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Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021

*GBD 2021 Causes of Death Collaborators**

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Summary

Background Regular, detailed reporting on population health by underlying cause of death is fundamental for public health decision making. Cause-specific estimates of mortality and the subsequent effects on life expectancy worldwide are valuable metrics to gauge progress in reducing mortality rates. These estimates are particularly important following large-scale mortality spikes, such as the COVID-19 pandemic. When systematically analysed, mortality rates and life expectancy allow comparisons of the consequences of causes of death globally and over time, providing a nuanced understanding of the effect of these causes on global populations.

Methods The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 cause-of-death analysis estimated mortality and years of life lost (YLLs) from 288 causes of death by age-sex-location-year in 204 countries and territories and 811 subnational locations for each year from 1990 until 2021. The analysis used 56 604 data sources, including data from vital registration and verbal autopsy as well as surveys, censuses, surveillance systems, and cancer registries, among others. As with previous GBD rounds, cause-specific death rates for most causes were estimated using the Cause of Death Ensemble model—a modelling tool developed for GBD to assess the out-of-sample predictive validity of different statistical models and covariate permutations and combine those results to produce cause-specific mortality estimates—with alternative strategies adapted to model causes with insufficient data, substantial changes in reporting over the study period, or unusual epidemiology. YLLs were computed as the product of the number of deaths for each cause-age-sex-location-year and the standard life expectancy at each age. As part of the modelling process, uncertainty intervals (UIs) were generated using the 2·5th and 97·5th percentiles from a 1000-draw distribution for each metric. We decomposed life expectancy by cause of death, location, and year to show cause-specific effects on life expectancy from 1990 to 2021. We also used the coefficient of variation and the fraction of population affected by 90% of deaths to highlight concentrations of mortality. Findings are reported in counts and age-standardised rates. Methodological improvements for cause-of-death estimates in GBD 2021 include the expansion of under-5-years age group to include four new age groups, enhanced methods to account for stochastic variation of sparse data, and the inclusion of COVID-19 and other pandemic-related mortality—which includes excess mortality associated with the pandemic, excluding COVID-19, lower respiratory infections, measles, malaria, and pertussis. For this analysis, 199 new country-years of vital registration cause-of-death data, 5 country-years of surveillance data, 21 country-years of verbal autopsy data, and 94 country-years of other data types were added to those used in previous GBD rounds.

Findings The leading causes of age-standardised deaths globally were the same in 2019 as they were in 1990; in descending order, these were, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, and lower respiratory infections. In 2021, however, COVID-19 replaced stroke as the second-leading age-standardised cause of death, with 94·0 deaths (95% UI 89·2–100·0) per 100 000 population. The COVID-19 pandemic shifted the rankings of the leading five causes, lowering stroke to the third-leading and chronic obstructive pulmonary disease to the fourth-leading position. In 2021, the highest age-standardised death rates from COVID-19 occurred in sub-Saharan Africa (271·0 deaths [250·1–290·7] per 100 000 population) and Latin America and the Caribbean (195·4 deaths [182·1–211·4] per 100 000 population). The lowest age-standardised death rates from COVID-19 were in the high-income super-region (48·1 deaths [47·4–48·8] per 100 000 population) and southeast Asia, east Asia, and Oceania (23·2 deaths [16·3–37·2] per 100 000 population). Globally, life expectancy steadily improved between 1990 and 2019 for 18 of the 22 investigated causes. Decomposition of global and regional life expectancy showed the positive effect that reductions in deaths from enteric infections, lower respiratory infections, stroke, and neonatal deaths, among others have contributed to improved survival over the study period. However, a net reduction of 1·6 years occurred in global life expectancy between 2019 and 2021, primarily due to increased death rates from COVID-19 and other pandemic-related mortality. Life expectancy was highly variable between super-regions over the study period, with southeast Asia, east Asia, and Oceania gaining 8·3 years (6·7–9·9) overall, while having the smallest reduction in life expectancy due to COVID-19 (0·4 years). The largest reduction in life expectancy due to COVID-19 occurred in Latin America and the Caribbean (3·6 years). Additionally, 53 of the 288 causes of death were highly concentrated in locations with less than 50% of the global population as of 2021,

and these causes of death became progressively more concentrated since 1990, when only 44 causes showed this pattern. The concentration phenomenon is discussed heuristically with respect to enteric and lower respiratory infections, malaria, HIV/AIDS, neonatal disorders, tuberculosis, and measles.

Interpretation Long-standing gains in life expectancy and reductions in many of the leading causes of death have been disrupted by the COVID-19 pandemic, the adverse effects of which were spread unevenly among populations. Despite the pandemic, there has been continued progress in combatting several notable causes of death, leading to improved global life expectancy over the study period. Each of the seven GBD super-regions showed an overall improvement from 1990 and 2021, obscuring the negative effect in the years of the pandemic. Additionally, our findings regarding regional variation in causes of death driving increases in life expectancy hold clear policy utility. Analyses of shifting mortality trends reveal that several causes, once widespread globally, are now increasingly concentrated geographically. These changes in mortality concentration, alongside further investigation of changing risks, interventions, and relevant policy, present an important opportunity to deepen our understanding of mortality-reduction strategies. Examining patterns in mortality concentration might reveal areas where successful public health interventions have been implemented. Translating these successes to locations where certain causes of death remain entrenched can inform policies that work to improve life expectancy for people everywhere.

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Introduction

For more than three decades, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has been systematically and comprehensively recording and analysing causes of human death stratified by age, sex, and time across the world.[1,2] This information has been used to guide policy solutions, reduce modifiable risk factors, monitor and evaluate national and sub-national health interventions, and ultimately improve health recommendations at both regional and local levels.[1] Assessing trends in cause-specific mortality is essential to inform health policy that must continuously evolve to account for rapid changes to the global health landscape, such as the COVID-19 pandemic.[3] Comprehensive updates to levels and trends in causes of death give insight into emerging global health challenges and can facilitate benchmarking in the case of a new pandemic or other events that can lead to a staggering loss of life. Therefore, documenting novel changes to mortality, such as an emerging pandemic, in real time, is important.

Causes of death are not uniformly distributed between populations; rather, large variability in the leading causes often reflects important social and geographical differences.[4] These differences can include access to and quality of health care, timeliness of health system responsiveness, and exposure to causes that are endemic to specific geographical locations.[4] Mortality patterns continually evolve, as some areas become successful in their reduction efforts, whereas other causes persist within specific locations. The past 30 years have seen improvements among many causes of mortality, some of which have considerably narrowed in geographical range and are now concentrated within smaller areas worldwide. This change enables us to identify the resulting areas of concentrated mortality—areas where deaths from that cause are occurring within a limited subset of the global population. Our analysis provides an opportunity to answer important epidemiological questions that have been at the forefront of global and public health discourse—eg, which causes have contributed to the largest increase or decrease in life expectancy, which locations are experiencing greater concentrations of preventable causes of death, and how has COVID-19 and other pandemic-related mortality (OPRM) affected life expectancy and the overall fatal burden of diseases? Regional variation in many of the leading causes of death remains evident in these most recent estimates, representing important opportunities for creating tailored health policy to improve disparities and alleviate concentrations of mortality.

GBD 2021 provides an updated, comprehensive set of the fatal burden of disease summarised with cause-specific mortality metrics and years-of-life-lost (YLLs) metrics for 288 causes by age and sex across 204 countries and territories from 1990 to 2021, an update from the previously published estimates covering 1990–2019. In this study, we present mortality concentrations and a decomposition analysis of life expectancy due to different causes of death and illustrate the impact of causes of death on global, regional, and country-specific life expectancy, as well as highlighting locations that are most affected by concentrated geographical mortality burden. As with previous iterations of GBD, this cycle incorporates newly available data sources and improved methodological approaches to re-estimate the entire time series, providing updated estimates that supersede all previous GBD cause-of-death publications. GBD 2021 includes an estimation of several different models for disease and injury outcomes. This manuscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.[5]

Research in context

Evidence before this study

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has provided regular updates on the complex patterns and trends in population health around the world since the first GBD publication in 1993. With each subsequent iteration, there have been important methodological updates, new datasets included, and an expanded list of causes, risk factors, and locations for which estimates of the burden of disease are produced. In 1993, mortality and years of life lost (YLLs) were reported for 107 categories of diseases that covered all possible causes of death, for eight regions. In the last GBD cycle—GBD 2019—estimates of mortality and YLLs were produced for 286 causes of death in 204 countries and territories, including all WHO member states, and for subnational locations in 21 countries and territories, for every year from 1990 to 2019. Although many groups have reported on national-level, cause-specific mortality and other population-health metrics, including the WHO World Health Statistics reports, GBD is the most detailed and transparent research effort to date. Further, estimates of COVID-19-related deaths in 2020 and 2021 have been reported by several sources, including GBD studies that have quantified excess mortality due to the pandemic within a subset of GBD locations. However, no previous publications have quantified the effect of COVID-19 on life expectancy, while considering the full spectrum of disease mortality over the past three decades, across all countries and territories. This study presents, for the first time, 288 causes of death from 1990 to 2021, complementary to the all-cause mortality findings presented in the GBD 2021 Demographics analysis. Combined, these studies provide a comprehensive view of all-cause and cause-specific mortality from 1990 to 2021.

Added value of this study

Alongside the all-cause mortality and life-expectancy assessments in companion publications for GBD 2021, this analysis delineates cause-specific mortality and its effect on life expectancy. This study includes a comprehensive decomposition analysis elucidating the primary cause of death influencing life expectancy on a global, regional, and national level. Additionally, we present causes of death and YLLs for all countries and territories, providing policy makers with valuable insights into variations in cause-specific mortality. This study is also the first of its kind to publish 2021 estimates of COVID-19-related deaths and YLLs for 204 countries and territories in the context of the global burden of disease. Although other publications have estimated deaths due to COVID-19, those deaths have not previously been compared with deaths from other causes. By modelling COVID-19 deaths within a hierarchy of mutually exclusive and collectively exhaustive causes of death, this study provides policy makers with information that is essential for setting health priorities around the world. To obtain more comprehensive insights from life expectancy, it is necessary to break it down into age-specific mortality, which is influenced by cause-specific mortality rates. We examined the effect of COVID-19 and other causes of death on life expectancy by decomposing death counts into different cause-specific mortality rates across various dimensions, including country or territory, region, super-region, and five distinct time periods: 1990–2000, 2000–2010, 2010–2019, 2019–2021, and 1990–2021. We could therefore systematically calibrate the COVID-19 pandemic against other causes of mortality over the period 1990–2021. Finally, our study identified several causes of death that exhibited increased geographical concentration over time—ie, causes with a disproportionate impact within a specific geographical area compared with the rest of the global observations. This analysis provides policy makers important information on regional variation and inequalities in cause-specific mortality. Also new to GBD 2021, we report on 12 additional causes of death: COVID-19 and other pandemic-related mortality, pulmonary arterial hypertension, and nine cancer types—hepatoblastoma, Burkitt lymphoma, other non-Hodgkin lymphoma, eye cancer, retinoblastoma, other eye cancers, soft tissue and other extraosseous sarcomas, malignant neoplasm of bone and articular cartilage, and neuroblastoma and other peripheral nervous-cell tumours. Granularity of the estimation of deaths in children younger than 5 years was enhanced by the addition of four new age groups: 1–5 months, 6–11 months, 12–23 months, and 2–4 years.

Implications of all the available evidence

Our study provides a full analysis of causes of death worldwide and across time, alongside the changing patterns in life expectancy precipitated by those causes. Increasing geographical concentration of mortality was observed for many causes of death, highlighting disparities between regions and substantial differences in cause-specific contributions to life expectancy. On a global scale, this information provides an opportunity to examine whether reductions in mortality were resilient to the onset of a novel pandemic. On a regional level, the estimates generated by our study provide important detail on the evolving impact of causes of death among countries, allowing crucial insight into differential success by geography, time, and cause. The comprehensive nature of GBD 2021 cause-of-death estimation provides valuable opportunities to learn from mortality gains and losses, helping to accelerate progress in reducing mortality.

Methods

Overview

In GBD 2021, we produced estimates for each epidemiological quantity of interest for 288 causes of death by age-sex-location-year for 25 age groups from birth to 95 years and older; for males, females, and both sexes combined; in 204 countries and territories grouped into 21 regions and seven super-regions; and for every year from 1990 to 2021. GBD 2021 also includes subnational analyses for 21 countries and territories

(appendix 1 section 2.1). An international network of collaborators provides, reviews, and analyses the available data to generate these metrics; GBD 2021 drew on the expertise of more than 11 000 collaborators from more than 160 countries and territories.

The methods used to generate these estimates closely followed those for GBD 2019.[6] These methods have been extensively peer reviewed over previous rounds of the GBD study[4,6–9] and as part of the peer-review process for GBD 2021. Here, we provide an overview of the methods with an emphasis on the main methodology changes since GBD 2019; a comprehensive description of the analytical methods for GBD 2021 is provided in appendix 1. Detailed descriptions of analytical methods and models for each cause of death are also available in a searchable online tool.

The GBD 2021 cause-of-death estimates described here include cause-specific mortality and the premature death metric (YLLs). We calculated YLLs as the number of deaths for each cause-age-sex-location-year multiplied by the standard life expectancy at each age (appendix 1 section 6.3). Standard life expectancy is calculated from the lowest age-specific mortality rate between countries.[10] Briefly, we estimated cause-specific death rates for 209 causes using the Cause of Death Ensemble model (CODEm), and we used alternative strategies to model causes with little data, substantial changes in reporting over the study period, or unusual epidemiology. The modelling strategy used for all causes of death can be found in appendix 1 (table S10). CODEm is a modelling tool developed specifically for GBD that assesses the out-of-sample predictive validity of different statistical models and covariate permutations and then combines the results from those assessments to produce cause-specific estimates of the burden of mortality. Methodological improvements for cause-of-death estimates in the present round of estimation focused on several key areas. First, cause-of-death data were updated to include age data for the following age groups younger than 5 years: 1–5 months, 6–11 months, 12–23 months, and 2–4 years. Second, we implemented enhanced methods to account for stochastic variation in cause-of-death data and improve the estimation of small cause fractions present in less common causes of death. Third, we added 199 new country-years of vital registration cause-of-death data, 5 country-years of surveillance data, 21 country-years of verbal autopsy data, and 94 country-years of other data types. Lastly, we incorporated COVID-19 and OPRM, which includes excess mortality associated with the COVID-19 pandemic, excluding deaths from COVID-19, lower respiratory infections, measles, malaria, and pertussis.

The GBD disease and injury hierarchy

GBD classifies diseases and injuries into a hierarchy with four levels that include both fatal and non-fatal causes. Level 1 causes include three broad aggregate categories (communicable, maternal, neonatal, and nutritional [CMNN] diseases; non-communicable diseases [NCDs]; and injuries) and Level 2 disaggregates those categories into 22 clusters of causes, which are further disaggregated into Level 3 and Level 4 causes. At the most detailed level, 288 fatal causes are estimated. For a full list of causes of death by level, see appendix 1 (table S2). For GBD 2021, we separately report on 12 causes of death for the first time: COVID-19, OPRM, pulmonary arterial hypertension, and nine cancer types: hepatoblastoma, Burkitt lymphoma, other non-Hodgkin lymphoma, eye cancer, retinoblastoma, other eye cancers, soft tissue and other extraosseous sarcomas, malignant neoplasm of bone and articular cartilage, and neuroblastoma and other peripheral nervous cell tumours.

See **Online** for appendix 1

For a **searchable repository of cause-specific model details** see https://www.healthdata.org/gbd/methods-appendices-2021

Data sources, processing, and assessing for completeness

For the **GBD data sources** see https://ghdx.healthdata.org/gbd-2021/sources

The GBD 2021 cause-of-death database included data sources identified in previous rounds of estimation in addition to 9248 new sources (appendix 1 table S5). We included multiple data types to capture the widest array of information, including vital registration and verbal autopsy for all 288 causes as well as survey, census, surveillance, cancer registry, police records, open-source databases, and minimally invasive tissue sampling. To standardise these data so that they can be compared by cause, age, sex, location, and time, we applied a set of data processing corrections. First, deaths with insufficient age data to estimate the GBD age groups or missing age and sex data underwent age and sex splitting to assign GBD age groups as well as sex (appendix 1 section 3.5). Additionally, garbage codes, which are non-specific, implausible, or intermediate, rather than underlying cause of death codes from the International Classification of Diseases, were redistributed to appropriate targets to assign the underlying cause of death.[11] We excluded data sources with more than 50% of all deaths assigned to major garbage codes (class 1 or class 2 garbage codes) in a given year for a specific location (location-year) to mitigate the potential for bias from these sources (appendix 1 section 3.7). For GBD 2021, we established a buffer system so that location-years that were included in the previous GBD cycle would not be dropped from the current cycle as long as less than 55% of all deaths were assigned to major garbage codes. This 5% buffer ensured greater consistency in data source inclusion from one cycle to the next.

Assessing data completeness illustrates the coverage from a data source on overall mortality for the country. Vital registration and verbal autopsy data completeness—a source-specific estimate of the percentage of total cause-specific deaths that are reported in a given location and year—was assessed by location-year, and sources with less than 50% completeness were excluded. We excluded 142 country-years of data because of completeness. As with garbage codes, we used a

5% buffer so that sources included in the previous GBD cycle would not be excluded from the current cycle if they had at least 45% completeness, allowing us to retain 24 country-years that had previously been dropped. We then multiplied the estimated all-cause mortality for each age-sex-location-year by the cause fraction for the corresponding age-sex-location-year to adjust all included sources to 100% completeness. Verbal autopsy and vital registration data availability, completeness, and quality rating for each location-year are available in appendix 1 (section 3), as well as full details on all data processing corrections.

Improvements in GBD 2021 to cause of death data processing and estimation

Adjustments for stochastic variation

In GBD 2021, we made two primary improvements to the methods used to reduce stochastic variation, most affecting causes of death with small sample sizes. First, we updated the Bayesian algorithm used in the noise reduction of these data to improve the preservation of real trends in data with large sample sizes, and imparted additional information from regional trends for data with small sample sizes. Second, the non-zero floor, a method that addresses distorted data shapes and nonsensical trends caused by small numbers when transformed to log space, was updated to be time-invariant and independent of demographic inputs. The full details of these two key improvements, as well as other improvements that address stochastic variation, can be found in appendix 1 (section 3.14).

COVID-19 and OPRM estimation

We derived COVID-19 and OPRM estimates from an analysis of the overall excess mortality due to the COVID-19 pandemic from January 1, 2020, to December 31, 2021. Full details of the estimation of excess mortality, COVID-19 deaths, and OPRM are provided in appendix 1 (section 5). To estimate excess mortality, we first developed a database of all-cause mortality by week and month after accounting for reporting lags, anomalies such as heat waves, and under-registration of deaths. Next, we developed an ensemble model to predict expected deaths in the absence of the COVID-19 pandemic for the years 2020 and 2021. In location and time combinations with data used for these models, we estimated excess mortality as observed mortality minus expected mortality. To estimate excess mortality for location-years without data, we developed a statistical model to directly predict the excess mortality due to COVID-19, using covariates that pertained to both the COVID-19 pandemic and background population-health-related metrics at the population level before SARS-CoV-2 emerged. Uncertainty was propagated through each step of this estimation procedure.[12]

To produce the final estimates of COVID-19 deaths used in GBD 2021, we used a counterfactual approach. The counterfactual estimates the number of deaths if infection detection rates were at the highest observed value for each location-year. Using the ratio of counterfactual over estimated excess deaths and the ratio of reported COVID-19 deaths over excess deaths, we calculated the ratio of total COVID-19 deaths over reported COVID-19 deaths and multiplied this figure by the number of reported COVID-19 deaths for our final estimates of COVID-19 deaths.[12]

To account for increases in excess mortality in 2020 and 2021 that could not be attributed to particular causes, we introduced a residual cause, OPRM. We identified four causes of death—lower respiratory infections, measles, malaria, and pertussis—as related to the COVID-19 pandemic and having reliable enough estimates to not contribute to OPRM. Thus, we calculated OPRM as the difference between excess mortality and the sum of deaths due to COVID-19 and these four causes.[12]

Presentation of cause-specific mortality estimates

Cause-specific mortality estimates for 2021 are given in death counts and age-standardised rates per 100 000 population, calculated using the GBD standard-population structure.[10] For changes over time, we present percentage changes over the period 1990–2021, and annualised rates of change as the difference in the natural log of the values at the start and end of the time interval divided by the number of years in the interval. We computed uncertainty intervals (UIs) for all metrics using the mean estimate across 1000 draws (appendix 1 sections 2–3), and 95% UIs are given as the 2·5th and 97·5th percentiles of that distribution.

Life-expectancy decomposition

The objective of life-expectancy decomposition is to analyse the difference in life expectancy by age and location, quantifying contributions from specific causes (appendix 1 section 7). We examined temporal trends in causes over continuous time periods across different locations. We aimed to identify the effect of causes of death on life expectancy by using three main decomposition steps. For this study, we investigated the top-20 Level 2 and Level 3 GBD causes contributing to change in life expectancy. The remaining causes were then combined as "other communicable and maternal disorders" or "other NCDs". The first step involved decomposing the difference in life expectancy by age. We calculated age-specific contributions to understand the variation in life expectancy across different age groups. In the second step, each age-specific contribution was further decomposed into cause-age-specific contributions. This analysis allowed for the identification of the specific causes of death that contributed to the differences in life expectancy within each age group. Finally, we aggregated the cause-age-specific contributions across age groups to produce cause-specific contributions to the overall difference

in life expectancy. This aggregation provided a comprehensive understanding of how different causes of death contributed to the observed variations in life expectancy. By applying this decomposition approach, we gain insights into the relative effect of different causes of death on changes in life expectancy by age and location.

Calculation of mortality concentration

Concentrated causes in GBD refer to causes that exhibit a disproportionate impact in a specific geographical subset of the data compared with the rest of the global observations. In GBD 2021, we used two different methods to identify these concentrated causes: coefficient of variation and mortality concentration.

Coefficient of variation

For each GBD cause, we calculated a coefficient of variation using standard statistical methods. This measure assesses the variability of a population relative to its mean.[13] The observations considered for this calculation were national, age-standardised, both-sex mortality rates, using the mean mortality rate between 2019 and 2021. Causes with larger coefficients of variation have data that are less centred around the mean and indicate a greater likelihood of a concentrated cause.

Mortality concentration

To identify concentrations of mortality—geographical locations or groups of locations with populations that are disproportionately affected by a particular cause—we first calculated the total number of all-age, both-sex deaths in 2021 by cause in each of the 811 subnational locations and sorted these locations by number of deaths in descending order. We then calculated the cumulative percentage of deaths by dividing location-specific cumulative deaths by the number of global deaths for each cause. When the cumulative percentage reached or exceeded 90% for a given cause, we divided the population of the geographical subset included in that cumulative percentage by the total global population in 2021, using population estimates from the GBD population model described in previous publications.[10,12] This identification of geographical subsets that contain at least 90% of deaths from a given cause but represent a comparatively small share of the global population was used to identify potential inequalities in the

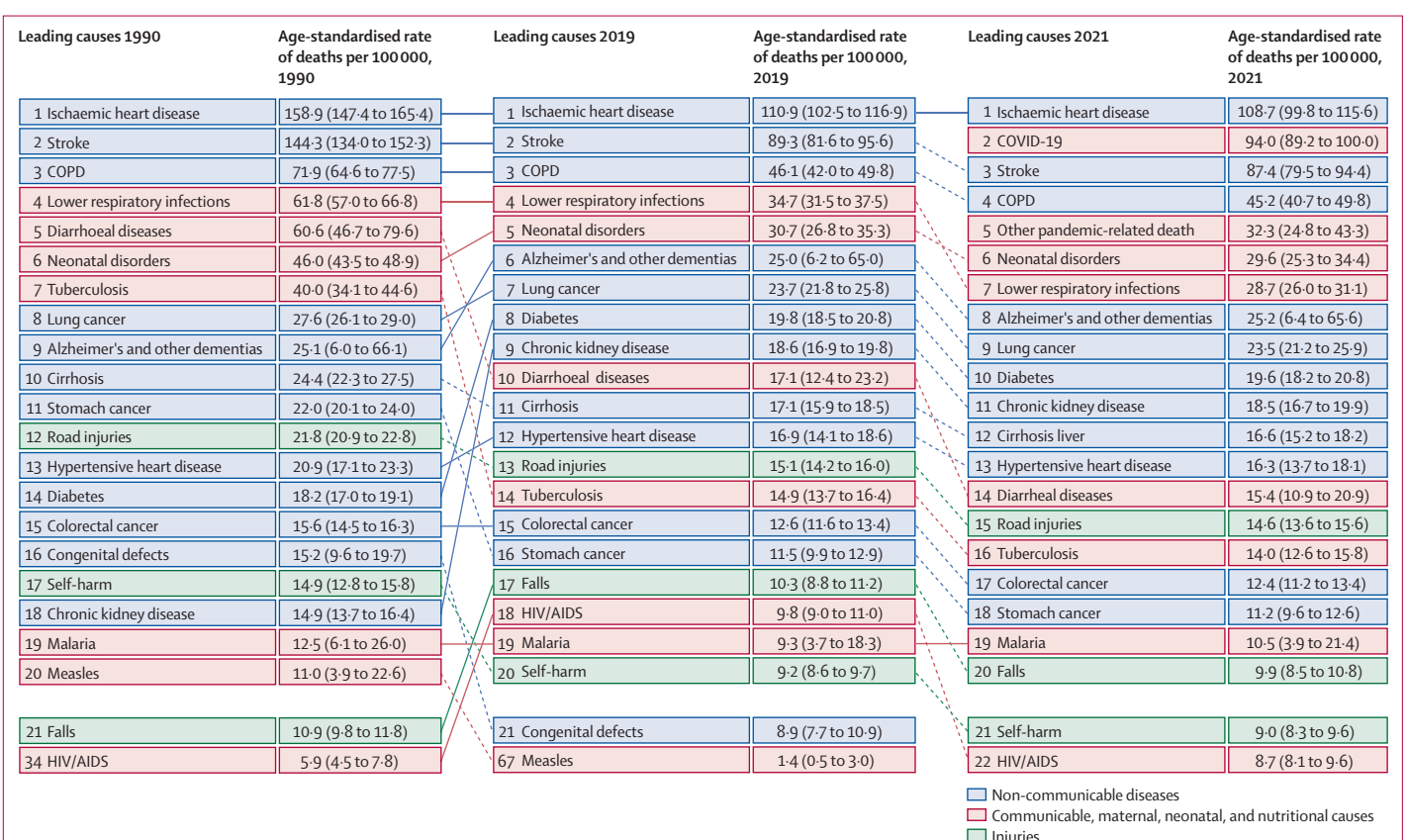


Figure 1: **Leading Level 3 causes of global deaths and age-standardised death rate per 100 000 population for males and females combined, 1990, 2019, and 2021**
Figure shows the 20 leading causes of death in descending order. Causes are connected by lines between time periods; solid lines represent an increase or lateral shift in ranking and dashed lines are decreases in rank. COPD=chronic obstructive pulmonary disease. Lung cancer=tracheal, bronchus, and lung cancer.

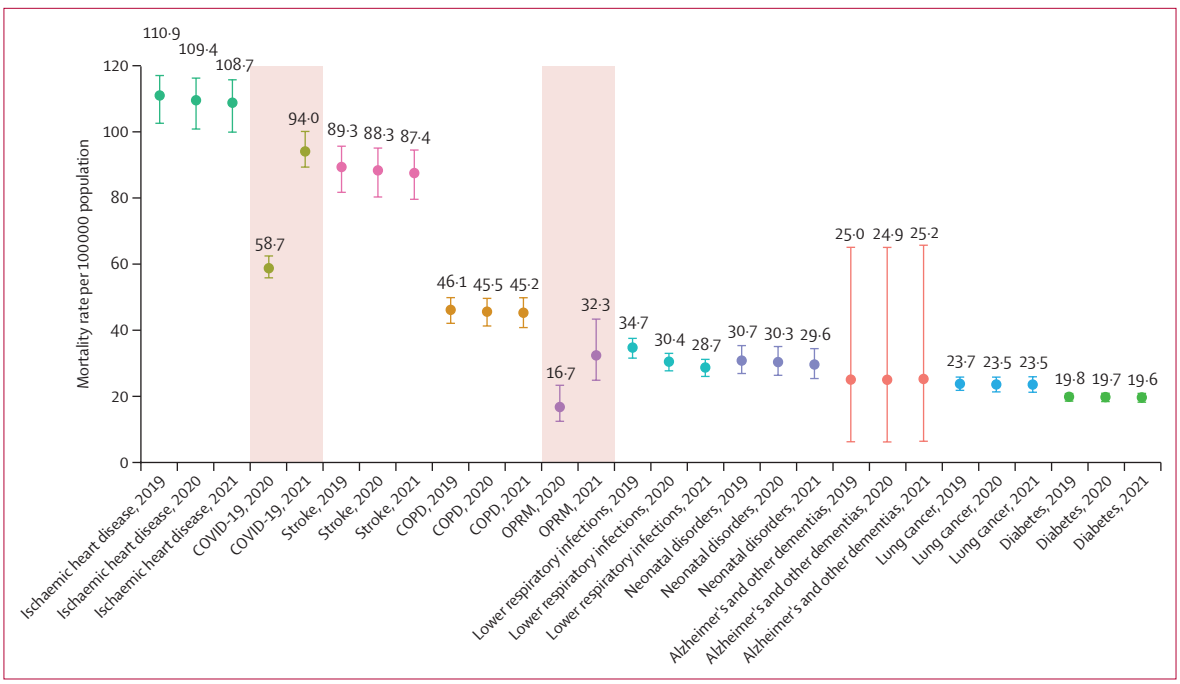


Figure 2: **Age-standardised mortality rate per 100 000 population for the ten leading Level 3 causes of death globally, 2019–21**
Whisker plot in which the y-axis represents the age-standardised mortality rate and the x-axis represents a selected cause-year. Causes are arranged from highest to lowest age-standardised mortality rate, with each cause assigned a distinct colour for identification. The whiskers represent the 95% uncertainty interval. COPD=chronic obstructive pulmonary disease. OPRM=other pandemic-related mortality.

incidence of mortality between locations and populations. In addition to identifying these concentrations of mortality in 2021, we repeated this same analysis for 1990. By comparing the respective proportions of affected global population in these two years, we were able to differentiate causes that showed increased, decreased, or unchanged concentrations of mortality. The causes highlighted in this study were those characterised by an age-standardised mortality rate greater than 0·5 per 100 000 population. The purpose of presenting mortality concentrations is to illustrate causes that are disproportionately affecting specific populations, when previously that cause affected large swaths of the population. Thus, we did not calculate the mortality concentration for causes that are endemic to certain regions, as the mortality rate is already known to be concentrated among specific parts of the global population. We excluded two endemic causes, Ebola virus disease and Chagas disease, from this calculation.

GBD research and reporting practices

This research is compliant with the Guidelines for Accurate and Transparent Health Estimates Reporting recommendations (GATHER; appendix 1 table S4).[14] Software packages used in the cause-of-death analysis for GBD 2021 were Python (version 3.10.4), Stata (version 13.1), and R (version 4.2.1). Statistical code used for GBD estimation is publicly available online.

See Online for appendix 2

To **view and download estimates from the GBD Results tool** see https://www.vizhub.healthdata.org/gbd-results

To **explore estimates of health burden using GBD Compare** see https://www.vizhub.healthdata.org/gbd-compare

For **summaries of results for each cause of death** see https://www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets

For the **statistical code** see http://ghdx.healthdata.org/gbd-2021/code

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

Estimates described in the Article are viewable in appendix 2. Detailed results for each cause of death in the analysis are available in downloadable form through the GBD Results tool and via visual exploration through the online tool GBD Compare. Summaries of results for each cause of death included in the analysis are available online.

Global causes of death

From 1990 to 2019, the annual rate of change in global deaths from all causes ranged from –0·9% (95% UI –2·7 to 0·8) to 2·4% (0·1 to 4·7; appendix 2 figure S1). The corresponding annual rates of change in the global age-standardised mortality rate ranged from –3·3% (–5·0 to –1·6) to 0·4% (–1·9 to 2·5). In 2020, however, the total number of deaths worldwide increased by 10·8% (6·4 to 15·4) compared with 2019, from 57·0 million deaths (54·9 to 59·5) in 2019 to 63·1 million deaths (60·6 to 65·9) in 2020. This trend persisted in 2021, with an increase of 7·5% (3·1 to 12·4) relative to 2020, to 67·9 million (65·0 to 70·8) deaths. The age-standardised mortality rate followed a similar pattern, increasing by 8·1% (3·9 to 12·4) in 2020 and

	Global	Central Europe, eastern Europe, and central Asia	High income	Latin America and Caribbean	North Africa and Middle East	South Asia	Southeast Asia, east Asia, and Oceania	Sub-Saharan Africa
2020								
1								
Cause	Ischaemic heart disease	Ischaemic heart disease	Ischaemic heart disease	COVID-19	Ischaemic heart disease	Ischaemic heart disease	Stroke	COVID-19
Age-standardised rate (per 100 000 population)	109·4 (100·7–116·1)	215·3 (199·2–225·7)	51·4 (45·1–54·6)	133·7 (121·5–145·3)	205·2 (182·7–225·6)	150·3 (139·7–162·2)	142·8 (123·9–159·8)	158·9 (148·5–170·0)
Number	8 840 000 (8 180 000–9 360 000)	1 410 000 (1 310 000–1 480 000)	1 290 000 (1 110 000–1 390 000)	799 000 (725 000–869 000)	760 000 (681 000–838 000	1 960 000 (1 820 000–2 110 000)	3 460 000 (3 030 000–3 880 000)	659 000 (615 000–706 000)
2								
Cause	Stroke	Stroke	COVID-19	Ischaemic heart disease	COVID-19	Chronic obstructive pulmonary disease	Ischaemic heart disease	Stroke
Age-standardised rate (per 100 000 population)	88·3 (80·2–95·0)	110·7 (102·7–115·6)	41·8 (40·8–42·8)	84·3 (77·2–89·4)	123·9 (106·8–137·1)	104·1 (92·3–117·0)	110·8 (97·3–124·6)	126·2 (113·4–140·4)
Number	7 140 000 (6 500 000–7 680 000)	726 000 (675 000–758 000)	930 000 (908 000–952 000)	496 000 (454 000–525 000)	483 000 (415 000–537 000)	1 230 000 (1 090 000–1 370 000)	2 570 000 (2 260 000–2 880 000)	481 000 (432 000–538 000)
3								
Cause	COVID-19	COVID-19	Stroke	Stroke	Stroke	COVID-19	Chronic obstructive pulmonary disease	Ischaemic heart disease
Age-standardised rate (per 100 000 population)	58·7 (55·8–62·4)	72·9 (64·1–81·7)	29·0 (24·7–31·2)	47·5 (43·4–50·5)	103·8 (92·0–115·6)	101·8 (95·0–108·5)	66·9 (57·4–77·0)	92·9 (83·1–103·0)
Number	4 800 000 (4 560 000–5 110 000)	467 000 (411 000–523 000)	764 000 (636 000–830 000)	278 000 (255 000–296 000)	370 000 (329 000–414 000)	1 320 000 (1 230 000–1 400 000)	1 500 000 (1 290 000–1 730 000)	346 000 (309 000–388 000)
4								
Cause	Chronic obstructive pulmonary disease	Other COVID-19 pandemic-related outcomes	Alzheimer's disease and other dementias	Diabetes mellitus	Hypertensive heart disease	Stroke	Tracheal, bronchus, and lung cancer	Lower respiratory infections
Age-standardised rate (per 100 000 population)	45·5 (41·2–49·6)	41·0 (32·9–51·9)	26·5 (6·74–65·1)	36·5 (33·9–38·9)	40·2 (32·0–46·7)	83·3 (75·7–90·4)	34·8 (29·0–41·0)	88·5 (77·8–98·2)
Number	3 650 000 (3 320 000–3 970 000	264 000 (212 000–333 000)	774 000 (198 000–1 900 000)	217 000 (202 000–231 000)	138 000 (110 000–160 000)	1 060 000 (969 000–1 150 000)	938 000 (783 000–1 110 000)	588 000 (494 000–686 000)
5								
Cause	Lower respiratory infections	Tracheal, bronchus, and lung cancer	Tracheal, bronchus, and lung cancer	Lower respiratory infections	Chronic kidney disease	Diarrhoeal diseases	Alzheimer's disease and other dementias	Malaria
Age-standardised rate (per 100 000 population)	30·4 (27·7–32·9)	25·5 (24·4–26·5)	25·9 (23·8–27·0)	32·8 (29·6–35·1)	37·9 (33·3–42·4)	50·2 (32·0–79·4)	27·9 (6·76–74·8)	67·9 (22·6–145·0)
Number	2 280 000 (2 080 000–2 460 000)	168 000 (161 000–174 000)	581 000 (526 000–610 000)	187 000 (169 000–200 000)	142 000 (125 000–159 000)	591 000 (381 000–940 000)	562 000 (136 000–1 490 000)	713 000 (251 000–1 480 000)
6								
Cause	Neonatal disorders	Cirrhosis and other chronic liver diseases	Chronic obstructive pulmonary disease	Chronic kidney disease	Other COVID-19 pandemic-related outcomes	Neonatal disorders	Lower respiratory infections	Tuberculosis
Age-standardised rate (per 100 000 population)	30·3 (26·3–35·0)	22·5 (21·7–23·3)	19·2 (16·9–20·3)	30·9 (28·3–33·1)	30·4 (11·4–52·0)	43·8 (37·2–51·6)	21·2 (18·9–23·6)	67·3 (56·7–77·8)
Number	1 910 000 (1 650 000–2 200 000)	131 000 (127 000–136 000)	490 000 (424 000–522 000)	184 000 (169 000–197 000)	121 000 (46 500–207 000)	672 000 (571 000–792 000)	424 000 (378 000–469 000)	378 000 (313 000–442 000)

(Table 1 continues on next page)

	Global	Central Europe, eastern Europe, and central Asia	High income	Latin America and Caribbean	North Africa and Middle East	South Asia	Southeast Asia, east Asia, and Oceania	Sub-Saharan Africa
(Continued from previous page)								
7								
Cause	Alzheimer's disease and other dementias	Alzheimer's disease and other dementias	Colon and rectum cancer	Chronic obstructive pulmonary disease	Diabetes mellitus	Lower respiratory infections	Hypertensive heart disease	HIV/AIDS
Age-standardised rate (per 100 000 population)	24·9 (6·16–65·0)	20·8 (4·88–55·3)	14·7 (13·2–15·6)	25·0 (22·5–26·5)	29·4 (26·4–32·3)	40·0 (35·8–44·7)	20·1 (14·1–24·8)	65·8 (59·9–73·2)
Number	1 890 000 (470 000–4 940 000)	136 000 (32 100–362 000)	344 000 (300 000–367 000)	144 000 (130 000–152 000)	113 000 (101 000–124 000)	522 000 (465 000–582 000)	459 000 (320 000–562 000)	539 000 (487 000–612 000)
8								
Cause	Tracheal, bronchus, and lung cancer	Lower respiratory infections	Chronic kidney disease	Interpersonal violence	Chronic obstructive pulmonary disease	Tuberculosis	Stomach cancer	Diarrhoeal diseases
Age-standardised rate (per 100 000 population)	23·5 (21·3–25·8)	19·5 (18·3–20·8)	14·0 (12·1–15·3)	23·5 (22·4–24·8)	26·9 (23·9–29·7)	34·2 (30·1–40·1)	18·4 (14·2–22·0)	57·0 (36·2–79·4)
Number	1 970 000 (1 780 000–2 160 000)	96 200 (91 200–101 000)	364 000 (307 000–399 000)	147 000 (140 000–155 000)	92 400 (82 500–102 000)	509 000 (450 000–597 000)	491 000 (380 000–589 000)	452 000 (324 000–588 000)
9								
Cause	Diabetes mellitus	Cardiomyopathy and myocarditis	Lower respiratory infections	Other COVID-19 pandemic-related outcomes	Alzheimer's disease and other dementias	Diabetes mellitus	Road injuries	Other COVID-19 pandemic-related outcomes
Age-standardised rate (per 100 000 population)	19·7 (18·4–20·9)	19·2 (17·9–20·4)	13·6 (11·8–14·6)	20·9 (10·3–33·3)	25·7 (6·30–67·6)	33·1 (29·8–36·0)	15·7 (13·9–17·6)	50·5 (31·3–70·8)
Number	1 630 000 (1 520 000–1 720 000)	113 000 (105 000–121 000)	361 000 (306 000–390 000)	125 000 (59 600–199 000)	73 600 (17 900–198 000)	419 000 (378 000–457 000)	380 000 (335 000–429 000)	245 000 (159 000–339 000)
10								
Cause	Chronic kidney disease	Colon and rectum cancer	Self-harm	Alzheimer's disease and other dementias	Lower respiratory infections	Other COVID-19 pandemic-related outcomes	Chronic kidney disease	Neonatal disorders
Age-standardised rate (per 100 000 population)	18·6 (16·9–19·9)	18·6 (17·6–19·4)	10·9 (10·5–11·2)	20·8 (5·14–53·8)	25·4 (22·4–28·5)	28·2 (18·5–39·5)	15·3 (13·4–17·0)	50·0 (42·1–59·2)
Number	1 500 000 (1 360 000–1 610 000)	122 000 (115 000–127 000)	149 000 (142 000–153 000)	119 000 (29 200–308 000)	103 000 (91 000–116 000)	370 000 (246 000–514 000)	376 000 (333 000–420 000)	889 000 (749 000–1 050 000)
2021								
1								
Cause	Ischaemic heart disease	Ischaemic heart disease	Ischaemic heart disease	COVID-19	Ischaemic heart disease	COVID-19	Stroke	COVID-19
Age-standardised rate (per 100 000 population)	108·7 (99·8–115·6)	213·6 (196·1–229·1)	51·0 (44·9–54·2)	195·4 (182·1–211·4)	202·8 (179·7–225·9)	156·5 (150·4–164·4)	141·1 (123·2–159·7)	271·0 (250·1–290·7)
Number	8 990 000 (8 290 000–9 550 000)	1 410 000 (1 290 000–1 510 000)	1 310 000 (1 120 000–1 400 000)	1 200 000 (1 110 000–1 290 000)	769 000 (679 000–863 000)	2 060 000 (1 980 000–2 170 000)	3 550 000 (3 100 000–4 020 000)	1 150 000 (1 060 000–1 240 000)
2								
Cause	COVID-19	COVID-19	COVID-19	Ischaemic heart disease	COVID-19	Ischaemic heart disease	Ischaemic heart disease	Stroke
Age-standardised rate (per 100 000 population)	94·0 (89·2–100·0)	168·8 (150·6–186·1)	48·1 (47·4–48·8)	83·8 (75·9–90·6)	172·4 (150·3–191·5)	149·1 (136·4–161·8)	110·4 (94·9–124·6)	124·7 (111·8–138·6)
Number	7 890 000 (7 490 000–8 400 000)	1 100 000 (982 000–1 210 000)	1 070 000 (1 060 000–1 090 000)	504 000 (457 000–545 000)	698 000 (608 000–777 000)	1 990 000 (1 820 000–2 160 000)	2 660 000 (2 290 000–3 000 000)	484 000 (432 000–544 000)

(Table 1 continues on next page)

	Global	Central Europe, eastern Europe, and central Asia	High income	Latin America and Caribbean	North Africa and Middle East	South Asia	Southeast Asia, east Asia, and Oceania	Sub-Saharan Africa
(Continued from previous page)								
3								
Cause	Stroke	Stroke	Stroke	Stroke	Stroke	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	Other COVID-19 pandemic-related outcomes
Age-standardised rate (per 100 000 population)	87·4 (79·5–94·4)	109·8 (101·6–116·6)	28·8 (24·5–30·9)	46·7 (42·3–50·2)	101·9 (89·2–114·4)	101·6 (90·3–114·2)	66·6 (56·2–77·7)	123·9 (87·7–159·5)
Number	7 250 000 (6 600 000–7 820 000)	725 000 (671 000–770 000)	771 000 (641 000–838 000)	279 000 (254 000–301 000)	372 000 (325 000–421 000)	1 230 000 (1 100 000–1 380 000)	1 560 000 (1 310 000–1 820 000)	584 000 (418 000–757 000)
4								
Cause	Chronic obstructive pulmonary disease	Other COVID-19 pandemic-related outcomes	Alzheimer's disease and other dementias	Other COVID-19 pandemic-related outcomes	Other COVID-19 pandemic-related outcomes	Stroke	Tracheal, bronchus, and lung cancer	Ischaemic heart disease
Age-standardised rate (per 100 000 population)	45·2 (40·7–49·8)	50·0 (34·8–68·7)	26·5 (6·74–64·8)	39·0 (22·5–58·4)	64·5 (34·4–100·6)	81·8 (74·2–89·6)	34·8 (28·8–41·1)	92·8 (83·3–103·5)
Number	3 720 000 (3 360 000–4 090 000)	321 000 (223 000–438 000)	792 000 (203 000–1 940 000)	236 000 (135 000–355 000)	265 000 (139 000–414 000)	1 070 000 (968 000–1 170 000)	970 000 (800 000–1 150 000)	352 000 (316 000–396 000)
5								
Cause	Other COVID-19 pandemic-related outcomes	Tracheal, bronchus, and lung cancer	Tracheal, bronchus, and lung cancer	Diabetes mellitus	Hypertensive heart disease	Other COVID-19 pandemic-related outcomes	Alzheimer's disease and other dementias	Lower respiratory infections
Age-standardised rate (per 100 000 population)	32·3 (24·8–43·3)	25·1 (23·7–26·6)	25·9 (23·8–27·0)	36·3 (33·2–39·3)	39·5 (31·3–46·3)	63·3 (50·4–77·2)	28·9 (7·41–78·6)	85·4 (75·3–95·0)
Number	2 690 000 (2 060 000–3 610 000)	167 000 (157 000–176 000)	591 000 (537 000–620 000)	221 000 (202 000–239 000)	138 000 (109 000–162 000)	838 000 (674 000–1 020 000)	608 000 (155 000–1 670 000)	563 000 (472 000–655 000)
6								
Cause	Neonatal disorders	Cirrhosis and other chronic liver diseases	Chronic obstructive pulmonary disease	Chronic kidney disease	Chronic kidney disease	Diarrhoeal diseases	COVID-19	Malaria
Age-standardised rate (per 100 000 population)	29·6 (25·3–34·4)	22·3 (21·0–23·5)	19·1 (16·8–20·2)	30·7 (27·8–33·5)	37·7 (32·7–42·8)	47·8 (30·2–75·7)	23·2 (16·3–37·2)	65·9 (23·6–136·7)
Number	1 830 000 (1 570 000–2 130 000)	131 000 (123 000–138 000)	495 000 (428 000–527 000)	187 000 (170 000–204 000)	145 000 (126 000–164 000)	573 000 (372 000–908 000)	606 000 (425 000–974 000)	704 000 (265 000–1 400 000)
7								
Cause	Lower respiratory infections	Alzheimer's disease and other dementias	Colon and rectum cancer	Lower respiratory infections	Diabetes mellitus	Neonatal disorders	Lower respiratory infections	Tuberculosis
Age-standardised rate (per 100 000 population)	28·7 (26·0–31·1)	20·8 (4·94–55·6)	14·7 (13·1–15·5)	30·4 (27·0–33·3)	29·3 (25·9–32·5)	42·0 (35·6–50·2)	20·9 (18·6–23·4)	65·8 (56·1–76·9)
Number	2 180 000 (1 980 000–2 360 000)	137 000 (32 500–370 000)	348 000 (304 000–372 000)	177 000 (157 000–194 000)	116 000 (102 000–129 000)	636 000 (538 000–760 000)	431 000 (384 000–482 000)	373 000 (313 000–439 000)
8								
Cause	Alzheimer's disease and other dementias	Cardiomyopathy and myocarditis	Chronic kidney disease	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	Lower respiratory infections	Hypertensive heart disease	HIV/AIDS
Age-standardised rate (per 100 000 population)	25·2 (6·36–65·6)	19·1 (17·5–20·7)	13·9 (12·0–15·1)	24·7 (22·1–26·4)	26·4 (23·2–29·6)	39·2 (34·2–44·6)	19·8 (14·0–24·3)	61·4 (55·8–68·5)
Number	1 960 000 (499 000–5 120 000)	112 000 (103 000–122 000)	368 000 (310 000–402 000)	145 000 (130 000–156 000)	92 700 (82 000–104 000)	516 000 (451 000–584 000)	470 000 (333 000–575 000)	515 000 (467 000–583 000)

(Table 1 continues on next page)

	Global	Central Europe, eastern Europe, and central Asia	High income	Latin America and Caribbean	North Africa and Middle East	South Asia	Southeast Asia, east Asia, and Oceania	Sub-Saharan Africa
(Continued from previous page)								
9								
Cause	Tracheal, bronchus, and lung cancer	Colon and rectum cancer	Lower respiratory infections	Interpersonal violence	Alzheimer's disease and other dementias	Tuberculosis	Stomach cancer	Diarrhoeal diseases
Age-standardised rate (per 100 000 population)	23·5 (21·2–25·9)	18·5 (17·4–19·6)	11·9 (10·2–12·7)	23·3 (21·7–24·8)	25·7 (6·22–66·8)	33·1 (29·0–39·1)	18·1 (14·4–21·8)	54·4 (33·9–76·7)
Number	2 020 000 (1 820 000–2 220 000)	122 000 (115 000–129 000)	321 000 (267 000–348 000)	147 000 (137 000–156 000)	73 900 (18 000–198 000)	501 000 (441 000–587 000)	500 000 (397 000–605 000)	434 000 (310 000–570 000)
10								
Cause	Diabetes mellitus	Lower respiratory infections	Self-harm	Alzheimer's disease and other dementias	Cirrhosis and other chronic liver diseases	Diabetes mellitus	Road injuries	Neonatal disorders
Age-standardised rate (per 100 000 population)	19·6 (18·2–20·8)	16·5 (15·4–17·7)	10·8 (10·4–11·0)	20·8 (5·18–54·3)	23·2 (20·2–26·8)	32·8 (29·5–36·1)	15·5 (13·6–17·5)	48·6 (40·3–58·1)
Number	1 660 000 (1 540 000–1 760 000)	82 800 (77 800–87 500)	148 000 (141 000–152 000)	121 000 (30 300–317 000)	99 600 (86 100–116 000)	426 000 (383 000–468 000)	379 000 (331 000–430 000)	873 000 (724 000–1 040 000)

Table 1: **Number of deaths and age-standardised mortality rates for ten leading Level 3 causes of death in 2020 and 2021, globally and by super-region, for all ages and males and females combined**

an additional 5·2% (1·0 to 9·7) in 2021. In 2020 and 2021, deaths from COVID-19 and OPRM changed the pattern of mortality for the leading causes of age-standardised death (figures 1, 2; table 1). At Level 3 of the GBD cause-classification hierarchy, the rankings of the four causes of death with the highest age-standardised mortality rates were the same in 2019 as they were in 1990, with each showing a steady decline in its age-standardised death rate (figure 1). These causes were, in descending order, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, and lower respiratory infections. In 2021, however, COVID-19 replaced stroke as the second leading cause of age-standardised death globally (with 94·0 deaths [95% UI 89·2 to 100·0] per 100 000 population), with stroke becoming the third leading cause. Additionally, OPRM—which includes excess mortality associated with the pandemic, excluding COVID-19, lower respiratory infections, measles, and pertussis causes—emerged as the fifth leading cause of age-standardised deaths in 2021; lower respiratory infections decreased from the fourth to the seventh leading cause. The effect of COVID-19 on age-standardised mortality was similar to that of chronic obstructive pulmonary disease in 2020 but increased by 60·2% (53·1 to 67·6) in 2021, becoming similar to that of stroke and ischaemic heart disease (figure 2; table 1).

COVID-19 and OPRM

Our estimates show that 4·80 million (95% UI 4·56–5·11) deaths due to COVID-19 occurred globally in 2020, and 7·89 million (7·49–8·40) in 2021. Age-standardised rates of death due to COVID-19 were highly variable among GBD super-regions (table 1). In 2021, the rankings from highest to lowest were sub-Saharan Africa (271·0 deaths [250·1–290·7] per 100 000 population); Latin America and the Caribbean (195·4 deaths [182·1–211·4] per 100 000 population); north Africa and the Middle East (172·4 deaths [150·3–191·5] per 100 000 population); central Europe, eastern Europe, and central Asia (168·8 deaths [150·6–186·1] per 100 000 population); south Asia (156·5 deaths [150·4–164·4] per 100 000 population); high income (48·1 deaths [47·4–48·8] per 100 000 population); and southeast Asia, east Asia, and Oceania (23·2 deaths [16·3–37·2] per 100 000 population; table 1).

Deaths from both COVID-19 and OPRM also varied substantially by age, with older ages being disproportionately affected (table 2). Individuals aged 70–74 years had the highest number of deaths from both COVID-19 and OPRM in 2020 and again in 2021. The highest percentage of total deaths from COVID-19 was found in those aged 40–44 years, whereas the highest mortality rate occurred in those aged 95 years and older. Death rates from OPRM were high among older age groups and among the youngest ages, with a rate of 141·2 deaths (95% UI 58·0–277·5) per 100 000 population for infants aged 0–6 days, and 77·3 deaths (44·0–118·0) per 100 000 population in infants aged 7–27 days. At a global scale, COVID-19 deaths and OPRM were slightly higher for males than for females in most age groups in 2021 (appendix 2 figure S5). Exceptions to this trend include those aged 90–94 years and those aged 95 years and older (appendix 2 figure S5).

	Deaths				Deaths per 100 000 population				Percentage of total deaths			
	COVID-19 2020	COVID-19 2021	Other COVID-19 pandemic-related outcomes 2020	Other COVID-19 pandemic-related outcomes 2021	COVID-19 2020	COVID-19 2021	Other COVID-19 pandemic-related outcomes 2020	Other COVID-19 pandemic-related outcomes 2021	COVID-19 2020	COVID-19 2021	Other COVID-19 pandemic-related outcomes 2020	Other COVID-19 pandemic-related outcomes 2021
Early neonatal	0	1	3518	3462	0·0	<0·1	141·4	141·2	0·0%	<0·1%	0·2%	0·2%
Late neonatal	3	5	5069	5641	<0·1	0·1	68·5	77·3	<0·1%	<0·1%	1·1%	1·3%
1–5 months	170	287	24269	26 647	0·3	0·5	44·4	49·6	<0·1%	<0·1%	3·1%	3·6%
6–11 months	234	394	20 478	30 883	0·4	0·6	31·7	48·9	<0·1%	0·1%	3·5%	5·5%
12–23 months	998	1644	19 042	30 550	0·8	1·3	14·5	23·8	0·2%	0·3%	3·7%	6·2%
2–4 years	8500	14 386	14 730	23 574	2·1	3·6	3·6	5·8	1·2%	2·1%	2·0%	3·4%
5–9 years	7052	11 393	5377	8196	1·0	1·7	0·8	1·2	1·9%	3·2%	1·5%	2·3%
10–14 years	8553	14 405	1588	2715	1·3	2·2	0·2	0·4	2·8%	4·8%	0·5%	0·9%
15–19 years	17 032	26 852	5932	12 576	2·8	4·3	1·0	2·0	3·1%	4·8%	1·1%	2·2%
20–24 years	25 528	40 743	8219	17 453	4·3	6·8	1·4	2·9	3·6%	5·5%	1·2%	2·4%
25–29 years	47 857	78 496	12581	28 816	8·1	13·3	2·1	4·9	5·9%	9·2%	1·6%	3·4%
30–34 years	81 232	137 979	21 625	49 808	13·4	22·8	3·6	8·2	7·9%	12·3%	2·1%	4·5%
35–39 years	112 228	195 380	29 877	69 402	20·5	34·8	5·5	12·4	9·0%	14·1%	2·4%	5·0%
40–44 years	165 337	287 099	44 391	102 041	33·5	57·4	9·0	20·4	10·3%	16·0%	2·8%	5·7%
45–49 years	207 940	355 388	55 989	124 899	44·0	75·1	11·8	26·4	10·1%	15·7%	2·7%	5·5%
50–54 years	253 491	426 785	67 629	147 651	57·7	95·9	15·4	33·2	9·1%	14·0%	2·4%	4·8%
55–59 years	336 162	564 508	90 815	191 441	87·5	142·7	23·6	48·4	9·0%	13·8%	2·4%	4·7%
60–64 years	460 769	774 879	125 433	262 008	146·1	242·1	39·8	81·9	9·8%	15·0%	2·7%	5·1%
65–69 years	564 371	957 557	155 431	321 301	209·4	347·1	57·7	116·5	9·4%	14·5%	2·6%	4·9%
70–74 years	585 549	989 888	156 931	325 295	298·7	480·9	80·1	158·0	8·8%	13·2%	2·4%	4·3%
75–79 years	539 515	861 796	135 849	276 402	417·1	653·4	105·0	209·6	7·9%	11·8%	2·0%	3·8%
80–84 years	551 014	888 813	146 084	277786	638·9	1014·8	169·4	317·2	7·5%	11·3%	2·0%	3·5%
85–89 years	427 770	658 875	106 842	191 824	959·3	1441·1	239·6	419·5	6·9%	10·0%	1·7%	2·9%
90–94 years	280 605	426 185	67 297	114 449	1608·9	2382·3	385·9	639·8	7·5%	10·8%	1·8%	2·9%
≥95 years	120 173	174 390	24 074	42 104	2298·6	3199·6	460·5	772·5	7·8%	10·7%	1·6%	2·6%

Table 2: **Number of deaths, age-standardised mortality rates, and percentage of total deaths due to COVID-19 and other pandemic-related mortality by age, globally**

Leading causes of global YLLs

The causes of death with the highest age-standardised YLL rates show shifting epidemiological trends from CMNN diseases to NCDs at Level 3 of the cause hierarchy (appendix 2 figure S2). Globally, the leading three causes of age-standardised YLLs in 1990 were all CMNN diseases. Ranked in descending order, these causes were neonatal disorders, lower respiratory infections, and diarrhoeal diseases. In 2019, neonatal disorders remained the leading cause of age-standardised YLLs, but the second and third leading causes were replaced by NCDs: ischaemic heart disease (ranked second) and stroke (ranked third). In 2021, COVID-19 was the second-leading cause of global age-standardised YLLs, making the leading two causes CMNN diseases (with neonatal disorders ranked first), with ischaemic heart disease ranked third. Among the leading causes of age-standardised YLLs, malaria was the only cause to show an increase in age-standardised YLL rates between 2019 and 2021 (ranking ninth in 2019 and seventh in 2021).

Decomposition of global life expectancy

We found long-standing positive trends in global life expectancy since the early 1990s, with steady increases occurring across each decade between 1990 and 2019 (appendix 2 table S4). Altogether, the global increase in life expectancy from 1990 to 2019 totalled 7·8 years (95% UI 7·1–8·5). In 2019–21, however, we found a global decline in life expectancy of 2·2 years due to deaths from COVID-19 and OPRM combined. This decrease was partly offset by reductions in other diseases, for a net reduction in global life expectancy of 1·6 years. Despite this notable reduction, we observed an overall increase in life expectancy of 6·2 years (5·4–7·0) across the entire study period. This decomposition analysis provides insights into the specific causes that influenced changes in life expectancy over the defined time periods. Among the various contributing factors to a change in life expectancy, the cause with the greatest effect on the increase in life expectancy worldwide was the reduction in deaths caused by enteric infections (figure 3). This category includes diarrhoeal, typhoid, and paratyphoid diseases. A reduction

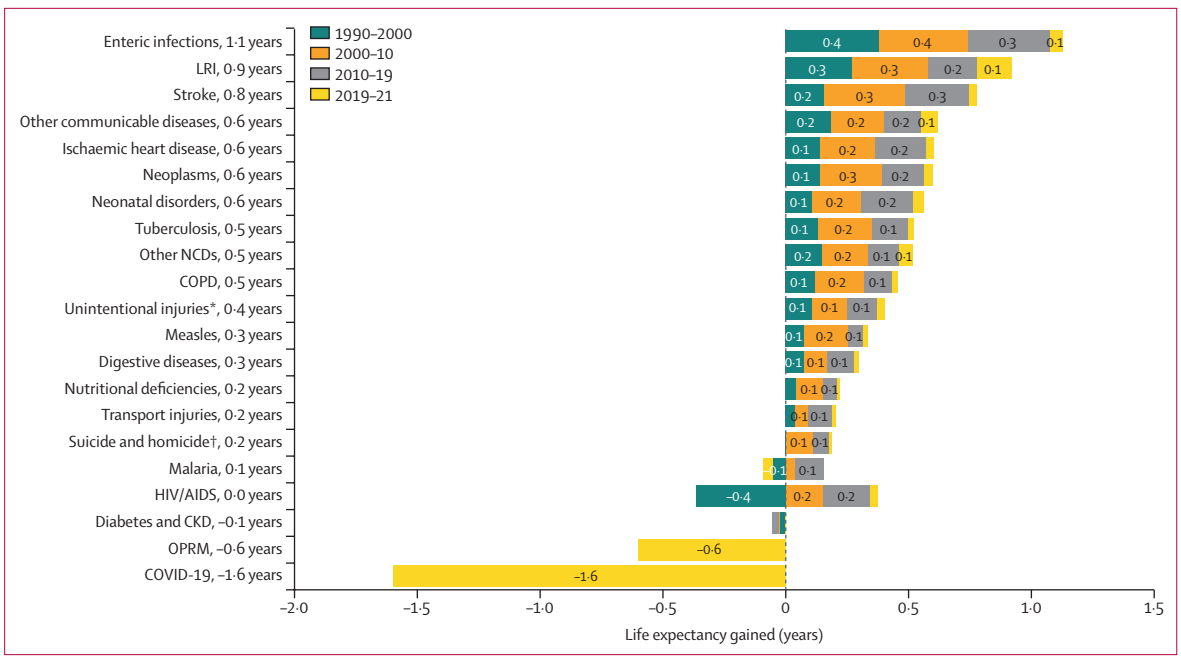


Figure 3: **Change in life expectancy attributable to leading causes of death for males and females combined, 1990–2000, 2000–10, 2010–19, and 2019–21, globally**

Each row represents the change in global life expectancy from 1990 to 2021 for a given cause. The total change in life expectancy is further broken down by different colours to represent changes over time periods. A bar to the right of 0 represents an increase in life expectancy due to changes in the given time period, and a bar to the left of 0 represents a decrease in life expectancy due to a given time period. For readability, labels indicating a change in life expectancy of less than 0·05 years are not shown. CKD=chronic kidney disease. COPD=chronic obstructive pulmonary disease. LRI=lower respiratory infection. NCD=non-communicable disease. OPRM=other pandemic-related mortality. *Does not include natural disasters. †Does not include war and terrorism.

in deaths from these diseases is responsible for a substantial increase in life expectancy of 1·1 years during 1990–2021, but this increase was most pronounced between 1990 and 2000 compared with other time periods. The second-largest effect on increasing life expectancy is attributed to the reduction in deaths from lower respiratory infection, contributing 0·9 years of gained life expectancy from 1990 to 2021. Other leading factors include reduced mortality from stroke, CMNN diseases, neonatal deaths, ischaemic heart disease, and neoplasms, each of which increased global life expectancy by 0·6–0·8 years over the study period. Changing rates of HIV/AIDS and malaria mortality both contributed positively to the overall global life expectancy in some years but negatively affected life expectancy in others. Beginning in 2000, reductions in HIV/AIDS-related mortality were evident following substantial negative effects in earlier years. Reductions in deaths from malaria, however, were less sustained, increasing life expectancy by 0·1 years from 2010 to 2019 but having no effect from 2019 to 2021. Across all causes, the largest effect on the change in global life expectancy was from COVID-19, which resulted in a decline of 1·6 years between 2019 and 2021.

Decomposition of super-region, regional, and country-level life expectancy

Each of the seven super-regions experienced an overall increase in life expectancy between 1990 and 2021, despite progress in each being differentially affected by COVID-19 (figures 4, 5). Southeast Asia, east Asia, and Oceania showed the highest gain, with a net improvement of 8·3 years (95% UI 6·7–9·9), while also being the least affected by COVID-19, which contributed a loss in life expectancy of just 0·4 years. The overall increase in life expectancy in southeast Asia, east Asia, and Oceania can largely be attributed to reduced mortality from chronic respiratory diseases, contributing to a gain of 1·2 years, whereas reduced mortality from stroke, lower respiratory infections, and neoplasms were among other causes that contributed to the 8·3-year (6·7–9·9) increase. The second-largest gain occurred in south Asia, where life expectancy increased by 7·8 years (6·7–8·9), which can be largely attributed to reduced mortality from enteric infectious diseases, contributing a substantial gain of 3·1 years in life expectancy. The largest reduction in overall life expectancy due to COVID-19 occurred in the super-region of Latin America and the Caribbean, which experienced a loss of 3·6 years. Reductions in deaths due to malaria throughout sub-Saharan Africa led to an increase in life expectancy of 0·8 years for the super-region.

The differential effect of COVID-19 on reduced life expectancy was observed across GBD regions (figure 6). Although most regions experienced overall improvements in life expectancy between 1990 and 2021, a reduction occurred in southern sub-Saharan Africa, which faced the greatest impact of HIV and was also

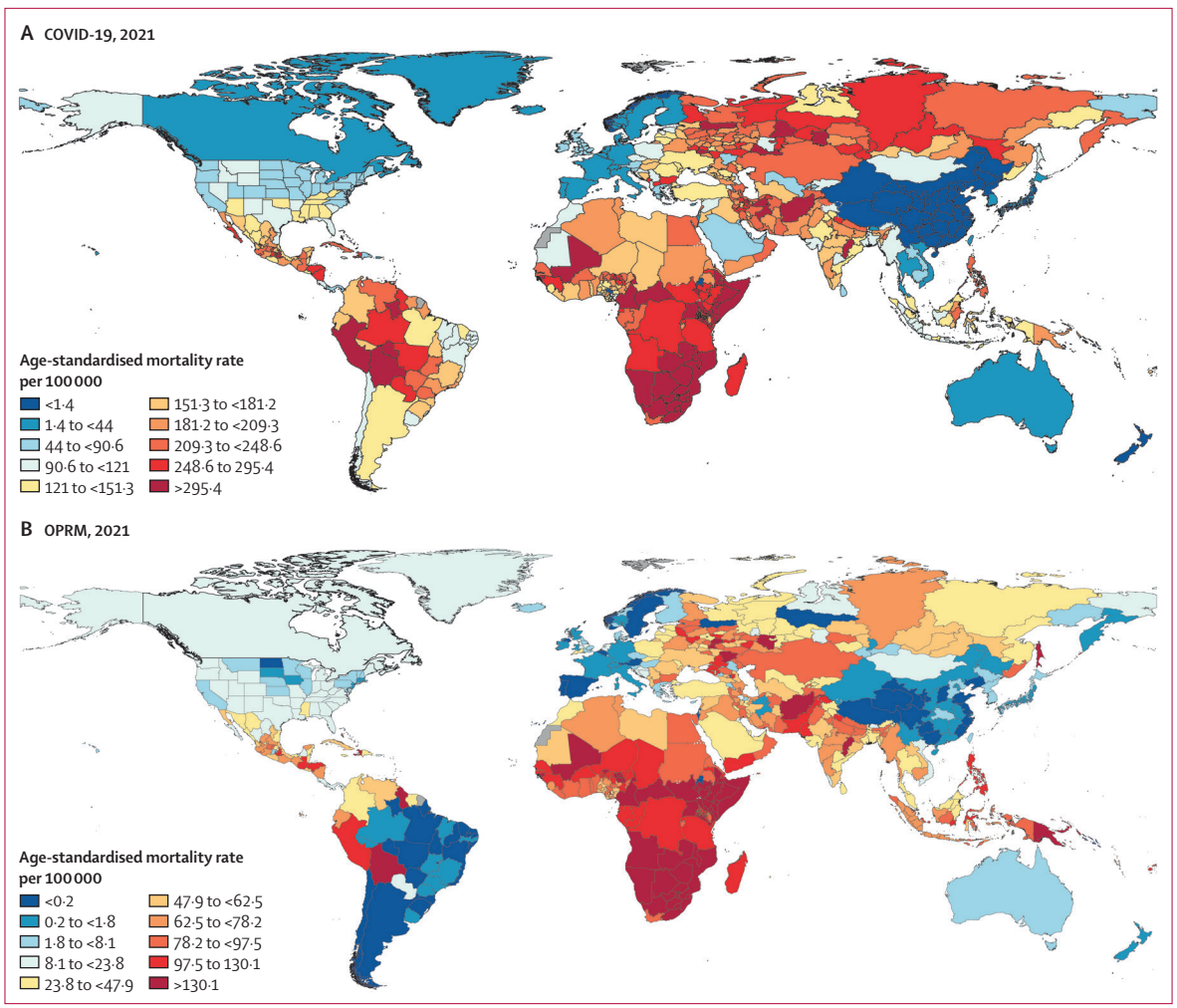


Figure 4: **Age-standardised mortality rate of COVID-19 and OPRM, 2021**
Global choropleth maps of COVID-19 (A) and OPRM (B) for 2021 that show sub-national detail where available. OPRM=other pandemic-related mortality.

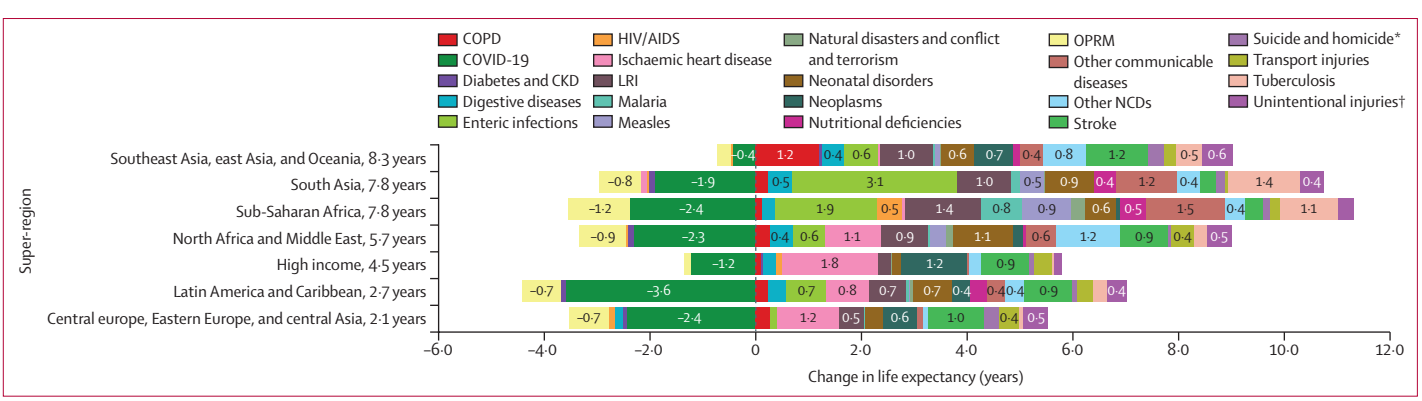


Figure 5: **Change in life expectancy attributable to leading causes of death among super-regions, 1990–2021**
Each row represents the change in life expectancy from 1990 to 2021 for a given super-region. A bar to the right of 0 represents an increase in life expectancy due to changes in the given cause, and a bar to the left of 0 represents a decrease in life expectancy for a given cause. For readability, labels indicating a change in life expectancy of less than 0·3 years are not shown. CKD=chronic kidney disease. COPD=chronic obstructive pulmonary disease. LRI=lower respiratory infection. NCD=non-communicable disease. OPRM=other pandemic-related mortality. *Does not include natural disasters. †Does not include war and terrorism.

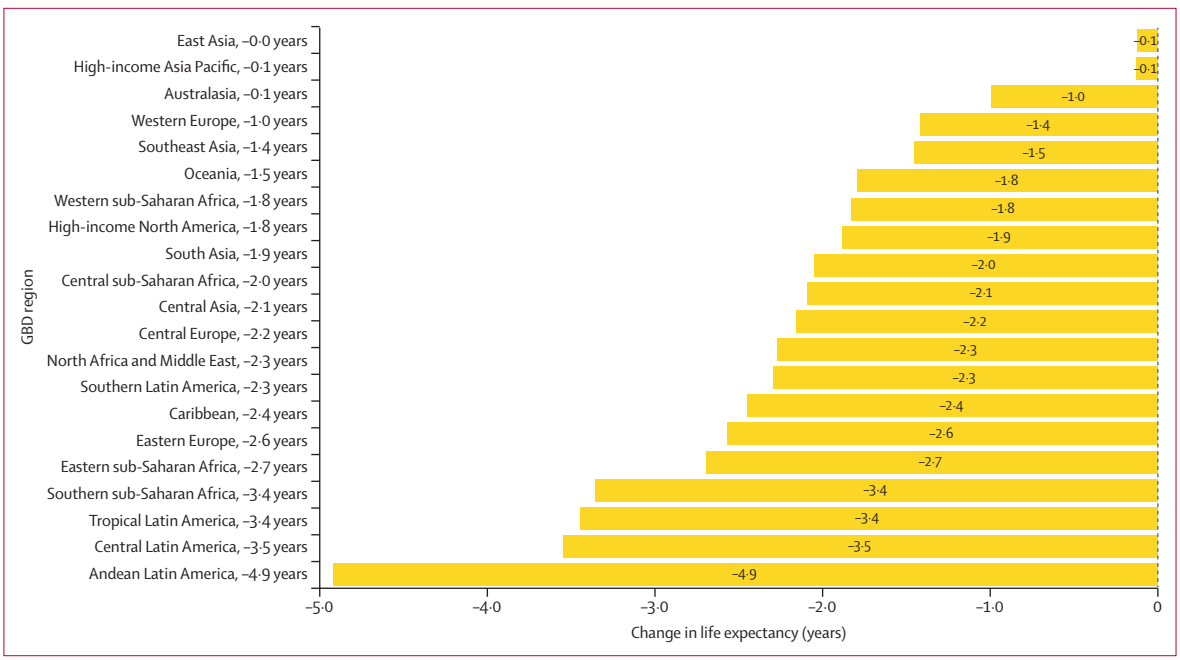


Figure 6: **Effect of COVID-19 on life expectancy by GBD region, 2019–21**
For readability, labels indicating a change in life expectancy of less than 0·05 years are not shown. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

heavily affected by COVID-19. The overall decrease in life expectancy of 4·3 years (95% UI 3·0–5·8) included a reduction of 2·4 years due to HIV/AIDS and 3·4 years due to COVID-19, which were only partly offset by reductions in mortality due to other causes. Notably, COVID-19 reduced life expectancy in Andean Latin America by 4·9 years, although the region had an overall gain of 2·6 years (1·0–4·1) between 1990 and 2021. The effect of COVID-19 in eastern sub-Saharan Africa, which resulted in a reduction in life expectancy of 2·7 years, was offset by steady improvements across many different causes, which resulted in the highest overall increase in life expectancy among GBD regions (10·7 years [9·0–12·2]). Control of enteric infections in this region contributed to an increase in life expectancy of 1·9 years, along with reductions in lower respiratory infections and tuberculosis, each of which contributed to an additional 1·6 years' increase in life expectancy. Each region in sub-Saharan Africa experienced reductions in the number of enteric infections, which improved life expectancy in those regions between 0·8 and 2·4 years.

HIV/AIDS had a substantial negative effect on life-expectancy trends in southern sub-Saharan Africa from 1990 to 2021 (appendix 2 figure S27). Despite improvements in each of the time periods 2000–2010, 2010–2019, and 2019–2021, this region was unable to recover the 9·0 years lost during 1990–2000. Although we found a net decline in deaths due to HIV/AIDS between 2000 and 2019, improvements slowed substantially from 2019 to 2021, when only 0·2 years in life expectancy were gained as a result of reduced HIV/AIDS mortality. Conversely, eastern sub-Saharan Africa had the highest level of recovery to their life expectancy among the regions, gaining 1·5 years of life expectancy over the entire study period.

In 1990, malaria-related deaths had almost no effect on life expectancy in eight of the 21 GBD regions (appendix 2 figure S13). By 2021, however, 90% of malaria deaths across all age groups occurred in locations with only 12% of the global population. Efforts to control malaria in various regions of sub-Saharan Africa have yielded modest gains in life expectancy. Central sub-Saharan Africa gained 0·7 years in life expectancy between 2000 and 2010, western sub-Saharan Africa gained 0·9 years during 2010–19, and eastern sub-Saharan Africa gained 0·7 years in 2000–10. Despite these advancements, many regions with malaria transmission experienced a decline in life expectancy from 2019 to 2021. The most noticeable reductions were in eastern sub-Saharan Africa, with a decrease of 0·2 years, followed by western sub-Saharan Africa, which lost 0·1 years in life expectancy over the same period.

At the national level, some of the highest gains in life expectancy between 1990 and 2021 occurred in the eastern region of sub-Saharan Africa (appendix 2 figure S12). Life expectancy in Ethiopia increased by 18·2 years (95% UI 16·3–19·8) as a result of reductions in deaths from many causes, most notably other communicable and maternal disorders (3·2 years), tuberculosis (3·1 years), and enteric infectious diseases (2·4 year). The largest reduction in life expectancy occurred in Lesotho, at 12·9 years (10·1–15·7), largely attributed to increased deaths from HIV/AIDS, which resulted in a reduction of 7·3 years (appendix 2 figures S12, S27, table S4).

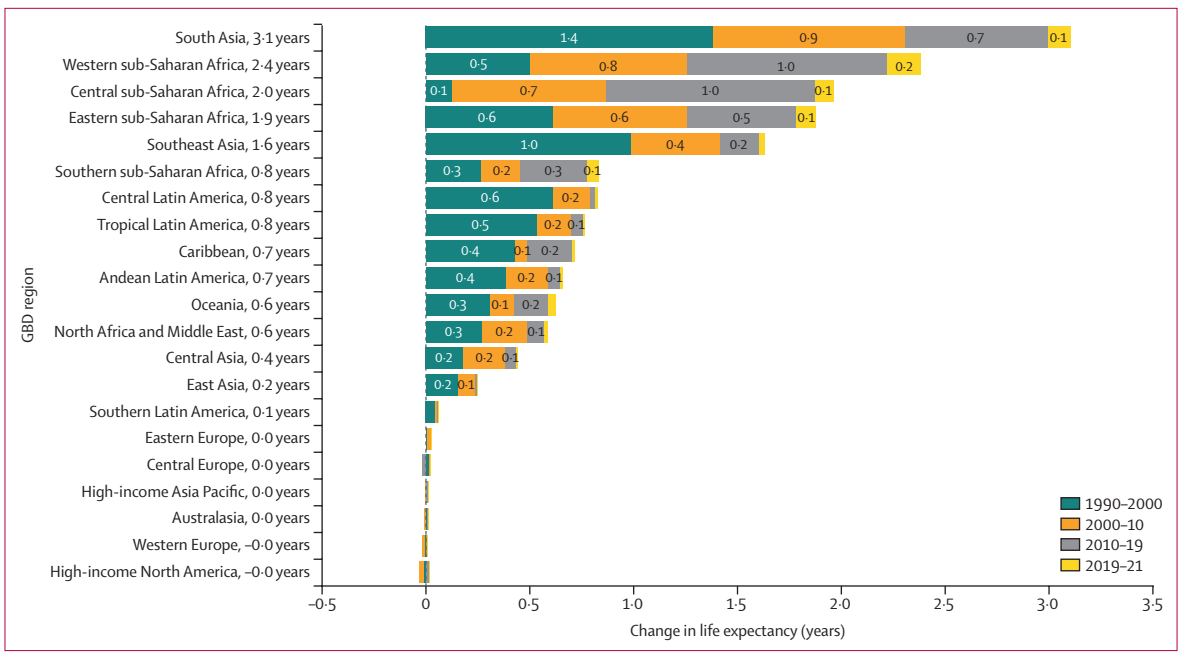


Figure 7: **Effect of enteric infectious diseases on life expectancy by time period and GBD region, 1990–2021**
For readability, labels indicating a change in life expectancy of less than 0·05 years are not shown. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

Effect of CMNN diseases on life expectancy and trends in mortality concentration

Among CMNN causes, several key trends emerged in their effect on global life expectancy and the localisation of deaths over time. First, the reduction of deaths due to enteric disease had a substantial impact on global life expectancy, with notable regional variations (figure 7). As 160 countries and territories made progress in reducing CMNN disease-related mortality, mortality concentration emerged. Deaths became more concentrated into certain countries or regions, persisting alongside advancements made in other parts of the world. An illustrative example is the shift in deaths due to enteric diseases in children younger than 5 years, with 90% of deaths occurring in locations containing 63% of the population of children younger than 5 years in 1990, decreasing to locations containing 51% of the population by 2021 (appendix 2 figure S28). Second, the reduction in the number of lower respiratory infections yielded positive effects on life expectancy in some regions. Regions such as Andean Latin America and western and eastern sub-Saharan Africa had gains of 1·6 years in life expectancy due to reduced deaths from lower respiratory infections. This progress is further underscored by the transformation from 90% of deaths from lower respiratory infections in children younger than 5 years occurring in locations with 71% of the population of the under-5 population in 1990 to 90% occurring in locations with 58% of the under-5 population by 2021, signalling substantial improvements in some regions and increased concentration of this cause in others (figure 8; appendix 2 figure S29). Third, HIV/AIDS had a substantial impact on life-expectancy trends, particularly in southern sub-Saharan Africa, and with 90% of deaths concentrated in locations containing 46% of the entire population and 39% of the under-5 population in 2021 (appendix 2 figures S27, S30). However, HIV/AIDS was less concentrated in 2021 than in 1990. Fourth, efforts to control malaria in sub-Saharan Africa resulted in modest gains in life expectancy. Similarly, 90% of malaria-related deaths in 2021 occurred in locations containing only 12% of the entire population and 20% of the under-5 population, showing mortality concentration (figure 5; appendix 2 figures S13, 31). Fifth, reductions in tuberculosis-related deaths had a positive effect on life expectancy across all regions, and changes in mortality rates indicated mortality concentration, with 90% of deaths occurring in locations containing 66% of the entire population in 1990, decreasing to 62% by 2021 (figure 9; appendix 2 figure S14). Lastly, although measles had a relatively small global effect on life expectancy, this cause showed high mortality concentration. The disease remained contained globally, with 90% of deaths concentrated in locations containing only 15% of the entire population and 24% of the under-5 population in 2021 (figure 3; appendix 2 figure S15).

Reductions in neonatal deaths contributed to a 0·6-year increase in global life expectancy. Also, 90% of neonatal deaths were concentrated in locations containing 71% of the population in 1990, decreasing to 51% by 2021 (appendix 2 figures S16, S34). Finally, nutritional deficiencies had a relatively small global impact on life expectancy but substantial effects on specific regions—eastern sub-Saharan Africa, central

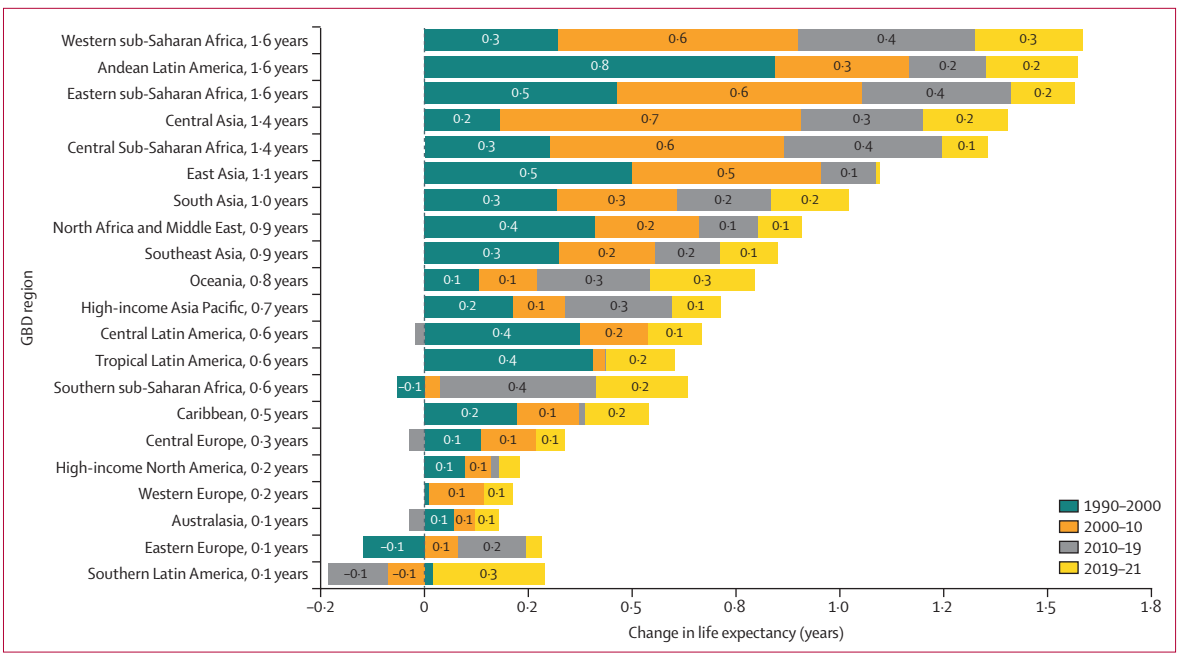


Figure 8: **Effect of lower respiratory infections on life expectancy by time period and GBD region, 1990–2021**
For readability, labels indicating a change in life expectancy of less than 0·05 years are not shown. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

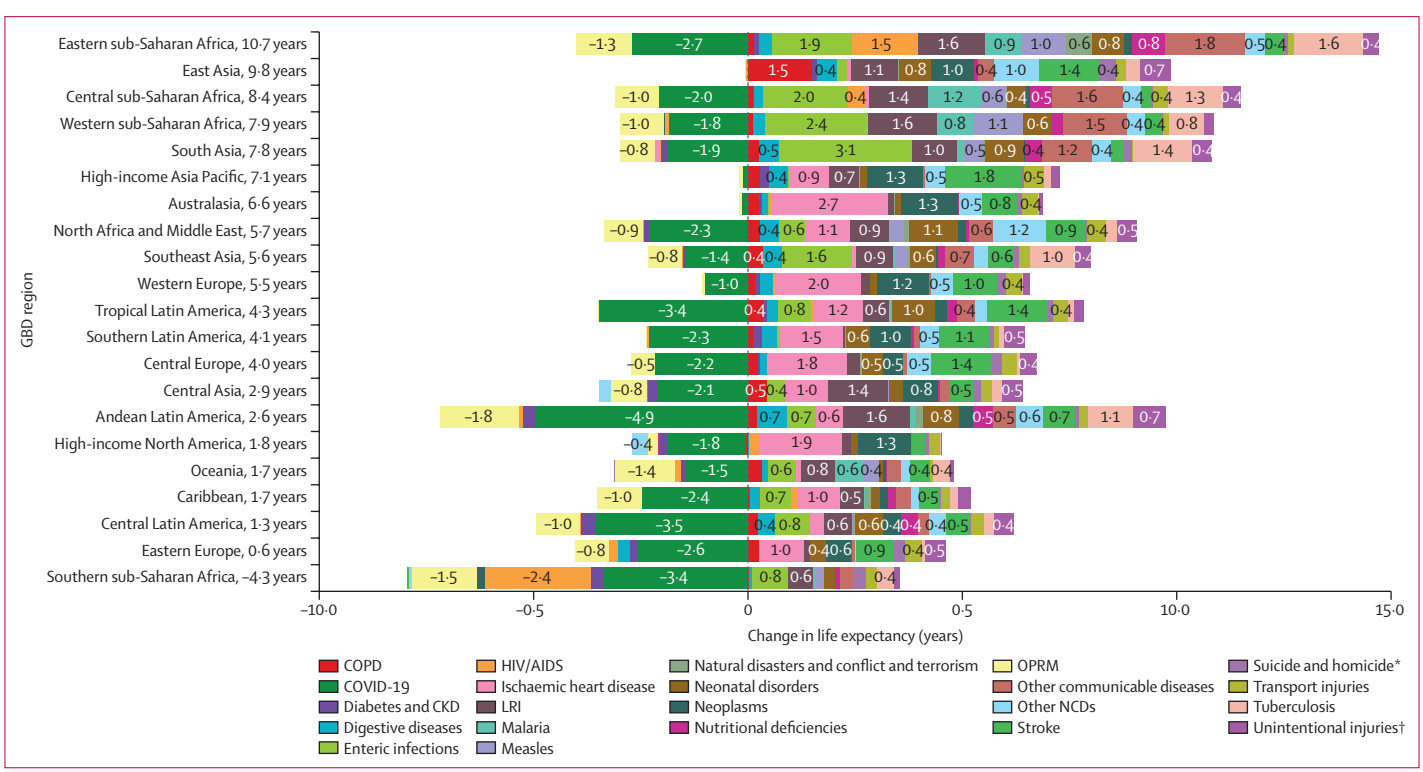


Figure 9: **Change in life expectancy attributable to leading causes of death among GBD regions, 1990–2021**
Each row represents the change in life expectancy from 1990 to 2021 for a given GBD region. A bar to the right of 0 represents an increase in life expectancy due to changes in the given cause, and a bar to the left of 0 represents a decrease in life expectancy for a given cause. For readability, labels indicating a change in life expectancy of less than 0·3 years are not shown. CKD=chronic kidney disease. COPD=chronic obstructive pulmonary disease. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. LRI=lower respiratory infection. NCD=non-communicable disease. OPRM=other pandemic-related mortality. *Does not include war and terrorism. †Does not include natural disasters.

sub-Saharan Africa, and south Asia saw notable increases. We found a shift towards mortality concentration, with 90% of nutritional deficiency-related deaths in children younger than 5 years concentrated in locations containing 49% of the population in this age group by 2021, compared with 59% in 1990 (appendix 2 figures S18, S35). Overall, CMNN diseases showed a large degree of mortality concentration.

Effect of NCDs on life expectancy and trends in mortality concentration

Among NCDs, several findings reflect their effect on global life expectancy and death concentration. Reductions in stroke led to a notable gain in life expectancy of 0·8 years, but stroke deaths were not concentrated, with 90% occurring in locations containing 84% of the global population (appendix 2 figures S23, S36). Similarly, ischaemic heart disease had a substantial effect on improvement to life expectancy, contributing 0·6 years to global life expectancy; yet, as with stroke, ischaemic heart disease showed little mortality concentration, with 90% of deaths concentrated in locations containing 84% of the population in 2021 (appendix 2 figures S17, S37). Neoplasms added 0·6 years to life expectancy, with high-income regions greatly benefiting; as with other NCDs, 90% of neoplasms deaths occurred in locations containing 86% of the population in 2021, indicating a consistent risk of dying from cancer regardless of geography (appendix 2 figures S19, S38). Chronic respiratory diseases contributed an increase of 0·5 years to life expectancy, with east Asia contributing the most to this increase through substantial improvements in mortality in China. Chronic respiratory diseases also showed little mortality concentration, with 90% of deaths occurring in locations containing 79% of the population (appendix 2 figures S20, S39). Digestive diseases and cirrhosis had a substantial negative effect on life expectancy, with little improvement from 2010 to 2019, and showed little mortality concentration (appendix 2 figures S21, S40). Diabetes and kidney diseases had a negative effect on life expectancy, resulting in a global loss of 0·1 years in life expectancy. This cause also had little mortality concentration, with 90% of deaths occurring in locations representing 89% of the population (appendix 2 figures S22, S41). Overall, NCDs largely did not show concentration, meaning that we did not observe mortality from these causes moving towards more restricted geographical areas (appendix 2 figure S42).

Effect of injuries on life expectancy and trends in mortality concentration

The reduction in transport injuries had a positive effect on life expectancy, contributing to a gain of 0·2 years. However, as with NCDs, transport injury-related mortality was not concentrated, with 90% of deaths concentrated in locations containing 88% of the population in 1990, decreasing slightly to 84% of the population by 2021 (appendix 2 figures S24, S43). Unintentional injuries also showed little mortality concentration, with 90% of deaths occurring in locations containing 88% of the population in 2021 (appendix 2 figures S26, S44). Lastly, the overall reduction in mortality rates from self-harm and interpersonal violence contributed to a 0·2-year increase in life expectancy with variable mortality concentration, showing concentration in central and tropical Latin America and South Africa, but not exclusively in these locations (appendix 2 figures S25, S45).

Discussion

Main findings

The COVID-19 pandemic has emerged as one of the most defining global health events of recent history. Our latest comprehensive estimates of cause-specific mortality give insight into the global landscape of disease before and during the first 2 years of the pandemic, revealing the important changes in disease-burden patterns that followed. After more than three decades of consistent improvements in global life expectancy and declining age-standardised death rates, COVID-19 reversed long-standing progress and disrupted trends in the epidemiological transition. As the second leading cause of age-standardised deaths in 2021, COVID-19 had a pronounced influence on the reduction in global life expectancy that occurred. The heterogeneous influence of the disease across the globe provides important insights for improving future pandemic preparedness and ensuring that nations are equitably equipped to respond to new outbreaks. Additionally, our analysis of geographical and temporal trends in mortality enables us to observe the changing patterns in causes of death worldwide. Many causes have exhibited a reduced geographical reach—a reflection of dedicated and persistent mitigation efforts to reduce the burden of certain causes, as well as potential changes to risk-factor exposure.[15] This study offers an opportunity to apply the lessons learned from these successes to further reduce deaths from causes that are now present within smaller, more concentrated areas throughout the world.

The COVID-19 pandemic

The emergence and spread of COVID-19 follows a similar pattern of regional heterogeneity that is common among many leading communicable causes of death, with higher rates of infection and increased fatalities occurring in lower-resource settings.[6,16,17] Although heterogeneity in COVID-19 outcomes in 2020 and 2021 varied by the income status of a country or territory, outcomes were also directly related to age, government actions to close borders, and the implementation of transmission-reduction policies.[18] This general pattern did not always hold true at the national level, however, where estimates from some high-income countries showed a much greater burden than would have been expected, indicating important opportunities for improved pandemic preparedness and response in these nations.[19] The varying effects across

locations emphasises the complexity of the pandemic. Diverse social, economic, and political influences contributed to the variations in death rates observed between locations. In general, areas with advanced health-care systems and robust medical facilities were better able to manage abrupt increases in the number of COVID-19 cases. By contrast, locations with poorer health-care infrastructure were less equipped to handle the surge in infections that occurred,[20] although strong health-care systems did not singularly influence the outcome of the pandemic.[19] Improving preparedness for future pandemics should also include engagement strategies to enhance the trust that individuals place in public health recommendations.[19] Additionally, identifying methods to enhance death-reporting systems[3] and overcome political obstacles to ensure accurate reporting will be crucial steps for monitoring COVID-19 and future pandemic occurrences.[21,22]

Our study shows that COVID-19 was one of the leading global causes of death during the first 2 years of the pandemic and provides an opportunity to delineate between the disease's direct and indirect mortality effects as well as its effect on life expectancy. As previously predicted,[3] COVID-19 shifted baseline patterns of mortality for diseases and injuries that were affected by physical-distancing measures and other government-mandated restrictions. Deferred care-seeking during the height of the pandemic also probably contributed to shifts in patterns of mortality for some diseases and injuries and might also have contributed to the emergence of pandemic-related deaths not attributable directly to COVID-19, lower respiratory infections, measles, malaria, or pertussis (OPRM). Deferred care-seeking might also have been a contributing factor in the notable divergence in the age distribution in deaths between COVID-19 and OPRM, whereby COVID-19 deaths were substantially higher in older ages, whereas the highest rate of OPRM was seen in older ages as well as in children younger than 23 months. Mortality might have increased in the youngest ages because caregivers might have hesitated to seek medical care during the peak of the virus's spread. Understanding these disparities is imperative for shaping future health policies and preparedness efforts.

Important trends in life expectancy

Advancements over the past three decades in the prevention and control of infectious diseases have contributed to increases in life expectancy in many locations, increasing the need to support populations living with NCDs.[23] The global decline in life expectancy that occurred in 2020 and 2021 confounds the longer-term trend of increase.[10] Our decomposition analysis suggests that this decline was predominantly a result of the pandemic (combined COVID-19 and OPRM), but the degree of severity varied greatly by location. Although large improvements in many causes—including HIV/AIDS and lower respiratory and enteric infections—somewhat counterbalanced the decline, the decrease in life expectancy was also compounded by increasing rates of mortality from other causes, such as diabetes and kidney diseases.

The effect of COVID-19 on life expectancy showed varying degrees of severity, ranging from a large loss of 4·9 years in Andean Latin America to almost no change in east Asia. From 1990 to 2021, reductions in many of the leading causes of death resulted in overall life-expectancy increases across most regions, despite heavy setbacks for many because of the COVID-19 pandemic. We found that despite Andean Latin America having the largest regional reduction in life expectancy due to the pandemic, overall life-expectancy reductions across the region were tempered by improvements in other causes, with reductions in rates of death from lower respiratory infections and neonatal disorders responsible for an increase in life expectancy of 2·6 years overall between 1990 and 2021. The impressive reductions in neonatal disorders throughout many countries in Andean Latin America have been attributed to the improvements made in implementing effective maternal and neonatal health intervention strategies.[24]

The reduction in life expectancy in southern sub-Saharan Africa also exceeded the global average by a substantial margin, with a reduction of 3·4 years due to COVID-19. Although life expectancy in the region was substantially affected by the COVID-19 pandemic, the reduction was also attributable to high mortality rates from HIV/AIDS. Some nations with high pandemic-related death tolls were among those already burdened by high rates of other infectious diseases. Several countries in southern sub-Saharan Africa navigated the challenges of the pandemic, alongside long histories of combatting some of the highest HIV/AIDS prevalence rates in the world.[25,26] A subset of countries were faced with a triple burden of COVID-19, HIV/AIDS, and tuberculosis.[27] The combined burden of these causes across southern sub-Saharan Africa was not offset by sufficient improvements in mortality from other causes, leading to an overall reduction in the region's life expectancy of more than 4 years over the entire study period.

Cause-specific patterns of mortality concentration

Estimates of mortality concentration reflect shifting patterns of disease over time, from diseases that have a widespread presence moving to more geographically reduced subsets of the global population. These changes highlight differences between populations and their progress towards reducing mortality due to diseases and injuries. These findings also provide an important opportunity to improve how best public health practices are applied to further disease reduction. Broadly, widespread declines in many communicable diseases resulted in mortality from these causes exhibiting more

concentrated geographical distributions in 2021 relative to patterns seen in 1990. The degree of mortality concentration estimated by this study for enteric and lower respiratory infections, malaria, HIV/AIDS, neonatal disorders, and tuberculosis reflects substantial global progress in reducing mortality from these causes over the study period, underscoring the success of several public health campaigns, global commitments, and improvements in communicable-disease programmes.[28–30] Estimates of mortality concentration can be used to examine where disease mitigation strategies have been successful, where they can be further implemented to reduce inequality, and where more research might be needed to develop effective treatment and intervention strategies.

Notably, our estimates support previous findings[31] that show deaths from malaria are becoming increasingly concentrated and are now particularly concentrated within western sub-Saharan Africa, with an additional corridor running through central Africa and into Mozambique. Countries in western sub-Saharan Africa with the highest under-5 death rates from malaria in 2021 included Burkina Faso, Sierra Leone, and Niger. This concentration of malaria mortality reflects both differential rates of population growth across Africa, as well as the varying rates of progress in reducing transmission, most notably by malaria nets treated with long-lasting insecticide and in strengthening case management.[32] At a time of growing threats to progress against malaria, including emerging parasite and vector resistance and budgetary pressures, but also amid promising new tools such as second vaccine for malaria, it is more important than ever that changing patterns of mortality are quantified and understood.[33,34]

Enteric infections showed large disease concentration. Under-5 deaths from enteric infections were largely concentrated within sub-Saharan Africa and south Asia. Countries in sub-Saharan Africa and south Asia with the highest under-5 death rates from enteric infections in 2021 included Chad, South Sudan, and the Central African Republic. There are many contributing factors that should be considered when examining how to reduce enteric infections in the remaining concentrated locations. Alongside the provision of oral rehydration solution and rotavirus vaccines, critical public health improvements such as in water, sanitation, and hygiene might have contributed to decreases in enteric deaths.[35,36] Childhood growth failure, also a leading risk factor for deaths from lower respiratory infections, malaria, and measles, must be addressed through interventions to improve women's health including anaemia, promotion of early exclusive breastfeeding, and management of acute malnutrition, among others.[37,38] Countries with the highest burden of infectious disease mortality in children younger than 5 years tend to be geographically clustered, suggesting multisectoral approaches are necessary to continue reducing mortality in the countries with the highest rates.[39]

A broad and recurring theme from this study is that reductions in enteric infections contributed to improved life expectancies over the past several decades. The reductions in childhood mortality associated with diarrhoeal diseases that have occurred across many parts of Africa[35,40–42] can also be partly explained by many combined local efforts in improved immunisation;[43] access to water, sanitation, and hygiene facilities;[12,44] breastfeeding;[45] oral rehydration therapy;[46] and zinc supplementation,[15] alongside global initiatives such as the Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea.[47] Given that enteric disease-related mortality and specifically diarrhoeal disease-related mortality continued to decline during the COVID-19 pandemic, the post-pandemic period might offer opportunities to accelerate progress on prevention and treatment. Diarrhoeal diseases are particularly amenable to public health intervention, and given this cause's high burden among children, we must continue to direct resources towards its prevention.[47,48] Several locations still do not have the necessary financing, governance, and political commitment to reduce rates of enteric infections.[49] To accelerate progress in reducing enteric disease-related mortality, routine and catch-up immunisation programmes must be strengthened and expanded, including building on the global success of the rotavirus roll-out[50] and countering disruptions in childhood immunisation during the pandemic.[51] Additionally, efforts should focus on advancing candidate vaccines against enterotoxigenic *Escherichia coli*, norovirus, and shigella.[51–55]

Our study also found that some vaccine-preventable diseases, such as measles, have shown widespread reductions in mortality rates and were geographically concentrated. Under-5 deaths from measles were concentrated within western and eastern sub-Saharan Africa. Although multiple factors contribute to decreases in infectious disease burden, improvements in measles mortality have largely been attributable to the global availability of a safe and effective vaccine against measles, producing life-long immunity, with two-dose efficacy exceeding 95%.[56] Measles incidence has decreased dramatically where vaccination efforts have been successful, including North America, South America, Europe, and Australia;[57–61] although, since 2016, endemic measles transmission has been re-established in ten countries that previously had achieved measles elimination.[61] We found that, as of 2021, measles mortality was concentrated in countries and regions with insufficient access to the measles vaccine, particularly in sub-Saharan Africa. Although valuable insights can be drawn from countries that have achieved measles control through effective vaccination programmes and surveillance systems, interventions still must be tailored to the affected communities and countries for successful reductions in mortality.[62]

Some infectious diseases, such as HIV/AIDS, also showed mortality concentration. Deaths from HIV/AIDS

were largely concentrated within sub-Saharan Africa, most notably southern sub-Saharan Africa. Countries in sub-Saharan Africa with the highest age-standardised mortality rate in 2021 included Lesotho, Eswatini, and Botswana. Countries in sub-Saharan Africa with the highest under-5 death rates from HIV in 2021 included Lesotho, Equatorial Guinea, and Guinea-Bissau. This concentration highlights how HIV-control campaigns, preventative measures,[63,64] improved treatment with the emergence of antiretroviral therapy,[65] access to testing and health care,[66] and research advancements might have contributed to the reduced global mortality of HIV. Despite these successes, substantial barriers remain to reducing HIV mortality, such as stigma discouraging people from accessing treatment and care,[67,68] insufficient health-care infrastructure,[69] access to testing,[70] coverage of antiretroviral therapy,[71] and complications due to co-occurring diseases such as tuberculosis and HIV.[72] Preventative measures are particularly important for the reduction of HIV mortality because HIV prevalence is the primary contributor to high mortality rates. Although countries can learn from successful HIV campaigns and strategies, global support is needed to ensure HIV treatment and preventative measures are accessible to all populations at risk.[70,73,74]

In many high-income nations, the overall rate of neonatal deaths decreased between 1990 and 2021, becoming more concentrated over time. Deaths from neonatal disorders in 2021 were concentrated within sub-Saharan Africa and south Asia.[75] Countries in these regions with the highest under-5 death rates from neonatal disorders in 2021 included Mali, South Sudan, and Sierra Leone. However, the disparity in mortality between high-income and low-income countries and regions highlights inequality in progress. Newborn care that can reduce mortality includes resuscitation, prevention of hypothermia and infection, in-facility delivery, and exclusive breastfeeding.[76,77] Neonatal mortality might be reduced globally if policy makers examine the strategies that led to successes elsewhere.[78]

Conversely, although the burden of many NCDs has also been reducing, these causes have typically not followed the same pattern of mortality concentration seen in CMNN diseases. These trends emphasise a key distinction in the spatial dynamics of NCDs compared with many communicable diseases. Although non-communicable causes might not exhibit the same degree of concentration as communicable causes, the mortality burden has changed in distribution, reducing over time in high-income countries and regions, while persisting in low-income countries and regions. Age-standardised mortality rates due to NCDs decreased in most locations within the high-income; Latin America and the Caribbean; north Africa and the Middle east; and central Europe, eastern Europe, and central Asia super-regions between 1990 and 2021. However, NCDs in the south Asia; sub-Saharan Africa; and southeast Asia, east Asia, and Oceania super-regions have either increased or decreased at notably lower levels in 2021 compared with in 1990. Examples of this trend include ischaemic heart disease, neoplasms, and stroke, all of which largely declined over the study period—although their reductions have been widely dispersed and not as targeted as the CMNN causes. These findings show that NCDs do not appear to be moving towards more condensed geographical locations over time in the same way that many CMNN diseases are, which could make interventions and policies more complex to implement.

Ultimately, the extent of mortality concentration reflects both the progress achieved in health-care advancements and the shortcomings that persist in their equitable implementation. Disease concentration is evidence that there are effective interventions and policies that have successfully reduced disease burden in many locations, but these innovations have not been equitably distributed throughout the world or have been ineffective at addressing the specific challenges certain populations face. There remains a global need to improve access to new interventions and vaccines, to invest in the implementation of validated public health policies, and to strategise with geographical sources of disease in mind. Future efforts should continue the ongoing mitigation of communicable diseases, focusing on locations where these causes have become more geographically concentrated, while also initiating efforts to combat chronic causes within low-resourced settings. Additionally, patterns of high geographical concentration among infectious causes and low geographical concentration among chronic causes reflect the global epidemiological transition, wherein mortality rates of infectious deaths declined throughout most years of our study. The increased concentration of a cause of death, particularly communicable diseases, illustrates success in mitigation that can be adapted within the countries and regions with mortality concentration identified in our study, with the potential to greatly reduce mortality from those causes of death.

Limitations

Methodological advancements have enabled GBD 2021 to produce cause-specific estimates of mortality more easily than in previous iterations; however, as with any study of this scope, there are several important limitations to acknowledge. Cause-specific limitations for every cause of death in GBD are detailed in appendix 1 (section 3). Here, we describe cross-cutting limitations with applicability across many causes. First, sparsity of data or unreliability of data from specific regions, time periods, or age groups can influence the accuracy of our estimates, particularly poor data quality and coverage from western, eastern, southern, and central sub-Saharan Africa and south Asia. Second, the quality of cause-of-death and verbal-autopsy data rely on accurately coded death certificates to the international standards set by the International Classification of Diseases and are

subject to the practice of the doctor completing the death certificate, who may or may not have received training to facilitate comparability of reporting underlying causes of death. This process is further complicated by comorbidities at the time of death, which might affect the accuracy of both vital-registration and verbal-autopsy data sources. A key data-processing method for GBD is the re-allocation of incorrectly or vaguely assigned deaths—referred to as garbage codes[11]—to a more accurate, plausible underlying cause of death. This step helps to create comparable cause-specific estimates of mortality by underlying cause. Third, GBD assesses quality of cause-of-death data partly by examining levels of completeness, which indicate the accuracy with which the vital registration can capture deaths that occur in a location-year, irrespective of the percentage of garbage coding. Data completeness depends on the percentage of well-certified data, which is not necessarily indicative of low garbage coding. Fourth, some sources of uncertainty, including the covariates used in models, are not captured in our estimation process. Fifth, we used a negative binomial modelling approach to improve our estimation of deaths for some causes with over-dispersed data, but do not have a standardised empirical approach for selecting causes to which we apply this method. Sixth, to provide estimates for locations with low levels of completeness, as well as to address the lags in data reporting that occur, our estimates for the most recent years depend more heavily on the modelling process. For causes where data are limited, providing estimates with appropriate uncertainty is preferable to providing no information. Seventh, in the calculation of life expectancy decomposition, there is instability when the difference in all-cause deaths is too small. In this case, we use the reduced Das Gupta equation (appendix 1 section 7). Additionally, to avoid assigning positive life-expectancy contributions to COVID-19-related causes, if the signs for the change in life expectancy and all-cause deaths were the same, we used the same reduced Das Gupta formula, except in the case that the cause in question was COVID-19-related (either COVID-19 or OPRM), when a modified version was used. When viewing life expectancy decomposition, it is important to understand the effects of fatal discontinuity events, such as earthquakes or conflict. If life-expectancy decomposition is calculated for 2 consecutive years, we can see the effect of unique, stochastic events, but for the longer time periods, the interpretation of the effect of these events will be misleading. This method works well with causes that have continuous time trends, and not for causes that have mortality spikes in select years and locations. This type of event confounds true health trends within a time period because the absence or presence of a disaster is seen as a change in life expectancy. Finally, this cycle of GBD contains additional limitations that pertain to modelling deaths and related mortality from the COVID-19 pandemic. The limitations of the methods used to calculate COVID-19 have been fully outlined in previous publications,[12] but it is important to reiterate that COVID-19 estimates are limited by data-source availability. The methods to estimate COVID-19-related deaths were especially limited in certain regions, such as sub-Saharan Africa, which means our estimates in these areas are solely driven by relationships with covariates. Future development of these data sources is crucial because estimates improve as the quality of the underlying data sources improves. Subsequent GBD cycles will provide revised estimates after additional data for recent years become available.

Future directions

In the next iteration of GBD, we will include over 100 location-years of vital registration and other data types that have been reported since GBD 2021 estimates were produced. Additionally, we will continue to expand the estimation of causes of death by disaggregating broad categories of causes of death into more detailed causes where available. These improvements aim to enhance precision and timeliness of estimates of COVID-19-related deaths and other cause of death. We also plan to simplify our approach to estimating COVID-19-related deaths. In lieu of the residual OPRM category reported in GBD 2021, we will use all available location-years of cause-of-death data to attribute mortality to specific causes, removing this residual category. We anticipate that this method will facilitate more timely and actionable insights for public health planning and policy making, especially as we expect to observe more regular and modellable mortality patterns in the post-pandemic years. Through these advancements, we will improve the utility and accuracy of the GBD study as a tool for effective public strategies.

Conclusion

Findings from GBD 2021 provide a comprehensive overview of long-term mortality trends along with important insights into the COVID-19 pandemic years. The COVID-19 pandemic fundamentally changed the landscape of global health and mortality. As a leading cause of death, COVID-19 reduced life expectancy in 2 years nearly as much as reductions in communicable and NCDs have improved it over decades. The changes in mortality caused by the pandemic were not predictable through the standard GBD estimation methods and required the development and application of novel estimation methods as the pandemic emerged in real time. These timely updates on causes of death are essential for monitoring progress, identifying prevailing health concerns, guiding targeted interventions, and optimising resource allocation. GBD 2021 shows that better life expectancy outcomes might be achieved by leveraging past successes in mortality reduction. If future policy efforts are guided by the successes made in countries and regions with effective disease-mitigation

programmes, such achievements might be replicated in locations where high mortality persists. While COVID-19 and other health challenges continue, GBD 2021 can offer valuable guidance for public health investment and policy making.

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Please see appendix 1 section 10 for more detailed information about individual author contributions to the research, divided into the following categories: managing the overall research enterprise; writing the first draft of the manuscript; primary responsibility for applying analytical methods to produce estimates; primary responsibility for seeking, cataloguing, extracting, or cleaning data; designing or coding figures and tables; providing data or critical feedback on data sources; developing methods or computational machinery; providing critical feedback on methods or results; drafting the manuscript or revising it critically for important intellectual content; and managing the estimation or publications process. The lead, corresponding, and senior authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

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Data sharing

To download the data used in these analyses, please visit the Global health Data Exchange GBD 2021 website (https://ghdx.healthdata.org/gbd-2021/sources).

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