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Trends and Disparities in cerebrovascular disease mortality among patients with bronchus and lung cancer in the United States, 1999-2020: A Population-Based Retrospective Study

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Abstract

Background

Bronchus and lung cancer are highly prevalent and fatal malignant tumors worldwide. Cerebrovascular disease is a leading cause of years of life lost among bronchus and lung cancer patients. However, previous studies have mostly been single-center and small-sample, lacking population-level mortality trends and population differences analysis.

Methods

A retrospective study was conducted based on the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research database to analyze the cerebrovascular disease-related mortality data of bronchus and lung cancer patients aged ≥ 25 years in the United States from 1999 to 2020. The Joinpoint regression model was used to analyze the trend of age-adjusted mortality rate and subgroup differences.

Results

Of the 3.5987 million bronchus and lung cancer-related deaths, 10,970 (0.3%) were attributed to cerebrovascular disease. The overall age-adjusted mortality rate decreased from 0.34 to 0.20 (Average Annual Percent Change =-2.44, $p < 0.001$), and slightly rebounded after 2014. Unspecified stroke as the main subtype, cerebral infarction shows a non-significant upward trend. Men aged 65 and above, non-Hispanic blacks and rural residents have higher age-adjusted mortality rate, with significant interstate differences.

Conclusion

From 1999 to 2020, the mortality rate of bronchus and lung cancer combined with cerebrovascular disease decreased overall but has stabilized in recent years. There are obvious group differences. Targeted optimization of cardio-cerebrovascular oncology management strategies is needed to mitigate health inequalities.

Contributions to the literature

Text box 1. Contributions to the literature
·This study is the first nationwide analysis of long-term trends and disparities in cerebrovascular disease mortality among U.S. bronchus and lung cancer patients based on big data.
·It reveals significant health inequalities across gender, race, urban/rural settings, and geographic regions, providing evidence for targeted interventions.
·The proposed integrated management strategy of “cardiovascular-cerebrovascular oncology” offers evidence-based support for multidisciplinary collaboration.

1. Introduction

Bronchus and lung cancer (LC), recognized as the malignant tumors with the highest morbidity and mortality rates globally, pose a significant threat to human life and health safety [1]. Over the past two decades, increased attention to LC risk factors such as smoking, along with innovations in screening technologies and optimization of comprehensive treatment plans, has contributed to a significant decline in LC incidence and mortality rates. Despite these improvements, the number of deaths attributed to LC remains greater than the combined total of deaths from colorectal, breast, and prostate cancers. And it has always ranked first in terms of mortality and incidence among malignant tumors in the United States, excluding gender factors[2].

In recent years, it has been found that the management of complications of LC in clinical practice significantly prolongs the survival period of LC patients, suggesting that the management of LC complications has become an increasingly important public health issue[3]. Studies have shown[4] that the median time from disease diagnosis to the occurrence of Cerebrovascular diseases (CEVD) events in LC is 1.3 years, making it the earliest malignant tumor to present CEVD. This indicates that CEVD, as the primary cause of Years of Life Lost (YLL) in adult patients with LC in the United States, has become increasingly important. Several studies have found that there is a complex bidirectional association between LC and CEVD[5, 6]. On the one hand, the procoagulant factors released by tumor cells in LC patients are prone to cause thrombosis in blood vessels, which in turn triggers CEVD. Meanwhile, direct damage to vascular endothelial cells caused by tumor metastasis, radiotherapy and chemotherapy drugs can lead to the destruction of vascular wall structure, thereby inducing hemorrhagic or ischemic cerebrovascular events[7]. On the other hand, LC and CEVD share multiple risk factors, such as smoking, advanced age, hyperlipidemia and hypertension, etc[8–10]. It is worth noting that the clinical manifestations of CEVD in LC patients may be atypical and are often masked by tumor-related symptoms, ultimately leading to delayed diagnosis and treatment, which also highlights the importance of CEVD in LC.

Previous studies have sought to analyze the onset characteristics and risk factors of CEVD in patients with LC[11–13]. However, most of these investigations were single-center studies with small sample sizes, which limited their national representativeness. Furthermore, they did not perform systematic analyses of the various subtypes of CEVD, including ischemic and hemorrhagic strokes. At the same time, Previous studies have lacked research on mortality trends based on large sample populations, especially regarding the differences among various demographic characteristics (such as gender, race, and region), where the existing evidence is even more limited.

Therefore, this study aims to explore the disease trends among different demographic characteristics by using a comprehensive database, and to identify potential racial and geographical differences that may guide the formulation of public health intervention measures and policies. Given the above complex correlations, this study aims to fill a key research gap, namely, to clarify the impact of geographical and demographic differences on LC and CEVD-related mortality. By leveraging the relevant data from the

Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database, this study aims to analyze the trends of LC and CEVD-related mortality from 1999 to 2020, and for the first time systematically explore the combined impact of multiple regions, races, and economic levels on LC and CEVD in the United States during this period. By delving deeply into its trend changes, not only can the group-level mortality rate changes related to LC and CEVD be revealed, but also the impact of racial and geographical differences can be further explored, providing evidence-based basis for formulating targeted disease prevention and control strategies for LC and CEVD.

2. Methods

2.1 Data source

This retrospective cross-sectional investigation examined temporal trends and demographic disparities in CEVD-attributed mortality among U.S. adults with LC during 1999–2020. Death certificate data were retrieved from the CDC WONDER database, which compiles nationwide mortality records and population estimates[14]. Cause-of-death coding followed the International Classification of Diseases, Tenth Revision(ICD-10)[15]. Eligible records were those in which CEVD (ICD-10 I60-I69) was recorded as the underlying cause of death, with LC (ICD-10 C34) noted as a contributing cause. Records with an undocumented cause of death were not considered. This ICD-10-based case definition follows the approach adopted in prior studies of LC and CEVD[16–18]. Ethical oversight was exempted as the dataset is anonymized, publicly accessible, and conforms to the STROBE reporting guidelines for observational research[19].

2.2 Data abstraction

This study retrieved the total population, death toll and AAMR for each state in the United States from 1999 to 2020. Stratification was performed according to gender, age group, race/ethnicity, geographical location, urbanization level and place of death. The analysis focused on adults aged 25 years and older. Age was categorized in 10-year intervals and also dichotomized for specific trend analyses (< 65 years vs. ≥65 years). This dichotomization has been frequently applied in previous investigations using the CDC WONDER data[20]. Racial and ethnic categories encompass Hispanic or Latino, Non-Hispanic (NH) White, NH Black or African American, NH American Indian or Alaska Native, and NH Asian or Pacific Islander. These classifications align with those previously used in analyses from the CDC WONDER database and are based on data reported on death certificates in compliance with the US Office of Budget and Management Guidelines[20]. To stratify the population geographically, we employed the Urban-Rural Classification Scheme from the National Center for Health Statistics and divided the counties into urban (large metropolitan area; population greater than 1 million), medium/small metropolitan area (population between 50,000-999,999), and rural (population lesser than 50,000) categories. Additionally, we divided the United States into four regions based on the US Census Bureau’s classification: Northeast, Midwest, South, and West[21].

2.3 Statistical analysis

Analyses involved calculating both Crude Mortality Rate (CR) and AAMR per 100,000 population. The AAMR was calculated by direct standardization to the 2000 U.S. standard population to control for variations in age structure across groups and time[22]. The trend of AAMR is determined by dividing the number of CEVD deaths in patients with combined LC by the number of all-cause deaths in patients with combined LC. We employed the Joinpoint regression model (Joinpoint V5.1.0, National Cancer Institute) to evaluate the trend of AAMRs in each subgroup[23]. By fitting the log-linear regression model, this model calculates the significance of AAMR over time. The annual percent change (APC) and its 95% confidence interval (CI) were estimated through Monte Carlo permutation procedures. A summary measure, the average annual percent change (AAPC), was subsequently derived as a weighted average of APC, accompanied by its 95% confidence interval, to depict the overall mortality trend across the entire 22-year interval. If the slope describing the change in mortality rate is significantly different from 0 in the two-tailed t-test, it is assumed that the APC shows an increasing or decreasing trend. The statistical significance was set at $P \leq 0.05$. Data processing and visualization were conducted with R version 4.4.3 and Excel.

3. Results

From 1999 to 2020, among 55,317,623 individuals aged 25 and above, there were a total of 3,598,758 all-cause deaths with LC, of which 10,970 deaths were associated with (0.3%) CEVD (Table 1, Supplemental Table 1). According to the statistics of the place of death, 59.65% of the deaths occurred in medical facilities, 13.07% in the deceased's homes, 15.92% in nursing homes or long-term care facilities, 7.78% in hospice care facilities, and 3.26% in other places (Supplemental Table 2).

Table.1. Baseline characteristics of all-cause mortality and cerebrovascular death among patients with comorbid bronchus and lung cancer

Demographic	All-Cause, n(%)	CEVD Related to Bronchus and Lung Cancer, n(%)
	n = 3,598,758	N = 10,970
Sex		
Male	2,008,809(55.82)	5,518(50.30)
Female	1,589,949(44.18)	5,452(49.70)
Age of death, year		
25–34	3,274(0.09)	2(0.02)
35–44	37,055(1.03)	38(0.35)
45–54	237,146(6.59)	331(3.02)
55–64	698,330(19.40)	1,434(13.07)
65–74	1,141,438(31.72)	3,337(30.42)
75–84	1,077,556(29.94)	3,999(36.45)
85+	403,959(11.22)	1,829(16.67)
Race and Ethnicity		
Hispanic or Latina	112,057(3.11)	298(2.72)
NH American Indian or Alaska Native	16,068(0.45)	49(0.45)
NH Asian or Pacific Islander	70,757(1.97)	255(2.32)
NH Black or African American	371,346(10.32)	1,120(10.21)
NH White	3,020,878(83.94)	9,236(84.19)
Census Region		
Region 1: Northeast	666,480(18.52)	1,841(16.78)
Region 2: Midwest	869,729(24.17)	2,753(25.10)
Region 3: South	1,440,290(40.02)	4,060(37.01)
Region 4: West	622,259(17.29)	2,316(21.11)

3.1. Demographic trends in mortality (overall)

The AAMR of CEVDs in LC patients decreased from 0.34 (95% CI: 0.31 to 0.36) in 1999 to 0.20 (95% CI: 0.18 to 0.21) in 2020, and the AAPC was − 2.44 (95% CI: -3.17 to -1.70, $p < 0.001$) (Fig. 1, Supplemental Table 4). Specifically, patients with LC combined with CEVDs showed a significant downward trend

before 2014 (APC: -4.41; 95% CI: -4.87 to -3.94; p < 0.001), followed by a mild increase (APC: 2.66; 95% CI: 0.08 to 5.31; p = 0.044) (Supplemental Table 3).

Finally, we also observed that the overall decline in AAMR in patients with LC combined with CEVDs was lower than that in the overall AAMR of LC during the same period (AAPC: -2.44 vs -2.52) (Fig. 2).

3.2. Subtypes of CEVDs among patients with bronchus and lung cancer

The most common cause of death among LC patients with CEVD is unspecified stroke (56.95%), followed by cerebral infarction (14.15%), hemorrhagic stroke (17.19%), and other cerebrovascular diseases (11.71%) (Fig. 3). The AAMR trend analysis over 22 years (Table 2) shows that the mortality rate of all CEVD subtypes decreased except for cerebral infarction. The decrease in AAPC was the largest among unspecified strokes (-4.46; 95% CI: -5.00 to -3.92; p < 0.001), the smallest among other cerebrovascular diseases (-1.39; 95% CI: -4.18 to 1.49; p = 0.341), and only cerebral infarction showed an upward trend in AAPC (0.71; 95% CI: -4.53 to 6.22; p = 0.796) (Supplemental Table 3).

Table 2
Trends in Age-Adjusted Mortality Rates of Cerebrovascular Death among patients with comorbid bronchus and lung cancer between 1999 and 2020, stratified by subtypes of CEVDs

		AAMR			
Year	Population, No.	Hemorrhagic Stroke (I60-I62)	Cerebral Infarction (I63)	Stroke, Unspecified (I64)	Other Cerebrovascular Diseases (I67, I69)
1999	180408769	0.05 (0.04–0.06)	0.03 (0.02–0.04)	0.22 (0.2–0.24)	0.04 (0.03–0.05)
2000	181984640	0.05 (0.04–0.06)	0.04 (0.03–0.05)	0.18 (0.16–0.2)	0.04 (0.03–0.05)
2001	184305128	0.05 (0.04–0.06)	0.03 (0.02–0.04)	0.19 (0.17–0.21)	0.03 (0.03–0.04)
2002	186208028	0.04 (0.03–0.05)	0.03 (0.02–0.04)	0.19 (0.17–0.21)	0.03 (0.03–0.04)
2003	188090429	0.04 (0.03–0.05)	0.03 (0.02–0.04)	0.16 (0.14–0.18)	0.04 (0.03–0.05)
2004	190205384	0.04 (0.04–0.06)	0.02 (0.01–0.03)	0.17 (0.15–0.19)	0.03 (0.02–0.04)
2005	192551384	0.04 (0.03–0.05)	0.03 (0.02–0.04)	0.16 (0.14–0.17)	0.03 (0.02–0.04)
2006	195019359	0.03 (0.02–0.03)	0.02 (0.01–0.03)	0.15 (0.14–0.17)	0.02 (0.02–0.03)
2007	197403777	0.05 (0.04–0.06)	0.03 (0.02–0.04)	0.14 (0.12–0.15)	0.03 (0.02–0.04)
2008	199795090	0.04 (0.03–0.05)	0.02 (0.01–0.03)	0.13 (0.11–0.14)	0.03 (0.02–0.04)
2009	202107016	0.04 (0.04–0.06)	0.02 (0.01–0.03)	0.14 (0.12–0.15)	0.02 (0.02–0.03)
2010	203891983	0.02 (0.02–0.03)	0.02 (0.01–0.03)	0.11 (0.1–0.13)	0.02 (0.02–0.03)
2011	206592936	0.04 (0.03–0.04)	0.02 (0.01–0.03)	0.12 (0.11–0.14)	0.01 (0.01–0.01)
2012	208826037	0.04 (0.03–0.05)	0.02 (0.01–0.03)	0.13 (0.11–0.15)	0.01 (0.01–0.02)
2013	211085314	0.03 (0.02–0.04)	0.02 (0.01–0.03)	0.1 (0.09–0.11)	0.02 (0.02–0.03)
2014	213809280	0.03 (0.02–0.04)	0.02 (0.01–0.03)	0.1 (0.09–0.12)	0.01 (0.01–0.02)

		AAMR			
2015	216553817	0.03 (0.02–0.03)	0.02 (0.01–0.03)	0.08 (0.07–0.09)	0.02 (0.02–0.03)
2016	218641417	0.03 (0.03–0.04)	0.03 (0.02–0.03)	0.1 (0.08–0.11)	0.03 (0.02–0.04)
2017	221447331	0.03 (0.02–0.04)	0.04 (0.03–0.05)	0.08 (0.07–0.1)	0.02 (0.01–0.02)
2018	223311190	0.03 (0.02–0.04)	0.06 (0.05–0.07)	0.09 (0.07–0.1)	0.02 (0.02–0.03)
2019	224981167	0.03 (0.02–0.04)	0.05 (0.05–0.06)	0.09 (0.07–0.1)	0.03 (0.02–0.04)
2020	226635013	0.03 (0.02–0.03)	0.04 (0.03–0.05)	0.09 (0.07–0.1)	0.03 (0.02–0.04)
Total	4473854489	0.03 (0.03–0.03)	0.03 (0.03–0.03)	0.13 (0.13–0.13)	0.03 (0.03–0.03)
Percentage of total CEVDs (%)		17.19	14.15	56.95	11.71
Annual Percentage of Change (%) (95% CI)		-1.90 (-3.05,0.74)	0.71 (-4.53,6.22)	-4.46 (-5.00,-3.92)	-1.39 (-4.18,1.49)

Age-adjusted mortality rate per 100,000 person-years, directly standardized to the 2000 US Census population. Abbreviations AAMR, age-adjusted mortality rate

3.3. Disparities in gender

During the study period, both the overall and gender-stratified AAMRs showed a trend of initially decreasing followed by increasing. The AAMRs of men were always higher than that of women (0.27vs 0.20), and the differences gradually became similar with the increase of years. For men, there was a downward trend from 1999 to 2015 (APC: -5.28; 95% CI: -5.82 to -4.74; $p < 0.001$), while there was an upward trend from 2015 to 2020 (APC: 4.01; 95% CI: 0.54 to 7.59; $p = 0.026$). For females, there was a downward trend from 1999 to 2014 (APC: -3.82; 95% CI: -4.75 to -2.87; $p < 0.001$), and an upward trend from 2014 to 2020 (APC: 3.71; 95% CI: -0.29 to 7.87; $p = 0.067$) (Fig. 4, Supplemental Tables 3 and 4).

Subsequently, we conducted a comparison of the number of CEVD-related deaths among LC patients of different age groups and genders from 1999 to 2020. Due to the de-identification processing of the CDC WONDER database, the database has been compressed for data with fewer than 10 deaths. Therefore, we are unable to obtain the specific number of deaths among American adults aged 25–34. Thus, only age group stratification has been conducted for adults over 35 years old. The results show that during the 22-year study period, the number of deaths among men aged 55–84 was consistently higher than

that among women, which is consistent with the basic trend of AAMR. However, among those under 55 and over 85 years old, the number of deaths among women exceeded that of men (Fig. 5).

3.4. Disparities in age group

When stratified by age, the AAMR of CEVD in the elderly patient group with LC (1.01) consistently exceeded that in the younger group (0.03). Among younger individuals, the AAMR remained relatively stable from 1999 to 2020 (APC: -0.13; 95% CI: -0.83 to 0.57; p = 0.697). Among the elderly, AAMR showed a downward trend from 1999 to 2013 (APC: -4.55; 95% CI: -5.33 to -3.77; p < 0.001), followed by a slight increase from 2013 to 2020 (APC: 1.27; 95% CI: -1.02 to 3.61; p = 0.260) (Fig. 6, Supplemental Tables 3 and 5).

3.5. Racial and ethnicity differences

When stratified by race or ethnicity, the highest AAMRs for adult LC-related CEVD was for NH Black or African American (0.27), followed by NH White (0.23), NH American Indian or Alaska Native (0.20), NH Asian or Pacific Islander (0.14) and Hispanic or Latino (0.09). Due to the low overall death toll, it is impossible to conduct trend analysis on the NH American Indian or Alaska Native population, the NH Asian or Pacific Islander, and the Hispanic or Latino population.

The AAMR trend change of NH Black or African American showed a trend of rising initially and then falling. Its AAMR showed a downward trend from 1999 to 2016 (APC: -4.20, 95% CI: -5.65 to -2.73, p < 0.001, and then showed an upward trend from 2016 to 2020 (APC: 12.45, 95% CI: -0.85 to 27.54, p = 0.066), but there was no statistical difference. The AAMR trend of NH White was similar: it showed a downward trend from 1999 to 2013 (APC: -4.56, 95% CI: -5.18 to -3.95, p < 0.001, an upward trend from 2013 to 2020 (APC: 1.48, 95% CI: -0.46 to 3.46, p = 0.126), but no statistical difference (Fig. 7, Supplemental Tables 3 and 6).

3.6. State-wise distribution

When stratified by different states, it ranges from the lowest Utah (0.07) to the highest Alaska (0.41). States in the top 90th percentile (Alaska, Washington, Oklahoma, Mississippi) have an AAMR approximately in the bottom 10th percentile (New Mexico, Arizona, Louisiana, Nevada). 2.4 times that of Utah (Figs. 8 and 9, Supplemental Table 7).

3.7. Census region

We found that during the research period, the AAMR of each census district generally showed a trend of first decreasing and then increasing, and their AAMRs were basically similar: Northeast (0.19), Midwest (0.24), South (0.22), and West (0.22). Northeastern AAMR showed a downward trend from 1999 to 2015 (APC: -4.76, 95% CI: -6.00 to -3.51, p < 0.001), slightly increased from 2015 to 2020 (APC: 5.25, 95% CI: -3.00 to 14.20, p = 0.204), but no significant statistical difference was observed. Both Midwestern and

Southern AAMRs decreased significantly from 1999 to 2013 (Midwest: -4.13, 95% CI: -5.36 to -2.89, p < 0.001; South: -4.30, 95% CI: -5.25 to -3.33, p < 0.001), slightly increased from 2013 to 2020 (Midwest: 1.71, 95% CI: -2.10 to 5.67, p = 0.363; South: 1.63, 95% CI: -1.25 to 4.59, p = 0.251). Western AAMR decreased significantly from 1999 to 2017 (APC: -4.30, 95% CI: -5.14 to -3.46, p < 0.001), and increased slightly from 2017 to 2020 (APC: 12.13, 95% CI: -1.07 to 27.09, p = 0.071), and no significant statistical difference was observed (Figs. 10 and 11, Supplemental Tables 3 and 8).

3.8. Urbanization

AAMR was consistently higher in nonmetropolitan areas than in metropolitan areas throughout the study period (0.25 vs 0.21). In nonmetropolitan areas, AAMR continued to decline from 1999 to 2020(APC: -2.30; 95% CI: -3.22 to -1.38; p < 0.001). AAMR in metropolitan areas continued to decline from 1999 to 2015(APC: -4.38; 95% CI: -5.01 to -3.75; p < 0.001), this was followed by a slight increase between 2015 and 2020(APC: 4.57,95% CI: 0.70 to 8.60, p = 0.023) (Fig. 12, Supplemental Tables 3 and 9).

4. Discussion

We conducted a comprehensive analysis of the 22-year mortality data from the CDC WONDER database to study the CEVD mortality patterns in patients with LC comorbidities. Over the 22-year study period, CEVD-related mortality among LC patients declined for most cerebrovascular subtypes, with the sole exception of cerebral infarction—a pattern that likely signals improved management of shared risk factors. Secondly, although the overall situation has improved, the gradual stabilization or slight increase in the overall mortality rate after 2015 suggests that the management of common risk factors for LC combined with CEVD, such as obesity, smoking and drinking, may have entered a plateau period. It also indicates that the treatment methods for CEVD, especially the targeted strategies for patients with LC combined with CEVD, need to be further updated.

As a key issue at the intersection of oncology and cardio-cerebrovascular diseases, CEVD is one of the most common serious complications during LC treatment and follow-up phases. This has also elevated the emerging discipline of cardio-cerebrovascular oncology to a central role in the comprehensive management of LC patients. Over the past two decades, significant progress has been made in the cardio-cerebrovascular care of LC patients. Cardiac imaging techniques such as echocardiography and cardiac magnetic resonance imaging have been used to assess cardiac function, and computed tomography coronary angiography has also been applied. Meanwhile, the application of artificial intelligence in the diagnosis, treatment and disease research of CEVD has greatly improved the prognosis of CEVD in LC patients[24, 25]. Although LC patients have made significant progress in CEVD, they still face a relatively high risk of CEVD disease, and the mortality rate in some specific groups is even gradually increasing. Behind this phenomenon lies the interwoven effect of multiple factors such as the tumor itself, treatment interventions, and underlying health conditions: On the one hand, the inflammatory factors secreted in large quantities by LC cells and the shed tumor cells can directly activate the body's coagulation system, damage the integrity of vascular endothelium, and thereby induce thrombosis. This may not only lead to ischemic cerebrovascular events but also cause tumor cell

hematogenous metastasis to cerebral blood vessels to form cancer thrombus, or directly invade the vascular wall to cause vascular stenosis and rupture. Ultimately, it leads to ischemic or hemorrhagic stroke; On the other hand, anti-tumor treatment methods such as radiotherapy and chemotherapy can also indirectly increase the risk of CEVD. For instance, nausea and vomiting related to radiotherapy and chemotherapy can lead to reduced food intake and insufficient blood volume in patients, while the vascular toxicity of chemotherapy drugs can further damage the vascular endothelium and intensify the risk of thrombosis. Behind this phenomenon lies the interwoven effect of multiple factors such as the tumor itself, treatment interventions, and underlying health conditions: On the one hand, the inflammatory factors secreted in large quantities by LC cells and the shed tumor cells can directly activate the body's coagulation system, damage the integrity of vascular endothelium, and thereby induce thrombosis. This may not only lead to ischemic cerebrovascular events but also cause tumor cell hematogenous metastasis to cerebral blood vessels to form cancer thrombus, or directly invade the vascular wall to cause vascular stenosis and rupture. Ultimately, it leads to ischemic or hemorrhagic stroke; On the other hand, anti-tumor treatment methods such as radiotherapy and chemotherapy can also indirectly increase the risk of CEVD. For instance, nausea and vomiting related to radiotherapy and chemotherapy can lead to reduced food intake and insufficient blood volume in patients, while the vascular toxicity of chemotherapy drugs can further damage the vascular endothelium and intensify the risk of thrombosis. The pathophysiological mechanism of the above-mentioned multi-factor superposition highlights the necessity of implementing individualized prevention and control strategies for high-risk populations with LC combined with CEVD, and also suggests that future research should focus on narrowing the epidemiological differences among different populations to alleviate the disease burden caused by this complication.

The gender stratification results showed that both the overall and gender-specific AAMR showed a trend of first decreasing and then increasing, and the AAMR of men was consistently higher than that of women during the study period. Interestingly, this gender disparity gradually dissipated over the years. Meanwhile, this study found that during the 22-year research period, the number of male deaths in the 55–84 age group was consistently higher than that of female deaths, which was basically consistent with the overall AAMR trend. However, among those under 55 and over 85, the number of female deaths exceeded that of male deaths. The above results show that there are gender differences in the AAMR of CEVD in LC patients. Men exhibited a persistently higher risk of CEVD during LC management, potentially attributable to their generally lower health awareness[26, 27].This makes CEVD-related risk factors such as hypertension, diabetes, smoking, alcohol abuse, and a high-fat, low-fiber diet more common in male patients[28–30]. However, with the general improvement of health awareness in society and the popularization of CEVD-related disease screening, the CEVD-related AAMR in male LC patients has shown a continuous downward trend. This has also directly contributed to the gradual narrowing of the AAMR gap between the two genders.

In contrast, the CEVD-related AAMR of female LC patients showed an upward trend after 2014. This suggests that there are certain deficiencies or inadequations in the health management of CEVD in

female LC patients, which is closely related to the fluctuations in female estrogen exposure levels caused by dietary structure and environmental changes. Its protective effects include promoting young endothelial phenotypes by increasing the bioavailability of nitric oxide and reducing inflammation and oxidative stress. In a meta-analysis, it was found that women with a reproductive age of less than 30 years had a 75% higher risk of stroke compared to those with a reproductive age of 36 to 38 years[31, 32].This association seems to be mainly driven by early menopause (under 40 years old) or mid-early menopause (40–44 years old). Interestingly, other studies have found that early or late menarche also seems to increase the risk of stroke[33, 34]. In premenopausal women, estrogen can reduce the formation of atherosclerotic lesions, but in randomized hormone replacement trials in postmenopausal women, an increase in coronary artery disease was observed[35]. This might be related to the fact that estrogen can enhance the calcification of existing atherosclerotic plaques by promoting osteoblast-like phenotypes in vascular smooth muscle cells[36], and the low level of estrogen after menopause may explain the susceptibility to brain injury in aging women[37], which is consistent with our research results. This suggests that in the future, we need to focus on managing the AAMR of CEVD in female LC patients, so as to alleviate the social burden caused by CEVD as a whole.

Through age-stratified analysis, it can be known that the AAMR of the elderly group was always higher than that of the young group, and the AAMR of the young group remained almost unchanged, while that of the elderly group showed a trend of first decreasing and then increasing. This suggests that the disease management of CEVD in the elderly group is somewhat lacking, which may be related to age-dependent endothelial dysfunction[38], Age-related physiological and pathological changes Conditions such as arteriosclerosis, decreased endothelial function and delayed ventricular filling will further increase the risk of atrial fibrillation[39]. In addition, the cognitive decline of the elderly and the reduction of social and economic resources will further complicate the management of atrial fibrillation, leading to a worse prognosis. With the further aggravation of population aging[40], this has led to an increase in the disease burden of CEVD among this population, which is also one of the reasons for the persistently high mortality rate. Meanwhile, treatment methods such as direct oral administration of anticoagulants, which can alleviate severe complications in oral anticoagulation therapy, have not been fully utilized in the elderly population due to low prescription rates, economic barriers, and medication compliance issues[41], which is also one of the reasons for the persistently high mortality rate.

Through the analysis of racial stratification, it can be known that the AAMR of NH Black or African American is the highest, followed by NH White, and the data of the other races are missing. Interestingly, both NH Black or African American and NH White showed a trend of first decreasing and then increasing. The increasing trend of NH Black or African American was more significant compared to that of NH White. This suggests that LC patients of NH Black or African American face a greater risk of CEVD. Socioeconomic gradients likely underpin this disparity: NH Black or African American decedents had, on average, lower income and educational attainment—factors consistently linked with reduced screening for vascular risk factors, poorer medication adherence, and delayed presentation for acute cerebrovascular events[42, 43]. Furthermore, NH Black or African Americans have relatively insufficient

management of diseases with high-risk factors for CEVD such as diabetes and hyperlipidemia[44], which further exacerbates the mortality risk of CEVD in this group.

By analyzing the AAMR of different states, it can be known that Alaska, Washington, Oklahoma and Mississippi have the highest mortality rates, while New Mexico, Arizona, Louisiana, Nevada and Utah have the lowest mortality rates. This suggests that there are significant differences in the AAMR of CEVD in LC patients among states. Among them, Utah has the lowest AAMR, which seems to be related to its lower smoking rate and higher health habits[45]. However, Mississippi, which is geographically close to Utah, has a higher AAMR, suggesting that even if the geographical location is close, The CEVD mortality rate of LC patients may also vary among states due to differences in cardio-cerebrovascular oncology care models, medical infrastructure, medical-related policy designations, and the disease burden of CEVD[46]. Those states that have been continuously declining may have implemented the comprehensive cardio-cerebrovascular oncology model or better thrombosis prevention programs earlier. This is worthy of comparative health system studies to identify scalable cardio-cerebrovascular risk mitigation strategies.

By analyzing the AAMR in different regions, it can be seen that the differences between the Northeast, Midwest, South and West regions are small. Although the AAMR of patients in each region showed a downward trend in the early stage, the AAMR of patients in all regions showed a certain rebound in the later period. Although this rebound is not significant, this suggests that the increase in AAMR of CEVD in LC patients is not limited to a certain region. This is an overall change trend. This may be because as the survival period of LC patients gradually extends, their CEVD-related disease risk factors are gradually exposed. At the same time, the cumulative damage caused by the inflammatory factors continuously secreted by LC is easy to appear in patients with long-term survival[47], Secondly, the long-term vascular toxicity of new anti-cancer treatments gradually becomes more significant. This lag is more likely to appear in LC patients with longer survival periods[48].

By analyzing the AAMR of urban and non-urban areas, we can see that the AAMR of non-urban areas is always higher than that of urban areas, and there is a slight increase in urban areas after 2015. Due to incomplete medical facilities, shortage of medical personnel, insufficient medical insurance coverage and poor overall health awareness[49], the AAMR of the population in non-urban areas is generally high. However, with the improvement of economic levels, patients in non-urban areas are more inclined to seek medical treatment in urban areas[46], which has led to critically ill patients originally in non-urban areas receiving centralized treatment in tertiary centers in urban areas. Meanwhile, due to reasons such as access barriers to CEVD specialties and incomplete medical facilities in non-urban areas, they only accept patients with milder conditions. These factors have jointly led to the decline of AAMR in non-urban areas, while it has increased in urban areas.

5. Limitations

The nationally representative CDC WONDER data used in this study ensures that the research results have good applicability and reliability, but there are still several inevitable limitations in this study. Firstly, the core data of this study originated from ICD codes and death certificates in the CDC WONDER database. The use of death certificate data affected the measurement error of CEVD as the cause of death by classification error bias, resulting in overestimation or underestimation of the results. Secondly, as the determination of the "underlying cause of death" and the "contributing cause of death" in the death certificate relies on the subjective judgment of the declarant and lacks a unified standardized determination process, this further intensifies the risk of classification bias. Thirdly, since this database does not include key clinical information such as tumor stage, pathological type, and treatment plan of LC patients, it is impossible to analyze the direct impact of treatment methods on the risk of CEVD occurrence. Fourth, the database compressed the data of subgroups with a death toll of less than 10, which made it impossible to carry out trend analysis for some ethnic minorities and age groups, and restricted in-depth exploration of health differences among these groups. Finally, the urban-rural classification, which originated from the 2013 National Center for Health Statistics classification in the United States, may no longer be a good indicator for measuring the contemporary distribution pattern of residents, especially in the context of population changes caused by the pandemic after 2020.

6. Conclusion

In conclusion, this study analyzed the changes in CEVD-related mortality among LC patients in different populations in the United States from 1999 to 2020. The research results suggest that although the overall mortality rate of LC patients combined with CEVD has shown a downward trend over the past 20 years, it has gradually stabilized in recent years. This suggests that further development of new therapeutic drugs, exploration of new multidisciplinary treatment strategies and targeted medical policies are still needed to alleviate the stabilizing mortality rate. At the same time, further clinical and population-based research is required to deeply understand the differences that still exist at the gender, age, racial and social levels even when the overall trend is declining or stabilizing.

Abbreviations

LC
Bronchus and lung cancer
CEVD
Cerebrovascular disease
YLL
Years of life lost
AAMR
Age–adjusted mortality rate
APC
Annual percent change
AAPC

Average annual percent change
CDC WONDER
Centers for Disease Control and Prevention's Wide–Ranging Online Data for Epidemiologic Research
ICD
10–International Classification of Diseases, 10th Revision
NH
Non–Hispanic
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology

Declarations

Ethics approval and consent to participate

This study used de-identified, publicly available data from the CDC WONDER database. According to national guidelines and institutional policy, analysis of such datasets does not require ethical approval or individual consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Not applicable.

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Author Contribution

SZ and ZT conceived and designed the study, collected data, and wrote the manuscript. WW and YL collected data. PY and XH contributed to data analysis tools. PS supervised the study and revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The datasets analyzed are publicly available from the CDC WONDER Multiple Cause of Death database: https://wonder.cdc.gov/mcd.html.

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Figures

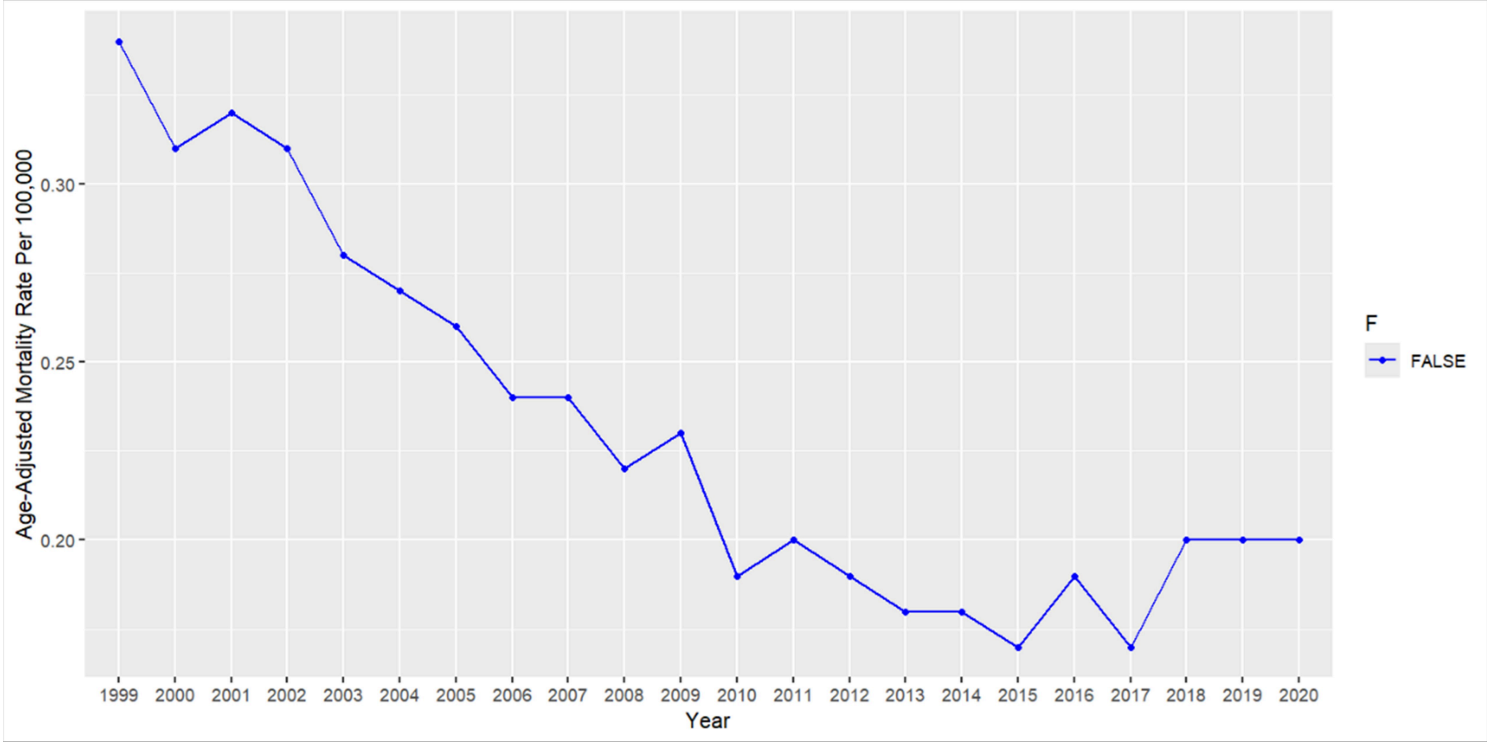


Figure 1

Trends in Age-Adjusted Mortality Rates of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020.

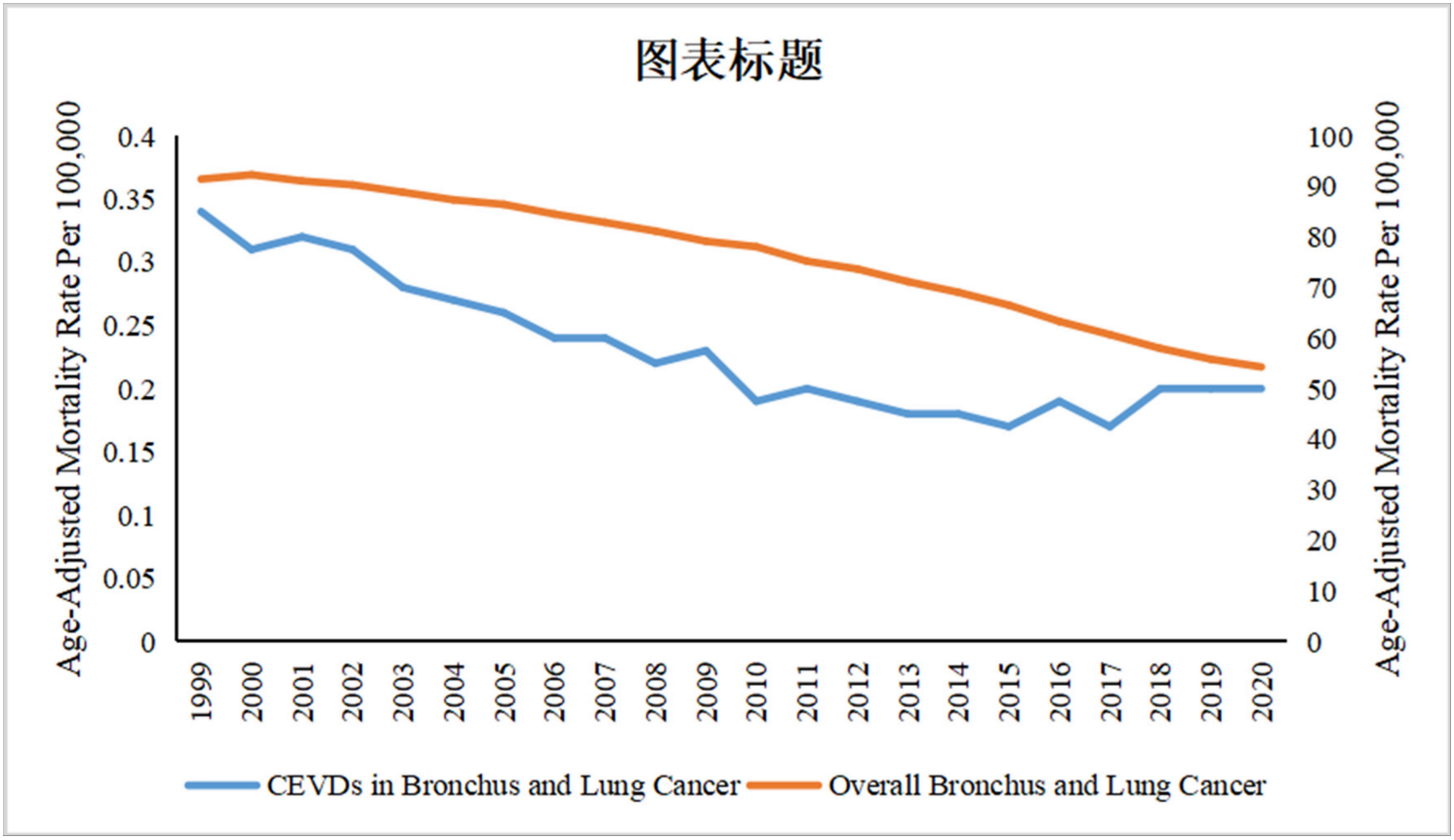


Figure 2

Comparison of Trends of Age-Adjusted Mortality Rate of CEVDs in Bronchus and Lung Cancer and Age-Adjusted Mortality Rate of Overall Bronchus and Lung Cancer

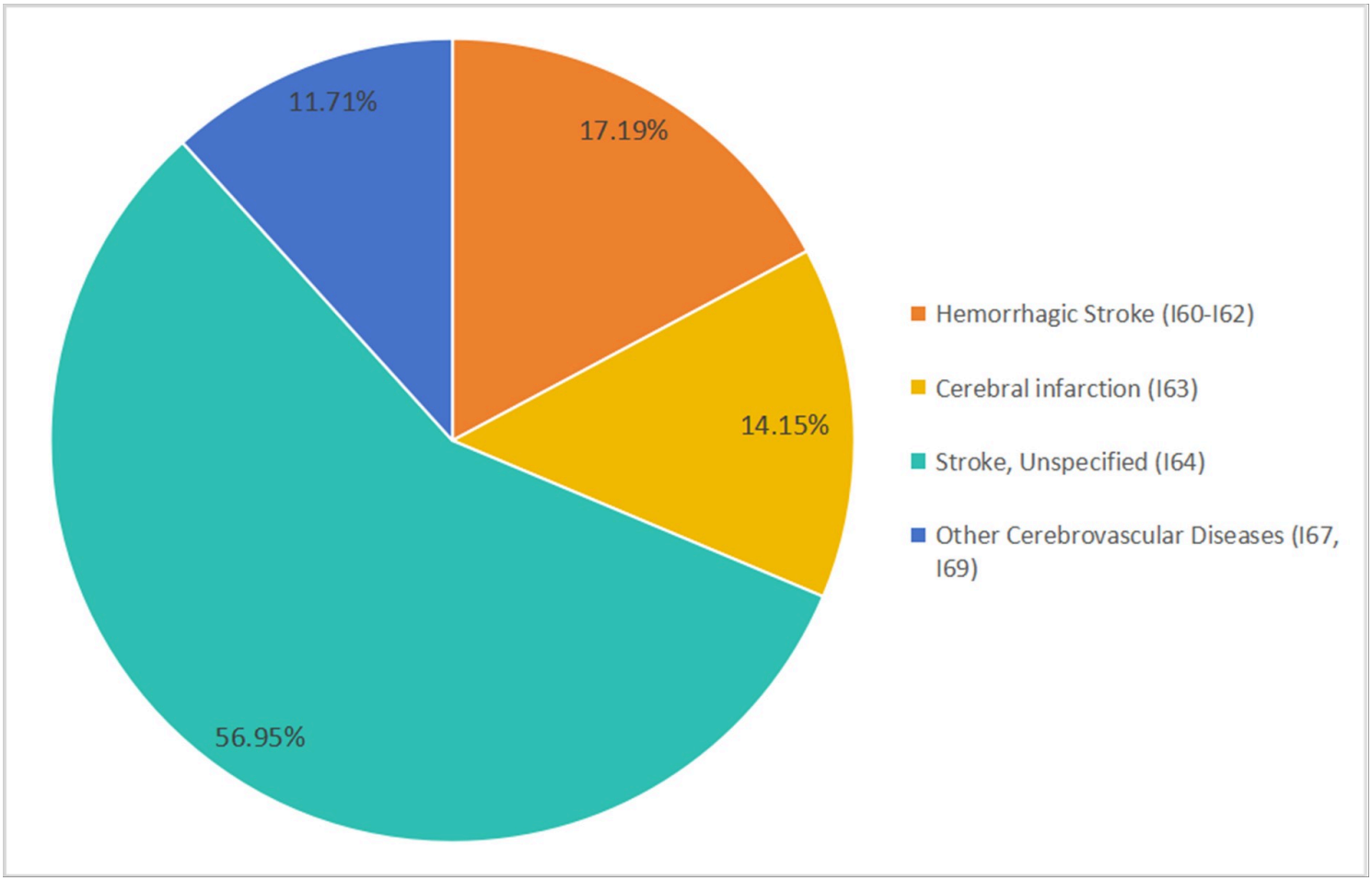


Figure 3

Etiologies of Cerebrovascular Deaths among Patients with Comorbid Bronchus and Lung Cancer

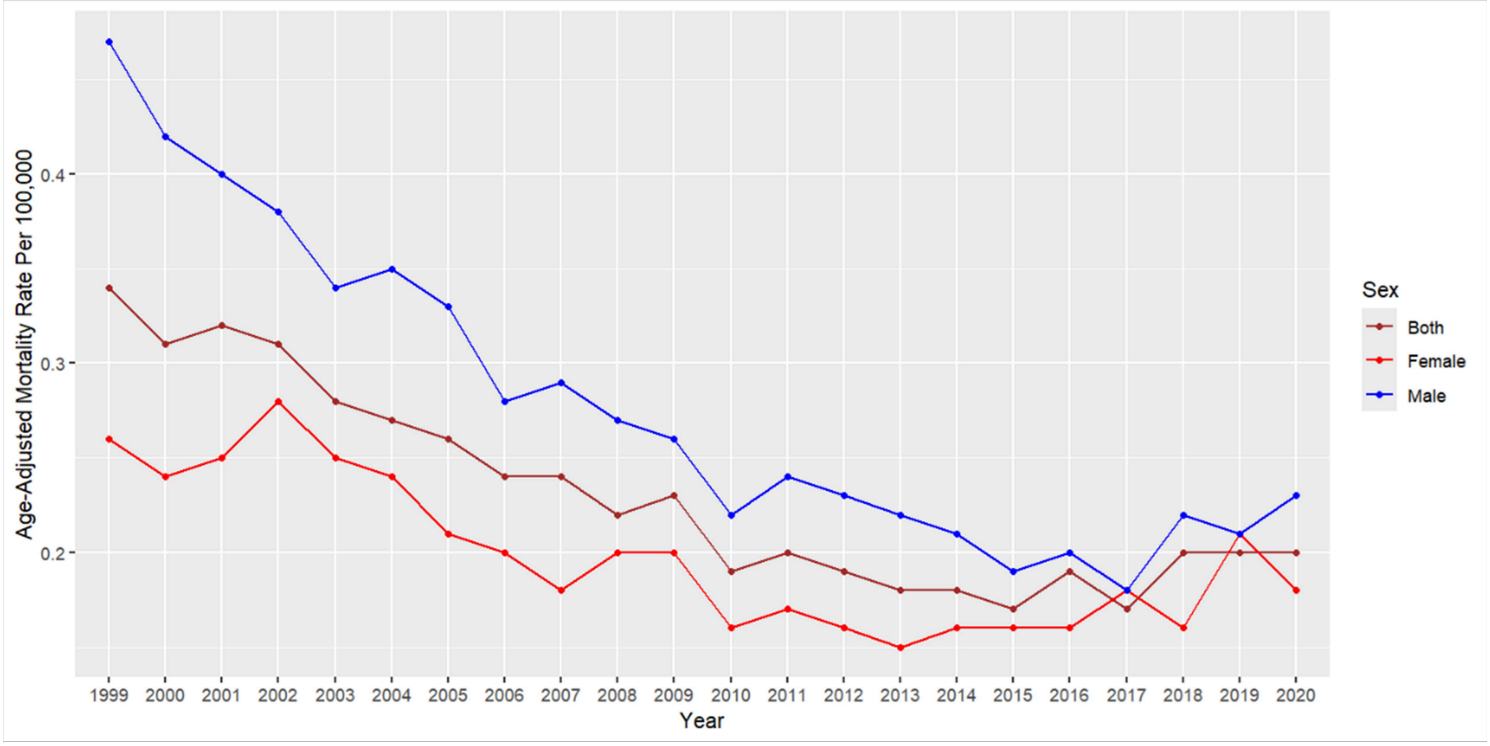


Figure 4

Trends in Age-Adjusted Mortality Rates of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by Gender

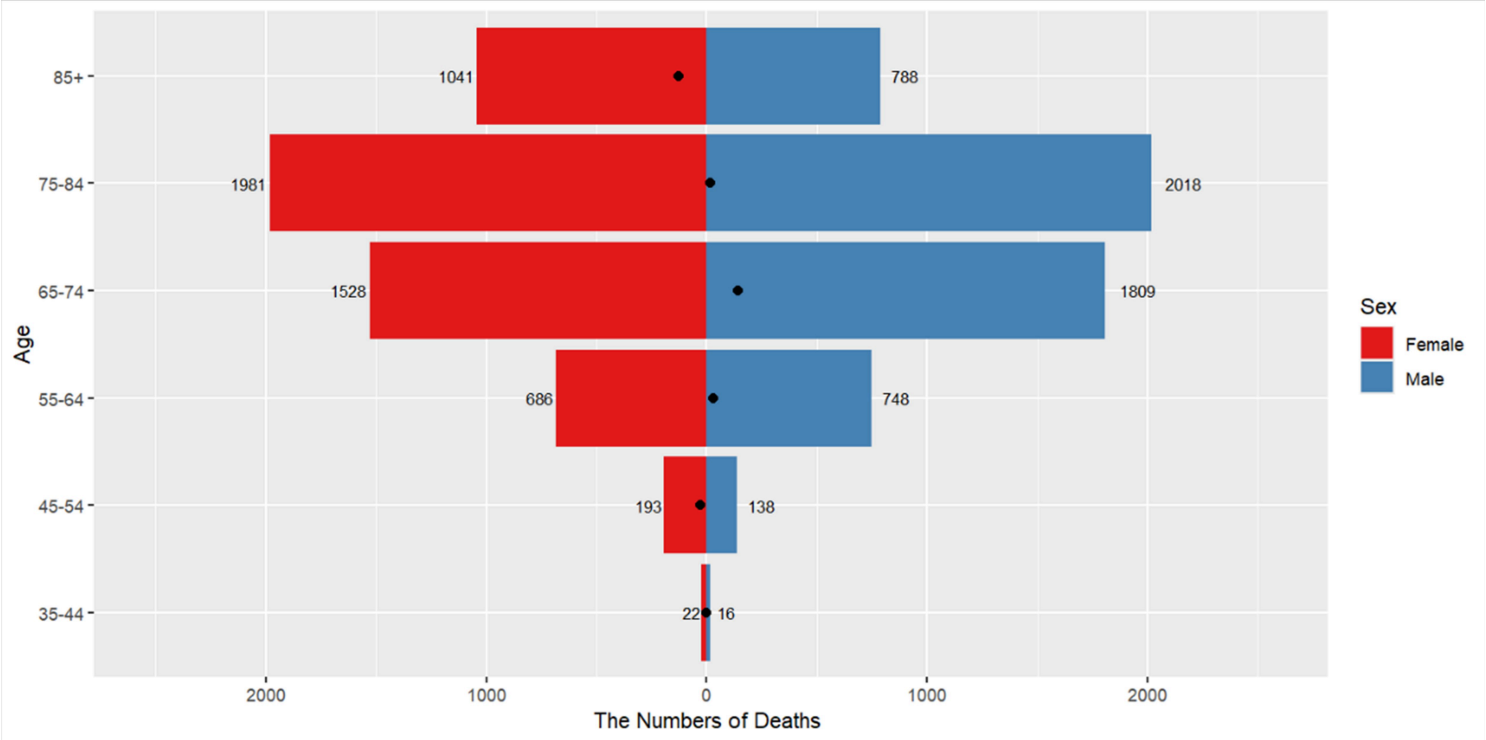


Figure 5

The numbers of deaths of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by Gender and Age Group

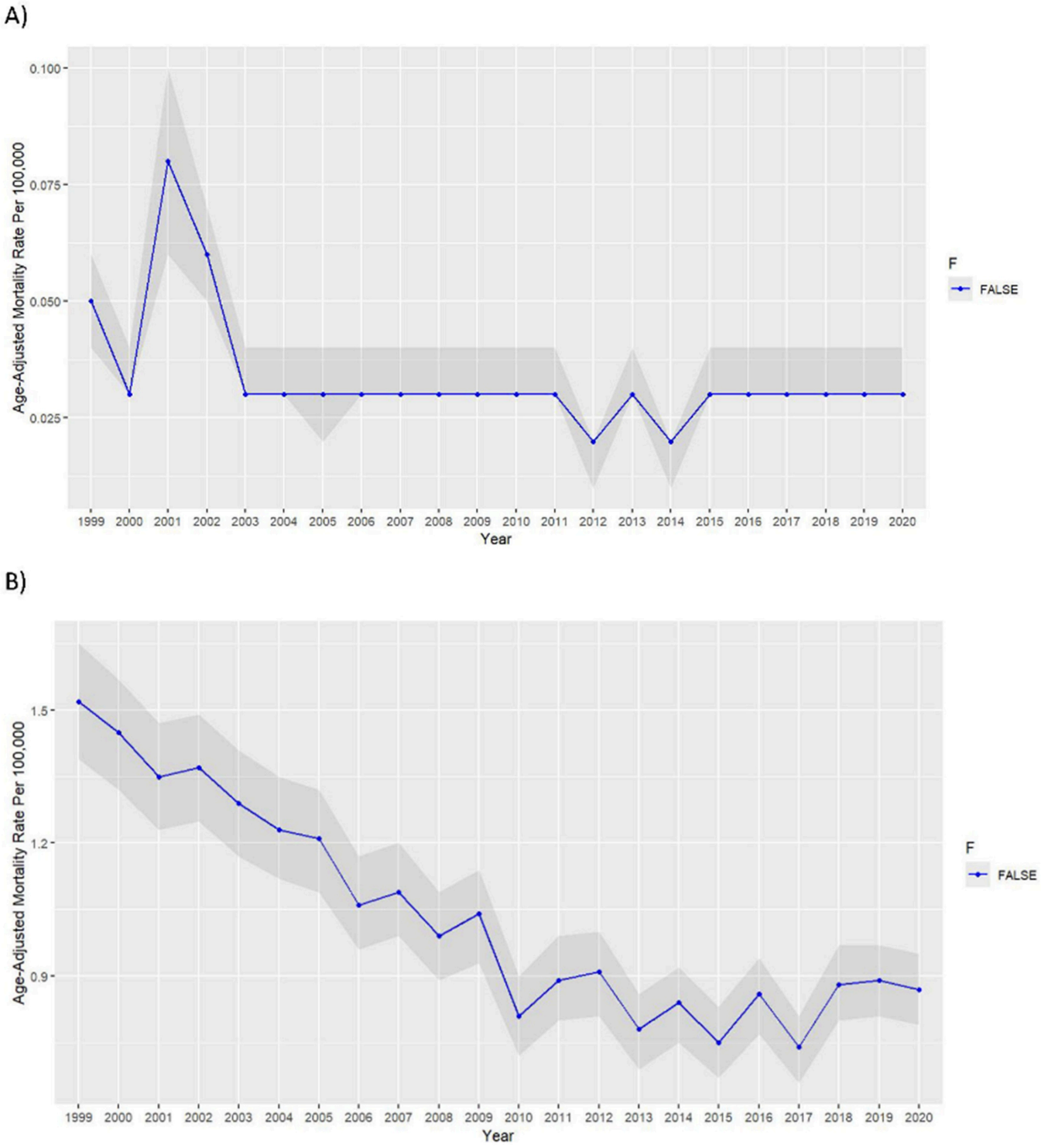


Figure 6

Trends in Age-Adjusted Mortality Rates of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by Age Group. A: < 65 years. B: ≥ 65 years.

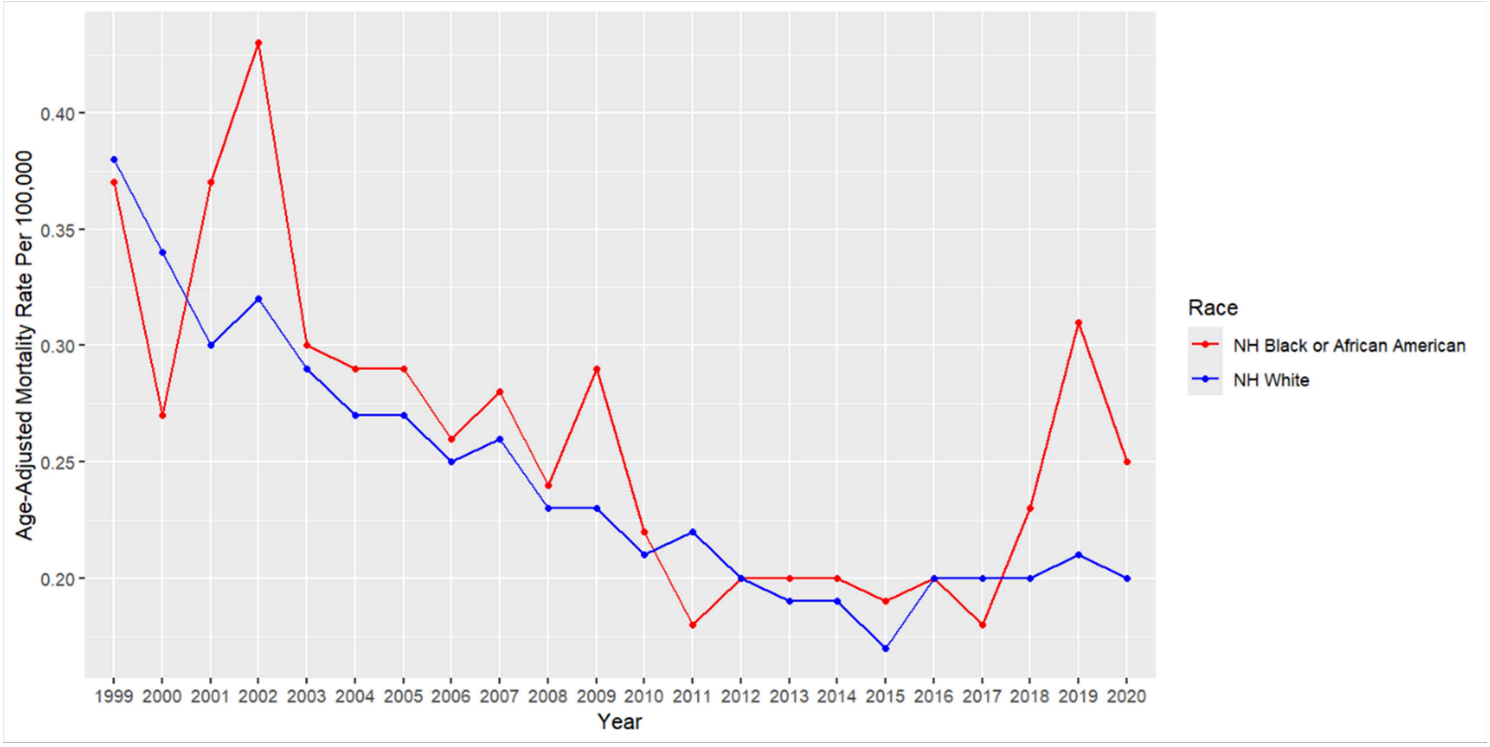


Figure 7

Trends in Age-Adjusted Mortality Rates of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by Races and Ethnicities.

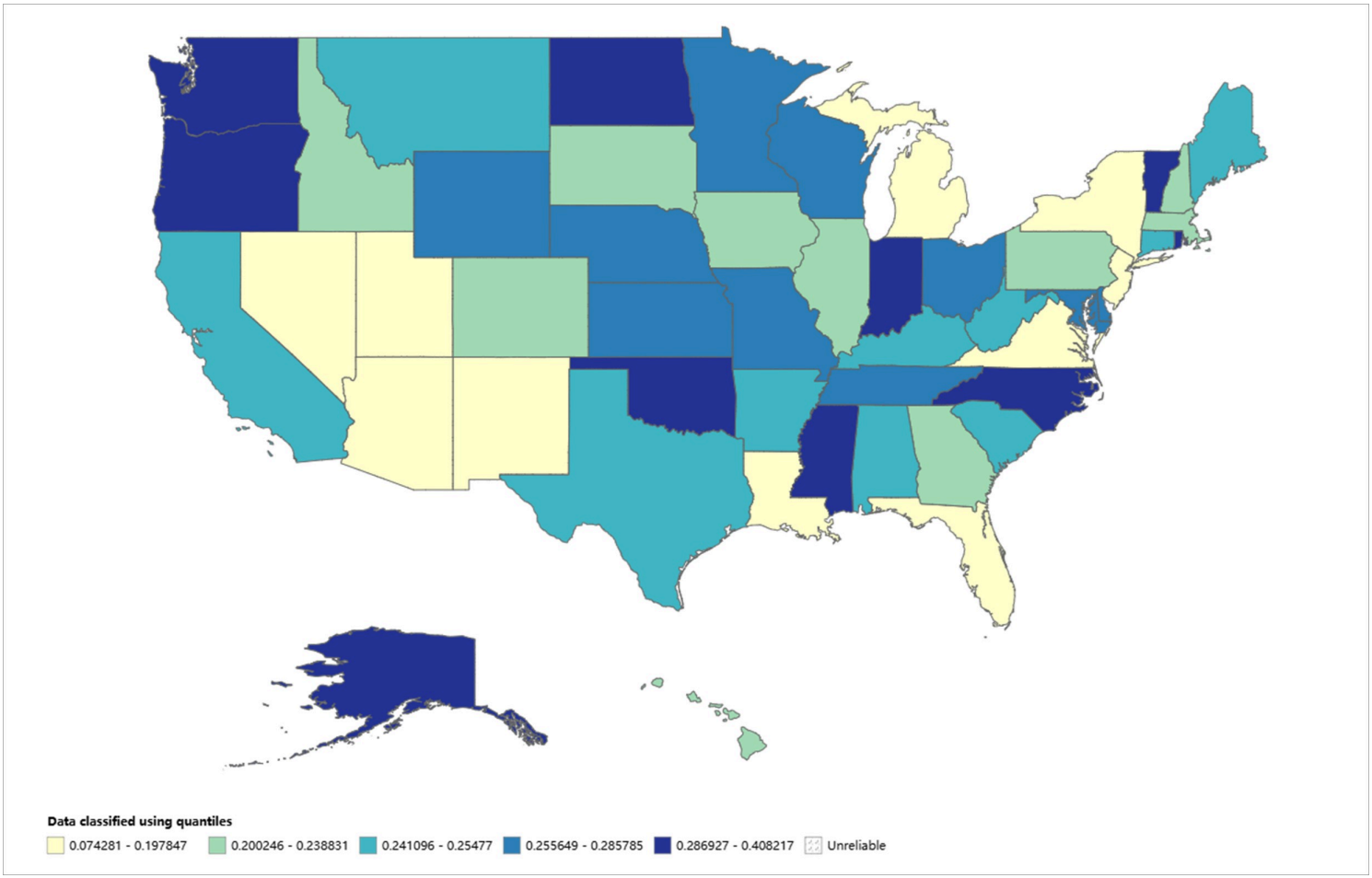


Figure 8

Age-Adjusted Mortality Rates of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by States

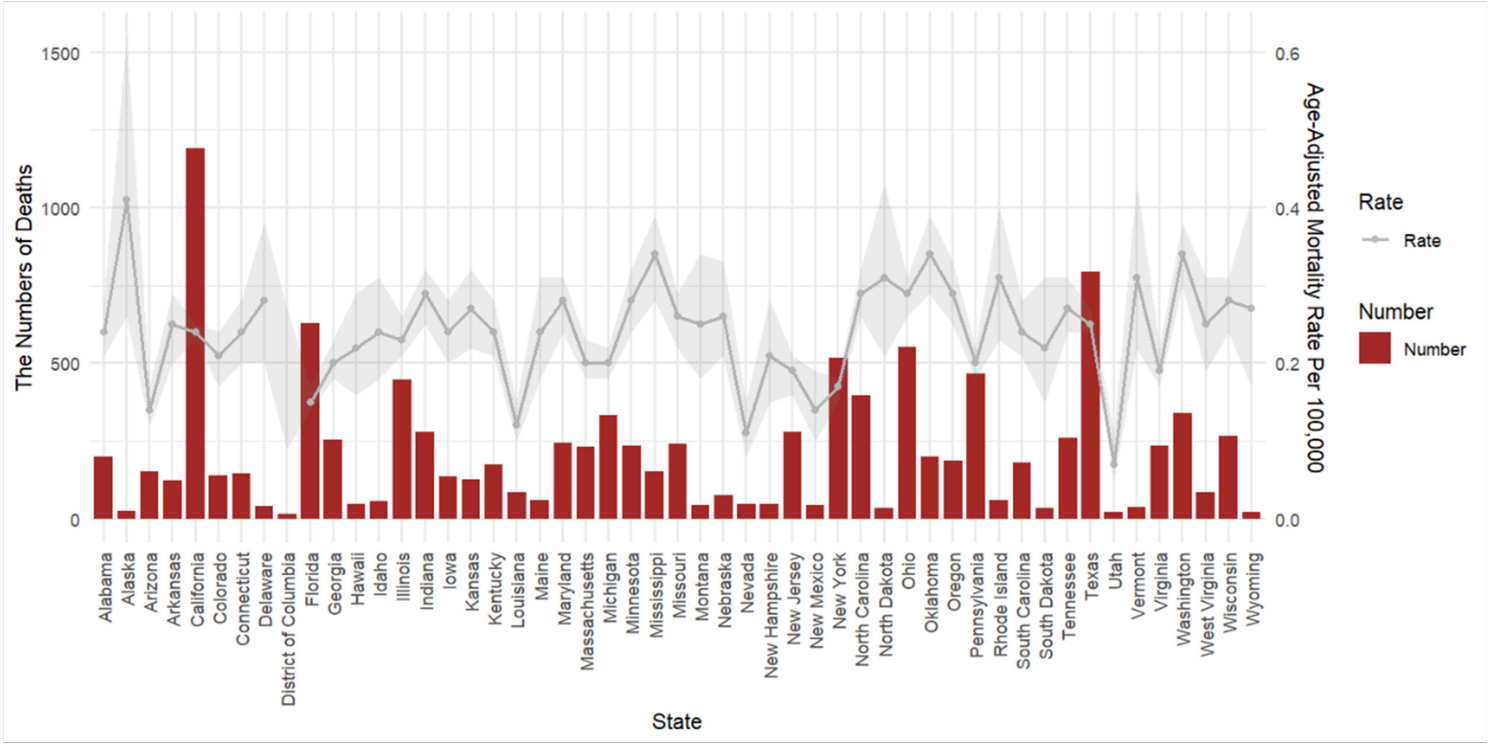


Figure 9

Age-Adjusted Mortality Rates and Deaths of Cerebrovascular Diseases among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by States

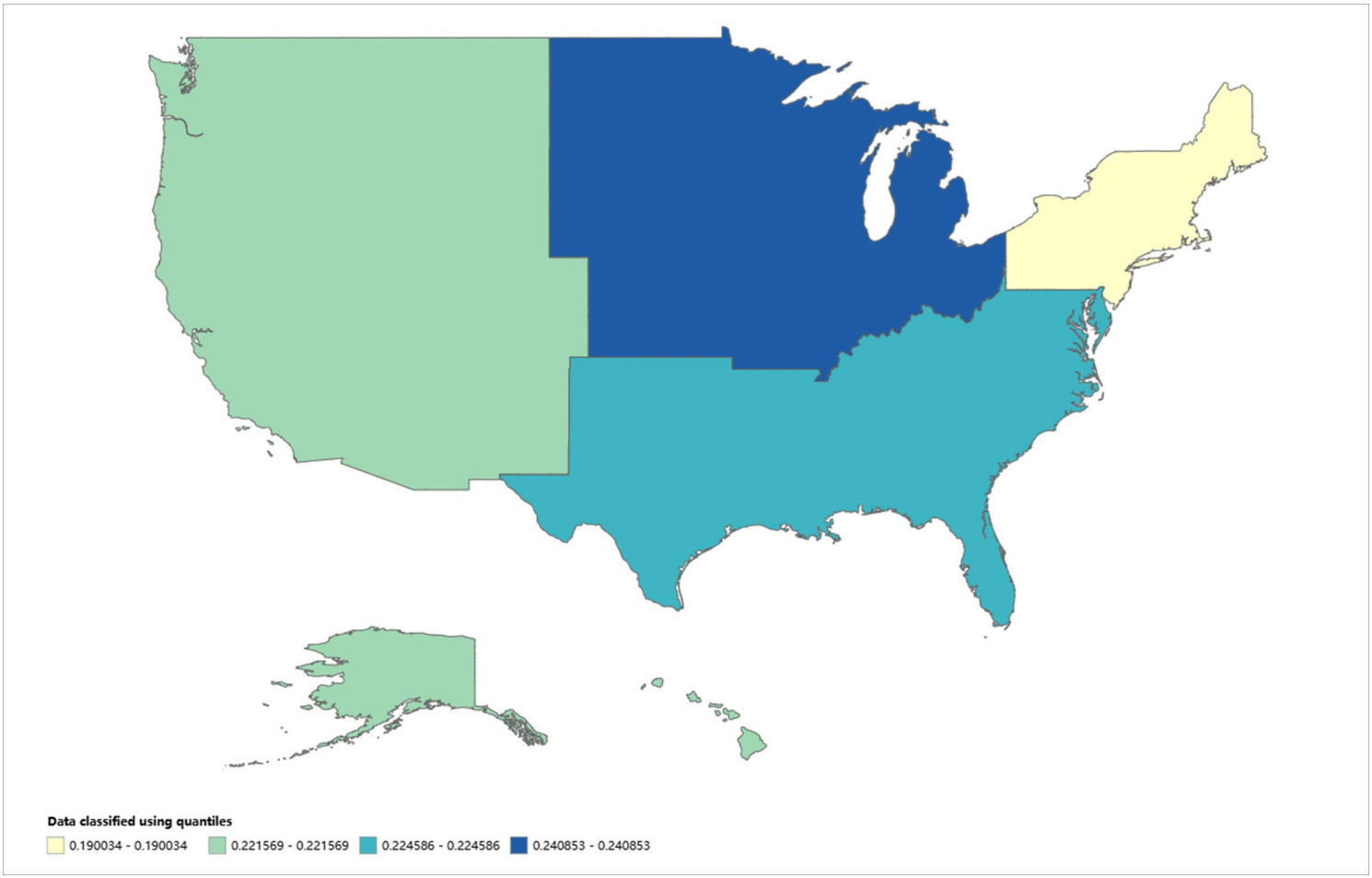


Figure 10

Age-Adjusted Mortality Rates of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by Census Region

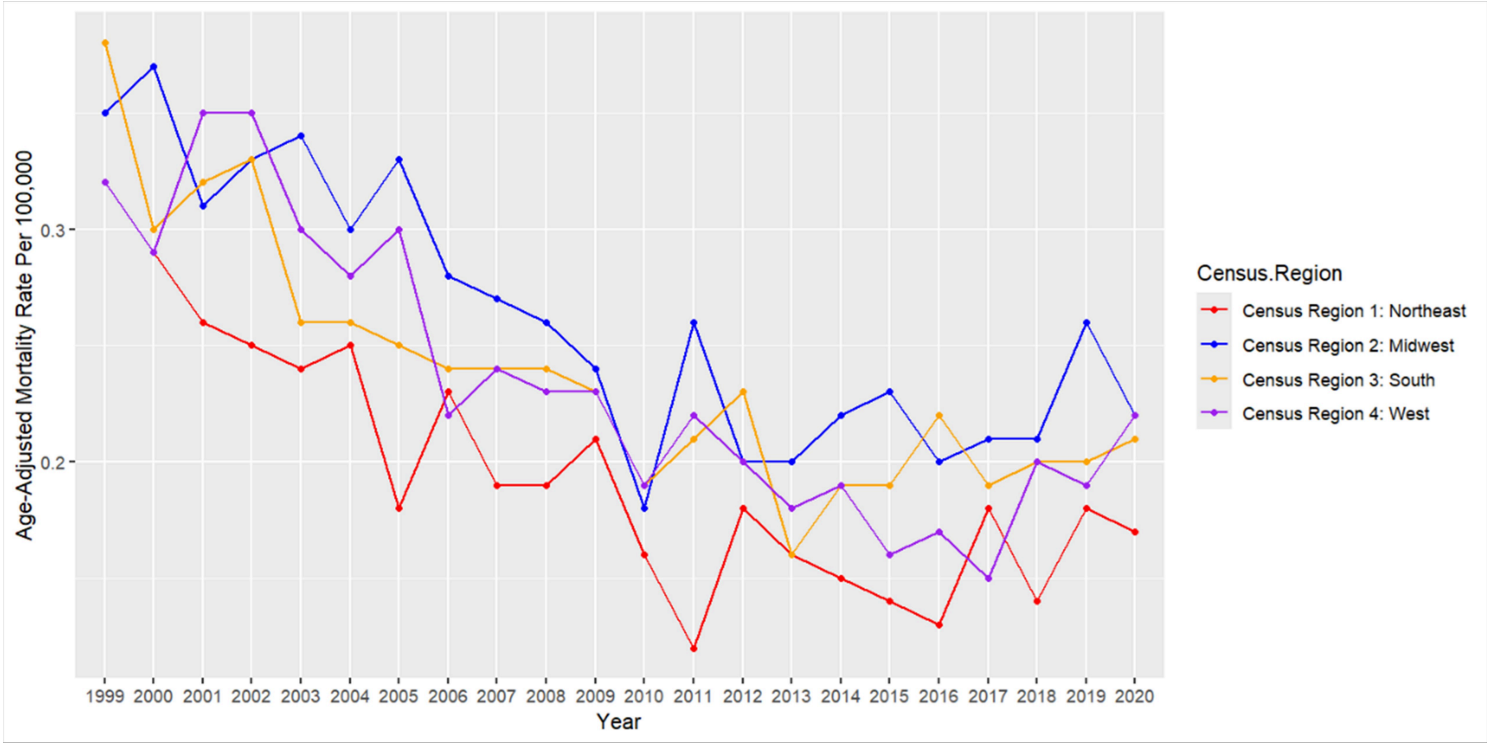


Figure 11

Trends in Age-Adjusted Mortality Rates of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by Census Region.

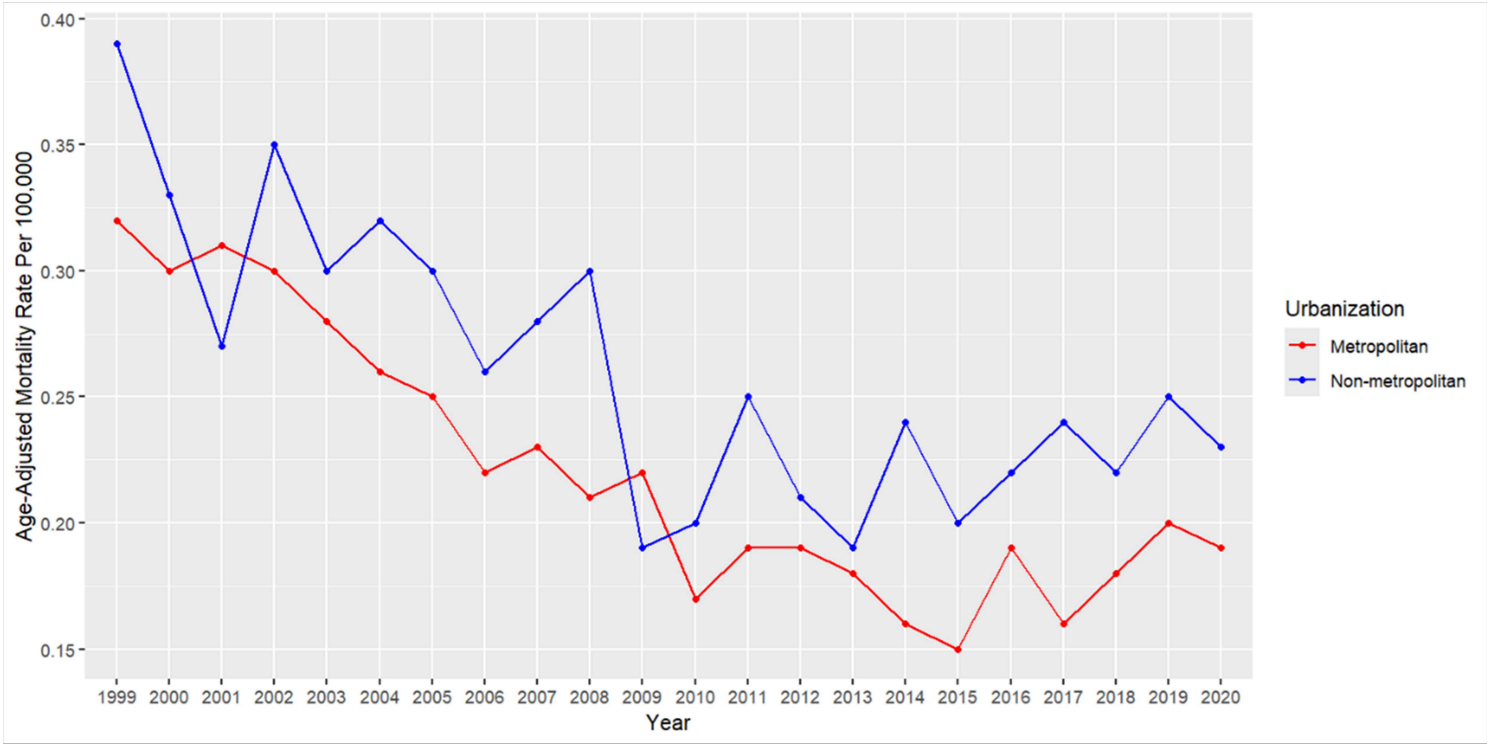


Figure 12

Trends in Age-Adjusted Mortality Rates of Cerebrovascular Death among Patients with Comorbid Bronchus and Lung Cancer between 1999 and 2020, Stratified by Urbanization.

Supplementary Files

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- Supplementarydata.docx