nature cardiovascular research

Article

https://doi.org/10.1038/s44161-023-00220-2

Excess cardiovascular mortality across multiple COVID-19 waves in the United States from March 2020 to March 2022

Received: 10 June 2022

Accepted: 24 January 2023

Published online: 27 February 2023

Check for updates

Lefei Han[1,2,6], Shi Zhao[3,6], Siyuan Li[4,6], Siyu Gu[1,2], Xiaobei Deng[4], Lin Yang[5] ✉ & Jinjun Ran[4] ✉

The COVID-19 pandemic has limited the access of patients with cardiovascular diseases to healthcare services, causing excess deaths. However, a detailed analysis of temporal variations of excess cardiovascular mortality during the COVID-19 pandemic has been lacking. Here we estimate time-varied excess cardiovascular deaths (observed deaths versus expected deaths predicted by the negative binomial log-linear regression model) in the United States. From March 2020 to March 2022 there were 90,160 excess cardiovascular deaths, or 4.9% more cardiovascular deaths than expected. Two large peaks of national excess cardiovascular mortality were observed during the periods of March–June 2020 and June–November 2021, coinciding with two peaks of COVID-19 deaths, but the temporal patterns varied by state, age, sex and race and ethnicity. The excess cardiovascular death percentages were 5.7% and 4.0% in men and women, respectively, and 3.6%, 8.8%, 7.5% and 7.7% in non-Hispanic White, Black, Asian and Hispanic people, respectively. Our data highlight an urgent need for healthcare services optimization for patients with cardiovascular diseases in the COVID-19 era.

Since the first reported case of the coronavirus disease 2019 (COVID-19) in December 2019, the pandemic has caused 18.2 million deaths worldwide in the first two years, including 5.9 million reported COVID-19 deaths and other deaths due to the pandemic (measured as excess mortality)[1]. As of July 2022, the United States have experienced multiple waves of the COVID-19 pandemic with different dominating SARS-CoV-2 variants and profiles in virulence, and over one million deaths due to COVID-19 infections have been reported[2]. Beyond the deaths directly caused by COVID-19, unexpected deaths have also increased dramatically among non-COVID-19 patients with chronic medical conditions such as cardiovascular diseases (CVDs)[3], diabetes[4], Alzheimer's disease[5] and renal failure[6]. The increased non-COVID-19 deaths could be partly explained by overburdened healthcare services, delayed admissions of patients and changed health-seeking behaviors[3,7–9]. During the pandemic, the healthcare authorities in the United States have reallocated healthcare resources to improve the service capacity for non-COVID-19 patients. However, the impact of multiple waves of the pandemic on other diseases warrants more in-depth evaluations.

The disruption of CVD management in the early phase of the pandemic has been reported worldwide. Studies in the United States reported a decline in hospitalizations of acute cardiovascular events and a dramatic increase in out-of-hospital cardiac arrest events and deaths[10,11]. Elevated numbers of CVD mortality were also observed

[1]School of Global Health, Chinese Center for Tropical Diseases Research, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [2]One Health Center, Shanghai Jiao Tong University–The University of Edinburgh, Shanghai, China. [3]JC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong SAR, China. [4]School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [5]School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, China. [6]These authors contributed equally: Lefei Han, Shi Zhao, Siyuan Li. ✉e-mail: l.yang@polyu.edu.hk; jinjunr@sjtu.edu.cn

in the United States and other countries in the early phase[3,12–15]. The continuing threats of the pandemic may bring profound impacts on patients with CVD. It is important to further investigate the indirect impact of the COVID-19 pandemic on patients with CVD within a longer observation period and explore temporal variations seen.

In this study, we estimated and compared the excess mortality due to CVDs across the multiple pandemic waves in the United States. These estimates may provide insights into the short- and long-term impacts of the COVID-19 pandemic on the circulatory system, which is important information for the authorities when optimizing the allocation of healthcare resources to CVD patients amid the ongoing pandemic.

Results

From 1 March 2020 to 26 March 2022, there were 1,946,662 documented CVD deaths reported by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) in the United States[16]. This exceeded the expected level of deaths by 4.9% (95% confidence interval (CI) 4.8%; 5.0%), which projected to 90,160 (95% CI 88,630; 91,609) excess CVD deaths, including 47,703 (95% CI 46,635; 48,653) in the period 2020–2021 and 42,457 (95% CI 41,170; 43,681) in the period 2021–2022 (Table 1).

We observed that the trajectory of nationwide excess CVD deaths had five waves during the period (Fig. 1), which coincided with the trajectory of COVID-19 deaths. The correlation between excess CVD deaths and COVID-19 deaths by state and wave are shown in Supplementary Table 1. During Wave I (1 March 2020 to 6 June 2020), we observed a sharp increase in excess CVD deaths. Specifically, there was an 8.6% (95% CI 8.4%; 8.8%) increase in deaths due to ischemic heart disease (IHD) and a 13.2% (95% CI 12.9%; 13.5%) increase in deaths due to hypertensive disease. During Wave II (7 June 2020 to 3 October 2020), the curves of COVID-19 deaths and excess CVD deaths were both milder. Although there was a large peak of COVID-19 during Wave III (4 October 2020 to 26 June 2021), the excess CVD deaths were lower compared to those in previous waves. The largest number of excess deaths was observed in Wave IV (27 June 2021 to 27 November 2021), which involved 90.2 deaths per million persons (95% CI 88.3; 92.2). During Waves IV and V (28 November 2021 to 26 March 2022), the trends of excess deaths for IHD, hypertensive disease, cerebrovascular disease and other diseases of the circulatory system were almost proportionally synchronous with the death curve of COVID-19. We did not observe excess deaths from heart failure throughout the whole study period. Among excess deaths due to CVDs, deaths due to IHD accounted for the largest proportion (49.0%) during the study period, followed by hypertensive disease (24.7%), cerebrovascular disease (19.0%) and other diseases of the circulatory system (15.6%).

The excess CVD mortalities and percentages varied by state and wave. During the study period, Mississippi, Maine, South Carolina, Vermont, Alabama, Oklahoma, Nebraska, Louisiana, Georgia and Tennessee were most affected (excess mortalities ranged from 491.2 to 844.4 per million persons). During Wave I, there were 31 states that showed notable increases in CVD deaths. Among them, New York and New Jersey showed the greatest increases in CVD deaths, with increases of 34.0% (95% CI 32.4%; 35.6%) and 23.3% (95% CI 22.8%; 23.8%), respectively, compared with the expected levels. During Wave II, the excess deaths expanded to 38 states and the excess percentage estimates were increased in most states. By contrast, the excess percentages in New York and New Jersey were largely mitigated. During the long period of Wave III, although a few southern states showed greater excess mortalities, the magnitudes of the excess percentage in CVD deaths were widely mitigated in many states. In Wave IV, there were broad increases in CVD deaths, with 46 states showing marked increases. The largest increases were shown in Vermont and Maine (excess percentage 36.9% (95% CI 34.3%; 39.5%) and 29.8% (95% CI 28.2%; 31.4%), respectively). In Wave V, the increased CVD deaths were still clearly observed in most states but the peaks were lower than they were in Wave IV (Fig. 2). A slight spatial autocorrelation of excess percentages was observed from Wave I to Wave III, but this vanished from Wave IV (Supplementary Table 39). In 2020–2021, there was a 7.2% (95% CI 7.1%; 7.3%) increase in IHD deaths, and a 4.7% (95% CI 4.5%; 4.9%) increase in 2021–2022. Substantial IHD death increases were observed in Wave I in New York (excess percentage 42.0% (95% CI 39.2%; 44.8%)) and New Jersey (excess percentage 30.7% (95% CI 30.0%; 31.4%)). The excess mortalities by state in the first and second pandemic years are shown in Fig. 3. The excess deaths, mortalities and percentages of CVD and its subtypes by state, COVID-19 pandemic wave and year of pandemic can be found in Extended Data Figs. 1 and 2 and Supplementary Tables 2–38.

Excess deaths and excess percentage changes of CVDs were disproportionally distributed by age, sex and race and ethnicity and showed different temporal patterns (Fig. 4, Extended Data Fig. 3 and Supplementary Table 40). We used another data source from the Wide-ranging Online Data for Epidemiologic Research (WONDER) database to investigate demographic disparities in excess CVD deaths[17]. The results showed that throughout the study period there was an 11.0% (95% CI 10.8%; 11.2%) excess percentage increase of CVD deaths in adults aged 20–64 years, a 5.6% (95% CI 5.5%; 5.7%) increase in adults aged 65–84 years and a 1.0% (95% CI 0.8%; 1.2%) increase in adults aged 85 years and over. The excess percentage of CVDs was larger in males (5.7% (95% CI 5.6%; 5.8%)) than in females (4.0% (95% CI 3.9%; 4.1%)). The excess percentage of CVDs was 8.8% (95% CI 8.6%; 9.0%) in non-Hispanic Black people, 7.5% (95% CI 7.1%; 7.9%) in non-Hispanic Asian people, 7.7% (95% CI 7.4%; 8.0%) in Hispanic people and 3.6% (95% CI 3.5%; 3.7%) in non-Hispanic White people. It should be noted that the estimates from the WONDER database might be slightly different from those from the NCHS database because of the different reference periods and slight discrepancies of total death counts in the two datasets (refer to Methods for details). Nevertheless, the results were generally robust for the main analyses and demographic subgroup analyses when using the periodic spline with various degrees of freedom in regression models (Supplementary Tables 41 and 42).

Discussion

That the COVID-19 pandemic indirectly led to increased CVD deaths has been reported in many countries during the initial phase of the pandemic. The existing evidence limited the study periods to half a year or one year and mainly focused on the whole period[3,13,15,18–25]. After more than two years of living with the pandemic, we updated the evaluation for a longer period. We found that, nationwide, increased CVD deaths have persisted throughout the two years and the trajectory of excess CVD deaths was almost coincident with the COVID-19 death waves in the United States. The spatial distribution of excess CVD mortality varied by region and COVID-19 death wave. New York and New Jersey suffered the most during the first pandemic wave but were mitigated subsequently. Broader increases in excess CVD deaths were shown in the second wave and slightly mitigated in the third wave. The fourth wave was the most severe across the United States, while the severity was moderately reduced in the fifth wave.

The COVID-19 pandemic has substantially interrupted cardiovascular medical care worldwide. Our findings were consistent with previous studies, showing that the excess CVD deaths were dominated by acute CVD events, which might require emergent treatments, including IHD, hypertensive disease and cerebrovascular disease[3,13,15,21,23,25]. During the pandemic, healthcare systems had to engage in substantial efforts against the COVID-19 pandemic, resulting in indirect disruption of the routine services and emergency services of cardiovascular medical care. This could be one explanation for the trajectory synchronization between COVID-19 deaths and excess CVD deaths. An international survey from 108 countries indicated that the volume of cardiac diagnostic testing declined by 64% in April 2020 compared with March 2019[26]. On the other hand, CVD patients may have been reluctant to seek medication in an effort to avoid in-hospital COVID-19 infection.

https://doi.org/10.1038/s44161-023-00220-2

Table 1 | Estimated excess mortality in CVDs in the United States from March 2020 to March 2022

Periods[a]	No. of observed deaths	No. of expected deaths (95% CI)	No. of excess deaths (95% CI)	Weekly average no. of estimated excess deaths (95% CI)	Excess mortality per million persons (95% CI)	Excess (%) (95% CI)[b]
CVDs						
Overall	1,946,662	1,856,502 (1,855,053; 1,858,032)	90,160 (88,630; 91,609)	835 (821; 848)	274.8 (270.1; 279.2)	4.9 (4.8; 5.0)
2020–2021	934,004	886,301 (885,351; 887,369)	47,703 (46,635; 48,653)	917 (897; 936)	145.9 (142.7; 148.8)	5.4 (5.3; 5.5)
2021–2022	1,012,658	970,201 (968,977; 971,488)	42,457 (41,170; 43,681)	758 (735; 780)	129.0 (125.1; 132.7)	4.4 (4.3; 4.5)
Wave I	251,248	238,595 (238,138; 239,056)	12,653 (12,192; 13,110)	904 (871; 936)	38.7 (37.3; 40.1)	5.3 (5.1; 5.5)
Wave II	287,889	268,278 (267,778; 268,740)	19,611 (19,149; 20,111)	1,154 (1,126; 1,183)	60.1 (58.6; 61.6)	7.3 (7.1; 7.5)
Wave III	685,194	671,734 (670,796; 672,696)	13,460 (12,498; 14,398)	354 (329; 379)	41.0 (38.1; 43.9)	2.0 (1.9; 2.1)
Wave IV	387,959	358,316 (357,662; 358,935)	29,643 (29,024; 30,297)	1,347 (1,319; 1,377)	90.2 (88.3; 92.2)	8.3 (8.1; 8.5)
Wave V	334,372	319,579 (318,732; 320,353)	14,793 (14,019; 15,640)	870 (825; 920)	44.8 (42.5; 47.4)	4.6 (4.3; 4.9)
Hypertensive disease						
Overall	259,073	236,790 (236,491; 237,113)	22,283 (21,960; 22,582)	206 (203; 209)	67.9 (66.9; 68.8)	9.4 (9.3; 9.5)
2020–2021	123,134	109,831 (109,641; 110,048)	13,303 (13,086; 13,493)	256 (252; 259)	40.7 (40.0; 41.3)	12.1 (11.9; 12.3)
2021–2022	135,939	126,959 (126,700; 127,236)	8,980 (8,703; 9,239)	160 (155; 165)	27.3 (26.4; 28.1)	7.1 (6.9; 7.3)
Wave I	32,865	29,025 (28,935; 29,116)	3,840 (3,749; 3,930)	274 (268; 281)	11.8 (11.5; 12.0)	13.2 (12.9; 13.5)
Wave II	37,590	32,981 (32,881; 33,074)	4,609 (4,516; 4,709)	271 (266; 277)	14.1 (13.8; 14.4)	14.0 (13.7; 14.3)
Wave III	90,663	85,335 (85,143; 85,533)	5,328 (5,130; 5,520)	140 (135; 145)	16.2 (15.6; 16.8)	6.2 (6.0; 6.4)
Wave IV	52,211	46,583 (46,445; 46,715)	5,628 (5,496; 5,766)	256 (250; 262)	17.1 (16.7; 17.5)	12.1 (11.8; 12.4)
Wave V	45,744	42,867 (42,683; 43,036)	2,877 (2,708; 3,061)	169 (159; 180)	8.7 (8.2; 9.3)	6.7 (6.3; 7.1)
IHD						
Overall	791,735	747,553 (746,861; 748,283)	44,182 (43,452; 44,874)	409 (402; 416)	134.7 (132.4; 136.8)	5.9 (5.8; 6.0)
2020–2021	385,660	359,873 (359,416; 360,388)	25,787 (25,272; 26,244)	496 (486; 505)	78.9 (77.3; 80.3)	7.2 (7.1; 7.3)
2021–2022	406,075	387,680 (387,101; 388,289)	18,395 (17,786; 18,974)	328 (318; 339)	55.9 (54.0; 57.6)	4.7 (4.5; 4.9)
Wave I	105,563	97,203 (96,983; 97,426)	8,360 (8,137; 8,580)	597 (581; 613)	25.6 (24.9; 26.3)	8.6 (8.4; 8.8)
Wave II	118,543	108,862 (108,622; 109,086)	9,681 (9,457; 9,921)	569 (556; 584)	29.6 (29.0; 30.4)	8.9 (8.7; 9.1)
Wave III	278,844	271,128 (270,680; 271,590)	7,716 (7,254; 8,164)	203 (191; 215)	23.5 (22.1; 24.9)	2.8 (2.6; 3.0)
Wave IV	155,190	142,970 (142,661; 143,263)	12,220 (11,927; 12,529)	555 (542; 570)	37.2 (36.3; 38.1)	8.5 (8.3; 8.7)
Wave V	133,595	127,389 (126,990; 127,753)	6,206 (5,842; 6,605)	365 (344; 389)	18.8 (17.7; 20.0)	4.9 (4.6; 5.2)
Heart failure						
Overall	177,317	189,516 (189,294; 189,752)	−12,199 (−12,435; −11,977)	−113 (−115; −111)	−37.2 (−37.9; −36.5)	−6.4 (−6.5; −6.3)
2020–2021	84,329	89,317 (89,174; 89,478)	−4,988 (−5,149; −4,845)	−96 (−99; −93)	−15.3 (−15.8; −14.8)	−5.6 (−5.8; −5.4)
2021–2022	92,988	100,200 (100,011; 100,398)	−7,212 (−7,410; −7,023)	−129 (−132; −125)	−21.9 (−22.5; −21.3)	−7.2 (−7.4; −7.0)
Wave I	23,503	24,302 (24,233; 24,373)	−799 (−870; −730)	−57 (−62; −52)	−2.4 (−2.7; −2.2)	−3.3 (−3.6; −3.0)
Wave II	25,690	26,778 (26,703; 26,848)	−1,088 (−1,158; −1,013)	−64 (−68; −60)	−3.3 (−3.5; −3.1)	−4.1 (−4.4; −3.8)
Wave III	61,560	68,624 (68,483; 68,770)	−7,064 (−7,210; −6,923)	−186 (−190; −182)	−21.5 (−22.0; −21.1)	−10.3 (−10.5; −10.1)
Wave IV	35,708	36,483 (36,384; 36,578)	−775 (−870; −676)	−35 (−40; −31)	−2.4 (−2.6; −2.1)	−2.1 (−2.4; −1.8)
Wave V	30,856	33,329 (33,197; 33,449)	−2,473 (−2,593; −2,341)	−145 (−153; −138)	−7.5 (−7.9; −7.1)	−7.4 (−7.8; −7.0)
Cerebrovascular disease						
Overall	338,832	321,674 (321,364; 322,001)	17,158 (16,831; 17,468)	159 (156; 162)	52.3 (51.3; 53.2)	5.3 (5.2; 5.4)
2020–2021	161,376	153,192 (152,990; 153,422)	8,184 (7,954; 8,386)	157 (153; 161)	25.0 (24.3; 25.7)	5.3 (5.2; 5.4)
2021–2022	177,456	168,481 (168,221; 168,756)	8,975 (8,700; 9,235)	160 (155; 165)	27.3 (26.4; 28.1)	5.3 (5.1; 5.5)
Wave I	42,331	40,769 (40,673; 40,866)	1,562 (1,465; 1,658)	112 (105; 118)	4.8 (4.5; 5.1)	3.8 (3.6; 4.0)
Wave II	50,081	46,768 (46,659; 46,867)	3,313 (3,214; 3,422)	195 (189; 201)	10.1 (9.8; 10.5)	7.1 (6.9; 7.3)
Wave III	120,154	115,898 (115,701; 116,101)	4,256 (4,053; 4,453)	112 (107; 117)	13.0 (12.4; 13.6)	3.7 (3.5; 3.9)
Wave IV	67,843	63,098 (62,955; 63,234)	4,745 (4,609; 4,888)	216 (210; 222)	14.4 (14.0; 14.9)	7.5 (7.3; 7.7)
Wave V	58,423	55,142 (54,963; 55,307)	3,281 (3,116; 3,460)	193 (183; 204)	9.9 (9.4; 10.5)	6.0 (5.7; 6.3)

Table 1 (continued) | Estimated excess mortality in CVDs in the United States from March 2020 to March 2022

Periods[a]	No. of observed deaths	No. of expected deaths (95% CI)	No. of excess deaths (95% CI)	Weekly average no. of estimated excess deaths (95% CI)	Excess mortality per million persons (95% CI)	Excess (%) (95% CI)[b]
Other diseases of the circulatory system						
Overall	379,705	365,650 (365300, 366019)	14,055 (13,686; 14,405)	130 (127; 133)	42.8 (41.7; 43.9)	3.8 (3.7; 3.9)
2020–2021	179,505	175,500 (175,269; 175,759)	4,005 (3,746; 4,236)	77 (72; 81)	12.3 (11.5; 13.0)	2.3 (2.2; 2.4)
2021–2022	200,200	190,150 (189,856; 190,459)	10,050 (9,741; 10,344)	179 (174; 185)	30.5 (29.6; 31.4)	5.3 (5.1; 5.5)
Wave I	46,986	47,584 (47,472; 47,697)	−598 (−711; −486)	−43 (−51; −35)	−1.8 (−2.2; −1.5)	−1.3 (−1.5; −1.1)
Wave II	55,985	53,274 (53,152; 53,388)	2,711 (2,597; 2,833)	159 (153; 167)	8.3 (8.0; 8.7)	5.1 (4.9; 5.3)
Wave III	133,973	132,295 (132,070; 132,526)	1,678 (1,447; 1,903)	44 (38; 50)	5.1 (4.4; 5.8)	1.3 (1.1; 1.5)
Wave IV	77,007	70,332 (70,174; 70,481)	6,675 (6,526; 6,833)	303 (297; 311)	20.3 (19.8; 20.8)	9.5 (9.3; 9.7)
Wave V	65,754	62,165 (61,964; 62,350)	3,589 (3,404; 3,790)	211 (200; 223)	10.9 (10.3; 11.5)	5.8 (5.5; 6.1)

[a]The overall pandemic period was from 1 March 2020 to 26 March 2022. The period of 2020–2021 was from 1 March 2020 to 27 February 2021. The period of 2021–2022 was from 28 February 2021 to 26 March 2022. The five pandemic waves were defined as Wave I (Week 10, 1 March 2020, to Week 23, 6 June 2020), Wave II (Week 24, 7 June 2020, to Week 40, 3 October 2020), Wave III (Week 41, 4 October 2020, to Week 25, 26 June 2021), Wave IV (Week 26, 27 June 2021, to Week 47, 27 November 2021) and Wave V (Week 48, 28 November 2021, to Week 12, 26 March 2022).
[b]Excess (%)=excess deaths/expected deaths×100.

Lockdown measures also provided a challenge for patients in terms of being able to access healthcare services. The under-diagnosis and postponement of patients receiving timely treatments left them at a higher risk of adverse cardiac outcomes[27]. Previous evidence demonstrated that during the pandemic, the weekly rates of hospitalization for acute coronary syndrome declined by 48% in Northern California, United States[28]. The incidence of out-of-hospital cardiac arrests increased in New York and many cities in Italy[11,29]. The number of patients with ST-segment elevation myocardial infarction (STEMI) admitted to hospitals declined and they experienced longer waits to receive treatments. An increased number of patients showed worsened presentation of STEMI, including increased infarct size, a larger extent of microvascular obstruction, a higher rate of intramyocardial haemorrhage and other complications worldwide[30–32]. In the United States, nearly a 38% decline in cardiac catheterization laboratory for STEMI activations has been reported during the early pandemic[33]. A study from the North American COVID-19 Myocardial Infarction Registry showed that, compared with patients who received the primary percutaneous coronary intervention in 2015–2019, patients in 2020 had 11–13 minutes longer door-to-balloon time regardless of confirming COVID-19 or not. In-hospital mortalities were 33% among STEMI patients with COVID-19 infection, 11% among STEMI patients with suspected COVID-19 infection and 4% among those during the period 2015–2019[34]. The reduction in primary percutaneous coronary intervention procedures and increased total ischemia time were also reported in many countries[35,36]. Our supplementary analysis also found excess deaths due to acute myocardial infarction accounted for about 29% of total excess CVD deaths in the past two years (Supplementary Table 43). These findings highlight the importance of maintaining healthcare delivery for individuals with acute CVD events during the pandemic.

In response to the ongoing pandemic, professional cardiovascular associations have published several guidelines and expert consensus to reflect and improve the capacity of cardiovascular care[37–43]. The procedure of healthcare services has been modified to balance routine cardiovascular services and COVID-involved cardiovascular services. Telemedicine also provides an opportunity to deliver healthcare services and has been used to monitor CVD progression[41,44–46]. By the end of 2020, emergency medical services in the United States had recovered somewhat when compared to the initial phase of the pandemic but were still lower than the pre-pandemic level[47]. A follow-up study[26] showed, in April 2021, that cardiac diagnostic test volume in high-income countries (that is, the United States) had almost recovered to pre-pandemic levels, though had yet to recover in lower-income countries[48]. Marked improvement was also shown in STEMI care, with a decreased in-hospital mortality rate and improved clinical outcomes in 2021 compared with 2020[49]. Although efforts were made to reallocate CVD healthcare resources, we still observed notable excess CVD deaths in 2021–2022. The potential for as yet unknown long-term impacts on CVD patients as a result of the pandemic could be another emerging issue.

As SARS-CoV-2 viruses persistently circulated, the long-term cardiac impact may emerge subsequently. Our study had a two-year observation period, which allowed us to investigate the combined consequence of acute effect and long-term effects on cardiovascular healthcare. Beyond IHD, hypertensive disease and cerebrovascular disease, we found that other excess deaths of the circulatory system increased since Wave IV. This might be partly attributed to a long-term disruption of cardiovascular healthcare. A nationwide or regional lockdown may lead to increased physical inactivity, poor dietary intake, interruption of long-term disease management, income loss and so on.[50,51]. Thus, patients with chronic CVD conditions may experience faster disease progression than expected. In addition, emerging evidence noted the sequelae of the post-COVID-19 cardiac syndrome, which may bring a profound impact as well. Persistent sinus tachycardia, postural orthostatic tachycardia syndrome, atrial arrhythmia, myocardial infarction, right ventricular dysfunction, heart failure, (non) IHD and cardiomyopathy have been reported among COVID-19 survivors[50,52–54]. Studies in the United States found that after being infected with SARS-CoV-2 for over 30 days, people had a higher risk of death and incident CVDs[54,55]. A UK study demonstrated that a history of COVID-19 hospitalization was associated with a three-time higher risk of adverse CVD events up to four months from diagnosis[56]. Further evaluation is warranted to disentangle the excess CVD deaths attributed to interrupted healthcare systems and cardiac sequelae of post-COVID-19 infection.

Few studies compared the differences in excess deaths across multiple waves of the COVID-19 pandemic, and we fill the gap here. The temporal trend of excess CVD deaths can be partly explained by the combined effects of transmission dynamics of different variants, politics for disease control, population immunity and reallocation of cardiovascular services[38,57]. First, the five COVID-19 waves had their specific dominant SARS-CoV-2 variants with different virulence and transmissibility, which may partly contribute to different magnitudes of pandemic severity. Although the weekly COVID-19 incidence in Wave I was much lower than in other waves, a sharp increase in excess CVDs deaths was shown during this period. The reason for this could be that the healthcare systems were underprepared at the beginning. Wave III

https://doi.org/10.1038/s44161-023-00220-2

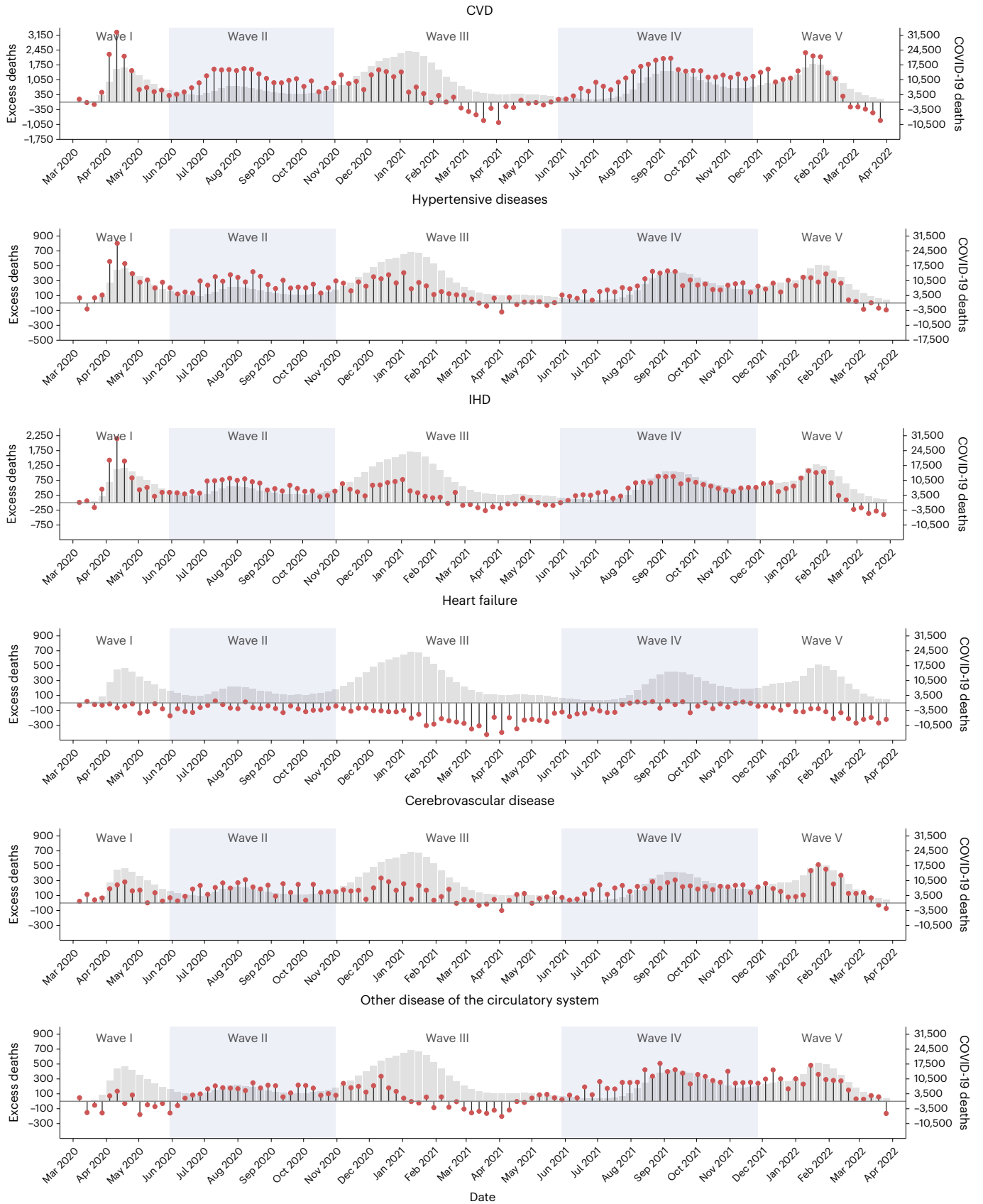


Fig. 1 | Weekly estimates of excess deaths for CVDs in the United States. Time-series estimates of excess death counts for overall CVDs and subtypes from 1 March 2020 to 26 March 2022. Cardiovascular subtypes include hypertensive disease, IHD, heart failure, cerebrovascular disease and other diseases of the circulatory system. The weekly estimates of excess deaths for any cardiovascular and subtype causes are shown as red points. As a comparison, the weekly number of deaths due to COVID-19 are shown as grey bar charts. The subtype 'other diseases of the circulatory system' includes pulmonary embolism, pericarditis, myocarditis, cardiac arrest and so on.

https://doi.org/10.1038/s44161-023-00220-2

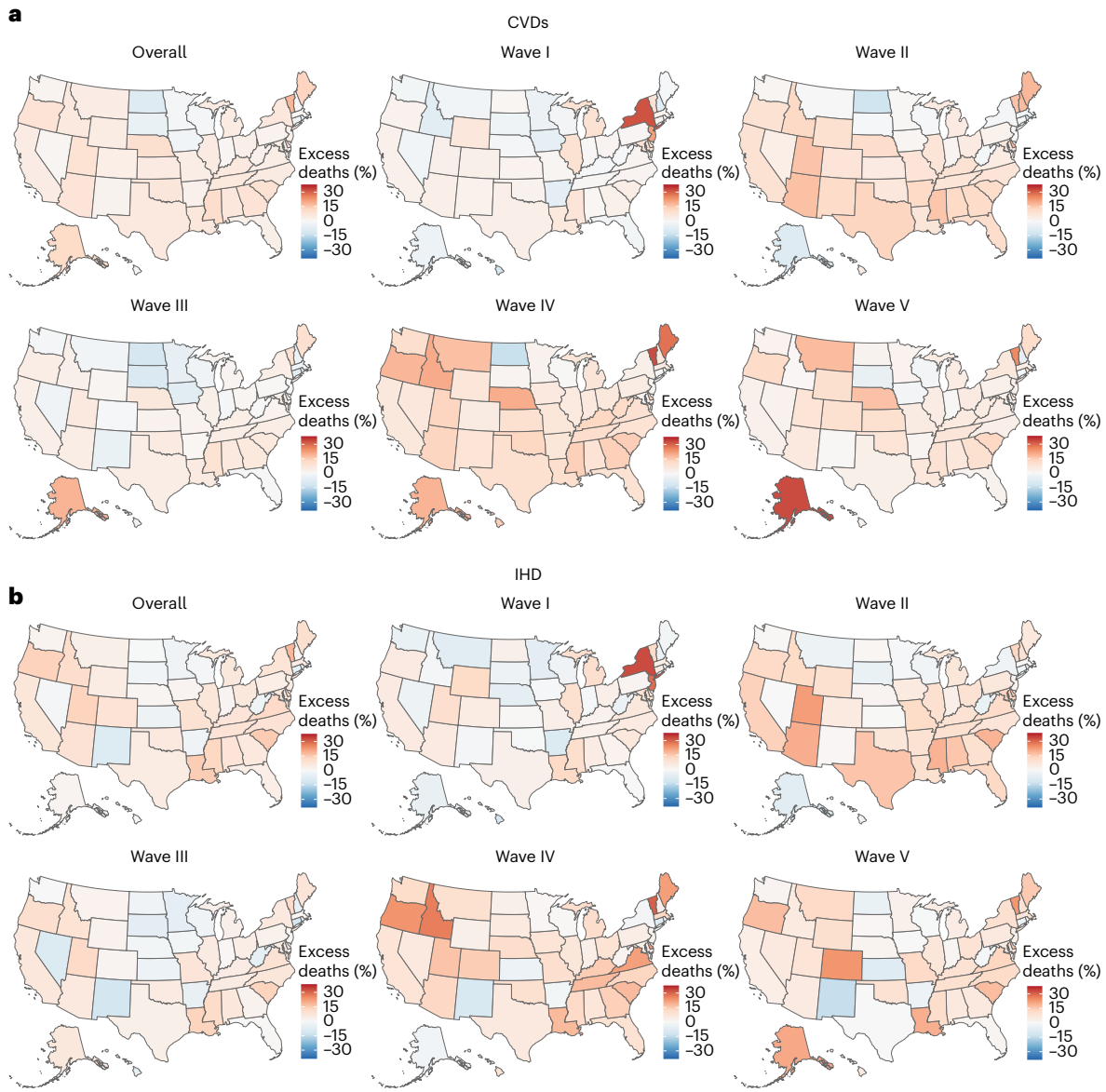


Fig. 2 | Maps of excess percentage of CVD deaths stratified by COVID-19 death wave in the United States. a,**b**, The excess death percentage estimates include overall CVDs (**a**) and IHD (**b**). The gradient colors from blue to red indicate the excess percentage estimates varied from negative to positive values across states. 'Overall' refers to the period from 1 March 2020 to 26 March 2022. The five waves were defined as Wave I (Week 10, 1 March 2020, to Week 23, 6 June 2020), Wave II (Week 24, 7 June 2020, to Week 40, 3 October 2020), Wave III (Week 41, 4 October 2020, to Week 25, 26 June 2021), Wave IV (Week 26, 27 June 2021, to Week 47, 27 November 2021) and Wave V (Week 48, 28 November 2021, to Week 12, 26 March 2022) according to COVID-19 death waves in the United States.

showed a large number of COVID-19 deaths, while excess CVD deaths decreased. The decline could be the result that healthcare resources have been made necessary reallocation. In addition, COVID-19 vaccines have been distributed since December 2020. About 54% of the US population, including 87% of people aged 65 years and over, had completed at least one dose of vaccination as of Wave III (June 2021)[58]. Moreover, the phenomenon that CVD deaths had a profound increase in Wave I and declined in Wave III was mainly among people aged 85 years or above, suggesting a possibility of mortality displacement in older people. This means that some deaths might have been brought forward by a few months due to the pandemic[59]. Nevertheless, persistently increased CVD deaths among the 20–84-year age group throughout the observational period suggests additional efforts should be adopted to protect those people. During Wave IV, when the transmission was dominated by the Delta variant with much increased transmissibility and virulence, the excess CVD mortality was largely increased. Despite the Omicron variant in Wave V showing the most transmissibility but much milder virulence, excess CVD mortality was still of significance. It highlights the importance of continuing to monitor healthcare resources for CVDs and optimizing the capacity under the varied scenario of the COVID-19 pandemic to protect CVD patients.

Some limitations of the study should be noted. First, the study used provisional death counts. Due to reporting delays, data incompleteness was likely and varied by state and time, especially for data in recent weeks. We retrieved the death counts of which the data completeness has been adjusted by NCHS and we excluded the most recent weeks to minimize the effect of reporting lag. We remarked that the statistical uncertainty for adjusting data completeness due to reporting delay may need to be accounted for to improve the assessment of the statistical uncertainty of excess deaths. In addition, the statistical uncertainty of the dispersion parameter of the fitted negative binomial distribution was neglected when constructing the 95% CI of excess death, which was suspected to have little effect on the main findings. Second, due to data availability, we only analyzed deaths that showed

https://doi.org/10.1038/s44161-023-00220-2

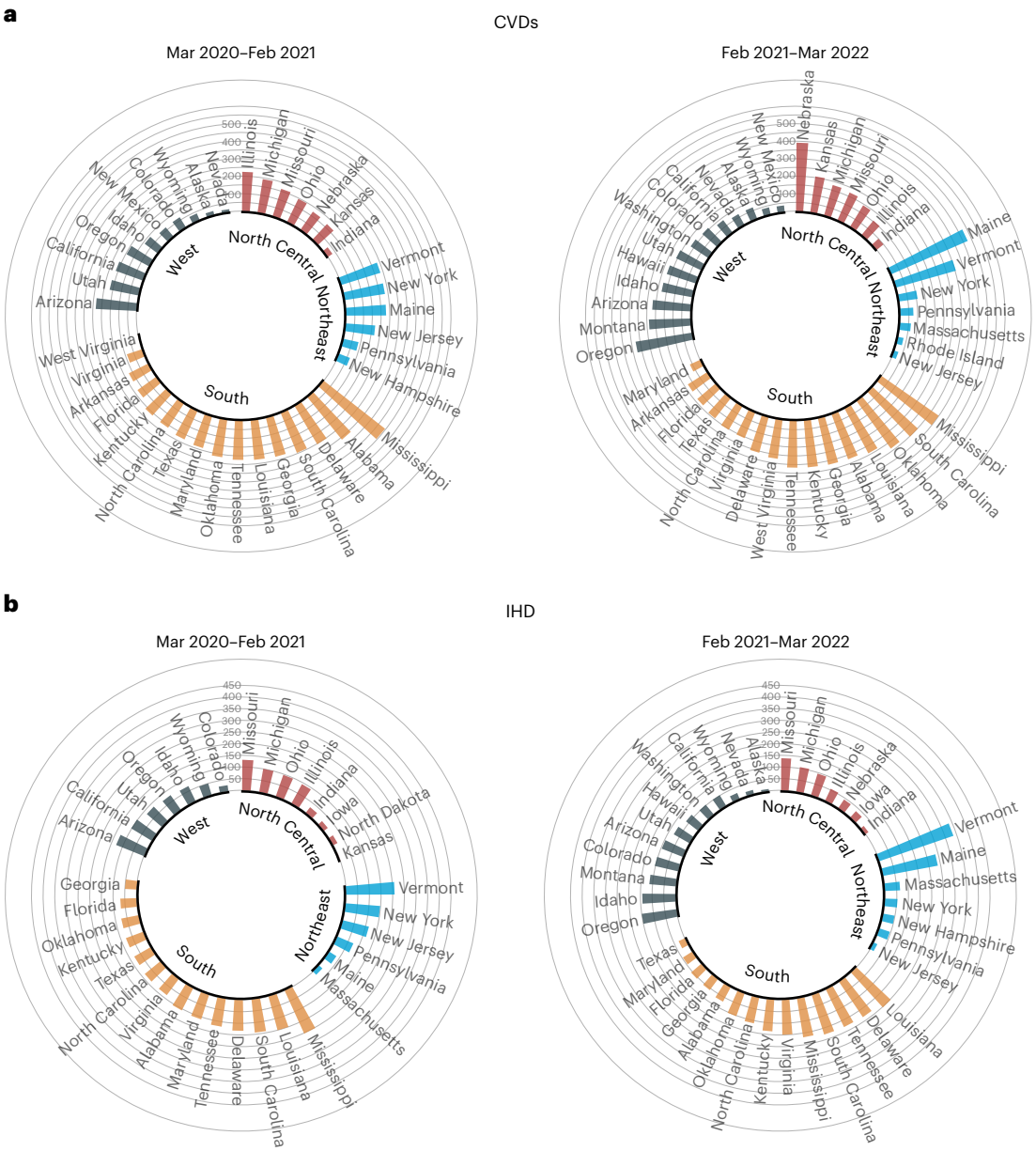


Fig. 3 | Annual excess mortalities of CVDs (per million persons) by states in the United States. a,**b**, The excess mortality estimates include overall CVDs (**a**) and IHD (**b**). These states were grouped into different color clusters according to their geographic regions, including North Central, Northeast, South and West. The period of 2020–2021 was from 1 March 2020 to 27 February 2021. The period of 2021–2022 was from 28 February 2021 to 26 March 2022. The states with negative estimated values were not shown.

CVD as the underlying cause of death on the death certificate. It was likely that some CVD deaths with the co-occurrence of CVD and COVID-19 were coded as COVID-19. The US CDC indicated that for about 95% of deaths with COVID-19 reported on the death certificate, COVID-19 was selected as their primary cause of death[16]. On the other hand, COVID-19 can also provoke adverse cardiovascular events, such as myocarditis, sudden cardiac death, heart failure and so on, resulting in additional deaths associated with CVD[43]. Our data was limited to differentiate the two situations. We also estimated excess mortality when CVD was listed as one of the multiple causes of death on the death certificate (Supplementary Table 44). The results may reflect the full impact of COVID-19 on CVD. In addition, despite CVD patients being asked to be screened for COVID-19 viruses and symptoms before receiving treatments since the improvement of testing capacity in May 2020[42,60], there might be some COVID-19 deaths that were misclassified to CVD due to the absence of testing, such as out-of-hospital deaths. These deaths might be more difficult to identify in our analysis. Third, individual data for CVDs were not publicly available in our study. Since previous evidence indicated that excess mortalities were disproportionally shown by race and ethnicity, age, sex and so on[61], we retrieved an alternative dataset from CDC WONDER to investigate the demographic disparities. However, death counts from the WONDER database were slightly less than those of the NCHS because demographic information was absent for some deaths, and we excluded some minority groups from the analysis. In addition, the reference period from WONDER only covered two years (2018–2019), shorter than the five years (2015–2019) covered by the main analyses. The estimates from WONDER might be slightly different from the main analyses but still added value to our understanding of the demographic disparities over time. Fourth, reporting findings may be prone to choose those subgroups with extreme values. It is of note that states with higher estimates may have different demographic structures. The infection control measures, healthcare sources and

https://doi.org/10.1038/s44161-023-00220-2

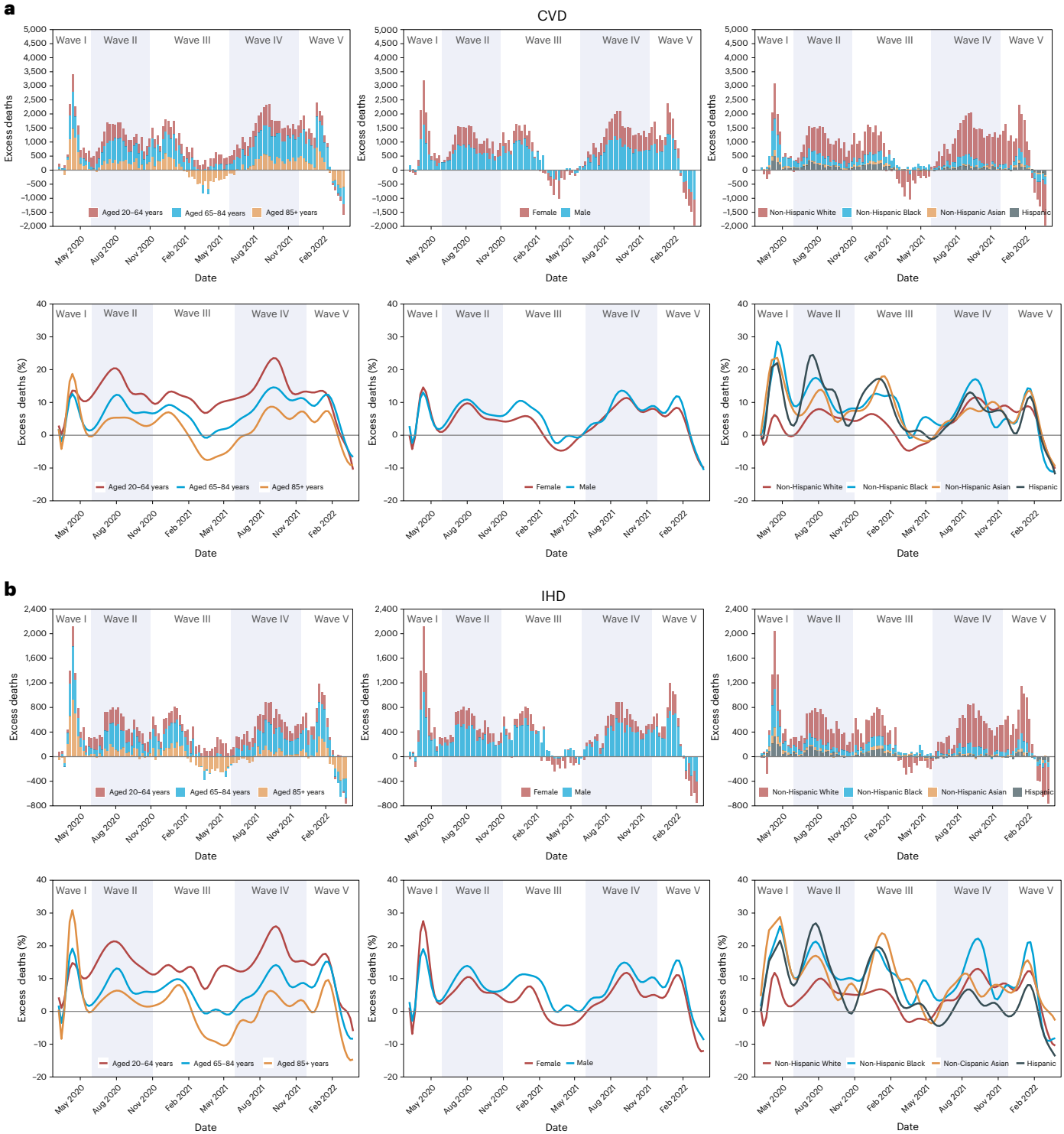


Fig. 4 | Weekly estimates of excess deaths and excess death percentages for CVDs by demographic characteristic in the United States. a,**b**, The excess estimates included overall CVDs (**a**) and IHD (**b**) from 1 March 2020 to 26 March 2022. For the two categories, panels of the upper and lower rows are weekly excess death estimates and excess death percentage estimates, respectively. Panels from left to right were subgroup analysis by age, sex and race and ethnicity, respectively. For age group stratification, the estimates are shown in red for people aged 20–64 years, blue for people aged 65–84 years and yellow for people aged 85 years or above. For sex stratification, the estimates are shown in red for females and blue for males. For race and ethnicity stratification, the estimates are shown in red for non-Hispanic White people, blue for non-Hispanic Black people, yellow for non-Hispanic Asian people, and grey for Hispanic people. The five COVID-19 death waves were defined as Wave I (Week 10, 1 March 2020, to Week 23, 6 June 2020), Wave II (Week 24, 7 June 2020, to Week 40, 3 October 2020), Wave III (Week 41, 4 October 2020, to Week 25, 26 June 2021), Wave IV (Week 26, 27 June 2021, to Week 47, 27 November 2021) and Wave V (Week 48, 28 November 2021, to Week 12, 26 March 2022).

socioeconomic states could also be different. The findings should be carefully interpreted.

In summary, excess cardiovascular mortality has been persistently observed in the first two years of the COVID-19 pandemic in the United States and its peaks were coincident with the peaks of COVID-19 mortality. This highlights the consistent burden of CVD deaths posed in healthcare systems even when COVID-19 activities waned in the community. In addition, the excess cardiovascular mortalities varied by state across multiple COVID-19 waves. Further study should clarify the mechanisms of its temporal–spatial pattern. As COVID-19 continues to pose threats to public health, it is important to monitor the mortality risk of non-COVID-19 causes, expand healthcare resources and optimize the healthcare capacity to maintain the treatment levels for cardiovascular or other chronic diseases in the era living with COVID-19.

Methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines and complies with all relevant ethical regulations. The study was exempt from ethical review and consent to participants because all data used in this study were publicly available, fully anonymized and aggregated without any identifiable information.

Data sources

We retrieved weekly death counts of the 50 US states and the District of Columbia between 4 January 2015 and 25 June 2022 from the NCHS of the CDC[16]. Death counts in the most recent weeks may suffer from incompleteness due to reporting delay. The issue has been adjusted by the NCHS and the technical procedure for data completeness adjustment was detailed elsewhere[16]. We only included the data up to March 2022 to further ensure the data completeness.

Deaths with the underlying causes of CVDs were identified according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). The death causes were classified as hypertensive diseases (ICD-10 code: I10–I15), IHD (I20-I25), heart failure (I50), cerebrovascular disease (I60–I69) and other diseases of the circulatory system (I00–I09, I26–I49, I51, I52, I70–I99)[16]. Other diseases of the circulatory system included pulmonary embolism, pericarditis, myocarditis, cardiac arrest and others. Deaths with an underlying cause of COVID-19 (diagnosed or stated on the death certificate) were excluded from our analyses. To calculate mortality rates, we retrieved annual population counts of each state during 2015–2020 from the US Census Bureau[62] and converted them into weekly data by linear interpolation. We used a first-order autoregressive model to smooth and project the population size at national and state level in 2021 and 2022.

The weekly death counts were available for most states of the United States. However, the NCHS suppressed the counts less than 10 to null value for a particular week/state due to the NCHS confidentiality standards. The suppression occurred in a few states with small population sizes and none of the national-level data was suppressed. The average number of weeks when the death counts were suppressed for CVD subgroup categories at the state level is comparable between 2015–2019 (10.3 weeks) and 2020–2022 (9.3 weeks). We performed interval censoring adjustment for the likelihood function (a negative binomial process) when such a suppressed situation occurred. We also found that the sum of the state-level estimates was in line with the national-level estimate, suggesting that such an issue might be trivial and thus that our results were unlikely to be sensitive to such an issue.

To the best of our knowledge, there is no formal definition of the COVID-19 pandemic waves, but it is commonly adopted that an 'epidemic wave' refers to a notable increase in COVID-19 cases or deaths that has a clear peak and then declines. We identified five pandemic waves according to the weekly surveillance data of COVID-19 deaths in the United States[2]. The starting calendar date of each wave depended on the week when death counts were at the trough between two consecutive waves and the wave ended on the day before the next wave. Thus, Wave I was from Week 10 (1 March 2020) to Week 23 (6 June 2020), Wave II was from Week 24 (7 June 2020) to Week 40 (3 October 2020), Wave III was from Week 41 (4 October 2020) to Week 25 (26 June 2021), Wave IV was from Week 26 (27 June 2021) to Week 47 (27 November 2021) and Wave V was from Week 48 (28 November 2021) to Week 15 (26 March 2022).

Main statistical analysis

Excess deaths were measured by the net difference between observed and expected death counts. The expected death counts (baseline) were estimated as counterfactual death counts by assuming no impacts of the COVID-19 pandemic from 1 March 2020 to 26 March 2022 for each cause of CVD mortality. Due to the overdispersion feature of the death count data, we used a fixed-effect negative binomial log-linear regression model to fit the weekly death data from 3 January 2015 to 29 February 2020. For the observed death counts y, we have the following negative binomial (NB) distribution:

$$(y|\mathbf{X}) \sim \mathrm{NB}\left(\mathrm{mean} = g(\mathbf{X\beta}),\ \mathrm{dispersion} = k\right), \tag{1}$$

where $g(\mathbf{X\beta}) = \exp(\mathbf{X\beta})$, $\mathbf{X}$ is the vector of observations, and k is the dispersion parameter such that the variance of $(y|\mathbf{X})$ is:

$$g(\mathbf{X\beta})\left[1 + \frac{g(\mathbf{X\beta})}{k}\right] = \exp(\mathbf{X\beta})\left[1 + \frac{\exp(\mathbf{X\beta})}{k}\right]. \tag{2}$$

We consider $\hat{\boldsymbol{\beta}} \sim \mathrm{Normal}(\boldsymbol{\beta}, \Sigma)$. Here, $\hat{\boldsymbol{\beta}}$ was treated as an asymptotically normal statistical estimator of the true regression parameter vector $\boldsymbol{\beta}$. The Σ denoted the covariance matrix of all regression parameters, which is to be estimated using the Delta method.

The fitted model was used to project the weekly death counts from 1 March 2020 to 26 March 2022. In the regression model, the state-specific weekly death rates were regressed by using the natural logarithm of population size as an offset from the natural logarithm of weekly death counts.

The time-varying pattern of death counts was decomposed into temporal trend and seasonality components. The temporal trend in the death sequence was adjusted with a linear term for the calendar year (from 2015 to 2022). The within-year periodicity (that is, seasonality) was parameterized using a periodic spline for epidemiological weeks (from Week 1 to Week 52) with four degrees of freedom. The periodic spline was used to fit the seasonality within one year and repeated for each year. To determine the degree of freedom of periodic spline, we fitted ten fixed-effect negative binomial log-linear regression models for each state with ten candidate degrees of freedom ranging from 3 to 12. For each degree of freedom, we fitted 51 state-level regression models using the maximum likelihood approach, and calculated their overall score of Akaike information criterion (AIC) as a measure of the tradeoff between goodness-of-fit and model complexity. According to the minimal value of AIC, the periodic spline with four degrees of freedom was selected for the main and subgroup analyses. It was of note that the selected degree of freedom here merely fixed the number of free parameters to capture the seasonality patterns, rather than to represent the seasonality term itself, which means different values of parameters were estimated for different states. Thus, the 51 regression models were fitted with state-specific patterns of both trend and seasonality.

With the estimates of expected death counts, we calculated the excess deaths (observed death counts − expected death counts), weekly average excess deaths (excess deaths/length of the observational period), excess mortality (excess deaths/population) and excess percentage (excess deaths/expected deaths × 100) for different subgroups. The statistical uncertainty of expected death counts was assessed by using 95% CI. The 95% CI of the mean death counts was constructed by mean estimate ± 1.96 s.e.m., and the s.e.m. was calculated by applying the Delta method with first-order Taylor approximation.

The spatial autocorrelation of excess estimates across states was measured by global Moran's *I* statistic in ArcGIS v.10.6. Any contiguous polygon was defined as the neighbor (that is, sharing a common border)[63]. Alaska and Hawaii were not involved in the calculation of Moran's *I* statistic because the two states are not adjacent to any other state. To control for the increased probability of false positives when conducting multiple comparisons, two-sided false discovery rate-adjusted *P* values <0.05 were considered statistically significant.

Subgroup statistical analysis for different age, sex and race and ethnicity strata

To explore the demographic disparities of excess mortality and their temporal patterns in subgroup populations, we also retrieved weekly death counts for different age (20–64 years, 65–84 years and 85+ years), sex (male and female) and race and ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian and Hispanic) groups from the CDC WONDER database[17]. We obtained the weekly death counts from the beginning of 2018 to 25 June 2022 through the Provisional Multiple Cause of Death database at the WONDER platform, which contained aggregated death counts of all US counties based on death certificates for US residents. The trend and seasonality of observed deaths of CVDs from the WONDER database were generally consistent with those from the NCHS database, though there were mild discrepancies. Consistent with the main analysis, death counts after 27 March 2022 were excluded considering the reporting lags. Deaths assigned to CVDs were also identified by ICD-10 codes, and were classified as hypertensive diseases (I10–I15), IHD (I20–I25), heart failure (I50), cerebrovascular disease (I60–I69) and other diseases of the circulatory system (I00–I09, I26–I49, I51, I52 and I70–I99).

Consistent with the regression model used for the main analysis, for each age, sex and race and ethnicity subgroup, we used a fixed-effect negative binomial log-linear regression model to fit the weekly death data from January 2018 to February 2020, respectively. The fitted model was used to project the weekly death counts from March 2020 to March 2022. The temporal trend in the death sequence was adjusted with a linear term for the calendar year. The within-year periodicity was parameterized using a periodic spline for epidemiological weeks with four degrees of freedom. We did not estimate the excess deaths for subgroups aged <20 years and some ethnic minorities (including American Indian, Alaska Native, Native Hawaiian and Other Pacific Islander) because death counts of those subgroups were sparse. Besides, a small number of deaths without demographic information were not included in the subgroup analysis.

Sensitivity analysis

Multiple strategies for sensitivity analysis were conducted for evaluating the robustness of results. First, for the main analyses and demographic subgroup analyses, we used the periodic spline with degrees of freedom at 8 and 12 (whereas a degree of freedom at 4 was used in the main model) to test the robustness of the fitting for the seasonal effect. Second, time series of death counts during the period 2016–2019 was fitted by using the negative binomial log-linear regression model to test the potential influence of different baseline selections on the prediction of death counts during the period 2020–2022 for the main analyses (Supplementary Tables 41 and 42).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All raw data in this study are publicly available and can be retrieved from the National Center for Health Statistics, Centers for Disease Control and Prevention (COVID-19 Death Data and Resources: https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm and Wide-ranging Online Data for Epidemiologic Research: https://wonder.cdc.gov/mcd.html).

Code availability

Statistical analyses, figures and maps were carried out using R statistical software, v.4.2.1. Code for the analysis conducted for the paper is available at https://github.com/ran1991/excessCVD.

References

1. Wang, H. et al. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. *Lancet* **399**, 1513–1536 (2022).
2. *Trends in Number of COVID-19 Cases and Deaths in the US Reported to CDC, by State/Territory* (Centers for Disease Control and Prevention, accessed 15 August 2022); https://covid.cdc.gov/covid-data-tracker/#trends_weeklydeaths_select_00
3. Wadhera, R. K. et al. Cardiovascular deaths during the COVID-19 pandemic in the United States. *J. Am. Coll. Cardiol.* **77**, 159–169 (2021).
4. Ran, J. et al. Increase in diabetes mortality associated with COVID-19 pandemic in the U.S. *Diabetes Care* **44**, e146–e147 (2021).
5. Gilstrap, L., Zhou, W., Alsan, M., Nanda, A. & Skinner, J. S. Trends in mortality rates among medicare enrollees with Alzheimer disease and related dementias before and during the early phase of the COVID-19 pandemic. *JAMA Neurol.* **79**, 342–348 (2022).
6. Han, L. et al. Changes in renal failure mortality during the COVID-19 pandemic in the United States. *J Nephrol.* **34**, 2167–2170 (2021).
7. Ball, S. et al. Monitoring indirect impact of COVID-19 pandemic on services for cardiovascular diseases in the UK. *Heart* **106**, 1890–1897 (2020).
8. Young, M. N., Iribarne, A. & Malenka, D. COVID-19 and cardiovascular health: this is a public service announcement. *J. Am. Coll. Cardiol.* **77**, 170–172 (2021).
9. Nadarajah, R. & Gale, C. P. Collateral cardiovascular damage during the COVID-19 pandemic. *Nat. Rev. Cardiol.* **19**, 81–82 (2022).
10. Bhatt, A. S. et al. Fewer hospitalizations for acute cardiovascular conditions during the COVID-19 pandemic. *J. Am. Coll. Cardiol.* **76**, 280–288 (2020).
11. Lai, P. H. et al. Characteristics associated with out-of-hospital cardiac arrests and resuscitations during the novel coronavirus disease 2019 pandemic in New York City. *JAMA Cardiol.* **5**, 1154–1163 (2020).
12. Kontopantelis, E. et al. Excess deaths from COVID-19 and other causes by region, neighbourhood deprivation level and place of death during the first 30 weeks of the pandemic in England and Wales: a retrospective registry study. *Lancet Reg. Health Eur.* **7**, 100144 (2021).
13. Brant, L. C. C. et al. Excess of cardiovascular deaths during the COVID-19 pandemic in Brazilian capital cities. *Heart* **106**, 1898–1905 (2020).
14. Grande, E. et al. Variation in cause-specific mortality rates in Italy during the first wave of the COVID-19 pandemic: a study based on nationwide data. *Int. J. Environ. Res. Public Health* **19**, 805 (2022).
15. Liu, J. et al. Excess mortality in Wuhan city and other parts of China during the three months of the covid-19 outbreak: findings from nationwide mortality registries. *Brit. Med. J.* **372**, n415 (2021).
16. *Excess Deaths Associated with COVID-19* (Centers for Disease Control and Prevention, accessed 20 July 20 2022); https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm
17. *National Center for Health Statistics Mortality Data on CDC WONDER* (Centers for Disease Control and Prevention, accessed 20 July 2022); https://wonder.cdc.gov/mcd.html

18. Woolf, S. H., Chapman, D. A., Sabo, R. T., Weinberger, D. M. & Hill, L. Excess deaths from COVID-19 and other causes, March-April 2020. *JAMA* **324**, 510–513 (2020).
19. Zhu, D., Ozaki, A. & Virani, S. S. Disease-specific excess mortality during the COVID-19 pandemic: an analysis of weekly US death data for 2020. *Am. J. Public Health* **111**, 1518–1522 (2021).
20. Woolf, S. H., Chapman, D. A., Sabo, R. T. & Zimmerman, E. B. Excess deaths Ffom COVID-19 and other causes in the US, March 1, 2020, to January 2, 2021. *JAMA* **325**, 1786–1789 (2021).
21. Banerjee, A. et al. Excess deaths in people with cardiovascular diseases during the COVID-19 pandemic. *Eur. J. Prev. Cardiol.* **28**, 1599–1609 (2021).
22. Bodilsen, J. et al. Hospital admission and mortality rates for non-covid diseases in Denmark during covid-19 pandemic: nationwide population based cohort study. *Brit. Med. J.* **373**, n1135 (2021).
23. Cannata, A. et al. Impact of the COVID-19 pandemic on in-hospital mortality in cardiovascular disease: a meta-analysis. *Eur. J. Prev. Cardiol.* **29**, 1266–1274 (2021).
24. Dorrucci, M. et al. Excess mortality in Italy during the COVID-19 pandemic: assessing the differences between the first and the second wave, Year 2020. *Front. Public Health* **9**, 669209 (2021).
25. Fox, D. K. et al. Impact of the COVID-19 pandemic on patients without COVID-19 with acute myocardial infarction and heart failure. *J. Am. Heart Assoc.* **11**, e022625 (2022).
26. Einstein, A. J. et al. International impact of COVID-19 on the diagnosis of heart disease. *J. Am. Coll. Cardiol.* **77**, 173–185 (2021).
27. Leong, D. P., Eikelboom, J. W. & Yusuf, S. The indirect consequences of the response to the COVID-19 pandemic. *J. Am. Coll. Cardiol.* **77**, 186–188 (2021).
28. Solomon, M. D. et al. The Covid-19 pandemic and the incidence of acute myocardial infarction. *N. Engl. J. Med.* **383**, 691–693 (2020).
29. Baldi, E. et al. Out-of-hospital cardiac arrest during the Covid-19 outbreak in Italy. *N. Engl. J. Med.* **383**, 496–498 (2020).
30. Pessoa-Amorim, G. et al. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. *Eur. Heart J. Qual. Care Clin. Outcomes* **6**, 210–216 (2020).
31. Lechner, I. et al. Impact of COVID-19 pandemic restrictions on ST-elevation myocardial infarction: a cardiac magnetic resonance imaging study. *Eur. Heart J.* **43**, 1141–1153 (2022).
32. Chew, N. W. S. et al. The global effect of the COVID-19 pandemic on STEMI Care: a systematic review and meta-analysis. *Can. J. Cardiol.* **37**, 1450–1459 (2021).
33. Garcia, S. et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. *J. Am. Coll. Cardiol.* **75**, 2871–2872 (2020).
34. Garcia, S. et al. Initial findings from the North American COVID-19 Myocardial Infarction Registry. *J. Am. Coll. Cardiol.* **77**, 1994–2003 (2021).
35. De Luca, G. et al. COVID-19 pandemic, mechanical reperfusion and 30-day mortality in ST elevation myocardial infarction. *Heart* **108**, 458–466 (2022).
36. De Luca, G. et al. Impact of COVID-19 pandemic on mechanical reperfusion for patients with STEMI. *J. Am. Coll. Cardiol.* **76**, 2321–2330 (2020).
37. Wyckoff, M. H. et al. 2021 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: summary from the Basic Life Support; Advanced Life Support; Neonatal Life Support; Education, Implementation, and Teams; First Aid Task Forces; and the COVID-19 Working Group. *Circulation* **145**, e645–e721 (2022).
38. ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2-care pathways, treatment, and follow-up. *Eur. Heart J.* **43**, 1059–1103 (2022).
39. Gluckman, T. J. et al. 2022 ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: a report of the American College of Cardiology Solution Set Oversight Committee. *J. Am. Coll. Cardiol.* **79**, 1717–1756 (2022).
40. Keshvani, N. et al. Heart failure quality of care and in-hospital outcomes during the COVID-19 pandemic: findings from the Get With The Guidelines-Heart Failure registry. *Eur. J. Heart Fail.* **24**, 1117–1128 (2022).
41. Rao, G. et al. Paradigm shifts in cardiac care: lessons learned from COVID-19 at a large New York health system. *Curr. Probl. Cardiol.* **46**, 100675 (2021).
42. Wood, D. A. et al. Safe reintroduction of cardiovascular services during the COVID-19 pandemic: from the North American Society leadership. *J. Am. Coll. Cardiol.* **75**, 3177–3183 (2020).
43. Katz, J. N. et al. COVID-19 and disruptive modifications to cardiac critical care delivery: JACC review topic of the week. *J. Am. Coll. Cardiol.* **76**, 72–84 (2020).
44. Eberly, L. A. et al. Telemedicine outpatient cardiovascular care during the COVID-19 pandemic: bridging or opening the digital divide? *Circulation* **142**, 510–512 (2020).
45. Treskes, R. W. et al. Effect of smartphone-enabled health monitoring devices vs regular follow-up on blood pressure control among patients after myocardial infarction: a randomized clinical trial. *JAMA Netw. Open* **3**, e202165 (2020).
46. Xu, H., Granger, B. B., Drake, C. D., Peterson, E. D. & Dupre, M. E. Effectiveness of telemedicine visits in reducing 30-day readmissions among patients with heart failure during the COVID-19 pandemic. *J. Am. Heart Assoc.* **11**, e023935 (2022).
47. Handberry, M. et al. Changes in emergency medical services before and during the COVID-19 pandemic in the United States, January 2018-December 2020. *Clin. Infect. Dis.* **73**, S84–s91 (2021).
48. Einstein, A. J. et al. Worldwide disparities in recovery of cardiac testing 1 year into COVID-19. *J. Am. Coll. Cardiol.* **79**, 2001–2017 (2022).
49. Garcia, S. et al. Trends in clinical presentation, management, and outcomes of STEMI in patients with COVID-19. *J. Am. Coll. Cardiol.* **79**, 2236–2244 (2022).
50. Raman, B., Bluemke, D. A., Lüscher, T. F. & Neubauer, S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *Eur. Heart J.* **43**, 1157–1172 (2022).
51. Kohli, P. & Virani, S. S. Surfing the waves of the COVID-19 pandemic as a cardiovascular clinician. *Circulation* **142**, 98–100 (2020).
52. Mitrani, R. D., Dabas, N. & Goldberger, J. J. COVID-19 cardiac injury: implications for long-term surveillance and outcomes in survivors. *Heart Rhythm* **17**, 1984–1990 (2020).
53. Ståhlberg, M. et al. Post-COVID-19 tachycardia syndrome: a distinct phenotype of post-acute COVID-19 syndrome. *Am. J. Med.* **134**, 1451–1456 (2021).
54. Xie, Y., Xu, E., Bowe, B. & Al-Aly, Z. Long-term cardiovascular outcomes of COVID-19. *Nat. Med.* **28**, 583–590 (2022).
55. Al-Aly, Z., Xie, Y. & Bowe, B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* **594**, 259–264 (2021).
56. Ayoubkhani, D. et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *Brit. Med. J.* **372**, n693 (2021).
57. Ge, Y. et al. Impacts of worldwide individual non-pharmaceutical interventions on COVID-19 transmission across waves and space. *Int. J. Appl. Earth Obs. Geoinf.* **106**, 102649 (2022).

58. *COVID-19 Vaccinations in the United States, Jurisdiction* (Centers for Disease Control and Prevention, accessed 21 May 2022); https://data.cdc.gov/Vaccinations/COVID-19-Vaccinations-in-the-United-States-Jurisdi/unsk-b7fc
59. Schwartz, J. Is there harvesting in the association of airborne particles with daily deaths and hospital admissions? *Epidemiology* **12**, 55–61 (2001).
60. Romero, L. et al. Health center testing for SARS-CoV-2 during the COVID-19 pandemic—United States, June 5–October 2, 2020. *MMWR Morb. Mortal. Wkly. Rep.* **69**, 1895–1901 (2020).
61. Shiels, M. S. et al. Racial and ethnic disparities in excess deaths during the COVID-19 pandemic, March to December 2020. *Ann. Intern. Med.* **174**, 1693–1699 (2021).
62. *Census Data* (The United States Census Bureau, accessed 20 July 2022); https://data.census.gov/cedsci/
63. ArcGIS Pro. *Spatial Autocorrelation (Global Moran's I) (Spatial Statistics)* https://pro.arcgis.com/en/pro-app/latest/tool-reference/spatial-statistics/spatial-autocorrelation.htm (2022).

Acknowledgements

This work was supported by the Shanghai Science and Technology Development Foundation, 22YF1421100 (J.R.) and Health Medical Research Fund—Commissioned Research on COVID-19, COVID1903007 (L.Y.). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the paper; and decision to submit the paper for publication. We thank S. Sun (Capital Medical University) and W. Cao (Peking University) for their helpful comments.

Author contributions

J.R. and L.H. conceived the study. S.L. and S.G. curated the data. J.R., L.H. and S.Z. performed the formal analysis. S.Z. was responsible for the methodology. J.R. and L.Y. provided the project administration. L.H. and S.L. did the visualization. L.H. and S.Z. wrote the original draft. J.R., L.Y. and X.D. reviewed and edited the paper. All authors contributed to the interpretation of data and read and approved the final paper.

Competing interests

The authors declare no competing interests.

Additional information

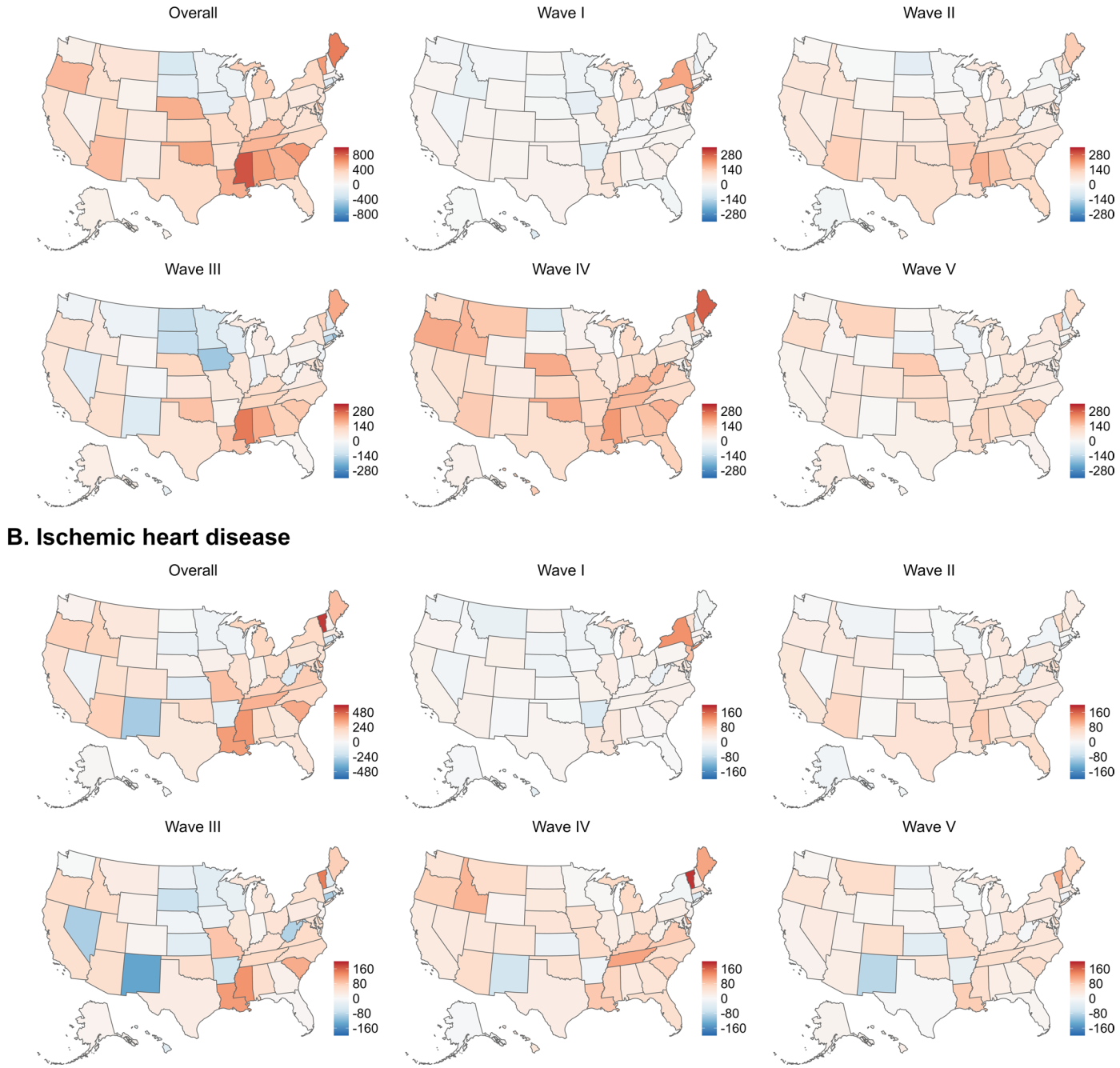
Extended data is available for this paper at https://doi.org/10.1038/s44161-023-00220-2.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44161-023-00220-2.

Correspondence and requests for materials should be addressed to Lin Yang or Jinjun Ran.

Peer review information *Nature Cardiovascular Research* thanks David Steinberg, Frits Rosendaal and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

https://doi.org/10.1038/s44161-023-00220-2

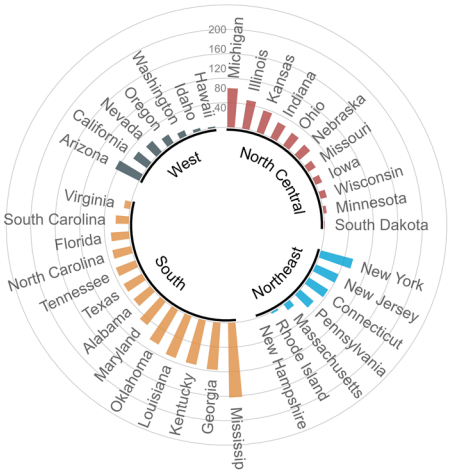


Extended Data Fig. 1 | Maps of excess mortalities of cardiovascular diseases (per million persons) stratified by COVID-19 death wave in the United States. The excess morality estimates include (**a**) overall cardiovascular diseases and (**b**) ischemic heart disease. The gradient colors from blue to red indicate the excess mortality estimates varied from negative to positive values across states. 'Overall' refers to the period from March 1, 2020, to March 26, 2022. The five waves were defined as Wave I (Week 10 March 1, 2020, to Week 23 June 6 2020), Wave II (Week 24 June 7 2020 to Week 40 October 3 2020), Wave III (Week 41 October 4 2020 to Week 25 June 26 2021), Wave IV (Week 26 June 27 2021 to Week 47 November 27 2021), and Wave V (Week 48 November 28 2021 to Week 12 March 26 2022) according to COVID-19 death waves in the United States.

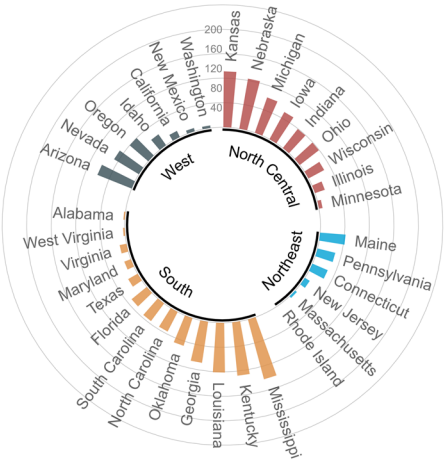
https://doi.org/10.1038/s44161-023-00220-2

A. Hypertensive disease

March.2020 - February.2021

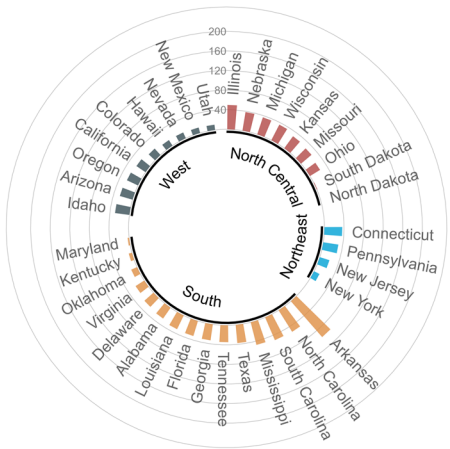


March.2021 - March.2022

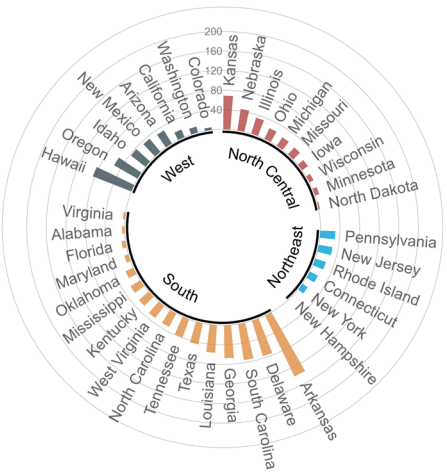


B. Cerebrovascular disease

March.2020 - February.2021

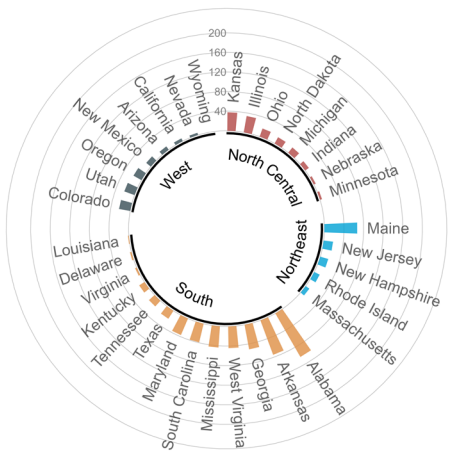


March.2021 - March.2022

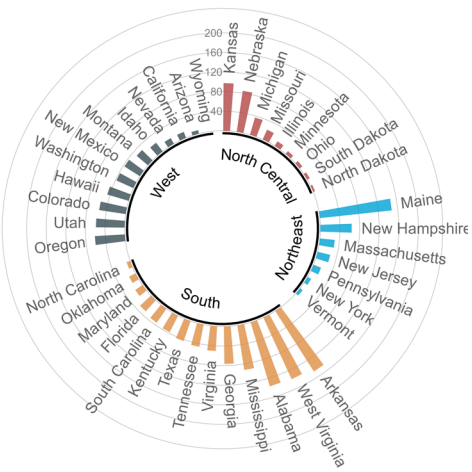


C. Other disease of the circulatory system

March.2020 - February.2021

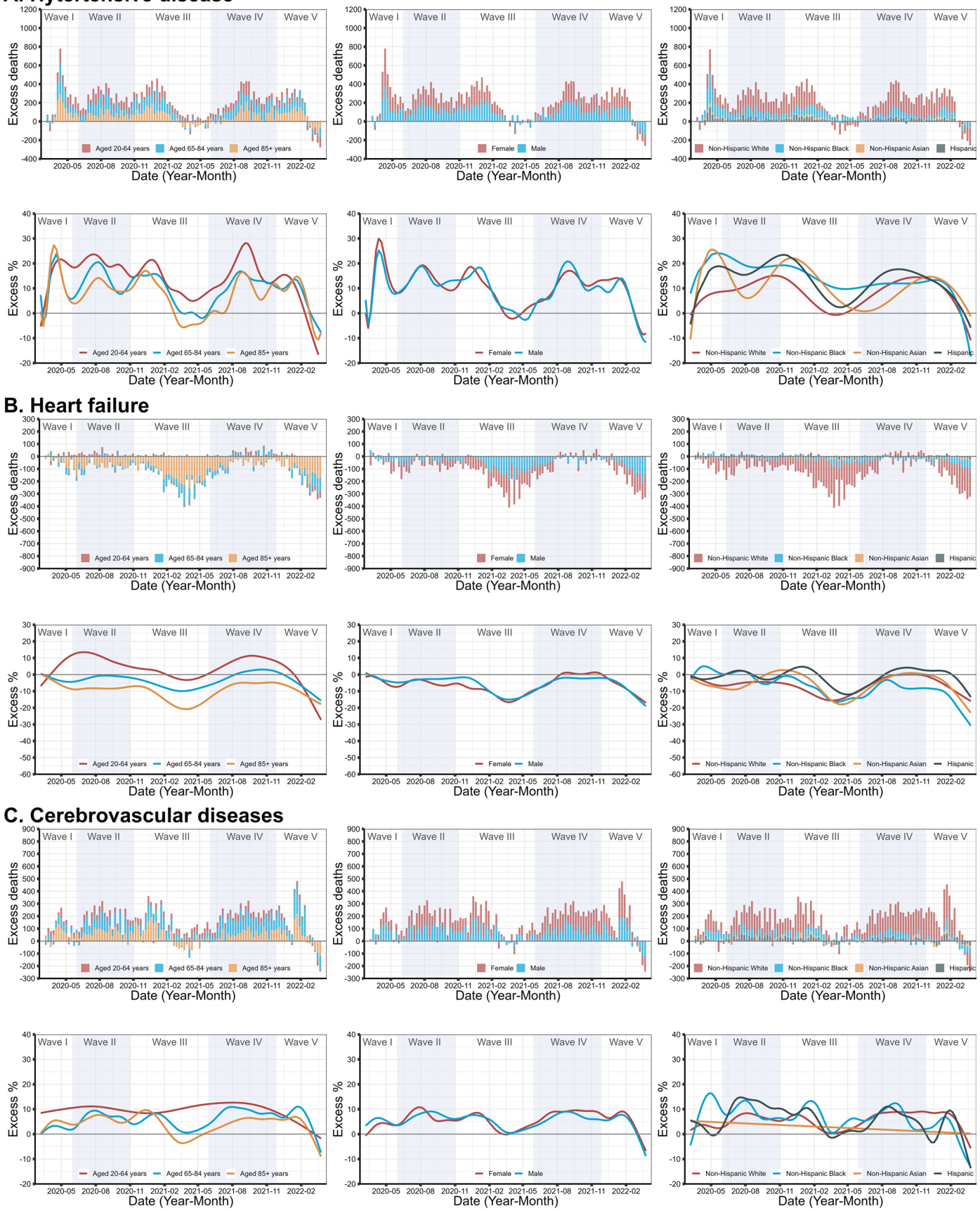


March.2021 - March.2022



Extended Data Fig. 2 | Annual excess mortalities of cardiovascular diseases (per million persons) by states in the United States. The excess mortality estimates include (**a**) hypertensive disease (**b**) cerebrovascular disease and (**c**) other diseases of the circulatory system. These states were grouped into different color clusters according to their geographic regions, including North Central, Northeast, South, and West. The period of 2020–2021 was from March 1, 2020, to February 27, 2021. The period of 2021-2022 was from February 28, 2021, to March 26, 2022. The states with negative estimated values were not shown.

https://doi.org/10.1038/s44161-023-00220-2



Extended Data Fig. 3 | See next page for caption.

https://doi.org/10.1038/s44161-023-00220-2

Extended Data Fig. 3 | Weekly estimates of excess deaths and excess percentage for subtype cardiovascular diseases by demographic characteristic in the United States. The excess estimates included (**a**) hypertensive disease, (**b**) heart failure, and (**c**) cerebrovascular disease from March 1, 2020, to March 26, 2022. For the three categories, panels of the upper and lower rows are weekly excess death estimates and excess percentage estimates, respectively. Panels from left to right were subgroup analysis by age, sex, and race and ethnicity, respectively. For age group stratification, the estimates are shown in red for people aged 20–64 years, blue for people aged 65–84 years and yellow for people aged 85 years or above. For sex stratification, the estimates are shown in red for females and blue for males. For race and ethnicity stratification, the estimates are shown in red for non-Hispanic White people, blue for non-Hispanic Black people, yellow for non-Hispanic Asian people, and grey for Hispanic people. The five COVID-19 death waves were defined as Wave I (Week 10 March 1, 2020, to Week 23 June 6 2020), Wave II (Week 24 June 7 2020 to Week 40 October 3 2020), Wave III (Week 41 October 4 2020 to Week 25 June 26 2021), Wave IV (Week 26 June 27 2021 to Week 47 November 27 2021), and Wave V (Week 48 November 28 2021 to Week 12 March 26 2022).

nature portfolio

Corresponding author(s): Jinjun Ran and Lin Yang

Last updated by author(s): Jan 11, 2023

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☒	☐ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	All data processing and cleaning was performed using the statistical software R.
Data analysis	Statistical analyses were carried out using R version 4.2.1, and scripts for the R language were available on GitHub at: https://github.com/ran1991/excessCVD. The spatial autocorrelation was measured by the global Moran's I statistic in ArcGIS 10.6.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data of weekly CVD death counts from January 2015 to May 2022 were publicly available in the CDC NCHS (National Center for Health Statistics: https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm). Data of CVD death by demographics from January 2018 to May 2022 were publicly available in the CDC WONDER (Wide-ranging Online Data for Epidemiologic Research: https://wonder.cdc.gov/mcd.html).

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Sex-specific excess cardiovascular mortalities were analyzed in this study. The sex-specific mortality data were retrieved from the CDC Wide-ranging Online Data for Epidemiologic Research database (WONDER) database: https://wonder.cdc.gov/controller/datarequest/D176. Sex information was collected based on the registration of death.
Population characteristics	Anonymous and aggregated data involving people who died from the underlying causes of cardiovascular diseases during Jan 2015 - Mar 2022 in the United States, aged 20 years above. Data retrieved from the CDC National Center for Health Statistics of the United States.
Recruitment	We used nationwide CVD mortality data retrieved from the Centers for Disease Control and Prevention of the United States.
Ethics oversight	The study is about secondary, aggregated, and anonymized data, so no ethical permission is required.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Cross-state time-series analysis of population level mortality
Research sample	N/A. The study was a nationwide analysis in the US including all historical CVD mortality data deaths. Thus, the results are generalizable to the US
Sampling strategy	N/A. We used all reported CVD deaths available for analysis.
Data collection	Weekly CVD death counts between January 4, 2015 and June 25, 2022 were retrieved from CDC NCHS (National Center for Health Statistics: https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm). Data for different age (20-64 years, 65-84 years, 85+ years), sex (male and female), and race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic) were retrieved from CDC WONDER (Wide-ranging Online Data for Epidemiologic Research: https://wonder.cdc.gov/mcd.html). Data collection and cleaning were performed by Lefei Han and Jinjun Ran, and the main analysis was conducted by Jinjun Ran and Shi Zhao.
Timing	The updated data were downloaded on July 23 2022.
Data exclusions	Concerning large residual incompleteness, we also excluded data from the most recent weeks (April and May 2022) before analysis.
Non-participation	N/A. Our data is nationwide counts of mortality and population based on a national registry.
Randomization	This is a cross-state time-series study using administrative data from the entire population in the US and includes no randomization.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging