Supplementary Materials

Mortality trends due to concomitant cardiovascular disease and cancer in the United States

eMethods 1. Bayesian Hierarchical Model

The primary objective of fitting a Bayesian hierarchical model was to test the robustness of the observed national mortality trend inflection points (e.g., around 2015 and 2018). Specifically, we aimed to evaluate whether these apparent inflection points might be confounded by concurrent, substantial shifts in other major public health crises that peaked during the same period. We therefore incorporated three state-level covariates known to have undergone changes circa our periods of interest: the drug overdose mortality rate, the opioid-related mortality rate, and the PM2.5 pollution level.

Rationale for Covariate Selection and Model Specification:

Adjusting for Concurrent Confounding: The epidemics of drug and opioid overdoses, as well as significant changes in air pollution, exhibited pronounced temporal fluctuations that overlapped with the inflection periods under study. Their state-level variations are plausibly linked to all-cause and cause-specific mortality. Including them as covariates in the model allows us to estimate and statistically "adjust for" their average effects on mortality levels. This enables a more isolated estimation of the immediate "level shifts" associated with the inflection periods (post_2015, post_2018) themselves, net of these concurrent crises.

Testing for Effect Modification of Trends: We specifically included interaction terms between each covariate and time. This tests a more nuanced hypothesis: whether the strength of the association between each covariate (e.g., the opioid crisis) and mortality itself changed over time. A significant interaction would indicate that the covariate not only affected the mortality level but also potentially contributed to shaping or modifying the trajectoryof the national trend. Controlling for this dynamic effect helps ascertain whether the identified inflection points are independent of the evolving impact of these covariates.

Inference for Underlying Drivers: If the inflection points remain statistically significant after adjusting for these strong, temporally coincident confounders, it strengthens the inference that the observed trend changes are more likely attributable to other, broader factors not directly measured here. This supports the discussion of potential drivers such as the cumulative cardiotoxicity of evolving cancer therapies or the increasing population prevalence of shared risk factors (e.g., obesity, physical inactivity).

Prior Selection and Computation:

We used weakly informative priors, which provide modest regularization to stabilize estimates but are dominated by the information in the likelihood function. The model was estimated using Hamiltonian Monte Carlo (MCMC) sampling via the brmspackage. We ran 4 Markov chains, each for 4,000 iterations (2,000 warm-up). Convergence was successfully assessed (all R-hat ≤ 1.01, effective sample sizes > 1,000). Analyses of Bayesian Hierarchical Model were performed using R version 4.3.3 (R Foundation).

eMethods 2. Approach to Multiple Comparisons in Stratified Analyses

The study involved numerous stratified trend analyses (by age, sex, race, and state) to identify disparities. To address the increased risk of Type I errors due to multiple testing, we applied the Benjamini-Hochberg (BH) procedure to control the False Discovery Rate (FDR) for the stratified Average Annual Percentage Change (AAPC) and Annual Percentage Change (APC) estimates.

The BH correction was applied to the p-values associated with the AAPC estimates from all subgroup-specific Joinpoint models. The AAPC provides a single, summary estimate of the trend over the entire study period for each subgroup, making it a suitable unit for multiplicity adjustment. The adjusted p-values (q-values) for each subgroup's AAPC are presented alongside the unadjusted p-values in Supplementary Tables S1-S3. For demographic subgroups (age, sex, race), the Annual Percentage Change (APC), which describe trends within specific temporal segments and are used to identify inflection points, were also subjected to the BH correction. The procedure was applied separately to the p-values of all APC segments within each demographic stratification. This step was crucial for ensuring the robustness in pinpointing the timing of trend inflection points across these subgroups. State-level analyses did not involve segment-specific APC comparisons, as the spatial disparity assessment relied solely on the summary AAPC metric. The adjusted p-values (q-values) for the APC in each subgroup are presented in Fig 1-4.

This dual-level correction strategy ensures rigorous control of the false discovery rate for our primary inferences: the FDR-corrected AAPC identifies which subgroups have significant overall trends, while the FDR-corrected APC provides a more robust estimation of inflection years for describing how those trends evolved over time within demographic subgroups.

Table S1. Trends of the ASMR attributable to comorbid cancer and cardiovascular disease by demographic characteristics in the United States during 2000-2023.

Index	Year	AAPC	*P*	*P*_adj
Total	2000-2023	-0.7823	0.0012	0.0012
Female	2000-2023	-0.6739	<0.0001	<0.0001
Male	2000-2023	-1.1174	<0.0001	<0.0001
15-44 years old	2000-2023	-0.5009	0.000669	0.000669
45-64 years old	2000-2023	-0.5561	<0.0001	<0.0001
65-74 years old	2000-2023	-1.0349	<0.0001	<0.0001
75-84 years old	2000-2023	-0.9609	<0.0001	<0.0001
85+ years old	2000-2023	-0.5713	0.0001	0.0002
American Indian or Alaska Native	2000-2023	-0.7669	0.0308	0.0308
Asian or Pacific Islander	2000-2023	-1.8915	<0.0001	<0.0001

Black or African American	2000-2023	-1.3453	<0.0001	<0.0001
White	2000-2023	-0.6977	<0.0001	<0.0001

*Note: *P* were adjusted for multiple comparisons using the Benjamini-Hochberg procedure within each stratification (FDR < 0.05). *P*_adj indicates the adjusted *P*. ASMR: age-standardized mortality rates.

Table S2. Posterior estimates from a Bayesian Hierarchical Model for the impact of covariates on trends in ASMR due to comorbid cancer and cardiovascular disease, 2000-2023.

Category	**Parameter**	**Estimate**	**95% CI**	**Sig.**
Time trends	Intercept	49.10	[44.96, 53.43]	
	Time (2000-2015)	-0.56	[-0.83, -0.30]	
	Post-2015 (2015-2018)	-17.41	[-23.76, -10.98]	*
	Post-2018 (2018-2023)	-19.66	[-26.61, -12.66]	*
	Time × Post-2015	1.20	[0.78, 1.60]	*
	Time × Post-2018	1.09	[0.69, 1.49]	*
Covariate main effects	Drug use disorder mortality	-1.41	[-4.04, 1.16]	
	Opioid use disorder mortality	1.15	[-2.07, 4.39]	
	PM2.5	-0.18	[-0.53, 0.16]	
Time interactions	Time × Drug use disorder mortality	0.14	[0.00, 0.29]	
	Time × Opioid use disorder mortality	-0.16	[-0.34, 0.02]	
	Time × PM2.5	0.03	[0.01, 0.06]	*

Note: N= 1,145 observations (51 states, 2000-2023). Model convergence was successful (all R-hat ≤ 1.01). The Intercept represents the estimated baseline level in the year 2000, prior to policy periods and with all centered covariates at their mean. Random effects SD: Intercept = 12.79, Time = 0.67 (corr = -0.70).

* indicates 95% credible interval does not include 0.

Table S3. Trends in the proportion of the ASMR attributable to comorbid cancer and cardiovascular diseases within the total ASMR, the cancer ASMR, and the cardiovascular disease ASMR in the United States from 2000 to 2023.

Index	Year	AAPC	*P*
Total ASMR	2000-2023	-0.0365	0.8766
Cancer ASMR	2000-2023	0.6339	<0.0001
Cardiovascular disease ASMR	2000-2023	1.2132	<0.0001

ASMR: age-standardized mortality rates.

Table S4. Trends of the ASMR attributable to comorbid cancer and cardiovascular disease in different state of the United States during 2000-2015 and 2015-2023, respectively.

State	2000-2015			2015-2023		
	AAPC	*P*	*P*_adj	AAPC	*P*	*P*_adj
Alabama	-2.7757	<0.0001	<0.0001	3.3126	0.0016	0.0042
Alaska	-3.6951	<0.0001	<0.0001	-2.254	<0.0001	<0.0001
Arizona	-2.4636	<0.0001	<0.0001	0.2358	0.7272	0.7418
Arkansas	-2.7274	0.1918	0.2223	2.7569	0.1193	0.1521
California	-0.2352	0.6604	0.6873	-0.6081	0.5911	0.6554
Colorado	-1.3631	0.0040	0.0053	2.5989	0.01564	0.0249
Connecticut	0.8095	0.0003	0.0005	2.8638	0.0024	0.0056
Delaware	-1.4398	<0.0001	<0.0001	0.0224	0.9146	0.9146
District of Columbia	-0.4770	0.5857	0.6223	4.5140	0.0006	0.0017
Florida	-1.4144	0.2464	0.2792	4.9975	0.0066	0.0125
Georgia	-2.8785	<0.0001	<0.0001	-4.3641	0.0042	0.0086
Hawaii	-0.0972	0.8211	0.8375	2.9852	0.0047	0.0093
Idaho	-0.1291	0.5830	0.6223	-0.8106	0.0363	0.0562
Illinois	-2.5324	<0.0001	<0.0001	8.2479	<0.0001	<0.0001
Indiana	-0.8660	0.0001	2.0071	2.6961	0.0018	0.0045
Iowa	-2.4448	<0.0001	<0.0001	1.1511	0.0114	0.0189
Kansas	-2.8612	<0.0001	<0.0001	3.8507	<0.0001	<0.0001
Kentucky	-2.4023	<0.0001	<0.0001	2.2052	0.09650	0.1262

Louisiana	-1.7623	<0.0001	<0.0001	5.2903	<0.0001	<0.0001
Maine	-2.9904	<0.0001	<0.0001	3.1317	<0.0001	<0.0001
Maryland	-3.3177	<0.0001	<0.0001	1.7845	<0.0001	0.0001
Massachusetts	-3.0444	0.0037	0.0052	-1.3094	0.2999	0.3477
Michigan	-0.8843	0.0473	0.0574	6.1096	<0.0001	<0.0001
Minnesota	-1.6374	<0.0001	<0.0001	2.3354	<0.0001	<0.0001
Mississippi	-2.8041	<0.0001	<0.0001	0.3429	0.6557	0.6967
Missouri	-0.2608	0.8507	0.8507	1.2254	0.0377	0.0365
Montana	-1.7489	<0.0001	<0.0001	2.5481	0.0025	0.0056
Nebraska	-1.5473	<0.0001	<0.0001	3.0256	0.0001	0.0004
Nevada	-0.4021	0.0018	0.0028	5.6939	<0.0001	0.0001
New Hampshire	-1.3851	0.0034	0.0049	1.3293	0.0115	0.0189
New Jersey	-2.4619	<0.0001	<0.0001	1.6027	<0.0001	<0.0001
New Mexico	-3.4770	<0.0001	<0.0001	4.6457	0.0113	0.0189
New York	-1.0939	<0.0001	<0.0001	4.0780	0.0003	0.0009
North Carolina	-0.3416	0.5783	0.6223	3.9716	0.0018	0.0045
North Dakota	-2.1882	<0.0001	<0.0001	-0.9557	<0.0001	<0.0001
Ohio	-3.2137	<0.0001	<0.0001	1.1098	0.0433	0.04010
Oklahoma	-2.5437	<0.0001	<0.0001	6.7809	0.0482	0.0486
Oregon	-4.3987	<0.0001	<0.0001	7.8847	<0.0001	<0.0001
Pennsylvania	-2.4514	<0.0001	<0.0001	1.8499	0.0484	0.04052
Rhode Island	-0.8928	0.0040	0.0053	2.5763	0.0443	0.0446
South Carolina	-1.4557	<0.0001	<0.0001	0.5049	0.7140	0.7418
South Dakota	-1.1264	<0.0001	<0.0001	5.2958	0.0027	0.0058
Tennessee	-0.4127	0.0180	0.0229	5.2504	<0.0001	<0.0001
Texas	-0.8000	0.0156	0.0204	2.1768	0.4484	0.5082
Utah	-0.4269	0.1362	0.1615	0.4863	0.1543	0.1830
Vermont	-3.4194	<0.0001	<0.0001	1.6776	0.1280	0.1592
Virginia	-1.7608	<0.0001	<0.0001	6.1599	0.0011	0.0030
Washington	-1.1287	<0.0001	<0.0001	3.2867	0.0085	0.0155
West Virginia	-3.5116	0.0466	0.0574	9.1685	<0.0001	0.0001
Wisconsin	-1.6837	<0.0001	<0.0001	0.6903	0.1448	0.1758

Wyoming	-0.9690	0.0011	0.0016	0.4313	0.6323	0.6862

Note: *P* were adjusted for multiple comparisons using the Benjamini-Hochberg procedure within each stratification (FDR < 0.05). *P*_adj indicates the adjusted .

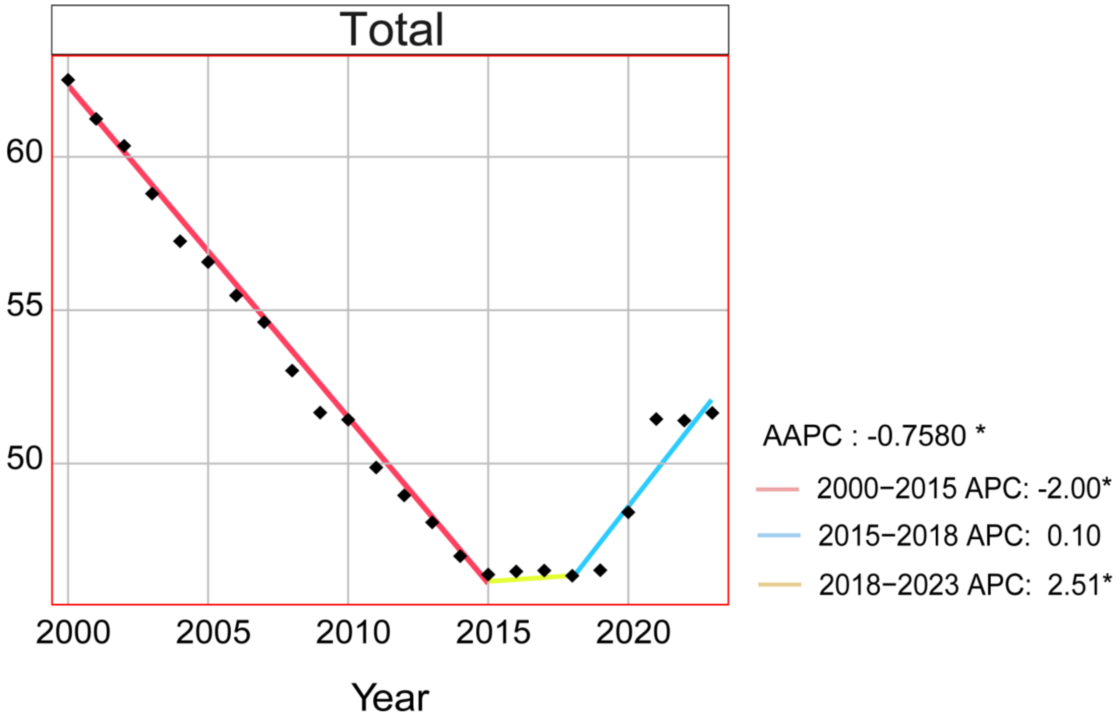

Figure S1. Trends in the ASMR attributable to comorbid cancer and cardiovascular disease using the 2010 US standard population among the total population in the United States, 2000-2023. ASMR: age-standardized mortality rates; APC: annual percent change. *: $P < 0.05$.