Incidence and Mortality Trends of Atrial Fibrillation/ Atrial Flutter in the United States 1990 to 2017

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Atrial fibrillation (AF) and flutter (AFL) are the most common clinically significant arrhythmias in older adults with an increasing disease burden due to an aging population. However, up-to-date trends in disease burden and regional variation remain unknown. In an observational study utilizing the Global Burden of Disease (GBD) database, age-standardized mortality and incidence rates for AF overall and for each state in the United States (US) from 1990 to 2017 were determined. All analyses were stratified by gender. The relative change in age-standardized incidence rate (ASIR) and age-standardized death rate (ASDR) over the observation period were determined. Trends were analyzed using Joinpoint regression analysis. The mean ASIR per 100,000 population for men was 92 (+/-8) and for women was 62 (+/-5) in the US in 2017. The mean ASDR per 100,000 population for men was 5.8 (+/-0.3) and for women was 4.4 (+/-0.4). There were progressive increases in ASIR and ASDR in all but 1 state. The states with the greatest percentage change in incidence were New Hampshire (+13.5%) and Idaho (+16.0%) for men and women, respectively. The greatest change regarding mortality was seen in Mississippi (+26.3%) for men and Oregon (+53.8%) for women. In conclusion these findings provide updated evidence of increasing AF and/or AFL incidence and mortality on a national and regional level in the US, with women experiencing greater increases in incidence and mortality rates. This study demonstrates that the public health burden related to AF in the United States is progressively worsening but disproportionately across states and among women. **(Am J Cardiol 2021;148:78−83)**

Atrial fibrillation (AF) is a heart rhythm disorder characterized by rapid disorganized electrical activity originating in the atrium which is associated with increased morbidity and mortality.[1,2] The likelihood of developing AF is complex and influenced by biological factors, environmental factors, genetics, epigenetics, and social determinants.[3-8] Studies have shown that the prevalence and incidence of AF have been increasing in North America and Europe from the 1970s to the beginning of the 21st century.[9] It is estimated that the prevalence of AF ranges from 2.7 to 6.1 million people in the United States (US) and this number is expected to increase to 12.1 million in 2030.[10] The upsurge in AF is straining the US healthcare system. The net incremental cost of AF was shown to be $8705 per patient and the national incremental cost was estimated to range between $6 and $26 billion based on prevalence data from 2004 to 2006.[11,12] Despite the growing public health challenge posed by AF, detailed up-to-date trends on the epidemiology of AF on a national and state level in the US remain limited. An accurate understanding of the current epidemiology of AF is crucial to the appropriate allocation of resources and therapies aimed at reducing the clinical and socioeconomic impact of the disease.

The objectives of this study were to determine current mortality and incidence rates for atrial fibrillation (AF) and/or flutter (AFL) overall and for each state in the US across a defined time period using the Global Burden of Disease database.

Methods

For this observational analysis of AF incidence and mortality, data collected for the Global Burden of Disease (GBD) study was utilized. The GBD methodology has been published previously and reports global results for health

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[1]Tweet: "Atrial Fibrillation/Flutter disease related incidence and mortality on rise across the United States."

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loss related to specific diseases: deaths and death rates, years of life lost due to premature mortality, prevalence and incidence. The study data are estimated annually and each round of results are internally consistent (i.e., cause-specific mortality estimates match all-cause mortality estimates). The data are made available publicly (http://ghdx.healthdata.org/gbd-results-tool).

In the GBD methodology, AF was defined as a diagnosis of AF or atrial flutter by ECG finding. GBD study attributes each death to a single underlying cause that began the series of events leading to death, in accordance with International Classification of Diseases (ICD)-10 principles. To estimate incidence and mortality of AF and/or flutter, GBD used a systematic review strategy to identify claims data for both in-patient and out-patient visits in the US. To address changes in coding practices of AF, GBD uses an approach which combines disease model (i.e., 'DisMod-MR') tool and cause of death ensemble model (i.e., 'CODEm') to estimate deaths from AF and AFL. These tools are used to pool disparate information on incidence, prevalence, and mortality for varying age groupings and from varying age groupings from data sources that use varying methods. This combined approach allows for more accurate estimate of the number of deaths attributable to AF and/or flutter. We extracted, incidence and mortality estimates for AF between 1990 and 2017 across 51 US states were extracted from the online data repository.

Age-standardized incidence and mortality data per 100,000 population categorized by state, gender, and year were extracted from the GBD Results Tool web-based system. For all age-standardized rates, GBD uses a standard population calculated as the non-weighted average across all countries of the percentage of the population in each 5-year age group for the years 2010 to 2035 from the United Nations Population Division's World Population Prospects (2012 revision) (GBD 2012, United Nations Department of Economics and Social Affairs Population Division). We computed relative change over the observation period by computing the difference between the start and end age-standardized incidence rates (ASIRs) and age-standardized death rates (ASDRs) for each gender in each country.

Trends were assessed using Joinpoint software (Version 4.5.0.1) provided by the United States National Cancer Institute Surveillance Research Program (28). Joinpoint regression analysis assesses changes in linear slope for mortality trends over time, as described previously (28). Briefly, it assesses the overall trends in mortality, initially with no Joinpoints, and tests for significant changes in the model with sequential addition of points where there is significant change in the slope of the line. The model also computes an estimated annual percentage change (EAPC) for each trend by fitting a regression line to the natural logarithm of the rates. The log-linear transformation allows us to approximation of normal distributions and by estimating the annual percentage change, it was possible to assess change in mortality trend at a constant percent per year. EAPCs are reported with 95% Confidence Intervals (CIs). This method of statistical analysis has been previously utilized by Hartley et.al[13]

Results

There were a total of 51 states or territories in the US each with 28 years of available data for analysis. Gender-specific, age-standardized incidence, and death per 100,000 population from Atrial fibrillation and/or Atrial flutter across 51 US states between 1990 and 2017 are shown in Supplementary Figures 1 and 2. There were no missing data elements. The mean 2017 incidence rate per 100,000 population for AF for men was 92 (+/-8) and the mean 2017 ASIR for women was 62 (+/-5). For men, the greatest incidence rates in 2017 were observed in Massachusetts (105 per 100,000 population), New Hampshire (105 per 100,000 population), Maine (104 per 100,000 population) and Connecticut (104 per 100,000 population). For women, the greatest incidence rates were observed in Ohio (69 per 100,000 population), West Virginia (69 per 100,000 population), Louisiana (68 per 100,000 population), and Delaware (68 per 100,000 population). The 2017 incidence rates for each state are represented graphically in Table 1A.

The mean 2017 AF ASDR per 100,000 population for men was 5.8 (+/-0.3) and the mean 2017 death rate for women was 4.4 (+/-0.4). For men, the greatest death rates were observed in New Hampshire (6.6 per 100,000 population), Maine (6.5 per 100,000 population), Montana (6.4 per 100,000 population), and Alaska (6.3 per 100,000 population). For women, the greatest death rates were observed in Oregon .7 per 100,000 population), Alaska (5.5 per 100,000 population), Montana (5.4 per 100,000 population), and Utah (5.1 per 100,000 population). The 2017 death rates for each state are represented graphically in Table 1B.

Across the 28-year study period, there was, overall, an increasing trend in the incidence of AF across the majority of US states. Among men, all states except District of Columbia (-1.7% change in men and a -1.9% in women) show increase in the incidence rate of AF/andAFL between 1990 and 2017. The greatest incidence rates for men in 2017 were clustered in the New England region. However, the states that showed the greatest percentage change in incidence for men were scattered throughout the Northeast, West coast, and South, with the top 5 being New Hampshire (+13.5%), California (+13.3%), Massachusetts (+13.0%), and Maine (+12.4%). Among females, all states except District of Columbia show an increase in the incidence rate of AF/AFL between 1990 to 2017. For women, the states with the greatest incidence rates and percentage change in incidence did not appear geographically clustered; with Idaho (+16.0%), California (+15.5%), Maine (+15.3%), and Washington (+14.6%) showing the highest increase. A summary of overall incidence rate percentage changes for both men and women are shown in Figure 1.

Apart from Alaska, where there was overall decrease in death rate in men (-8.4%) and in women (-2.9%), there were overall increasing death rates in both men and women in the majority of states. The greatest percentage increases were, for men: Mississippi (+26.3%), Oklahoma (+26.3%), Idaho (+24.9%), and Kentucky (+23.4%); and for women: Oregon (+53.8%), Montana (+47.2%), Utah (+44.8%), and Nebraska (+40.0%). A summary of overall mortality rate percentage changes for both men and women are shown in Figure 2.

Table 1A
Age-standardized incidence rates from 1990 and 2017 organized by gender (per 100,000 population)

Age standardized incidence rates 1990 and 2017				
	Male		Female	
State	1990	2017	1990	2017
Alabama	82.26	88.91	55.34	59.61
Alaska	82.5	89.49	54.48	58.46
Arizona	85.81	94.75	57.15	64.6
Arkansas	79.94	84.9	54.33	57.26
California	79.04	89.35	52.2	60.1
Colorado	80.25	88.16	52.27	57.43
Connecticut	92.56	103.62	59.02	66.78
Delaware	91.32	102.24	59.71	67.79
District of Columbia	69.91	68.42	49.21	47.7
Florida	89.36	100.25	59.71	67.27
Georgia	83.46	90.55	55.44	60.56
Hawaii	81.06	87.76	50.53	52.34
Idaho	82.79	92.44	56.36	65.24
Illinois	83.34	90.78	55.89	61.54
Indiana	86.8	95.51	58.06	64.73
Iowa	80.52	85.37	52.9	54.66
Kansas	83.39	91.2	54.89	60.16
Kentucky	87.72	96.39	59.99	67.44
Louisiana	86.24	95.62	59.7	68.1
Maine	92.79	104.24	58.6	66.39
Maryland	87.02	96.12	56.56	63.71
Massachusetts	92.81	104.92	57.79	66.63
Michigan	85.8	95.06	57.47	64.78
Minnesota	82.97	90.59	52.32	55.24
Mississippi	77.55	80.64	52.88	55.89
Missouri	87	96.15	59.61	67.76
Montana	84.42	94.14	55.87	62.86
Nebraska	83.98	92.45	54.73	60.5
Nevada	81.16	86.92	54.85	59.5
New Hampshire	92.26	104.76	58.12	66.27
New Jersey	88.87	99.04	57.19	63.71
New Mexico	73.15	75.06	49.08	50.12
New York	91.09	101.77	59.09	66.42
North Carolina	85.42	93.84	56.1	61.65
North Dakota	76.54	78.51	54.36	60.05
Ohio	89.7	99.76	60.71	68.92
Oklahoma	82.83	90.19	57.22	63.94
Oregon	84.55	93.4	55.59	63.06
Pennsylvania	90.94	100.79	59.36	66.2
Rhode Island	87.4	95.79	56.77	62.53
South Carolina	87.13	95.68	55.95	61.19
South Dakota	81.57	88.48	55.62	61.88
Tennessee	83.56	91.06	56.31	62.11
Texas	83.32	91.38	56.64	64.45
Utah	77.18	82	52.85	56.33
Vermont	87.5	97.25	56.26	62.93
Virginia	84.16	92.07	56.59	61.62
Washington	86.06	96.37	56.18	64.14
West Virginia	86.57	94.53	60.92	68.56
Wisconsin	85.84	94	55.76	61.67
Wyoming	75.52	78.53	50.87	52.39

Table 1B
Age-standardized death rates from 1990 and 2017 organized by gender (per 100,000 population)

Age Standardized Death Rates 1990 and 2017				
	Male		Female	
State	1990	2017	1990	2017
Alabama	4.7	5.66	3.27	4.26
Alaska	7.04	6.32	5.76	5.44
Arizona	4.99	5.67	3.51	4.17
Arkansas	4.58	5.49	3.22	4.07
California	4.67	5.41	3.18	3.85
Colorado	4.8	5.7	3.33	4.4
Connecticut	5.29	5.96	3.59	4.47
Delaware	5.81	6.04	3.91	4.57
District of Columbia	4.63	4.83	3.98	3.74
Florida	4.78	5.78	3.42	4.25
Georgia	4.9	5.76	3.43	4.3
Hawaii	4.8	5.44	3.33	3.61
Idaho	5.05	6.3	3.75	5.05
Illinois	4.87	5.42	3.36	4.02
Indiana	5.03	5.86	3.54	4.36
Iowa	4.71	5.41	3.19	3.86
Kansas	4.84	5.75	3.29	4.25
Kentucky	4.9	6	3.54	4.66
Louisiana	4.84	5.82	3.59	4.42
Maine	5.41	6.44	3.65	4.69
Maryland	5.21	5.78	3.55	4.12
Massachusetts	5.22	6.11	3.47	4.35
Michigan	4.96	5.69	3.48	4.21
Minnesota	4.95	5.67	3.3	4.25
Mississippi	4.46	5.64	3.15	4.06
Missouri	4.94	5.78	3.54	4.44
Montana	5.29	6.3	3.73	5.48
Nebraska	5.01	6.03	3.36	4.72
Nevada	5.41	5.53	3.85	4.2
New Hampshire	5.39	6.59	3.78	4.82
New Jersey	5.03	5.71	3.38	3.92
New Mexico	4.6	5.02	3.18	3.6
New York	4.89	5.6	3.32	4.01
North Carolina	4.93	5.73	3.53	4.47
North Dakota	4.91	5.79	3.37	4.4
Ohio	5.14	5.99	3.63	4.6
Oklahoma	4.63	5.79	3.39	4.62
Oregon	5.21	6.28	3.73	5.77
Pennsylvania	5.12	5.91	3.53	4.34
Rhode Island	4.8	5.87	3.36	4.23
South Carolina	4.91	5.98	3.43	4.28
South Dakota	4.78	5.62	3.29	4.44
Tennessee	4.77	5.64	3.36	4.32
Texas	4.85	5.65	3.45	4.32
Utah	4.84	5.7	3.62	5.16
Vermont	5.36	5.91	3.83	4.35
Virginia	5.08	5.66	3.52	4.19
Washington	5.15	5.87	3.58	4.34
West Virginia	4.91	5.98	3.6	4.71
Wisconsin	5.11	5.89	3.44	4.13
Wyoming	5.21	5.69	3.53	4.48

Supplementary Figures 1 and 2 demonstrate an overall increasing trend in incidence and death rate for most of the US states. Supplementary tables 1A and 1B present the results of a Joinpoint analyses for ASIRs for AF between 1990 to 2017 in men and women, respectively. Supplementary Tables 2A and 2B present the results of Joinpoint analyses for ASDRs. In each of these tables, EAPCs in rates for periods covered by each trend are reported. Significant trend changes in ASIRs and ASDRs are reported. There are significant increasing trends in AF

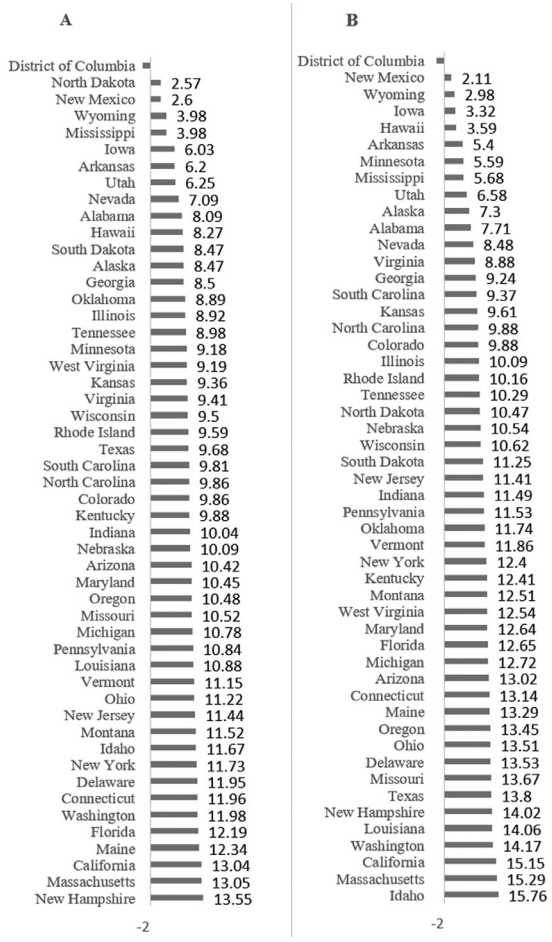

Figure 1. Percentage change in incidence rate between 1990 and 2017 from Atrial Fibrillation / Atrial Flutter across United States for men (*A*) and women (*B*).

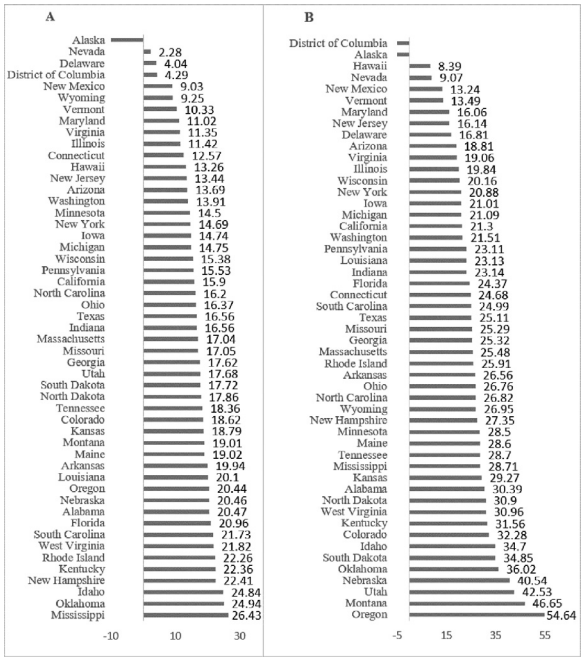

Figure 2. Percentage change in death rate between 1990 and 2017 from Atrial Fibrillation / Atrial Flutter across United States for men (*A*) and women (*B*).

incidence in most states for men and women. Lastly, an inflection point in 2001 is notable for increased incidence and mortality rates for both genders across most states.

Discussion

This study reports recent data relating to the epidemiology of atrial fibrillation (AF) and/or flutter (AFL) on a national and state level in the United States over a 28-year period. All regions of the US, apart from the District of Columbia, experienced an increase in AF incidence rates. The Northeast region was notable for having the highest incidence rates amongst men. While current incidence rates among states were higher for men than women, women had greater increases in incidence rates over the study period. In contrast to prior studies, our study showed a significant increase in mortality rates with the exception of the District of Columbia and Alaska. Furthermore, while overall mortality rates were higher in men, women had a significantly greater increase in mortality across most states over the study period. These data suggest that the public health burden related to AF in the US is progressively worsening, particularly since 2001, but disproportionately between states.

Incidence rates for AF in the US are expected to increase because of the aging US population and increased surveillance. However, studies from Europe and North America show discrepancy in the trend in AF incidence rates.[14–16] The world-wide incidence of AF in 1990 was 60.7 per 100,000 person-years in males and 43.8 in females. In 2010, the world-wide incidence had increased to 77.5 per person-years in males and 59.5 in females.[17] Fifty year follow up of the Framingham Heart Study participants showed age-adjusted incidence was 3.7 and 2.5 per 1000 person-years among men and women, respectively, in the early time period of the study compared with 13.4 and 8.5 per 1000 person years among men and women respectively in the most recent time period.[18]

Prior studies have demonstrated that AF is associated with increased mortality, but survival has been trending upward over time. Globally, the mortality associated with AF has increased 2-fold in women and 1.9-fold in men.[17] In Medicare beneficiaries over 65 years of age, the age and sex-adjusted mortality at 30 days and 1 year was 11% and 25%, respectively, in 2007.[15] In a community-based cohort of new-onset AF, the most common causes of death within 4 months of AF diagnosis were coronary artery disease (22%), heart failure (14%), and ischemic stroke (10%) and beyond 4 months were heart failure (16%), coronary artery disease (15%), and ischemic stroke (7%).[19] In 1998, the Framingham Heart Study established that AF was associated with an increased risk of death in males (OR 1.5; 95% CI 1.2 to 1.8) and females (OR 1.9; 95% CI 1.5 to 2.2),[1] Nonetheless, long term follow-up of Framingham Heart Study participants showed a 25% decrease over time in multivariable-adjusted mortality following AF onset when comparing the first to final time periods of the study.[18] This study also showed a 73.5% decline in stroke risk after AF onset when comparing the first to final time periods of the study. Similarly, a long-term Danish study showed a decrease in population-adjusted mortality from the first to last 5 year period by 20% in men and 18% in women.[20] The

same researchers reported an improving trend in stroke mortality from 1980 to 2002.[21] On the other hand, the 2000-2010 community study of Olmstead County, MN showed that age- and gender-adjusted mortality rates did not change over time.[16] In contrast, our study showed a significant increase in mortality rates from 1990 to 2017. The exceptions were the District of Columbia for females and Alaska for both genders. The reason for the discrepancy in mortality trends in relation to AF is unclear and outside the scope of this study. This may, in part, be due to the underutilization of anticoagulation in AF.[22,23] In the US National Cardiovascular Data Registry of outpatients with AF, less than one half of high-risk patients (defined as those with CHA2DS2-VASc score $\geq$ 4) were receiving anticoagulation.[23] It has been shown that AF patients not treated with anticoagulation had 2.1-fold increased risk of recurrent stroke and 2.4-fold increase risk of recurrent severe stroke.[24]

Additionally, it is known that genetics confer survival advantage to females over males for most disease states except autoimmune diseases.[25,26] While mortality related to AF was higher across all states for men, in general women had significantly greater increases in mortality over the study period compared with men. The greatest percentage increase in mortality for men was in Mississippi which had 26% increase in mortality from 1990 to 2017, while 16 states had greater than 30% increases in mortality for women. In fact, Oregon had a 54% increase in AF-related mortality for women. While there were no regional patterns for mortality among men, among women the greatest percentage increases in mortality rates were in the West and Mountain West and included Oregon Montana, Utah, and Nebraska.

Unlike prior studies, this study for the first time shows an inflection point in 2001 at which time there was a significant increase in the trend for both AF incidence and mortality in both genders across most states. The explanation for this finding would be speculative and outside the scope of this study. Nevertheless, this key finding has important public health implications and underscores the necessity of understanding the current epidemiology of AF.

Several limitations should be considered when interpreting the results of this study. First this is an observational study subject to limitations and biases of any observational study. Second, the GBD dataset did not distinguish between AF and AFL, or patterns of AF − such as paroxysmal or persistent − and therefore analysis could not be performed on these arrhythmia subsets. Third, the GBD database does not distinguish between clinical relevant or symptomatic cases and subclinical AF/AFL. Fourth, this database primarily relies upon hospital administrative data across various regional geographic regions, which stem from varying practices and quality care across hospitals

In conclusion, AF incidence and mortality rates are increasing across all states in the US, with the exceptions of the District of Columbia and Alaska. The upward trends have accelerated for most states since 2001 and women have experienced greater increases in incidence and mortality rates. This study demonstrates that the public health burden related to atrial fibrillation in the United States is progressively worsening particularly since 2001 but disproportionately across states and among women.

The burden of AF is worsening in the United States disproportionately among states and women and is an ever-increasing public health challenge

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.02.014.

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