

Trends and Disparities in Mortality Involving Co-Documented Sepsis and Obesity in the United States, 1999–2024: A Serial Cross-Sectional Study

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Abstract

Background

Sepsis and obesity are each major public health burdens in the United States, and their co-occurrence has not previously been characterized using multiple-cause-of-death (MCD) surveillance, which captures conditions recorded anywhere on the death certificate rather than only the underlying cause. We examined long-term national trends and disparities in mortality involving co-documented sepsis and obesity.

Methods

In this retrospective serial cross-sectional study, we used Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) multiple-cause-of-death data to identify United States deaths among adults aged 25 years or older, from 1999 through 2024, in which sepsis and obesity were both recorded anywhere on the death certificate. Age-adjusted mortality rates (AAMRs) per 100,000 population were calculated overall and by sex, Hispanic origin, race and ethnicity, census region, urbanization, and state. Temporal trends were assessed using Joinpoint regression, with annual percentage change and average annual percentage change estimated for each identified trend segment.

Results

From 1999 through 2024, 64,163 deaths involved co-documented sepsis and obesity. The overall AAMR rose from 0.41 (95% CI, 0.38–0.44) per 100,000 in 1999 to a peak of 2.95 (95% CI, 2.88–3.02) in 2021, then declined to 1.46 (95% CI, 1.42–1.51) in 2024, tracing a steady rise (1999–2018), a sharp pandemic-era acceleration (2018–2021), and a partial reversal (2021–2024). Mortality was consistently higher among women, non-Hispanic American Indian/Alaska Native and Native Hawaiian/Pacific Islander decedents, and residents of the South and nonmetropolitan counties, with the highest state-level burden in Oklahoma.

Conclusions

Mortality involving co-documented sepsis and obesity rose substantially in the United States over 25 years, driven by a pandemic-era surge that has only partially reversed, and disproportionately burdened women, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Black populations, and residents of the South and rural America. These findings support continued multiple-cause-of-death surveillance and identify actionable public health and policy priorities: targeted expansion of rural and equity-focused sepsis-care quality improvement, and integration of obesity prevention into infection-mortality prevention strategy.

Clinical trial number: not applicable.

Background

Sepsis remains a major public health burden in the United States. In 2022, approximately 2.4 million inpatient stays involved sepsis, and 14.2% of hospitalizations in which sepsis was the principal diagnosis ended in in-hospital death.[1] Obesity represents another major public health challenge: during August 2021–August 2023, the age-adjusted prevalence of obesity among US adults aged 20 years or older was 40.3%, including 9.7% with severe obesity.[2] Given the substantial burdens of both conditions, understanding mortality in which sepsis and obesity are recorded together has important implications for public health surveillance and prevention.

Obesity has been associated with greater susceptibility to serious infections and sepsis. In the prospective, population-based REGARDs cohort, class III obesity was associated with a higher risk of a future sepsis event.[3] More recently, a large multicohort study found progressively higher risks of severe infection-related hospitalization and death across increasing obesity classes.[4] Proposed explanations include chronic inflammation and obesity-associated disruption of immune-cell metabolism and function, which can impair host responses to infection.[5]

Nevertheless, the relationship between obesity and outcomes after sepsis onset remains complex. A 2026 systematic review and meta-analysis of 12 retrospective studies involving 130,755 adults with sepsis found that elevated body mass index was associated with lower pooled short- and long-term mortality, consistent with the reported “obesity paradox.”[6] Similar findings have been reported in a large US cohort of 55,038 hospitalized adults meeting Sepsis-3 criteria, although the estimated association varied according to the analytic approach and adjustment for illness severity.[7] These studies address prognosis after sepsis has developed rather than population-level mortality trends, which this study examines instead.

Mortality statistics based solely on the underlying cause of death may underrepresent sepsis-related mortality because sepsis is frequently recorded as a contributing rather than the underlying cause; in a national analysis, sepsis was designated as the underlying cause in only 22% of death certificates on which it was mentioned.[8] Multiple-cause-of-death data reflect all medical information reported on death certificates and permit the evaluation of conditions that contributed to death whether or not they were selected as the underlying cause.[9] To our knowledge, national long-term trends and disparities in mortality involving co-documented sepsis and obesity have not previously been characterized. Characterizing these patterns may strengthen mortality surveillance, identify populations experiencing disproportionate burdens, support the prioritization of prevention efforts, and inform public health and healthcare policy. Accordingly, we examined national trends and demographic, geographic, and urban–rural disparities in mortality involving co-documented sepsis and obesity among US adults aged 25 years or older using CDC WONDER multiple-cause-of-death data from 1999 through 2024.

Methods

Study design and data source

This retrospective serial cross-sectional study used the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death databases to examine mortality involving co-documented sepsis and obesity among US residents aged 25 years or older from 1999 through 2024. The lower age limit was selected because estimates among younger adults frequently contained suppressed or statistically unreliable cells.

Data for 1999–2020 were obtained from the Final Multiple Cause of Death database, which uses bridged-race population estimates. Data for 2021–2024 were obtained from the Multiple Cause of Death Single-Race database. Because the population denominator and race-classification frameworks differ between these database eras, analyses were conducted separately where direct concatenation was not methodologically appropriate. The final CDC WONDER queries were completed on July 22, 2026.

CDC WONDER provides publicly available, de-identified, aggregate mortality data. Therefore, institutional review board approval and informed consent were not required.

Study population and case definition

Eligible deaths were those in which at least one prespecified septicemia-related code and at least one obesity code were recorded anywhere on the same death certificate. Neither sepsis nor obesity was required to be the underlying cause of death.

Septicemia-related deaths were identified using the following International Classification of Diseases, Tenth Revision codes: A02.1, A20.7, A22.7, A26.7, A32.7, A39.4, A40.0–A40.3, A40.8–A40.9, A41.0–A41.5, A41.8–A41.9, A42.7, and B37.7. Obesity was identified using codes E66.0, E66.1, E66.2, E66.8, and E66.9. Codes within each condition set were combined using OR, and the septicemia-related and obesity code sets were combined using AND. The same co-documentation logic was applied throughout the study period. A reproducible summary of the query and analysis criteria is provided in Supplementary Table S1.

The expanded septicemia-related code set was used to capture the broader death-certificate burden of mortality involving sepsis-related diagnoses. Throughout this study, the term sepsis refers to this prespecified ICD-10-based surveillance definition and does not imply clinically adjudicated Sepsis-3 organ dysfunction.

Mortality measures and subgroup variables

The primary outcome was the annual age-adjusted mortality rate (AAMR) per 100,000 population for deaths involving co-documented sepsis and obesity. AAMRs were calculated by direct standardization to

the 2000 US standard population. Annual death counts, population denominators, crude mortality rates, AAMRs, 95% confidence intervals, and AAMR standard errors were retained where available.

Mortality patterns were evaluated overall and by sex, Census region, Hispanic origin, race and ethnicity, urbanization category, and state.

State-level AAMRs were pooled separately for 1999–2020 and 2021–2024 and displayed descriptively using choropleth maps. State estimates were not analyzed using Joinpoint regression and were not formally compared across the two database eras.

Urbanization analyses for 1999–2020 used the 2013 National Center for Health Statistics Urban–Rural Classification Scheme. Annual AAMRs and corresponding standard errors were available for this period and were evaluated using Joinpoint regression. For 2021–2024, the age-restricted grouped urbanization query returned death counts only, without population denominators, crude mortality rates, AAMRs, or standard errors; urbanization findings for that period were therefore summarized descriptively as counts only, without rate comparisons or Joinpoint modeling.

Race and ethnicity analyses

Historical race analyses used the 1999–2020 bridged-race framework. Joinpoint modeling during this period was restricted to non-Hispanic Black and non-Hispanic White decedents because these were the only groups with complete and reliable annual AAMR and standard-error series across all 22 years: non-Hispanic American Indian or Alaska Native estimates included 2 suppressed and 8 unreliable years, and non-Hispanic Asian or Pacific Islander estimates included 5 suppressed and 7 unreliable years, so both groups were summarized using pooled estimates but excluded from historical Joinpoint modeling.

Contemporary race and ethnicity analyses used the 2018–2024 Single-Race Multiple Cause of Death database and included six mutually exclusive non-Hispanic race groups together with Hispanic or Latino decedents of any race. The contemporary groups were non-Hispanic American Indian or Alaska Native, non-Hispanic Asian, non-Hispanic Black, non-Hispanic Native Hawaiian or Other Pacific Islander, non-Hispanic White, non-Hispanic more than one race, and Hispanic or Latino of any race. Reproducible query criteria for these race and Hispanic-origin definitions are provided in Supplementary Table S14.

Because the historical bridged-race and contemporary single-race classifications are not directly comparable, these analyses were conducted and interpreted separately and were not combined into a continuous race-specific time series. The magnitude of this non-comparability was assessed directly for the 2018–2020 overlap years (Supplementary Table S20).

Annual AAMRs were estimated for each contemporary race and ethnicity group. Pooled 2021–2024 AAMRs were compared using non-Hispanic White decedents as the reference group. Absolute rate differences and rate ratios were calculated using unrounded pooled AAMRs. For rate differences, 95% confidence intervals were derived by combining the variances of the group-specific and reference

AAMRs under an assumption of independent estimates. For rate ratios, 95% confidence intervals were calculated on the logarithmic scale using the delta method and then exponentiated.

Exploratory Joinpoint analyses were also performed for the 2018–2024 annual AAMR series for each contemporary race and ethnicity group. Because each series contained only seven annual observations, a maximum of one joinpoint was permitted.

Historical rates based on fewer than 20 deaths were considered statistically unreliable. Contemporary rates were evaluated using the applicable CDC WONDER reliability criterion based on relative confidence-interval width. Hispanic-origin records categorized as Not Stated were retained only for counts-based quality-control assessment and were excluded from rate-based comparisons because valid population denominators and AAMRs were not available (Supplementary Tables S26-S27). Race and ethnicity findings reflect surveillance estimates rather than biological differences.

Joinpoint trend analysis

Temporal trends in annual AAMRs were evaluated using the Joinpoint Regression Program, version 6.1.0, developed by the National Cancer Institute. Year was specified as the independent variable and AAMR as the dependent variable. Log-linear models incorporated annual AAMR standard errors using the heteroscedastic-errors option.

Models were fitted using the grid-search method with default spacing. A maximum of four joinpoints was permitted for the longer annual series. Contemporary 2018–2024 race and ethnicity models were limited to a maximum of one joinpoint because of the shorter observation period. No breakpoint was forced at 2020.

The optimal number and location of joinpoints were selected using the weighted Bayesian information criterion. Empirical Quantile 95% confidence intervals were estimated using 5,001 resamples.

Annual percentage changes were calculated for each identified trend segment. Average annual percentage changes were calculated across the full prespecified interval for each modeled series. Annual percentage changes and average annual percentage changes were considered statistically significant when their 95% confidence intervals excluded zero.

Numerical differences between subgroup estimates were not interpreted as statistically significant unless a formal comparison had been performed.

Joinpoint analyses were conducted for the overall population and for eligible annual series defined by sex, Census region, Hispanic origin, historical race, contemporary race and ethnicity, and urbanization during 1999–2020.

Sensitivity analyses

Two sensitivity analyses were performed.

First, a narrower sepsis-definition sensitivity analysis was conducted using only ICD-10 codes A40–A41 for septicemia, retaining the obesity requirement, co-documentation logic, age threshold, study period, and all other eligibility criteria unchanged from the primary analysis. Annual AAMRs and corresponding standard errors were analyzed using the same Joinpoint specifications as the primary overall series.

Second, a descriptive COVID-19 underlying-cause analysis was conducted for 2020–2024 within the primary expanded-code cohort. Deaths for which U07.1 was recorded as the underlying cause were identified. These deaths were subtracted from the corresponding annual eligible death counts, and the proportion of each annual cohort with COVID-19 as the underlying cause was calculated.

Deaths in which U07.1 appeared only as a contributing cause were not identified. Post-exclusion AAMRs were not calculated because suppressed age-specific cells prevented valid direct standardization and because age-adjusted rates are not additive. No post-exclusion Joinpoint models or formal between-series tests were performed.

Data suppression, reliability, and quality control

CDC WONDER suppresses death counts of 1–9. Suppressed values were retained as missing and were not imputed. Rates designated as unreliable under the applicable CDC WONDER criteria were not used for trend modeling.

All reported estimates were checked for internal consistency against the corresponding CDC WONDER and Joinpoint outputs.

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement; the completed checklist is provided in Supplementary Table S28.

Use of AI tools

During the preparation of this work, the authors used artificial intelligence tools to assist with manuscript formatting and language editing. The authors reviewed and edited all AI-assisted content, verified the accuracy of the underlying data and analysis independently, and take full responsibility for the content of this publication.

Results

Study population and overall temporal trends

From 1999 through 2024, 64,163 deaths among US adults aged 25 years or older involved co-documented sepsis and obesity, with both conditions recorded anywhere on the death certificate. Of these, 37,434 deaths (58.3%) were among female decedents and 26,729 (41.7%) were among male decedents. The annual number of deaths increased from 734 in 1999 to a peak of 7,460 in 2021, then declined to 3,989 in 2024 (Table 1 and Supplementary Table S4).

Table 1. Deaths involving co-documented sepsis and obesity among US adults by subgroup, 1999-2024

Characteristic	Deaths, No.	% of Total
Overall	64,163	100.0
Sex		
Female	37,434	58.3
Male	26,729	41.7
Hispanic origin		
Hispanic	6,748	10.5
Non-Hispanic	57,226	89.2
Not stated	189	0.3
Census region		
Northeast	8,611	13.4
Midwest	13,210	20.6
South	26,794	41.8
West	15,548	24.2

Abbreviations: none. Percentages are of the 64,163 total deaths. Hispanic-origin percentages sum to 100.0% including records categorized as Not Stated, which were retained for counts-based quality control only (Supplementary Tables S26-S27) and excluded from rate-based analyses. Census region percentages sum to 100.0%. Full annual death counts by subgroup are provided in Supplementary Tables S4-S9.

Table 2. Age-Adjusted Mortality Rates (AAMR) and Average Annual Percent Change (AAPC), by Subgroup, 1999-2024

Subgroup	AAMR, 1999 (95% CI)	Peak AAMR, 2021 (95% CI)	AAMR, 2024 (95% CI)	AAPC, 1999- 2024 (95% CI)
Overall	0.41 (0.38-0.44)	2.95 (2.88-3.02)	1.46 (1.42-1.51)	4.02 (3.01-4.96)
Female	0.49 (0.45-0.54)	2.96 (2.87-3.06)	1.57 (1.51-1.64)	3.52 (2.49-4.41)
Male	0.31 (0.28-0.35)	2.87 (2.78-2.98)	1.35 (1.28-1.41)	4.84 (3.94-5.78)
Hispanic	0.26 (0.18-0.37)	3.38 (3.18-3.59)	1.12 (1.01-1.24)	3.25 (1.60-5.12)
Non-Hispanic	0.42 (0.39-0.45)	2.83 (2.76-2.91)	1.51 (1.46-1.56)	4.18 (3.19-5.03)
Northeast	0.36 (0.29-0.42)	1.55 (1.43-1.67)	0.88 (0.79-0.97)	3.13 (2.34-4.24)
Midwest	0.42 (0.36-0.49)	2.38 (2.24-2.52)	1.21 (1.12-1.31)	4.28 (3.49-5.70)
South	0.41 (0.36-0.46)	3.73 (3.61-3.86)	1.88 (1.79-1.96)	4.80 (3.87-5.81)
West	0.49 (0.42-0.56)	3.24 (3.10-3.40)	1.45 (1.36-1.55)	3.50 (2.34-4.54)
A40-A41 sensitivity definition	0.41 (0.38-0.44)	2.95 (2.88-3.02)	1.46 (1.42-1.51)	4.01 (3.01-5.06)

Abbreviations: AAMR, age-adjusted mortality rate per 100,000 population; AAPC, average annual percent change; CI, confidence interval. This table includes only the subgroups with a continuous 1999-2024 observation period. Historical race (1999-2020), contemporary race and ethnicity (2018-2024), and urbanization category (1999-2020) use different observation windows because of differing CDC WONDER database eras and are presented separately in Supplementary Tables S2-S3 and S15-S25. All AAPCs shown were statistically significant (95% CI excluded zero).

The overall age-adjusted mortality rate (AAMR) increased from 0.41 per 100,000 population (95% CI, 0.38 to 0.44) in 1999 to 2.95 (95% CI, 2.88 to 3.02) in 2021, before declining to 1.46 (95% CI, 1.42 to 1.51) in 2024. Despite the post-2021 decline, the 2024 AAMR remained 3.6 times the 1999 rate. Across 1999-2024, the AAMR increased by an average of 4.02% per year (95% CI, 3.01% to 4.96%). Joinpoint analysis identified three significant phases: an increase during 1999-2018 (annual percent change [APC], 4.35%; 95% CI, 2.78% to 5.71%), a sharp acceleration during 2018-2021 (APC, 33.60%; 95% CI, 18.90% to 40.51%), and a decline during 2021-2024 (APC, -20.59%; 95% CI, -28.30% to -14.62%) (Figure 1, Table 2, and Supplementary Tables S2-S4).

Trends by sex

Female decedents had numerically higher AAMRs than male decedents at both endpoints. Among female decedents, the AAMR was 0.49 (95% CI, 0.45 to 0.54) in 1999, peaked at 2.96 (95% CI, 2.87 to 3.06) in 2021, and declined to 1.57 (95% CI, 1.51 to 1.64) in 2024. The corresponding AAMRs among male decedents were 0.31 (95% CI, 0.28 to 0.35), 2.87 (95% CI, 2.78 to 2.98), and 1.35 (95% CI, 1.28 to 1.41), respectively. The full-period average annual percent change (AAPC) was 3.52% (95% CI, 2.49% to 4.41%) among female decedents and 4.84% (95% CI, 3.94% to 5.78%) among male decedents. Both groups followed the same three-phase pattern. During 2018-2021, the APC was 30.58% (95% CI, 15.89% to 37.65%) among female decedents and 35.90% (95% CI, 23.94% to 42.62%) among male decedents; during 2021-2024, the respective APCs were -18.46% (95% CI, -26.48% to -12.25%) and -22.58% (95% CI, -28.95% to -17.24%) (Supplementary Tables S2, S3, and S5 and Supplementary Figure S2).

Trends by Hispanic origin

Among Hispanic decedents, the AAMR increased from 0.26 (95% CI, 0.18 to 0.37) in 1999 to 3.38 (95% CI, 3.18 to 3.59) in 2021, then declined to 1.12 (95% CI, 1.01 to 1.24) in 2024. Among non-Hispanic decedents, the corresponding AAMRs were 0.42 (95% CI, 0.39 to 0.45), 2.83 (95% CI, 2.76 to 2.91), and 1.51 (95% CI, 1.46 to 1.56). The full-period AAPC was 3.25% (95% CI, 1.60% to 5.12%) among Hispanic decedents and 4.18% (95% CI, 3.19% to 5.03%) among non-Hispanic decedents. The 2018-2021 increase was numerically steeper among Hispanic decedents (APC, 50.61%; 95% CI, 28.93% to 64.68%) than among non-Hispanic decedents (APC, 30.90%; 95% CI, 16.78% to 37.34%), followed by corresponding declines during 2021-2024 (APC, -33.95%; 95% CI, -42.69% to -26.35%; and APC, -18.30%; 95% CI, -25.91% to -12.44%, respectively) (Supplementary Tables S2, S3, and S6 and Supplementary Figure S3).

Regional, urban-rural, and state patterns

AAMRs peaked in 2021 in each Census region. In that year, the AAMR was highest numerically in the South (3.73; 95% CI, 3.61 to 3.86), followed by the West (3.24; 95% CI, 3.10 to 3.40), Midwest (2.38; 95% CI, 2.24 to 2.52), and Northeast (1.55; 95% CI, 1.43 to 1.67). By 2024, the respective AAMRs were 1.88 (95% CI, 1.79 to 1.96), 1.45 (95% CI, 1.36 to 1.55), 1.21 (95% CI, 1.12 to 1.31), and 0.88 (95% CI, 0.79 to 0.97). Full-period AAPCs ranged from 3.13% (95% CI, 2.34% to 4.24%) in the Northeast to 4.80% (95% CI, 3.87% to 5.81%) in the South. All regions increased significantly during 2018-2021 and declined significantly during 2021-2024 (Supplementary Tables S2, S3, and S7 and Supplementary Figure S4).

Urbanization-specific rate analyses were limited to 1999-2020. In 2020, AAMRs were numerically highest in micropolitan (2.92; 95% CI, 2.69 to 3.16) and noncore counties (2.85; 95% CI, 2.57 to 3.12), and lowest in large fringe metropolitan counties (1.50; 95% CI, 1.40 to 1.60). Full-period AAPCs were significant in all six urban-rural categories and were numerically largest in noncore (7.78%; 95% CI, 5.84% to 9.26%) and micropolitan counties (7.76%; 95% CI, 5.87% to 9.29%). For 2021-2024, only counts were available;

counts were lower in 2024 than in 2021 in each urbanization category and were not interpreted as rate comparisons (Supplementary Tables S2, S3, S8, and S9 and Supplementary Figure S5).

In pooled state estimates for 1999-2020, Oklahoma had the highest AAMR (2.0 per 100,000), followed by Vermont (1.5) and West Virginia (1.4); Connecticut, Massachusetts, and Virginia each had an AAMR of 0.5. In the separate 2021-2024 pooled estimates, Oklahoma (6.6), South Carolina (6.1), and Delaware (4.6) had the highest AAMRs, whereas Maine (0.5), Connecticut (0.6), and Massachusetts (0.8) had the lowest (Supplementary Tables S10 and S11 and Supplementary Figures S9 and S10).

Race and ethnicity

Historical bridged-race and contemporary single-race results were analyzed separately. During 1999-2020, pooled AAMRs were 1.83 (95% CI, 1.67 to 1.98) among non-Hispanic American Indian or Alaska Native decedents, 1.39 (95% CI, 1.36 to 1.42) among non-Hispanic Black decedents, 0.84 (95% CI, 0.83 to 0.85) among non-Hispanic White decedents, and 0.19 (95% CI, 0.18 to 0.21) among non-Hispanic Asian or Pacific Islander decedents. Complete reliable annual series were available only for non-Hispanic Black and non-Hispanic White groups. Among non-Hispanic Black decedents, the AAMR increased nonsignificantly during 1999-2018 (APC, 2.37%; 95% CI, -0.11% to 3.86%) and then increased during 2018-2020 (APC, 33.03%; 95% CI, 7.66% to 45.69%); the 1999-2020 AAPC was 4.96% (95% CI, 3.24% to 6.15%). Among non-Hispanic White decedents, the AAMR increased during 1999-2003 (APC, 13.12%; 95% CI, 5.61% to 47.69%), was not significantly changed during 2003-2018 (APC, 4.31%; 95% CI, -5.36% to 5.16%), and increased during 2018-2020 (APC, 21.46%; 95% CI, 7.21% to 32.20%); the full-period AAPC was 7.48% (95% CI, 6.20% to 9.71%) (Supplementary Tables S15-S17, S21-S23, and Supplementary Figure S7).

In the mutually exclusive contemporary comparison pooled over 2021-2024, non-Hispanic Native Hawaiian or Other Pacific Islander decedents had the highest AAMR (6.39; 95% CI, 5.21 to 7.78), corresponding to a rate ratio of 3.20 (95% CI, 2.63 to 3.88) relative to non-Hispanic White decedents. The AAMR was 5.20 (95% CI, 4.66 to 5.80) among non-Hispanic American Indian or Alaska Native decedents (rate ratio, 2.60; 95% CI, 2.33 to 2.90) and 2.88 (95% CI, 2.78 to 2.98) among non-Hispanic Black decedents (rate ratio, 1.44; 95% CI, 1.39 to 1.50). The reference AAMR among non-Hispanic White decedents was 2.00 (95% CI, 1.96 to 2.03). AAMRs were 1.86 (95% CI, 1.79 to 1.94) among Hispanic or Latino decedents of any race, 1.16 (95% CI, 0.97 to 1.37) among non-Hispanic decedents reporting more than one race, and 0.25 (95% CI, 0.21 to 0.29) among non-Hispanic Asian decedents (Supplementary Table S19).

In exploratory 2018-2024 Joinpoint models based on seven annual observations, each contemporary race and ethnicity group had a joinpoint in 2021, with significant increases during 2018-2021 and significant declines during 2021-2024. Full-period AAPCs were not significant for six of the seven groups; the exception was the non-Hispanic more-than-one-race group (AAPC, 10.21%; 95% CI, 0.50% to 23.94%).

These short-series estimates were considered exploratory (Supplementary Tables S18, S21, S24, and S25 and Supplementary Figure S8).

Sensitivity analyses

The narrower A40-A41 sepsis-definition sensitivity analysis identified 64,020 deaths, 143 fewer than the expanded-code primary analysis. Its AAMR increased from 0.41 (95% CI, 0.38 to 0.44) in 1999 to 2.95 (95% CI, 2.88 to 3.02) in 2021, then declined to 1.46 (95% CI, 1.42 to 1.51) in 2024. The full-period AAPC was 4.01% (95% CI, 3.01% to 5.06%), and the same three temporal phases were retained: 1999-2018 (APC, 4.18%; 95% CI, 2.48% to 5.72%), 2018-2021 (APC, 33.17%; 95% CI, 16.97% to 40.03%), and 2021-2024 (APC, -19.58%; 95% CI, -27.53% to -13.79%) (Supplementary Tables S2, S3, and S12 and Supplementary Figure S6).

During 2020-2024, 5,492 of 26,275 deaths in the primary cohort (20.9%) had COVID-19 (U07.1) recorded as the underlying cause. The proportion was 27.4% in 2020, peaked at 40.3% in 2021, and declined to 15.8% in 2022, 3.2% in 2023, and 2.0% in 2024. After subtracting these deaths, the remaining annual counts were 3,797 in 2020, 4,457 in 2021, 4,500 in 2022, 4,118 in 2023, and 3,911 in 2024. Post-exclusion AAMRs were not calculated (Supplementary Table S13).

Discussion

Principal findings

In this national analysis of 64,163 US deaths with co-documented sepsis and obesity from 1999 through 2024, age-adjusted mortality rose more than seven-fold before 2021, then declined by roughly half through 2024, tracing three statistically distinct phases: a steady rise (1999–2018), a sharp pandemic-era acceleration (2018–2021), and a partial retreat (2021–2024). Burden was consistently higher among women, non-Hispanic American Indian/Alaska Native and Native Hawaiian/Pacific Islander decedents, residents of the South and of nonmetropolitan counties, and, in state-level estimates, Oklahoma specifically.

Comparison with the wider CDC WONDER multiple-cause-of-death literature

Because sepsis is under-captured when only the underlying cause of death is coded, we used multiple-cause-of-death (MCD) data rather than underlying-cause data.[8] Four recent 2025–2026 CDC WONDER MCD analyses of sepsis co-documented with other chronic conditions provide a relevant benchmark. Sepsis co-documented with cancer declined from 1999 to a 2018 inflection (annual percent change [APC], -1.32%), rose sharply through 2021 (APC, +2.17%), then declined again through 2023 (APC, -3.65%).[10] Sepsis co-documented with diabetes followed a similar pattern (APC, -1.22% to 2018;

+18.14% to 2021; –12.25% to 2023).[11] By contrast, sepsis co-documented with acute kidney injury[12] and with cardiogenic shock (average annual percent change, 5.39%)[13] rose across the full period. What is consistent across all four studies, and what we regard as external validation of our own finding, is a shared 2018–2021 upward inflection followed by attenuation or decline from 2021 onward, regardless of comorbidity.[10-13] These studies also converge with ours on much of who bears the excess burden: non-Hispanic Black and American Indian/Alaska Native decedents, Southern residence, and nonmetropolitan residence recur as high-burden groups across most of them.[10-13] Male sex, however, is the typical pattern in this comparator literature,[10-13] making our finding of higher female AAMRs throughout the period a genuine point of divergence, discussed below. Similarly, our finding that non-Hispanic Native Hawaiian/Other Pacific Islander decedents had the highest contemporary AAMR is not corroborated by this literature and should be treated as a novel finding warranting confirmation. To our knowledge, this is the first MCD analysis to characterize the sepsis-obesity intersection specifically, complementing this emerging body of CDC WONDER work on sepsis co-documented with cancer, diabetes, acute kidney injury, and cardiogenic shock, and extending it to a comorbidity pair defined by a modifiable, prevalent risk factor rather than another acute or chronic disease process.[10-13]

The obesity–sepsis paradox: a different question than the one we asked

A substantial clinical literature, the so-called “obesity paradox,” reports that among patients who have already developed sepsis or another critical illness, higher body mass index (BMI) is paradoxically associated with better, not worse, survival.[14] A 2025 narrative review similarly concluded that obesity confers a survival benefit across multiple types of critical illness, including sepsis, with no clear mortality association once patients reach a very high BMI.[15] Consistent with this, a 2026 meta-analysis of 12 retrospective studies (130,755 adults with sepsis) found elevated BMI associated with lower short-term (odds ratio, 0.75), 28-/30-day (odds ratio, 0.74), and long-term (odds ratio, 0.68) mortality, an inverse association persisting even at BMI ≥ 40 kg/m². [6] A US cohort of 55,038 hospitalized adults meeting Sepsis-3 criteria showed the same pattern.[7] Proposed mechanisms include greater metabolic energy reserve, an anti-inflammatory adipokine profile, endotoxin-neutralizing lipoproteins, adrenal-steroid and renin-angiotensin activation, cardioprotective effects, and prevention of muscle wasting,[14] with additional contributions proposed from adipokine signaling (elevated resistin and visfatin)[16] and stress-induced “browning” of white adipose tissue.[17] Our findings do not contradict this literature because they measure a different question. The paradox describes conditional survival after sepsis has already occurred; [6],[7],[14] our study measures population-level absolute mortality burden, which can rise even as per-patient prognosis improves, because it is also driven by rising obesity prevalence (40.3% of US adults by 2021–2023), [2] rising sepsis incidence and detection, and increased joint documentation on certificates. We cannot distinguish, with death-certificate data, whether obesity was a bystander comorbidity, a contributor to fatal infection, or a marker of the frailty that made a septic episode fatal, a

limitation the paradox literature itself flags alongside reverse causality and BMI misclassification.[14] We therefore present our results as a surveillance-level complement to, not a test of, the paradox.

Sex disparities

Contrary to the comparator MCD literature, where male mortality consistently exceeded female,[10-13] we found higher AAMRs among women throughout. This is plausible given national obesity-prevalence data: age-adjusted obesity prevalence is modestly higher among women than men overall (41.4% vs 39.3%) and substantially higher among non-Hispanic Black women (56.0%).[2] A higher female obesity prevalence could plausibly translate into higher female co-documented mortality without any difference in per-episode case-fatality by sex. We flag this as a plausible, literature-consistent explanation rather than a demonstrated mechanism, since our ecological data cannot partition the sex difference from other unmeasured factors.

Racial, ethnic, regional, and rural disparities

The markedly elevated AAMRs among non-Hispanic American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and Black decedents echo a broader sepsis-disparities literature attributing excess mortality to structural determinants rather than biological difference. A Yale-led coalition-based intervention study frames these gaps as products of structural racism amenable to organizational-level intervention, reporting more sepsis complications, care-bundle deviations, and readmissions among Black and Latinx patients than non-Hispanic White patients.[18] Regional and rural excess mortality mirrors the rural-urban gap reported in the parallel MCD literature, including higher rural AAMRs in diabetes-sepsis mortality,[11] plausibly reflecting reduced intensive-care access, longer transport times, and critical-access hospital strain. We did not measure regional obesity prevalence directly and are not aware of a citation linking our regional pattern to it; we therefore attribute our regional findings to healthcare-access and critical-care-capacity explanations instead.

The pandemic-era acceleration and partial reversal

The sharp 2018–2021 acceleration coincided with COVID-19; our sensitivity analysis found COVID-19 was the underlying cause in 20.9% of eligible deaths from 2020–2024 (40.3% in 2021 alone), confirming the pandemic materially contributed to, but did not fully explain, the surge. Obesity is an independently established risk factor for severe COVID-19 and for a broad range of infections generally,[4] through mechanisms including chronic inflammation and disrupted immune-cell metabolism.[5] The pandemic therefore likely acted as an acute stressor on an already-rising trend. The subsequent 2021–2024 decline is harder to attribute definitively, but three non-exclusive contributors merit discussion. First, waning COVID-19 mortality after 2021 mechanically reduced a major driver of the surge. Second, hospital-level sepsis quality-improvement programs, including protocolized bundles, alert systems, and

“code sepsis” teams, have lowered observed-to-expected sepsis mortality ratios (1.14 to 0.73 in one center over 2017–2022),^[19] and continued national uptake could plausibly contribute to a real decline independent of COVID-19. Third, and more speculatively, the 2021 approval and rapid uptake of GLP-1 receptor agonists coincides with our observed decline; in the SELECT trial of semaglutide in adults with overweight or obesity and cardiovascular disease, semaglutide reduced infection-related deaths (hazard ratio, 0.71; 95% CI, 0.51-0.98) and COVID-19 deaths (hazard ratio, 0.66; 95% CI, 0.44-0.96) versus placebo.^[20] We raise this only as a hypothesis-generating explanation; our ecological design cannot establish individual-level causality or rule out confounding by simultaneous changes in COVID-19 mortality, coding practice, or care delivery.

Strengths and limitations

This study's principal strength is its use of MCD data, which captures sepsis and obesity wherever recorded on the certificate rather than only when selected as the underlying cause, an important distinction given how infrequently sepsis is coded as the underlying cause even when clinically present.^[8] Limitations include those inherent to all death-certificate surveillance: certificate-level diagnoses are not clinically adjudicated against Sepsis-3 criteria and are subject to coding variation over time and by facility; obesity is likely underreported on death certificates, which may bias co-documentation counts toward more severe or more thoroughly documented cases; the co-occurrence of two conditions does not establish that either caused death or that they interacted causally; and the 2018–2020 switch from bridged-race to single-race classification precludes a single continuous race-specific time series, which we addressed by analyzing the two eras separately (Supplementary Table S20). As with any ecological time-series analysis, our findings describe population-level associations and trends and cannot be used to infer individual-level risk or establish causal mechanisms for the disparities or inflection points described.

Public health and policy implications

These findings carry direct implications for surveillance, clinical practice, and policy. First, national mortality surveillance for sepsis should continue to incorporate MCD methodology and obesity co-documentation specifically, since underlying-cause-only surveillance would have missed the great majority of this burden.^{[8],[9]} Second, the concentration of excess mortality in the South, in nonmetropolitan counties, and among American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Black populations identifies concrete targets for resource allocation: expansion of rural critical-care and telehealth-supported sepsis-recognition capacity, and continued investment in structural-racism-focused, coalition-based quality-improvement models with a demonstrated track record of narrowing sepsis-care gaps.^[18] Third, hospital-level adoption of protocolized sepsis bundles remains an actionable, evidence-based lever for reducing mortality broadly, including among patients with obesity, and should be prioritized in the highest-burden facilities and regions identified here.^[19] Fourth, given the

established relationship between obesity and infection risk,[4] obesity prevention and treatment, including equitable access to effective pharmacologic therapies,[20] should be considered a component of sepsis-mortality prevention strategy at the population level. Finally, our results argue for sustained post-pandemic vigilance: the 2021–2024 decline left 2024 mortality still more than three times its 1999 level, indicating this burden, though past its pandemic peak, remains a growing, not resolved, public health problem. Future research should prioritize prospective validation of these certificate-based trends against clinically adjudicated Sepsis-3 cohorts, and, given the pandemic-era decline coinciding with rising GLP-1 receptor agonist use, a targeted evaluation of these agents' effect on infection-related and sepsis-specific mortality at the population level.

Conclusion

Mortality involving co-documented sepsis and obesity in the United States rose substantially from 1999 to 2024, driven by a pandemic-era surge that has only partially reversed, and fell unevenly across the population, disproportionately burdening women, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Black communities, and residents of the South and rural America. These findings are relevant beyond descriptive surveillance: they identify specific populations and regions where sepsis-mortality prevention efforts involving obesity should be prioritized, and they support continued multiple-cause-of-death surveillance, equity-focused sepsis-care quality improvement, and integration of obesity prevention into infection-mortality prevention strategy as actionable public health and policy priorities.

Abbreviations

AAMR, age-adjusted mortality rate; AAPC, average annual percentage change; APC, annual percentage change; CDC, Centers for Disease Control and Prevention; CI, confidence interval; COVID-19, coronavirus disease 2019; GLP-1, glucagon-like peptide-1; ICD-10, International Classification of Diseases, Tenth Revision; MCD, multiple cause of death; NHANES, National Health and Nutrition Examination Survey; NHOPI, Native Hawaiian or Other Pacific Islander; RECORD, REporting of studies Conducted using Observational Routinely-collected Data; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; WONDER, Wide-ranging Online Data for Epidemiologic Research.

Declarations

Ethics approval and consent to participate

This study used publicly available, de-identified, aggregate mortality data from the CDC WONDER Multiple Cause of Death database and did not involve identifiable individual-level data or direct

interaction with human participants. No ethics approval was required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are publicly available in the CDC WONDER Multiple Cause of Death database, <https://wonder.cdc.gov/mcd.html>.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

M.A conceptualization, data curation, analysis, original draft, revision.

M.R data curation, analysis.

S.T data curation, analysis.

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Figures

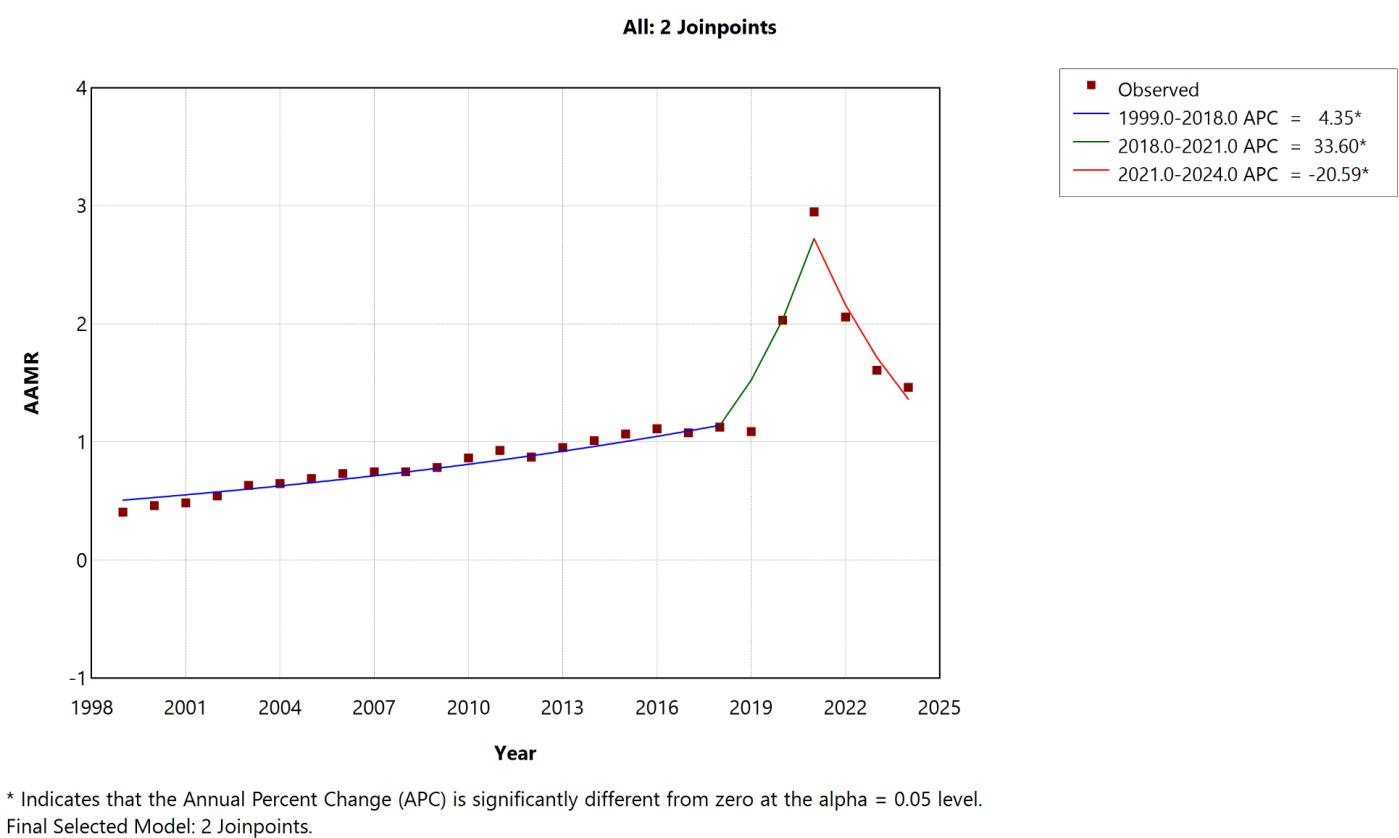


Figure 1

Overall age-adjusted mortality trends involving co-documented sepsis and obesity, United States, 1999-2024. Points show observed annual age-adjusted mortality rates (AAMRs) per 100,000 population among US adults aged 25 years or older. Lines show the fitted Joinpoint regression segments identified for the

overall population, colored by trend phase: blue indicates the 1999-2018 segment (APC, 4.35%), green indicates the 2018-2021 segment (APC, 33.60%), and red indicates the 2021-2024 segment (APC, -20.59%); this color coding distinguishes the three statistically distinct phases of the trend rather than any subgroup. Asterisks denote annual percent changes (APCs) whose 95% confidence interval excluded zero. Underlying data and full confidence intervals are reported in Supplementary Tables S2-S4; this figure is reproduced from Supplementary Figure S1.

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