Excess diabetes mellitus-related deaths during the COVID-19 pandemic in the United States

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eClinicalMedicine
2022;54: 101671
Published online 23 September 2022
https://doi.org/10.1016/j.eclinm.2022.101671

Summary

Background Diabetes mellitus (DM) is a critical risk factor for severe SARS-CoV-2 infection, and SARS-CoV-2 infection contributes to worsening glycemic control. The COVID-19 pandemic profoundly disrupted the delivery of care for patients with diabetes. We aimed to determine the trend of DM-related deaths during the pandemic.

Methods In this serial population-based study between January 1, 2006 and December 31, 2021, mortality data of decedents aged ≥25 years from the National Vital Statistics System dataset was analyzed. Decedents with DM as the underlying or contributing cause of death on the death certificate were defined as DM-related deaths. Excess deaths were estimated by comparing observed versus expected age-standardized mortality rates derived from mortality during 2006-2019 with linear and polynomial regression models. The trends of mortality were quantified with joinpoint regression analysis. Subgroup analyses were performed by age, sex, race/ethnicity, and state.

Findings Among 4·25 million DM-related deaths during 2006-2021, there was a significant surge of more than 30% in mortality during the pandemic, from 106·8 (per 100,000 persons) in 2019 to 144·1 in 2020 and 148·3 in 2021. Adults aged 25-44 years had the most pronounced rise in mortality. Widened racial/ethnic disparity was observed, with Hispanics demonstrating the highest excess deaths (67·5%; 95% CI 60·9-74·7%), almost three times that of non-Hispanic whites (23·9%; 95% CI 21·2-26·7%).

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Interpretation The United States saw an increase in DM-related mortality during the pandemic. The disproportionate rise in young adults and the widened racial/ethnic disparity warrant urgent preventative interventions from diverse stakeholders.

Funding National Natural Science Foundation of China.

Keywords: Mortality; Epidemiology; Disparity; Temporal trend; Predictive analysis

Research in context

Evidence before this study

We searched PubMed for human studies that reported excess diabetes mellitus (DM)-related mortality from inception to April 3, 2022, using the search terms (((diabetes mellitus[MeSH Terms])) AND (COVID-19[MeSH Terms])) AND (mortality[MeSH Terms]), with no language restrictions. A total of 211 articles were identified. The majority of the reports focused on the association between diabetes mellitus and outcomes of SARS-CoV-2 infection, presenting their results as hazard ratios. There were two articles reporting excess DM-related mortality in the U.S. during the pandemic. However, these studies were limited by defining diabetes only as the primary contributing cause of death on the death certificate. As DM is often an underlying comorbidity rather than a direct contributor to death, underreporting is a major concern in these studies. No study so far has presented the excess DM-related death by quantifying the difference in trend between expected and observed mortality.

Added value of this study

To the best of our knowledge, this is the first study with the longest follow-up period of 15 years, which quantified the excess DM-related death during the COVID-19 pandemic compared to long-term mortality trends and investigated the disparities across age, sex, racial/ethnic groups, and state. This serial cross-sectional study of a nationwide database including more than 4·25 million DM-related deaths during 2006-2021 in the United States reported a 33% excess mortality related to DM was observed during the COVID-19 pandemic. SARS-CoV-2 infection was the major contributor to the observed excess mortality, accounting for two-thirds of the excess death. An increase in deaths was observed in all age and sex groups, but the younger adults aged 25-44 had the steepest rise in mortality, with both young males and females aged 25-44 demonstrating mortality rates 70% more than the expected values. There was a widened disparity across racial/ethnic groups during the pandemic. Unexpectedly, Hispanics had the most pronounced rise in mortality among all racial/ethnic groups, nearly three times that of non-Hispanic Whites (67·5% vs. 23·9).

Implications of all the available evidence

We quantified the distressing increase in DM-related mortality during the COVID-19 pandemic and highlighted the augmented disparities across different subgroups. DM-related mortality was disproportionately affected by the pandemic compared to all-cause mortality in the general population. The considerable contribution of SARS-CoV-2 infection to the excess DM-related mortality warrants quality-of-care surveillance to formulate healthcare improvement initiatives. Our findings have crucial implications for public health strategies in the context of any public health crisis. The widened disparities across age, racial/ethnic groups, and states have implications for policymaking to tailor performance incentives for preventative practices.

Introduction

The expanding non-communicable diseases (NCDs) epidemic including diabetes mellitus (DM) and the ongoing COVID-19 pandemic are two serious threats to public health globally.[1] In the United States (U.S.), about 11·3% of the population (37·3 million people) are living with DM.[2] The coronavirus disease 2019 (COVID-19) pandemic has had a broad and rippling effect on people's health. As a risk factor for contracting SARS-CoV-2, DM is the second most prevalent chronic disease (10%) among individuals treated for COVID-19.[3] Mounting evidence has established the relationship of DM with increased risk of severe SARS-CoV-2 infection and mortality.[3–6] A Swedish study reported that patients with type 2 diabetes had 1·4 times the likelihood of COVID-related hospitalization and intensive care unit admission, and 1·5 times the likelihood of death.[6] During the pandemic, the disruption in the healthcare system, stay-at-home mandate, and delay in clinic follow-ups has led to a decrease in outpatient visits and laboratory testing, and a rise in telemedicine visits and medication refill by mail order among patients with diabetes.[7] As a result, there have been growing reports of worsening glycemic control and a rise in episodes of diabetic ketoacidosis during the first few months of the pandemic.[8]

Excess death associated with the COVID-19 pandemic has been investigated by previous studies;[9,10] however, there have been limited reports of excess death specifically related to DM during the pandemic.[6,11,12] Most presented COVID-related mortality among people with DM as hazard ratios. So far, no study has presented the excess DM-related death by quantifying the difference in trend between expected and observed mortality. Using nationally representative data from the U.S., our study aims to examine and visualize the trend of DM-related mortality between 2006 and 2021, quantify the excess death related to DM during the COVID-19 pandemic, and investigate the disparities across age, sex, racial/ethnic groups, and state.

Methods

Study design and study population

This study is a population-based time series analysis combined with predictive analysis between January 1, 2006 and December 31, 2021 on decedents in the U.S. Data were obtained from the National Vital Statistics System (NVSS) dataset through the Center for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) website. The database contained annual death data of more than 99% of decedents in 50 U.S. states and the District of Columbia. Each record in the database represented the death data of one decedent. The data were updated through April 16, 2022. We also collected demographic data including age, sex, race/ethnicity, geographical region, and cause of death. Since all data from NVSS were publicly available and completely de-identified, the study did not seek approval from the institutional review board. The study is compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Definitions

Death data associated with DM among U.S. adults aged 25 years and above were collected from January 1, 2006 to December 31, 2021. DM was defined according to the tenth edition of the international classification of diseases (ICD-10): E10 to E14). The corresponding ICD-10 codes for the causes of death were I00-I97 for cardiovascular disease, C00-C97 for cancer, U07·1 for COVID-19, F01-F99+G00-G98 for nervous and mental diseases, and J00-J98 for respiratory disease. Deaths were attributable to COVID-19 if COVID-19 was listed as the primary cause of death on the death certificate. By the same token, deaths attributable to a certain disease were determined by the primary cause of death on the death certificate. Since DM is usually regarded as the mediator but not the disease that directly leads to death, DM-related deaths should not be restricted to only deaths listed as the primary contributing cause of death. This could result in possible underestimation of DM-related mortality, an issue encountered in Ran et al's study.[11] Our study employed a broader definition of DM-related deaths, which were defined as deaths with DM listed as the primary contributing cause of death or one of the underlying causes of death to avert bias. In other words, decedents with DM on any position of the cause of death on the death certificate were defined as DM-related death. Age stratification was defined as 25–44, 45–64, and ≥65 years, and further stratified by ten years in the appendix (p 4-5 and p 8). Race/ethnicity was defined as non-Hispanic Alaska Indians/American Natives, non-Hispanic Asians, non-Hispanic Blacks, Hispanics, and non-Hispanic Whites.

Statistical analysis

Demographic characteristics of decedents with DM were presented as frequencies with percentages. The crude mortality rate was calculated by dividing the annual DM-related deaths by the total U.S. population of the corresponding year. Next, age-standardized mortality rates (ASMR, per 100,000 persons) were calculated by multiplying the age-specific mortality rates by the number of persons in each age group of the standard population (the direct standardization method). The age structure was divided every ten years from 25 to 85+ based on the 2000 U.S. Census Standard Population.

To quantify DM-related mortality during the pandemic, we conducted a predictive analysis to determine the expected mortality rates in 2020 and 2021 using ASMR from 2006 to 2019, followed by a comparison between the observed and expected mortality rates in 2020 and 2021. We tested time series regression models including ARIMA, ARMA, linear regression, and polynomial regression according to the data distribution. The most appropriate model was then selected by referring to the model fit and the significance between the variables. For analysis that used the linear regression model, we used the ordinary least squares method to determine the expected rates and the R square to determine the goodness of fit of each model. For data with non-linear distribution, we performed polynomial regression to predict the mortality rates during the pandemic. The formula, goodness of fit, and significance of each model were shown in the appendix (p 2).

We also performed joinpoint regression analysis, a piecewise linear regression that utilizes the grid search method, combined with Monte Carlo Permutation test to determine the significance of the trend. The magnitude of the overall trends was presented by segments with annual percentage change (APC) with 95% confidence interval (CI) and their associated P values. Joinpoint regression suggests if the trend could be best explained by a single (no joinpoint) or ≥2 (≥1 joinpoint) segments. Subgroup analyses by age, sex, race/ethnicity (according to the U.S. Office of Management and Budget definition), and state were performed. Sex-specific mortality rates were examined within the age groups. Subgroups with ≤20 deaths were excluded due to the concern of unreliable estimation. In addition, we used spatial autocorrelation to evaluate the spatial distribution of DM-related mortality in the U.S. (appendix p14).

All analyses were performed using National Cancer Institute's joinpoint regression (Joinpoint Trend Analysis Software version 4·9·0·0; National Cancer Institute, Bethesda, MD), R 4·0·2 statistical software (data management), and PyCharm 3·9·0 (predictive analysis). Two-sided P value with threshold of significance at 0·05 was used.

Ethics statement
Since all data from NVSS were publicly available and completely de-identified, the study did not seek approval from the institutional review board.

Role of funding source
The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of this manuscript. JZ, YHY, FJ had full access to all the data used in this study and all authors had final responsibility for the decision to submit for publication.

Results

Decedent population and characteristics
A total of 4,243,254 DM-related deaths among adults aged 25 years and older were documented during 2006-2021. Most deaths occurred in the older age group (age 65 or older) (76%). Male (54%) outnumbered females (46%). A majority of decedents were non-Hispanic Whites (71%), followed by non-Hispanic Blacks (15%) and Hispanics (10%) (appendix p 3).

The overall ASMR (per 100,000 persons) for DM-related death decreased gradually from 2006 (116·1) to 2015 (103·9). Following a slight rise to 106·8 in 2019, there was a surge in mortality in 2020 (144·1, 33·3% excess mortality) and remained high in 2021 (148·3, 35·3% excess mortality) (Figure 1A and Table 1). The rise in excess DM-related mortality was higher than that observed for excess all-cause mortality in the total population in 2020 (15·3%, 95%CI 13·2-17·4%) and 2021 (17·8%, 95%CI 15·2-20·6%), respectively (Table 1). On joinpoint analysis, the increase for segment 2019-2021 translated to an APC of 18·7% (95%CI 15·3-22·2%), which was in stark contrast to the incremental increase between 2015 and 2019 (APC 1·8%; 95%CI 0·4-3·3%). Of note, about two-thirds of the excess DM-related deaths were associated with SARS-CoV-2 infection during the pandemic (Figure 1A).

Diabetes-related mortality by age
Figure 1 and Table 1 present the trend of DM-related mortality from 2006 to 2021, stratified by age. The highest ASMR was seen among the elderly across the entire study period. Before the pandemic, despite a significant decreasing trend of mortality in middle-aged and the elderly, there was a steady increase in DM-related mortality for younger adults (aged 25-44 years) (figure D, G, J). During the pandemic, all age groups experienced a noticeable growth in mortality. Of note, the steepest rise in mortality was seen in younger adults, as evidenced by the highest excess death (+54·0% in 2020 and +77·2% in 2021) and an APC of 37·1% (95%CI 26·2-48·9%) (Table 1 and figure D). Despite harboring the highest disease burden, the elderly showed the smallest difference in mortality between the pre-pandemic and pandemic periods. Furthermore, all-cause ASMR, APC, and excess deaths for DM-related mortality stratified by age in ten years wide were shown in the appendix (p 4-5 and p 8).

Diabetes-related mortality by sex
Mortality stratified by sex showed a persistently higher mortality burden for males compared to females during the study period (Figure 1B, C). Before the pandemic, females exhibited a steeper decline in mortality (APC -1·9%; 95%CI -2·2-[-1·6]%) between 2006 and 2015 than males (APC -0·9%; 95%CI -1·1-[-0·6]%). During the pandemic, the mortality rates for both sex groups soared. The observed mortality rates are higher than the corresponding expected mortality, around 30% versus 40% for males and females, respectively (Table 1).

In age- and sex-stratified analyses (Figure 1, Table 2, and appendix p 9-10), a high excess death was observed across all sex-age subgroups during the pandemic. The greatest increase was noted in both younger males (75·8%) and females (78·2%) with the mortality nearly double that of the expected rates in 2021. For the sharp rise during the COVID-19 pandemic, joinpoint analysis revealed an APC of 36·2% (95%CI 24·9-48·5%) for young females and 37·2% (95%CI 24·9-50·8) for young males. Those over 65 of both sex groups saw the smallest percent increase in mortality across the three age groups during the pandemic.

Diabetes-related mortality by race/ethnicity
Before the pandemic, the overall decline of mortality was similar for all racial/ethnic groups except for non-Hispanic American Indians/Alaska Natives (Table 1 and appendix p 11). In 2020, all racial/ethnic groups saw a difference between observed and expected mortality, and a widening disparity was found. The sharpest rise in mortality was found in Hispanics (+67·5%), followed by non-Hispanic Blacks (+58·7%), non-Hispanic Asians (+50·1%), and non-Hispanic AI/AN, while the lowest APC was found in non-Hispanic Whites

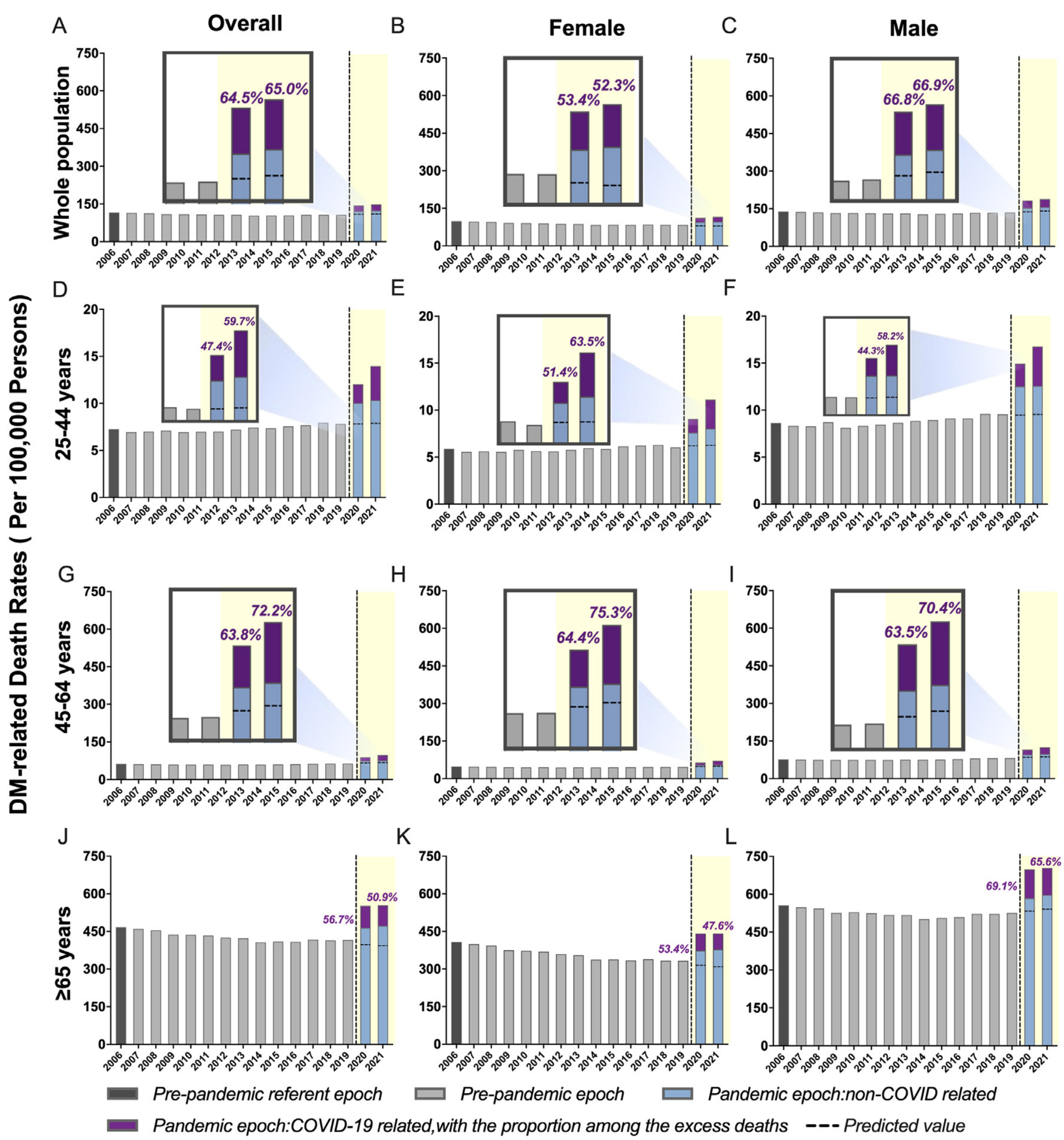

Figure 1. Temporal trends in diabetes mellitus (DM)-related deaths and excess deaths during the COVID-19 pandemic, by sex, further stratified by age. (A) Overall population, (B) Female, (C) Male, (D) Aged at 25–44 years old in overall population, (E) Aged at 25–44 years old in female, (F) Aged at 25–44 years old in male, (G) Aged at 45–64 years old in overall population, (H) Aged at 45–64 years old in female, (I) Aged at 45–64 years old in male, (J) Aged more than 65 years old in overall population, (K) Aged more than 65 years old in female, (L) Aged more than 65 years old in male. DM-related deaths rates (per 100,000 persons) increased across all subgroups during the pandemic. The observed mortality rates were above the predicted mortality rates (dashed horizontal line). Depicted by purple bars, DM-related deaths associated with COVID-19 was almost or more than 50% across the subgroups during pandemic. COVID-19 related decedent was defined as DM-related death with COVID-19 recorded as one of the causes on the death certificate.

(+23·9%). The mortality increase among Hispanics was nearly three times that of non-Hispanic Whites. Different racial/ethnic groups had similar trends in mortality among males and females (Table 2).

Cause of death related to diabetes mellitus

Figure 2 displays the multiple causes of mortality for decedents with DM-related death. Before the pandemic, two major underlying causes of death were

	Age-standardized mortality rate (per 100,000 persons)							Trend segment	
	2006 (Pre-Pandemic Referent Epoch)	2020 (Pandemic Epoch 1)			2021 (Pandemic Epoch 2)			Year	APC [95%CI]
		Observed	Predicted [95%CI]	% Increase [‡]	Observed	Predicted [95%CI]	% Increase [‡]		
Multiple cause of death[∫]	116·1	144·1	108·1	**+33·3**	148·3	109·6	**+35·3**	2006—2015	-1·3** [-1·5 to -1·0]
	[115·6-116·5]	[143·7-144·6]	[106·1-111·1]	**[30·5-36·2]**	[147·9 - 148·8]	[107·1-112·2]	**[31·7-39·0]**	2015—2019	1·8* [0·4 to 3·3]
								2019—2021	18·7** [15·3 to 22·2]
Multiple cause of death[∬]	116·1	123·1	108·1	**+13·8**	126·3	109·6	**+15·2**	2006—2014	-1·4** [-1·7 to -1·1]
(non-COVID-19)	[115·6-116·5]	[122·6-123·5]	[106·1-110·1]	**[11·4-16·4]**	[125·8 - 126·7]	[107·1-112·2]	**[12·1-18·4]**	2014—2019	0·9* [0·0 to 1·8]
								2019—2021	9·2** [6·2 to 12·3]
Underlying cause of death[∭]	36·3	38·1	34·1	**+11·7**	38·4	34·8	**+10·4**	2006—2009	-3·6* [-7·1 to -0·1]
	[36·0-36·5]	[37·8-38·3]	[32·9-35·3]	**[7·2-16·7]**	[38·2 - 38·7]	[33·2-36·4]	**[4·9-16·5]**	2009-2018	0·0 [-0·8 to 0·8]
								2018—2021	6·1** [2·4 to 10·1]
Age									
25-44 years	7·3	12·0	7·8	**+54·0**	14·0	7·9	**+77·2**	2006—2019	1·1** [0·7 to 1·5]
	[7·1-7·4]	[11·8-12·3]	[7·6-8·0]	**[46·6-61·8]**	[13·7 - 14·2]	[7·6-8·1]	**[68·4-86·6]**	2019—2021	37·1** [26·2 to 48·9]
45-64 years	62·2	89·3	65·9	**+35·4**	97·7	67·7	**+44·3**	2006—2014	-0·6** [-0·9 to -0·2]
	[61·7-62·8]	[88·7-89·9]	[65·1-66·8]	**[32·7-38·2]**	[97·0 - 98·3]	[66·5-68·8]	**[41·0-47·8]**	2014—2019	2·4** [1·3 to 3·5]
								2019—2021	24·6** [20·5 to 28·9]
≥65 years	467·4	552·2	397·2	**+39·0**	554·3	393·0	**+41·1**	2006—2015	-1·6** [-1·9 to -1·3]
	[465·2-469·6]	[550·2-554·2]	[385·9-408·6]	**[34·6-43·6]**	[552·3 - 556·3]	[380·4-405·6]	**[36·2-46·3]**	2015—2019	1·5 [-0·2 to 3·2]
								2019—2021	16·5** [12·7 to 20·4]
Sex									
Female	99·1	112·4	79·8	**+40·9**	115·8	78·6	**+47·4**	2006—2015	-1·9** [-2·2 to -1·6]
	[98·5-99·7]	[111·9-113·0]	[77·4-82·2]	**[36·2-45·9]**	[115·3 - 116·4]	[73·6-83·5]	**[42·0-53·2]**	2015—2019	1·0 [-0·7 to 2·7]
								2019—2021	17·5** [13·6 to 21·6]
Male	139·0	183·1	137·8	**+32·9**	188·4	140·3	**+34·2**	2006—2015	-0·9** [-1·1 to -0·6]
	[138·2-139·8]	[182·3-183·9]	[135·5-140·1]	**[30·2-35·7]**	[187·6 - 189·2]	[137·3-143·3]	**[30·9-37·7]**	2015—2019	2·4** [1·1 to 3·6]
								2019—2021	18·8** [15·8 to 21·8]
Race and ethnicity[#]									
Non-Hispanic Whites	105·3	124·9	100·8	**+23·9**	N/A	102·2	N/A	2006—2018	-0·7** [-1·0 to -0·4]
	[104·8-105·8]	[124·4-125·4]	[99·0-102·6]	**[21·2-26·7]**		[99·9-104·6]		2018—2020	12·7** [7·2 to 18·5]
Non-Hispanic Blacks	202·2	240·9	151·8	**+58·7**	N/A	148·7	N/A	2006—2018	-2·1** [-2·5 to -1·7]
	[200·0-204·4]	[239·0-242·8]	[145·5-158·1]	**[51·1-66·9]**		[141·7-155·7]		2018—2020	20·7** [12·5 to 29·5]
Hispanics	141·8	196·2	117·1	**+67·5**	N/A	117·8	N/A	2006—2018	-1·9** [-2·3 to -1·5]
	[139·6-144·0]	[194·5-198·0]	[113·3-120·9]	**[60·9-74·7]**		[112·9-122·7]		2018—2020	26·9** [18·7 to 35·7]
Non-Hispanic AI/AN					N/A		N/A		

Table 1 *(Continued)*

	Age-standardized mortality rate (per 100,000 persons)							Trend segment	
	2006 (Pre-Pandemic Referent Epoch)	2020 (Pandemic Epoch 1)			2021 (Pandemic Epoch 2)			Year	APC [95%CI]
		Observed	Predicted [95%CI]	% Increase ‡	Observed	Predicted [95%CI]	% Increase ‡		
	191·5	275·2	184·0	**+49·5**		183·6		2006–2018	-0·4 [-0·9 to 0·1]
	[182·3–200·7]	[267·1–283·2]	[178·5-189·6]	**[40·9-58·7]**		[177·5-189·8]		2018–2020	17·9** [8·9 to 27·7]
Non-Hispanic Asians	89·5	110·5	73·6	**+50·1**	N/A	72·6	N/A	2006–2018	-1·5** [-2·0 to -1·1]
	[87·0–91·9]	[108·7–112·2]	[70·6-76·5]	**[42·1-58·9]**		[69·3-75·8]		2018–2020	18·8** [10·4 to 27·9]
Reference									
Total population	1183·8	1254·4	1088·3	**+15·3**	1287·6	1093·0	+17·8	2006–2019	-0·6** [-0·8 to -0·4]
	[1182·2–1185·3]	[1253·1–1255·8]	[1069·9-1106·6]	**[13·2-17·4]**	[1286·2-1289·0]	[1069·2-1116·8]	[15·2-20·6]	2019–2021	10·9** [6·5 to 15·5]

***Table 1*: All-cause age-standardized mortality rate and annual percentage change (APC) for Diabetes Mellitus (DM)-related mortality in U.S. adults by age group, sex, and race and ethnicity, 2006-2021.**

Note:**p* value<0·05.

***p* value<0·01.

ʃMultiple cause of death: Deaths caused by various causes including DM.

ʃʃExcluded decedents with COVID-19 infection as the underlying cause of death.

ʃʃʃUnderlying cause of death: The disease or injury which initiated the train of events leading directly to death. Namely decedents with DM listed as the primary cause of death.

‡Denotes the % of increase from predicted to observed value.

#Race and ethnicity from 2006 to 2020.

Non-Hispanic AI/AN:Non-Hispanic American Indian/Alaska Native.

	Age-standardized mortality rate (per 100,000 persons)							Trend segment	
	2006 (Pre-Pandemic Referent Epoch)	2020 (Pandemic Epoch 1)			2021 (Pandemic Epoch 2)			Year	APC [95%CI]
		Observed	Predicted [95%CI]	% Increase ‡	Observed	Predicted [95%CI]	% Increase ‡		
Female									
25-44 years	5·9	9·1	6·2	**+46·1**	11·1	6·2	**+78·2**	2006—2019	0·9** [0·4 to 1·4]
	[5·6-6·1]	[8·8-9·4]	[6·0-6·4]	**[37·1-56·1]**	[10·8-11·4]	[6·0-6·5]	**[66·9-89·9]**	2019—2021	36·2** [24·9 to 48·5]
45-64 years	48·6	64·3	48·0	**+33·9**	71·4	49·2	**+45·1**	2006—2019	-0·1 [-0·5 to 0·4]
	[47·9-49·3]	[63·6-65·1]	[47·0-49·1]	**[29·6-38·4]**	[70·6-72·2]	[47·9-50·5]	**[39·7-50·7]**	2019—2021	28·3** [17·5 to 40·0]
≥65 years	407·6	440·9	314·8	**+40·1**	441·1	308·7	**+42·9**	2006—2016	-2·1** [-2·3 to -1·8]
	[405·0-402·1]	[438·5-443·3]	[305·4-324·2]	**[35·3-45·2]**	[438·7-443·4]	[298·4-319·1]	**[37·5-48·6]**	2016—2019	1·5 [-2·0 to 5·2]
								2019—2021	15·8** [11·7 to 19·9]
Non-Hispanic Whites	87·5	94·9	76·3	**+24·4**	N/A	76·8	N/A	2006—2018	-1·4** [-1·7 to -1·1]
	[86·9-88·1]	[94·3-95·5]	[74·4-78·2]	**[20·6-28·4]**		[74·4-79·3]		2018—2020	11·9** [6·1 to 18·0]
Non-Hispanic Blacks	184·9	201·6	136·2	**+48·0**	N/A	136·5	N/A	2006—2018	-2·7** [-3·1 to -2·4]
	[182·3-187·5]	[199·3-203·8]	[132·5-139·8]	**[42·5-53·9]**		[131·7-141·3]		2018—2020	19·6** [12·3 to 27·4]
Hispanics	125·7	155·5	89·9	**+72·9**	N/A	87·7	N/A	2006—2018	-2·4** [-2·8 to -2·0]
	[123·0-128·4]	[153·4-157·6]	[86·3-93·5]	**[64·1-82·5]**		[83·7-91·6]		2018—2020	24·6** [16·1 to 33·7]
Non-Hispanic AI/AN	177·9	222·7	150·4	**+48·1**	N/A	148·7	N/A	2006—2018	-1·3** [-1·7 to -0·9]
	[166·2-189·5]	[213·0-232·4]	[145·7-155·1]	**[37·3-59·5]**		[143·5-153·9]		2018—2020	17·0** [9·0 to 25·5]
Non-Hispanic Asians	77·5	85·0	59·4	**+43·0**	N/A	58·2	N/A	2006—2018	-2·0** [-2·5 to -1·5]
	[74·5-80·5]	[82·9-87·0]	[56·6-62·2]	**[33·4-53·7]**		[55·1-61·3]		2018—2020	16·2** [6·7 to 26·5]
Male									
25-44 years	8·6	14·9	9·5	**+58·1**	16·8	9·5	**+75·8**	2006—2019	1·2** [0·7 to 1·7]
	[8·3-8·9]	[14·6-15·3]	[9·1-9·8]	**[49·1-67·8]**	[16·4-17·2]	[8·9-10·2]	**[65·4-86·9]**	2019—2021	37·2** [24·9 to 50·8]
45-64 years	76·7	115·5	84·8	**+36·3**	125·3	87·1	**+43·9**	2006—2014	-0·2 [-0·5 to 0·1]
	[75·8-77·6]	[114·5-116·6]	[83·2-86·3]	**[33·4-39·3]**	[124·2-126·4]	[85·7-88·5]	**[40·4-47·4]**	2014—2019	2·6** [1·7 to 3·5]
								2019—2021	24·5** [21·1 to 28·0]
≥65 years	555·9	698·7	532·5	**+31·2**	704·0	540·7	**+30·2**	2006—2015	-1·1** [-1·4 to -0·8]
	[552·1-559·8]	[695·2-702·2]	[521·5-543·5]	**[27·9-34·7]**	[700·5-707·5]	[526·3-555·0]	**[26·2-34·4]**	2015—2019	2·1* [0·6 to 3·6]
								2019—2021	16·6** [13·2 to 20·1]
Non-Hispanic Whites	129·0	161·5	130·7	**+23·6**	N/A	133·2	N/A	2006—2018	-0·3* [-0·6 to -0·0]
	[128·1-129·9]	[160·7-162·4]	[128·8-132·6]	**[21·2-26·1]**		[130·7-135·6]		2018—2020	13·1** [7·7 to 18·8]
Non-Hispanic Blacks	226·4	295·8	203·1	**+45·6**	N/A	207·0	N/A	2006—2018	-1·4** [-1·8 to -0·9]
	[222·7-230·2]	[292·4-299·1]	[197·4-208·8]	**[40·0-51·5]**		[199·6-214·4]		2018—2020	21·6** [12·3 to 31·7]
Hispanics	162·5	246·1	143·1	**+71·9**	N/A	144·3	N/A	2006—2018	-1·4** [-1·8 to -1·0]
	[158·8-166·1]	[243·1-249·1]	[138·4-147·9]	**[64·4-79·9]**		[138·2-150·4]		2018—2020	28·6** [20·2-37·5]

Table 2 *(Continued)*

	2006 (Pre-Pandemic Referent Epoch)	2020 (Pandemic Epoch 1) Observed	2020 Predicted [95%CI]	2020 % Increase ‡	2021 (Pandemic Epoch 2) Observed	2021 Predicted [95%CI]	2021 % Increase ‡	Trend segment Year	APC [95%CI]
Non-Hispanic AI/AN	208·9	337·4	223·8	**+50·7**	N/A	225·0	N/A	2006–2018	0·4 [-0·4 to 1·2]
	[193·7-224·0]	[324·1-350·6]	[212·8-234·9]	**[38·0-64·8]**		[212·8-237·2]		2018–2020	18·7* [3·9 to 35·5]
Non-Hispanic Asians	105·4	142·9	97·3	**+46·9**	N/A	98·7	N/A	2006–2018	-1·1** [-1·6 to -0·7]
	[101·2-109·5]	[139·8-146·0]	[92·9-101·6]	**[37·6-57·1]**		[93·1-104·4]		2018–2020	20·8** [12·1 to 30·1]

Age-standardized mortality rate (per 100,000 persons)

***Table 2:* All-cause age- and sex-standardized mortality rate and annual percentage change (APC) for Diabetes Mellitus (DM)-related mortality in U.S. adults with Diabetes Mellitus (DM), by age group and race and ethnicity, 2006–2021.**

Note: * p value <0·05.

** p value <0·01.

‡Denotes the % of increase from predicted to observed value.

Race and ethnicity from 2006 to 2020.

cardiovascular disease and diabetes, accounting for more than 60% of deaths (Figure 2A). During the COVID-19 pandemic, SARS-CoV-2 infection accounted for about two-thirds of excess deaths (Figures 1A and 2B). We also demonstrated increased mortality rates in all top causes of death, with nervous and mental disease- and cancer-related mortality having the highest increased percent difference (appendix p 6).

Diabetes-related mortality by region

Significant state-level variation of DM-related mortality was observed during the COVID-19 pandemic (Figures 3A, 3B). Appendix (p 7) highlighted the states with the highest and lowest mortality in 2020, and appendix (p 12) depicted the state-level mortality in descending order and differences in mortality between 2019–2020 and 2020–2021 (p 13). From 2020 to 2021, while Oklahoma, Mississippi and Kentucky remained the top 3 states with the highest mortality throughout the pandemic, we saw a shift of highest mortality from clusters in the plains and the District of Columbia to Texas and some states in the Southeast. On the other hand, Connecticut and Massachusetts continued to have the lowest mortality. Between 2019 and 2020, all states suffered from an increase in mortality, with the most extreme found in the District of Columbia, followed by Mississippi and Oklahoma. In addition to marking the highest mortality, Oklahoma and Southeastern states like Kentucky and Mississippi still suffered the most significant rise in mortality between 2020 and 2021, while about a third of the states already saw a decline. Between 2020 and 2021, Rhode Island and the District of Columbia then demonstrated the largest drop among all states. In addition, spatial autocorrelation was used to assess the spatial distribution of DM-related ASMR in 2020 and 2021. The Midwest (South Dakota, Nebraska) and South (Oklahoma, Texas, and Mississippi) of the U.S. formed a high-high cluster of DM-related mortality, whereas aggregation of regions with low-low ASMR clustered in the Northeast of the U. S. in 2021 (local Moran analysis, $p < 0.001$) (Figure 3D).

Discussion

This temporal trend study showed a 33% excess mortality related to DM during the COVID-19 pandemic in the U.S. SARS-CoV-2 infection contributed to around two-thirds of the excess mortality. DM-related mortality rates in 2021 in both young males and females (aged 25 to 44 years) were about 70% more than the expected rates, and the younger adults saw the steepest increasing trend when compared to those over 65 and the middle-aged group. An accentuated disparity across racial/ethnic groups during the pandemic was also observed. Interestingly, among all racial/ethnic groups, the increasing trend was highest in Hispanics, nearly three

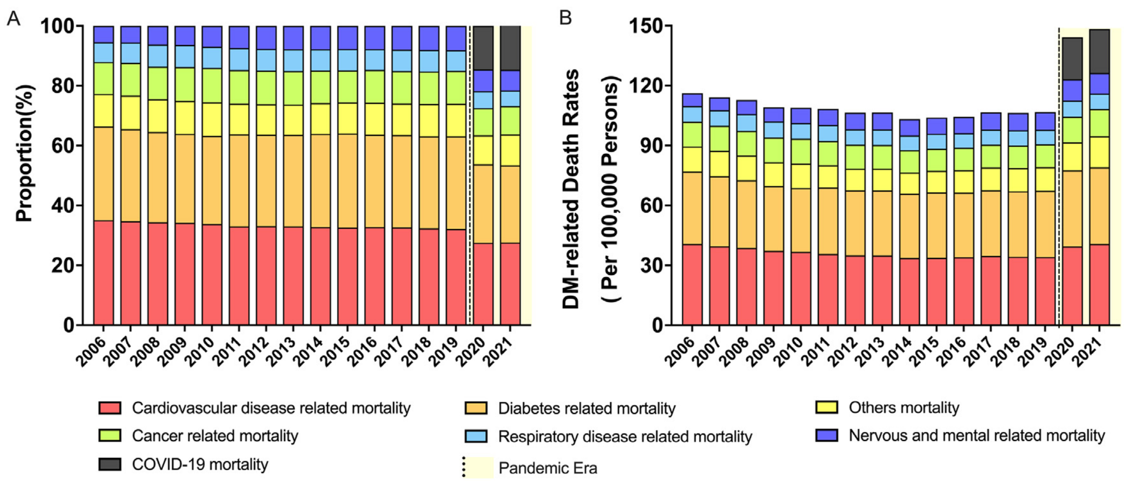

Figure 2. Causes of deaths related to diabetes mellitus (DM) presented by (A) the proportion and (B) the age-standardized mortality rate (ASMR) of different causes of death. The change in proportion of causes of death after the emergence of SARS-CoV-2 infection and the absolute change of all causes of death were shown.

times that of Non-Hispanic Whites (67·5% vs. 23·9%), contrary to the "Hispanic Health paradox" as previously reported,[13] which refers to paradoxically better health outcomes among Hispanics in the United States compared to non-Hispanic Whites, despite having more disadvantaged socioeconomic profiles. Lastly, we presented the state-level variation in DM-related death during the pandemic. Taken together, we demonstrated that the distressing increase in diabetes-related mortality during the pandemic could be explained by the SARS-CoV-2 infection and disparities, and that DM-related mortality was disproportionately affected by the pandemic compared to all-cause mortality in the general population.

There are several explanations that may account for the substantial excess death related to DM during the COVID-19 pandemic. The bi-directional relationship between DM and COVID-19 has been well-established. Diabetes mellitus is a critical risk factor for severe SARS-CoV-2 infection, intensive care unit admission, and mortality,[4–6] and SARS-CoV-2 infection contributes to insulin resistance and worsening glycemic control through intricate pathways.[14,15] During the pandemic, the stay-at-home mandate resulted in substantial physical inactivity, more TV-viewing time, less healthy dietary habits, and more psychological stress, which in turn exacerbates metabolic diseases such as diabetes and leads to a greater risk of COVID-19-related hospitalization.[16] In addition, diabetes-related outpatient visits and laboratory testing fell noticeably,[7,17] signifying a gap in healthcare delivery for DM patients. Congruent with our results, a nationwide cohort study in the UK found a similar increase in mortality among people with type 2 diabetes at the start of the pandemic.[17] Compared to this study, our study provided a more comprehensive overview of diabetes-related mortality over the course of 15 years. Additionally, we were able to highlight and quantify the difference in trends before and during the pandemic with trend segment analysis and reporting of APC, as well as variations in mortality by age, sex, race/ethnicity, and state.

Through the collective effort in health policy and clinical care, both the U.S. and multi-country analyses have demonstrated a continued decline of all-cause mortality among individuals with diabetes over the past two decades, up until 2017.[18–20] However, after adding the most updated data, we showed that the overall DM-related death increased slightly but without statistical significance between 2015 and 2019.

Before the pandemic, contrary to the overall downward trend in mortality from 2006–2019, we saw a steady rise among individuals with diabetes mellitus aged 25 to 64, in line with previous literature.[19] Ali et al.'s nationwide study from 1999 through 2010 found that adults younger than 44 years of age were less likely to meet glycemic control targets and participate in preventative practices than older adults.[21] Younger adults were also reported to have a higher additional mortality risk from diabetes and higher rates of death from hyperglycemic crisis.[19]

Upon examination of diabetes-related mortality stratified by age, adults aged 65 or older demonstrated the highest mortality rate in our study, both before and during the pandemic. Age is an important risk factor for type 2 diabetes, and the elderly are more likely to require care in the intensive care unit or die from SARS-CoV-2 infection.[3,22] Noticeably, during the COVID-19 pandemic, we saw a surge in mortality, which translates to a higher additional mortality risk, in patients between the age of 25 to 44 rather than in the oldest age group, which is in line with previous studies.[23–25] For the older population, many other medical conditions besides diabetes contribute to a patient's

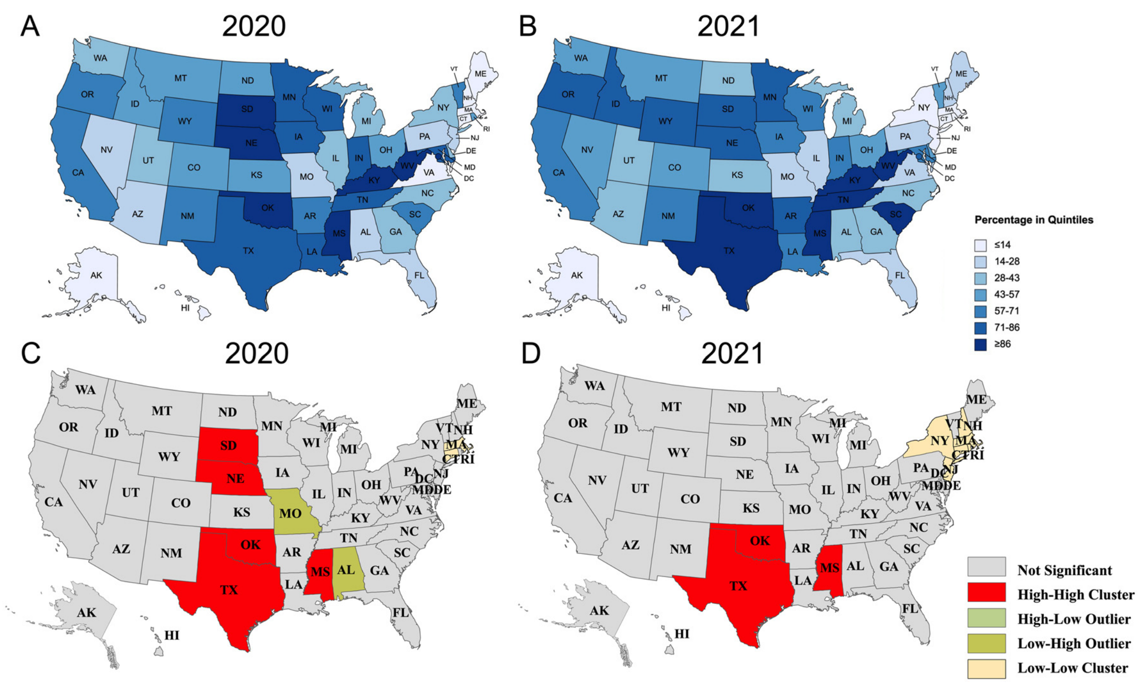

Figure 3. State-level variation and local Moran-spatial autocorrelation analysis of diabetes mellitus (DM)-related deaths during the COVID-19 Pandemic. State-level Variation of mortality in 2020 (A) and 2021 (B); Local Moran-spatial autocorrelation analysis of DM-related deaths in both 2020 (C) and 2021 (D) showed a positive spatial autocorrelation with high DM-related mortality clustered in the Eastern U.S.

death, thereby mitigating the effect of diabetes on mortality.[24] This result is further corroborated by the fact that an overwhelming majority of young people with diabetes avoided or delayed medical care during the pandemic.[8,26] Younger adults also reported difficulty in access to medications, and were less likely to adhere to COVID-19 prevention measures and have health insurance. Of note, even with the implementation of nationwide COVID-19 vaccination measures, we still saw an obvious increase in mortality from 2020 to 2021 in younger and middle-aged adults, whereas the elderly saw a slight decline.

Disparities in mortality were also observed between genders and ethnicities. Although previous literature reported a higher risk of COVID-19-related morbidity and mortality in men than in women, possibly due to biological factors (e.g. augmented immune response) and behavioral factors (e.g. more smoking and alcohol use),[27]our study exhibited a comparable rising trend during the pandemic. Furthermore, our study extends findings from prior work that described the disproportionate burden of morbidity and mortality in the Blacks and Latino populations compared to the White population,[12,28] and highlighted an accentuated racial/ethnic disparity in DM-related death during the pandemic. In our study, non-Hispanic AI/AN and Blacks showed the highest *absolute* mortality rates as in the pre-pandemic era, and during the pandemic they experienced a significantly higher *relative* increase in excess DM-related mortality than non-Hispanic Whites.

These observations may be attributable to the deep-rooted health and socioeconomic inequality among racial/ethnic minorities. Racial/ethnic minorities were also found to have a higher prevalence of diabetes and obesity, poorer glycemic control, more sedentary lifestyle, and higher occupational risks.[13,28,29]

To our knowledge, our study is the first to report all DM-related mortality at the state level before and during the pandemic. There was a significant inter-state variation in DM-related mortality, ranging from 324·1 (per 100,000 persons) for Oklahoma to 71·6 for Connecticut in 2021. Oklahoma, Mississippi and Kentucky remained the top 3 states with the highest mortality during the pandemic, and several states in the Southeast and the Southwest saw higher mortality. Several explanations could account for the discrepancies, including the severity of the pandemic, baseline medical resources, vaccination coverage, and socioeconomic characteristics such as household income. Consistent with our findings, even before the pandemic, previous work by Alva et al. demonstrated hotspots of highest DM-related mortality in Oklahoma, most of the Southeast except for Virginia, followed by some states in the Great Lakes.[30]

DM-related mortality reflects the magnitude of COVID-19 burden on patients with DM and is to some extent associated with the quality of care for DM.

Attention should also be brought to states with higher mortality to identify areas in need of improvement for DM care. Despite having fewer underlying health conditions, young adults were most affected by the pandemic among all age groups. Future research may focus on the investigation of potential mechanisms underlying these findings. Our findings have crucial implications for public health strategies in the context of any public health crisis. They may help policymakers with quality-of-care surveillance to formulate healthcare improvement initiatives and tailor performance incentives for preventive practices. Studies with detailed demographic, clinical characteristics, and delivery of diabetes care are also needed to identify the risk factors and vulnerable populations to inform policy change in preparation for the new normalcy.

A key strength of our study was the long-term longitudinal analysis of data from an authoritative national center which captures more than 99% of deaths in 51 U.S. states from Jan 2006 through Dec 2021. Second, our study design allows investigation into the excess death related to DM during the pandemic by including DM as both the primary cause of death and one of the causes of death on the death certificate, which is a clear distinction from previous work.[10] Furthermore, predictive analyses quantified the excess death attributable to the COVID-19 pandemic, and results were further consolidated by robust subgroup analyses by demographic, clinical, and geographic characteristics.

This study has limitations. The major limitation is that the ascertainment of DM status could not be directly obtained by identifying DM as a cause of death on the death certificate. In the U.S., underreporting of diabetes on the death certificate is common, in part because DM is often an underlying comorbidity rather than a direct contributor to death. Less than 50% of decedents with DM actually had DM listed among the causes of death on the death certificate.[31–33] Based on previous studies, reporting of diabetes anywhere on the death certificate did not change over time from 1970-2007.[31,33] However, the association between both diabetes and obesity and COVID-19-related mortality, established very early on in the pandemic, may have served to increase awareness and therefore increase the ascertainment of diabetes status on death certificates during the pandemic. A proportion of the apparent 33% increase in diabetes-related deaths may have therefore been attributable to this factor.

On the contrary, during the pandemic, when clinical loading increased, the underreporting and misclassification of DM-related deaths may be more pronounced. However, all these underscore the importance of this issue we are investigating because even with potential underreporting, the excess deaths related to DM during the pandemic was very high. Second, the component of race/ethnicity in 2021 was different from 2020 and before (with an additional subgroup named "more than one race" in 2021). Therefore, we only presented 2020 data in race/ethnicity. Lastly, the COVID-19 pandemic began in the U.S. in March 2020. Thus, 2020 includes three months where SARS-CoV-2 infections were not contributing to mortality. For simplicity, mortality rates were presented by the year so the impact of COVID-19 on the mortality rate in 2020 might be underestimated.

In conclusion, our study quantified the excess DM-related death during the COVID-19 pandemic. There was a 33% excess mortality related to DM during the pandemic, and two-thirds of which were attributable to SARS-CoV-2 infection. The increase in DM-related mortality, disproportionate rise in young adults, and the widened disparities across age, sex, racial/ethnic subpopulations and states warrant interventions from diverse stakeholders.

Contributors

All authors: Data interpretation and approval the manuscript. FL, XG, XH, YHY, YW, FJ: Study design. XDS, JZ: Method design. FL, XG, XH, JZ, JL, NG, LZ, YHY, FJ: Data analysis. FL, XG, AHH, JL, YHY: Drafting of the manuscript. JZ, YJ, MGK, LZ, FJ: Critical review of the manuscript. YW: Critical revision of the manuscript. JZ, YHY, FJ: Study conception and study supervision.

Data sharing statement

The NVSS can be accessed through this website: https://wonder.cdc.gov/mcd-icd10-provisional.html.

Declaration of interests

Professor Ji is the speaker of Gilead Sciences, MSD and Ascletis, and he is the consulting and advisory board of Gilead Sciences and MSD. All other authors declare no competing interests.

Acknowledgements

The study was supported by National Natural Science Foundation of China (11971375). The funding body did not play any roles in the design, conduction or reporting of the study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101671.

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