Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021

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Summary

Background Detailed, comprehensive, and timely reporting on population health by underlying causes of disability and premature death is crucial to understanding and responding to complex patterns of disease and injury burden over time and across age groups, sexes, and locations. The availability of disease burden estimates can promote evidence-based interventions that enable public health researchers, policy makers, and other professionals to implement strategies that can mitigate diseases. It can also facilitate more rigorous monitoring of progress towards national and international health targets, such as the Sustainable Development Goals. For three decades, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has filled that need. A global network of collaborators contributed to the production of GBD 2021 by providing, reviewing, and analysing all available data. GBD estimates are updated routinely with additional data and refined analytical methods. GBD 2021 presents, for the first time, estimates of health loss due to the COVID-19 pandemic.

Methods The GBD 2021 disease and injury burden analysis estimated years lived with disability (YLDs), years of life lost (YLLs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries using 100 983 data sources. Data were extracted from vital registration systems, verbal autopsies, censuses, household surveys, disease-specific registries, health service contact data, and other sources. YLDs were calculated by multiplying cause-age-sex-location-year-specific prevalence of sequelae by their respective disability weights, for each disease and injury. YLLs were calculated by multiplying cause-age-sex-location-year-specific deaths by the standard life expectancy at the age that death occurred. DALYs were calculated by summing YLDs and YLLs. HALE estimates were produced using YLDs per capita and age-specific mortality rates by location, age, sex, year, and cause. 95% uncertainty intervals (UIs) were generated for all final estimates as the 2·5th and 97·5th percentiles values of 500 draws. Uncertainty was propagated at each step of the estimation process. Counts and age-standardised rates were calculated globally, for seven super-regions, 21 regions, 204 countries and territories (including 21 countries with subnational locations), and 811 subnational locations, from 1990 to 2021. Here we report data for 2010 to 2021 to highlight trends in disease burden over the past decade and through the first 2 years of the COVID-19 pandemic.

Findings Global DALYs increased from 2·63 billion (95% UI 2·44–2·85) in 2010 to 2·88 billion (2·64–3·15) in 2021 for all causes combined. Much of this increase in the number of DALYs was due to population growth and ageing, as indicated by a decrease in global age-standardised all-cause DALY rates of 14·2% (95% UI 10·7–17·3) between 2010 and 2019. Notably, however, this decrease in rates reversed during the first 2 years of the COVID-19 pandemic, with increases in global age-standardised all-cause DALY rates since 2019 of 4·1% (1·8–6·3) in 2020 and 7·2% (4·7–10·0) in 2021. In 2021, COVID-19 was the leading cause of DALYs globally (212·0 million [198·0–234·5] DALYs), followed by ischaemic heart disease (188·3 million [176·7–198·3]), neonatal disorders (186·3 million [162·3–214·9]), and stroke (160·4 million [148·0–171·7]). However, notable health gains were seen among other leading communicable, maternal, neonatal, and nutritional (CMNN) diseases. Globally between 2010 and 2021, the age-standardised DALY rates for HIV/AIDS decreased by 47·8% (43·3–51·7) and for diarrhoeal diseases decreased by 47·0% (39·9–52·9). Non-communicable diseases contributed 1·73 billion (95% UI 1·54–1·94) DALYs in 2021, with a decrease in age-standardised DALY rates since 2010 of 6·4% (95% UI 3·5–9·5). Between 2010 and 2021, among the 25 leading Level 3 causes, age-standardised DALY rates increased most substantially for anxiety disorders (16·7% [14·0–19·8]), depressive disorders (16·4% [11·9–21·3]), and diabetes (14·0% [10·0–17·4]). Age-standardised DALY rates due to injuries decreased globally by 24·0% (20·7–27·2) between 2010 and 2021, although improvements were not uniform across locations, ages, and sexes. Globally, HALE at birth improved slightly, from 61·3 years (58·6–63·6) in 2010 to 62·2 years (59·4–64·7) in 2021. However, despite this overall increase, HALE decreased by 2·2% (1·6–2·9) between 2019 and 2021.

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Interpretation Putting the COVID-19 pandemic in the context of a mutually exclusive and collectively exhaustive list of causes of health loss is crucial to understanding its impact and ensuring that health funding and policy address needs at both local and global levels through cost-effective and evidence-based interventions. A global epidemiological transition remains underway. Our findings suggest that prioritising non-communicable disease prevention and treatment policies, as well as strengthening health systems, continues to be crucially important. The progress on reducing the burden of CMNN diseases must not stall; although global trends are improving, the burden of CMNN diseases remains unacceptably high. Evidence-based interventions will help save the lives of young children and mothers and improve the overall health and economic conditions of societies across the world. Governments and multilateral organisations should prioritise pandemic preparedness planning alongside efforts to reduce the burden of diseases and injuries that will strain resources in the coming decades.

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Introduction

Comprehensive estimates of the global burden of disease have a crucial role in improving understanding of the impact of diseases and injuries on population health and assessing progress towards international health targets. Since the early 1990s, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has systematically and comprehensively produced estimates of global health and health loss across stratified age groups, locations, and sexes.[1,2] In 2020, the COVID-19

Research in context

Evidence before this study

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 is a comprehensive study of global health loss. GBD 2021 provides current information on the distribution and burden of diseases and injuries across time, age, sex, location, and sociodemographic group. GBD quantifies burden using disability-adjusted life-years (DALYs), a metric introduced in the World Bank's 1993 World Development Report and since adopted as a key measure of disease burden by WHO, the UN, the World Bank, and governmental agencies around the world. The previous GBD cycle, GBD 2019, estimated prevalence, incidence, and burden as years lived with disability, years of life lost to premature mortality, DALYs, and healthy life expectancy for 369 diseases and injuries in 204 countries and territories, from 1990 to 2019, across age groups and by sex. While other groups have reported on DALYs and other population health metrics in recent years, including the WHO World Health Statistics 2020 report and national-level burden of disease studies, GBD remains the most comprehensive disease burden research effort to date.

Added value of this study

GBD 2021 includes 19 189 new data sources for DALYs, 12 new causes, and other important methodological updates. Notably, we disaggregated the under-5 age group, providing more detailed age-based estimates of burden for young children. GBD 2021 reports ten non-COVID-19-related causes for the first time: pulmonary arterial hypertension, hepatoblastoma, Burkitt lymphoma, other non-Hodgkin lymphoma, eye cancer (including retinoblastoma and other eye cancers as distinct causes), soft tissue and other extraosseous sarcomas, malignant neoplasm of bone and articular cartilage, neuroblastoma, and other peripheral nervous cell tumours. Another important advancement of GBD 2021 is the addition of the impact of the COVID-19 pandemic on disease burden. GBD 2021 includes the estimation of burden for COVID-19, post-COVID-19 condition (also known as long COVID), other pandemic-related outcomes, and the effect of COVID-19 on other selected diseases and injuries. By modelling the burden of COVID-19 and related outcomes within a mutually exclusive and collective exhaustive cause hierarchy, this Article provides both policy makers and practitioners with scientific and evidence-based insights to help guide decision making, priority setting, and resource allocation from subnational to global levels. Policy makers benefit from robust evidence to formulate effective policies, while practitioners gain actionable insights for programme design and implementation. This report's global perspective aids in coordinated resource allocation, fostering collaborative efforts to address interconnected health challenges efficiently, such that it provides a comprehensive toolkit to inform and enhance decision-making processes across various levels of governance and practice.

Implications of all the available evidence

Timely and comprehensive estimates of disease burden are crucial for making health-related policy decisions. At the global level, in this study we found that the burden of diseases and injuries shifted in 2021 compared with previous years, with COVID-19 imposing additional health loss as the leading cause of burden in 2021. Neonatal disorders, ischaemic heart disease, and stroke continued to be among the leading causes of DALYs globally in 2021, as in every year of the previous decade. These findings highlight the importance of continuing to prioritise non-communicable disease prevention and treatment policies, along with health system improvements and ongoing COVID-19 vaccination and other transmission-prevention efforts.

pandemic shifted global health priorities to control transmission of SARS-CoV-2 and respond to added demands on health services. Since then, COVID-19 has transitioned from being a new threat requiring emergency response, to an infectious disease that populations need to live with and manage. Within this context, systematic and up-to-date analysis of disease burden by cause, age, sex, location, and year assumes an even more important function. The results generated by such analyses provide the evidence base on which the emergence of COVID-19 can be better understood, as well as the altered burden of disease landscape that ensued in 2020 and 2021 after the novel coronavirus circulated widely.

GBD 2021 highlights new and existing health threats that require prioritisation on international public health agendas. GBD 2021 estimates will allow up to date identification of health disparities within and between populations, enabling evaluation of how these have changed over time, quantify health gains, and, in turn, identify policies or interventions that present the most promising opportunities for impact in the post-COVID-19 era. GBD 2021 estimates are given for 371 diseases and injuries (including 95 communicable, maternal, neonatal, and nutritional [CMNN] diseases, 234 non-communicable diseases, and 40 injuries); 204 countries and territories; 21 countries with subnational locations; 25 age groups; females, males, and both sexes combined; and for the years 1990–2021. Here, we report prevalence, incidence, years lived with disability (YLDs; quantifying non-fatal health loss), years of life lost (YLLs; quantifying fatal health loss), disability-adjusted life-years (DALYs; quantifying both years lost to premature mortality and years lived with disability), and healthy life expectancy (HALE; quantifying expected years of life lived in good health). We focused on estimates between 2010 and 2021 to highlight trends in disease burden over the past decade and in 2020 and 2021, the first 2 years of the COVID-19 pandemic. In this manuscript we provide high-level findings of GBD 2021. The estimation of causes of deaths and YLLs for GBD 2021 are summarised elsewhere.[3]

There have been key data and methodological updates for GBD 2021, which are summarised in the Methods section. Notably, to our knowledge, GBD 2021 is the first publication to provide comprehensive burden estimates for COVID-19 as an infectious disease inclusive of post-COVID-19 condition (also known as long COVID; disability caused by remaining symptoms after initial SARS-CoV-2 infection has been cleared[4]), other COVID-19 pandemic-related outcomes, and the effect of COVID-19 on the burden of selected diseases. GBD 2021 findings therefore supersede those from GBD 2019 and all previous GBD rounds. This manscript was produced as part of the GBD Collaborator Network and in accordance with the GBD Protocol.[5]

Methods

Overview

In this section, we provide an overview of the burden estimation process for GBD 2021, with further details provided in appendix 1. Methods used to generate burden estimates closely followed those for GBD 2019; however, here we summarise new or updated processes since GBD 2019. Methods used to generate GBD 2021 estimates are also available online. Here we report GBD 2021 estimates of incidence, point prevalence (hereafter referred to as prevalence), YLDs, YLLs, and DALYs for 371 diseases and injuries along with estimates of HALE. Estimates were produced by sex (female and male) and age (25 age groups from birth to age 95 years and older) for 204 countries and territories, including subnational estimates for 21 countries and territories. GBD 2021 provides annual estimates between 1990 and 2021; however, in this report we have focused on estimates between 2010 to 2021 to highlight trends over the past decade and the first 2 years of the COVID-19 pandemic. We also present these metrics stratified by Socio-demographic Index (SDI), a composite measure of lag-distributed income per capita, average years of education for those aged 15 years or older, and fertility rates among females younger than 25 years (appendix 1 section 4).

See Online for appendix 1

For more on **methods to generate GBD 2021 estimates** see https://ghdx.healthdata.org/gbd-2021

An international network of over 10 000 collaborators from more than 150 countries and territories provided, reviewed, or analysed the available data to generate GBD metrics. GBD 2021 complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER);[6] a completed GATHER checklist is provided in appendix 1 (table S3). Analyses were completed using Python (version 3.10.4), Stata (version 13.1), and R (version 4.2.1).

Geographical hierarchy

GBD 2021 produced estimates for 204 countries and territories, grouped into 21 regions and seven super-regions. GBD regions, and in turn GBD super-regions, are made up of countries and territories that are geographically close, epidemiologically similar, and share similar distributions of causes of death. Subnational estimates were produced for the following 21 countries and territories: Brazil, China, Ethiopia, India, Indonesia, Italy, Iran, Japan, Kenya, Mexico, New Zealand, Nigeria, Norway, Pakistan, the Philippines, Poland, Russia, South Africa, Sweden, the UK, and the USA. Subnational analyses were conducted at the first level of administrative organisation within each country, except for New Zealand (which was conducted by Māori ethnicity), Sweden (by Stockholm and non-Stockholm), the UK (by local government authorities), Kenya (by county), and the Philippines (by province). Since GBD 2019, the GBD location hierarchy has included all WHO Member States. At the most detailed level, we generated estimates for 983 specific locations. A full list of the geographical hierarchy is in appendix 1 (table S1).

Disease and injury hierarchy

The 371 diseases and injuries included in GBD 2021 were organised within a cause hierarchy with four levels plus the Level 0 aggregate of all causes. Level 1 consisted of other COVID-19 pandemic-related outcomes and three broad aggregate categories: CMNN diseases; non-communicable diseases; and injuries. Level 2 included 22 clusters of causes that each fell within a Level 1 category. Level 3 included 175 causes of which 132 were specific causes and 43 were clusters of Level 4 causes. Level 4 consisted of 302 specific causes, including 170 specific causes that each fell within the 43 Level 3 clusters of causes and the 132 Level 3 specific causes that were not further disaggregated at Level 4. Overall, 365 causes had non-fatal outcomes, and 288 causes had fatal outcomes. A full list of causes by level is in appendix 1 (table S2).

Data sources

DALY estimates for GBD 2021 were informed by 100 983 data sources (including 19 189 sources newly used in 2021). Included among these data sources were 75 459 data sources on non-fatal causes, among which 36 916 were data sources on incidence, 22 236 were data sources on prevalence, and 45 were data sources on other epidemiological measures (eg, remission). Information on data sources for YLLs for GBD 2021 have been reported elsewhere.[3] For non-fatal estimates, data sources included scientific literature, household survey data, epidemiological surveillance data, disease registry data, clinical informatics data, and other sources (appendix 1 section 3.1.1). Cause-specific literature reviews are described in detail in appendix 1 (section 8) and include searches of online research databases, government and international organisation websites, published reports, primary data sources, and contributions of datasets by GBD Collaborators. Multiple data types were included to capture the widest array of epidemiological information pertaining to a cause. Fatal estimates, methods, and data sources are discussed in full detail elsewhere.[3] Data sources were identified from vital registration, verbal autopsy, registry, survey, police, or surveillance data across all countries and territories. As with any given release of GBD, we sought to incorporate as much available data from around the world as possible into our estimates. We receive data not only through literature reviews, but also through proactive data seeking and through the work of collaborators in our network to identify new datasets and sources.

Prevalence, incidence, and YLDs

YLDs were calculated with a microsimulation process that used estimated age-sex-location-year-specific prevalent counts of non-fatal disease sequelae (consequences of a disease or injury) for each cause and disability weights for each sequela as the inputs.

Data processing

Epidemiological data with known biases (eg, alternative case definitions or measurement methods) were adjusted with correction factors estimated by network meta-regressions using MR-BRT (meta-regression—Bayesian, regularised, trimmed; appendix 1 section 3.3).[7] MR-BRT encompasses a series of statistical models—namely, linear and non-linear mixed effects models—and fitting procedures (appendix 1 section 3.5). Input data to estimate correction factors consisted of pairs of estimates where two case definitions or measurement methods were available for the same age-sex-location-year. For example, the correction factor used to adjust past-year prevalence estimates of anxiety disorders down to reflect point prevalence (the gold-standard recall period for this cause) was informed by available past-year prevalence data matched with point prevalence data on age, sex, location, and year (cause-specific corrections applied to the data using MR-BRT are in appendix 1 [section 8]). Input data not reported by sex were adjusted using the cause-specific pooled within-study sex ratio. Input data not reported by age and sex underwent age-sex splitting. Age-specific estimates from sources reporting by age and by sex (but not by age-sex) were adjusted using the within-source sex ratio to provide age-sex-specific estimates. Input data representing an age span greater than 25 years were split into granular age-specific estimates via an alternative age pattern that was estimated with available data from other sources (appendix 1 section 3.3.5).

Clinical informatics data also underwent various forms of data processing, as detailed in appendix 1 (section 3.2). Clinical sources included data on inpatient hospital admissions, outpatient visits (including to general practitioners), and health insurance claims. Data from inpatient hospital admissions reporting a single diagnosis were adjusted to account for readmissions, non-primary diagnoses, and outpatient care. The fraction of unique inpatient cases and ratios between primary and non-primary diagnoses, and inpatient and outpatient care, were extracted from data sources containing this level of detail at the individual level. Age-sex-specific ratios were then estimated by cause using MR-BRT, and inpatient data were adjusted accordingly. Estimates of total inpatient admission rates per capita for each location, year, age, and sex were used to scale inpatient sources that were incomplete for the population. Inpatient sources were additionally transformed using a scalar derived from the Healthcare Access and Quality Index to account for varying health-care access by location.[8] These adjustments aim to produce standardised, population-level clinical estimates of incidence and prevalence.

Statistical analyses of prevalence estimates

For most diseases and injuries, prevalence and incidence were modelled using DisMod-MR 2.1 (Disease Modelling Meta-Regression; version 2.1). DisMod-MR 2.1 is a Bayesian disease modelling meta-regression tool that

generates internally consistent estimates of prevalence, incidence, remission, and mortality by sex, location, year, and age group. The tool also produced these measures for locations with missing raw epidemiological data by estimating prevalence across a cascade down the five levels of the GBD geographical hierarchy. Epidemiological data from locations higher in the hierarchy served as priors for the estimation of the epidemiological parameter from locations lower in the hierarchy. DisMod-MR 2.1 also uses location-level covariates to inform prevalence and incidence for locations with missing data. More detail on DisMod-MR 2.1 is in appendix 1 (section 3.6) and has been published elsewhere.[9] For some causes, spatiotemporal Gaussian process regression (ST-GPR) disease models were used instead of DisMod-MR 2.1. ST-GPR is a set of regression methods that allow us to analyse heterogeneous and incomplete data requiring statistical smoothing over time, age, and location. More detail on ST-GPR is in appendix 1 (section 3.4). Custom models were used for causes where DisMod-MR 2.1 or ST-GPR could not adequately model prevalence or incidence. Details about cause-specific methods are in appendix 1 (section 8).

Severity distribution and disability weights

Prevalence and incidence were split into sequela-specific prevalence and incidence for non-fatal causes for which disability varied across a spectrum of severity. Sequela categories varied by non-fatal cause—for instance, categories could represent asymptomatic, mild, moderate, and severe sequelae. Estimates of the proportion of cases in each sequela category for most non-fatal causes were calculated via analysis of the Medical Expenditure Panel Survey (known as MEPS; appendix 1 section 3.8).[10] Severity proportions for remaining non-fatal causes were estimated from an analysis of the US National Epidemiologic Survey on Alcohol and Related Conditions,[11,12] the 1997 Australian National Survey of Mental Health and Wellbeing,[13] or from published survey data sourced from literature reviews. Details on severity proportions by cause are in appendix 1 (section 8). Crude YLD rates were estimated by multiplying sequela-specific prevalence by their respective disability weights. Disability weights represent health loss from a sequela on a scale ranging from 0 (equivalent to no health loss) to 1 (equivalent to death). Disability weights were derived from community surveys of the general population from Bangladesh, Hungary, Indonesia, Italy, Peru, Sweden, Tanzania, the Netherlands, and the USA, and an open internet survey available in English, Spanish, and Mandarin.[14,15] Participants of the surveys were presented pairs of lay descriptions of health states and asked which of the two was the healthier state. Lay descriptions were created by experts, used non-clinical language, and were 35 words or shorter in length. Responses were then anchored between 0 and 1 via population health equivalence questions where respondents were asked to compare the benefit of lifesaving or disease-prevention programmes. More detail on the estimation of disability weights is provided elsewhere[14,15] and in appendix 1 (section 3.9).

Comorbidity

YLDs underwent a comorbidity correction to account for the co-occurrence of non-fatal causes in the population and to allow for YLDs to be additive across the GBD 2021 cause hierarchy. The co-occurrence of non-fatal causes was simulated within a population of 20 000 simulated individuals for every age, sex, location, and year. The probability of each simulated individual having each sequela was equal to its prevalence. Each simulated individual was then assigned a cumulative disability weight on the basis of a multiplicative function of all the disability weights assigned to the simulated individual. Sequela-specific disability weights were adjusted accordingly and the YLD rate for each sequela was calculated. YLD counts were then estimated as the YLD rate multiplied by the age-sex-location-year-specific population. More detail on this comorbidity simulation is in appendix 1 (section 3.10).

New for GBD 2021

For GBD 2021, we further disaggregated all estimates for age groups younger than 5 years into those aged 0–6 days, 7–27 days, 1–5 months, 6–11 months, 12–23 months, and 2–4 years. The relatively broad grouping of 1–4-year-old children in previous iterations of the GBD study limited our ability to make targeted recommendations regarding the burden from neonatal disorders given that the risk factors, health services, supportive equipment needs, and caregiver needs vary considerably within this age group. GBD 2021 reports two new COVID-19-related causes: COVID-19 at Level 3 (including the burden due to long COVID, modelled as a sequela for COVID-19), and other COVID-19 pandemic-related outcomes at Level 1 (appendix 1 table S2). Other COVID-19 pandemic-related outcomes included excess mortality associated with the pandemic minus mortality directly due to COVID-19, lower respiratory infections, measles, malaria, and pertussis, because there was a reduction in deaths from these causes during the pandemic[3] and, hence, we removed that effect on mortality first before calculating other pandemic-related deaths. For the first time, GBD 2021 also reports on five additional Level 3 causes (pulmonary arterial hypertension, eye cancer, soft tissue and other extraosseous sarcomas, malignant neoplasm of bone and articular cartilage, and neuroblastoma and other peripheral nervous cell tumours), and five additional Level 4 causes (hepatoblastoma, Burkitt lymphoma, other non-Hodgkin lymphoma, retinoblastoma, and other eye cancers; appendix 1 table S2). The decision to model and report new causes is manifold and considers such factors as data availability, policy concerns, research

priorities, and methodological refinements. Processes used to incorporate these causes into GBD 2021 are in appendix 1 (section 8). Additionally, the prevalence estimates for major depressive disorder and anxiety disorders were adjusted for the impact of the COVID-19 pandemic using data sourced from a systematic review that informed a meta-regression in MR-BRT. This model was then used to adjust pre-pandemic prevalence of these two disorders estimated via DisMod-MR 2.1 (appendix 1 section 8).[16]

Deaths and YLLs

YLLs were calculated as the product of estimated age-sex-location-year-specific deaths and the standard life expectancy at the age death occurred for a given cause. This process is summarised here, with detailed information provided in affiliated GBD 2021 publications featuring causes of death and YLLs,[3] as well as updated demographic parameters.[17]

Data processing

GBD 2021 methods follow principles from the ICD, 11th edition, whereby each death is assigned to the underlying cause that initiated events leading to death. Vital registration data reporting assigned ICD so-called garbage codes (a term used in GBD to represent non-specific codes, implausible codes, or intermediate rather than underlying cause of death codes) were assigned to the most likely cause of death via redistribution algorithms.[18] These algorithms were derived from published studies, expert consultation, or regression on data sources reporting multiple causes of death.[3]

Statistical analyses of mortality estimates

Cause of death estimates for most diseases and injuries were modelled via the Cause of Death Ensemble model (CODEm). CODEm uses an ensemble of statistical models while also systematically testing combinations of covariates on the basis of their out-of-sample predictive validity. It then combines results to estimate deaths by location, age, sex, and year for a given cause. CODEm was run by sex and separately for countries and territories with and without extensive complete vital registration data to decrease the likelihood of uncertainty inflation from data with high heterogeneity. Multiple iterations of out-of-sample predictive validity for each model were assessed, and models with the smallest root-mean-square error were weighted to generate an ensemble model for a given cause. Other customised modelling strategies were used to estimate deaths for a small group of causes with unique epidemiology, important changes in reporting practices, or a scarcity of data. These modelling strategies included the use of prevalence, incidence, case-fatality data, or data related to sub-causes to inform cause of death estimates; further discussions of these methods are available elsewhere.[3]

DALYs and HALE

YLDs and YLLs were summed to calculate DALYs by location, age, sex, year, and cause (appendix 1 section 5). HALE was estimated as a complementary measure to DALYs, representing a population's average number of years of life spent in good health. HALE values were calculated using age-specific mortality rates and YLDs per capita. The method used to estimate HALE was unchanged from previous GBD cycles.[19] The method was presented by Sullivan,[20] and is described in appendix 1 (section 6). Both DALYs and HALE were estimated by location, age, sex, and year, and DALYs also by cause.

Data presentation, annual rate of change, uncertainty, and SDI

GBD 2021 metrics were estimated as counts, all-age and age-specific rates per 100 000 population, and age-standardised rates per 100 000 population, calculated using the GBD standard population structure. We present percentage changes over specified time periods (eg, 2010–21), 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. All calculations were conducted 500 times to generate draw-level estimates. The number of computations per process was reduced from 1000, as in previous GBD iterations, to 500 for GBD 2021 because simulation testing revealed the final estimates and their uncertainty were not affected by this reduction. Final estimates represent the mean estimate across 500 draws, and 95% uncertainty intervals (UIs) are represented by the 2·5th and 97·5th percentile values across the draws. Uncertainty was propagated at each step in the estimation process.

Sociodemographic development has been a leading contributor to health gains over the three decades for which GBD has previously tracked changes in burden by location.[21] In this Article, we also present an analysis of burden for locations across SDI quintiles. SDI is a composite indicator representing the geometric mean of three parameters: the lag-distributed income per capita, average years of schooling, and the fertility rate in females younger than 25 years for a given location. SDI scores were rescaled from 0 (lowest income and years of schooling, and highest fertility) to 100 (highest income and years of schooling, and lowest fertility). This process is further explained in appendix 1 (section 4).

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

We generated results using GBD methods to analyse data between 2010 and 2021 to highlight trends in disease burden over the past decade and through the first 2 years

of the COVID-19 pandemic (2020 and 2021). We present prevalence and incidence results for causes at Level 3 of the GBD cause hierarchy and DALY estimates for all causes combined and individual causes or cause groups at Levels 1–3 of the hierarchy. DALY estimates are presented at the global level, by SDI quintile, GBD regions, and countries and territories.

Global trends in prevalence and incidence

The number of prevalent cases and age-standardised prevalence and their rank by cause and sex in 2010 and 2021 are presented in appendix 2 (tables S1–S6). Globally, the most prevalent Level 3 diseases and injuries during 2021 (across ages and sexes) were oral disorders (3·69 billion [95% UI 3·40–4·00] cases at any given point during the year), headache disorders (2·81 billion [2·60–3·03]), and haemoglobinopathies and haemolytic anaemias, which includes inherited blood disorders (2·19 billion [2·12–2·27]; appendix 2 table S4). These causes also had the highest age-standardised prevalence of all Level 3 causes (appendix 2 tables S1, S2, S3). There were only minimal changes among the 20 most prevalent causes since 2010.

The Level 3 causes with the highest incidence globally in 2021 (across ages and sexes) were upper respiratory infections (12·8 billion [95% UI 11·4–14·5] new cases), diarrhoeal diseases (4·67 billion [4·11–5·22]), and oral disorders (3·74 billion [3·31–4·22]). These three causes also had the highest incidence globally for all sexes combined since 2010. The number of incident cases and age-standardised incidence and rank by cause, age, and sex, for 2010 and 2021, are in appendix 2 (tables S7, S8, S9, S10, S11, S12).

There were 2·28 billion (95% UI 2·18–2·37) incident cases of COVID-19 globally in 2021, equivalent to an age-standardised incidence rate of 28 955·3 (27 708·3–30 143·2) per 100 000 population (appendix 2 tables S7, S10). This was an increase from 1·63 billion (1·55–1·69) incident cases of COVID-19 globally in 2020, equivalent to an age-standardised incidence rate of 20 819·8 (19 908·0–21 681·5) per 100 000 (appendix 2 table S7, S10). Although males and females had similar incidence rates of COVID-19 across years (appendix 2 tables S8, S9, S11, S12), females were affected by long COVID at twice the rate of males (63·2% [59·7–66·3] of people with long COVID were female and 36·8% [33·7–40·3] were male in 2020–21; sequela-level estimates not shown).

Global trends in DALYs between 2010 and 2021

The global number of all-cause DALYs remained steady between 2010 (2·63 billion [95% UI 2·44–2·85]) and 2019 (2·61 billion [2·36–2·88]); however, global all-cause DALYs increased to 2·76 billion (2·50–3·04) in 2020 and to 2·88 billion (2·64–3·15) in 2021 (appendix 2 table S13). Yet, there was a decrease in the global age-standardised DALY rate per 100 000 population, which accounts for the impact of population growth and ageing, between 2010 (39 352·9 [36 554·8–42 641·1]) and 2019 (33 763·6 [30 685·4–37 225·2]), equivalent to a 14·2% (10·7–17·3) decrease in the global age-standardised all-cause burden (appendix 2 table S13). However, the global age-standardised DALY rate per 100 000 population increased between 2019 and 2020 by 4·1% (1·8–6·3), to 35 143·0 (32 052·1–38 678·8) in 2020, and by 7·2% (4·7–10·0) between 2019 and 2021, to 36 206·8 DALYs (33 039·5–39 638·7) in 2021 (appendix 2 table S13).

Across the Level 1 causes, non-communicable diseases contributed the highest burden globally and was the only disease group for which DALYs increased between 2010 and 2021, from 1·47 billion (95% UI 1·32–1·64) in 2010 to 1·73 billion (1·54–1·94) in 2021 (appendix 2 table S13). This increase was mostly due to population growth and ageing (165 of 204 countries increased in population between 2010 and 2021), because the age-standardised DALY rates decreased between 2010 and 2021 by 6·4% (3·5–9·5), from 22 209·8 (19 961·7–24 705·4) to 20 783·1 (18 495·1–23 377·4) DALYs per 100 000 population. DALYs for CMNN diseases decreased from 876 million (816–939) in 2010 to 831 million (761–909) in 2021. The age-standardised DALY rate for CMNN diseases decreased by 12·9% (5·1–19·2) between 2010 and 2021, from 13 062·8 (12 173·8–14 002·1) to 11 373·3 (10 360·3–12 517·3) DALYs per 100 000. DALYs due to injuries decreased from 284 million (266–305) in 2010 to 248 million (227–272) in 2021 (appendix 2 table S13). The age-standardised DALY rate due to injuries decreased by 24·0% (20·7–27·2) from 2010 to 2021, from 4080·1 (3821·4–4385·6) to 3098·9 (2837·2–3404·5) DALYs per 100 000. However, most of the health gains from injuries occurred between 2010 and 2019 (a decrease of 20·8% [17·7–23·6] in age-standardised DALY rate) as opposed to between 2019 and 2021 (a decrease of 4·1% [1·1–6·7]).

See Online for appendix 2

In total, 15 non-communicable diseases, seven CMNN diseases, two types of injuries, and other COVID-19 pandemic-related outcomes featured within the 25 leading Level 3 causes of DALYs in 2021 (figure 1). Between 2010 and 2020, neonatal disorders, ischaemic heart disease, and stroke were the leading causes of DALYs for all ages and sexes combined. In 2020, COVID-19 emerged as the fourth leading cause of all-age DALYs. In 2021, it became the leading cause of DALYs, surpassing neonatal disorders, ischaemic heart disease, and stroke. Other COVID-19 pandemic-related outcomes was the 24th leading cause of DALYs in 2020 and the eighth leading cause in 2021. The emergence of both these causes in 2020 reversed the decline in DALYs due to CMNN diseases, causing an increase of 18·0% (95% UI 13·8–22·5) in age-standardised DALY rates between 2019 and 2021. However, there were substantial health gains among other leading CMNN diseases, most notably for HIV/AIDS (with a decrease in the age-standardised DALYs rate of 47·8% [43·3–51·7]

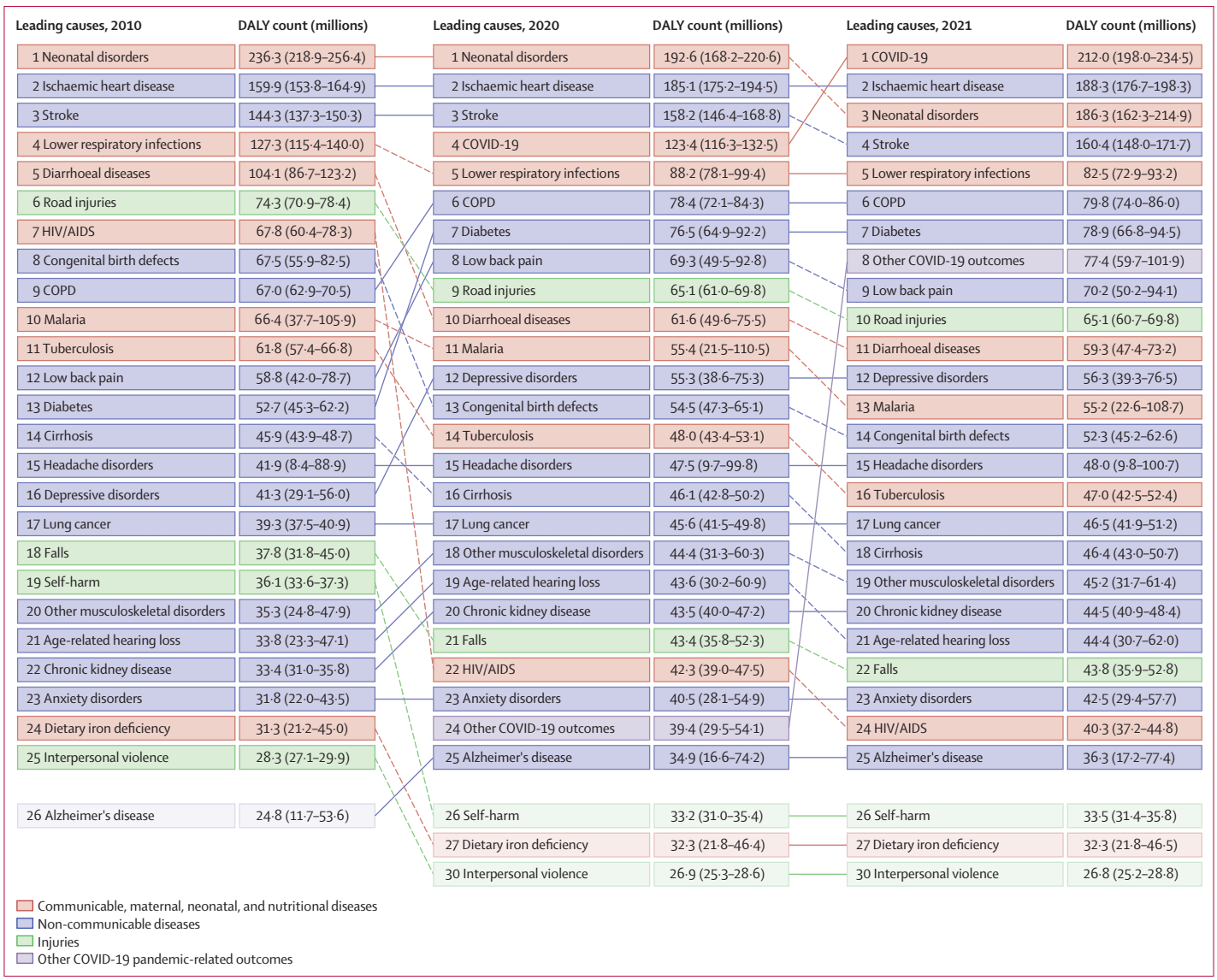


Figure 1: **Leading 25 Level 3 causes of global DALYs in 2010, 2020, and 2021, for both sexes combined, and all ages**
Causes are connected by lines between time periods, where solid lines represent an increase or no change in rank and dashed lines represent a decrease in rank. Faded colours indicate that the cause is not within the top 25 causes of DALYs for that year. Data in parentheses are 95% uncertainty intervals. COPD=chronic obstructive pulmonary disease. DALY=disability-adjusted life-year.

between 2010 and 2021) and diarrhoeal diseases (decrease of 47·0% [39·9–52·9]). The smallest health gain among the CMNN diseases was observed for neonatal disorders (decrease in age-standardised DALY rate of 17·1% [4·9–25·9]), which was in the top three leading causes of DALYs in 69 of 204 countries and territories in 2021.

Among the non-communicable diseases featured in figure 1 as the leading Level 3 causes of DALYs in 2021, the largest health gains between 2010 and 2021 were observed for congenital birth defects (with a decrease in the age-standardised DALY rate of 20·9% [95% UI 2·7–30·4], cirrhosis and other chronic liver diseases (a decrease of 18·3% [10·9–26·5]), and stroke (a decrease of 16·9% [11·7–21·9]; appendix 2, table S25). However, age-standardised DALYs also increased by 14·0% (10·0–17·4) for diabetes, 16·4% (11·9–21·3) for depressive disorders, and 16·7% (14·0–19·8) for anxiety disorders. The two types of injury explaining the most burden globally in 2021 (figure 1) decreased in age-standardised DALY rates between 2010 and 2021. Between 2010 and 2021, age-standardised DALYs for road injuries decreased by 22·9% (18·5–27·1), from 1049·4 (1001·8–1108·3) per 100 000 in 2010 to 808·9 (752·7–865·8) per 100 000 in 2021 and falls decreased by 6·9% (4·0–10·2), from 570·9 (480·7–678·2) per 100 000 in 2010 to 531·2 (437·3–638·8) per 100 000 in 2021. However, most of this change occurred before 2019,

when the rate was 839·9 (788·0–899·3) DALYs per 100 000 for road injuries and 536·7 (442·8–643·0) per 100 000 for falls. Age-standardised DALY rates and number of DALYs by cause and location for 2010, 2019, 2020, and 2021 are presented in appendix 2 table S13.

Figure 2 shows the distribution of global DALYs across age groups for females and males in 2021 for Level 2 causes, COVID-19, and other COVID-19 pandemic-related outcomes (the equivalent plot for 2020 is in appendix 2 [figure S1]; age-specific rates for 2021 are in appendix 2 [figure S2]). In 2021, males accounted for 1·55 billion (95% UI 1·43–1·69) global DALYs and females for 1·33 billion (1·19–1·48) global DALYs. In females, COVID-19 was the leading Level 3 cause of DALYs in 2021 (80·2 million [73·1–92·5] DALYs) followed by neonatal disorders (79·9 million [70·3–91·0]; appendix 2 table S14). In males, COVID-19 was also the leading cause of DALYs (132 million [124–143] DALYs), followed by ischaemic heart disease (115 million [108–123]) and neonatal disorders (106 million [91·2–124]; appendix 2 table S15). Most of the burden due to neonatal disorders in 2021 occurred during the first 6 days after birth and burden imposed by neonatal conditions decreased sharply with age

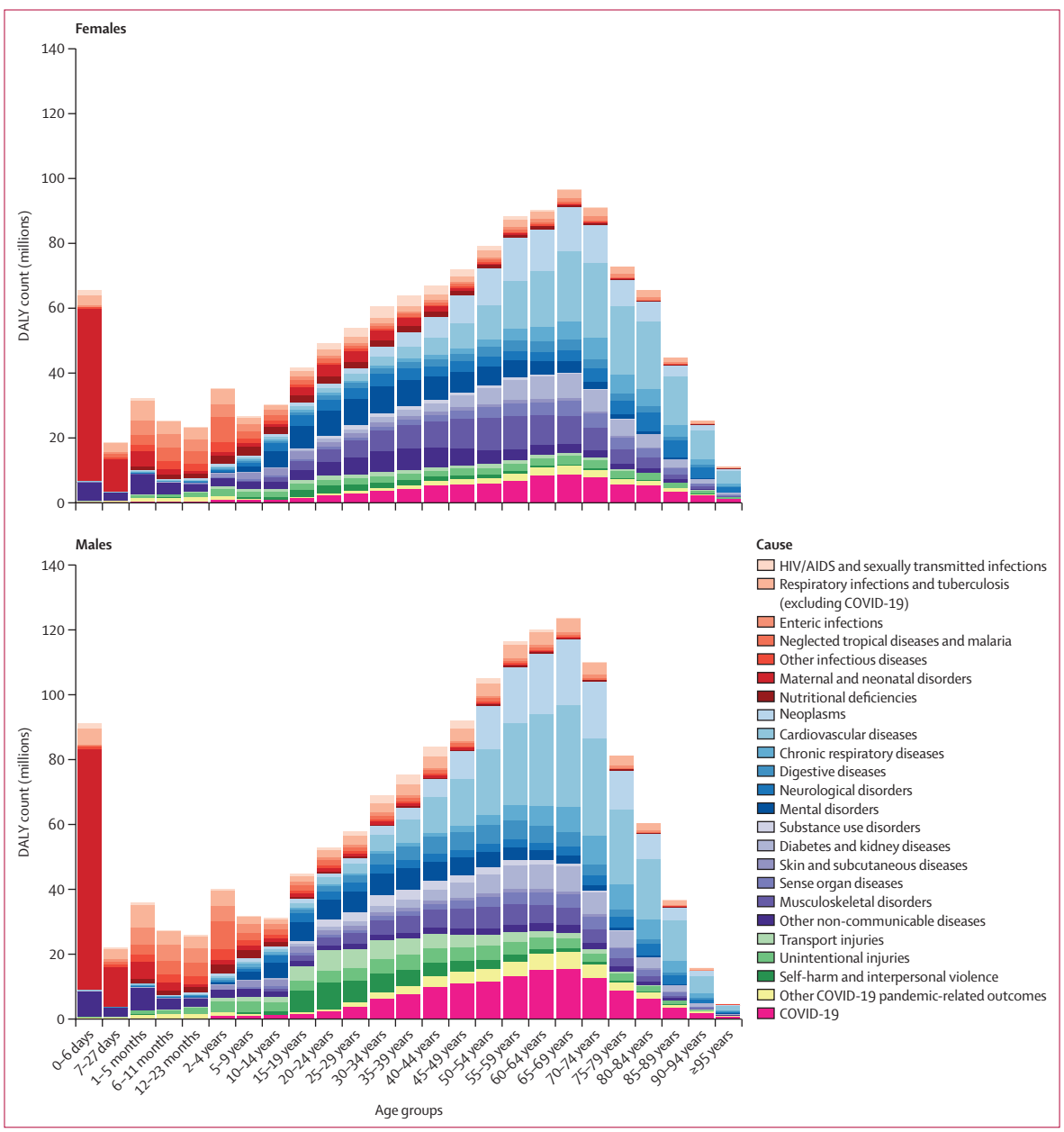


***Figure 2*: The distribution of global DALYs by age and sex for Level 2 causes, COVID-19, and other COVID-19 pandemic-related outcomes in 2021**
DALY=disability-adjusted life-year.

thereafter. Despite similar age-standardised incidence rates of COVID-19 between females and males, the age-standardised DALY rate for COVID-19 was greater among males (3247·9 [3057·9–3521·4] per 100 000 males; 8·5% [7·6–9·5] of male DALYs) than females (1822·6 [1651·0–2125·7] per 100 000 females; 6·1% [5·3–7·0] of female DALYs). Males also had a larger age-standardised rate of DALYs due to other COVID-19 pandemic-related outcomes (1220·4 [909·4–1630·9] DALYs per 100 000) than did females (705·2 [503·6–945·9] per 100 000; appendix 2 tables S14, S15). Older populations had greater health loss due to COVID-19 than did younger populations, with individuals aged 50–69 years having 5834·8 (5515·1–6302·5) DALYs per 100 000 and individuals aged 70 years and older having 11 584·1 (11 067·8–12 262·5) DALYs per 100 000 due to COVID-19 in 2021 (appendix 2 figure S2). This trend was also evident for other COVID-19 pandemic-related outcomes, which accounted for 1911·6 (1429·8–2677·6) DALYs per 100 000 population aged 50–69 years, and 3572·6 (2701·0–4791·8) per 100 000 population aged 70 years and older globally (appendix 2 figure S2).

Decomposition of DALYs into YLDs and YLLs

Global all-cause DALYs in 2021 were composed of 907 million (95% UI 680–1170) YLDs (equivalent to 31·3% [25·4–37·5] of total DALYs and an age-standardised rate of 11 031·9 [8279·5–14 272·4] YLDs per 100 000; appendix 2 table S16) and 1·98 billion (1·87–2·10) YLLs (equivalent to 68·7% [62·5–74·6] of total DALYs and an age-standardised rate of 25 175·4 [23 693·7–26 906·6] YLLs per 100 000; appendix 2 table S19). Global YLDs increased from 738 million (550–959) in 2010 and YLLs increased from 1·89 billion (1·82–1·96) in 2010. All-cause, age-standardised YLD rates, which account for population growth and ageing, remained relatively stable between 2010 and 2021, with only a 2·6% (1·3–4·8) increase globally (appendix 2 table S16).

	Cause	YLDs 2021			Percentage change, 2010–21	
		Percentage of all-cause YLDs	Count (millions)	Age-standardised rate (per 100 000)	YLD count	Age-standardised rate
1	Low back pain	7·7% (6·5 to 9·1)	70·2 (50·2 to 94·1)	832·2 (595·9 to 1115·3)	19·4% (17·9 to 20·8)	–2·4% (–2·9 to –1·8)
2	Depressive disorders	6·2% (5·0 to 7·8)	56·3 (39·3 to 76·5)	681·2 (475·3 to 924·0)	36·5% (31·7 to 41·7)	16·4% (11·9 to 21·3)
3	Headache disorders	5·2% (1·2 to 10·4)	48·0 (9·80 to 101)	588·4 (117·6 to 1245·7)	14·4% (12·7 to 17·8)	0·3% (–1·1 to 1·4)
4	Age-related and other hearing loss	4·9% (3·9 to 5·9)	44·4 (30·7 to 62·0)	525·9 (364·2 to 731·9)	31·6% (30·0 to 33·1)	2·5% (1·7 to 3·3)
5	Other musculoskeletal disorders	4·8% (3·6 to 6·2)	43·0 (29·6 to 59·2)	507·2 (349·5 to 698·0)	28·7% (26·7 to 30·8)	6·3% (5·6 to 7·0)
6	Anxiety disorders	4·7% (3·6 to 6·0)	42·5 (29·4 to 57·7)	524·3 (363·3 to 716·2)	33·7% (30·7 to 37·0)	16·7% (14·0 to 19·8)
7	Diabetes mellitus	4·5% (3·9 to 5·2)	41·2 (29·0 to 56·5)	477·0 (336·1 to 653·3)	62·9% (60·3 to 65·8)	25·9% (24·0 to 28·1)
8	Dietary iron deficiency	3·6% (2·8 to 4·2)	32·3 (21·8 to 46·5)	423·7 (285·3 to 611·0)	3·2% (0·9 to 5·2)	–7·3% (–9·4 to –5·5)
9	Blindness and vision loss	3·2% (2·4 to 4·4)	29·2 (19·0 to 42·9)	342·8 (224·2 to 503·6)	32·9% (27·4 to 38·6)	2·6% (–2·5 to 7·7)
10	Gynaecological diseases	3·0% (2·5 to 3·7)	27·4 (19·1 to 38·2)	334·0 (232·7 to 467·5)	15·3% (14·0 to 16·8)	1·4% (0·6 to 2·3)
11	Falls	2·7% (2·3 to 3·0)	24·2 (16·8 to 32·8)	288·6 (200·9 to 391·7)	21·4% (19·2 to 23·3)	–3·5% (–4·7 to –2·6)
12	Oral disorders	2·6% (1·7 to 3·6)	23·2 (13·8 to 35·0)	275·9 (164·2 to 416·8)	25·1% (21·4 to 28·6)	0·4% (–2·6 to 3·3)
13	Neonatal disorders	2·4% (2·0 to 2·8)	21·7 (15·7 to 27·3)	282·7 (204·9 to 356·1)	24·9% (13·8 to 35·3)	13·5% (3·6 to 22·9)
14	Osteoarthritis	2·3% (1·4 to 4·5)	21·3 (10·2 to 42·9)	244·5 (117·1 to 493·1)	36·9% (35·2 to 38·5)	2·4% (1·3 to 3·5)
15	Neck pain	2·2% (1·7 to 2·9)	20·4 (13·6 to 28·9)	242·3 (162·6 to 342·8)	22·0% (19·4 to 24·6)	1·4% (1·0 to 1·9)
16	Stroke	1·7% (1·3 to 2·0)	15·2 (11·0 to 19·4)	178·7 (128·9 to 227·6)	29·1% (25·4 to 32·8)	–1·2% (–4·0 to 1·5)
17	COPD	1·7% (1·3 to 2·1)	14·9 (12·4 to 17·1)	174·4 (145·5 to 201·0)	29·1% (24·8 to 33·3)	–2·5% (–5·7 to 0·5)
18	Schizophrenia	1·7% (1·2 to 2·2)	14·8 (10·9 to 19·1)	177·8 (131·6 to 228·9)	16·3% (14·9 to 17·8)	0·0% (–0·9 to 0·9)
19	COVID-19	1·6% (0·6 to 3·6)	14·3 (5·14 to 33·7)	176·4 (63·1 to 418·9)	..	..
20	Alzheimer's disease and other dementias	1·3% (1·0 to 1·6)	11·6 (7·96 to 15·3)	141·9 (97·7 to 187·2)	45·7% (44·1 to 47·2)	2·6% (1·7 to 3·5)
21	Autism spectrum disorders	1·3% (0·8 to 2·0)	11·5 (7·84 to 16·3)	147·6 (100·2 to 208·1)	12·9% (11·9 to 13·7)	0·7% (–0·2 to 1·4)
22	Alcohol use disorders	1·2% (1·0 to 1·5)	11·0 (7·68 to 15·3)	132·3 (92·3 to 184·5)	6·8% (3·4 to 10·5)	–8·1% (–10·8 to –5·4)
23	Asthma	1·1% (0·9 to 1·4)	10·2 (6·50 to 15·0)	131·1 (84·0 to 194·7)	2·1% (0·2 to 4·4)	–11·1% (–12·8 to –8·9)
24	Drug use disorders	1·0% (0·8 to 1·3)	9·23 (6·54 to 11·8)	114·1 (80·9 to 145·5)	26·2% (22·5 to 30·1)	13·9% (10·9 to 17·2)
25	Other mental disorders	1·0% (0·7 to 1·3)	8·96 (5·72 to 13·5)	106·6 (68·2 to 160·7)	19·5% (18·4 to 21·0)	–0·2% (–0·8 to 0·2)

Data in parentheses are 95% uncertainty intervals. Count data are presented to three significant figures, and rates and percentage change data are presented to one decimal place. COPD=chronic obstructive pulmonary disease. YLDs=years lived with disability.

Table: **Top 25 leading Level 3 causes of global YLDs, ranked from 1 to 25, in 2021 across all ages, for both sexes combined, YLD counts, age-standardised rates, and percentage change between 2010 and 2021**

21 non-communicable diseases, three CMNN diseases, and one injury featured within the 25 leading Level 3 causes of YLDs globally in 2021 (table). The top three causes of YLDs, across all ages and sexes combined, were all non-communicable diseases: low back pain (70·2 million [95% UI 50·2–94·1] YLDs), depressive disorders (56·3 million [39·3–76·5] YLDs), and headache disorders (48·0 million [9·80–101] YLDs). Among the 25 leading Level 3 causes of YLDs, we observed the largest increase in age-standardised YLD rates between 2010 and 2021 in diabetes, anxiety disorders, depressive disorders, drug use disorders, and neonatal disorders (table). COVID-19, which was the leading contributor to the increase in DALYs in 2021 (figure 1), did not feature as prominently as a leading cause of YLDs, ranking as the 19th leading Level 3 cause of YLDs in 2021 (14·3 million [5·14–33·7] YLDs; table), up from 41st in 2020 (4·95 million [1·79–11·4] YLDs; appendix 2 table S16).

Global YLLs increased non-significantly (4·6% [95% UI –0·9 to 10·7]) between 2010 and 2021 (appendix 2

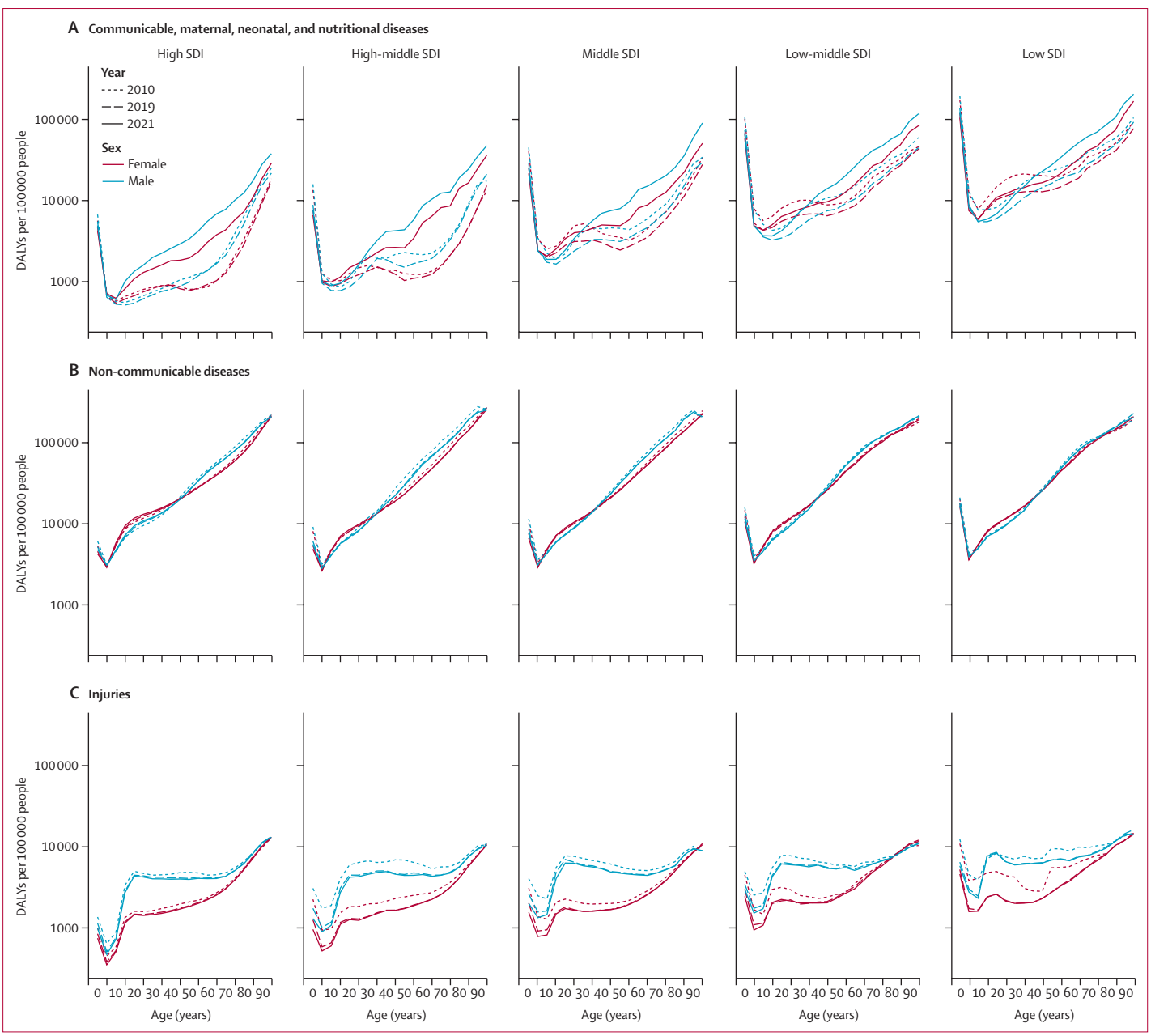


Figure 3: **Age-specific DALY rates for Level 1 causes of communicable, maternal, neonatal, and nutritional diseases (A), non-communicable diseases (B), and injuries (C), by age, sex, year, and SDI quintile**

The y-axis shows DALYs per 100 000 population on a logarithmic scale. DALY=disability-adjusted life-year. SDI=Socio-demographic Index.

table S19). However, relative to YLDs, a larger decrease of 12·0% (6·4 to 16·8) in age-standardised YLL rates was found between 2010 (28 595·8 [27 568·9 to 29 636·5] per 100 000) and 2021 (25 175·4 [23 693·7 to 26 906·6] per 100 000). The top three causes of YLLs, across all ages and sexes, in 2021 were: COVID-19 (198 million [187–211] YLLs), ischaemic heart disease (184 million [173–195]), and neonatal disorders (165 million [141–191]; appendix 2 table S19). Age-standardised YLD and YLL rates, and the number of YLDs and YLLs by cause, location, and sex for 2010, 2019, 2020, and 2021 are in appendix 2 (tables S16, S17, S18, S19, S20, S21).

Trends in DALYs by SDI, location, age, and sex

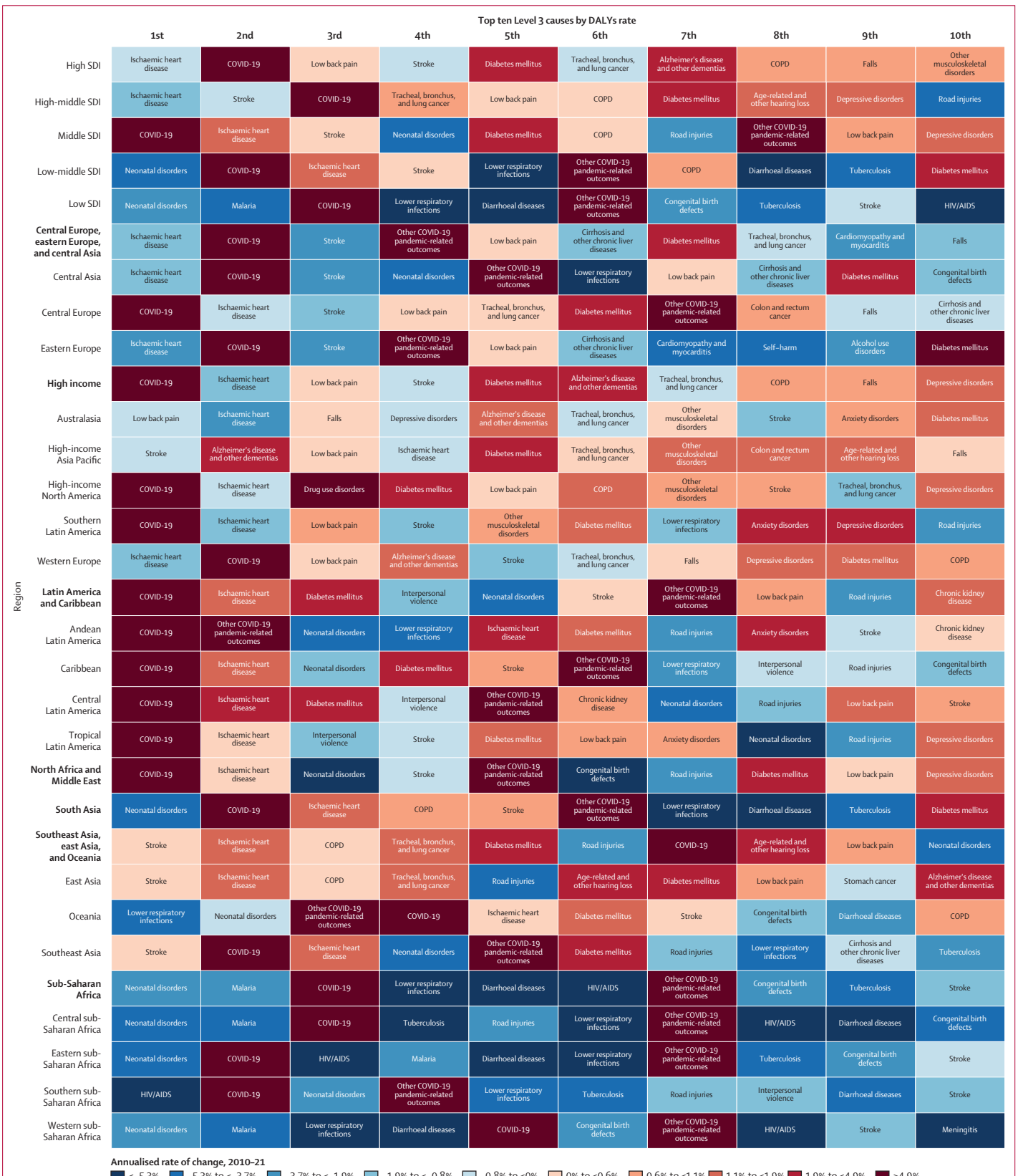
Trends in DALYs at the global level were informed by complex patterns of cause-specific burden across location, age, and sex. Age-standardised DALY rates for non-communicable diseases in males in 2021 ranged from 18 489·4 (95% UI 16 343·7–21 105·5) DALYs per 100 000 population in the high SDI quintile to 24 964·7 (22 503·7–27 556·8) per 100 000 in the low-middle SDI quintile. In females age-standardised DALY rates ranged from 17 167·4 (14 340·9–20 435·8) per 100 000 in the high SDI quintile to 24 072·6 (21 230·1–27 461·6) per 100 000 in the low SDI quintile (appendix 2 table S22). Across all SDI quintiles, age-specific DALY rates from non-communicable diseases decreased with increasing age from 0–6 days through to 5–9 years, and then increased gradually with age from this point on (figure 3).

Age-standardised DALY rates for CMNN diseases in males in 2021 ranged from 2902·3 (95% UI 2750·4 to 3092·7) per 100 000 in the high SDI quintile to 28 861·0 (26 081·7 to 32 375·0) per 100 000 in the low SDI quintile. In females, they ranged from 2014·2 (1816·0 to 2272·9) per 100 000 in the high SDI quintile to 24 040·3 (21 630·5 to 26 984·8) per 100 000 in the low SDI quintile (appendix 2 table S22). Age-standardised DALY rates for CMNN diseases decreased between 2010 and 2021 in the low SDI quintile (by 19·3% [12·2 to 25·8]) and the low-middle SDI quintile (by 13·9% [7·1 to 19·7]). Age-standardised DALY rates for CMNN diseases decreased at lower rates in the middle SDI quintile (by 4·9% [–2·0 to 10·8]), whereas (due to the emergence of COVID-19) rates increased for both the high-middle SDI quintile (by 26·9% [20·1 to 34·6]) and the high SDI quintile (by 63·9% [54·9 to 73·8]). Except for the high SDI quintile, age-specific DALY rates for CMNN diseases were higher in females than males in age groups younger than 25 years, and higher among males than females in age groups including those aged 25 years and older. In the high SDI quintile, DALY rates for CMNN diseases were higher among males than among females across most of the lifespan (figure 3).

Age-standardised DALY rates for injuries in males in 2021 ranged from 3050·8 (95% UI 2784·5–3395·9) per 100 000 in the high SDI quintile to 5958·8 (5266·7–6754·1) per 100 000 in the low SDI quintile. In females, age-standardised DALY rates ranged from 1384·7 (1206·2–1607·8) per 100 000 in the high-middle SDI quintile to 2787·9 (2414·0–3214·2) per 100 000 in the low SDI quintile (appendix 2 table S22). Age-standardised DALY rates for injuries decreased between 2010 and 2021 in all locations, ranging from a decrease of 31·7% (26·3–36·2) in the low SDI quintile to a decrease of 12·3% (10·4–14·2) in the high SDI quintile. Across all SDI quintiles, DALY rates for injuries emerged 0–6 days after birth, declined between the age groups of 7–27 days after birth and 5–9 years, and increased with age thereafter. From age 20 years and older, DALY rates for injuries in males remained relatively stable with increasing age and males aged 15–49 years in low SDI locations had similar DALY rates from injuries in 2021 (6854·7 [6203·9–7633·6] DALYs per 100 000) as they did in 2010 (7317·5 [6689·3–8064·0] per 100 000, a decrease of 6·3% [0·6–11·7]), whereas the DALY rates for females increased quite steadily with age from age 20 years (figure 3).

Drivers of changes in DALYs by location are further illustrated in figure 4, which shows the ten leading Level 3 causes of DALYs in 2021 and their annualised rate of change between 2010 and 2021 by region, super-region, and SDI quintile. In the low SDI quintile, seven of the ten leading Level 3 causes of DALYs were CMNN diseases, led by neonatal disorders (77·9 million [95% UI 65·4 to 92·8] DALYs), malaria (39·7 million [16·2 to 77·3]), and COVID-19 (33·7 million [30·8 to 38·2]; appendix 2 table S23). Age-standardised DALY rates per 100 000 due to these three causes were highest in the low SDI quintile (neonatal disorders: 4599·0 [3868·8 to 5449·4]; malaria: 2872·3 [1135·3 to 5709·5]; COVID-19: 5646·7 [5223·4 to 6170·2]), and lowest in the high SDI quintile (neonatal disorders: 536·1 [477·1 to 596·7]; malaria: 0·0 [0·0 to 0·1]; COVID-19: 1220·2 [1148·4 to 1341·9]; appendix 2 table S22). As SDI increased, more non-communicable diseases emerged in the top ten leading causes of DALYs (figure 4). In the high SDI quintile, eight of the ten leading Level 3 causes of DALYs were non-communicable diseases, led by ischaemic heart disease (23·5 million [21·5 to 24·7] DALYs), low back pain (15·9 million [11·5 to 21·2]), and stroke (15·2 million [13·7 to 16·4]); appendix 2 table S23). However, the age-standardised rate of DALYs due to ischaemic heart disease was lowest in the high SDI quintile (1133·9 [1053·0 to 1185·9] per 100 000) and highest in the low-middle SDI quintile

Figure 4: **Leading ten Level 3 causes of DALYs in 2021 by SDI quintile, region, super-region, and annualised rate of change between 2010 and 2021**
Level 3 causes are ranked by attributable DALYs from left (first) to right (tenth) for each GBD region and SDI quintile, with GBD super-regions in bold. Leading ten Level 3 causes of DALYs are ranked according to 2021 DALYs counts. COPD=chronic obstructive pulmonary disease. DALY=disability-adjusted life-year. SDI=Socio-demographic Index.


Top ten Level 3 causes by DALYs rate
1st
2nd
3rd
4th
5th
6th
7th
8th
9th
10th
Region
High SDI
Ischaemic heart disease
COVID-19
Low back pain
Stroke
Diabetes mellitus
Tracheal, bronchus, and lung cancer
Alzheimer's disease and other dementias
COPD
Falls
Other musculoskeletal disorders
High-middle SDI
Ischaemic heart disease
Stroke
COVID-19
Tracheal, bronchus, and lung cancer
Low back pain
COPD
Diabetes mellitus
Age-related and other hearing loss
Depressive disorders
Road injuries
Middle SDI
COVID-19
Ischaemic heart disease
Stroke
Neonatal disorders
Diabetes mellitus
COPD
Road injuries
Other COVID-19 pandemic-related outcomes
Low back pain
Depressive disorders
Low-middle SDI
Neonatal disorders
COVID-19
Ischaemic heart disease
Stroke
Lower respiratory infections
Other COVID-19 pandemic-related outcomes
COPD
Diarrhoeal diseases
Tuberculosis
Diabetes mellitus
Low SDI
Neonatal disorders
Malaria
COVID-19
Lower respiratory infections
Diarrhoeal diseases
Other COVID-19 pandemic-related outcomes
Congenital birth defects
Tuberculosis
Stroke
HIV/AIDS
Central Europe, eastern Europe, and central Asia
Ischaemic heart disease
COVID-19
Stroke
Other COVID-19 pandemic-related outcomes
Low back pain
Cirrhosis and other chronic liver diseases
Diabetes mellitus
Tracheal, bronchus, and lung cancer
Cardiomyopathy and myocarditis
Falls
Central Asia
Ischaemic heart disease
COVID-19
Stroke
Neonatal disorders
Other COVID-19 pandemic-related outcomes
Lower respiratory infections
Low back pain
Cirrhosis and other chronic liver diseases
Diabetes mellitus
Congenital birth defects
Central Europe
COVID-19
Ischaemic heart disease
Stroke
Low back pain
Tracheal, bronchus, and lung cancer
Diabetes mellitus
Other COVID-19 pandemic-related outcomes
Colon and rectum cancer
Falls
Cirrhosis and other chronic liver diseases
Eastern Europe
Ischaemic heart disease
COVID-19
Stroke
Other COVID-19 pandemic-related outcomes
Low back pain
Cirrhosis and other chronic liver diseases
Cardiomyopathy and myocarditis
Self–harm
Alcohol use disorders
Diabetes mellitus
High income
COVID-19
Ischaemic heart disease
Low back pain
Stroke
Diabetes mellitus
Alzheimer's disease and other dementias
Tracheal, bronchus, and lung cancer
COPD
Falls
Depressive disorders
Australasia
Low back pain
Ischaemic heart disease
Falls
Depressive disorders
Alzheimer's disease and other dementias
Tracheal, bronchus, and lung cancer
Other musculoskeletal disorders
Stroke
Anxiety disorders
Diabetes mellitus
High-income Asia Pacific
Stroke
Alzheimer's disease and other dementias
Low back pain
Ischaemic heart disease
Diabetes mellitus
Tracheal, bronchus, and lung cancer
Other musculoskeletal disorders
Colon and rectum cancer
Age-related and other hearing loss
Falls
High-income North America
COVID-19
Ischaemic heart disease
Drug use disorders
Diabetes mellitus
Low back pain
COPD
Other musculoskeletal disorders
Stroke
Tracheal, bronchus, and lung cancer
Depressive disorders
Southern Latin America
COVID-19
Ischaemic heart disease
Low back pain
Stroke
Other musculoskeletal disorders
Diabetes mellitus
Lower respiratory infections
Anxiety disorders
Depressive disorders
Road injuries
Western Europe
Ischaemic heart disease
COVID-19
Low back pain
Alzheimer's disease and other dementias
Stroke
Tracheal, bronchus, and lung cancer
Falls
Depressive disorders
Diabetes mellitus
COPD
Latin America and Caribbean
COVID-19
Ischaemic heart disease
Diabetes mellitus
Interpersonal violence
Neonatal disorders
Stroke
Other COVID-19 pandemic-related outcomes
Low back pain
Road injuries
Chronic kidney disease
Andean Latin America
COVID-19
Other COVID-19 pandemic-related outcomes
Neonatal disorders
Lower respiratory infections
Ischaemic heart disease
Diabetes mellitus
Road injuries
Anxiety disorders
Stroke
Chronic kidney disease
Caribbean
COVID-19
Ischaemic heart disease
Neonatal disorders
Diabetes mellitus
Stroke
Other COVID-19 pandemic-related outcomes
Lower respiratory infections
Interpersonal violence
Road injuries
Congenital birth defects
Central Latin America
COVID-19
Ischaemic heart disease
Diabetes mellitus
Interpersonal violence
Other COVID-19 pandemic-related outcomes
Chronic kidney disease
Neonatal disorders
Road injuries
Low back pain
Stroke
Tropical Latin America
COVID-19
Ischaemic heart disease
Interpersonal violence
Stroke
Diabetes mellitus
Low back pain
Anxiety disorders
Neonatal disorders
Road injuries
Depressive disorders
North Africa and Middle East
COVID-19
Ischaemic heart disease
Neonatal disorders
Stroke
Other COVID-19 pandemic-related outcomes
Congenital birth defects
Road injuries
Diabetes mellitus
Low back pain
Depressive disorders
South Asia
Neonatal disorders
COVID-19
Ischaemic heart disease
COPD
Stroke
Other COVID-19 pandemic-related outcomes
Lower respiratory infections
Diarrhoeal diseases
Tuberculosis
Diabetes mellitus
Southeast Asia, east Asia, and Oceania
Stroke
Ischaemic heart disease
COPD
Tracheal, bronchus, and lung cancer
Diabetes mellitus
Road injuries
COVID-19
Age-related and other hearing loss
Low back pain
Neonatal disorders
East Asia
Stroke
Ischaemic heart disease
COPD
Tracheal, bronchus, and lung cancer
Road injuries
Age-related and other hearing loss
Diabetes mellitus
Low back pain
Stomach cancer
Alzheimer's disease and other dementias
Oceania
Lower respiratory infections
Neonatal disorders
Other COVID-19 pandemic-related outcomes
COVID-19
Ischaemic heart disease
Diabetes mellitus
Stroke
Congenital birth defects
Diarrhoeal diseases
COPD
Southeast Asia
Stroke
COVID-19
Ischaemic heart disease
Neonatal disorders
Other COVID-19 pandemic-related outcomes
Diabetes mellitus
Road injuries
Lower respiratory infections
Cirrhosis and other chronic liver diseases
Tuberculosis
Sub-Saharan Africa
Neonatal disorders
Malaria
COVID-19
Lower respiratory infections
Diarrhoeal diseases
HIV/AIDS
Other COVID-19 pandemic-related outcomes
Congenital birth defects
Tuberculosis
Stroke
Central sub-Saharan Africa
Neonatal disorders
Malaria
COVID-19
Tuberculosis
Road injuries
Lower respiratory infections
Other COVID-19 pandemic-related outcomes
HIV/AIDS
Diarrhoeal diseases
Congenital birth defects
Eastern sub-Saharan Africa
Neonatal disorders
COVID-19
HIV/AIDS
Malaria
Diarrhoeal diseases
Lower respiratory infections
Other COVID-19 pandemic-related outcomes
Tuberculosis
Congenital birth defects
Stroke
Southern sub-Saharan Africa
HIV/AIDS
COVID-19
Neonatal disorders
Other COVID-19 pandemic-related outcomes
Lower respiratory infections
Tuberculosis
Road injuries
Interpersonal violence
Diarrhoeal diseases
Stroke
Western sub-Saharan Africa
Neonatal disorders
Malaria
Lower respiratory infections
Diarrhoeal diseases
COVID-19
Congenital birth defects
Other COVID-19 pandemic-related outcomes
HIV/AIDS
Stroke
Meningitis
Annualised rate of change, 2010–21
<–5·3%
–5·3% to <–3·7%
–3·7% to <–1·9%
–1·9% to <–0·8%
–0·8% to <0%
0% to <0·6%
0·6% to <1·1%
1·1% to <1·9%
1·9% to <4·9%
≥4·9%

(3137·8 [2912·4 to 3360·9] per 100 000). The largest changes in age-standardised DALY rates for ischaemic heart disease between 2010 and 2021 ranged from a decrease of 1·4% (–6·5 to 8·6) in low SDI locations to a decrease of 26·0% (20·6 to 31·3) in high-middle SDI locations. The age-standardised rate of DALYs due to low back pain was highest in the high SDI quintile (1094·3 [792·2 to 1459·2] per 100 000) and was lowest in the middle SDI quintile (717·5 [512·8 to 962·4] per 100 000). However, the age-standardised DALY rate due to stroke was lowest in high SDI locations (730·5 [665·3 to 786·6] per 100 000) and highest in low SDI locations (2462·9 [2203·8 to 2735·2] per 100 000). The smallest change in age-standardised DALY rates due to stroke was estimated to be for low SDI locations (decrease of 9·6% [2·5 to 15·8]), whereas the largest decrease was estimated to be for high-middle SDI locations (26·0% [20·6 to 31·3]).

For eight of 21 GBD regions, the leading cause of burden was COVID-19 (figure 4). However, COVID-19 did not feature within the top ten leading Level 3 causes of DALYs in Australasia, high-income Asia Pacific, or east Asia in 2021. The annualised rate of change for number of DALYs between 2010 and 2021 was largest for drug use disorders in high-income North America (6·5% [6·0–7·1]) and diabetes in eastern Europe (5·5% [4·9–6·2]).

The leading Level 3 causes of age-standardised DALY rates by location in 2021 are shown in figure 5 (the equivalent map for 2020, and for 2020 by sex, are in appendix 2 [figures S3, S4, S5, S6, S7]). COVID-19 was the leading cause of age-standardised DALY rates in 95 (47%) of 204 countries and territories. Despite the large burden from COVID-19 in these locations—including many in the super-region of sub-Saharan Africa—neonatal disorders, diarrhoeal diseases, malaria, or HIV/AIDS persisted as the leading Level 3 causes of burden in 17 countries and territories in sub-Saharan Africa. Ischaemic heart disease continued to be the leading cause of burden in nine countries and territories in north Africa and the Middle East, five countries and territories in western Europe, and six countries and territories in central Asia. Low back pain was the most burdensome cause in Canada (in high-income North America), and all locations in Australasia. Stroke was the most burdensome cause in all locations in east Asia.

Trends in HALE by location and year

We estimated global HALE at birth of 61·3 years (95% UI 58·6 to 63·6) in 2010, 63·6 years (60·7 to 66·2) in 2019, and 62·2 years (59·4 to 64·7) in 2021 (appendix 2 table S24). HALE at birth increased by 1·4% (0·4 to 2·4) between 2010 and 2021. However, HALE decreased by

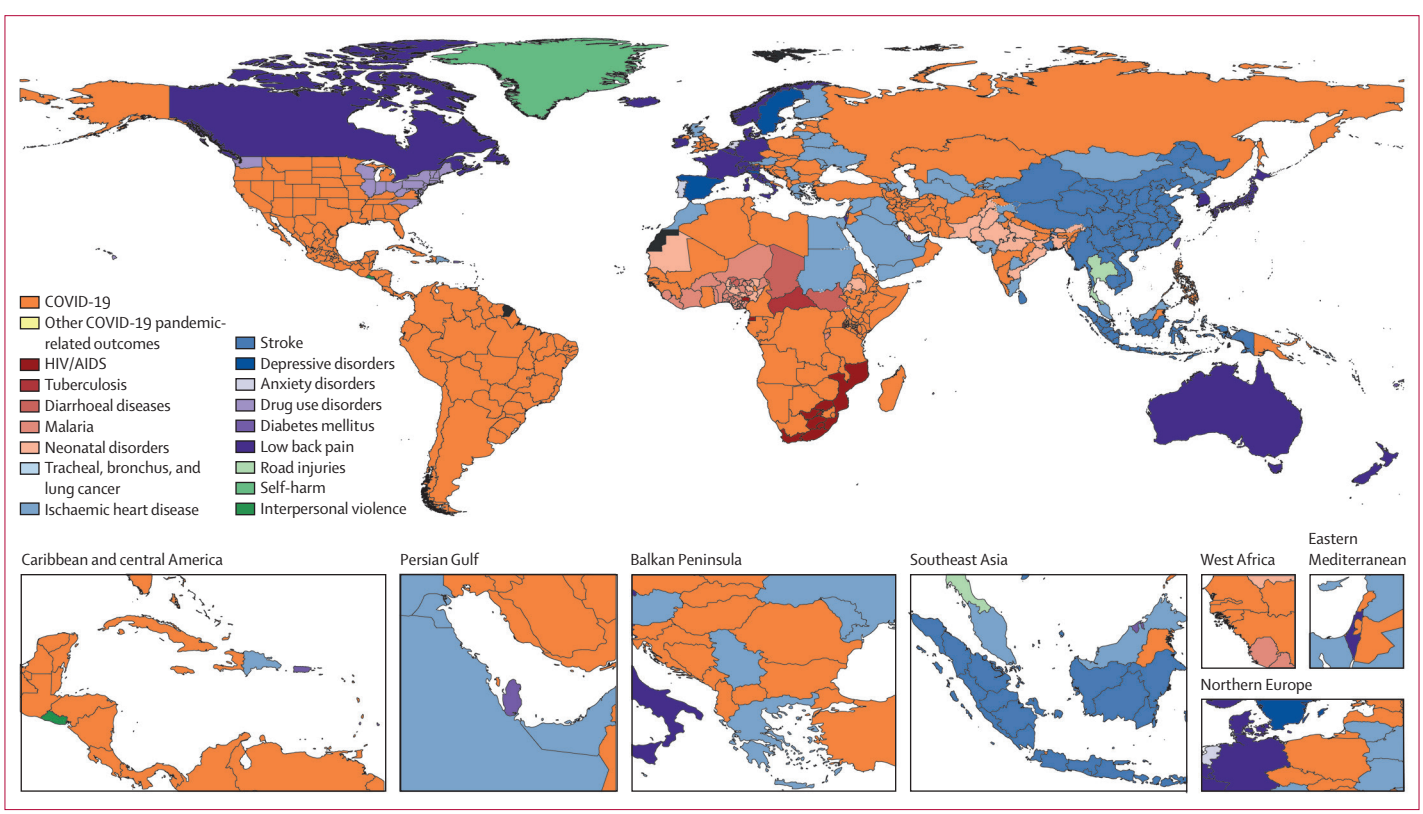


Figure 5: **Leading Level 3 causes of age-standardised DALY rates by location, all ages, both sexes, in 2021**
Dotted lines indicate disputed territories. DALY=disability-adjusted life-year.

2·2% (1·6 to 2·9) between 2019 and 2021. For 2021, we estimated higher HALE at birth in high SDI locations (68·5 years [65·2 to 71·3]) than in low SDI locations (54·4 years [51·6 to 56·7]). We estimated the greatest change in HALE at birth between 2010 and 2021 for low SDI locations (a change of 4·2% [1·9 to 6·0], from 52·2 years [49·6–54·3] in 2010). By comparison, we estimated minimal changes in HALE at birth within high SDI locations between 2010 and 2021 (a change of –0·5% [–0·8 to –0·2], from 68·9 years [65·7 to 71·6] in 2010). We estimated that HALE at birth increased between 2010 and 2021 for 11 of 21 GBD regions, with the largest increases estimated for the Caribbean, where HALE increased by 19·7% (16·5 to 23·3), from 50·4 years (47·9 to 52·6) in 2010 to 60·4 years (57·4 to 63·0) in 2021. We also found that HALE at birth decreased between 2010 and 2021 in six of 21 GBD regions. The largest decrease in HALE at birth was observed in Andean Latin America, which decreased by 5·4% (3·8 to 7·0), from 65·9 years (62·8 to 68·3) in 2010 to 62·3 years (59·4 to 64·7) in 2021.

We estimated improvement in HALE at birth in 59 (29%) of 204 countries and territories between 2010 and 2021 (appendix 2 table S24). Among them, there were 30 countries and territories where HALE at birth increased by more than 2 years between 2010 and 2021. Haiti had the largest improvement in HALE at birth (an increase of 90·2% [95% UI 77·1–104·6], from 27·4 years [25·5–29·3] in 2010 to 52·1 years [48·2–55·4] in 2021) due to the Haiti earthquake in 2010 and recovery thereafter. The next largest improvements were observed in Eswatini (an increase of 11·8% [6·2–19·2], from 41·1 years [38·5–43·7] in 2010 to 45·9 years [43·1–48·7]) and Côte d'Ivoire (an increase of 9·7% [5·8–13·5], from 50·0 years [47·4–52·3] in 2010 to 54·9 years [51·8–57·8] in 2021). In 43 countries and territories, we estimated HALE at birth to decrease between 2010 and 2021, and in 21 countries and territories, HALE at birth decreased by more than 2 years between 2010 and 2021. The largest reduction in HALE at birth was observed in Peru (a decrease of 7·4% [5·2–9·8], from 68·0 years [64·6–70·7] in 2010 to 63·0 years [60·1–65·4] in 2021) and Venezuela (a decrease of 6·9% [3·7–10·1], from 65·4 years [62·4–68·0] in 2010 to 60·9 years [57·7–64·0] in 2021).

Discussion

In 2020 and 2021, global health outcomes, as measured by age-standardised DALY rates, worsened for the first time in three decades. From 1990 to 2019, GBD analyses showed consistent and rather encouraging improvements in overall health outcomes at the population level. During this period, achievements by the global health community included reductions in vaccine-preventable deaths and improvements in under-5 mortality rates,[3,17] contributing to the trend of people living longer. However, as a global epidemiological transition occurs wherein the greatest share of disease burden shifts from communicable diseases to non-communicable diseases, populations are living longer but in poorer health. GBD 2021 reports a new global trend: the global number of DALYs and age-standardised DALY rates increased in both 2020 and 2021. This is a setback from the gains in overall human health at the global population level over the past three decades, and the evidence suggests that the COVID-19 pandemic was the inflection point for the reversal in progress. GBD 2021 quantified the health impacts of COVID-19 during some of the worst phases of the pandemic. Estimates of health loss caused by the COVID-19 pandemic provide the global health community—researchers, practitioners, and policy makers—with comprehensive health metrics about the immediate and long-term health needs of the populations most affected. The shared knowledge base provided by GBD 2021 can help stakeholders at all levels of responsibility—from multilateral agencies and national governments to local organisations—identify systemic inefficiencies that must be addressed in preparation for future pandemics and other global health crises.[22] DALYs are a useful metric to understand the effects of the COVID-19 pandemic on population health because they capture overall disease burden by measuring how diseases and injuries reduce years of healthy living. The estimation of DALYs up to 2021 also provides an important new benchmark for evaluating progress towards Sustainable Development Goal 2030 targets. GBD 2021 presents new opportunities for mutual understanding and accountability by countries and territories in their responses to the health inequalities persisting in their populations.

Important trends

The profound impact of the COVID-19 pandemic affected population health at the global level, the reverberations of which continue to be detected through population-level scientific studies.[16,23–26] GBD 2021 found that the burden of COVID-19, as measured by DALYs, increased between 2020 and 2021. In 2020, the global all-age incidence of COVID-19 was 1·63 billion (95% UI 1·55–1·69) cases, equivalent to an age-standardised incidence rate of 20 819·8 (19 908·0–21 681·5) cases per 100 000. Global COVID-19 incidence increased to 2·28 billion (2·18–2·37) in 2021, equivalent to an age-standardised incidence rate of 28 955·3 (27 708·3–30 143·2) per 100 000. The distribution of DALYs due to COVID-19 was mostly driven by deaths and YLLs (as opposed to YLDs). Although in 2021 males and females had similar COVID-19 incidence rates, the age-standardised DALY rates for males were higher than for females. We found that, in addition to the sex disparities, both COVID-19 incidence and DALY rates were higher in low SDI locations than in high SDI locations. DALYs from other COVID-19 pandemic-related outcomes followed similar trends as DALYs due to COVID-19, in that they were higher in males than in females and highest in the low SDI quintile.

When shifting our focus from burden imposed directly by COVID-19 to the secondary impacts of the pandemic, other trends emerged. In the cases of both long COVID (data not shown) and depressive and anxiety disorders, the burden was driven by YLDs in 2020 and 2021 and was greater in females than males. The health consequences of the pandemic were unevenly distributed across demographic groups and geographical locations, which exacerbated existing socioeconomic inequities.[27] Government responses to the health-care challenges presented by the COVID-19 pandemic were varied, and susceptible populations were most affected as a result. The delivery of care and services—whether basic and routine care like vaccinations or immediate COVID-19 medical aid—was hampered.[28] Our estimation of burden for COVID-19 accounted for the roll-out of COVID-19 vaccines across countries and territories in 2021. Due to use of face masks, physical distancing, and other non-pharmaceutical interventions deployed during the COVID-19 pandemic, we found evidence that the burden of some other infectious diseases (eg, influenza and respiratory syncytial virus) in some locations was reduced, the effects of which were incorporated into our excess mortality estimations.[23] Locations with strained and under-resourced health systems faced overwhelming structural challenges in securing swift and sufficient supplies of vaccine, which compromised vaccine delivery to high-risk populations,[29] and further affected progress in responding to the burden imposed by the pandemic in under-resourced locations in 2021.[25]

As the pandemic recedes and COVID-19 becomes an endemic disease, a new global health landscape is becoming visible. In addition to COVID-19, six CMNN diseases were in the top 25 leading Level 3 causes of DALYs globally in 2021 (neonatal disorders, lower respiratory infections, diarrhoeal diseases, malaria, tuberculosis, and HIV/AIDS). DALY counts for each of these causes had decreased since 2010, with reductions in age-standardised DALY rates between 2010 and 2021 ranging from a decrease of 17·1% (95% UI 4·9 to 25·9) for neonatal disorders to a decrease of 47·8% (43·3 to 51·7) for HIV/AIDS. As anticipated with the global epidemiological transition,[3,17] the decrease in burden from CMNN diseases between 2010 and 2021 was largely driven by a decrease in age-standardised YLL rates (which decreased by 15·1% [6·7 to 22·2]) rather than YLD rates (which decreased by 4·5% [–3·6 to 20·7], appendix 2 tables S26, S27). The progress on reducing the burden of CMNN diseases must preserve momentum, particularly across low SDI locations. Neonatal disorders remained the third-leading cause of DALYs worldwide in 2021 and was in the top three leading causes of DALYs in 69 of 204 countries and territories. While the global community made progress in curtailing deaths and YLLs from neonatal disorders between 2010 and 2021 (19·5% [7·0 to 29·5] reduction in age-standardised YLL rates between 2010 and 2021),[3] many still experience the non-fatal health consequences of neonatal disorders throughout their lifespan. The age-standardised DALY rates of diarrhoeal diseases decreased by 47·0% (39·9 to 52·9) between 2010 in 2021 due primarily to progress in the management of its risk factors among children younger than 5 years.[30] However, the decrease in burden of diarrhoeal diseases was not evenly distributed across SDI locations or groups aged 5 years and older and remained one of the top ten leading causes of DALYs in 50 countries and territories in 2021. As with diarrhoeal diseases, the global burden of HIV/AIDS also decreased. Increasing treatment coverage and preventive strategies, particularly advances in antiretroviral therapy and the implementation of treatment-as-prevention programmes,[31] reduced HIV/AIDS burden globally in 2021. In 2021, however, HIV/AIDS remained in the top ten leading causes of DALYs in 39 countries and territories and was the leading cause of DALYs in Congo (Brazzaville), Equatorial Guinea, Djibouti, Malawi, Mozambique, Zambia, Botswana, Eswatini, Lesotho, and South Africa. Global treatment coverage is not increasing at a sufficient rate to meet the joint UNAIDS targets to globally diagnose 95% of people living with HIV, provide treatment to 95% of people diagnosed, and achieve viral suppression in 95% of people on treatment by 2030.[32] Progress to slow down transmission, increase treatment rates, and prevent HIV-related deaths is urgently required.

Between 2010 and 2021, DALYs from non-communicable diseases increased by 17·6% (95% UI 13·8 to 21·0) due to the ageing and growing global population,[17] with only a moderate improvement in corresponding age-standardised DALY rates (decrease of 6·4% [3·5 to 9·5] between 2010 and 2021; appendix 2 table S25). The non-communicable disease burden was distributed widely across the world's populations, irrespective of age, sex, or socioeconomic circumstance, which presents both immediate and long-term challenges to health-care systems.[16,33,34] Cardiovascular diseases—notably, Level 3 causes including ischaemic heart disease and stroke—were in the top five leading sources of global DALYs in 190 countries and territories in 2021. Changes in age-standardised DALY rates from 2010 to 2021 for stroke ranged from decreases of 9·6% (2·5 to 15·8) in low SDI locations to decreases of 24·9% (17·3 to 31·7) in high-middle SDI locations, whereas for ischaemic heart disease changes in age-standardised DALY rates ranged from a decrease of 1·4% (–6·5 to 8·6) in low SDI locations to a decrease of 26·0% (20·6 to 31·3) in high-middle SDI locations. Ischaemic heart disease and stroke share many modifiable risk factors and opportunities for intervention. The increasing global burden from diabetes between 2010 and 2021, alongside established risk factors for cardiovascular diseases (eg, high blood pressure, high cholesterol, high BMI, kidney dysfunction, ambient and household air pollution, physical inactivity, and tobacco use) are known contributors to stagnating progress on reducing the burden from cardiovascular diseases.[35]

Intervention strategies targeting modifiable risks, especially approaches with demonstrated success, such as tobacco control and blood pressure-lowering and cholesterol-lowering strategies,[35] will help reduce the overall burden of non-communicable diseases. In addition to prevention through the management of risk factors, the negative health effects of cardiovascular disease can be mitigated through timely intervention for acute events and surgical procedures. However, geographical disparities between high-income countries and low-income and middle-income countries in access to and quality of cardiac surgical care must be addressed,[36,37] which would help populations for whom the burden of cardiovascular diseases is greatest receive the necessary care and treatment.

We estimated that 31·3% (95% UI 25·4–37·5) of global DALYs in 2021 were due to YLDs. The leading contributors of global YLDs were non-communicable diseases: low back pain, depressive disorders, and headache disorders. Low back pain was the largest contributor of global all-cause YLDs in 2021, with a decrease in the age-standardised YLD rate of only 2·4% (1·8–2·9) since 2010. Globally, prevalent cases and YLDs from low back pain increased with age—peaking in the 85–89 year age group—presenting huge challenges to countries with ageing populations.[38] Clinical guidelines for treatment and prevention include education, self-care, physical therapy, medication, non-surgical treatments, and surgery.[39,40] Not only are some of these treatment options costly, but also, when used in isolation, rarely address the complex nature of low back pain. A holistic approach to the burden imposed by low back pain, addressing its biological, social, and psychological components, with further research into the efficacy of diagnostic and preventive options, would advance our ability to manage this considerable source of disability worldwide.

The efficacy and cost-effectiveness of treatment options for depressive disorders across low-income, middle-income, and high-income settings have been established by existing research.[16] These include the use of self-care (eg, web-based therapy), primary care, and community outreach programmes to deliver psychological and pharmacological interventions, hospital care, and specialist services.[41] Although mental health interventions are effective and cost-effective, and public opinions regarding the benefits of seeking treatment for mental disorders are becoming more supportive, we estimated there were 332 million (95% UI 298–376) cases of depressive disorders globally in 2021. Cases were distributed across the entire lifespan but were most common among females between age groups 15–19 years and 60–64 years. In many instances, depressive disorders are rarely detected at their onset, and only a small proportion of individuals receive the evidence-based treatment packages considered to be minimally adequate.[34,41] This is also the case for other disabling and burdensome mental disorders, such as anxiety disorders and schizophrenia, and substance use disorders. The findings of GBD 2021 underline the need for an enhanced response to address mental and substance use disorders through expanded financial commitments and improved service quality and access. The need to intensify our efforts to minimise the negative health consequences of mental and substance use disorders is urgent in the wake of shock events, like the COVID-19 pandemic, natural disasters, and military conflicts.[16] Additionally, many mental disorders are prevalent during childhood or early adulthood, when other risk factors such as bullying victimisation and childhood maltreatment can occur.[16,42] Early interventions with population-based prevention strategies targeting these risk factors and promoting the social and emotional development of younger populations will lead to positive outcomes. Interventions that can address the increasing burden of drug use disorders are also urgently required, particularly for opioid use disorders. Opioid substitution therapy can decrease opioid use and health risks involved with injecting drugs. The effects of an opioid overdose can be reversed with use of the opioid antagonist naloxone, the availability of which ought to be expanded alongside training on safe and effective administration for pharmacists, health-care providers, individuals at risk of opioid overdose, their family members, and social service agencies that work with substance users.[43]

Approximately 2·81 billion (95% UI 2·60 to 3·03) individuals had migraine or tension-type headache in 2021, with females aged 15–49 years being most affected. Interventions targeting the management of symptoms exist, but we found no sign of improvement in the burden of these disorders between 2010 and 2021 (with a 0·3% [–1·1 to 1·4] increase in age-standardised YLD rates). In addition to opportunities to scale up treatment strategies, more work is required to establish the modifiable risk factors of headache disorders.[44]

Among the leading 25 causes of YLDs, we observed the largest increase in global age-standardised YLD rates for diabetes between 2010 and 2021 (25·9% [95% UI 24·0–28·1]). An increase in the age-standardised rate was evident in all 204 countries and territories between 2010 and 2021. This increase in age-standardised YLD rates for diabetes was largely driven by type 2 diabetes and the increasing rates of obesity globally. Type 2 diabetes is preventable and, in some instances, reversible with early detection and adequate care.[33,45,46] GBD 2021 estimates that 525 million (490–565) people had diabetes in 2021; however, without global intervention, a separate GBD 2021 analysis has forecast that more than 1·31 billion people worldwide will have diabetes by 2050.[33] Any coordinated response to the escalating burden of diabetes must target the underlying causes of obesity and help remove the social and logistical barriers to accessing care and services.

The overall burden imposed by injuries was driven by deaths and YLLs, both of which decreased between 2010 and 2021. Reductions in the burden of injuries were not

distributed equally across time, sex, and location. The travel restrictions and physical distancing measures implemented in some countries and territories to control the spread of SARS-CoV-2 during the COVID-19 pandemic might have contributed to small decreases in road accidents in 2020 and 2021; however, data and evidence on this have been inconsistent.[3] Our estimates indicated that most of the health gains from injuries occurred between 2010 and 2019 as opposed to between 2019 and 2021. Burden from injuries was highest in low SDI locations, where exposure to forces of nature (ie, natural disasters) increased the burden due to injuries in 2010 for both males and females. Despite this, males aged 15–49 years in low SDI locations had similar DALY rates from injuries in 2021 as they did in 2010. The leading injuries among males aged 15–49 years in the low SDI quintile in 2021 were road injuries, conflict and terrorism, and interpersonal violence (data not shown). Males were more affected by these injuries than their female counterparts, for whom we saw a substantial decrease in burden from injuries in the same period (decrease of 45·8% [40·9–50·1] since 2010; data not shown). Although populations in many countries and territories are living safer and longer lives, more effort is required to reach those same standards for many others, especially those living in low SDI locations.

Globally, HALE at birth improved from 61·3 years (95% UI 58·6–63·6) in 2010 to 62·2 years (59·4–64·7) in 2021. GBD 2021 provides an important baseline from which we can track the extent to which life expectancies rebound and progress in HALE accelerates after 2021. Between 2010 and 2021, we observed improvements in HALE at birth in 59 countries and territories, with people living in low SDI locations having larger gains than those living in high SDI locations. Faster progress in the sociodemographic circumstances in low SDI locations resulted in larger gains in life expectancy and HALE at birth between 2010 and 2021.

Limitations

GBD estimates of health and health loss evolve across cycles because of the addition of new data, important improvements made to the burden estimation pipeline, and instability in datasets and processes, which we try to minimise wherever possible. Inconsistencies in the availability of primary epidemiological data remain a limitation and source of instability within GBD analyses. Our estimates depend on the out-of-sample predictive validity of modelling processes in cases where data are insufficient to produce burden estimates for all 204 countries and territories (by year, sex, and age). Although this approach cannot fully replace high quality primary data, it ensures that populations or causes with no or little data are not excluded from important benchmarking exercises intended for burden estimation. With any given GBD release, there might be extant data not identified or incorporated, which is a key part of the rationale for ongoing cycles of releases, rather than a single update. For the primary data available, our data processing methods account for known sources of variation wherever possible, but fully disentangling variation in our estimates is not always possible due to measurement error and reporting inaccuracies. There are problems with the quality and collection of primary data, such as flawed methodologies and potential under-reporting of illnesses, which is a recurring limitation for GBD that can be continually improved on by strengthening data-collection systems. Our identification of reference and alternative case definitions for epidemiological data undergoing bias correction can further inform survey design in future data collection efforts. Our estimation of 95% UIs is also an area requiring further improvement. Our analyses are intended to capture uncertainty from a range of data types and processes (eg, from stochastic variation in input data, age–sex splitting, bias corrections, and other data manipulations or statistical approaches), but it is difficult to capture all sources of uncertainty across the entire burden estimation pipeline.

Our estimation of YLDs is restricted by several factors. Due to data sparsity, severity distributions do not capture variation by access to treatments for major causes contributing to YLDs. The development of new approaches to model changes in severity by health-care access for depressive and anxiety disorders is underway and could provide a solution to this issue in future GBD cycles.[47] The quality and accuracy of comorbidity corrections also requires improvement. Our comorbidity correction adjusted for the difference between the average disability weight for one sequela and the multiplicatively combined disability weight for multiple sequelae (ie, independent comorbidity). This approach underestimates the comorbidity between sequelae especially for causes (eg, mental disorders) where the comorbidity distribution is reliant on the range of disorders experienced. Limitations related to our estimation of YLLs are discussed in detail elsewhere.[3]

The estimation of DALYs for specific diseases and injuries also has distinct limitations, and these are presented in greater detail in appendix 1 (section 8) and topic-specific publications. Notably, for GBD 2021, challenges associated with collecting data and modelling a novel disease like COVID-19 were present. Modelling COVID-19, long COVID, and other COVID-19 pandemic-related outcomes presented analytical challenges for a range of reasons. First, data on COVID-19 outcomes (eg, cases, deaths, hospital admissions, and seroprevalence) were of highly variable quality and completeness, which required novel methods for standardisation.[23,25,26] Second, approaches for estimating excess mortality, which were used to estimate the extent of other COVID-19 pandemic-related mortality, can produce quite divergent results in some locations.[17] Third, we found considerable

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heterogeneity in case definition and instrumentation used to measure long COVID. We concentrated on estimates for three major symptom clusters associated with long-term health loss from COVID-19 because these would not be captured by GBD cause estimates. Cohort data suggest that these three clusters capture the most severe outcomes reported at 3 months or longer after initial infection but are not a complete capture of all long COVID symptoms.[24] However, we had limited ability in GBD 2021 to capture the specific indirect effects of COVID-19, both in modelling fatal and non-fatal outcome estimations. In future analyses, the combined effect of changing virus variants, vaccinations, and past infection on the occurrence of long COVID will need to be evaluated. Due to sparsity of data from long COVID follow-up studies, particularly from low-income and middle-income settings, we were unable to fully assess variation in the occurrence, severity, or duration of long COVID between locations. As more data become available from the pandemic era, the ability to more fully and specifically estimate the indirect effect of the COVID-19 pandemic across many causes is likely to improve. Work to address these limitations in future data collection efforts is in development and will be incorporated into future iterations of GBD.[24]

Future directions

Efforts by GBD research teams to include new causes and locations, secure new epidemiological data, more precisely correct for measurement error, and capture uncertainty within burden estimates are ongoing areas of priority. Because forecasts of future health trends are of great value to policy makers, forecasting the burden of disease under reference and alternative risk exposure scenarios is another ongoing area of high priority. There also remains a need to analyse the long-term effects of COVID-19 and develop tools and analytical frameworks that can measure the hidden burden of the pandemic. Developing and refining analytical tools to better understand the extent of the burden imposed by COVID-19 will also assist pandemic planning and preparedness. More streamlined incorporation of location-level covariates capturing the effect of the pandemic is being tested within our cause of death and prevalence modelling for the next GBD cycle. The use of DisMod-AT, an updated version of DisMod-MR, to estimate prevalence is also proceeding for several causes. We expect DisMod-AT to produce more accurate trends over age and time within our prevalence estimates, including the integration of the effect of population shock events. We also expect to incorporate severity distributions by health-care access for several causes in the next GBD cycle and continue work to eventually produce dependent comorbidity corrections. Our burden estimation processes are constantly evolving to provide the most comprehensive and accurate information to stakeholders. However, areas of innovation and methods development also need to be staggered to allow us to respond to emerging trends and the ever-evolving public health landscape.

Conclusion

In 2020 and 2021, the global all-cause burden of disease increased for the first time in three decades. This reversal in progress was due to three main factors: (1) the direct health impacts of COVID-19; (2) the indirect health consequences of COVID-19 and the pandemic, such as the effect on mental disorders; and (3) fallout from overburdened health service systems and uncoordinated policy responses to the COVID-19 pandemic. The effect of the pandemic, as measured by DALYs, was unevenly distributed by age, sex, and location, exacerbating many existing inequalities. As the world starts to recover, continuing gains for other CMNN diseases must not stall. Urgent priority needs to be given to prevalent and disabling non-communicable diseases that have seen insufficient or no improvement despite several calls to action—notably, cardiovascular diseases, musculoskeletal disorders (ie, low back pain), and mental disorders. Ultimately, GBD 2021 results illustrate the need for our global community to come together in a multidisciplinary and coordinated response to deliver not just better survival rates, but healthier and safer outcomes for our ever growing and ageing population.

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Please see appendix 1 section 8 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.

Declaration of interests

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Data sharing

To download the data used in these analyses, please visit the GBD 2021 Sources Tool. The statistical code used in GBD 2021 is available online.

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

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

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