

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*



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.

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*Collaborators are listed at the end of the Article

Correspondence to:
Prof Simon I Hay, Institute for
Health Metrics and Evaluation,
University of Washington,
Seattle, WA 98195, USA
sihay@uw.edu

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

See Online for appendix 1

(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.

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.

Data sources, processing, and assessing for completeness

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

For the GBD data sources see
<http://ghdx.healthdata.org/gbd-2021>

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 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

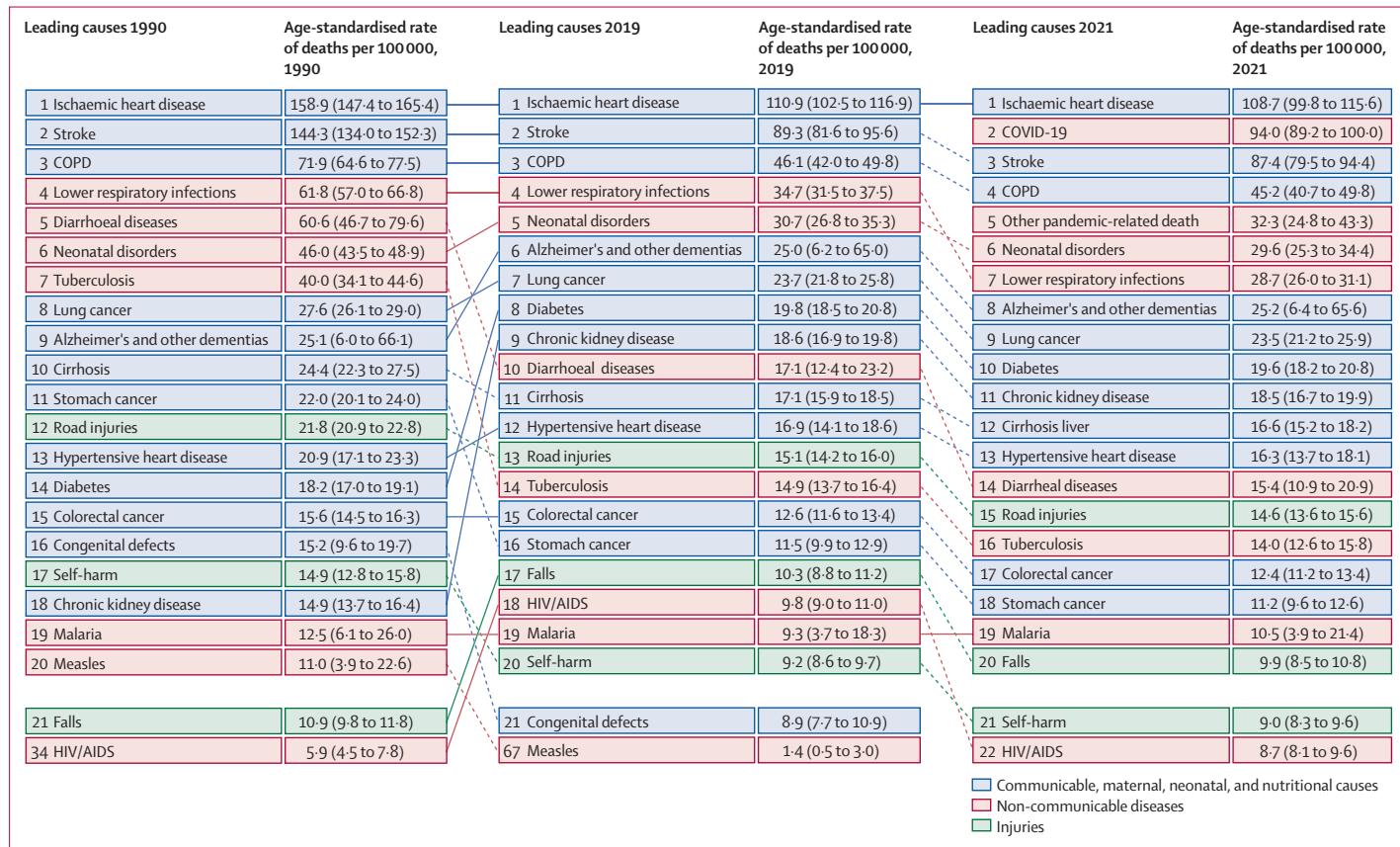


Figure 1: Leading Level 3 causes of global deaths and age-standardised death rate per 100 000 population for males and females combined, 1990, 2019, and 2021

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.

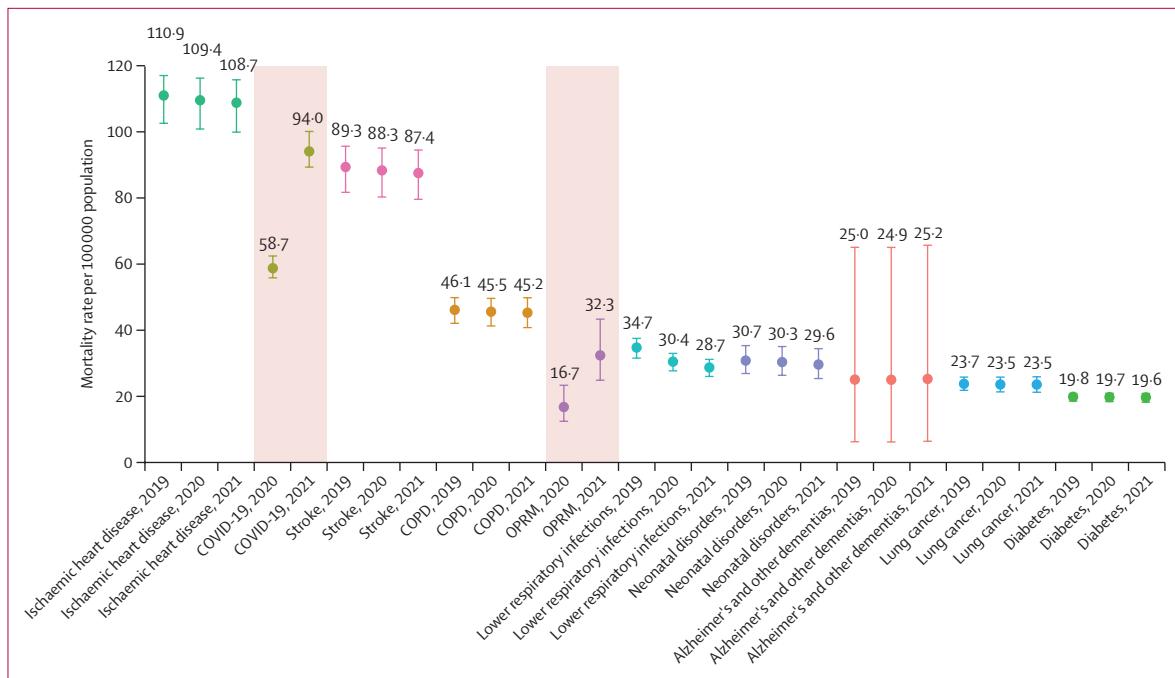


Figure 2: Age-standardised mortality rate per 100 000 population for the ten leading Level 3 causes of death globally, 2019–21

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.

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.

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

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 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

See Online for appendix 2

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

	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
	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)
	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)
2	Cause	Stroke	Stroke	COVID-19	Ischaemic heart disease	COVID-19	Chronic obstructive pulmonary disease	Ischaemic heart disease
	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)
	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)
3	Cause	COVID-19	COVID-19	Stroke	Stroke	Stroke	COVID-19	Chronic obstructive pulmonary 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)
	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)
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
	Age-standardised rate (per 100 000 population)	45.5 (41.2–49.6)	41.0 (32.9–51.9)	26.5 (6.7–65.1)	36.5 (33.9–38.9)	40.2 (32.0–46.7)	83.3 (75.7–90.4)	34.8 (29.0–41.0)
	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)
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
	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 (6.7–74.8)
	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 (386 000–1 490 000)
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
	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)
	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)

(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
	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)
	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)
8	Cause	Tracheal, bronchus, and lung cancer	Lower respiratory infections	Chronic kidney disease	Interpersonal violence	Chronic obstructive pulmonary disease	Tuberculosis	Stomach cancer
	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)
	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)
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
	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)
	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)
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
	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)
	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)
2021								
1	Cause	Ischaemic heart disease	Ischaemic heart disease	Ischaemic heart disease	COVID-19	Ischaemic heart disease	COVID-19	Stroke
	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)
	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)
2	Cause	COVID-19	COVID-19	COVID-19	Ischaemic heart disease	COVID-19	Ischaemic heart disease	Ischaemic heart disease
	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)
	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)
								544 000 (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	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 (425 000–1 670 000)	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)

(Table 1 continues on next page)

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).

	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)								
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
	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)
	Number	1960 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)
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
	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)
	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)
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
	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)
	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)
								48.6 (40.3-58.1)
								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

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).

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

	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	26647	0·3	0·5	44·4	49·6	<0·1%	<0·1%	3·1%	3·6%
6–11 months	234	394	20478	30883	0·4	0·6	31·7	48·9	<0·1%	0·1%	3·5%	5·5%
12–23 months	998	1644	19042	30550	0·8	1·3	14·5	23·8	0·2%	0·3%	3·7%	6·2%
2–4 years	8500	14386	14730	23574	2·1	3·6	3·6	5·8	1·2%	2·1%	2·0%	3·4%
5–9 years	7052	11393	5377	8196	1·0	1·7	0·8	1·2	1·9%	3·2%	1·5%	2·3%
10–14 years	8553	14405	1588	2715	1·3	2·2	0·2	0·4	2·8%	4·8%	0·5%	0·9%
15–19 years	17032	26852	5932	12576	2·8	4·3	1·0	2·0	3·1%	4·8%	1·1%	2·2%
20–24 years	25528	40743	8219	17453	4·3	6·8	1·4	2·9	3·6%	5·5%	1·2%	2·4%
25–29 years	47857	78496	12581	28816	8·1	13·3	2·1	4·9	5·9%	9·2%	1·6%	3·4%
30–34 years	81232	137979	21625	49808	13·4	22·8	3·6	8·2	7·9%	12·3%	2·1%	4·5%
35–39 years	112228	195380	29877	69402	20·5	34·8	5·5	12·4	9·0%	14·1%	2·4%	5·0%
40–44 years	165337	287099	44391	102041	33·5	57·4	9·0	20·4	10·3%	16·0%	2·8%	5·7%
45–49 years	207940	355388	55989	124899	44·0	75·1	11·8	26·4	10·1%	15·7%	2·7%	5·5%
50–54 years	253491	426785	67629	147651	57·7	95·9	15·4	33·2	9·1%	14·0%	2·4%	4·8%
55–59 years	336162	564508	90815	191441	87·5	142·7	23·6	48·4	9·0%	13·8%	2·4%	4·7%
60–64 years	460769	774879	125433	262008	146·1	242·1	39·8	81·9	9·8%	15·0%	2·7%	5·1%
65–69 years	564371	957557	155431	321301	209·4	347·1	57·7	116·5	9·4%	14·5%	2·6%	4·9%
70–74 years	585549	989888	156931	325295	298·7	480·9	80·1	158·0	8·8%	13·2%	2·4%	4·3%
75–79 years	539515	861796	135849	276402	417·1	653·4	105·0	209·6	7·9%	11·8%	2·0%	3·8%
80–84 years	551014	888813	146084	277786	638·9	1014·8	169·4	317·2	7·5%	11·3%	2·0%	3·5%
85–89 years	427770	658875	106842	191824	959·3	1441·1	239·6	419·5	6·9%	10·0%	1·7%	2·9%
90–94 years	280605	426185	67297	114449	1608·9	2382·3	385·9	639·8	7·5%	10·8%	1·8%	2·9%
≥95 years	120173	174390	24074	42104	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

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 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

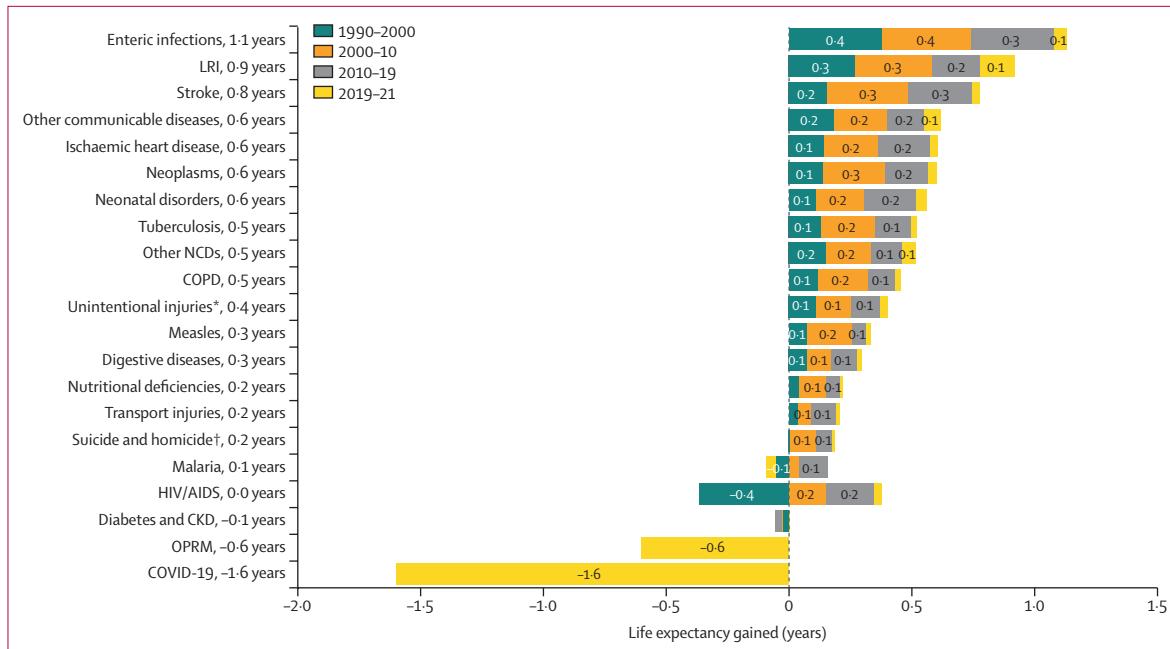


Figure 3: Change in life expectancy attributable to leading causes of death for males and females combined, 1990–2000, 2000–10, 2010–19, and 2019–21, globally

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.

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 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,

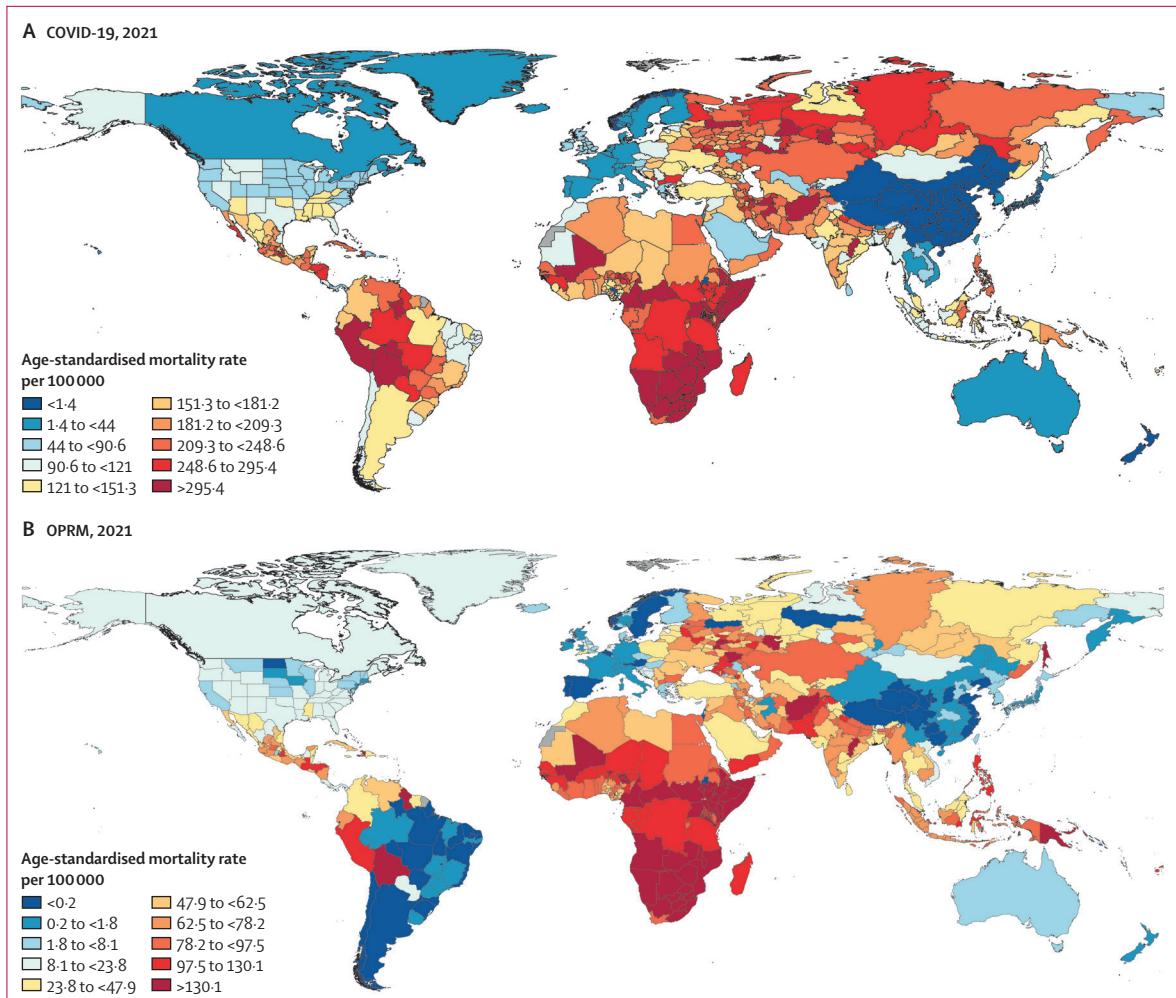


Figure 4: Age-standardised mortality rate of COVID-19 and OPRM, 2021

Global choropleth maps of COVID-19 (A) and OPRM (B) for 2021 that show sub-national detail where available. OPRM=other pandemic-related mortality.

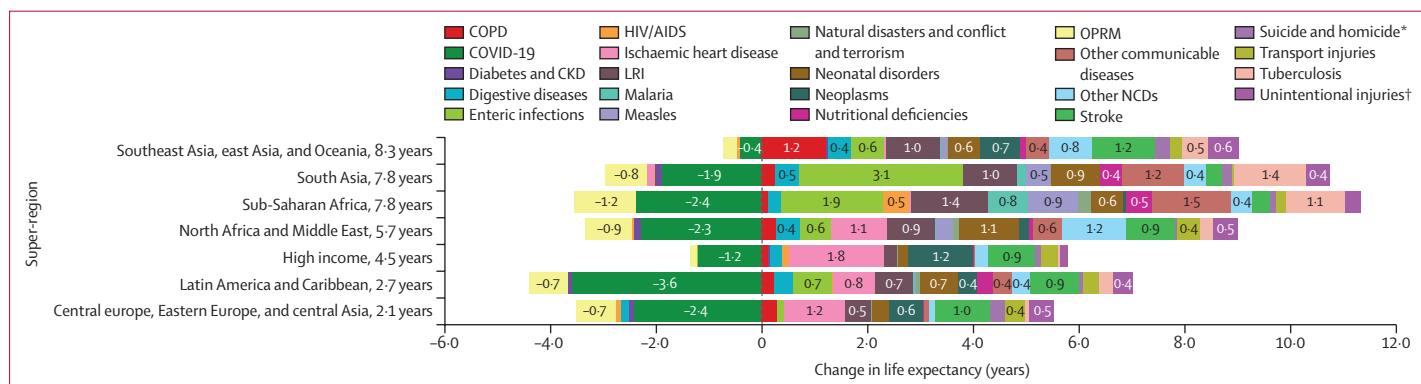


Figure 5: Change in life expectancy attributable to leading causes of death among super-regions, 1990–2021

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.

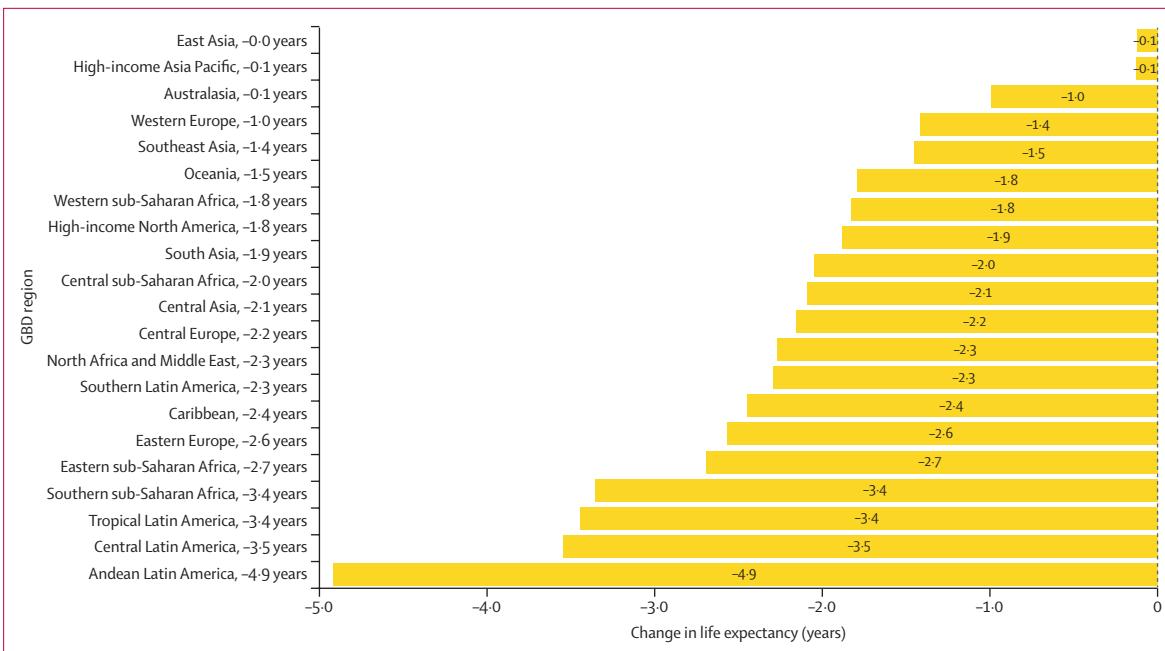


Figure 6: Effect of COVID-19 on life expectancy by GBD region, 2019-21

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.

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).

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

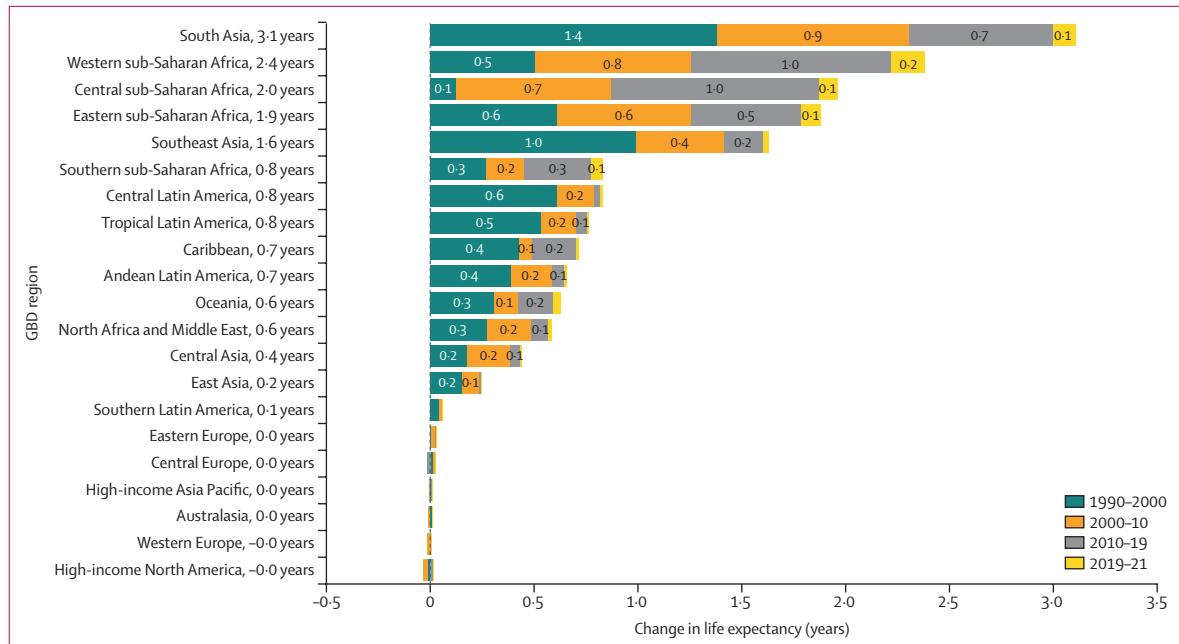


Figure 7: Effect of enteric infectious diseases on life expectancy by time period and GBD region, 1990–2021

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.

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, S31). 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 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

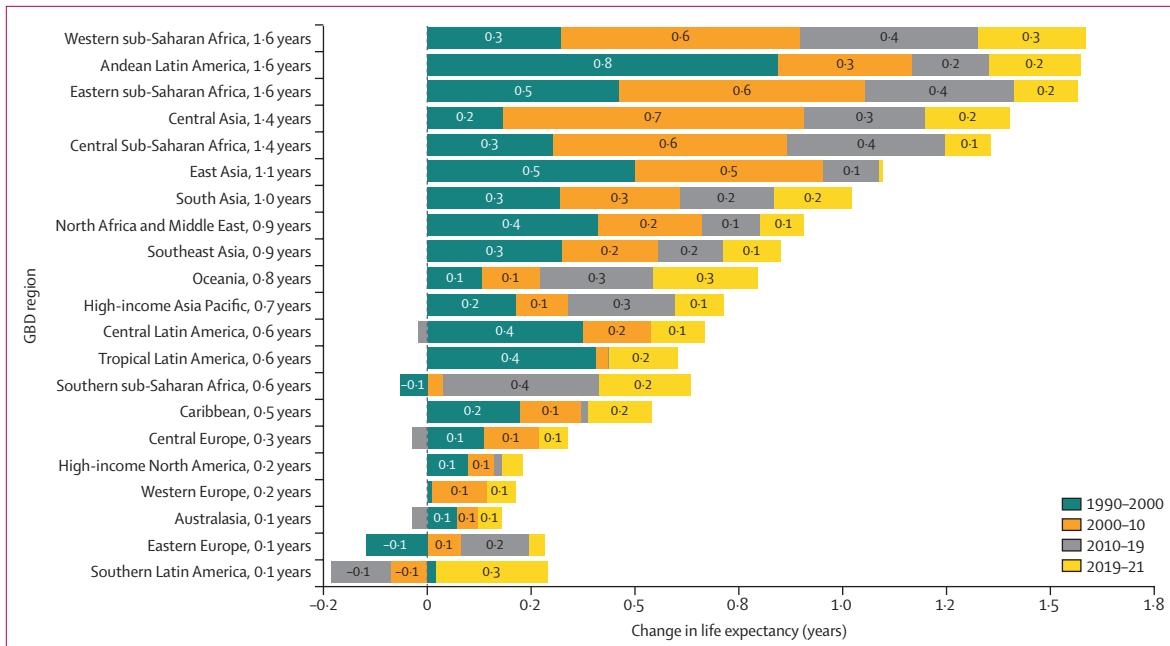


Figure 8: Effect of lower respiratory infections on life expectancy by time period and GBD region, 1990–2021

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.

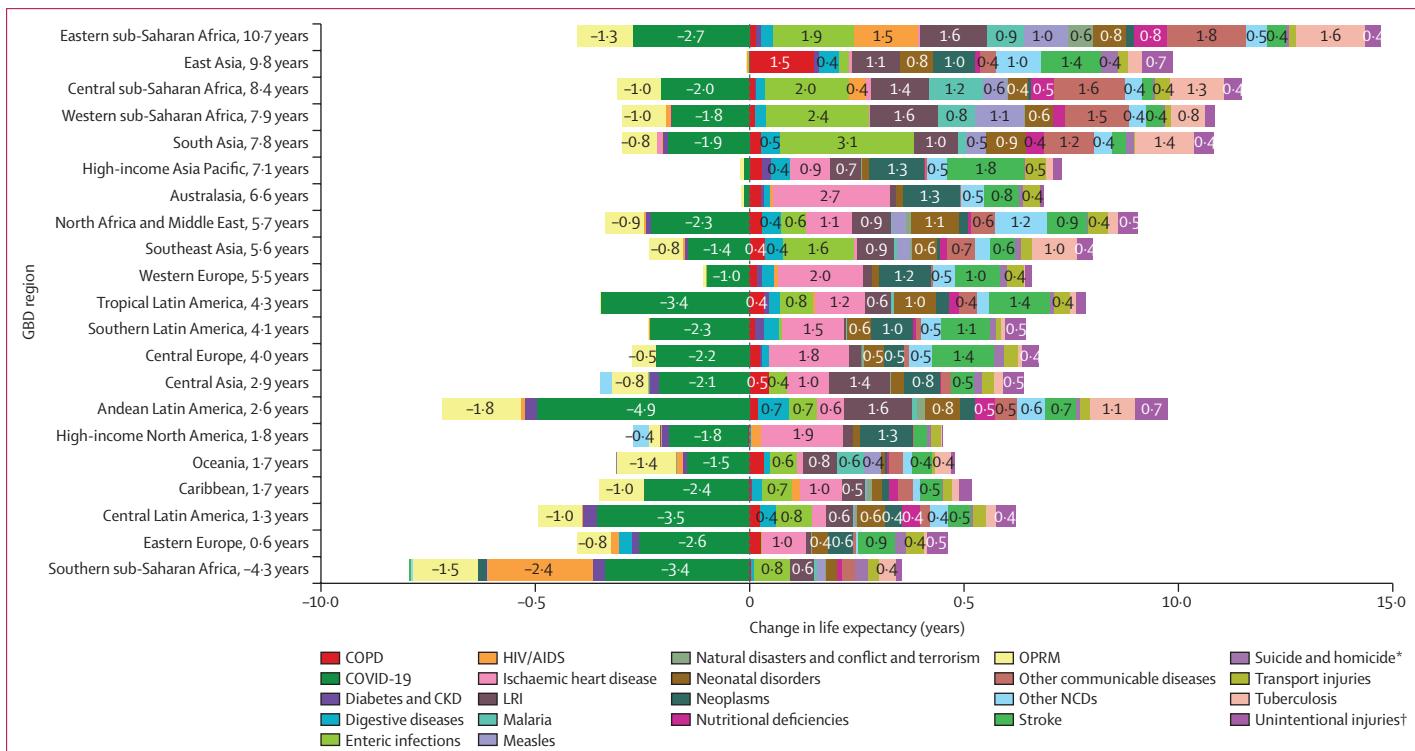


Figure 9: Change in life expectancy attributable to leading causes of death among GBD regions, 1990–2021

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.

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 systems³ 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 findings³¹ 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-out⁵⁰ 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 codes⁷¹—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.

GBD 2021 Causes of Death Collaborators

Mohsen Naghavi*, Kanyin Liane Ong*, Amiral Ali, Hazim S Ababneh, Yohannes Habtegiorgis Abate, Cristiana Abbafati, Rouzbeh Abbasgholizadeh, Mohammadreza Abbasian, Mohsen Abbasi-Kangevari, Hedayat Abbastabar, Samar Abd ElHafeez, Michael Abdelmasseh, Sherief Abd-Elsalam, Ahmed Abdelwahab, Mohammad Abdollahi, Mohammad-Amin Abdollahifar, Meriem Abdoun, Deldar Morad Abdulah, Auwal Abdullahi, Mesfin Abebe, Samrawit Shawel Abebe, Aidin Abedi,

Kedir Hussein Abegaz, E S Abhilash, Hassan Abidi, Olumide Abiodun, Richard Gyan Aboagye, Hassan Abolhassani, Meysam Abolmaali, Mohamed Abouzid, Girma Beressa Aboye, Lucas Guimaraes Abreu, Woldu Aber Abhra, Dariush Abtahi, Samir Abu Rumeileh, Hasan Abualruz, Bilyaminu Abubakar, Eman Abu-Ghribieh, Niveen ME Abu-Rmeileh, Salahdein Aburuz, Ahmed Abu-Zaid, Manfred Mario Kokou Accrombessi, Tadele Girum Adal, Abdu A Adamu, Isaac Yeboah Addo, Giovanni Addolorato, Akindele Olupelumi Adebiyi, Victor Adekanmbi, Abiola Victor Adepoju, Charles Oluwaseun Adetunji, Juliana Bunmi Adetunji, Temitayo Esther Adeyeoluwa, Daniel Adedayo Adeyinka, Olorunsola Israel Adeyomoye, Biruk Adie Adie Admass, Qorinah Estiningtyas Sakilah Adnani, Saryia Adra, Anuoluwapo Adeyimika Afolabi, Muhammad Sohail Afzal, Saira Afzal, Suneth Buddhika Agampodi, Pradyumna Agasthi, Manik Aggarwal, Shahin Aghamiri, Feleke Doyore Agide, Antonella Agodi, Anurag Agrawal, Williams Agyemang-Duah, Bright Opoku Ahinkorah, Aqeel Ahmad, Danish Ahmad, Firdos Ahmad, Muayyad M Ahmad, Sajjad Ahmad, Shahzaib Ahmad, Tauseef Ahmad, Keivan Ahmadi, Amir Mahmoud Ahmadzade, Ali Ahmed, Ayman Ahmed, Haroon Ahmed, Luai A Ahmed, Mehrunnisha Sharif Ahmed, Meqdad Saleh Ahmed, Muktar Beshir Ahmed, Syed Anees Ahmed, Marjan Ajami, Budi Aji, Essona Matatoma Akara, Hossein Akbarialabadi, Karolina Akinosoglou, Tomi Akinyemiju, Mohammed Ahmed Akkaif, Samuel Akyirem, Hanadi Al Hamad, Syed Mahfuz Al Hasan, Fares Alahdab, Samer O Alalalmeh, Tariq A Alalwan, Ziyad Al-Aly, Khurshid Alam, Manjurul Alam, Noore Alam, Rasmieh Mustafa Al-amer, Fahad Mashhour Alanezi, Turki M Alanzi, Sayer Al-Azzam, Almaza Albakri, Mohammed Albashtawy, Mohammad T AlBataineh, Jacqueline Elizabeth Alcalde-Rabanal, Khalifah A Aldawsari, Wafa A Aldhaleei, Robert W Aldridge, Haileselasie Berhane Alema, Mulubirhan Assefa Alemayohu, Sharifullah Alemi, Yihun Mulugeta Alemu, Adel Ali Saeed Al-Gheethi, Khalid F Alhabib, Fadwa Alhalqa Naji Alhalqa, Mohammed Khaled Al-Hanawi, Abid Ali, Amjad Ali, Liaqat Ali, Mohammed Usman Ali, Rafat Ali, Shahid Ali, Syed Shujait Shujait Ali, Gianfranco Alicandro, Sheikh Mohammad Alif, Reyhaneh Alikhani, Yousef Alimohamadi, Ahmednur Adem Aliyi, Mohammad A M Aljasir, Syed Mohamed Aljunid, Francois Alla, Peter Allebeck, Sabah Al-Marwani, Sadeq Ali Ali Al-Maweri, Joseph Uy Almazan, Hesham M Al-Mekhlafi, Louay Almidani, Omar Almidani, Mahmoud A Alomari, Basem Al-Omari, Jordi Alonso, Jaber S Alqahtani, Shehabaldin Alqalyoobi, Ahmed Yaseen Alqutaibi, Salman Khalifah Al-Sabah, Zaid Altaany, Awais Altaf, Jaffar A Al-Tawfiq, Khalid A Altirkawi, Deborah Oyine Aluh, Nelson Alvis-Guzman, Hassan Alwafi, Yaser Mohammed Al-Worafa, Hany Aly, Safwat Aly, Karem H Alzoubi, Reza Amani, Azmeraw T Amare, Prince M Amegbor, Edward Kwabena Ameyaw, Tarek Tawfiq Amin, Alireza Amindarolzarbi, Sohrab Amiri, Mohammad Hosein Amirzade-Iraqi, Hubert Amu, Dickson A Amugsi, Ganiyu Adeniyi Amusa, Robert Ancuceanu, Deanna Anderlini, David B Anderson, Pedro Prata Andrade, Catalina Liliana Andrei, Tudorel Andrei, Colin Angus, Abhishek Anil, Sneha Anil, Amir Anoushiravani, Hossein Ansari, Ansariadi Ansariadi, Alireza Ansari-Moghaddam, Catherine M Antony, Ernoiz Antriyandarti, Davood Anvari, Saeid Anvari, Saleha Anwar, Sumadi Lukman Anwar, Razique Anwer, Anayochukwu Edward Anyasodor, Muhammad Aqeel, Juan Pablo Arab, Jalal Arabloo, Mosab Arafat, Aleksandr Y Aravkin, Demelash Areda, Abdulfatai Aremu, Olatunde Aremu, Hany Arifin, Mesay Arkew, Benedetta Armocida, Michael Benjamin Arndt, Johan Ärnlöv, Mahwish Arooj, Anton A Artamonov, Judie Arulappan, Raphael Taiwo Aruleba, Ashokan Arumugam, Malke Asaad, Mohsen Asadi-Lari, Akeza Awealom Asgedom, Mona Asghariahmadabad, Mohammad Asghari-Jafarabadi, Muhammad Ashraf, Armin Aslani, Thomas Astell-Burt, Mohammad Athar, Seyyed Shamsadin Athari, Bantalem Tilaye Tilaye Atinifu, Habtamu Wondmagegn Atlaw, Prince Atorkey, Maha Moh'd Wahbi Atout, Alok Atreya, Avinash Aujayeb, Marcel Ausloos, Abolfazl Avan, Atalel Fentahun Awedew, Amlak Mulat Aweke, Beatriz Paulina Ayala Quintanilla, Haleh Ayatollahi, Jose L Ayuso-Mateos, Seyed Mohammad Ayyoubzadeh, Sina Azadnajafabad, Rui M S Azevedo, Ahmed Y Azzam, Darshan B B,

Abraham Samuel Babu, Muhammad Badar, Ashish D Badiye, Soroush Baghdadi, Nasser Bagheri, Sara Bagherieh, Sulaiman Bah, Saeed Bahadorikhali, Najmeh Bahmanzari, Ruhai Bai, Atif Amin Baig, Jennifer L Baker, Abdulaziz T Bako, Ravleen Kaur Bakshi, Senthilkumar Balakrishnan, Madhan Balasubramanian, Ovidiu Constantin Baltatu, Kiran Bam, Maciej Banach, Soham Bandyopadhyay, Palash Chandra Banik, Hansi Bansal, Kannu Bansal, Franca Barbic, Martina Barchitta, Mainak Bardhan, Erfan Bardideh, Suzanne Lyn Barker-Collo, Till Winfried Bärnighausen, Francesco Barone-Adesi, Hiba Jawdat Barqawi, Lope H Barrero, Amadou Barrow, Sandra Barteit, Lingkan Barua, Zarrin Basharat, Azadeh Bashiri, Afisu Basiru, Pritish Baskaran, Buddha Basnyat, Quique Bassat, João Diogo Basso, Ann V L Basting, Sanjay Basu, Kavita Batra, Bernhard T Baune, Mohsen Bayati, Nebiyou Simegnew Bayileyegn, Thomas Beaney, Neeraj Bedi, Massimiliano Beghi, Emad Behboudi, Priyamadhaba Behera, Amir Hossein Behnoush, Masoud Behzadifar, Maryam Beiranvand, Diana Fernanda Bejarano Ramirez, Yannick Béjot, Sefealem Assefa Belay, Chalie Mulu Belete, Michelle L Bell, Muhammad Bashir Bello, Olorunjuwon Omolaja Bello, Luis Belo, Apostolos Beloukas, Rose Grace Bender, Isabela M Bensenor, Azizullah Beran, Zombor Berezvai, Alemshet Yirga Berhie, Betyna N Berice, Robert S Bernstein, Gregory J Bertolacci, Paulo J G Bettencourt, Kebede A Beyene, Devidas S Bhagat, Akshaya Srikanth Bhagavathula, Neeraj Bhala, Ashish Bhalla, Dinesh Bhandari, Kayleigh Bhangdia, Nikha Bhardwaj, Pankaj Bhardwaj, Prarthna V Bhardwaj, Ashish Bhargava, Sonu Bhaskar, Vivek Bhat, Gurjit Kaur Bhatti, Jasvinder Singh Bhatti, Manpreet S Bhatti, Rajbir Bhatti, Zulfiqar A Bhutta, Boris Bikbov, Jessica Devin Bishai, Catherine Bisignano, Francesca Bisulli, Atanu Biswas, Bijit Biswas, Saeid Bitaraf, Bikes Destaw Bitew, Veera R Bitra, Tone Bjørge, Micheal Kofi Boachie, Mary Sefa Boampong, Anca Vasilica Bobirca, Virginia Bodolica, Adam Olalekan Bodunrin, Eyob Ketema Bogale, Kassawmar Angaw Bogale, Somayeh Bohlouli, Obasanjo Afolabi Bolarinwa, Archith Boolor, Milad Bonakdar Hashemi, Aime Bonny, Kaustubh Bora, Berrak Bora Basara, Hamed Borhany, Arturo Borzutzky, Souad Bouaoud, Antoine Boustany, Christopher Boxe, Edward J Boyko, Oliver J Brady, Dejana Braithwaite, Luisa C Brant, Michael Brauer, Alexandra Brazinova, Javier Brazo-Sayavera, Nicholas J K Breitborde, Susanne Breitner, Hermann Brenner, Andrei Nikolaeivich Briko, Nikolay Ivanovich Briko, Gabrielle Britton, Julie Brown, Traolach Brugha, Norma B Bulamul, Lemma N Bulto, Danilo Buonsenso, Richard A Burns, Reinhard Busse, Yasser Bustanji, Nadeem Shafique Butt, Zahid A Butt, Florentino Luciano Caetano dos Santos, Daniela Calina, Luis Alberto Cámera, Luciana Aparecida Campos, Ismael R Campos-Nonato, Chao Cao, Yin Cao, Angelo Capodici, Rosario Cárdenas, Sinclair Carr, Giulia Carreras, Juan J Carrero, Andrea Carugno, Cristina G Carvalheiro, Felix Carvalho, Márcia Carvalho, Joao Mauricio Castaldelli-Maia, Carlos A Castañeda-Orjuela, Giulio Castelpietra, Ferrán Catalá-López, Alberico L Catapano, Maria Sofia Cattaruzza, Christopher R Cederoth, Luca Cegolon, Francieli Cebranel, Muthia Cenderadewi, Kelly M Cercy, Ester Cerin, Muge Cevik, Joshua Chadwick, Yaacoub Chahine, Chiranjib Chakraborty, Promit Ananya Chakraborty, Jeffrey Shi Kai Chan, Raymond N C Chan, Rama Mohan Chandika, Eeshwar K Chandrasekar, Chin-Kuo Chang, Jung-Chen Chang, Gashaw Sisay Chanie, Periklis Charalampous, Vijay Kumar Chattu, Pankaj Chaturvedi, Victoria Chatzimavridou-Grigoriadou, Akhilanand Chaurasia, Angela W Chen, An-Tian Chen, Catherine S Chen, Haowei Chen, Meng Xuan Chen, Simiao Chen, Ching-Yu Cheng, Esther T W Cheng, Nicolas Cherbuin, Wondimye Ashenafi Cheru, Ju-Huei Chien, Odgerel Chimed-Ochir, Ritesh Chimoriya, Patrick R Ching, Jesus Lorenzo Chirinos-Caceres, Abdula Chitheer, William C S Cho, Bryan Chong, Hitesh Chopra, Sonali Gajanan Choudhari, Rajiv Chowdhury, Devasahayam J Christopher, Isaac Sunday Chukwu, Eric Chung, Erin Chung, Eunice Chung, Sheng-Chia Chung, Muhammad Chutiyami, Zinhle Cindi, Iolanda Cioffi, Mareli M Claassens, Rafael M Claro, Kaleb Coberly, Rebecca M Cogen, Alyssa Columbus, Haley Comfort, Joao Conde, Samuele Cortese,

Paolo Angelo Cortesi, Vera Marisa Costa, Simona Costanzo, Ewerton Cousin, Rosa A S Couto, Richard G Cowden, Kenneth Michael Cramer, Michael H Criqui, Natália Cruz-Martins, Silvia Magali Cuadra-Hernández, Garland T Culbreth, Patricia Cullen, Matthew Cunningham, Maria Paula Curado, Sriharsha Dadana, Omid Dadras, Siyu Dai, Xiaochen Dai, Zhaoli Dai, Lachlan L Dalli, Giovanni Damiani, Jiregna Darega Gela, Jai K Das, Saswati Das, Subasish Das, Ana Maria Dascalu, Nihar Ranjan Dash, Mohsen Dashti, Anna Dastiridou, Gail Davey, Claudio Alberto Dávila-Cervantes, Nicole Davis Weaver, Kairat Davletov, Diego De Leo, Katie de Luca, Aklilu Tamire Debele, Shayom Debopadhyay, Louisa Degenhardt, Azizallah Dehghan, Lee Deitesfeld, Cristian Del Bo', Ivan Delgado-Enciso, Berecha Hundessa Demessa, Andreas K Demetriades, Ke Deng, Xinlei Deng, Edgar Denova-Gutiérrez, Niloofar Deravi, Nebiyu Dereje, Nikolaos Dervenis, Emin Dervišević, Don C Des Jarlais, Hardik Dineshbhai Desai, Rupak Desai, Vinod Gnana Chellaiyan Devanbu, Syed Masudur Rahman Dewan, Arkadeep Dhali, Kuldeep Dharma, Meghnath Dhimal, Sameer Dhingra, Vishal R Dhulipala, Diana Dias da Silva, Daniel Diaz, Michael J Diaz, Adriana Dima, Delaney D Ding, Huanghe Ding, Ricardo Jorge Dinis-Oliveira, M Ashworth Dirac, Shirin Djalalinia, Thao Huynh Phuong Do, Camila Bruneli do Prado, Saeid Doaei, Masoud Dodangeh, Milad Dodangeh, Sushil Dohare, Klará Georgieva Dokova, Christiane Dolecek, Regina-Mae Villanueva Dominguez, Wanyue Dong, Deepa Dongarwar, Mario D'Oria, Fariba Dorostkar, E Ray Dorsey, Wendel Mombaqué dos Santos, Rajkumar Doshi, Leila Doshmangir, Robert Kokou Dowou, Tim Robert Driscoll, Haneil Larson Dsouza, Viola Dsouza, Mi Du, John Dube, Bruce B Duncan, Andre Rodrigues Duraes, Senbagam Duraisamy, Oyewole Christopher Durojaiye, Laura Dwyer-Lindgren, Paulina Agnieszka Dzianach, Arkadiusz Marian Dziedzic, Abdel Rahman E'mar, Ejemai Eboreime, Alireza Ebrahimi, Chidiebere Peter Echieh, Hisham Atan Edinur, David Edvardsson, Kristina Edvardsson, Defi Efendi, Ferry Efendi, Diyan Ermawan Effendi, Terje Andreas Eikemo, Ebrahim Eini, Michael Ekholenetiale, Temitope Cyrus Ekuandio, Iman El Sayed, Iffat Elbarazi, Teshome Bekele Elema, Noha Mousaad Eleman, Frank J Elgar, Islam Y Elgendi, Ghada Metwally Tawfik ElGohary, Hala Rashad Elhabashy, Muhammed Elhadi, Waseem El-Huneidi, Legesse Tesfaye Elilo, Omar Abdelsadek Abdou Elmeliqy, Mohamed A Elmonem, Mohammed Elshaer, Ibrahim Elsobaby, Theophilus I Emeto, Luchuo Engelbert Bain, Ryenchindorj Erkhembayar, Christopher Imokhuede Esezobor, Babak Eshrati, Sharareh Eskandarieh, Juan Espinosa-Montero, Habtamu Esubalew, Farshid Etaee, Natalia Fabin, Adewale Oluwaseun Fadaka, Adeniyi Francis Fagbamigbe, Ayesha Fahim, Saman Fahimi, Aliasghar Fakhri-Demeshghieh, Luca Falzone, Mohammad Fareed, Carla Sofia e Sá Farinha, MoezAllIslam Ezzat Mahmoud Faris, Pawan Sirwan Faris, Andre Faro, Abidemi Omolara Fasanmi, Ali Fatehizadeh, Hamed Fattahi, Nelsenius Klau Fauk, Pooria Fazeli, Valery L Feigin, Alireza Feizkhah, Ginenus Fekadu, Xiaoru Feng, Seyed-Mohammad Fereshtehnejad, Abdullah Hamid Feroze, Daniela Ferrante, Alize J Ferrari, Nuno Ferreira, Getahun Fetensa, Bikila Regassa Feyisa, Irina Filip, Florian Fischer, Joanne Flavel, David Flood, Bobirca Teodor Florin, Nataliya A Foigt, Morenike Oluwatoyin Folayan, Artem Alekseevich Fomenkov, Behzad Foroutan, Masoud Foroutan, Ingeborg Forthun, Daniela Fortuna, Matteo Foschi, Kayode Raphael Fowobaje, Kate Louise Francis, Richard Charles Franklin, Alberto Freitas, Joseph Friedman, Sara D Friedman, Takeshi Fukumoto, John E Fuller, Blima Fux, Peter Andras Gaal, Muktar A Gadanya, Abhay Motiramji Gaidhane, Santosh Gaihre, Emmanuela Gakidou, Yaseen Galali, Natalie C Galles, Silvano Gallus, Mandukhai Ganbat, Aravind P Gandhi, Balasankar Ganesan, Mohammad Arfat Ganiyani, MA Garcia-Gordillo, William M Gardner, Jalaj Garg, Naval Garg, Rupesh K Gautam, Semiu Olatunde Gbadamosi, Tilaye Gebri Gebi, Miglas W Gebregergis, Mesfin Gebrehiwot, Teferi Gebru Gebremeskel, Simona Roxana Georgescu, Tamirat Getachew, Peter W Gething, Molla Getie, Keyghobad Ghadiri, Sulmaz Ghahramani, Khalid Yaser Ghailan, Mohammad-Reza Ghasemi,

Ghazal Ghasempour Dabaghi, Afsaneh Ghasemzadeh, Ahmad Ghashghaei, Fariba Ghassemi, Ramy Mohamed Ghazy, Ajnish Ghimire, Sama Ghoba, Maryam Gholamalizadeh, Asadollah Gholamian, Ali Gholamrezaebeh, Nasim Gholizadeh, Mahsa Ghorbani, Pooyan Ghorbani Vajargah, Aloke Gopal Ghoshal, Paramjit Singh Gill, Tiffany K Gill, Richard F Gillum, Themba G Ginindza, Alem Girmay, James C Glasbey, Elena V Gnedovskaya, Laszlo Göböös, Myron Anthony Godinho, Amit Goel, Ali Golchin, Mohamad Goldust, Mahaveer Golechha, Pouya Goleij, Nelson G M Gomes, Philimon N Gona, Sameer Vali Gopalani, Giuseppe Gorini, Houman Goudarzi, Alessandra C Goulart, Bárbara Niebla García Goulart, Anmol Goyal, Ayman Grada, Simon Matthew Graham, Michal Grivna, Giuseppe Grossi, Shi-Yang Guan, Giovanni Guarducci, Mohammed Ibrahim Mohialdeen Gubari, Mesay Dechasa Gudeta, Avirup Guha, Stefano Guicciardi, Rafael Alves Guimarães, Snigdha Gulati, Damitha Asanga Gunawardane, Sasidhar Gunturu, Cui Guo, Anish Kumar Gupta, Bhawna Gupta, Manoj Kumar Gupta, Mohak Gupta, Rajat Das Gupta, Rajeev Gupta, Sapna Gupta, Veer Bala Gupta, Vijai Kumar Gupta, Vivek Kumar Gupta, Lami Gurmessia, Reyna Alma Gutiérrez, Farrokh Habibzadeh, Parham Habibzadeh, Rasool Haddadi, Mostafa Hadei, Najah R Hadi, Nils Haep, Nima Hafezi-Nejad, Alemayehu Hailu, Arvin Haj-Mirzaian, Esam S Halboub, Brian J Hall, Sebastian Haller, Rabih Halwani, Randah R Hamadeh, Sajid Hameed, Samer Hamidi, Erin B Hamilton, Chieh Han, Qiuxia Han, Asif Hanif, Nasrin Hanifi, Graeme J Hankey, Fahad Hanna, Md Abdul Hannan, Md Nuruzzaman Haque, Harapan Harapan, Arief Hargono, Josep Maria Haro, Ahmed I Hasaballah, Ikramul Hasan, M Tasdik Hasan, Hamidreza Hasani, Mohammad Hasanian, Abdiwahab Hashi, Md Saquib Hasnain, Ikrama Hassan, Soheil Hassanipour, Hadi Hassankhani, Johannes Haubold, Rasmus J Havmoeller, Simon I Hay, Jiawei He, Jeffrey J Hebert, Omar E Hegazi, Golnaz Heidari, Mohammad Heidari, Mahsa Heidari-Foroozan, Bartosz Helfer, Dalia Hendrie, Brenda Yuliana Herrera-Serna, Claudiu Herteliu, Hamed Hesami, Kamal Hezam, Catherine L Hill, Yuta Hiraike, Ramesh Holla, Nobuyuki Horita, Md Mahbub Hossain, Sahadat Hossain, Mohammad-Salar Hosseini, Hassan Hosseinzadeh, Mehdi Hosseinzadeh, Ahmad Hosseinzadeh Adli, Mihuela Hostiuc, Sorin Hostiuc, Mohamed Hsairi, Vivian Chia-rong Hsieh, Rebecca L Hu, Chengxi Hu, Junjie Huang, Michael Hultström, Ayesha Humayun, Tsegaye Gebreyes Hundie, Javid Hussain, M Azhar Hussain, Nawfal R Hussein, Foziya Mohammed Hussien, Hong-Han Huynh, Bing-Fang Hwang, Segun Emmanuel Ibitoye, Khalid S Ibrahim, Pulwasha Maria Iftikhar, Desta Ijo, Adalia I Ikiroma, Kevin S Ikuta, Paul Chukwudi Ikwegbue, Olayinka Stephen Ilesanmi, Irena M Ilic, Milena D Ilic, Mohammad Tarique Imam, Mustapha Immurana, Sumant Iramdar, Endang Indriasiyah, Muhammad Iqhrammullah, Arnaud Iradukunda, Kenneth Chukwuemeka Iregbu, Md Rabiul Islam, Sheikh Mohammed Shariful Islam, Farhad Islami, Faisal Ismail, Nahlah Elkudssiah Ismail, Hiroyasu Iso, Gaetano Isola, Masao Iwagami, Chidozie C D Iwu, Ihoghoosa Osamuyi Iyamu, Mahalaxmi Iyer, Linda Merin J, Jalil Jaafari, Louis Jacob, Kathryn H Jacobsen, Farhad Jadidi-Niaragh, Morteza Jafarinia, Abdollah Jafarzadeh, Khushleen Jaggi, Kasra Jahankhani, Nader Jahannmehr, Haitham Jahrami, Nityanand Jain, Ammar Abdulrahman Jairoun, Abhishek Jaiswal, Elham Jamshidi, Mark M Janko, Abubakar Ibrahim Jatau, Sabzali Javadov, Tahereh Javaheri, Sathish Kumar Jayapal, Shubha Jayaram, Rime Jebai, Sun Ha Jee, Jayakumar Jeganathan, Anil K Jha, Ravi Prakash Jha, Heng Jiang, Yingzhao Jin, Olatunji Johnson, Mohammad Jokar, Jost B Jonas, Tamas Joo, Abel Joseph, Nitin Joseph, Charity Ehimwenma Joshua, Grace Joshy, Jacek Jerzy Jozwiak, Mikk Jürisson, Vaishali K, Billingsley Kaambwa, Ali Kabir, Zubair Kabir, Vidya Kadashetti, Dler Hussein Kadir, Rizwan Kalani, Laleh R Kalankesh, Leila R Kalankesh, Feroze Kaliyadan, Sanjay Kalra, Vineet Kumar Kamal, Sivesh Kahir Kamarajah, Rajesh Kamath, Zahra Kamiab, Naser Kamyari, Thaniigaivelan Kanagasabai, Tanuj Kanchan, Himal Kandel, Arun R Kanmanthareddy, Edmund Wedam Kanmiki, Kehinde Kazeem Kanmodi, Suthanthira Kannan S,

Sushil Kumar Kansal, Rami S Kantar, Neeti Kapoor, Mehrdad Karajizadeh, Shama D Karanth, Reema A Karasneh, Ibraheem M Karaye, André Karch, Asima Karim, Salah Eddin Karimi, Arman Karimi Behnagh, Faizan Zaffar Kashoo, Qalandar Hussein Abdulkarim Kasnazani, Hengameh Kasraei, Nicholas J Kassebaum, Molly B Kassel, Joonas H Kauppila, Navjot Kaur, Norita Kawakami, Gbenga A Kayode, Foad Kazemi, Sina Kazemian, Tahseen Haider Kazmi, Getu Mosisa Kebebew, Adera Debella Kebede, Fassikaw Kebede, Tibebeleslassie S Keflie, Peter Njenga Keiyoro, Cathleen Keller, Jaimon Terence Kelly, John H Kempen, Jessica A Kerr, Emmanuel Kesse-Guyot, Himanshu Khajuria, Amirmohammad Khalaji, Nauman Khalid, Anees Ahmed Khalil, Alireza Khalilian, Faham Khamesipour, Ajmal Khan, Asaduzzaman Khan, Gulfaraz Khan, Ikramullah Khan, Imteyaz A Khan, M Nuruzzaman Khan, Maseer Khan, Mohammad Jobair Khan, Moien AB Khan, Zeeshan Ali Khan, Mahammed Ziauddin Khan suheb, Shaghayegh Khanmohammadi, Khaled Khatab, Fatemeh Khatami, Haitham Khatatbeh, Moawiah Mohammad Khatatbeh, Armin Khavandegar, Hamid Reza Khayat Kashani, Feriha Fatima Khidri, Elaheh Khodadoust, Mohammad Khorgamphar, Moein Khorimali, Zahra Khorrami, Ahmad Khosravi, Mohammad Ali Khosravi, Zemene Demelash Kifle, Grace Kim, Jihee Kim, Kwanghyun Kim, Min Seo Kim, Yun Jin Kim, Ruth W Kimokoti, Kasey E Kinzel, Adnan Kisa, Sezer Kisa, Desmond Klu, Ann Kristin Skrindo Knudsen, Jonathan M Kocarnik, Sonali Kochhar, Timea Kocsis, David S Q Koh, Ali-Asghar Kolahi, Kairi Kolves, Farzad Kompani, Gerbrand Koren, Soewarta Kosen, Karel Kostev, Parvaiz A Koul, Sindhura Lakshmi Koulmane Laxminarayana, Kewal Krishan, Hare Krishna, Varun Krishna, Vijay Krishnamoorthy, Yuvraj Krishnamoorthy, Kris J Krohn, Bartholemey Kuate Defo, Burcu Kucuk Bicer, Md Abdul Kuddus, Mohammed Kuddus, Ilari Kuitunen, Mukhtar Kulimbet, Vishnutheertha Kulkarni, Akshay Kumar, Ashish Kumar, Harish Kumar, Manasi Kumar, Rakesh Kumar, Madhulata Kumari, Fantahun Tarekegn Kumie, Satyajit Kundu, Om P Kurmi, Asep Kusnali, Dian Kusuma, Alexander Kwarteng, Ilias Kyriopoulos, Hmwe Hmwe Kyu, Carlo La Vecchia, Ben Lacey, Muhammad Awwal Ladan, Lucie Laflamme, Abraham K Lagat, Anton C J Lager, Abdelilah Lahmar, Daphne Teck Ching Lai, Dharmesh Kumar Lal, Ratilal Laloo, Tea Lallukka, Hilton Lam, Judit Lám, Kelsey R Landrum, Francesca Lanfranchi, Justin J Lang, Berthold Langguth, Van Charles Lanssingh, Ariane Laplante-Lévesque, Bagher Larjani, Anders O Larsson, Savita Lasrado, Zohra S Lassi, Kamaluddin Latief, Kaveh Latifinaibin, Paolo Lauriola, Nghi Huu Hanh Le, Thao Thi Thu Le, Trang Diep Thanh Le, Caterina Ledda, Jorge R Ledesma, Munjae Lee, Paul H Lee, Seung Won Lee, Shaun Wen Huey Lee, Wei-Chen Lee, Yo Han Lee, Kate E LeGrand, James Leigh, Elvynna Leong, Temesgen L Lerango, Ming-Chieh Li, Wei Li, Xiaopan Li, Yichong Li, Zhihui Li, Virendra S Ligade, Andrew Tiyamike Makhiringa Likaka, Lee-Ling Lim, Stephen S Lim, Megan Lindstrom, Christine Linehan, Chaojie Liu, Gang Liu, Jue Liu, Runben Liu, Shiwei Liu, Xiaofeng Liu, Xuefeng Liu, Erand Llanaj, Michael J Loftus, Rubén López-Bueno, Platon D Lopukhov, Arianna Maever Loreche, Stefan Lorkowski, Paulo A Lotufo, Rafael Lozano, Jailos Lubinda, Giancarlo Lucchetti, Alessandra Lugo, Raimundas Lunevicius, Zheng Feei Ma, Kelsey Lynn Maass, Nikolaos Machairas, Monika Machoy, Farzan Madadizadeh, Christian Madsen, Aurea M Madureira-Carvalho, Azzam A Maghazachi, Sandeep B Maharaj, Soleiman Mahjoub, Mansour Adam Mahmoud, Aireza Mahmoudi, Elham Mahmoudi, Razzagh Mahmoudi, Azeem Majeed, Irsra Fatima Makhdoom, Elaheh Malakan Rad, Venkatesh Maled, Reza Malekzadeh, Armaan K Malhotra, Kashish Malhotra, Ahmad Azam Malik, Iram Malik, Deborah Carvalho Malta, Abdullah A Mamun, Pejman Mansouri, Mohammad Ali Mansournia, Lorenzo Giovanni Mantovani, Sajid Maqsood, Bishnu P Marasini, Hamid Reza Marateb, Joemer C Maravilla, Agustina M Marconi, Parham Mardi, Mirko Marino, Abdoljalal Marjani, Gabriel Martinez, Bernardo Alfonso Martinez-Guerra, Ramon Martinez-Piedra, Daniela Martini, Santi Martini, Francisco Rogerlândio Martins-Melo, Miquel Martorell, Wolfgang Marx, Sharmin Maryam, Roy Rillera Marzo, Anthony Masaka, Awoke Masrie, Stephanie Mathieson, Alexander G Mathioudakis, Manu Raj Mathur,

Jishanth Mattumpuram, Richard Matzopoulos, Richard James Maude, Andrea Maugeri, Pallab K Maulik, Mahsa Mayeli, Maryam Mazaheri, Mohsen Mazidi, John J McGrath, Martin McKee, Anna Laura W McKown, Susan A McLaughlin, Steven M McPhail, Enkeleint A Mechili, John Robert Caraboo Medina, Rishi P Mediratta, Jitendra Kumar Meena, Rahul Mehra, Kamran Mehrabani-Zeinabad, Entezar Mehrabi Nasab, Tesfahan Mekene Meto, Gebrekirios Gebremichael Meles, Max Alberto Mendez Mendez-Lopez, Walter Mendoza, Ritesh G Menezes, Belayneh Mengist, Alexios-Fotios A Mentis, Sultan Ayoub Meo, Haftu Asmerom Meresa, Atte Meretoja, Tuomo J Meretoja, Abera M Mersha, Bezwit Afework Mesfin, Tomislav Mestrovic, Kukulege Chamila Dinushi Mettananda, Sachith Mettananda, Peter Meylakhs, Adquate Mhlanga, Laurette Mhlanga, Tianyue Mi, Tomasz Miazgowski, Georgia Micha, Irmrina Maria Michalek, Ted R Miller, Edward J Mills, Le Huu Nhat Minh, GK Mini, Pouya Mir Mohammad Sadeghi, Andreea Mirica, Antonio Mirijello, Erkin M Mirrakhimov, Mizan Kiros Mirutse, Maryam Mirzaei, Awoke Misganaw, Ashim Mishra, Sanjeev Misra, Philip B Mitchell, Prasanna Mithra, Chaitanya Mittal, Mohammadreza Mobayen, Madeline E Moberg, Ashraf Mohamadkhani, Jama Mohamed, Mouhand F H Mohamed, Nouh Saad Mohamed, Sakineh Mohammad-Alizadeh-Charandabi, Soheil Mohammadi, Abdollah Mohammadian-Hafshejani, Noushin Mohammadifard, Hassen Mohammed, Hussen Mohammed, Mustapha Mohammed, Salahuddin Mohammed, Shafiu Mohammed, Viswanathan Mohan, Hoda Mojiri-Forushani, Amin Mokari, Ali H Mokdad, Sabrina Molinaro, Mariam Molokhia, Sara Morntazmanesh, Lorenzo Monasta, Stefania Mondello, Mohammad Ali Moni, AmirAli Moodi Ghalibaf, Maryam Moradi, Yousef Moradi, Maziar Moradi-Lakeh, Maliheh Moradzadeh, Paula Moraga, Lidia Morawska, Rafael Silveira Moreira, Negar Morovatdar, Shane Douglas Morrison, Jakub Morze, Jonathan F Mosser, Rohith Motappa, Vincent Mougin, Simin Mouodi, Parsa Mousavi, Seyed Ehsan Mousavi, Amin Mousavi Khanegah, Emmanuel A Mpoly, Matias Mrejen, Sumaira Mubarik, Lorenzo Muccioli, Ulrich Otto Mueller, Faraz Mughal, Sumoni Mukherjee, Francesc Mulita, Kavita Munjal, Efrén Murillo-Zamora, Fungai Musaigwa, Khaled M Musallam, Ahmad Mustafa, Ghulam Mustafa, Saravanan Muthupandian, Raman Muthusamy, Muhammad Muzaffar, Woojae Myung, Ahamarshan Jayaraman Nagarajan, Gabriele Nagel, Pirouz Naghavi, Aliya Naheed, Ganesh R Naik, Gurudatta Naik, Firzan Nainu, Sanjeev Nair, Hastyar Hama Rashid Najmuldeen, Noureddin Nakhostin Ansari, Vinay Nangia, Atta Abbas Naqvi, Sreenivas Narasimha Swamy, Aparna Ichalangod Narayana, Shumaila Nargus, Bruno Ramos Nascimento, Gustavo G Nascimento, Samar Nasehi, Abdulqadir J Nashwan, Zuhair S Natto, Javid Nauman, Muhammad Naveed, Biswa Prakash Nayak, Vinod C Nayak, Athare Nazri-Panjaki, Rawlance Ndejo, Sabina Onyinye Nduaguba, Hadush Negash, Ionut Negoi, Ruxandra Irina Negoi, Serban Mircea Negru, Seyed Aria Nejadghaderi, Chakib Nejjari, Evangelia Nena, Samata Nepal, Marie Ng, Haruna Asura Nggada, Georges Nguefack-Tsague, Josephine W Ngunjiri, Anh Hoang Nguyen, Dang H Nguyen, Hau Thi Hien Nguyen, Phat Tuan Nguyen, Van Thanh Nguyen, Robina Khan Niazi, Katie R Nielsen, Yeshambel T Nigatu, Taxiarchis Konstantinos Nikolouzakis, Ali Nikoobar, Fatemeh Nikoomanesh, Amin Reza Nikpoor, Dina Nur Anggraini Ningrum, Chukwudi A Nnaji, Lawrence Achilles Nnyanzi, Efaq Ali Noman, Shuhei Nomura, Mamoonah Noreen, Nafise Noroozi, Bo Norrvig, Jean Jacques Noubiap, Amanda Novotney, Chisom Adaobi Nri-Ezedi, George Ntaios, Mpiko Ntsekhe, Virginia Nuñez-Samudio, Dieta Nurrika, Jerry John Nutor, Bogdan Oancea, Kehinde O Obamiro, Mary Aigbiremo Oboh, Ismail A Odetokun, Nkechi Martina Odogwu, Martin James O'Donnell, Michael Safo Oduro, Akinyemi O D Ofakunrin, Abiola Ogunkoya, Ayodipupo Sikiru Oguntade, In-Hwan Oh, Hassan Okati-Aliabad, Sylvester Reuben Okeke, Akinkunmi Paul Okeke, Osaretin Christabel Okonji, Andrew T Olagunju, Muideen Tunbosun Olaiya, Matthew Idowu Olatubi, Gláucia Maria Moraes Oliveira, Isaac Iyinoluwa Olufadewa, Bolajoko Olubukunola Olusanya, Jacob Olusegun Olusanya,

Yinka Doris Oluwafemi, Hany A Omar, Ahmed Omar Bali, Goran Latif Omer, Maureene Auma Ondayo, Sokking Ong, Obinna E Onwujekwe, Kenneth Ikenna Onyedibe, Michal Ordak, Orish Ebere Orisakwe, Verner N Orish, Doris V Ortega-Altamirano, Alberto Ortiz, Wael M S Osman, Samuel M Ostroff, Uchechukwu Levi Osuagwu, Adrian Otoi, Nikita Ostavnov, Stanislav S Ostavnov, Amel Ouyahia, Guoqing Ouyang, Mayowa O Owolabi, Yaz Ozten, Mahesh Padukudru P A, Alicia Padron-Monedero, Jagadish Rao Padubidri, Pramod Kumar Pal, Tamás Palicz, Claudia Palladino, Raffaele Palladino, Raul Felipe Palma-Alvarez, Feng Pan, Hai-Feng Pan, Adrian Pana, Paramjot Panda, Songhomitra Panda-Jonas, Seithikurippu R Pandi-Perumal, Helena Ullyarthar Pangaribuan, Georgios D Panos, Leonidas D Panos, Ioannis Pantazopoulos, Anca Mihaela Pantea Stoian, Paraskevi Papadopoulou, Romil R Parikh, Seoyeon Park, Ashwaghosh Parthasarathi, Ava Pashaei, Maja Pasovic, Roberto Passera, Deepak Kumar Pasupula, Hemal M Patel, Jay Patel, Sangram Kishor Patel, Shankargouda Patil, Dimitrios Patoulias, Venkata Suresh Pathipati, Uttam Paudel, Hamidreza Pazoki Toroudi, Spencer A Pease, Amy E Peden, Paolo Pedersini, Umberto Pensato, Veincent Christian Filipino Pepito, Emmanuel K Peprah, Prince Peprah, João Perdigão, Marcos Pereira, Maria F P Peres, Arokiasamy Perianayagam, Norberto Perico, Richard G Pestell, Konrad Pesudovs, Fanny Emily Petermann-Rocha, William A Petri, Hoang Tran Pham, Anil K Philip, Michael R Phillips, Daniela Pierannunzio, Manon Pigeolet, David M Pigott, Thomas Pilgrim, Zahra Zahid Piracha, Michael A Piradov, Saeed Pirouzpanah, Nishad Plakkal, Evgueni Plotnikov, Vivek Podder, Dimitri Podighe, Suzanne Polinder, Kevan R Polkinghorne, Ramesh Poluru, Ville T Ponkilainen, Fabio Porru, Maarten J Postma, Govinda Raj Poudel, Akram Pourshams, Naeimeh Pourtaheri, Sergio I Prada, Pranil Man Singh Pradhan, Thejeswar N Prakasham, Manya Prasad, Akila Prashant, Elton Junio Sady Prates, Daniel Prieto Alhambra, TINA PRISCILLA, Natalie Pritchett, Bharathi M Purohit, Jagadeesh Puvvula, Nameer Hashim Qasim, Ibrahim Qatteq, Asma Saleem Qazi, Gangzhen Qian, Suli Qiu, Maryam Faiz Qureshi, Mehrdad Rabiee Rad, Amir Radfar, Raghu Anekal Radhakrishnan, Venkatraman Radhakrishnan, Hadi Raeisi Shahraki, Quinn Rafferty, Alberto Raggi, Pankaja Raghav Raghav, Nasiru Raheem, Fakher Rahim, Md Jyllur Rahim, Vafa Rahimi-Movaghfar, Md Mosfequr Rahman, Mohammad Hifz Ur Rahman, Mosiur Rahman, Muhammad Aziz Rahman, Amir Masoud Rahmani, Shayan Rahmani, Vahid Rahamanian, Sathish Rajaa, Prashant Rajput, Ivo Rakovac, Shakthi Kumaran Ramasamy, Sheena Ramazanu, Kritika Rana, Chhabi Lal Ranabhat, Nemanja Rancic, Amey Rane, Chythra R Rao, Indu Ramachandra Rao, Mithun Rao, Sowmya J Rao, Drona Prakash Rasali, Davide Rasella, Sina Rashedi, Vahid Rashedi, Mohammad-Mahdi Rashidi, Ashkan Rasouli-Saravani, Azad Rasul, Giridhara Rathnaiah Babu, Santosh Kumar Rauniyar, Ramin Ravangard, Nakul Ravikumar, David Laith Rawaf, Salman Rawaf, Lal Rawal, Reza Rawassizadeh, Bharat Rawlley, Rabail Zehra Raza, Christian Razo, Elrashdy Moustafa Mohamed Redwan, Faizan Ur Rehman, Lennart Reifels, Robert C Reiner Jr, Giuseppe Remuzzi, Luis Felipe Reyes, Maryam Rezaei, Nazila Rezaei, Negar Rezaei, Mohsen Rezaeian, Taeho Gregory Rhee, Mavra A Riaz, Antonio Luiz P Ribeiro, Jennifer Rickard, Hannah R Riva, Hannah Elizabeth Robinson-Oden, Célia Fortuna Rodrigues, Mónica Rodrigues, Leonardo Roever, Emma Lynn Best Rogowski, Peter Rohlloff, Debby Syahru Romadlon, Esperanza Romero-Rodríguez, Michele Romoli, Luca Ronfani, Gholamreza Roshandel, Gregory A Roth, Himanshu Sekhar Rout, Nitai Roy, Priyanka Roy, Enrico Rubagotti, Guilherme de Andrade Ruela, Susan Fred Rumisha, Tilleye Runghien, Godfrey M Rwegerera, Andrzej Rynkiewicz, Chandan S N, Aly M A Saad, Zahra Saadatian, Korosh Saber, Maha Mohamed Saber-Ayad, Morteza SaberiKamarposhti, Siamak Sabour, Simona Sacco, Perminder S Sachdev, Rajesh Sachdeva, Basema Saddik, Adam Saddler, Bashdar Abuzed Sadee, Ehsan Sadeghi, Erfan Sadeghi, Farideh Sadeghian, Mohammad Reza Saeb, Umar Saeed, Fahimeh Safaeinejad, Sher Zaman Safi, Rajesh Sagar, Amene Saghzadeh, Dominic Sagoe, Fatemeh Saheb Sharif-Askari,

Narjes Saheb Sharif-Askari, Amirhossein Sahebkar, Soumya Swaroop Sahoo, Umakanta Sahoo, Monalisha Sahu, Zahra Saif, Mirza Rizwan Sajid, Joseph W Sakshaug, Nasir Salam, Payman Salamat, Afeez Abolarinwa Salami, Luciane B Salaroli, Mohamed A Saleh, Sana Salehi, Marwa Rashad Salem, Mohammed Z Y Salem, Sohrab Salimi, Hossein Samadi Kafil, Sara Samadzadeh, Saad Samargandy, Yoseph Leonardo Samodra, Abdallah M Samy, Juan Sanabria, Francesca Sanna, Damian Francesco Santomauro, Itamar S Santos, Milena M Santric-Milicevic, Bruno Piassi Sao Jose, Made Ary Sarasmita, Sivan Yegnanarayana Iyer Saraswathy, Aswini Saravanan, Babak Saravi, Yaser Sarikhani, Tamay Sarkar, Rodrigo Sarmiento-Suárez, Gargi Sachin Sarode, Sachin C Sarode, Arash Sarveazad, Brijesh Sathian, Thirunavukkarasu Sathish, Maheswar Satpathy, Abu Sayeed, Md Abu Sayeed, Mete Saylan, Mehdi Sayyah, Nikolaos Scarmeas, Benedikt Michael Schaarschmidt, Markus P Schlaich, Winfried Schlee, Maria Inês Schmidt, Ione Jayce Ceola Schneider, Art Schuermans, Austin E Schumacher, Aletta Elisabeth Schutte, Michaël Schwarzinger, David C Schwebel, Falk Schwendicke, Mario Šekerija, Siddharthan Selvaraj, Sabyasachi Senapati, Subramanian Senthilkumaran, Sadaf G Sepanlou, Dragos Serban, Yashendra Sethi, Feng Sha, Maryam Shabany, Amir Shafaat, Mahan Shahie, Nilay S Shah, Pritik A Shah, Syed Mahboob Shah, Saeed Shahabi, Attaullah Shahbandi, Izza Shahid, Samiah Shahid, Wajeehah Shahid, Hamid R Shahsavar, Moyad Jamal Shahwan, Ahmed Shaikh, Masood Ali Shaikh, Alireza Shakeri, Ali S Shalash, Sunder Sham, Muhammad Aaqib Shamim, Mehran Shams-Beyranvand, Hina Shamshad, Mohammad Anas Shamsi, Mohd Shanawaz, Abhishek Shankar, Sadaf Sharfaei, Amin Sharifan, Javad Sharifi-Rad, Rajesh Sharma, Saurab Sharma, Ujjawala Sharma, Vishal Sharma, Rajesh P Shastri, Amin Shavandi, Maryam Shayan, Amr Mohamed Elsayed Shehabeldine, Aziz Sheikh, Rahim Ali Sheikhi, Jiabin Shen, Adithi Shetty, B Suresh Kumar Shetty, Pavanchand H Shetty, Peilin Shi, Kenji Shibuya, Desalegn Shiferaw, Mika Shigematsu, Min-Jeong Shin, Youn Ho Shin, Rahman Shiri, Reza Shirkoohi, Nebyu Aniley Shitaye, Aminu Shittu, Ivy Shie, K M Shivakumar, Velizar Shivarov, Farhad Shokraneh, Azad Shokri, Sina Shool, Seyed Afshin Shorofi, Sunil Shrestha, Kerem Shuval, Emmanuel Edwar Siddig, João Pedro Silva, Luís Manuel Lopes Rodrigues Silva, Soraya Silva, Colin R Simpson, Anjali Singal, Abhinav Singh, Balbir Bagicha Singh, Garima Singh, Jasbir Singh, Narinder Pal Singh, Paramdeep Singh, Surjit Singh, Dhirendra Narain Sinha, Robert Sinto, Md Shahjahan Siraj, Sarah Brooke Sirota, Freddy Sitas, Shravan Sivakumar, Valentin Yurievich Skryabin, Anna Aleksandrovna Skryabina, David A Sleet, Bogdan Socea, Anton Sokhan, Ranjan Solanki, Shipra Solanki, Hamidreza Soleimani, Sameh S M Soliman, Suhang Song, Yimeng Song, Reed J D Sorensen, Joan B Soriano, Ireneous N Soyiri, Michael Spartalis, Sandra Spearman, Chandrashekhar T Sreeramareddy, Vijay Kumar Srivastava, Jeffrey D Stanaway, Muhammad Haroon Stanikzai, Benjamin A Stark, Joseph R Starnes, Antonina V Starodubova, Caroline Stein, Dan J Stein, Fridolin Steinbeis, Caitlyn Steiner, Jamie D Steinmetz, Paschalis Steiropoulos, Aleksandar Stevanović, Leo Stockfelt, Mark A Stokes, Stefan Stortecsky, Vetriselvan Subramaniyan, Muhammad Suleman, Rizwan Suliankatchi Abdulkader, Abida Sultana, Haitong Zhe Sun, Jing Sun, Johan Sundström, David Sunkersing, Katharina S Sunnerhagen, Chandan Kumar Swain, Lukasz Szarpak, Mindy D Szeto, Miklós Szócska, Payam Tabaei Damavandi, Rafael Tabarés-Seisdedos, Seyed Mohammad Tabatabaei, Ozra Tabatabaei Malazy, Seyed-Amir Tabatabaeizadeh, Shima Tabatabai, Mohammad Tabish, Jyothi Tadkamadla, Santosh Kumar Tadakamadla, Yasaman Taheri Abkenar, Moslem Taheri Soodejani, Jabeen Taiba, Ken Takahashi, Iman M Talaat, Ashis Talukder, Mircea Tampa, Jacques Lukenze Tamuzi, Ker-Kan Tan, Sarmila Tandukar, Haosu Tang, Hong K Tang, Ingan Ukuur Tarigan, Mengistie Kassahun Tariku, Md Tariqijaman, Elvis Enowbeyang Tarkang, Razieh Tavakoli Oliaee, Seyed Mohammad Tavangar, Nuno Taveira, Yibekal Manaye Tefera, Mohamad-Hani Temsah, Reem Mohamad Hani Temsah, Masayuki Teramoto, Riki Tesler, Enoch Teye-Kwadjo, Rishu Thakur, Pugazhenthan Thangaraju, Kavumpurathu Raman Thankappan,

Samar Tharwat, Rasiah Thayakaran, Nihal Thomas, Nikhil Kenny Thomas, Azalea M Thomson, Amanda G Thrift, Chern Choong Chern Thum, Lau Caspar Thygesen, Jing Tian, Ales Tichopad, Jansje Henny Vera Ticoalu, Tala Tillawi, Tenaw Yimer Tiruye, Mariya Vladimirovna Titova, Marcello Tonelli, Roman Topor-Madry, Adetunji T Toriola, Anna E Torre, Mathilde Touvier, Marcos Roberto Tovani-Palone, Jasmine T Tran, Nghia Minh Tran, Domenico Trico, Samuel Joseph Tromans, Thien Tan Tri Tai Truyen, Aristidis Tsatsakis, Guesh Mebrahtom Tsegay, Evangelia Eirini Tsermpini, Munkhtuya Tumurkhuu, Kang Tung, Stefanos Tyrovolas, Sayed Mohammad Nazim Uddin, Aniefiok John Udoakang, Arit Udo, Atta Ullah, Irfan Ullah, Saeed Ullah, Sana Ullah, Srikanth Umakanthan, Chukwuma David Umeokonkwo, Brigid Unim, Bhaskaran Unnikrishnan, Carolyn Anne Unsworth, Era Upadhyay, Daniele Urso, Jibrin Sammani Usman, Seyed Mohammad Vahabi, Asokan Govindaraj Vaithinathan, Rohollah Valizadeh, Sarah M Van de Velde, Jef Van den Eynde, Orsolya Varga, Priya Vart, Shoban Babu Varthy, Tommi Juhani Vasankari, Milena Vasic, Siavash Vaziri, Balachandar Vellingiri, Narayanaswamy Venketasubramanian, Nicholas Alexander Verghese, Madhur Verma, Massimiliano Veroux, Georgios-Ioannis Verras, Dominique Vervoort, Jorge Hugo Villafane, Gabriela Ines Villanueva, Manish Vinayak, Francesco S Violante, Maria Viskadourou, Sergey Konstantinovich Vladimirov, Vasily Vlassov, Bay Vo, Stein Emil Vollset, Avina Vongpradith, Theo Vos, Isidora S Vujcic, Rade Vukovic, Hatem A Wafa, Yasir Waheed, Richard G Warnai, Cong Wang, Ning Wang, Shu Wang, Song Wang, Yanzhong Wang, Yuan-Pang Wang, Muhammad Waqas, Paul Ward, Emebet Gashaw Wassef, Stefanie Watson, Stephanie Louise Watson Watson, Kosala Gayan Weerakoon, Melissa Y Wei, Robert G Weintraub, Daniel J Weiss, Ronny Westerman, Joanna L Whisnant, Taweewat Wiangkham, Dakshitha Praneeth Wickramasinghe, Nuwan Darshana Wickramasinghe, Angga Wilandika, Caroline Wilkerson, Peter Willeit, Shadrach Wilson, Marcin W Wojewodzic, Demewoz H Woldegebreal, Axel Walter Wolf, Charles D A Wolfe, Yohannes Addisu Wondimagegne, Yen Jun Wong, Utoomporn Wongsin, Ai-Min Wu, Chenkai Wu, Felicia Wu, Xinsheng Wu, Zenghong Wu, Juan Xia, Hong Xiao, Yang Xie, Suowen Xu, Wang-Dong Xu, Xiaoyue Xu, Yvonne Yiru Xu, Ali Yadollahpour, Kazumasa Yamagishi, Danting Yang, Lin Yang, Yuichiro Yano, Yao Yao, Habib Yaribeygi, Pengpeng Ye, Sisay Shewasinad Yehualashet, Metin Yesiltepe, Subah Abderehim Yesuf, Saber Yezli, Siyan Yi, Amanuel Yigezu, Arzu Yigit, Vahit Yigit, Paul Yip, Malede Berihun Yismaw, Yazachew Yismaw, Dong Keon Yon, Naohiro Yonemoto, Seok-Jun Yoon, Yuyi You, Mustafa Z Younis, Zabihollah Yousefi, Chuanhua Yu, Yong Yu, Faith H Yuh, Siddhesh Zadey, Vesna Zadnik, Nima Zafari, Fathiah Zakhram, Nazar Zaki, Sojib Bin Zaman, Nelson Zamora, Ramin Zand, Moein Zangiabadian, Heather J Zar, Iman Zare, Armin Zarrintan, Mohammed G M Zeari, Zahra Zeinali, Hajun Zhang, Jianrong Zhang, Jingya Zhang, Liqun Zhang, Yunquan Zhang, Zhi-Jiang Zhang, Hanqing Zhao, Chenwen Zhong, Juxiao Zhou, Bin Zhu, Lei Zhu, Makan Ziafati, Magdalena Zielińska, Osama A Zitoun, Mohammad Zoladl, Zhiyong Zou, Liesl J Zuhkle, Alimuddin Zumla, Elri Zweck, Samer H Zyoud, Eve E Wool†, and Christopher J L Murray†.

*Joint first authors. †Joint senior authors

Affiliations

Institute for Health Metrics and Evaluation (Prof M Naghavi PhD, K L Ong PhD, C M Antony MA, A Y Aravkin PhD, M B Arndt PhD, A V L Basting MPH, R G Bender MSc, B N Berice MPH, G J Bertolacci BS, K Bhangdia MS, J D Bishai BA, C Bisignano MPH, Prof M Brauer DSc, K M Cercy BS, C S Chen BA, E Chung MD, E Chung MSc, K Coberly BS, R M Cogen BA, H Comfort MPH, E Cousin PhD, G T Culbreth PhD, M Cunningham MSc, X Dai PhD, N Davis Weaver MPH, Prof L Degenhardt PhD, L Deitesfeld MA, M A Dirac MD, R V Dominguez BS, L Dwyer-Lindgren PhD, Prof V L Feigin PhD, A J Ferrari PhD, J E Fuller MLIS, Prof E Gakidou PhD, N C Galles MPH, W M Gardner MPH, S Ghoba MS, E B Hamilton MPH, C Han BA, Prof S I Hay FMedSci, J He MSc, R L Hsu, K S Ikuta MD, N J Kassebaum MD, M B Kassel BA, C Keller MPH, K E Kinzel MSPH, J M Kocarnik PhD, K J Krohn MPH, H H Kyu PhD, J R Ledesma MPH, K E LeGrand MPH, Prof S S Lim PhD, M Lindstrom PhD, Prof R Lozano MD, K L Maass PhD, A L W McKown MA, S A McLaughlin PhD, T Mestrovic PhD, M E Moberg MS, A H Mokdad PhD, J F Mosser MD, V Mougin BA, A Novotney MPH, S M Ostroff PhD, Y Ozten MS, M Pasovic MEd, S A Pease BS, D M Pigott PhD, N Pritchett DrPH, Q Rafferty BA, C Razo PhD, R C Reiner Jr PhD, H E Robinson-Oden MLIS, G A Roth MD, T Runghien MSc, D F Santomauro PhD, A E Schumacher PhD, S B Sirota MA, R J D Sorensen PhD, S Spearman MS, J D Stanaway PhD, B A Stark MA, C Stein PhD, C Steiner MPH, A M Thomson BA, A E Torre BS, N A Verghese BA, Prof S Vollset DrPH, A Vongpradith BA, Prof T Vos PhD, S Watson MS, J L Whisnant MPH, C Wilkerson MPH, S Wilson BS, Y Xu MPH, F H Yuh MPA, E E Wool MPH, Prof C J L Murray DPhil), Department of Health Metrics Sciences, School of Medicine (Prof M Naghavi PhD, A Y Aravkin PhD, E Cousin PhD, X Dai PhD, M A Dirac MD, L Dwyer-Lindgren PhD, Prof E Gakidou PhD, Prof S I Hay FMedSci, N J Kassebaum MD, H H Kyu PhD, Prof S S Lim PhD, Prof R Lozano MD, A Misganaw PhD, A H Mokdad PhD, E A Mpolya PhD, D M Pigott PhD, R C Reiner Jr PhD, G A Roth MD, J D Stanaway PhD, C Stein PhD, Prof S Vollset DrPH, Prof T Vos PhD, Prof C J L Murray DPhil), Department of Applied Mathematics (A Y Aravkin PhD), Department of Global Health (M B Arndt PhD, S Kochhar MD, K R Nielsen MD, R J D Sorensen PhD, Z Zeinali MD), School of Medicine (Prof E J Boyko MD), Department of Internal Medicine (Y Chahine MD), Department of Cardiology (Y Chahine MD), Department of Health Systems and Population Health (A W Chen MSc), Department of Pediatrics (E Chung MD, K R Nielsen MD), Department of Family Medicine (M A Dirac MD), Department of Neurology (R Kalani MD), Department of Anesthesiology & Pain Medicine (N J Kassebaum MD, V Krishnamoorthy MD), Division of Plastic and Reconstructive Surgery (S D Morrison MD), Henry M Jackson School of International Studies (S M Ostroff PhD), Division of Cardiology (G A Roth MD), University of Washington, Seattle, WA, USA; Faculty of Medicine (A Aali MD), Department of Neuroscience (A Ahmadzade MD), Dental Research Center (E Bardideh DDS), Orthodontics Department (M Ghorbani DDS), Clinical Research Development Unit (N Morovatdar MD), Applied Biomedical Research Center (A Sahebkar PhD), Biotechnology Research Center (A Sahebkar PhD), Department of Medical Informatics (S Tabatabaei PhD), Clinical Research Development Unit (S Tabatabaei PhD), Department of Medical Genetics (N Zafari MD), Mashhad University of Medical Sciences, Mashhad, Iran; Radiation Oncology (H S Ababneh MD), Department of Orthopaedic Surgery (A Ebrahimi MD), Division of Cardiology (I Y Elgendi MD, D H Nguyen BS), Department of Radiology (A Haj-Mirzaian MD, X Liu PhD), Cardiovascular Research Center (A Schuermans BSc), Massachusetts General Hospital, Boston, MA, USA; Department of Clinical Governance and Quality Improvement (Y H Abate MSc), Aleta Wondo Hospital, Aleta Wondo, Ethiopia; Department of Juridical and Economic Studies (C Abbafati PhD), Department of Public Health and Infectious Diseases (M S Cattaruzzi PhD), La Sapienza University, Rome, Italy; Doheny Eye Institute (R Abbasgholizadeh MD), Doheny Image Reading and Research Lab (DIRRL) (L Almidani MSc), Center for Social Medicine (J Friedman PhD), Department of Environmental Health Sciences (M Khorgamphar BA), Department of Health Policy Management (M Khorgamphar BA), General Internal Medicine and Health Services Research (M Y Wei MD), University of California Los Angeles, Los Angeles, CA, USA; Department of Orthopedic Surgery (M Abbasian MD), Department of Pediatrics (S Aly MD), T.H. Chan School of Public Health (Prof T W Bärnighausen MD), P M S Pradhan MD, E Zweck MD), Center for Primary Care (S Basu PhD), Harvard Business School (F Caetano dos Santos PhD), Department of Epidemiology (S Carr MS), Department of Health Policy and Management (H Ding MPH), Division of Cardiology (I Y Elgendi MD), Department of Neurological Surgery at Brigham and Women's Hospital (A H Feroze MD), Department of Ophthalmology (Prof J H Kempen MD), Department of Global Health and Population (Z Li PhD, P Rohloff MD), Department of Health Policy and Oral

Epidemiology (Z S Natto DrPH), Department of Global Health and Social Medicine (M Pigeolet MD), Beth Israel Deaconess Medical Center (S Sharfaei MD), Division of General Internal Medicine (Prof A Sheikh MD), Harvard University, Boston, MA, USA; Department of Orthopaedic Surgery (M Abbasian MD), Department of Anesthesiology (D Abtahi MD, S Salimi MD, A Shakeri MD), Department of Biotechnology (S Aghamiri PhD), National Nutrition and Food Technology Research Institute (M Ajami PhD), Urology Department (M Bonakdar Hashemi MD), Internal Medicine Department of SBMU (H Borhany MD), School of Medicine (N Deravi MD, M Heidari-Foroozan BSc, S Nejadghaderi MD, S Rahmani MD, M Zangiabadian MD), Department of Community Nutrition (S Doaei PhD, A Mokari PhD), Medical Genetics (M Ghasemi PhD), Cancer Research Center (M Gholamalizadeh PhD), Obesity Research Center (A Haj-Mirzaian MD), Urology and Nephrology Research Center (H Hesami MD), Ophthalmic Research Centre (H Hesami MD), Department of Immunology (K Jahankhani MSc, A Rasouli-Saravani PhD), Department of Health Policy and Management (N Jahanmehr PhD), Safety Promotion and Injury Prevention Research Center (N Jahanmehr PhD), Department of Neurosurgery (H Khayat Kashani MD), Ophthalmology and Vision Science (Z Khorrami PhD), Social Determinants of Health Research Center (A Kolahi MD, A Nikoobar DipSc, M Rashidi MD), Department of Epidemiology (S Sabour PhD), Traditional Medicine and Materia Medica Research Center (F Safaeinejad PhD), Ophthalmic Research Center (ORC) (M Shayan MD), Emergency Department (S Shool MD), Department of Medical Education (S Tabatabai PhD), Shahid Beheshti University of Medical Sciences, Tehran, Iran (S Nasehi MSc); Non-communicable Diseases Research Center (M Abbasi-Kangevari MD, S Azadnajafabad MD, S Momtazmanesh MD, P Mousavi MD, S Rahmani MD, M Rashidi MD, N Rezaei MD, N Rezaei PhD), Advanced Diagnostic and Interventional Radiology Research Center (H Abbastabar PhD), The Institute of Pharmaceutical Sciences (TIPS) (Prof M Abdollahi PhD), School of Pharmacy (Prof M Abdollahi PhD), Research Center for Immunodeficiencies (H Abolhassani PhD, A Saghazadeh MD), Tehran Heart Center (R Alikhani MD, E Mehrabi Nasab MD), Universal Scientific Education and Research Network (USERN) (M Amirzade-Iraqi DDS), Digestive Diseases Research Institute (A Anoushvarani MD, S Fahimi MD), Prof R Malekzadeh MD, A Mohamadkhani PhD, Prof A Pourshams MD, S G Sepanlou MD), Department of Health Information Management (S Ayyoubzadeh PhD), Translational Ophthalmology Research Center (N Bahmanzadeh PhD), School of Medicine (A Behnoush BS, N Hafezi-Nejad MD, A Khalaji BS, S Khanmohammadi MD, M Mayeli MD, S Mohammadi MD, S Momtazmanesh MD), Iranian Research Center for HIV/AIDS (O Dadras DrPH), Multiple Sclerosis Research Center (S Eskandarieh PhD), Department of Ophthalmology (Prof F Ghassemi MD, A Mahmoudi MD), Department of Health in Emergencies and Disasters (M Hadei PhD), Department of Virology (A Hosseinzadeh Adli PhD), Cardiac Primary Prevention Research Center (S Kazemian MD), Department of Cardiac Electrophysiology (S Kazemian MD), Center for Research and Training in Skin Diseases and Leprosy (F Khamesipour PhD), Urology Research Center (Prof F Khatami PhD), Sina Trauma and Surgery Research Center (A Khavandegar MD, M Khormali MD, Prof V Rahimi-Movaghhar MD, F Sadeghi PhD, Prof P Salamat MD, S Shool MD), Children's Medical Center (F Kompani MD), Endocrinology and Metabolism Research Institute (Prof B Larjani FACE, N Rezaei PhD, O Tabatabaei Malazy PhD), Department of Cardiology (E Mahmoudi MD, P Mansouri MD, S Raschedi MD), Department of Pediatric Cardiology (Prof E Malakan Rad MD), Department of Epidemiology and Biostatistics (M Mansournia PhD), Department of Physiotherapy (Prof N Nakhostin Ansari PhD), Research Center for War-affected People (Prof N Nakhostin Ansari PhD), Department of Pharmacology (N Noroozi DVM), Sina Trauma Research Center (M Shabany PhD), Department of Neurology (M Shafie MD), Department of Medicine (A Shahbandi MD), Department of Pharmaceutical Care (A Sharifan PharmD), Research Center for Rational Use of Drugs (A Sharifan PharmD), Cancer Research Center (R Shirkoohi PhD), Cancer Biology Research Center (R Shirkoohi PhD), Department of Pathology (Prof S Tavangar MD), Faculty of Medicine

(S Vahabi MD), Tehran University of Medical Sciences, Tehran, Iran; Department of Epidemiology (S Abd ElHafeez DrPH), Biomedical Informatics and Medical Statistics Department (I El Sayed PhD), Pediatric Dentistry and Dental Public Health Department (Prof O A A Elmely PhD), Department of Tropical Health and Parasitology (R M Ghazy PhD), Department of Pathology (Prof I M Talaat PhD), Alexandria University, Alexandria, Egypt; Department of Surgery (M Abdelmasset MD, Prof J Sanabria MD), Marshall University, Huntington, WV, USA; Department of Tropical Medicine and Infectious Diseases (S Abd-Elsalam PhD), Tanta University, Tanta, Egypt; Department of Internal Medicine (A Abdelwahab MD), Section of General Internal Medicine (Prof A Agrawal PhD), Baylor College of Medicine, Houston, TX, USA; Department of Small Animal Clinical Sciences (M Abdollahifar PhD), Department of Community Health and Epidemiology (D A Adeyinka PhD), University of Saskatchewan, Saskatoon, SK, Canada; Department of Medicine (Prof M Abdoun B.Med.Sc.), University of Setif Algeria, Sétif, Algeria; Community and Maternity Nursing Unit (D M Abdulah MPH), Department of Pathology and Microbiology (M S Ahmed MSc), University of Duhok, Duhok, Iraq; Department of Physiotherapy (A Abdulla PhD), Department of Community Medicine (Prof M A Gadanya FMCPh), Department of Nursing Science (M Ladan PhD), Bayero University Kano, Kano, Nigeria; Department of Rehabilitation Sciences (A Abdulla PhD, M U Ali MSc, M Khan MPH, J S Usman PhD), School of Nursing (S Tyrovolas PhD), Hong Kong Polytechnic University, Hong Kong, China; Department of Midwifery (M Abebe MSc), Department of Public Health (T L Lerango MPH, Y A Wondimagegne PhD), Dilla University, Dilla, Ethiopia; Department of Public Health (S Abebe MPH), Department of Medical Laboratory Sciences (M Arkew MSc), School of Public Health (W A Cheru PhD, A Masrie MPH), Department of Health Policy and Management (A T Debele MSc), Health Sciences Department of Oncology Nursing (T G Gebi MSc), School of Nursing and Midwifery (T Getachew MSc, A D Kebede MSc), Department of Clinical Pharmacy (M D Gudeha MSc), School of Medical Laboratory Sciences (H A Meresa MSc), Haramaya University, Harar, Ethiopia; Department of Neurosurgery (A Abedi MD), Keck School of Medicine (A Abedi MD), Department of Radiology (A Gholamrezaezaad MD), Mark and Mary Stevens Neuroimaging and Informatics Institute (S Salehi MD), University of Southern California, Los Angeles, CA, USA; Department of Biostatistics (K H Abegaz PhD), Near East University, Nicosia / TRNC, Turkey; Department of Biostatistics and Health Informatics (K H Abegaz PhD), Madda Walabu University, Bale Robe, Ethiopia; Department of Botany (E S Abhilash PhD), Sree Narayana Guru College Chelannur, Kozhikode, India; Laboratory Technology Sciences Department (H Abidi PhD), Department of Nursing (M Zoladil PhD), Yasuj University of Medical Sciences, Yasuj, Iran; Department of Community Medicine (O Abiodun MPH), Babcock University, Ilishan-Remo, Nigeria; Department of Family and Community Health (R G Aboagye MPH), Department of Population and Behavioural Sciences (H Amu PhD, E E Tarkang PhD), Department of Health Policy Planning and Management (M K Boachie PhD), Department of Medical Epidemiology and Biostatistics (R K Dowou MPhil), Institute of Health Research (M Immurana PhD, D Klu PhD), Department of Microbiology and Immunology (V N Orish PhD), University of Health and Allied Sciences, Ho, Ghana; Department of Medical Biochemistry and Biophysics (H Abolhassani PhD), Department of Global Public Health (Prof P Albeck MD, Prof L Laflamme PhD), Department of Neurobiology, Care Sciences and Society (Prof J Ärnlöv PhD, S Fereshtehnejad PhD), Department of Medical Epidemiology and Biostatistics (Prof J J Carrero PhD), Department of Physiology and Pharmacology (C R Cederroth PhD), Department of Molecular Medicine and Surgery (Prof J H Kauppinen MD), Aging Research Centre (A C J Lager PhD), Karolinska Institute, Stockholm, Sweden; Department of Neurosurgery (M Abolmaali MD), Pars Advanced and Minimally Invasive Medical Manners Research Center (Y Alimohamadi PhD), Health Management and Economics Research Center (J Arabloo PhD, H Ayatollahi PhD), Department of Epidemiology (M Asadi-Lari PhD), Department of Health Information Management (H Ayatollahi PhD), School of Medicine (M Dodangeh MD), Department of Medical Laboratory Sciences (F Dorostkar PhD), Preventive Medicine

and Public Health Research Center (B Eshrati PhD, M Moradi-Lakeh MD), Department of Ophthalmology (H Hasani MD, M Ziafati MD), Minimally Invasive Surgery Research Center (A Kabir MD), Endocrine Research Center (A Karimi Behnagh MD), Department of Echocardiography (A Karimi Behnagh MD), Eye Research Center (H Kasraei MD), Educational Development Center (E Khodadoust MD), Department of Anesthesiology (K Latifinaibin MD), Gastrointestinal and Liver Diseases Research Center (M Moradi-Lakeh MD), Department of Physiology (H Pazoki Toroudi PhD), Physiology Research Center (H Pazoki Toroudi PhD), Colorectal Research Center (A Sarveazad PhD), Iran University of Medical Sciences, Tehran, Iran (M Moradi MD); Khatami Al-anbia Hospital (M Abolmaali MD), Shefi Neuroscience Research Center, Tehran, Iran; Department of Physical Pharmacy and Pharmacokinetics (M Abouzid PharmD), Poznan University of Medical Sciences, Poznan, Poland; Department of Public Health (G B Aboye MSc), Madda Walabu University, Addis Ababa, Ethiopia; Department of Nutrition and Dietetics (G B Aboye MSc), USAID-JSI Digital Health Activity (B H Demessa MPH), Jimma University, Addis Ababa, Ethiopia; Department of Pediatric Dentistry (Prof L G Abreu PhD), Department of Internal Medicine (Prof L C Brant PhD, Prof A P Ribeiro MD), Department of Nutrition (Prof R M Claro PhD), Department of Maternal and Child Nursing and Public Health (Prof D C Malta PhD, E J S Prates BS), Department of Clinical Medicine (Prof B R Nascimento PhD), Clinical Hospital (Prof B R Nascimento PhD), Centre of Telehealth (Prof A P Ribeiro MD), Department of Infectious Diseases and Tropical Medicine (B P Sao Jose PhD), Federal University of Minas Gerais, Belo Horizonte, Brazil; Department of Adult Health Nursing (W A Abhra MSc), Department of Nursing (A Girmay MSc, G M Tsegay MSc), Aksum University, Aksum, Ethiopia; Department of Neurology (S Abu Rumeileh MD), Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; Department of Nursing (H Abualrutz PhD), Al Zaytoonah University of Jordan, Amman, Jordan; Department of Pharmacology and Toxicology (B Abubakar PhD), Department of Veterinary Microbiology (M B Bello PhD), Department of Veterinary Public Health and Preventive Medicine (A Shittu MSc), Usmanu Danfodiyo University, Sokoto, Sokoto, Nigeria; Nigerian Institute of Medical Research (B Abubakar PhD), Nigerian Institute of Medical Research, Lagos, Nigeria; Clinical Sciences Department (F Abu-Gharbieh PhD, S Adra MD, H J Barqawi MPhil, N R Dash MD, Prof R Halwani PhD, Prof A A Maghazachi PhD, M M Saber-Ayad MD, N Saheb Sharif-Askari PhD, Prof I M Talaat PhD), College of Medicine (F Ahmad PhD, Prof R Halwani PhD, Prof B Saddik PhD, M A Saleh PhD), Department of Pharmacy Practice and Pharmacotherapeutics (Prof K H Alzoubi PhD, Prof H A Omar PhD), Department of Physiotherapy (A Arumugam PhD), Department of Basic Biomedical Sciences (Y Bustanji PhD), Sharjah Institute for Medical Research (N M Eleman PhD), Department of Basic Medical Sciences (W El-Huneidi PhD, A Karim PhD), Department of Clinical Nutrition and Dietetics (M E M Faris PhD), Department of Finance and Economics (Prof M Hussain PhD), Sharjah Institute of Medical Sciences (F Saheb Sharif-Askari PhD), Department of Medicinal Chemistry (S S M Soliman PhD), University of Sharjah, Sharjah, United Arab Emirates (K A Altirkawi MD); Institute of Community and Public Health (Prof N M Abu-Rmeileh PhD), Birzeit University, Ramallah, Palestine; Department of Therapeutics (Prof S Aburuz PhD), Institute of Public Health (L A Ahmed PhD, I Elbarazi DrPH, Prof S M Shah PhD), College of Medicine and Health Sciences (Prof M Grivna PhD, J Nauman PhD), Department of Medical Microbiology & Immunology (Prof G Khan PhD), Family Medicine Department (M A Khan MSc), Department of Food, Nutrition and Health (Prof S Maqsood PhD), Department of Computer Science and Software Engineering (Prof N Zaki PhD), United Arab Emirates University, Al Ain, United Arab Emirates; College of Pharmacy (Prof S Aburuz PhD), Department of Clinical Nursing (Prof M M Ahmad PhD), University of Jordan, Amman, Jordan; Department of Surgery (A Abu-Zaid MD), College of Pharmacy (R M H Temsah PharmD), Alfaisal University, Riyadh, Saudi Arabia; College of Graduate Health Sciences (A Abu-Zaid MD), Department of Neurology (R Zand MD), University of Tennessee, Memphis, TN, USA; Department of Disease Control

(M M K Accrombessi PhD), Department of Infectious Disease Epidemiology (O J Brady PhD), Department of Non-Communicable Disease Epidemiology (M Iwagami PhD), Department of Health Services Research and Policy (Prof M McKee DSc), London School of Hygiene & Tropical Medicine, London, UK; Department of Clinical Research (M M K Accrombessi PhD), Clinical Research Institute of Benin (IRCB), Abomey-Calavi, Benin; Department of Public Health (T G Adal MPH), Wolkite University, Wolkite, Ethiopia; Department of Global Health (A A Adamu PhD), South African Centre for Epidemiological Modelling and Analysis (SACEMA) (L Mhlanya PhD), Department of Epidemiology (J L Tamuzi MSc), Department of Industrial Psychology (E Teye-Kwadjo PhD), Stellenbosch University, Cape Town, South Africa; Cochrane South Africa (A A Adamu PhD), Burden of Disease Research Unit (R Matzopoulos PhD), Risk and Resilience in Mental Disorders Unit (Prof D J Stein MD), South African Medical Research Council, Cape Town, South Africa (C A Nnaji MPH); Centre for Social Research in Health (I Y Addo PhD, S R Okeke PhD), St George and Sutherland Clinical School (H Akbarialabad MD), National Drug and Alcohol Research Centre (Prof L Degenhardt PhD), School of Medicine (P K Maulik PhD), School of Psychiatry (Prof P B Mitchell MD), School of Public Health and Community Medicine (A E Peden PhD, Prof A E Schutte PhD), Centre for Primary Health Care and Equity (CPHCE) (P Peprah MSc, F Sitas PhD), School of Optometry and Vision Science (Prof K Pesudovs PhD), Faculty of Medicine and Health (S Sharma PhD), The George Institute for Global Health (I Ye MPH), University of New South Wales, Sydney, NSW, Australia; Quality and Systems Performance Unit (I Y Addo PhD), Cancer Institute NSW, Sydney, NSW, Australia; Internal Medicine and Alcohol Related Disease Unit (Prof G Addolorato MD), Department of Woman and Child Health and Public Health (D Buonsenso MD), Fondazione Policlinico Universitario A Gemelli IRCCS (Agostino Gemelli University Polyclinic IRCCS), Rome, Italy; Department of Medical and Surgical Sciences (Prof G Addolorato MD), Università Cattolica di Roma (Catholic University of Rome), Rome, Italy; Department of Community Medicine (A O Adebiyi MD, A A Afolabi MPH, O S Ilesanmi PhD), Department of Veterinary Medicine (T E Adeyeoluwa PhD), Department of Epidemiology and Medical Statistics (M Ekhlonenete MSc, A F Fagbamigbe PhD, K R Fowobaje MSc), Faculty of Public Health (M Ekhlonenete MSc, I I Olufadewa MHS), Department of Health Promotion and Education (S E Ibitoye MPH, A Ogunkoya MPH), College of Medicine (A P Okekunle PhD), Department of Medicine (Prof M O Owolabi DrM), University of Ibadan, Ibadan, Nigeria; Department of Community Medicine (A O Adebiyi MD, O S Ilesanmi PhD), Department of Medicine (A S Oguntade MSc, Prof M O Owolabi DrM), Department of Oral and Maxillofacial Surgery (A A Salami BDS), University College Hospital, Ibadan, Ibadan, Nigeria; Department of Obstetrics and Gynecology (V Adekanbi PhD), University of Texas Medical Branch, Galveston, TX, USA; Department of HIV and Infectious Diseases (A V Adepoju MD), Jhpiego, Abuja, Nigeria; Department of Adolescent Research and Care (A V Adepoju MD), Adolescent Friendly Research Initiative and Care, Ado Ekiti, Nigeria; Department of Microbiology (Prof C O Adetunji PhD), Edo State University Uzairue, Iyamho, Nigeria; Department of Biochemistry (J B Adetunji PhD), Osun State University, Osogbo, Nigeria; Department of Biosciences and Biotechnology (T E Adeyeoluwa PhD, A J Udoakang PhD), Department of Physiology (O I Adeyomoye PhD), Department of Microbiology (O O Bello PhD, Y D Oluwafemi PhD), Department of Biological Sciences (T C Ekundayo PhD), University of Medical Sciences, Ondo, Ondo, Nigeria; Department of Public Health (D A Adeyinka PhD), Federal Ministry of Health, Abuja, Nigeria; Anesthesia (B A Admass MSc), Institute of Public Health (B D Bitew PhD), Department of Environmental and Occupational Health and Safety (B D Bitew PhD), Department of Clinical Pharmacy (G S Chanje MSc), Department of Pharmacology (Z D Kifle MSc), University of Gondar, Gondar, Ethiopia; Faculty of Medicine (Q E S Adnani PhD), Center of Excellence in Higher Education for Pharmaceutical Care Innovation (Prof M J Postma PhD), Universitas Padjadjaran (Padjadjaran University), Bandung, Indonesia; Department of Life Sciences (M S Afzal PhD), University of Management and Technology, Lahore, Pakistan; Department of Community Medicine

(Prof S Afzal PhD), King Edward Memorial Hospital, Lahore, Pakistan; Department of Public Health (Prof S Afzal PhD), Public Health Institute, Lahore, Pakistan; Department of Community Medicine (Prof S B Agampodi MD, N D Wickramasinghe MD), Department of Parasitology (Prof K G Weerakoon PhD), Rajarata University of Sri Lanka, Anuradhapura, Sri Lanka; New Initiatives (Prof S B Agampodi MD), International Vaccine Institute, Seoul, South Korea; Department of Cardiovascular Medicine (P Agasthi MD), Mayo Clinic, Scottsdale, AZ, USA; Department of Internal Medicine (M Aggarwal MD, A Boustany MD, M Gupta MD), Department of Pediatrics (Prof H Aly MD, A E'mar MD), Lerner Research Institute (X Liu PhD), Cleveland Clinic, Cleveland, OH, USA; Department of Health Education and Health Promotion (F D Agide PhD), Department of Public Health (N Dereje PhD, L T Eilo MPH), Wachemo University, Hossana, Ethiopia; Department of Medical and Surgical Sciences and Advanced Technologies "GF Ingrassia" (Prof A Agodi PhD, M Barchitta PhD, A Maugeri PhD, Prof M Veroux PhD), Department of Biomedical and Biotechnological Sciences (L Falzone PhD, G Grossi PhD), Department of General Surgery and Medical-Surgical Specialties (Prof G Isola PhD), Department of Clinical and Experimental Medicine (C Ledda PhD), University of Catania, Catania, Italy; Trivedi School of Biosciences (Prof A Agrawal PhD), Ashoka University, Sonipat, Haryana 131029, India; Department of Geography and Planning (W Agyemang-Duah MSc), Department of Biomedical and Molecular Sciences (A Nkipoor PhD), Queen's University, Kingston, ON, Canada; School of Public Health (B O Ahinkorah MPHil), School of Nursing and Midwifery (M Chutiyami PhD), University of Technology Sydney, Sydney, NSW, Australia; Department of Medical Biochemistry (A Ahmad PhD), Department of Pediatrics (Prof G Mustafa MD), Department of Pharmacology (M Tabish MPharm), Shaqra University, Shaqra, Saudi Arabia; School of Medicine and Psychology (D Ahmad PhD), National Centre for Epidemiology and Population Health (Y Alemu MPH, G Joshy PhD), Research School of Population Health (N Bagheri PhD, R A Burns PhD, Prof N Cherbuin PhD), Australian National University, Canberra, ACT, Australia; Public Health Foundation of India, Gandhinagar, India (D Ahmad PhD); Department of Health and Biological Sciences (S Ahmad PhD), Abasya University, Peshawar, Pakistan; Department of Natural Sciences (S Ahmad PhD), Gilbert and Rose-Marie Chagoury School of Medicine (L Roever PhD), Lebanese American University, Beirut, Lebanon; Department of Medical Oncology (S Ahmad MD), Department of Medicine (M Ganiyani MD), Miami Cancer Institute, Miami, FL, USA; Department of Community Medicine and Preventive Health (S Ahmad MD), King Edward Medical University Lahore, Lahore, Pakistan; Department of Epidemiology and Health Statistics (T Ahmad MS), Southeast University, Nanjing, China; School of Public Health (K Ahmadi PhD, S Basu PhD), Department of Primary Care and Public Health (T Beaney MSc, Prof A Majeed MD, R Palladino MD, Prof S Rawaf MD), WHO Collaborating Centre for Public Health Education and Training (D L Rawaf MRCS), Imperial College London, London, UK; Faculty of Pharmaceutical Sciences (K Ahmadi PhD), UCSI University, Kuala Lumpur, Malaysia; Department of Pharmacy Practice (A Ahmed PhD), Riphah Institute of Pharmaceutical Sciences, Islamabad, Pakistan; Division of Infectious Diseases and Global Public Health (IDGPH) (A Ahmed PhD), University of California, San Diego, CA, USA; Institute of Endemic Diseases (A Ahmed MSc), Unit of Basic Medical Sciences (E S Siddig MD), University of Khartoum, Khartoum, Sudan; Swiss Tropical and Public Health Institute (A Ahmed MSc), University of Basel, Basel, Switzerland; Department of Biosciences (H Ahmed PhD), COMSATS Institute of Information Technology, Islamabad, Pakistan; Department of Nursing (M S Ahmed MSc), Majmaah University, Al Majmaah, Saudi Arabia; Department of Epidemiology (M B Ahmed MPH, D Shiferaw MPH), Department of Surgery (N S Bayilegyn MD), Jimma University, Jimma, Ethiopia; Australian Center for Precision Health (M B Ahmed MPH), Department of Allied Health and Human Performance (T Y Tiruye PhD), University of South Australia, Adelaide, SA, Australia; Brody School of Medicine (S Ahmed PhD), Department of Internal Medicine (S Alqalyobi MD), Department of Computer Science (A O Bodunrin MSc), Department of Physiology (M Tumurkhui PhD), Diabetes & Obesity Institute and Physiology (K Tung PhD), East Carolina University, Greenville, NC, USA (R T Aruleba PhD); Department of Food and Nutrition Policy and Planning Research (M Ajami PhD), National Institute of Nutrition, Tehran, Iran; Faculty of Medicine and Public Health (B Aji DrPH), Jenderal Soedirman University, Purwokerto, Indonesia; Moyen Mono Health District (E Akara MD), Ministry of Health, Tohoun, Togo; Department of Internal Medicine (K Akinosoglou PhD), University of Patras, Patras, Greece; Department of Internal Medicine and Infectious Diseases (K Akinosoglou PhD), University General Hospital of Patras, Patras, Greece; Department of Population Health Sciences (T Akinyemiju PhD), Duke Global Health Institute (T Akinyemiju PhD, M M Janki PhD, C Wu PhD), Department of Anesthesiology (V Krishnamoorthy MD), Center for the Study of Aging and Human Development (Y Yao MD), Duke University, Durham, NC, USA; Department of Cardiology (M A Akkaif PhD), Fudan University, Shanghai, China; Yale School of Nursing (S Akyirem MRes), School of the Environment (Prof M L Bell PhD, Y Song PhD), School of Medicine (R G Bender MSc), Department of Internal Medicine (F Etaee MD), Department of Dermatology (M Goldust MD), Department of Psychiatry (W Li PhD, T G Rhee PhD), Department of Radiology and Biomedical Imaging (X Liu PhD), Yale University, New Haven, CT, USA; Department of Geriatric and Long Term Care (H Al Hamad MD, B Sathian PhD), Rumailah Hospital (H Al Hamad MD), Department of Nursing Education & Research (A J Nashwan MSc), Hamad Medical Corporation, Doha, Qatar; Division of Public Health Sciences (S Al Hasan PhD), Washington University School of Medicine, St Louis, MO, USA; McWilliams School of Biomedical Informatics (F Alahdab MSc), UTHealth, Houston, TX, USA; Department of Biomedical Informatics, Biostatistics, and Epidemiology (F Alahdab MSc), University of Missouri, Columbia, MO, USA; Department of Clinical Sciences (S O Alalalmeh BPharm., O E Hegazi BPharm.), Center for Medical and Bio-Allied Health Sciences Research (Prof M J Shahwan PhD, M A Shamsi PhD, S H Zyoud PhD), Ajman University, Ajman, United Arab Emirates; Department of Biology (T A Alalwan PhD), University of Bahrain, Sakhir, Bahrain; John T. Milliken Department of Internal Medicine (Z Al-Aly MD), Department of Surgery (Y Cao DSc, Prof A T Toriola MD, C Wang MPH), Brown School (C Wang MPH), Washington University in St. Louis, St. Louis, MO, USA; Clinical Epidemiology Center (Z Al-Aly MD), US Department of Veterans Affairs (VA), St Louis, MO, USA; Murdoch Business School (K Alam PhD), Murdoch University, Perth, WA, Australia; Department of Bioengineering (M Alam PhD), Department of Nutrition and Food Studies (S Tyrovolas PhD), George Mason University, Fairfax, VA, USA; Prevention Division (N Alam MPH), Department of Medicine (V Kulkarni MS), Digital Health and Informatics Directorate (Prof S M McPhail PhD), Queensland Health, Brisbane, QLD, Australia; Centre for Environment and Population Health (N Alam MPH), Griffith University, Nathan, QLD, Australia; School of Nursing (R M Al-amer PhD), Department of Basic Medical Sciences (R A Karasneh PhD, M M Khatatbeh PhD), Yarmouk University, Irbid, Jordan; School of Nursing and Midwifery (R M Al-amer PhD), Translational Health Research Institute (R Chimoriya PhD), Department of Engineering (G R Naik PhD), Western Sydney University, Sydney, NSW, Australia; Department of Health Information Management and Technology (T M Alanzi PhD), Department of Public Health (Prof S Bah PhD), Division of Forensic Medicine (Prof R G Menezes MD), Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia (F M Alanezi PhD); Department of Clinical Pharmacy (Prof S Al-Azzam PharmD, Prof K H Alzoubi PhD), Department of Rehabilitation Sciences and Physical Therapy (Prof M A Alomari PhD), Jordan University of Science and Technology, Irbid, Jordan; Department of Medicine (A Albakri MD), Royal Jordanian Medical Services, Amman, Jordan; Department of Community and Mental Health (Prof M Albashtawy PhD), Al al-Bayt University, Mafrqa, Jordan; Faculty of Medicine (Prof M T AlBataineh PhD), Yarmouk University, Irbid, Jordan; Center for Health Systems Research (J E Alcalde-Rabanal PhD, S M Cuadra-Hernández PhD, D V Ortega-Altamirano DrPH), Center for Nutrition and Health Research (I R Campos-Nonato PhD, E Denova-Gutiérrez DSc), National Institute of Public Health, Cuernavaca, Mexico; Department of Pediatrics (K A Aldawsari MD), Nicklaus Children's Hospital, Miami, FL, USA; Heart Center (K A Aldawsari MD), Biostatistics, Epidemiology, and Science Computing Department (S Yezli PhD), King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia; Division of Gastroenterology and

Hepatology (W A Aldhaleei MD), Mayo Clinic, Jacksonville, FL, USA; Institute of Health Informatics (R W Aldridge PhD), Department of Health Informatics (S Chung PhD), Department of Behavioural Science and Health (S Hossain MS), Institute of Epidemiology and Health Care (J Kim MSc), Division of Psychology and Language Sciences (M Kumar PhD), Institute of Cardiovascular Science (A S Oguntade MSc), Department of Population Health Sciences (D Sunkersing PhD), Department of Infection (Prof A Zumla PhD), University College London, London, UK; Department of Public Health (H B Alema MPH), Aksum University, Axum, Ethiopia; Department of Epidemiology (M Alemayohu MPH), Department of Environmental Health (A A Asgedom PhD), School of Public Health (G G Meles MPH), Mekelle University, Mekelle, Ethiopia; Unit of Epidemiology & Medical Statistics (M Alemayohu MPH), University of Verona, Verona, Italy; Global Health Entrepreneurship (S Alemi PhD), Tokyo Medical and Dental University, Tokyo, Japan; Department of Epidemiology and Biostatistics (Y Alemu MPH, K A Bogale MPH), College of Medicine and Health Science (A Amare PhD), Department of Midwifery (A M Aweke MSc), College of Medicine and Health Sciences (S A Belay MSc), School of Health Science (A Y Berhie MSc), Department of Health Promotion and Behavioural Science (E K Bogale MPH), Anaesthesiology (F T Kumie MSc), Department of Surgery (N A Shitaye MD), Department of Pharmacy (M Yismaw MSc), Department of Pharmacology (Y Yismaw MSc), Bahir Dar University, Bahir Dar, Ethiopia; Global Centre for Environmental Remediation (A A S Al-Gheethi PhD), School of Medicine and Public Health (P Atorkey MPhil), University of Newcastle, Newcastle, NSW, Australia; Cooperative Research Centre for Contamination Assessment and Remediation of the Environment, Newcastle, NSW, Australia (A A S Al-Gheethi PhD); Department of Cardiac Sciences (Prof K F Alhabib MD), Section of Adult Hematology (Prof G M T ElGohary MD), Department of Physiology (Prof S A Meo PhD), Pediatric Intensive Care Unit (M Temsah MD), King Saud University, Riyadh, Saudi Arabia; College of Nursing (Prof F A N Alhalaiqa PhD), College of Dental Medicine (S A A Al-Maweri PhD), Department of Physical Education (Prof M A Alomari PhD), QU Health (M Mohammed PhD), Department of Population Medicine (Prof G Rathnaiah Babu PhD), Qatar University, Doha, Qatar; Psychological Sciences Association, Amman, Jordan (Prof F A N Alhalaiqa PhD); Department of Health Services and Hospital Administration (M K Al-Hanawi PhD), Health Economics Research Group (M K Al-Hanawi PhD), Department of Family and Community Medicine (N S Butt PhD), Department of Pediatric Dentistry (Prof O A A Elmelygi PhD), Rabigh Faculty of Medicine (A A Malik PhD), Department of Dental Public Health (Z S Natto DrPH), Department of Community Medicine (S Samargandy PhD), King Abdulaziz University, Jeddah, Saudi Arabia; Department of Zoology (A Ali PhD), Department of Botany (Prof I Khan PhD), Abdul Wali Khan University Mardan, Mardan, Pakistan; Department of Biotechnology and Genetic Engineering (A Ali PhD, M Waqas PhD), Hazara University Mansehra, Mansehra, Pakistan; Department of Biological Sciences (L Ali PhD, A S Qazi PhD, R Z Raza PhD), National University of Medical Sciences (NUMS), Rawalpindi, Pakistan; Department of Medical Rehabilitation (Physiotherapy) (M U Ali MSc), Department of Human Pathology (Prof H A Nggada MD), University of Maiduguri, Maiduguri, Nigeria; Department of Biosciences (R Ali MPhil, N Salam PhD), Centre for Interdisciplinary Research in Basic Sciences (CIRBSc) (S Anwar PhD, M A Shamsi PhD), Jamia Millia Islamia, New Delhi, India; Centre for Biotechnology and Microbiology (S Ali PhD), Center for Biotechnology and Microbiology (S S Ali PhD, M Suleman PhD), University of Swat, Charbagh, Pakistan; Department of Pathophysiology and Transplantation (G Alicandro PhD), Università degli Studi di Milano (University of Milan), Milan, Italy; Cystic Fibrosis Center (G Alicandro PhD), Fondazione IRCCS Ospedale Maggiore Policlinico IRCCS 'Ca' Granda Maggiore Policlinico' Hospital Foundation, Milan, Italy; School of Public Health and Preventive Medicine (S M Alif PhD), School of Public Health and Preventative Medicine (Prof M Asghari-Jafarabadi PhD), Department of Human Centered Computing (M Hasan MSc), Department of Infectious Diseases (M J Loftus MBBS), Department of Medicine (Prof K R Polkinghorne PhD, Prof A G Thrift PhD), Monash University, Melbourne, VIC, Australia; Department of Public Health (A A Aliyi MPH), Madda Walabu University, Goba, Ethiopia; Medical Laboratories (M A M Aljasir PhD), Qassim University, Buraydah, Saudi Arabia; Department of Molecular and Clinical Pharmacology (M A M Aljasir PhD), Institute of Infection and Global Health (Prof A Beloukas PhD), Liverpool Orthopaedic and Trauma Service (S M Graham PhD), Department of Surgery (Prof R Lunevicius DSc), Institute of Population Health Sciences (M R Mathur PhD), University of Liverpool, Liverpool, UK; Department of Health Policy and Management (Prof S M Aljunid PhD), Department of Surgery (S K Al-Sabah MD), Kuwait University, Kuwait, Kuwait; International Centre for Casemix and Clinical Coding (Prof S M Aljunid PhD), National University of Malaysia, Bandar Tun Razak, Malaysia; Bordeaux School of Public Health (Prof F Alla PhD), University of Bordeaux, Bordeaux, France; Department of Dentistry (S Al-Marwani MSc), Independent Consultant, Sana'a, Yemen; Public Health and Community Medicine (S Al-Marwani MSc), Independent Consultant, Irbid, Jordan; Department of Medicine (J U Almazan PhD, Prof D Poddighe PhD), Nazarbayev University, Astana, Kazakhstan; Department of Parasitology (Prof H M Al-Mekhlafi PhD), Department of Paediatrics (Prof H Ariffin MD), University of Malaya Medical Centre (Prof H Ariffin MD), Department of Medicine (L Lim MRCP), University of Malaya, Kuala Lumpur, Malaysia; Department of Parasitology (Prof H M Al-Mekhlafi PhD), Sana'a University, Sana'a, Yemen; Wilmer Eye Institute (L Almidani MSc), Department of Radiology and Radiological Science (A Amindarolzarbi MD, N Hafezi-Nejad MD), Department of Biostatistics (A Columbus MS), Department of Epidemiology (T G Hundie MD), Department of Neurosurgery (F Kazerni MD), Department of Health Policy and Management (D Vervoort MD), Division of Cardiology (M Viskadourou MD), Department of International Health (H Zhang MS), Johns Hopkins University, Baltimore, MD, USA (E Jamshidi PharmD); Department of Urology (O Almidani MSc), Department of Cardiac Surgery (L Göbölös PhD), Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates; Nuffield Department of Surgical Sciences (O Almidani MSc, S Bandyopadhyay BA), Nuffield Department of Medicine (B Basnyat MD, Prof R J Maude PhD), Oxford Centre for Global Health Research (C Dolecek PhD), Nuffield Department of Population Health (B Lacey PhD), University of Oxford, Oxford, UK; Department of Epidemiology and Population Health (B Al-Omari PhD), Khalifa University of Science, Technology & Research, Abu Dhabi, United Arab Emirates; Research Program of Epidemiology and Public Health (J Alonso MD), Pompeu Fabra University, Barcelona, Spain; Department of Experimental and Health Sciences (J Alonso MD), Biomedical Research Networking Center in Epidemiology and Public Health (CiberESP), Madrid, Spain; Department of Respiratory Care (J S Alqahtani PhD), Prince Sultan Military College of Health Sciences, Dammam, Saudi Arabia; Independent Consultant, Greenville, NC, USA (S Alqalyoubi MD), Department of Prosthodontics and Implant Dentistry (A Alqtaibi PhD), Taibah University, Medinah, Saudi Arabia; Department of Prosthodontics (A Alqtaibi PhD), Ibb University, Ibb, Yemen; Jaber Al Ahmad Al Sabah Hospital (S K Al-Sabah MD), Ministry of Health, Kuwait, Kuwait; Department of Basic sciences (Z Altaany PhD), Yarmouk University, Irbid, Jordan; Institute of Molecular Biology and Biotechnology (A Altaf PhD, Prof M Ashraf PhD, S Shahid PhD), University College of Medicine & Dentistry (Prof M Arooj PhD), Department of Oral Biology (A Fahim PhD), University Institute of Public Health (S Hameed MPH, A Hanif PhD, A A Malik PhD, S Nargus PhD), University Institute of Diet and Nutritional Sciences (A Khalil PhD), Department of Technology (M Muzaffar MBA), Research Centre for Health Sciences (RCHS) (M Muzaffar MBA, S Shahid PhD), Department of Physics (W Shahid PhD), The University of Lahore, Lahore, Pakistan (M A Riaz Mcom); Department of Specialty Internal Medicine (Prof J A Al-Tawfiq MD), Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia; Department of Medicine (Prof J A Al-Tawfiq MD), Indiana University School of Medicine, Indianapolis, IN, USA; Lisbon Institute of Global Mental Health (D O Aluh MSc), Nova University of Lisbon, Lisboa, Nigeria; Clinical Pharmacy and Pharmacy Management (D O Aluh MSc), University of Nigeria Nsukka, Nsukka, Nigeria; Research Group in Hospital Management and Health Policies (Prof N Alvis-Guzman PhD), Universidad de la Costa (University of the Coast), Barranquilla,

Colombia; Research Group in Health Economics (Prof N Alvis-Guzman PhD), University of Cartagena, Cartagena, Colombia; Department of Clinical Pharmacology and Toxicology (H Alwafi PhD), Department of Medical Genetics (M Athar PhD), Science and Technology Unit (M Athar PhD), Institute of Center and Research Studies (F Rehman PhD), Umm Al-Qura University, Makkah, Saudi Arabia; Department of Medical Sciences (Prof Y M Al-Worafi PhD), Azal University for Human Development, Sana'a, Yemen; Department of Clinical Sciences (Prof Y M Al-Worafi PhD), University of Science and Technology of Fujairah, Fujairah, United Arab Emirates; Department of Pediatric Cardiology (S Aly MD), Boston Children's Hospital, Boston, MA, USA; Interdisciplinary Graduate Program in Human Toxicology (R Amani DVM), University of Iowa, Iowa City, IA, USA; Health Policy Research Center (R Amani DVM, S Ghahramani MD, H Kasraei MD, Y Sarikhani PhD, S Shahabi PhD), Health Information Management (A Bashiri PhD), Health Human Resources Research Center (M Bayati PhD), Trauma Research Center (P Fazeli MSc, M Karajizadeh PhD), Department of Medical Immunology (P Fazeli MSc), Shiraz Neuroscience Research Center (M Jafarinia PhD, R Tavakoli Oliaee PhD), Non-communicable Disease Research Center (Prof R Malekzadeh MD, S G Sepanlou MD), Department of Epidemiology and Biostatistics (H Raeisi Shahraki PhD), Department of Health Services Management (R Ravangard PhD), Department of Biostatistics (E Sadeghi PhD), Shiraz University of Medical Sciences, Shiraz, Iran; School of Medicine (A Amare PhD), School of Public Health (M Du MSC, V Podder HSC), Adelaide Medical School (T K Gill PhD, Prof C L Hill MD), Robinson Research Institute (Z S Lassi PhD, H Mohammed PhD), Centre for Heart Rhythm Disorders (J Noubiap MD), University of Adelaide, Adelaide, SA, Australia; School of Global Public Health (P M Amegbor PhD, S D Friedman BA, E K Peprah PhD), Department of Child and Adolescent Psychiatry (Prof S Cortese PhD), The Center for Drug Use and HIV Research (CDUHR) (P Meylakhs PhD), New York University, New York, NY, USA; School of Graduate Studies (E K Ameyaw MPhil), Lingnan University, Hong Kong, China; Public Health and Community Medicine Department (Prof T T Amin MD), Department of Neurophysiology (Prof H R Elhabashy MD), Cairo University, Cairo, Egypt; Medicine, Quran and Hadith Research Center (S Amiri PhD), Baqiyatallah University of Medical Sciences, Tehran, Iran; Department of Maternal and Child Wellbeing (D A Amugsi PhD), African Population and Health Research Center, Nairobi, Kenya; Department of Medicine (G A Amusa MD), Department of Pediatrics (A O D Ofakunrin MSc), University of Jos, Jos, Nigeria; Department of Internal Medicine (G A Amusa MD), Department of Pediatrics (A O D Ofakunrin MSc), Jos University Teaching Hospital, Jos, Nigeria; Faculty of Pharmacy (Prof R Anculeanu PhD), Department of Cardiology (C Andrei PhD), Department of Internal Medicine and Rheumatology (A V Bobirca PhD), Ophthalmology Department (A Dascalu PhD), Department of General Surgery (B T Florin PhD, I Negoi PhD, D Serban PhD, B Socea PhD), Department of Dermatology and Venereology (Prof S R Georgescu PhD), Department of Internal Medicine (M Hostiuc PhD), Department of Legal Medicine and Bioethics (S Hostiuc PhD), Department of Anatomy and Embryology (R I Negoi PhD), Department of Diabetes, Nutrition and Metabolic Diseases (A Pantea Stoian PhD), Department of Dermatology (M Tampa PhD), Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Centre for Sensorimotor Performance (D Anderlini MD), Department of Urology (Prof E Chung MD), School of Public Health (A J Ferrari PhD, D F Santomauro PhD), Institute for Social Science Research (E Kammi MPH, A A Mamun PhD, J C Maravilla PhD), School of Health and Rehabilitation Sciences (A Khan PhD, M Moni PhD), School of Dentistry (R Laloo PhD), Queensland Brain Institute (Prof J J McGrath MD), The University of Queensland, Brisbane, QLD, Australia (J T Kelly PhD); Neurology Department (D Anderlini MD), Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; Faculty of Medicine (D B Anderson PhD), School of Architecture, Design, and Planning (Prof T Astell-Burt PhD), Menzies Centre for Health Policy and Economics (M Balasubramanian PhD), School of Pharmacy and Charles Perkins Centre (Z Dai PhD), School of Public Health (Prof T R Driscoll PhD, H K Tang PhD), Sydney Medical School (S Islam PhD), Save Sight Institute (H Kandel PhD, Prof S L W Watson PhD, Y You PhD),

Department of Public Health (M Khan PhD), Asbestos Diseases Research Institute (J Leigh MD), Kolling Institute (S Mathieson PhD), Sydney Musculoskeletal Health (S Mathieson PhD), School of Veterinary Science (B B Singh PhD), Menzies Centre for Health Policy (F Sitas PhD), University of Sydney, Sydney, NSW, Australia; Department of Health Care Management (P P Andrade MD), Prof R Busse PhD, S Mohammed PhD), Technical University of Berlin, Berlin, Germany; European University, Lisbon, Portugal (P P Andrade MD); Department of Statistics and Econometrics (Prof T Andrei PhD, Prof M Ausloos PhD, Prof C Hertelius PhD, A Mirica PhD, A Otoiu PhD), Faculty of Management (A Dima PhD), Bucharest University of Economic Studies, Bucharest, Romania; School of Health and Related Research (C Angus MSc), Department of Infection and Tropical Medicine (O C Durojaiye MPH), Department of Psychology (A Yadollahpour PhD), University of Sheffield, Sheffield, UK; Department of Pharmacology (A Anil MD, M Shamim MBBS, S Singh MD, S B Varthy MD), Department of Community Medicine and Family Medicine (P Baskaran MD, P Bhardwaj MD, M K Gupta MD, Prof P R Raghav MD), Department of Anatomy (Prof N Bhardwaj MD, H Krishna MD), School of Public Health (P Bhardwaj MD), Department of Forensic Medicine and Toxicology (T Kanchan MD), Department of Surgical Oncology (Prof S Misra MCh), Department of Pharmacology and Research (A Saravanan MD), Department of Community Medicine (G Singh MD), All India Institute of Medical Sciences, Jodhpur, India; All India Institute of Medical Sciences, Bhubaneswar, India (A Anil MD); Department of Obstetrics and Gynecology (S Anil MBBS), Ernakulam Medical Centre, Palarivattom, Kochi, India; Department of Epidemiology and Biostatistics (Prof H Ansari PhD, Prof A Ansari-Moghaddam PhD), Department of Health Promotion (A Nazri-Panjaki MSc), Health Promotion Research Center (H Okati-Aliabad PhD), Zahedan University of Medical Sciences, Zahedan, Iran; School of Public Health (A Ansariadi PhD), Faculty of Pharmacy (F Nainu PhD), Hasanuddin University, Makassar, Indonesia; Agribusiness Study Program (E Antriyandarti DrAgrSc), Sebelas Maret University, Surakarta, Indonesia; Department of Parasitology (D Anvari PhD), Department of Dermatology (N Gholizadeh MD), Department of Medical-Surgical Nursing (S Shorofi PhD), Department of Environmental Health (Prof Z Yousefi PhD), Mazandaran University of Medical Sciences, Sari, Iran; Department of Parasitology (D Anvari PhD), Department of Pharmacology (Prof B Foroutan PhD), Iranshahr University of Medical Sciences, Iranshahr, Iran; Regenerative Medicine, Organ Procurement, and Transplantation Multi-disciplinary Center (S Anvari MD), School of Health (S Doaei PhD), Department of Social Medicine and Epidemiology (A Feizkhah MD), Department of Medical-Surgical Nursing (P Ghorbani Vajargah MSc), Gastrointestinal and Liver Diseases Research Center (S Hassanipour PhD), Caspian Digestive Disease Research Center (S Hassanipour PhD), Department of Environmental Health Engineering (J Jaafari PhD), Guilan University of Medical Sciences, Rasht, Iran; School of Chemical and Life Sciences (SCLS) (S Anwar PhD), Jamia Hamdard, New Delhi, India; Department of Surgery (S Anwar PhD), Gadjah Mada University, Yogyakarta, Indonesia; Department of Pathology (R Anwer PhD), Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia; School of Dentistry and Medical Sciences (A E Anyasodor PhD), Charles Sturt University, Orange, NSW, Australia; Department of Psychology (M Aqeel PhD, M Aqeel PhD), Foundation University Islamabad, Rawalpindi, Pakistan; Department of Medicine (J Arab MD), Department of Epidemiology and Biostatistics (F Barbic PhD), Western University, London, ON, Canada; Gastroenterology Department (J Arab MD), Pediatric Infectious Diseases and Immunology (A Borzutzky MD), Pontifical Catholic University of Chile, Santiago, Chile; College of Pharmacy (M Arafat PhD), Al Ain University, Abu Dhabi, United Arab Emirates; College of Art and Science (D Areda PhD), Ottawa University, Surprise, AZ, USA; School of Life Sciences (D Areda PhD), Arizona State University, Tempe, AZ, USA; Department of Veterinary Pharmacology and Toxicology (A Aremu PhD), Department of Veterinary Physiology and Biochemistry (A Basiru PhD), Department of Veterinary Public Health and Preventive Medicine (I A Odetokun PhD), University of Ilorin, Ilorin, Nigeria; Department of Public Health (O Aremu PhD), Birmingham City University, Birmingham, UK; Department of Cardiovascular, Endocrine-metabolic Diseases and Aging (B Armocida MSc, B Unim PhD), National Institute of Health, Rome, Italy; Division of Tropical and

Humanitarian Medicine (B Armocida MSc), University of Geneva, Geneva, Switzerland; School of Health and Social Studies (Prof J Ärnlöv PhD), Dalarna University, Falun, Sweden; Department of Biophysics (A Artamonov PhD), A.A. Timiryazev Institute of Plant Physiology (M V Titova PhD), Russian Academy of Sciences, Moscow, Russia; Department of Maternal and Child Health (J Arulappan DSc), Sultan Qaboos University, Muscat, Oman; Department of Community Medicine and Rehabilitation (A Arumugam PhD), Department of Nursing (Prof D Edvardsson PhD), Umeå University, Umeå, Sweden; Department of Plastic Surgery (M Asaad MD), Health Science Center (D Dongarwar MS), University of Texas, Houston, TX, USA; International Relations Department (M Asadi-Lari PhD), Development of Research and Technology Center (S Djalalinia PhD), Centre for Primary Health Care Network Management (H Fattahi PhD), Ministry of Health and Medical Education, Tehran, Iran; Neurological Surgery Department (M Asghariahmadabad MD), School of Nursing (J Nutor PhD), Department of Epidemiology and Biostatistics (M Teramoto MD), University of California San Francisco, San Francisco, CA, USA; Cabrini Research (Prof M Asghari-Jafarabadi PhD), Cabrini Health, Malvern, VIC, Australia; Department of Aging Research Institute (A Aslani MD), Department of Radiology (M Dashti MD), A Ghasemzadeh MD, A Zarrintan MD), Department of Health Policy and Management (L Doshmangir PhD), School of Nursing and Midwifery (H Hassankhani PhD), Research Center for Evidence-Based Medicine (M Hosseini MD), Department of Virology (A Hosseinzadeh Adli PhD), Department of Immunology (F Jadidi-Niaragh PhD), School of Management and Medical Informatics (L R Kalankesh PhD), Social Determinants of Health Research Center (S Karimi PhD, Prof S Mohammad-Alizadeh-Charandabi PhD), Midwifery Department (Prof S Mohammad-Alizadeh-Charandabi PhD), Department of Community Medicine (S Mousavi MD), Molecular Medicine Research Center (S Pirouzpanah PhD), Drug Applied Research Center (H Samadi Kafil PhD), Tabriz University of Medical Sciences, Tabriz, Iran; Department of Immunology (S Athari PhD), Department of Critical Care and Emergency Nursing (N Hanifi PhD), Zanjan University of Medical Sciences, Zanjan, Iran; School of Nursing and Midwifery (B T Atinatu MSc), Department of Pediatrics and Child Health Nursing (S S Yehualashet MSc), Debre Berhan University, Debre Berhan, Ethiopia; Department of Biomedical sciences (H W Atlaw MSc), Department of Public Health (H Esubalew MPH), Department of Nursing (A M Mersha MSc), Department of Clinical Midwifery (B A Mesfin B.Med.Sc.), Arba Minch University, Arba Minch, Ethiopia; Hunter New England Population Health, Wallsend, NSW, Australia (P Atorkey MPhil); Faculty of Nursing (M M W Atout PhD), Philadelphia University, Amman, Jordan; Department of Forensic Medicine (A Atreya MD), Lumbini Medical College, Palpa, Nepal; Northumbria HealthCare NHS Foundation Trust, Newcastle upon Tyne, UK (A Aujayeb MBBS); School of Business (Prof M Ausloos PhD), Department of Health Sciences (Prof T Brugha MD, P H Lee PhD, S J Tromans PhD), University of Leicester, Leicester, UK; Robarts Research Institute (A Avan MD), The University of Western Ontario, London, ON, Canada; Department of Surgery (A F Awedew MD), Addis Ababa University, Debre Tabor, Ethiopia; The Judith Lumley Centre (B Ayala Quintanilla PhD), School of Nursing and Midwifery (Prof D Edvardsson PhD, F Efendi PhD, M Rahman PhD), Department of Public Health (H Jiang PhD, Prof C Liu PhD), La Trobe University, Melbourne, VIC, Australia; San Martin de Porres University, Lima, Peru (B Ayala Quintanilla PhD); Department of Psychiatry (Prof J L Ayuso-Mateos PhD), Department of Medicine (Prof A Ortiz MD), Hospital Universitario de La Princesa (Princess University Hospital) (Prof J B Soriano MD), Universidad Autónoma de Madrid (Autonomous University of Madrid), Madrid, Spain; Biomedical Research Networking Center for Mental Health Network (CIBERSAM) (Prof J L Ayuso-Mateos PhD), National School of Public Health (F Catalá-López PhD, A Padron-Monedero PhD), Institute of Health Carlos III, Madrid, Spain; Department of Sciences (Prof R M S Azevedo PhD), Therapeutic and Diagnostic Technologies Department (Prof N Cruz-Martins PhD), Toxicology Research Unit (TOXRUN) (Prof D Dias da Silva PhD, Á M Madureira-Carvalho PhD), Cooperativa de Ensino Superior Politécnico e Universitário (CESPU) (University Polytechnic Higher Education Cooperative), Gandra, Portugal; Department of Neurovascular Research (A Y Azzam MBBCh),

Nested Knowledge, Inc., Saint Paul, MN, USA; Faculty of Medicine (A Y Azzam MBBCh), October 6 University, 6th of October City, Egypt; Kasturba Medical College, Mangalore (D B B MD, R Holla MD, M Rao MD), Department of Physiotherapy (A S Babu PhD, Prof V K PhD), Department of Health Policy (V Dsouza MSc), Prasanna School of Public health (R Kamath MHA), Department of Pharmacy Management (V S Ligade PhD), Department of Forensic Medicine (A Mishra MD), Manipal College of Dental Sciences (Prof A I Narayana PhD, Prof R A Radhakrishnan PhD), Department of Forensic Medicine and Toxicology (Prof V C Nayak MD), Manipal TATA Medical College (M Rahman PhD), Department of Community Medicine (C R Rao MD), Department of Nephrology (I Rao DM), Manipal Academy of Higher Education, Manipal, India; Department of Medicine (A S Babu PhD), Melbourne School of Population and Global Health (H Jiang PhD, L Reifels PhD), School of Health Sciences (A Meretoja MD), Department of General Practice (J Zhang MD), University of Melbourne, Melbourne, VIC, Australia; Gomal Center of Biochemistry and Biotechnology (M Badar PhD), Gomal University, Dera Ismail Khan, Pakistan; Department of Forensic Science (A D Badiye PhD, H Bansal MSc, N Kapoor PhD), Government Institute of Forensic Science, Nagpur, India; Division of Orthopaedics (S Baghdadi MD), Children's Hospital of Philadelphia, Philadelphia, PA, USA; Health Research Institute (N Bagheri PhD), University of Canberra, Canberra, ACT, Australia; School of Medicine (S Bagheri BSc, G Ghasempour Dabaghi MD, M Rabiee Rad MD), Department of Environmental Health Engineering (A Fatehizadeh PhD), Cardiac Rehabilitation Research Center (K Mehrabani-Zeinabad PhD), Department of General Surgery (P Mir Mohammad Sadeghi MD), Isfahan Cardiovascular Research Institute (N Mohammadifard PhD), Department of Medical Physics (K Saber PhD), Musculoskeletal Research Center (A Shafaat MS), Isfahan University of Medical Sciences, Isfahan, Iran; NanoElectronics and Photonics Systems (MEPHOS) (S Bahadorikhali PhD), Universitat Rovira i Virgili, Tarragona, Spain; School of Public Affairs (R Bai MD), Nanjing University of Science and Technology, Nanjing, China; International Medical School (A A Baig PhD), Management and Science University, Alam, Malaysia; Center for Clinical Research and Prevention (J L Baker PhD), Bispebjerg University Hospital, Frederiksberg, Denmark; Department of Neurosurgery (A T Bako PhD), Houston Methodist Hospital, Houston, TX, USA; Maternal and Child Health Unit (R K Bakshi MD), Department of Biostatistics (V K Kamal PhD), Indian Council of Medical Research, New Delhi, India; (D K Lal MD); Division of Biological Sciences (S Balakrishnan PhD), Tamil Nadu State Council for Science and Technology, Chennai, India; Health Care Management Department (M Balasubramanian PhD), Flinders Health and Medical Research Institute (N B Bularu PhD), College of Nursing and Health Sciences (L N Bulto PhD), College of Medicine and Public Health (T G Gebremeskel PhD, B Kaambwa PhD, G R Naik PhD), Health Economics Unit (B Kaambwa PhD), Department of Nursing and Health Sciences (S Shorofi PhD), Flinders University, Adelaide, SA, Australia; Center of Innovation, Technology and Education (CITE) (Prof O C Baltatu PhD), Institute of Biomedical Engineering (Prof L A Campos PhD), Anhembi Morumbi University, São José dos Campos, Brazil; Department of Medicine (K Bam MPH, M T Olaiya PhD), School of Nursing and Midwifery (D Bhandari PhD), Stroke and Ageing Research, Victorian Heart Institute (L L Dalli PhD), Department of Neuroscience (Prof C A Unsworth PhD), Monash University, Clayton, VIC, Australia; Department of Hypertension (Prof M Banach PhD), Medical University of Lodz, Lodz, Poland; Polish Mothers' Memorial Hospital Research Institute, Lodz, Poland (Prof M Banach PhD); Department of Neurosurgery (S Bandyopadhyay BA), School of Psychology (Prof S Cortese PhD), Faculty of Medicine (R Thayakaran PhD), University of Southampton, Southampton, UK; Department of Non-communicable Diseases (P C Banik MPhil, L Barua MPH), Bangladesh University of Health Sciences, Dhaka, Bangladesh; Department of Medicine (K Bansal MD), Department of Neurology (S Sivakumar MD), University of Massachusetts Medical School, Worcester, MA, USA; Department of Medicine (K Bansal MD), Department of Cardiovascular Medicine (A K Jha MD), Saint Vincent Hospital, Worcester, MA, USA; Department of Biomedical Sciences (F Barbic PhD), Humanitas University, Milan, Italy; Miami Cancer Institute (M Bardham MD), Baptist Health South

Florida, Miami, FL, USA; School of Psychology (Prof S L Barker-Collo PhD), School of Pharmacy (K A Beyene PhD), University of Auckland, Auckland, New Zealand; Heidelberg Institute of Global Health (HIGH) (Prof T W Bärnighausen MD, S Bartelt PhD, S Chen DSc), Heidelberg University, Heidelberg, Germany; Department of Translational Medicine (F Barone-Adesi PhD), University of Eastern Piedmont, Novara, Italy; Department of Industrial Engineering (Prof L H Barrero DSc), Pontifical Javeriana University, Bogota, Colombia; Department of Epidemiology (A Barrow MPH), D Braithwaite PhD, D D Ding BS, D Yang MPH), College of Medicine (M J Diaz BS), UF Health Cancer Center (S D Karanth PhD), Department of Computer and Information Science and Engineering (P Naghavi MSc), University of Florida, Gainesville, FL, USA; Department of Public & Environmental Health (A Barrow MPH), University of The Gambia, Brikama, The Gambia; Alpha Genomics, Islamabad, Pakistan (Z Basharat PhD); Department of Tuberculosis (B Basnyat MD), Birat Nepal Medical Trust, Kathmandu, Nepal; Barcelona Institute for Global Health (Prof Q Bassat MD), Universitat de Barcelona (University of Barcelona), Barcelona, Spain; Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain (Prof Q Bassat MD); Faculty of Pharmacy (J D Basso PharmD, S Silva MSc), Coimbra Chemistry Centre (J D Basso PharmD), Department of Geography and Demography (M Rodrigues PhD), Coimbra Institute for Biomedical Imaging and Translational Research (S Silva MSc), University of Coimbra, Coimbra, Portugal; Department of Medical Education (K Batra PhD), University of Nevada Las Vegas, Las Vegas, NV, USA; Department of Psychiatry (Prof B T Baune PhD), Institute for Epidemiology and Social Medicine (A Karch MD), University of Münster, Münster, Germany; Department of Psychiatry (Prof B T Baune PhD), Melbourne Medical School, Melbourne, VIC, Australia; School of Public Health (Prof N Bedi MD), Dr. D. Y. Patil University, Mumbai, India; Clinical Nutrition (R M Chandika PhD), Department of Epidemiology (S Dohare MD, K Y Ghailan PhD, M Khan MD), Department of Maxillofacial Surgery and Diagnostic Sciences (E S Halboub PhD), Department of Health Education and Promotion (M Shanawaz MD), Jazan University, Jazan, Saudi Arabia (Prof N Bedi MD); Department of Mental Health (M Beghi MD), AUSL Romagna, Ravenna, Italy; Department of Basic Sciences (E Behboudi PhD), Khoj University of Medical Sciences, Khoj, Iran; Department of Community Medicine and Family Medicine (P Behera MD), All India Institute of Medical Sciences, BHUBANESWAR, India; Department of Epidemiology (M Heidari-Foroozan BSc, S Khanmohammadi MD, S Nejadghaderi MD, S Rashedi MD, H Soleimani MD), Endocrinology and Metabolism Research Institute (A Khalajei BS), Non-Communicable Diseases Research Center (NCDRC), Tehran, Iran (A Behroush BS); Social Determinants of Health Research Center (M Behzadifar PhD), Lorestan University of Medical Sciences, Khorramabad, Iran; Division of Pulmonary, Critical Care, and Sleep (M Beiranvand PhD), University of Florida, Jacksonville, FL, USA; Department of Medicine (D F Bejarano Ramirez BN), El Bosque University, Bogota, Colombia; Transplant Service (D F Bejarano Ramirez BN), University Hospital Foundation Santa Fe de Bogotá, Bogota, Colombia; Department of Neurology (Prof Y Béjot PhD), University Hospital of Dijon, Dijon, France; Dijon Stroke Registry (Prof Y Béjot PhD), University of Burgundy, Dijon, France; National Data Management Center (NDMC) for Health, Burden of Disease Unit (C M Belete MSc, W A Cheru PhD), National Data Management Center for Health (A Misganaw PhD), Ethiopian Public Health Institute, Addis Ababa, Ethiopia; Land Administration and Use Bureau (C M Belete MSc), Academia Sinica, Bahir Dar, Ethiopia; Infectious Disease Research Department (M B Bello PhD), King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; Department of Biological Sciences (L Belo PhD), Research Unit on Applied Molecular Biosciences (UCIBIO) (L Belo PhD, Prof F Carvalho PhD, V M Costa PhD, Prof D Dias da Silva PhD, J P Silva PhD), Associated Laboratory for Green Chemistry (LAQV) (M Carvalho PhD, N G M Gomes PhD), Department of Chemical Sciences (R A S Couto MD), Institute for Research and Innovation in Health (Prof N Cruz-Martins PhD), Public Health and Forensic Sciences, and Medical Education Department (Prof R J Dinis-Oliveira PhD), Department of Community Medicine, Information and Health Decision Sciences (A Freitas PhD), Department of Chemistry (N G M Gomes PhD), Department of Chemical Engineering (Prof C F Rodrigues PhD), University of Porto, Porto, Portugal; Department of Biomedical Sciences (Prof A Beloukas PhD), University of West Attica, Athens, Greece; Department of Internal Medicine (I M Bensenor PhD, I S Santos PhD), Department of Psychiatry (Prof J Castaldelli-Maia PhD, Prof M F P Peres MD, Y Wang PhD), Center for Clinical and Epidemiological Research (I S Santos PhD), University of São Paulo, São Paulo, Brazil; School of Medicine (A Beran MD, J T Tran BS), Indiana University, Indianapolis, IN, USA; Institute of Marketing (Z Bereczai PhD), Corvinus University of Budapest, Budapest, Hungary; Competition Economics and Market Research Section (Z Bereczai PhD), Hungarian Competition Authority, Budapest, Hungary; Hubert Department of Global Health (R S Bernstein MD), School of Medicine (A O Fasanmi PhD, E L B Rogowski MPH), Department of Family and Preventive Medicine (T Sathish PhD), Rollins School of Public Health (Prof D A Sleet PhD), Emory University, Atlanta, GA, USA; Butte County Department of Public Health, Chico, CA, USA (R S Bernstein MD); Faculty of Medicine (P J G Bettencourt PhD), Catholic University of Portugal, Rio de Mouro, Portugal; Department of Pharmaceutical and Administrative Sciences (K A Beyene PhD), University of Health Sciences and Pharmacy in St. Louis, St Louis, MO, USA; Department of Forensic Chemistry (D S Bhagat PhD), Government Institute of Forensic Science, Aurangabad, Aurangabad, India; Department of Public Health (A S Bhagavathula PhD), North Dakota State University, Fargo, ND, USA; Institutes of Applied Health Research and Translational Medicine (N Bhala PhD), Queen Elizabeth Hospital Birmingham, Birmingham, UK; Institute of Applied Health Research (N Bhala PhD), NIHR Global Health Research Unit on Global Surgery (J C Glasbey MSc), University of Birmingham, Birmingham, UK; Department of Internal Medicine (Prof A Bhalla MD), Post Graduate Institute of Medical Education and Research, Chandigarh, India; Public Health Research Laboratory (D Bhandari PhD), Department of Biotechnology (B P Marasini PhD), Faculty of Humanities and Social Sciences (U Paudel PhD), Department of Community Medicine (P M S Pradhan MD), Tribhuvan University, Kathmandu, Nepal; Department of Hematology Oncology (P V Bhardwaj MD), University of Massachusetts Medical School, Springfield, MA, USA; Department of Internal Medicine (A Bhargava MD), Wayne State University, Detroit, MI, USA; Global Health Neurology Lab (S Bhaskar PhD), NSW Brain Clot Bank, Sydney, NSW, Australia; Department of Neurology and Neurophysiology (S Bhaskar PhD), South West Sydney Local Health District and Liverpool Hospital, Sydney, NSW, Australia; Department of Internal Medicine (V Bhat MBBS), St. John's National Academy of Health Sciences, Bangalore, India; Medical Lab Technology (G K Bhatti PhD), University Centre for Research and Development (S Kalra DM), Chandigarh University, Mohali, India; Department of Human Genetics and Molecular Medicine (Prof J S Bhatti PhD, S Senapati PhD, U Sharma PhD), Department of Zoology (B Vellingiri PhD), Central University of Punjab, Bathinda, India; Department of Botanical and Environmental Sciences (Prof M S Bhatti PhD), Department of Pharmaceutical Sciences (R Bhatti PhD), Guru Nanak Dev University, Amritsar, India; Centre for Global Child Health (Prof Z A Bhutta PhD), Temerty Faculty of Medicine (V Chatta MD), Division of Neurology (S Fereshtehnejad PhD), Department of Neurosurgery (A K Malhotra MD), University of Toronto, Toronto, ON, Canada; Centre of Excellence in Women & Child Health (Prof Z A Bhutta PhD), Division of Women and Child Health (J K Das MD), Department of Pediatrics (Z S Lassi PhD), Department of Family Medicine (Prof S M Shah PhD), Aga Khan University, Karachi, Pakistan; Scientific-Tools.Org, Bergamo, Italy (B Bikbov MD); Department of Biomedical and NeuroMotor Sciences (Prof F Bisulli PhD), Department of Biomedical and Neuromotor Sciences (A Capodici MD, S Guicciardi MD, L Muccioli MD), Department of Medical and Surgical Sciences (Prof F S Violante MD), University of Bologna, Bologna, Italy; UOC Clinica Neurologica (Prof F Bisulli PhD), IRCCS Istituto delle Scienze Neurologiche di Bologna (Institute of Neurological Sciences of Bologna), Bologna, Italy; Department of Neurology (Prof A Biswas DM), Department of GI Surgery (A Dhali MBBS), Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital, Kolkata, India; Community & Family Medicine (B Biswas MD), All India Institute of Medical Sciences, Deoghar, India; Department of

Biostatistics and Epidemiology (Prof S Bitaraf PhD), Department of Orthodontics (E Eini DDS), Education Development Center (M Sayyah MD), Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Faculty of Health Sciences (V R Bitra PhD), Department of Internal Medicine (G M Rwegeera MD), University of Botswana, Gaborone, Botswana; Department of Global Public Health and Primary Care (Prof T Bjørge PhD, A Hailu PhD), Department of Psychosocial Science (D Sagoe PhD), University of Bergen, Bergen, Norway; Department of Research (M W Wojewodzic PhD), Cancer Registry of Norway, Oslo, Norway (Prof T Bjørge PhD); SAMRC Centre for Health Economics and Decision Science (PRICELESS SA) (M K Boachie PhD), University of the Witwatersrand, Johannesburg, South Africa; Department of Sociology and Social Work (M S Boampong PhD), Department of Biochemistry and Biotechnology (A Kwarteng PhD), Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; School of Business Administration (Prof V Bodolica PhD), American University of Sharjah, Sharjah, United Arab Emirates; Department of Veterinary Medicine (S Bohlouli PhD), Islamic Azad University, Kermanshah, Iran; Discipline of Public Health Medicine (O A Bolarinwa MSc, T G Ginindza PhD), School of Nursing and Public Health (E E Tarkang PhD), University of KwaZulu-Natal, Durban, South Africa; Department of Internal Medicine (A Boloor MD), Department of Forensic Medicine and Toxicology (H L Dsouza MD, V Krishna MD, Prof B K Shetty MD, P H Shetty MD), Department of General Medicine (J Jeganathan MD), Department of Community Medicine (N Joseph MD, P Mithra MD, R Motappa MD), Department of Obstetrics and Gynaecology (A Shetty MS), Kasturba Medical College, Mangalore (Prof B Unnikrishnan MD), Manipal Academy of Higher Education, Mangalore, India; Faculty of Medicine and Pharmaceutical Sciences (A Bonny MD), University of Douala, Douala, Cameroon; Department of Cardiology (A Bonny MD), Centre Hospitalier Montfermeil (Montfermeil Hospital Center), Montfermeil, France; Regional Medical Research Centre, North East Region (K Bora MD), Indian Council of Medical Research, Dibrugarh, India; General Directorate of Health Information Systems (B Bora Basara PhD), Ministry of Health, Ankara, Turkiye; Department of Medicine (Prof S Bouaoud MD), Faculty of Medicine (Prof A Ouyahia PhD), University Ferhat Abbas of Setif, Setif, Algeria; Department of Epidemiology and Preventive Medicine (Prof S Bouaoud MD), University Hospital Saadna Abdenour, Setif, Algeria; Department of Earth, Environment, and Equity (C Boxe PhD), Division of General Internal Medicine (R F Gillum MD), Department of Community and Family Medicine (R F Gillum MD), Howard University, Washington, DC, USA; General Medicine Service (Prof E J Boyko MD), Department of Veterans Affairs, Seattle, WA, USA; Cancer Population Sciences Program (D Braithwaite PhD), University of Florida Health Cancer Center, Gainesville, FL, USA; School of Population and Public Health (Prof M Brauer DSc, P A Chakraborty MPH, I O Iyamu MD, D P Rasali PhD), School of Nursing (A Pashaei MSc), University of British Columbia, Vancouver, BC, Canada; Institute of Epidemiology (A Brazinova MD), Comenius University, Bratislava, Slovakia; Department of Sports and Computer Science (J Brazo-Sayavera PhD), Universidad Pablo de Olavide (Pablo de Olavide University), Seville, Spain; Department of Psychiatry and Behavioral Health (Prof N J K Breitborde PhD), Department of Psychology (Prof N J K Breitborde PhD), Division of Cardiovascular Medicine (A Guha MD), Ohio State University, Columbus, OH, USA; Institute for Medical Information Processing, Biometry, and Epidemiology (S Breitner DSc), Ludwig Maximilian University of Munich, Munich, Germany; Institute of Epidemiology (S Breitner DSc), Helmholtz Zentrum München German Research Center for Environmental Health, Neuherberg, Germany; Division of Clinical Epidemiology and Aging Research (Prof H Brenner MD), German Cancer Research Center, Heidelberg, Germany; Biomedical Department (A N Brikoff PhD), Bauman Moscow State Technical University, Moscow, Russia; Department of Epidemiology and Evidence-Based Medicine (Prof N I Brikoff DSc, P D Lopukhov PhD), I.M. Sechenov First Moscow State Medical University, Moscow, Russia; Department of Neuroscience (G Britton PhD), University of Panama, Ancon, Panama; Infectious Diseases Department (G Britton PhD), Gorgas Memorial Institute for Health Studies, Panama City, Panama; Department of Injury (J Brown PhD), Global Women's Health Program (P Cullen PhD), The George Institute for Global Health, Newtown, NSW, Australia; Faculty of

Medicine (J Brown PhD), School of Population Health (P Cullen PhD, Z Dai PhD, X Xu PhD), School of Psychiatry (Prof P S Sachdev MD), University of New South Wales, Kensington, NSW, Australia; Global Health Research Institute (D Buonsenso MD), Università Cattolica del Sacro Cuore (Catholic University of Sacred Heart), Rome, Italy; Department of Biopharmaceutics and Clinical Pharmacy (Y Bustanji PhD), The University of Jordan, Amman, Jordan; School of Public Health Sciences (Z A Butt PhD, O A Zitoun MD), University of Waterloo, Waterloo, ON, Canada; Al Shifa School of Public Health (Z A Butt PhD), Al Shifa Trust Eye Hospital, Rawalpindi, Pakistan; Department of Clinical Pharmacy (Prof D Calina PhD), University of Medicine and Pharmacy of Craiova, Craiova, Romania; Department of Internal Medicine (Prof L A Cámera MD), Hospital Italiano de Buenos Aires (Italian Hospital of Buenos Aires), Buenos Aires, Argentina; Board of Directors (Prof L A Cámera MD), Argentine Society of Medicine, Buenos Aires, Argentina; College of Health Sciences (Prof L A Campos PhD), Abu Dhabi University, Abu Dhabi, United Arab Emirates; Dana-Farber Cancer Institute, Boston, MA, USA (C Cao MPH); Management and Healthcare (EMbeDS) (A Capodici MD), Sant'Anna School of Advanced Studies, Pisa, Italy; Department of Health Care (Prof R Cárdenas DSc), Metropolitan Autonomous University, Mexico City, Mexico; Oncological Network, Prevention and Research Institute (G Gorini MD), Institute for Cancer Research, Prevention and Clinical Network, Florence, Italy (G Carreras PhD); Dermatology Unit (A Carugno MD), Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII (Territorial Healthcare Company Pope John XXIII), Bergamo, Italy; Department of Pediatrics (C G Carvalheiro PhD), University of São Paulo, Ribeirão Preto, Brazil; Department of Pediatrics (C G Carvalheiro PhD), Clinical Hospital of Ribeirão Preto, Ribeirão Preto, Brazil; Instituto de Investigação, Inovação e Desenvolvimento (Institute of Research Innovation and Development) (M Carvalho PhD), University Fernando Pessoa, Porto, Portugal; Colombian National Health Observatory (C A Castañeda-Orjuela MD), National Institute of Health, Bogota, Colombia; Epidemiology and Public Health Evaluation Group (C A Castañeda-Orjuela MD), National University of Colombia, Bogota, Colombia; Department of Medicine (G Castelpietra PhD), University of Udine, Udine, Italy; Department of Mental Health (G Castelpietra PhD), Healthcare Agency "Friuli Occidentale", Pordenone, Italy; Clinical Epidemiology Program (F Catalá-López PhD), Ottawa Hospital Research Institute, Ottawa, ON, Canada; Department of Pharmacological and Biomolecular Sciences (Prof A L Catapano PhD), IRCCS Istituto Ortopedico Galeazzi (Galeazzi Orthopedic Institute IRCCS) (G Damiani MD), Department of Clinical Sciences and Community Health (Prof C La Vecchia MD), Department of Food, Environmental and Nutritional Sciences (Prof D Martini PhD), University of Milan, Milan, Italy; MultiMedica Sesto San Giovanni IRCCS, Sesto S. Giovanni, Italy (Prof A L Catapano PhD); Department of Otolaryngology, Head and Neck Surgery (C R Cederoth PhD), University of Tubingen, Tübingen, Germany; Department of Medical, Surgical & Health Sciences (L Cegolon PhD), Department of Medical, Surgical, and Health Sciences (Prof M D'Orsi MD), University of Trieste, Trieste, Italy; Public Health Unit (L Cegolon PhD), University Health Agency Giuliano-Isontina (ASUGI), Trieste, Italy; Department of Nutrition (Prof F Cembranel DSc), Federal University of Santa Catarina, Florianópolis, Brazil; College of Public Health, Medical, and Veterinary Sciences (M Cenderadewi MPHTM), Prof R C Franklin PhD, A E Peden PhD), Department of Public Health and Tropical Medicine (T I Emeto PhD), James Cook University, Townsville, QLD, Australia (K O Obamiro PhD); Department of Public Health (M Cenderadewi MPHTM), University of Mataram, Mataram, Indonesia; Mary MacKillop Institute for Health Research (Prof E Cerin PhD), Faculty of Health Sciences (G R Poudel PhD), Australian Catholic University, Melbourne, VIC, Australia; School of Public Health (Prof E Cerin PhD), Department of Periodontology and Implant Dentistry (K Deng PhD), Department of Urban Planning and Design (C Guo PhD), Centre for Suicide Research and Prevention (Prof P Yip PhD), Department of Social Work and Social Administration (Prof P Yip PhD), University of Hong Kong, Hong Kong, China; Infection and Global Health Research (M Cevik MD), University of St Andrews, St Andrews, UK; Regional Infectious Diseases Unit (M Cevik MD), Department of Clinical Effectiveness (A I Ikiroma PhD),

NHS National Services Scotland, Edinburgh, UK; ICMR School of Public Health (J Chadwick MD), Division of Epidemiology and Biostatistics (V K Kamal PhD), National Institute of Epidemiology, Chennai, India; Department of Biotechnology (Prof C Chakraborty PhD), Adamas University, Kolkata, India; Skeletal Aging & Orthopedic Surgery (Prof C Chakraborty PhD), Hallym University, Chuncheon, South Korea; Heart Failure and Structural Heart Disease Unit (J Chan MBChB), Cardiovascular Analytics Group, Hong Kong, China; Department of Medicine and Therapeutic (R N C Chan MBChB), Prince of Wales Hospital, Hong Kong, China; Department of Anesthesiology and Perioperative Medicine (E K Chandrasekar MD), School of Medicine (Prof S Xu PhD), University of Rochester, Rochester, NY, USA (E Dorsey MD); Institute of Epidemiology and Preventive Medicine (C Chang PhD), National Taiwan University, Taipei City, Taiwan; Department of Psychological Medicine (C Chang PhD), Department of Twin Research and Genetic Epidemiology (M Mazidi PhD), Faculty of Life Sciences and Medicine (M Molokhia PhD), Institute of Psychiatry, Psychology & Neuroscience (D Urso MD), School of Population Health and Environmental Sciences (H A Wafa MPH, Y Wang PhD, Prof C D A Wolfe MD), King's College London, London, UK; College of Medicine (J Chang PhD), National Taiwan University, Taipei, Taiwan; Department of Nursing (J Chang PhD), National Taiwan University Hospital, Taipei, Taiwan; Department of Public Health (P Charalampous PhD, S Polinder PhD, F Porru MD), Department of Medical Informatics (Prof D Prieto Alhambra PhD), Erasmus University Medical Center, Rotterdam, Netherlands; Department of Community Medicine (V Chattu MD), Datta Meghe Institute of Medical Sciences, Sawangi, India; Center for Cancer Epidemiology (Prof P Chaturvedi MD), Homi Bhabha National Institute (HBNI), Mumbai, India; Department of Endocrinology (V Chatzimavridou-Grigoriadou MD), Department of Mathematics (O Johnson PhD), Division of Immunology, Immunity to Infection and Respiratory Medicine (A G Mathioudakis PhD), Division of Psychology and Mental Health (F Mughal FRCCP), University of Manchester, Manchester, UK; Department of Endocrinology (V Chatzimavridou-Grigoriadou MD), Christie Hospital NHS Foundation Trust, Manchester, UK; Oral Medicine and Radiology (A Chaurasia MD), King George's Medical University, Lucknow, India; Fuwai Hospital (A Chen PhD), Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; Department of Computer Science (A Chen PhD), University of Texas Austin, Austin, TX, USA; Clinical Research Center (H Chen MB), Southern Medical University, Guangzhou, China; Department of Internal Medicine (D Flood MD), University of Michigan, Ann Arbor, MI, USA (M Chen BDS); Ocular Epidemiology Research Group (Prof C Cheng MD), Singapore Eye Research Institute, Singapore, Singapore; Ophthalmology & Visual Sciences Academic Clinical Program (Prof C Cheng MD), National Dental Research Institute Singapore (G G Nascimento PhD), Duke-NUS Medical School, Singapore, Singapore; Department of Paediatrics (E T W Cheng MBChB, S Dai PhD), School of Pharmacy (G Fekadu MSc), Jockey Club School of Public Health and Primary Care (J Huang MD, C Zhong MD), Department of Medicine & Therapeutics (Y Jin MD), Department of Medicine and Therapeutics (L Lim MRCP), The Chinese University of Hong Kong, Hong Kong, China; Department of Laboratory Medicine (J Chien PhD), Taichung Tzu-Chi Hospital Buddhist Tzu-Chi Medical Foundation, Tainzh, Taiwan; Department of Medical Laboratory Science and Biotechnology (J Chien PhD), Central Taiwan University of Science and Technology, Taichung, Taiwan; Department of Public Health and Health Policy (O Chimed-Ochir PhD), Hiroshima University, Hiroshima, Japan; Westmead Clinical School (R Chimoriya PhD), University of Sydney, Sydney, Australia; Division of Infectious Diseases (P R Ching MD), School of Medicine (H Ding MPH), Virginia Commonwealth University, Richmond, VA, USA; Department of Public Health, Administration, and Social Sciences (J L Chirinos-Caceres DrPH), Cayetano Heredia University, Lima, Peru; Iraq Field Epidemiology Training Program (I-FETP) (A Chitheer MD), Ministry of Health, Baghdad, Iraq; Department of Clinical Oncology (W C S Cho PhD), Queen Elizabeth Hospital, Hong Kong, China; Department of Medicine (B Chong MBBS), Saw Swee Hock School of Public Health (Prof D S Q Koh PhD, Prof D S Q Koh PhD, S Yi PhD), School of Medicine (M Ng PhD), Leadership Institute for Global Health Transformation (LIGHT) (S Ramazanu PhD), Department of Surgery (K Tan PhD), Yong Loo Lin School of Medicine (Prof N Venketasubramanian MBBS), National University of Singapore, Singapore, Singapore; Department of Biosciences (H Chopra PhD), Center for Global Health Research (M Fareed PhD, S Muthupandian PhD), Department of Public Health Dentistry (Prof G Mini PhD), Saveetha Dental College and Hospitals (M R Tovani-Palone PhD), Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, India; Department of Community Medicine (Prof S G Choudhari MD, Prof A M Gaidhane MD), Datta Meghe Institute of Medical Sciences, Wardha, India; Department of Epidemiology (S O Gbadamosi MD, R Jebai MPH), Florida International University, Miami, FL, USA (Prof R Chowdhury PhD); Department of Epidemiology (Prof R Chowdhury PhD), Institute of Social and Preventive Medicine (M Ganbat MPH), Department of Neurology (L D Panos MD), Department of Emergency Medicine (I Pantazopoulos PhD), Department of Cardiology (T Pilgrim MD, S Stortecy MD), University of Bern, Bern, Switzerland; Department of Pulmonary Medicine (Prof D J Christopher MD), Department of Endocrinology, Diabetes and Metabolism (Prof N Thomas PhD), Christian Medical College and Hospital (CMC), Vellore, India; Department of Paediatric Surgery (I S Chukwu B.Med.Sc.), Federal Medical Centre, Umuahia, Nigeria; Department of AndroUrology (Prof E Chung MD), AndroUrology Centre, Brisbane, QLD, Australia; Health Data Research UK, London, UK (S Chung PhD); Department of Genetics (Z Cindi PhD), School of Veterinary Medicine (F Musaigwa PhD), Department of Biostatistics Epidemiology and Informatics (J Puvvula PhD), University of Pennsylvania, Philadelphia, PA, USA; Department of Food, Environmental and Nutritional Sciences (I Cioffi PhD, C Del Bo' PhD, M Marino PhD), University of Milan, Milano, Italy; Department of Biochemistry and Microbiology (M M Claassens PhD), University of Namibia, Windhoek, Namibia; Department of Paediatrics and Child Health (M M Claassens PhD), Stellenbosch University, Tygerberg, South Africa; Nova Medical School (J Conde PhD), Nova University of Lisbon, Lisbon, Portugal; School of Medicine and Surgery (P A Cortesi PhD, Prof L G Mantovani DSc), University of Milan Bicocca, Monza, Italy; Department of Epidemiology and Prevention (S Costanzo PhD), IRCCS Neuromed, Pozzilli, Italy; Department of Psychology (R G Cowden PhD), University of the Free State, Park West, South Africa; Department of Psychology (K M Cramer PhD), Office of Institutional Analysis (J Dube MA), University of Windsor, Windsor, ON, Canada; Department of Family Medicine and Public Health (Prof M H Criqui MD), University of California San Diego, La Jolla, CA, USA; Department of Epidemiology (Prof M p Curado PhD), Accamargo Cancer Center, São Paulo, Brazil; Department of Internal Medicine (S Dadana MD), Cheyenne Regional Medical Center, Cheyenne, WY, USA; School of Clinical Medicine (S Dai PhD), Hangzhou Normal University, Hangzhou, China; Department of Dermatology (G Damiani MD), Lerner College of Medicine (L Göbölös PhD), Harrington Heart and Vascular Institute (A Guha MD), Department of Quantitative Health Science (X Liu PhD), Department of Neonatology (I Qatteea MD), Department of Nutrition and Preventive Medicine (Prof J Sanabria MD), Case Western Reserve University, Cleveland, OH, USA; Department of Public Health (J Darega Gela MPH), Ambo University, Ambo, Ethiopia; Department of Biochemistry (S Das MD), Ministry of Health and Welfare, New Delhi, India; Ingram School of Engineering (S Das PhD), Texas State University, San Marcos, TX, USA; Ophthalmology Department (A Dascalu PhD), Emergency University Hospital Bucharest, Bucuresti, Romania; 2nd University Ophthalmology Department (A Dastiridou MD), Department of Ophthalmology (N Dervenis MD), Second Department of Cardiology (D Patoulias PhD), Aristotle University of Thessaloniki, Thessaloniki, Greece; Ophthalmology Department (A Dastiridou MD), University of Thessaly, Greece; Department of Global Health and Infection (Prof G Davey MD), Brighton and Sussex Medical School, Brighton, UK; School of Public Health (Prof G Davey MD, N Dereje PhD, D H Woldegebre MPH), Center for Food Science and Nutrition (T B Elema MA), Medical Laboratory Science (M Getie MSc), Emergency Department (D Ijo MSc), Department of Health Management Information Systems (D Ijo MSc), Addis Ababa University, Addis Ababa, Ethiopia; Department of Population and Development (C A Dávila-Cervantes PhD), Latin American Faculty of Social Sciences Mexico, Mexico City, Mexico; Health

Research Institute (K Davletov PhD), Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan; Australian Institute for Suicide Research and Prevention (Prof D De Leo DSc, Prof K Kolves PhD), Griffith University, Mount Gravatt, QLD, Australia; Discipline of Chiropractic (K de Luca PhD), CQ University, Brisbane, QLD, Australia; Medical College (S Debopadhyia BS), Albany Medical College, Albany, NY, USA; Department of Epidemiology and Community Medicine (A Dehghan PhD), Fasa University of Medical Sciences, Fasa, Iran; School of Medicine (I Delgado-Enciso DSc), University of Colima, Colima, Mexico; Department of Research (I Delgado-Enciso DSc), Colima State Health Services, Colima, Mexico; Department of Neurosurgery (A K Demetriades MD), Global Health Governance Programme (J Patel BSc), Centre for Medical Informatics (Prof A Sheikh MD), Usher Institute (Prof C R Simpson PhD), College of Medicine and Veterinary Medicine (G Verras MD), University of Edinburgh, Edinburgh, UK; Department of Neurosurgery (A K Demetriades MD), National Health Service Scotland, Edinburgh, UK; Epidemiology Branch (X Deng PhD), National Institute of Health, Durham, NC, USA; St Paul's Eye Unit (N Dervenis MD), Royal Liverpool University Hospital, Liverpool, UK; Department of Forensic Medicine (E Dervišević PhD), University of Sarajevo, Sarajevo, Bosnia and Herzegovina; Department of Forensic Medicine (E Dervišević PhD), Universiti Kebangsaan Malaysia Medical Centre, Sarajevo, Bosnia and Herzegovina; Department of Psychiatry (Prof D C Des Jarlais PhD, S Guntur MD), The Zena and Michael A. Wiener Cardiovascular Institute (V R Dhulipala MD), Institute of Critical Care Medicine (A Shaikh MD), Department of Cardiology (M Vinayak MD), Icahn School of Medicine at Mount Sinai, New York, NY, USA (A Shaikh MD); Graduate Medical Education (H D Desai MD), Gujarat Adani Institute of Medical Sciences, Bhuj, India; Division of Cardiology (R Desai MBBS), Atlanta Veterans Affairs Medical Center, Decatur, GA, USA; Department of Community Medicine (V G C Devanbu MD), Chettinad Academy of Research and Education, Chennai, India; Department of Pharmacy (S Dewan PhD, M R Islam PhD), University of Asia Pacific, Dhaka, Bangladesh; Pharmacology Department (S Dewan PhD), Center for Life Sciences Research Bangladesh, Dhaka, Bangladesh; Division of Pathology (K Dhamo PhD), ICAR-Indian Veterinary Research Institute, Bareilly, India; Research Department (M Dhimal PhD), B P Marasini PhD, U Paudel PhD), Research Section (A Ghimire BSc), Nepal Health Research Council, Kathmandu, Nepal; Department of Pharmacy Practice (S Dhingra PhD), National Institute of Pharmaceutical Education and Research, Hajipur, India; Faculty of Science (Prof D Diaz PhD), National Autonomous University of Mexico, Mexico City, Mexico; Toxicology Research Unit (TOXRUN) (Prof R J Dinis-Oliveira PhD), Advanced Polytechnic and University Cooperative (CESPU), Gandra, Portugal; Department of Medicine (T H Do MD), Can Tho University of Medicine and Pharmacy, Can Tho, Viet Nam; Center for Health Sciences (C B do Prado MSc), Federal University of Espírito Santo, Vitória, Brazil; Department of Biostatistics (M Dodangeh Mcom), Independent Consultant, Tehran, Iran; Department of Social Medicine and Health Care Organisation (K G Dokova PhD), Medical University "Prof. Dr. Paraskev Stoyanov", Varna, Bulgaria; Mahidol Oxford Tropical Medicine Research Unit (C Dolecek PhD), Mahidol University, Bangkok, Thailand; School of Elderly Care Services and Management (W Dong MD), Nanjing University of Chinese Medicine, Nanjing, China; Cardio-Thoraco-Vascular Department (Prof M D'Oria MD), Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy; Departamento de Responsabilidade Social (Department of Social Responsibility) (W M dos Santos PhD), Hospital Alemão Oswaldo Cruz (Oswaldo Cruz German Hospital), São Paulo, Brazil; Brazilian Centre for Evidence-based Healthcare (W M dos Santos PhD), Joanna Briggs Institute, São Paulo, Brazil; Department of Cardiology (R Doshi MD), St. Joseph's University Medical Center, Paterson, NJ, USA; Department of Forensic Medicine and Toxicology (H L Dsouza MD), Kasturba Medical College Mangalore, Mangalore, India; Department of Periodontology (M Du MSc), Shandong University, Jinan, China; Postgraduate Program in Epidemiology (Prof B B Duncan MD, Prof B N G Goulart DSc, Prof M I Schmidt MD), Federal University of Rio Grande do Sul, Porto Alegre, Brazil; School of Medicine (Prof A R Duraes PhD), Institute of Collective Health (Prof M Pereira PhD, Prof D Rasella PhD), Federal University of Bahia,

Salvador, Brazil; Department of Internal Medicine (Prof A R Duraes PhD), Escola Bahiana de Medicina e Saúde Pública (Bahiana School of Medicine and Public Health), Salvador, Brazil; Department of Biotechnology (S Duraismay PhD), SRM Institute of Science and Technology (SRMIST), Kattankulathur, India; Child Health Analytics Research Program (P A Dzianach PhD, Prof P W Gething PhD, F Sanna PhD, D J Weiss PhD), Geospatial Health and Development Team (J Lubinda PhD, A Saddler PhD), The Malaria Atlas Project (S F Rumisha PhD), Telethon Kids Institute, Perth, WA, Australia; Department of Conservative Dentistry with Endodontics (A M Dziedzic DSc), Medical University of Silesia, Katowice, Poland; Department of Psychiatry (E Eboreime PhD, E Tsermpini PhD), Dalhousie University, Halifax, NS, Canada; Department of Psychiatry (E Eboreime PhD), University of Alberta, Edmonton, AB, Canada; Division of Cardiothoracic Vascular Surgery (C P Echiel FWACS), University of Calabar, Calabar, Nigeria; Division of Cardiothoracic Surgery (C P Echiel FWACS), University of Arizona, Tucson, AZ, USA; School of Health Sciences (H A Edinur PhD), Universiti Sains Malaysia (University of Science Malaysia), Kubang Kerian, Malaysia; College of Science, Health and Engineering (K Edvardsson PhD), La Trobe University, Bundoora, VIC, Australia; Department Pediatric Nursing (D Efendi MSN), Faculty of Public Health (D Kusuma DSc), Centre for Family Welfare (K Latief Master of Epidemiology), University of Indonesia, Depok, Indonesia; Neonatal Intensive Care Unit (D Efendi MSN), University of Indonesia Hospital, Depok, Indonesia; Department of Community Health Nursing (F Efendi PhD), Department of Epidemiology (A Hargono DMD), Faculty of Public Health (S Martini PhD), Universitas Airlangga (Airlangga University), Surabaya, Indonesia; Research Center for Public Health and Nutrition (D E Effendi MA), National Research and Innovation Agency Republic of Indonesia (BRIN), Jakarta, Indonesia (A Kusnali LLB, H U Pangaribuan MSc); Centre for Global Health Inequalities Research (CHAIN) (Prof T Eikemo PhD), Department of Circulation and Medical Imaging (J Nauman PhD), Norwegian University of Science and Technology, Trondheim, Norway; Department of Food Science and Nutrition (T B Elema MA), Arsi University, Asella, Ethiopia; School of Population and Global Health (Prof F J Elgar PhD), McGill University, Montreal, QC, Canada; Department of Internal Medicine and Hematology Unit (Prof G M T ElGohary MD), Department of Entomology (A M Samy PhD), Medical Ain Shams Research Institute (MASRI) (A M Samy PhD), Neurology Department (Prof A S Shalash PhD), Ain Shams University, Cairo, Egypt; Faculty of Medicine (M Elhadi MD), University of Tripoli, Tripoli, Libya; Egypt Center for Research and Regenerative Medicine (ECRRM), Cairo, Egypt (M A Elmonem PhD); Department of Clinical Pathology (M Elshaer MD), Faculty of Pharmacy (M A Saleh PhD), Rheumatology and Immunology Unit (S Tharwat MD), Mansoura University, Mansoura, Egypt; Department of Infectious Diseases and Public Health (I Elsobhy PhD), City University of Hong Kong, Hong Kong, China; Department of Animal Medicine (I Elsobhy PhD), Cardiovascular Department (Prof A M A Saad MD), Zagazig University, Zagazig, Egypt; Lincoln International Institute for Rural Health (L Engelbert Bain PhD), University of Lincoln, Lincoln, UK; Department of International Cyber Education (R Erkhembayar MD), Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; Department of Paediatrics (C I Esezobor MB), Department of Psychiatry (A T Olagunju MD), University of Lagos, Lagos, Nigeria; Department of Paediatrics (C I Esezobor MB), Lagos University Teaching Hospital, Lagos, Nigeria; Department of Obesity, Diabetes and Cardiovascular Risk (Prof J Espinosa-Montero PhD), National Institute of Public Health Mexico, Cuernavaca, Mexico; Independent Consultant, Bologna, Italy (N Fabin MD); Department of Anesthesia (A O Fadaka PhD), Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; Department of Biotechnology (A O Fadaka PhD), School of Pharmacy (O C Okonji MSc), University of the Western Cape, Cape Town, South Africa; Research Centre for Healthcare and Community (A F Fagbamigbe PhD), Faculty of Health and Life Sciences (O P Kurmi PhD), Coventry University, Coventry, UK; Department of Food Hygiene and Quality Control (A Fakhri-Demeshghieh DVM), University of Tehran, Tehran, Iran; Epidemiology and Biostatistics Unit (L Falzone PhD), IRCCS Pascale, Naples, Italy; Dissemination Division (C S e Farinha MSc), National Institute of Statistics, Lisbon, Portugal;

Activity Planning and Control Unit (C S e Farinha MSc), Directorate-General of Health (DGS), Lisbon, Portugal; Department of Biology (P S Faris PhD), Department of Food Technology (Y Galali ResM, B A Sadee PhD), Department of Statistics (D H Kadir PhD), Salahaddin University-Erbil, Erbil, Iraq; Department of Biology (P S Faris PhD), Department of Nutrition and Dietetics (Y Galali ResM, B A Sadee PhD), Cihan University-Erbil, Erbil, Iraq; Department of Psychology (Prof A Faro PhD), Federal University of Sergipe, São Cristóvão, Brazil; Satcher Health Leadership Institute (A O Fasammi PhD), Morehouse School of Medicine, Atlanta, GA, USA; Centre for Health Policy Research (Prof P Ward PhD), Torrens University Australia, Adelaide, SA, Australia (N K Faulk MSc); Institute of Resource Governance and Social Change, Kupang, Indonesia (N K Faulk MSc); National Institute for Stroke and Applied Neurosciences (Prof V L Feigin PhD), Auckland University of Technology, Auckland, New Zealand; Third Department of Neurology (E V Gnedovskaya PhD), Research Center of Neurology, Moscow, Russia (Prof V L Feigin PhD, Prof M A Piradov DSc); Department of Pharmacy (G Fekadu MSc), Department of Nursing (G Fetensa MSc, L Gurmessa MSc, G M Kebebew MSc), Institute of Health Sciences (B R Feyisa MPH), Wollega University, Nekemte, Ethiopia; School of Medicine (X Feng PhD), Department of Psychology (C Hu PhD), Tsinghua Vanke School of Public Health (Z Li PhD), Tsinghua University, Beijing, China; Department of Translational Medicine (D Ferrante PhD), University of Piemonte Orientale, Italy, Novara, Italy; Department of Social Sciences (Prof N Ferreira PhD), University of Nicosia, Nicosia, Cyprus; Department of Psychiatry (I Filip MD), Kaiser Permanente, Fontana, CA, USA; School of Health Sciences (I Filip MD), A.T. Still University, Mesa, AZ, USA; Institute of Public Health (F Fischer PhD), Departement of Surgery (N Haep MD), Department of Neurology (S Samadzadeh MD), Department of Infectious Diseases and Respiratory Medicine (F Steinbeis MD), Charité Universitätsmedizin Berlin (Charité Medical University Berlin), Berlin, Germany; School of Social Sciences (J Flavel PhD), Stretton Health Equity, Adelaide, SA, Australia; Center for Research in Indigenous Health (D Flood MD), Maya Health Alliance, Tecpán, Guatemala; Institute of Gerontology (N A Foigt PhD), National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine; Department of Child Dental Health (Prof M O Folayan FWACS), Obafemi Awolowo University, Ile-Ife, Nigeria; Clinical Science Department (Prof M O Folayan FWACS), Nigerian Institute of Medical Research, Yaba, Nigeria; Department of Cell Biology and Biotechnology (A A Fomenkov PhD), K.A. Timiryazev Institute of Plant Physiology, Moscow, Russia; Department of Medical Parasitology (M Foroutan PhD), Faculty of Medicine (M Foroutan PhD), Department of Public Health (N Kamyari PhD), Department of Pharmacology (H Mojiri-Forushani PhD), Abadan University of Medical Sciences, Abadan, Iran; Department of Disease Burden (I Forthun PhD, A S Knudsen PhD, C Madsen PhD), Norwegian Institute of Public Health, Bergen, Norway; Healthcare Innovation Department (D Fortuna MSc), Regional Agency for Health and Social Care of Emilia-Romagna, Bologna, Italy; Department of Biotechnological and Applied Clinical Sciences (DISCAB) (M Foschi MD), Department of Neurology (Prof S Sacco MD), University of L'Aquila, L'Aquila, Italy; Department of Neuroscience (M Foschi MD), Hospital Santa Maria delle Croci, Ravenna, Italy; Child Survival Unit (K R Fowabaje MSc), Centre for African Newborn Health and Nutrition, Ibadan, Nigeria; Centre for Adolescent Health (K L Francis MBiostat, J A Kerr PhD), Department of Critical Care and Neurosciences (Prof R G Weintraub MB), Murdoch Childrens Research Institute, Parkville, VIC, Australia; Center for Health Technology and Services Research (CINTESIS), Porto, Portugal (A Freitas PhD); Department of Dermatology (T Fukumoto PhD), Kobe University, Kobe, Japan; Department of Pathology (Prof B Fux PhD), Department of Integrated Health Education (Prof L B Salaroli PhD), Federal University of Espírito Santo, Vitória, Brazil; Health Services Management Training Centre (P A Gaal PhD, T Joo PhD, J Lám PhD, T Palicz MD), Karoly Racz Doctoral School of Clinical Medicine (T Kocsis MSc), Faculty of Health and Public Administration (M Szócska PhD), Semmelweis University, Budapest, Hungary; Department of Applied Social Sciences (P A Gaal PhD), Sapientia Hungarian University of Transylvania, Târgu-Mureş, Romania; Department of Community Medicine (Prof M A Gadanya FMCPh), Aminu Kano Teaching Hospital, Kano, Nigeria; Institute of Applied Health Sciences (S Gaihre PhD), University of Aberdeen, Aberdeen, UK;

Department of Environmental Health Sciences (S Gallus DSc, A Lugo PhD), Mario Negri Institute for Pharmacological Research, Milan, Italy; Department of Research Publication (M Ganbat MPH), Zaigal Research Institute, Ulaanbaatar, Mongolia, Mongolia; Department of Community Medicine and Family Medicine (A P Gandhi MD), All India Institute of Medical Sciences, Nagpur, India; Institute of Health and Wellbeing (B Ganesan PhD), Federation University, Churchill, VIC, Australia; Department of General Medicine (M Ganiyani MD), Grant Medical College & Sir J.J. Group of Hospitals, Mumbai, India; Faculty of Business and Management (M García-Gordillo PhD), Universidad Autónoma de Chile (Autonomous University of Chile), Talca, Chile; Division of Cardiovascular Medicine (J Garg MD), Medical College of Wisconsin, Milwaukee, WI, USA; University School of Management and Entrepreneurship (N Garg PhD, R Sharma PhD), Delhi Technological University, Delhi, India; Department of Pharmacology (Prof R K Gautam PhD), Indore Institute of Pharmacy, Indore, India; Department of Midwifery (M W Gebregergis MSc), Department of Medical Laboratory Sciences (H Negash MSc), Adigrat University, Adigrat, Ethiopia; Department of Environmental Health (M Gebrehiwot DSc), Department of Public Health (F M Hussien MPH, F M Hussien MPH), Wollo University, Dessie, Ethiopia; Reproductive and Family Health (T G Gebremeskel PhD), Axum College of Health Science, Axum, Ethiopia; Department of Dermatology (Prof S R Georgescu PhD), "Victor Babes" Clinical Hospital of Infectious and Tropical Diseases, Bucharest, Romania; School of Population Health (Prof P W Gething PhD, D J Weiss PhD), School of Public Health (D Hendrie PhD, T R Miller PhD), Curtin University, Perth, WA, Australia; Infectious Disease Research Center (Prof K Ghadiri MD), Pediatric Department (Prof K Ghadiri MD), Universal Scientific Education and Research Network (USERN) (P Goleij MSc), Department of Rehabilitation and Sports Medicine (M Mirzaei MSc), Research Center for Environmental Determinants of Health (Prof E Sadeghi PhD), Department of Infectious Disease (Prof S Vaziri MD), Kermanshah University of Medical Sciences, Kermanshah, Iran; Center of Health Management (K Y Ghailan PhD), Aden University, Aden, Yemen; School of Public Health (A Ghashghaei BSc), Department of Food Hygiene and Safety (Prof R Mahmoudi PhD), Qazvin University of Medical Sciences, Qazvin, Iran; Young Researchers and Elite Club (A Gholamian MSc), Islamic Azad University, Rasht, Iran; Department of Biology (A Gholamian MSc), Islamic Azad University, Tehran, Iran; Respiratory Medicine Department (Prof A G Ghoshal MD), National Allergy Asthma Bronchitis Institute, Kolkata, India; Department of Respiratory Medicine (Prof A G Ghoshal MD), Fortis Hospital, Kolkata, India; Warwick Medical School (Prof P S Gill DM), University of Warwick, Coventry, UK (J W Sakshaug PhD); Westmead Applied Research Centre (M A Godinho MBBS), University of Sydney, Westmead, NSW, Australia; Department of Hepatology (Prof A Goel DM), Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; Department of Applied Cell Sciences (A Golchin PhD), Cellular and Molecular Medicine Institute (A Golchin PhD), Urmia University of Medical Sciences, Urmia, Iran (R Valizadeh PhD); Department of Health Systems and Policy Research (M Golechha PhD), Indian Institute of Public Health, Gandhinagar, India; Department of Genetics (P Goleij MSc), Sana Institute of Higher Education, Sari, Iran; Department of Exercise and Health Sciences (P N Gona PhD), University of Massachusetts Boston, Boston, MA, USA; Hudson College of Public Health (S V Gopalani MPH), University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; Department of Health and Social Affairs (S V Gopalani MPH), Government of the Federated States of Micronesia, Palikir, Federated States of Micronesia; Department of Respiratory Medicine (H Goudarzi PhD), Center for Environmental and Health Sciences (H Goudarzi PhD), Hokkaido University, Sapporo, Japan; Department of Epidemiology (Prof A C Goulart PhD), Universidade de São Paulo (University of São Paulo), São Paulo, Brazil; Blood and Marrow Transplantation and Cellular Therapy Program (A Goyal MD), Division of Pediatric Hospital Medicine (R P Mediratta MD), Stanford University, Palo Alto, CA, USA; Department of Dermatology (A Grada MD), Health Informatic Lab (T Javaheri PhD), Department of Computer Science (R Rawassizadeh PhD), Boston University, Boston, MA, USA; Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences (S M Graham PhD, Prof D Prieto Alhambra PhD), Nuffield

Department of Medicine (T Runghien MSc), Nuffield Department of Primary Care Health Sciences (T Tillawi MD), Oxford University, Oxford, UK; Department of Public Health and Preventive Medicine (Prof M Grivna PhD), Charles University, Prague, Czech Republic; Department of Epidemiology and Biostatistics (S Guan MD), Anhui Medical University, Hefei, China; Post Graduate School of Public Health (G Guarducci MD), University of Siena, Siena, Italy; Department of Family and Community Medicine (M I M Gubari PhD), University Of Sulaimani, Sulaimani, Iraq; Health Directorate (S Guicciardi MD), Local Health Authority of Bologna, Bologna, Italy; Faculty of Nursing (Prof R A Guimarães PhD), Federal University of Goiás, Goiânia, Brazil; Department of General Surgery (S Gulati MD), Dignity Health, Phoenix, AZ, USA; Department of Community Medicine (D A Gunawardane MD), University of Peradeniya, Kandy, Sri Lanka; Department of Psychiatry (S Gunturu MD), Bronxcare Health System, Bronx, NY, USA; Department of Internal Medicine (A K Gupta PharmD), Faculty of Medicine and Health Sciences (Prof N P Singh MD), Shree Guru Gobind Singh Tricentenary University, Gurugram, India; Non-communicable Division (NCD) (A K Gupta PharmD), Indian Council of Medical Research, Delhi, India; Department of Public Health (B Gupta PhD), Department of Health and Education (F Hanna PhD), Torrens University Australia, Melbourne, VIC, Australia; Department of Epidemiology and Biostatistics (R Gupta MPH), Department of Health Promotion, Education, and Behavior (T Mi PhD), University of South Carolina, Columbia, SC, USA; Centre for Noncommunicable Diseases and Nutrition (R Gupta MPH), BRAC University, Dhaka, Bangladesh; Department of Preventive Cardiology (Prof R Gupta MD), Eternal Heart Care Centre & Research Institute, Jaipur, India; Department of Medicine (Prof R Gupta MD), Mahatma Gandhi University Medical Sciences, Jaipur, India; Department of Toxicology (S Gupta MSc), Shriram Institute for Industrial Research, Delhi, India; School of Medicine (V Gupta PhD), Institute for Mental and Physical Health and Clinical Translation (IMPACT) (W Marx PhD), Deakin University, Geelong, VIC, Australia; School of Biotechnology (V Gupta PhD), Dublin City University, Glasnevin, Ireland; Faculty of Medicine Health and Human Sciences (Prof V K Gupta PhD), Macquarie Medical School (Y You PhD), Macquarie University, Sydney, NSW, Australia; Department of Epidemiology and Psychosocial Research (R A Gutiérrez PhD), Ramón de la Fuente Muñiz National Institute of Psychiatry, Mexico City, Mexico; Global Virus Network, Middle East Region, Shiraz, Iran (F Habibzadeh MD); School of Medicine (P Habibzadeh MD), University of Maryland, Baltimore, MD, USA; Department of Pharmacology and Toxicology (R Haddadi PhD), Hamadan University of Medical Sciences, Hamadan, Iran; Department of Clinical Pharmacology and Medicine (Prof N R Hadi PhD), University of Kufa, Najaf, Iraq; Clinician Scientist Program (N Haep MD), Berlin Institute of Health, Berlin, Germany; NYU Shanghai, Shanghai, China (B J Hall PhD); Department of Infectious Disease Epidemiology (S Haller MD), Robert Koch Institute, Berlin, Germany; Department of Public Health (S Haller MD), Charité Institute of Public Health, Berlin, Germany; Department of Family and Community Medicine (Prof R R Hamadeh PhD), College of Medicine and Medical Sciences (H Jahrami PhD), Arabian Gulf University, Manama, Bahrain; School of Health and Environmental Studies (Prof S Hamidi DrPH), Hamdan Bin Mohammed Smart University, Dubai, United Arab Emirates; Department of Nephrology (Q Han PhD), Beijing Chao-ying Hospital, Capital Medical University, Beijing, China; Centre for Neuromuscular and Neurological Disorders (Prof G J Hankey MD), The University of Western Australia, Perth, WA, Australia; Perron Institute for Neurological and Translational Science, Perth, WA, Australia (Prof G J Hankey MD); Department of Biochemistry and Molecular Biology (Prof M Hannan PhD), Bangladesh Agricultural University, Mymensingh, Bangladesh; Department of Anatomy (Prof M Hannan PhD), Dongguk University, Gyeongju, South Korea; Department of Population Science and Human Resource Development (Prof M Haque PhD, Prof M Rahman PhD, M Rahman DrPH), Department of Mathematics (M Kuddus PhD), University of Rajshahi, Rajshahi, Bangladesh; Medical Research Unit (H Harapan PhD), Universitas Syiah Kuala (Syiah Kuala University), Banda Aceh, Indonesia; Research Unit (J M Haro MD), University of Barcelona, Barcelona, Spain; Biomedical Research Networking Center for Mental Health Network (CiberSAM), Barcelona, Spain (J M Haro MD); Department of Zoology and Entomology

(A I Hasaballah PhD, M G M Zeariya PhD), Department of Plant and Microbiology (A M E Shehabeldine PhD), Al-Azhar University, Cairo, Egypt; Department of Pharmaceutical Technology (I Hasan MPharm), University of Dhaka, Dhaka, Bangladesh; Department of Radiology (M Hasanian MD), Arak University of Medical Sciences, Arak, Iran; Department of Public Health (A Hashi PhD), Jigjiga University, Jigjiga, Ethiopia; Department of Pharmacy (Prof M S Hasnain PhD), Palamau Institute of Pharmacy, Daltonganj, India; Public Health Department (I Hassan MPH), Dalhatu Araf Specialist Hospital, Lafia, Nigeria; Department of Public Health (I Hassan MPH), Federal University of Lafia, Lafia, Nigeria; Independent Consultant, Tabriz, Iran (H Hassankhani PhD); Department of Diagnostic and Interventional Radiology and Neuroradiology (J Haubold MD), Prof B M Schaarschmidt MD), Institute of Artificial Intelligence in Medicine (J Haubold MD), University Hospital Essen, Essen, Germany; Skane University Hospital (R J Havmoeller PhD), Skane County Council, Malmö, Sweden; Faculty of Kinesiology (Prof J J Hebert PhD), University of New Brunswick, Fredericton, NB, Canada; School of Allied Health (Prof J J Hebert PhD), Murdoch University, Murdoch, WA, Australia; Independent Consultant, Santa Clara, CA, USA (G Heidari MD); Community-Oriented Nursing Midwifery Research Center (M Heidari PhD), Department of Epidemiology and Biostatistics (A Mohammadian-Hafshejani PhD), Department of Health in Disasters and Emergencies (R Sheikhi B.Hlth.Sci), Shahrood University of Medical Sciences, Shahrood, Iran; Institute of Psychology (B Helfer PhD), University of Wroclaw, Wroclaw, Poland; Meta Research Centre (B Helfer PhD), University of Wroclaw, Wroclaw, Poland; Departamento de Salud Oral (Department of Oral Health) (B Y Herrera-Serna PhD), Universidad Autónoma de Manizales (Autonomous University of Manizales), Manizales, Colombia; School of Business (Prof C Hertelius PhD), London South Bank University, London, UK; Department of Microbiology (K Hezam PhD), Department of Applied Microbiology (E A Noman PhD), Taiz University, Taiz, Yemen; School of Medicine (K Hezam PhD), Nankai University, Tianjin, China; Rheumatology Department (Prof C L Hill MD), The Queen Elizabeth Hospital, Woodville, SA, Australia; Division for Health Service Promotion (Y Hiraike PhD), Department of Mental Health (Prof N Kawakami PhD), Department of Global Health Policy (S Nomura PhD, S K Rauniyar PhD), University of Tokyo, Tokyo, Japan; Department of Pulmonology (N Horita PhD), Yokohama City University, Yokohama, Japan; National Human Genome Research Institute (NHGRI) (N Horita PhD), National Institutes of Health, Bethesda, MD, USA; Social and Environmental Health Research (M Hossain MPH), Nature Study Society of Bangladesh, Khulna, Bangladesh; Department of Health Promotion and Community Health Sciences (M Hossain MPH), Texas A&M University, College Station, TX, USA; Department of Public Health and Informatics (S Hossain MS), Jahangirnagar University, Dhaka, Bangladesh; School of Health and Society (H Hosseinzadeh PhD), University of Wollongong, Wollongong, NSW, Australia; Institute of Research and Development (Prof M Hosseinzadeh PhD), Faculty of Medicine (H T H Nguyen MD), Institute for Research and Training in Medicine, Biology and Pharmacy (H T H Nguyen MD), Duy Tan University, Da Nang, Viet Nam; Department of Computer Science (Prof M Hosseinzadeh PhD), Diplomacy and Public Relations Department (A Omar Bali PhD), University of Human Development, Sulaymaniyah, Iraq; Department of Clinical Legal Medicine (S Hostiuc PhD), National Institute of Legal Medicine Mina Minovici, Bucharest, Romania; Faculty of Medicine of Tunis (Prof M Hsairi MPH), University Tunis El Manar, Tunis, Tunisia; Department of Health Services Administration (V Hsieh PhD), Department of Occupational Safety and Health (Prof B Hwang PhD), China Medical University, Taichung, Taiwan; Department of Surgical Sciences (M Hultström PhD), Department of Medical Cell Biology (M Hultström PhD), Department of Medical Sciences (Prof A O Larsson PhD, Prof J Sundström PhD), Uppsala University, Uppsala, Sweden; Department of Public Health and Community Medicine (Prof A Humayun PhD), Shaikh Zayed Postgraduate Medical Institute, Lahore, Pakistan; Department of Biological Sciences and Chemistry (Prof J Hussain PhD), Natural and Medical Sciences Research Center (A Khan PhD, A Ullah MS, S Ullah MSc, M Waqas PhD), School of Pharmacy (A K Philip PhD), University of Nizwa, Nizwa, Oman; Department of Social Sciences and Business (Prof M Hussain PhD),

Roskilde University, Roskilde, Denmark; Department of Biomolecular Sciences (N R Hussein PhD), Department of Biology (K S Ibrahim PhD), University of Zakho, Zakho, Iraq; International Master Program for Translational Science (H Huynh BS), Department of Global Health and Health Security (K Latief Master of Epidemiology), International Ph.D. Program in Medicine (L Minh MD), Research Center for Artificial Intelligence in Medicine (L Minh MD), Graduate Institute of Biomedical Informatics (D N A Ningrum MPH), School of Public Health (Y L Samodra MPH, Y L Samodra MPH), Department of Clinical Pharmacy (M A Sarasmith PharmD), Global Health and Health Security Department (U Wongsin PhD), Taipei Medical University, Taipei, Taiwan; Department of Occupational Therapy (Prof B Hwang PhD), Asia University, Taiwan, Taichung, Taiwan; Health Policy and Management Department (P M Iftikhar MD), City University of New York, New York, NY, USA; Division of Infectious Diseases (K S Ikuta MD), Veterans Affairs Greater Los Angeles, Los Angeles, CA, USA; Department of Pathology (P C Ikwegbue MSc), School of Public Health and Family Medicine (R Matzopoulos PhD, C A Nnaji MPH), Division of Cardiology (Prof M Ntsekhe PhD), Department of Paediatrics and Child Health (Prof H J Zar PhD, Prof L J Zuhlke PhD), Department of Medicine (Prof L J Zuhlke PhD), University of Cape Town, Cape Town, South Africa; Faculty of Medicine (I M Ilic PhD), Prof M M Santric-Milicevic PhD, A Stevanović MD, I S Vujić PhD), School of Public Health and Health Management (Prof M M Santric-Milicevic PhD), School of Medicine (R Vukovic PhD), University of Belgrade, Belgrade, Serbia; Department of Epidemiology (Prof M D Ilic PhD), University of Kragujevac, Kragujevac, Serbia; College Of Pharmacy (M Imam PhD), Prince Sattam Bin Abdulaziz University, Al Khari, Saudi Arabia; Division of Gastroenterology and Hepatology (S Imdam MD), University of Arkansas for Medical Sciences, Little Rock, AR, USA; National Research and Innovation Agency, Jakarta, Indonesia (E Indriasiyah PhD, I U Tarigan PhD); Faculty of Public Health (M Iqbalullah PhD), Universitas Muhammadiyah Aceh, Banda Aceh, Indonesia; Department of Medicine (A Iradukunda MD), University of Burundi, Bujumbura, Burundi; Research Department (A Iradukunda MD), ARNECH Research and Consulting Office, Bujumbura, Burundi; Department of Medical Microbiology (K C Iregbu MD), University of Abuja, Abuja, Nigeria; Department of Medical Microbiology (K C Iregbu MD), National Hospital, Abuja, Nigeria; Institute for Physical Activity and Nutrition (S Islam PhD), Department of Psychology (M A Stokes PhD), Deakin University, Burwood, VIC, Australia; Department of Surveillance and Health Services Research (F Islami PhD), American Cancer Society, Atlanta, GA, USA; Clinical Laboratory (F Ismail PhD), Tobruk University, Tobruk, Libya; Blood Transmitted Diseases (F Ismail PhD), National Center for Disease Control, Tobruk, Libya; Department of Clinical Pharmacy & Pharmacy Practice (Prof N Ismail PhD), Asian Institute of Medicine, Science and Technology, Kedah, Malaysia; Malaysian Academy of Pharmacy, Puchong, Malaysia (Prof N Ismail PhD); Public Health Department of Social Medicine (Prof H Iso MD), Graduate School of Medicine (Prof K Yamagishi MD), Osaka University, Suita, Japan; Department of Health Services Research (M Iwagami PhD), Research and Development Center for Health Services (Prof K Yamagishi MD), University of Tsukuba, Tsukuba, Japan; School of Health Systems and Public Health (C C D Iwu MPH), University of Pretoria, Pretoria, South Africa; Knowledge Translation Program (I O Iyamu MD), Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada; Department of Biotechnology (M Iyer PhD), Karpagam Academy of Higher Education (Deemed to be University), Coimbatore, India; Department of Orthodontics & Dentofacial Orthopedics (L J BDS), Department of Oral Pathology and Microbiology (Prof G S Sarode PhD), Prof S C Sarode PhD, Dr D. Y. Patil University, Pune, India; Research and Development Unit (L Jacob MD), Biomedical Research Networking Center for Mental Health Network (CiberSAM), Sant Boi de Llobregat, Spain; Faculty of Medicine (L Jacob MD), University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France; Department of Health Studies (K H Jacobsen PhD), University of Richmond, Richmond, VA, USA; Department of Immunology (Prof A Jafarzadeh PhD), Research Center for Hydatid Disease in Iran (F Khamesipour PhD), Kerman University of Medical Sciences, Kerman, Iran; Department of Immunology (Prof A Jafarzadeh PhD), Family Medicine Department (Z Kamiab MD), Clinical Research Development Unit (Z Kamiab MD), Department of Epidemiology and Biostatistics (Prof M Rezaeian PhD), Rafsanjan University of Medical Sciences, Rafsanjan, Iran; Department of Nephrology (K Jaggi MD), San Mateo Medical Center, San Mateo, CA, USA; Department of Nephrology (K Jaggi MD), Mills Peninsula Medical Center, Burlingame, CA, USA; Department of Psychiatry (Z Saif MBA), Ministry of Health, Manama, Bahrain (H Jahrami PhD); Statistics Unit (N Jain MD), Riga Stradiņš University, Riga, Latvia; Department of Health and Safety (A A Jairoun PhD), Dubai Municipality, Dubai, United Arab Emirates; Centre for Community Medicine (A Jaiswal MD), Department of Preventive Oncology (J K Meena MD), Centre for Dental Education and Research (B M Purohit MDS), Department of Psychiatry (Prof R Sagar MD), Department of Radiation Oncology (A Shankar MD), All India Institute of Medical Sciences, New Delhi, India; School of Pharmacy and Pharmacology (A Jatau PhD), Menzies Institute for Medical Research (F Pan PhD, J Tian PhD), University of Tasmania, Hobart, TAS, Australia; Department of Physiology (Prof S Javadov PhD), University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico; Centre of Studies and Research (S Jayapal PhD), Ministry of Health, Muscat, Oman; Department of Biochemistry (Prof S Jayaram MD), Government Medical College, Mysuru, India; Department of Epidemiology and Health Promotion (Prof S Jee PhD), Department of Preventive Medicine (K Kim MD), Yonsei University, Seoul, South Korea; Department of Community Medicine (R P Jha MSc), Dr. Baba Saheb Ambedkar Medical College & Hospital, Delhi, India; Department of Community Medicine (R P Jha MSc), Banaras Hindu University, Varanasi, India; Zoonoses Research Center (M Jokar DVM), Islamic Azad University, Karaj, Iran; Department of Clinical Sciences (M Jokar DVM), Department of Public Health (Y Sarikhani PhD), Jahrom University of Medical Sciences, Jahrom, Iran; Institute of Molecular and Clinical Ophthalmology Basel, Basel, Switzerland (Prof J B Jonas MD); Department of Ophthalmology (Prof J B Jonas MD), Heidelberg University, Mannheim, Germany; Hungarian Health Management Association (T Palicz MD), Hungarian Health Management Association, Budapest, Hungary (T Joo PhD); Department of Gastroenterology and Hepatology (A Joseph MD), Department of Biomedical Data Science (S Park MD), Department of Radiology (S Ramasamy MD), Stanford University, Stanford, CA, USA; Department of Economics (C E Joshua BSc), National Open University, Benin City, Nigeria; Department of Family Medicine and Public Health (J J Jozwiak PhD), University of Opole, Opole, Poland; Institute of Family Medicine and Public Health (M Jürisson PhD), University of Tartu, Tartu, Estonia; School of Public Health (Z Kabir PhD), University College Cork, Cork, Ireland; Department of Oral and Maxillofacial Pathology (V Kadashetti MDS), Department of Public Health Dentistry (Prof K M Shivakumar PhD), Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, India; Social Determinants of Health Research Center (L R Kalankesh PhD), Faculty of Medicine (Z Saadatian PhD), Infectious Diseases Research Center (Z Saadatian PhD), Gonabadi University of Medical Sciences, Gonabadi, Iran; Department of Dermatology (F Kaliyadan MD), King Faisal University, Hofuf, Saudi Arabia; Department of Endocrinology (S Kalra DM), Bharti Hospital Karnal, Karnal, India; Northern Oesophagogastric Cancer Unit (S K Kamarajah BSc), Newcastle University, Newcastle, UK; Care and Public Health Research Institute (CAPHRI) (R Kamath MHA), Maastricht University, Maastricht, Netherlands; School of Graduate Studies (T Kanagasabai PhD), Meharry Medical College, Nashville, TN, USA; Sydney Eye Hospital (H Kandel PhD), South Eastern Sydney Local Health District, Sydney, NSW, Australia; Division of Cardiology (A R Kanmanthareddy MD), Creighton University, Omaha, NE, USA; College of Public Health (A R Kanmanthareddy MD), Department of Environmental, Agricultural and Occupational Health (J Taiba MPH), University of Nebraska Medical Center, Omaha, NE, USA; Regional Institute for Population Studies (E Kanmiki MPH), University of Ghana, Accra, Ghana; Faculty of Dentistry (K K Kanmodi MPH), University of Puthisastra, Phnom Penh, Cambodia; Office of the Executive Director (K K Kanmodi MPH), Campaign for Health and Neck Cancer Education (CHANCE) Programme (A A Salami BDS), Cephas Health Research Initiative Inc, Ibadan, Nigeria; Department of Community Medicine (S Kannan S MD), ESIC Medical College and Hospital Chennai, Chennai, India;

Dr. S S Bhatnagar University Institute of Chemical Engg. & Technology (Prof S K Kansal PhD), Department of Anthropology (Prof K Krishan PhD), Institute of Forensic Science & Criminology (V Sharma PhD), Panjab University, Chandigarh, India; The Hansjörg Wyss Department of Plastic and Reconstructive Surgery (R S Kantar MD), Nab'a Al-Hayat Foundation for Medical Sciences and Health Care, New York, NY, USA; Cleft Lip and Palate Surgery Division (R S Kantar MD), Global Smile Foundation, Norwood, MA, USA; School of Health Professions and Human Services (I M Karaye MD), Hofstra University, Hempstead, NY, USA; Department of Anesthesiology (I M Karaye MD), Montefiore Medical Center, Bronx, NY, USA; Department of Physical Therapy and Health Rehabilitation (F Z Kashoo MSc), Majmaah University, Majmaah, Saudi Arabia; Gastrointestinal Center (Q H A Kasnazani MD), Anwar Shyxa Medical City, Sulaimanyah, Iraq; Department of Digestive Surgery (Q H A Kasnazani MD), Kurdistan Higher Council For Medical Specialities, Sulaimanyah, Iraq; Surgery Research Unit (Prof J H Kauppile MD), Center for Environmental and Respiratory Health Research (I Shiu PhD), Martti Ahtisaari Institute (I Shiu PhD), University of Oulu, Oulu, Finland; Department of ENT (N Kaur MS), Dr. B. R. Ambedkar State Institute of Medical Sciences (AIMS), Mohali, India; International Research Center of Excellence (G A Kayode PhD), Institute of Human Virology Nigeria, Abuja, Nigeria; Julius Centre for Health Sciences and Primary Care (G A Kayode PhD), Copernicus Institute of Sustainable Development (G Koren PhD), Utrecht University, Utrecht, Netherlands; Community Medicine Department (T H Kazmi FCPS), Shalamar Medical & Dental College, Lahore, Pakistan; Public Health (F Kebede MPH), Woldia University, Woldia, Ethiopia; Institute of Biological Chemistry and Nutrition (T S Keflie PhD), University Hohenheim, Stuttgart, Germany; Open, Distance and eLearning Campus (Prof P N Keiyo PhD), Department of Psychiatry (M Kumar PhD), School of Public Health (R G Wamai PhD), University of Nairobi, Nairobi, Kenya; Eye Unit (Prof J H Kempen MD), MyungSung Medical College, Addis Ababa, Ethiopia; Department of Psychological Medicine (J A Kerr PhD), University of Otago, Christchurch, New Zealand; Department of Human Nutrition (E Kesse-Guyot PhD), National Research Institute for Agriculture, Food and Environment, Jouy-en-Josas, France; University Sorbonne Paris Nord (E Kesse-Guyot PhD), Department of Health, Medicine and Human Biology (M Touvier PhD), Sorbonne Paris Nord University, Bobigny, France; Amity Institute of Forensic Sciences (H Khajuria PhD, B P Nayak PhD), Amity Institute of Pharmacy (K Munjal PhD), Amity University, Noida, India; College of Health Sciences (N Khalid PhD), Abu Dhabi University, Abu Dhabi, United Arab Emirates; Department of Biostatistics (Prof A Khalilian PhD), Mazandaran University of Medical Sciences, Mazandaran, Iran; Department of Pediatrics (I A Khan MD), Center for Pharmacoepidemiology and Treatment Science (A Parthasarathi MD), Rutgers University, New Brunswick, NJ, USA; Population Science Department (M Khan PhD), Jatiya Kabi Kazi Nazrul Islam University, Mymensingh, Bangladesh; Primary Care Department (M A Khan MSc), NHS North West London, London, UK; Department of Medicine (Z A Khan MD), Independent Consultant, Hyderabad, India; Department of Critical Care Medicine (M Z Khan suheb MD), St. Luke's Aurora Medical Center, Milwaukee, WI, USA; College of Health, Wellbeing and Life Sciences (Prof K Khatab PhD), Sheffield Hallam University, Sheffield, UK; College of Arts and Sciences (Prof K Khatab PhD), Ohio University, Zanesville, OH, USA; Faculty of Nursing (H Khatatbeh PhD), Jerasl University, Jerasl, Jordan; Department of Biochemistry (F Khidri PhD), Liaquat University Of Medical and Health Sciences, Jamshoro, Pakistan; Department of Epidemiology (A Khosravi PhD), Center for Health Related Social and Behavioral Sciences Research (F Sadeghian PhD), Shahroud University of Medical Sciences, Shahroud, Iran; Molecular Medicine Department (M Khosravi PhD), Pasteur Institute of Iran, Tehran, Iran; Department of Pediatrics (G Kim MD), Case Western Reserve University School of Medicine, Cleveland, OH, USA; Division of Pediatric Hospital Medicine (G Kim MD), University Hospitals Rainbow Babies and Children's Hospital, Cleveland, OH, USA; Cardiovascular Disease Initiative (M Kim MD), Broad Institute of MIT and Harvard, Cambridge, MA, USA; School of Traditional Chinese Medicine (Y Kim PhD), Xiamen University Malaysia, Sepang, Malaysia; Millennium Prevention, Westwood, MA, USA (R W Kimokoti MD); School of Health Sciences

(Prof A Kisa PhD), Kristiania University College, Oslo, Norway; Department of International Health and Sustainable Development (Prof A Kisa PhD), Tulane University, New Orleans, LA, USA; Department of Nursing and Health Promotion (S Kisa PhD), Faculty of Health Sciences (Prof A W Wolf PhD), Oslo Metropolitan University, Oslo, Norway; Global Healthcare Consulting, New Delhi, India (S Kochhar MD); Independent Consultant, Jakarta, Indonesia (S Kosen MD); Department of Epidemiology (Prof K Kostev PhD), IQVIA, Frankfurt, Germany; Department of Gynecology (Prof K Kostev PhD), Philipps-Universität Marburg, Marburg, Germany; Department of Internal and Pulmonary Medicine (Prof P A Koul MD), Sheri Kashmir Institute of Medical Sciences, Srinagar, India; Kasturba Medical College, Mangalore (S Koulmane Laxminarayana MD), Manipal Academy of Higher Education, Udupi, India; Evidence Synthesis Unit (Y Krishnamoorthy MD), Partnership for Research, Opportunity, Planning, Upskilling, and Leadership (PROPUL) Evidence, Chennai, India; Department of Demography (Prof B Kuade Defo PhD), Department of Social and Preventive Medicine (Prof B Kuade Defo PhD), University of Montreal, Montreal, QC, Canada; Faculty of Medicine (B Kucuk Bicer PhD), Gazi University, Ankara, Turkey; Department of Biochemistry (Prof M Kuddus PhD), College of Public Health & Health Informatics (R Kumar PhD), Department of Public Health (M G M Zeariya PhD), University of Hail, Hail, Saudi Arabia; Department of Pediatrics (I Kuitunen PhD), Kuopio University Hospital, Kuopio, Finland; Institute of Clinical Medicine (I Kuitunen PhD), University of Eastern Finland, Kuopio, Finland; Department of Health Research (M Kulimbert MSc), Atchabarov Scientific Research Institute of Fundamental and Applied Medicine (M Kulimbert MSc), Kazakh National Medical University, Almaty, Kazakhstan; Cardiothoracic Surgery (A Kumar MD), UN Mehta Institute of Cardiology and Research Center, Ahmedabad, India; Cardiothoracic Surgery (A Kumar MD), Medanta Hospital, Gurugram, India; Department of Internal Medicine (A Kumar MD), Cabrini Institute, Akron, OH, USA; Department of Food Technology (Prof H Kumar PhD), Shri Vishwakarma Skill University, Palwal, India; Department of Biotechnology (Prof H Kumar PhD), Amity Institute of Biotechnology (M Kumari PhD, E Upadhyay PhD), Amity University Rajasthan, Jaipur, India; Global Health Institute (S Kundu MPH), North South University, Dhaka, Bangladesh; Department of Nutrition and Food Science (S Kundu MPH), Department of Biochemistry and Food Analysis (N Roy PhD), Department of Post-Harvest Technology and Marketing (A Sayeed MSc), Patuakhali Science and Technology University, Patuakhali, Bangladesh; Department of Medicine (O P Kurmi PhD), Department of Health Research Methods, Evidence and Impact (E J Mills PhD), Department of Psychiatry and Behavioural Neurosciences (A T Olagunju MD), McMaster University, Hamilton, ON, Canada; Department of Health Services Research and Management (D Kusuma DSc), City University of London, London, UK; Department of Health Policy (I Kyriopoulos PhD), London School of Economics and Political Science, London, UK; National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, Oxford, UK (B Lacey PhD); Institute for Social and Health Sciences (Prof L Laflamme PhD), University of South Africa, Pretoria, South Africa; International Maize and Wheat Improvement Center (CIMMYT), El Batan, Mexico (A K Lagat BS); Department of Basic Sciences (A K Lagat BS), Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya; Stockholm County Council Surveillance and Analysis Centre for Epidemiology and Community Medicine, Stockholm, Sweden (A C J Lager PhD); Department of Family Medicine (A Lahmar MD), University of Medicine, Oujda, Morocco; School of Digital Science (D T C Lai PhD), Institute of Applied Data Analytics (D T C Lai PhD), Faculty of Science (E Leong PhD), Universiti Brunei Darussalam (University of Brunei Darussalam), Bandar Seri Begawan, Brunei; Department of Public Health (Prof T Lallukka PhD); Department of Virology (F Zakharn PhD), University of Helsinki, Helsinki, Finland (T J Meretoja MD); Institute of Health Policy and Development Studies (Prof H Lam PhD), National Institutes of Health, Manila, Philippines; NEVES Society for Patient Safety, Budapest, Hungary (J Lám PhD); Department of Epidemiology (K R Landrum MSc), University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; Duke Global Health Institute (K R Landrum MSc), Duke University, Durham, USA; Department of Health Sciences (DISSAL) (F Lanfranchi MD), University of Genoa, Genoa, Italy; Centre for

Surveillance and Applied Research (J J Lang PhD), Public Health Agency of Canada, Ottawa, ON, Canada; Department of Psychiatry and Psychotherapy (B Langguth PhD, W Schlee PhD), University of Regensburg, Regensburg, Germany; Chief Medical Office (Prof V C Lansingh PhD), HelpMeSee, New York, NY, USA; Mexican Institute of Ophthalmology, Queretaro, Mexico (Prof V C Lansingh PhD); Department of Behavioural Sciences and Learning (A Laplante-Lévesque PhD), Linköping University, Linköping, Sweden; Department of Clinical Chemistry and Pharmacology (Prof A O Larsson PhD), Uppsala University Hospital, Uppsala, Sweden; Department of Otorhinolaryngology (S Lasrado MS), Father Muller Medical College, Mangalore, India; International Society Doctors for the Environment, Arezzo, Italy (P Lauriola MD); Faculty of Medicine (N Le MD), Department of General Medicine (V T Nguyen MD), University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Viet Nam (T T Le MD, T D T Le MD); Department of Cardiovascular Research (N Le MD), Methodist Hospital, Merrillville, IN, USA; Independent Consultant, Ho Chi Minh City, Viet Nam (T D T Le MD); Department of Medical Science (M Lee PhD), Ajou University School of Medicine, Suwon, South Korea; Department of Precision Medicine (Prof S W Lee MD), Sungkyunkwan University, Suwon-si, South Korea; School of Pharmacy (S W Lee PhD), Monash University, Bandar Sunway, Malaysia; School of Pharmacy (S W H Lee PhD), Taylor's University Lakeside Campus, Subang Jaya, Malaysia; The Department of Family Medicine (W Lee PhD), University of Texas, Galveston, TX, USA; Department of Preventive Medicine (Prof Y Lee PhD, Prof S Yoon PhD), Korea University, Seoul, South Korea (Prof M Shin PhD); Department of Health Promotion and Health Education (M Li PhD), National Taiwan Normal University, Taipei, Taiwan; Department of Health Management Center (X Li PhD), Fudan University, Shanghai, China; National Clinical Research Center for Cardiovascular Diseases (Y Li PhD), Chinese Academy of Medical Sciences, Shenzhen, China; Directorate of Quality Management and Digital Health (A T M Likaka MPH), Ministry of Health, Lilongwe, Malawi; UCD Centre for Disability Studies (C Linehan PhD), University College Dublin, Dublin, Ireland; School of Life Sciences (G Liu PhD), University of Technology Sydney, Ultimo, NSW, Australia; Centre for Inflammation (G Liu PhD), Centenary Institute, Camperdown, NSW, Australia; Department of Epidemiology and Biostatistics (Prof J Liu PhD), China Center for Health Development Studies (Y Yao MD), School of Public Health (H Zhang MS), Institute of Child and Adolescent Health (Z Zou MD), Peking University, Beijing, China; Center for Evidence-Based Medicine and Clinical Research (R Liu MD), School of Public Health and Management (Y Yu MS), Hubei University of Medicine, Shiyan, China; National Center for Chronic and Noncommunicable Disease Control and Prevention (N Wang PhD, P Ye MPH), Chinese Center for Disease Control and Prevention, Beijing, China (Prof S Liu PhD); Department of Molecular Epidemiology (E Llanaj PhD), German Institute of Human Nutrition Potsdam-Rehbrücke, Potsdam, Germany; German Center for Diabetes Research (DZD), München-Neuherberg, Germany (E Llanaj PhD); Department of Infectious Diseases (M J Loftus MBBS), Alfred Health, Melbourne, VIC, Australia; Department of Physical Medicine and Nursing (R López-Bueno PhD), University of Zaragoza, Zaragoza, Spain; Department of Musculoskeletal disorders (R López-Bueno PhD), National Research Centre for the Working Environment, Copenhagen, Denmark; National Institutes of Health (A Loreche BS), Department of Epidemiology and Biostatistics (J C Medina MD), University of the Philippines Manila, Manila, Philippines; School of Medicine and Public Health (A Loreche BS), Center for Research and Innovation (V F Pepito MSc), Ateneo De Manila University, Pasig City, Philippines; Institute of Nutritional Sciences (Prof S Lorkowski PhD), Friedrich Schiller University Jena, Jena, Germany; Competence Cluster for Nutrition and Cardiovascular Health (nutriCARD), Jena, Germany (Prof S Lorkowski PhD); Department of Medicine (Prof P A Lotufo DrPH), University of Sao Paulo, Sao Paulo, Brazil; School of Medicine (Prof G Lucchetti PhD), Federal University of Juiz de Fora, Juiz de Fora, Brazil; Department of General Surgery (Prof R Lunevicius DSc), Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK; Centre for Public Health and Wellbeing (Z Ma PhD), University of the West of England, Bristol, UK; 2nd Department of Propaedeutic Surgery (N Machairas PhD),

Department of Biophysics (Prof P Papadopoulou PhD), 3rd Department of Cardiology (M Spartalis PhD), University of Athens, Athens, Greece; Periodontal Department (Prof M Machoy PhD), Department of Propedeutics of Internal Diseases & Arterial Hypertension (Prof T Miazgowski MD), Pomeranian Medical University, Szczecin, Poland; Department of Biostatistics and Epidemiology (F Madadizadeh PhD), Yazd University of Medical Sciences, Yazd, Iran; Laboratório de Farmacognosia (LAQV)(Associated Laboratory for Green Chemistry (Á M Madureira-Carvalho PhD), Universidade do Porto (University of Porto), Porto, Portugal; School of Pharmacy (S B Maharaj DBA), University of the West Indies, St. Augustine, Trinidad and Tobago; Planetary Health Alliance, Boston, MA, USA (S B Maharaj DBA); Cellular and Molecular Biology Research Center (Prof S Mahjoub PhD), Department of Clinical Biochemistry (Prof S Mahjoub PhD), Social Determinants of Health Research Center (S Mouodi PhD), Babol University of Medical Sciences, Babol, Iran; Department of Clinical and Hospital Pharmacy (M A Mahmoud PhD), Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia; Department of Psychology (I F Makhdoom PhD), University of Sargodha, Sargodha, Pakistan; Department of Forensic Medicine (Prof V Maled MD), Shri Dharmasthala Manjunatheshwara University, Dharwad, India; Department of Forensic Medicine (Prof V Maled MD), Department of Infectious Diseases and Microbiology (P A Shah MBBS), Rajiv Gandhi University of Health Sciences, Bangalore, India; Department of Internal Medicine (K Malhotra MBBS), Dayanand Medical College and Hospital, Ludhiana, India; Department of Electrical Engineering (I Malik PhD), Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia; Laboratory of Public Health (Prof L G Mantovani DSc), Instituto Auxologico Italiano IRCCS (Italian Auxological Institute), Milan, Italy; Biomedical Engineering Research Center (CREB) (H Marateb PhD), Universitat Politècnica de Catalunya (Barcelona Tech - UPC), Barcelona, Spain; Department of Artificial Intelligence (H Marateb PhD), Smart University of Medical Sciences, Tehran, Iran; University Health Services (A M Marconi MD), University of Wisconsin- Madison, Madison, WI, USA; Centro de Estudio e Investigación para la prevención y el tratamiento de las adicciones (Center for the Study and Investigation of Addiction Prevention and Treatment) (A M Marconi MD), Universidad de Buenos Aires (University of Buenos Aires), Buenos Aires, Argentina; Non-communicable Diseases Research Center (P Mardi MD), School of Medicine (M Shams-Beyranvand MSc), Alborz University of Medical Sciences, Karaj, Iran; Department of Biochemistry (A Marjani PhD), Joint, Bone, Connective tissue, Rheumatology Research Center (JBCRC) (M Moradzadeh PhD), Golestan Research Center of Gastroenterology and Hepatology (G Roshandel PhD), Golestan University of Medical Sciences, Gorgan, Iran; Department of Economics (Prof G Martinez PhD), Autonomous Technology Institute of Mexico, Mexico City, Mexico; Department of Infectious Diseases (B A Martinez-Guerra MSc), Instituto Nacional de Nutrición Salvador Zubirán (Salvador Zubiran National Institute of Medical Sciences and Nutrition), Mexico City, Mexico; Noncommunicable Diseases and Mental Health Department (R Martinez-Piedra BSc), Pan American Health Organization, Washington, DC, USA; Indonesian Public Health Association, Surabaya, Indonesia (S Martini PhD); Campus Fortaleza (F R Martins-Melo PhD), Federal Institute of Education, Science and Technology of Ceará, Fortaleza, Brazil; Department of Nutrition and Dietetics (M Martorell PhD), Centre for Healthy Living (M Martorell PhD), University of Concepción, Concepción, Chile; Department of Pharmacy (S Maryam PharmD), Bahauddin Zakariya University, Multan, Pakistan; Faculty of Humanities and Health Sciences (Prof R R Marzo MD), Curtin University, Malaysia, Sarawak, Malaysia; Jeffrey Cheah School of Medicine and Health Sciences (Prof R R Marzo MD), School of Pharmacy (Y Wong PhD), Monash University, Subang Jaya, Malaysia; Faculty of Health and Education (A Masaka MSc), Botho University-Botswana, Gaborone, Botswana; North West Lung Centre (A G Mathioudakis PhD), Manchester University NHS Foundation Trust, Manchester, UK; Health Policy Research (M R Mathur PhD), Public Health Foundation of India, Gurugram, India; Department of Medicine (J Mattumpuram MD), University of Louisville, Louisville, KY, USA; Department of Epidemiology (Prof R J Maude PhD), Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand; Research Division (P K Maulik PhD),

The George Institute for Global Health, New Delhi, India; Department of Social Medicine and Family (M Mazaheri PhD), Dezful University of Medical Sciences, Dezful, Iran; National Centre for Register-based Research (Prof J J McGrath MD), Aarhus University, Aarhus, Denmark; Australian Centre for Health Services Innovation (Prof S M McPhail PhD), Queensland University of Technology, Kelvin Grove, QLD, Australia; Department of Healthcare (E A Mechili PhD), University of Vlora, Vlora City, Albania; Clinic of Social and Family Medicine (E A Mechili PhD), Laboratory of Toxicology (T K Nikolouzakis PhD), Department of Medicine (Prof A Tsatsakis DSc), University of Crete, Heraklion, Greece; Department of Global Health (J C Medina MD), University of the Ryukyus, Nishihara, Japan; Department of Food Science and Technology (R Mehra PhD), Maharishi Markandeshwar (Deemed to be University), Ambala, India; Department of Public Health (T Mekene Meto MPH), Arba Minch University, Arbaminch, Ethiopia; Department of Medical Oncology and Hematology (M A M Mendez-Lopez PhD), Kantonsspital St. Gallen, St. Gallen, Switzerland; Peru Country Office (W Mendoza MD), United Nations Population Fund (UNFPA), Lima, Peru; Department of Public Health (B Mengist MPH), Department of Epidemiology and Biostatistics (M K Tariku MPH), Public Health Department (T Y Tiruye PhD), Department of Human Nutrition and Food Sciences (E G Wassie MSc), Debre Markos University, Debre Markos, Ethiopia; International Dx Department (A A Menthis MD), BGI Genomics, Copenhagen, Denmark; Neurology Unit (A Meretoja MD), Breast Surgery Unit (T J Meretoja MD), Helsinki University Hospital, Helsinki, Finland; University Centre Varazdin (T Mestrovic PhD), University North, Varazdin, Croatia; Department of Pharmacology (Prof K D Mettananda PhD), Department of Paediatrics (Prof S Mettananda DPhil), University of Kelaniya, Ragama, Sri Lanka; Clinical Medicine Department (Prof K D Mettananda PhD), North Colombo Teaching Hospital, Ragama, Sri Lanka; University Paediatrics Unit (Prof S Mettananda DPhil), Colombo North Teaching Hospital, Ragama, Sri Lanka; International Centre for Health Economics, Management, and Policy (P Meylakhs PhD), National Research University Higher School of Economics, St. Petersburg, Russia; Stritch School of Medicine (A Mhlanga PhD), Loyola University Chicago, Chicago, IL, USA; Department of Preventive Medicine (L Mhlanga PhD), Department of Medicine (N S Shah MD), Northwestern University, Chicago, IL, USA; Anaesthesiology Department (G Micha PhD), Helena Venizelou General and Maternity Hospital, Athens, Greece; Department of Epidemiology (I Michalek PhD), National Cancer Registry (I Michalek PhD), Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; Pacific Institute for Research & Evaluation, Calverton, MD, USA (T R Miller PhD); Global Institute of Public Health (Prof G Mini PhD), Ananthapuri Hospitals and Research Institute, Trivandrum, India; Department of Medical Sciences (A Mirjello MD), IRCCS Casa Sollievo della Sofferenza General Hospital (IRCCS Home for the Relief of Suffering General Hospital), San Giovanni Rotondo, Italy; Internal Medicine Programme (Prof E M Mirrakhimov PhD), Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan; Department of Atherosclerosis and Coronary Heart Disease (Prof E M Mirrakhimov PhD), National Center of Cardiology and Internal Disease, Bishkek, Kyrgyzstan; Office of the Minister (M K Mirutse MPH), Federal Ministry of Health, Addis Ababa, Ethiopia; Department of Forensic Medicine and Toxicology (C Mittal MD), Dr. B. C. Roy Multi-Specialty Medical Research Centre, Kharagpur, India; Burn and Regenerative Medicine Research Center (Prof M Mobayen MD), Guilan University of Medical Sciences, rasht, Iran; College of Applied and Natural Science (J Mohamed MSc), University of Hargeisa, Hargeisa, Somalia; Department of Internal Medicine (M F H Mohamed MSc), Brown University, Providence, RI, USA; Molecular Biology Unit (N S Mohamed MSc), Bio-Statistical and Molecular Biology Department (N S Mohamed MSc), Sirius Training and Research Centre, Khartoum, Sudan; Department of Public Health (H Mohammed MPH, Y M Tefera MPH), Dire Dawa University, Dire Dawa, Ethiopia; Department of Pharmaceutical Sciences (S Mohammed PhD), Notre Dame of Maryland University, Baltimore, MD, USA; Department of Pharmacy (S Mohammed PhD), Mizan-Tepi University, Mizan, Ethiopia; Health Systems and Policy Research Unit (S Mohammed PhD), Ahmadu Bello University, Zaria, Nigeria; Department of Diabetology (V Mohan DSc), Madras Diabetes Research

Foundation, Chennai, India; Department of Diabetology (V Mohan DSc), Dr. Mohan's Diabetes Specialities Centre, Chennai, India; Institute of Clinical Physiology (S Molinaro PhD), National Research Council, Pisa, Italy; Clinical Epidemiology and Public Health Research Unit (L Monasta DSc, L Ronfani PhD), Burlo Garofolo Institute for Maternal and Child Health, Trieste, Italy; Department of Biomedical and Dental Sciences and Morphofunctional Imaging (Prof S Mondello MD), Messina University, Messina, Italy; Faculty of Medicine (A Moodi Ghalibaf MD), Infectious Diseases Research Center (F Nikoomanesh PhD), Medical Toxicology & Drug Abuse Research Center (M Rezaei MD), Birjand University of Medical Sciences, Birjand, Iran; Department of Epidemiology and Biostatistics (Y Moradi PhD), Social Determinants of Health Research Center (A Shokri PhD), Kurdistan University of Medical Sciences, Sanandaj, Iran; Computer, Electrical, and Mathematical Sciences and Engineering Division (P Moraga PhD), King Abdullah University of Science and Technology, Thuwal, Saudi Arabia; International Laboratory for Air Quality and Health (Prof L Morawska PhD), School of Public Health and Social Work (N Wang PhD), Queensland University of Technology, Brisbane, QLD, Australia; Department of Public Health (Prof R S Moreira PhD), Oswaldo Cruz Foundation, Recife, Brazil; Department of Public Health (Prof R S Moreira PhD), Federal University of Pernambuco, Recife, Brazil; Department of Biology and Biological Engineering (J Morze PhD), Chalmers University of Technology, Gothenburg, Sweden; College of Medical Sciences (J Morze PhD), SGMK Copernicus University, Warsaw, Poland; Epidemiology Department (S Mousavi MD), Aging Research Institute, Tabriz, Iran; Department of Fruit and Vegetable Product Technology (Prof A Mousavi Khanegah PhD), Prof. Wacław Dąbrowski Institute of Agricultural and Food Biotechnology State Research Institute, Warsaw, Poland; Department of Health and Biomedical Sciences (E A Mpolya PhD), Nelson Mandela African Institution of Science and Technology, Arusha, Tanzania; Research Department (M Mrejen PhD), Instituto de Estudos para Políticas de Saúde (IEPS), São Paulo, Brazil; Unit of Pharmacotherapy, Epidemiology and Economy (S Mubarik MS), University Medical Center Groningen (Prof M J Postma PhD), Department of Internal Medicine (P Vart PhD), University of Groningen, Groningen, Netherlands; Competence Center of Mortality-Follow-Up of the German National Cohort (R Westerman DSc), Federal Institute for Population Research, Wiesbaden, Germany (Prof U O Mueller MD); Center for Population and Health, Wiesbaden, Germany (Prof U O Mueller MD); School of Medicine (F Mughal FRCGP), Keele University, Keele, UK; Knowledge Management Department (S Mukherjee PhD), Prahlad Omkarwati Foundation (POF), Mumbai, India; Independent Consultant, New Delhi, India (S Mukherjee PhD); Department of Surgery (F Multa PhD), G Verrass MD), General University Hospital of Patras, Patras, Greece; Faculty of Medicine (F Multa PhD), Department of Internal Medicine (G Ntaios PhD), Department of Emergency Medicine (I Pantazopoulos PhD), University of Thessaly, Larissa, Greece; Clinical Epidemiology Research Unit (E Murillo-Zamora PhD), Mexican Institute of Social Security, Villa de Alvarez, Mexico; Postgraduate in Medical Sciences (E Murillo-Zamora PhD), Universidad de Colima, Colima, Mexico; Research & Innovation Department (Prof K M Musallam MD), Burjeel Medical City, Abu Dhabi, United Arab Emirates; Department of Internal Medicine (A Mustafa MD), Staten Island University Hospital Northwell Health, Staten Island, NY, USA; Department of Pediatrics & Pediatric Pulmonology (Prof G Mustafa MD), Institute of Mother & Child Care, Multan, Pakistan; Prince Fahad bin Sultan Chair for Biomedical Research (S Muthupandian PhD), University of Tabuk, Tabuk, Saudi Arabia; Centre for Infectious Diseases (Prof R Muthusamy PhD), Saveetha Medical College and Hospitals (S R Pandi-Perumal MSc), Centre of Molecular Medicine and Diagnostics (COMManD) (Prof S Patil PhD), Saveetha University, Chennai, India; Department of Neuropsychiatry (W Myung PhD), Department of Food and Nutrition (A P Okekunle PhD), Seoul National University, Seoul, South Korea; Research and Analytics Department (A J Nagarajan MTech), Initiative for Financing Health and Human Development, Chennai, India; Department of Research and Analytics (A J Nagarajan MTech), Bioinsilico Technologies, Chennai, India; Institute of Epidemiology and Medical Biometry (Prof G Nagel PhD), Ulm University, Ulm, Germany; Initiative for Non Communicable Diseases (A Naheed PhD), Maternal and Child Health Division

(A Sayeed MSc, M Siraj MSc), Nutrition and Clinical Services Division (M Tariquijaman MSc), International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; Comprehensive Cancer Center (G Naik MPH), Department of Health Policy & Organization (M Rahim MA), Department of Health Services Administration (M Rahim MA), Department of Psychology (D C Schwebel PhD), University of Alabama at Birmingham, Birmingham, AL, USA; Department of Pulmonary Medicine (S Nair MD), Government Medical College Trivandrum, Trivandrum, India; Health Action by People, Trivandrum, India (S Nair MD); Department of Medical Laboratory Analysis (H H Najmuldeen PhD), Cihan University Sulaimaniya Research Center (CUSRC) (H N Qasim PhD), Cihan University Sulaymaniyah, Sulaymaniyah, Iraq; Suraj Eye Institute, Nagpur, India (V Nangia MD); School of Pharmacy (A Naqvi PhD), University of Reading, Reading, UK; Mysore Medical College and Research Institute (Prof S Narasimha Swamy MD), Government Medical College, Mysore, India; Department of Biotechnology (M Naveed PhD), University of Central Punjab, Lahore, Pakistan; Department of Disease Control and Environmental Health (R Ndejo MSc), Makerere University, Kampala, Uganda; School of Pharmacy (S O Nduaguba PhD), West Virginia University, Morgantown, WV, USA; Department of General Surgery (I Negoi PhD), Fourth Department of General Surgery (D Serban PhD), Emergency University Hospital Bucharest, Bucharest, Romania; Department of Cardiology (R I Negoi PhD), Cardio-Aid, Bucharest, Romania; Department of Oncology (S Negru MD), Victor Babes University of Medicine and Pharmacy, Timisoara, Romania; Faculty of Medicine (Prof C Nejari PhD), Euromed University of Fes, Fez, Morocco; Faculty of Medicine (Prof C Nejari PhD), University Sidi Mohammed Ben Abdellah, Fez, Morocco; Department of Medicine (E Nena MD, P Steiropoulos MD), Democritus University of Thrace, Alexandroupolis, Greece; Department of Community Medicine (S Nepal MD), Kathmandu University, Palpa, Nepal; Department of Histopathology (Prof H A Nggada MD), University of Maiduguri Teaching Hospital, Maiduguri, Nigeria; Department of Public Health (G Nguefack-Tsague PhD), University of Yaoundé I, Yaoundé, Cameroon; Department of Biological Sciences (J W Ngunjiri DrPH), University of Embu, Embu, Kenya; Department of General Medicine (A H Nguyen MD), Thai Binh University of Medicine and Pharmacy, Thai Binh City, Viet Nam; Department of Medical Engineering (D H Nguyen BS), University of South Florida, Tampa, FL, USA; Department of Surgery (P T Nguyen MD), Danang Family Hospital, Danang, Viet Nam; International Islamic University Islamabad, Islamabad, Pakistan (R K Niazi PhD); Institute for Mental Health and Policy (Y T Nigatu PhD), Centre for Addiction and Mental Health, Toronto, ON, Canada; Department of General Surgery (T K Nikolouzakis PhD), University Hospital of Heraklion, Heraklion, Crete, Greece; Public Health Department (D N A Ningrum MPH), Universitas Negeri Semarang (State University of Semarang), Kota Semarang, Indonesia; Center for Public Health (L A Nnyanzi PhD), Teesside University, Middlesbrough, UK; Faculty of Applied Sciences and Technology (E A Noman PhD), Universiti Tun Hussein Onn Malaysia, Johor, Malaysia; Department of Health Policy and Management (S Nomura PhD), Keio University, Tokyo, Japan; Department of Microbiology and Molecular Genetics (M Noreen PhD), The Women University Multan, Multan, Pakistan; Department of Clinical Sciences (Prof B Norrving PhD), Lund University, Lund, Sweden; Department of Paediatrics (C A Nri-Ezedi MD), Nnamdi Azikiwe University, Awka, Nigeria; The Cardiac Clinic (Prof M Ntsekhe PhD), Groote Schuur Hospital, Cape Town, South Africa; Unit of Microbiology and Public Health (V Nuñez-Samudio PhD), Institute of Medical Sciences, Las Tablas, Panama; Department of Public Health (V Nuñez-Samudio PhD), Ministry of Health, Herrera, Panama; Department of Public Health (D Nurriki PhD), Banten School of Health Science, South Tangerang, Indonesia; Ministry of Research, Technology and Higher Education (D Nurriki PhD), Higher Education Service Institutions (LL-DIKTI) Region IV, Bandung, Indonesia; Department of Applied Economics and Quantitative Analysis (Prof B Oancea PhD), University of Bucharest, Bucharest, Romania; Disease Control and Elimination (M A Oboh PhD), Medical Research Council Unit, The Gambia, Banjul, The Gambia; Division of General Internal Medicine (N M Odogwu PhD), Mayo Clinic, Rochester, MN, USA; School of Public Health (N M Odogwu PhD), Department of

Epidemiology and Community Health (R R Parikh MD), Department of Surgery (J Rickard MD), University of Minnesota, Minneapolis, MN, USA; Department of Medicine (M J O'Donnell PhD), National University of Ireland - Galway, Galway, Ireland; PSSM Data Sciences, Pfizer Research & Development (M Oduro PhD), Pfizer Inc., Groton, CT, USA; Department of Preventive Medicine (I Oh PhD), Department of Pediatrics (Prof D Yon MD), Kyung Hee University, Seoul, South Korea; Independent Consultant, Sydney, NSW, Australia (S R Okeke PhD); Department of Nursing Science (M I Olatubu PhD), Bowen University, Iwo, Nigeria; Cardiology Department (G M M Oliveira PhD), Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; Slum and Rural Health Initiative Research Academy (I Olufadewa MHS), Slum and Rural Health Initiative, Ibadan, Nigeria; Centre for Healthy Start Initiative, Lagos, Nigeria (B O Olusanya PhD, J O Olusanya MBA); Department of Pharmacology and Toxicology (Prof H A Omar PhD), Beni-Suef University, Beni-Suef, Egypt; Surgery Department (G L Omer MD), Sulaimani University, Sulaimani, Iraq; ENT Department (G L Omer MD), Tor Vergata University of Rome, Rome, Italy; School of Public Health (M A Ondayo PhD), Moi University, Eldoret, Kenya; Department of Environmental Health and Biology (M A Ondayo PhD), University of Eldoret, Eldoret, Kenya; Non-communicable Disease Prevention Unit (S Ong FAMS), Ministry of Health, Bandar Seri Begawan, Brunei; Early Detection & Cancer Prevention Services (S Ong FAMS), Pantai Jerudong Specialist Centre, Bandar Seri Begawan, Brunei; Department of Pharmacology and Therapeutics (Prof O E Onwujekwe PhD), University of Nigeria Nsukka, Enugu, Nigeria; Department of Biomedical Sciences (K I Onyedibe PhD), Mercer University School of Medicine, Macon, GA, USA; Department of Pharmacotherapy and Pharmaceutical Care (M Ordahl PhD), Department of Biochemistry and Pharmacogenomics (M Zielińska MPharm), Medical University of Warsaw, Warsaw, Poland; University of Port Harcourt, Port Harcourt, Nigeria (Prof O E Orisakwe PhD); Sickle Cell Unit (V N Orish PhD), Ho Teaching Hospital, Ho Municipality, Ghana; Department of Nephrology and Hypertension (Prof A Ortiz MD), The Institute for Health Research Foundation Jiménez Diaz University Hospital, Madrid, Spain; Department of Biology (W M S Osman PhD), Khalifa University, Abu Dhabi, United Arab Emirates; School of Medicine (U L Osuagwu PhD), Translation Health Research Institute (K Rana PhD), Western Sydney University, Campbelltown, NSW, Australia; Department of Optometry and Vision Science (U L Osuagwu PhD), University of KwaZulu-Natal, KwaZulu-Natal, South Africa; Laboratory of Public Health Indicators Analysis and Health Digitalization (N Ostavnov BA, S S Ostavnov PhD), Department of Information Technologies and Management (S K Vladimirov PhD), Moscow Institute of Physics and Technology, Dolgoprudny, Russia; Department of Project Management (S S Ostavnov PhD), Department of Health Care Administration and Economics (Prof V Vlassov MD), National Research University Higher School of Economics, Moscow, Russia; Division of Infectious Diseases (Prof A Ouyahia PhD), University Hospital of Setif, Setif, Algeria; Department of General Surgery (G Ouyang MD), Central South University, ChangSha, China; Department of Respiratory Medicine (Prof M P A P DNB), Department of Oral and Maxillofacial Surgery (C S N PhD), Jagadguru Sri Shivaratreeswara University, Mysore, India; Department of Forensic Medicine and Toxicology (J Padubidri MD), Kasturba Medical College, Mangalore, Mangalore, India; Department of Neurology (Prof P K Pal DM), National Institute of Mental Health and Neurosciences, Bengaluru, India; Research Institute for Medicines (C Palladino PhD, Prof J Perdigão PhD), Prof N Taveira PhD, Universidade de Lisboa (University of Lisbon), Lisbon, Portugal; Department of Public Health (R Palladino MD), University of Naples Federico II, Naples, Italy; Department of Mental Health (R F Palma-Alvarez PhD), Hospital Universitari Vall d'Hebron (Vall d'Hebron University Hospital), Barcelona, Spain; Department of Psychiatry, Mental Health and Addictions (R F Palma-Alvarez PhD), Vall d'Hebron Institut de Recerca (Vall d'Hebron Research Institute), Barcelona, Spain; Department of Epidemiology and Biostatistics (Prof H Pan PhD), Anhui Medical University, Hefei, China; Department of Public Health (A Pana PhD), Babes Bolyai University, Cluj Napoca, Romania; Department of Health Metrics (A Pana PhD), Center for Health Outcomes & Evaluation, Bucharest, Romania; School of Public Health (P Panda MPH), Asian Institute of Public Health University,

Bhubaneswar, India; Privatpraxis, Heidelberg, Germany (S Panda-Jonas MD); Division of Research and Development (S R Pandi-Perumal MSc), Lovely Professional University, Phagwara, India; Department of Ophthalmology (G D Panos PhD), Nottingham University Hospitals Queen's Medical Centre Campus, Nottingham, UK; Division of Ophthalmology & Visual Sciences (G D Panos PhD), People in Psychiatry and Applied Psychology (F Shokraneh PhD), University of Nottingham, Nottingham, UK; Department of Science and Mathematics (Prof P Papadopoulou PhD), Derei-The American College of Greece, Athens, Greece; Research Center (A Parthasarathi MD), Allergy Asthma and Chest Center, Mysore, India; Department of Medical Sciences (R Passera PhD), University of Torino, Torino, Italy; Department of Imaging (R Passera PhD), AOU Città della Salute e della Scienza di Torino, Torino, Italy; Cardiology Department (D Pasupula MD), MercyOne North Iowa Medical Center, Mason City, IA, USA; Department of Physiotherapy (H M Patel PhD), Charotar University of Science and Technology, Anand, India; School of Dentistry (J Patel BSc), University of Leeds, Leeds, UK; Department of Poverty, Gender and Youth (S K Patel PhD), Population Council, New Delhi, India; College of Dental Medicine (Prof S Patil PhD), Roseman University of Health Sciences, South Jordan, UT, USA; Second Department of Internal Medicine (D Patoulias PhD), European Interbalkan Medical Center, Thessaloniki, Greece; Department of Internal Medicine (V Pathipati MD), Advent Health, Palm Coast, FL, USA; Department of Hospital Medicine (V Pathipati MD), Sound Physicians, Palm Coast, FL, USA; Clinical Research Department (P Pedersini MSc), J H Villaflor PhD), IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy; Department of Neurology (U Pensato MD), IRCCS Humanitas Research Hospital, Milan, Italy; International Institute for Educational Planning (IIEP) (Prof M F P Peres MD), Albert Einstein Hospital, São Paulo, Brazil; Department of Development Studies (Prof A Perianayagam PhD), Department of Fertility Studies (U Sahoo PhD), International Institute for Population Sciences, Mumbai, India; Mario Negri Institute for Pharmacological Research, Bergamo, Italy (N Perico MD, Prof G Remuzzi MD); Pennsylvania Cancer and Regenerative Medicine Center (R G Pestell MD), Baruch S Blumberg Institute, Doylestown, PA, USA; Department of Medicine (R G Pestell MD), Xavier University School of Medicine, Woodbury, NY, USA; Facultad de Medicina (F E Petermann-Rocha PhD), Universidad Diego Portales (Diego Portales University), Santiago, Chile; School of Cardiovascular and Metabolic Health (F E Petermann-Rocha PhD), University of Glasgow, Glasgow, UK; School of Medicine (W A Petri MD), University of Virginia, Charlottesville, VA, USA; School of Medicine (H Pham MD), Department of Epidemiology (H K Tang PhD), Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Viet Nam; Shanghai Mental Health Center (Prof M R Phillips MD), Shanghai Jiao Tong University, Shanghai, China; Department of Psychiatry (Prof M R Phillips MD), Department of Neurology (Prof N Scarmeas PhD), Columbia University, New York, NY, USA; National Centre for Disease Prevention and Health Promotion (D Pierannunzio PhD), National Institute of Health, Roma, Italy; Department of Pediatric Orthopedic Surgery (M Pigeolet MD), Hôpital Necker - Enfants Malades, Paris, France; International Center of Medical Sciences Research, Islamabad, Pakistan (Z Z Piracha PhD); Department of Neonatology (N Plakkal MD), Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India; Research School of Chemistry and Applied Biomedical Sciences (E Plotnikov PhD), Tomsk Polytechnic University, Tomsk, Russia; Mental Health Research Institute (E Plotnikov PhD), Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, Russia; Medical College (V Podder HSC), Tairunnessa Memorial Medical College and Hospital, Gazipur, Bangladesh; Clinical Academic Department of Pediatrics (Prof D Poddighe PhD), University Medical Center (UMC), Astana, Kazakhstan; Department of Data Management and Analysis (R Poluru PhD), The INCLEN Trust International, New Delhi, India; Department of Orthopedics and Traumatology (V T Pankilainen PhD), University of Tampere, Tampere, Finland; Non-communicable Diseases Research Center (N Pourtaheri PhD), Bam University of Medical Sciences, Bam, Iran; Centro de Investigaciones Clínicas (Clinical Research Center) (S I Prada PhD), Fundación Valle del Lili (Valle del Lili Foundation), Cali, Colombia; Universidad ICESI, (S I Prada PhD); Division of Medical Oncology and Hematology (Prof T N Prakasham DM), Department of Dermatology venereology and

leprosy-DVL (Prof T PRISCILLA MD), Apollo Institute of Medical Sciences and Research, Hyderabad, India; Department of Clinical Research and Epidemiology (M Prasad MD), Institute of Liver and Biliary Sciences, New Delhi, New Delhi, India; Department of Biochemistry (Prof A Prashant PhD), Jagadguru Sri Shivaratreeswara University, Mysuru, India; Department of Cardiology (G Qian MS), Third Military Medical University, Chongqing, China; The Department of Gynecology (S Qiu MD), Sun Yat-sen University, Guangzhou, China; Medical Sciences Education Department (M Qureshi MD), Western University of Health Sciences, Pomona, CA, USA; Cardiovascular Research Center (M Rabiee Rad MD), Isfahan Cardiovascular Research Institute, Isfahan, Iran; College of Medicine (A Radfar MD), University of Central Florida, Orlando, FL, USA; Department of Medical Oncology (Prof V Radhakrishnan MD), Cancer Institute (W.I.A), Chennai, India; UO Neurologia, Salute Pubblica e Disabilità (The Neurology, Public Health and Disability Unit) (A Raggi PhD), Fondazione IRCCS Istituto Neurologico Carlo Besta (IRCCS Foundation Carlo Besta Neurological Institute), Milan, Italy; Pathology Department (N Raheem FMCPATH), Mobiddo Adama University Teaching Hospital -Yola, Yola, Nigeria; Department of Health Sciences (Prof F Rahim PhD), Cihan University-Sulaymaniyah, Sulaymaniyah, Iraq; Cihan University Sulaimaniyah Research Center (CUSRC), Sulaymaniyah, Iraq (Prof F Rahim PhD); Institute of Health and Wellbeing (M Rahman PhD), Federation University Australia, Berwick, VIC, Australia; Future Technology Research Center (A Rahmani PhD), National Yunlin University of Science and Technology, Yunlin, Taiwan; Department of Public Health (V Rahamanian PhD), Torbat Jam Faculty of Medical Sciences, Torbat Jam, Iran; Department of Community Medicine (S Rajaa MD), Employees' State Insurance Model Hospital, Chennai, India; Centre for Chronic Disease Control, New Delhi, India (P Rajput PhD); European Office for the Prevention and Control of Noncommunicable Diseases (I Rakovac PhD), World Health Organization (WHO), Moscow, Russia; Research Department (C L Ranabhat PhD), Science, Technology and Natural Resources Department (S Tandukar PhD), Policy Research Institute, Kathmandu, Nepal; Health and Public Policy Department (C L Ranabhat PhD), Global Center for Research and Development, Kathmandu, Nepal; Centre for Clinical Pharmacology (N Rancic PhD), University of Defence in Belgrade, Belgrade, Serbia; Centre for Clinical Pharmacology (N Rancic PhD), Medical College of Georgia at Augusta University, Belgrade, Serbia; Health Economics and Outcomes Research Department (A Rane MS), Agios Pharmaceuticals, Cambridge, MA, USA; Department of Pharmaceutical Economics and Policy (A Rane MS), Massachusetts College of Pharmacy and Health Sciences, Boston, MA, USA; Department of Oral Pathology (S Rao MDS), Sharavathi Dental College and Hospital, Shimogga, India; Data Analytic Services (D P Rasali PhD), British Columbia Centre for Disease Control, Vancouver, BC, Canada; University of Social Welfare and Rehabilitation Sciences, Tehran, Iran (V Rashedi PhD); Department of Geography (A Rasul PhD), Soran University, Soran, Iraq; Section of Pulmonary and Critical Care Medicine (N Ravikumar MD), University of Chicago, Chicago, IL, USA; Inovus Medical, St Helens, UK (D L Rawaf MRCS); Academic Public Health England (Prof S Rawaf MD), Public Health England, London, UK; School of Health, Medical and Applied Sciences (L Rawal PhD), CQ University, Sydney, NSW, Australia; Internal Medicine Department (B Rawley MD), State University of New York, Syracuse, NY, USA; Department of Biological Sciences (Prof E M M Redwan PhD), King Abdulaziz University, Jeddah, Egypt; Department of Protein Research (Prof E M M Redwan PhD), Research and Academic Institution, Alexandria, Egypt; Grenoble Computer Science Laboratory (LIG) (F Rehman PhD), University of Grenoble Alpes, Grenoble, France; Unisabana Center for Translational Science (L F Reyes PhD), Universidad de La Sabana (Savannah University), Chia, Colombia; Critical Care Department (L F Reyes PhD), Clinica Universidad De La Sabana (Savannah University Clinic), Chia, Colombia; Department of Public Health Sciences (T G Rhee PhD), University of Connecticut, Farmington, CT, USA; Department of Surgery (J Rickard MD), University Teaching Hospital of Kigali, Kigali, Rwanda; Department of Medical Education (H R Riva MPAS), Texas Tech University, El Paso, TX, USA; Department of Dermatology (H R Riva MPAS), University of Colorado Denver, Aurora, CO, USA; 1H-TOXRUN - One Health Toxicology Research Unit

(Prof C F Rodrigues PhD), Instituto Universitário de Ciências da Saúde (CESPU), Paredes, Portugal; Department of Clinical Research (L Roever PhD), Federal University of Uberlândia, Uberlândia, Brazil; Institute for Health Metrics and Evaluation (E L B Rogowski MPH), University of Washington, Seattle, USA; Center for Indigenous Health Research (P Rohlff MD), Wuqu' Kawoq Maya Health Alliance, Tecpan, Guatemala; Faculty of Nursing (D S Romadlon PhD), Chulalongkorn University, Bangkok, Thailand; Clinical and Epidemiological Research in Primary Care (GICEAP) (E Romero-Rodríguez PhD), Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Cordoba, Spain; Maurizio Bufalini Hospital, Cesena, Italy (M Romoli MD); Department of Analytical and Applied Economics (Prof H S Rout PhD), C K Swain MPhil, UGC Centre of Advanced Study in Psychology (M Satpathy PhD), Utkal University, Bhubaneswar, India; Department of Labour (P Roy PhD), Directorate of Factories, Government of West Bengal, Kolkata, India; Centro de Investigación Palmira (Palmira Research Center) (E Rubagotti PhD), Corporación Colombiana de Investigación Agropecuaria AGROSAVIA (Colombian Agricultural Research Corporation), Bogota, Colombia; Advanced Campus Governador Valadares (Prof G d Ruela MSc), Juiz de Fora a Federal University, Governador Valadares, Brazil; Nursing Department (Prof G d Ruela MSc), Universidade Presidente Antônio Carlos (President Antônio Carlos University), Governador Valadares, Brazil; Department of Health Statistics (S F Rumisha PhD), National Institute for Medical Research, Dar es Salaam, Tanzania; Department of Cardiology and Internal Medicine (Prof A Rynkiewicz PhD), University of Warmia and Mazury, Olsztyn, Poland; Department of Medical Pharmacology (M M Saber-Ayad MD), Public Health and Community Medicine Department (M R Salem MD), Cairo University, Giza, Egypt; Faculty of Computing and Informatics (M SaberiKamarposhni PhD), Multimedia University, Cyberjaya, Malaysia; Neuropsychiatric Institute (Prof P S Sachdev MD), Prince of Wales Hospital, Randwick, NSW, Australia; Department of Cardiology (R Sachdeva MD), Department of Veterans Affairs, Decatur, GA, USA; Department of Cardiology (R Sachdeva MD), Medical College of Georgia at Augusta University, Augusta, GA, USA; Department of Pharmaceutical Chemistry (Prof M R Saeb PhD), Medical University of Gdańsk, Gdańsk, Poland; Multidisciplinary Laboratory Foundation University School of Health Sciences (FUSH) (Prof U Saeed PhD), Foundation University, Islamabad, Pakistan; International Center of Medical Sciences Research (ICMSR), Islamabad, Pakistan (Prof U Saeed PhD); Faculty of Medicine, Bioscience and Nursing (S Z Safi PhD), MAHSA University, Selangor, Malaysia; Interdisciplinary Research Centre in Biomedical Materials (IRCBM) (S Z Safi PhD), COMSATS Institute of Information Technology, Lahore, Pakistan; Department of Community Medicine and Family Medicine (S Sahoo MD, M Verma MD), Department of Anatomy (A Singal PhD), Department of Radiodiagnosis (P Singh MD), All India Institute of Medical Sciences, Bathinda, India; Department of Preventive & Social Medicine (M Sahu MD), All India Institute of Hygiene & Public Health, Kolkata, India; Department of Statistics (M R Sajid PhD), University of Gujarat, Pakistan, Gujarat, Pakistan; Institute for Employment Research, Nuremberg, Germany (J W Sakshaug PhD); Technology Management Department (Prof M Z Y Salem PhD), University College of Applied Sciences, Gaza, Palestine; School of Economics and Management (Prof M Z Y Salem PhD), University of Kassel, Kassel, Germany; Department of Neurology (S Samadzadeh MD), University of Southern Denmark, Odense, Denmark; Policy and Epidemiology Group (D F Santomauro PhD), Queensland Centre for Mental Health Research, Wacol, QLD, Australia; Pharmacy Study Program (M A Sarasmita PharmD), Udayana University, Badung, Indonesia; Independent Consultant, Thiruvananthapuram, India (S Y Saraswathy PhD); Indira Gandhi Medical College and Research Institute, Puducherry, India (A Saravanan MD); Department of Orthopaedics and Trauma Surgery (B Saravi PhD), University of Freiburg, Freiburg, Germany; Department of Orthopaedics (B Saravi PhD), Loretto Hospital Freiburg, Freiburg, Germany; Department of Food Processing Technology (T Sarkar PhD), West Bengal State Council of Technical Education, Malda, India; Department of Health and Society (Prof R Sarmiento-Suárez MPH), University of Applied and Environmental Sciences, Bogota, Colombia; National School of Public Health (Prof R Sarmiento-Suárez MPH), Carlos III Health Institute, Madrid, Spain; Faculty of Health & Social Sciences (B Sathian PhD), Bournemouth University, Bournemouth, UK; Udyam-Global Association for Sustainable Development, Bhubaneswar, India (M Satpathy PhD); National Centre for Epidemiology and Population Health (M Sayeed MS, A Talukder MSc), Australian National University, Acton, ACT, Australia; Market Access Division (M Saylan MD), Bayer, Istanbul, Türkiye; Department of Neurology (Prof N Scarneaux PhD), National and Kapodistrian University of Athens, Athens, Greece; Dobney Hypertension Centre (Prof M P Schlaich MD), University of Western Australia, Perth, WA, Australia; Hypertension and Kidney Disease Laboratory (Prof M P Schlaich MD), Baker Heart and Diabetes Institute, Melbourne, VIC, Australia; Department of Health Sciences (I J C Schneider PhD), Federal University of Santa Catarina, Araranguá, Brazil; Department of Cardiovascular Sciences (A Schuermans BSc, J Van den Eynde BSc), Katholieke Universiteit Leuven, Leuven, Belgium; Cardiovascular Program (X Xu PhD), The George Institute for Global Health, Sydney, NSW, Australia (Prof A E Schutte PhD), Prof J Sundström PhD; Department of Methodology and Innovation in Prevention (M Schwarzinger MD), University Hospital of Bordeaux, France, Bordeaux, France; University of Bordeaux (M Schwarzinger MD), The National Institute of Health and Medical Research (Inserm), Bordeaux, France; Clinic for Conservative Dentistry and Periodontology (Prof F Schwendicke PhD), University Hospital of the Ludwig-Maximilians-University Munich, Munich, Germany; Department of Medical Statistics (M Šekerija PhD), University of Zagreb, Zagreb, Croatia; Department of Epidemiology and Prevention of Chronic Noncommunicable Diseases (M Šekerija PhD), Croatian Institute of Public Health, Zagreb, Croatia; Faculty of Dentistry (S Selvaraj PhD), AIMST University, Bedong, Malaysia; Emergency Department (S Senthilkumaran MD), Manian Medical Centre, Erode, India; Department of Medicine and Surgery (Y Sethi MBBS), Government Doon Medical College, Dehradun, India; Center for Biomedical Information Technology (F Sha PhD), Shenzhen Institutes of Advanced Technology, Shenzhen, China; Department of Community Health (M Shabany PhD), Aja University of medical sciences, Tehran, Iran; HepatoPancreatoBiliary Surgery and Liver Transplant Department (P A Shah MBBS), Healthcare Global Limited Cancer Care Hospital, Bangalore, India; Division of Preventive Cardiology (I Shahid MBBS), Houston Methodist Academic Institute, Houston, TX, USA; Department of Chemistry (H Shahsavari PhD), Institute for Advanced Studies in Basic Sciences (IASBS), Zanjan, Iran; Independent Consultant, Karachi, Pakistan (M A Shaikh MD); Department of Pathology and Laboratory Medicine (S Sham MD), Northwell Health, New York, NY, USA; Research Institute of Pharmaceutical Sciences (H Shamshad PhD), International Center for Chemical and Biological Sciences (S Ullah MSc), University of Karachi, Karachi, Pakistan; Department of Clinical Review and Safety (S Sharfaei MD), Baim Institute for Clinical Research, Boston, MA, USA; Facultad de Medicina (Faculty of Medicine) (J Sharifi-Rad PhD), Universidad del Azuay (University of Azuay), Cuenca, Ecuador; Department of Physiotherapy (S Sharma PhD), Kathmandu University, Dhulikhel, Nepal; Department of Microbiology (R P Shastri PhD), Yenepoya University, Mangalore, India; Department of Engineering (A Shavandi PhD), Free University of Brussels, Brussels, Belgium; Department of Ophthalmology (M Shayan MD), Harvard Medical School, Boston, MA, USA; Psychology Department (J Shen PhD), University of Massachusetts Lowell, Boston, MA, USA; Friedman School of Nutrition Science and Policy (P Shi PhD), Tufts University, Boston, MA, USA; Tokyo Foundation for Policy Research, Tokyo, Japan (Prof K Shibuya MD); Department of Public Health (D Shiferaw MPH), Dambi Dollo University, Dembi Dollo, Ethiopia; National Institute of Infectious Diseases, Tokyo, Japan (M Shigematsu PhD); Department of Pediatrics (Prof Y Shin PhD), CHA University, Seoul, South Korea; Department of Pediatrics (Prof Y Shin PhD), CHA Gangnam Medical Center, Seoul, South Korea; Finnish Institute of Occupational Health, Helsinki, Finland (R Shiri PhD); Department of Clinical Immunology and Hematology (V Shivarov PhD), Sofamed University Hospital, Sofia, Bulgaria; Department of Genetics (V Shivarov PhD), Sofia University "St. Kliment Ohridski", Sofia, Bulgaria; Department of Public Health and Primary Care (F Shokraneh PhD, Prof P Willeit PhD), Yusuf Hamied Department of Chemistry (H Z Sun PhD), University of Cambridge, Cambridge, UK; School of Pharmacy (S Shrestha PharmD), Monash

University, Selangor Darul Ehsan, Malaysia; The Cooper Institute, Dallas, TX, USA (K Shuval PhD); Department of Medical Microbiology and Infectious Diseases (E E Siddig MD), Erasmus University, Rotterdam, Netherlands; Center of Potential and Innovation of Natural Resources (Prof L M R Silva PhD), Polytechnic Institute of Guarda, Guarda, Portugal; Health Sciences Research Centre (Prof L M R Silva PhD), University of Beira Interior, Covilhã, Portugal; School of Health (Prof C R Simpson PhD), Victoria University of Wellington, Wellington, New Zealand; Department of Dentistry (A Singh MD), All India Institute of Medical Sciences, Bhopal, India; School of Public Health & Zoonoses (B B Singh PhD), Guru Angad Dev Veterinary & Animal Sciences University, Ludhiana, India; Department of Community Medicine (G Singh MD), Lady Hardinge Medical College, New Delhi, India; Department of Paediatrics (J Singh MD), All India Institute of Medical Sciences, Bilaspur, India; Department of Epidemiology (D N Sinha PhD), School of Preventive Oncology, Patna, India; Department of Epidemiology (D N Sinha PhD), Healis Sekhsaria Institute for Public Health, Mumbai, India; Department of Internal Medicine (R Sinto MD), University of Indonesia, Jakarta Pusat, Indonesia; Department of Internal Medicine (R Sinto MD), Dr. Cipto Mangunkusumo National Hospital, Jakarta Pusat, Indonesia; Clinical Branch (V Y Skryabin MD), Moscow Research and Practical Centre on Addictions, Moscow, Russia; Addiction Psychiatry Department (V Y Skryabin MD), Russian Medical Academy of Continuous Professional Education, Moscow, Russia; Department of Infectious Diseases and Epidemiology (A A Skryabina MD), Department of Internal Disease (A V Starodubova DSc), Pirogov Russian National Research Medical University, Moscow, Russia; Division of Injury Prevention (Prof D A Sleet PhD), The Bizzell Group, Atlanta, GA, USA; Department of Surgery (B Socea PhD), "Sf. Pantelimon" Emergency Clinical Hospital Bucharest, Bucharest, Romania; Department of Infectious Diseases (A Sokhan PhD), Kharkiv National Medical University, Kharkiv, Ukraine; Department of Systemic Pathology (R Solanki MD), Touro College of Osteopathic Medicine, Middletown, NY, USA; Department of Pathology (R Solanki MD), American University of the Caribbean School of Medicine, Cupecoy, Saint Martin; Department of Biochemistry (S Solanki MD), Other, Barbados; Department of Health Policy and Management (S Song PhD), University of Georgia College of Public Health, Athens, GA, USA; Centro de Investigación Biomédica en Red Enfermedades Respiratorias (CIBERES) (Center for Biomedical Research in Respiratory Diseases Network), Madrid, Spain (Prof J B Soriano MD); Hull York Medical School (I N Soyiri PhD), University of Hull, Hull City, UK; Division of Community Medicine (C T Sreeramareddy MD), International Medical University, Kuala Lumpur, Malaysia; Amity Institute of Biotechnology (V K Srivastava PhD), Amity University Rajasthan, Jaipur, Jaipur, India; Department of Biological Sciences (V K Srivastava PhD), Indian Institute of Science Education and Research, Bhopal, Bhopal, India; Public Health Department (M Stanikzai MPH), Kandahar University, Kandahar, Afghanistan; Department of Pediatric Cardiology (J R Starnes MD), Vanderbilt University Medical Center, Nashville, TN, USA; Department of Research and Learning (J R Starnes MD), Lwala Community Alliance, Rongo, Kenya; Nutrition and Dietetics Department (A V Starodubova DSc), Federal Research Institute of Nutrition, Biotechnology and Food Safety, Moscow, Russia; Institute for Health Metrics and Evaluation (J D Steinmetz PhD), University of Washington, Seattle, WA, USA; Occupational and Environmental Medicine Department (L Stockfelt PhD), Institute of Neuroscience and Physiology (Prof K S Sunnerhagen PhD), Institute of Health and Care Sciences (Prof A W Wolf PhD), University of Gothenburg, Gothenburg, Sweden; School of Medicine (V Subramaniyan PhD), Monash University, Sunway, Malaysia; School of Life Sciences (M Suleman PhD), Xiamen University, China, Xiamen, China; National Institute of Epidemiology (R Suliankatchi Abdulkader MD), Indian Council of Medical Research, Chennai, India; Mental Health Research (A Sultana MD), Independent Consultant, Khulna, Bangladesh; Division of Global Mental Health (A Sultana MD), EviSyn Health, Khulna, Bangladesh; Rural Health Research Institute (Prof J Sun PhD), Charles Sturt University, Bathurst, NSW, Australia; Institute of Integrated Intelligence and Systems (Prof J Sun PhD), Griffith University, QLD, Australia; Department of Neurocare (Prof K S Sunnerhagen PhD), Sabzevar University of Medical Sciences, Gothenburg, Sweden; Department of Clinical Outcomes

(Prof L Szarpak PhD), Maria Skłodowska-Curie Medical Academy, Warsaw, Poland; Department of Clinical Research and Development (Prof L Szarpak PhD), LUXMED Group, Warsaw, Poland; Department of Dermatology (M D Szeto BS), University of Colorado, Aurora, CO, USA; Department of Neurology (P Tabaei Damavandi MD), Neurocenter of Southern Switzerland (NSI), Lugano, Switzerland; Department of Medicine (Prof R Tabarés-Seisdedos PhD), University of Valencia, Valencia, Spain; Carlos III Health Institute (Prof R Tabarés-Seisdedos PhD), Biomedical Research Networking Center for Mental Health Network (CiberSAM), Madrid, Spain; Department of Basic Medical Sciences (S Tabatabaeizadeh PhD), Department of Internal Medicine (S Tabatabaeizadeh PhD), Islamic Azad University, Mashhad, Iran; Dentistry and Oral Health, Rural Clinical Sciences (J Tadkamadla PhD), La Trobe University, Bendigo, VIC, Australia; School of Dentistry and Oral Health (S K Tadkamadla PhD), Griffith University, Gold Coast, QLD, Australia; Living Systems Institute (Y Taheri Abkenar PharmD), Department of Health and Community Sciences (A Udooh PhD), University of Exeter, Exeter, UK; Department of Biostatistics and Epidemiology (M Taheri Soodejani PhD), Shahid Sadoughi University of Medical Sciences, Yazd, Iran; University of Western Australia, Perth, NSW, Australia (Prof K Takahashi PhD); University of Occupational and Environmental Health, Kitakyushu, Japan (Prof K Takahashi PhD); Statistics Discipline (A Talukder MSc), Khulna University, Khulna, Bangladesh; Department of Dermato-Venereology (M Tampa PhD), Dr. Victor Babes Clinical Hospital of Infectious Diseases and Tropical Diseases, Bucharest, Romania; Department of Medicine (J L Tamuzi MSc), Northlands Medical Group, Omuthiya, Namibia; State Key Laboratory of Numerical Modeling for Atmospheric Sciences and Geophysical Fluid Dynamics (LASG) (H Tang PhD), Chinese Academy of Sciences, Beijing, China; University Institute "Egas Moniz", Monte da Caparica, Portugal (Prof N Taveira PhD); Health Management Department (R Tesler PhD), Ariel University, Ariel, Israel; Department of Psychology (E Teye-Kwadjo PhD), University of Ghana, Legon, Ghana; Wellbeing Preventable and Chronic Diseases Division (R Thakur PhD), Menzies School of Health Research, Alice Springs, NT, Australia; Charles Darwin University, Alice Springs, NT, Australia (R Thakur PhD); Department of Pharmacology (P Thangaraju MD), All India Institute of Medical Sciences, Raipur, India; Public Health Department (Prof K R Thankappan MD), Amrita Institute of Medical Sciences, Kochi, India; Institute of Applied Health Research (R Thayakaran PhD), University of Birmingham, Birmingham, UK, UK; Department of Gastroenterology (N K Thomas MD), PSG Institute of Medical Sciences and Research, Coimbatore, India; Department of Psychiatry (C C Thum MB), Hospital Sultan Abdul Aziz Shah Universiti Putra Malaysia, Serdang, Malaysia; National Institute of Public Health (Prof L C Thygesen PhD), University of Southern Denmark, Copenhagen, Denmark; Faculty of Biomedical Engineering (A Tichopad PhD), Czech Technical University, Prague, Czech Republic; Faculty of Public Health (J H V Ticoalu MPH), Universitas Sam Ratulangi, Manado, Indonesia; Laboratory of Public Health Indicators Analysis and Health Digitalization (M V Titova PhD), Moscow Institute of Physics and Technology, Moscow, Russia; Department of Medicine (Prof M Tonelli MD), Department of Oncology (L Yang PhD), University of Calgary, Calgary, AB, Canada; Institute of Public Health (R Topor-Madry PhD), Jagiellonian University Medical College, Kraków, Poland; Agency for Health Technology Assessment and Tariff System, Warsaw, Poland (R Topor-Madry PhD); Nutritional Epidemiology Research Team (EREN) (M Touvier PhD), National Institute for Health and Medical Research (INSERM), Paris, France; SRM College of Pharmacy (M R Tovani-Palone PhD), SRM Institute of Science and Technology (SRMIST), Chennai, India; Department of Health (N M Tran MD), Children's Hospital 1, Ho Chi Minh City, Viet Nam; Department of Surgical, Medical, Molecular Pathology and Critical Care Medicine (D Trico MD), University of Pisa, Pisa, Italy; Adult Learning Disability Service (S J Tromans PhD), Leicestershire Partnership National Health Service Trust, Leicester, UK; School of Medicine (T T Truyen MD), Nam Can Tho University, Can Tho, Viet Nam; Environmental Sciences Program (S Uddin PhD), Asian University for Women, Chittagong, Bangladesh; Department of Geography (S Uddin PhD), University of Victoria, Victoria, BC, Canada; Department of Rehabilitation and Health Sciences (I Ullah PhD), Iqra University,

Islamabad, Pakistan; Department of Zoology (S Ullah PhD), Division of Science and Technology (S Ullah PhD), University of Education, Lahore, Lahore, Pakistan; Department of Paraclinical Sciences (S Umakanthan MD), The University of the West Indies, St. Augustine, Trinidad and Tobago; Department of Community Medicine (C D Umeokonkwo MPH), Alex Ekwueme Federal University Teaching Hospital Abakaliki, Abakaliki, Nigeria; Institute of Health and Wellbeing (Prof C A Unsworth PhD), Federation University Australia, Churchill, VIC, Australia; Center for Neurodegenerative Diseases and the Aging Brain (D Urso MD), University of Bari, Tricase, Italy; Department of Physiotherapy (J S Usman PhD), Bayero University, Kano, Kano, Nigeria; College of Health and Sport Sciences (A G Vaithianathan MSc), University of Bahrain, Salmania, Bahrain; Department of Social Sciences (Prof S M Van de Velde PhD), Universiteit Antwerpen, Antwerpen, Belgium; Department of Public Health and Epidemiology (O Varga PhD), University of Debrecen, Debrecen, Hungary; UKK Institute, Tampere, Finland (Prof T J Vasankari MD); Faculty of Medicine and Health Technology (Prof T J Vasankari MD), Tampere University, Tampere, Finland; Institute of Public Health of Serbia, Belgrade, Serbia (M Vasic PhD); Department of Human Genetics & Molecular Biology (B Vellingiri PhD), Bharathiar University, Coimbatore, India; Raffles Neuroscience Centre (Prof N Venketasubramanian MBBS), Raffles Hospital, Singapore, Singapore; Department Pediatric Hematology and Oncology (G I Villanueva MD), Hospital de Clinicas Jose de San Martin (Jose de San Martin Clinical Hospital), Ciudad Autonoma de Buenos Aires, Argentina; Occupational Health Unit (Prof F S Violante MD), Sant'Orsola Malpighi Hospital, Bologna, Italy; Department of Molecular Epidemiology (S K Vladimirov PhD), Research Institute for Systems Biology and Medicine, Moscow, Russia; Faculty of Information Technology (B Vo PhD), HUTECH University, Ho Chi Minh City, Viet Nam; Department of Pediatric Endocrinology (R Vukovic PhD), Mother and Child Healthcare Institute of Serbia "Dr Vukan Cupic", Belgrade, Serbia; Office of Research, Innovation, and Commercialization (ORIC) (Prof Y Waheed PhD), Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad, Pakistan; Gilbert and Rose-Marie Chagoury School of Medicine (Prof Y Waheed PhD), Lebanese American University, Byblos, Lebanon; Department of Cultures, Societies and Global Studies (R G Wamai PhD), Northeastern University, Boston, MA, USA; Department of Neurosurgery (S Wang MD), School of Public Health (J Xia PhD), Capital Medical University, Beijing, China; Department of Gastroenterology (S Wang PhD), Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China; Department of Medicine (M Y Wei MD), Greater Los Angeles VA Healthcare System, Los Angeles, CA, USA; Cardiology Department (Prof R G Weintraub MB), Royal Children's Hospital, Melbourne, VIC, Australia; Department of Physical Therapy (T Wiangkham PhD), Naresuan University, Phitsanulok, Thailand; Department of Surgery (D P Wickramasinghe MD), University of Colombo, Colombo, Sri Lanka; Department of Nursing (A Wilandika MKep), Universitas Aisyiyah Bandung, Bandung, Indonesia; Department of Medical Statistics, Informatics and Health Economics (Prof P Willeit PhD), Medical University Innsbruck, Innsbruck, Austria; Department of Chemical Toxicology (M W Wojewodzic PhD), Norwegian Institute of Public Health, Oslo, Norway; Department of Nutrition (D H Woldegebreal MPH), University of California Davis, Davis, CA, USA; NIHR Biomedical Research Centre (Prof C D A Wolfe MD), Guy's and St. Thomas' Hospital and Kings College London, London, UK; The Second Affiliated Hospital (Prof A Wu MD), Wenzhou Medical University, Wenzhou, China; Global Health Research Center (C Wu PhD), Duke Kunshan University, Kunshan, China; Department of Food Science and Human Nutrition (Prof F Wu PhD), Michigan State University, East Lansing, MI, USA; School of Public Health (Shenzhen) (X Wu MPH), Sun Yat-sen University, Shenzhen, China; Division of Gastroenterology (Prof Z Wu PhD), Huazhong University of Science and Technology, Wuhan, China; School of Public Health (H Xiao PhD), Zhejiang University, Zhejiang, China; Department of Public Health Science (H Xiao PhD), Fred Hutchinson Cancer Research Center, Seattle, WA, USA; Department of Behavior and Operation Management (Y Xie MD), Beijing Advanced Innovation Center for Big Data-based Precision Medicine, Beijing, China; Department of Endocrinology (Prof S Xu PhD), University of Science and Technology of China, Hefei,

China; School of Public Health (Prof W Xu MD), Southwest Medical University, Luzhou, China; Department of Cancer Epidemiology and Prevention Research (L Yang PhD), Alberta Health Services, Calgary, AB, Canada; Faculty of Medicine (Y Yano MD), Department of Public Health (N Yonemoto PhD), Juntendo University, Tokyo, Japan; Research Center of Physiology (H Yaribegi PhD), Semnan University of Medical Sciences, Semnan, Iran; Department of Pharmacology, Physiology & Neuroscience (M Yesiltepe PhD), Rutgers University, Newark, Turkiye; Clinical Investigation Unit (M Yesiltepe PhD), Ankara City Hospital, Ankara, Turkiye; Department of Family Medicine (S A Yesuf MSc), St. Peter's Specialized Hospital, Addis Ababa, Ethiopia; Independent Consultant, Addis Ababa, Ethiopia (S A Yesuf MSc); KHANA Center for Population Health Research, Phnom Penh, Cambodia (S Yi PhD); Trinity College Institute for Neuroscience (A Yigezu MPH), School of Medicine (A Yigezu MPH), Trinity College Dublin, Dublin, Ireland; Department of Health Management (A Yiğit PhD, V Yiğit PhD), Süleyman Demirel Üniversitesi (Süleyman Demirel University), Isparta, Turkiye; Pharmacy Department (Y Yismaw MSc), Alkan Health Science, Business and Technology College, Bahir Dar, Ethiopia; Department of Neuropsychopharmacology (N Yonemoto PhD), National Center of Neurology and Psychiatry, Kodaira, Japan; Department of Health Policy and Management (Prof M Z Younis PhD), Jackson State University, Jackson, MS, USA; School of Business & Economics (Prof M Z Younis PhD), Universiti Putra Malaysia (University of Putra Malaysia), Kuala Lumpur, Malaysia; Department of Epidemiology and Biostatistics (Prof C Yu PhD), School of Medicine (Z Zhang PhD), Wuhan University, Wuhan, China; Association for Sociably Applicable Research (ASAR), Pune, India (S Zadey MS); Department of Emergency Medicine (S Zadey MS), Global Emergency Medicine Innovation and Implementation (GEMINI) Research Center, Durham, NC, USA; Epidemiology and Cancer Registry Sector (Prof V Zadnik PhD), Institute of Oncology Ljubljana, Ljubljana, Slovenia; Faculty of Medicine and Health Sciences (F Zakham PhD), Hodeidah University, Hodeidah, Yemen; Department of Health Sciences (S Zaman MSc), James Madison University, Harrisonburg, VA, USA; Hospital San Juan de Dios, Tarija, Bolivia (N Zamora MD); Department of Neuroscience (R Zand MD), Geisinger Health System, Danville, PA, USA; Unit on Child & Adolescent Health (Prof H J Zar PhD), Medical Research Council South Africa, Cape Town, South Africa; Research and Development Department (I Zare BSc), Sina Medical Biochemistry Technologies, Shiraz, Iran; Victorian Comprehensive Cancer Centre, Melbourne, VIC, Australia (J Zhang MD); School of Public Policy and Administration (J Zhang BA), Xi'an Jiaotong University, Xi'an, China; Medical Oncology Department of Gastrointestinal Cancer (L Zhang MS), Cancer Hospital of Dalian University of Technology, Shenyang, China; School of Biomedical Engineering, Faculty of Medicine (L Zhang MS), Dalian University of Technology, Dalian, China; School of Public Health (Y Zhang PhD), Hubei Province Key Laboratory of Occupational Hazard Identification and Control (Y Zhang PhD), Wuhan University of Science and Technology, Wuhan, China; College of Traditional Chinese Medicine (H Zhao MD), Hebei University, Baoding, China; Computational Bioscience Research Center (J Zhou PhD), King Abdullah University of Science and Technology, Jeddah, Saudi Arabia; School of Public Health and Emergency Management (B Zhu PhD), Southern University of Science and Technology, Shenzhen, China; School of Life Sciences (L Zhu PhD), Yunnan University, Kunming, China; College of Medicine (O A Zitoun MD), Sulaiman Alrajhi University, Al Bukairiyah, Saudi Arabia; NIHR Biomedical Research Centre (NIHR-BRC) (Prof A Zumla PhD), University College London Hospitals, London, UK; Department of Cardiology, Pulmonology, and Vascular Medicine (E Zweck MD), Heinrich-Heine-University, Duesseldorf, Germany; School of Physics (S H Zyoud PhD), Universiti Sains Malaysia (University of Science Malaysia), Penang, Malaysia

Contributors

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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events from BMS, Pfizer, Medtronic, Amgen, NovoNordisk, and Servier; support for attending meetings and/or travel from Medtronic; leadership or fiduciary role in other board, society, committee or advocacy group, unpaid, with the French Neurovascular Society; all outside the submitted work. M Bell reports grants or contracts from US EPA, NIH, High Tide Foundation, Health Effects Institute, Yale Women Faculty Forum, Environmental Defense Fund, Yale Climate Change and Health Center, Wellcome Trust Foundation, Robert Wood Johnson Foundation, and the Hutchinson Postdoctoral Fellowship (all paid to their institution); Consulting fees from Clinique; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or education events from Colorado School of Public Health, Duke University, University of Texas, Data4Justice, Korea University, Organization of Teratology Information Specialists, University of Pennsylvania, Boston University, IOP Publishing, NIH, Health Canada, PAC-10, UKRI, AXA Research Fund Fellowship, Harvard University and the University of Montana; Support for attending meeting and/or travel from Colorado School of Public Health, University of Texas, Duke University, Boston University, University of Pennsylvania, Harvard University, American Journal of Public Health, Columbia University and Harvard University; Leadership or fiduciary role in other board, society, committee or advocacy group, unpaid with Fifth National Climate Assessment and Lancet Countdown, Johns Hopkins Advisory Board, Harvard external advisory committee for training grant, WHO Global Air Pollution and Health Technical Advisory group and the National Academies Panels and Committee; and paid with the US EPA Clean Air Scientific Advisory Committee (CASAC); outside the submitted work. L Belo reports other financial or non-financial interests with UCIBIO – FFUP through support from FCT in the scope of the project UIDP/04378/2020 and UIDB/04378/2020 of UCIBIO and the project LA/P/0140/2020 of i4HB, all outside the submitted work. R S Bernstein reports other financial or non-financial support as a full-time Medical Consultant employee of the California Department of Public Health in the Center for Heal Care Quality; outside the submitted work. P J G Bettencourt reports patents planned, issued, or pending (WO2020229805A1, BR112021022592A2, EP3965809A1, OA1202100511, US2023173050A1, EP4265271A2, and EP4275700A2); other financial or non-financial interests with the Botnar Foundation as project reviewer, outside the submitted work. S Bhaskar reports grants or contracts from the Japan Society for the Promotion of Science (JSPS), Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) and JSPS and the Australian Academy of Science; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid with Rotary District 9675 as the district chair, Global Health & Migration Hub Community as Chair and Manager (Berlin, Germany), PLOS One, BMC Neurology, Frontiers in Neurology, Frontiers in Stroke, Frontiers in Public Health and the BMC Medical Research Methodology as an Editorial Board Member, and as a Member of the College of Reviewers (Canadian Institutes of Health Research, Canada); outside the submitted work. B Bikbov reports grants or contracts from the European Commission and The University of Rome; Support for attending meetings/travel from the European Renal Association; Leadership or fiduciary role in other board, society, committee or advocacy group, unpaid in an advocacy group with the International Society of Nephrology and unpaid on the Western Europe Regional Board of the International Society of Nephrology; Other financial or non-financial support from Scientific-Tools.org; outside the submitted work. A Biswas reports consulting fees from INTAS Pharmaceuticals Ltd, India, Lupin Pharmaceuticals, Ltd, India, and Alkem Laboratories, India as personal payments; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Roche Diagnostics, India, as personal payments; all outside the submitted work. E J Boyko reports payment or Honoria for lectures, presentations, speakers' bureaus, manuscript writing or education events from the Korean Diabetes Association, Diabetes Association of the R.O.C (Taiwan), the American Diabetes Association, and the International Society for the Diabetic Foot; Support for attending meetings and/or travel from the Korean Diabetes Association; Diabetes Association of the R.O.C (Taiwan), International Society for the Diabetic Foot; outside the submitted work. M Carvalho reports other financial or non-financial interests from LAQV/REQUIMTE, University of Porto (Porto, Portugal) and acknowledges the

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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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