Global, regional, and national characteristics of the main causes of increased disease burden due to the covid-19 pandemic: time-series modelling analysis of global burden of disease study 2021

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ABSTRACT

OBJECTIVE

To quantify and identify the main causes of increased disease burden due to coronavirus disease 2019 (covid-19) pandemic.

DESIGN

Time-series modelling study.

DATA SOURCE

Global Burden of Disease Study 2021.

MAIN OUTCOME MEASURES

Absolute and relative rate differences were calculated, along with their 95% confidence intervals (95% CIs), between the observed and expected rates for 174 causes of increases in incidence, prevalence, disability adjusted life years (DALYs) and deaths in 2020-2021. A statistically significant increase was indicated if the 95% CIs of the rate differences were above 0.

RESULTS

Globally, the rate of age standardised DALYs increased in absolute difference per 100 000 and relative rate difference by 97.9 (95% CI 46.9 to 148.9) and 12.2% (95% CI 5.8% to 18.5%) for malaria, 83.0 (79.2 to 86.8) and 12.2% (11.7% to 12.8%) for depressive disorders, and 73.8 (72.2 to 75.4) and 14.3% (14.0% to 14.7%) for anxiety disorders, which were prominent and statistically significant, followed by stroke, tuberculosis, and ischaemic heart disease. Additionally, the age standardised incidence and prevalence per 100 000 significantly increased for depressive disorders (618.0 (95% CI 589.3 to 646.8) and 414.2 (394.6 to 433.9)) and anxiety disorders (102.4 (101.3 to 103.6) and 628.1 (614.5 to 641.7)), as well as notable rises in age standardised prevalence for ischaemic heart disease (11.3 (5.8 to 16.7)) and stroke (3.0 (1.1 to 4.8)). Furthermore, age standardised mortality due to malaria significantly increased (1.3 (0.5 to 2.1) per 100 000). Depressive and anxiety disorders were the most predominant causes of increased DALY burden globally, especially among females; while malaria had the most severe increased DALY burden in the African region, typically affecting children younger than five years; and stroke and ischaemic heart disease in the European region and in individuals aged 70 and older.

CONCLUSION

The covid-19 pandemic significantly increased the burden of several non-covid conditions, particularly mental health disorders, malaria in young children in the African region, and stroke and ischaemic heart disease in older adults, with notable disparities across age and sex. These findings underscore the urgent need to strengthen health system resilience, enhance integrated surveillance, and adopt syndemic-informed strategies to support equitable preparedness for future public health emergencies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Throughout the covid-19 pandemic, numerous healthcare services faced severe disruptions, which hindered efforts to prevent and control the disease burden from various causes

A comprehensive and systematic quantitative assessment of the covid-19 pandemic's impact on the disease burden of other causes is still needed

WHAT THIS STUDY ADDS

The impact of the covid-19 pandemic on global disease burden of 174 causes in 2020-2021 was systematically quantified and main causes with increased burden were identified

Globally, the burden of depressive and anxiety disorders, as well as malaria in children in the African region, and stroke and ischaemic heart disease in older adults most notably increased during the pandemic compared with other causes

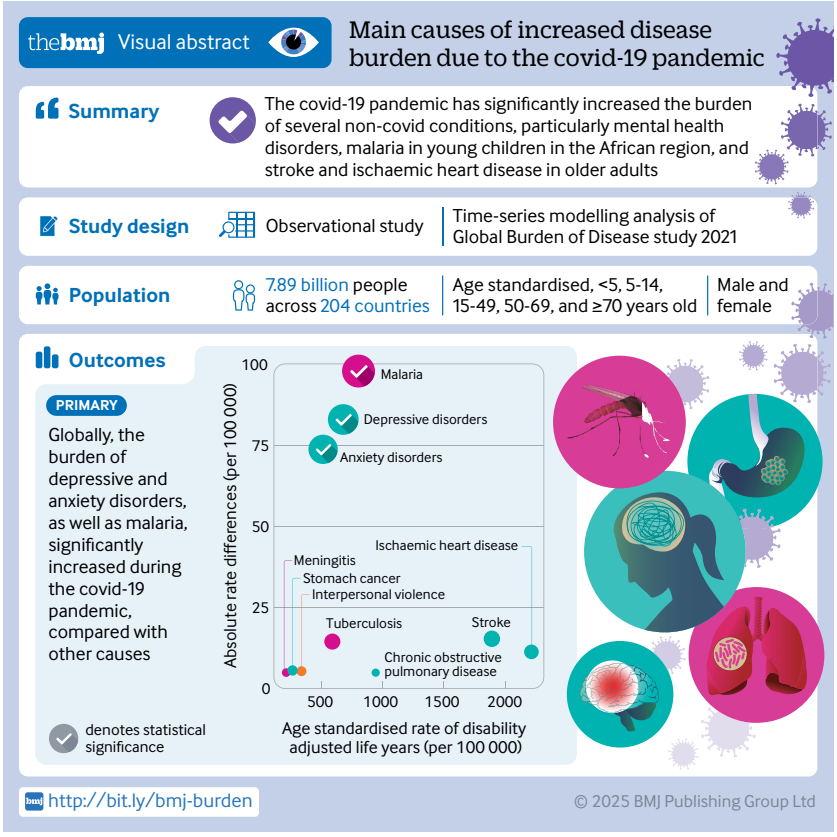
Introduction

In the early 2020, coronavirus disease 2019 (covid-19) swiftly triggered a global pandemic, causing profound harm to the global public health and socioeconomic landscape.[1] Declared a public health emergency of international concern by the World Health Organization in 2020,[2] the covid-19 disease has caused substantial damage to human health, including immune system impairment, increased susceptibility to infections, systemic inflammation, and long term sequelae.[3 4] An estimated 15.9 million (95% uncertainty intervals 14.7-17.2) people worldwide died from the covid-19 pandemic in 2020 and 2021, leading to a global average reduction in life expectancy of 1.6 years. Additionally, mortality among individuals aged 15 years and older increased by 22% for males and 17% for females.[5]

Additionally, the rapid surge in covid-19 cases, particularly severe cases and fatalities, resulted in widespread shortages of medical resources in many countries.[6 7] Most healthcare services were severely affected during the pandemic, leading to interruptions in many diseases prevention and control, such as

delays in case detection and diagnosis, treatment interruptions, and disruptions to routine childhood vaccination coverage.[8-10] This situation had an important impact on the burden of various causes, including communicable, maternal, neonatal, and nutritional diseases; non-communicable diseases; and injuries. According to WHO, if health service disruptions resulted in a 25-50% decrease in the identification and management of tuberculosis cases over a three month period during the covid-19 pandemic, worldwide tuberculosis deaths could increase by around 0.2-0.4 million.[11] Notably, the pandemic has also led to interruptions in the identification and management of neglected tropical diseases because of reduced financial support and staffing.[12] In 2020, a substantial increase in cases of anxiety and depression was observed, potentially linked to the covid-19 pandemic and the associated containment measures.[13] Estimates suggest that, during the pandemic period, neonatal and maternal fatalities increased globally due to overwhelmed and disrupted healthcare services.[14] In the United States, the pandemic resulted in a large increase in injury related mortality among young individuals.[15] Moreover, incidents of self-harm and interpersonal violence were also reported to have surged during the lockdown in India.[16]

While the direct impact of covid-19 on human health is well established, a scarcity of systematic research and evaluation regarding the pandemic's effect on other causes of disease burden remain scarce. Addressing these gaps is crucial for understanding the broader health impacts of the pandemic, helping to manage causes particularly susceptible to increased burdens and improving public health security in future equitable events or other public health emergencies.[5 17] Based on the Global Burden of Disease Study 2021 (GBD 2021),[18-20] we collected data for the burden of 174 causes from 1990 to 2021. We developed time-series models to simulate the disease burden of those causes in 2020 and 2021 under a scenario without covid-19, across various regions, age groups, and sexes. This method allowed us to quantify the impact of the covid-19 pandemic on the disease burden of other causes.



Methods

Overview

This study analysed 174 causes of disease burden (all level 3 causes in GBD 2021) for which data were available from 1990-2021, excluding covid-19 disease. Level 3 causes were chosen due to their balance between clinical specificity and data completeness, and because they are widely used for cross-national comparison and burden estimation. These causes are also considered the most stable and relevant to policy for comparative assessment across countries and over time. Covid-19 disease was excluded by design because our objective was to assess the indirect impacts of the pandemic on other causes. Rare conditions or causes with incomplete or inconsistent time-series data across countries were excluded, either because they were not available or not reported at the level 3 resolution in the GBD 2021 database. A complete list of the included level 3 causes is provided in supplementary table 1. Additionally, supplementary table 2 provides definitions and explanations of key academic terms used in this study to help non-specialist readers to better understand the content.

We used time-series models, including the autoregressive integrated moving average (ARIMA) model and the ARIMA-long short-term memory (ARIMA-LSTM) hybrid model, to analyse the incidence, prevalence, disability adjusted life years (DALYs), and deaths for 174 causes of disease burden in 2020 and 2021. We calculated the average absolute and relative rate differences and their 95% confidence intervals (95% CIs) between the observed and expected rates for 2020-2021 to quantify the impact of the pandemic. This helped to identify the main causes with increases in incidence, prevalence, DALYs, and deaths compared with scenario in which the covid-19 pandemic did not happen in 2020-2021.

Data sources

We obtained data for the incidence, prevalence, DALYs, and deaths for 174 causes, which included annual cases, rates, and age standardised rates of incidence, prevalence, disability adjusted life years, and deaths, along with their 95% uncertainty interval, by age and sex across 204 countries and territories (hereafter countries) from 1990 to 2021. We obtained these data from the Global Health Data Exchange query

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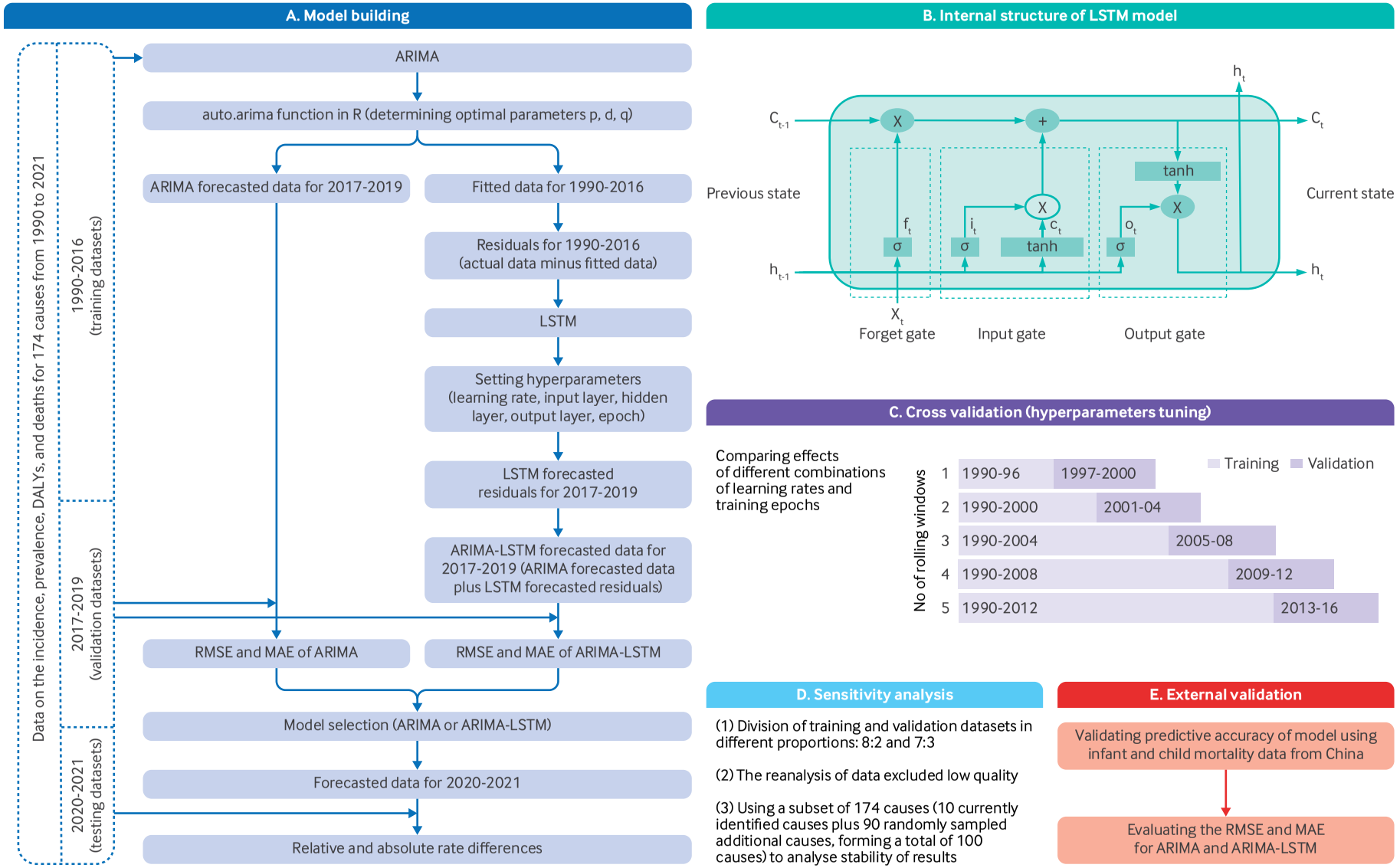

Fig 1 | Overview of the analytical pipeline for model development and evaluation. ARIMA=autoregressive integrated moving average model; LSTM=long short-term memory (ARIMA-LSTM); MAE=mean absolute error; RMSE=root mean squared error

tool (https://vizhub.healthdata.org/gbd-results).[18-20] The countries were further categorised into six WHO regions (Western Pacific Region, South-East Asia Region, Region of the Americas, European Region, Eastern Mediterranean Region, and African Region). We categorised age into five groups (<5, 5-14, 15-49, 50-69, and ≥70 years old).

Models

The ARIMA is a classic time-series predictive model that combines the autoregressive part, integrated part, and moving average part.[21] The LSTM model introduces three types of gates—forget, input, and output gates—which control the flow of information, enhancing the model's predictive effectiveness and accuracy for time-series data.[22] The hybrid ARIMA-LSTM model combines the strengths of ARIMA and LSTM, leveraging their respective advantages. By integrating these methods, this combined model comprehensively captures complex data features, improving modelling predictive accuracy.[23]

Model training and parameter tuning

This study used time-series modelling with historical data. The yearly incidence, prevalence, DALYs, and mortality of each cause from 1990 to 2016 constituted the training dataset. The subsequent period, 2017-2019, was used as the validation dataset to evaluate the predictive performance of the ARIMA and hybrid ARIMA-LSTM models. For the ARIMA model, data from 1990 to 2016 was used to determine optimal parameters (p, d, q) by use of the auto.arima function in R software,[24] followed by forecasting for the years 2017-2019. For the ARIMA-LSTM model, the ARIMA model fitted data from 1990 to 2016 to calculate residuals. Subsequently, the ARIMA model forecasted data for 2017-2019 (Y1), and LSTM predicted residual values for 2017-2019 (Y2). The final prediction of the ARIMA-LSTM model was derived from the sum of Y1 and Y2 (fig 1).[25]

For the LSTM model, we used an expanding window cross-validation strategy on the training dataset (1990-2016) to select hyperparameters and evaluate the potential risk of overfitting.[26] The LSTM model was structured with an input layer and an output layer, both of dimension 1, and a hidden layer containing 32 neurons. We conducted expanding windows validation to optimise the hyperparameters, focusing on the effects of learning rate and training epochs. Specifically, we tested combinations of learning rate (0.01, 0.05) and training epochs (100, 200, 300). The results showed that a learning rate of 0.01 with 200 epochs led the model to reach a local minimum in prediction error, resulting in the smallest root mean squared error and mean absolute error (supplementary table 3).[27] Therefore, the final LSTM model retained a single hidden layer with 32 neurons, a learning rate of 0.01, and 200 epochs.

Model validation, selection, and testing

For each cause, both ARIMA and ARIMA-LSTM models were fitted, and their performance was evaluated using root mean squared error and mean absolute error on the validation dataset (2017-2019). We selected the ARIMA-LSTM model only when it outperformed the ARIMA model on both metrics (the lower root mean squared error and lower mean absolute error); otherwise, we used the ARIMA model. Root mean squared error and mean absolute error values for both the ARIMA and ARIMA-LSTM models, for each cause, were provided in supplementary table 1. Finally, after determining the suitable model (ARIMA or ARIMA-LSTM), we used data from 1990 to 2019 to forecast values for 2020 and 2021 (fig 1). We calculated the average absolute and relative rate differences, along with their 95% CIs, between the observed and expected rates for 2020-2021 to quantify the increases in incidence, prevalence, DALYs, and deaths. We assessed the 95% CIs of the absolute and relative rate differences, with 95% CIs above 0 indicating a statistically significant increased burden.

Additionally, to further validate the model's performance, we used external datasets (infant and child deaths data in China) to validate the predictive accuracy of ARIMA and ARIMA-LSTM models.

Sensitivity analysis

We conducted three types of sensitivity analysis to assess the stability of the results (fig 1). First, we tested different data splits (eg, 8:2 (1990-2013 for training and 2014-2019 for validation) or 7:3 (1990-2010 for training and 2011-2019 for validation)) to evaluate whether the current 9:1 split (1990-2016 for training and 2017-2019 for validation) was appropriate for model selection. Next, we evaluated the impact of excluding low quality data for the primary results based on the study published in *The Lancet*,[28] which provided data quality scores of age standardised mortality within the GBD database for each country and territory on a scale from 0 (worst) to 5 (best). We performed the same time-series predictions and calculated the relative and absolute rate differences, after removing data from countries with the worst data quality, for each cause between the observed and predicted values for 2020-2021, identifying the main causes with an increased burden. Finally, we further assessed the stability of the results by using a subset of 174 causes, which included the 10 currently identified causes and 90 randomly sampled additional causes.

Software

We used Microsoft Excel 2016 for data extraction and storage, and R (version 4.2.1) and Python (version 3.9) for data cleaning, model construction, analysis, and visualisation.

Patient and public involvement

This study was a modelling study and systematic analysis based on data from the Global Burden of Disease Study 2021. Our work relied entirely on

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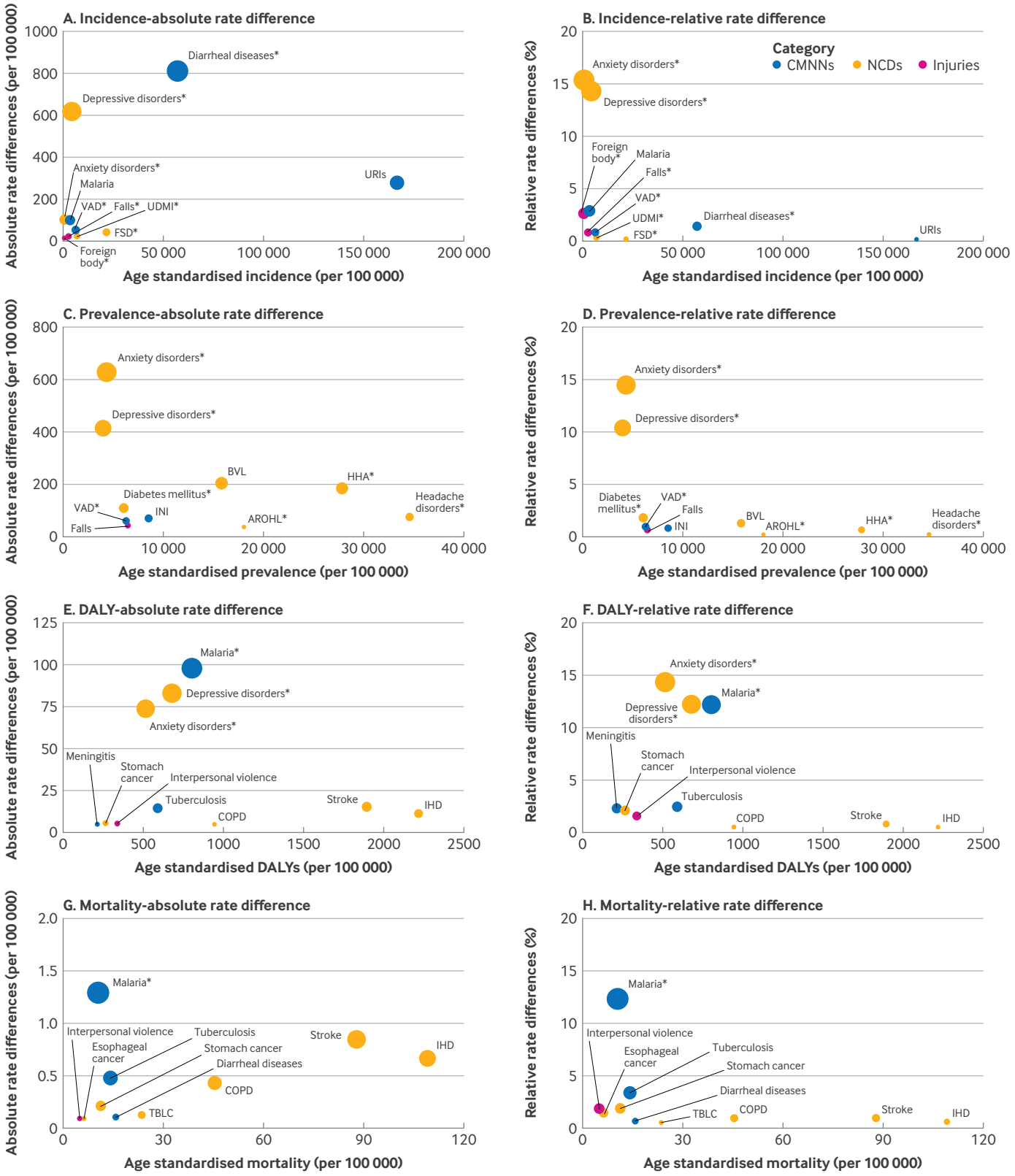

Fig 2 | The global main causes of increased burden during the covid-19 pandemic, by rate difference, standardised by age. (A) Incidence-absolute rate differences; (B) incidence-relative rate differences; (C) prevalence-absolute rate differences; (D) prevalence-relative rate differences; (E) DALYs-absolute rate differences; (F) DALYs-relative rate differences; (G) mortality-absolute rate differences; (H) mortality-relative rate differences. The asterisk (*) denotes statistical significance. AROHL=age related and other hearing loss; BVL=blindness and vision loss; CMNNs=communicable, maternal, neonatal, and nutritional diseases; COPD=chronic obstructive pulmonary disease; DALYs=disability adjusted life years; FSD=fungal skin diseases; HHA=hemoglobinopathies and haemolytic anaemias; IHD=ischaemic heart disease; INI=intestinal nematode infections; NCDs=non-communicable diseases; TBLC=tracheal, bronchus, and lung cancer; UDMI=urinary diseases and male infertility; URIs=upper respiratory infections; VAD=vitamin A deficiency

Fig 3 | Main causes with increased burden by sex, standardised by age. (A) Incidence in women and (B) men; (C) prevalence in women and (D) men; (E) DALYs in women and (F) men; (G) mortality in women and (H) men. The orange lines represent an increase in ranking, while the blue lines indicate either no change or a decrease. DALYs=disability adjusted life years.*Statistical significance

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Fig 4 | Main causes of burden with increased burden by age. (A-E) incidence by age; (F-J) prevalence by age; (K-O) DALYs by age; (P-T) deaths by age; *statistical significance. Alzheimer's disease=Alzheimer's disease and other dementias; Blindness=blindness and vision loss; Cirrhosis=cirrhosis and other chronic liver diseases; COPD=chronic obstructive pulmonary disease; DALYs=disability adjusted life years; Gallbladder disorder=gallbladder and biliary diseases; Haemoglobinopathies=haemoglobinopathies and haemolytic anaemias; Hearing loss=age-related and other hearing loss; Intellectual disability=idiopathic developmental intellectual disability; Malnutrition=protein-energy malnutrition; Nematode infections=intestinal nematode infections; Nutritional deficiencies=other nutritional deficiencies; STIs excluding HIV=sexually transmitted infections excluding HIV; TBLC=tracheal, bronchus, and lung cancer; Trypanosomiasis=African trypanosomiasis; Upper digestive diseases=upper digestive system diseases; URIs=upper respiratory infections; Urinary/infertility=urinary diseases and male infertility

secondary data from the GBD database, which involved neither the diagnosis nor treatment of any specific condition nor any primary data collection or direct interaction with participants. Therefore, no patients or members of the public were involved in formulating the research questions or outcomes, collecting or analysing the data, interpreting the results, or writing the manuscript.

Results

Main causes of increased burden globally

Globally, the top 10 causes with the highest absolute rate differences were identified from 174 causes (fig 2, supplementary figure 1). Significant increases in age standardised rates of incidence, prevalence, and DALYs for depressive and anxiety disorders were observed. The absolute increases in age standardised DALYs and mortality for malaria ranked highest. This indicates that during the 2020-2021 covid-19 pandemic, depressive and anxiety disorders, along with malaria, were most notably affected, with a significant rise in disease burden compared with other causes. Moreover, of the 174 causes analysed, 38 causes showed a significant increase in at least one metric (supplementary table 4).

The absolute age standardised rates of incidence values for depressive and anxiety disorders increased by 618.0 (95% CI 589.3 to 646.8) and 102.4 (101.3 to 103.6) per 100 000, with relative increases of 14.3% and 15.4%, respectively (fig 2A-B and supplementary table 5). The absolute age standardised prevalence values for these disorders rose by 414.2 (394.6 to 433.9) and 628.1 (614.5 to 641.7) per 100 000, with relative increases of 10.4% and 14.5% (fig 2C-D, supplementary table 5). The absolute age standardised DALY values increased by 83.0 (79.2 to 86.8) and 73.8 (72.2 to 75.4) per 100 000, with relative increases of 12.2% and 14.3% (fig 2E-F and supplementary table 5). The absolute increases in age standardised DALYs for malaria were 97.9 (46.9 to 148.9) and for mortality were 1.3 (0.5 to 2.1) per 100 000, with relative increases of 12.2% and 12.3%, respectively (fig 2E-H and supplementary table 5).

Additionally, significant increases in the absolute rate differences of age standardised prevalence per 100 000 were observed for ischaemic heart disease and stroke. Ischaemic heart disease rose by 11.3 (5.8 to 16.7), and stroke by 3.0 (1.1 to 4.8) (supplementary table 4). The burden of both diseases was particularly pronounced among individuals aged 70 years and above, with prevalence at 169.0 (100.8 to 237.1) for ischaemic heart disease and 27.0 (14.4 to 39.6) for stroke.

Main causes of increased burden by sex

The main causes of increased incidence and prevalence varied between sexes (fig 3A-D). The rise in the burden of depressive and anxiety disorders was more pronounced in women , while headache disorders saw a significant increase in men. Vitamin A deficiency had a higher incidence and prevalence in men, whereas haemoglobinopathies and haemolytic anaemias were more prevalent in women. Additionally, the incidence of fungal skin diseases and urinary diseases, as well as the prevalence of cirrhosis and other chronic liver diseases, noticeably increased in women. In men, the prevalence of blindness and vision loss, and age related hearing loss significantly increased. The patterns for DALYs and deaths (fig 3E-H) were relatively consistent across sexes, with the most notable increases in DALYs observed in depressive disorders, malaria, and anxiety disorders, and the highest rise in mortality noted as a result of malaria.

Main causes of increased burden by age

The impact of the covid-19 pandemic on disease burdens of other causes also varied across age groups (fig 4 and supplementary table 5). The burden of depressive and anxiety disorders significantly increased in individuals aged five years and older. The highest absolute increase in disease burden for depressive and anxiety disorders was in the 15-49 years age group, with significant increases in incidence, prevalence, and DALYs (supplementary table 5). The largest relative rate differences were in the 5-14 years age group, with increases of 22.6% (depressive) and 17.6% (anxiety) for incidence, 19.5% (depressive) and 17.3% (anxiety) for prevalence, and 21.3% (depressive) and 17.1% (anxiety) for DALYs.

Malaria related DALYs and deaths had the most significant increase in children under five years old. The absolute increase in DALYs was 769.0 per 100 000, while deaths increased by 8.8 per 100 000. The relative rate differences were 13.3% for DALYs and 13.6% for deaths. Additionally, upper respiratory infections had the greatest increase among children under 5 years. For individuals aged 15-49 years, the incidence and prevalence of headache disorders markedly increased, while the incidence of diarrheal diseases significantly increased in those aged 50 years and older.

Leading causes of increased burden by countries

For the age standardised rates of incidence, depressive disorders were the leading cause in 96 countries, particularly in the European and Eastern Mediterranean Regions. Diarrheal diseases were the leading cause in 69 countries, especially in the South-East Asia and African Regions. Upper respiratory infections were the leading cause in 22 countries, primarily in the Regions of Americas (supplementary figure 2A and supplementary figure 3A). Regarding age standardised prevalence, globally, anxiety disorders showed the highest increase in 134 countries. Depressive disorders were foremost in 17 countries, while malaria led in 13 countries (supplementary figure 2B and supplementary figure 3B). In terms of age standardised DALYs, depressive (60 countries) and anxiety disorders (56 countries) stood out as major causes, with concentrations in the Americas, South-East Asia, and European Regions. Malaria was most prevalent in 25 countries primarily within the African Region (fig 5 and supplementary figure 3C). For age

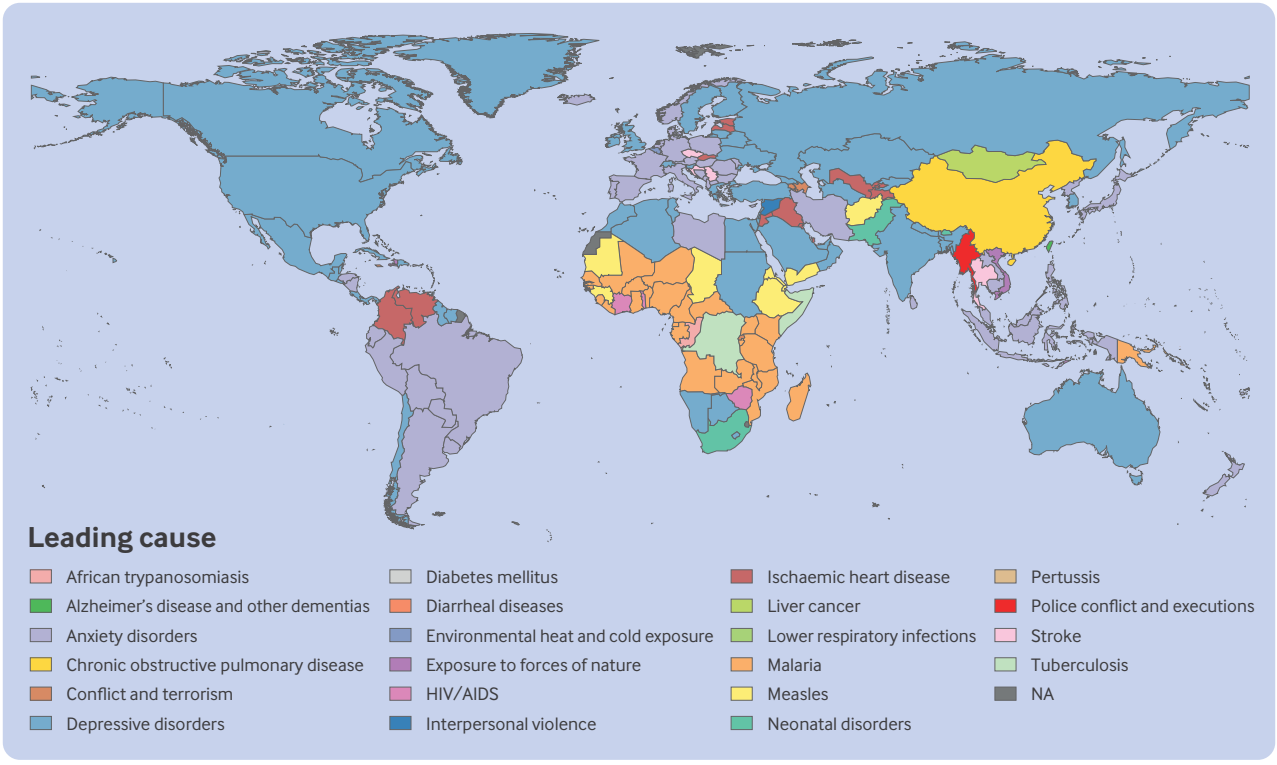

Fig 5 | Leading causes of increased disability adjusted life years by countries and territories. The leading causes refer to the causes with the largest absolute rate differences between the observed and predicted rates for 2020-2021, but this does not imply that each rate difference is statistically significant. NA=not available

standardised mortality, ischaemic heart disease was the leading causes in 51 countries and stroke in 24 countries, primarily in the Americas and European Regions; malaria was the leading cause in 24 countries primarily within the African Region (supplementary figure 2C and supplementary figure 3D).

Time-series models performance and sensitivity analysis

The median root mean squared error and mean absolute error values for the 174 global causes in the validation sets were as follows: 0.3 and 0.2 for incidence, 0.7 and 0.6 for prevalence, 0.6 and 0.5 for DALYs, and 0.02 and 0.02 for deaths (supplementary figure 4). In external validation, the model also showed relatively high predictive accuracy, with root mean squared error and mean absolute error at 3.5 and 3.3, 1.6 and 1.5, respectively (supplementary figure 5). Compared with the external validation with a root mean squared error of around 3.5, the proposed method has a relatively good generalisation error. In the sensitivity analysis, the root mean squared error and mean absolute error values were greater when the training and validation set split was 8:2 or 7:3, compared with the 9:1 split. This trend suggests that the current 9:1 split of the training and validation sets is optimal for minimising error, thereby supporting model comparison and selection.

An analysis excluding low quality data showed that the results remained largely consistent with our main findings, suggesting that our conclusions are robust. Among the top 10 causes across the four indicators, the absolute rate differences for most causes showed no significant changes before and after excluding low quality data, as indicated by overlapping 95% CIs (supplementary figure 6). Furthermore, when subsets of the 174 causes were analysed, the top 10 causes with the largest absolute and relative rate differences were fully consistent with the main results (supplementary figure 7).

Discussion

Principal findings

This study explored the indirect health impacts of the covid-19 pandemic by analysing 174 causes across all regions, age groups, and sexes, and identifies the main causes with the largest increases in incidence, prevalence, DALYs, and deaths attributable to pandemic related disruptions. Our findings indicate that the impact of the covid-19 pandemic varied across different causes and show notable disparities by sex, age group, and region, thereby providing a comprehensive and nuanced picture of the pandemic's indirect effects on disease burden. The disease burden of depressive and anxiety disorders showed a significant increase across all sexes and among individuals older than five years. Malaria emerged as the leading contributor to increased disease burden among children younger than five years old, particularly in the African Region. Among individuals aged 70 and older, stroke accounted

for the largest increase in disease burden. Compared with men, women had a greater increase in the burden of depressive and anxiety disorders, self-harm, and sexually transmitted infections (excluding HIV), and Alzheimer's disease and other dementias. By contrast, men had a greater increase in the burden of stroke, tuberculosis, chronic obstructive pulmonary disease, ischaemic heart disease, and interpersonal violence. The leading causes of the increased burden by country may be influenced by the local baseline disease burden of these causes. Therefore, it is crucial to consider each nation's specific context and data to understand the variations in leading causes across countries.

Impact of the covid-19 pandemic on global health

Our study identified a surge in the burden of depressive and anxiety disorders associated with the covid-19 pandemic, aligning with previous research that has reported similar trends.[13 29] In 2020, the global prevalence of anxiety and depression increased by more than 25%, with women being nearly twice as likely to be affected as men.[13] SARS-CoV-2 infection can trigger an abnormal response of the immune system, leading to chronic low level inflammation,[30] which may affect the balance of neurotransmitters, especially 5-hydroxytryptophan and dopamine.[31] These are related to the regulation of emotions, thereby increasing the risk of depressive and anxiety disorders. The increasing challenges of social isolation and lifestyle changes during the pandemic have heightened the occurrence of depressive and anxiety disorders, particularly in women, especially in the absence of conventional psychological support.[32] This critical secondary public health challenge warrants urgent and sustained attention. Although the WHO Mental Health Action Plan 2013-2030 recognizes mental health and psychosocial support as essential components of emergency response,[33] translating this framework into actionable policies remains a challenge. To strengthen implementation in the post-pandemic era, countries should integrate mental health into national emergency preparedness plans, invest in primary level mental health services, expand access to evidence based digital interventions, and prioritise support for populations at high risk, particularly women, who have been disproportionately affected. Additionally, enhanced mental health surveillance and long term outcome evaluation are essential to inform more equitable and responsive mental health policies.

Meanwhile, the covid-19 pandemic has led to an increased disease burden of chronic, time sensitive, and prognostically severe causes such as stroke and ischaemic heart disease.[34 35] In response to the large influx of covid-19 cases, medical resources were prioritised for pandemic control, resulting in a significant reduction in the capacity for stroke care in many hospitals.[36] These findings underscore the urgent need to build more resilient healthcare systems that can sustain essential services during public health emergencies. Emergency preparedness plans should explicitly include strategies to preserve and prioritise acute care pathways for cardiovascular and cerebrovascular conditions. Methods could involve establishing parallel service systems that separate infectious disease response from critical non-communicable disease care, investing in telemedicine infrastructure, and enhancing pre-hospital triage and referral systems to ensure timely treatment for stroke and acute cardiac events.

Additionally, malaria burden significantly increased among children under five, particularly in the African Region, as did the tuberculosis burden. During the covid-19 pandemic, healthcare resources were reallocated, services were disrupted, and public health priorities shifted toward immediate crisis response.[37] These disruptions led to reduced screening, diagnosis, and treatment efforts for malaria and tuberculosis, undermining ongoing surveillance systems and control programmes.[38-40] Global health targets have prioritised these diseases, including the WHO End TB Strategy,[41] the Global Technical Strategy for Malaria 2016-2030,[42] and SDG 3.3 of the United Nations Sustainable Development Goals,[43] which aims to end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases by 2030. However, our findings suggest that the covid-19 pandemic has posed substantial challenges to achieving these goals, particularly in the case of malaria control. In response, we recommend reallocating resources to strengthen malaria and tuberculosis prevention programmes in regions of high burden, aiming to offset the pandemic related setbacks in disease control efforts. In particular, ensuring the continuity and accessibility of essential services during health emergencies, such as through decentralisation or mobile outreach, is critical to sustaining progress. Furthermore, future pandemic responses should be tailored to mitigate indirect health harm by integrating preparedness strategies into existing infectious disease control frameworks.

Our study also highlights key limitations in current public health systems when responding to pandemics or other public health emergencies of international concern, including disrupted monitoring of diseases not related to covid-19,[44] inconsistent data quality across countries,[45] and the lack of integrated early warning systems to capture cross disease impacts.[46] To address these gaps, we propose the development of a multidisease integrated surveillance system, a digitally integrated and multi-tiered platform that consolidates real-time data across infectious, non-communicable, and mental health conditions. Initially, this system would focus on high burden, time sensitive respiratory infections such as covid-19, influenza, and respiratory syncytial virus, and gradually expand to include chronic and mental health conditions to support syndemic informed policy making. The multidisease integrated surveillance system could be introduced through a phased approach, leveraging existing national and international systems with support from WHO and regional partners such as the WHO covid-19 integrated surveillance, which has expanded from the influenza based Global Influenza Surveillance and Response

System to include multiple respiratory pathogens.[47] Through interoperable design and coordinated governance, the multidisease integrated surveillance system could improve early detection of indirect health impacts, enable more targeted interventions, and strengthen health system resilience for future pandemics and other global health emergencies. In addition, artificial intelligence (AI) can enhance the sensitivity and timeliness of disease surveillance by enabling automated integration and anomaly detection across multiple data sources, such as clinical records, laboratory results, and social media.[48] Using machine learning models, AI can predict disease trends and identify potential public health threats, thereby supporting more precise decision making. In resource limited settings, AI can also help to compensate for workforce shortages and improve the efficiency and reach of outbreak responses.

Moreover, the implementation of public health and social measures during the covid-19 pandemic, while critical for mitigating viral transmission, may have inadvertently exacerbated disruptions to routine health services, potentially influencing the disease burden of other causes.[36 37] Evidence suggests that a well chosen combination of public health and social measures, including less disruptive and costly measures (eg, gathering restrictions), can be just as effective as more intrusive and drastic interventions.[49] Appropriately implemented measures can also play a synergistic role in controlling specific diseases. For example, during the covid-19 pandemic, widespread public health and social measures, such as mask wearing requirements in public settings, event cancellations, and crowd gathering restrictions, led to a significant reduction in the incidence of seasonal influenza and respiratory syncytial virus globally.[50 51] Therefore, selection of appropriate measures is crucial by assessing transmission risks, cost effectiveness, and social acceptability in future pandemic responses, which should strive to mitigate these indirect health setbacks while preserving the observed reductions in certain infections (eg, through smart use of public health and social measures).[52 53]

Strengths and limitations of this study

This study quantified the indirect health impacts of the covid-19 pandemic across 174 diseases and injuries, covering all ages, sexes, and regions. It offers a broader scope than prior cause-specific studies and identifies key contributors to increased burden—particularly mental health disorders, malaria in young children in the African region, and ischaemic heart disease and stroke in older adults—while showing significant sex and age disparities. In addition to robust analysis, we provide actionable, policy relevant recommendations, including the development of the multidisease integrated surveillance system and the application of AI to improve health system preparedness.

Our study has several limitations that should be acknowledged. Firstly, the data have some limitations. These include the uneven quality of data across regions, potential underreporting and delayed diagnoses during the covid-19 pandemic, and the limited time span of available data (only 30 years, from 1990 to 2019). These factors may affect the accuracy and comparability of cross-country estimates. With longer time-series and more representative data, a more comprehensive and robust assessment of the pandemic's impact on disease burden could be achieved. Secondly, our time-series models (ARIMA and ARIMA-LSTM), despite rigorous validation and sensitivity analyses, may not fully capture the complexity and heterogeneity of pandemic related disruptions, especially those influenced by unmeasured confounding factors, due to their reliance on historical trends and assumption of temporal continuity. Thirdly, although our study included all 174 causes at level 3 from the GBD database, the GBD framework does not capture all health conditions. In particular, certain rare diseases and region specific issues are not separately represented. These omissions may lead to an underestimation of the pandemic's indirect health impacts, limit the generalisability of our findings, and obscure health disparities across populations. Moreover, important related causes such as long covid were also not included and warrant further investigation as relevant data become available.

To further improve our understanding of disease burden in the post-pandemic era, future research should focus on several key areas. Firstly, emerging health conditions with their increasing public health relevance and widespread impact, such as long covid, should be incorporated into burden of disease frameworks. Secondly, novel methods are needed to strengthen data collection for rare diseases and region specific health issues, which remain under-represented in global datasets and are often subject to estimation uncertainty. Thirdly, we encourage continued improvement and expansion of international databases to enhance data quality, coverage, and timeliness. These efforts will help enable more accurate, representative, and policy relevant assessments of global health impacts.

Conclusions and policy implications

The covid-19 pandemic led to significant indirect increases in disease burden for specific causes, particularly mental health disorders (especially depression and anxiety), malaria in children under five years in the African region, and ischaemic heart disease and stroke in older adults. These impacts showed notable disparities by sex and age, highlighting vulnerable populations that were disproportionately affected. The pandemic led to major setbacks to global health targets, including the WHO Mental Health Action Plan 2013-2030, WHO's 2030 goals for malaria and tuberculosis. Overall, the covid-19 pandemic disrupted essential health services, weakened disease surveillance, and widened health inequalities; altogether exposing critical gaps in health system resilience, particularly in low resource settings. Future responses to potential pandemics or other public health emergencies of international concern

must extend beyond infection control to address long term, syndemic health impacts. Strengthening of resilient health systems, including the development of integrated surveillance platforms, such as the multidisease integrated surveillance system and the application of AI, will be critical for early detection, targeted interventions, and equitable public health preparedness.

Contributors: SY conceived the study. CC developed, programmed the model, and analysed the data. YC and JQ tested and validated the model. SY, CC, and WZ visualised the results and drafted the manuscript. SY, CC, WZ, KC, MC, RQ, JM, JQ, XW, JC, HZ, AD, QF, JZ, YY, and ND checked the data and interpreted the results. SY and YC proposed revisions to the manuscript. All authors read and approved the final manuscript. SY is the guarantor. CC, WZ, and YC contributed equally. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required: this study uses publicly available, aggregated data from the GBD study and no individual patient data were involved.

Data sharing: Publicly available datasets (Global Burden of Disease study 2021) were analysed in this study. The data can be found here: https://ghdx.healthdata.org/gbd-results-tool.

Participants: No individual level data or human participants were directly involved; the study refers to the existing aggregated data from the GBD database.

Code availability: Time-series modelling code used in this study is available at https://github.com/zwk-research/code_1.git.

Transparency: The lead author (SY) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patients and public communities: We will seek to ensure transparent and accessible communication of our findings with patient and public audiences in future dissemination efforts. The findings of this study will be disseminated through plain language summaries shared via social media platforms such as WeChat, Weibo, and hospital newsletters, as well as through knowledge sharing activities conducted in collaborative workshops involving healthcare professionals, researchers, and community stakeholders.

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