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ORIGINAL RESEARCH

Temporal Trends in Substance Use and Cardiovascular Disease–Related Mortality in the United States

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BACKGROUND: There are limited data on substance use (SU) and cardiovascular disease (CVD)–related mortality trends in the United States. We aimed to evaluate SU+CVD–related deaths in the United States using the Centers for Disease Control and Prevention Wide-Ranging, Online Data for Epidemiologic Research database.

METHODS AND RESULTS: The Multiple Cause-of-Death Public Use record death certificates were used to identify deaths related to both SU and CVD. Crude, age-adjusted mortality rates, annual percent change, and average annual percent changes with a 95% CI were analyzed. Between 1999 and 2019, there were 636 572 SU+CVD-related deaths (75.6% men, 70.6% non-Hispanic White individuals, 65% related to alcohol). Age-adjusted mortality rates per 100 000 population were pronounced in men (22.5 [95% CI, 22.6–22.6]), American Indian or Alaska Native individuals (37.7 [95% CI, 37.0–38.4]), nonmetropolitan/rural areas (15.2 [95% CI, 15.1–15.3]), and alcohol-related death (9.09 [95% CI, 9.07 to 9.12]). The overall SU+CVD-related age-adjusted mortality rates increased from 9.9 (95% CI, 9.8–10.1) in 1999 to 21.4 (95% CI, 21.2–21.6) in 2019 with an average annual percent change of 4.0 (95% CI, 3.7–4.3). Increases in SU+CVD-related average annual percent change were noted across all subgroups and were pronounced among women (4.8% [95% CI, 4.5–5.1]), American Indian or Alaska Native individuals, younger individuals, nonmetropolitan areas, and cannabis and psychostimulant users.

CONCLUSIONS: There was a prominent increase in SU+CVD-related mortality in the United States between 1999 and 2019. Women, non-Hispanic American Indian or Alaska Native individuals, younger individuals, nonmetropolitan area residents, and users of cannabis and psychostimulants had pronounced increases in SU+CVD mortality.

Key Words: cardiovascular disease ■ cardiovascular mortality ■ mortality trend ■ substance use

A lifetime prevalence of substance use (SU) is reported at ≈10% in the general United States (US) population.[1] It is well-known that SU disorder can disturb physical health, mental status, and social well-being.[1] Several substances, such as alcohol, opioids, stimulants, sedatives, and cannabis are associated with increased cardiovascular disease (CVD) risk, including coronary artery disease, heart failure, and arrhythmias.[2–6] In patients with pre-existing cardiovascular conditions, SU further heightens the risk of CVD-related mortality and morbidity.[7]

Survival rates of CVD have improved substantially in the past decades due to improvements in overall cardiovascular care, although the trends have plateaued.[8] In contrast, rates of SU and SU-related death have continued to increase.[7] Additionally,

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CLINICAL PERSPECTIVE

What Is New?

- Substance use and cardiovascular disease–related mortality in the United States between 1999 and 2019 has been on the continuous rise.
- There is heterogeneity in the trend of substance use and cardiovascular disease–related mortality, with women, non-Hispanic American Indian or Alaska Native individuals, younger individuals, nonmetropolitan area residents, and users of cannabis and psychostimulants having more pronounced increases in substance use and cardiovascular disease mortality.

What Are the Clinical Implications?

- Identifying the high-risk groups is crucial for prioritizing preventive measures aiming to reduce substance use and cardiovascular disease–related mortality in these populations.

Nonstandard Abbreviations and Acronyms

AAMR	age-adjusted mortality rate
AAPC	average annual percentage change
APC	annual percentage change
NH	non-Hispanic
SU	substance use

studies demonstrate that CVD-related mortality associated with psychotropic drugs has been escalating.[9] However, the temporal changes in CVD-related mortality associated with various categories of SU have yet to be well characterized. Additionally, it is unclear whether temporal trends in SU-related CVD mortality are impacted by sex, ethnicity, and geographic region in the United States. Therefore, we assessed these trends in SU-related CVD deaths in the United States using the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (WONDER) database.

METHODS

Deaths occurring within the United States related to CVD and SU were extracted from the CDC WONDER database.[10] The Multiple Cause-of-Death Public Use record death certificates were used to analyze deaths in which SU and CVD were both mentioned as contributing or underlying causes of death on nationwide death certificates. This database has previously been used in several other studies to determine CVD mortality trends.[11,12] Patients with SU were identified with *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes provided in supplementary files, and patients with CVD were identified with *ICD-10-CM* codes I00-I99 (diseases of the circulatory system) in patients ≥25 years of age as previously described.[12–14] Smoking/tobacco use was not included in primary analyses as a form of SU. If a patient had multiple SU listed on the death certificate, they would be counted once for SU-related death. However, in a subgroup by drug category, they would be accounted for all drug category separately listed on the death certificate. *ICD* codes of intentional substance overdoses were included in our analysis, whereas accidental or assault by substance were not included (Table S1). Institutional Review Board approval was not sought because the CDC WONDER database contains publicly available, anonymized data. All data and materials have been made publicly available and can be accessed at https://wonder.cdc.gov/. Informed consent was not required due to the nature of the publicly available deidentified data.

SU+CVD-related deaths, population size, and location of death (including medical facilities [outpatient, emergency room, inpatient, death on arrival or status unknown], home, hospice, and nursing home/long-term care facility) were extracted. Demographics (sex, race and ethnicity, and age) and regional information (urban–rural and state) were extracted from 1999 to 2019. Races and ethnicities were defined as non-Hispanic (NH) White, NH Black, Hispanic, Native American or Alaska Native, and NH Asian or Pacific Islander patients. These racial and ethnic categories have previously been used within analyses from the CDC WONDER database and rely on reported data on death certificates.[10] Age groups were defined as 25–39, 40–54, 55–69, 70–84, and 85+ years of age. The CDC WONDER database provides age-adjusted mortality rates in preset 10-year intervals for adults. Therefore, we were unable to include patients 18 to 24 years of age within the analyses. For urban–rural classifications, the 2013 National Center for Health Statistics Urban–Rural Classification Scheme was used to divide the counties into metropolitan (large central metropolitan, large fringe metropolitan, medium metropolitan, and small metropolitan) and nonmetropolitan (micropolitan and noncore) categories.[15] Regions were classified into Northeast, Midwest, South, and West according to the Census Bureau definitions.

Crude and age-adjusted mortality rates (AAMRs) per 100 000 population were determined. Crude mortality rates were determined by dividing the number of SU+CVD-related deaths by the corresponding US population of that year. As previously described, AAMRs were calculated by standardizing the SU+CVD-related deaths to the year 2000 US population.[16] The

Joinpoint Regression Program (Joinpoint V 4.9.0.0, National Cancer Institute) was used to determine trends in AAMR using annual percent change (APC).[17] This method identifies significant changes in AAMR over time by fitting a series of joined straight lines on a log scale where temporal variation occurred. For data containing 17 to 21 time points, the guidelines recommend that the analysis identifies a maximum of 3 inflection points across the study period.[18] Therefore, the Joinpoint regression statistical software was set to determine a maximum of 3 Joinpoints (21 years of analysis were included) where significant temporal variation existed in the trend. APCs with 95% CI for the AAMR were calculated at the identified line segments linking Joinpoints using the Monte Carlo permutation test. The weighted average of the APCs was calculated and reported as average APCs (AAPCs) and corresponding 95% CIs as a summary of the reported mortality trend for the entire study period. APCs were considered increasing or decreasing if the slope describing the change in mortality did not have CIs that crossed zero. Statistical significance was inferred based on nonoverlapping CIs.

RESULTS

Population Characteristics

Between 1999 and 2019, there was a total of 51 998 560 deaths in the United States. There were 29 455 193 deaths related to CVD in people ≥25 years of age, of which 636 572 (2.2%) also had SU listed as concomitant cause of death. Of all SU+CVD-related deaths, 75.6% were men, and 70.6%, 15.9%, 9.8%, 1.9%, and 1.2% were NH White, NH Black, Hispanic, American Indian or Alaska Native, and NH Asian or Pacific Islander individuals, respectively. Only 0.7% of race and ethnicity data were missing. Among SU+CVD deaths, the most common age range was 55 to 69 years (39.1% of SU+CVD-related deaths), followed by 40 to 54 years (36.8%), 70 to 84 years (12.1%), 25 to 39 years (10.3%), and 85+ years (1.7%) (Table S2). When stratified by substance category (not mutually exclusive), alcohol accounted for the most SU+CVD-related deaths (65%), followed by opioids (13.7%), cocaine (9.8%), stimulants (6.5%), sedatives (4.1%), and cannabis (0.5%) (Table S3). Of 575 920 SU+CVD-related deaths with location available on place of death, 274 503 (47.7%) occurred in medical facilities, 26 812 (4.6%) occurred in nursing/long-term care homes, 10 211 (1.8%) occurred in hospice, and 264 394 (45.9%) occurred at home (Table S4).

Age-Adjusted Mortality Rates per 100 000

The overall CVD-related AAMR (independent of contributing SU) was 654.0 (95% CI, 653.8–654.3), and overall SU-related AAMR (independent of contributing CVD) was 43.6 (95% CI, 43.6–43.7) (Table; Table S5). The overall SU+CVD-related AAMR from 1999 to 2019 was 14.3 (95% CI, 14.3–14.3) per 100 000 individuals. During this period, ischemic heart disease (4.8) had the highest SU+CVD-related AAMR, followed by heart failure (2.0), cerebrovascular accident (1.2), and aortic dissection (0.1) (Table S6). The overall SU+CVD-related AAMR was 22.5 (95% CI, 22.6–22.6) in men and 6.8 in women (95% CI, 6.7–6.8) (Figure 1; Table S7), and was highest in American Indian or Alaska Native individuals (37.7 [95% CI, 37.0–38.4]), followed by NH Black individuals (20.3 [95% CI, 20.1–20.4]), NH White individuals (14.1 [95% CI, 14.0–14.1]), Hispanic individuals (13 [95% CI, 12.9–13.1]), and NH Asian or Pacific islander individuals (3.6 [95% CI, 3.5–3.7]) (Figure 2; Table S8). Nonmetropolitan/rural areas had higher SU+CVD-related AAMR than metropolitan/urban areas (15.2 [95% CI, 15.1–15.3] versus 14.1 [95% CI, 14.1–14.1]) (Figure 3; Table S9). District of Columbia had the highest SU+CVD-related AAMR at 25.4, whereas Virginia had the lowest SU+CVD-related AAMR at 8.1 (Figure 4; Table S10). States with AAMRs greater than the 90th percentile were the District of Columbia, Nevada, Alaska, Oklahoma, and Wyoming, whereas states with AAMRs less than the tenth percentile were Virginia, New Jersey, Illinois, Pennsylvania, and Alabama. Individuals aged 55 to 69 years had the highest SU+CVD-related AAMR (25.1 [95% CI, 25.0–25.2]), followed by 40 to 54 years (17.5 [95% CI, 17.4–17.6]), 70 to 84 years (15.6 [95% CI, 15.5–15.7]), age 85+ years (9.4 [95% CI, 9.2–9.6]), and 25 to 39 (5.0 [95% CI, 5.0–5.0]) (Figure 5; Table S11).

Regarding substance category, alcohol+CVD-related AAMR was the highest (9.09 [95% CI, 9.07–9.12]), followed by opioids (2.04 [95% CI, 2.03–2.06]), cocaine (1.45 [95% CI, 1.44–1.46]), stimulants (0.95 [95% CI, 0.94–0.96]), sedatives (0.6 [95% CI, 0.6–0.61]), and cannabis (0.07 [95% CI, 0.068–0.073]) (Figure 6; Tables S12 through S15).

Although smoking/tobacco use was not included as a substance for the purpose of this study, for underlying CVD mortality, CVD+SU AAMR was 4.7 (95% CI, 4.7–4.7), while CVD+SU+smoking AAMR was 1.0 (95% CI, 1.0–1.0).

Temporal Trends

Between 1999 and 2019, overall CVD-related death (independent of contributing SU) decreased with an AAPC of –1.5% (95% CI, –1.6 to –1.4) (Figure S1). However, over this period, the overall SU-related death (Figure S2) (independent of contributing CVD) increased with an AAPC of 3.9% (95% CI, 3.2–4.7). Overall, the SU+CVD-related AAMR increased from

Table. Age-Adjusted Mortality Rates With Average Annual Percentage Changes of Substance Use, Cardiovascular Disease, and Substance Use+Cardiovascular Disease–Related Mortality in the United States, 1999 to 2019

	Age-adjusted rate per 100 000 population							
	Year 1999	95% CI (%)	Year 2019	95% CI (%)	Overall from 1999–2019	95% CI (%)	AAPC (%)	95% CI (%)
SU-related mortality	30.0	29.8 to 30.3	64.1	63.8 to 64.5	43.6	43.6 to 43.7	3.9	3.2 to 4.7
Alcohol	19.8	19.5 to 20.0	32.1	31.8 to 32.3	24.16	24.1 to 24.2	2.4	2.2 to 2.6
Cannabis	0.05	0.04 to 0.06	0.62	0.59 to 0.65	0.22	0.21 to 0.22	14.7	12.5 to 16.8
Cocaine	3.0	2.9 to 3.1	8.8	8.7 to 9.0	4.5	4.49 to 4.53	6.6	3.6 to 9.7
Opioid	4.9	4.7 to 5.0	23.5	23.3 to 23.7	11.89	11.85 to 11.92	8.3	6.9 to 9.7
Sedative-hypnotics	1.3	1.25 to 1.36	6.3	6.2 to 6.4	3.75	3.73 to 3.76	8.5	7.3 to 9.8
Stimulants	0.4	0.37 to 0.43	9.7	9.6 to 9.8	2.54	2.53 to 2.56	18.1	15.1 to 22.2
CVD-related mortality	798.5	797.2 to 799.8	595.6	594.6 to 596.5	654	653.8 to 654.3	–1.5	–1.6 to –1.4
SU+CVD-related mortality	9.9	9.8 to 10.1	21.4	21.2 to 21.6	14.3	14.3 to 14.3	4.0	3.7 to 4.3
Sex								
Male	16.6	16.3 to 16.8	33.1	32.8 to 33.5	22.5	22.5 to 22.6	3.6	2.8 to 4.3
Female	4.1	4.0 to 4.2	10.5	10.3 to 10.6	6.8	6.7 to 6.8	4.8	4.5 to 5.1
Race and ethnicity								
NH American Indian or Alaska Native	25.3	22.0 to 28.6	58.9	55.2 to 62.5	37.7	37.0 to 38.4	5.4	4.4 to 6.4
NH Asian or Pacific Islander	2.4	2.0 to 2.8	4.9	4.6 to 5.3	3.6	3.5 to 3.7	3.5	3 to 4.1
NH Black or African American	20.3	19.6 to 21.0	26.5	25.9 to 27.1	20.3	20.1 to 20.4	1.6	0.4 to 2.9
Hispanic	12.4	11.8 to 13.1	16.9	16.5 to 17.4	13.0	12.9 to 13.1	1.6	1.2 to 2
NH White	8.4	8.2 to 8.5	22.6	22.3 to 22.8	14.1	14.0 to 14.1	5.1	4.8 to 5.5
Age, y*								
25–39	3.1	3 to 3.3	8.2	8 to 8.4	5.3	5.0 to 5.0	5.3	3.9 to 6.6
40–54	11.8	11.5 to 12.1	24.1	23.7 to 24.5	17.5	17.4 to 17.6	3.8	2.9 to 4.7
55–69	15.7	15.3 to 16.2	40.9	40.4 to 41.1	25.1	25.0 to 25.2	4.9	4.3 to 5.5
70–84	14.2	13.7 to 14.7	22.5	21.9 to 23.0	15.6	15.5 to 15.7	2.5	2.1 to 2.9
85+	10.4	9.4 to 11.4	11.9	11.1 to 12.8	9.4	9.2 to 9.6	0.9	–0.6 to 2.5
Urbanization								
Rural	9.0	8.7 to 9.4	24.7	24.2 to 25.3	15.2	15.1 to 15.3	5.0	4.6 to 5.4
Urban	10.1	9.9 to 10.2	20.8	20.6 to 21.0	14.1	14.1 to 14.1	3.8	3.5 to 4.1
Substance								
Alcohol	7.5	7.3 to 7.6	12.7	12.5 to 12.8	9.09	9.07 to 9.12	2.7	2.5 to 3
Cannabis	0.017	0.012 to 0.025	0.2	0.18 to 0.22	0.07	0.07 to 0.07	12.7	10.9 to 14.5
Cocaine	0.94	0.9 to 0.99	2.23	2.17 to 2.29	1.45	1.4 to 1.5	5.1	1.9 to 8.4
Opioid	0.76	0.72 to 0.8	3.6	3.52 to 3.68	2.04	2.03 to 2.06	8.7	7.1 to 10.4
Sedative-hypnotics	0.21	0.19 to 0.23	0.97	0.93 to 1.01	0.6	0.6 to 0.61	9.4	7.7 to 11.1
Stimulants	0.17	0.15 to 0.19	3.2	3.13 to 3.28	0.95	0.94 to 0.96	16.8	13.9 to 19.9

AAPC indicates average annual percentage change; CVD, cardiovascular disease; NH, non-Hispanic; and SU, substance use.
*Crude mortality rates.

9.9 (95% CI, 9.8–10.1) in 1999 to 21.4 (95% CI, 21.2–21.6) in 2019, with an AAPC of 4.0% (95% CI, 3.7–4.3) (Figure 1). The SU and CVD-related AAMR increased from 1999 to 2012 at an APC of 2.8 (95% CI, 2.4–3.2), which then accelerated to 6.2 (95% CI, 5.5–6.8) from 2012 to 2019. The SU+CVD-related AAMR increased between 1999 and 2019 in both women (AAPC, 4.8% [95% CI, 4.5–5.1]) and men (3.6% [95% CI, 2.8–4.3]). (Figure 1).

The AAPC in SU+CVD-related AAMRs and crude mortality rates increased across all ethnicities and age groups from 1999 to 2019. SU+CVD-related AAMR increased in American Indian or Alaska Native individuals (AAPC, 5.4% [95% CI, 4.4–6.4]), NH White

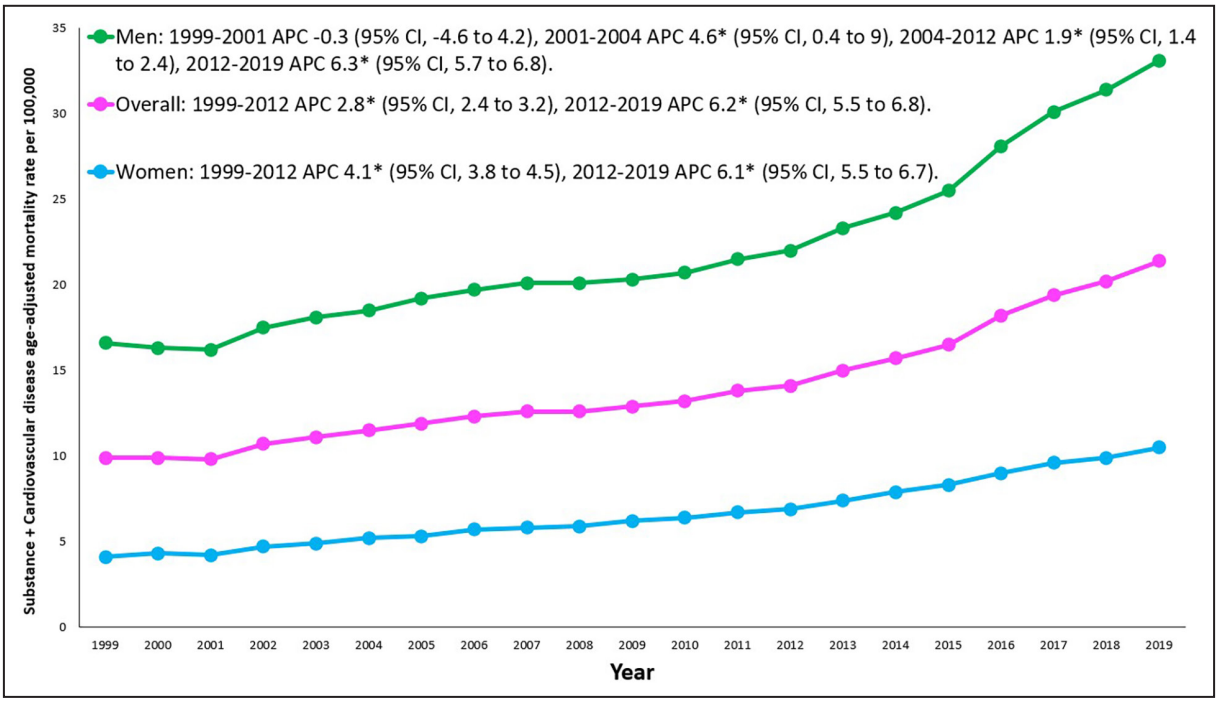

Figure 1. Overall and sex-stratified substance use+cardiovascular disease–related age-adjusted mortality rates in the United States, 1999 to 2019.
*The APC is significantly different from zero at α=0.05. APC indicates annual percentage change.

individuals (AAPC, 5.1% [95% CI, 4.8–5.5]), NH Asian or Pacific Islander individuals (AAPC, 3.5% [95% CI, 3 to 4.1]), Hispanic individuals (AAPC, 1.6% [95% CI, 1.2–2]), and NH Black individuals (AAPC, 1.6% [95% CI, 0.4–2.9%]) (Figure 2). Nonmetropolitan/rural areas (5% [95% CI, 4.6–5.4]) had higher AAPC in SU+CVD

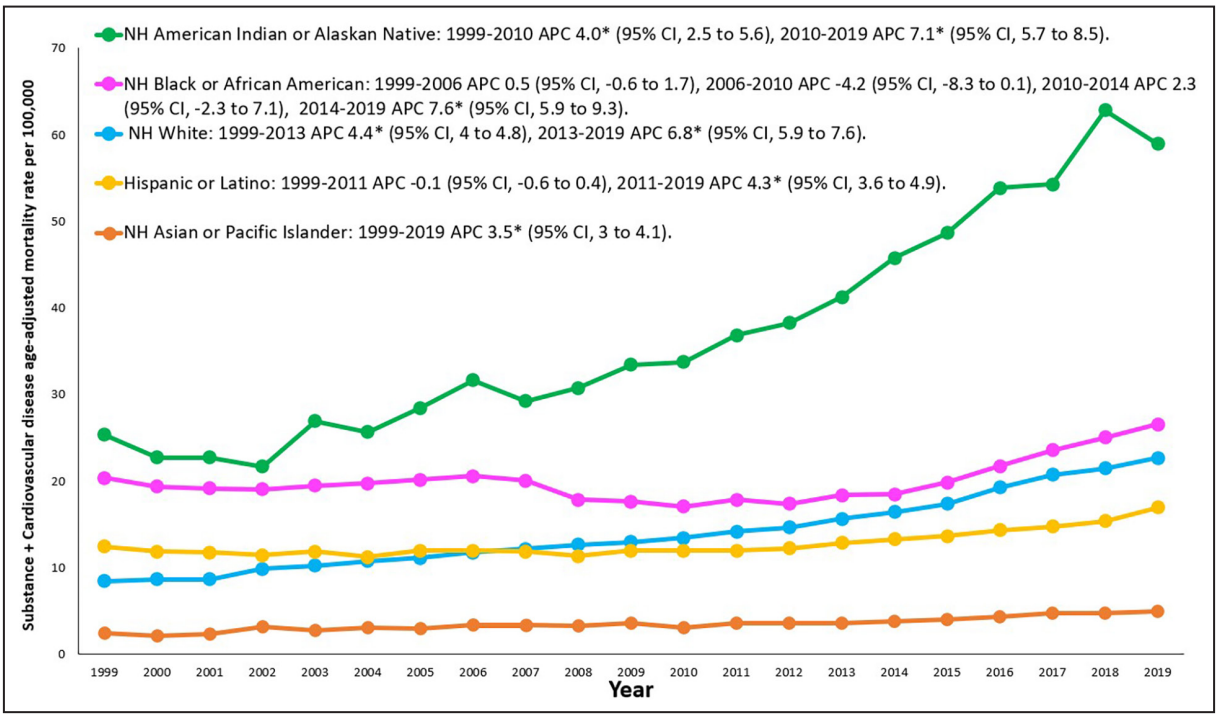

Figure 2. Race- and ethnicity-stratified substance use+cardiovascular disease–related age-adjusted mortality rates in the United States, 1999 to 2019.
*The APC is significantly different from zero at α=0.05. APC indicates annual percentage change; and NH, non-Hispanic.

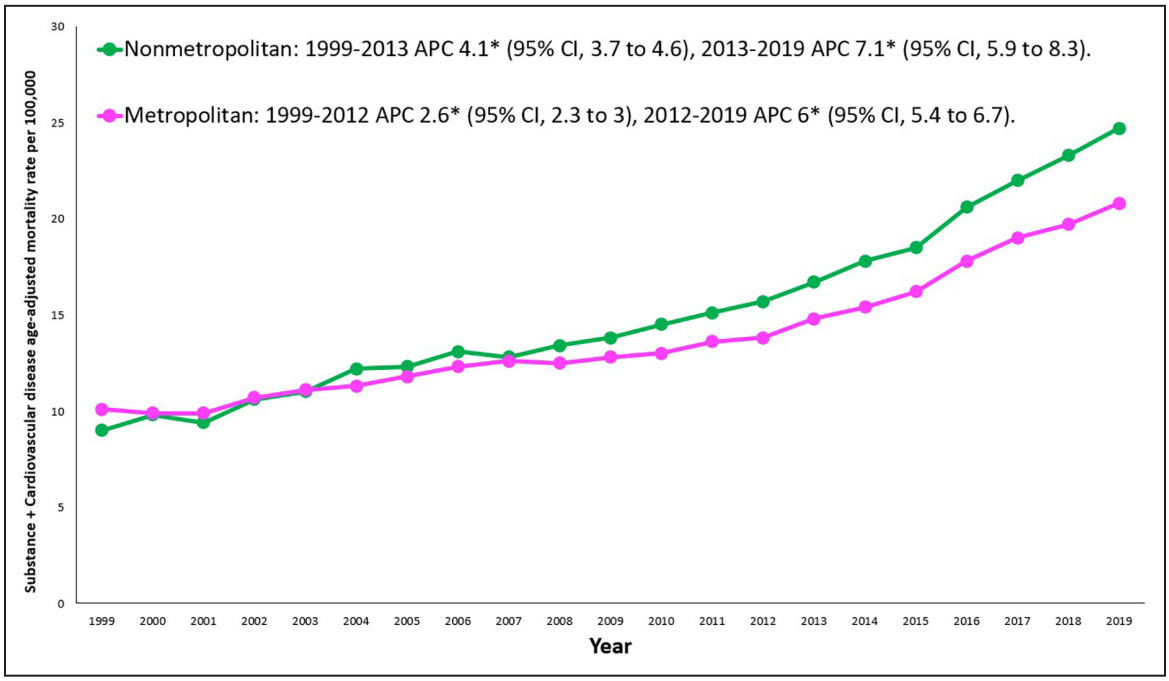

Figure 3. Substance use+cardiovascular disease–related age-adjusted mortality rates of metropolitan and nonmetropolitan areas in the United States, 1999 to 2019.
*The APC is significantly different from zero at α=0.05. APC indicates annual percentage change.

AAMR than metropolitan/urban areas (3.8% [95% CI, 3.5–4.1]) (Figure 3). SU+CVD-related crude mortality rates increased in age range 25 to 39 years (AAPC, 5.3% [95% CI, 3.9–6.6]), 55 to 69 years (AAPC, 4.9% [95% CI, 4.3–5.5]), 40 to 54 years (AAPC, 3.8% [95% CI, 2.9–4.7]), 70 to 84 years (AAPC, 2.5% [95% CI,

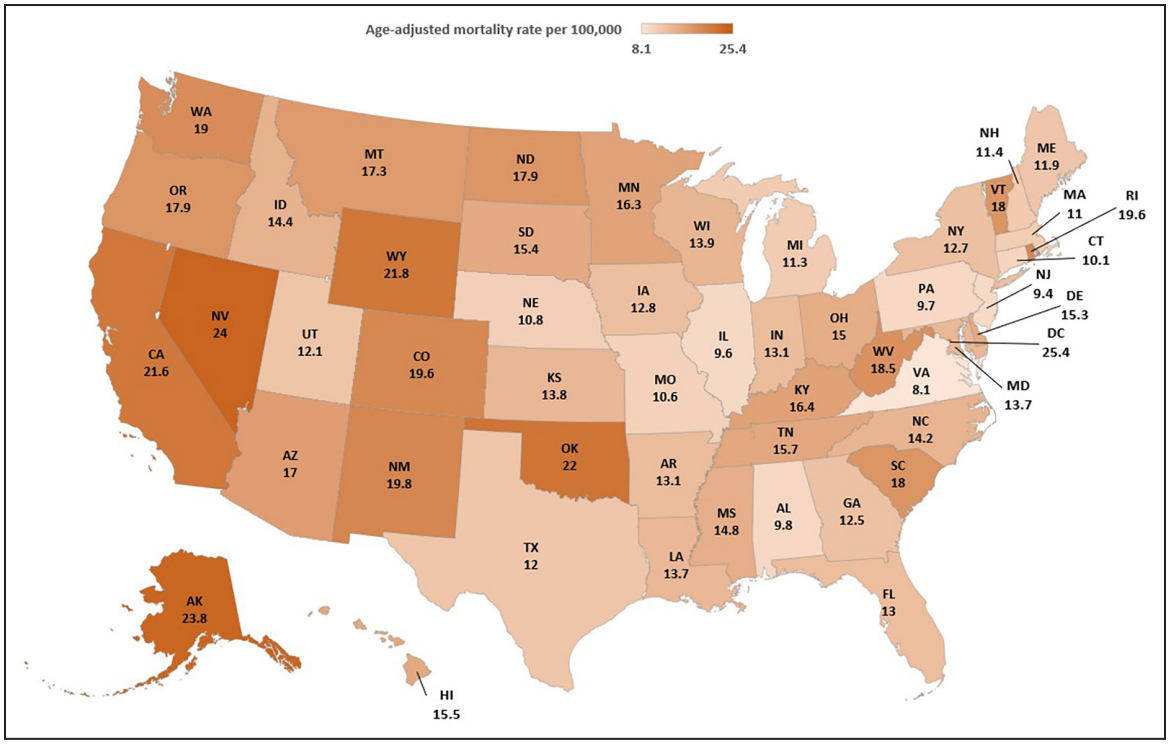

Figure 4. Geographic map demonstrating substance use+cardiovascular disease–related age-adjusted mortality rates by states in the United States, 1999 to 2019.

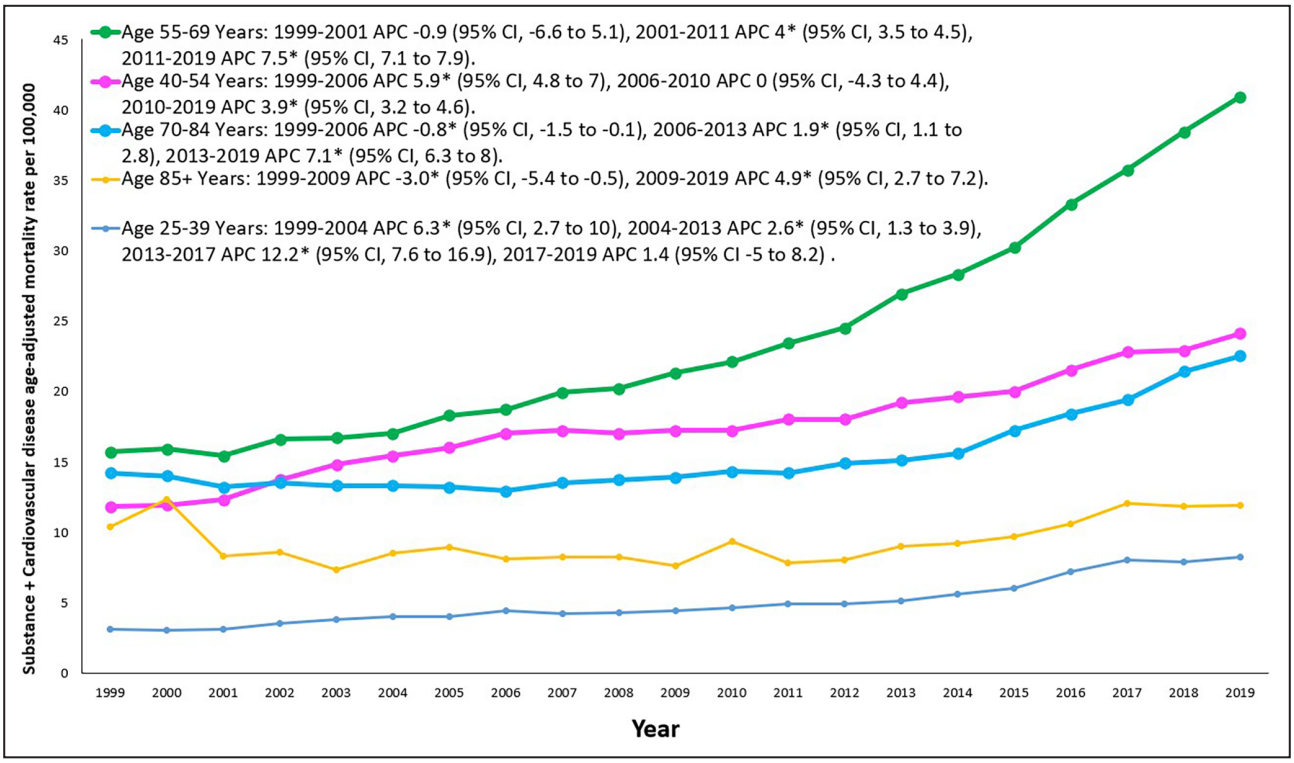

Figure 5. Age-stratified substance use+cardiovascular disease–related age-adjusted mortality rates in the United States, 1999 to 2019.

*The APC is significantly different from zero at α=0.05. APC indicates annual percentage change.

2.1–2.9]), and 85+ years (AAPC, 0.9% [95% CI, -0.6 to 2.5]) (Figure 5).

Regarding AAMR of SU+CVD-related mortality stratified by substance category, between 1999 and 2019, cannabis had the highest AAPC (12.7% [95% CI, 10.9–14.5]), followed by sedatives (9.4% [95% CI, 7.7–11.1]), opioids (8.7% [95% CI, 7.1–10.4]), cocaine (5.1%, [95% CI, 1.9–8.4]), and alcohol had the lowest AAPC (2.7% [95% CI, 2.5–3]) (Figure 6).

DISCUSSION

Our analysis of SU+CVD trends in the United States between 1999 and 2019 demonstrates several important findings. Despite a reduction in overall CVD mortality during this period, SU+CVD-related mortality increased at an average of 4% per year. Men, American Indian or Alaska Native individuals, the 55- to 69-year age group, and nonmetropolitan areas demonstrated the highest AAMRs in their demographic subgroups. In 2019, alcohol, opioids, stimulants (methamphetamines), and cocaine were the most common SU contributors to SU+CVD mortality. The temporal increase in SU+CVD during the study period was pronounced in women, American Indian or Alaska Native and NH White individuals, younger individuals, nonmetropolitan areas, and users of stimulants. The increase in SU+CVD-related AAMR has particularly accelerated since 2012. These results have important public health implications by identifying high-risk groups that may benefit from targeted efforts to reduce substance-associated CVD mortality.

Substances evaluated in our analysis, including alcohol, cannabis, cocaine, opioids, and stimulants, have multiple cardiovascular effects and are associated with the development of cardiomyopathy, arrhythmias, microvascular disease, and coronary artery disease, particularly in the case of cocaine and stimulants.[2–6,19–21] SU may also be associated with the progression of CVD due to reduced health literacy and adherence to medical care.[22] Among the substances evaluated in our study, alcohol was the most common to be associated with SU+CVD-related death, more than 4 times opioids, the second-highest substance. While cannabis had the lowest SU+CVD-related absolute AAMR throughout analysis, it demonstrated a large increase in AAPC over the study period. This could be due to a nationwide increase in use in the setting of permissive laws, especially in the younger age group and White individuals,[7,23–25] or due to increased potency of tetrahydrocannabinol in cannabis products in recent years.[26] On the other hand, low absolute mortality rates of cannabis+CVD suggest that targeting other SU may yield more substantial improvement in CVD mortality. Large percent increases in

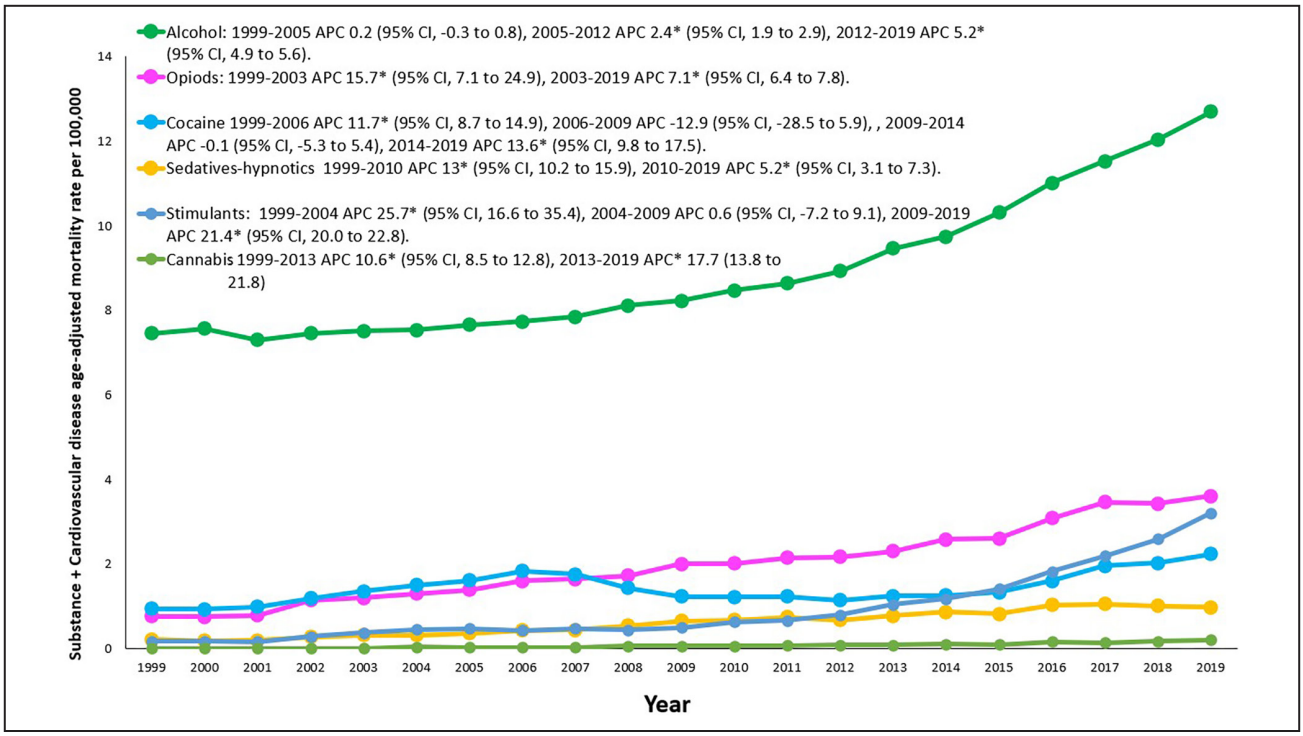

Figure 6. Substance use+cardiovascular disease–related age-adjusted mortality rates stratified by substance in the United States, 1999 to 2019.
*The APC is significantly different from zero at α=0.05. APC indicates annual percentage change.

SU+CVD were also seen among stimulant use, particularly between 2010 and 2019, where stimulants were the fastest-growing category of SU+CVD. Stimulants, particularly methamphetamines, are associated with significant cardiotoxicity and have become an epidemic across certain geographic regions in the United States.[14,27] These findings further reinforce the growing role of stimulants as a contributor to CVD mortality.

Our results indicate that men have higher SU+CVD-related AAMR, likely related to a higher SU rate among men and generally lower mortality among women from CVD conditions.[28] Both men and women experienced increases in SU+CVD-related AAMRs throughout the study periods. AAPC was pronounced in women at almost 5% a year, concordant with data from the National Vital Statistics System indicating a notable increase in SU usage and overdose rate especially among middle-aged women.[29] Vulnerabilities leading to SU have been shown to vary between men and women, with greater psychosocial burdens, higher rates of comorbid mood disorders, and higher barriers to SU treatment in women, all potentially contributing to a rise in SU+CVD.[30] Therefore, additional efforts to address the growing use of SU geared towards unique sex-based barriers may be of value to improve SU+CVD mortality trends.

We also highlight substantial racial disparities in the rates of SU+CVD, which expands on the prior literature in this important area. We found that American Indian or Alaska Native individuals had the highest absolute AAMRs and had a pronounced increase in SU+CVD-related AAMR during the study period, with the AAMR almost double the second-highest group (NH Black individuals). There may be several reasons for racial differences in SU+CVD. Prior studies have noted that White and American Indian individuals were more likely to use alcohol and develop alcohol use disorder. In contrast, Black individuals were more likely to use illicit drugs (including cocaine or stimulants).[31] Differences in baseline use may be further exacerbated by disparities in SU treatment, where White individuals were more likely to undergo substance abuse treatment and with higher treatment success rate.[32,33] Additionally, racial and ethnic minority groups have higher SU-related death despite similar or lower SU rates,[31,33] which may highlight barriers in health care and other socioeconomic inequalities. Racial disparities may also coincide with economic disparities based on social factors as contributors to both SU and SU+CVD, although prior studies have suggested heterogeneity in risk of SU disorder between individuals from different socioeconomic levels.[34–36] Our results suggest that targeting efforts to identify and address causes in racial differences in SU+CVD mortality may be an important component of addressing known racial disparities in overall CVD outcomes.[37]

Our results also demonstrate that SU+CVD AAMR is more prominent in rural areas than urban areas,

with trends particularly diverging over the last decade. Differences in SU+CVD may be one of the explanations for previous studies that have highlighted higher CVD mortality in rural compared with urban regions.[38] Rural differences in SU have been attributed to socioeconomic vulnerabilities and access to health delivery systems in general[39] and SU treatment in particular,[40] and will require further evaluation.

Lastly, when examined by age groups, we found that although younger adults had lower SU+CVD AAMR than older individuals, those aged 25 to 39 years had pronounced AAPC increase during the study period. These results are concordant with the data demonstrating a surge in SU use in young adults living in the United States.[25] Increases in SU+CVD in younger populations are particularly alarming because younger patients have otherwise low rates of traditional CVD mortality, and targeting SU use in younger adults should remain an essential target of public health intervention.

This study has several limitations. The accuracy of the CDC WONDER data set depends on use of *ICD* codes, which may have resulted in misclassification of causes of death. Although we included *ICD* codes of intentional substance overdose, we did not include *ICD* codes of accidental or assault by substance. Overdose deaths are not specifically addressed in our analysis because the focus was primarily on SU+CVD-associated mortality, although differentiating overdose from primarily CVD causes may be difficult. Individual drug categories for certain substances such as methamphetamines are not well characterized by *ICD-10* codes. Still, important categories such as *ICD 10* codes stimulants have been associated with good accuracy for classifying methamphetamine use.[41] Compared with other studies using *ICD* codes to identify SU mortality, we have used a broader definition with more inclusive *ICD* codes to capture more patients with a history of SU,[42] although we could not independently verify the accuracy of these codes for SU. Using *ICD* codes, we were not able to specifically identify or differentiate users of alternative form of the substances (for instance, patients who used cannabis extracts). Smoking as a form of SU contributor to mortality is not evaluated in this analysis because the focus was primarily on other SU, and multivariable analyses adjusted for contributing smoking could not be performed in this data set. However, smoking was listed as a contributing source in ≈20% of individuals with CVD+SU mortality and may therefore mediate some of the SU-related mortality in this analysis. Patients with concurrent smoking+SU will require further evaluation in future studies. Additionally, our results suggest that patients with SU should be screened and offered management for concurrent high-risk CVD comorbidities including smoking. Reasons for heterogeneity in outcome differences among States were not examined, though they may be related to the higher prevalence of SU because AAMRs are a result of both prevalence and case fatality. Lastly, additional data on variables that may be important contributors to SU and CVD mortality, such as socioeconomic status, income level, mental health, and other comorbid conditions, were not able to be evaluated in our study.

CONCLUSIONS

Our analysis demonstrates a prominent increase in SU+CVD-related mortality in the United States between 1999 and 2019, with the most pronounced increases among women, American Indian or Alaska individuals, younger individuals, those living in nonmetropolitan areas, and users of cannabis and psychostimulants. When looking at the most recent data in year 2019, AAMR was higher among men, American Indian or Alaska Native individuals, those 55 to 69 years old, nonmetropolitan areas, and users of alcohol, opioids, stimulants (methamphetamines), and cocaine. Additional public health efforts targeting SU may be valuable to reduce CVD mortality.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S15
Figures S1–S2

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