounding in our analyses. However, as the unadjusted outcomes comprised only four of the 119 extracted observations, confounding was likely a minimal effect.

In addition, studies on COPD risk are prone to double-counting due to the umbrella nature of the disease and reporting estimates for overall COPD and each disease separate. We extracted and reported results separately for COPD, chronic bronchitis and emphysema when studies provided disaggregated data. However, this can still lead to overlapping populations, which may inflate effect estimates, compromising the reliability of meta-analysis results and subsequent decision-making.[39] We addressed this issue through conducting sensitivity analyses for incidence and mortality risk that included only one observation per study-prioritizing results based on overall COPD definition to reduce bias from overlapping definitions. The sensitivity analyses showed no change in the effect on incidence risk but reported a non-significant difference in lung cancer mortality risk between individuals with and without COPD which differed from the main analysis.

In our search, we found only one study[86] which examined lung cancer risk by COPD severity stages, but that study was excluded from the analyses as its results were not comparable to those of the included studies. Still, studies show that the prognosis of lung cancer worsens with increasing COPD severity.[87] Therefore, future studies must consider stratifying the risk outcomes by COPD severity stages.

In conclusion, US adults with COPD, particularly those with emphysema and a smoking history, are at an increased risk for lung cancer incidence and mortality compared to those without COPD. As COPD-associated morbidity and mortality continue

to increase, further research is needed on the risks associated with COPD, especially among different subgroups, and the intersectional ways in which COPD and lung cancer risk manifest.

Data Sharing Statement

The data underlying this article are available in the article and in its online Supplementary Materials.

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Author Contributions

All authors made significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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