

Mortality Trends and Demographic Patterns in Unspecified Diabetes Mellitus with Peripheral Circulatory Complications: A CDC WONDER Analysis (1999–2023)

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Abstract

Background

Diabetes mellitus(DM) and resulting Peripheral Circulatory Complications(PCC) contribute significantly to mortality. This study aimed to analyze the national trends related to unspecified Diabetes Mellitus with Peripheral Circulatory Complications (ICD code E14.5) among US adults stratified by demographic and geographical parameters.

Methods

Data were abstracted using the CDC WONDER database. Age-adjusted mortality rates(AAMRs) were calculated, and temporal trends were analyzed using the Join point Regression Program (Version 5.0.2). Annual percentage Changes(APCs) with 95% confidence intervals were calculated. Data were stratified by gender, age group, race/ethnicity, U.S. Census Region, states, and urbanization Status.

Results

From 1999–2023, 193,818 deaths occurred from unspecified DM with PCC. Overall AAMR declined from 2.6 to 1.3 per 100,000 (APC – 6.3%, 95% CI: -10.53 to -5.70, $p < 0.001$), with an initial rise during 1999–2001 (APC + 17.52%, 95% CI: 4.04 to 30.94, $p < 0.05$). Males had consistently higher mortality than females. Adults aged ≥ 65 years bore the highest burden (AAMR 15.05). Racial disparities persisted, with Non-Hispanic Blacks showing disproportionately high rates. Geographically, the South Census Region (AAMR 2.56) and non-metropolitan areas (AAMR 2.5) had elevated mortality. State-level variation was substantial, with the District of Columbia highest (4.0) and Utah lowest (1.2). Inpatient settings (47.8%) and nursing homes (25.1%) were the most common places of death. Sensitivity analysis excluding 2020–2021 confirmed trend robustness (AAPC – 4.11%, $p < 0.05$).

Conclusions

Mortality related to unspecified DM with PCC has declined overall in the US over the past two decades, yet disparities persist. High mortality findings in males, older adults, the South Census, and non-metropolitan regions highlight the need for targeted public health interventions in southern and non-metropolitan areas.

Highlights

- National mortality showed an overall decline from 1999-2023 (AAPC: -4.11%) despite an early rise (1999-2001 APC: +17.52%).

- Males and adults aged ≥ 65 years consistently had the highest mortality burden (AAMR 15.05 per 100,000).
- Inpatient settings (47.8%) and nursing homes (25.1%) were the most common places of death.
- Non-metropolitan areas and Southern Census Region had persistently higher AAMRs (2.5 vs 2.3 per 100,000).
- State-level variation was substantial, with District of Columbia highest (4.0) and Utah lowest (1.2).
- Sensitivity analysis excluding COVID-19 years (2020-2021) confirmed the robustness of long-term trends.

INTRODUCTION

Diabetes mellitus is a chronic disease marked by persistent high blood sugar levels caused either by insufficient insulin production or the body's inability to effectively use the insulin produced. It affects people of all ages, genders, and regions, making it one of the leading causes of global morbidity and mortality (1). Currently, approximately half a billion people worldwide are living with diabetes, and this number is expected to increase by more than 50% over the next 25 years, with projections suggesting 360 million individuals will be affected by 2030 (2, 3). Unspecified diabetes mellitus with peripheral circulatory complications refers to impaired glucose regulation accompanied by vascular damage in the extremities. The term 'unspecified' is used when the exact type of diabetes (type 1 or type 2) causing these complications has not been determined. This condition can progress to severe complications including critical limb ischemia and even amputation(4) .

The vascular complications of diabetes are the most serious manifestations of the disease. The primary causes of death in individuals with DM are largely attributed to coronary artery disease, along with elevated risks of stroke and peripheral vascular disease, known as macrovascular complications(5) . Among these ,peripheral circulatory complications including peripheral artery disease (PAD) ,diabetic foot ulcers, and gangrene stand out as among the most severe and disabling outcomes, substantially increasing the risk of lower limb amputation and premature death. In United states, approximately 8.5 million adults with T2DM have PAD, with annual diagnoses increasing by 1.3% since 2015, disproportionately impacting racial minorities and low-income(5) .

The pathophysiological mechanisms of peripheral circulatory complications in DM are multifactorial. The factors which are increased in diabetes mellitus such as oxidative stress, inflammation, atherothrombosis and endothelial dysfunction are critical to development of circulatory complications(6). A study reports that if PAD is identified on the basis of an ABI of < 0.90 , its prevalence in patients with diabetes may be as high as 29%(7) .The burden of diabetes related vascular disease is well documented, existing studies have predominantly focused on Type 2 diabetes mellitus associated with broad macrovascular complications like myocardial infarction and stroke .The critically important mortality data captured by international classification of disease 10 revision (ICD-10) code E14.5(unspecified diabetes mellitus with peripheral circulatory complications)(4) remains an under

recognized area. This code is often used when type of diabetes is not specified and has a high potential for underreporting of T2DM related peripheral vascular deaths making E14.5 an important marker of hidden disease burden.

Despite this critical association between unspecified diabetes and PCC, no U.S. study has comprehensively evaluated mortality specifically attributed to ICD-10 code E14.5, including sex, racial, and demographic disparities. Therefore, this study provides the first long-term analysis (1999–2023) of mortality trends for unspecified DM with PCC using CDC WONDER data.

Our objectives were to: (1) characterize overall mortality trends for E14.5 over 25 years; (2) identify disparities by sex, age group, race/ethnicity, and geographic region; (3) evaluate urbanization-based differences; and (4) assess the impact of the COVID-19 pandemic through sensitivity analysis. This novel approach fills a critical gap by isolating the specific burden of E14.5 from broader DM complications codes used in previous analyses, providing precise evidence to guide targeted prevention in vulnerable populations.

The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (10).

METHODS

Study setting and Cohort

The mortality data was obtained from CDC WONDER online web interface, a comprehensive database of death certificate data from the fifty states of the USA as well as the District of Columbia from years (1999–2023)(8). The Multiple Cause-of-Death Public Use record death certificates were utilized to find records in which unspecified DM and peripheral circulatory complication were mentioned as multiple cause of death on nationwide death certificates. This database has previously been used to determine trends in mortality of DM and MI. Patients were identified using the International Classification of Diseases 10th Revision Clinical Modification (ICD-10-CM) codes using ICD code E14.5 referring to unspecified diabetes mellitus with peripheral circulatory complications, specifically capturing cases where type of diabetes was not documented but a definitive peripheral circulatory complication was present(9). This study did not require Institutional review board approval, as we used a publicly available, de-identified dataset provided by the government. No further data cleaning or manipulation was performed on raw mortality counts provided by CDC ensuring strong adherence to the source data standards. The study was conducted according to the reporting standards outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (10) .

Data Extraction

Data were extracted and analyzed across multiple stratifications including demographics (age groups 24–44 years ,45–64 years ,and 65–85 years, these age groups cutoffs were selected because they correspond to life stage transitions relevant to potential vascular risks associated with diabetes and to align with prior epidemiologic studies evaluating diabetes associated vascular mortality and allow comparability across different age groups, Ex categorized as male or female; and race/ethnicity categorized as white, Black or African American, Hispanic or Latino, Asian or Pacific Islander, and American Indian or Alaska Native) from 1999 to 2023. Trends in mortality were evaluated based on state-specific variations, U.S. census regions (Northeast, Midwest, South, West), and urbanization status categorized as (metropolitan or non-metropolitan) based on the 2013 National Center for Health Statistics Urban-Rural Classification Scheme(11). Additionally ,place of death was examined based on facility type including medical facility (inpatient, outpatient or ER ,dead on arrival, unknown status), decedent's home, unknown place of death, hospice facility and nursing home or long term care facility.

Statistical analysis

The data were presented as age-adjusted mortality rates (AAMRs) and crude death rates (CRs). AAMRs were derived by applying age-specific mortality rates to the 2000 U.S. standard population, producing a weighted average that facilitates equitable evaluations of mortality rates among different populations or time periods (12). AAMRs were employed to evaluate mortality trends by race/ethnicity, gender, census region, state, and urban–rural classification, while CRs were utilized for age-group analyses because comparisons were within fixed age groups. This approach preserve the actual mortality burden within each age specific group preventing over adjustments that could distort comparisons. Join point regression was applied to log transformed AAMRs to model annual percent changes on multiplicative scales.

Trend analyses were performed using the Join point regression program version 5.0.2 (13) to estimate annual percentage changes (APCs), with corresponding 95% confidence intervals (CIs). A maximum of three join points were allowed following the National Cancer Institute(NCI) guidelines(14) for time series analysis spanning a period of 25 years. The Join point software identifies the simplest join point model by starting with the fewest join points and sequentially assessing the statistical significance of adding additional joinpoints up to a predefined maximum, with Monte Carlo permutation tests (15) .To determine whether APCs represented increasing or decreasing trends, the slope of mortality rate changes was evaluated for significant deviation from zero using a two-tailed t-test. A pairwise comparison between groups was conducted to assess the parallelism of trends. A p value of < 0.05 was regarded as statistically significant.

Human Subjects and Ethics

This study used publicly available, de-identified aggregate mortality data obtained from the CDC WONDER database (Wide - ranging Online Data for Epidemiologic Research). As the data set contains no personal identifiers and is accessible to the public, this analysis does not contain human subjects

research and does not require institutional review board (IRB) approval. The data were accessed for research purposes on 10 October 2024. No identifiable information was available to the authors at any stage of the study. Sensitivity analysis was carried out excluding 2020 and 2021 to reduce and identify whether the COVID-19 pandemic caused distortions in the mortality patterns.

RESULTS

Collectively 193,818 deaths occurred in patients with Diabetes Mellitus with peripheral circulatory complications. Most deaths occurred in inpatient settings (47.80%), followed by Nursing homes (25.10%), decedents' homes (20.40%), hospice facilities (3.70%), and others (3.00%). A higher proportion of deaths were recorded in males (55.80%) aged 65–85 years and above (Supplementary Tables 1 and 2 show related deaths stratified by sex, race and place of death), (Fig. 1 shows the overall summary of the study, illustrating the relationships between the major variables, analytical approach, and key findings.) (Fig. 2 shows the distribution of deaths by place of occurrence).

Annual Mortality Trends for Peripheral Circulatory Complications in Patients with Diabetes Mellitus:

The overall age-adjusted mortality rate (AAMR) in patients with diabetes mellitus with peripheral circulatory complications declined from 2.6 (95% CI: 2.5 to 2.7) in 1999 to 1.3 (95% CI: 1.3 to 1.4) in 2023 (refer to Supplementary Table 1, Fig. 1 for details). Analysis identified 3 join points indicating three distinct trend segments. A significant rise in mortality was exhibited from 1999 to 2001 (APC: 17.52; 95% CI: 4.04 to 30.94; $p < 0.05$), followed by a significant decline from 2001 to 2016 (APC: -6.33; 95% CI: -10.53 to -5.70; $p < 0.001$). From 2016 to 2023, a non-significant decrease was seen (APC: -0.12; 95% CI: -4.53 to 16.45; $p > 0.05$) (Supplementary Table 3 shows APCs stratified by gender, race, urbanization, and census region) (Fig. 3 shows overall annual AAMR and APCs).

Sex-Stratified Mortality Trends for Peripheral Circulatory Complications in Patients with Diabetes Mellitus:

A higher AAMR was observed in males across all years as compared to females. Join point regression revealed 3 join points each in males and females.

In males, a declining trend was observed from 1999 to 2018 (APC: -4.88; 95% CI: -5.57 to -3.97; $p < 0.05$). A rise was observed from 2018 to 2021 (APC: 5.92; 95% CI: 0.78 to 9.35; $p < 0.05$), followed by a sharp decline from 2021 to 2023 (APC: -11.84; 95% CI: -16.88 to -4.10; $p < 0.05$). The changes in the mortality rate were statistically significant ($p < 0.05$). In females, a rise in the trend was noted from 1999 to 2001 (APC: 17.05; 95% CI: 5.15 to 19.4; $p < 0.05$), followed by a decrease from 2001 to 2016 (APC: -7.46; 95% CI: -11.15 to 6.85; $p < 0.05$). Another decline was observed from 2016 to 2023, which was non-significant (APC: -0.57; 95% CI: -5.46 to 17.21; $p > 0.05$) (See Supplementary tables 3 for details.) (Supplementary

Table 4 shows overall and gender-stratified annual AAMR.) (Fig. 4 shows a gender-stratified mortality pattern).

Age Groups Stratified Mortality Trends for Peripheral Circulatory Complications in Patients with Diabetes Mellitus:

Most age groups demonstrated declining mortality throughout the study period with varied magnitude and consistency. The highest AAMR was observed among those aged 65–85 + years (15.05), followed by those aged 45–64 years (1.84), and the lowest was observed among those aged 25–44 years (0.12) (Fig. 1). Trend analysis revealed 3 joinpoints for the 25–44 and 45–64 age groups, while 4 joinpoints were obtained for the older age group (65–85 + years).

Among the age group of 25–44 years, an increase was noted from 1999 to 2003 (APC: 8.67; 95% CI: 2.28 to 23.0; $p < 0.05$), followed by a significant decrease from 2003 to 2006 (APC: -23.49; 95% CI: -28.9 to -11.9; $p < 0.05$), and another decrease from 2006 to 2023 was observed, which was not significant (APC: -0.03; 95% CI: -1.58 to 2.41; $p > 0.05$).

Among the age group of 45–64 years, a significant decrease in the trend was noted from 1999 to 2018 (APC: -4.27; 95% CI: -5.86 to -3.09; $p < 0.05$), followed by a significant increase from 2018 to 2021 (APC: 8.87; 95% CI: 1.0 to 12.7; $p < 0.05$), and another significant decrease from 2021 to 2023 (APC: -12.9; 95% CI: -19.69 to -2.77; $p < 0.05$).

The individuals aged 65–85 + years demonstrated the following mortality pattern: a significant rise was observed from 1999 to 2001 (APC: 21.07; 95% CI: 7.25 to 35.46; $p < 0.05$), followed by a significant decline from 2001 to 2018 (APC: -6.17; 95% CI: -7.87 to -5.48; $p < 0.05$). From 2018 to 2021, a non-significant increase in trend was observed (APC: 6.44; 95% CI: -11.14 to 10.20; $p > 0.05$), followed by a significant increase from 2021 to 2023 (APC: -12.54; 95% CI: -20.54 to -0.17; $p < 0.05$) (Supplementary Table 5 shows AAMRs across age groups) (Fig. 5 shows mortality trends across age groups).

Race/Ethnicity Stratified Mortality Trends for Peripheral Circulatory Complications in Patients with Diabetes Mellitus:

Hispanic or Latino accounted for 8.79% of total deaths. Most deaths were reported in non-Hispanics (91.2%). Among non-Hispanics, White individuals comprised the highest proportion of total deaths (70.5%), followed by Black or African Americans (17.9%), Asian or Pacific Islanders (1.73%), and the lowest deaths were reported in American Indian or Alaska Native (0.90%). The trend analysis highlighted 3 joinpoints for most of the races except for NH American Indians or Alaska Natives for which 2 joinpoints were demonstrated.

Among Hispanics or Latinos, a non-significant increase was noted from 1999 to 2003 (APC: 4.75; 95% CI: -1.09 to 18.90; $p > 0.05$). From 2003 to 2008, a significant drop was noted (APC: -12.16; 95% CI: -18.36 to -8.21; $p < 0.05$), followed by another significant decline from 2008 to 2023 (APC: -5.96; 95% CI: -7.33 to -0.40; $p < 0.05$).

Among NH American Indians or Alaska Natives, the mortality declined from 1999 to 2018 (APC: -6.36; 95% CI: -17.51 to 11.17), followed by a rise from 2018 to 2023 (APC: 6.74; 95% CI: -5.78 to 43.03); these trends were not significant ($p > 0.05$).

For Asian or Pacific Islanders, a non-significant rise was noted from 1999 to 2002 (APC: 11.88; 95% CI: -6.35 to 58.66; $p > 0.05$), followed by a significant decrease from 2002 to 2021 (APC: -9.83; 95% CI: -14.50 to -9.36; $p < 0.05$). From 2021 to 2023, a gradual non-significant decrease was noted (APC: -0.0009; 95% CI: -0.14 to 0.13; $p > 0.05$).

Among Blacks, a significant increase was observed from 1999 to 2001 (APC: 20.70; 95% CI: 0.55 to 42.58; $p < 0.05$), followed by a significant decrease from 2001 to 2016 (APC: -8.37; 95% CI: -14.02 to -7.50; $p < 0.05$). From 2016 to 2023, a slight, non-significant rise was noted (APC: 0.004; 95% CI: -5.19 to 17.11; $p > 0.05$).

Among White, a significant rise from 1999 to 2001 was noted (APC: 17.06; 95% CI: 4.29 to 28.88; $p < 0.05$), followed by a significant decline from 2001 to 2014 (APC: -5.93; 95% CI: -10.21 to -5.19; $p < 0.05$). From 2014 to 2023, a decline was observed that was not significant (APC: -1.23; 95% CI: -3.87 to 8.83; $p > 0.05$) (Supplementary Tables 3, and 6 show APC and annual AAMR across different races.) (Figs. 1 and 6 show mortality trends across races throughout the study period).

Geography-Stratified Mortality Trends for Peripheral Circulatory Complications in Patients with Diabetes Mellitus:

Trends stratified by states:

substantial disparities were observed across U.S. states, reflecting variations in demographics, health care access, and disease burden. The highest AAMR was seen in the District of Columbia (4.0), and the lowest was observed in Utah (1.2). The states falling in the top 90th percentile included Rhode Island (2.8), Vermont (2.8), Maryland (3.05), Mississippi (3.1), South Carolina (3.15), and the District of Columbia (4.0), and the states falling in the lowest 10th percentile included Utah (1.2), Wyoming (1.2), Alaska (1.25), Idaho (1.25), Nevada (1.3), and Colorado (1.4) (Supplementary Table 7, Figs. 1 and Supplementary Fig. 1 indicate mortality burden across U.S. states).

Trends stratified by Census Region:

The South exhibited the highest AAMR (2.56; 95% CI: 2.46 to 2.64), while the lowest was noted in the West (2.07; 95% CI: 1.97 to 2.18). The joinpoint regression model indicated 3 joinpoints each for the Northeast, Midwest, and South, and 4 joinpoints for the West. The Northeast demonstrated a significant decrease from 1999 to 2017 (APC: -5.65; 95% CI: -13.04 to -2.55; $p < 0.05$), followed by a significant increase from 2017 to 2020 (APC: 4.98; 95% CI: 2.57 to 7.04; $p < 0.05$); another sharp significant decrease was noted from 2020 to 2023 (APC: -10.20; 95% CI: -12.54 to -8.33; $p < 0.05$). The Midwest demonstrated similar trends, a significant decrease from 1999 to 2018 (APC: -4.34; 95% CI: -10.29 to -2.41; $p < 0.05$), a significant increment from 2018 to 2021 (APC: 6.40; 95% CI: 1.76 to 9.54; $p < 0.05$), and a significant decline from 2021 to 2023 (APC: -12.92; 95% CI: -18.73 to -6.15; $p < 0.05$). The South followed a similar course; the trend showed a significant decrease in mortality from 1999 to 2018 (APC: -4.41; 95% CI: -5.28 to -3.81; $p < 0.05$) then a significant increment from 2018 to 2021 (APC: 8.76; 95% CI: 3.15 to 12.36; $p < 0.05$) followed by a sharp decline from 2021 to 2023 (APC: -10.92; 95% CI: -16.08 to -3.41; $p < 0.05$). The West demonstrated a non-significant gradual rise from 1999 to 2015 (APC: 0.56; 95% CI: -1.73 to 8.34; $p > 0.05$), followed by a significant decrease from 2015 to 2018 (APC: -8.96; 95% CI: -11.09 to -6.18; $p < 0.05$). From 2018 to 2021, a non-significant rise was observed (APC: 2.49; 95% CI: -0.25 to 4.97; $p > 0.05$), and a significant decline from 2021 to 2023 (APC: -17.77; 95% CI: -22.40 to -14.15; $p < 0.05$) (Supplementary Tables 3, 8, and Fig. 1 and supplementary Fig. 2 demonstrate AAMR and APC across various census regions).

Trends stratified by urbanization:

Non-metropolitan areas maintained a higher AAMR than metropolitan areas (2.5 vs 2.3). The overall mortality curve showed 2 joinpoints for metropolitan areas and 3 joinpoints for non-metropolitan areas. For metropolitan areas, a significant increase was noted from 1999 to 2001 (APC: 16.13; 95% CI: 0.11 to 29.23; $p < 0.05$), followed by a significant decline from 2001 to 2020 (APC: -6.21; 95% CI: -7.56 to -5.58; $p < 0.05$). Non-metropolitan areas exhibited comparable trends, with a significant climb from 1999 to 2001 (APC: 18.22; 95% CI: 8.24 to 29.25; $p < 0.05$), a significant drop from 2001 to 2018 (APC: -4.71; 95% CI: -6.54 to -4.30; $p < 0.05$), followed by a non-significant rise from 2018 to 2020 (APC: 11.24; 95% CI: -3.36 to 19.17; $p > 0.05$) (Supplementary Tables 3 and 9 and Fig. 1 and supplementary Fig. 3 show mortality trends stratified by urbanization in the U.S. across the study period).

Sensitivity analysis:

To account for distortions in mortality reporting during the COVID-19 pandemic, joinpoint analyses were repeated after excluding 2020–2021. The direction and magnitude of trends remained consistent. The overall trend exhibited decreasing mortality from 1999 to 2023 (AAPC: -4.11; 95% CI: -5.51 to -2.70; $p < 0.05$). The decrease was more prominent among females (AAPC: -6.52; 95% CI: -3.78 to -7.19; $p < 0.05$). The older age group (65–85+ years) exhibited the most prominent decline (AAPC: -2.94; 95% CI: -4.36 to -1.50; $p < 0.05$). The Asians exhibited the most decline (AAPC: -6.76; 95% CI: -8.80 to -4.67; $p < 0.05$). Geographical trends revealed a prominent decline in the Midwest (AAPC: -3.44; 95% CI: -4.50 to -2.37; $p < 0.05$) and in the metropolitan area (AAPC: -4.40; 95% CI: -5.88 to -2.89; $p < 0.05$) (Refer to supplementary Table 10 for details).

DISCUSSION

This study provides unparalleled detail of U.S. death rates from peripheral circulatory complications of diabetes mellitus over 25 years. Joinpoint regression reveals time-dependent changes across sex, age, race, state of residence, and degree of rurality. The all-cause age-standardized mortality shows a steady decline between 1999 and 2023 without interruption. Nevertheless, persistent subgroup disparities and time-dependent perturbations reveal structural and biological vulnerability that threaten broad-based gains. This rigorous approach uniquely identifies the COVID-19 disruptions and rural disparities missed by previous studies(16)(17)(20). Its merging of the analysis of long-term epidemiological trends with mechanistic and systemic explanations makes it an indispensable tool for informing targeted interventions and framing public health policy.

Increased mortality evident in men reflects a combination of higher baseline cardiovascular and metabolic risks, such as smoking and hypertension, further exacerbated by behavioral predispositions of delayed healthcare engagement. Consequently, men manifest advanced macrovascular disease. By contrast, women demonstrate lower but more variable mortality rates. These likely reflect a predominance of microvascular disease that is more difficult to detect, along with gender biases in vascular referrals resulting in underdiagnosis (16)(23)(24). These sex-specific mechanisms require the development of gender-specific diagnostic strategies. Improved microvasculature assessment benefits women. Selective vascular screening benefits men. These approaches would help improve early detection and reduce the mortality burden for men.

Age stratification reveals unique biological and clinical complexities. Older adults (≥ 65 years) suffer the highest mortality burden from cumulative chronic atherosclerosis accumulation, impaired tissue blood supply, and enhanced susceptibility to infections that exacerbate ischemic limb damage. Middle-aged adults exhibit an increasing mortality burden based on the accelerating rates of obesity and metabolic syndrome. These factors accelerate vascular disease through chronic inflammation and endothelial dysfunction. While the absolute mortality rates are lower among younger adults, observed trends indicate a growth in the prevalence of early-onset diabetes with progressive vascular disease. This again highlights the paramount importance of primary prevention and early treatment strategies for this younger age group.(18)(24)

A profound investigation of racial and ethnic inequities reveals extensive and persistent disparities. Mortality rates among non-Hispanic Black populations are two to three times higher compared to Whites, particularly in rural regions. This is attributable to socioeconomic disadvantage, limited access to vascular specialists, fragmented care coordination, and delayed revascularizations despite comparable disease severity (20)(23). Poverty in numerous rural, predominantly Black regions impairs medication adherence and regular follow-up. This leads to a more rapid disease progression of peripheral artery disease and late-stage presentations, making them difficult to manage. Systemic racism and implicit bias further impact referral practices and the timeliness of intervention. Hispanic populations face similar challenges due to language and cultural barriers that promote access issues,

although some improvement has been documented regarding specialty diabetes programs. Asian and Pacific Islander populations demonstrate decreased prevalence of adverse cardio-metabolic risk factors and better access to urban healthcare services. Their mortality rates decrease with the most significant deviation. American Indian and Alaska Native populations manifest erratic patterns of mortality due to small population size and significant health system shortages, which pose major obstacles to specialized vascular and limb preservation care (17)(20)(23). Racial disparities will be best addressed with culturally tailored interventions and system-wide changes to improve health care equity and accessibility for under-resourced communities and races facing the highest mortalities.

The disparities in mortality patterns are further compounded by geographic considerations. Southern states, particularly Mississippi, South Carolina, and the District of Columbia, tend to have the highest death rates. Higher prevalence of diabetes drives this. Underlying factors include entrenched poverty and prevalent obesity epidemics. A deficit of vascular specialists runs parallel to a shortage of multidisciplinary teams for the care of diabetic feet(17)(24). Rural non-metropolitan areas significantly amplify such disparities due to travel distances impeding access to care, reduced availability of options for screening, and greater reliance on emergency medicine for limb preservation. Death rates increase disproportionately in these regions. For Black adults living in rural areas, diabetes mortalities are more than twice as high as those of their urban counterparts. This points out how Black populations and rural groups are experiencing a high burden of mortality. Urban areas, on the other hand, have low mortality rates because of better accessibility to vascular surgeries and comprehensive programs for the preservation of limbs. Disparities in the gradient for Black rural populations point to large-scale interaction between race and place, wherein systems of inequality dramatically elevate risks for vascular health.

Policy actions must rapidly target tele-vascular hubs, mobile screening units, incentivize providers to practice in rural areas, and expand multidisciplinary teams. These interventions would help in managing this crisis of disparities observed in mortality patterns where some groups suffer more than others, effectively (16)(17)(24). Studies of the location of deaths reveal fragmented care: almost 50% of deaths occur in hospitals, reflecting advanced acute complications among vulnerable diabetics. Another quarter of deaths occur in nursing homes, reflecting multimorbidity and frailty among aging populations. Low rates of home and hospice deaths reflect significant gaps in the management of chronic diseases and the integration of palliative care for advanced vascular disease in the community. This points to a tremendous opportunity to improve the quality of life for patients by expanding home wound care and hospice services. (18)

Different from prior CDC WONDER analyses that focused primarily on amputations or shorter periods, the breadth of this study over 25 years and enhanced joinpoint regression methods, along with efficient sensitivity analysis, reveal trend inflection points not previously reported. It directly quantifies the transient mortality disruptions from the COVID-19 pandemic and specifically explores the interactive effects of urbanization and race, providing both temporal and demographic granularity. These findings

establish unique associations between epidemiological trends and health care access with biological vulnerabilities (16)(17)(20)(21)(22).

Recent bibliometric analyses have documented the rapid emergence of large language models such as ChatGPT in medical research, with exponential growth rates of approximately 27% per month and particular relevance to internal medicine, clinical decision support, and medical education [26]. While our study employed traditional epidemiological methods through CDC WONDER and Joinpoint regression, future investigations into diabetes-related peripheral circulatory complications mortality could benefit from integrating machine learning approaches to analyze larger datasets, identify subtle nonlinear trends, and integrate diverse data sources. However, as these analyses emphasize, careful consideration must be given to algorithmic bias, data privacy, validation against established epidemiological standards, and the potential for exacerbating healthcare disparities if AI tools are deployed without appropriate safeguards in resource-limited settings [26]. The intersection of traditional epidemiology and emerging AI methodologies offers promising avenues for a more nuanced understanding of mortality patterns while maintaining scientific rigor.

What this research contributes is the advancement from descriptive epidemiology to mechanistic and systemic analysis. It explains how a decline in overall mortality conceals continued rural and racial inequalities. Without addressing these racial and rural disparities, mortality trends and prevalence associated with peripheral circulatory complications as a consequence of diabetes mellitus won't be improved. It reveals, for the first time, the impact of the pandemic on health care resilience, identifying nodes at which global health emergencies erase significant gains. The granular findings inform specific public health measures: expansion of vascular access in rural areas, development of race-conscious multidisciplinary teams, sex- and age-based implementation of screening protocols, and enhancement of resilience in chronic care systems. The integrative approach yields an approach that ensures progress in mortality equates to health equity and sustainable development.(19)(20)(23)

The COVID-19 pandemic brought to light the fragile aspect of chronic disease management. It temporarily obviated gains in mortality rate reductions across multiple subgroups. The current study's 25-year longitudinal assessment, with joinpoint regression methodologies, offers clear temporal resolution regarding subtle changes in this epidemic that were missed previously. Importantly, the sensitivity analysis excluding the pandemic years (2020–2021) showed that the direction and magnitude of mortality trends remained consistent, confirming the robustness of our findings. Notably, it provides critical information to inform immediate health policy and clinical action. Effective responses should target the rapid implementation of telehealth-supported vascular care to remote and resource-constrained regions. Multidisciplinary diabetic foot teams must be expanded to match the patients' racial representations to overcome cultural and medical barriers. There is a dire need for incentivization toward redirecting vascular experts into resource-poor areas, especially the groups that suffer the most, including the Black racial groups and rural residents, and the Districts falling in the 90th percentile with respect to age-adjusted mortality rates. Health systems must bolster crisis preparedness and resilience to maintain gains during future disruptions.

America stands at a crossroads for vascular health. Failing to take decisive action has the potential to harden the current unacceptable pattern of avoidable early deaths among the nation's most disadvantaged diabetic population. The mechanistic insights and extensive subgroup analyses from this trial represent solid guidance toward the translation of statistical benefits into durable, equitable health outcomes, so that, especially those groups that are facing the burden of the highest mortality, are considered the main target for interventions, and mortality associated with diabetes could be reduced. Achieving substantial equity in the face of entrenched disparities requires rapid, coordinated, and concentrated efforts to topple entrenched systemic barriers and fully realize the full promise of modern diabetes management (19)(20)(23)(25).

STUDY LIMITATIONS:

This analysis is limited by reliance on data from death certificates, which are subject to misclassification of peripheral circulatory disease and variable attribution of diabetes as a cause of death. The ecological design prohibits conclusions of causality on an individual level. Sample sizes for some racial subgroups—most notably American Indian and Alaska Native populations—are small, resulting in unreliable trend estimates. Despite these limitations, the methodology is consistent with standard epidemiological criteria from CDC WONDER (16)(17)(20) and affords sound national and subgroup characterization. Also, the efficient sensitivity analysis added in our study's joint point analysis adds to the accuracy of findings and eliminates any minor errors.

CONCLUSION

Our study shows mortality trends associated with peripheral circulatory complications as a consequence of diabetes mellitus in the United States over a period of 25 years, from 1999 to 2023. These trends demonstrate that although marked advances in diabetes vascular treatment have lowered overall death rates related to peripheral circulation, strong disparities persist based on sex, age, race/ethnicity, and geography. Men suffer the macrovascular consequences more profoundly due to exposure to risk factors and delays in care, while older adults bear the chronic burden of vascular damage. Blacks and Hispanics, especially those living in rural southern territories, suffer death rates two to three times higher compared to Whites and urban dwellers. The communities face systemic issues, including limited access, provider shortages, economic disadvantage, and pervasive bias that fuels risk. The COVID-19 pandemic clearly exposed the fragility of these gains, resulting in short-term increased mortality among the vulnerable. This study's rigorous, long-term analytical approach clearly exposes these nuances. To safeguard and extend gains, immediate attention needs to be focused on advancing telehealth-supported vascular services to resource-poor areas, expanding culturally sensitive multidisciplinary care, encouraging the distribution of vascular specialists, and reinforcing the resilience of chronic care systems. Failing to do so in earnest threatens to make permanent avoidable early deaths among America's most vulnerable diabetic patients. This research frames an evidence-based scheme that the nation should use to translate statistical gains into enduring, equitable vascular health outcomes that are fair to the overall population so that no underprivileged group suffers.(19)(20)(23)(25)

Abbreviations

AAMR

Age-Adjusted Mortality Rate

APC

Annual Percent Change

AAPC

Average Annual Percent Change

CDC

Centers for Disease Control and Prevention

ICD

10-International Classification of Diseases, 10th Revision

Declarations

Ethics Approval and Consent to Participate

This study used publicly available, de-identified data from CDC WONDER and was exempt from institutional review board approval.

Consent for Publication

Not applicable.

Availability of Data and Materials

The dataset analyzed in this study is publicly available on the CDC WONDER online database (<https://wonder.cdc.gov/>). No special access permissions were required.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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Authors' Contributions

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Arooj Ihsan Ullah: Writing – original draft, Writing – review & editing.

Safiullah Soomro: Writing – original draft, Writing – review & editing.

Fizzah Ikram Ul Haq: Writing – original draft, Writing – review & editing.

All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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Figures

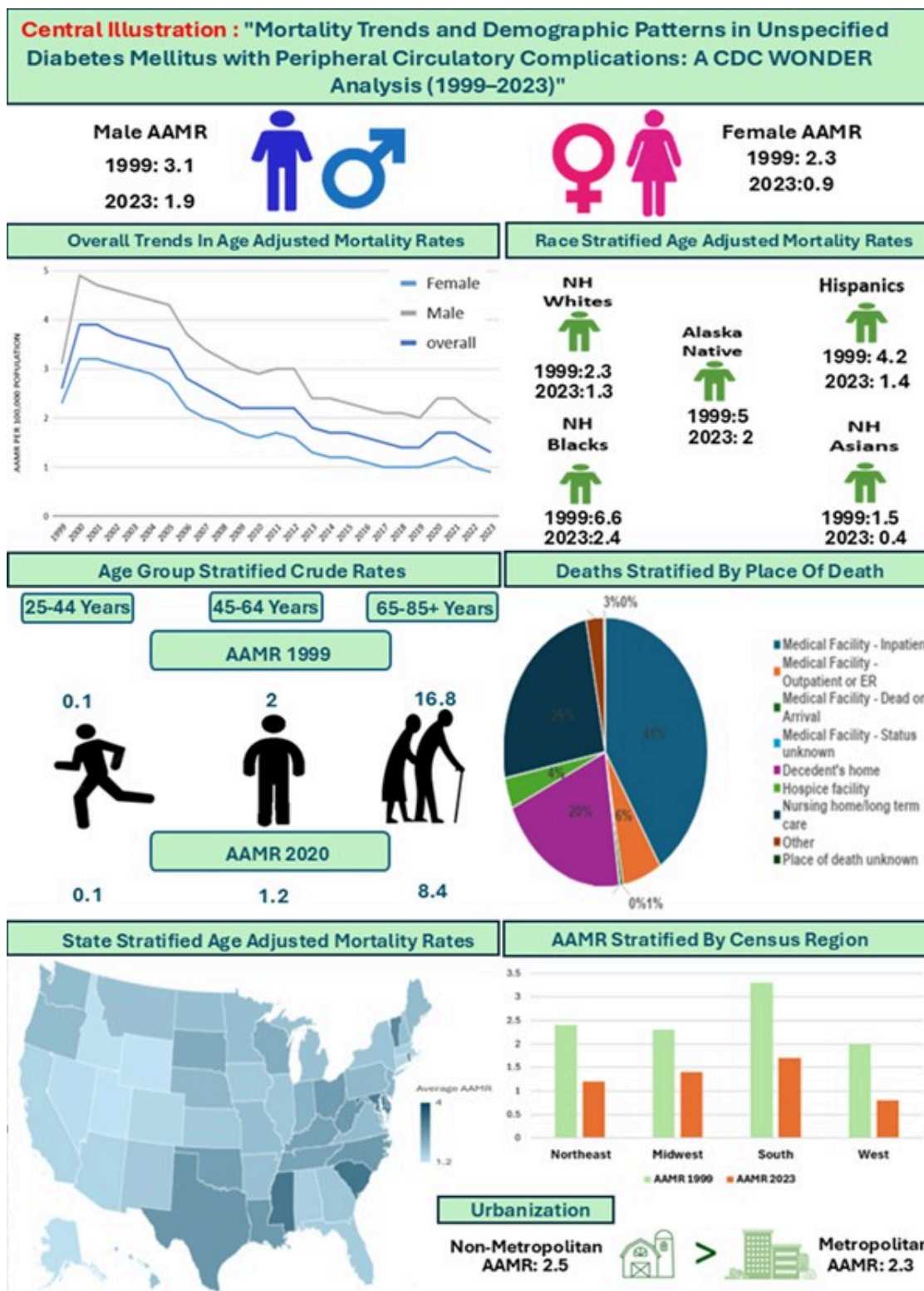


Figure 1

(Central Illustration): Patterns and distribution of mortality related to Unspecified Diabetes Mellitus with Peripheral Circulatory Complications in the U.S. from 1999 to 2023, emphasizing age-adjusted mortality trends across sex, race, urbanization level, and geographic region.

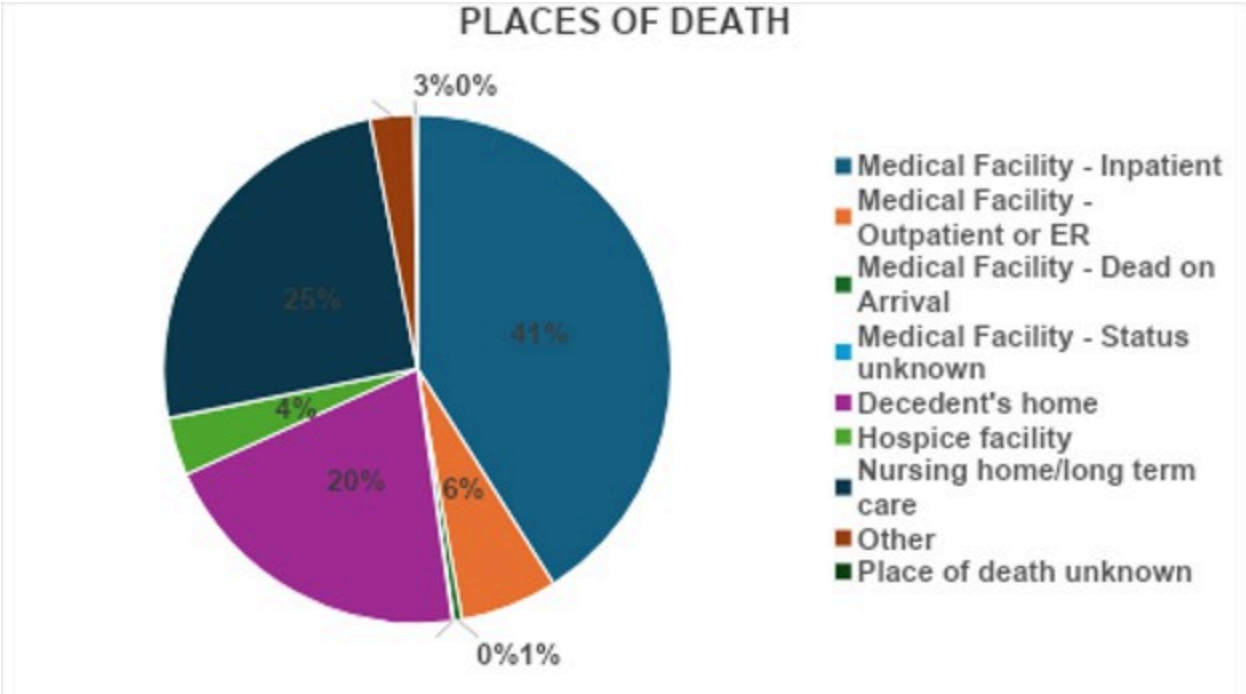


Figure 2

Distribution of Unspecified Diabetes Mellitus with Peripheral Circulatory Complications related deaths by place of occurrence in the U.S. (1999–2023).

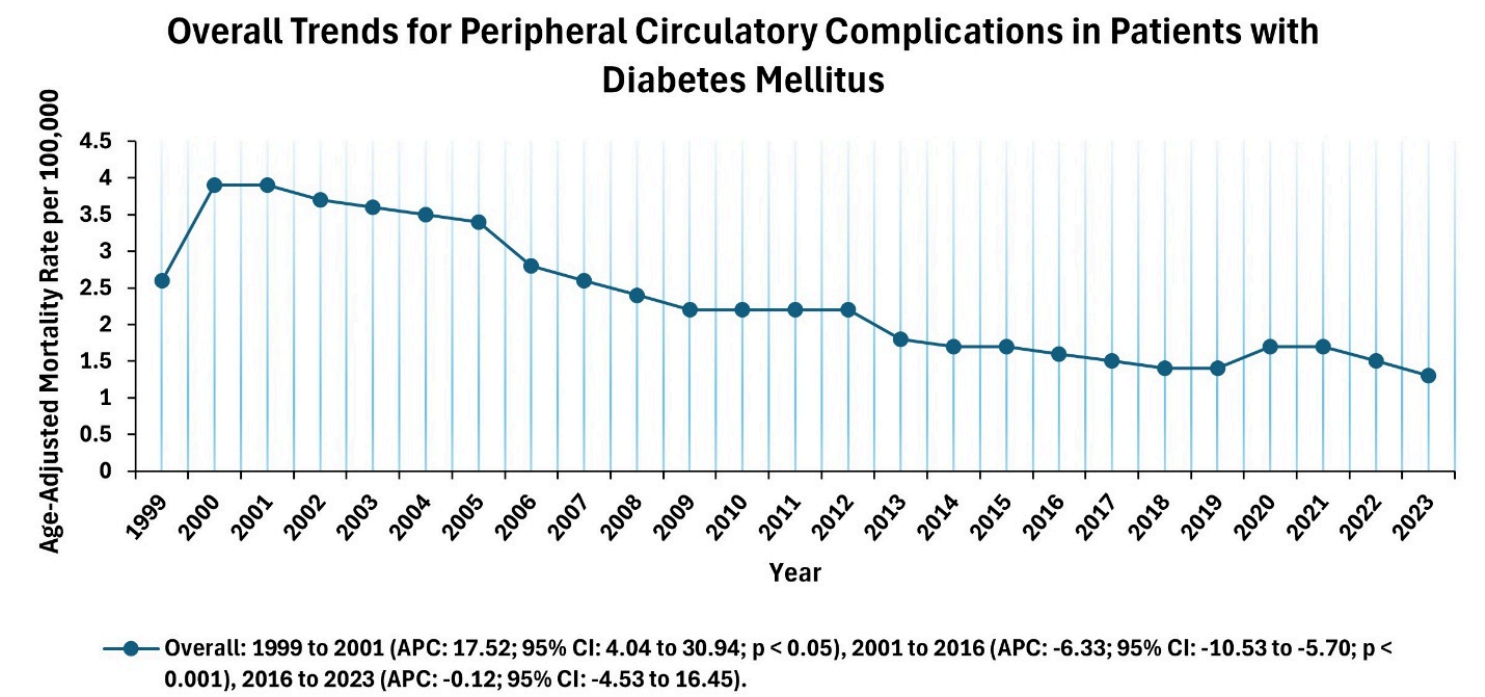


Figure 3

Overall Trends in Age-Adjusted Mortality Rate in Unspecified Diabetes Mellitus with Peripheral Circulatory Complications in the U.S. from 1999 to 2023. Rates are per 100,000, age-adjusted to 2000

U.S. standard.

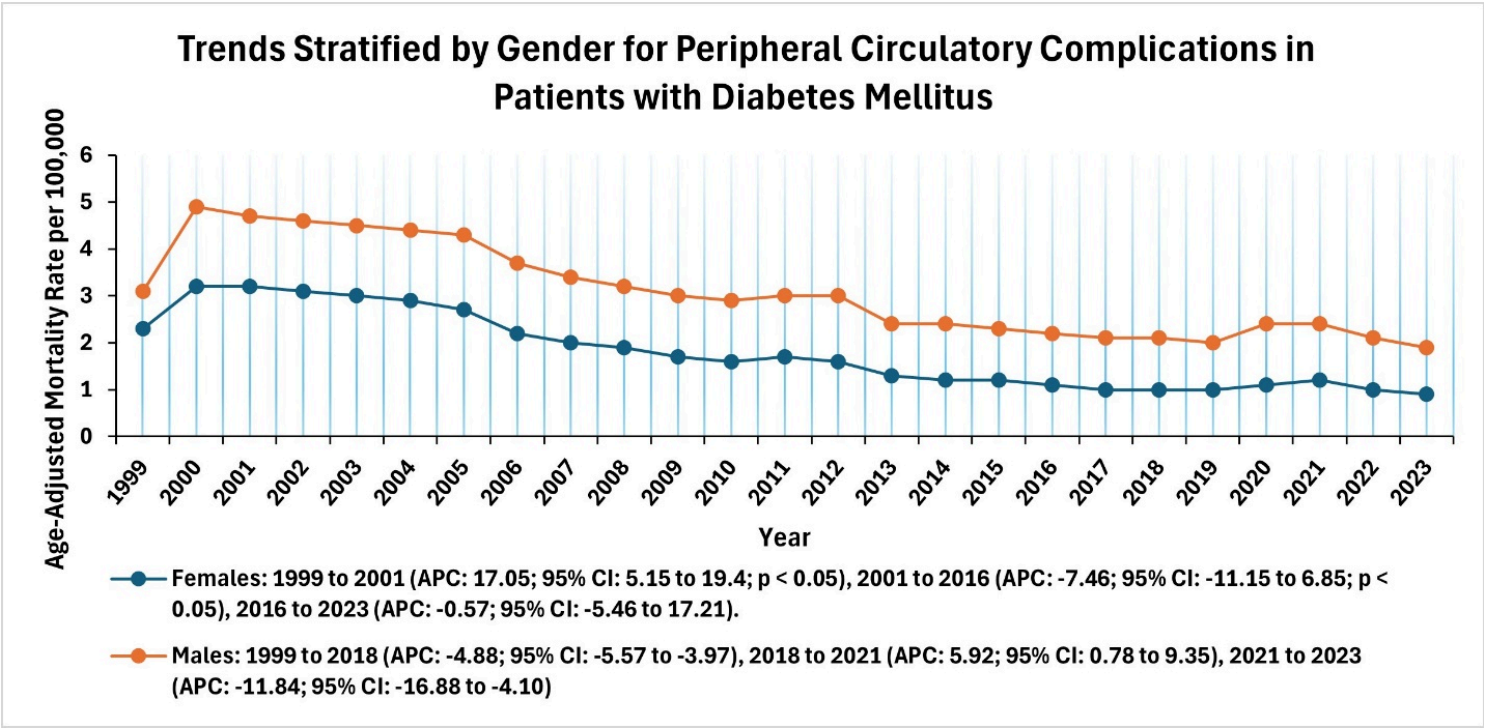


Figure 4

Trends in Age-Adjusted Mortality Rate in Unspecified Diabetes Mellitus with Peripheral Circulatory Complications Stratified by Sex in the U.S. from 1999 to 2023.

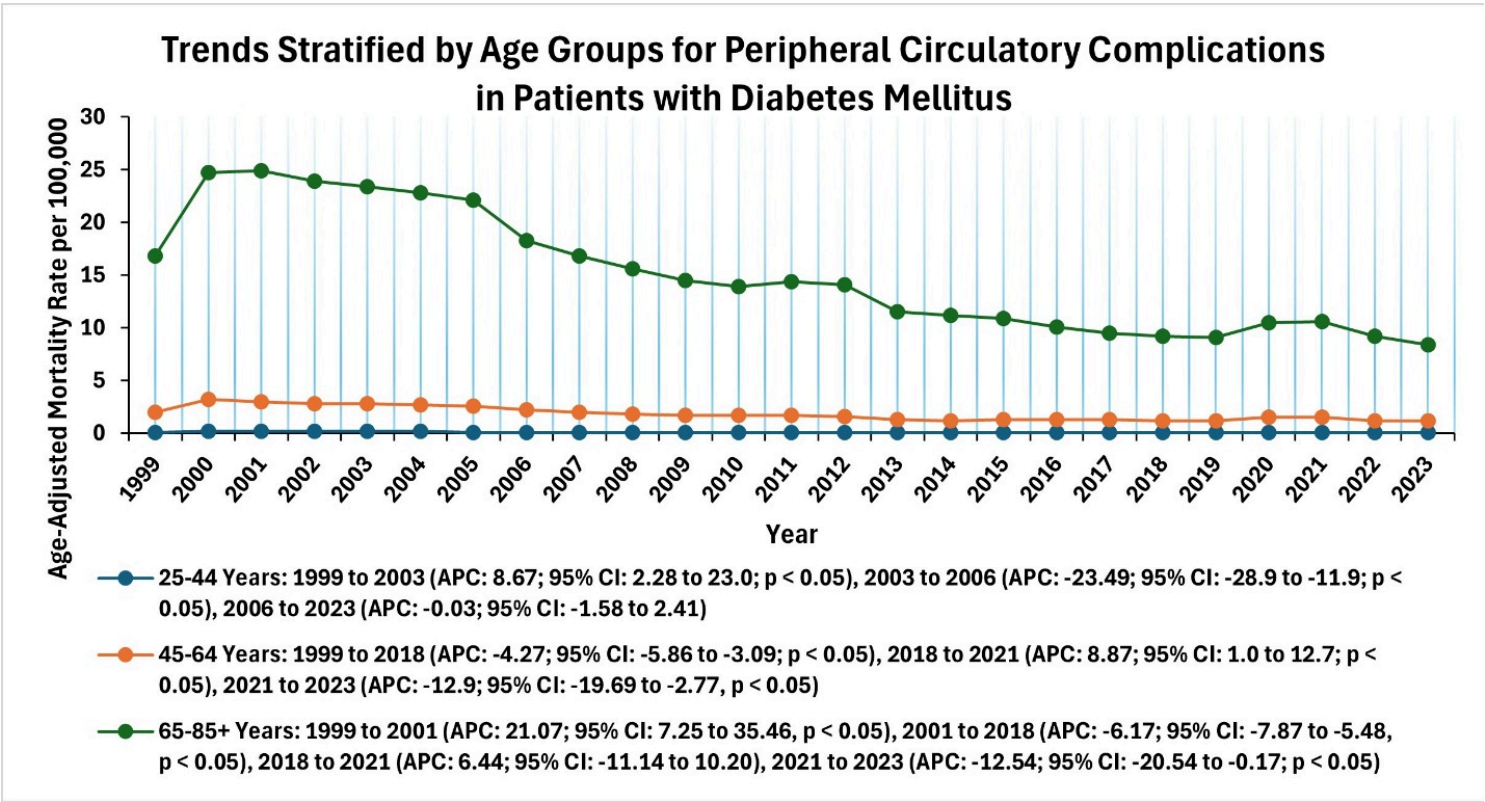


Figure 5

Trends in Age-Adjusted Mortality Rate in Unspecified Diabetes Mellitus with Peripheral Circulatory Complications Stratified by Age Groups in the U.S. from 1999 to 2023.

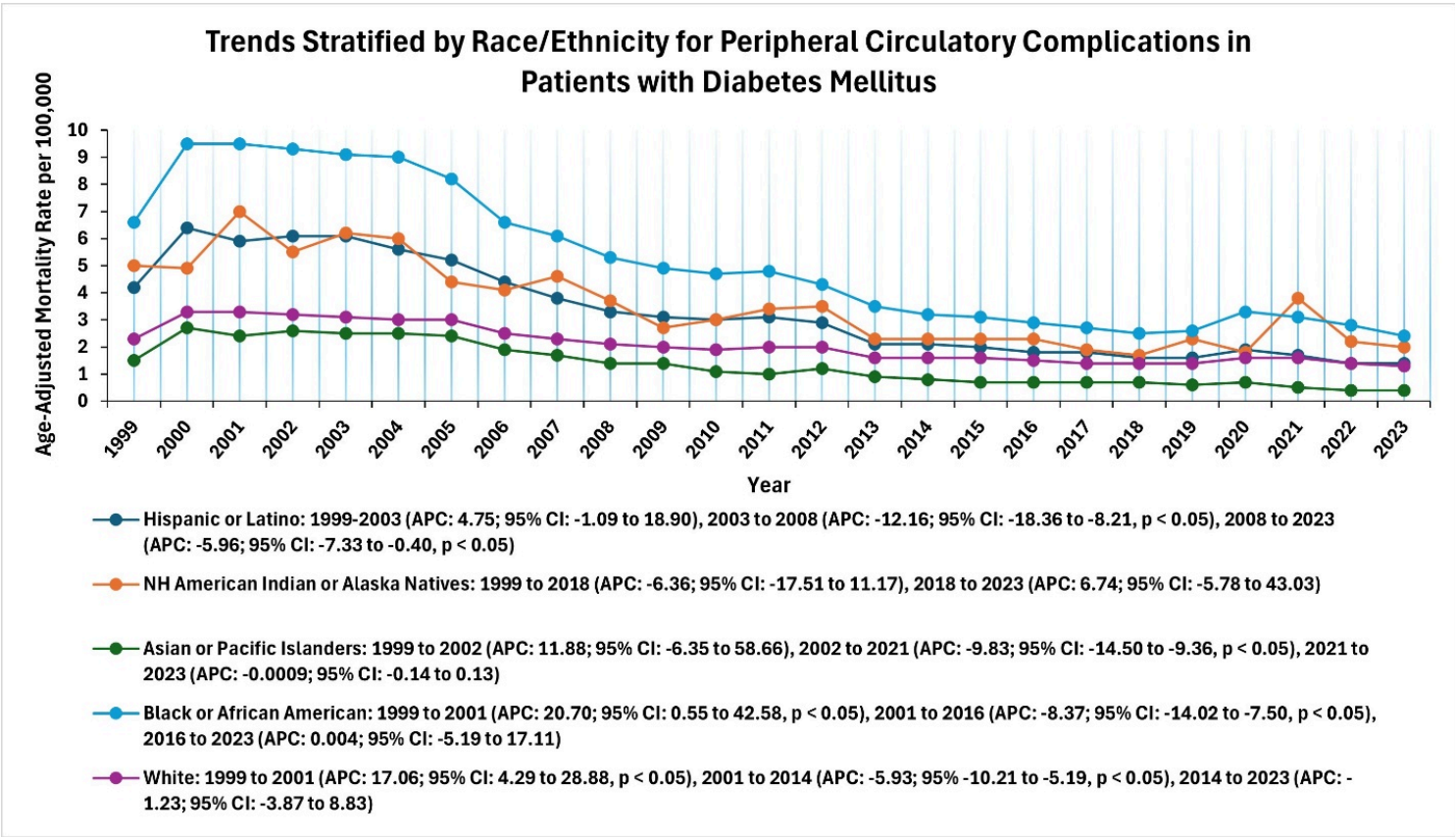


Figure 6

Trends in Age-Adjusted Mortality Rate in Unspecified Diabetes Mellitus with Peripheral Circulatory Complications Stratified by Race/Ethnicity in the U.S. from 1999 to 2023. NH = Non-Hispanic.

Supplementary Files

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