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Early View

Research letter

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Changing Trends in Age-Adjusted Pulmonary Fibrosis Mortality in the United States: a Joinpoint Regression Analysis

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To the Editor,

The prevalence of pulmonary fibrosis mortality has been shown to steadily rise from 1979 to 2010 in the United States and from 2001 to 2013 across the European Union.(1-5) However, it is unknown if similar trends are being seen in the U.S. in recent years. By evaluating the National Center for Health Statistics underlying cause-of-death (UCOD) database, the current study updates previous analyses and uses a Joinpoint regression model for determining changes in the trend of pulmonary fibrosis deaths in the United States, from 1999 to 2017.

Data were obtained from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research.(6) This program contains data on death certificates for U.S. residents. Each death certificate contains a single UCOD, up to twenty additional multiple contributing causes, and demographic data. The primary aim was to describe temporal trends in death rates attributable to pulmonary fibrosis (ICD-10 [international classification of diseases, 10th revision] code J84.1) as the UCOD.

Age-adjusted mortality rates were computed by the direct method to the projected year 2000 U.S. population. Trends in mortality rate from pulmonary fibrosis were calculated stratified by age, sex, race and geographic area of residence.

Among subjects in whom pulmonary fibrosis is the UCOD, the coexistence of comorbid conditions or contributing causes-of-death such as infections (e.g. possibly triggering acute exacerbations of pulmonary fibrosis) may influence the clinical course and survival of pulmonary fibrosis.(7) Therefore, to gain understanding on the potential burden of contributing causes-of-death on pulmonary fibrosis mortality secular trends, the yearly estimates of pneumonia and influenza (J09-J18), septicemia (A40-A41), heart failure (I50), ischemic heart disease (I20-I25), pulmonary heart disease (I26-I28), chronic obstructive pulmonary disease (J40-J44), diabetes (E10-E14), cerebrovascular disease (I60-I69) and lung cancer (C34) were

examined. These conditions were included since they are among the ten leading causes-of-death in the United States.(8)

The years in the study period at which change in mortality occurred and was statistically significantly different (i.e., increased or decreased trend) or remained stable, the annual percentage change, and the average annual percentage change from 1999 to 2017 was computed with the Joinpoint software (version 4.6). For each annual percentage change (APC), 95% confidence intervals (CI) were calculated based on a t-distribution. Allowing as few as two observed time points in the beginning, ending, and middle line segments (including the joinpoints), a maximum of two joinpoints were searched for using the Grid search algorithm and the Bayesian Information Criterion test and an overall alpha level of 0.05.(9)

From 1999-2017, pulmonary fibrosis was recorded as the UCOD in 230,900 decedents in the United States. During this time period, the age-adjusted mortality rate increased by an average of 0.7% per year. Overall, age-adjusted mortality rates were highest in men, in non-Hispanic whites and in the Midwestern United States. Also, crude rates increased with age (Table).

During the study period, two segmented trends were identified by the joinpoint analyses (1999-2004 and 2004-2017). The age-adjusted mortality rate increased from 1999 (32.9 per 1,000,000 population) until reaching a peak in 2004 (42.3 per 1,000,000 population; APC 4.0%). Subsequently, the age-adjusted mortality rate for pulmonary fibrosis decreased from 42.3 per 1,000,000 population in 2004 to 36.4 per 1,000,000 population in 2017, with an annual percent reduction of 0.6%. Age-adjusted mortality trends for pulmonary fibrosis as multiple cause-of-death (i.e., pulmonary fibrosis-related death) had a trajectory analogous to the trends of pulmonary fibrosis listed as the UCOD. One joinpoint was identified at 2003. From

1999-2003 the APC was 2.2% (95%CI 1.2%, 3.2%) and from 2003-2017 the APC was -0.8% (95%CI -0.9%, -0.7%); average APC -0.1% [95%CI -0.3%, 0.1%]).

APC trends in age-adjusted mortality from pulmonary fibrosis stratified by sex, race and geographic region were similar to overall trends, with significant increases or stable changed from 1999 that lasted 5 to 6 years before either leveling off or significantly decreasing (Table). Within subgroups defined by race and gender, while White men had an increase in the age-adjusted mortality average APC, Black women experienced a decreased trend from 1999-2017. Stable trends were observed among other gender/racial groups (Table, average APC). All U.S. geographic regions had stable trends except the Northeastern United States that experienced significant increases in mortality over the study period. A mortality reduction was observed in decedents under age 65, yet significant increases in mortality rates were observed among adults ≥85 years-old.

Pneumonia and influenza infection were the most prevalent contributing causes-of-death associated with pulmonary fibrosis. Notably, during the study period, compared to June through November, the average number of deaths among subjects with pulmonary fibrosis was higher from December through May—influenza season (951; 95%CI 928, 975 vs. 1,074; 95%CI 1,045, 1,102). From 1999-2017, stable average annual percentage trends were observed in all but two (pulmonary heart disease, average annual increase of 1.3%; 95%CI 0.5%, 2.1%; cerebrovascular disease, average annual decrease of -2.0%; 95%CI -2.8%, -1.1%) of the nine contributing causes-of-death (Table).

Prior studies have indicated a rise in pulmonary fibrosis related mortality in the U.S. since the 1970's.(2-4) Although the increase in the age-adjusted mortality rate of 4% points per year during 1999-2004 and in pulmonary fibrosis deaths in older adults notably out-

numbering younger age groups supports prior epidemiological findings, the age-adjusted mortality has declined 0.6% annually from 2004-2017. The observed recent slight decline in overall death rates may be attributed to several important findings. First, it is possible that improved recognition and awareness of non-IPF interstitial lung diseases has been increasing. Second, the decrease in age-adjusted mortality in pulmonary fibrosis concurred with significant downward trends in pneumonia and influenza mortality rates over the same interval (decreasing 3.7% per year from 2004-2017). These estimates of averted disease burden may be attributed to improvements in pneumococcal and seasonal influenza vaccination or targeted prophylaxis in the nation.(10) Similarly, the decrease in ischemic heart disease (2004-2017) and cerebrovascular complications (1999-2017) attributed to improvements in control of hypertension, hyperlipidemia, and smoking cessation may have also contributed to the decreasing trend in pulmonary fibrosis mortality since 2004.(11, 12) Lastly, it is unclear if enhanced disease awareness, access to specialized care and antifibrotic therapy, improvement in comorbid disease management, supportive care and lung transplant survival have contributed to the decelerating mortality rates in recent years.

This study is limited by potential misclassification of death certificate codes which may influence the interpretation of our findings. Notwithstanding the reported inaccuracies in death certificate data, the overall declining trends from 2004-2017 seem unlikely to be solely explained by yearly coding errors and underreporting.

The 2004 joinpoint marks a new trend (2004-2017) that differs significantly from 1999-2004. It is possible that the 2004 joinpoint represents differences in the quality of reporting vital statistics data compared to other years. However, sensitivity analysis showed that if a preceding or following year was chosen, the trend lines would be unchanged (e.g., the average APC for 2003-2017 and 2005-2017 was -0.5% [95%CI -0.9%, -0.1%] and -0.7% [95%CI -0.9%, -0.4%], respectively). Lastly, the trends in pulmonary fibrosis mortality may be due to variation in influenza rates by season, rather than reflecting variation in the rate of the true incidence of mortality from pulmonary fibrosis.

Despite the decline in death rates from 2004-2017, the positive average APC of overall age-adjusted mortality rates from 1999-2017 highlights remaining challenges in addressing the burden of pulmonary fibrosis in the United States.

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Table. Age-adjusted and trends in annual percent change in mortality rates due to pulmonary fibrosis as the underlying cause of death by demographic characteristic in the United States, 1999–2017.

	Pulmonary Fibrosis Mortality		Annual Percent Change, % (95% CI) [&]		Average Annual Percent Change, % (95% CI) [#]
Variable	**No. of Deaths (%)**	**Age-Adjusted Rate per 1,000,000 (95% CI)**	**Trend 1**	**Trend 2**	**1999-2017**
Overall	230,900 (100)	37.91 (37.7, 38.1)	1999-2004 4.0 (2.3, 5.8)	2004-2017 -0.6 (-1.0, -0.3)	0.7 (0.2, 1.1)
Sex					
Men	123,387 (53.4)	49.65 (49.4, 49.9)	1999-2005 3.0 (1.1, 5.0)	2005-2017 -0.5 (-1.1, 0.1)	0.6 (0.0, 1.3)
Women	107,513 (46.6)	29.77 (29.6, 29.9)	1999-2004 4.1 (2.1, 6.2)	2004-2017 -1.1 (-1.5, -0.7)	0.3 (-0.2, 0.9)
Race					
White, Non-Hispanic	194,633 (84.2)	39.4 (39.2, 39.6)	1999-2004 4.2 (2.5, 6.0)	2004-2017 -0.4 (-0.7, 0)	0.9 (0.4, 1.4)
Men	105,659 (45.7)	52.2 (51.9, 52.5)	1999-2004 3.7 (2.0, 5.5)	2004-2017 -0.1 (-0.5, 0.2)	0.9 (0.4, 1.4)
Women	88,974 (38.5)	30.4 (30.2, 30.6)	1999-2004	1999-2017	0.6 (-0.1, 1.2)

			4.5 (2.4, 6.8)	-0.9 (-1.4, -0.5)	
Black, Non-Hispanic	11,685 (5.1)	20.9 (20.5, 21.3)	1999-2005 1.8 (-1.4, 5.1)	2005-2017 -2.3 (-3.3, -1.2)	-0.9 (-2.1, 0.2)
Men	5,388 (2.3)	25.1 (24.4, 25.8)	1999-2005 3.5 (-0.2, 7.4)	2005-2017 -2.5 (-3.6, -1.3)	-0.5 (-1.8, 0.8)
Women	6,297 (2.7)	18.8 (18.3, 19.2)	-	-	-1.6 (-2.2, -0.9)
Hispanic	17,430 (7.5)	42.9 (42.3, 43.6)	-	-	-0.5 (-1.1, 0.1)
Men	8,624 (3.7)	50.2 (49.1, 51.4)	-	-	-0.3 (-0.9, 0.4)
Women	8,806 (3.8)	37.7 (36.9, 38.5)	1999-2005 3.2 (-0.7, 7.2)	2005-2017 -1.7 (-2.7, -0.6)	-0.1 (-1.4, 1.3)
Census Region					
Northeast	38,839 (16.8)	31.8 (31.5, 32.1)	1999-2005 4.2 (1.9, 6.5)	2005-2017 -0.2 (-0.9, -0.7)	1.2 (0.4, 2.0)
Midwest	57,746 (25.0)	41.41 (41.1, 41.7)	1999-2005 4.1 (1.9, 6.4)	2005-2017 -0.9 (-1.5, -0.2)	0.8 (0.0, 1.5)
South	86,705 (37.5)	39.47 (39.2, 39.7)	1999-2004 3.2 (1.3, 5.1)	2004-2017 -0.4 (-0.8, 0.0)	0.6 (0.0, 1.1)
West	47,610 (20.6)	37.17 (36.8, 37.5)	1999-2004 2.7 (1.0, 4.3)	2004-2017 -1.6 (-2.1, -1.1)	-0.2 (-0.8, 0.4)
Age-Groups*					
35-44	1,607 (0.7)	1.9 (1.90, 2.09)	-	-	-3.5 (-4.9, -2.2)
45-54	6,655 (2.9)	8.3 (8.07, 8.47)	-	-	-2.5 (-3.2, -1.8)
55-64	20,291 (8.8)	31.7 (31.3, 32.2)	-	-	-1.8 (-2.3, -1.4)
65-74	51,776 (22.4)	124.5 (123.4, 125.5)	1999-2004 3.1 (1.0, 5.1)	2004-2017 -1.9 (-2.3, -1.5)	-0.6 (-1.1, 0.0)
75-84	87,318 (37.8)	348.3 (346.0, 350.6)	1999-2006 3.6 (1.9, 5.4)	2006-2017 -0.6 (-1.4, 0.2)	1.0 (0.2, 1.8)
≥85	62,443 (27.1)	626.3 (621.4, 631.2)	1999-2005 4.6 (2.8, 6.4)	2005-2017 0.7 (0.3, 1.2)	2.0 (1.4, 2.6)
Contributing Causes of Death+					

Pneumonia and influenza	29,162 (12.6)	4.8 (4.7, 4.8)	1999-2004 6.9 (-0.6, 15)	2004-2017 -3.7 (-4.3, -3)	-1.2 (-3.6, 1.2)
Ischemic heart disease	25,871 (11.2)	4.3 (4.2, 4.3)	1999-2007 1.9 (-0.8, 4.7)	2007-2017 -2.8 (-4.8, -0.8)	-0.7 (-2.2, 0.8)
Heart failure	24,987 (10.8)	4.1 (4.0, 4.1)	-	-	0.5 (-0.3, 1.3)
COPD	23,280 (10.1)	3.8 (3.8, 3.9)	-	-	1.1 (-0.4, 2.6)
Diabetes	16,030 (6.9)	2.6 (2.6, 2.7)	-	-	0.5 (-0.3, 1.3)
Pulmonary heart disease	15,550 (6.7)	2.5 (2.5, 2.6)	-	-	1.3 (0.5, 2.1)
Septicemia	5,559 (2.4)	0.9 (0.9, 0.9)	1999-2008 5.0 (2.6, 7.4)	2008-2017 -0.3 (-2.0, 1.5)	2.6 (-0.1, 5.4)
Cerebrovascular disease	3,734 (1.6)	0.6 (0.6, 0.6)	-	-	-2.0 (-2.8, -1.1)
Lung cancer	1,792 (0.8)	0.3 (0.3, 0.3)	-	-	-1.1 (-2.4, 0.3)

CI = confidence interval; COPD = chronic obstructive pulmonary disease.

The annual percent change or average annual percent change is significant if confidence intervals do not cross zero (P <0.05).

[&] Years included are linear segments that have different slopes and are connected at the time point where a change in trend occurs (referred to as joinpoint). For example, for the overall variable one joinpoint was identified at 2004 and two-line segments or time periods (trend 1: 1999-2004, and trend 2: 2004-2017). If data not shown, it is because there are not joinpoints and regression analysis of all time points each year shows no meaningful departures from a linear trend.

[#] The average annual percent change is a weighted average of the annual percent changes, with the weights equal to the length of the joinpoint segments.

* Unable to calculate age-adjusted rates for age groups. These numbers represent crude rates and confidence intervals.

[+] The National Center for Health Statistics multiple cause-of-death data include conditions that are important contributors to death (i.e., the disease or injury that contributed to the fatal outcome) but were not reported as the underlying cause (i.e., the disease or injury that initiated the chain of morbid events leading directly to death).