

Rising Burden and Future Projections of Tobacco-Associated Ischemic Heart Disease Mortality in the United States: A CDC WONDER and Joinpoint Regression Analysis, 1999–2035

Khadeeja Ali Hamzah

Baghdad University Al-Kindy College of Medicine

Muhammad Shahzaib

King Edward Medical College of Medicine

Safa Gul

Cardiology faculty, Northwest Institute of Health Sciences

Abduallah Muataz Taha Al-Ibraheem

Baghdad University Al-Kindy College of Medicine

Nuha Mohammed Saleh Al_hawy

nuhamuhammadsaleh@gmail.com

Faculty of medicine Sana'a University

Tushar Kanti Bhadra

National Institute of Cardiovascular Diseases

Yousif Hameed Kurmasha

College of Medicine, University of Kufa

Research Article

Keywords:

Posted Date: September 29th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10995442/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background:

Tobacco use is a major modifiable risk factor for ischemic heart disease (IHD) and contributes to atherosclerosis, inflammation, endothelial dysfunction, and thrombosis. Although overall IHD mortality in the United States has declined over recent decades, the temporal patterns and population-level disparities in IHD mortality among individuals with documented tobacco use remain incompletely characterized.

Objective:

To evaluate temporal trends, demographic and geographic disparities, and future projections of tobacco-associated IHD mortality among U.S. adults aged ≥ 25 years from 1999 through 2024, with projections through 2035.

Methods:

We conducted a retrospective population-based study using the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause-of-Death database. Tobacco-associated IHD deaths were identified among adults aged ≥ 25 years when IHD (ICD-10 codes I20–I25) was listed as the underlying cause of death and tobacco use was documented as a contributing condition. Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated using the 2000 U.S. standard population. Temporal trends were evaluated using Joinpoint regression to estimate annual percent changes (APCs) and average annual percent changes (AAPCs). Autoregressive integrated moving average (ARIMA) models were used to project mortality through 2035.

Results:

A total of 953,967 tobacco-associated IHD deaths were identified between 1999 and 2024. Overall AAMRs increased significantly from 1999 to 2005 (APC, 40.78%; 95% CI, 30.22–52.20) and continued to increase from 2005 to 2020, although at a slower rate (APC, 2.40%; 95% CI, 1.36–3.46). From 2020 to 2024, AAMRs declined nonsignificantly (APC, – 4.07%; 95% CI, – 9.69 to 1.91), while the overall trend remained significantly increasing (AAPC, 9.38%; 95% CI, 7.17–11.65). Mortality was consistently higher among males and older adults and varied substantially across racial/ethnic, regional, and urbanization groups. Black or African American individuals had the greatest overall increase in AAMR (AAPC, 10.13%; 95% CI, 7.89–12.41), while rural and micropolitan populations experienced a particularly high mortality burden. ARIMA projections indicated that the overall AAMR may decline from 11.69 per 100,000 in 2024 to 9.13 per 100,000 by 2035; however, important subgroup disparities are expected to persist, with projected increases among adults aged 65–74 years, Black or African American individuals, and nonmetropolitan populations.

Conclusions:

Tobacco-associated IHD mortality increased substantially in the United States from 1999 to 2024, despite a nonsignificant decline during 2020–2024. Although overall mortality is projected to decline through 2035, substantial demographic and geographic disparities are expected to persist, with increasing mortality projected in several high-risk populations. Targeted tobacco cessation, equitable cardiovascular prevention, and improved access to preventive and cardiovascular care are needed to reduce the burden of tobacco-associated IHD mortality.

Introduction

Ischemic heart disease (IHD) remains a major cause of cardiovascular death despite long-term improvements in prevention and treatment. In the Global Burden of Disease 2019 analysis, cardiovascular diseases, mainly IHD and stroke were the leading cause of global mortality with cardiovascular deaths increasing from 12.1 million in 1990 to 18.6 million in 2019 (1). U.S. surveillance data also continue to show a substantial burden from coronary heart disease and related cardiovascular outcomes (2). Recent U.S. mortality database studies have reported that IHD mortality has not declined evenly across the population, with persistent differences by sex, race/ethnicity, geographic region, and urban-rural status (3, 4).

Tobacco exposure is a well-established modifiable risk factor for ischemic cardiovascular disease. Cigarette smoke contributes to endothelial dysfunction, oxidative stress, inflammation, adverse lipid changes, and thrombus formation, mechanisms that can promote atherosclerosis and coronary events (5, 6). In a nationally representative U.S. cohort, current smokers lost more than 10 years of life expectancy compared with non smokers, while cessation before 40 years of age reduced most of the excess mortality risk associated with continued smoking (7).

Most prior mortality analyses have examined all IHD deaths or model-based estimates of smoking-attributable IHD mortality. These approaches are useful, but they differ from death-certificate analyses in which tobacco use is recorded as a contributing condition. A Global Burden of Disease-based study examined smoking-attributable IHD mortality in China, India, Indonesia, the United States, and Russia, the five countries with the highest number of smokers, from 1990 to 2019 (8). A separate CDC WONDER analysis of tobacco-associated stroke mortality used a death-certificate approach and found increasing demographic and geographic disparities among tobacco-associated stroke deaths (9).

Therefore, this study aimed to characterize national trends in tobacco-associated ischemic heart disease mortality among U.S. adults aged 25 years and older from 1999 to 2024 and to estimate future mortality patterns through 2035. We also examined whether these trends differed across major demographic and geographic groups including sex, race, age, census region, and urbanization status. By focusing on deaths with documented tobacco use this study provides contemporary evidence on the evolving burden and disparities of tobacco-associated IHD mortality in the United States.

Methods

2.1 Data source and study design

This retrospective cross-sectional study utilized mortality data from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database to evaluate national mortality trends in ischemic heart disease (IHD) among individuals with documented tobacco use in the United States from 1999 to 2024. Mortality data were obtained from the Multiple Cause-of-Death (MCOD) database, which compiles death certificate information submitted from all 50 states and the District of Columbia. Causes of death were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) coding system (10).

Decedents with ischemic heart disease were identified using ICD-10 codes I20–I25 as the underlying cause of death. Cases were included if tobacco use or tobacco-related exposure was recorded as a contributing condition on the death certificate. Only deaths in which IHD was listed as the primary underlying cause and tobacco use was concurrently documented were included in the analysis. These ICD-10 classifications have been widely used in prior epidemiologic studies investigating ischemic heart disease patterns in the United States as well as tobacco (9, 11, 12).

Because the CDC WONDER database contains publicly available, de-identified data, Institutional Review Board (IRB) approval and informed consent were not required. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

2.2 Study population and variables

The study included adults aged ≥ 25 years. Individuals younger than 25 years were excluded because of the relatively low burden of tobacco-associated ischemic heart disease mortality in younger populations and to ensure stability in age-adjusted mortality calculations.

Mortality data were stratified according to demographic and geographic variables, including age group, sex, race/ethnicity, census region, and urbanization status. Age categories were divided into 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥ 85 years. Race/ethnicity groups included White, Black or African American, American Indian or Alaska Native, Asian or Pacific Islander, and Hispanic populations, as categorized within CDC WONDER.

Geographic analyses were performed across the four United States Census regions (Northeast, Midwest, South, and West). Urbanization status was classified according to the National Center for Health Statistics (NCHS) Urban–Rural Classification Scheme and categorized as large central metropolitan, large fringe metropolitan, medium metropolitan, small metropolitan, micropolitan, and noncore (rural) counties (13).

2.3 Statistical analysis

Crude mortality rates (CMRs) and age-adjusted mortality rates (AAMRs) per 100,000 population were calculated for tobacco-associated ischemic heart disease mortality. Crude mortality rates were derived by dividing annual death counts by the corresponding yearly United States population estimates. AAMRs were calculated using direct standardization based on the 2000 US standard population to account for differences in age distribution across demographic groups and over time.

Temporal trends in AAMRs from 1999 to 2024 were analyzed using the Joinpoint Regression Program (Version 5.1.0; National Cancer Institute, Bethesda, Maryland, USA) (14). Joinpoint regression identifies statistically significant changes in mortality trends by fitting a series of connected log-linear regression models. Annual percent changes (APCs) were estimated for individual trend segments, while the average annual percent change (AAPC) summarized the overall mortality trend across the study period.

A maximum of three joinpoints was permitted in accordance with National Cancer Institute recommendations. Positive APC or AAPC values indicated increasing mortality trends, whereas negative values indicated declining trends. Statistical significance was assessed using a two-sided t-test, with p-values < 0.05 considered statistically significant.

average (ARIMA) models. The optimal ARIMA specification was selected separately for the overall population and each prespecified subgroup based on model fit and diagnostic performance, including the Akaike information criterion (AIC), Bayesian information criterion (BIC), mean absolute error (MAE), root mean square error (RMSE), mean absolute percentage error (MAPE), and residual autocorrelation assessed using the Ljung-Box test (15). Forecasting analyses were performed overall and stratified by sex, race/ethnicity, age group, census region, urbanization category, and place of death.

Result

Overall:

A total of 953,967 deaths from tobacco-associated ischemic heart disease (IHD) were identified in the United States between 1999 and 2024 (Supporting Information in Table S1)

Age-adjusted mortality rates (AAMRs) for tobacco-associated ischemic heart disease (IHD) exhibited an overall upward trend in the US between 1999 and 2024. Significant rise was seen from 1999 to 2005 (APC: 40.78; 95% CI: 30.22–52.20), followed by a slight but substantial increase from 2005 to 2020 (APC: 2.40; 95% CI: 1.36–3.46), and a nonsignificant fall from 2020 to 2024 (APC: –4.07; 95% CI: –9.69 to 1.91). Throughout the study period, the overall trend showed a significant increase (AAPC: 9.38; 95% CI: 7.17–11.65), implying a consistent increase in the mortality burden (Fig. 1 presents the overall temporal trend in age-adjusted mortality rates (AAMRs) from 1999 to 2024 and illustrates the major changes in mortality over the study period. Table 1 summarizes the annual percent changes and average annual percent change, while Supplementary Table S2 provides the detailed annual AAMR estimates).

Table 1
Annual Percent Change (APC) in Age-Adjusted Mortality Rates (AAMRs) for Tobacco-Associated Ischemic Heart Disease Among Adults Aged ≥ 25 Years in the United States, 1999–2024

Year Interval	APC (95% CI)
Overall	
1999–2005	40.78 (30.22–52.20)
2005–2020	2.4 (1.36–3.46)
2020–2024	-4.07(-9.69-1.91)
Sex	
Women	
1999–2001	-5.17 (-27.74-24.44)
2001–2004	73.39 (40.76-113.58)
2004–2016	3.1 (2.38–3.82)
2016–2024	0.6 (-1.55-0.37)
Men	
1999–2005	41.88 (30.98–53.69)
2005–2020	2.33 (1.27–3.39)
2015–2024	-4.76 (-10.35-1.18)
Race	
American Indian or Alaska Native	
1999–2005	39.37 (22.83–58.14)
2005–2024	-0.40 (-1.41-0.62)
Asian or Pacific Islander	
1999–2006	35.27 (25.57–45.73)
2006–2020	1.16 (0.03–2.31)
2020–2024	-5.51 (-10.7–0.03)
Black or African American	
1999–2005	37.81 (27.12–49.41)
2005–2020	3.96 (2.91–5.01)
2020–2024	-2.34 (-7.33-2.91)
White	
1999–2005	41.01 (30.50-52.37)
2005–2020	2.46 (1.41–3.51)
2020–2024	-3.4 (-9.73-2.1)
Census Region	
Northeast	
1999–2005	59.67 (44.07–76.95)
2005–2024	-0.47 (-1.21-0.28)
Midwest	
CI, Confidence Interval; NH, non-Hispanic	

Year Interval	APC (95% CI)
1999–2005	36.91 (24.94–50.04)
2005–2011	12.43 (5.75–19.54)
2011–2024	-0.15 (-1.24-0.95)
South	
1999–2005	33.59 (22.5-45.69)
2005–2021	3.01 (1.93–4.1)
2021–2024	-5.35 (-14.68-5.01)
West	
1999–2001	-4.52 (-28.08-26.76)
2001–2004	58.69 (26.8-98.59)
2004–2021	1.51 (1.04–1.98)
2021–2024	-5.24 (-10.003–0.22)
Urban-rural classification	
Large Central Metro	
1999–2005	44.29 (30.26–59.84)
2005–2020	1.54 (0.35–2.75)
Large Fringe Metro	
1999–2005	46.35 (33.77–60.13)
2005–2020	1.15 (0.13–2.17)
Medium Metro	
1999–2002	11.1(0.16–23.23)
2002–2005	57.57 (39.39–78.13)
2005–2020	2.49 (2.17–2.81)
Small Metro	
1999–2005	33.83(23.97–44.46)
2005–2020	3.14 (2.16–4.13)
Micropolitan (Nonmetro)	
1999–2005	39.57 (28.36–51.75)
2005–2020	3.17 (2.15–4.21)
NonCore (Nonmetro)	
1999–2001	2.06 (-32.94-55.33)
2001–2004	52.19 (10.28-110.03)
2004–2015	6.58 (5.14–8.04)
2015–2020	0.81 (-2.32-4.05)
Age Groups	
Age 35–44 years	
1999–2005	27.78 (20.73–35.23)
2005–2021	2.24 (1.34–3.15)
CI, Confidence Interval; NH, non-Hispanic	

Year Interval	APC (95% CI)
2021–2024	-6.61 (-15.33-3.02)
Age 45–54 years	
1999–2001	2.8 (-22.23-35.88)
2001–2005	36.46 (23.37–50.96)
2005–2012	4.64 (2.45–6.87)
2012–2021	0.29 (-0.97-1.57)
2021–2024	-6.06 (-11.85-0.12)
Age 55–64 years	
1999–2005	29.51(21.54–38.01)
2005–2020	3.72 (2.84–4.61)
2020–2024	-4.34 (-8.96-0.53)
Age 65–74 years	
1999–2005	36.83 (26.98–47.45)
2005–2020	2.34 (1.32–3.37)
2020–2024	-2.56 (-7.61-2.77)
Age 75–84 years	
1999–2005	48.19 (35.01–62.65)
2005–2018	2.02 (0.49–3.57)
2018–2024	-2.69 (-6.28-1.04)
Age 85 + years	
1999–2005	62.34 (44.83–81.98)
2005–2018	2.79 (1.42–4.18)
2018–2024	-1.80 (-5.06-1.56)
CI, Confidence Interval; NH, non-Hispanic	

Trends by Sex:

Males consistently exhibited higher mortality rates than females throughout the study period, with a total of 672,230 male deaths compared with 281,737 female deaths (**Supporting Information in Table S1. AAMRs by sex and race/ethnicity, 1999–2024**)

Among females, the AAMR increased substantially from 2001 to 2004 (APC, 73.39%; 95% CI, 40.76–113.58), followed by a continued significant increase through 2016 (APC, 3.10%; 95% CI, 2.38–3.82), and subsequently remained stable. Overall, female mortality demonstrated a significant increase during the study period (AAPC, 7.74%; 95% CI, 4.47–11.10). Among males, the AAMR increased significantly from 1999 to 2005 (APC, 41.88%; 95% CI, 30.98–53.69), followed by a sustained significant increase through 2020 (APC, 2.33%; 95% CI, 1.27–3.39). Overall, male mortality also increased significantly (AAPC, 9.41%; 95% CI, 7.15–11.72) (Fig. 2 **presents sex-specific AAMR trends from 1999 to 2024 and illustrates the persistent difference in mortality between males and females. Supplementary Table S2 provides the detailed annual mortality estimates by sex, while Table 1 summarizes the corresponding temporal trends**).

Trends by Age:

Age-specific analysis revealed significant variation in mortality patterns. AAMRs climbed dramatically across all age groups from 1999 to 2005, with APCs ranging from 27.78 (35–44 years) to 62.34 (85 + years), and then continued to increase throughout the 2010s. The overall trend showed a progressive increase with age, from an AAPC of 6.69 (95% CI: 4.83–8.59) among individuals aged 35 to 44 years to 13.45 (95% CI: 10.38–16.61) among individuals aged 85 years and above (Fig. 3 **presents the age-group-specific crude mortality rate (CMR) trends from 1999**

to 2024 and illustrates the differences in mortality patterns across age groups. Supplementary Table S3 provides the detailed age-group-specific mortality estimates, while Table 1 summarizes the associated trend estimates).

Trends by Race and Ethnicity:

White individuals accounted for the majority of deaths ($n = 852,655$), followed by Black or African American ($n = 83,472$), Asian or Pacific Islander ($n = 9,196$), and American Indian or Alaska Native ($n = 7,315$) individuals. Mortality increased significantly across all racial and ethnic groups over the study period. Black or African American individuals had the greatest overall increase in AAMR (AAPC, 10.13%; 95% CI, 7.89–12.41), with a sustained increase through 2020 (APC, 3.96%; 95% CI, 2.91–5.01). Among White individuals, AAMR increased sharply from 1999 to 2005 (APC, 41.01%; 95% CI, 30.50–52.37), followed by a continued increase through 2020 (APC, 2.46%; 95% CI, 1.41–3.51), yielding an overall AAPC of 9.47% (95% CI, 7.26–11.74). American Indian or Alaska Native individuals demonstrated a significant increase from 1999 to 2005 (APC, 39.37%; 95% CI, 22.23–58.14), followed by a stable trend, with an overall AAPC of 7.96% (95% CI, 4.82–11.19). Asian or Pacific Islander individuals showed a significant increase through 2020, followed by the only significant recent decline among racial and ethnic groups from 2020 to 2024 (APC, –5.51%; 95% CI, –10.70 to –0.03); however, mortality remained significantly increased overall (AAPC, 8.55%; 95% CI, 6.18–10.96) (Fig. 4 presents race- and ethnicity-specific AAMR trends from 1999 to 2024 and illustrates the substantial differences in mortality trajectories across racial and ethnic groups. Supplementary Tables S1 and S4 provide the detailed mortality estimates, while Table 1 summarizes the temporal trends across these groups.).

Trends by Region:

According to regional analysis, mortality patterns varied among census regions. In the Northeast, AAMRs rose dramatically from 1999 to 2005 (APC: 59.67; 95% CI: 44.07–76.95) and then stabilized, with an overall AAPC of 11.49 (95% CI: 8.86–14.18) whereas in the Midwest, AAMRs grew significantly from 1999 to 2011, with a notable acceleration from 2005 to 2011 (APC: 12.43; 95% CI: 5.75–19.54), for an overall AAPC of 10.82 (95% CI: 8.06–13.65). A significant rise was seen in mortality rate in the South through 2021 (AAPC: 8.53; 95% CI: 6.01–11.11). In the West, AAMRs increased significantly from 2001 to 2004 (APC: 58.69; 95% CI: 26.80–98.59), but decreased dramatically in 2021–2024 (APC: –5.24; 95% CI: –10.00 to –0.22), resulting in the lowest overall AAPC across census areas (5.70; 95% CI: 2.27–9.25) (Fig. 5 presents AAMR trends across the four U.S. Census regions from 1999 to 2024 and illustrates the geographic variation in mortality trajectories. Supplementary Table S5 provides the detailed region-specific mortality estimates, while Table 1 summarizes the associated temporal trends).

Trends by Urbanization:

From 1999 to 2005, AAMRs increased significantly across all urbanization categories, with the largest overall increase observed in Micropolitan (nonmetropolitan) areas (AAPC: 12.48; 95% CI: 8.99–15.11), followed by Large Fringe Metro (AAPC: 12.41; 95% CI: 6.65–15.23) and Large Central Metro areas (AAPC: 12.27; 95% CI: 9.14–15.48). Medium metropolitan areas experienced a significant acceleration from 2002 to 2005 (APC: 57.57; 95% CI: 39.39–78.13), resulting in an overall AAPC of 10.25 (95% CI: 7.95–12.60) whereas noncore (nonmetropolitan) areas showed a substantial increase from 2001 to 2004 (APC: 52.19; 95% CI: 10.28–110.03) and maintained growth through 2015 (APC: 6.58; 95% CI: 5.14–8.04), for an overall AAPC of 10.22 (95% CI: 4.31–16.46) (Fig. 6 presents AAMR trends according to urbanization level from 1999 to 2024 and illustrates the differences in mortality patterns between metropolitan and nonmetropolitan areas. Supplementary Table S6 provides the detailed urbanization-specific mortality estimates, while Table 1 summarizes the associated temporal trends).

Place of Death:

Among 953,945 tobacco-related IHD patients, the person's home was the most common place of death (404,286; 42.4%), followed by medical facility-inpatient settings (241,711; 25.3%) and nursing home/long-term care facilities (87,656; 9.2%) (Supporting Information in Table S7).

Forecasted Mortality Trends:

ARIMA models demonstrated adequate model fit and residual diagnostics across the overall population and prespecified subgroups. The selected models were characterized by acceptable AIC and BIC values, low forecasting errors, and nonsignificant Ljung–Box tests, indicating no significant residual autocorrelation and adequate model specification (Table 2 summarizes the selected ARIMA models and their forecasting performance).

Table 2
Optimal ARIMA models and forecasting performance metrics for tobacco-associated ischemic heart disease mortality across overall and subgroup analyses.

Dataset	Group	Model	AIC	BIC	MAE	RMSE	MAPE (%)	Ljung-Box p	Ljung-Box	ADF p-value
Overall		ARIMA(4, 2, 1)	66.63	73.69	0.455184	0.67003	5.1167	0.8058	White noise	0.6298
Age Groups ^a	35–44 years	ARIMA(0,1,0) with drift	-18.86	-16.42	0.1083	0.150219	7.7356	0.8667	White noise	0.5846
	45–54 years	ARIMA(4, 2, 1)	45.39	52.46	0.281202	0.424105	4.1925	0.8423	White noise	0.9272
	55–64 years	ARIMA(0,2,1)	96.96	99.31	1.044078	1.589702	5.8808	0.8936	White noise	0.9198
	65–74 years	ARIMA(0,1,0) with drift	137.37	139.81	2.187137	3.417525	7.9846	0.913	White noise	0.5232
	75–84 years	ARIMA(4, 2, 1)	166.22	173.28	3.632516	5.402191	6.3095	0.8035	White noise	0.543
	85 + years	ARIMA(0,2,1)	183.76	186.12	5.974691	9.672209	7.8854	0.9123	White noise	0.5367
Census Region	Census Region 1: Northeast	ARIMA(0,2,1)	84.13	86.49	0.761051	1.225743	9.0484	0.7766	White noise	0.3138
	Census Region 2: Midwest	ARIMA(2,2,0)	78.72	82.25	0.786834	1.036197	7.9408	0.9311	White noise	0.99
	Census Region 3: South	ARIMA(4,1,0) with drift	81.12	88.43	0.620143	0.900187	7.6448	0.5173	White noise	0.4188
	Census Region 4: West	ARIMA(1,1,0)	61.71	64.14	0.471825	0.750687	7.2761	0.9518	White noise	0.4191
Gender	Female	ARIMA(4, 2, 1)	39.2	46.27	0.267258	0.383502	5.8089	0.8827	White noise	0.4789
	Male	ARIMA(4, 2, 1)	89.43	96.5	0.708762	1.071061	5.0184	0.734	White noise	0.6622
Race	American Indian or Alaska Native	ARIMA(0,1,0)	96.88	98.1	1.141949	1.582502	13.5244	0.5494	White noise	0.4682
	Asian or Pacific Islander	ARIMA(2, 2, 1)	11.77	16.48	0.180611	0.244016	12.4683	0.8819	White noise	0.8188
	Black or African American	ARIMA(0,1,0) with drift	58.23	60.67	0.52423	0.701922	9.5605	0.9852	White noise	0.728
	White	ARIMA(4, 2, 1)	69.32	76.39	0.47849	0.70873	5.1202	0.8999	White noise	0.6328
Urbanization	Large Central Metro	ARIMA(0,1,0) with drift	54.91	57	0.515617	0.794579	11.9448	0.9544	White noise	0.4537
	Large Fringe Metro	ARIMA(1,1,0)	61.92	64.01	0.614909	0.93376	8.9017	0.4631	White noise	0.4658
Abbreviations: ARIMA, autoregressive integrated moving average; AIC, Akaike information criterion; BIC, Bayesian information criterion; MAE, mean absolute error; RMSE, root mean square error; MAPE, mean absolute percentage error; ADF, Augmented Dickey–Fuller test. The selected ARIMA models, along with AIC, BIC, ADF test results, and Ljung–Box statistics, are presented for the overall analysis and subgroup analyses according to age, sex, race, census region, urbanization level, and place of death. Model performance was evaluated using MAE, RMSE, and MAPE. Ljung–Box p-values > 0.05 indicate that residuals approximated white noise, supporting adequate model fit.										
a Crude mortality rates were used for age-group analyses, whereas age-adjusted mortality rates were used for all other subgroup analyses.										

Dataset	Group	Model	AIC	BIC	MAE	RMSE	MAPE (%)	Ljung-Box p	Ljung-Box	ADF p-value
	Medium Metro	ARIMA(0,1,2) with drift	55.01	59.19	0.518747	0.702789	7.6148	0.9891	White noise	0.2331
	Micropolitan (Nonmetro)	ARIMA(0,1,0) with drift	73.6	75.69	0.857763	1.239936	10.0978	0.8355	White noise	0.665
	NonCore (Nonmetro)	ARIMA(0,1,0) with drift	69.22	71.31	0.911059	1.117095	9.7629	0.7293	White noise	0.5204
	Small Metro	ARIMA(0,1,0) with drift	68.63	70.72	0.736176	1.101467	9.6382	0.8162	White noise	0.3313
Place of Death	Decedent's home	ARIMA(0,1,0) with drift	424.49	426.93	778.984351	1065.511377	10.2655	0.7936	White noise	0.0932
	Hospice facility	ARIMA(1,1,0)	296.89	299.32	53.011003	82.016778	14.445	0.9594	White noise	0.9574
	Medical Facility - Dead on Arrival	ARIMA(0,1,0)	280.11	281.33	50.121615	61.781571	12.9649	0.2235	White noise	0.9264
	Medical Facility - Inpatient	ARIMA(0,2,1)	406.14	408.5	555.237556	992.730143	6.8919	0.8336	White noise	0.5804
	Medical Facility - Outpatient or ER	ARIMA(0,2,1)	364.36	366.71	292.7877	415.91954	6.3244	0.8373	White noise	0.8997
	Nursing home/long term care	ARIMA(0,2,1)	356.36	358.72	234.931668	354.220402	8.8394	0.7315	White noise	0.6402
	Other	ARIMA(4,1,0) with drift	316.55	323.86	70.80572	99.782589	8.1711	0.985	White noise	0.0737
Abbreviations: ARIMA, autoregressive integrated moving average; AIC, Akaike information criterion; BIC, Bayesian information criterion; MAE, mean absolute error; RMSE, root mean square error; MAPE, mean absolute percentage error; ADF, Augmented Dickey–Fuller test. The selected ARIMA models, along with AIC, BIC, ADF test results, and Ljung–Box statistics, are presented for the overall analysis and subgroup analyses according to age, sex, race, census region, urbanization level, and place of death. Model performance was evaluated using MAE, RMSE, and MAPE. Ljung–Box p-values > 0.05 indicate that residuals approximated white noise, supporting adequate model fit.										
a Crude mortality rates were used for age-group analyses, whereas age-adjusted mortality rates were used for all other subgroup analyses.										

ARIMA-based estimates suggest that age-adjusted mortality rates (AAMRs) for tobacco-associated IHD will continue to drop over the next decade (Fig. 7 presents the historical AAMR trends from 1999 to 2024 together with ARIMA-based forecasts through 2035 and illustrates the projected evolution of mortality over the coming decade. Supplementary Figure S1 provides the detailed overall forecast trajectory.). The AAMR is projected to drop from 11.69 per 100,000 in 2024 to 9.48 per 100,000 in 2034 (95% CI: –5.93 to 24.89), with a broader 2035 prediction interval (point estimate 9.13; 95% CI: –8.14 to 26.41), indicating growing uncertainty over time.

Sex-specific forecasts indicate persisting disparities (Supplementary Figure S2 presents the projected sex-specific AAMRs from 2025 to 2035; Table S8 provides the detailed annual forecast estimates by sex). Male AAMRs are expected to decrease from 18.13 in 2024 to 12.94 in 2034 (95% CI: –13.11 to 38.98), while female rates are expected to remain steady, falling from 6.34 to 5.91 (95% CI: –2.41 to 14.24) throughout the same period.

Age-stratified forecasts reveal a significantly greater burden among older individuals (Supplementary Figure S3). The AAMR for the 65–74 age group is expected to increase from 46.86 in 2024 to 62.75 in 2034 (95% CI: 40.71–84.80), whereas the AAMR for the 85 + age group is expected to decrease from 114.81 to 88.60 (95% CI: –56.17 to 233.37) (Supplementary Table S9 provides the detailed age-specific forecasts).

Regional differences persist (Supplementary Figure S4) with the South is expected to have the highest AAMR by 2034 (16.68; 95% CI: 11.27–22.09), followed by the West (8.05; 95% CI: 1.12–14.98), while the Northeast (5.11; 95% CI: –22.33 to 32.56) and Midwest (7.09; 95% CI: –16.70 to 30.88) are projected to decline (Table S10 provides the detailed regional forecasts).

According to Racial and ethnic projections, Black or African American individuals are expected to have the biggest growth, from 11.27 in 2024 to 15.21 in 2034 (95% CI: 10.68–19.74), while White individuals are expected to experience a decline from 12.48 to 10.14 (95% CI: –7.02 to

27.30) (Supporting Information in Supplementary Figure S5 and Supplementary Table S11, provide the detailed race- and ethnicity-specific forecasts.).

Urbanization-based forecasts show that nonmetropolitan areas will continue to face the greatest burden (Supplementary Figure S6). Micropolitan (Nonmetro) and Noncore (Nonmetro) AAMRs are expected to increase to 32.86 (95% CI: 23.32–42.39) and 33.06 (95% CI: 24.47–41.65) by 2034, respectively, compared to 14.76 (95% CI: 8.65–20.87) in Large Central Metro regions (Supporting Information in Supplementary Figure S6 and Supplementary Table S12, provide the detailed urbanization-specific forecasts).

ARIMA estimates indicate that deaths in the deceased's home will rise from 28,171.9 in 2025 to 38,430.7 by 2035 (95% CI: 31,221.5–45,639.8), while hospice deaths remain stable (1,630.5 to 1,602.7; 95% CI: 164.3–3,041.0) (Figure S7 illustrates these projected patterns, and Supplementary Table S13 provides the detailed forecasts.).

Discussion

This study evaluated long-term trends and future projections of tobacco-attributable ischemic heart disease (IHD) mortality in the United States from 1999 to 2024 using Joinpoint regression and ARIMA forecasting. Overall, age-adjusted mortality rates (AAMRs) increased significantly during the study period, with a rapid rise between 1999 and 2005, followed by a slower but sustained increase until 2020. Although mortality showed a nonsignificant decline after 2020, the overall trend remained upward. Forecast analysis suggests that overall AAMRs will gradually decline over the next decade; however, substantial disparities are expected to persist across sex, age, race and ethnicity, geographic region, and urbanization.

The overall increase in tobacco-associated IHD mortality reflects the persistent cardiovascular consequences of tobacco exposure despite decades of tobacco-control initiatives. Smoking accelerates atherosclerosis through endothelial dysfunction, oxidative stress, inflammation, platelet activation, and thrombosis, substantially increasing the risk of myocardial infarction and cardiovascular death (16). Although smoking prevalence has declined nationally, the cumulative effects of long-term smoking, together with population aging and persistent tobacco use in vulnerable populations, likely explain the continued increase in mortality observed in this study. The modest decline after 2020 may indicate the beneficial effects of smoking cessation programs, improved cardiovascular prevention, and advances in the management of ischemic heart disease (17, 18).

Sex-specific analyses demonstrated consistently higher mortality among males than females throughout the study period. Men experienced a significant increase in mortality from 1999 to 2020, while females also showed a marked increase, particularly during the early 2000s (19, 20). Higher smoking prevalence, greater cumulative tobacco exposure, and a higher burden of traditional cardiovascular risk factors among men likely contribute to these findings. Nevertheless, the continued increase among women is concerning and may reflect changing smoking behaviors, increasing obesity and diabetes prevalence, and improved survival from competing diseases that allows cardiovascular disease to become more prominent (21, 22). Forecasts indicate that male mortality will remain substantially higher than female mortality despite projected declines in both groups, emphasizing the need for sex-specific prevention and smoking cessation strategies (23).

Age-stratified analyses demonstrated progressively increasing mortality with advancing age. Individuals aged 85 years and older experienced the greatest overall increase during the study period, while forecast models suggest that mortality among adults aged 65–74 years may continue to rise over the next decade (18). These findings are expected because older adults accumulate longer durations of tobacco exposure and have a higher prevalence of hypertension, diabetes, dyslipidemia, and other comorbidities that amplify cardiovascular risk. Although younger adults had lower mortality rates, significant increases across all age groups indicate that tobacco continues to contribute to premature cardiovascular disease throughout adulthood (1).

Marked racial and ethnic disparities were observed. Black or African American individuals experienced the largest overall increase in mortality and are projected to have the greatest future burden. These disparities likely reflect differences in socioeconomic status, healthcare access, preventive cardiovascular care, smoking cessation resources, and the prevalence of cardiovascular risk factors. American Indian or Alaska Native populations also experienced substantial increases, consistent with the disproportionately high tobacco use reported in these communities (22, 24). In contrast, Asian or Pacific Islander individuals were the only racial group to demonstrate a significant decline after 2020, suggesting potential benefits from lower smoking prevalence, improved healthcare access, and successful prevention strategies. White individuals showed sustained increases through 2020 but are projected to experience declining mortality over the next decade (25).

Regional analyses demonstrated considerable geographic variation. The Northeast showed the highest overall increase during the study period, whereas the South maintained persistently elevated mortality and is projected to experience the highest AAMRs by 2034. These findings likely reflect regional differences in smoking prevalence, socioeconomic conditions, healthcare accessibility, and implementation of tobacco-control policies (26). The projected declines in the Northeast and Midwest may indicate greater effectiveness of public health interventions and cardiovascular prevention programs, whereas the continuing burden in the South highlights the need for stronger tobacco-control measures and improved cardiovascular risk management (27).

Urbanization analyses further demonstrated important geographic inequalities. Mortality increased across all urbanization categories, but micropolitan and noncore rural areas experienced the greatest overall burden and are projected to continue having the highest mortality rates over the next decade (20). Rural communities often face limited healthcare infrastructure, physician shortages, lower availability of smoking cessation services, delayed diagnosis of cardiovascular disease, and greater socioeconomic disadvantage. In contrast, large metropolitan areas are expected to maintain comparatively lower mortality, likely reflecting better access to preventive healthcare and specialized cardiovascular services (22).

Forecast analyses suggest a gradual decline in overall tobacco-associated IHD mortality through 2034, indicating potential benefits of continued reductions in cigarette smoking and improvements in cardiovascular care. However, these encouraging trends should be interpreted cautiously because prediction intervals widened over time, indicating greater uncertainty in long-term estimates. Moreover, projected increases among older adults, Black individuals, Southern residents, and rural populations demonstrate that current public health strategies have not benefited all populations equally. Future interventions should therefore prioritize high-risk groups through targeted smoking cessation programs, equitable healthcare access, aggressive cardiovascular risk factor control, and policies addressing socioeconomic disparities (16, 28).

This study has several strengths. It utilized nationally representative mortality data spanning 26 years, standardized age-adjusted mortality rates, Joinpoint regression to identify significant temporal changes, and ARIMA modeling to estimate future trends. Comprehensive subgroup analyses by sex, age, race and ethnicity, region, and urbanization provide valuable insights into population-level disparities that can guide public health planning.

Several limitations should also be considered. Mortality estimates relied on death certificate data, which may be affected by coding errors or misclassification. The ecological design precludes causal inference at the individual level, and information regarding smoking intensity, duration, secondhand smoke exposure, socioeconomic status, and treatment history was unavailable. In addition, ARIMA projections assume continuation of historical trends and may not account for future policy changes, emerging tobacco products, or unexpected public health events.

conclusion

tobacco-associated IHD mortality increased significantly in the United States between 1999 and 2024 despite recent signs of stabilization. Although overall mortality is projected to decline over the next decade, disparities are expected to persist among males, older adults, Black individuals, Southern residents, and rural populations. Strengthening tobacco-control policies, expanding access to smoking cessation services, and implementing targeted cardiovascular prevention strategies remain essential to reducing the future burden of tobacco-related ischemic heart disease.

Declarations

Conflicts of interest:

None.

Ethics approval and consent to participate:

This study used publicly available, de-identified data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database and did not involve human participants or identifiable private information. As such, institutional ethics approval and informed consent were not required, in accordance with national regulations and institutional policies. The study complies with the ethical standards of the Declaration of Helsinki.

Clinical Trial Number

Not applicable

Consent for publication:

Not applicable

Author Contribution

Khadeeja Ali Hamzah: Conceptualization, methodology, data curation, formal analysis, investigation, writing original draft, and writing review and editing; Muhammad Shahzaib: methodology, data curation, statistical analysis, investigation, and writing review and editing; Safa Gul: data curation, statistical analysis, investigation, and writing review and editing; Abdullah Muataz Taha Al-Ibraheem: data curation, investigation, literature review, and writing review and editing; Nuha Mohammed Saleh Al_hawy: investigation, interpretation of results, writing review and editing, and corresponding author responsibilities; Tushar Kanti Bhadra: data curation, investigation, interpretation of results, and writing review and editing; Yousif Hameed Kurmasha: methodology, statistical analysis, interpretation of results, writing, review and editing, and critical revision of the manuscript. All authors contributed to the interpretation of the findings, critically reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Acknowledgements:

None.

Sources of funding: None.

Data Availability

This study used publicly available, de-identified data from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER).

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. *Journal of the American College of Cardiology*. Elsevier Inc.; 2020. pp. 2982–3021. .010 PubMed PMID: 33309175.
2. Palaniappan LP, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. 2026 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation*. 2026;153(9). 10.1161/CIR.0000000000001412.
3. Ibrahim R, Salih M, Gomez Tirambulo CV, Takamatsu C, Lee JZ, Fortuin D, et al. Impact of Social Vulnerability and Demographics on Ischemic Heart Disease Mortality in the United States. *JACC: Adv*. 2023;2(7). 10.1016/j.jacadv.2023.100577.
4. Naveed MA, Ahmed F, Eltawansy S, Ali A, Afzaal Z, Azeem B, et al. Trends and disparities in ischemic heart disease mortality in the United States: an analysis of CDC WONDER database, 1999–2020. *Coron Artery Dis*. 2025;36(8):662–70. 10. 1097/MCA.0000000000001550 PubMed PMID: 40632641.
5. Kondo T, Nakano Y, Adachi S, Murohara T. Effects of tobacco smoking on cardiovascular disease. *Circulation J Japanese Circulation Soc*. 2019;1980–5. 10.1253/circj.CJ. -19-0323 PubMed PMID: 31462607.
6. Higashi Y. Smoking cessation and vascular endothelial function. *Hypertension Research*. Springer Nature; 2023. pp. 2670–8. 10.1038/s41440-023- 01455-z PubMed PMID: 37828134.
7. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, et al. 21st-Century Hazards of Smoking and Benefits of Cessation in the United States. *N Engl J Med*. 2013;368(4):341–50. 10.1056/nejmsa1211128 . PubMed PMID: 23343063.
8. Tang S, Meng J, Zhao X, Sun W. Trends of ischemic heart disease mortality attributable to smoking in the five countries with the highest number of smokers during 1990–2019: an age-period-cohort analysis. *Archives of Medical Science*. Termedia Publishing House Ltd.; 2024. pp. 43–53. 10.5114/aoms/182886.
9. Hassan W, Nabi R, Rath S, Javeid A, Ali D, Haseeb B, et al. Stroke-related mortality trends among tobacco users in the U.S.: A 21-year retrospective analysis of national data from the CDC WONDER database. *J Stroke Cerebrovasc Dis*. 2025;34(10). 10.1016/j.jstrokecerebrovasdis.2025.108436 . PubMed PMID: 40848956.
10. Multiple Cause of Death Data on CDC WONDER. Accessed May 2. 2026. <https://wonder.cdc.gov/mcd.html>
11. Naveed MA, Ahmed F, Eltawansy S, Ali A, Afzaal Z, Azeem B, Kashan M, Aman K, Ahmed M, Jain H, Kamil O. Trends and disparities in ischemic heart disease mortality in the United States: an analysis of CDC WONDER database, 1999–2020. *Coron Artery Dis*. 2025;36(8):662–70.
12. Shahab SH, Maryam Z, Naqvi SM, Ahmed M, Matloob A, Masood HG, Umair E, Khalid M, Talha M, Rehman UU. Trends and disparities in liver failure-related mortality in adults with mental and behavioral disorders due to tobacco use: A retrospective analysis. *Medicine*. 2026;105(20):e48719.
13. Ingram DD, Franco SJ. NCHS urban-rural classification scheme for counties. *Vital Health Stat* 2. 2012;(154):1–65.

14. National Cancer Institute. Number of Joinpoints. Joinpoint Help System. Accessed May2,2026.
<https://surveillance.cancer.gov/help/joinpoint/setting-parameters/method-and-parameters-tab/number-of-joinpoints>
15. Schaffer AL, Dobbins TA, Pearson SA. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. *BMC Med Res Methodol*. 2021;21(1):58.
16. U.S. Department of Health and Human Services. Smoking cessation: a report of the Surgeon General. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2020.
17. Rose JJ, Krishnan-Sarin S, Exil VJ, Hamburg NM, Fetterman JL, Ichinose F, et al. Cardiopulmonary impact of electronic cigarettes and vaping products: a scientific statement from the American Heart Association. *Circulation*. 2023;148(8):703–28.
10.1161/CIR.0000000000001160.
18. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. 2024 Heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2024;149(8):e347–913. 10.1161/CIR.0000000000001209.
19. Dennison Himmelfarb CR, Benowitz NL, Blank MD, Bhatnagar A, Chase PJ, Davis EM, et al. Impact of smokeless oral nicotine products on cardiovascular disease: implications for policy, prevention, and treatment. *Circulation*. 2025;151(1):e1–21.
10.1161/CIR.0000000000001293.
20. Cross SH, Mehra MR, Bhatt DL, Nasir K, O'Donnell CJ, Califf RM, et al. Rural-urban differences in cardiovascular mortality in the US, 1999–2020. *JAMA*. 2022;328(18):1850–2. 10.1001/jama.2022.18546.
21. Bhatnagar A, Maziak W, Eissenberg T, Ward KD, Thurston G, King BA, et al. Water pipe (hookah) smoking and cardiovascular disease risk: a scientific statement from the American Heart Association. *Circulation*. 2019;139(19):e917–36. 10.1161/CIR.0000000000000671.
22. Singh GK, Siahpush M. Widening rural-urban disparities in life expectancy, U.S., 1969–2009. *Am J Prev Med*. 2014;46(2):e19–e29.
10.1016/j.amepre.2013.10.017
23. Piano MR, Benowitz NL, Fitzgerald GA, Corbridge S, Heath J, Hahn E, et al. Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment. *Circulation*. 2010;122(15):1520–44. 10.1161/CIRCULATIONAHA.110.948364.
24. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*. 2004;43(10):1731–7. 10.1016/j.jacc.2003.12.047.
25. Banks E, Joshy G, Weber MF, Liu B, Grenfell R, Egger S, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. *BMC Med*. 2019;17(1):128. 10.1186/s12916-019-1351-4.
26. GBD 2021 Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and territories, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2024;403(10440):2162–203. 10.1016/S0140-6736(24)00933-4.
27. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56–528. 10.1161/CIR.0000000000000659.
28. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet*. 2006;368(9536):647–58. 10.1016/S0140-6736(06)69249-0.

Figures

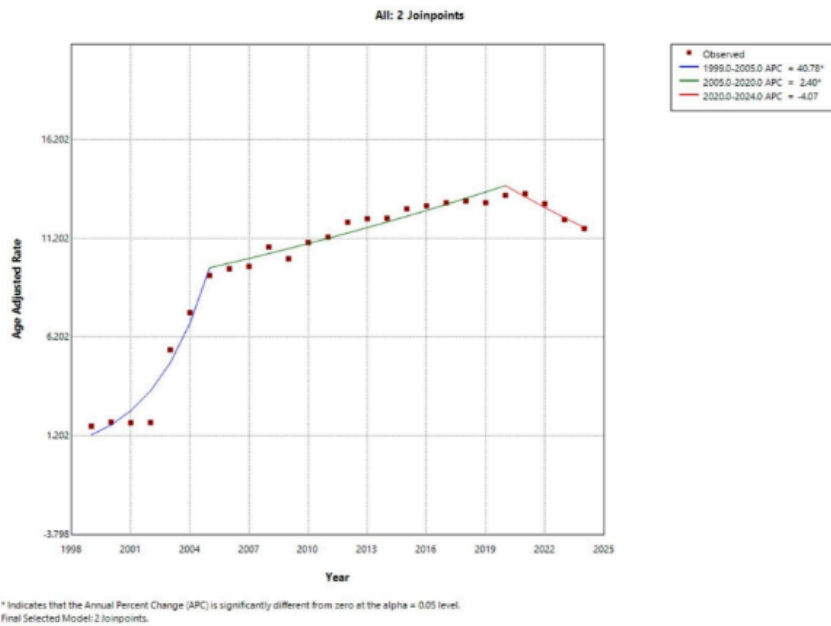


Figure 1

Trends in Age-Adjusted Mortality Rates (AAMRs) for Tobacco-Associated Ischemic Heart Disease Among Adults Aged ≥25 Years in the United States, 1999–2024.

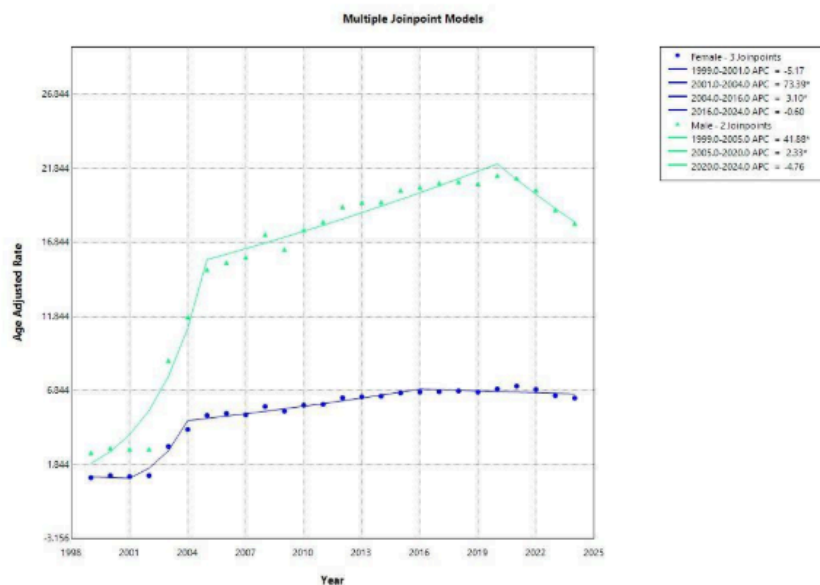


Figure 2

Trends in Age-Adjusted Mortality Rates (AAMRs) for Tobacco-Associated Ischemic Heart Disease Among Adults Aged ≥25 Years in the United States, Stratified by Sex, 1999–2024.

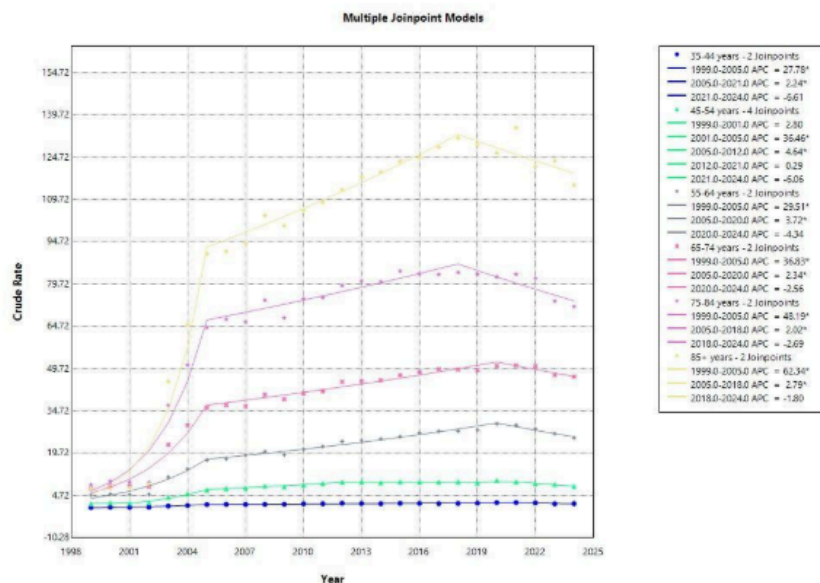


Figure 3

Trends in Crude Mortality Rates (CMRs) for Tobacco-Associated Ischemic Heart Disease Among Adults Aged ≥ 25 Years in the United States, Stratified by Age Group, 1999–2024.

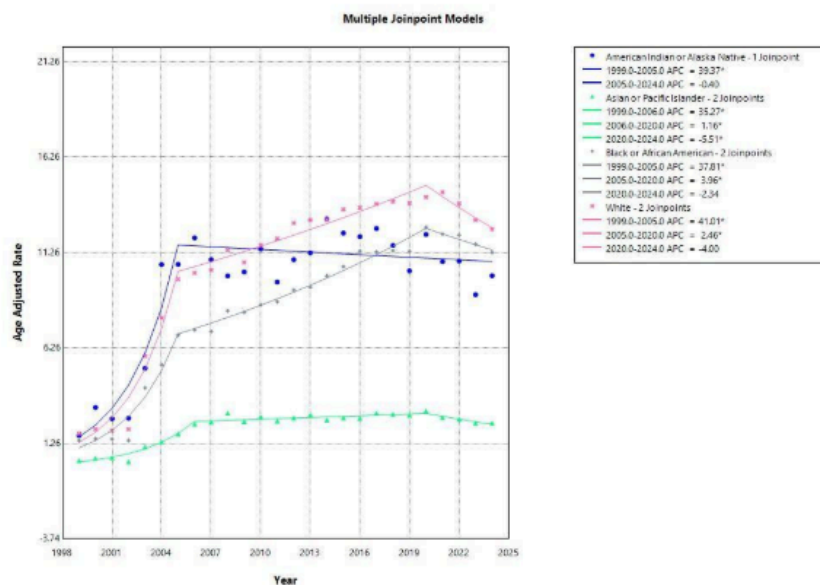


Figure 4

Trends in Age-Adjusted Mortality Rates (AAMRs) for Tobacco-Associated Ischemic Heart Disease Among Adults Aged ≥ 25 Years in the United States, Stratified by Race/Ethnicity, 1999–2024

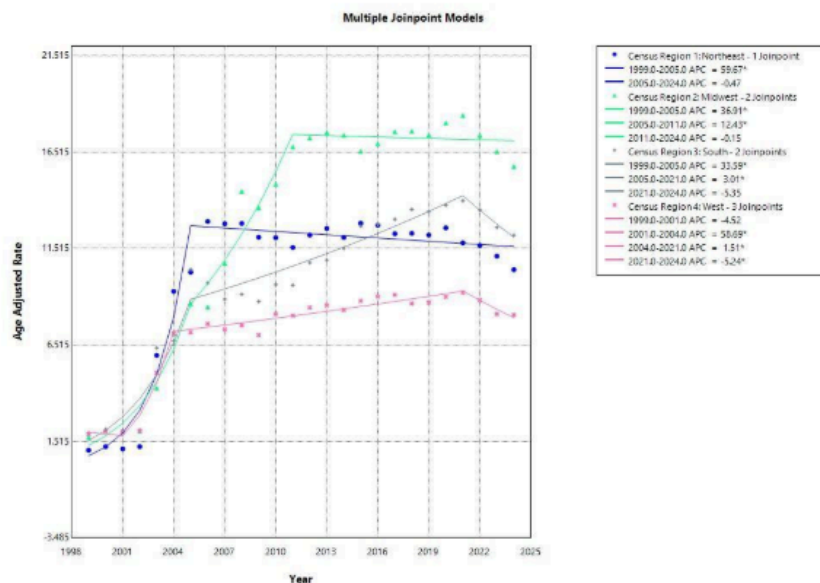


Figure 5

Trends in Age-Adjusted Mortality Rates (AAMRs) for Tobacco-Associated Ischemic Heart Disease Among Adults Aged ≥25 Years in the United States, Stratified by U.S. Census Region, 1999–2024.

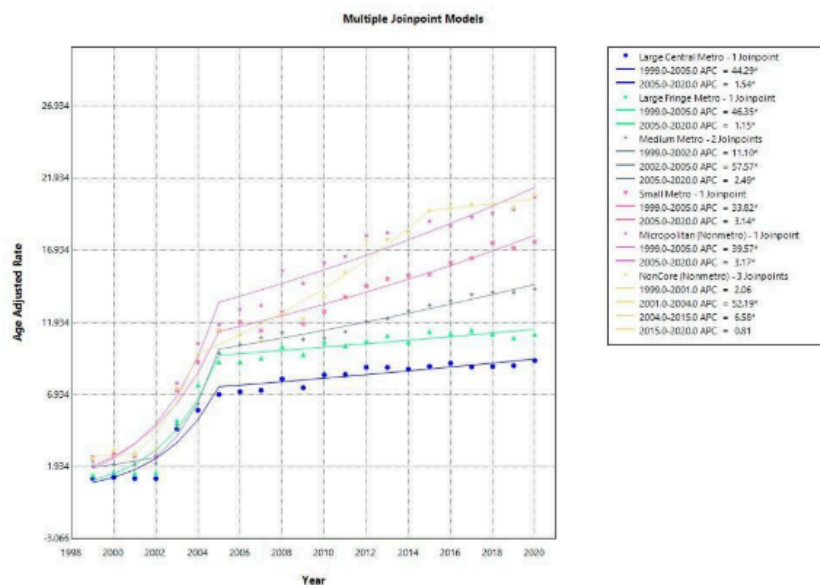


Figure 6

Trends in Age-Adjusted Mortality Rates (AAMRs) for Tobacco-Associated Ischemic Heart Disease Among Adults Aged ≥25 Years in the United States, Stratified by Urbanization Level, 1999–2024.

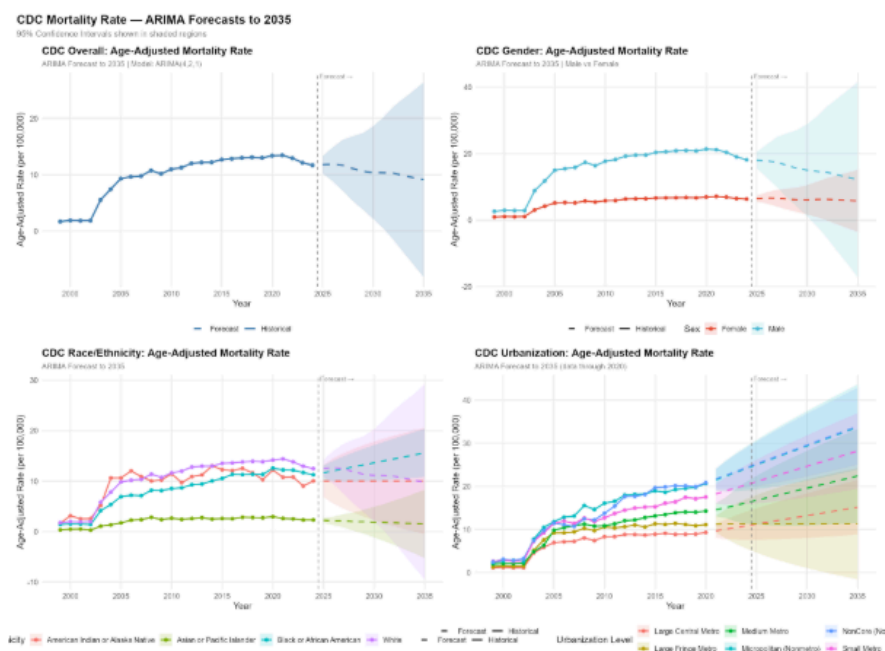


Figure 7

Historical Trends and ARIMA Forecasts of Age-Adjusted Mortality Rates (AAMRs) for Tobacco-Associated Ischemic Heart Disease Among Adults Aged ≥ 25 Years in the United States, Overall and Stratified by Sex, Race/Ethnicity, and Urbanization Level, 1999–2035.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Maintables8.docx](#)
- [Supplementarymaterials7.docx](#)