Letter

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# Trends in cardiovascular–kidney–metabolic–related mortality among US adults, 1999–2023

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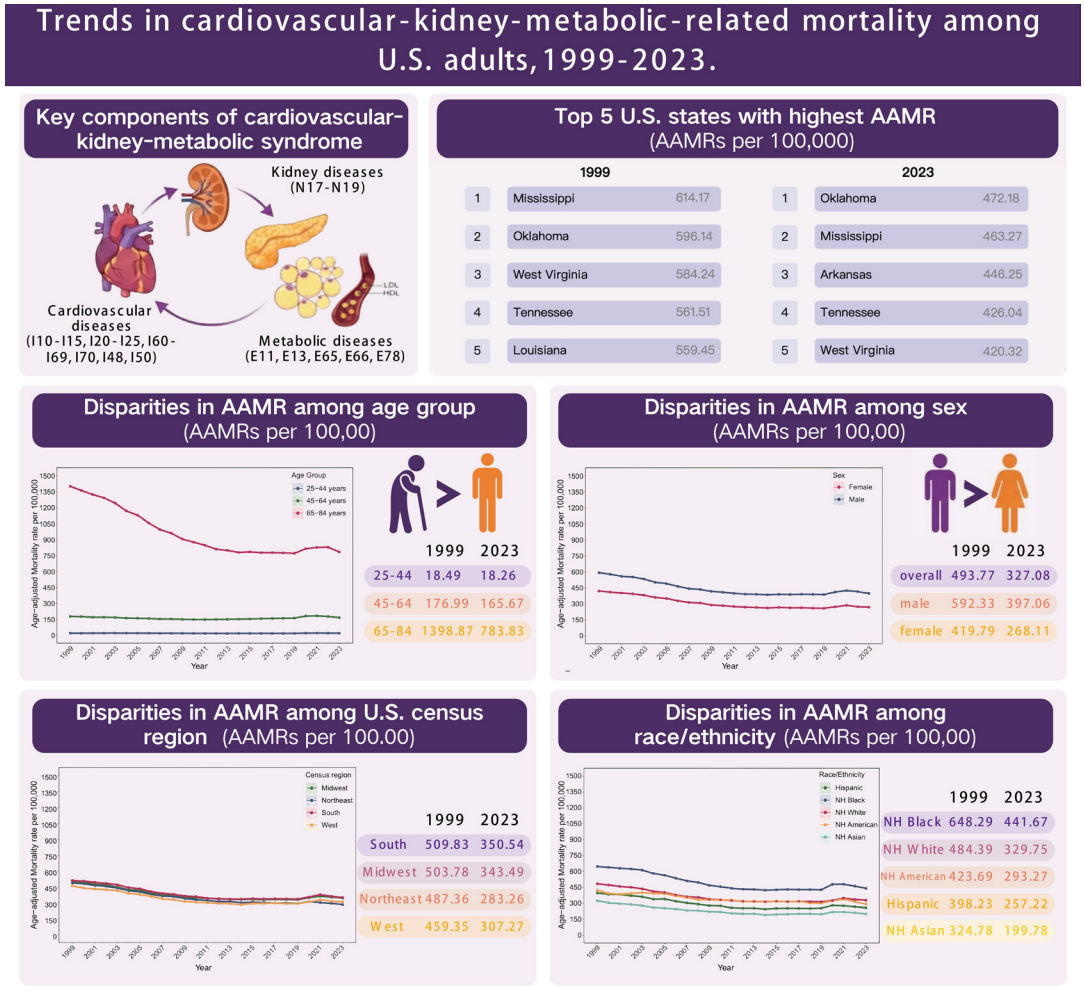
## Graphical abstract




CKM-related age-adjusted mortality rates among US adults, 1999–2023: stratification by age, sex, race/ethnicity, and US census region, with state-level comparisons.

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Supplemental Digital Content is available for this article.

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| Nonstandard Abbreviations and Acronyms | |
|---|---|
| **AAMR** | age-adjusted mortality rate |
| **AAPC** | average annual percent change |
| **AHA** | American Heart Association |
| **APC** | annual percent change |
| **CDC** | Centers for Disease Control and Prevention |
| **CI** | confidence interval |
| **CKM** | cardiovascular–kidney–metabolic |
| **COVID-19** | coronavirus disease 2019 |
| **CVD** | cardiovascular disease |
| **NH** | non-Hispanic |
| **WONDER** | Wide-ranging Online Data for Epidemiologic Research |

## 1. Introduction

Emerging evidence highlights the complex interplay among cardiovascular disease (CVD), chronic kidney disease, and metabolic risk factors. To capture these multidirectional relationships, the American Heart Association (AHA) introduced cardiovascular–kidney–metabolic (CKM) syndrome in 2023.[1] The global burden of these conditions is striking: CVD accounted for approximately 19.1 million deaths in 2020,[2] chronic kidney disease caused nearly 1.2 million deaths in 2017[3]—representing a 41.5% increase since 1990—and diabetes contributed to almost 1.7 million deaths in 2021.[4] In the United States, CKM syndrome affects an estimated 33%–40% of adults as of 2023, positioning it as a leading driver of mortality.[5] Yet despite its high prevalence and profound health impact, long-term trends in CKM-related mortality among US adults remain unexplored. To address this, we used the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) database to analyze trends and sociodemographic disparities in CKM-related mortality among US adults aged 25 years and older from 1999 to 2023.

## 2. Methods

This study analyzed mortality data from the CDC WONDER database, which compiles death certificate information for all US residents. We included adults aged ≥ 25 years who died from CKM causes between 1999 and 2023. CKM-related deaths were defined as the underlying cause of death using the International Classification of Disease (ICD)-10 codes, encompassing cardiovascular diseases (I10–I15, I20–I25, I60–I69, I70, I48, I50), kidney diseases (N17–N19), and metabolic diseases (E11, E13, E65, E66, E78). Given that ICD-10 codes do not directly correspond to the AHA CKM staging framework, this definition represents an aggregated CKM-related mortality category rather than formal stage-based CKM mortality. We extracted age-adjusted mortality rates (AAMRs) per 100,000 population, with corresponding 95% confidence intervals (CIs), stratified by age group, sex, race/ethnicity, and US census region. Temporal trends were assessed using Joinpoint regression (version 5.1.0.0) to estimate annual percent change (APC) and average APC (AAPC), allowing up to four joinpoints based on permutation tests and the Bayesian Information Criterion (BIC). Because AAMR is not available for the ≥ 85-year age group, trend analyses were restricted to age groups for which age-adjusted rates could be consistently calculated. Statistical significance was determined using two-sided $p$-values < 0.05. Because the CDC WONDER database contains deidentified, publicly available government data, institutional review board approval was not required.

## 3. Results

Between 1999 and 2023, there were 20,227,498 CKM-related deaths in the United States. The overall AAMR declined from 493.77 (95% CI: 492.73–494.80) in 1999 to 327.08 (95% CI: 326.40–327.77) in 2023 (AAPC: −1.70, 95% CI: −2.16 to −1.24) (Table S1, Supplemental Digital Content, https://links.lww.com/CARES/A7). To assess the impact of the coronavirus disease 2019 (COVID-19) pandemic on CKM-related mortality, we identified deaths involving COVID-19 using ICD-10 code U07.1. In 2020, the total number of CKM-related deaths increased modestly to 898,977; however, 153,005 of these deaths (17.02%) listed COVID-19 as a contributing cause (Note S1, Supplemental Digital Content, http://links.lww.com/CARES/A8).

Stratified by age, the highest AAMR was observed among adults aged 65 to 84 years, and this group experienced a significant decline in mortality between 1999 and 2023 (AAPC: −2.34; 95% CI: −2.80 to −1.88). By contrast, the lowest AAMR was consistently observed in adults aged 25 to 44 years. Mortality rates in younger and middle-aged adults remained relatively stable over the study period, with no significant changes observed in either the 25 to 44 years group (AAPC: 0.02; 95% CI: −0.46 to 0.51) or the 45- to 64-year group (AAPC: −0.26; 95% CI: −0.54 to 0.01). Sex-specific analyses indicated that males consistently had higher mortality rates than females. For males, the AAMR declined from 592.33 (95% CI: 590.45–594.20) in 1999 to 397.06 (95% CI: 395.90–398.22) in 2023 (AAPC: −1.69, 95% CI: −2.18 to −1.20), with a similar trend observed in females (AAPC: −1.86, 95% CI: −2.36 to −1.35).

In race-specific analyses, non-Hispanic (NH) Black individuals consistently had the highest AAMR throughout the study period, followed by NH White, American Indian/Alaska Native, Hispanic, and NH Asian populations. Among NH Black individuals, the AAMR declined from 648.29 (95% CI: 644.12–652.46) in 1999 to 441.67 (95% CI: 439.08–444.26) in 2023 (AAPC: −1.60, 95% CI: −1.90 to −1.29). This pattern of decline was similarly observed among other racial/ethnic groups. Regionally, the South had the highest AAMR throughout 1999 to 2023, followed by the Midwest, Northeast, and

West. The Northeast saw the largest overall decline in AAMR (AAPC: –2.22, 95% CI: –2.72 to –1.71). Initially, the Northeast had higher rates than the West, but by 2020, this trend reversed. At the state level, Mississippi and Oklahoma—both located in the South—had the nation's highest AAMRs.

## 4. Discussion

This nationwide analysis revealed a significant overall decline in CKM-related mortality among US adults from 1999 to 2023. However, this favorable trend was interrupted by a temporary reversal between 2019 and 2021. Persistent disparities were evident: mortality rates remained highest among men, older adults, and NH Black individuals. Geographic variation was also marked, with the greatest burden concentrated in the Southern United States. Together, these findings underscore the substantial influence of sociodemographic and environmental factors on CKM-related mortality. In parallel, advances in pharmacotherapy, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and nonsteroidal mineralocorticoid receptor antagonists, along with improved screening and early intervention in high-risk populations (e.g., diabetes, hypertension, kidney disease), may have further improved patient outcomes.[6] The rebound in mortality rates between 2019 and 2021, followed by a slow decline, is most likely attributable to the COVID-19 pandemic,[7] reflecting both its direct cardiovascular complications and the indirect effects of healthcare disruption.

Building on the overall decline in mortality, our findings show that men consistently exhibit higher CKM-related mortality rates than women. Several mechanisms may underlie this disparity. Sex hormones, particularly estrogen, confer protective effects by enhancing nitric oxide production, promoting arterial dilation, reducing atherosclerosis, and influencing fat distribution and metabolism, which may partially explain lower obesity prevalence among women.[8] Estrogen also appears to mitigate kidney injury, though most evidence comes from animal studies, and human data remain limited.[9] Age-related differences were also pronounced, with the highest mortality consistently observed among older adults. This pattern reflects the cumulative burden of molecular and cellular aging, as well as the increasing proportion of elderly individuals in the population. Substantial racial and ethnic disparities were observed, with NH Black adults experiencing disproportionately high mortality,[6] likely due to structural racism, limited healthcare access, and inequities in chronic disease management (Note S2, Supplemental Digital Content, http://links.lww.com/CARES/A9). In contrast, NH Asian adults showed lower mortality, potentially reflecting greater preventive care engagement and treatment adherence. Geographic disparities further reinforced these patterns. The pronounced and sustained mortality burden observed in the Southern United States underscores the importance of targeted investment in prevention, primary care capacity, and chronic disease management infrastructure[10] (Note S3, Supplemental Digital Content, http://links.lww.com/CARES/A10).

Several limitations should be acknowledged. First, the use of ICD-10 codes from death certificates may introduce misclassification, potentially biasing mortality estimates. Second, broad ICD-10 categories could result in the overinclusion of cardiovascular deaths not directly related to CKM. This approach, while epidemiologically significant, may inadvertently include subtypes such as nonhypertensive stroke, which have a lower metabolic association with CKM. Future research could benefit from sensitivity analyses that exclude these subtypes to better clarify the metabolic basis of CKM-related mortality. Additionally, the lack of detailed clinical and socioeconomic data in the CDC WONDER database limits our ability to control for residual confounding, which could influence the observed associations. Finally, the AHA CKM framework is still evolving, and future versions may incorporate additional metabolic factors, such as liver function and sleep, which could refine the framework and influence subsequent analyses. This study is intentionally conservative to maximize specificity, but we acknowledge that expanding the CKM definition could yield different prevalence estimates. Such expanded definitions warrant further investigation in future studies to better understand the full scope of CKM-related mortality and its determinants.

## Acknowledgements

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## Ethical statement

This study used publicly available, de-identified data from the CDC WONDER database. As no identifiable human subjects were involved, institutional review board approval and informed consent were not required.

## Conflicts of interest

The authors have no conflicts of interest to disclose.

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## Data availability statement

The data underlying this article are publicly available from the CDC WONDER database at wonder.cdc.gov/deaths-by-underlying-cause.html.

## Author contributions

QW and TXW designed the study and wrote the manuscript. QW and JQW performed data extraction, quality assessment, and data analysis. MJC supervised the study and critically revised the manuscript. All authors contributed to the interpretation of the results and approved the final version of the manuscript.

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