The *Lancet* Commission on 21st century global threats to health

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Executive Summary

This report from the *Lancet* Commission on 21st century global threats to health lays out a foresight-driven, health-focused approach to identifying and prioritising major threats to global health over the remainder of the century. We argue that recent global shocks (including COVID-19, Ebola Bundibugyo virus disease, major geopolitical conflict, accelerating climate impacts, rapid shifts in development assistance, and the emergence of powerful artificial intelligence [AI] systems) show how quickly assumptions about stability can be overturned—and why governments and multilateral institutions must counter short-termism and localism with systematic, repeatable risk assessment and preparedness planning.

Commission core goals

The Commission has two central aims: (1) to characterise the likely leading future threats to health with quantitative forecasts where possible and structured qualitative methods where data are insufficient (eg, malicious AI use or nuclear conflict with nuclear famine); and (2) to promote solutions and cross-cutting actions, including innovation where current tools are inadequate, and strategies that reduce risk across multiple threats simultaneously. A consistent theme is that harms will be unequally distributed, often falling most heavily on people with low income and marginalised populations, because existing inequalities shape exposure, vulnerability, and resilience.

Conceptual framework and metric: expected amenable disability-adjusted life-years

The Commission deliberately adopts an inclusive definition of threat: the largest causes of future health loss that are amenable to policy action. To quantify and compare threats, this report uses expected cumulative amenable disability-adjusted life-years (DALYs) from 2025 to 2100, defined as the difference between a plausible best and a plausible worst scenario for each threat. In other words, threats are measured by the expected cumulative magnitude of death and disability combined that could be reduced through policy action by the end of the 21st century. By including both fatal and non-fatal health outcomes, we are accounting for more than just survival. At the same time, by focusing on health impacts, we are not taking into consideration other dimensions of wellbeing. This design—ie, measuring threats by the difference between their plausible worst and best scenarios—emphasises actionable leverage (what societies can reasonably reduce), rather than worst possible outcome narratives (ie, measuring threats solely by their harm in the worst-case outcome).

Key methodological choices made in this Commission include a 75-year horizon to 2100, chosen for practical and political utility, while acknowledging arguments for shorter or longer horizons. We use a reference scenario (what would happen if trends in key risk factors and other drivers in health were to continue) to identify which of several hundred diseases, risk factors, social drivers, and other factors fall into four categories based on cumulative DALYs: extinction potential, major catastrophic risks, major risks and causes, and the wider threat landscape. We focus on expected burden (not risk-adjusted burden), rather than applying explicit societal risk-aversion adjustments. Although our primary metric is cumulative expected amenable burden, we do recognise that malicious use of AI, including bioweapons, and nuclear conflict with nuclear famine carry risks of extinction in the next 75 years.

For extinction potential and major catastrophic threats, we estimate cumulative expected amenable DALYs. Amenable DALYs are defined as the difference between an empirically derived plausible best and plausible worst scenario for each threat. By focusing on the range of what is possible, as defined by these two scenarios, we provide a solution to the well known problem that forecasts themselves can alter policy action, often called reflexivity.

Reference scenario: what is most likely if current trajectories of risks and other drivers persist

The reference scenario developed for this Commission builds on the Institute for Health Metrics and Evaluation (IHME) and Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) forecasting infrastructure,

Lancet 2026; 408: 1603–61

Published **Online** October 11, 2026 https://doi.org/10.1016/S0140-6736(26)01714-9

This online publication has been corrected. The corrected version first appeared at thelancet.com on October 15, 2026

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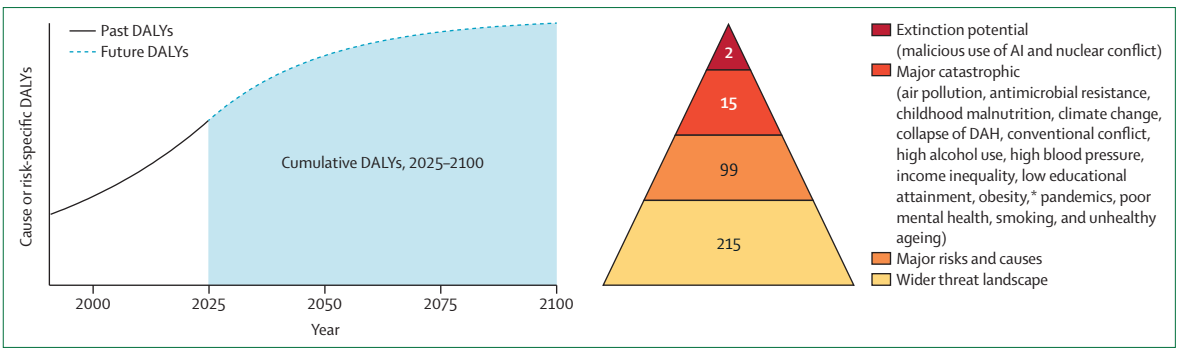


Figure 1: **Pyramid of threats**
The pyramid shows diseases, injuries, risks, socioeconomic factors, and other threats classified by severity of harm (ie, cumulative attributable DALYs). The graph schematic shows cumulative DALY calculation per health entity estimated using the reference scenario. The dashed reference scenario forecasts each cause or risk forward to 2100; the shaded area is the cumulative burden (DALYs) accumulated between 2025 and 2100. Major catastrophic and extinction potential threats met the Commission criteria accounting for more than 1 billion cumulative DALYs to the end of the century. AI=artificial intelligence. DAH=development assistance for health. DALYs=disability-adjusted life-years. *Obesity refers to the cluster of high BMI, poor diet, and low physical activity risks.

incorporating trends in major risk factors, socioeconomic drivers, and cause-specific mortality patterns, and extending forecasts to 2100 with explicit additions for threats such as pandemics, climate pathways, war, and inequality. In this most probable future if trends in key drivers continue, life expectancy and healthy life expectancy generally improve, but healthy life expectancy rises more slowly, implying more years lived with chronic disability as populations age and non-communicable diseases dominate.

Important drivers of the reference scenario include poverty and educational attainment. Given the slow expected economic growth in sub-Saharan Africa and continued population growth, the number of people living in extreme poverty is expected to rise until late in the century, slowing progress in health outcomes. Although many risk drivers are expected to decline, in terms of population rates, obesity and fasting plasma glucose will steadily increase. The reference scenario highlights how the trajectory of global health is profoundly affected by what happens to economic growth in sub-Saharan Africa, particularly in the Sahel.

The pyramid of threats

By using the cumulative burden estimated for diseases and risk factors plus qualitative assessments for nuclear conflict and the malicious use of AI, we divided hundreds of potential threats (diseases, injuries, socioeconomic drivers, and other threats) into a pyramid of threats with four categories: threats with the potential to lead to human extinction by 2100, major catastrophic threats, major risks and causes, and the wider threat landscape (figure 1). Threats with extinction potential, which represent the first category of the pyramid, include nuclear conflict with nuclear famine and the malicious use of AI, including bioweapons development. Other extinction risks such as asteroid collision and supervolcanoes were not included because the probabilities of these events occurring in the next 75 years were deemed to be extremely low. Other potential extinction threats, such as mirror life, were also excluded because of insufficient evidence. The second category in the threat pyramid was composed of threats that are forecasted to cause more than 1 billion cumulative DALYs by 2100 in the reference scenario. To reduce the number of threats in the major catastrophic risk category, we excluded some that we judged already had sufficient policy attention and global health expenditure, such as ischaemic heart disease and several site-specific cancers. 15 threats were included in the major catastrophic threats category: air pollution, antimicrobial resistance, childhood malnutrition, climate change, collapse of development assistance for health (DAH), conventional conflict, high alcohol use, high blood pressure, income inequality, low educational attainment, naturally occurring pandemics (not AI-enabled), obesity (combining high BMI, poor diet, and low activity), poor mental health, smoking, and unhealthy ageing.

Our assessment of cumulative burden in the reference scenario suffers from the problem of reflexivity. To make a future scenario, we must build into the modelling explicit or implicit assumptions about policy action, such as government efforts to reduce CO_2 emissions. However, forecasts might alter governments' willingness to take action, creating self-defeating prophecies. For the top two categories of threats in the pyramid, we seek to solve the reflexivity problem by focusing on the range of plausible outcomes in the future rather than a single reference scenario.

Quantifying expected amenable burden

For each of the threats with extinction potential and the major catastrophic threats, we sought to empirically estimate a plausible worst and plausible best scenario. The expected values for plausible best and worst scenarios are the product of the probability of each event in each year and the average harm the event will cause, with scenarios following the average trajectory of expected values from a range of possible best and worst trajectories

(figure 2A–C). Figure 2D shows an illustration of the concept of plausible best and plausible worst for a threat and how the reference scenario falls between these two bounds; the exact trajectory that might unfold will be determined by the policy response. There is, of course, uncertainty for the plausible best and plausible worst trajectories. We focus on the average across trajectories in a scenario, called the expectation; figure 2D shows the expected amenable burden. The emphasis is on the term plausible; we approach the definition of plausible trajectories for each threat by examining the level of each threat across countries from 1990 to present. To ground the plausible best and worst in observed experience, we drew on stochastic frontier analysis, a method that traces how the extremes of one variable (eg, disease burden) shift with explanatory variables (eg, development level). A replicable method using stochastic frontier analysis and capturing time trends in the best and worst scenarios across countries was developed. In addition, to ensure that trajectories for plausible best and plausible worst outcomes represent changes in a threat that are plausible, we identified the most rapid rates of increase or decrease (ie, the extremes of velocity) for each threat. The combination of constraints for level and velocity can be used to generate plausible future trajectories for each country and threat. The space between the plausible best and plausible worst trajectory provides an assessment of the zone of the possible. This logic has already been used in the climate community, where comparisons between high-emission scenarios such as the Representative Concentration Pathway (RCP) 8.5 and low-emission scenarios such as RCP2.6 are common.

Plausible best and plausible worst trajectories for each threat were generated for each country. Using the IHME forecasting platform, which is a full cohort-component competing risks framework, we generated age-specific, sex-specific, cause-specific, and location-specific estimates of mortality and non-fatal outcomes. Cohort component modelling means we follow each current age-group and future birth cohort forward through time; competing risks means that if someone survives a plausible best-scenario death at a younger age, this will mean more deaths at older ages in the future. We defined the difference between these two scenarios as expected amenable burden. Cumulating this over the 75-year period of analysis provides estimates of cumulative expected amenable DALYs for each threat.

The Commission compares threats by their cumulative expected amenable DALYs, using country-level analyses (204 countries and territories) across age, sex, and cause, and identifies substantial geographical heterogeneity in amenable burdens (ie, priorities differ sharply by country). Figure 3 shows the amenable burden for each threat, with the extinction potential threats highlighted in red. The results show the expectation of the difference between plausible best and plausible worst scenarios, meaning that it accounts for the probability of a particular outcome and the DALY loss in each outcome. In this plot, a 1% probability of 10 billion DALYs and a 10% probability of 1 billion DALYs will be the same expected value. Figure 3 is not a ranking of policy priority and should not be read as one. Its purpose is to apply one standardised method—the gap between a plausible best and a plausible worst scenario—to threats that are conventionally assessed in separate literatures using incompatible metrics. For this reason, threats are listed alphabetically rather than ordered by magnitude, with extinction potential threats highlighted in red. A threat with a lower expected amenable burden can warrant less, equal, or greater urgency, either because it carries a tail risk of catastrophe or because important pathways of harm remain unquantified; this consideration applies with particular force to climate change, where several pathways are not yet fully quantified and where the uncertainty runs in both directions. The 17 threats range from 1·02 billion DALYs (95% UI 0·673–1·62) to 23·1 billion DALYs (19·5–26·9). For comparison, the COVID-19 pandemic caused approximately 500 million DALYs. The largest cumulative expected amenable burden is from obesity.

Our assessment of climate change harm is substantially larger than older baseline assessments, such as WHO's 2014 quantitative risk assessment (which projected 250 000 additional deaths annually between 2030 and 2050 based on a narrower set of pathways).

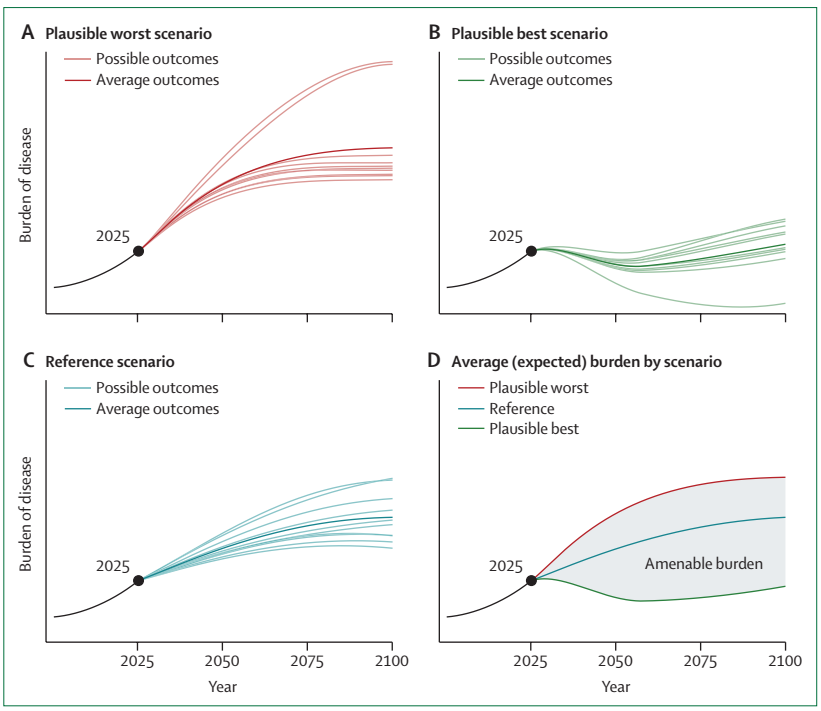


Figure 2: **Possible and expected outcomes of disease burden by scenario**
Illustrative disease burden under each scenario is uncertain, with multiple possible outcomes (A, B, and C). Expected burden is the average burden across possible outcomes. (D) The shaded area represents an estimate of amenable burden.

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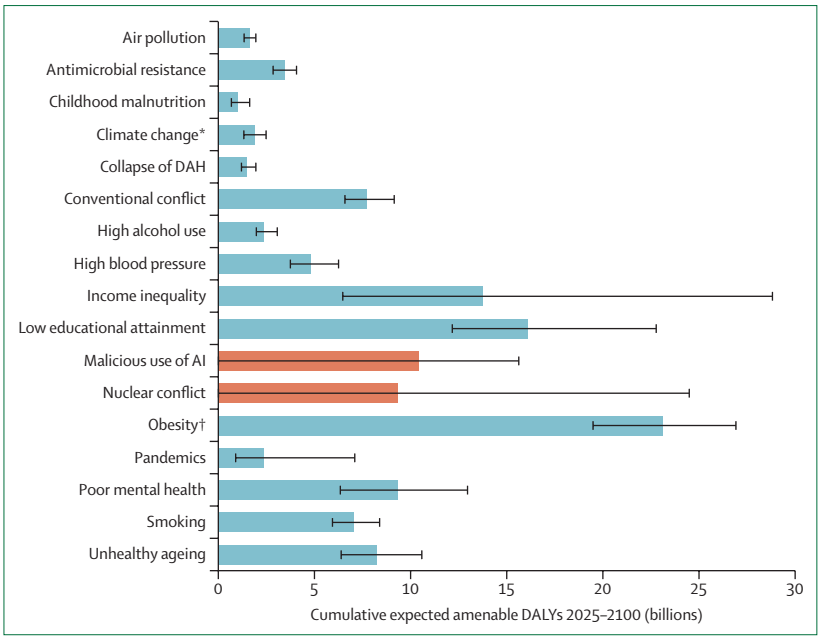


Figure 3: **Cumulative expected amenable DALYs related to each of the 17 threats, with uncertainty intervals**
DALYs are cumulative from 2025 to 2100, with cumulative expected amenable DALYs referring to the difference in cumulative DALYs between the plausible best and plausible worst scenario for each threat. Expected amenable burden measures the health loss that could be averted, not the priority a threat should receive. Threats are listed alphabetically rather than ordered by magnitude. A threat with a lower expected value might still warrant urgent action, particularly where it carries a tail risk of catastrophe or where important pathways remain unquantified. 95% uncertainty intervals are given as lines. Red bars denote threats with extinction potential. AI=artificial intelligence. DAH=development assistance for health. DALYs=disability-adjusted life-years. *Climate change refers to direct health pathways only, not economic disruption, biodiversity loss, or other dimensions. †Obesity refers to the cluster of high BMI, poor diet, and low physical activity risks.

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Panel 1: Enablers: conditions that determine whether societies can reduce threats

- Trust (and the need for a science of trust enhancement)
- Functioning global governance for problems no country can solve alone
- Sustainable health-system financing, especially in low-resource settings amid development assistance for health volatility
- Pro-equity policies that reduce vulnerability and strengthen social cohesion
- Resilient food systems
- National capacity to plan for rapid demographic and social change
- Human rights (including sexual and reproductive health and rights)
- Equitable universal health coverage, with a focus on quality, efficiency, and affordability

However, our findings align closely with the escalating risks identified in recent World Bank analyses and the increasingly severe indicators tracked by the annual Lancet *Countdown on health and climate change*. Our estimates are also similar in magnitude to the effects estimated with econometric methods by Carleton and colleagues, which is often used in the social cost of carbon literature. Nevertheless, given that global mean surface temperature is likely to increase by another 1·5°C to 2·5°C in the rest of this century, new pathways of effect for climate change might emerge that are not currently supported by empirical evidence. Climate change-amenable DALYs could reasonably increase in future evaluations.

Beyond threat-by-threat analysis, the Commission identifies enabling factors that shape preparedness, mitigation, and adaptation capacity across many risks. Many of these enabling factors are intertwined, with the potential to influence each other (panel 1).

The report culminates in three cross-cutting recommendations intended to shift governments and institutions from reactive to anticipatory action (panel 2).

Panel 2: Three headline recommendations

1. Build and fund threat-ready health systems with dedicated capabilities for foresight, prevention, preparedness, and protection—grounded in strong systems and durable financing rather than ad hoc crisis response.
2. Dramatically increase investment in breakthrough innovation even in the current times of uncertainty and pressure on government budgets where existing tools are insufficient (eg, platform vaccines, new antibiotics, obesity therapeutics, climate mitigation, and atmospheric carbon removal) alongside governance to manage high-risk technologies (eg, frontier artificial intelligence [AI] systems and AI-enabled biological design tools).
3. Create a recurring Monitor of 21st Century Global Threats to Health to update threat assessments, track science and data, and regularly present findings to major political and security forums to counter neglect cycles.

Introduction

In the past 6 years, the COVID-19 pandemic has reminded the world that unexpected or unforeseen events can dramatically alter human health and human society. The Russian invasion of Ukraine is another event radically altering European governments' assessment of security. Recent shifts in US foreign policy have exacerbated policy uncertainty. Climate trends unfolding steadily over the past century and accelerating since 1980 have now been firmly planted in the policy agendas of many states. Abrupt reductions in development assistance for health (DAH; see appendix pp 129–131 for a complete list of acronyms and their definitions) have disrupted delivery programmes in low-income countries. These are just a few examples of how events or trends that have not been obvious in past data are emerging as critical dimensions of government and intergovernmental agenda setting. The dramatic increase in artificial intelligence (AI) and large language model capabilities in

the early 2020s is another example of developments that are transforming the sense of stability, order, and predictability in many domains of human endeavour.

A core function of government at every level, and of intergovernmental collective action, is to use foresight to anticipate, prepare for, and, where possible, prevent future threats to health and wellbeing. The *Lancet* Commission on 21st century global threats to health is fundamentally an exercise in using foresight to anticipate the major future threats to health, identify ways in which societies can prepare for threats, take actions to prevent or reduce threats, mitigate the harm from threats if and when they emerge, and facilitate adaptation at the individual, community, and societal level. In this Commission report, we will outline how we think about threats, how we quantify their probability and the distribution of potential harms, and what could be done by societies to address more than one threat at a time.

The Commission analysis is timely because short-termism and its companion, localism—the unfortunate focus of most politicians and governments on issues that are close geographically or that might occur in the very near future—limit the effectiveness of governments and the international community in addressing future threats. The cycles of concern and neglect about pandemics are a classic example of how short-termism adversely affects governments' ability to anticipate, prepare, and prevent. Localism often means that governments are unlikely to fund action to address critical needs in low-resource settings that are far away and do not influence collective voter sentiment. Declines in official development assistance[1] (ODA) observed in 2025 and 2026 might also reflect some increases in localism. Systematic risk assessment can help address short-termism, especially if the assessment is put in front of decision makers, the media, and the public on a regular schedule. Providing clarity on the potential effects of future systemic risks on the most vulnerable throughout the world might also counteract localism and promote equity. Existing risk assessments, although useful, are not comprehensive, often have insufficient quantitative analysis to support their conclusions, and do not focus on what can be changed in the future.

More specifically, the goals for the Commission are two-fold. First, to use quantitative and qualitative analysis to characterise the leading threats to health in the future. This is done with the full appreciation that there will always be rare, high-impact events that cannot be anticipated, but the analysis presented here can help characterise the subset of risks that can be quantified, alongside newly emerging risks that can be approximated with more subjective methods, such as AI. All assessments of the future course of human development will be highly uncertain, but attempts at quantification or qualitative assessment can increase attention to key threats. The second goal is to promote awareness of solutions for each of these threats, advocate for innovation where existing solutions are insufficient, and search for actions that can be taken to address multiple threats in the future.

The Commission uses a two-step process to consider a wide range of threats. First, we use a scenario describing what might happen if current trends in key drivers continue, classifying a wide range of threats into four groups: extinction potential, major catastrophic threats, major risks and causes, and other threats. Second, for extinction potential and major catastrophic threats, we develop a formalised assessment of the future expected burden that is amenable to change, defined as the difference between a plausible best and a plausible worst scenario for each threat (with plausible best and worst scenarios each reflecting an expected value for that threat, calculated as the product of the probability of each event in each year times the harm that would occur). These threats are then quantified by the cumulative expected magnitude of disease burden that could be reduced through policy action by the end of the 21st century. Expected amenable burden measures both death and disability but not other dimensions of wellbeing. Measuring threats by their amenability emphasises actionable leverage and offers an alternative to catastrophe narratives that measure threats solely by their harm in a worst-case outcome.

A given threat, such as climate change, will have differential effects on different communities and on specific individuals, households, or groups within each community. In general, the effects of most of the threats examined will be greatest on the most vulnerable, particularly people with low income and groups who are marginalised in each society due to factors such as gender, race, ethnicity, or age. The effect of health challenges today is strongly modulated by these existing inequalities, and this will also hold in the future. Understanding the evolution of inequalities will necessarily be part of understanding future threats. Some threats might affect everyone nearly equally (such as asteroid collisions or nuclear winter). Although the focus of the Commission is on global threats, we will attempt where possible to understand which communities and individuals will be most affected in the future. Our analysis is done at the country level, providing material for future in-depth investigations into the effect of global threats at the regional and national level. However, country-level estimates should be interpreted with greater caution than regional or global aggregates. The appendix (pp 5–102) details the data quality constraints applied throughout the modelling process, including the exclusion of countries with populations below 1 million from frontier fitting. Developing systematic indicators of empirical evidence strength by country is being explored for future iterations of this work.

Many cross-cutting factors influence both the likelihood of a threat occurring and the distribution of its harms. These factors include poverty, food systems, political

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See **Online** for appendix

structures, unregulated markets, and myriad other factors that shape not only who is most exposed to harm but also who benefits from new protective solutions. Diffusion of innovations theory predicts that new technologies reach groups and countries with greater resources, capacity, and access first, meaning that, without deliberate action, future innovations risk compounding rather than reducing existing inequalities.[2] Where relevant in both the assessment of major threats and in proposed actions recommended by the Commission, we will return to some of these cross-cutting factors. Because inequality and lack of education are such important determinants of current and future health impact, we also analyse the burden that can be addressed by reducing inequality and low levels of education as threats themselves.

The Commission is divided into nine sections: the framework for threat assessment, the reference scenario or most probable future if trends in current drivers continue, identification of the pyramid of threats, analysis of amenability for extinction potential and major catastrophic threats, analyses of specific threats, comparative magnitude of threats, limitations, enabling factors, and main recommendations.

Section 1: Our framework for threat assessment

Many threat assessment frameworks have been adopted by governments and corporations for constructing risk registries.[3–6] Other organisations report on major risks or threats; for example, the World Economic Forum produces a global risks report that surveys businesses and other leaders to report on perceived major risks. Research groups have been created, such as the Centre for the Study of Existential Risk at the University of Cambridge, to examine some major threats. Other centres devoted to understanding catastrophic risk include the Future of Humanity Institute (University of Oxford), the Global Catastrophic Risk Institute, the Berkeley Existential Risk Initiative (University of California), Stanford Existential Risks Initiative, the African Futures and Innovation programme (Institute for Security Studies), and the Pardee Center for International Futures (University of Denver). Some authors have used the Drake equation[7] to infer the survival rate of civilisations.[8] The increasing number of these groups studying catastrophic risk highlights the concern at many levels in society about understanding future risks.

For the Commission, we have leveraged this literature but developed a new and explicit framework focused on threats to both the fatal and non-fatal components of health. Developing this framework has required both conceptual clarity on what we want to assess and the extension of forecasting and foresight methods so that modern Bayesian statistical methods can be used to help inform the work. While developing this body of work, we have developed a strategy to both assess what is probabilistically most likely to occur if trends in current drivers continue and implemented bounds on the range of future scenarios, represented by each threat using plausible best and worst cases. The nature of what is plausible in the future and the relationship to technical innovation or technical breakthroughs will be a key theme.

1.1 What is a threat?

Some would define a threat by emphasising the stochastic or unpredictable nature of certain events such as pandemics, wars, or natural disasters. But this emphasis on the periodicity or cadence of events when defining a threat could mean that the largest cause of poor health in the future that is amenable to change could be ignored simply because it is evolving more slowly. For example, global temperature is changing slowly in a predictable manner, but most would not discount this as a threat simply because of the speed of change or its predictability. To avoid excluding from consideration factors that change slowly or can be predicted with more certainty, we have chosen the most inclusive definition of a threat—namely, the largest causes of health loss cumulatively over the relevant period of consideration. Given the extensive work of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) to quantify diseases and risks since 1990 and forecast them through the year 2050,[9] we have adopted cumulative expected disability-adjusted life-years (DALYs) related to each threat as the initial metric for the Commission threat definition. In a second step, we have prioritised large threats by how amenable they are to change. Amenable DALYs are defined as the difference in death and disability combined between plausible worst-case and plausible best-case scenarios.

Other dimensions of threats are crucial for social prioritisation of action. For example, in addition to increasing DALYs, some threats such as climate change might lead to upheaval in economies, the need for migration, and political instability. These other important dimensions of individual wellbeing and societal stability are vital; however, we do not assess these aspects of each threat. Our assessment is consciously focused on health, and we recognise that it is only one of many dimensions that should be taken into consideration when establishing overall priorities for action. These other dimensions can go well beyond human wellbeing to encompass impacts on the planet, such as biodiversity.

Using both quantitative and, in a limited number of cases, qualitative methods, we seek to first characterise each threat in terms of cumulative DALYs over the period of concern. For the extinction potential and major catastrophic threats, we also evaluated how much of the future burden is amenable to change. The period of concern and how much each threat can be changed deserve further exploration. Although our primary mode of analysis is a threat-by-threat evaluation, there are many important interactions between threats that are discussed later in this Commission report.

1.2 What is the right timeframe for the analysis?

What is the right timeframe for the analysis to help governments, intergovernmental bodies, and communities take action to improve future wellbeing? The Sustainable Development Goals (SDGs) were set covering a 15-year period from 2015 to 2030, as were the Millennium Development Goals from 2000 to 2015.[10] The UN Secretary-General extended the window of consideration out to 2050 in the Summit of the Future, held during the UN General Assembly in 2024.[11] The climate community routinely provides the world with climate forecasts out to 2100, but many analyses of the full social costs of carbon argue for a longer vision out to 2300.[12–14] Going even farther, there is a community of philanthropists, philosophers, and activists calling for a very long-term view of human prospects going out thousands or even millions of years.[15–19]

Determining the right timeframe for the Commission analysis involves several considerations. To help the Commission advance its own thinking, we convened a meeting of philosophers to specifically advise on the right timeframe for assessment of threats; a more complete account of this view is published in a companion piece.[20] First, some philosophers argue that only consequences for individuals alive today should be considered in the projections of the future.[16] A less extreme formulation of the preference for living individuals over potential future individuals argues for a discount on future potential lives. The philosophical argument for either view is grounded in the notion that living individuals, if harmed, have a right to complain, whereas potential people may not. The enhanced focus on the effects on those currently living stems from the tradition of personal ethics rather than population ethics. Second, some economists argue for discounting the future (as embedded in the social cost of carbon literature, for example), including in cost–benefit analyses, when the value of future human lives is monetised and discounted. Discounting can be of two types. Humans and some social decision makers manifest pure myopia, namely they simply value the present more than the future. This notion of pure myopia, that future wellbeing is less valuable than current wellbeing, has been widely criticised in the philosophical literature.[16,21–27] Others use discounting as an omnibus mechanism to capture factors correlated with time,[28–30] such as the risk of global catastrophe or the increasing uncertainty of risk assessments in the future due to technological innovation, wars, and other developments.[31] The Stern Review on the Economics of Climate Change[32] discounted the future at 0·1% per year for catastrophic risk. Although there is some convenience in using this heuristic approach to discounting, Amartya Sen, and others, argue it is preferable to explicitly address factors such as uncertainty.[33] Third, some argue that we should evaluate threats over the timeframe that current actions, whether harmful or helpful, will have a major impact. Greenhouse gases emitted today can affect the world for centuries, so why would we exclude harms from current actions from consideration of global threats? Fourth, as we model further into the future, uncertainty in estimates might increase. At some point, uncertainty might be so great as to make assessment extremely difficult. Some argue we should adjust our future considerations for this increasing uncertainty. This proposal, however, is complicated by the fact that uncertainty is not always greater further into the future. For example, the uncertainty that a pandemic will occur in any given year might be very great, but the uncertainty in the cumulative probability of a pandemic over the next century might be much smaller.[34,35] Finally, practical considerations of gaining political or public support for analyses that span too long an interval might limit the utility of these analyses. There is likewise a risk that forecasts of reference scenarios that prove inaccurate could be used to undermine trust in science more broadly; our use of scenario ranges rather than point predictions is intended in part to reduce this vulnerability.

Considering these issues, the Commission has decided to evaluate threats from the present to 2100, namely the next 75 years; this is also around the average global lifespan for the next generation.[36] The actual trajectory of the world population affects estimates of the total harm from threats. Whether the world population rises and then levels off, or instead peaks and steadily declines, makes a considerable difference to the threat assessments and influences how far into the future we should conduct these calculations. For example, our cohort-component model of future population suggests that the global population peaks in 2064 at 9·7 billion[37] and then steadily declines to 4·6 billion in 2200. Of note, the companion piece from the group of philosophers argues that the timeframe of 2100 is too short.[20] 2100 does not even cover the timeframe of the expected lifespan of all individuals living today. We have chosen to focus on 2100 for practical computation and political acceptability, but recognise the need to push models further into the future for some uses, particularly for threats such as climate change and nuclear conflict, whose health consequences extend beyond this timeframe. We might also revisit this in future iterations of the work.

1.3 Expected DALYs or risk-adjusted expected DALYs?

Some governments have expressed a preference for risk aversion, which in practice means assigning greater than expected weight to large problems. For example, the EU[38,39] has formally adopted the precautionary principle, which can be represented as a form of risk aversion. The philosophical literature has formalised decision-theoretic frameworks to capture risk aversion in social decision making.[40] Although these frameworks have been proposed and widely discussed, in practice adopting this approach is challenging. First, in repeated decision making at the societal level, total and average outcomes

will be worse[41] if risk aversion is taken into consideration because we might choose to act on problems with a small probability of very bad outcomes while ignoring problems that are on average larger but with lower probabilities of very bad outcomes. Second, what level of risk aversion would be appropriate? There are also few, if any, practical applications of formal risk aversion that have been documented. However, it is likely that some political leaders have informally considered risk aversion in some of their decision making. Of note, the meeting of philosophers had a nearly unanimous view that formal risk aversion would not be appropriate for evaluating 21st-century global threats to health. The Commission has decided to not consider risk aversion in the calculation of amenable DALYs related to each threat over the next 75 years. Cumulative amenable DALYs thus reflect expected risk; the tail of the distribution is weighted by the probabilities of those more extreme outcomes.

Another common approach to the issue of risk aversion is to report separately on the probability of an outcome and the harm of the outcome.[42] This approach shifts the onus of considering risk aversion onto the user or reader of the results. In our experience, however, many users of the results might struggle with making sense of the two independent dimensions of threat assessment. We have adopted the practice of focusing on the expectation of burden, and for the extinction potential and major catastrophic risks, the expectation of amenable burden, which simplifies the presentation and comparison of results. Our ultimate approach, outlined in this section, which largely focuses on the expected values of threats for most risks, is supplemented by special consideration for threats with extinction risk, in line with arguments that extinction risks (ie, nuclear conflict and malicious use of AI) warrant special attention.[43,44] Focusing on the expectation of burden, which is the product of probability and harm, means that some threats that have the potential to cause a very high degree of harm but with a very low probability of that harm occurring will have a moderate expected value of burden. Designating such threats as having extinction potential acknowledges the possibility of the tail risk of extinction while still allowing for comparison of expected harm across threats.

1.4 Reference scenarios and reflexivity

We begin by first estimating a reference scenario, that is, what we think is probabilistically most likely to occur if current trends continue. In some published literature, the reference scenario is often referred to as a forecast depending on the field, such as in economic forecasting; reference scenarios have been published for the GBD on a country-by-country basis out to 2050 with methods developed by the Institute for Health Metrics and Evaluation (IHME).[9] The reference scenario includes within it the expected changes in key drivers of future health; in other words, the reference scenario is conditional on actions that are likely to be taken. As Robert E Lucas[45] has argued, if we ignore endogenous policy and individual responses, forecasts will likely be incorrect. In the case of climate change, the reference scenario takes into consideration that countries will act to reduce annual greenhouse gas emissions such that they peak in 2040 and then decline, following the Representative Concentration Pathway 4.5 (RCP4.5) and Coupled Model Intercomparison Project, version 6 (CMIP6) ensemble.[46,47] However, the RCP4.5 scenario includes considerable action to decarbonise energy and transport sectors and suggests that global carbon emissions per unit gross domestic product (GDP) would drop to levels that have never been observed in any country. What if reference scenario forecasts conditional on these actions undermine the political consensus to take action?

The possibility that the future is a function of the forecast has been referred to by many terms: self-defeating or self-fulfilling forecasts, reflexivity, or endogenous response.[48,49] Although it substantially increases the analytical work required, we have decided to address this issue explicitly by estimating two alternative scenarios for each threat for extinction potential risks and major catastrophic risks in addition to the reference scenario. Specifically, we develop a plausible worst and a plausible best scenario for each threat that distinguishes it from implausible, often highly aspirational scenarios. The difference between the cumulative burden in the plausible best and worst scenarios, after accounting for competing risks (see section 1.7 for details), will then be the estimate of cumulative expected amenable DALYs related to each threat over the period from 2025 to 2100. For our approach to be credible, we need to articulate first principles for choosing plausible best and worst alternative scenarios that avoid the pitfalls of underestimating or overestimating each threat. Proposals for how to operationalise this are discussed in the following paragraph.

Defining the amenable nature of each threat as the difference between a plausible best and plausible worst scenario has a profound impact on the results of threat assessment. For example, given current knowledge and technology, the difference between plausible best and plausible worst scenarios for the impact of supervolcanoes would arguably be zero. In terms of our deliberations, we would then give no priority to addressing supervolcanoes as a 21st century global threat to health. This decision does not mean that there is no risk of supervolcanoes, only that according to current knowledge, this risk is not amenable to change. There is a second more polemic effect of this approach: in the literature on some threats, comparisons are made between plausible worst-case scenarios and some previous state of nature, such as in the climate change literature with comparisons to preindustrial levels of temperature. No plausible best

scenario for the 21st century suggests that preindustrial levels of temperature can be achieved, so we would not use this comparison to assess climate change impacts for the Commission. Specifically for climate change, there is an exception to this observation; namely, the possibility of breakthrough innovation. We have chosen not to incorporate breakthrough innovation in our plausible best scenarios; the reasons for which are discussed in section 3.

1.5 Quantitative and qualitative methods

Wherever possible, we use observations of the past and statistical models to try and characterise both the reference scenario and alternative scenarios (making different assumptions on the trajectory for aspects of the risk such as greenhouse gas emissions). Some threats such as the development of unaligned artificial general intelligence (ie, AI that is proficient in all aspects of human intelligence, whose goals do not align with those of humanity) or the use of AI to create super pathogens by terrorists, have not occurred to date. In cases where a threat has never appeared, statistical models cannot be built on past data. In these cases, we have resorted to using qualitative methods to estimate the risk of an event. The literature has three approaches to solicit these probabilities: expert opinion, public opinion, or superforecasters (people who consistently make unusually accurate predictions about future events).[50] Comparison of these three estimates shows that, on average, superforecasters produce lower probabilities than experts or, where available, the general public. Experts tend to overestimate the probabilities of bad outcomes and simultaneously overestimate the potential for new technical progress. Since we have only used qualitative approaches for assessing the risk of AI and the risk of nuclear conflict with nuclear famine, both expert biases might be at play. For our qualitative assessment of malicious use of AI and nuclear conflict with nuclear famine, we have used both expert and superforecaster assessments.[51] Notably, the two risks with extinction potential this century are also those that require the use of the subjective assessments of probabilities of extinction.

1.6 Scenarios affect future population size: total versus average and harm versus benefit

Full dynamic modelling of future population health poses some core philosophical and practical challenges above and beyond the inherent uncertainty in future scenarios. At the heart of these issues is the reality that different actions or evolution of threats will change the number (as well as the specific makeup) of future populations. How should these changes be taken into account? For example, increasing the scale-up of education will lower fertility (due to a number of factors, including increased female control over resources and fertility choices, use of birth control, labour market involvement, and shifting cultural norms and roles, etc)[37,52] and thus affect future population due to fewer births but also increased lifespan. The fertility effects would be quite large, so that in an alternative scenario of more rapid scale-up of education, fewer healthy life-years would be lived, but there would also be fewer DALYs due to both reduced fertility and reductions in age-specific death rates and prevalence of diseases.

These types of problems are often captured in the debates between those who desire to maximise total wellbeing in the future (through aggregation of wellbeing across all future individuals) versus those who want to maximise some other metric that removes the effect of total population size, such as average wellbeing. There are compelling philosophical arguments against either position,[16,53–56] which is at least testament to the complexity of this issue. One aspect that has not been explored fully to date is the focus on aggregated harm, in our case aggregated DALYs. A key concern about total wellbeing is that efforts to increase the birth rate would, all other things being equal, automatically increase future total wellbeing. Undesirable policies that violate human rights, such as restricting access to contraceptives, could in some cases increase total wellbeing by increasing the future population. This scenario is often called the pro-natalist critique of total measures of wellbeing. On the other hand, average wellbeing in the future could be increased through equally undesirable actions that worsen the survival of those with low levels of wellbeing.

We have opted to evaluate threats using total expected DALYs, or, more specifically, total expected amenable DALYs in the second stage of our analysis. DALYs are by their nature a negative measure, a measure of harm. Aggregation of a negative measure is not subject to the automatic pro-natalist critique of aggregated wellbeing. Increasing the birth rate would, all other things being equal, increase DALYs. Because aggregation of DALYs appears not to be subject to pro-natalist concerns, we believe our measure of cumulative amenable DALYs is a practical approach to the total versus average problems that have plagued many welfare economics discussions.

1.7 Competing risks framework

Many studies on global threats, such as the health impacts of climate change, pandemics, or conflicts, estimate the number of deaths related to a threat or compare one future with an alternative future. For single-year or short-term assessments, deaths or averted deaths are a reasonable metric. When a longer timeframe is used, however, deaths are a fundamentally poor metric. A simple thought experiment shows the problem. For the current population over age 40 years, when evaluating health impacts over the next 75 years, no deaths are avertable because by age 115 years, effectively all people will have died regardless of the threat scenario. Since death cannot be averted, only accelerated or delayed, the evaluation of threats needs to take into account a

time-based metric (such as DALYs, so that earlier or later death translates into years of life lived). There is also a second inference from this thought experiment. If, in a plausible best scenario, more children survive to be adults, then those adults will eventually die from a range of non-communicable diseases (NCDs) and other conditions more common at older ages, such as dementia; a concept known as competing risks. In other words, averting deaths from one cause does not eliminate those deaths completely but instead returns survivors to the population who remain at risk for other causes of death at older ages. Competing risks can therefore have complex and potentially counter-intuitive effects on future deaths and population across different scenarios. To adequately capture the true amenable burden associated with a threat across causes and over time (ie, to account for the effects of reduced or increased mortality in an earlier age-time period on later mortality and population), a full cohort-component competing risks modelling framework needs to be used. The cohort-component method is the standard demographic approach to forecast population, in which the population is aged forward by age and sex based on scenario-specific fertility, mortality, and migration rates.

Section 2: What is the most probable future if current trends in key drivers persist: the reference scenario

We use the IHME Future Health Scenarios framework, which has been used to generate a reference scenario to 2050, published previously.[9] This set of statistical models is fit to the curated GBD estimates of outcomes and risks from 1990 to 2023 to produce forecasts of disease burden by cause, country, age, and sex for mortality and morbidity. The modelling approach has three components. First, predicting the trajectory for the 88 risk factors in the GBD analysis and select interventions. Second, removing the effect of risk factors modelled in the first component from the GBD estimates of cause-specific mortality rates and fitting general models for each risk-deleted cause to social and economic drivers. Third, an autoregressive model for cause-specific and all-cause mortality that captures factors not explained by either trends in risk factors or socioeconomic drivers. The framework also uses all-cause mortality forecasts in conjunction with forecasts of fertility and migration to produce internally consistent forecasts of population. This combination of modelling strategies allows for a model that has both out-of-sample predictive validity and can be used to explore various alternative scenarios based on the trajectory of risk factors and socioeconomic drivers. Additional details on this modelling strategy are described in the appendix (pp 5–61).

We extend the reference scenario[9] to 2100 and include the effect of threats that have been elaborated for the work of the Commission; we have not included the qualitative assessment of the risks of malicious AI or nuclear conflict in the reference scenario, as these are based on subjective assessments. These additions to the previously published model include pandemics, additional climate change pathways, a more detailed model of conventional war, and explicit modelling of income inequality. We have further updated the previously published reference scenario with various updates of GBD risks and drivers. Details are provided in the appendix. As the models are fit to GBD results, all the limitations of the GBD study also pertain to the reference scenario.

For the work of the Commission, we have also made changes to how the underlying socioeconomic drivers of risk-deleted mortality are modelled. The Socio-demographic Index (SDI) is an index extensively used in GBD that combines lag-distributed income per capita, average years of schooling, and the total fertility rate below age 25 years.[57] This combined measure of a location's social and economic development is a better predictor of underlying mortality than any of the three variables on their own, and it solves a major problem of collinearity between all three variables in the statistical analysis. Underlying cause of death (after removing the effect of risk factors) has been modelled as a function of SDI for many causes and populations. However, to better capture the variation in income distribution across countries and its effect on health outcomes in the future—ie, create a more equity-sensitive SDI—we have modified the computation of SDI to capture aspects of income distribution. We have tested many different formulations of this more equity-sensitive SDI and found the version that is most predictive of health outcomes. This predictive validity is achieved through using median household consumption per capita instead of lag-distributed income per capita. Median household consumption per capita captures the effect in some countries, particularly oil-producing states, where high lag-distributed income per capita does not affect consumption in the majority of households. It also captures the extremes of income distribution where the bottom 50% consume dramatically less than the top 50% of households. Due to smoothing of consumption over time by households, consumption per capita tends to be more stable and resistant to shocks. We tested other formulations, such as using household consumption per capita of the bottom decile or quintile, but median was the most predictive of health outcomes. This equity-sensitive SDI is also more predictive of age-specific mortality rates than the SDI alone, confirming the longstanding literature that the distribution of income or consumption is an important determinant of health.[58–60]

We have developed a dynamic model of GDP growth that captures the interaction between economic growth and CO_2 emissions and the consequent effect of temperature change on economic growth. To date, this is the only model that captures the complex bidirectional,

causal interaction between climate and economic growth. Figure 4A shows the forecasted global trends in GDP from this model used in the reference scenario. This model has several advantages. First, it captures the effect of demographic change on economic growth by first modelling GDP per working-age adult and then multiplying by the expected number of working-age adults in the future from demographic forecasts. Second, human capital improvement is captured in the models as an important driver of the GDP growth rate. Third, agricultural GDP per worker is also a function of temperature; namely, higher temperatures reduce agricultural GDP. Fourth, it includes the well characterised tendency for GDP per capita growth rates to slow as economies become larger. Notably, GDP forecasts used for the reference scenario are much lower than those used in the CMIP6 climate scenarios[61] and closer to those produced for select countries by the Organisation for Economic Co-operation and Development (OECD).[62] The differences in GDP forecasts are most extreme in parts of sub-Saharan Africa, where some Intergovernmental Panel on Climate Change scenarios have GDP per capita growing 12-fold over the next 75 years compared with minimal growth in the past 75 years. Slower expected growth in sub-Saharan Africa increases the effect of many threats in that region compared with higher GDP per capita forecasts. Figure 4B shows that if economic growth follows the modelled trajectories, the gap in absolute terms and in relative terms between low-income and high-income countries will widen, not narrow.

Unfortunately, the combination of much higher population growth rates in the low-income nations, combined with relatively slow expected economic growth in these nations despite demographic shifts, means the number of individuals living in extreme poverty (defined

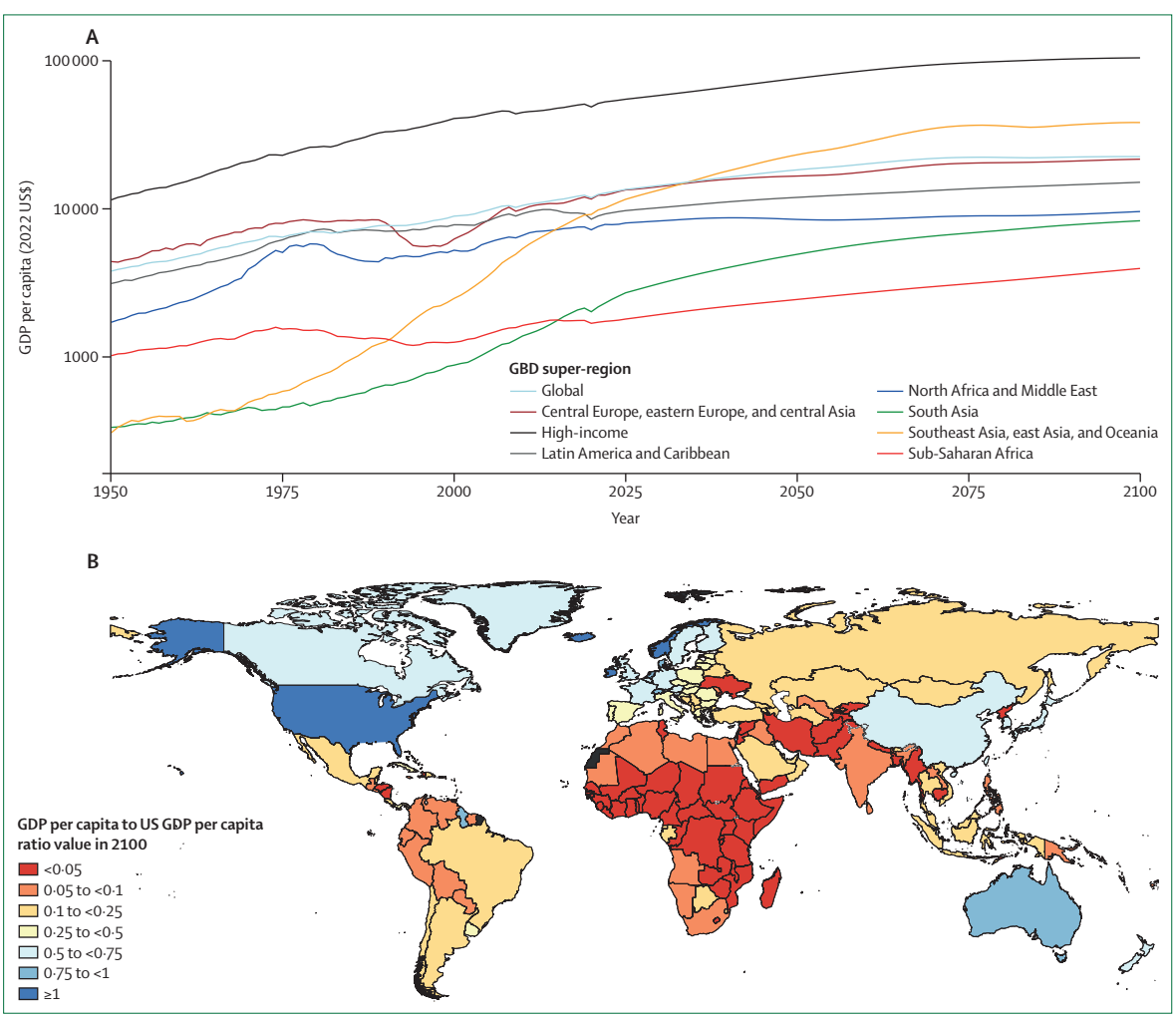


Figure 4: **Historic and forecasted trends in GDP per capita**
(A) Projected trends in GDP per capita, globally, and by GBD super-region (1950–2100). These trends are used in the reference scenario. GDP per capita is in 2022 US$. (B) Map of the ratio of GDP per capita to US GDP per capita in 2100, for 204 countries and territories; forecasts presented in this panel are for the reference scenario. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. GDP=gross domestic product.

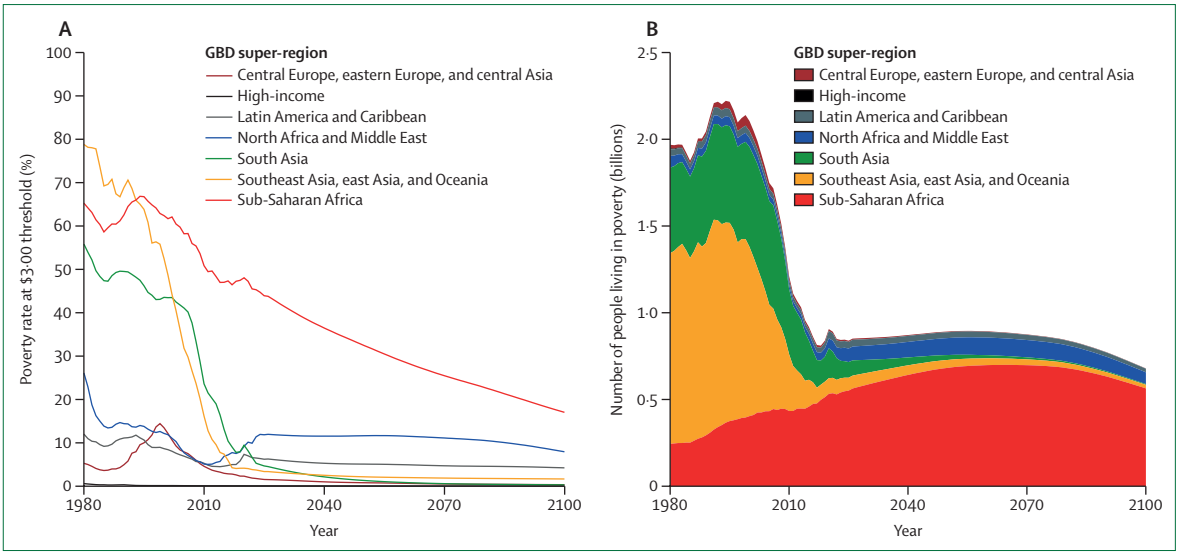


Figure 5: **Historic and forecasted trends in extreme poverty by GBD super-region, 1980–2100**
Extreme poverty rate (A) and number of people living in extreme poverty (B) by GBD super-region, 1980–2100. Extreme poverty is defined as less than $3·00 per day in 2021 purchasing power parity-adjusted dollars. Forecasts presented in this figure are for the reference scenario. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

as less than $3·00 a day in 2021 purchasing power parity-adjusted dollars) in sub-Saharan Africa will increase until late in the century (figure 5).

Extreme poverty rates and counts declined in much of the world over the past 40 years (figure 5), particularly in southeast Asia, east Asia, and Oceania and in south Asia. In much of sub-Saharan Africa, however, slow economic growth accompanied by rapid population growth has contributed to increased numbers of people in extreme poverty that will continue to increase in the coming decades. Climate models show that these same areas of sub-Saharan Africa are likely to experience the most impactful increases in temperature.[61] Rising extreme poverty in a world with declining DAH will create populations that might be under severe duress.

The reference scenario for educational attainment at age 25–29 years is based on the relationship between change in educational attainment and the level of educational attainment (appendix p 140). Empirical fitting of this relationship suggests that educational attainment will stop increasing when education levels reach 17·2 years of schooling among males and 18·5 years among females. Using these relationships, we get the mean level of education forecasted to 2100 by GBD super-region (appendix p 141). The functional form of the curves suggests that countries appear to follow conserved trajectories in change in educational attainment. Rates of change in educational attainment at age 25–29 years are not related to income per capita after controlling for level of education. In the reference scenario, this leads to more progress in educational attainment in sub-Saharan Africa, for example, than in GDP per capita. Because educational attainment is such a powerful driver of fertility and mortality, these trends have an important effect on the reference scenario.[63] Moreover, the divergence in economic growth and educational attainment might also contribute to intensified out-migration in some parts of sub-Saharan Africa, which will likely be compounded by climate change.

Future trends in health also depend on the trends in a number of key behavioural, environmental, and metabolic risk factors. For the reference scenario, trends in these risk factors by location are modelled with an ensemble modelling approach that forecasts past trends into the future using a variety of different models. The mix of models used for the forecast is based on out-of-sample predictive validity testing. The appendix (p 142) shows the global trends for key risk factors driving future change. We expect notable increases in the next 75 years in high adult BMI, high blood pressure, and high temperature. Other drivers such as smoking and child wasting are expected to decline.

Demographic change, both ageing of populations and the relative shift in global population share over the century, has important implications for many health threats. Figure 6 shows global population in the reference scenario is expected to peak at 9·51 billion (95% UI 8·75–10·4) people in 2064 and then decline. Over the next 75 years, the share of the world's population that lives in sub-Saharan Africa is expected to increase from 15·3% (14·7–16·1) in 2025 to 36·7% (33·4–40·2) in 2100. This dramatic shift in global population towards sub-Saharan Africa will shift the global disease patterns more towards those seen in this super-region. Declines in global population influence our assessment of the DALYs

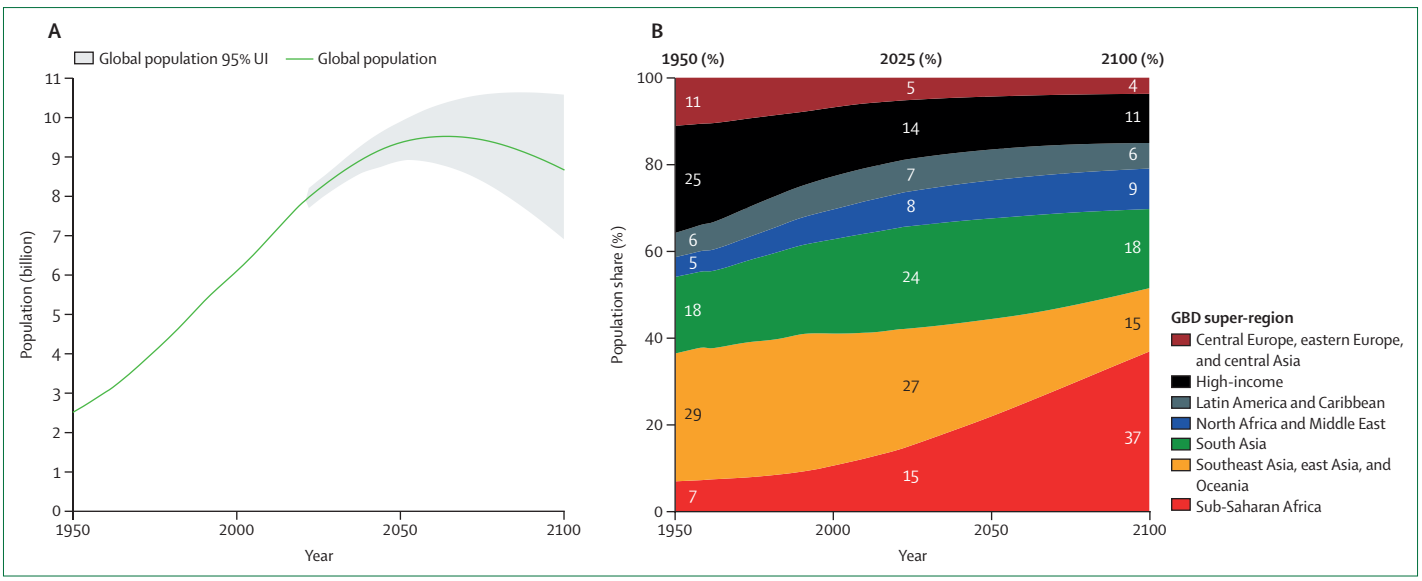


Figure 6: **Historic and forecasted trends in global population, 1950–2100**
Global population trajectory (A) and composition of global population by GBD super-region (B), 1950–2100. Forecasts presented in this figure are for the reference scenario. The forecasted population in 2100 is 8·7 billion and the peak population is 9·5 billion in 2064. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

attributable to each threat over the rest of the century. Because we use a dynamic model of the population, changes in different scenarios alter future population size and distribution by changing the death rates and, in some cases, the birth rates as well. The phenomenon of competing risks is particularly important in interpreting our findings. If, for example, an intervention rapidly reduces future tobacco consumption, the individuals who do not die from tobacco-related diseases will be exposed to other conditions, such as dementia or cancers, leading to increases in death numbers from those other conditions.

Despite the threats outlined in this Commission report, we expect life expectancy to improve over the century for both males and females in the reference scenario (figure 7). General improvement in life expectancy is all the more remarkable given worsening factors such as climate change, obesity, or mental disorders. From 2025 to 2100, healthy life expectancy at the global level is expected to increase by only 5·69 years (95% UI 1·82–8·21) compared with 8·65 years (3·99–11·69) for life expectancy. The slower progress in healthy life expectancy means the population, on average, will spend more years in poor health in the future than today due to conditions such as mental disorders, musculoskeletal disorders, or diabetes that have a larger effect on years lived with disability (YLDs) than years of life lost (YLLs).

The appendix (p 143) shows the evolution of future deaths broken down into 22 major causes or clusters of causes. At the global level, the number of deaths will increase due to population growth and ageing even though the age-standardised rates for most (not all)

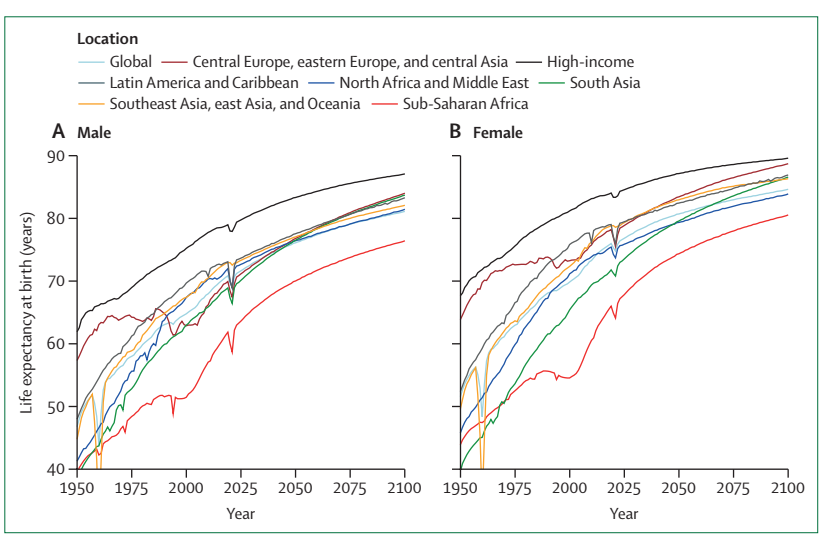


Figure 7: **Historic and forecasted trends in life expectancy at birth by sex, 1950–2100**
Life expectancy at birth for males (A) and females (B) globally and by GBD super-region, 1950–2100. Forecasts presented in this figure are for the reference scenario. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

diseases are declining. The epidemiological transition captured in the reference scenario will play out in all regions. No country will have a preponderance of burden due to communicable, maternal, neonatal, and nutritional disorders by the end of the century, but the share due to this cluster of poverty-related conditions remains stubbornly large in low-income regions late in the century (appendix pp 144–45).

Figure 8 shows the global cumulative disease burden (measured in DALYs) between 2025 and 2100 by GBD level 3 cause in the reference scenario. NCDs will

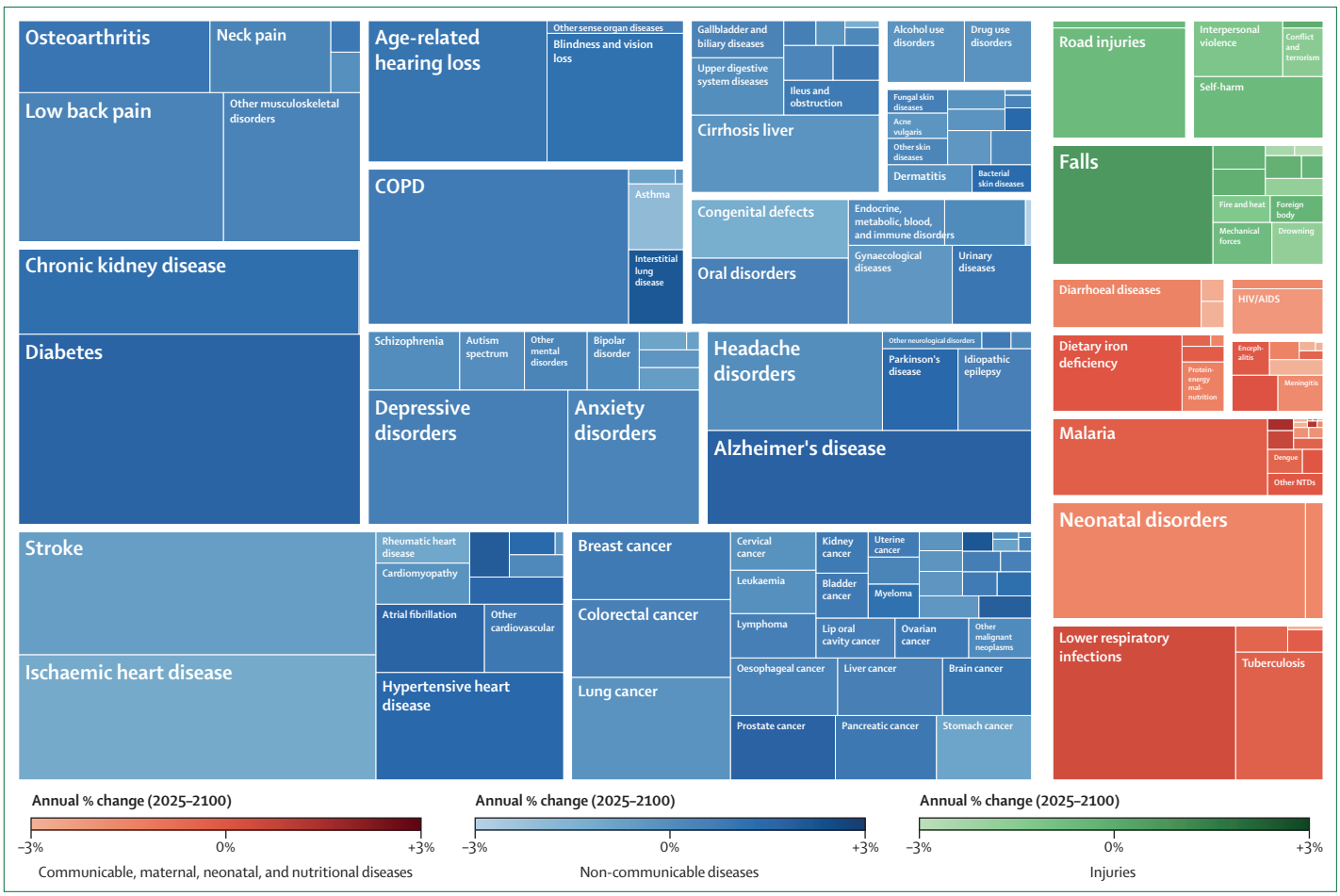


Figure 8: **Global cumulative DALYs due to GBD level 3 causes from 2025 to 2100**
Forecasts presented in this figure are for the reference scenario. Non-communicable diseases are shown in blue; communicable, maternal, neonatal, and nutritional diseases in red; and injuries in green. COPD=chronic obstructive pulmonary disease. DALYs=disability-adjusted life-years. NTDs=neglected tropical diseases. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

dominate the global disease burden over the next 75 years (shown in blue). The largest contributors to NCDs will be diabetes, ischaemic heart disease, stroke, and chronic obstructive pulmonary disease (COPD). There are also large contributions expected from musculoskeletal disorders, mental disorders, hearing loss, and vision loss. Among injuries, road traffic injuries and falls will likely make the largest contributions. The large number of causes that are still prominent over the century highlights how NCDs cannot be reduced to a small number of conditions. Surprisingly, because of demographic shifts towards low-income countries, communicable, maternal, neonatal, and nutritional disorders will still be major contributors, with particularly prominent contributions from neonatal disorders, malaria, pneumonias, and tuberculosis.

Using standard GBD methods, we can approximate future attributable burden by risk factor and cumulate the future attributable DALYs by risk (figure 9). Given the obesity pandemic and its link to fasting plasma glucose, the largest future risks are high fasting plasma glucose and high BMI, followed by high blood pressure and diet. Air pollution, tobacco, and malnutrition remain major future risks in terms of attributable burden. Non-optimal temperature (heat and cold), alcohol, and occupational exposures come next in the list of future attributable burden.

The reference scenario is simply what is likely to occur based on observed trends and relationships, but breakthrough technology can alter these futures, as can unexpected events. The uncertainty in the reference scenario is large, and the gaps between nations can be much larger or smaller than the average result emphasised here.

Section 3: The pyramid of threats

Using the reference scenario, the Commission classified a large set of diseases, risks, socioeconomic factors, and other threats into a pyramid of severity. Figure 1 shows this pyramid. At the top, we included the two threats that carry extinction potential between now and 2100. These were malicious AI, including using AI to create new

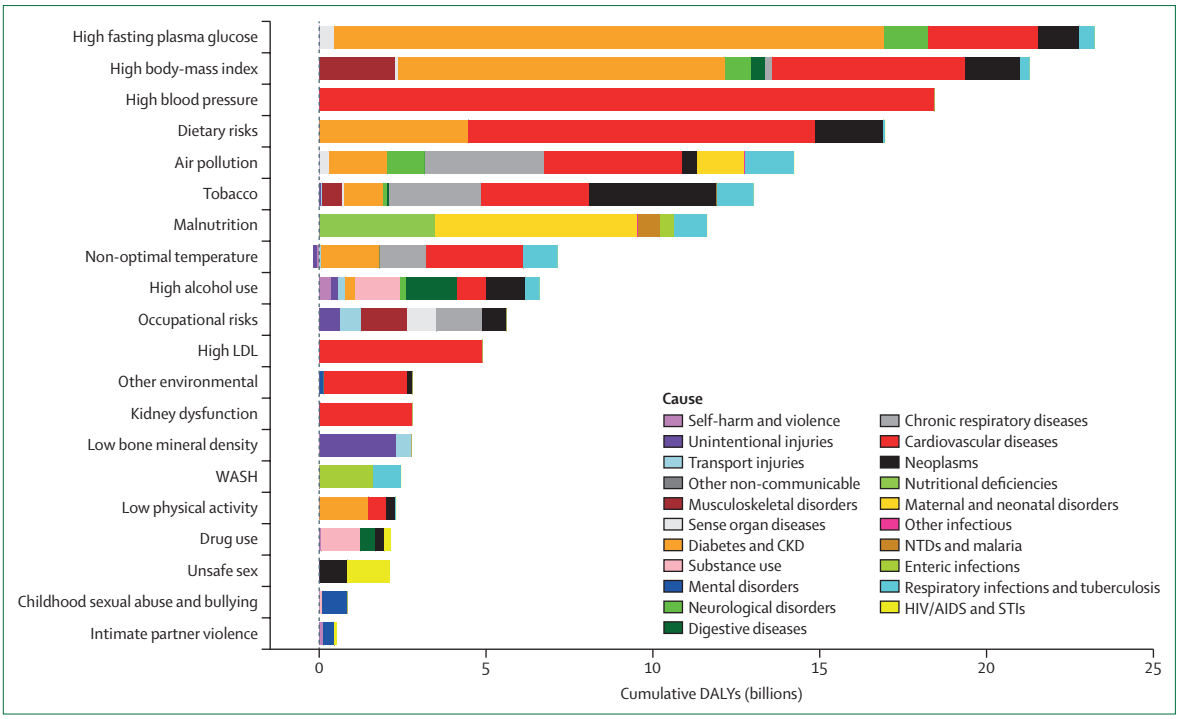


Figure 9: **Global cumulative DALYs attributable to GBD Level 2 risk factors by cause**
DALYs are cumulative from 2025 to 2100. CKD=chronic kidney disease. DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. NTDs=neglected tropical diseases. STIs=sexually transmitted infections. WASH=water, sanitation, and hygiene.

bioweapons, and nuclear conflict with nuclear famine. Of note, these threats do not have formal quantitative models supporting their assessment and depend critically on subjective assessments. Other authors, such as Vaclav Smil[64] and Toby Ord,[18] have explored other potential threats that could be considered as having extinction potential. First, asteroid collision with the Earth and supervolcano eruption can, in theory, cause human extinction. However, we did not include them in our pyramid of threats because the probability of these events between now and 2100 was exceedingly low, resulting in low amenable burden. Existing technology also has extremely limited ability to mitigate a celestial object large and fast enough to cause existential risk, notwithstanding the 2022 NASA Double Asteroid Redirection Test, which showed that kinetic deflection is feasible for a small asteroid.[65] Second, mirror life (ie, manufactured, self-replicating organisms composed entirely of mirror-image biological molecules) was the source of considerable discussion. We ultimately did not include mirror life as an extinction potential threat for the following reasons. The technology to create mirror bacteria does not yet exist, although it might in the next one to three decades. The publication and call to action in a paper published in *Science* coauthored by 38 scientists on the risks of mirror life has already led to many, if not all, of the labs working on mirror life stopping work.[66] If mirror life were to be developed, it would be by bad actors empowered by AI. As such, we believe the AI threat, including bioweapons, encompasses the bad actor nature of mirror life. In addition, since publication of the *Science* paper, academic commentary has questioned the plausibility of some assumptions underlying the claim that mirror life could pose a catastrophic threat. For example, David Perrin's response to the *Science* article argues that mirror organisms might face substantial biological and metabolic barriers, and that it should not be assumed that existing immune systems would be entirely ineffective against mirror bacteria.[67]

The second category of the pyramid of threats is major catastrophic risks. We included in this category threats that met several criteria. First, based on our reference scenario, the threats account for more than 1 billion cumulative DALYs to the end of the century. For reference, 1 billion DALYs is equivalent to two COVID-19 pandemics, showing that these are critical threats for governments and the global community to address. In addition to causing more than 1 billion DALYs in the reference scenario, there was a reasonable expectation that the analysis of amenability would show substantial scope for policy action. Finally, we excluded some diseases for which funding and policy attention is already at a high level, such as ischaemic heart disease and site-specific cancers. We identified 15 threats in the major catastrophic risk category: air pollution, antimicrobial resistance, childhood malnutrition, climate change, collapse of DAH, conventional conflict, high alcohol use, high blood pressure, income inequality,

low educational attainment, naturally occurring pandemics, obesity, poor mental health, smoking, and unhealthy ageing.

The third category is major risks and causes made up of 99 diseases and risks considered in the reference scenario, all of which will cause more than 500 million DALYs to 2100. Diseases and risks causing less than that are in the fourth and largest category of other risks and causes.

Some potential threats were not modelled in the reference scenario and were excluded for a variety of reasons. First, we excluded threats with insufficient data for robust quantitative modelling (eg, exposure to plastics, heavy metal pollution other than lead, and pesticides) where global exposure data or exposure–response relationships were insufficient to support credible projections to 2100. For some potential threats, such as declining institutional trust, we chose to put these as broader enabling (or disenabling) factors that are discussed in section 8. These enabling factors are much harder to quantify in terms of burden, given current knowledge and data, but are nevertheless crucial to understand. The distinction between some broader socioeconomic drivers and some enabling factors reflects both the availability of methods and the directness of the health pathway. For example, income inequality and low educational attainment have established, measurable DALY burdens, whereas enabling conditions such as governance, trust, and institutional capacity operate even further upstream, shaping societies' capacity to respond to threats across the board rather than generating independently attributable health loss.

Based on the pyramid of threats, we undertook the second stage of the analysis of extinction potential threats and major catastrophic risks, focusing on estimating how much of the future burden was amenable to action. The 17 threats identified in the two top categories of the threat pyramid represent the Commission's best current analysis and will be assessed annually in light of new data, emerging evidence, and unforeseen developments, as detailed in section 9.

Section 4: Assessing amenability of extinction potential and major catastrophic threats: plausible best and worst scenarios

To quantify the health harm from each of the extinction potential and major catastrophic threats that are amenable to policy action, we estimated the difference in cumulative expected DALYs between a plausible best and plausible worst scenario. To ensure our estimates remain conceptually comparable and grounded in reality—rather than aspirational advocacy—we standardised the creation of these scenarios with a three-step historical analysis (with necessary exceptions for unprecedented threats such as nuclear conflict and malicious AI). The analysis of the amenable zone of action in the future also provides a solution to the problem of reflexivity, namely that our reference scenario assumes certain policy actions in the future that could be affected by our forecasts.

We used flexible splines with stochastic frontier analysis to bound the historically observed highest and lowest levels of a threat as a function of SDI or GDP per capita. Historical data were assessed for time-dependence, namely whether there is empirical evidence that the plausible best or plausible worst is shifting over time. Where there was compelling evidence for these shifts, we incorporated time-varying frontiers into the definition of plausible best and worst at a given year in the future. We calculated upper and lower bounds on the rates of change observed across countries over the period 1990 to present to ensure trajectory transitions are also plausible, preventing models from predicting dramatic, unrealistic shifts over very short periods (velocity frontiers).

Our scenarios incorporate historical rates of technical innovation, but they explicitly exclude hypothetical breakthrough technologies (eg, cheap nuclear fusion or atmospheric carbon removal). Breakthroughs are inherently unpredictable and could equally reduce harm in both the best and worst scenarios. Therefore, excluding them prevents bias in calculating the cumulative amenable DALYs, although future research and development prioritisation research should consider modelling these separately.

Figure 2 illustrates the construct for plausible worst and plausible best scenarios. The zone defined between the two curves in panel D is the zone of the possible. The reference scenario lies between the two boundaries and is one possible future conditional on a particular set of policy actions. Considering the whole zone gives us a more robust sense of what is possible, not subject to self-defeating or self-fulfilling forecasts. The area between the plausible best and plausible worst curves, which represents cumulative amenable DALYs, also provides policy makers with a sense of how much their actions can alter the trajectory of human health. Both the plausible worst and plausible best trajectories are expected values, that is, the product of probability times harm in each scenario. The different trajectories within plausible best and plausible worst are weighted by their probabilities to generate the expectation (or average) trajectory for each scenario. An extinction potential threat does not automatically have the largest amenable burden because this assessment takes into account the probability of the extinction event occurring.

Because the Commission chose to evaluate threats to the end of the century, the degree of uncertainty varies substantially across the 17 threats. Established risks such as tobacco use or child malnutrition rely on extensive historical datasets, resulting in narrower uncertainty bounds in the future scenarios. Conversely, threats lacking a well established evidence base regarding future trajectories or intervention efficacy—such as malicious use of AI and nuclear conflict with nuclear

famine—carry high uncertainty, but the extensive policy discussion underway and their potential magnitude demand their inclusion.

Section 5: Quantification of cumulative expected amenable DALYs for extinction potential and major catastrophic threats

This section outlines how we developed plausible best-case and plausible worst-case scenarios and the implied amenable burden by age, sex, cause, and location for each extinction potential and major catastrophic threat. More complete detail on the analysis of each of these threats, including the construction of the reference, plausible best, and plausible worst scenarios for each threat, is described in the appendix (pp 5–102).

5.1 Air pollution

Ambient particulate air pollution accounted for 4·42% (95% UI 3·57–5·40) of global DALYs in 2023 and has been slowly increasing in terms of both the number of DALYs and the share of total DALYs attributable to this risk.[68] These increases reflect population shifts and ageing of the population in exposure areas into the age groups with NCDs affected by ambient air pollution. Although there has been progress reducing ambient particulate pollution in high-income countries, in some parts of Latin America and Asia, exposure remains high, despite notable improvements in the latter region. Ambient particulate air pollution is correlated with SDI and GDP per capita (appendix p 146).

$PM_{2·5}$ (particulate matter pollution) concentration is weakly correlated with CO_2 emissions. The largest driver of $PM_{2·5}$ concentration is national policy regulating industrial, power generation, transport, and agricultural emissions.[69] Because $PM_{2·5}$ is also related to income per capita, its effects tend to decline over the course of the century in the reference scenario. Using stochastic frontier analysis, we put upper and lower bounds on the level of $PM_{2·5}$ concentration observed at different levels of nine features: location-specific GDP per capita, global GDP per capita, population density, CO_2 emissions, mean annual temperature, annual days of precipitation, mean annual wind speed, $PM_{2·5}$ emissions from wildfires, and an indicator variable for Persian Gulf states. In the plausible best scenario, global $PM_{2·5}$ concentration steadily drops before plateauing around 2070 (figure 10). In the plausible worst-case scenario, $PM_{2·5}$ slightly increases throughout the century with notable shifts in concentration by region.

Given the large regulatory scope to reduce $PM_{2·5}$ at any given level of income per capita, the difference in DALYs between the scenarios is large. Cumulative amenable DALYs are 1·64 billion (95% UI 1·33–1·95), with the largest potential amenable DALYs in south Asia. Like smoking, air pollution is a threat for which the policy prescription is well known and demonstrated effective in many settings. However, implementing regulations to reduce air pollution can impose costs at any given level of GDP per capita. We have not quantified the economic impact of the regulation required to reduce $PM_{2·5}$. In some cases, such as India, the cost might be political rather than economic, as high $PM_{2·5}$ levels are related to agricultural practices, which the government is reluctant to regulate.

5.2 Antimicrobial resistance

Antimicrobial resistance occurs when bacteria, viruses, fungi, and parasites evolve and no longer respond to the drugs designed to kill them, making infections harder to treat. Antimicrobial resistance has been recognised as a global health threat for decades, since concerns of the emergence of penicillin-resistant *Staphylococcus aureus* strains in hospital settings were raised post-World War 2.[70] The emergence of methicillin-resistant *S aureus* in the 1960s complicated treatment protocols and increased mortality rates[71] and became a prevalent cause of hospital-acquired infections worldwide.

Throughout the subsequent decades, the overuse and misuse of antibiotics in human medicine and potentially in agriculture exacerbated rates of antimicrobial resistance for some pathogen–drug combinations. By the early 2000s, multidrug-resistant tuberculosis and resistance in pathogens such as *Neisseria gonorrhoeae* and *Plasmodium falciparum* posed substantial treatment challenges.[72,73] In 2014, WHO published its first global report on antimicrobial resistance surveillance, highlighting the widespread occurrence of resistance across multiple regions and the critical need for comprehensive monitoring and intervention strategies.[74]

Despite increasing attention on this threat, such as the WHO's Global Action Plan on AMR in 2015,[75] a 2016 UN General Assembly resolution,[76] and the adoption of SDG indicator 3.d.2[77]—which aims to reduce bloodstream infections caused by antimicrobial resistance—progress

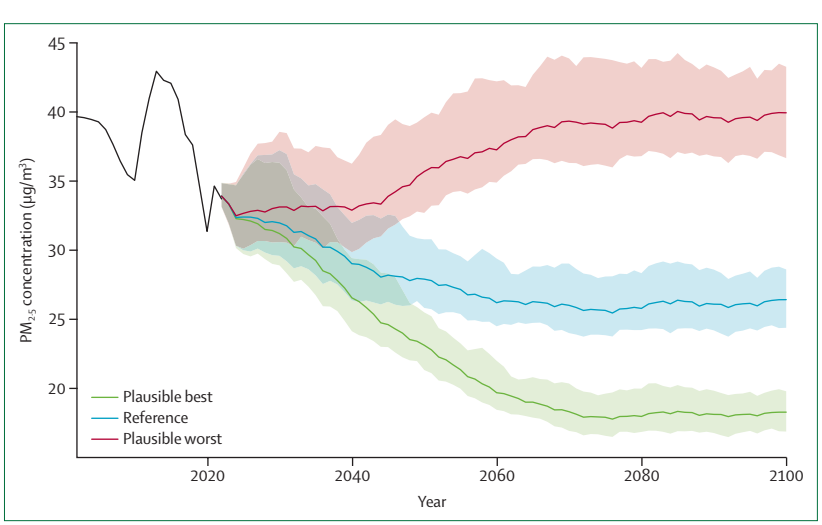


Figure 10: **Global $PM_{2·5}$ concentration scenarios, 2002–2100**
$PM_{2·5}$=particulate matter pollution.

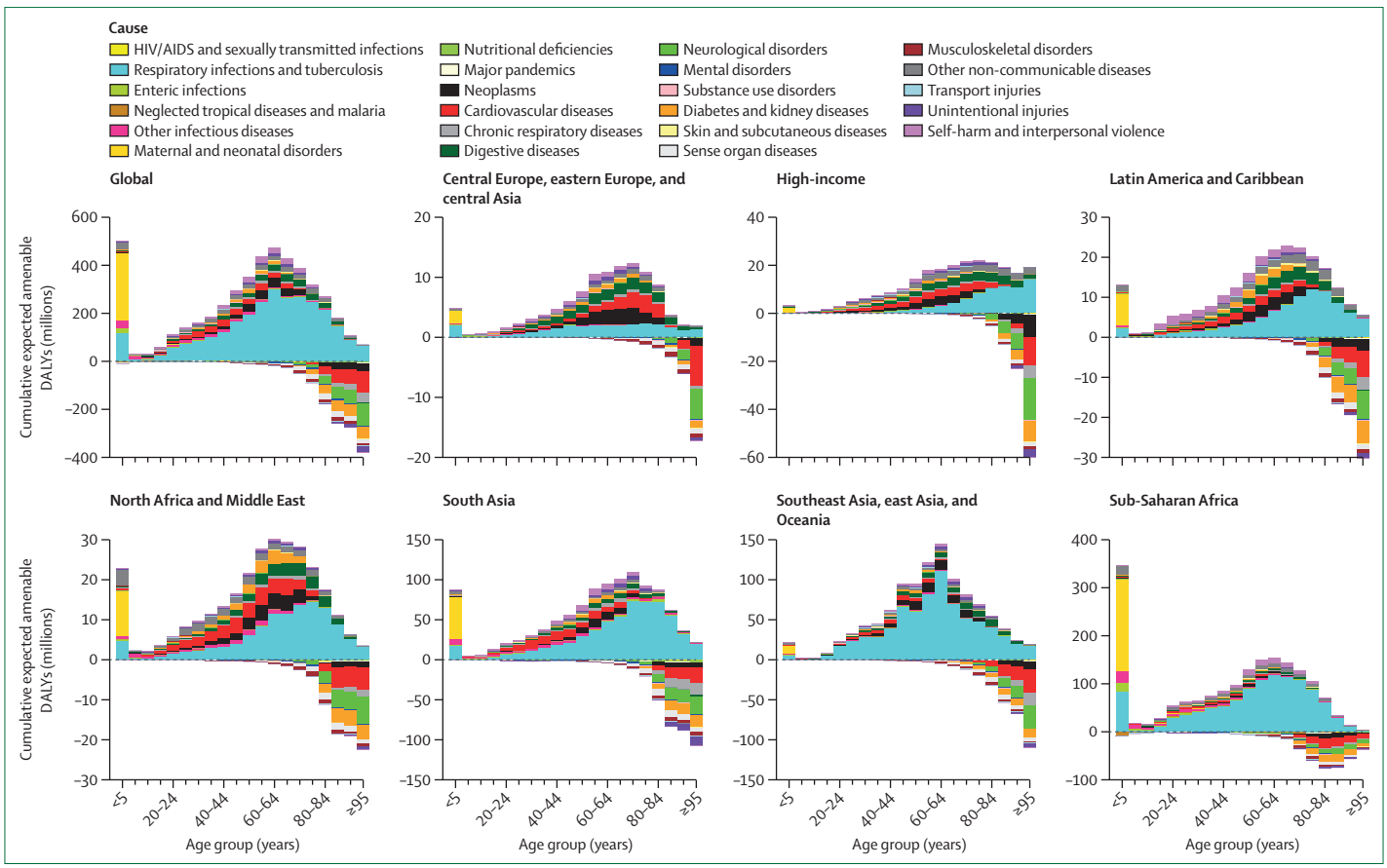


Figure 11: **Cumulative expected amenable DALYs related to antimicrobial resistance by age and cause, globally and by GBD super-region**
DALYs are cumulative from 2025 to 2100, with cumulative expected amenable DALYs referring to the difference in cumulative DALYs between the plausible best and plausible worst scenario for each threat. DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

in mitigating this threat has been uneven. A study on the global burden of antimicrobial resistance in 2019 estimated that 4·95 million deaths associated with bacterial antimicrobial resistance and 1·27 million deaths attributable to bacterial antimicrobial resistance occurred in 2019 alone.[78]

A 2024 study, published in the *Lancet*,[79] represents the most comprehensive assessment of the global burden of antimicrobial resistance from 1990 to 2021, with forecasts extending to 2050. This study shows trends in antimicrobial resistance burden vary widely based on age group: from 1990 to 2021, deaths due to antimicrobial resistance decreased by 50% among children younger than five years (likely due to increased vaccination, better sanitation, and improved access to health care); however, during the same period, deaths due to antimicrobial resistance increased by over 80% in adults aged 70 years and older (likely associated with ageing populations, higher rates of hospital-acquired infections, and increased antibiotic use in long-term care settings).[79] Regional disparities are also highlighted in this study, with the highest antimicrobial resistance mortality rates found in sub-Saharan Africa and south Asia, where insufficient access to quality health care and high antibiotic misuse contribute to resistance. By contrast, high-income regions have lower antimicrobial resistance mortality rates but experience a rising burden among older adults and hospitalised patients.

We have constructed plausible best and worst scenarios by fitting stochastic frontiers to antimicrobial resistance burden as a function of GDP per capita for 19 (Level 2) causes (appendix pp 61–103). Our scenarios bundle improvements in drug quality, access, and prescribing together with biological resistance, as these are correlated with GDP per capita. These plausible best and plausible worst scenarios for each of the 19 causes have been combined to get an overall plausible worst and overall plausible best scenario for antimicrobial resistance.

Figure 11 shows the cumulative amenable DALY for each GBD super-region by cause due to antimicrobial resistance. The largest amenable burden is related to respiratory infections and tuberculosis, but with contributions from a wide range of other causes where iatrogenic infections with drug-resistant pathogens are

common. The prominence of DALYs related to these other causes is greater in north Africa and the Middle East; central Europe, eastern Europe, and central Asia; the high-income super-region; and Latin America and the Caribbean than in the three other super-regions or globally. In total, we estimate 3·44 billion (95% UI 2·84–4·06) cumulative amenable DALYs related to antimicrobial resistance.

5.3 Childhood malnutrition

Child growth failure, including stunting, wasting, and underweight, accounted for 13·2% (95% UI 9·87–15·3) of global DALYs in 1990 and declined to 3·03% (1·82–3·93) of global DALYs in 2023.[68] This decrease is largely due to three factors: the shift in population to older age groups; the reduction in malnutrition-related causes due to other reasons such as lower respiratory infections and diarrhoeal diseases; and the decline in prevalence of stunting, wasting, and underweight. The progress in reducing child malnutrition has slowed since 2019 as the global birth cohort has shifted towards low-income countries with higher rates, such as in the Sahel region. Progress at the national level, however, can obscure substantial variation within countries. Within countries, child growth failure remains concentrated among the lowest-income households, meaning that national-level progress in reducing stunting, wasting, and underweight can mask persistent high rates among the most vulnerable populations.

In the reference scenario, we expect all three measures of childhood malnutrition to continue to decline. Figure 12 shows the relationship between child underweight and SDI, with upper and lower bounds estimated with stochastic frontier analysis. In general, the correlation between measures of childhood malnutrition and GDP per capita is quite high (0·7). There is a unique pattern where stunting in south Asia is higher than expected for GDP per capita, and wasting is higher than expected in parts of sub-Saharan Africa. Although the correlation between sociodemographic development and child growth failure is high, there is still considerable variation at any given level of SDI. The wide scope between the plausible best and plausible worst frontiers translates into considerable policy scope to lower the burden of child malnutrition at any given level of development.

Cumulative amenable DALYs related to child growth failure total 1·02 billion (95% UI 0·673–1·62). This assessment of the threat does not take into account the relationship between stunting of children and human capital development. Continued high rates of stunting might have long-term effects on cognitive function and ultimately on economic productivity. Child growth failure, particularly stunting, might also decrease school performance. The World Bank's human capital index has emphasised the crucial role of stunting in the measurement of human capital and ultimate economic output. Expanding the scope of the threat analysis to include economic growth might give more priority to childhood malnutrition and its link to food systems.

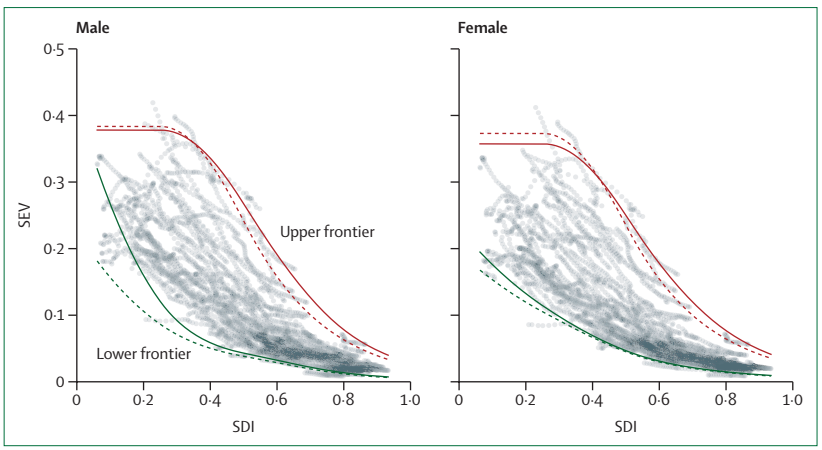


Figure 12: **Relationship between child underweight and SDI, 1990–2021**
Each country-year of child underweight SEV, a severity-weighted measure of exposure, and SDI level is depicted by a grey point. For 2021, upper frontiers are depicted by solid red lines, and lower frontiers by solid green lines. For 1990, upper frontiers are depicted by dashed red lines, and lower frontiers by dashed green lines. SEV=summary exposure value. SDI=Socio-demographic Index.

5.4 Climate change

In 2023, heat contributed to 17·5 million DALYs or 0·6% of global burden.[68] In 2014, WHO forecasted the effects of climate change on health through heat-related mortality in elderly people, mortality associated with coastal flooding, diarrhoeal disease mortality in children younger than 15 years, malaria, dengue, and stunting.[80] A decade later (2024), the World Bank evaluated a narrower set of pathways: dengue, malaria, diarrhoea, stunting, and extreme heat.[81] Although both analyses recognised that there were other potential pathways, WHO and the World Bank concluded these were the only pathways for which there was sufficient evidence to quantify specific effects. The Commission sought to expand the set of pathways analysed through which climate change directly and indirectly affects human health. Climate, more than some of the other threats, is expected to have highly heterogeneous impacts across countries, with the greatest burdens often in the lowest-income and most vulnerable communities.

Although climate change will profoundly affect human welfare through non-health mechanisms, such as the economic devastation of local agriculture or physical loss and damage from extreme weather, the scope of this analysis remains strictly focused on quantifiable human health outcomes. Another major pathway for climate impact will be through mass migration, but that has also not been considered for lack of reliable information on population movement at the required resolution. To date, there are no global models of location-specific migration built from population data that could be used. WHO and

World Bank analyses, for example, used national population estimates from the United Nations Population Division of the Department of Economic and Social Affairs World Population Prospects, which assumes the distribution within countries remains constant. The UNPD models do not consider climate change.

Evaluated health pathways

To study the health impacts of climate change, we built upon and elaborated on existing epidemiological and climatological models, largely using the CMIP6 ensemble. We evaluated the expected amenable health burden mediated through the following core pathways: direct effects of temperature (both increased heat and decreased cold) on multiple infectious, non-communicable, and injury causes (eg, lower respiratory infections and road injuries); direct and indirect effects of tropical cyclones; direct and indirect effects of floods including diarrhoeal diseases, cholera, and NCDs; exposure to wildfire and non-wildfire fine particulate matter ($PM_{2·5}$) exacerbated by climate change; shifting ecological suitability of malaria and dengue; increased food insecurity and malnutrition; and reductions in rural income per person in agrarian societies. Table 1 outlines the pathways included and evaluated for this analysis.

Some pathways were partially included in the analysis (table 1), such as the effects on water, sanitation, and hygiene via the impacts of flooding on cholera and diarrhoeal disease, and the health effects resulting from health-system disruption, through impacts on respiratory and cardiovascular disease following tropical cyclones and floods. Climate change might also alter the ecology and transmission of additional pathogens beyond malaria and dengue. We evaluated cause-specific mortality in relation to daily temperature for 40 infectious diseases and found sufficient evidence of a relationship for lower respiratory infections, but not other infectious diseases. In addition, we included the effect of storms and floods on diarrhoea, cholera, and lower respiratory infections. Although climate change has the potential to amplify other threats through systems-level disruptions, we evaluated many pathways and included those for which the strength of evidence supported inclusion, with additional details described in table 1.

Given the breadth of the included pathways, causes, ages, and locations, this analysis is the most comprehensive to date of the overall future global health impact on climate change. The more limited WHO 2014 analysis indicated an additional 250 000 deaths per year from 2030 to 2050 due to climate change.[80] In 2024, the World Bank updated the WHO analysis (but excluded the coastal flooding pathway) with a focus on climate change-related mortality in 69 low-income and middle-income countries (LMICs), including extreme heat, diarrhoeal disease, malaria, dengue, and undernutrition. This analysis forecasted 63·9 million cumulative deaths from 2026 to 2100 for a middle of the road (Shared Socioeconomic Pathway [SSP]2-4.5) scenario and 131·2 million deaths for a higher emission, regional rivalry (SSP3-7.0) scenario.[81] Notably, this analysis indicated three-fold higher mortality than the WHO analysis, despite the restriction to 69 countries. Differences in methodology for estimating malaria and in socioeconomic and population estimates are likely factors accounting for this difference.[81] Other analyses have focused specifically on the direct effects of temperature or air pollution and indicate the importance of these pathways.

Several proposed pathways were excluded from our primary DALY modelling due to limited effect sizes or highly uncertain causal mechanisms. The pathway proposing reduced micronutrient content in crops grown under higher CO_2 concentrations was excluded, for example. The projected effect is comparatively very small, and micronutrient deficiencies currently contribute a minor fraction to global DALYs. The hypothesis that climate stress will lead to increased interstate wars was excluded. Current conflict literature indicates that, while plausible, specific pathways are not well established and effects on inter-group violence are small, especially in comparison to other drivers.[82–85] Interpersonal violence, often included in climate-conflict analyses, was explicitly included in our temperature analysis as a cause of death. Drought is also suggested to negatively affect health, for example through reduced food and water security or mental health effects. CMIP6 models predict increased drought in specific locations; however, quantification is challenged as model uncertainty indicates that the location of future drought is more reliably projected than its severity. There is insufficient direct, large-scale epidemiological evidence for claims that rising sea levels and subsequent saltwater intrusion into fresh water will broadly increase hypertension rates. Regional famine was also excluded as a standalone modelled pathway as its occurrence depends on governance, market access, and humanitarian response and no CMIP6 models project famine events directly. The average health effects of regional famines are partially captured through the child malnutrition and rural income pathways. Consistent with this approach, GBD 2023 documents a 67% decline in global protein-energy malnutrition mortality between 1990 and 2023, from 9·1 to 3·0 deaths per 100 000 people.[86] Other proposed pathways including climate change leading to increases in BMI, antimicrobial resistance, and lower educational attainment are not supported by panel data analysis (table 1). However, climate change nonetheless acts as a systemic risk amplifier and has the potential to affect the magnitude of several of the other threats assessed in this Commission in ways that are not yet reflected in the data.

Climate change will likely act as a major threat multiplier for human migration, compounding existing economic and cultural drivers. High-income nations are already highly urbanised, and most models predict

	Mechanism	Status	Basis or rationale
Pathways quantified in the analysis			
Ambient heat and cold (mortality)	Direct effect of high and low ambient temperature on mortality, via the temperature–mortality, exposure–response relationship applied across all locations and populations; this analysis evaluated 130 causes of death and found significant associations with 16 distinct causes (stroke, hypertensive heart disease, ischaemic heart disease, cardiomyopathy and myocarditis, COPD, lower respiratory infections, type 2 diabetes, chronic kidney disease, road injuries, drowning, exposure to forces of nature or mechanical forces, other unintentional injuries, self-harm, interpersonal violence, and other transport injuries)	Included	Starting with all (N=176) level 3 causes in the GBD cause hierarchy, we first reduced the set of potential causes by excluding causes (n=44) for which no deaths were recorded in our mortality datasets; we also excluded two causes for which vital registration data are not used to model mortality due to known inconsistencies in classification practices across countries (ie, dementia and protein-energy malnutrition); we estimated relative risk surfaces and uncertainties for all remaining (n=130) level 3 causes in the GBD cause hierarchy; non-significant relationships were observed for 114 causes, including many infectious diseases; these direct effects of temperature are the dominant pathway in our analysis, consistent with previous WHO (replicated in the recent World Bank analysis[81]) and stand-alone analyses
Ambient heat and cold morbidity (non-fatal)	Non-fatal direct effects of high and low ambient temperature; this includes most of the distinct causes indicated for temperature-related mortality; stroke, hypertensive heart disease, cardiomyopathy and myocarditis, COPD, lower respiratory infections, chronic kidney disease, road injuries, drowning, exposure to forces of nature or mechanical forces, other unintentional injuries, self-harm, interpersonal violence, and other transport injuries	Included	Temperature amenable DALYs currently reflect morbidity for the causes listed; non-fatal heat morbidity is comparatively modest, relative to mortality
Non-wildfire ambient air pollution ($PM_{2·5}$; mortality and morbidity)	Captures contributions of climate-relevant emissions to ambient air pollution concentrations; under lower emission climate scenarios, emissions of (fossil fuel-related) air pollutants will also decrease; this pathway also captures the interaction between emissions with temperature and other climate variables that act to increase $PM_{2·5}$ concentrations; $PM_{2·5}$ acts on ischaemic heart disease, stroke, lung cancer, lower respiratory infections, COPD, dementia, and type 2 diabetes	Included	The second dominant pathway; together with heat, accounts for the large majority of quantified climate-attributable DALYs, at a magnitude consistent with previous stand-alone analyses; the inclusion of this pathway is a unique addition in this work compared with previous WHO and World Bank analyses
Wildfire $PM_{2·5}$ air pollution (mortality and morbidity)	Captures change in wildfire-derived $PM_{2·5}$ under different climate scenarios; includes same causes as non-wildfire $PM_{2·5}$ (ischaemic heart disease, stroke, lung cancer, lower respiratory infections, COPD, dementia, and type 2 diabetes)	Included	In some locations, changes in climate lead to changes in land area burned and subsequent emissions of $PM_{2·5}$ in wildfire smoke; modelled separately from non-wildfire $PM_{2·5}$ and accounts for air pollution amenable DALYs, with substantial regional variation
Malaria (mortality and morbidity)	Vector-borne transmission governed by climatic suitability (temperature, precipitation, and flooding), with estimates accounting for malaria development assistance for health, GDP per capita, and urbanisation	Included	Modelled with climate suitability covariates, economic indicators and vector-survival relationships, with sampling across CMIP6 models to propagate climate uncertainty; in much of west and central sub-Saharan Africa, under warmer climate scenarios malaria suitability decreases, whereas in parts of eastern sub-Saharan Africa, suitability increases as temperatures warm in higher altitude areas; overall, malaria suitability decreases throughout most of the tropics and subtropics; malaria suitability (but not burden) increases in mid-latitudes as middle-income and low-income countries effectively control malaria
Dengue (mortality and morbidity)	Vector-borne transmission governed by climatic suitability (temperature, precipitation, and flooding), with estimates accounting for malaria development assistance for health, GDP per capita, and urbanisation	Included	Modelled with climate suitability covariates, economic indicators, and dengue-specific vector-survival relationships, with sampling across CMIP6 models to propagate climate uncertainty; dengue suitability increases but burden is much smaller compared with malaria
Child malnutrition (temperature pathway; mortality and morbidity)	High ambient temperature and altitude effects on child undernutrition (stunting, wasting, and underweight), and associated cause-specific mortality (lower respiratory infections, measles, diarrhoea, and protein-energy malnutrition)	Included	The analysis is based on household-level micro-data from all DHS and MICS surveys with geocoding that account for household consumption separately from heat exposure; multiple metrics of heat exposure were tested; days over 30°C was the most predictive of child growth failure
Income/GDP effect on income inequality	Climate change alters rural and urban income growth, which propagates through the (equity-sensitive) SDI and the income-inequality threat to a wide range of risk factors (eg, metabolic, occupational, and behavioural) and cause-specific (NCDs, infectious diseases, maternal and neonatal disorders, and injuries) mortality and morbidity	Included	The empirical relationship between climate and rural and urban income growth was formally modelled and embedded in the scenarios—a major addition prompted by the climate–health community; the model accounts for the endogenous connection between economic growth emissions and temperature change
Flood-related direct effects	Climate change can lead to increases in flooding; this pathway includes direct deaths due to injuries, drowning, and electrocution	Included	The analysis captures the direct mortality effects of fluvial floods via injuries and drowning using relationships derived from the EM-DAT database; floods make a relatively small contribution to amenable burden relative to the temperature and air pollution pathways, but are important in specific locations
Flood-related indirect effects	Climate change can lead to increases in flooding; flooding contaminates water supplies and disrupts essential services, leading to indirect effects including diarrhoeal disease, cholera transmission, and cardiovascular and respiratory disease	Included	Indirect effects on diarrhoeal disease, transmission of cholera, and cardiovascular and respiratory disease, based on published systematic reviews; the effects on cardiovascular and respiratory disease are hypothesised to operate through disruption of essential services, supply chains, and health systems

(Table 1 continues on next page)

	Mechanism	Status	Basis or Rationale
(Continued from previous page)			
Hypertension	Reported associations between heat exposure and hypertension-related morbidity and reduced life expectancy in hypertensive patients	Included	The analysis includes the association between heat exposure and hypertensive-associated outcomes, including many cardiovascular diseases, diabetes, and chronic kidney disease, and this is true for both morbidity and mortality (life expectancy) outcomes; given that we model the direct association between temperature and cardiovascular disease (stroke, hypertensive heart disease, ischaemic heart disease, cardiomyopathy and myocarditis, type 2 diabetes, and chronic kidney disease), our analysis actually captures more of this impact than would an analysis restricted to impacts via hypertension; adding a separate pathway exclusively via hypertension would be double-counting
Tropical cyclone mortality and morbidity	Tropical cyclones lead to direct deaths (eg, injuries, drowning, and electrocution)	Included	The direct deaths from tropical cyclones are captured via the EM-DAT database; tropical cyclones on the global scale have caused, on average, 2000 deaths in a typical year since 2000, with some high event years reaching over 100 000 deaths; this pathway will likely remain a comparatively small contributor to the burden in the future compared with the effects of heat
Tropical cyclone-related indirect effects	Tropical cyclones leading to indirect effects on cardiovascular disease and respiratory diseases, on both mortality and morbidity	Included	Indirect effects from cardiovascular and respiratory disease are captured from the epidemiological literature; these effects are partially attributable to medical support disruptions, environmental contamination, and psychosocial stress; tropical cyclones are a very small pathway relative to the dominant heat and air-pollution pathways and even relative to fluvial floods
Pathways partially included			
WASH	Droughts, floods, storms, sea-level rise, and saline intrusion disrupt water, sanitation, and hygiene services, affecting diarrhoeal disease and other outcomes	Partially included	Captured in part as effects of floods on cholera and diarrhoeal disease are included; diarrhoeal disease is by far the largest cause related to WASH
Malnutrition via food-system disruption (eg, floods, droughts, and extreme weather)	Crop, supply-chain, and economic-loss pathways drive food insecurity and undernutrition	Partially included	The temperature pathway to child malnutrition is included; income effects are captured via the GDP and inequality pathway; increased drought might lead to famine in the future but CMIP6 does not model this; average effects of climate change over the past 35 years are implicitly captured in the malnutrition analysis
Health-system disruption	Damage to infrastructure, reduced health-worker performance under increased heat, supply-chain disruption, and demand surges during extreme events degrade care quality and access	Partially included	The MCC published relative risks of mortality by cause outcomes after extreme weather events, including health-system disruption; this pathway is included for tropical cyclones and floods
Other infectious diseases (additional vector-borne, water-borne, food-borne, soil-borne, and fungal disease)	Climate alters the range, seasonality, and intensity of transmission for a broad set of pathogens beyond malaria and dengue	Partially included	Using daily mortality data, we have tested for the infectious disease relationships and found one star or higher relationships for lower respiratory infections but not for other infectious diseases; separate from this pathway, we include the effect of extreme weather events on diarrhoea, cholera, and lower respiratory infections as well; in addition, we have included pathway models for dengue and malaria; we do not expect indirect effects on other infectious diseases to result in large numbers of amenable DALYs
Conventional conflict pathway of climate change	Climate stress might raise the risk of armed conflict, with direct and indirect health consequences	Partially included	The linkage between climate and conflict remains quite controversial in the political science literature; PRIO strenuously argues that once political variables are accounted for there is no statistical association between climate and conflict; Mach and colleagues[83] polled conflict researchers in 2019 and found conflict ranked 14th of 16 variables related to climate; our analysis does include the link between temperature and interpersonal violence, but does not include intergroup conflict, as these effects are small, especially in comparison to other drivers, and might be subject to reverse causality; adjusting by SDI, statistical analysis of GBD 2023 panel data (204 countries, 1990–2023) finds no significant association between temperature and conflict and terrorism DALY rates once location and year fixed effects are applied (coefficient –0·457, p>0·05)
Pathways considered but not included			
Pandemics and spillover events	Climate change is hypothesised to raise the frequency of zoonotic spillover and pandemic emergence	Not included (as a climate pathway)	The relationship between pandemic occurrence and temperature was empirically tested over ~400 years and no association was found in the regression analysis; the independently estimated increase in large-pandemic risk is carried in the pandemics module; the rising risk might in part reflect climate-related drivers of spillover, although other drivers are more commonly cited
Antimicrobial resistance	Climate conditions might accelerate the selection and spread of resistant organisms	Not included (as a climate pathway)	The evidence linking climate observed antimicrobial resistance rates is not strong; for example, statistical analysis of antimicrobial resistance age-standardised rates and temperature finds no association; statistical analysis of this relationship using GBD panel data shows no significant relationship between mean annual temperature and antimicrobial resistance attributable death rates; a regression of log antimicrobial resistance attributable DALY rates on mean temperature with location and year fixed effects showed no statistical significance (coefficient –0·002, p>0·05); adjusting the model by SDI did not modify the direction or significance (coefficient +0·004, p>0·05)

(Table 1 continues on next page)

	Mechanism	Status	Basis or Rationale
(Continued from previous page)			
Mental health (climate-related)	Post-disaster PTSD, anxiety, depression, and distress associated with extreme events and slow-onset change	Not included (as a climate pathway)	Exclusion was a conscious decision after careful deliberation; GBD mental health experts expressed scepticism about direct effects of heat, rainfall, and other climate variables on mental health per se; the observed association might partly reflect media coverage of climate rather than direct climate effects; the direct effect of heat on risk of suicide is included in the analysis; the evidence on post-disaster mental disorders after extreme events is stronger but likely a small contributor to global DALYs
Educational attainment	Climate disruption can reduce the performance in the education of children exposed to heat during early childhood	Not included (as a climate pathway)	GBD 2023 panel data (204 countries, 1990–2023) finds no temperature association with mean years of schooling once country and year fixed effects are applied (coefficient –0·040, p=0·38); income per capita is the dominant predictor; attainment tracks development, not temperature; reduced performance of children exposed to extreme heat in early childhood might well work through child growth failure, for which there is considerable literature on cognitive function; this mechanism working on specific children is not captured in the analysis; a regression of mean years of education among women aged 25–29 years (204 countries, 1990–2023) on mean temperature with location and year fixed effects showed no statistical significance (coefficient –0·040, p>0·05); adjusting the model by lag-distributed income did not modify the direction or significance (coefficient –0·048, p>0·05)
Sea level rise	Inundation, displacement, and saline intrusion threaten health and survival in low-lying states and Small Island Developing States	Not included	The main direct health effect of sea level rise is via migration, which is not directly quantifiable in this analysis; as sea level rise is a slow-onset phenomenon, it is unlikely to cause substantial direct mortality beyond storm surges; relative risks and direct deaths in EM-DAT do capture storm surge effects already and are reflected in the tropical cyclone death rates; in the future, the Monitor will hopefully capture the effects of climate on migration, including storm surges
Droughts	Drought affects nutrition, water security, livelihoods, and mental health	Not included	Although CMIP6 models predict increased probability and severity of drought in a consistent set of locations (the Mediterranean, western North America, the Amazon, southern Africa, and Australia) under all scenarios, the severity of droughts are highly uncertain and highly sensitive to which drought metrics are used; between-model uncertainty is high, indicating that the location of future drought is more reliably projected than its severity; mapping from drought to famine is problematic because famine is a sociopolitical phenomenon; a good example is despite repeated droughts in parts of India, there has not been a famine in 50 years because of the policy response
Obesity and high BMI	Climate change is proposed to raise obesity by worsening food insecurity, shifting diet, and reducing physical activity under extreme heat	Not included	The GBD data on obesity levels from 1990 to 2023 do not support a positive pathway: the relationship between high-BMI summary exposure value and annual mean temperature is generally negative (higher temperatures associated with lower obesity prevalence), and statistical analysis of this relationship does not yield a robust positive climate–obesity effect; taking into account SDI, country fixed effects, and caloric intake per capita, the temperature coefficient is small, non-significant, and not robust in sign (–0·001, p>0·05), whereas SDI remains the consistent and significant driver of high BMI-exposure (coefficient +0·260, p<0·001)

CMIP6=Coupled Model Intercomparison Project 6. COPD=chronic obstructive pulmonary disease. DALYs=disability-adjusted life-years. DHS=Demographic and Health Surveys. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. GDP=gross domestic product. MCC=Multi-Country Multi-City Collaborative Research Network. MICS=Multiple Indicator Cluster Surveys. NCDs=non-communicable diseases. $PM_{2.5}$=particulate matter pollution. PTSD=post-traumatic stress disorder. SDI=Socio-demographic Index. WASH=water, sanitation, and hygiene.

Table 1: **Pathways by which climate change can affect health: coverage in the Commission analysis**

steady, global urbanisation throughout this century.[87–89] However, as certain regions become increasingly unliveable and as sea-level rise displaces coastal communities, internal and international migration will accelerate. Robust climate migration modelling currently suffers from a lack of granular, origin-to-destination data. Evaluating the potential health consequences of this migration requires forecasts at fine scale spatial resolution since effects and even their direction will be highly localised. Although there is potential for stress to be placed on health-care resources in locations receiving migrant populations, migration will also lead to lower exposure to heat and other climate stresses. When more accurate assessments become available, they will likely reduce the modelled health impacts of climate change, as households actively adapt by moving away from highly climate-stressed environments. Because our current models cannot perfectly capture this adaptive migration, the amenable burden estimates presented here potentially overestimate the realised harm.

Modelling scenarios and amenable burden

Rather than developing bespoke scenarios for global mean surface temperature based on greenhouse gas emissions relative to GDP, we used the established CMIP6 ensemble scenarios. The CMIP project was first developed by the World Climate Research Programme in 1995 and was initiated to produce and compare modelled projections of past, present, and future climate parameters to improve understanding of inter-relationships and to forecast the magnitude of future climate change and the impact of various emissions scenarios. The sixth (CMIP6) phase is now completed, and CMIP7 is beginning to produce results. CMIP models use Representative

Concentration Pathways (RCPs) to define future emissions and climate forcing scenarios as inputs to simulate future climate. Each RCP is associated with an increase in global mean surface temperature by 2081–2100, relative to the 1850–1900 preindustrial baseline. In our work we defined the amenable climate DALYs as the difference in health outcomes between a high-emissions scenario (RCP8.5, with a projected global mean surface temperature increase of 4·4°C) and a low-emissions scenario (RCP2.6, with a projected global mean surface temperature increase of 1·8°C). Although we use the same levels of radiative forcing as in other CMIP-based analyses, we explicitly do not incorporate the shared socioeconomic pathways, as these inherently incorporate external assumptions regarding population dynamics and economic conditions. The appendix provides details on the modelling strategies for each of the pathways included in the analysis (pp 37–59). By using RCP8.5 and RCP2.6, we are likely increasing the estimated amenable DALYs due to climate change compared with applying the principles of plausible best and plausible worst to CO_2 emissions per unit GDP. We estimated plausible best and plausible worst greenhouse gas emissions and global mean surface temperature and found that plausible worst is closer to RCP7.0 than RCP8.5, and also found that plausible best has higher emissions and a higher global mean surface temperature than RCP2.6. Importantly, in CMIP7, the highest emissions scenario is substantially lower than that of the RCP8.5 scenario included in our analysis, resulting in an estimated global mean surface temperature increase of approximately 3·5°C above pre-industrial levels.[90]

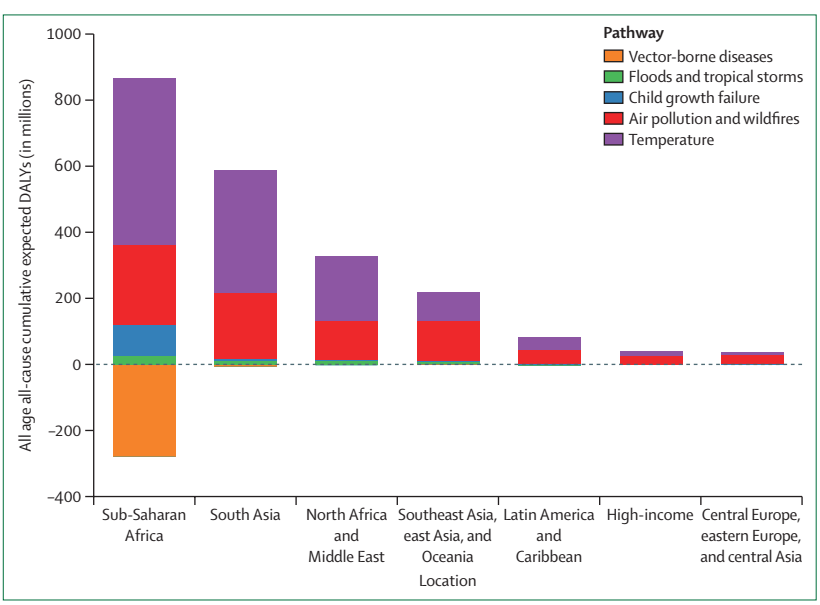


Figure 13: **Cumulative expected amenable DALYs by climate pathway for each GBD super-region**
DALYs are cumulative from 2025 to 2100, with cumulative expected amenable DALYs referring to the difference in cumulative DALYs between the plausible best and plausible worst scenario for each threat.
DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study

CMIP7's shift away from RCP8.5 reflects a more recent understanding of the highest plausible level of emissions and implies that the amenable DALYs included in our analysis are based on a difference in emissions that is larger than anticipated.

On the other hand, the CMIP6 ensemble partly includes some of the low probability but high impact tipping points that have been discussed in the literature.[91] The tail risks, which are not included in any of the CMIP6 ensemble members, include melting of the Greenland ice sheet and full instead of partial Atlantic Meridional Overturning Circulation (AMOC) collapse. Melting of the Greenland ice sheet this century is assigned extremely low probability. Full AMOC collapse has been modelled, and the effects depend on which emissions scenario will unfold; in RCP8.5 it might be net beneficial for Europe but in RCP4.5 temperatures in northwestern Europe will be reduced by as much as 2°C. Future work on climate change, particularly the CMIP7 ensembles, will hopefully include more of these tail risks in their assessments.

Figure 13 shows the amenable burden in each super-region by climate pathway, emphasising that the largest effects will be in sub-Saharan Africa. The majority of climate-induced harm is mediated through the direct effects of extreme heat, predominantly affecting sub-Saharan Africa and south Asia. Increased air pollution (mostly from non-wildfire $PM_{2·5}$) represents the second-most substantial pathway, followed by child growth failure, and then tropical storms and floods. Across climate scenarios to 2100, malaria and dengue contribute a small and heterogeneous share of the net global DALY burden, with their combined effect substantially outweighed by temperature and $PM_{2·5}$ pathways. Globally, malaria shows a net negative amenable burden, with an estimated –244 million (95% UI –656 to 123) DALYs under RCP8·5 compared with RCP2.6, reflecting the inverted U-shaped relationship between temperature and transmission suitability, whereby many high-burden regions become too warm for optimal transmission. These reductions are most evident across parts of western sub-Saharan Africa and contribute to lower burden in younger age groups in those settings. However, this global decline masks important location-specific increases, particularly in some eastern sub-Saharan African and select high-altitude locations where warming shifts conditions closer to optimal transmission. Dengue, in contrast to malaria, contributes only a minor proportion of global DALYs across all scenarios, with relatively small changes in incidence and mortality compared with other climate-sensitive pathways. It should be noted, however, that dengue is increasing in three scenarios, including the reference scenario, but most of that increase is not correlated with temperature per se but with the spread of the virus into new peri-urban and urban areas. Overall, the net effect of vector-borne diseases is a modest reduction in global

DALYs under higher warming scenarios, but this is more than offset by increases in the burden from non-communicable diseases driven by temperature and air pollution. Vector-borne diseases have very little effect in high-income and upper middle-income countries because above certain thresholds of income per capita, public health authorities, health services, and households find ways to protect themselves from mortality from malaria and dengue. These results underscore that, although malaria dynamics are highly sensitive to climate, their global contribution to total climate-attributable DALYs is limited, and the direction of their effect varies substantially by geography. For both diseases, these effects are likely to be overestimated, as the increasing roll out of vaccines, relatively newly available for both diseases, is expected to impact disease burden.

When analysed by super-region, the predominant health effects manifest as NCDs (appendix pp 147–48). Extreme heat and $PM_{2·5}$ heavily drive exacerbations in cardiovascular diseases, chronic respiratory conditions, lower respiratory infections, diabetes, and kidney diseases. In high-income countries, there is a notable increase in dementia driven by escalating $PM_{2·5}$ exposure.

As with other threats, certain causes have a negative amenable burden in older age groups due to the concept of competing risks, wherein in the low-emissions (RCP2.6) scenario, more individuals survive to older ages, where they subsequently die from age-related causes that would have been pre-empted by early climate-related mortality in the RCP8.5 scenario (appendix p 149; this is distinct from the negative amenable DALYs related to vector-borne diseases).

Aggregate impact and future trajectories

The health effects of climate change will scale steadily towards the end of the century. By 2100, the difference in life expectancy between the high-emission and low-emissions scenarios is projected to exceed 2 years in highly vulnerable regions such as the Sahel region of Africa. Country-specific differences in life expectancy are shown in figure 14.

Taking all evaluated pathways into account, cumulative amenable DALYs related to climate change total 1·89 billion (95% UI 1·32–2·48). This magnitude of harm is substantially larger than older baseline assessments, such as WHO's 2014 quantitative risk assessment, which projected 250 000 additional deaths annually between 2030 and 2050 based on a narrower set of risks.[80] However, our findings align closely with the increasingly severe indicators tracked by the annual Lancet *Countdown on Health and Climate Change*.

If carbon emissions do not reach net-zero or negative levels within this century, global mean surface temperatures will continue to rise indefinitely. Although climate change represents a massive global health burden, it could escalate into an extinction threat in subsequent centuries if emissions are not curtailed. As with all threats in this Commission report, our baseline statistical forecasts do not account for the potential rapid development of breakthrough mitigation technologies, possibly accelerated by advances in AI. The widespread deployment of fusion energy, highly efficient direct air capture, or geoengineering could dramatically alter the climate trajectory in the latter half of this century and beyond.

5.5 Collapse of DAH

Given the cuts to DAH that were announced in 2025 by a number of governments, most notably the USA, it is reasonable to evaluate the threat to global health posed by the potential collapse of solidarity between nations. Our latest assessment of changes to DAH suggests a reduction of 9·7% overall from 2024 to 2025.[92] This

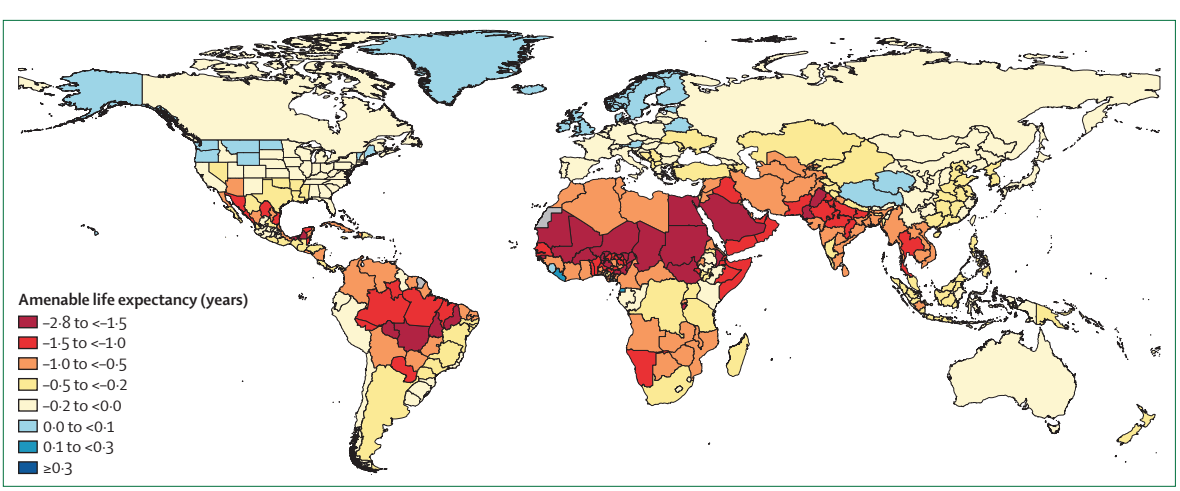


Figure 14: **Map of amenable life expectancy related to climate change in 2100, for 204 countries and territories**
A negative difference in life expectancy indicates that life expectancy will be lower in 2100 in the high emission scenario (RCP8.5) compared to the low emissions scenario (RCP2.6), and vice versa for a positive difference in life expectancy. RCP=Representative Concentration Pathway

assessment, however, is quite uncertain, as the latest budgets passed in the USA suggest smaller cuts than initially announced, but when these funds will be dispersed remains unclear. The UK government has reduced ODA to 0·3% of gross national income as of 2025 to fund increased defence spending.[93] France and Germany have also reduced DAH. In the past several decades, ODA had broad political support, including commitments by many high-income countries to reach 0·7% of GDP to support ODA; in the UK for example, ODA reached this level in 2013, but it has subsequently declined, falling below 0·7% in 2021 and then abruptly cut in 2025.[1] Overall, across donor countries, ODA, including support for Ukraine, declined to 0·33% of gross national income for donor countries in 2024[94] and to just 0·26% in 2025.[95]

DAH is an overlapping construct with ODA that encompasses not only grants but also financial resources from international financial institutions targeting the health sector. In addition, DAH includes philanthropic resources not included in ODA. ODA also includes non-health financing, with 2023 ODA for health totalling around 7% of ODA, approximately US$16 billion.[96] In the same year, total DAH totalled $65 billion, emphasising the prominent role of the development banks, philanthropies, and non-governmental organisations.[97] DAH has an important and direct effect on vaccination programmes through the support of Gavi, the Vaccine Alliance, bed nets and the roll out of other malaria interventions, tuberculosis programmes, antiretroviral therapy for HIV, and neglected tropical diseases programmes, to name only a subset. The full short-term impacts of DAH reductions remain uncertain as there are ongoing changes to US government (historically the largest source of DAH) allocations through the US State Department; the US administration is actively negotiating bilateral compacts with recipient nations as part of their new global health strategy.

One challenging question is what Ministries of Finance in low-income or lower-middle-income countries will do if DAH is substantially reduced. For example, will they increase funding for the health sector, a phenomenon known as compensatory spending? Statistical analyses suggest there might not be compensatory spending when resources decline.[92] In other words, Ministries of Finance might not fill some or even any of the gap created by declines in DAH, due to severe fiscal constraints on governments, particularly in the setting of increasing debt service payments. The Accra Reset[98] is an initiative stimulated by certain heads of government to rethink global health financing, with an emphasis on increased autonomy. Assuming no compensatory spending, in our plausible worst scenario DAH declines to roughly half the amount of DAH disbursed in 2024, which was estimated based on the observed lower bound of ODA per a donor country's gross national income relative to their GDP, and in our plausible best scenario, we assume that DAH increases from historic highs as a percentage of GDP at the rate observed from 2000 to present.

A key question is how to translate reductions in funding into increases in DALYs. There are two strategies: use the observed overall relationship between funding, including DAH and domestic resources and health outcomes, or analyse the likely effect of reductions of DAH on specific programmes such as vaccination, malaria, or HIV. Past analyses have suggested that global health action has saved child lives in low-income countries on average at a cost of US$ 3000–5000 per life.[99] Lastuka and colleagues[100] have also computed the incremental cost per additional year of healthy life (equivalent to a DALY reduction) with stochastic frontier analysis. These costs depend on the country's GDP per capita and range from US$ 2140 (95% UI 1604–3940) for upper-middle-income countries to US$ 312 (226–670) for low-income countries.[100]

A more standardised approach, and the one we have taken here, is to analyse the relationship between age-specific health spending per capita and age-specific cause-specific mortality adjusted for risk factors that are not under the direct effect of the health system. Details of this approach are provided in the appendix (pp 104–07), including fitting frontiers for each age group, controlling for broader social and environmental risk factors. We estimate the amenable DALYs due to DAH by using the plausible best and plausible worst scenarios for DAH, estimates of the age-profile DAH targets,[101] and the stochastic frontiers, and holding the level of inefficiency in each country constant. As a final step, to maintain comparability to other threats, we analyse the deaths averted in the plausible best compared with the plausible worst, while taking into account competing risks.

This analysis suggests cumulative amenable DALYs related to DAH come to 1·50 billion (95% UI 1·20–1·95). The distribution by super-region suggests that 69·8% (65·9–73·2) of amenable DALYs would be in sub-Saharan Africa. The impact of the collapse of DAH is smaller than many other threats but highly concentrated in the lowest-income regions.

5.6 Conventional conflict

GBD 2023 suggests that from 1990 to 2023, there were 3·77 million (95% UI 3·04–4·97) deaths and 329 million (255–466) DALYs from both interstate and civil conflicts.[68,86] These numbers, although large, represent 0·211% (0·170–0·277) of global deaths and 0·357% (0·279–0·492) of global DALYs. Given geopolitical developments including rising tension between China and the USA, the Russian invasion of Ukraine, and the Israel–Gaza–Lebanon conflicts, the US–Israel–Iran conflicts, and more, there is understandably increased concern about both conventional and nuclear conflict.

Several organisations attempt to track conventional conflicts, including Uppsala Conflict Data Program,[102]

the Peace Research Institute Oslo,[103] the Armed Conflict Location and Event Data,[104] and the Project Mars dataset.[105] These databases produce reports of specific engagements on specific dates in specific locations, often using newspapers and other independent observers, and are a rich source to understand trends in conventional war. Nevertheless, conflict deaths, both of combatants and non-combatants, are often highly controversial; groups on various sides of a conflict might have incentives to over-report or under-report. Even in recent conflicts such as Gaza, the reported number of casualties from various groups varies from 49 271 to 78 525.[106] Another example is the very wide range of deaths reported from the conflict in Tigray, Ethiopia, from 8946 to 16 291;[107] one major database reported the higher number of 600 000 deaths based on unconfirmed reports.[108,109] Despite these limitations, however, these ongoing efforts provide an overall assessment of the magnitude of conventional conflict. Figure 15 shows a map of civil and interstate conflicts and their recorded magnitude since 1800, highlighting that conventional conflict has concentrated in certain geographical areas. Conflicts that occurred before 1990 were not included in the frontier analysis.

These databases have been analysed to predict future conflicts at the geospatial level. Using a generalised spatiotemporal causal inference model to estimate indirect deaths due to conventional conflict, we forecasted the number of conflict deaths through 2100 under a reference scenario, with wide UIs. These estimates include both direct and indirect deaths, the latter resulting from the knock-on effects of conflict on health services and other infrastructure. The model uses infant mortality rates, population density, GDP per capita (purchasing power parity), and previous mortality rates as covariates. The cumulative DALYs from conventional conflict, including estimated direct and indirect non-fatal injuries, are 547 million (95% UI 424–722) for 2025–2100, under the reference scenario. At the country level, DALYs were disproportionately distributed, with countries in north Africa and the Middle East bearing the highest burden.

For our plausible best and worst scenarios, we have used stochastic frontier analysis to set upper and lower boundaries on the number of conflict deaths per capita as a function of SDI. Given the dramatic variation in rates observed in the super-regions of sub-Saharan Africa and north Africa and the Middle East compared with other super-regions, we have fit frontiers on conventional conflict separately for these two super-regions. To capture the highly stochastic nature of conflicts, and that most conflicts do not run at the same intensity for decades, the frontier fitting has been conducted on average conflict death rates over the period 1990–2021. Death rates include both combatant and non-combatant casualties. Given that interstate conflicts have two (or more) states involved, we have used the SDI in the location where the deaths occur.

Although amenable deaths are a highly imperfect measure (section 1.7), much of the literature on conflict is framed in terms of deaths averted. For comparability, we have therefore modelled amenable deaths as well as amenable DALYs for this threat. Using the competing risks framework, we estimated 81·1 million (95% UI 65·0–98·0) cumulative amenable deaths between 2025 and 2100 at the global level, with 64·2 million (50·9–77·9) of those deaths in sub-Saharan Africa. This burden is 21·5 times greater than the number of amenable deaths

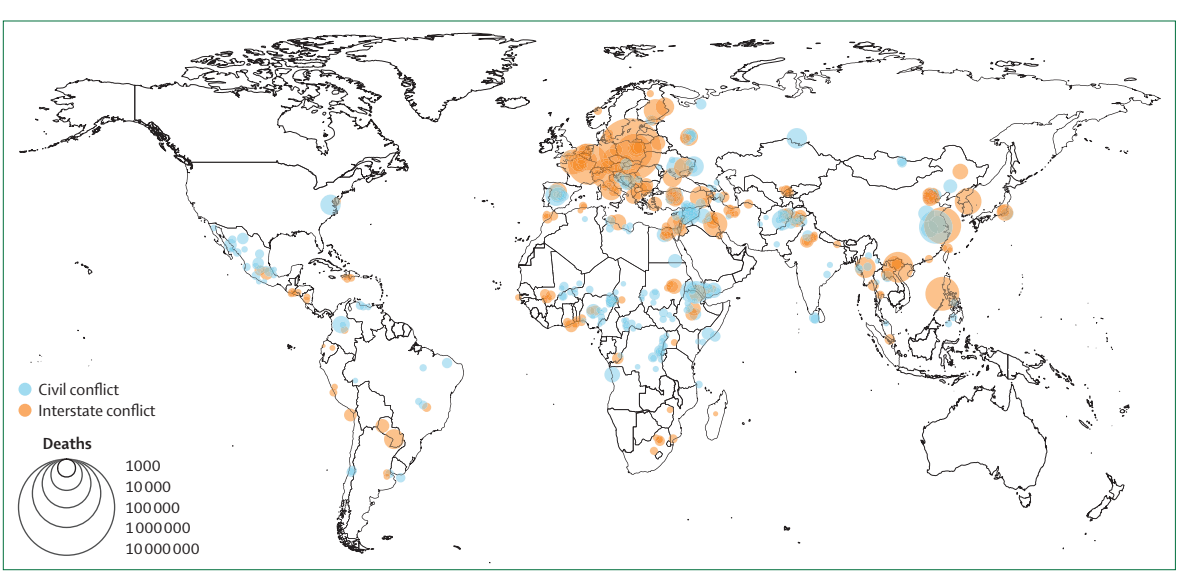


Figure 15: **Geographic distribution of conventional wars, 1800–2023**
Each bubble represents a campaign (Project Mars, 1800–2011)[105] or conflict (UCDP GED, 2012–23),[102] sized by total deaths (killed in action for Project Mars; all battle deaths for UCDP). Orange denotes interstate conflict; blue denotes civil conflict. Multi-theatre wars such as WWI and WWII are disaggregated into separate campaigns to reflect their true geographical spread. GED=Georeferenced Events Database UCDP=Uppsala Conflict Data Program.

observed in the past 35 years. The large number of amenable deaths compared with past observations is due to the wide range of country-specific death rates used in fitting stochastic frontier analyses. As conflict has a comparatively young age of death and thus a high ratio of DALYs to deaths, the global cumulative amenable DALYs is 7·71 billion (6·58–9·14). The large number of cumulative amenable DALYs from conventional conflict is a function of the wide range in plausible best and plausible worst scenarios. The effect of conflict on migration, such as the mass exodus from Syria, has not been included in these calculations.

5.7 High alcohol use

As a leading risk factor for attributable disease burden and premature mortality worldwide, high alcohol use remains a pervasive and escalating threat to global public health.[68] Unlike the relatively stagnant global trajectory of smoking,[110] the global burden of alcohol is forecasted to worsen in the coming decades in the reference scenario.

Although recent discourse frequently highlights declines in consumption within certain high-income countries, particularly driven by cultural shifts and reduced drinking prevalence among younger demographics,[111] this localised progress obscures a deteriorating global picture. In many LMICs, rapid economic development, rising disposable incomes, and aggressive expansion by the multinational alcoholic beverage industry are driving a steep upward trajectory in consumption.[112] Consequently, the global amenable gap is actively expanding.

The burden of disease attributable to alcohol is complex, manifesting through both acute, immediate harms and chronic, long-term pathologies. This bimodal distribution of risk affects both young and ageing populations across multiple domains. Alcohol is a primary driver of liver cirrhosis, alcoholic hepatitis, and acute pancreatitis. The carcinogenic properties of ethanol and its metabolite, acetaldehyde, substantially elevate the risk of cancers of the liver, breast, colorectum, oesophagus, and upper aerodigestive tract. Heavy consumption is a major contributor to ischaemic heart disease, ischaemic stroke, atrial fibrillation and flutter, and haemorrhagic stroke. This pattern is complicated by the cardioprotective effects of mild drinking levels; while the presence of cardioprotective effects is controversial, a recent burden of proof analysis suggests that the balance of evidence supports the effect.[113] Crucially, unlike smoking, a proportion of alcohol's attributable DALYs stems from its acute psychoactive effects, leading to road traffic injuries, interpersonal violence, and self-harm, predominantly among younger demographics.

The reference scenario suggests epidemiological divergence between high-income countries and LMICs. In high-income countries, public health campaigns, changing generational habits, and taxation have begun to bend the curve downward. However, in emerging markets, the alcoholic beverage industry is successfully employing marketing strategies that are largely restricted elsewhere.

Effective, evidence-based countermeasures exist, embodied in the WHO SAFER initiative:[114] strengthen restrictions on availability, advance drink-driving countermeasures, facilitate access to screening and interventions, enforce bans on advertising and sponsorship, and raise prices through excise taxes. Yet, implementation remains highly fragmented, leaving populations vulnerable to the aggressive marketing of a hazardous substance.[115] Emerging evidence suggests that obesity medicines might also reduce alcohol consumption, particularly among heavy drinkers, which could represent a pathway through which obesity medicines affect the high alcohol threat.[116]

To quantify the amenable burden of high alcohol use, we analysed population-level exposure against SDI and log GDP per capita. Similar to smoking, modelling reveals a profound variance in consumption rates among countries with identical levels of economic development. However, alcohol consumption is heavily modulated by diverse cultural, religious, and historical contexts. Despite these baseline cultural differences, the stochastic frontier analysis shows a wide amenable range. Robust policy interventions, particularly pricing mechanisms, marketing bans, and availability restrictions, have proven capable of altering consumption trajectories across all SDI quintiles. The cross-country variance observed explicitly illustrates that rising alcohol consumption is not an unavoidable byproduct of economic growth, but rather a modifiable policy failure.

Cumulative amenable DALYs are due to a diverse set of causes spanning from younger ages through to age 80 years, with prominent contributions from self-harm and interpersonal violence, unintentional injuries, transport injuries, digestive diseases, cardiovascular disease, cancers, and tuberculosis (appendix p 150). The cumulative amenable DALYs related to high alcohol use total 2·35 billion (95% UI 1·97–3·06) by 2100. The largest contributions are in the super-regions of sub-Saharan Africa and southeast Asia, east Asia, and Oceania.

The baseline trajectory for global alcohol consumption points upward, causing the gap between the reference scenario and the plausible best scenario to widen substantially over time. Failing to implement optimal policies will increase future burden.

5.8 High systolic blood pressure

High systolic blood pressure (SBP) remains one of the most pervasive, lethal, and fundamentally modifiable physiological risk factors in global health. High SBP exemplifies the complex intersection of changing global diets, physical activity, and varying capacities of primary care systems.

The global trajectory of high SBP is currently defined by an intense epidemiological tug-of-war between rising risk and rising access to treatment. In many regions,

particularly across the Americas, north Africa and the Middle East, and Oceania, the burden of SBP-attributable DALYs is rising. This escalation is inextricably linked to the global increase of BMI; the profound physiological connection between obesity and hypertension is actively driving up baseline population blood pressure faster than clinical systems can manage it.[68,117] There are also claims that temperature might contribute to rising SBP; this association is perhaps borne out by the strong link between temperature and a range of cardiovascular diseases.

Strong evidence from cohort studies and randomised clinical trials has established links to many key outcomes.[118,119] High SBP acts as a systemic, mechanical stressor on the vascular system, serving as the dominant driver for several of the world's leading causes of death. The attributable disease burden is heavily concentrated in: cardiovascular disease, where SBP is the primary global risk factor for ischaemic heart disease, haemorrhagic stroke, and ischaemic stroke; renal failure, where chronic, unmanaged high blood pressure is a leading cause of hypertensive kidney disease and broader chronic kidney disease progression; and in other vascular pathologies it greatly contributes to aortic aneurysms, peripheral artery disease, and hypertensive heart disease.

Although the obesogenic environment drives blood pressure upward, this force is being actively counterbalanced in select regions by two major public health successes. First, population-level sodium reduction, as dietary sodium is a potent driver of hypertension. Certain nations have achieved remarkable reductions in population-level SBP through coordinated salt reduction policies. Japan, for instance, has successfully used public health campaigns, cultural shifts, and industry cooperation to steadily lower population salt intake over decades, yielding massive dividends in reduced stroke mortality.[120,121] Secondly, pharmacological interventions have been implemented in many high-income and rapidly developing nations. The expansion of primary care has dramatically increased access to cheap, effective generic antihypertensive medications (such as angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics).

To quantify the amenable burden of high SBP, we modelled population-level exposure against SDI. As with other behavioural and metabolic risks, there is a large observational variance among countries at identical levels of economic development. This variance across countries reflects both the drivers of risk as well as the individual and population-level coverage of effective interventions.

This variance shows that high SBP is highly responsive to intervention. The amenable DALYs can be actively captured through a combination of population-wide and clinical strategies: environmental and dietary policies, such as implementing mandatory salt reformulation targets for processed foods, enforcing clear front-of-package warning labels for high-sodium products, and using taxation to disincentivise highly processed, sodium-dense foods; health system strengthening through expanding universal screening protocols and adopting standardised treatment algorithms, such as the WHO's HEARTS technical package, which emphasises protocol-based management and improved access to combination therapies; and upstream metabolic interventions, including aggressively addressing the upstream BMI and obesity drivers through urban planning for physical activity, sugar-sweetened beverage taxes, and improved access to novel anti-obesity medications.

By estimating the upper and lower bounds of these policy implementations out to the end of the century, we establish the plausible best and plausible worst scenarios. The cumulative amenable DALYs from high SBP by 2100 total 4·79 billion (95% UI 3·74–6·25).

Because blood pressure interventions, whether a reduction in dietary salt or the initiation of a daily pill, can alter cardiovascular risk almost immediately, this threat presents one of the fastest return-on-investments in global health. Failing to aggressively target this amenable gap will allow the rising tide of global obesity to overwhelm current clinical gains, resulting in an unprecedented and entirely preventable surge in cardiovascular and renal mortality.

5.9 Income inequality

In the deliberations of the Commission, the underlying importance of the interlinkages between poverty and inequality with poor health was frequently emphasised. Inequality is a driver of health within each nation that is highly amenable to economic and social policy (taxation, subsidies, transfers, and programmes). Although amenable to intervention, there is also real political resistance in some countries to redistributive policies. Inequality between nations is also important but far less amenable to plausible policy action other than through multilateral and bilateral efforts such as ODA, trade agreements, and subsidised loans through the development banks.

A vast literature links poverty or some other measure of household financial power to health outcomes.[122–124] The connection for many specific health outcomes or risk factors with income and absolute or relative poverty has been well established. For this analysis, we developed plausible best and plausible worst scenarios examining the relationship between median household consumption per capita and lag-distributed income (appendix p 151). We adopted median household consumption as the most predictive distribution-sensitive measure of household financial power after extensive testing of various formulations, including extreme poverty and household consumption per capita for various deciles. These measures were evaluated with out-of-sample predictive validity for models of age-specific mortality fit on the data from 1950 to 2023 for all countries and territories.

These scenarios primarily capture the distributional dimension of inequality rather than the relative inequality presented in the Wilkinson hypothesis,[125] which holds that income disparities within societies carry independent health effects beyond absolute income levels to the extent that more inclusive growth correlates with lower within-society inequality; however, our measure might indirectly reflect some of these dynamics.

For estimating the frontiers to develop plausible best and plausible worst scenarios, we have excluded the major petroleum exporting states, which we found to have profoundly lower median consumption per capita than other locations. The level of inequality in these economies has not been observed outside of petrostates and would be implausible in non-petrostates. Using median consumption per capita in the construction of SDI leads to an equity-sensitive measure of economic power, as it focuses on the median rather than the mean, and is more aligned with welfare than average income. Equity-sensitive SDI affects the plausible better and worse scenarios through two pathways. First, the model for underlying mortality includes the equity-sensitive SDI. Second, for risk factors with an established relationship to SDI, the equity-sensitive SDI is included as a driver in the risk factor forecast model. The impact of inequality, both through risk factor changes and more direct pathways such as access to health services or social services, is captured through this approach. Plausible better and worse scenarios use both frontiers on the level of median consumption per capita and on the velocity of change in median consumption per capita. The net effect on equity-sensitive SDI is shown in the appendix (p 152), which shows reference, plausible best, and plausible worst SDI trajectories by GBD super-region.

The cumulative number of DALYs from 2025 to 2100 that is amenable to improvements in income inequality from the levels found in the worst scenario to the best scenario is extremely large, at 13·8 billion (95% UI 6·50–28·8). At the global level, this amenable burden represents 5·57% (2·59–11·1) of the forecasted total cumulative DALYs (for 2025–2100) across all causes under the reference scenario. This is equivalent to the DALYs of more than 25 COVID-19 pandemics. Figure 16 shows the cumulative amenable DALYs related to income inequality by age, Level 2 cause, and GBD super-region. Any cause that is above the null line (ie, positive amenable DALYs) is reduced in the plausible best scenario in that age group compared with the plausible worst scenario. For causes below the null line, the opposite is true: due to competing causes, there are more DALYs due to that cause in the plausible best than in the plausible worst scenario in that age group. Reducing income inequality has a profound, positive effect on neonatal causes in sub-Saharan Africa, for example. In high-income countries, reducing income inequality reduces the burden from many causes but might actually lead to more neoplasm DALYs in older ages. This comparison also includes effects mediated through changes in population size because of fertility changes.

To better understand the opposite relationships of income inequality to cardiovascular disease and cancers, we compared age-specific DALY rates (removing population impact) for these two cause groups over time from 2025 to 2100 across super-regions (appendix p 153). Notably, in high-income countries where the net cumulative amenable burden is slightly negative, the contrasting scenario differences between cardiovascular disease (positive amenable) and cancers (negative amenable) are very small and the absolute effect of the income inequality threat is minor. In sub-Saharan Africa, the scenario difference in DALY rates was much larger for cardiovascular disease (positive amenable) than cancer (negative amenable). Also at play are strong downward trends for cardiovascular disease rates in both the plausible best and worst scenarios in all age groups, whereas cancers declined at slower rates than cardiovascular disease in younger age groups and were stable or slightly increasing in the older age groups. These patterns result from a strong inverse relationship between cardiovascular disease and SDI, so the plausible best scenario lowers its age-specific rates enough that net amenable DALY counts fall despite the competing risk effect of additional survivors. Many cancers are positively associated with SDI, and age-specific cancer rates are higher in the plausible best scenario. The inverse effect of SDI on scenario difference in cancer rates is much smaller than the corresponding effect on cardiovascular disease, so that competing risks play a stronger role for cancers.

Because inequality is so large in some sub-Saharan African countries, the largest potential gains are in this GBD super-region. Reducing income inequality affects both communicable, maternal, neonatal, and nutritional disorders causes and NCDs, and its impacts are across all age groups. The breakdown by cause reveals that maternal and neonatal conditions feature prominently in the amenable burden, which might appear disproportionate given that NCDs dominate absolute projected DALYs. This reflects high amenability where income gains have a proportionally larger effect on maternal and neonatal outcomes and the gap between best and worst scenarios is wide. The potential impacts of reducing income inequality on health outcomes can be evaluated by looking at the difference in life expectancy between the plausible worst and plausible best scenarios in 2100. Amenable life expectancy in 2100 varies by country, ranging from 9·83 years (95% UI 1·24–18·9) lower in the United Arab Emirates in the worst scenario than in the best scenario to 0·671 years (0·0445–1·48) higher in Switzerland (appendix p 155).

One concern about this framing of the range of inequality between plausible best and worst is that we are assuming future trends in GDP per capita are not influenced by redistributive policies. In economics, there is considerable

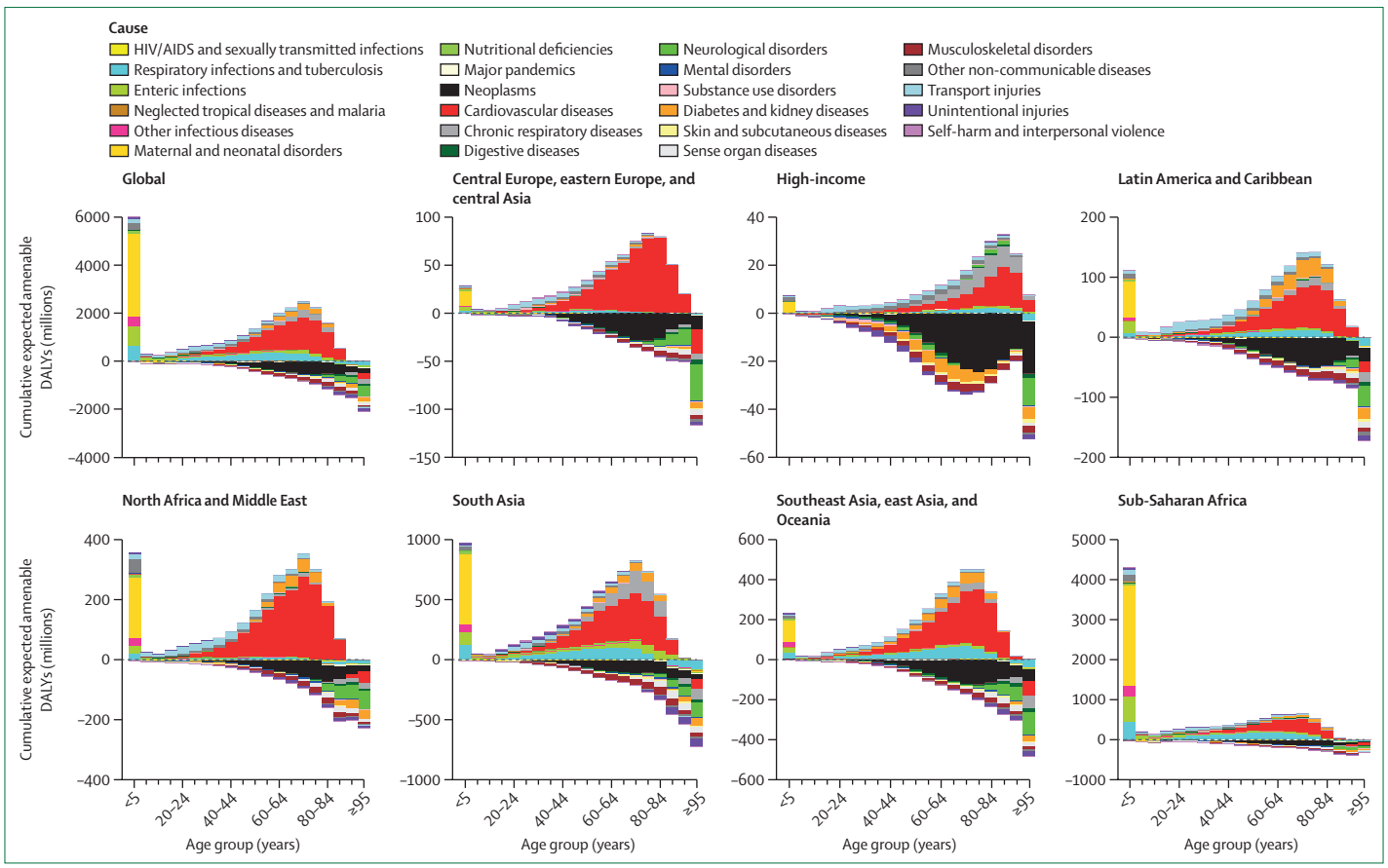


Figure 16: **Cumulative expected amenable DALYs related to income inequality by age and cause, globally and by GBD super-region**
DALYs are cumulative from 2025 to 2100, with cumulative expected amenable DALYs referring to the difference in cumulative DALYs between the plausible best and plausible worst scenario for each threat. DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

literature on the equity–efficiency trade-off but also considerable controversy.[126–128] The idea is that efforts to redistribute income aggressively can lead to reduced GDP per capita growth. Some development economists have also argued that inequality can hamper growth through mechanisms such as underinvestment in human capital formation. In the observed data on the ratio of median consumption per capita to GDP per capita, we tested for this relationship and found that as the ratio increases (meaning inequality decreases), GDP per capita growth is slower. More radical redistribution leading to median consumption per capita above the upper bound, shown in the appendix (p 151), might further limit growth. The empirical literature on this trade-off is highly contested, with studies finding heterogeneous effects depending on country income level, time horizon, and the shape of the distribution.[129–132] The controversy on the trade-off between growth and the health gains from redistribution, if causal, could complicate the prioritisation of this strategy.

5.10 Low educational attainment

Extensive literature has repeatedly shown that educational attainment has a nearly linear effect on the risk of child and adult mortality.[133,134] The relationship between maternal education and child mortality has been recognised for many decades. The pathways through which education shapes health outcomes include health behaviours, health literacy, autonomy in decision making, health-care access and navigation, employment and income, and more, all of which mediate the relationship between educational attainment and morbidity and mortality across the life course.[135,136] Evidence has also shown a strong relationship between paternal education and child mortality, controlling for maternal education,[137] as well as between parental education and health in younger years and own education and health in adulthood.[138] In line with this evidence, our analysis uses parental education as the predictor of health outcomes below age 20 years and own education thereafter. Multiple studies also show that across high-income and middle-income countries and some low-income countries, adult mortality is also related to educational attainment for males and females.[133,139] Educational attainment of women of reproductive age is also the most important determinant of fertility levels, with higher education being associated with lower fertility.[140] Therefore, raising

educational attainment has a dual effect on DALYs over the course of the century: profoundly decreasing total population and decreasing death rates.

As noted in the reference scenario discussion (section 2), we expect educational attainment to improve in the coming decades, with considerable catch-up occurring, narrowing educational attainment gaps between low-income and high-income countries. We found that growth in educational attainment observed in the past 50 years has been largely uncorrelated with GDP growth rates. Empirically, the best predictor of the velocity of educational attainment growth is the current level of education; further progress in educational attainment is largely a function of how much progress has already been made, with slow increases in populations with very low educational attainment, an acceleration through an average of approximately 8–10 years of education, and slower progress in populations with very high educational attainment. We likewise found that historically, north Africa and the Middle East have had much faster growth rates for female educational attainment than other regions. As part of these long-term trends, we also expect that in nearly all countries, female educational attainment will be higher than male; already female attainment is higher than male attainment in the younger cohorts in most middle-income and all high-income countries, and the forecasts show this trend is likely to continue (appendix pp 156–59).

We have constructed plausible best and worst scenarios by fitting frontiers on change in years of education in the group aged 25–29 years. We assume that, as cohorts, age-maximum education has been achieved by age 30 years. We recognise that some graduate education can and does occur after age 30; however, education after this age has comparatively little effect on overall educational levels. Given the unusual pattern of extremely rapid progress in educational attainment in some countries in north Africa and the Middle East and then equally rapid reductions in the rate of progress, we have also examined fit constraints on acceleration (appendix p 160). Figure 17 shows the cumulative amenable DALYs related to low education by age, level 2 cause, and GBD super-region. In contrast to income inequality reduction, accelerated attainment of education has much more diverse effects across causes, ages, and super-regions. Although the effect on child causes is especially large, meaningful reductions also occur across a broad range of causes in young and middle-aged adults. More individuals surviving childhood and young adulthood does mean more deaths from cancers, neurological causes, and others at older ages. Similar factors are at work here as described for the income inequality threat (appendix p 154)

Cumulatively from 2025 to 2100, the global number of DALYs amenable to increases in educational attainment is 16·1 billion (95% UI 12·2–22·8), equivalent to 6·53% (5·30–8·79) of cumulative reference DALYs due to all causes in the reference scenario. More than 60% (67·7% [63·2–72·9]) of the amenable DALYs due to low education are in sub-Saharan Africa because of population shifts and because that region currently has the lowest level of educational attainment. More than half (61·9% [57·2–67·3]) of the amenable burden is in children and adolescents (aged 0–19 years), and more than half (54·1% [50·4–58·0]) is attributable to communicable, maternal, neonatal, and nutritional disorders DALYs.

Education has a dual effect on mortality and fertility, leading to large effects of faster or slower educational attainment. Our analysis has taken into consideration the range of possible increases in educational attainment observed across countries. Faster increases in educational attainment would very substantially alter the trajectory of population growth in sub-Saharan Africa, particularly west Africa. In the plausible best scenario of educational attainment, for example, global population would peak at 9·29 billion (95% UI 8·69–9·95) in 2056, compared with 9·51 billion (8·75–10·4) in 2064 in the reference scenario (see section 2). Our plausible best scenario for education is grounded in observed rates of change in educational attainment at each level of educational attainment. However, such progress on education would require prioritisation of education by national governments. Given the small fiscal space for many low-income countries, prioritisation would be facilitated by development assistance for education. The contrasts in the amenable burden for low educational attainment and income inequality by age, sex, cause, and location are interesting given they are both distal drivers of health outcomes operating through multiple mechanisms. The primary reasons for these contrasts stem from where income inequality is high for a given level of development and likewise where educational attainment is low for a given level of attainment.

5.11 Malicious use of AI, including creation of bioweapons using AI

Progress in AI has accelerated rapidly since the advent of transformer architectures. Global investment has swelled correspondingly. Private AI investment in 2024 reached US$ 109·1 billion in the USA, US$ 9·3 billion in China, and US$ 4·5 billion in the UK (with generative AI alone attracting US$ 33·9 billion globally), and cumulative global AI investments and announced infrastructure deals now exceed US$ 1 trillion.[141] Tech companies and state actors globally are competing to develop increasingly advanced foundational models, while an ever-growing ecosystem of start-ups embed AI into everyday functions. Benchmark tests for coding, general science, and mathematics are being steadily surpassed, and predictions for agentic large language models suggest near-term tools capable of replacing many human activities. Some analysts project the realisation of artificial general intelligence within the next 5–15 years, although a consensus definition of artificial general intelligence remains elusive.

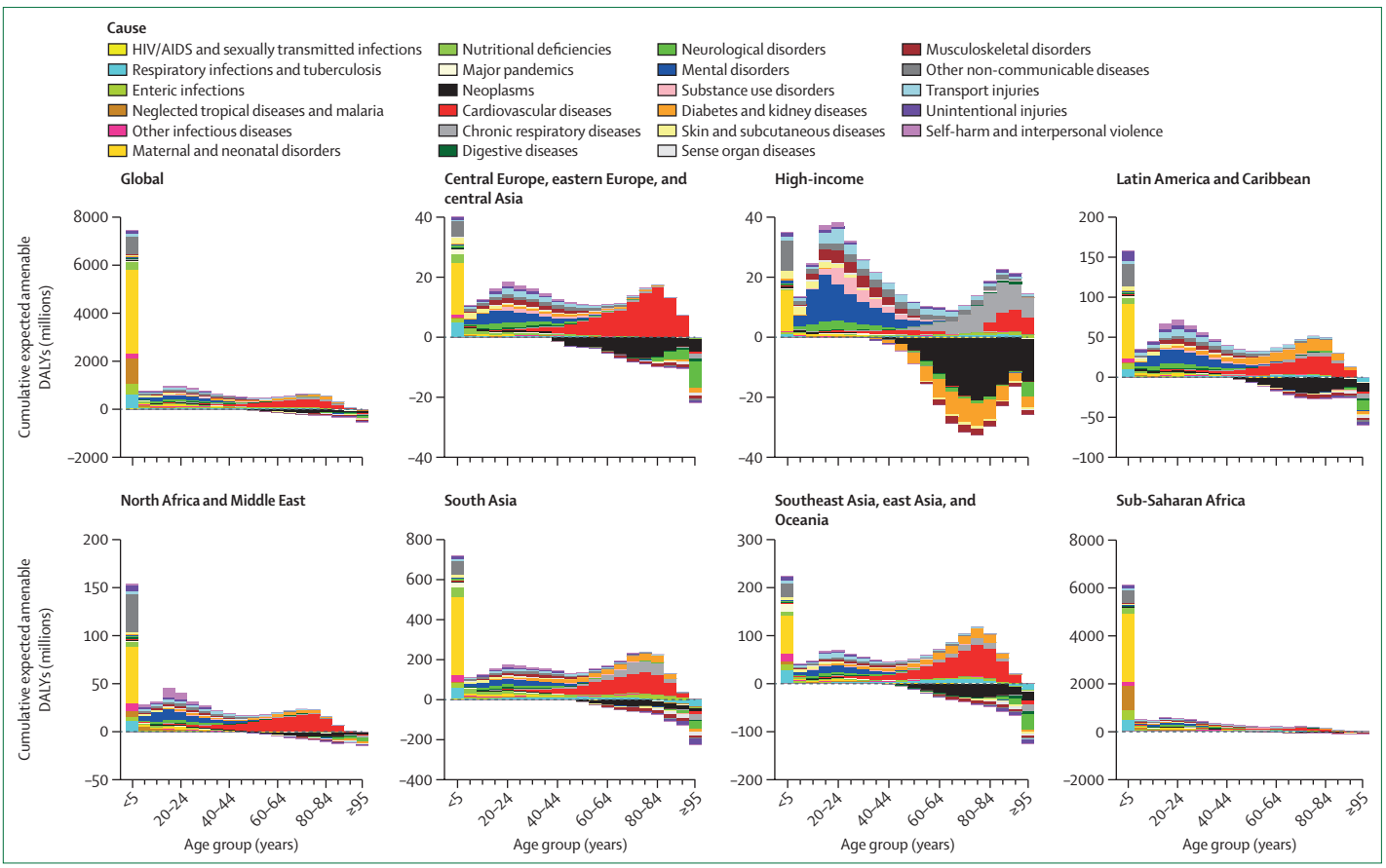


Figure 17: **Cumulative expected amenable DALYs related to low education by age and cause, globally and by GBD super-region**
DALYs are cumulative from 2025 to 2100, with cumulative expected amenable DALYs referring to the difference in cumulative DALYs between the plausible best and plausible worst scenario for each threat. DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

Although AI's potential to advance health and wellbeing is enormous, including reducing the risk of and harm caused by many of the other threats in this Commission report, the risk of catastrophic harm is equally profound. A growing coalition of voices across policy, industry, and academia is calling for robust safeguards before future models are capable of precipitating global catastrophes. No malicious AI event of a truly global magnitude has occurred to date; therefore, fitting empirical statistical models is impossible. Consequently, risk quantification relies heavily on published surveys, forecasting tournaments, and elicited expert judgement.

Given the subjective nature of AI forecasting, disentangling specific outcomes is challenging. However, the risks broadly manifest across three main pathways. The first pathway involves pathogens, with AI used maliciously to design and synthesise highly lethal, novel biological agents, greatly lowering the barrier to entry for bad actors. Second, the integration of AI into critical societal infrastructure leading to cascading failures or malicious exploitation. These systems issues include AI hallucinations being incorporated into clinical practice guidelines, the creation of mass political deepfakes, AI-enhanced ransomware targeting health-care facilities, autonomous weapons, autonomous nuclear weapons, and the catastrophic disruption of financial institutions.[142,143] The final pathway is loss of control through the emergence of agentic, unaligned artificial general intelligence. This loss of control includes AI systems creating subgoals that lead to the seeking of human disempowerment or elimination, particularly if such agents autonomously gain access to financial networks, key infrastructure, or physical tools in the real world.

Crucially, not all AI risks present the same intervention challenges. Systems issues are currently the most amenable to conventional governance and intervention. Risks can be actively mitigated through interventions such as the robust cybersecurity hardening of health-care and financial databases, strict regulatory frameworks for clinical AI integration, and digital watermarking mandates. Pathogen risks are moderately amenable; they can be restricted by implementing mandatory screening for DNA synthesis orders, screening of reagent sales needed for DNA and RNA synthesis, securing lab

environments, managed access to biological data, and legally restricting access to biological design models. These are illustrative examples, as effective restriction will require a broad set of coordinated interventions agreed upon globally. Loss of control scenarios remain the least amenable to standard policy interventions. Preventing these outcomes relies heavily on solving fundamental, open technical problems in AI alignment and achieving unprecedented international coordination to monitor and regulate massive computing clusters and training runs, including developing and implementing policy frameworks for controlling AI models with the largest potential for catastrophic misuse. Since progress in AI development is mostly private sector-driven, governments lack leadership and depth of understanding to effectively design and implement regulations. That said, there have been several recent developments in AI governance, including the creation of the UK AI Security Institute[144] and the White House Executive Order, *Promoting Advanced Artificial Intelligence Innovation and Security*.[145]

Efforts to quantify the risk of AI-related catastrophe (defined as death of at least 10% of the global population) and extinction by 2100 show wide divergence between forecasting groups: median estimates from super-forecasters were 2·1% for catastrophe and 0·4% for extinction, whereas AI domain experts estimated 12·0% for catastrophe and 3·0% for extinction. Most aggregate group estimates place extinction risk under 10%, although notable individual commentators estimate it to be substantially higher. The Forecasting Research Institute did a standardised, long-run tournament to elicit assessments from both AI domain experts and superforecasters (individuals with proven track records of predictive accuracy), described in more detail in the appendix (pp 109–14). Over prolonged interaction, the estimates of the two groups did not converge. Domain experts estimated substantially higher probabilities for extreme outcomes compared with superforecasters, highlighting the profound uncertainty in the field.

Plausible best-case scenarios envision no major AI events leading to mass casualties or extinction achieved through regulatory mechanisms for the three pathways. We construct plausible worst-case scenarios using the sum of the median plus three median absolute deviations of the expert and superforecaster judgements. To calculate the upper bound of our uncertainty interval, we add two absolute median deviations to this point estimate. The expectation value of deaths and DALYs are calculated from these probabilities (appendix pp 109–14). Based on this qualitative and largely subjective assessment, the amenable DALYs related to malicious AI are estimated at 10·4 billion (95% UI 0·00–15·6), cumulatively for 2025–2100. Although this figure is not much larger than some other massive global health threats (such as pandemics or obesity, diet, and physical activity), it carries a non-zero risk of total extinction, which is why it is grouped as an extinction potential threat along with nuclear war with nuclear famine. We note that, as is the case for our assessment of nuclear war, our assessment of amenable burden for malicious AI combines a potentially immense consequence with a probability that is much less than one. As this assessment is substantially more tenuous than other threats, we have not included this outcome in the reference scenario. However, if we did incorporate these risks, it would reduce forecasted life expectancy in each year by approximately 3–4 years by 2100. Arguably, our assumption that loss of control is amenable to policy intervention is not well substantiated. As such, our estimates of amenable cumulative DALYs due to malicious AI might be exaggerated.

5.12 Naturally occurring pandemics

When COVID-19 spread around the world and eventually led to 18·1 million (95% UI 17·2–18·7) deaths and 547 million (499–618) DALYs between 2020 and 2023,[68,86] a toll amplified by pre-existing social inequalities and chronic-disease burden, concentrated in deprived and comorbid populations,[146] many health-system leaders were taken unaware. Forecasts of life expectancy from 2019 or before from the UN, IHME, the Wittgenstein Centre,[37,147] and various national authorities did not account for the possibility of a major pandemic. Because there was insufficient attention paid to the potential for large scale health harm from pandemics, the world was ill-prepared to respond. However, statistical analysis of past pandemics reveals that we should not have been surprised by the magnitude of the COVID-19 pandemic.[148,149]

Several analyses of past recorded pandemics and epidemics suggest that death counts follow a heavy-tailed distribution, meaning that exceptionally large outbreaks happen more often than would be expected under a normal distribution.[149,150] We have built on this literature to develop models of the expected range of pandemic-related deaths over the next 75 years. By examining how this modelling approach fits to data from before 1950 compared with 1950 to present, we have also assessed how robust this statistical approach is likely to be.

There are four components to the assessment. First, using two published sources[149,150] as a starting point, supplemented by more detailed assessments of some pandemics such as the Spanish Flu or HIV, we have reviewed all reported pandemics and large-scale epidemics from 1600 to present. We developed formal inclusion criteria defining pandemic-level events based on five dimensions: magnitude (≥100 000 population-scaled deaths), novel pathogen emergence or antigenic shift, defined temporal boundaries, spatiotemporal uniqueness, and aetiological attribution, producing a curated dataset of 61 events (see appendix p 63 for a full listing of these events along with sources). We excluded from our analysis pandemics before 1600 based on the

notion that reporting was less likely to be accurate in earlier periods. Because earlier pandemics occurred when global population was considerably smaller, we have scaled previous estimates of deaths from pandemics by the ratio of current population to the population at the time.[151–154] This approach effectively shifts the distribution of reported pandemic sizes upward for events further back in time.

Figure 18 shows the database of pandemics from 1600 to present where the height and size of the points equal the scaled number of deaths, and the colours depict different time periods since 1600. Two distinct tiers of events are visible, separated at the model's empirically chosen threshold of 3 million population-scaled deaths: moderate pandemics (100 000 to 3 million scaled deaths, n=50) and catastrophic pandemics (above 3 million, n=17). The frequency of moderate pandemics below 3 million deaths appears to have declined in the 20th century, whereas the frequency of catastrophic pandemics has not shown a corresponding decline. By the nature of the data, this distribution includes all pandemics, including, in principle, bioterrorism, however, there has not been a bioterrorist threat causing enough deaths to appear on the figure. For the Commission, bioterrorist threats are included under the assessment of malicious use of AI.

Second, for pandemics larger than 100 000 scaled deaths, we fit a two-component mixture distribution to evaluate the shape of the distribution of size over 100 000 (appendix pp 23–25). According to the database of past pandemics, for pandemics causing more than 100 000 deaths, the expected size is 5·26 million (95% UI 3·02–20·0) deaths (see appendix p 161 for the fit of the mixture distribution to the historical pandemic database).

Third, we predict the probability each year of a naturally occurring pandemic (ie, not an AI-enabled pandemic) of over 100 000 deaths by fitting models to past event rates (appendix pp 23–25). Rather than fitting a single rate to



Figure 18: **Historical pandemic deaths database, 1600–present**
The number of deaths for each pandemic are population-adjusted by the ratio of the current population to the population at the time. The largest pandemics have been labelled. PLE=pandemic-level events.

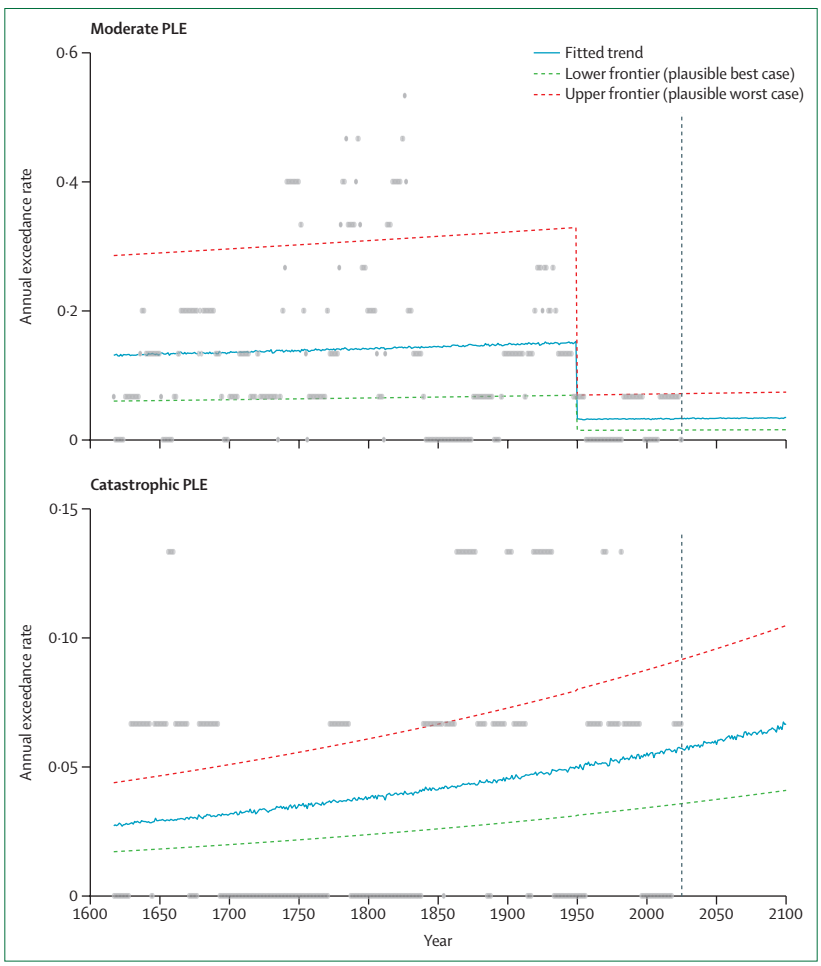


Figure 19: **Observed and projected annual exceedance rates for pandemic-level events by severity tier, 1600–2100**

PLEs are categorised into two severity tiers: moderate (100 000–3 million deaths; top panel) and catastrophic (over 3 million deaths; bottom panel). Grey points depict observed PLE rates within sliding windows. The blue solid line shows the fitted reference rate trajectory for each tier. The green dashed line shows the lower (plausible best case) and the red dashed lines shows the upper (plausible worst case) stochastic-frontier envelopes around the reference. The plausible worst and best cases are typical adverse and optimistic rates, not extremes: they shift the reference rate trajectory by the mean of the one-sided inefficiency component, so some grey points might lie above or below them. For the moderate tier, this trajectory incorporates a structural break at 1950, reflecting the mid-twentieth-century advances in modern medicine, sanitation, and public health; the catastrophic tier shows no comparable break and instead rises over the record. The vertical grey dashed line at 2025 marks the boundary between the historical period and the 2026–2100 forecast horizon. PLE=pandemic-level events.

all events, we model the occurrence rate separately for moderate pandemics (100 000 to 3 million deaths) and catastrophic pandemics (above 3 million), reflecting the distinct temporal dynamics visible in the historical record (figure 19). The rate of moderate pandemics has declined over time, consistent with improvements in public health; notably, the mid-20th century marks a step change in this decline, coinciding with the widespread adoption of antibiotics, modern vaccines, and organised surveillance systems. The rate of catastrophic pandemics, by contrast, shows no evidence of decline, consistent with claims that pandemic risk is increasing due to increased mixing between humans and wild animals in marginal forest zones.[155] These claims come from examining a very short time period, but given the sparsity of pandemics, longer time periods are needed to characterise the trends. Whether an emerged pathogen becomes catastrophic, however, also depends on how widely it spreads, not only on the conditions of its emergence. Air travel has compressed the effective distance from any local outbreak,[156] and migration and displacement might add further geographical seeding routes.[157] Urbanisation is double-edged in this regard: as rural populations shift to cities, they move away from such animal-interface interactions,[158] yet the urban densities they enter might favour onward human-to-human transmission,[159] and rural population growth is still increasing in some countries. There are claims that climate change is correlated with spillover events, although formal testing in our occurrence model found no statistical association. Precision population mapping at the pixel level suggests that the land area with human occupation has changed from 0·20 million km² to 0·32 million km² in the past 25 years, and when examining rural areas, it has changed from 0·14 million km² to 0·25 million km². Although these are large relative increases, the total area covered by settlements remains extremely small, around 0·2–0·3% of the land area of the Earth.[160]

Multiplying each tier's forecasted event rate by the tier-specific average pandemic size and projected population growth yields an expected cumulative pandemic death toll. Sensitivity analysis shows that the choice of model parameters and the cutoffs used to transition from one distributional assumption to another have minimal effect on the overall estimate. To test the robustness of this approach, we fit a model with data up to 1950 and compared the predictions of this model with observed deaths from 1951 to 2025. The prediction was consistent with the observed number of deaths over the past 75 years, lending credibility to the forecasts for the next 75 years.

Fourth, to define plausible best-case and worst-case scenarios for pandemics that are empirically based on observed experiences, we applied stochastic frontier analysis to the tier-specific rate trajectories to derive upper and lower bounds on pandemic frequency for each tier (figure 19). Some might argue that the best scenario could be much lower if the average size of a pandemic were lower than the estimated 5 million deaths. However, the historical record is too sparse to estimate a separate time-varying severity distribution. The range in cumulative pandemic burden between the best and worst scenarios from 2025 to 2100 is 103 million deaths and 6·7 billion DALYs (without accounting for competing risks). The plausible best and plausible worst scenarios are run through the cohort-component competing risks model to assess amenable DALYs due to pandemics. We estimate 2·39 billion (95% UI 0·896–7·09) amenable DALYs due to pandemics, which equates to

0·972% (0·399–2·72) of the reference scenario cumulative DALYs.

These totals are a global estimate of the health loss from pandemics; how that loss arises as deaths and disability within any society is shaped by its health systems, social protection, and supply chains, not by the pathogen alone. Technical breakthroughs in the area of pandemics could also potentially alter the expected number of deaths. For example, an effective pan-influenza vaccine could reduce the risk of this pathogen contributing to future pandemics. Research on vaccines with broad effectiveness for other respiratory viruses can also make a substantial difference. AI-enabled acceleration of medical-countermeasure design, development, and delivery, together with broader innovation in research, manufacturing, and financing, could substantially increase the amenability of pandemics if resourced and deployed at scale. These breakthroughs are not captured in the assessment of best and worst plausible scenarios. The work of the Coalition for Epidemic Preparedness Innovations and its 100 Days Mission can also alter the expected burden of these conditions.

5.13 Nuclear conflict and potential nuclear famine

Nuclear conflict causes health harm through multiple channels. A nuclear detonation produces immediate fatalities from the blast wave, thermal radiation, and ionising radiation. Survivors face long-term consequences including burn injuries, excess leukaemia and solid cancers, and elevated rates of anxiety disorder and PTSD,[161,162] as documented among atomic bomb survivors in Hiroshima and Nagasaki.[163,164] Societies suffer from subsequent supply chain disruptions; resource sparsity; depleted food production, including from reduced inputs such as seed and fertiliser, disrupted food storage and transport, pollution, and more; and resulting conflict, government upheaval, infrastructure failure (potentially exacerbated by electromagnetic pulse), and other detrimental economic and social consequences. Beyond these direct and indirect health effects, a sufficiently large nuclear exchange could inject enough particulate matter into the upper atmosphere to suppress global temperatures and disrupt agricultural production for years, a phenomenon known as nuclear famine.[165,166] Nuclear famine would affect all regions of the world, including those far from the conflict itself, through reduced caloric availability and cascading food-system failures. The devastation that could result from nuclear war cannot be overstated. Nuclear conflict is accordingly recognised by superforecasters as one of the few threats with extinction potential to humanity, alongside malicious AI.[18] The risk is not hypothetical: we found that between 1948 and 2010, 22 nuclear weapon accidents and 21 close calls were recorded. Future nuclear conflicts could occur due to multiple distinct mechanisms, including nuclear exchange arising from international crises between nuclear powers, accidental detonation of nuclear warheads, terrorist use of nuclear devices, and AI deployment of nuclear weapons (included in the malicious use of AI threat in section 5.11), among others.

We considered modelling nuclear conflicts along a spectrum of severity, from limited regional exchanges to full-scale nuclear conflict, but the non-extinction scenarios collectively accounted for only a few percentage points of the total extinction risk estimate. The extinction threat of nuclear war cannot be estimated with the methods and datasets employed for most other threats in this report, which rely on GBD data of past health trends around the globe. To quantitatively estimate the burden of nuclear war through 2100, we relied on forecasts of nuclear war-caused extinction (defined as resulting in a global population of less than 5000), as well as of nuclear war events leading to death of at least 10% of the global population (nuclear catastrophe), by 2100, from superforecasters and nuclear war experts. These forecasts were refined during a 4-month forecasting-persuasion tournament in 2022, published in a 2025 study independent of this report (appendix pp 114–17).[167]

For more on the **Coalition for Epidemic Preparedness Innovations** see https://cepi.net/

The methods used to calculate amenable burden using these forecasts are also detailed in the appendix (pp 114–17). In brief, the extinction and catastrophe probability estimates of each survey respondent are used to calculate an expectation value for nuclear war burden through 2100. These expectation values are used as the plausible worst scenario, and the plausible best scenario is defined as zero nuclear-attributed deaths and DALYs. Thus, the cumulative plausible worst and amenable burdens used here are identical. It is worth reiterating that we have not, given the uncertainties involved, included the expected risk of nuclear conflict into the overall reference scenario reported in section 2. Combining the responses of all respondents creates a distribution of each cumulative amenable measure (deaths, DALYs, YLLs, and YLDs). The value reported for each burden measure is the 95th percentile of these values. Upper and lower uncertainty bounds are obtained by respectively adding and subtracting one standard deviation from the 95th percentile value, for each distribution (deaths, DALYs, YLLs, and YLDs). While nuclear war with nuclear famine could cause extinction, in our analysis, we use the expectation of harm for each threat in each scenario, namely the product of probability and severity. The amenable burdens for nuclear war and the malicious use of AI combine the immense consequence of these threats being realised (leading to extinction or catastrophe) with estimates of the probability of such events occurring, which have been judged by superforecasters and experts to be less than one by several orders of magnitude.

Applying this approach resulted in 133 million (95% UI 0·00–339) cumulative amenable deaths and 9·35 billion (0·00–24·5) cumulative amenable DALYs globally by 2100 for the nuclear conflict threat. The burden was unevenly distributed: sub-Saharan Africa bore the highest burden (2·97 billion [0·00–7·77] DALYs,

42·4 million [0·00–110] deaths), followed by south Asia (burden 2·03 billion [0·00–5·11] DALYs, 29·2 million [0·00–69·4] deaths); southeast Asia, east Asia, and Oceania (burden 1·64 billion [0·00–4·24] DALYs, 22·1 million [0·00–54·2] deaths); high-income (burden 0·954 billion [0·00–2·63] DALYs, 14·5 million [0·00–39·4] deaths); north Africa and the Middle East (0·834 billion [0·00–2·15] DALYs, 11·7 million [0·00–29·9] deaths); Latin America and the Caribbean (0·595 billion [0·00–1·68] DALYs, 8·52 million [0·00–23·7] deaths); and central Europe, eastern Europe, and central Asia (burden 0·351 billion [0·00–0·937] DALYs, 4·85 million [0·00–12·8] deaths). Most notably, sub-Saharan Africa bears the highest burden despite having no nuclear weapons, owing to nuclear extinction probability and its young age structure. These risks would reduce global forecasted life expectancy in each year by approximately 3 to 4 years by 2100.

The burden of nuclear war could be decreased by at least two mechanisms. First, if nuclear stockpiles are progressively reduced below the threshold at which sufficient particulates would be injected into the upper atmosphere to disrupt global agriculture, the risk of nuclear famine is eliminated. The second is whether the effects of nuclear famine can be mitigated through alternative food sources such as resilient crops and non-traditional food production. Our analysis suggests that preventing confrontations between nuclear powers is central to reducing health risks. Although accidental detonations and terrorist use are serious concerns, the greatest dangers arise from international crises. Recent shifts in Russian nuclear doctrine are especially concerning. Global non-proliferation efforts, including the Treaty on the Non-Proliferation of Nuclear Weapons[168] and the Treaty on the Prohibition of Nuclear Weapons,[169] and stockpile reduction initiatives must be reinforced. Empirical political science evidence suggests limitations of nuclear deterrence: nuclear weapons are poor instruments of coercion,[170] alliances with nuclear-armed powers appear more stabilising than acquisition,[171] and stationing weapons in non-nuclear states might not enhance security. Health-care professionals can enhance these efforts through health-risk assessments, following the model of the International Physicians for the Prevention of Nuclear War.[172] Engaging the public is also crucial, as public opinion can constrain political leaders; the current high level of public support for nuclear weapons use is particularly concerning.[173]

5.14 Obesity

The cluster of high BMI (overweight and obesity), poor diet, and low physical activity together already accounted for 10·4% (95% UI 5·40–13·4) of total DALYs in 2023. For communication simplicity, we label this cluster simply as obesity for the rest of this section. In previous forecasts, it has been estimated that the number of adults with overweight or obesity will rise to approximately 3·80 billion (3·39–4·04) by 2050, with the fastest growth occurring in sub-Saharan Africa and the highest prevalence in north Africa and the Middle East and Oceania.[174] Overweight and obesity, largely a consequence of poor diet and low physical activity, is increasing in every country in the world; there remains substantial uncertainty in the relative contributions of changes in diet and physical activity to the accelerating obesity pandemic in many parts of the world. Evidence from the National Health and Nutrition Examination Survey that it has peaked and declined in the USA due to the use of obesity medicines (eg, glucagon-like peptide-1) has wide UIs and might be premature.[175,176] Together, these three factors are linked to 54 health outcomes, such as cardiovascular diseases and type 2 diabetes, supported by careful and rigorous evidence scoring. In our reference scenario, we forecast that global overweight and obesity will increase to 60% of adults and nearly one-third of children and adolescents in 2050.[174,177]

Given the universal rise in overweight and obesity, the nearly universal increase in caloric availability in national diets,[178] and the decline in physical activity associated with rising income per capita, the reference scenario forecasts a major global impact of this cluster of behavioural risks. In general, BMI increases as SDI increases, but there is a wide range of BMI values at the same level of SDI (appendix p 162). The slope of the BMI and SDI relationship, particularly at higher levels of SDI, is steep. There are also clear cases of increases in BMI at the same level of SDI within a country or between countries over time. The trends in BMI are not just a function of income-related changes in diet and physical activity but also include changes that are not income-related. Many hypotheses have been proposed for these non-income-related changes: changes in the food supply, the widespread use of high-fructose corn syrup, widespread consumption of fast food, food deserts, increased use of ultra-processed food, removal of physical activity from schools, the emphasis on avoiding fat in the diet leading to increased caloric intake, declining sleep quality and quantity, etc.[179–181] Policies to reduce BMI, as evidenced by the overall trends in BMI, have failed to date. The political feasibility of achieving the plausible best scenario is a legitimate concern given the food and beverage industry's considerable influence over regulatory environments.

To define a plausible best scenario, grounded in observed data, we examine the data for BMI and SDI since 1990 and use stochastic frontier analysis to set bounds on the summary exposure level for BMI for each level of SDI. The summary exposure value is a risk-weighted summary of the full distribution of BMI. The frontiers are also time-varying (appendix pp 162–63). The upper bound defines the plausible worst scenario and the lower bound the plausible best scenario. We have repeated the analysis for diet and physical activity to define plausible best and worst for this risk cluster. Given

that the levels of BMI, at a given level of SDI, are changing over time, we have allowed the plausible worst frontier to increase as a function of year. Velocity frontiers for each component are provided in the appendix (pp 61–102, 117).

Given the proven effectiveness of obesity medicines,[182] with the second-generation products producing 20% or larger decreases in weight, the availability, affordability, and uptake of these products might have a profound effect on the cluster of BMI and diet. Trials with a triple agonist have shown 28% reductions in weight.[183] To take these products into account, we have modified the plausible best scenario to reduce BMI summary exposure value (a severity-weighted measure of exposure) by 10%, assuming global obesity drug coverage of 50% of those with overweight or obesity, with an average 20% reduction in weight in those taking the drug. Given that 44% of people with hypertension are estimated to be on treatment globally,[184] assuming that we can reach 50% coverage in the coming decades with obesity medicines is plausible. These numbers are arbitrary but roughly match the coverage of the population with other chronic risks. Figure 20 shows the plausible worst, reference, and plausible best scenarios, with and without obesity medicine coverage included trajectories for global BMI. The difference between plausible best with and without the assumed scale-up of obesity medicines is quite small, highlighting that even before these drugs were available, there is marked variation in obesity at the same level of development across countries. Figure 21 shows the cumulative amenable DALYs attributable to high BMI, poor diet, and low physical activity combined by age and cause, broken down by super-region. Unlike some other threats, the nexus of these three factors primarily affects chronic kidney disease, diabetes, cardiovascular diseases, and cancers, with smaller effects on musculoskeletal disorders, dementia, and more. Notably, this analysis includes all 28 outcomes associated with high BMI, diet, and physical activity that are included in GBD. High BMI is also associated with adverse maternal health outcomes, including gestational diabetes, pregnancy complications, and difficult labour, with rates rising alongside global obesity prevalence. DALYs averted in the plausible best scenario compared with plausible worst lead to increases in a range of causes at older ages through competing risks, reflecting that reducing obesity, while highly beneficial overall, also results in more people living longer with other conditions.[185] Rising obesity among older adults, whose joints and organs have reduced buffering capacity, increasingly compounds multimorbidity and compromises physical function and social independence. This effect is universal across regions, with large impacts even in the lower-income super-region of sub-Saharan Africa.

From 2025 to 2100, the cumulative number of DALYs amenable to reductions in this obesity-related cluster of risks from the levels found in the worst to those in the best scenarios is enormous; cumulative amenable DALYs for 2025–2100 is 23·1 billion (95% UI 19·5–26·9). This amenable burden equates to over 9% (9·40% [8·73–10·1]) of the cumulative DALYs in the reference scenario. This large number is a reflection of both the size of the burden already associated with these risks and the increasing trend in BMI. Like climate change, the rise in BMI is slow and steady, but when accumulated over the century, the amenable burden is very large. Even the plausible best scenario, which is grounded in data from as early as 1990, projects a slow increase in BMI. With breakthrough technology, even more ambitious best scenarios might make the size of the cumulative amenable DALYs even larger.

The relationship between obesity and poverty is worth noting. Previous research has drawn attention to the inverted U-shaped curve for household income per capita and obesity, with the lowest rates in the extreme poor, rates peaking around US$ 5000 per capita and then lower rates at higher incomes.[186] This suggests that as LMICs industrialise and household incomes rise, many populations will move into the middle-income range where obesity risk is highest, with the burden increasingly concentrated in LMICs in the coming decades. On top of this general pattern, the entire curve at every level of income has been steadily increasing over the past several decades. This increase in obesity at any given level of household income is quite profound, substantially larger than the cross-sectional relationship between household income and obesity in any given country. The complex dynamics of obesity are also illustrated by the fact that obesity rates tend to be higher at the country level in high-income countries than in low-income countries. This steady rise has the potential to widen health inequalities, with the greatest burden falling on lower-income groups within high-income countries and on populations in LMICs, where metabolic complications arise at lower BMI thresholds.

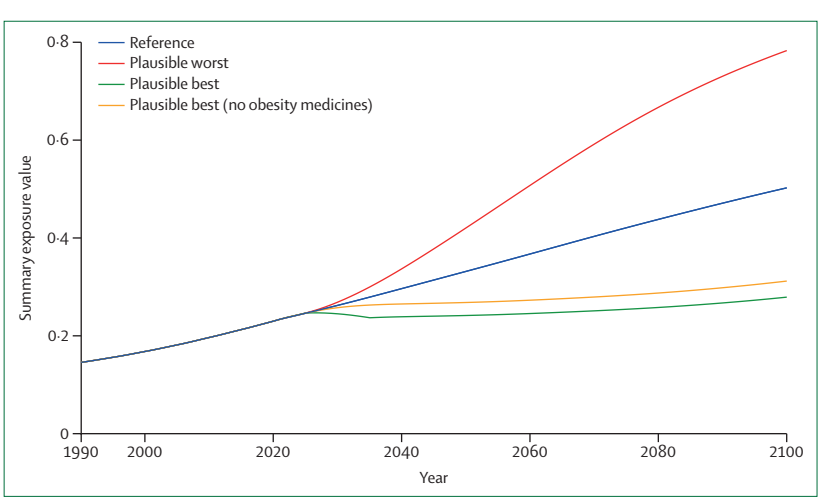


Figure 20: **Time series of adult BMI summary exposure value scenarios globally, 1990–2100**

Within countries, the relationship between household income and high BMI, poor diet, and low physical activity is uneven, with access to effective interventions varying substantially by socioeconomic status. The availability, affordability, and uptake of obesity medicines and similar treatments will likely follow existing socioeconomic gradients, raising the prospect of widening within-country health inequalities if access is not actively managed.

The literature on food systems[187] is in part attempting to call attention to the potential for improving human health by adjusting food intake. The scenario described in some of the food system analyses assumes that diet can be dramatically altered beyond the observed bounds of diet over the past 35 years and at a velocity of diet change that has not been observed. The difference in magnitude in their assessment is partly related to a very ambitious best scenario, converting the world to an optimal risk diet by 2050, whereas our best scenario is based on the empirically observed fastest velocity for change in diet. Food systems are also an important driver of greenhouse gas emissions, which are covered in the section on climate (section 5.4). Policy actions can be taken to reduce BMI and increase physical activity that do not alter greenhouse gas emissions by a large component, and actions can be taken on greenhouse gas emissions that do not dramatically alter diet and physical activity; therefore, we have chosen to keep the analysis of diet, physical activity, and BMI distinct from the analysis of climate change. Although there are clear potential linkages, there is also clear room to address each threat through independent policies.

5.15 Poor mental health

Based on the epidemiological baseline established by GBD 2023, poor mental health represents an important threat to human health and to global human capital and wellbeing.[68,86] The burden of mental disorders is rising in many regions. Rather than viewing variations in global prevalence as mere artifacts of inconsistent data, the Commission views these geographical disparities as evidence of a modifiable risk landscape.

Although high-income regions such as Australasia and western Europe have documented the steepest upward trajectories in prevalence of mental disorders over the past two decades, other global regions maintain

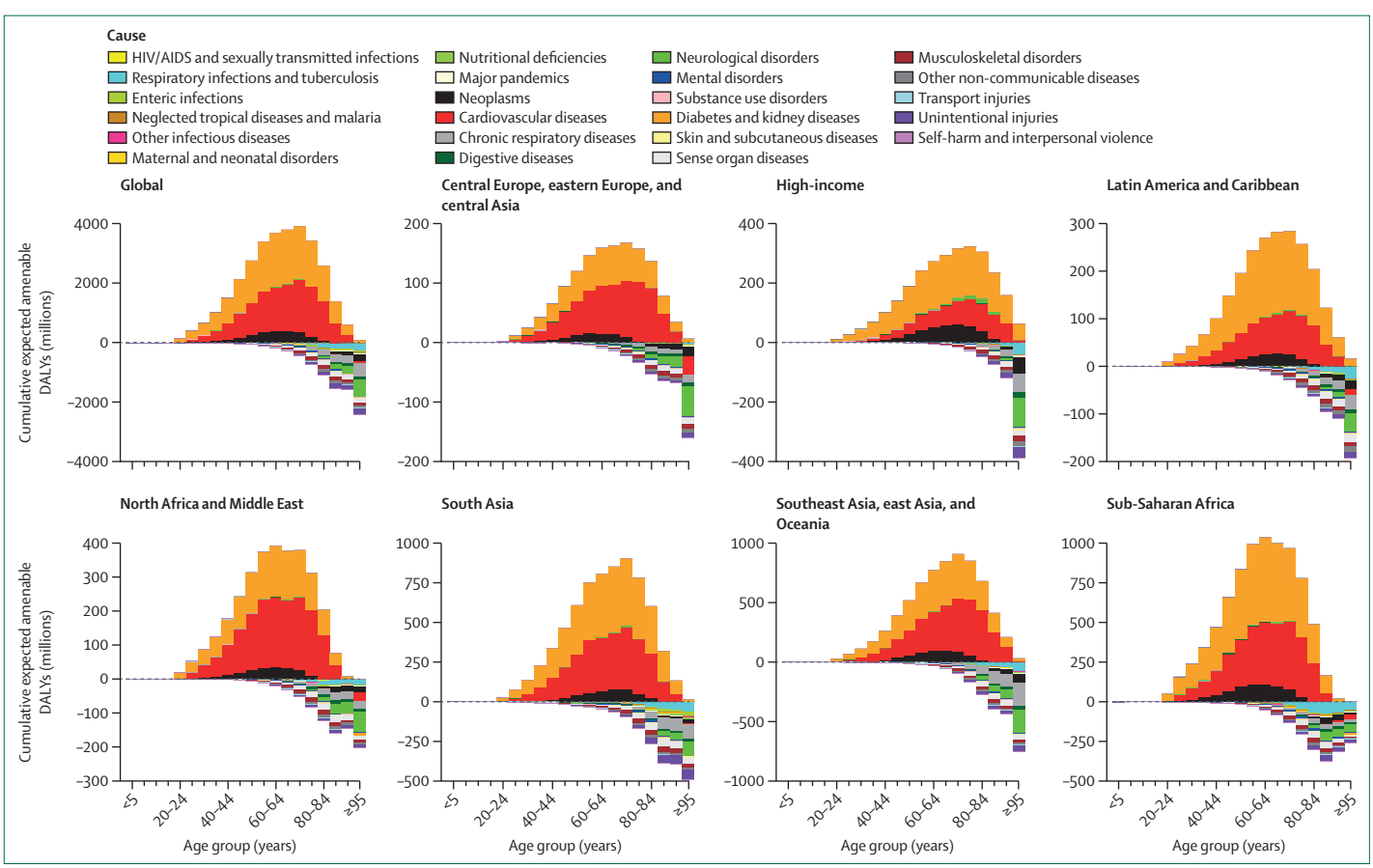


Figure 21: **Cumulative expected amenable DALYs related to obesity by age and cause, globally and by GBD super-region**
DALYs are cumulative from 2025 to 2100, with cumulative expected amenable DALYs referring to the difference in cumulative DALYs between the plausible best and plausible worst scenario for each threat. Obesity refers to the cluster of high BMI, poor diet, and low physical activity risks. DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

substantially lower baseline rates.[68] Even if the precise sociocultural, environmental, or structural protective factors driving these lower rates are not yet fully mapped, this wide variance establishes an amenable range. The variance suggests that escalating rates of anxiety and depression are not universally inevitable but are strongly influenced by modifiable societal and environmental conditions. This variation is also evident within countries, where lower-income groups face greater exposure to the social and economic drivers of poor mental health and are much less likely to receive appropriate treatment than higher-income groups.

The morbidity associated with poor mental health is substantial, heavily concentrating in the early decades of life, therefore having long-term consequences on global demographic and economic potential. Mental disorders and expressions of distress represent the single largest driver of disease burden for adolescents (aged 10–24 years) globally, accounting for 46·8 million (95% UI 32·9–66·6) DALYs in 2023 alone.[68] The capacity to mitigate this burden is severely fractured by global inequality. Systematic reviews indicate that a mere 6% of adolescents and children in LMICs receive appropriate treatment for mental disorders, compared with 43% in high-income countries.[188] Importantly, the Commission considers poor mental health a non-fatal threat, with 100% of cumulative amenable DALYs due to YLDs, because self-harm, not mental disorders, is the direct cause of death in cases of suicide. The relationship between mental disorders and self-harm is important, although epidemiologically complex. Major depressive disorder, which has a global prevalence exceeding 2900 cases per 100 000, increases the risk of suicide by 7·64 times.[189] Interestingly, although global age-standardised suicide rates have shown general declines, plateauing in western Europe and dropping sharply in parts of Asia, these macro-trends mask localised spikes in suicide among specific young demographics in high-income nations.

The COVID-19 pandemic administered a severe, acute shock to global mental health, likely driven by social isolation, grief, and profound economic uncertainty. Crucially, the evidence suggests that in heavily affected regions, the pandemic did not merely create a temporary spike, but catalysed and magnified existing upward trends in anxiety and depressive disorders.[190] Understanding that post-pandemic baseline rates have permanently shifted in many populations is crucial for forecasting future disease burdens.

To estimate the plausible best and plausible worst scenarios for the Commission's threat assessment, we use the robust regional trends identified between 2000 and 2019, combined with post-pandemic baselines. Because mental health epidemiology is complex, we draw our bounds from aggregate regional trends rather than extreme outlier countries. Mental disorder prevalence fails to stabilise and continues to compound at the highest observed regional growth rates recorded between 2000 and 2019. Global policy, social interventions, and improved psychiatric care access cause high-burden regions to stabilise and gradually converge towards the lower prevalence rates observed in more resilient global regions.

The cumulative amenable DALYs from poor mental health by the end of the century total 9·35 billion (95% UI 6·34–13·0). This figure underscores that mental health is not merely an actionable threat to 21st-century global health; investment in child and adolescent psychiatric care, structural social support, and cross-sectoral as well as cross-cultural research into opportunities for prevention of mental disorders and their consequences offers a substantial opportunity to avert burden in the coming decades.

5.16 Smoking

Tobacco consumption remains a profoundly destructive force in global public health. In 2023, tobacco smoking ranked as the third-leading cause of attributable disease burden worldwide, accounting for 5·78% (95% UI 4·82–7·12) of all DALYs.[68] Despite over two decades of international coordination under the WHO Framework Convention on Tobacco Control, the global trajectory of tobacco use remains highly concerning. Although high-income countries have achieved notable progress in reducing smoking prevalence, particularly among males, population growth and aggressive industry expansion in LMICs have offset these gains. Current forecasts suggest that the absolute number of cigarettes smoked globally will remain largely stagnant in the coming decades.

The 5·78% of global DALYs attributed to smoking is driven by a wide array of related diseases. Tobacco use is a primary driver of ischaemic heart disease and stroke, causing profound endothelial damage and promoting atherosclerosis. Smoking is the overwhelming global driver of COPD and exacerbates the severity of respiratory infections. Beyond being the primary cause of tracheal, bronchus, and lung cancers, tobacco use substantially increases the risk of cancers of the larynx, pharynx, oesophagus, pancreas, and bladder.

Further complicating this landscape is the marked increase in e-cigarette use, particularly among adolescents and young adults. Observational evidence suggests that youth e-cigarette initiation is associated with subsequent combustible tobacco use and elevated rates of nicotine dependence. However, the extent to which this reflects a causal gateway effect versus shared vulnerability factors remains an area of active investigation.[191,192]

Efforts to implement radical, endgame tobacco policies have largely faltered, although the recent passing of the Tobacco and Vapes Act 2026 in the UK promises to create the world's first tobacco-free generation (by banning the sale of tobacco to anyone born after a certain year).[193] A similar bill passed in

New Zealand but did not survive the first transition of governments.[194]

Meanwhile, less politically fraught and highly effective efforts embodied in the WHO MPOWER framework (monitoring use, protecting from smoke, offering help to quit, warning about dangers, enforcing marketing bans, and raising taxes) have yielded positive results, but implementation at the global level remains painfully slow due to relentless interference by the tobacco industry.[195]

To quantify the amenable burden of tobacco, we modelled smoking prevalence against SDI using stochastic frontier analysis (appendix p 118). At the highest levels of SDI, smoking prevalence generally converges and declines. At lower and middle SDI levels, there is large variation. Two countries with identical GDP per capita can have vastly different smoking rates. This wide variance explicitly shows the amenable range and proves that high tobacco consumption is not an inevitable consequence of economic development; rather, there is tremendous scope for policy interventions to alter tobacco consumption at any level of economic development.

Figure 22 shows cumulative amenable DALYs related to smoking by age, cause, and super-region. Reducing smoking to the levels of the plausible best scenario has large, positive effects on the burden of cancers, cardiovascular diseases, and chronic respiratory disease in most regions. In south Asia and particularly in sub-Saharan Africa, the age structure and background epidemiology mean there is also considerable amenable burden from respiratory infections and tuberculosis, much more than in other regions. The amenable burden from chronic respiratory conditions is the highest in south Asia due to high background rates. Very large competing risks phenomena are clear in all regions, with more of the population surviving until old age and experiencing death in those age groups due to a wide range of causes.

The cumulative amenable DALYs from smoking that could plausibly be averted through optimal policy (compared with the worst plausible trajectory) total 7·06 billion (95% UI 5·93–8·38) by the end of the century. The largest share of cumulative amenable DALYs is in southeast Asia, east Asia, and Oceania, although a few super-regions contribute more than 1 billion DALYs. The Commission's construct of measuring amenable burden in DALYs fully accounts for these competing risks. Consequently, the amenable burden computed for 2050 appears smaller than a simple subtraction of raw attributable deaths might suggest, as it accurately reflects the complex realities of ageing demographics.

Some critics might argue that our 7·06 billion DALY estimate is conservative. By anchoring our plausible best scenario to the lowest currently observed levels of smoking at given GDPs, we might be underestimating the potential effect of radical, untested policies (such as the aforementioned cohort bans). If global discourse shifts and aggressive endgame policies are widely adopted, the true amenable range could be larger. However, given the historical resilience of global cigarette consumption when the prevalence of smoking gets below 8% and the aggressive marketing tactics of the tobacco industry, anchoring our scenarios in empirically observed policy frontiers provides the most scientifically defensible estimate.

5.17 Unhealthy ageing

An unprecedented demographic shift is underway due to population ageing, with increases in life expectancy being observed around the world. This trend is occurring not only in high-income countries, but also in lower-income, high-fertility countries. Global life expectancy reached 73·8 years (95% UI 73·6–74·1) in 2023,[36] and we forecast it to reach 78·4 (75·9–80·6) years by 2050, despite short-term declines due to COVID-19.[196] This increase is due to increased life expectancy at older ages and decreased infant and child mortality. The average age of the population is also strongly influenced by lower fertility rates. Broadly speaking, this trend is a marker of societies' success; advancements in medical care, improved economic conditions, poverty reduction, greater access to education, and progress in gender equality have all contributed to increased life expectancy.

But many countries are ill-prepared to deal with this change. People living longer does not necessarily mean they are spending those years in full health. Disability and chronic diseases disproportionately affect those in their later years, including musculoskeletal disorders, mental disorders, diabetes, and neurodegenerative diseases such as dementia. In fact, the difference between life expectancy and healthy life expectancy has been increasing, negatively affecting health and care systems. From 1990 to 2010, each 1-year increase in life expectancy at birth was associated with just a 10-month increase in healthy life expectancy.[197] Recent analyses have found similar trends, with the difference between life expectancy and healthy life expectancy increasing in periods between 2000 and 2019, particularly for females.[198] Within countries, the widening gap between life expectancy and healthy life expectancy is not uniform: disability and chronic disease burden in later life is disproportionately concentrated among lower-income groups, amplifying existing inequalities into old age.

Some societies have started to prepare for the inevitable, with countries such as Switzerland and Singapore scoring highly in Chen and colleagues' Global Ageing Society Index,[199] which measures countries' readiness for population ageing in terms of wellbeing, productivity and engagement, equity, cohesion, and security. Countries that can prepare can reap the benefits of reduced health-care costs, enhanced productivity and knowledge-sharing from older people, and more

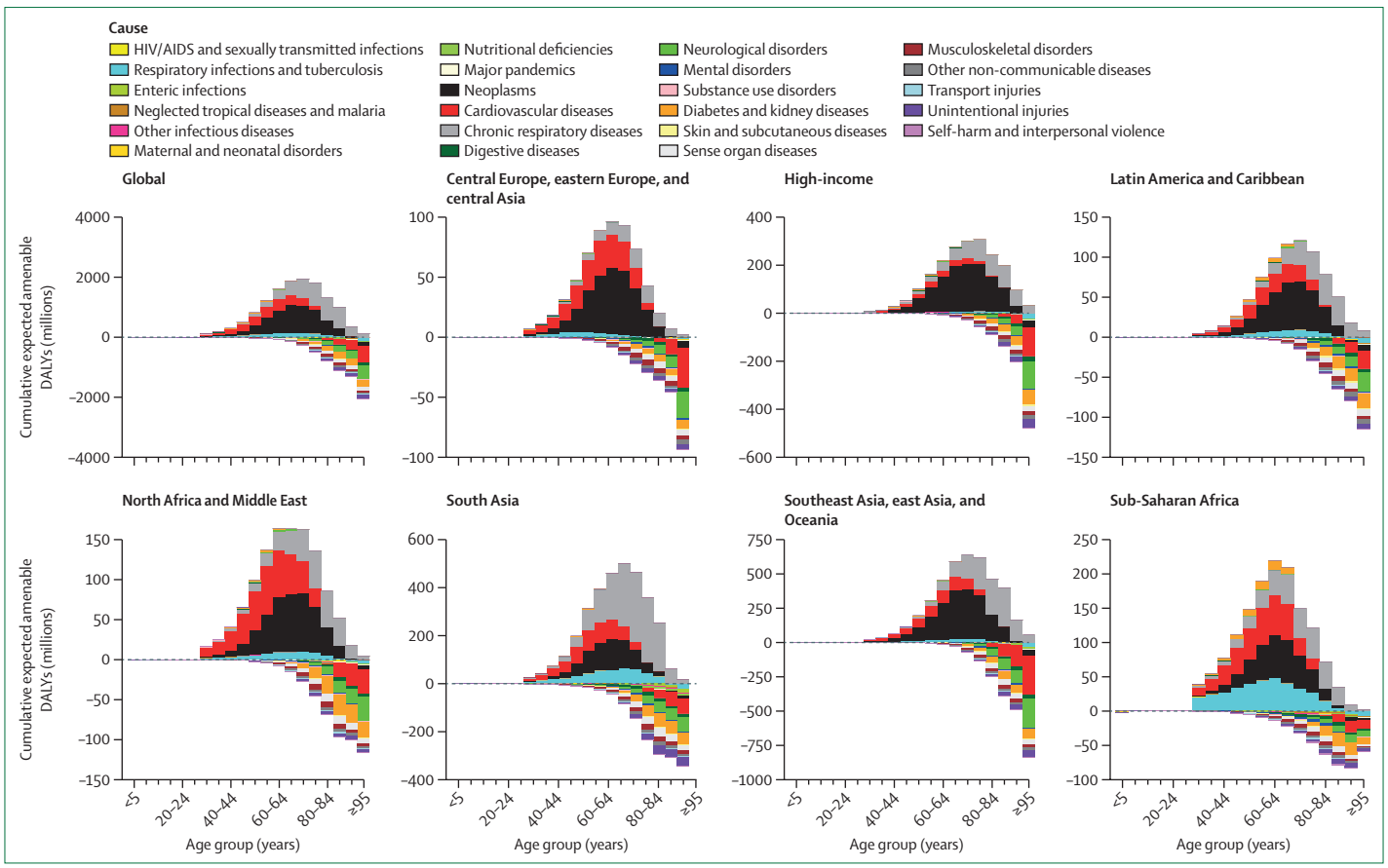


Figure 22: **Cumulative expected amenable DALYs related to smoking by age and cause, globally and by GBD super-region**
DALYs are cumulative from 2025 to 2100, with cumulative expected amenable DALYs referring to the difference in cumulative DALYs between the plausible best and plausible worst scenario for each threat. DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

sustainable demographic transitions. Currently, most countries are not prioritising this coming shift, meaning that the difference between healthy life expectancy and life expectancy is likely to continue to grow. As a result, more people around the world are spending their last years of life greatly affected by ill-health, and communities and countries will struggle to keep up with the burden.

To define plausible worst and plausible best scenarios for unhealthy ageing, we examined YLD rates for each age group across countries and time. For the age groups older than 60 years, we used stochastic frontier analysis to put boundaries on the highest and lowest levels of YLDs, observed at each level of age-specific mortality (appendix p 118). There is considerable variation in YLD rates, particularly from mental disorders, diabetes, and musculoskeletal disorders, across countries within each age group as a function of the age-specific death rate. We have assumed this entire gap is amenable to intervention even if we do not have a complete understanding of the variation across locations, such as the contribution from exercise or the contribution from social and cultural factors. Based on these assumptions, there is a huge cumulative amenable burden in all regions from unhealthy ageing. The global cumulative amenable DALYs total 8·26 billion (95% UI 6·38–10·6).

Section 6: Comparative magnitude of different threats

The analysis of the reference scenario and plausible best and worst scenarios for each of the 17 threats (with the exception of nuclear conflict and malicious use of AI, for which only plausible worst scenarios were estimated) has been done at the country level for 204 countries and territories, by age, sex, and cause. This analysis provides tremendous detail that can be used to explore how different threats affect different locations across all scenarios. Although we have highlighted that amenable deaths in long-run assessments such as 75 years are an intrinsically flawed metric, the appendix (pp 132–36) provides these numbers for each threat broken down by super-region to facilitate comparisons with other published threat-specific studies. A better metric that we have emphasised in the threat-specific discussions is cumulative amenable expected DALYs, namely the gap

	Global	Central Europe, eastern Europe, and central Asia	High-income	Latin America and Caribbean	North Africa and Middle East	South Asia	Southeast Asia, east Asia, and Oceania	Sub-Saharan Africa
Air pollution								
Cumulative amenable count (in millions)	1640 (1330–1950)	74·5 (56·9–92·8)	85·4 (66·1–105)	92·4 (70·5–111)	248 (198–324)	431 (311–564)	319 (262–364)	392 (310–498)
Cumulative amenable as a percent of reference	0·670% (0·518–0·794)	0·705% (0·507–0·920)	0·304% (0·236–0·389)	0·542% (0·397–0·709)	1·16% (0·899–1·44)	0·782% (0·545–0·996)	0·596% (0·455–0·720)	0·664% (0·543–0·782)
Antimicrobial resistance								
Cumulative amenable count (in millions)	3440 (2840–4060)	76·7 (57·4–103)	130 (65·1–195)	148 (85·5–206)	212 (154–265)	706 (479–959)	778 (606–970)	1380 (1130–1720)
Cumulative amenable as a percent of reference	1·40% (1·17–1·69)	0·722% (0·538–0·979)	0·460% (0·245–0·697)	0·863% (0·511–1·19)	0·988% (0·760–1·21)	1·27% (0·905–1·79)	1·45% (1·13–1·87)	2·34% (2·02–2·69)
Child malnutrition								
Cumulative amenable count (in millions)	1020 (673–1620)	7·18 (3·98–11·9)	1·66 (0·465–3·65)	14·7 (8·46–26·9)	27·4 (15·7–41·0)	106 (69·1–170)	43·4 (30·9–62·7)	818 (513–1280)
Cumulative amenable as a percent of reference	0·413% (0·281–0·651)	0·0676% (0·0365–0·109)	0·00584% (0·00179–0·0121)	0·0853% (0·0521–0·146)	0·127% (0·0771–0·189)	0·190% (0·127–0·281)	0·0806% (0·0581–0·116)	1·37% (0·996–2·04)
Climate change								
Cumulative amenable count (in millions)	1890 (1320–2480)	38·3 (14·2–58·9)	41·4 (5·59–79·2)	81·3 (51·8–114)	327 (236–443)	589 (394–792)	219 (170–270)	595 (259–948)
Cumulative amenable as a percent of reference	0·776% (0·535–1·02)	0·364% (0·142–0·527)	0·147% (0·0190–0·268)	0·478% (0·315–0·635)	1·51% (1·04–1·95)	1·08% (0·702–1·44)	0·409% (0·309–0·503)	1·02% (0·435–1·62)
Collapse of development assistance for health								
Cumulative amenable count (in millions)	1500 (1200–1950)	19·9 (12·4–33·9)	0·183 (–0·298 to 1·23)	30·2 (21·4–45·4)	167 (118–233)	183 (126–267)	55·9 (43·4–75·8)	1050 (857–1360)
Cumulative amenable as a percent of reference	0·611% (0·495–0·764)	0·186% (0·118–0·300)	0·000649% (–0·00109 to 0·00424)	0·176% (0·126–0·252)	0·774% (0·574–1·01)	0·329% (0·247–0·422)	0·104% (0·0789–0·133)	1·77% (1·54–2·05)
Conventional conflict								
Cumulative amenable count (in millions)	7710 (6580–9140)	60·5 (52·2–73·0)	24·1 (17·5–36·1)	349 (319–396)	482 (402–593)	828 (672–977)	474 (426–549)	5500 (4550–6570)
Cumulative amenable as a percent of reference	3·15% (2·59–3·81)	0·572% (0·467–0·689)	0·0861% (0·0583–0·134)	2·05% (1·69–2·46)	2·26% (1·73–2·94)	1·50% (1·21–1·85)	0·883% (0·733–1·07)	9·34% (7·51–11·2)
High alcohol use								
Cumulative amenable count (in millions)	2350 (1970–3060)	90·2 (52·7–141)	209 (147–293)	146 (103–197)	109 (80·8–145)	466 (262–838)	562 (452–694)	767 (608–1070)
Cumulative amenable as a percent of reference	0·957% (0·781–1·20)	0·847% (0·507–1·27)	0·742% (0·499–1·02)	0·850% (0·599–1·13)	0·508% (0·388–0·640)	0·837% (0·488–1·38)	1·05% (0·846–1·32)	1·30% (1·07–1·57)
High blood pressure								
Cumulative amenable count (in millions)	4790 (3740–6250)	154 (74·3–252)	270 (212–339)	289 (222–378)	735 (534–1010)	1070 (778–1350)	859 (649–1100)	1410 (1100–1870)
Cumulative amenable as a percent of reference	1·95% (1·45–2·45)	1·46% (0·731–2·48)	0·965% (0·735–1·29)	1·69% (1·21–2·22)	3·44% (2·45–4·56)	1·95% (1·40–2·47)	1·60% (1·15–2·12)	2·39% (1·92–2·98)
Income inequality								
Cumulative amenable count (in millions)	13 800 (6470–28 800)	160 (–92·8 to 555)	–146 (–274 to 35·3)	347 (–99·0 to 1140)	1380 (448–3550)	3710 (1950–5900)	999 (309–2200)	7310 (4090–15100)
Cumulative amenable as a percent of reference	5·57% (2·59–11·1)	1·49% (–0·909 to 4·98)	-0·517% (–0·916 to 0·130)	2·01% (–0·618 to 6·06)	6·38% (2·20–15·2)	6·70% (3·59–10·3)	1·86% (0·560–3·89)	12·2% (6·78–23·6)
Low education attainment								
Cumulative amenable count (in millions)	16 100 (12 200–22 800)	191 (94·9–326)	164 (68·1–282)	714 (447–1160)	490 (252–781)	2770 (1760–4140)	910 (607–1340)	10 900 (8380–15300)
Cumulative amenable as a percent of reference	6·53% (5·30–8·79)	1·78% (0·985–2·88)	0·576% (0·255–0·969)	4·14% (2·89–6·23)	2·26% (1·27–3·20)	4·97% (3·63–6·79)	1·68% (1·18–2·41)	18·3% (15·9–22·7)
Malicious use of AI								
Cumulative amenable count (in millions)	10 400 (0·00–15 600)	404 (0·00–606)	1080 (0·00–1620)	668 (0·00–998)	948 (0·00–1420)	2130 (0·00–3190)	1810 (0·00–2710)	3370 (0·00–5060)
Cumulative amenable as a percent of reference	4·21% (0·00–6·30)	3·81% (0·00–5·71)	3·95% (0·00–5·92)	3·87% (0·00–5·80)	4·47% (0·00–6·70)	3·89% (0·00–5·84)	3·37% (0·00–5·05)	5·56% (0·00–8·34)

(Table 2 continues on next page)

	Global	Central Europe, eastern Europe, and central Asia	High-income	Latin America and Caribbean	North Africa and Middle East	South Asia	Southeast Asia, east Asia, and Oceania	Sub-Saharan Africa
(Continued from previous page)								
Nuclear conflict								
Cumulative amenable count (in millions)	9350 (0·00–24 500)	351 (0·00–937)	954 (0·00–2630)	595 (0·00–1680)	834 (0·00–2150)	2030 (0·00–5110)	1640 (0·00–4240)	2970 (0·00–7770)
Cumulative amenable as a percent of reference	3·74% (0·00–9·30)	3·28% (0·00–8·27)	3·47% (0·00–8·74)	3·45% (0·00–8·76)	3·84% (0·00–9·51)	3·77% (0·00–8·75)	3·01% (0·00–7·50)	4·95% (0·00–12·3)
Obesity								
Cumulative amenable count (in millions)	23 100 (19 500–26 900)	967 (804–1140)	2080 (1730–2440)	1730 (1420–2030)	2310 (1890–2780)	5010 (4140–6070)	4640 (3820–5210)	6400 (5220–7730)
Cumulative amenable as a percent of reference	9·40% (8·73–10·1)	9·10% (8·03–10·2)	7·36% (6·72–8·21)	10·1% (9·19–11·2)	10·7% (9·54–12·1)	9·05% (8·17–10·0)	8·60% (7·95–9·41)	10·8% (9·76–11·7)
Pandemics								
Cumulative amenable count (in millions)	2390 (896–7090)	74·7 (29·8–203)	184 (74·2–485)	133 (52·4–354)	226 (90·9–665)	464 (152–1370)	342 (135–977)	966 (353–3030)
Cumulative amenable as a percent of reference	0·972% (0·399–2·72)	0·709% (0·285–1·94)	0·656% (0·273–1·71)	0·779% (0·311–2·03)	1·06% (0·436–2·91)	0·835% (0·303–2·24)	0·636% (0·261–1·72)	1·63% (0·670–4·95)
Poor mental health								
Cumulative amenable count (in millions)	9350 (6340–13 000)	361 (262–481)	1350 (959–1770)	751 (525–997)	1000 (687–1360)	2030 (1340–2840)	1380 (971–1890)	2470 (1640–3480)
Cumulative amenable as a percent of reference	3·78% (2·83–4·88)	3·39% (2·51–4·51)	4·76% (3·72–5·97)	4·37% (3·28–5·69)	4·65% (3·34–6·10)	3·65% (2·60–4·87)	2·55% (1·94–3·28)	4·16% (3·09–5·41)
Smoking								
Cumulative amenable count (in millions)	7060 (5930–8380)	348 (290–409)	1020 (851–1210)	406 (336–485)	688 (575–806)	1740 (1360–2470)	1860 (1580–2190)	1010 (845–1340)
Cumulative amenable as a percent of reference	2·89% (2·28–3·53)	3·30% (2·60–4·19)	3·64% (2·77–4·62)	2·39% (1·81–3·06)	3·22% (2·54–3·96)	3·15% (2·28–3·83)	3·48% (2·70–4·41)	1·71% (1·40–2·03)
Unhealthy ageing								
Cumulative amenable count (in millions)	8260 (6380–10 600)	334 (259–423)	1210 (930–1530)	652 (496–837)	798 (602–1010)	2030 (1510–2720)	2040 (1540–2630)	1190 (910–1500)
Cumulative amenable as a percent of reference	3·35% (2·75–3·96)	3·14% (2·63–3·72)	4·29% (3·72–5·03)	3·79% (3·14–4·54)	3·70% (3·06–4·37)	3·66% (2·76–4·37)	3·78% (3·16–4·55)	2·01% (1·58–2·45)

DALYs=disability-adjusted life-years. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study.

Table 2: **Cumulative expected amenable DALYs in millions and as a percent of reference for 17 threats, globally and by GBD super-region**

between the cumulative expected DALYs in the plausible best and plausible worst scenarios. Table 2 provides details by threat and by super-region. Notably, by using a full cohort-component competing risks framework (section 1.7), our assessments of amenable burden are substantially reduced compared with assessments that do not take into account competing risks; on average across a range of threats, we have found that estimates of amenable DALYs (and deaths) are reduced by around 50% when competing risks are factored in.

Figure 3 shows the cumulative amenable DALYs related to each of the 17 threats, with uncertainty intervals in terms of billions of DALYs. In total from all diseases and injuries, the reference scenario has 246 billion (95% UI 213–284) cumulative DALYs. Comparing cumulative amenable burden to what is expected in the reference scenario provides some idea of comparative magnitude not only across threats but relative to the totality of health problems. All these extinction potential and major catastrophic threats are very large, with amenable burden ranging from 1·02 billion (0·673–1·62) to 23·1 billion (19·5–26·9). This range of amenable DALYs equates to a range of 0·413% (0·281–0·651) of all forecasted DALYs to 9·40% (8·73–10·1). The largest threat in terms of cumulative amenable DALYs is the combination of high BMI (overweight and obesity), poor diet, and low physical activity. The next largest threats are low educational attainment and income inequality, both of which also contribute greater than 5% of cumulative DALYs. For low educational attainment, amenable DALYs come about equally from reduced disease rates associated with higher education and a reduced population from lower fertility. The next largest expected amenable DALYs are the two extinction potential threats: malicious use of AI and nuclear conflict with nuclear famine. Although both threats can cause human extinction before the end of the century under certain circumstances, on an expected-value basis, their cumulative amenable DALYs are estimated to be below

those of the three largest targets. These two estimates are, however, far more uncertain than the others: they rest on expert judgement rather than statistical models and carry wide uncertainty that includes the possibility of much larger burdens. The comparison reflects the difference in weighing the expectation of all outcomes and focusing on the worst outcome, namely extinction, and should not be read as placing these threats low among priorities.

Different threats have differential geographical effects, as shown in the appendix (p 164). Obesity, for example, is the leading threat for all super-regions except sub-Saharan Africa, for which low educational attainment has the largest effect. This is followed by income inequality, which is also second-leading for south Asia. Conventional conflict also disproportionately burdens sub-Saharan Africa, whereas this super-region is expected to experience proportionately less burden related to smoking and unhealthy ageing than other super-regions. The high-income super-region is disproportionately affected by poor mental health but contributes negative cumulative DALYs related to income inequality. Other super-regional patterns are shown in the appendix (p 164).

Different threats likewise affect different disease clusters in different ways. Some threats largely affect communicable, maternal, neonatal, and nutritional disorders, such as low education, income inequality, antimicrobial resistance, pandemics, the collapse of DAH, and child malnutrition. Others, such as obesity, smoking, unhealthy ageing, poor mental health, and high blood pressure, largely affect NCDs. The appendix (p 165) highlights the complex interplay that a full competing risks framework provides. For some causes of some threats, the cumulative amenable burden is negative; for example, negative injury and communicable, maternal, neonatal, and nutritional disorders DALYs related to obesity. This negative value is because, in the plausible best scenario, with much less obesity, more people survive to be exposed to injuries and communicable, maternal, neonatal, and nutritional disorders than in the plausible worst scenario.

Table 3 shows the rank distributions for each threat, highlighting how some threats are much more geographically heterogeneous than others. Obesity ranges from the leading threat in 154 countries and territories to the fourth-leading threat in nine countries. By contrast, income inequality ranges from the leading threat in 19 countries and territories to the lowest (17th-leading) threat in 70 countries. Several other threats have almost as large a range of rankings across countries as income inequality: low educational attainment, unhealthy ageing, and conventional war. Pandemics and nuclear conflict, which likely have a global distribution, have a much narrower range of ranks than some more differentiated threats. The table shows that the priority by threat will vary profoundly by country and region.

Section 7: Limitations

This Commission is a first attempt to compare a wide range of global health threats within a single conceptual and quantitative framework, and its conclusions should be read with several limitations in mind. As with any novel undertaking, we expect future iterations of the analysis will further refine the analysis, especially as

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Air pollution	0	0	0	0	0	0	0	5	14	19	21	28	30	26	27	17	17
Antimicrobial resistance	0	1	1	1	1	0	0	7	15	41	71	46	12	4	4	0	0
Child malnutrition	0	0	0	0	0	0	3	1	1	0	2	0	4	25	59	48	61
Climate change	0	0	0	0	1	0	0	2	8	2	6	25	34	47	29	33	17
Collapse of DAH	0	0	0	1	2	0	1	1	9	8	12	6	9	13	39	73	30
Conventional conflict	7	5	16	16	3	9	7	12	14	13	9	15	32	28	14	4	0
High alcohol use	0	0	0	0	0	0	13	23	23	21	28	18	27	18	14	11	8
High blood pressure	0	0	1	1	2	10	59	48	44	23	12	2	1	1	0	0	0
Income inequality	19	44	11	7	2	9	8	6	3	6	3	1	6	2	2	5	70
Low educational attainment	22	17	25	9	4	7	15	24	13	11	10	11	8	11	6	11	0
Malicious use of AI	1	16	45	79	46	12	5	0	0	0	0	0	0	0	0	0	0
Nuclear conflict	0	0	9	23	82	66	18	6	0	0	0	0	0	0	0	0	0
Obesity	154	26	15	9	0	0	0	0	0	0	0	0	0	0	0	0	0
Pandemics	0	0	0	0	0	0	10	21	21	29	19	41	32	23	7	0	1
Poor mental health	0	53	35	27	24	27	24	10	4	0	0	0	0	0	0	0	0
Smoking	0	2	11	15	18	54	24	21	18	19	4	4	7	5	2	0	0
Unhealthy ageing	1	40	35	16	19	10	17	17	17	12	7	7	2	1	1	2	0

Data are number of countries for which each threat corresponds to the given rank, from 1 to 17, based on highest number of cumulative expected amenable DALYs. AI=artificial intelligence. DAH=development assistance for health. DALYs=disability-adjusted life-years.

Table 3: **Rank distributions of cumulative expected amenable DALYs for each threat for 204 countries and territories**

new data and new scientific findings on threats are published.

The central metric, cumulative expected amenable DALYs, depends on how the plausible-best and plausible-worst scenarios are constructed for each threat. Where those scenarios are anchored in observed historical variation, through frontier bounds on exposure, they are empirically grounded. Where they rest on expert judgement for unprecedented events, they are necessarily more uncertain. The amenable burden reported here is the gap between these scenarios and is therefore a function of how they are defined rather than a prediction of what will occur. DALYs are a particularly useful and comprehensive measure of disease burden because they combine both fatal and non-fatal health outcomes into a single, standardised metric; however, no single measure can capture all components of lost wellbeing, particularly from harms that are difficult to quantify the impact of, or that have only indirect effects on health outcomes.

Any forecasted scenario, including the 75-year horizon to 2100 reported on here, entails uncertainty, which in most cases expands the further into the future scenarios are run. The world will change over this period in ways no model can anticipate through structural disruptions or technological breakthroughs. For this reason, the Commission focuses on amenable burden (the difference between scenarios) rather than point predictions. We also report 95% uncertainty intervals around future disease burden, but because these intervals are themselves estimates, in practice they cover about 93% of the predicted distribution rather than exactly 95% (appendix pp 35–37). The reference scenario is explicitly framed not as what will happen but rather what would happen if trends in the key drivers continue.

For two threats—nuclear conflict and the malicious use of AI—estimates rest on structured expert elicitation and superforecaster judgement rather than the statistical models used for the other threats. These estimates are inherently more uncertain than those of the other threats, and should not be treated as precise estimates. Superforecaster predictions typically concern events several months to a few years in the future, and the accuracy of superforecaster predictions has only been evaluated on such short timescales. The 75-year forecast we provide here greatly exceeds this range, and the confidence that should be placed in superforecaster predictions through the end of the century cannot be quantitatively evaluated. There is, however, at present no alternative to using these more subjective approaches. Ignoring such critical threats as nuclear conflict with nuclear famine and malicious use of AI is not a credible option.

The basis for excluding specific causal pathways for individual threats is set out in the relevant subsections of section 5. As the published literature evolves, future iterations of this analysis might well incorporate other pathways of action for specific threats.

The forecasts and scenarios are grounded in GBD estimates, for which some threats have more limited data or have variable data quality by geography. The extensive list of data and methods limitations for the GBD, well documented in many GBD publications, also apply here.

The climate analysis quantifies the dominant health pathways, with the full scope of pathways evaluated and the basis for each inclusion or exclusion decision set out in table 1. On scenario choice, the Commission uses RCP8.5 as the plausible worst case and RCP2.6 as the plausible best case. CMIP7 has replaced RCP8.5 as the highest emission scenario in favour of a high emission scenario with lower peak emissions, reflecting more recent emissions trends, including decreases in the costs and dissemination of renewable energy. This change means using RCP8.5 as our high emissions scenario likely overstates the amenable climate burden at the upper bound; at the same time, standard CMIP6 ensembles incorporate some, but not all, high-impact tail risks, such as abrupt shifts in Arctic and Antarctic sea ice and Tibetan plateau ice, or full collapse of the Atlantic Meridional Overturning Circulation or shifts in the south Asian and west African monsoons, which would push in the opposite direction. Our climate analysis also does not include the potential health effects that could occur via reduced nutrition, water insecurity, livelihoods, and mental health due to drought. Although climate models predict increased probability and severity of drought in a consistent set of locations, drought severity magnitude is highly uncertain. Another limitation of the climate analysis (and conventional conflict analysis) is the absence of a geospatial migration forecast model. Migration models at the pixel level that reflect climate change and conflict as well as the impacts of economic migration are an urgent priority. Given that the effects of sea level rise are also expected to act mainly via displacement, this climate change pathway has also not been included in our analysis.

The Commission discussed whether we should handle the climate change threat within the stochastic frontier framework that was applied to the majority of threats or use the contrast between RCP8.5 and RCP2.6. We landed on the latter, which leads to a larger amenable burden attributable to climate change compared with the stochastic frontier analysis approach, but we will assess our own plausible best and worst emissions frontiers in future iterations of this work. Of note, the stochastic frontier analysis approach yields global mean surface temperature changes more in line with CMIP7 high emissions scenarios.

The timeframe of analysis (through 2100) was selected after considerable deliberation. However, several threats, namely climate change and nuclear conflict, might have much larger effects on the global population in the decades and centuries following 2100. These effects are not reflected in our estimates of amenable burden.

Our results compare the burden that could be averted under the scenarios we specify. The results are not a ranking of policy priority and should not be read as one. We group the threats into tiers rather than a single order, and list them alphabetically within tiers, because a threat with a lower expected amenable burden might still require urgent action, either because it carries a tail risk of catastrophe or because important pathways of harm remain unquantified. This consideration applies with particular force to climate change. Our climate estimates rest largely on observed exposure–response relationships, which might not capture the unprecedented conditions, non-linear responses, and compounding interactions across environmental, biological, and social systems that a substantially warmer world could bring, and several pathways that could prove important, including migration, drought effects on nutrition and conflict, and sea-level rise, are not yet fully quantified. The uncertainty is therefore large and runs in both directions: our use of RCP8.5 as the plausible worst case might overstate the burden at the upper bound, while the unquantified and potentially non-linear pathways might lead us to understate it. The estimates for nuclear conflict and for the malicious use of AI are uncertain in a different way, resting on expert judgement over a horizon that cannot be validated, and should be read as indicative rather than precise. Where our findings differ from previous expectations, they are better treated as a reason for closer scrutiny and continued monitoring than as settled conclusions.

Section 8: Enablers

The quantification of cumulative amenable DALYs from two threats with extinction potential and 15 major catastrophic threats has identified a wide range of challenges, but it also suggests opportunities to improve health in the 21st century. These opportunities hinge on the presence of strong institutions, effective governance, and efficient service delivery systems, pillars that the Commission highlighted repeatedly when discussing mitigation and adaptation strategies. Central to these efforts is the element of trust, reflected by consistency, accountability, and integrity, as a foundation for resilience and a strong determinant of health intervention success. Achieving meaningful progress will require not only technical solutions but also robust societal and institutional foundations that foster collaboration and accountability.

There are powerful interlinkages between the extinction potential and major catastrophic threats that we have formally evaluated, meaning that actions to address one threat might either help or hinder the reduction of harm from other threats. Some of our recommendations follow from these connections. The interlinkages between threats are well demonstrated by climate change. For example, there are clear connections to pandemics through populations moving into areas with wildlife due to out-migration from heat-stressed zones; to child malnutrition through potential reductions in food output; to the interaction between heat and particulate pollution; and to antimicrobial resistance and mental health. Other interlinkages are also evident. For instance, income inequality can magnify the effect of threats in the most disadvantaged communities. The nature of the interlinkages prioritises policies that can address shared drivers across many threats. This pattern of interlinking, mutually reinforcing threats operating within conditions of social inequality reflects what has been described as a syndemic,[200] a concept that can help articulate how compounded harms arise when threats cluster and interact, and why cross-cutting enablers such as equity, trust, and health-system capacity are so central to the Commission's overall framework.

We have identified a key set of enabling factors that shape how societies will respond to threats in the future, as quantifying future threats alone is insufficient. Public health is full of examples in which potential threats were known, and protection plans were in place, yet effective action failed. These enablers are thus the backbone for the success of our primary recommendations and are foundational to whether societies will be able to act on identified threats. Each of the enablers is important well beyond the specific 21st century threats to health. For each enabler, recommendations for future action are possible and have been addressed in the existing broad health and development literature. However, we must recognise that, in many cases, there has been little progress on these enablers or, in some cases, declines.

8.1 Trust

Trust serves as a stabilising force, enabling societies to anticipate, mitigate, and adapt. Conversely, distrust can amplify harm, as shown during the COVID-19 pandemic, when scepticism about vaccine efficacy and public-health interventions such as distancing or mask-wearing undermined strategies to contain the virus. Although trust is a core enabler of a wide range of effective action, specific actions that can be taken to build trust have not been well studied. Broad trust is present in some societies but not others, but this does not yet provide insights into concrete actions that can be taken in low-trust societies. The most effective efforts to build trust are often examples of where governments or other institutions have delivered successful interventions valued by the local community. Trust in public health institutions is built over time, in non-emergency conditions, and cannot be manufactured rapidly in the face of an acute crisis. As Larson and colleagues have argued,[201] trustworthiness is accumulated over time through sustained engagement, transparency, and responsiveness, and its absence, when crises strike, cannot be quickly repaired.

Although there are not yet compelling studies on how to enhance trust, it is clear that a track record of successful programme implementation tailored to a particular context can build trust in a particular community.

Likewise, failure of programme delivery or examples of failed programmes can undermine trust. Because survey data show declines in trust and the important role of trust in successful responses to threats such as the COVID-19 pandemic, more work on understanding how to increase trust is a priority. We need a science of determinants of trust and trust enhancement in the future and a strategy to regain trust in science.

The connection between trust and governance takes different forms across the 17 threats assessed. In some cases (eg, naturally occurring pandemic and malicious use of AI), trust hinges on credible, transparent institutions that can show competence and good faith. In others (eg, obesity, alcohol, tobacco, and climate change) trust depends on whether affected populations perceive interventions as acting in their interests rather than excessively constraining their freedoms. Governance frameworks that fail to account for these distinctions risk undermining the interventions they are designed to implement. The Commission therefore treats trust as a substantive dimension of governance, not merely a precondition for it, and one that must be actively cultivated across all 17 threats.

8.2 Functioning global collaborative leadership to facilitate mutual action when national action alone is insufficient

Our analysis highlights that collective action between nations and within nations can create huge opportunities to reduce the harm from global health threats. Collective action is necessary for a number of the threats, such as the malicious use of AI, nuclear conflict, obesity, antimicrobial resistance, and climate change, which cannot be solved by governments or other actors acting for their own national populations alone. History has shown us that geographical borders cannot contain such threats, necessitating collective action. The concept of necessary mutual action has been the reason for the development of many of the existing global governance structures.

Although the multilateral system is far from perfect, multilateral institutions are a crucial mechanism for orchestrating collective action along with other models such as the Coalition for Epidemic Preparedness Innovations. Efforts such as creating dialogue between nations who are close to or in conflict, setting international standards for equitable migration, or negotiating complex arrangements to reduce carbon emissions are of utmost importance. At the same time, reassuring nations that multilateral institutions can operate fairly, efficiently, and effectively in different arenas, including health and education, will be essential. Global governance, particularly for health, might require reform to address concerns about efficiency and fairness.

Effective governance of health threats requires more than institutional coordination. It requires attention to how power and resources are distributed, how decisions are legitimised, and how conflicts between public and private interests are managed. Governance frameworks that assume goodwill and aligned incentives will be insufficient. They must instead be designed for when political interests conflict, ensuring decisions are made transparently, with meaningful participation, and with recourse when institutions fall short.

Commercial interests warrant explicit attention. Many of the Commission's identified threats involve industries whose economic incentives have delayed or weakened public health action. The gap between evidence and policy is often not a failure of knowledge but a consequence of commercial opposition. Governance frameworks must be capable of managing these conflicts and insulate health policy from undue commercial influence.

8.3 Sustainable health-system financing for low-resource countries

Substantial and abrupt declines in DAH in certain programmes, such as the United States Agency for International Development, have been disruptive for service provision, and have endangered the lives of children and adults. Progress made in recent decades against problems such as maternal and child health, malaria, HIV, tuberculosis, or neglected tropical diseases might be unravelled. This moment, although alarming, might also be an opportunity to redesign public health systems in lower resource settings, emphasising national prioritisation based on real, local data. The Accra Reset is an effort to mobilise discussion and strategy on how global health financing might be more effective in the future and support national goals.[98] Effective health programmes require local ownership, and donor funding in the past has, in many cases, limited governments' abilities to steward their own health systems. Although increased local accountability is highly desirable, limited fiscal space, given the debt burden in some countries, might severely limit the ability of these governments to fill the gap left by declines in DAH in the short to medium term.

Lessons learned over the past decades on what leads to effective financing emphasise investment in the most cost-effective technologies and delivery strategies, capable leadership and management of health systems, country ownership, and predictable financing. Sustainable financing is a crucial enabler of many health system actions, including effectively addressing global threats. Enactment of several financing reforms, including those recommended by the G20 High Level Independent Panel on Pandemic Preparedness and Response,[202] has already begun; if these efforts are implemented at scale, the Commission will incorporate associated outcome data into revised scenario bounds in the future.

8.4 Pro-equity policies

Analysis of the linkages between measures of income distribution and health shows the potential to improve

health through increased income redistribution or transfer payments. There are many other dimensions of equity in addition to the distribution of household consumption quantified as a threat. These other dimensions, including race, ethnicity, and educational attainment, vary across countries and can drive health disparities independently of income. Pro-equity policies go well beyond reducing income inequality and include factors such as affordable healthy food, clean water, and safe environments. Trends within countries are showing reduced inequality, although it is likely that asset inequality might not be declining to the same degree or even increasing. Income redistribution policies are in practice mostly national or local political decisions. However, enhanced focus on the potential of reduced inequality to reduce threats and enhance national security can bring increased attention to the benefit of income redistribution. Examination of the relationship between various measures of income inequality and GDP per capita highlights that, across countries, there is considerable variability in inequality at the same level of GDP per capita. Reducing inequality should also go beyond income or consumption and encompass other forms of inequality that operate on other dimensions such as race, ethnicity, political viewpoint, or gender. These non-income dimensions of equity, including differential exposure to environmental hazards, unequal access to education and health care, and structural discrimination, can drive health disparities independently of income levels. Nevertheless, the potential for an equity–growth trade-off implies there can be circumstances where too much redistribution might reduce health.

Inequality, along each of these dimensions, operates within countries as much as between them, and often determines who is most exposed to a health threat, who can access protection when threats materialise, and who is most likely to be left behind when resources are mobilised. The COVID-19 pandemic showed this clearly, where excess mortality was concentrated among lower-income workers, ethnic minority communities, and older populations, where structural disadvantage amplified biological and social vulnerability. Pro-equity policy frameworks must include explicit monitoring of within-country distributional outcomes.

8.5 Food systems

Resilient food systems serve as a cross-cutting enabler because of the breadth of their connections to the 17 priority threats. Most directly, the structure and functioning of food systems shape dietary environments and thereby influence obesity, childhood malnutrition, and high blood pressure—three threats that together account for a substantial share of amenable DALYs. Food production practices also bear on several additional threats: intensive livestock operations contribute to antimicrobial resistance through routine antibiotic use, expand the human–animal interface relevant to pandemic risk through zoonotic spillover, and generate greenhouse gas emissions and particulate matter that exacerbate both climate change and air pollution. Food insecurity has a bidirectional relationship with conventional conflict, serving as both a driver and a consequence, and is independently associated with poor mental health outcomes. In nuclear conflict scenarios, the capacity to sustain food production under conditions of reduced sunlight and trade disruption is a principal determinant of whether regional nuclear exchange escalates into global famine. Across lower-income settings, food systems are among the largest sources of employment and livelihood, linking their stability to income inequality and, through the established pathway from childhood nutrition to cognitive development and school performance, to educational attainment. Food system resilience also reduces the vulnerability of populations to abrupt reductions in DAH by strengthening local capacity to maintain nutritional status independently of external financing. The decline in famine-related mortality in recent decades has been substantially enabled by coordinated international humanitarian action, including the World Food Programme; current reductions in funding for such programmes place this progress at risk.[203] Building food systems that are diverse, climate-adapted, nutritionally oriented, and less reliant on antimicrobials could attenuate risk across a majority of the 17 threats simultaneously, making this a key enabling factor.

8.6 National capability to plan for rapid demographic change

Rapid changes are underway for most societies as outlined in the reference scenario: over the next 25 years, many countries will experience a decrease in working-age populations either in numbers or as a share of the population, alongside a surge in the population older than 65 years. These demographic changes require a transformation in how societies are organised, including changing policy concerning the welcoming of migrants, adjusting social organisation for an inverted population pyramid, and shifting health systems to tackle NCDs, a shift accelerated by climate change. The demographic changes will also challenge the financial sustainability of critical institutions such as social health insurance and social security.

Countries with the capacity to plan for rapid demographic change will be in a much stronger position to anticipate, prepare for, and respond to this coming transition. Solutions for profound changes will need to be tailored to each country's epidemiological, social, and economic circumstances. But even in the face of considerable variability in the optimal strategies to deal with change, governments and societies will need the capability to understand the different future trajectories for society and start planning for needed changes over much longer time frames than is the norm.

Short-termism at the national level will make it all too easy to avoid difficult reckoning with the looming challenges. Creating national capacity in government, academia, and NGOs for long-term analysis that can foster an honest and open discussion of the problems and options is one key step towards addressing these problems. The required skillsets to map out strategies to deal with the coming transitions will be broad, including forecasting or foresight, economic policy analysis, demography, epidemiology, and other disciplines. Successful models to deal with the demographic, health, digital, and social transformations will need to reflect national or subnational cultural identities and diverse groups within societies. In some countries, there is already strong capacity to undertake this type of strategic analysis, but in many others, substantial investment is needed in creating this capacity.

8.7 Commitment to human rights including sexual and reproductive health and rights

Reinforcing the value of human rights is key to the aims of this Commission. Human rights doctrine has been a powerful force for improving living standards and broadening access to health care. In terms of the threats under discussion, it is important that responses take a human rights lens and a social justice approach, recognising that not all will be affected equally, and provide due attention to those most adversely impacted.

Two central components of human rights that deserve specific attention of this Commission include the promotion of gender equality and sexual and reproductive health and rights. These two elements intersect and cut across a number of the 17 threats identified. For example, regarding unhealthy ageing, women are more likely to live longer—and more years in ill-health—than men, while the AIDS pandemic highlighted how serious the transmission of sexual diseases and infections can become, particularly among underserved populations.

The *Lancet*–Guttmacher Commission on Sexual and Reproductive Health and Rights described sexual and reproductive health and rights as "fundamental to people's health and survival, to sustainable development, and to the wellbeing of humanity".[204] On the back of this, the Commission proposed a comprehensive sexual and reproductive health and rights package, which can both promote good health and act as a safety net to current and future health threats. HIV/AIDS, the Zika virus, and recently mpox all show how threats to health can have gendered and sexual and reproductive health and rights elements, which is why it is so important that there is collaboration across Ministries of Health, Justice, Finance, and Education to promote a human rights approach to health care that takes the needs of all populations into account and ensures comprehensive access to sexual and reproductive health and rights. On a further note, investing in sexual and reproductive health and rights and gender equality has also been proven to have a number of beneficial effects for health and wellbeing overall, from ensuring girls have the right to pursue an education to improving maternal health outcomes.[205]

8.8 Advancing equitable universal health coverage with quality, efficiency, and affordability

Health systems are the platform through which many preventive actions and solutions for the amenable burden can be delivered. Preventive care can delay or curb many of the threats pertaining to NCDs while also promoting overall health throughout the life course. Taking a preventive rather than a curative approach can often be more cost-effective in the longer term.

In strengthening health systems, the universal health coverage agenda advocates for governments to commit to providing universal health coverage for their citizens. Universal health coverage is increasingly recognised as a continuum, as systems vary by the breadth and depth of coverage provided. Access to preventative and curative clinical services can reduce the effect of threats, including obesity (the nexus of high BMI, poor diet, and low activity), smoking, pandemics, climate change, and mental health. Within these efforts, taking a life-course approach is crucial as health needs and risks change depending on what phase of life people are at, something particularly important as countries experience demographic transitions. Currently, evidence suggests that the health systems in LMICs have not been adequately organised to ensure quality health-care for working-age and older adults.[206,207]

Although many existing universal health coverage efforts address access for the majority of the population, there are frequently underserved populations in each country that have little or no access to services. These underserved populations are identified through efforts to examine zero-dose children for vaccination, or the last mile for some services such as HIV care. All these efforts have the same focus, identifying where the groups that are largely excluded from existing systems are. Reaching these groups requires a workforce that extends beyond formal clinical services. Community health workers and others providing informal care are central to last-mile delivery, surveillance, and trust-building in underserved communities, but depend on sustained investment in training, remuneration, and supervision to be effective.

Section 9: Recommendations for addressing 21st-century global threats to health

There are many specific recommendations formulated by international commissions, UN high-level panels, and agency reports to address specific threats. Some threats, such as pandemics, climate change, or nuclear conflict, have received more global attention in the past decade than others that have perhaps not risen to the same level of global awareness. One emerging threat, malicious use

of AI, is also receiving considerable attention, with some governments proposing action plans and calls by some companies to increase research on alignment. We have three main recommendations that specifically address multiple threats. The set of enabling factors we have described in section 8 are critical as well, but our contribution as a Commission is to highlight these three actions that can alter the trajectory of human health this century.

9.1 Recommendation 1: Build and fund threat-ready health systems

The key to successfully dealing with the complex threats reviewed in this Commission report is to develop what we call threat-ready health systems. Despite the diverse nature of those threats, there are several common attributes of an appropriate response to all of them. The most important thing is to imbue the health system with a state of readiness, which requires the following elements: (1) foresight, including forecasting to anticipate threats; (2) preventive measures to avoid threats, building on in many cases primary health-care systems; (3) preparedness plans to respond effectively to threats; and (4) protection strategies to mitigate harm, including through optimised food environments. A health system with the capability to carry out these four elements of readiness is a threat-ready health system. Threat-ready health systems need to be grounded in strong public health and primary health care, including routine data monitoring systems, capable of identifying the effects of emerging threats and delivering targeted, timely responses. After the COVID-19 pandemic, a number of countries have taken measures to enhance pandemic preparedness, but we call for systems to anticipate, prevent, and prepare for a much broader set of threats. The threat-specific analyses in this report outline prevention and mitigation strategies for each, and countries should translate these into sustained, strategic prevention programmes, which, alongside threat-ready health systems, represent the most cost-effective response.

At the national level, the most important action to address threats is to build health systems with the capability to understand the nature of threats, and to prioritise funding for action to anticipate, prepare, and respond to these threats as they emerge. Often, global threats are ignored in funding decisions because they are in the distant future or they are so stochastic in nature they can be ignored in the short-term. Being threat-ready requires each nation to understand what threats are most important to their circumstances and, crucially, to then take action to build priority for actions to make their health systems threat-ready into their government budget allocation processes.

Threat-ready health systems require a dedicated unit within government that is focused exclusively on anticipating threats, including the full range outlined in this Commission report. Many governments have national emergency response plans, but being threat-ready requires broadening that notion. National risk registries are a helpful step, but countries often need a broader and more systemic view. To be effective, the dedicated unit will need to be connected to the rest of government through the appropriate mechanism since many solutions will require action across different departments and agencies. These health systems also require investing in the capability of national, regional, and local governments to anticipate, plan for, and respond to threats. Finally, monitoring the uptake and reach of threat-ready health system investments is required, tracking whether benefits are reaching low-resource settings and marginalised populations, to ensure implementation does not widen existing inequalities in exposure, protection, and resilience.

At the national level, government budget allocation processes should prioritise funding to support these actions, alongside investments in frontline training, public awareness, and systemic risk registries, ensuring health systems are truly threat-ready. Threat-ready health systems and sustainable health financing are inherently interlinked. Although readiness focuses on anticipation, prevention, preparedness, and response to threats, financing mechanisms provide the foundation to make readiness a reality. Building and funding these systems requires not only technical capacity but also strategic prioritisation of resources at national and international levels. The future forecasted in this report is not inevitable. The reference scenario describes where current trends lead, but the trajectory of the next 75 years depends on the policy choices that governments, institutions, and societies make. In conclusion, our Commission proposes a holistic action framework grounded in science, human rights, and solidarity. A vision rooted in trust, equity, and innovation is vital to address emerging global health threats.

9.2 Recommendation 2: Dramatically increase investment in innovation to create breakthrough solutions for key threats

Breakthrough innovation can alter the future burden of disease even more than our assessment of plausible best and worst cases has suggested. For example, with the development of fusion technology and improved technology to remove carbon from the atmosphere, global mean surface temperature could be lowered to pre-industrial levels. Rapid advances in AI in the past three years hold out the promise of accelerated innovation in biology and other fields. It is not implausible that such technologies could emerge in the next 75 years. It is also not guaranteed.

Breakthroughs, when they do come, also need to be made available more equitably than in the past. Scientific and technological innovation must be matched by equitable access and governance in the public interest.

The COVID-19 pandemic showed that rapid scientific progress does not automatically translate into equitable protection. Lower-income countries faced sustained delays, and the systems governing intellectual property, manufacturing capacity, and export controls were not designed with global equity as a priority. The Commission recommends that investments in innovation be explicitly paired with commitments to affordability, transparency, regulatory capacity strengthening in lower-income settings, and governance frameworks that ensure the benefits of these technologies are broadly shared. Efforts such as the G20 global coalition for local and regional production, innovation, and equitable access can play an important role.

Many other examples of breakthrough technical innovation that can address the threats have been identified: pan-strain vaccines for key pathogens, cheaper and more widely manufactured oral obesity medications with fewer side-effects, or new classes of effective antibiotics, to mention just a few. Not all the 17 threats need breakthrough innovation, such as income inequality, where existing redistributive policies and mechanisms suffice, but many on our list of 17 could benefit substantially from innovation.

Innovation requires investment and, in many cases, a long-term perspective. Private sector companies are incredible engines of innovation, but often their horizon is skewed to the short run (years or one decade, not 75 years) and skewed to high-income consumers. Investment with a long-term perspective and a truly global perspective might need to come through direct government research and development spending.

Although the private sector often drives technological advancements, addressing global challenges requires an inclusive approach that combines both public and private efforts. Governments and multilateral organisations must play a pivotal role in addressing market failures and supporting foundational science and innovation that might not yield immediate profits but have profound global benefits. For instance, fostering innovation ecosystems through incubators, accelerators, and mechanisms to support startups and deep tech companies can create pathways for transformative breakthroughs. Supporting local manufacturing and establishing centres of excellence worldwide can also help ensure equitable access to innovation. These goals are also reflected in global initiatives such as the UN's Technology Facilitation Mechanism,[208] which was established to strengthen international collaboration on science, technology, and innovation for sustainable development, particularly by supporting inclusive innovation ecosystems in LMICs.

A variety of policy strategies have been deployed to incentivise innovation, including advance market commitments, public–private partnerships such as the Coalition for Epidemic Preparedness Innovations, innovation prizes such as the XPrize, and research and development tax credits. These tools can be tailored to address specific threats, such as antibiotic resistance, obesity, climate change, or pandemic preparedness. In addition, emerging technologies such as AI for epidemiological surveillance and early detection represent key opportunities for innovation that can be scaled to benefit diverse populations. However, these innovations require robust ecosystems to thrive with consistent access to funding for sustained benefit. Crucially, innovation aimed at reducing these threats must incorporate safety and security considerations from the outset, and much of this work can happen at the level of technology design rather than depending solely on government regulation.

Addressing systemic barriers to innovation, such as corruption, conflicts of interest, excessive regulation, and inequitable governance structures, is equally important. Participatory and inclusive governance models can help tackle these challenges and ensure that innovation benefits are shared equitably across regions. Furthermore, innovation should not focus solely on technological breakthroughs; improvements in management, financing, and policy frameworks can also play transformative roles in addressing global threats.

To achieve transformative change, governments and global stakeholders should work collaboratively to create enabling environments that foster innovation, equitable partnerships, and systemic solutions. Although breakthrough innovation holds immense promise, it requires sustained investment, visionary leadership, and a commitment to addressing underlying systemic challenges to ensure that solutions are impactful, inclusive, and beneficial for all.

9.3 Recommendation 3: Create the Monitor of 21st Century Global Threats to Health

Understanding and prioritising global threats to health requires robust, comparative assessments of their magnitude and impact over time. For example, the finding that obesity is the number one threat in the majority of countries can recalibrate decision-makers' expectations, influence priority-setting, and catalyse targeted action. Likewise, the findings on the strong interconnections between social determinants and health trajectories this century can build support from the health sector for intersectoral action. However, the science of understanding threats can evolve quickly, so assessments should be updated regularly to remain relevant and impactful. For example, we have not included mirror life as a threat in this assessment, but the evidence on the potential of mirror life to cause harm might evolve quickly.

Equally important is ensuring that these findings are communicated effectively to decision makers at multiple levels, fostering both immediate and long-term responses to address the rampant short-termism, localism, and fragmented governance frequently seen in global and

national contexts. The Commission proposed the establishment of the Monitor of 21st Century Global Threats to Health. This initiative would serve as the cornerstone for a regular updating and quantification of cumulative amenable DALYs projected to the end of the 21st century, building upon the methods and results developed in the initial Commission report to produce outputs designed for both scientific audiences and policy makers. Assessment findings would be presented at global, regional, and national levels to ensure relevance and applicability across varying governance contexts. The Monitor would operate on an annual cycle, with scientific and policy oversight provided by an independent advisory committee convening biannually to review threats and guide thematic focus. Sustained operation would depend on securing funding through a combination of institutional partnerships and philanthropic support.

The regular assessment would cover new evidence on the 17 threats included in this assessment and new threats where evidence has emerged to support including them in the evaluation. Over time, it should also track the nature and strength of interactions between threats. The regular assessment would also have a special theme, such as focusing on a single threat or an underlying driver such as distrust. The special theme component of the assessment would sustain policy-maker engagement, enhance accountability, and build targeted momentum for action. This format will allow the Monitor to maintain flexibility, allowing adjustments to threat categories or rankings as new risks emerge or existing ones evolve. Updates on the state of science and data related to these threats will also be included, working to foster trust in the findings and addressing the growing deterioration of public confidence in science. The Monitor could draw inspiration from the European Commission's scoreboard approach, which has proven effective in stimulating government action by providing comparative assessments across nations.[209]

The findings should be presented on a regular basis to the G20 Joint Task Force on Finance and Health, which emerged from the 2021 G20 High Level Independent Panel report on financing the global commons for pandemic preparedness and response and was formalised under Italy's G20 Presidency that year.[202] This arrangement would ensure assessments become a standing agenda item. This venue would provide an unparalleled platform to influence global health and finance strategies, ensuring global threats to health are consistently discussed and incorporated into decision-making processes. Expanding this engagement to include the G7 and other regional bodies such as the African Union, EU, OECD, and the Association of Southeast Asian Nations could further amplify the impact.

Recognising the intersection between health threats, national security, and regional policies, findings should also be shared annually at forums such as the Munich Security Conference to engage the national security establishment and Inter-Parliamentary Union meetings to inform legislators that have the power to allocate resources. Another important venue would be the World Economic Forum, which brings together political leaders, business leaders, and thought leaders in different fields. The framing of major health threats as issues of national and individual security could broaden the audience and strengthen the case for action. To translate findings into national action, the Monitor will engage finance ministries alongside health ministries, ensuring that threat assessments reach decision makers with direct control over resource allocation. The development of handbooks or guides tailored for political audiences could further enhance this outreach.

The regular risk assessment should be presented to the World Health Assembly and the UN Secretary-General, with efforts to integrate findings into discussions during the UN General Assembly week each September. This approach would enhance visibility among global leaders and encourage intergovernmental collaboration on health threats. Presenting findings during the UN General Assembly week would ensure that they are highlighted during one of the most influential annual gatherings of global leaders. This timing could reinforce the urgency of addressing health threats and encourage coordinated global action, integrating them into speeches, reports, and advocacy materials to amplify their impact.

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Declaration of interests

SAb reports support for the present manuscript from BRAC International. KB reports grants or contracts from the US National Institutes for Health (NIH) and the Gates Foundation; and support for attending meetings and/or travel from the National University of Singapore and Nanyang Technological University, all outside the submitted work. HC-T reports support from the present manuscript from the Institute for Health Metrics and Evaluation, University of Washington. SD reports support for attending meetings and/or travel from the UK Government; and leadership or fiduciary roles in society, committee, or advocacy groups, paid or unpaid, as the Director of Genomics PLC, Special Envoy for Global Antimicrobial Resistance for the UK Government (Honorary), non-executive board member of

Clinton Health Access Initiative, Chair of the Centre for Science and Policy Leaders Fellowship, Advisory Board Member for the Institute of Health Metrics and Evaluation, Trustee of the Pearce Gould Charitable Trust, Trustee of Gates Cambridge, and Chair of the Trustees, The Trinity Challenge, and is the Master of Trinity College, Cambridge, all outside the submitted work. JLD reports grants or contracts from the Gates Foundation, Gates Ventures, and the National Pharmaceutical Council; and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from the University of Hong Kong, all outside the submitted work. LACG reports support for attending meetings and/or travel from the Institute for Health Metrics and Evaluation for meetings related to the *Lancet* Commission on 21st Century Threats to Health's Secretariat. SJHa reports support for the present manuscript from the Institute for Health Metrics and Evaluation; and leadership or fiduciary roles in board, society, committee or advocacy groups, paid or unpaid, with the Coalition for Epidemic Preparedness Innovations (CEPI) as Chair of the Board, outside the submitted work. NTL reports grants or contracts from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); and royalties or licenses from Civilização Brasileira/Grupo Editorial Record; all outside the submitted work. CJLM reports support for the present manuscript from The John Stanton and Teresa Gillespie Family Foundation and Pax Sapiens. KP reports support for the present manuscript from The John Stanton and Teresa Gillespie Family Foundation and Pax Sapiens. PP reports grants or contracts from the Gates Foundation; consulting fees from the Gates Foundation; support for attending meetings and/or travel from the Institute for Health Metrics and Evaluation for meetings related to the *Lancet* Commission on 21st Century Threats to Health's Secretariat; participation on a data safety monitoring board or advisory board as part of the Global Burden of Disease Independent Advisory Committee with IHME; and leadership or fiducuiary role in other board, society, committee or advocacy group, paid or unpaid, as Chair with Programme for Research in Epidemic Preparedness and Response (PREPARE) Singapore, Chair of the Strategy Board for the Pasteur Network, Chair of the Japan Institute of Health Security, and as Independent Director of Biocon Biologics and Biological E MRCeS; all outside the submitted work. CS reports support for attending meetings and/or travel from the Institute for Health Metrics and Evaluation for meetings related to the Lancet Commission on 21st Century Threats to Health's Secretariat; leadership or fiduciary role in other board, society, committee or advocacy group, unpaid, as Chair of a 2024 global health committee in Norway; and is the CEO of an independent research institute in Norway. YYT reports support for attending meetings and/or travel from the Institute for Health Metrics and Evaluation for meetings related to the Lancet Commission on 21st Century Threats to Health's Secretariat. JPU reports support for attending meetings and/or travel from the World Bank. JE-LW reports support from the present manuscript from the Lancet Commission on 21st Century Global Health Threats; grants or contracts from the National Medical Research Council, Singapore; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from the Lee Kuan Yew School of Public Policy Senior Fellowship in Public Service Programme; support for attending meetings and/or travel from National Taiwan University, University of Pittsburgh, Nikkei Asia, and the National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, outside the submitted work. AEY reports support for the present manuscript from The John Stanton and Teresa Gillespie Family Foundation and Pax Sapiens; and grants or contracts from the Gates Foundation, outside the submitted work. All other authors declare no competing interests.

Acknowledgments

We thank Senait Fisseha, Lan Xue, and Anita Zaidi, Commissioners on the *Lancet* Commission on 21st century global threats to health, for their support of this work. We thank Tashrik Ahmed, Brooke Anderson, Joan Ballester, Oliver Brady, Joan Casey, Alex de Sherbinin, Rosie Green, Solomon Hsiang, Swathi Manchikanti, Rachel Nethery, Maquines Odhiambo Sewe, Robbie M Parks, Poornima Prabhakaran, Waleska Teixeira Caiaffa, and Gregory Wellenius for the invaluable technical advice and input they provided at the Commission's consultation on the impact of climate change on health. We thank Chrisoula Andreou, Erika Blacksher, Mark Budolfson, Timothy Campbell, Nir Eyal, Maddalena Ferranna, Daniel Hausman, Anders Herlitz, Petra Kosonen, Kacper Kowalczyk, Adam Lerner, Andreas Mogensen, Michael Otsuka, Melinda A Roberts, Jeffrey Sanford Russell, Robert Steel, and Bastian Steuwer for the invaluable input they provided at the Commission's bioethics consultation on the philosophical considerations underlying the report's timelines and its approach to risk and uncertainty. We thank Henrik Urdal for the invaluable input he provided at the Commission's Bellagio convening on threat assessment, governance, and cross-cutting strategies.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

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