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Acquisition, analysis, or interpretation of data: Wang, Luo, Dugas, Werner.
Drafting of the manuscript: Wang, Luo, Dugas, Gao, Agarwal.
Critical revision of the manuscript for important intellectual content: Wang, Luo, Agarwal, Werner.
Statistical analysis: Wang, Luo.
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Leading Causes of Death in the US During the COVID-19 Pandemic, March 2020 to October 2021

In 2020, heart disease and cancer were the leading causes of death in the US, accounting for 1.29 million deaths, followed by COVID-19, accounting for 350 000 deaths.[1-3] The pandemic may also have indirectly led to increases in other causes of death, including heart disease, diabetes, Alzheimer disease, and unintentional injuries.[2,4] We examined the leading causes of death in the US, overall and in various age groups, from March 2020 to October 2021.

Methods | We obtained final national death certificate data for 2020 and provisional data for 2021 from the Centers for Disease Control and Prevention (accessed May 5, 2022[5]). We excluded data more recent than October 2021 because they were incomplete. We determined the 5 leading causes of death by year and age group, and compared the period March to December 2020 with the period January to October 2021. Because the data are publicly available, the study did not require institutional review board review.

Results | From March 2020 to October 2021, heart disease (20.1%), cancer (17.5%), COVID-19 (12.2%), accidents (6.2%), and stroke (4.7%) were the most common causes of death in the US. There were 2.875 million deaths in March to December 2020 and 2.855 million deaths in January to October 2021; the 5 leading causes of death were the same in each year. Among those older than 1 year, the number of deaths increased across age groups.

Deaths from cancer, heart disease, and COVID-19 accounted for the largest number of deaths in every group aged 55 years and older (**Table**, **Figure**). The leading 3 causes of death in these age groups were the same in 2020 and 2021. Among people aged 85 years and older, COVID-19 was ranked as the second leading cause of death in 2020 (110 000 deaths, 12.8% of deaths), and third in 2021 (69 000, 8.9% of deaths). Among those aged 45 to 54 years, COVID-19 was the fourth leading cause of death in 2020 (17 000 deaths, 10.4% of deaths), following heart disease, cancer, and accidents; in 2021, however, it was the leading cause of death (30 000 deaths, 16.8% of deaths).

In both time periods, accidents accounted for the largest number of deaths in every age group 1 to 44 years. Compared with 2020, COVID-19 increased from the fifth (6100 deaths) to the second leading cause of death (13 000 deaths) among those aged 35 to 44 years in 2021, became the fourth leading cause of death in 2021 among those aged 25 to 34 years (5000 deaths), and those aged 15 to 24 years (1100 deaths).

Discussion | From March 2020 to October 2021, COVID-19 accounted for 1 in 8 deaths in the US and was a top 5 cause of death in every age group aged 15 years and older. Cancer and heart disease deaths exceeded COVID-19 deaths overall and in most age groups, whereas accidents were the leading cause of death among those aged 1 to 44 years. Compared with the 2020 time period, deaths from COVID-19 in the 2021 time period decreased in ranking among those aged 85 years or older but increased in ranking among those aged 15 to 54 years, and became the leading cause of death among those aged 45 to 54 years.

The increased ranking of COVID-19 as a leading cause of death in some age groups is consistent with a downward age shift in the distribution of COVID-19 deaths in the US in 2021 compared with 2020,[6] perhaps driven by higher COVID-19 vaccination rates in 2021 in the oldest age groups.

The pandemic also has had indirect effects on other causes of death in the US. From 2019 to 2020, death rates increased for heart disease, accidents, stroke, Alzheimer disease, and diabetes.[2] Potential explanations are fear of accessing health care or misattribution of COVID-19 deaths to other causes.[4] Accidental deaths (including drug overdoses and unintentional alcohol poisoning), assault, and suicide remain major causes of death in the US, particularly in younger age groups; the pandemic may have contributed to some of these deaths.

Our analysis was limited by potential misclassification of the cause of death and incomplete death data for 2021, although we included a lag of 6 months to increase the

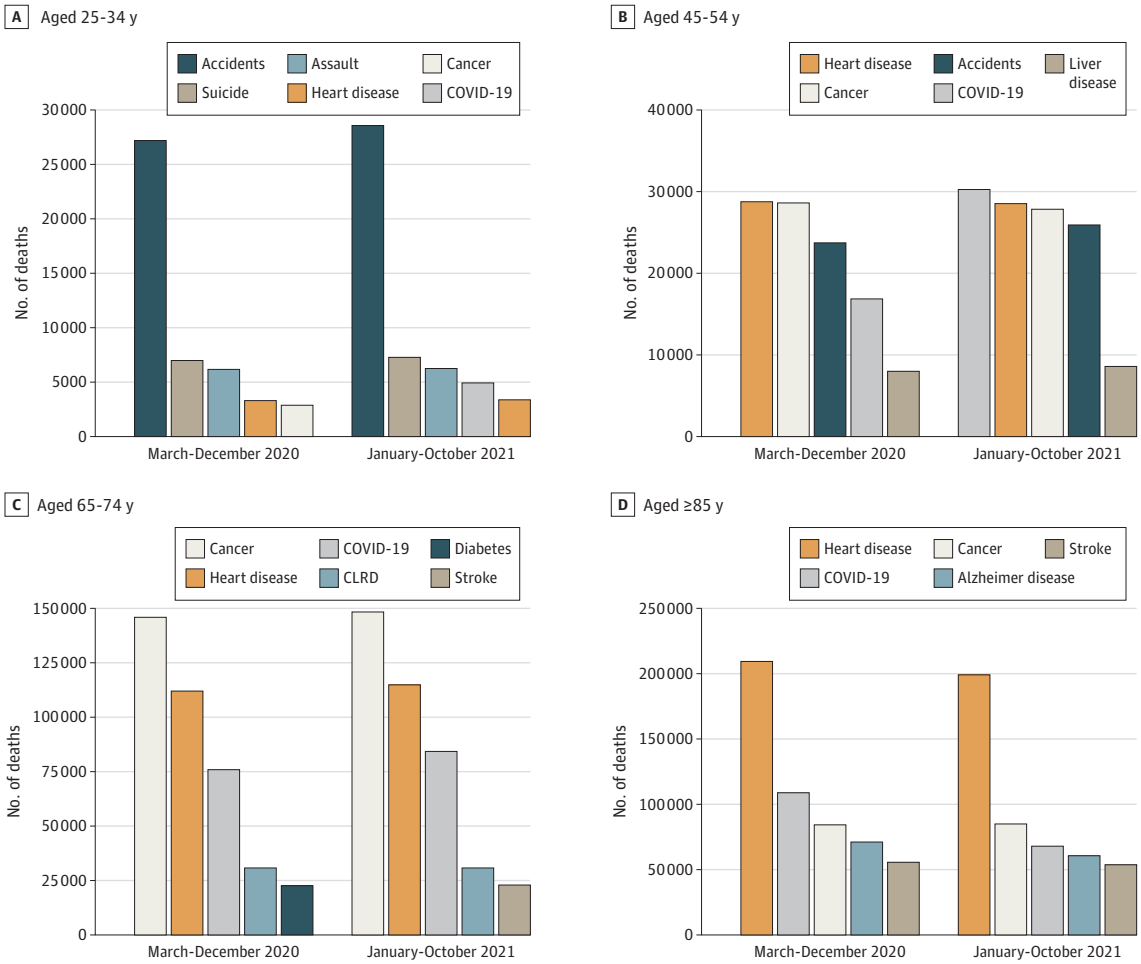
Table. Five Leading Causes of Death by Age Group From March to December 2020 and January to October 2021

	March to December 2020						January to October 2021					
Age group	Total	Cause 1	Cause 2	Cause 3	Cause 4	Cause 5	Total	Cause 1	Cause 2	Cause 3	Cause 4	Cause 5
<1 y												
Cause		Congenital malformations	Low birth weight	SIDS	Accidental deaths[a]	Pregnancy complications		Congenital malformations	Low birth weight	SIDS	Accidental deaths[a]	Pregnancy complications
No.	16 000	3400	2600	1100	1000	910	17 000	3300	2400	1100	1100	920
1-4 y												
Cause		Accidental deaths[a]	Congenital malformations	Assault	Cancer	Heart disease		Accidental deaths[a]	Congenital malformations	Assault	Cancer	Heart disease
No.	2900	1000	300	250	250	90	3100	1100	320	250	240	100
5-14 y												
Cause		Accidental deaths[a]	Cancer	Suicide	Assault	Congenital malformations		Accidental deaths[a]	Cancer	Suicide	Assault	Congenital malformations
No.	4700	1400	660	490	410	260	4900	1500	670	510	390	280
15-24 y												
Cause		Accidental deaths[a]	Assault	Suicide	Cancer	Heart disease		Accidental deaths[a]	Assault	Suicide	COVID-19	Cancer
No.	31 000	13 000	5600	5100	1100	730	32 000	13 000	5500	5400	1100	1100
25-34 y												
Cause		Accidental deaths[a]	Suicide	Assault	Heart disease	Cancer		Accidental deaths[a]	Suicide	Assault	COVID-19	Heart disease
No.	63 000	27 000	7100	6200	3400	3000	69 000	29 000	7400	6300	5000	3500
35-44 y												
Cause		Accidental deaths[a]	Heart disease	Cancer	Suicide	COVID-19		Accidental deaths[a]	COVID-19	Heart disease	Cancer	Suicide
No.	90 000	27 000	10 000	8900	6100	6100	104 000	30 000	13 000	11 000	9300	6500
45-54 y												
Cause		Heart disease	Cancer	Accidental deaths[a]	COVID-19	Chronic liver disease		COVID-19	Heart disease	Cancer	Accidental deaths[a]	Chronic liver disease
No.	163 000	29 000	29 000	24 000	17 000	8000	179 000	30 000	29 000	28 000	26 000	8700
55-64 y												
Cause		Cancer	Heart disease	COVID-19	Accidental deaths[a]	CLRD		Cancer	Heart disease	COVID-19	Accidental deaths[a]	Diabetes
No.	375 000	92 000	74 000	42 000	25 000	15 000	395 000	90 000	74 000	60 000	28 000	15 000
65-74 y												
Cause		Cancer	Heart disease	COVID-19	CLRD	Diabetes		Cancer	Heart disease	COVID-19	CLRD	Stroke
No.	574 000	146 000	112 000	76 000	31 000	23 000	597 000	149 000	115 000	85 000	31 000	23 000
75-84 y												
Cause		Heart disease	Cancer	COVID-19	CLRD	Stroke		Heart disease	Cancer	COVID-19	CLRD	Stroke
No.	699 000	139 000	136 000	97 000	40 000	36 000	681 000	138 000	136 000	82 000	38 000	37 000
≥85 y												
Cause		Heart disease	COVID-19	Cancer	Alzheimer	Stroke		Heart disease	Cancer	COVID-19	Alzheimer	Stroke
No.	857 000	210 000	110 000	85 000	72 000	56 000	774 000	200 000	85 000	69 000	61 000	55 000
Total												
Cause		Heart disease	Cancer	COVID-19	Accidental deaths	Stroke		Heart disease	Cancer	COVID-19	Accidental deaths	Stroke
No.	2 875 000	580 000	501 000	351 000	172 000	133 000	2 855 000	571 000	502 000	346 000	185 000	134 000

Abbreviations: CLRD, chronic lower respiratory disease; SIDS, sudden infant death syndrome.

[a] Accidental deaths include transportation accidents, drug overdoses, alcohol-related deaths, and other accidental deaths.

Figure. Leading Causes of Death in the US, March to December 2020 and January to October 2021



Bars indicate the number of deaths for each of the 5 most common causes of death by age group for those aged 25 to 34 years, 45 to 54 years, 65 to 74 years, and those aged 85 years and older. Colors are consistent by cause across age groups; however, scales differ. COVID-19 indicates coronavirus disease 2019; CLRD: chronic lower respiratory disease.

completeness of the provisional data. Moreover, because our analysis only extended through October 2021, it does not include deaths that occurred during the Omicron wave of the pandemic of late 2021 and early 2022.

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COMMENT & RESPONSE

Considerations for Generic-to-Generic Levothyroxine Switching

To the Editor I am thankful to Brito et al[1] for considering the clinical effect of switching US Food and Drug Administration–approved generic levothyroxine products in their recent comparative effectiveness research study. The authors included adults who filled generic levothyroxine preparations from any of the 3 most common manufacturers: Mylan, Sandoz, and Lannett. All 3 of these preparations are AB1 rated, as they meet bioequivalence requirements to an AB1-rated reference drug. The Mylan and Sandoz products were rated to Lannett's Unithroid. However, Mylan was not compared with the Sandoz product, so they are not technically therapeutically equivalent. Pharmacists may view all AB1-rated products as equivalent. All 3 products have a common microcrystalline cellulose excipient, likely resulting in similar dissolution characteristics and bioavailability. The reader should not extend this apparent clinical interchangeability beyond these 3 similar generics, as the authors acknowledged.

The effect of residual endogenous thyroid function on these outcomes is a shared concern.[1] Less than 2% of patients had athyreosis. This would be most applicable to the nearly one-third of patients who likely had no underlying hypothyroidism[2] and were included in the nearly 60% ingesting no more than 50 µg and the 87% with a daily dosage less than 100 µg. I believe this residual function results in a buffering effect on clinical outcomes, making it difficult to detect differences in bioavailability.

On the basis of clinical experiences following substitution of levothyroxine products during manufacturing disruptions[3] and introduction of reformulated (pharmacokinetically equivalent) products,[4] the European Thyroid Association[5] recommends caution, counseling, and follow-up testing in patients who have switched from 1 product to another.

I agree that the results of the study by Brito et al[1] are not applicable to switching from brand-name to generic products. The aforementioned limitations should have softened the conclusion that switching generic levothyroxine products is unlikely to have substantial implications for treatment effects. When patients report that their dispensed LT4 tablets look different, I will be moderately reassured if they are on low doses of the products addressed by Brito et al. I will still offer a worried patient a thyrotropin check and follow-up visit in 6 weeks to allay their anxiety, maintaining the patient-physician relationship.

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To the Editor In their recent comparative effectiveness research article, Brito et al[1] compared thyrotropin (TSH) levels in patients prescribed generic levothyroxine products who continued taking the same generic product with those who switched among generic products. From an initial population of 15 829 patients in a large administrative database, mean TSH levels and the proportion of patients with markedly abnormal TSH levels 6 weeks to 12 months after the index date of initial TSH assessment did not significantly differ in 2780 propensity-matched pairs of switchers and nonswitchers. This is an important study using levothyroxine therapy to address the broader question of whether generic products are interchangeable.

Although mean TSH levels and the proportion of deviating TSH levels would not be expected to statistically significantly differ with various generic products, those mean parameters do not provide information about the variations in a given individual. Such individual variations are more clinically relevant than population analyses. Brito et al[1] also should have reported on the intraindividual changes in TSH levels and, if possible, in thyroxine levels as well as the proportion of patients with new deviating TSH levels in switchers and nonswitchers. In addition, a Bland-Altman plot[2] would have more effectively provided information about individual outliers. In patients receiving a daily levothyroxine dosage of more than 100 µg, standard deviations of TSH level and TSH level change from baseline were more than 2-fold greater in switchers than in nonswitchers. This subgroup of patients may have experienced larger variations of TSH and/or thyroxine levels following generic switches compared with patients receiving lower doses.

It is time for all studies on generic products, including bioequivalence studies, to report both mean and individual data. The former is important from a public health perspective, but the latter is more relevant from a medical and therapeutic perspective.