Population-Based Study

Chronic Pain-Associated Mortality in the United States: A Population-Based Study, 1999-2023

Ali Al-Salahat, MBChB[1], Mittal Prajapati, MBBS[1-3], Ali Bin Abdul Jabbar, MBBS[2], Jyotsna Nagda, MD[3], Peter Staats, MD[4], and Laxmaiah Manchikanti, MD[5]

From: [1]Neurology Department, Creighton University, Omaha, NE; [2]Department of Internal Medicine, Creighton University, Omaha, NE; [3]Beth Israel Deaconess Medical Center, Department of Anesthesia, Critical Care and Pain Medicine, Harvard Medical School, Boston, MA; [4]National Spine and Pain Centers, Atlantic Beach, FL; [5]Pain Management Centers of America, Paducah, KY; Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY; Department of Anesthesiology, School of Medicine, LSU Health Sciences Center, Shreveport, LA

Address Correspondence: Ali Al-Salahat, MBChB, Neurology Department, Creighton University Omaha, NE
E-mail: alsalahatmd@gmail.com

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Background: Chronic pain is increasingly recognised as a disease with substantial morbidity, yet large-scale data on chronic pain-associated mortality trends and disparities are lacking.

Objective: To examine nationwide temporal trends and demographic disparities in chronic pain-associated mortality in the US from 1999 to 2023.

Methods: Death certificate data from the Centres for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database (1999-2023) were extracted. All deaths with chronic pain listed as a contributing cause were included (n = 67,417), reporting chronic pain (ICD-10 codes R52.1 and R52.2). Age-adjusted mortality rates (AAMRs) per 1,000,000 population, standardized to the 2000 US population. Trends were analysed using Joinpoint regression and represented by annual percentage changes (APCs) with 95% confidence intervals.

Results: Among 67,417 chronic pain-associated deaths (61.5% female), AAMR increased from 1.97 per 1,000,000 in 1999 to 10,72 per 1,000,000 in 2023 (average APC, +6.3%; 95% CI5.8% to 6.8%). Increases in AAMR were noted across both sexes (females; average APC, 6.1%; males: 6.6%), age groups (≥ 55 years: average APC, 6.5%; < 55 years: 4.7%), race/ethnicities (non-Hispanic White; average APC, 6.3%; non-Hispanic Black: 10.4% to 2019 then stable; Hispanic: similar acceleration), and regions (all average APCS, 5.3% to 6.3%). Females and those ≥ 55 years had higher AAMRS; the South had the highest burden (33.9% of deaths).

Conclusion: These findings revealed a marked rise in chronic pain-associated mortality, disproportionately affecting females, older adults, non-Hispanic White individuals, and the South, signalling chronic pain as a public health concern. Enhanced documentation, interventions targeting comorbidities and disparity-focused policies are urgently needed to mitigate this burden.

Key words: Chronic pain, pain, intractable pain, mortality, health care disparities

Key Message: Chronic pain-associated mortality in the United States increased nearly tenfold between 1999 and 2023, with notable disparities by age, sex, race/ethnicity, and region. These findings highlight chronic pain as a growing public health concern and underscore the need for improved documentation, targeted interventions, and equity-focused pain management policies.

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The definition of Pain was revised by the International Association for the Study of Pain (IASP) in 2020 as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (1). Persistent or recurrent pain for more than 3 months may be classified as chronic pain (CP) (2). CP is viewed by the IASP as a chronic, debilitating condition by itself (3). This view highlights the substantial morbidity and disability conferred by CP. National estimates from the United States (US) Centers for Disease Control and Prevention (CDC) reported a 20.9% prevalence of CP during 2021 in adults, i.e., one in 5 individuals (4).

The consequences of CP involve complex biopsychosocial interactions (1,2). CP can suppress immune function, decrease brain grey matter, alter gene expression, and lead to a phenotypic switch in the peripheral nervous system (PNS) (2,3,5). In people with CP, the neurons in the central nervous system (CNS) can become hyper-sensitive to stimulation in a phenomenon described as central sensitization (5-7). Neuroinflammation not only impacts the CNS but also affects the PNS and the immune system (8). When left unchecked, inflammatory responses can become dysregulated and have been implicated in a wide range of pathological conditions, including cancer, cardiovascular disease, metabolic disorders, and neurodegenerative diseases such as Alzheimer's disease. Chronic inflammation disrupts normal cellular signalling and tissue homeostasis, contributing to the progression and severity of these illnesses (8).

Mortality associated with CP is underestimated and under-documented. CP is associated with substance abuse, psychiatric disorders, polypharmacy with medication-related problems, physical inactivity, low-quality lifestyle, poor diet, and financial difficulties (9-11). Studies have also demonstrated that people with CP have increased all-cause mortality through opioid prescriptions (12). Additionally, cardiovascular disease-associated mortality has been described to have a dose-response relationship with the duration and degree of CP (13). While the etiology of increased mortality is not entirely clear, there is a growing body of evidence to show that CP-associated mortality (CPAM) may represent a public health concern. There is no data on CPAM, especially its temporal trends and demographic disparities.

This study aimed to examine demographic disparities in CPAM trends nationwide in the US from 1999 to 2023. We analyzed temporal trends in overall CPAM and differences in sex, race/ethnicity, age groups, and regions across the US. This data can help inform national and international policies related to CP and raise public awareness of CP.

Methods

Study design and participants

This population-based retrospective study followed the RECORD reporting guidelines. We extracted data on CP-related deaths (CPRD) in the US from the CDC Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database. The CDC WONDER database derives data from death certificates filed in state vital statistics offices. It collects them from all states and the District of Columbia into a national database by the National Centre for Health Statistics (NCHS) (14). The entire US population, which is based on US Census Bureau estimates, is used as a denominator for the mortality data (14,15). We separately queried the Multiple Cause of Death Files for 1999-2020 and 2018-2023 and merged them for analysis (16,17). The International Classification of Diseases (ICD), 10th Revision, Clinical Modification codes R52.1 and R52.2 were used to identify CP (18).

Stratification Groups

Data extracted for analysis consisted of biological sex, Race/Ethnicity, age groups (< 55 years, ≥ 55 years), and US Census region (West, South, Midwest, Northeast). Biological sex included female or male. Race/ethnicity was divided into non-Hispanic (NH) White, NH Black, and Hispanic based on what was listed on the patient's death certificate. Age groups were divided into young adults (< 55 years) and older adults (≥ 55 years) to have enough deaths to allow comparison and analysis. Data on other Ethnic groups (NH Asian or Pacific Islander, NH American Indian, etc.) could not be examined because of suppressed data for many years in each subgroup.

Statistical Analysis

Age-adjusted mortality rates (AAMR) per 1,000,000 and crude number of deaths related to CP were calculated. AAMR controls the variation in age distribution to allow data comparisons. It was also standardized using the 2000 US standard population (19). The Joinpoint Regression Program (Joinpoint version 5.4.0 available from the National Cancer Institute, Bethesda, Maryland) was utilized to analyze temporal trends from

1999 to 2023 (20). Using the Monte Carlo permutation test, we calculated the annual percentage change (APC) with 95% confidence intervals (CIs) for the AAMRs for the line segments linking a Joinpoint. The weighted average of the APCs was calculated and reported as average APCs (AAPC) with their 95% CIs. APC and AAPCs were considered to increase or decrease if the slope describing the change in mortality over the time interval significantly differed from zero using a 2-tailed t-test. Statistical significance was set at $P \leq 0.05$ (21). The study was exempt from institutional review board approval because the dataset from the CDC WONDER is anonymized, publicly available, and deidentified.

Results

Overall Mortality

There were 67,417 CPRD over the study period in the US. The number of CPRD increased by 745.65% from 1999 to 2023. The CP-related AAMR (CP-AAMR) increased from 1.97 per 1,000,000 in 1999 to 10.72 per 1,000,000 in 2023. From 1999 to 2013, the APC for CP-AAMR was +9.54%, and continued to increase from 2013 to 2023. Table 1 shows the total CPRD and CP-AAMR over the study period and by the stratification groups.

Sex-Based Disparities

Of all CPRD, 41,498 (61.55%) were female individuals, and 25,919 (38.45%) were male individuals. In female individuals, the AAMR increased significantly from 2.1 in 1999 to 10.4 in 2013 (APC +9.32%, 95% CI: 8.21 to 11.05) and increased to 11.61 in 2023. In male individuals, the AAMR accelerated from 1.71 in 1999 to 7.94 in 2014 (APC +9.60%, 95% CI: 8.58 to 11.17), and further increased to 9.36 in 2023 (Fig. 1). The AAPCs for female and male individuals were +6.05 (95% CI: 5.55 to 6.77) and +6.61 (95% CI: 6.13 to 7.32), respectively.

Race/Ethnicity-Based Disparities

Regarding race/ethnicity-based differences, 62,389 CPRD involved NH White individuals, and only 3,678 and 2,594 involved NH Black and Hispanic individuals, respectively. The AAMR for NH White individuals increased significantly (AAPC +6.34, 95% CI: 5.89 to 6.97) throughout the study period but showed rapid acceleration between 1999 and 2013 (Fig. 2). For NH Black individuals, the AAMR increased significantly from 0.54 in 1999 to 6.45 in 2019 (APC = +10.43, 95% CI: 9.55 to 12.42), but stabilized between 2019 and 2023. The AAMR in Hispanic individuals showed similar acceleration from 1999 to 2021, but showed no significant change from 2021 to 2023.

Table 1. *Changes in chronic pain-related deaths and age-adjusted mortality rates from 1999 to 2023, stratified by age group, biological sex, region and race/ethnicity.*

	1999		2023		AAPC (95% CI)	APC segment 1 (95% CI, years)	APC segment 2 (95% CI, years)
	No.	AAMR	No.	AAMR			
Total	541	1.97	4,577	10.72	6.28 (5.86 to 6.89)	9.54 (8.53 to 10.97, 1999-2013)	1.88 (0.64 to 2.91, 2013-2023)
Age group							
< 55	67	0.29	437	1.87	4.71 (3.79 to 5.92)	0.085 (-2.83-0.39, 1999-2015)	7.59 (4.16-15.88, 2015-2023)
≥ 55	474	8.16	4,140	43.26	6.45 (6.02 to 7.08)	8.30 (7.56 to 9.61, 1999-2015)	2.84 (0.97 to 4.22, 2015-2023)
Biological Sex							
Female	351	2.10	2,734	11.61	6.05 (5.55 to 6.77)	9.32 (8.21 to 11.05, 1999-2013)	1.64 (0.14 to 2.85, 2013-2023)
Male	190	1.71	1,843	9.36	2.76 (2.23 to 3.30)	9.54 (8.53 to 10.97, 1999-2014)	1.81 (0.28 to 3.09, 2014-2023)
Race/Ethnicity							
NH White	520	2.15	4,129	11.85	6.34 (5.89 to 6.97)	9.69 (8.65 to 11.18, 1999-2013)	1.81 (0.58 to 2.89, 2013-2023)
NH Black	14	0.54	326	7.02	8.57 (7.74 to 9.96)	10.43 (9.55 to 12.42, 1999-2019)	-0.31 (-9.19 to 5.11, 2019-2023)
Hispanic	12	1.10	187	3.96	5.22 (3.80 to 8.45)	7.79 (6.72 to 12.14, 1999-2021)	-19.38 (-34.70 to 2.91, 2021-2023)
Region							
Northeast	59	1.04	541	6.81	6.31 (5.53 to 7.52)	8.42 (7.21 to 11.25, 1999-2015)	2.21 (-1.95 to 4.58, 2015-2023)
Midwest	150	2.31	849	9.52	5.32 (4.67 to 6.22)	8.78 (7.72 to 10.55, 1999-2015)	-1.26 (-4.02 to 0.79, 2015-2023)
South	172	1.79	1,661	10.24	6.12 (5.52 to 6.96)	8.09 (7.19 to 9.73, 1999-2016)	1.45 (-1.95 to 3.65, 2016-2023)
West	153	3.11	1,526	15.73	6.08 (5.68 to 6.64)	11.25 (10.14 to 12.65, 1999-2012)	0.28 (-0.57 to 1.11, 2012-2023)

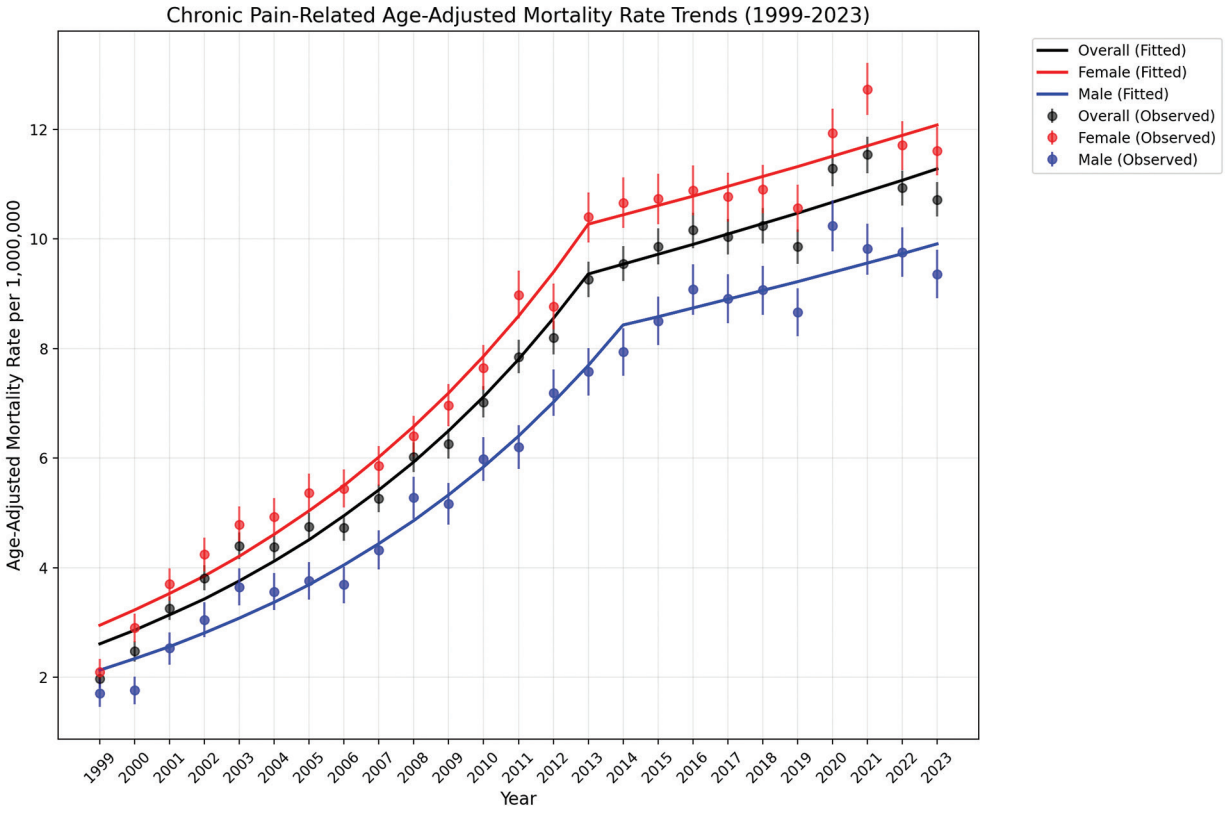


Fig. 1. *Trends in chronic pain-related age-adjusted mortality rates from 1999 to 2023 stratified by biological sex.*

Age Group-based Comparison

The majority of the CPRD involved individuals aged 55 years or more (56,013 or 83.1%), and 16.9% were aged less than 55 years. Both age groups showed a significant increase in CPAM across the study period (AAPC: +4.71, 95% CI: 3.79 to 5.92, for < 55 years and +6.45, 95% CI: 6.02 to 7.08, for ≥ 55 years). However, the AAMR for the younger age group had a significant decrease from 2012 to 2023 (APC -4.26, 95% CI: -6.34 to -2.54). Figure 3 shows the temporal trends in AAMR stratified by the age groups.

Region-Based Disparities

In terms of regional differences, the South (33.94%) had the highest proportion of CPRD, followed by the West (30.71%), then the Midwest (22.33%), and the Northeast (11.58%). All regions experienced significant increases in CPAM, with varying points where stability was achieved, as detailed in Table 1 and illustrated in Fig. 4. The AAPCs across the study period for all regions were statistically significant and ranged between +5.32 and +6.31 (Fig. 5).

Discussion

This nationwide analysis revealed several notable findings. There was a significant increase in CPAM from 1999 to 2023 in the US, which was found regardless of age group, biological sex, race/ethnicity, or regions. The CP-AAMR increased almost 10 times over the study period. Death linked to CP occurred more in female individuals and older individuals compared to male individuals and younger individuals. The older age group (≥ 55 years) had the most marked and consistent increase in AAMR over the entire period. Additionally, we found significant and important disparities in CPAM by race/ethnicity and regions.

There are multiple factors that may explain the rising deaths linked to CP. First, CP is increasingly being recognised as a disease rather than a symptom (2,3). Moreover, there is growing evidence for an association between CP and mortality (9,12,13). This has led to increased awareness among healthcare professionals on CPAM and, hence, improved documentation of CP on death certificates as a contributing cause of death

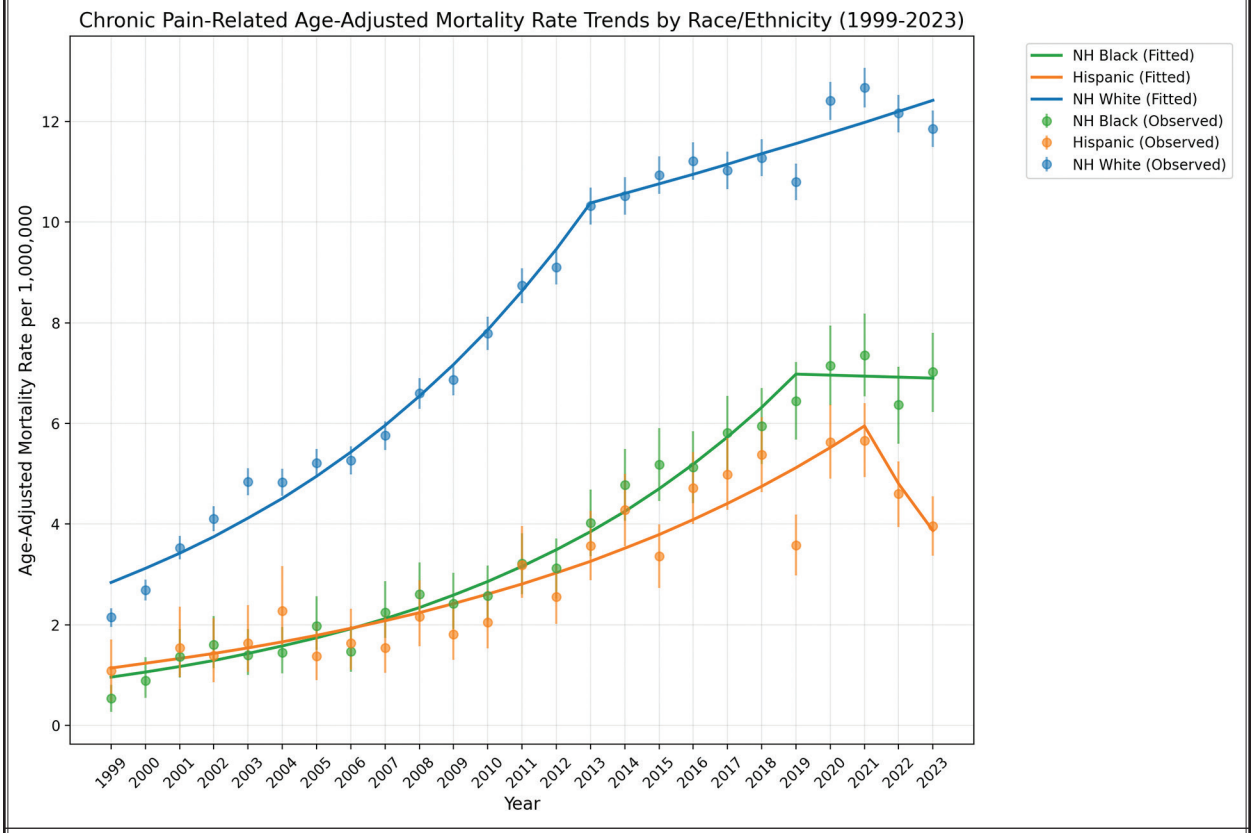


Fig. 2. *Trends in chronic pain-related age-adjusted mortality rates from 1999 to 2023 stratified by race/ethnicity.*

(CCD). Second, studies showed that among pain-free individuals in 2019, the incidence rate of new-onset CP was 52.4 cases per 1000 person-years (22). The growing incidence and burden of CP may partly explain the rising CPAM. Third, excess mortality in people with CP was found to be associated with low physical activity, poor quality diet, high body mass index, and smoking; these factors lead to a higher cardiovascular risk profile in people with CP (23). Co-morbid depression, anxiety, substance abuse, opioid dependence, and sleep disturbances are more common in people with CP, leading to poorer health overall (12,24). People with CP also have increased cardiovascular-associated and cancer-associated mortality (13,25). Over this time period, there has been a marked increase in the use of opioids. Interestingly, chronic opioid use has been linked to increased cancer risk in some studies (26). Third, the financial burdens placed on people with CP are substantial. They suffer from frequent hospital visits and admissions, medical/psychiatric co-morbidities, diagnostic testing, prescription drug use, and overall increased healthcare utilisation (2,11,27). This is compounded by higher unemployment rates and reduced productivity in people with CP compared to those without CP (11,28). Lastly, the biological complications of CP, as well as the use of opioid medications, such as neuroinflammation, central sensitization, and poor immune function, may lead to cardiovascular dysregulation and an increased risk of infections (2,5-9,13). Our findings uncover an impending public health crisis involving rising deaths from CP.

Female individuals are affected by CP more than male individuals, with epidemiological studies showing prevalence rates of 34.3% in the former compared to 26.7% in the latter (4). Our findings are consistent with previous studies. We found that both female and male individuals had a notable increase in CPAM, but female individuals showed consistently higher AAMR. The gap between female and male individuals was also widening over the study period, highlighting the growing sex-based disparities in CP.

The age group-based comparison in CPAM uncovered interesting findings in our study. The older age group showed a consistent uptrend in CPAM across the study, while the younger age group showed a period of

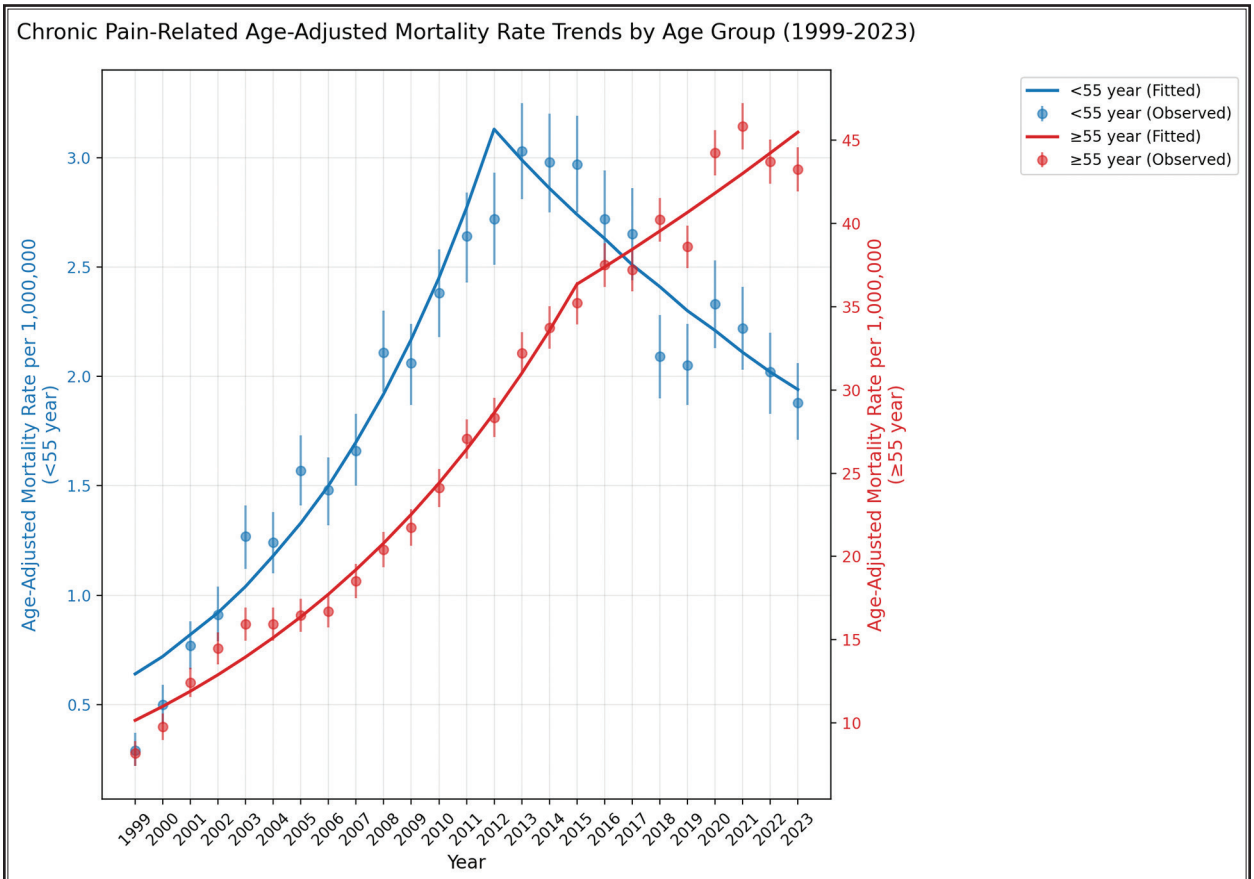


Fig. 3. *Trends in chronic pain-related age-adjusted mortality rates from 1999 to 2023 stratified by age group (< 55 years and ≥ 55 years).*

decline after 2012. Elderly people with CP were found to have a very high prevalence of polypharmacy, with reports of 89.5% having a minimum of 5 medications (10,29). Excess polypharmacy (≥ 10 prescriptions) is also problematic in elderly people with CP (10,29). We may postulate that this is a potential factor leading to excess CPAM in elderly people. The peak in CPAM in the younger age group around 2012 might have coincided with the peak of opioid prescriptions in the US, which occurred around 2010 with a decline afterwards (30). In addition, public intervention efforts and CDC guidelines related to opioid prescriptions may have contributed to the halt and decline of CPAM in the younger age group (31,32).

Racial/ethnic disparities in CPAM were significant in our results. CPAM was largely reported in NH White individuals. Studies examining racial/ethnicity-related disparities in CP showed that White and Black individuals had close prevalence rates, with the latter showing higher high-impact CP than White individuals; Hispanic individuals had the lowest CP prevalence (33). We revealed that CPAM significantly increased across all racial/ethnic groups but was mainly reported in NH White individuals. These findings may point to a problem related to under-reporting and under-documenting of CP as a CCD in NH Black and Hispanic individuals. The higher prevalence of high-impact CP in Black individuals may also account for the higher AAPC across the study period in NH Black individuals compared to NH White and Hispanic individuals (33). Regional disparities were also prominent in our results. The South showed the largest burden of CPAM compared to other regions, and all regions showed an initial increase followed by a period of stability. Studies show that the South has the highest rates of opioid prescriptions and opioid use disorders, possibly accounting for our findings (34,35).

CP may be considered a public health crisis given its substantial health, economic, and psychosocial impacts. National efforts, such as the National Pain Strategy (2016), may have slowed the rise in CP, as shown in our

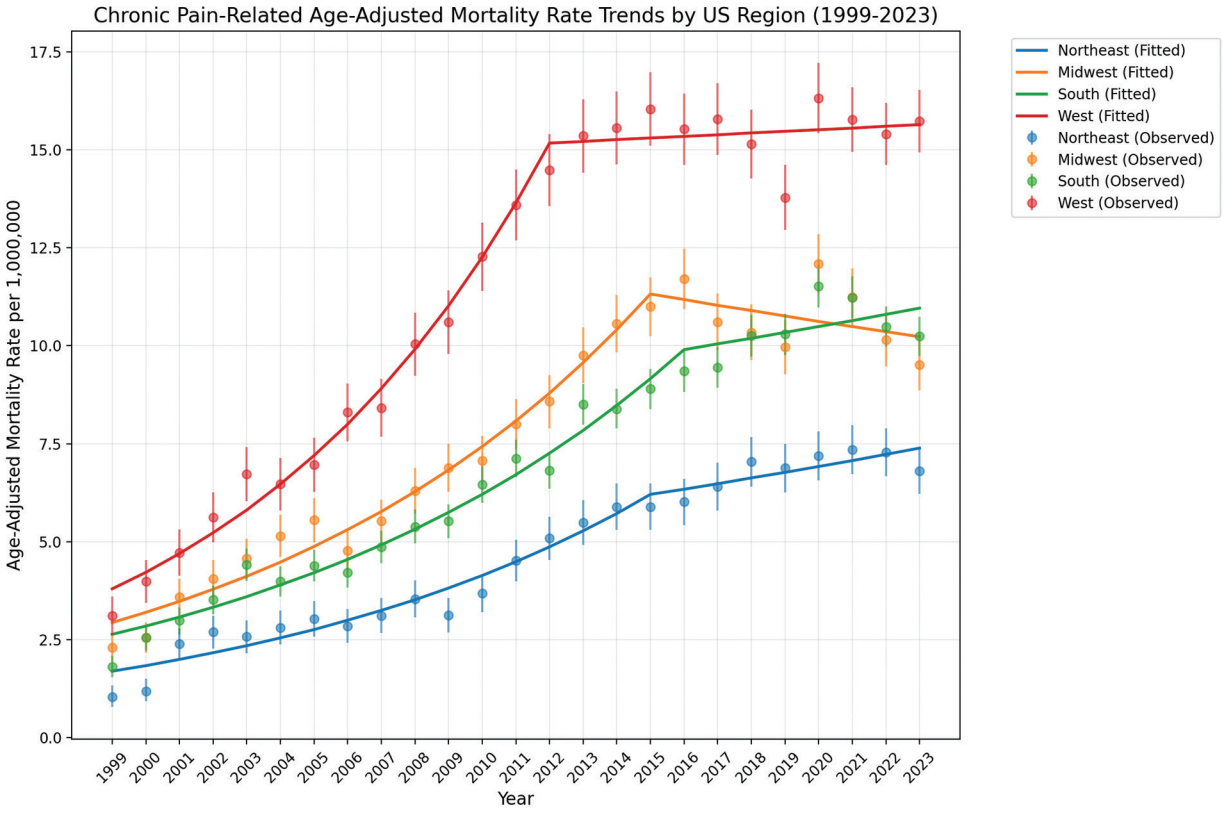


Fig. 4. *Trends in chronic pain-related age-adjusted mortality rates from 1999 to 2023 stratified by region.*

study, with CPAM relatively stabilising in recent years. This study highlights the urgent need for more targeted regulations, policies, guidelines, and public awareness campaigns related to CP. This data can be instrumental for healthcare administrators and policymakers to formulate action plans and policies to tackle the growing CP burden.

Limitations relating to this study mainly involve reliance on administrative billing codes documented on death certificates. This may expose the data to potential misclassification bias. Under-reporting is undoubtedly an issue when it pertains to CP being documented as a CCD on death certificates. CDC suppresses the counts of fewer than 10 in CDC WONDER data to protect confidentiality, and death rates are labelled unreliable for a count of less than 20 per the CDC WONDER data use agreement. Due to this reason, we were limited in analysing disparities in certain ethnic groups, such as NH Asian or Pacific Islander, NH American Indian or Alaska Native, due to low counts. Lastly, social determinants of health could contribute to the patient's death and were not reported on death certificates.

This represents the first large-scale analysis of CPAM in the US across the span of 24 years. The principal finding was a significant up-trend in deaths linked to CP regardless of sex, race/ethnic groups, age groups, or region. Significant disparities were uncovered in CPAM, which could guide physicians, policymakers, and healthcare administrators in the fight against CP. Future work may focus on identifying the underlying and contributing causes of death in people with CP.

Contributors

AA: conceptualization, data curation, methodology, visualization, writing -original draft; MP: conceptualization, methodology, visualization, writing -original draft; AB: data curation, formal analysis, methodology, writing -review & editing; JN: writing -original draft, writing -review & editing, supervision; PS: writing -original draft, writing -review & editing, supervision; LM: writing -original draft, writing -review & editing, supervision.

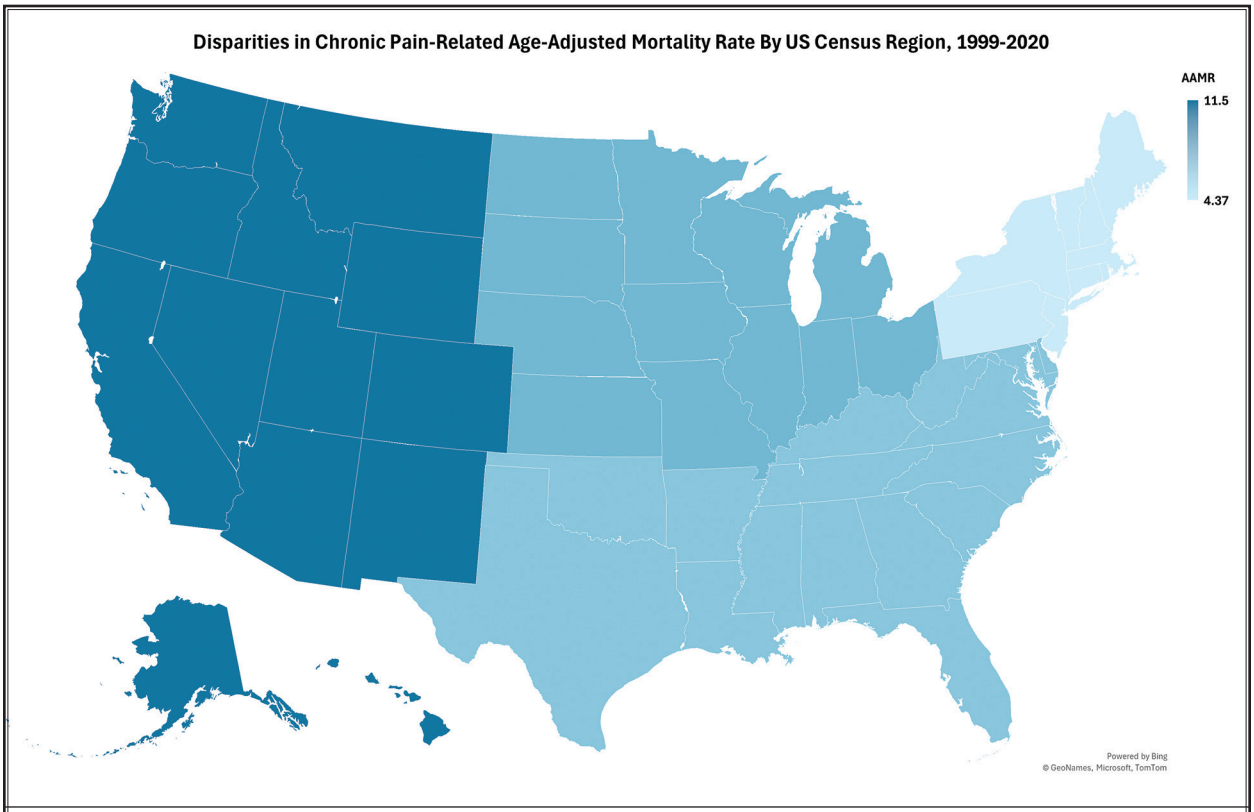


Fig. 5. *Regional differences in chronic pain-related age-adjusted mortality rates by region for the period 1999-2020.*

Data Sharing

Data analyzed in this study is publicly available from the CDC WONDER database and can be provided upon request.

Ethics Committee Approval

The study was exempt given that data used is publicly available and de-identified.

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