Original Research

COPD With Lung Cancer Among Older United States Adults: Prevalence, Diagnostic Timeliness, and Association With Earlier Stage Tumors

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Keywords**:** COPD; lung cancer; epidemiology; Medicare

Abbreviations: **COPD=** chronic obstructive pulmonary disease**, SES=** socioeconomic status, **CCI**= Charlson Comorbidity Score Index, **NSCLC**= non-small cell lung cancer, **SCLC**= Small cell lung cancer. **SEER**= Surveillance, Epidemiology and End Results, **AJCC**= the American Joint Committee on Cancer staging system, **NHWs**= Non-Hispanic White, **NHBs**= Non-Hispanic Black, **AIAN**= American Indian/Alaskan Native, **NHPI**= Native Hawaiian or Pacific Islander (NHPI), **AECOPD=** acute exacerbation of COPD, **PR**= Prevalence ratio, **PD**= Prevalence difference, **CI**= Confidence interval, **CLR**=UCL/ LCL= Confidence limit ratio =Upper confidence limit/ lower confidence limit, **CLD**= UCL-LCL= Confidence limit difference= Upper confidence limit - lower confidence limit, **RPR**= Ratio of prevalence ratios, **DID**= Difference in prevalence differences.

Funding Support:
The National Cancer Institute: R01-CA-264176
The National Institute of Environmental Health Sciences: 2T32ES007018-46

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Date of Acceptance: May 24, 2024 | ***Publication Online Date*:** June 5, 2024

Citation: Metwally EM, Lund JL, Drummond MB, Peacock Hinton S, Poole C, Thompson CA. COPD with lung cancer among older United States adults: prevalence, diagnostic timeliness, and association with earlier stage tumors. *Chronic Obstr Pulm Dis.* 2024; Published online June 5, 2024.
https://doi.org/10.15326.jcopdf.2024.0489

This article has an online supplement.

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Abstract.

Rationale: COPD is a common comorbidity among patients with lung cancer, and an important determinant of their outcomes, however it is commonly underdiagnosed.

Objective: To estimate the prevalence of COPD among a cohort of U.S. lung cancer patients, the timing of COPD diagnosis relative to their lung cancer diagnosis, and the association between earlier diagnosis of COPD and stage of lung cancer, with consideration of patient sociodemographic modifying factors.

Methods: We conducted an analysis of the Medicare-linked Surveillance, Epidemiology and End Results (SEER) database including patients aged 68+ years who were diagnosed with lung cancer between 2008 to 2017. **Exposure:** Prevalence of COPD was identified using claims and subclassified based on the timing of its diagnosis relative to the lung cancer diagnostic episode: "pre-existing" if diagnosed > 3 months before lung cancer, and "concurrent" if diagnosed around the same time as the lung cancer (+/-3 months). **Outcome:** Stage of cancer at diagnosis (early vs. late).

Results: Among 159,542 patients with lung cancer, 73.5% had COPD. Among those with COPD, 65.6% were diagnosed "early", i.e., > 3 months before their lung cancer. We observed a positive association between pre-existing COPD diagnosis and early-stage lung cancer (Prevalence ratio= 1.27; 95% CI= 1.23 - 1.30), in adjusted models which was stronger for male, Non-Hispanic Black, and Hispanic patients.

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Conclusions: Seven out of ten patients with lung cancer have COPD, however many don't receive their COPD diagnosis until around the time of lung cancer diagnosis. Among these patients, early COPD diagnosis may improve early detection of lung cancer.

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Introduction

Lung cancer is the most common cause of cancer-related death worldwide.[1] The 5-year survival of lung cancer ranges between 62% for early stage disease to 8% for late stage, with important disparities among racial minorities in the United States (U.S.).[1] Survival from lung cancer depends on tumor type, access to care, and preexisting comorbidities.[2,3] Chronic obstructive pulmonary disease (COPD) is a common comorbidity among patients with lung cancer and an independent risk factor for lung cancer regardless of smoking history.[4] Previous studies reported that the annual incidence of lung cancer is ~5x higher among patients with COPD compared to the general population.[5] Further, severe COPD is a competing cause of death among patients with lung cancer.[6] Both diseases are frequently diagnosed among older adult populations when patients are more likely to be frail, impacting their treatment tolerance, quality of life and survival.[7] Therefore, several calls[8,9,10,11] have emphasized the importance of including COPD in risk prediction models to improve ongoing efforts for diagnosis of lung cancer at an early-stage where curable treatment is available, and quality of life as well as survival are boosted.

However, COPD is frequently underdiagnosed in the general population, among participants in lung cancer screening, and patients with new lung cancer diagnoses.[12,13] Reports from previous studies showed that underdiagnosis of COPD is higher among populations at high risk to develop and die from lung cancer such as racial minorities and populations with low socioeconomic status (SES) in US.[14,15] Non-Hispanic Black (NHBs) populations are less likely to have a COPD diagnosis regardless of the severity of airflow obstruction,[16] and more likely to develop lung cancer at younger ages and less smoking intensity compared to non-Hispanic White

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

(NHWs) populations.[17] Low SES has been shown to be associated with greater risk of both COPD and lung cancer.[18]

Little is known about prevalence and timing of COPD diagnosis among patients with lung cancer and across different racial and SES backgrounds in U.S. Further, there is lack of evidence about whether a pre-existing COPD diagnosis is associated with earlier-stage lung cancer at diagnosis.[19] Therefore, in the present study we sought to estimate the prevalence of COPD diagnosis among patients diagnosed with lung cancer, the timing of COPD diagnosis relative to the start of their lung cancer diagnostic episode, and, among those with both COPD and lung cancer, the association between timing of COPD diagnosis and lung cancer stage at diagnosis.

Methods

Data source

We used the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) linked to Medicare fee-for-service (FFS) insurance claims data from the Centers for Medicaid and Medicare Services (CMS). The SEER-Medicare data reflects linkage of two large population-based sources of data to provide detailed information about Medicare beneficiaries with cancer. We used the SEER database which includes data from 21 cancer registries and represents approximately 40% of the US population.[20] The SEER tumor registry file includes patient sociodemographic, and tumor characteristics. The Medicare claims file includes all details of reimbursed health care services that occurred in different settings (e.g., hospitals, physician offices, outpatient clinics) from the time of patient's Medicare enrollment until disenrollment or death.

Study Population

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

The study population included Medicare beneficiaries who were diagnosed with primary invasive lung cancer between 2008 to 2017. To ensure we captured all relevant pre-diagnostic healthcare utilization in the Medicare FFS claims, patients were included if they had continuous enrollment in Medicare Parts A and B without health maintenance organization (HMO) coverage in the 36 months before diagnosis until 3 months after lung cancer diagnosis (or until death). Given the typical start of Medicare coverage at age 65 years in the US and our requirement of 3 years of continuous enrollment to reduce COPD misclassification,[21] we included patients 68 years of age and older. We excluded patients who were diagnosed at autopsy/death certificate, had lung cancer staged in situ, had previous history of cancer or were younger than 68-years-old at diagnosis (**Supplement Figure E1**).

Index Date

To characterize the healthcare episode in which the lung cancer was first detected, we used a published and validated algorithm[22] that identifies the earliest ICD-9/10 claim code associated with lung cancer within +/- 1 month of the SEER diagnosis month. This "index date" approximates the start of the cancer care episode, i.e., when care delivery for the suspected lung cancer began. If no Medicare claims were found within +/- 1 month of the SEER diagnosis month, the index date was imputed as the 15th day of SEER month.

COPD Diagnosis and Timing

We used a validated claims-based algorithm[23] to identify occurrence of one or more COPD diagnosis codes (ICD-9 491, 491.2, 492, 496 and ICD-10 J40, J41, J43.0, J43.1, J43.2, J43.8, J43.9, J44) from all Medicare claims in the 36 months before, to 3 months after, the index date. We further classified COPD based on its timing relative to the lung cancer diagnostic episode. Patients whose earliest COPD related claims occurred during the lung cancer peri-

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

diagnosis period, -3 to +3 months around the index date were classified as having "concurrent COPD"; all others were classified as having "pre-existing COPD". This framing reflects our hypothesis, that some patients might not receive their COPD diagnosis until after the start of the lung cancer diagnostic episode, i.e., during pre-treatment evaluation of lung cancer (e.g., Pulmonary function testing). It also reflects precedent for defining the "peri-diagnosis" period in healthcare utilization data.[24, 25] (**Figure 1**).

Outcome.

We used the SEER summary stage to classify lung cancer stage at diagnosis into (localized, regional, distant). Further, we used the TNM American Joint Committee on Cancer staging system 8th edition (AJCC) to classify the SEER stage into early- (localized SEER stage) versus late stage (regional and distant SEER stage).[26] The outcome of interest was early stage versus late-stage of lung cancer at diagnosis

Covariates.

We examined sociodemographic characteristics from the SEER registry including age at lung cancer diagnosis, sex (female/male), race and ethnicity categorized as Non-Hispanic White (NHWs), Non-Hispanic Black (NHBs), Hispanic, American Indian/Alaskan Native (AIAN), Native Hawaiian or Pacific Islander (NHPI), Asian American, Mixed Race and Other Race, marital status (married/partnered vs. not), census-tract indicators of SES (Yost US-based quintile) and poverty,[27] county rurality (Metro, urban, Rural), SEER registry region (East, South, Midwest, West), and year of lung cancer diagnosis (2008-2017). Tumor characteristics included histology: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and other invasive lung cancer, and tumor stage using SEER summary stage.

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Clinical characteristics from Medicare claims included healthcare utilization including frequency of inpatient stays, outpatient, and emergency department visits in the year prior to the index date. We used a case definition algorithm to identify occurrence of acute exacerbation of COPD (AECOPD) in the year before the index date as per the following: one or more occurrences of diagnosis codes (ICD-9 518.81, 518.82, 518.84, 786.09,799.1, 491.21, 491.22 or ICD-10 J44. 1). We estimated comorbidity burden using the Klabunde modified Charlson Comorbidity Score Index (CCI)[28] using claims in the 12 months before the index date, classifying patients into four groups (0, 1, 2, 3+) based on comorbidity score for each patient. Our comorbidity score excluded COPD so we can compare patients with and without COPD.

Statistical analysis.

We calculated descriptive statistics of sociodemographic, clinical and tumor characteristics comparing lung cancer patients with and without COPD and based on timing of COPD diagnosis (pre-existing vs. concurrent) relative to the index date. We used generalized linear models with Poisson distribution and identity link (to estimate prevalence difference: PD) and log link (to estimate prevalence ratio: PR) and corresponding 95% confidence intervals for the association between pre-existing (vs. concurrent) COPD diagnosis with early (vs. late) lung cancer stage at diagnosis among patients with COPD only. We fit two models: age adjusted and a fully adjusted model for age, sex, area-level SES, year of diagnosis, SEER region, CCI, and frequency of healthcare utilization (HCU). We didn't adjust for race in our regression models to avoid ignoring its discriminatory effect on the association,[29] but instead we reported PD and PR across all measured race and ethnicity groups. We also conducted subgroup analysis to examine possible modification of the association by sex, race and ethnicity, and SES using the same

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

method reported above for the main association PD and PR. We considered p-value <0.3 to be sufficient to reject the null hypothesis for the subgroup analyses.

All analyses were conducted using SAS, version 9.4 (SAS Institute Inc). This study was reviewed and approved as exempt by The University of North Carolina at Chapel Hill Institutional Review Board (#22-2998). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies. [30]

Results.

Our final study sample included 159,542 patients with lung cancer diagnosed between 2008 and 2017 (**Figure 2**). The mean age (SD) was 77.6 (6.6) years, the population has slightly more females (51.5%) than males, 85% of patients were NHWs, 6.7% were NHBs, 3.8% were Hispanic, 3.8% were Asian, 0.3% were AIAN and 0.2% were of NHPI race and ethnicity. Reflecting the SEER regions, 83.4% of patients were residents of metropolitan areas, 22.4% lived in areas of highest poverty, and 16.5% lived in lowest SES neighborhood quantile. Lung cancer was diagnosed at an early-stage for 21.5% of patients, 79.6% were diagnosed with non-small cell lung cancer (NSCLC), while 11.1% had small-cell lung cancer (SCLC). (**Table 1**).

A total of 117,202 (73.5%) of our study patients had evidence of COPD diagnosis in the 36 months prior to 3 months after their index date. Compared to patients without COPD, patients with COPD were more likely to be younger, male, more NHWs (86.3 vs. 81.5%), less NHBs (6.7 vs. 7%), less Hispanic (3.5 vs. 4.6%), and more likely to live in poverty and in low SES neighborhoods. Clinically, they were more likely to have 3 or more comorbidities other than COPD (19 vs. 11.7%), more healthcare utilization related to any medical condition at inpatient,

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

outpatient, and emergency department settings, and more likely to get diagnosed with early-stage lung cancer (22.7 vs. 18%) compared to patients without comorbid COPD. (**Table 1**).

Among 117,202 patients with comorbid COPD and lung cancer, 76,872 (65.6%) had pre-existing COPD diagnosis (evidence of COPD-related healthcare utilization >3 months before index date), while 40,330 (34.4%) had concurrent COPD diagnosis (evidence of COPD-related healthcare utilization only during the +/- 3 months from the index date). Patients with pre-existing COPD diagnosis were more likely to be older, female, NHWs, and had lower area level SES. Clinically, they had more comorbidities other than COPD, more healthcare utilization related to any medical condition at inpatient, outpatient, and emergency department settings, more AECOPD, and they were more likely to get diagnosed with early-stage lung cancer (24.9 vs. 18.6%) compared to patients with concurrent COPD diagnosis. (**Table 2**)

Association analysis. We observed a positive association between pre-existing (vs. concurrent) COPD diagnosis and early-stage (vs. late-stage) lung cancer at diagnosis. The age-adjusted PR (95% CI) was 1.34 (1.31 to 1.38) and PD (95% CI) was 0.063 (0.057 to 0.069). The association persisted after adjusting for age, sex, area-level SES, CCI, healthcare utilization during one year before lung cancer diagnosis, year of cancer diagnosis, and SEER registry region, fully adjusted PR (95%) CI was 1.27 (1.23 to 1.30) and fully adjusted PD was 0.048 (0.040 to 0.055). (**Table 3**)

Subgroup (Effect measure modification) association analyses. We observed some heterogeneity in the association between timing of COPD diagnosis and stage of lung cancer at diagnosis across patient groups by race and sex. On the additive scale, the adjusted PD (95% CI) for NHWs was 0.048 (0.040 to 0.057), while the PD for Hispanic was 0.084 (0.049 to 0.120), and the difference in PDs (interaction contrast) between Hispanic and NHWs was 0.036 (-0.0002 to 0.072). On the multiplicative scale, the adjusted PR for NHBs was 1.37 (1.22 to 1.54), while

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

the PR for NHWs was 1.26 (1.22 to 1.30) and the ratio of NHBs to NHWs PRs was 1.11 (0.94 to 1.30). The adjusted PR (95% CI) for males was 1.33 (1.28 to 1.39), while for females was 1.21 (1.16 to 1.26), and the ratio of male to female PRs (95% CI) was 1.09 (1.04 to 1.16). In addition, there was some heterogeneity observed across patient groups by census-tract level of SES (Yost US-based quintile) (**Supplement Table 1 & Figures 3,4**).

Discussion.

The present study responds to several calls[9,10, 31,32] for population-based evidence regarding underdiagnosis of COPD among patients with lung cancer in the US. We studied prevalence and diagnosis timing of COPD relative to the start of the lung cancer diagnostic episode, approximated by an index date, among older Medicare beneficiaries with lung cancer. We found that three quarters of patients with lung cancer had comorbid COPD, of whom two thirds had COPD diagnosis at least 3 months before lung cancer diagnosis (pre-existing COPD), while the remainder had their COPD diagnosis around the time (-/+ 3 months) of lung cancer diagnosis. Among patients with comorbid COPD and lung cancer, pre-existing COPD diagnosis was positively associated with early-stage lung cancer diagnosis, particularly among Hispanic and NHBs (compared to NHWs) and for males (compared to females).

Previous estimates of comorbid COPD diagnosis among patients with lung cancer varies widely between 20 to 90%.[33,25, 34] This might be due to inconsistent diagnostic indicators of COPD used across practices where COPD is often self-reported or electronic health records (EHRs) documented without evidence of obstructive pulmonary function testing (PFT).[35] In the present study, more than one third of patients with comorbid COPD and lung cancer didn't have evidence of their COPD diagnoses until +/-3 months of lung cancer diagnosis. There is scarcity of data about timing of COPD diagnosis relative to lung cancer diagnosis in the US, however,

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

few studies from other countries reported a high rate of COPD underdiagnosis at the time of lung cancer diagnosis. A recent study of administrative data linked to cancer registry from Canada observed that 18.5% of patients were undiagnosed with COPD until +/-3 months of lung cancer diagnosis. They reported 30% lower odds of late stage diagnosis among patients with COPD, especially those with pre-existing COPD diagnosis.[25] In a study from Spain, 60% of patients had their COPD diagnosed less than 6 months before lung cancer diagnosis.[34] Another study from Spain, 71.5% of patients had their COPD diagnosed around the time of lung cancer diagnosis.[36] A study from China reported a very high rate (93%) of COPD underdiagnosis at the time of lung cancer diagnosis.[37] Some of these studies reported higher proportion of early-stage lung cancer among patients with pre-existing COPD diagnosis, but only one[25] of them quantified the association between timing of COPD diagnosis and stage of lung cancer at diagnosis.

Our adjusted models indicated a positive association between pre-existing COPD diagnosis and early-stage lung cancer at diagnosis among patients with both conditions. Patients with pre-existing COPD diagnosis had several characteristics may have increased their chance of healthcare encounters, and accordingly early-stage lung cancer, such as being female, NHW, suffering from more comorbidities, AECOPD, and having higher healthcare utilization at inpatient, outpatient, and emergency department settings before lung cancer diagnosis compared to patients with a concurrent COPD diagnosis. These characteristics are frequently associated with higher incidence of early-stage lung cancer through symptomatic or incidental diagnosis, or through participation in lung cancer screening.[38]

Our subgroup analyses revealed That Males, Hispanics, and NHBs were more likely to have early-stage lung cancer diagnosis when they had pre-existing COPD compared to women and NHWs. These findings are critical because racial minorities have higher incidence, late-stage

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

at diagnosis and mortality from lung cancer, compared to NHWs in the US. [39,40, 41,42] Lung cancer is the leading cause of death among NHBs and Hispanic men and the second leading cause of death among Hispanic women.[43] Moreover, several studies have reported substantial racial disparities in COPD diagnosis among Black populations in the US. In a cross-sectional analysis of The COPD Genetic Epidemiology (COPDGene) study, NHBs had higher chance of undiagnosed COPD regardless severity of airflow limitation compared to NHWs. [16] For sex differences, several studies reported that men are more likely to have concurrent COPD diagnosis[16] and late-stage lung cancer diagnosis compared to women.[44]

Several factors might explain underdiagnosis of COPD such as nonspecific COPD symptoms that are often unrecognized or attributed to advancing age or smoking by the patient [45] or overlooked by the healthcare provider who is focusing on management of other health conditions commonly cooccurring in elderly populations.[46] Further, underutilization of spirometry to confirm COPD diagnosis in primary care settings might affect consistency of COPD diagnosis and management.[35] In the context of lung cancer, underdiagnosis of COPD might have critical implications such as decreased motivation to quit smoking, progression of the disease, decreased eligibility for lung cancer surgical treatment, and increased healthcare utilization.[47] However, previous studies[34,48] reported that majority of patients with comorbid COPD have mild to moderate severity of airflow limitation which make them eligible for surgical treatment when their lung cancer is diagnosed at an early stage.

Strengths and Limitations.

We used large population-based data of SEER-Medicare which represent ~ 40% of US population 65 years and older and include populations of diverse racial and SES backgrounds. Our findings of positive association between COPD diagnostic timeliness and stage of lung

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

cancer are novel and should inform ongoing research for early detection of lung cancer. However, our study isn't without limitations. First, our use of medical claims to identify COPD diagnosis could be prone to misclassification. To minimize misclassification bias, we used a diagnosis algorithm with a sensitivity of 85% and a specificity of 78.4% used across multiple settings.[49] Second, it is impossible to know for certain that the earliest ICD code observed during the study period reflects incident COPD diagnosis. Therefore, we limited our study population to those with at least 3 years of continuous enrollment to capture all possible healthcare encounters before lung cancer diagnosis. Our approach aligns and improves upon SEER-Medicare recommendations of requiring at least 2 years of claims data to conclude evidence of first diagnosis of chronic conditions such as COPD.[50] Third, we lacked data about COPD severity and smoking which might better explained the association between timing of COPD diagnosis and stage of lung cancer at diagnosis. However, we adjusted for other important confounders that might contribute to this association such as HCU during the year before lung cancer diagnosis and comorbidities. In addition, we conducted a simple quantitative bias analysis for unmeasured smoking and COPD severity, and it didn't fully account for the measured association (**Supplement**).

Conclusions.

Approximately, seven out of ten patients with lung cancer in the U.S. had comorbid COPD; of whom one third didn't receive their COPD diagnosis until around the time of lung cancer diagnosis. Timely COPD diagnosis is associated with early-stage lung cancer at diagnosis, especially among high-risk population such as racial minorities in the US. Our findings add to the growing body of evidence about the importance of timely COPD diagnosis to achieve earlier stage of lung cancer diagnosis and better patient outcomes.

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Acknowledgment

Author guarantor statement: Sharon Peacock Hinton is responsible for data integrity of this study.

Author contributions: Eman M. Metwally, Caroline A. Thompson, Jennifer L. Lund, M. Bradley Drummond, and Charles Poole contributed to study conception, design, and interpretation. Sharon Peacock Hinton contributed to data acquisition and analysis. Eman M. Metwally, Caroline A. Thompson and Charles Poole contributed to the analysis. Eman M. Metwally drafted the report, and all authors revised it critically.

California Cancer Registry Acknowledgment: The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 1NU58DP007156; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors.

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Conflict of Interest.

Dr. Metwally receives salary and research support from the National Institute of Environmental Health Sciences: 2T32ES007018.

Dr. Caroline Thompson receives salary support from The University of North Carolina at Chapel Hill and research support from the National Cancer Institute, the National Library of Medicine, the Centers for Disease Control, Academy Health, and the Gordon and Betty Moore Foundation. She has no other financial interests to disclose.

Dr. Lund receives funding from F-Hoffman La-Roche grant. Spouse was formerly employed by and owned a stock in GSK.

Dr. Drummond has no relevant conflicts of interest relates to this manuscript.

Dr. Poole has no relevant conflicts relates to this manuscript.

Mrs. Peacock has no relevant conflicts relates to this manuscript.

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

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Table 1. Sociodemographic, clinical and tumor characteristics of patients diagnosed with lung cancer with and without COPD.

Characteristics	**Overall** N (Col%)	**Lung cancer with comorbid COPD** N (Col%)	**Lung cancer without comorbid COPD** N (Col%)
All patients, N (%)	159,542 (100)	117,202 (73.5)	42,340 (26.5)
Age (at time of cancer diagnosis)			
Mean (SD)	77.6 (6.6)	77.2 (6.3)	78.5 (7.1)
Groupings, N (%)			
68-69	16,513 (10.4)	12,374 (10.6)	4,139 (9.8)
70-74	44,036 (27.6)	33,664 (28.7)	10,372 (24.5)
75-79	40,748 (25.4)	30,914 (26.4)	9,834 (23.2)
80-84	32,101 (20.1)	23,358 (19.9)	8,743 (20.7)
85+	26,144 (16.4)	12,374 (10.6)	9,252 (21.9)
Sex			
Female	83,793 (51.5)	59,282 (50.6)	22,807 (53.9)
Male	77,453 (48.5)	57,920 (49.4)	19,533 (46.1)
Race & ethnicity			
Non-Hispanic White	135,665 (85)	101,176 (86.3)	34,489 (81.5)
Non-Hispanic Black	10,680 (6.7)	7,721 (6.6)	2,959 (7)
Hispanic	6,036 (3.8)	4,104 (3.5)	1,932 (4.6)
Asian American	5,988 (3.8)	3,395 (2.9)	2,593 (6.1)
American Indian or Alaskan Native	528 (0.3)	381 (0.3)	147 (0.4)
Native Hawaiian or another Pacific Islander	390 (0.2)	261 (0.2)	129 (0.3)
Multiracial	72 (0.1)	44 (0.04)	28 (0.1)
Unspecified /Unknown race *	183	120	63
Marital/ Partner status			

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Yes	54,473 (48.9)	39,586 (47.8)	14,887 (52)
No	56,981 (51.1)	43,251 (52.2)	13,730 (48)
Unknown *	48,088	34,365	13,723
Residence			
Metro	133,092 (83.4)	96,427 (82.3)	36,665 (86.6)
Urban	23,400 (14.8)	18,273 (15.6)	5,127 (12.1)
Rural †	3,050 (1.9)	2,495 (2.1)	545 (1.3)
SEER registry region			
East	64,156 (40.2)	46,493 (39.7)	17,663 (41.7)
South	34,700 (21.8)	27,611 (23.6)	7,089 (16.7)
Midwest	14,491 (9.1)	11,048 (9.4)	3,443 (8.1)
West	46,195 (29)	32,050 (27.4)	14,145 (33.5)
% Poverty indicator census tract (Quartiles)			
Highest poverty rate	32,559 (22.6)	22,622 (21.6)	9,937 (25.4)
Upper Middle poverty rate	39,243 (27.3)	27,919 (26.6)	11,324 (28.9)
Lower Middle poverty rate	43,657 (30.3)	32,535 (31)	11,122 (28.4)
Lowest poverty rate	28,498 (19.8)	21,743 (20.7)	6,755 (17.3)
Unknown *	15,585	12,383	3,202
Neighborhood SES (US-based Quantile)			
Lowest SES	24,936 (16.2)	19,768 (17.5)	5,168 (12.8)
Lower Middle SES	27,336 (17.8)	21,221 (18.8)	6,115 (15.1)
Middle SES	29,190 (19)	21,869 (19.4)	7,294 (18)
Upper Middle SES	33,826 (22)	24,393 (21.6)	9,433 (23.3)
Highest	38,272 (25)	25,856 (22.9)	12,517 (30.9)
Unknown *	5,881	4,068	1,813
Modified Charlson Comorbidity Score Index (COPD is excluded) ‡			

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0	73,364 (46)	50,054 (42.7)	23,310 (55.1)
1	37,635 (23.6)	28,298 (24.1)	9,337 (22.1)
2	21,291 (13.4)	16,560 (14.1)	4,731 (11.2)
3+	27,252 (17.1)	22,290 (19)	4,962 (11.7)
Healthcare utilization in the one year before lung cancer diagnosis Number of visits Mean (SD)			
Emergency department visit-days	0.9 (1.6)	1 (1.8)	0.6 (1.1)
Outpatient visit-days	26.3 (24.7)	27.8 (25.7)	22.1 (21.3)
Inpatient days	0.5 (1)	0.6 (1.1)	0.3 (0.7)
Cancer Diagnosis Year			
2008-2012	84,978 (53.3)	62,441 (53.3)	22,537 (53.2)
2013-2017	74,564 (46.7)	54,761 (46.7)	19,803 (46.8)
Tumor histology			
Non-small cell lung cancer	126,961 (79.6)	92,205 (78.7)	34,756 (82.1)
Small Cell lung cancer	17,711 (11.1)	14,177 (12.1)	3,534 (8.4)
Other lung cancer	14,870 (9.3)	10,820 (9.2)	4,050 (9.5)
SEER Summary Stage			
Localized	32,271 (21.5)	25,121 (22.8)	7,150 (18)
Regional	34,887 (23.2)	27,199 (24.6)	7,688 (19.3)
Remote	83,068 (55.3)	58,106 (52.6)	24,962 (62.7)
Unknown *	9,316	6,776	2,540
Early vs. Late Stage at diagnosis			
Early stage	32,271 (21.5)	25,121 (22.8)	7,150 (18)
Late stage	171,955 (78.5)	85,305 (77.2)	32,650 (82)
Unknown *	9,316	6,776	2,540
Source of index date			

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Earliest lung cancer-related claim	142,798 (89.5)	106,993 (91.3)	35,805 (84.6)
Imputed as 15th of the SEER month	16,744 (10.5)	10,209 (8.7)	6,535 (15.4)

*Unknown / missing data were not included in calculations of percentage.

†Number of patients with unknown recorded residence were less than 11 and thus were added to the rural category without changing the category percentage.

‡COPD was excluded from the CCI to compare between patients with and without COPD.

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Table 2. Sociodemographic, clinical and tumor characteristics of patients with pre-existing versus concurrent COPD diagnosis relative to lung cancer diagnosis

Characteristics	**Overall** N (Col%)	**Lung cancer with pre-existing COPD diagnosis** N (Col%)	**Lung cancer with concurrent COPD diagnosis** N (Col%)
All patients, N (row%)	117,202 (73.5)	76,872 (65.6)	40,330 (34.4)
Age (at time of cancer diagnosis)			
Mean (SD)	77.2 (6.3)	77.4 (6.3)	77 (6.3)
Grouping N (%)			
68-69	12,374 (10.6)	7,718 (10)	4,656 (11.5)
70-74	33,664 (28.7)	21,694 (28.2)	11,970 (29.7)
75-79	30,914 (26.4)	20,531 (26.7)	10,383 (25.8)
80-84	23,358 (19.9)	15,545 (20.2)	7,813 (19.4)
85+	16, 892(14.4)	11,384 (14.8)	5,508 (13.7)
Sex			
Female	60,722 (50.4)	39,655 (51.6)	19,627 (48.7)
Male	59,721 (49.6)	37,217 (48.4)	20,703 (51.3)
Race & ethnicity			
Non-Hispanic White	103,887 (86.3)	67,239 (87.5)	33,937 (84.2)
Non-Hispanic Black	8,079 (6.7)	4,693 (6.1)	3,028 (7.5)
Hispanic	4,225 (3.5)	2,508 (3.3)	1,596 (4)
Asian American	3,422 (2.8)	1,910 (2.5)	1,485 (3.7)
American Indian or Alaskan Native	396 (0.3)	145 (0.2)	109 (0.3)
Native Hawaiian or another Pacific Islander	266 (0.2)	272 (0.4)	116 (0.3)
Multiracial	45 (0.04)	22 (0.03)	22 (0.1)

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Unspecified /Unknown *	120	83	37
Marital/Partner status			
Yes	39,586 (47.8)	25,005 (46.2)	14,581 (50.7)
No	43,251 (52.2)	29,093 (53.8)	14,158 (49.3)
Unknown *	34,365	22,774	11,591
Residence			
Metro	96,427 (82.3)	62,486 (81.3)	33,941 (84.2)
Urban	18,273 (15.6)	12,638 (16.4)	5,635 (14)
Rural †	2,602 (2.1)	1,743 (2.3)	752 (1.9)
SEER registry region			
East	46,493 (39.7)	30,100 (39.2)	16,393 (40.7)
South	27,611 (23.6)	18,585 (24.2)	9,026 (22.4)
Midwest	11,048 (9.4)	7,482 (9.7)	3,566 (8.8)
West	32,050 (27.4)	20,705 (26.9)	11,345 (28.1)
% Poverty indicator census tract			
Highest poverty (20 to 100%)	22,622 (21.6)	14,074 (20.6)	8,548 (23.3)
Upper Middle poverty (10 to <20%)	27,919 (26.6)	18,005 (26.4)	9,914 (27.1)
Lower Middle poverty (5 to < 10%)	32,535 (31)	22,511 (31.5)	11,024 (30.2)
Lowest poverty (0 to < 5%)	21,743 (20.7)	14,606 (21.7)	7,137 (19.5)
Unknown *	12,383	8,676	3,707
Neighborhood SES (US-based quantile)			
Lowest SES	19,768 (17.5)	13,608 (18.3)	6,413 (16.1)
Lower Middle SES	21,221 (18.8)	14,392 (19.4)	6,990 (17.6)
Middle SES	21,869 (19.4)	14,532 (19.6)	7,538 (18.9)
Upper Middle SES	24,393 (21.6)	15,773 (21.3)	8,771 (22)
Highest	25,856 (22.9)	15,894 (21.4)	10,085 (25.3)
Unknown *	4,068	2,673	1,427
Modified Charlson Comorbidity Score Index (COPD is excluded) ‡			

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0	50,054 (42.7)	28,611 (37.2)	21,443 (53.2)
1	28,928 (24.2)	19,118 (24.9)	9,180 (22.8)
2	16,560 (14.1)	11,893 (15.5)	4,666 (11.6)
3 +	22,290 (19)	17,249 (22.4)	5,041 (12.5)
Claims for Acute exacerbation of COPD (**AECOPD**) one year before lung cancer diagnosis			
Yes	24,245 (20.7)	19,595 (25.5)	4,650 (11.5)
No	92,957 (79.3)	57,277 (74.5)	35,680 (88.5)
Healthcare utilization in the one year before lung cancer diagnosis Number of visits Mean (SD)			
Emergency department visit-days	1 (1.8)	1.2 (2)	0.6 (1.1)
Outpatient visit-days	27.8 (25.7)	31.2 (27.3)	21.1 (20.6)
Inpatient days	0.6 (1.1)	0.7 (1.2)	0.3 (0.7)
Cancer Diagnosis Year			
2008-2012	62,441 (53.3)	40,174 (52.3)	22,267 (55.2)
2013-2017	54,761 (46.7)	36,698 (47.7)	18,063 (44.8)
Tumor histology			
Non-small cell lung cancer	92,205 (78.7)	59,004 (76.8)	33,201 (82.3)
Small Cell lung cancer	14,177 (12.1)	9,546 (12.4)	4,631 (11.5)
Other lung cancer	10,820 (9.2)	8,322 (10.8)	2,498 (6.2)
SEER Summary Stage at diagnosis			
Localized	25,121 (22.8)	17,910 (25)	7,211 (18.6)
Regional	27,199 (24.6)	17,410 (24.3)	9,789 (25.3)
Remote	58,106 (52.6)	36,406 (50.8)	21,700 (56.1)
Unknown *	6,776	5,146	1,630
Early versus late stage at diagnosis			
Early stage	25,121 (22.8)	17,910 (25)	7,211 (18.6)
Late stage	85,305 (77.2)	53,816 (75)	31,489 (81.4)

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Unknown *	6,776	5,146	1,630
Source of index date			
Earliest lung cancer-related claim	106,993 (91.3)	69,106 (89.9)	37,887 (93.9)
Imputed as 15th of SEER month	10,209 (8.7)	7,766 (10.1)	2,443 (6.1)

* Unknown / missing data were not included in calculations of percentage.

† Number of patients with unknown recorded residence were less than 11 and thus were added to the rural category without changing the category percentage.

‡ COPD was excluded from the CCI to compare between patients with and without COPD.

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Table 3. Association between COPD diagnostic timeliness (pre-existing vs. concurrent) and stage of lung cancer at diagnosis (early vs. late)

Adjusted models	Prevalence Ratio (95% CI)	CLR	Prevalence Difference (95% CI)	CLD
Age adjusted model	1.34 (1.31 to 1.38)	1.05	0.063 (0.057 to 0.069)	0.01
***Fully adjusted model**	1.27 (1.23 to 1.30)	1.06	0.048 (0.040 to 0.055)	0.01

***Fully adjusted model** for age at cancer diagnosis, sex, socioeconomic status (SES), year of cancer diagnosis, SEER Registry Region, Charlson Comorbidity Score Index (CCI) and healthcare utilization days during the one year before lung cancer diagnosis at inpatient, outpatient, emergency department settings. **PR**= Prevalence ratio, **PD**= Prevalence difference, **CI**= Confidence interval, **CLR**=UCL/ LCL= Confidence limit ratio =Upper confidence limit/ lower confidence limit, **CLD**= UCL-LCL= Confidence limit difference= Upper confidence limit - lower confidence limit.

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Figure 1

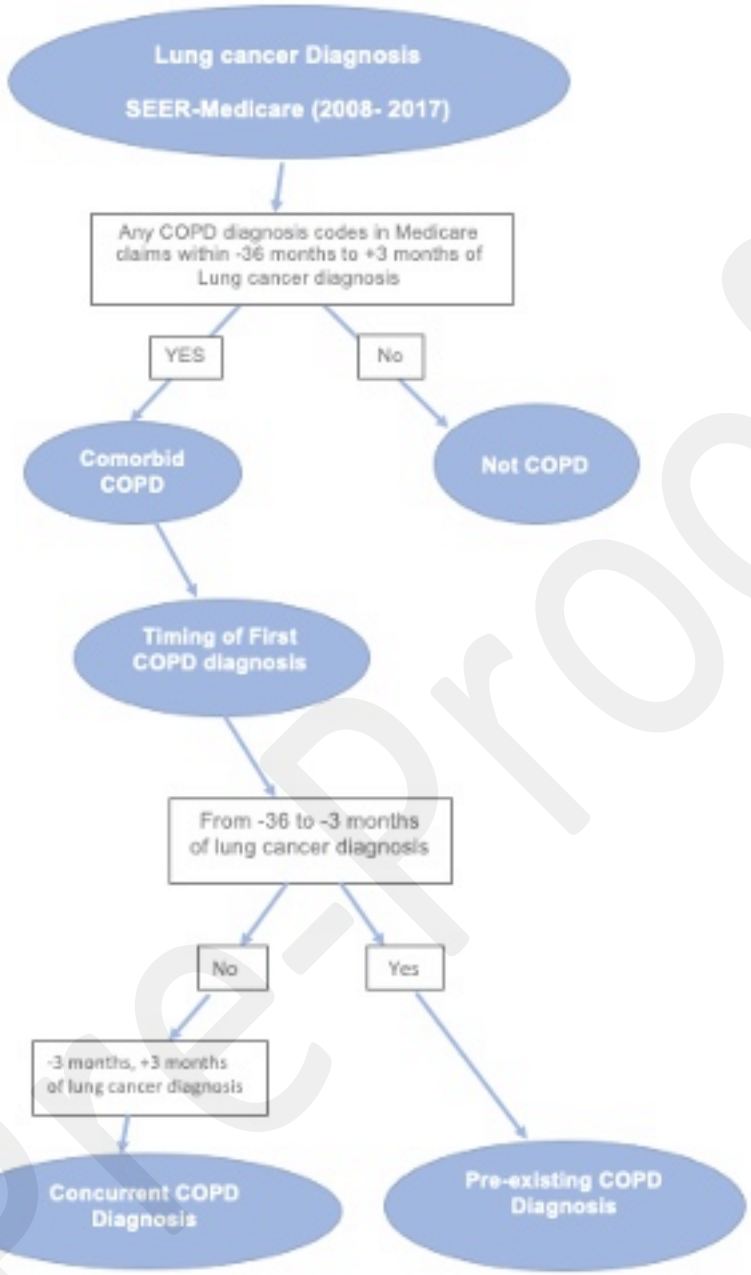

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Figure 2

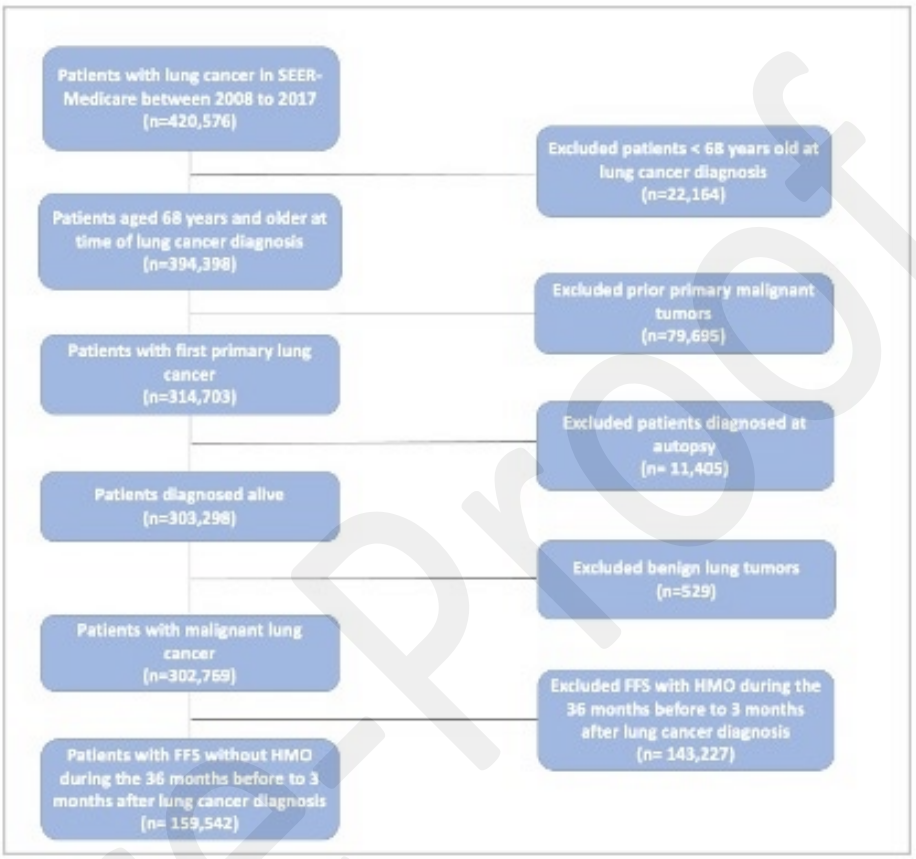

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Figure 3

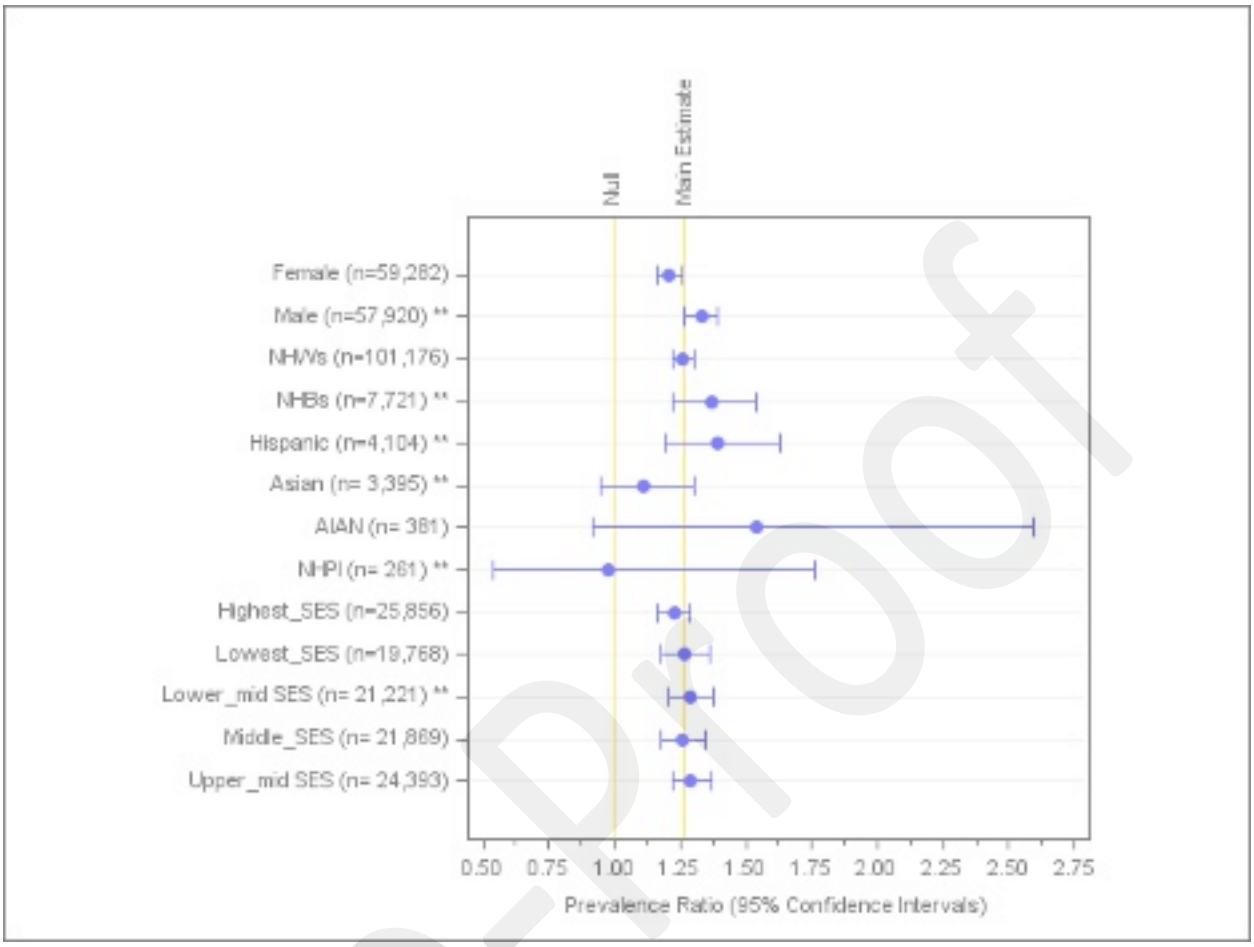

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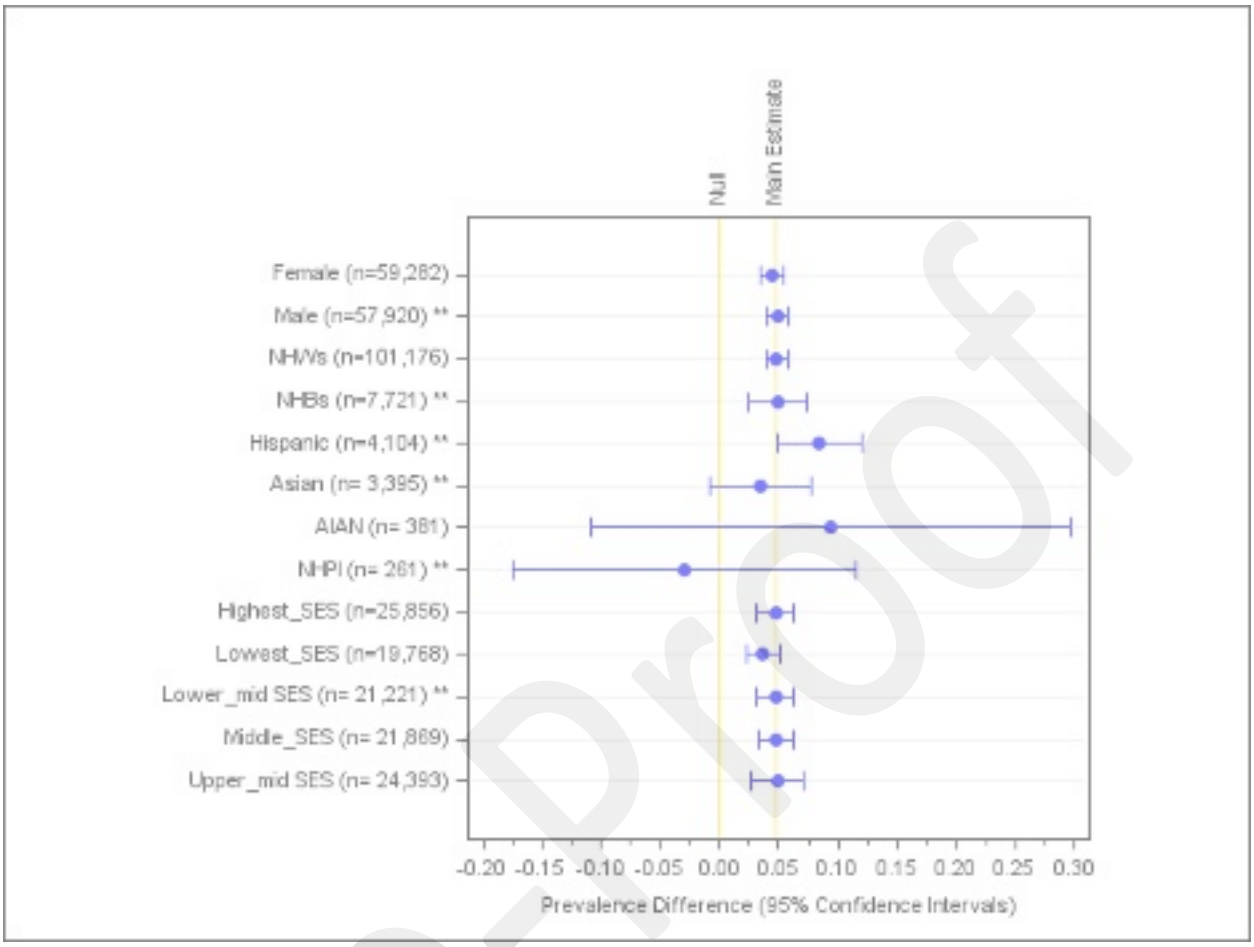
Figure 4



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Online Supplement

Supplementary Tables and figures

Supplement Table1. Subgroup analyses for the association between timing of COPD diagnosis and stage of lung cancer at diagnosis by sex, race and ethnicity, and census tract measure of socioeconomic status.

Subgroup	**Ratio of prevalence ratios (RPR) (95% CI); P-value ***	**Difference in prevalence differences (DID) (95% CI); P-value ***
SEX (ref= "female")		
Females	PR= 1.21 (1.16 to 1.26)	PD= 0.045 (0.035 to 0.055)
Males	PR= 1.33 (1.28 to 1.39)	PD= 0.049 (0.040 to 0.058)
Contrast between males and females estimates	RPR [b]= 1.09 (1.04 to 1.16); **<0.001**	DID [c]= 0.004 (-0.009 to 0.018); 0.50
RACE (ref= NHWs)		
NHWs	PR= 1.26 (1.22 to 1.30)	PD= 0.048 (0.040 to 0.057)
NHBs	PR= 1.37 (1.22 to 1.54)	PD= 0.049 (0.024 to 0.074)
Contrast between NHWs and NHBs estimates	RPR= 1.09 (0.97 to 1.22); **0.16**	DID=0.001 (-0.025 to 0.027); 0.9
Hispanic	PR= 1.39 (1.19 to 1.63)	PD= 0.084 (0.049 to 0.120)
Contrast between Hispanic and NHWs estimates	RPR= 1.11 (0.94 to 1.30); **0.22**	DID= 0.036 (-0.0002 to 0.072); **0.05**
Asian	PR= 1.11 (0.95 to 1.30)	PD= 0.034 (-0.008 to 0.077)

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Contrast between Asian and NHWs estimates	RPR= 0.88 (0.75 to 1.04); **0.20**	DID= -0.014 (-0.057 to 0.029); 0.52
AIAN	PR= 1.54 (0.92 to 2.59)	PD= 0.094 (-0.109 to 0.297)
Contrast between AIAN and NHWs estimates	RPR= 1.22 (0.72 to 2.06); 0.45	DID= 0.079 (-0.066 to 0.224); **0.29**
NHPI	PR= 0.98 (0.54 to 1.76)	PD= -0.030 (-0.175 to 0.115)
Contrast between NHPI and NHWs estimates	RPR= 0.78 (0.43 to 1.40); **0.05**	DID= -0.078 (-0.224 to 0.067); **0.29**
Mixed	PR= 0.87 (0.49 to 1.57)	PD= -0.036 (-0.287 to 0.216)
Contrast between Mixed and NHWs estimates	RPR= 0.69 (0.39 to 1.25); **0.22**	DID= -0.084 (-0.336 to 0.168); 0.51
SES (ref=Highest SES)		
Highest SES	PR= 1.23 (1.16 to 1.29)	PD= 0.047 (0.032 to 0.062)
Lowest SES	PR= 1.27 (1.18 to 1.36)	PD= 0.037 (0.023 to 0.051)
Contrast between Lowest and Highest SES estimates	RPR= 1.03 (0.94 to 1.13); 0.50	DID= -0.010 (-0.030 to 0.010); **0.30**
Lower Middle SES	PR= 1.29 (1.21 to 1.38)	PD= 0.047 (0.032 to 0.062)
Contrast between Lower Middle and Highest SES estimates	RPR= 1.05 (0.97 to 1.15); **0.26**	DID= 0.000 (-0.020 to 0.021); 1
Middle SES	PR= 1.26 (1.18 to 1.35)	PD= 0.047 (0.033 to 0.062)
Contrast between Middle and Highest SES estimates	RPR= 1.03 (0.95 to 1.12); 0.50	DID= -0.000 (-0.021 to 0.021); 1
Upper Middle SES	PR= 1.29 (1.22 to 1.37)	PD= 0.049 (0.027 to 0.071)

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Contrast between Upper Middle and Highest SES estimates	RPR= 1.05 (0.97 to 1.14); **0.20**	DID= 0.008 (-0.012 to 0.029); 0.43

*Subgroup /effect measure modification (EMM) analysis adjusted for age at cancer diagnosis, sex, socioeconomic status (SES), year of diagnosis, SEER Registry Region, Charlson Comorbidity Score Index (CCI) and all healthcare utilization during the one year before lung cancer diagnosis. P-value < 0.3 threshold is considered statistically significant to reject the Null hypothesis and is presented in bold.

RPR= Ratio of prevalence ratios, **DID**= Difference in prevalence differences.

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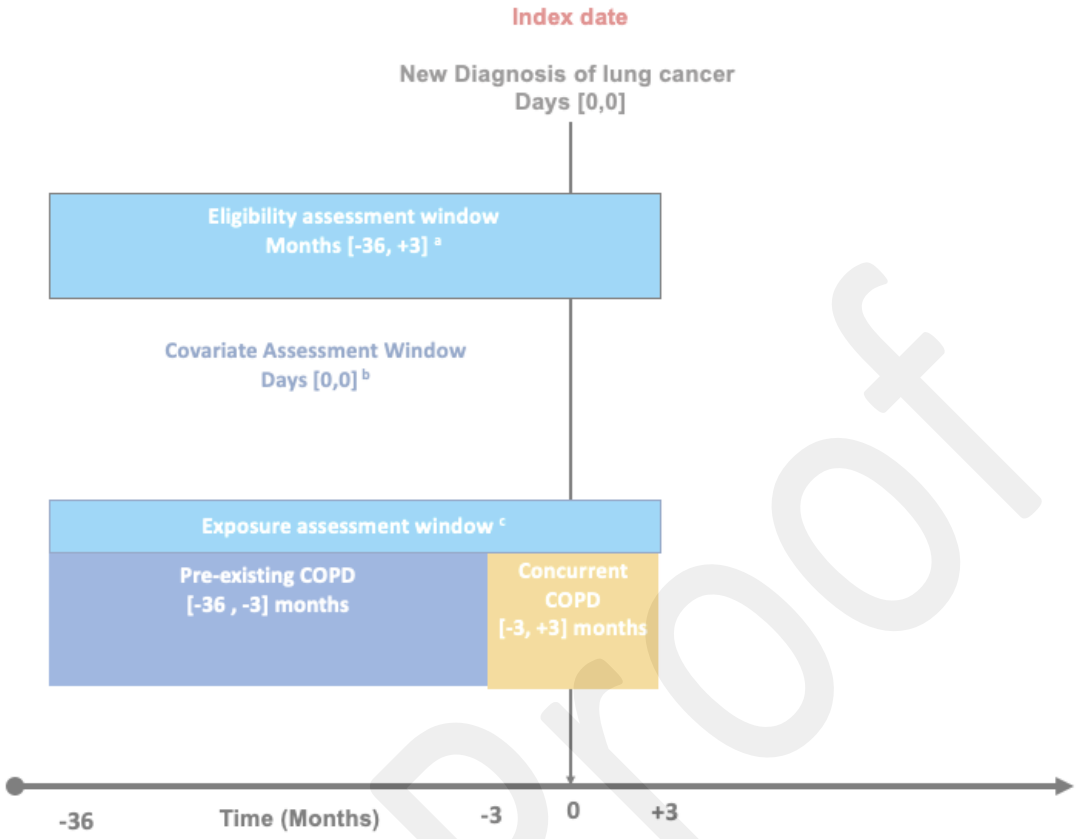

Supplement Figure E1. Patient assessment windows and study timeline

a. Exclusion criteria include age <68years, previous diagnosis of cancer, lung cancer diagnosed before 2008 or after 2017, in situ tumor, patient was diagnosed at autopsy or only on death certificate, any enrollment in Health Maintenance Organization (HMO) Medicare plan or any gaps in Medicare fee for service (FFS) parts A, B enrollment from 36 months prior to 3 months after lung cancer diagnosis.

b. Covariates assessment window includes assessing sociodemographic, clinical, and tumor characteristics.

c. Exposure includes evidence of claim-based diagnosis of chronic obstructive pulmonary disease (COPD) during the 36 months prior to 3 months after lung cancer diagnosis using the international classification of disease diagnosis codes versions 9 and 10 (ICD9, ICD10).

Published online June 5, 2024 https://doi.org/10.15326/jcopdf.2024.0489

Simplified Bias analyses using the Rothman Epi Sheets Available at:
https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=http://krothman.hostbyet2.com/episheet.xls&ved=2ahUKEwiQxcu_y72FAxXoD1kFHRIYDCoQFnoECA0QAQ&usg=AOvVaw0cealnxt2WCri6B9YnQ9_n

- **Direction of the bias** for both COPD severity and smoking is expected to be upward bias (overestimated observed association estimate) because both confounders have positive association with the exposure (COPD diagnosis timing) and outcome (early-stage lung cancer diagnosis).

- **Bias parameters:**

1- **Unmeasured COPD severity:**

Bias parameters based on reviewing literature are:

Prevalence of severe COPD among those with pre-existing COPD diagnosis= 0.3

Prevalence of severe COPD among those with concurrent COPD diagnosis= 0.1

Possible association between severe COPD and early-stage lung cancer was set to 2 scenarios:

RR= 1.2, RR=1.5

Observed PR between COPD diagnosis timing and early-stage lung cancer "unadjusted for severe COPD"	Assumed RR between severe COPD and early stage of lung cancer	**Corrected PR**
1.34	1.2	1.29
1.34	1.5	1.22

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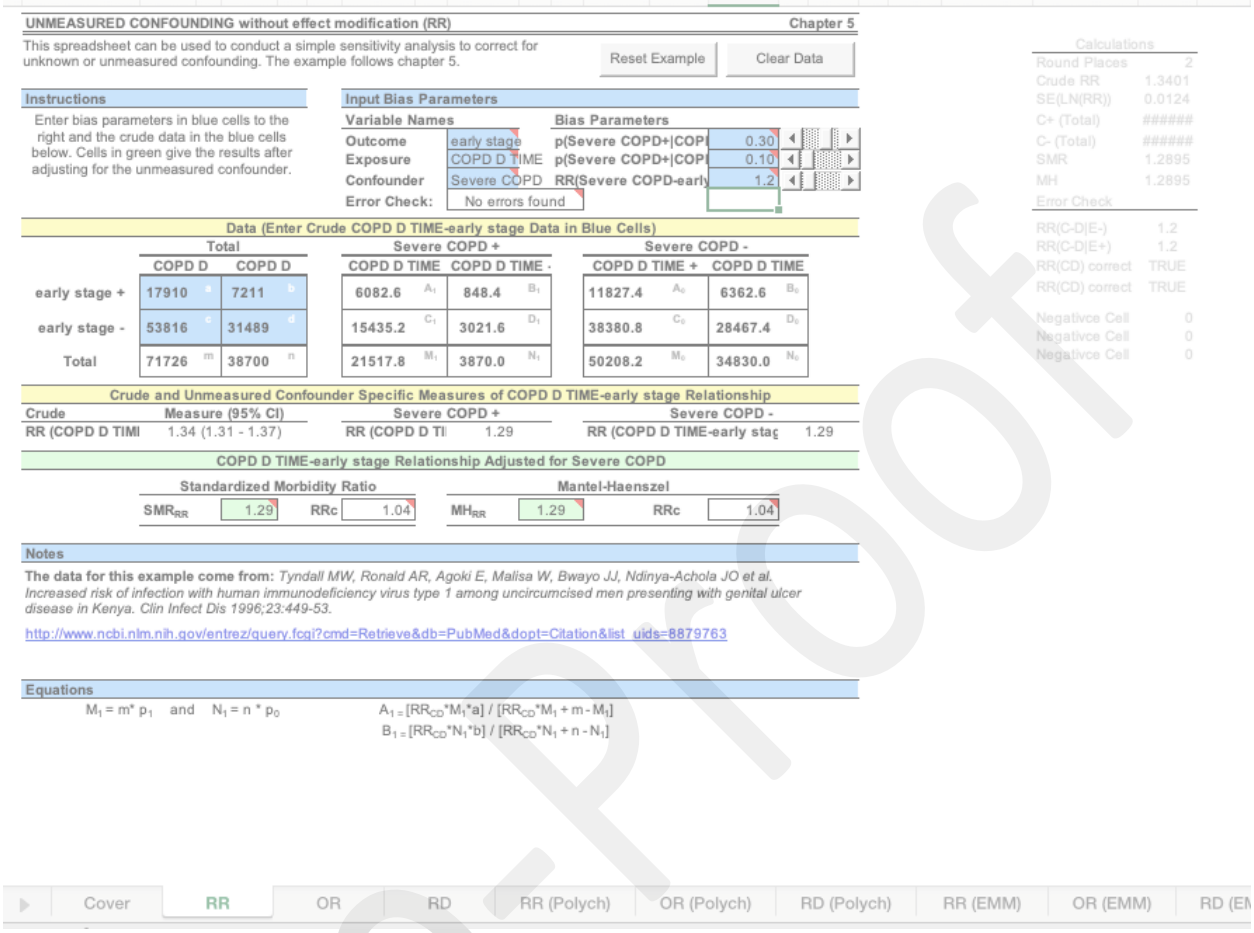
Scenario 1: RR between severe COPD and early stage of lung cancer =1.2



UNMEASURED CONFOUNDING without effect modification (RR) — Chapter 5

This spreadsheet can be used to conduct a simple sensitivity analysis to correct for unknown or unmeasured confounding. The example follows chapter 5.

Reset Example | Clear Data

Instructions

Enter bias parameters in blue cells to the right and the crude data in the blue cells below. Cells in green give the results after adjusting for the unmeasured confounder.

Input Bias Parameters

Variable Names		Bias Parameters	
Outcome	early stage	p(Severe COPD+|COPD	0.30
Exposure	COPD D TIME	p(Severe COPD+|COPD	0.10
Confounder	Severe COPD	RR(Severe COPD-early	1.2
Error Check:	No errors found		

Data (Enter Crude COPD D TIME-early stage Data in Blue Cells)

	Total		Severe COPD +		Severe COPD -	
	COPD D	COPD D	COPD D TIME	COPD D TIME -	COPD D TIME +	COPD D TIME
early stage +	17910 a	7211 b	6082.6 A_1	848.4 B_1	11827.4 A_0	6362.6 B_0
early stage -	53816 c	31489 d	15435.2 C_1	3021.6 D_1	38380.8 C_0	28467.4 D_0
Total	71726 m	38700 n	21517.8 M_1	3870.0 N_1	50208.2 M_0	34830.0 N_0

Crude and Unmeasured Confounder Specific Measures of COPD D TIME-early stage Relationship

Crude	Measure (95% CI)	Severe COPD +		Severe COPD -	
RR (COPD D TIMI	1.34 (1.31 - 1.37)	RR (COPD D TI	1.29	RR (COPD D TIME-early stag	1.29

COPD D TIME-early stage Relationship Adjusted for Severe COPD

Standardized Morbidity Ratio				Mantel-Haenszel			
SMR_{RR}	1.29	RRc	1.04	MH_{RR}	1.29	RRc	1.04

Notes

The data for this example come from: *Tyndall MW, Ronald AR, Agoki E, Malisa W, Bwayo JJ, Ndinya-Achola JO et al. Increased risk of infection with human immunodeficiency virus type 1 among uncircumcised men presenting with genital ulcer disease in Kenya. Clin Infect Dis 1996;23:449-53.*

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8879763

Equations

$M_1 = m^* p_1$ and $N_1 = n * p_0$

$A_1 = [RR_{CD}*M_1*a] / [RR_{CD}*M_1 + m - M_1]$

$B_1 = [RR_{CD}*N_1*b] / [RR_{CD}*N_1 + n - N_1]$

Calculations

Round Places	2
Crude RR	1.3401
SE(LN(RR))	0.0124
C+ (Total)	######
C- (Total)	######
SMR	1.2895
MH	1.2895
Error Check	
RR(C-D|E-)	1.2
RR(C-D|E+)	1.2
RR(CD) correct	TRUE
RR(CD) correct	TRUE
Negativce Cell	0
Negativce Cell	0
Negativce Cell	0

Cover | RR | OR | RD | RR (Polych) | OR (Polych) | RD (Polych) | RR (EMM) | OR (EMM) | RD (EM

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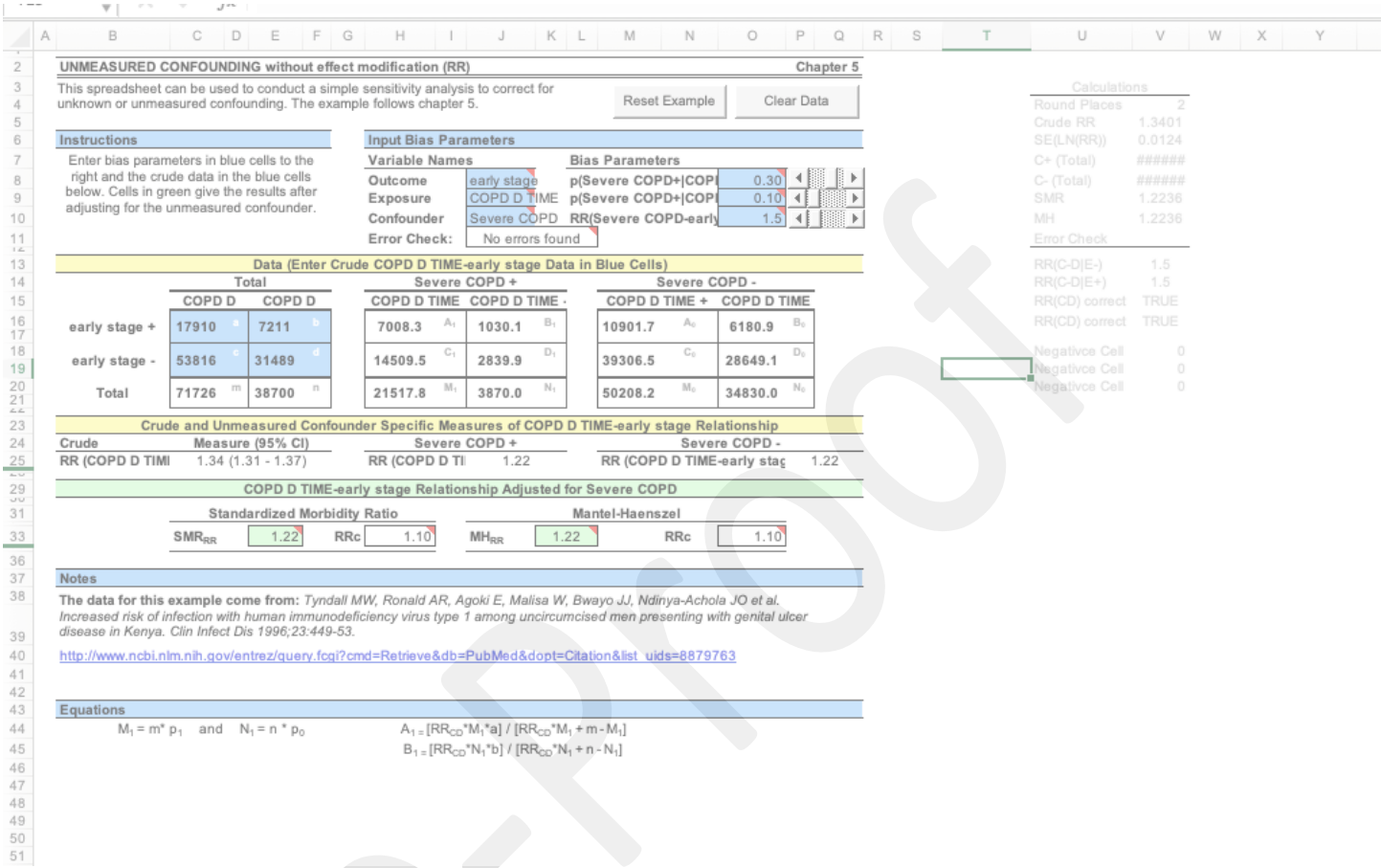
Scenario 2: RR between severe COPD and early stage of lung cancer =1.5



UNMEASURED CONFOUNDING without effect modification (RR) — Chapter 5

This spreadsheet can be used to conduct a simple sensitivity analysis to correct for unknown or unmeasured confounding. The example follows chapter 5.

Reset Example | Clear Data

Instructions

Enter bias parameters in blue cells to the right and the crude data in the blue cells below. Cells in green give the results after adjusting for the unmeasured confounder.

Input Bias Parameters

Variable Names		Bias Parameters	
Outcome	early stage	p(Severe COPD+|COPI	0.30
Exposure	COPD D TIME	p(Severe COPD+|COPI	0.10
Confounder	Severe COPD	RR(Severe COPD-early	1.5
Error Check:	No errors found		

Data (Enter Crude COPD D TIME-early stage Data in Blue Cells)

	Total		Severe COPD +		Severe COPD -	
	COPD D	COPD D	COPD D TIME	COPD D TIME -	COPD D TIME +	COPD D TIME
early stage +	17910 a	7211 b	7008.3 A_1	1030.1 B_1	10901.7 A_0	6180.9 B_0
early stage -	53816 c	31489 d	14509.5 C_1	2839.9 D_1	39306.5 C_0	28649.1 D_0
Total	71726 m	38700 n	21517.8 M_1	3870.0 N_1	50208.2 M_0	34830.0 N_0

Crude and Unmeasured Confounder Specific Measures of COPD D TIME-early stage Relationship

Crude	Measure (95% CI)	Severe COPD +		Severe COPD -	
RR (COPD D TIMI	1.34 (1.31 - 1.37)	RR (COPD D TI	1.22	RR (COPD D TIME-early stag	1.22

COPD D TIME-early stage Relationship Adjusted for Severe COPD

Standardized Morbidity Ratio			Mantel-Haenszel		
SMR_{RR}	1.22	RRc 1.10	MH_{RR}	1.22	RRc 1.10

Notes

The data for this example come from: *Tyndall MW, Ronald AR, Agoki E, Malisa W, Bwayo JJ, Ndinya-Achola JO et al. Increased risk of infection with human immunodeficiency virus type 1 among uncircumcised men presenting with genital ulcer disease in Kenya. Clin Infect Dis 1996;23:449-53.*

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8879763

Equations

$M_1 = m^* p_1$ and $N_1 = n * p_0$

$A_1 = [RR_{CD}{}^*M_1{}^*a] / [RR_{CD}{}^*M_1 + m - M_1]$

$B_1 = [RR_{CD}{}^*N_1{}^*b] / [RR_{CD}{}^*N_1 + n - N_1]$

Calculations

Round Places	2
Crude RR	1.3401
SE(LN(RR))	0.0124
C+ (Total)	######
C- (Total)	######
SMR	1.2236
MH	1.2236
Error Check	
RR(C-D|E-)	1.5
RR(C-D|E+)	1.5
RR(CD) correct	TRUE
RR(CD) correct	TRUE
Negative Cell	0
Negative Cell	0
Negative Cell	0

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2- Unmeasured smoking:

Bias parameters are:

Prevalence of ever smoking among those with known (pre-existing) COPD diagnosis= 0.9

Prevalence of ever smoking among those with Unknown (concurrent) COPD diagnosis= 0.8

Possible association between ever smoking and early-stage lung cancer was set to 2 scenarios.

RR= 1.3, RR=1.5

Observed PR between COPD diagnosis timing and early-stage lung cancer "unadjusted for severe COPD"	Assumed RR between smoking and early stage of lung cancer	**Corrected PR**
1.34	1.3	1.29
1.34	1.5	1.31

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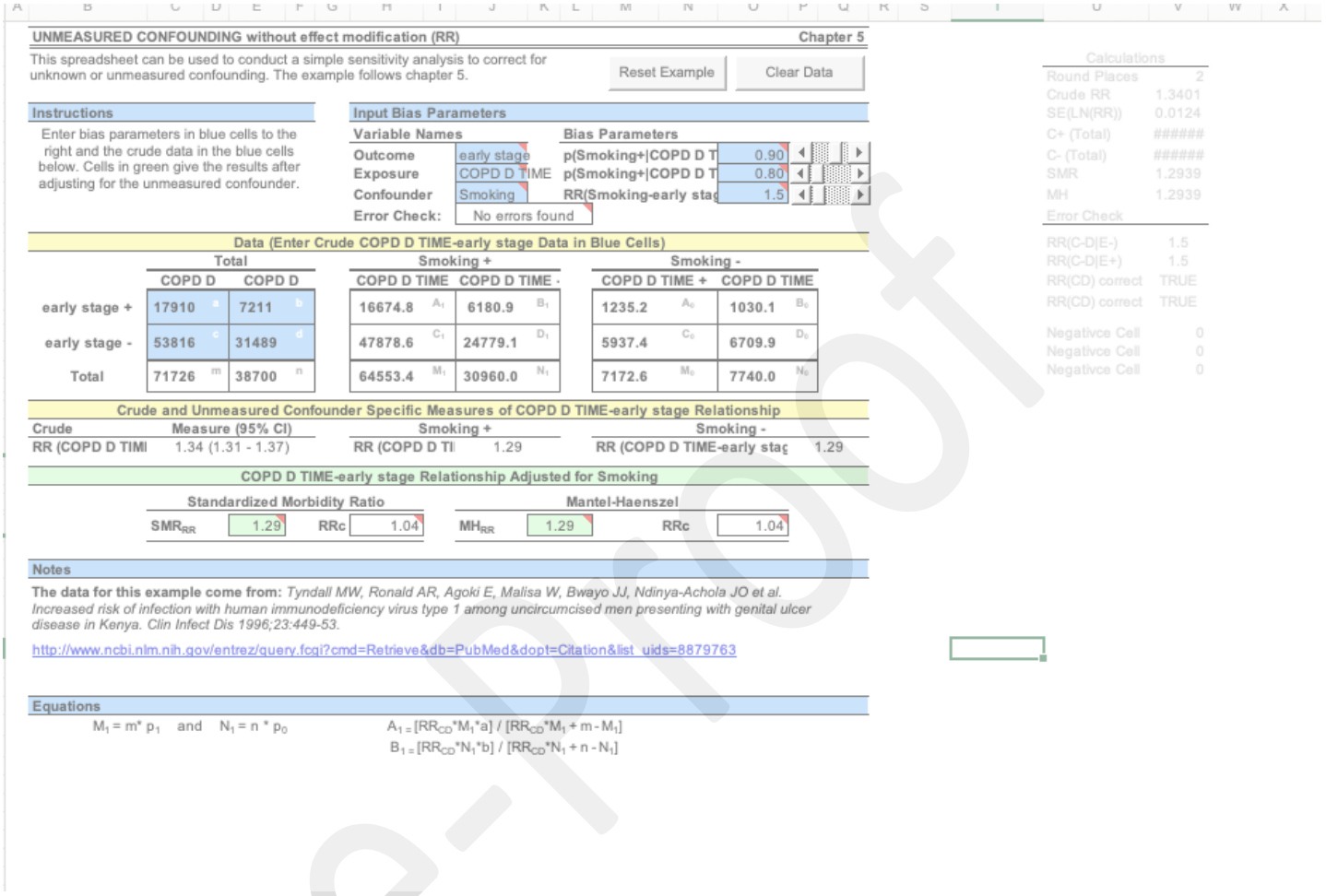
Scenario 1: RR between smoking and early diagnosis of lung cancer= 1.5



UNMEASURED CONFOUNDING without effect modification (RR) — Chapter 5

This spreadsheet can be used to conduct a simple sensitivity analysis to correct for unknown or unmeasured confounding. The example follows chapter 5.

Reset Example | Clear Data

Instructions

Enter bias parameters in blue cells to the right and the crude data in the blue cells below. Cells in green give the results after adjusting for the unmeasured confounder.

Input Bias Parameters

Variable Names		Bias Parameters	
Outcome	early stage	p(Smoking+|COPD D T	0.90
Exposure	COPD D TIME	p(Smoking+|COPD D T	0.80
Confounder	Smoking	RR(Smoking-early stag	1.5
Error Check:	No errors found		

Data (Enter Crude COPD D TIME-early stage Data in Blue Cells)

	Total		Smoking +		Smoking -	
	COPD D	COPD D	COPD D TIME	COPD D TIME -	COPD D TIME +	COPD D TIME
early stage +	17910 a	7211 b	16674.8 A_1	6180.9 B_1	1235.2 A_0	1030.1 B_0
early stage -	53816 c	31489 d	47878.6 C_1	24779.1 D_1	5937.4 C_0	6709.9 D_0
Total	71726 m	38700 n	64553.4 M_1	30960.0 N_1	7172.6 M_0	7740.0 N_0

Crude and Unmeasured Confounder Specific Measures of COPD D TIME-early stage Relationship

Crude	Measure (95% CI)	Smoking +		Smoking -	
RR (COPD D TIMI	1.34 (1.31 - 1.37)	RR (COPD D TI	1.29	RR (COPD D TIME-early stag	1.29

COPD D TIME-early stage Relationship Adjusted for Smoking

Standardized Morbidity Ratio			Mantel-Haenszel		
SMR_{RR}	1.29	RRc 1.04	MH_{RR}	1.29	RRc 1.04

Notes

The data for this example come from: *Tyndall MW, Ronald AR, Agoki E, Malisa W, Bwayo JJ, Ndinya-Achola JO et al. Increased risk of infection with human immunodeficiency virus type 1 among uncircumcised men presenting with genital ulcer disease in Kenya. Clin Infect Dis 1996;23:449-53.*

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8879763

Equations

$M_1 = m^* p_1$ and $N_1 = n * p_0$

$A_1 = [RR_{CD}{}^*M_1{}^*a] / [RR_{CD}{}^*M_1 + m - M_1]$

$B_1 = [RR_{CD}{}^*N_1{}^*b] / [RR_{CD}{}^*N_1 + n - N_1]$

Calculations

Round Places	2
Crude RR	1.3401
SE(LN(RR))	0.0124
C+ (Total)	######
C- (Total)	######
SMR	1.2939
MH	1.2939
Error Check	
RR(C-D|E-)	1.5
RR(C-D|E+)	1.5
RR(CD) correct	TRUE
RR(CD) correct	TRUE
Negativce Cell	0
Negativce Cell	0
Negativce Cell	0

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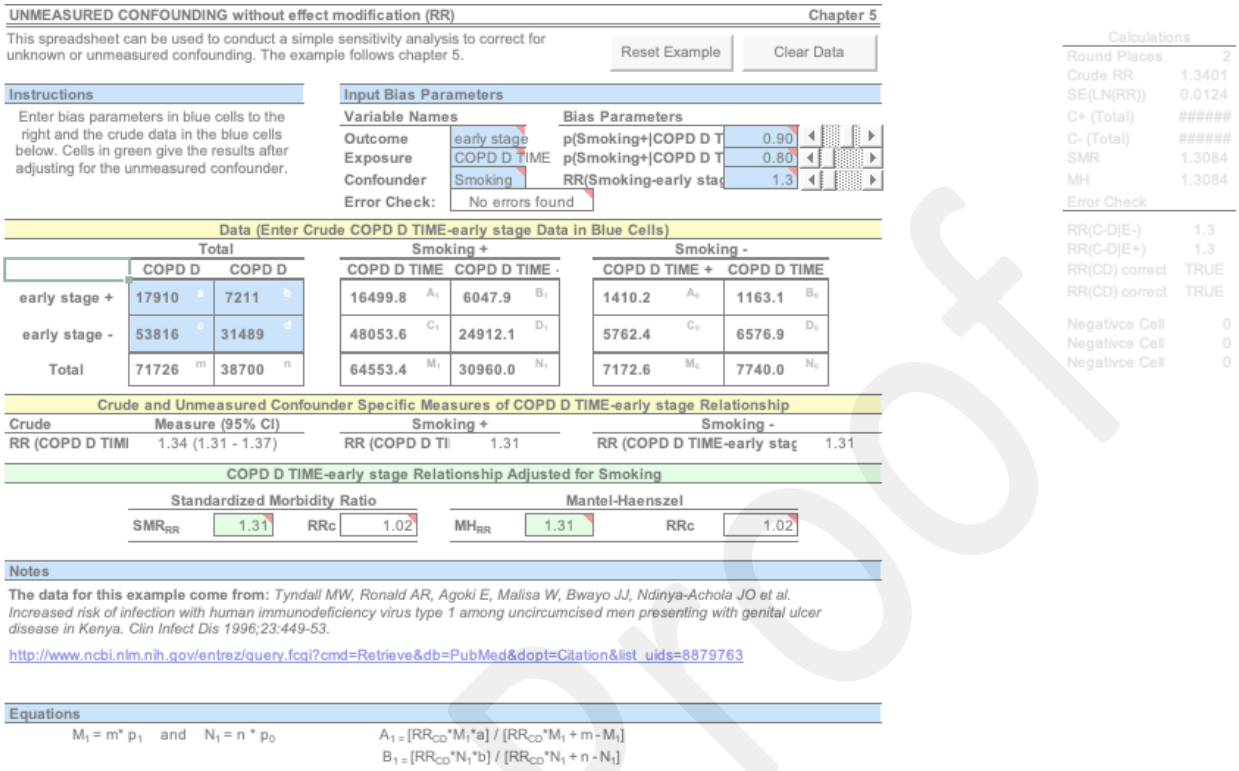
Scenario 2: RR between smoking and early diagnosis of lung cancer= 1.3



UNMEASURED CONFOUNDING without effect modification (RR) — Chapter 5

This spreadsheet can be used to conduct a simple sensitivity analysis to correct for unknown or unmeasured confounding. The example follows chapter 5.

Reset Example | Clear Data

Instructions

Enter bias parameters in blue cells to the right and the crude data in the blue cells below. Cells in green give the results after adjusting for the unmeasured confounder.

Input Bias Parameters

Variable Names		Bias Parameters	
Outcome	early stage	p(Smoking+|COPD D T	0.90
Exposure	COPD D TIME	p(Smoking+|COPD D T	0.80
Confounder	Smoking	RR(Smoking-early stag	1.3
Error Check:	No errors found		

Data (Enter Crude COPD D TIME-early stage Data in Blue Cells)

	Total		Smoking +		Smoking -	
	COPD D	COPD D	COPD D TIME	COPD D TIME -	COPD D TIME +	COPD D TIME
early stage +	17910 a	7211 b	16499.8 A_1	6047.9 B_1	1410.2 A_0	1163.1 B_0
early stage -	53816 c	31489 d	48053.6 C_1	24912.1 D_1	5762.4 C_0	6576.9 D_0
Total	71726 m	38700 n	64553.4 M_1	30960.0 N_1	7172.6 M_0	7740.0 N_0

Crude and Unmeasured Confounder Specific Measures of COPD D TIME-early stage Relationship

Crude	Measure (95% CI)	Smoking +		Smoking -	
RR (COPD D TIMI	1.34 (1.31 - 1.37)	RR (COPD D TI	1.31	RR (COPD D TIME-early stag	1.31

COPD D TIME-early stage Relationship Adjusted for Smoking

Standardized Morbidity Ratio			Mantel-Haenszel		
SMR_{RR}	1.31	RRc 1.02	MH_{RR}	1.31	RRc 1.02

Notes

The data for this example come from: *Tyndall MW, Ronald AR, Agoki E, Malisa W, Bwayo JJ, Ndinya-Achola JO et al. Increased risk of infection with human immunodeficiency virus type 1 among uncircumcised men presenting with genital ulcer disease in Kenya. Clin Infect Dis 1996;23:449-53.*

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8879763

Equations

$M_1 = m^* p_1$ and $N_1 = n * p_0$

$A_1 = [RR_{CD}{}^*M_1{}^*a] / [RR_{CD}{}^*M_1 + m - M_1]$

$B_1 = [RR_{CD}{}^*N_1{}^*b] / [RR_{CD}{}^*N_1 + n - N_1]$

Calculations

Round Places	2
Crude RR	1.3401
SE(LN(RR))	0.0124
C+ (Total)	######
C- (Total)	######
SMR	1.3084
MH	1.3084
Error Check	
RR(C-D|E-)	1.3
RR(C-D|E+)	1.3
RR(CD) correct	TRUE
RR(CD) correct	TRUE
Negativce Cell	0
Negativce Cell	0
Negativce Cell	0

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