Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010

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Summary

Background Reliable and timely information on the leading causes of death in populations, and how these are changing, is a crucial input into health policy debates. In the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010), we aimed to estimate annual deaths for the world and 21 regions between 1980 and 2010 for 235 causes, with uncertainty intervals (UIs), separately by age and sex.

Methods We attempted to identify all available data on causes of death for 187 countries from 1980 to 2010 from vital registration, verbal autopsy, mortality surveillance, censuses, surveys, hospitals, police records, and mortuaries. We assessed data quality for completeness, diagnostic accuracy, missing data, stochastic variations, and probable causes of death. We applied six different modelling strategies to estimate cause-specific mortality trends depending on the strength of the data. For 133 causes and three special aggregates we used the Cause of Death Ensemble model (CODEm) approach, which uses four families of statistical models testing a large set of different models using different permutations of covariates. Model ensembles were developed from these component models. We assessed model performance with rigorous out-of-sample testing of prediction error and the validity of 95% UIs. For 13 causes with low observed numbers of deaths, we developed negative binomial models with plausible covariates. For 27 causes for which death is rare, we modelled the higher level cause in the cause hierarchy of the GBD 2010 and then allocated deaths across component causes proportionately, estimated from all available data in the database. For selected causes (African trypanosomiasis, congenital syphilis, whooping cough, measles, typhoid and parathyroid, leishmaniasis, acute hepatitis E, and HIV/AIDS), we used natural history models based on information on incidence, prevalence, and case-fatality. We separately estimated cause fractions by aetiology for diarrhoea, lower respiratory infections, and meningitis, as well as disaggregations by subcause for chronic kidney disease, maternal disorders, cirrhosis, and liver cancer. For deaths due to collective violence and natural disasters, we used mortality shock regressions. For every cause, we estimated 95% UIs that captured both parameter estimation uncertainty and uncertainty due to model specification where CODEm was used. We constrained cause-specific fractions within every age-sex group to sum to total mortality based on draws from the uncertainty distributions.

Findings In 2010, there were 52·8 million deaths globally. At the most aggregate level, communicable, maternal, neonatal, and nutritional causes were 24·9% of deaths worldwide in 2010, down from 15·9 million (34·1%) of

Lancet 2012; 380: 2095–128

This online publication has been corrected. The corrected version first appeared at thelancet.com on February 22, 2013

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For **interactive versions of figures 1, 4, and 6–9** see http://healthmetricsandevaluation.org/gbd/visualizations/regional

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46·5 million in 1990. This decrease was largely due to decreases in mortality from diarrhoeal disease (from 2·5 to 1·4 million), lower respiratory infections (from 3·4 to 2·8 million), neonatal disorders (from 3·1 to 2·2 million), measles (from 0·63 to 0·13 million), and tetanus (from 0·27 to 0·06 million). Deaths from HIV/AIDS increased from 0·30 million in 1990 to 1·5 million in 2010, reaching a peak of 1·7 million in 2006. Malaria mortality also rose by an estimated 19·9% since 1990 to 1·17 million deaths in 2010. Tuberculosis killed 1·2 million people in 2010. Deaths from non-communicable diseases rose by just under 8 million between 1990 and 2010, accounting for two of every three deaths (34·5 million) worldwide by 2010. 8 million people died from cancer in 2010, 38% more than two decades ago; of these, 1·5 million (19%) were from trachea, bronchus, and lung cancer. Ischaemic heart disease and stroke collectively killed 12·9 million people in 2010, or one in four deaths worldwide, compared with one in five in 1990; 1·3 million deaths were due to diabetes, twice as many as in 1990. The fraction of global deaths due to injuries (5·1 million deaths) was marginally higher in 2010 (9·6%) compared with two decades earlier (8·8%). This was driven by a 46% rise in deaths worldwide due to road traffic accidents (1·3 million in 2010) and a rise in deaths from falls. Ischaemic heart disease, stroke, chronic obstructive pulmonary disease (COPD), lower respiratory infections, lung cancer, and HIV/AIDS were the leading causes of death in 2010. Ischaemic heart disease, lower respiratory infections, stroke, diarrhoeal disease, malaria, and HIV/AIDS were the leading causes of years of life lost due to premature mortality (YLLs) in 2010, similar to what was estimated for 1990, except for HIV/AIDS and preterm birth complications. YLLs from lower respiratory infections and diarrhoea decreased by 45–54% since 1990; ischaemic heart disease and stroke YLLs increased by 17–28%. Regional variations in leading causes of death were substantial. Communicable, maternal, neonatal, and nutritional causes still accounted for 76% of premature mortality in sub-Saharan Africa in 2010. Age standardised death rates from some key disorders rose (HIV/AIDS, Alzheimer's disease, diabetes mellitus, and chronic kidney disease in particular), but for most diseases, death rates fell in the past two decades; including major vascular diseases, COPD, most forms of cancer, liver cirrhosis, and maternal disorders. For other conditions, notably malaria, prostate cancer, and injuries, little change was noted.

Interpretation **Population growth, increased average age of the world's population, and largely decreasing age-specific, sex-specific, and cause-specific death rates combine to drive a broad shift from communicable, maternal, neonatal, and nutritional causes towards non-communicable diseases. Nevertheless, communicable, maternal, neonatal, and nutritional causes remain the dominant causes of YLLs in sub-Saharan Africa. Overlaid on this general pattern of the epidemiological transition, marked regional variation exists in many causes, such as interpersonal violence, suicide, liver cancer, diabetes, cirrhosis, Chagas disease, African trypanosomiasis, melanoma, and others. Regional heterogeneity highlights the importance of sound epidemiological assessments of the causes of death on a regular basis.**

Funding **Bill & Melinda Gates Foundation.**

Introduction

Cause-specific mortality is arguably one of the most fundamental metrics of population health. The rates and numbers of people who die, where, at what age, and from what, is a crucial input into policy debates, planning interventions, and prioritising research for new health technologies. Trends in causes of death provide an important geographical summary of whether society is or is not making progress in reducing the burden of premature (and especially avoidable) mortality and where renewed efforts are needed. If a health information system is not providing timely and accurate information on causes of death by age and sex, major reforms are required to provide health planners with this essential health intelligence.

Despite the importance of tracking causes of death and the tradition since 1893 of standardisation of definitions and coding for causes of death in the International Classification of Diseases and Injuries (ICD), global assessments of causes of death are a major analytical challenge. Vital registration systems that include medical certification of the cause of death captured about 18·8 million deaths of an estimated annual total of 51·7 million deaths in 2005, which is the latest year for which the largest number of countries (100) reported deaths from a vital registration system. Even for these deaths, the comparability of findings on the leading causes of death is affected by variation in certification skills among physicians, the diagnostic and pathological data available at the time of completing a death certificate, variations in medical culture in choosing the underlying cause, and legal and institutional frameworks for governing mortality reporting.[1–5] For the remaining deaths that are not medically certified, many different data sources and diagnostic approaches must be used from surveillance systems, demographic research sites, surveys, censuses, disease registries, and police records to construct a consolidated picture of causes of death in various populations. Because of the variety of data sources and their associated biases, cause of death assessments are inherently uncertain and subject to vigorous debate.[6–8]

Efforts to develop global assessments for selected causes began in the 1980s.[9–11] These efforts were motivated partly because the sum of various disease-specific estimates substantially exceeded the estimated number of deaths in

the world, particularly for children.[12] Lopez and Hull[11] attempted to develop a set of estimates of mortality in children younger than 5 years (under-5 mortality) by cause consistent with all-cause mortality data in 1983. The Global Burden of Disease study 1990 (GBD 1990) was the first comprehensive attempt to do so, and included 134 causes covering all age groups. The GBD 1990 cause of death approach was applied with some refinements to yield estimates of causes of death for 1999, 2000, 2001, 2002, 2004, and 2008.[13–17] Over this period, special attention was paid to priority diseases such as malaria, HIV/AIDS, and tuberculosis. The Child Health Epidemiology Reference Group (CHERG) also produced estimates of under-5 mortality from 16 causes that summed to estimates of deaths in children younger than 5 years for 2000–03, 2008, and 2010,[18–20] partly using the GBD 1990 approach combined with other methods, and putting special emphasis on the use of verbal autopsy as a source of data in low-income settings. Additionally to these comprehensive approaches, the tradition of disease-specific analyses that began in the 1980s with global cancer mortality has continued and intensified. In the past 5 years, for example, articles and reports have been published on global mortality from maternal causes,[21–24] malaria,[25,26] tuberculosis,[27,28] HIV/AIDS,[29] road traffic accidents,[30] site-specific cancers,[31,32] and diabetes,[33] among others.[34,35] These assessments of individual causes are based on diverse epidemiological approaches of varying scientific rigour, and, moreover, are not constrained to sum to estimates of all-cause mortality from demographic sources.

Global cause of death assessments can be characterised in four dimensions: the universe of raw data identified and examined, efforts to evaluate and enhance quality and comparability of data, the statistical modelling strategy, and whether causes of death are constrained to sum to all-cause mortality. First, in terms of the universe of data, the various iterations of the GBD and CHERG analysis of deaths in children younger than 5 years have made substantial use of data on causes of death from systems that attempt to capture the event of death. Other single-cause analyses, such as the annual UNAIDS efforts to estimate HIV-related deaths, measles estimates,[34] the World Malaria Report,[26] the WHO Global TB Control Report,[28] and many others have used data on disease incidence or prevalence and on case-fatality rates combined in a model of natural history progression. Second, perhaps the area of greatest variation in the published studies is the efforts to assess and enhance the quality and comparability of available data. These efforts often include very specific steps undertaken for different data sources and are frequently poorly documented. Third, in the past two decades, efforts to develop statistical models for causes of death have become more sophisticated. Compositional models that estimate cause fractions for several causes at once were first applied to global health by Salomon and Murray[36] and have been used extensively by CHERG but only for a subset of causes. GBD revisions for 1999, 2000, 2001, 2002, 2004, and 2008 have used these compositional models to allocate deaths according to three broad cause groups: communicable, maternal, neonatal, and nutritional causes; non-communicable diseases; and injuries. More recently, the array of modelling strategies used for causes of death has been broadened to include spatial-temporal Gaussian process regression,[22,37] mixed effects hierarchical models, and ensemble models.[38] Given the profusion of statistical modelling options, an important innovation has been the reporting of out-of-sample predictive validity to document the performance of complex models.[22,38]

Finally, in view of the developments in the field of mortality and cause of death estimation, for the GBD 2010 we completely re-evaluated all aspects of the GBD analytical strategy, including demographic estimation of all-cause mortality.[39,40] Because of the huge increase in published verbal autopsy studies and the availability in the public domain of cause of death data from government vital registration sources (130 countries), the universe of data has expanded substantially. Assessing and enhancing the quality and comparability of data can now take into account time trends in cause of death data from 1980 to 2010 that provide important insights into changes in certification and coding. Borrowing from other scientific fields, we have changed our analytical approach (see below) to an ensemble modelling strategy to generate more realistic uncertainty intervals (UIs) and more accurate predictions.[38] These innovations have been used in estimating mortality for an expanded GBD 2010 cause list of 291 causes compared with 134 in the GBD 1990 Study; of the 291 causes, 235 are causes of mortality, whereas the remaining causes account for years lived with disability (YLDs) but not deaths. We use a unified framework for all causes such that the sum of cause-specific estimates equals the number of deaths from all causes in each country or region, period, age group, and sex. This creates a link between the systematic analysis of data on all-cause mortality reported by Wang and colleagues[40] and results by cause presented here. In this Article, we provide a summary overview of the vast array of data and methods that have gone into this revision of the GBD, as well as what we believe are the key global and regional findings of importance for health priority debates.

Methods

Some general aspects of the analytical framework such as the creation of the 21 GBD regions and the full hierarchical cause list including the mapping of the ICD to the GBD 2010 cause list are reported elsewhere.[39] Although results are reported in this Article at the regional level for 1990 and 2010, the cause of death analysis has been undertaken at the country level for 187 countries from 1980 to 2010. Use of longer time series improves the performance of many types of estimation models; data from before 1980, however, are much sparser for developing countries so we restricted the analysis to 1980–2010.

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Database development

Over the 5-year duration of the GBD 2010, we sought to identify all published and unpublished data sources relevant to estimating causes of death for 187 countries from 1980 to 2010. Depending on the cause, various sources of data were used. We briefly outline in the following text the main types of data identified and how they were used. The appendix (p 2) provides a summary of the site-years of data identified by broad type of data system and the number of site-years by GBD region (the data presented in the appendix are mapped at the most detailed level for a given study; the aggregate levels are created by combining the detailed levels). Of the GBD regions, central sub-Saharan Africa had the most limited evidence base with data on only 27 causes from at least one country.

For vital registration with medical certification of causes of death, we identified 2798 site-years of data from 130 countries between 1980 and 2010. 3% of the site-years were coded with ICD 8, 44% with ICD 9, 40% with ICD 10, 12% with country-specific tabulations of ICD 8, ICD 9, and ICD 10, and 1% with non-ICD tabulations. Additionally, there is country to country variation in the detail used to report causes of death included in national reporting lists—namely, the basic tabulation list for ICD 9, the ICD 10 tabulation list, three-digit and four-digit detail, and special reporting lists. Overall, we identified 25 variants of cause of death reporting lists in use from 1980 to 2010 across all sources of vital registration.

The verbal autopsy data were collected through sample registration systems, demographic surveillance systems, or surveys. Verbal autopsy is a means for ascertaining the cause of death of individuals and the cause-specific mortality fractions in populations with incomplete vital registration systems. A trained interviewer uses a structured questionnaire to ask about the signs, symptoms, and demographic characteristics of a recently deceased individual from the next of kin. We identified 486 site-years of published and unpublished verbal autopsy data across 66 countries, of which 10% were nationally representative. Verbal autopsy data are highly heterogeneous: studies use different instruments, different cause lists from single causes to full ICD cause lists, different methods for assigning cause of death based on a completed verbal autopsy, different recall periods, and different age groups, quite apart from cultural differences in the interpretation of specific questions. The appendix (p 25) provides a full listing of the sources used for all verbal autopsy and non-vital registration data organised by country.

Population-based cancer registries provide an important source of data on incidence of cancers in various countries. We identified 2715 site-years of cancer registry data across 93 countries. Some registries also track cancer mortality and provide plausible data on the mortality-to-incidence ratio by age, sex, and site. Following the methods developed by Forouzanfar and colleagues,[31] we developed estimated mortality-to-incidence ratios for all major cancers by age, sex, and country. We estimated the log of the mortality-to-incidence ratio as a function of national income per head with random effects for country, year, and age. The estimated mortality-to-incidence ratios were used to map cancer registry data on incidence to expected deaths that have been incorporated into the database. Mortality-to-incidence ratios by country, age, and sex are available on request.

In most countries, police and crime reports are an important source of information for some types of injuries, notably road injuries and interpersonal violence. The police reports used in this analysis were obtained from published studies, national agencies, and institutional surveys such as the UN Crime Trends survey and the WHO Global Status Report on Road Safety Survey.[30,41] By comparing with other sources such as vital registration data, we assessed whether police reports were likely to be complete and cover the entire country. In total, we included in the analysis 1129 site-years of police reports from 122 countries from 1980 to 2010 that met our criteria.

We identified 32 site-years of burial and mortuary data in 11 countries from ministries of health, published reports, and mortuaries themselves. Because of known bias in the epidemiological composition of burial and mortuary data, we only used information on the fraction of injuries due to specific sub-causes from these sources. These proportionate fractions of injury deaths due to specific causes were transformed into fractions of all causes by multiplying by the fraction of all deaths due to injuries estimated from a model for all injuries.

Multiple demographic and health surveys, other surveys, and censuses provide data on the fraction of deaths in the reproductive age groups that are pregnancy-related. We identified 1557 survey years with sibling history data, and a further 52 household survey years or census years of data covering 61 countries. We also identified 56 surveys or censuses with information on injury mortality across 65 survey years or census years.

We identified eight countries with nationally representative maternal mortality surveillance systems covering 83 site-years and five GBD regions. Some surveillance systems were based on prospective verbal autopsy. Surveillance data on the number of maternal deaths, or the maternal mortality ratio multiplied by births, were converted into cause fractions by dividing by the total number of deaths estimated in the reproductive age groups.

Additionally, we included 21 site-years of data based on deaths in health facilities. However, we chose to only incorporate deaths due to injury from this source because of known bias. We adjusted data for bias using a revised version of the hospital adjustment method, which uses more data and is more consistent with the GBD cause list developed by Murray and colleagues in 2007.[42] This method attempts to correct for selection bias in the deaths that occur in hospital. Finally, we used only the fraction of injury deaths due to specific injuries from these sources and converted them to fractions of deaths

from all causes following the method described for burial and mortuary data.

Assessement and enhancement of data quality and comparability

We assessed and enhanced data quality following six steps outlined in more detail here:

Step 1 consists of the assessment of completeness of death recording in each source. In settings where a data source does not capture all deaths in a population, the cause composition of deaths captured might be different from those that are not. Murray and Lopez[43] postulated in the GBD 1990 that deaths recorded in countries with incomplete vital registration would more likely originate from wealthier sectors of populations for which the cause of death structure was skewed towards non-communicable rather than communicable diseases, communicable diseases being more common in those who cannot afford appropriate treatment. They proposed a correction based on the assumption that this inequality in death rates within a country was uniform across countries. This approach was used in subsequent GBD revisions and in some of the CHERG[19,44] analyses when making use of vital registration data.

There are reasons, however, to also be concerned that deaths recorded in systems with low coverage might be biased towards selected causes that are more likely to occur in hospital. Many vital registration systems begin with in-hospital deaths and progressively capture deaths in the community. Murray and colleagues[42] showed that the fraction of deaths in hospital was higher for acute causes for which death was not immediate but occurred over a matter of days such as for some maternal causes. Further, evidence on subnational mortality patterns[45] clearly shows that the assumption of uniform inequality is unlikely to be true; nor is the assumption that deaths are registered in order, from the richest to the poorest communities. For the GBD 2010, we assessed the completeness of vital registration or sample registration data over age 5 years using the most accurate variants of death distribution methods: synthetic extinct generations, the generalised growth balance method, and a hybrid of the two.[46] We assessed completeness for under age 5 years by comparing registration data with survey and census data on child mortality. More details on how the synthesis of these methods was done are provided by Wang and colleagues.[40] Completeness is often substantially different for child and adult deaths; in some regions such as Latin America, child completeness is usually lower than adult completeness, but other patterns are observed in Asia.[40] Completeness levels must also be interpreted with caution. Some systems, for example in Turkey, capture deaths relatively completely in selected administrative units only. That is, completeness of registration might be high but coverage is not.

For adults, few vital registration or sample registration datapoints exist with completeness lower than 70% in the database. Because completeness is often lower for deaths in children younger than 5 years compared with that in individuals older than 5 years, we investigated the effect of including data on causes of death with completeness lower than 70% (see appendix p 49 for more detail). We re-ran cause of death models for the major causes of death in children younger than 5 years in five different ways: excluding all data with completeness lower than 30%, lower than 40%, lower than 50%, lower than 60%, and lower than 70%. At the global level, the number of deaths estimated in 2010 for acute respiratory infections and diarrhoea, for example, differ by 0·9% and 1·2%, respectively, between models that include all data and those that exclude data where death registration for children younger than 5 years is less than 70% complete. The difference is slightly larger in 1980, for which including all data leads to higher numbers than excluding the incomplete data. Even in the 1980s at the regional or country level, the differences are small enough that we chose to use all available data. These sensitivity analyses suggest that, at least for major causes of child death, no consistent evidence of selection bias towards causes of death in richer populations exists.

To assess completeness is feasible for vital registration and sample registration data but not for small-scale studies on verbal autopsy, which might not detect all deaths through household recall. In fact, household recall often yields a substantial undercount of deaths.[47,48] In the absence of evidence on the cause of death pattern in recalled versus not recalled deaths, we have made the simplifying assumption that verbal autopsy cause fractions are representative of the study population; the CHERG analyses of verbal autopsy data make the same assumption.[19,20]

Step 2 consists of mapping revisions and variants of the ICD (see appendix p 50 for more detail). Vital registration data and some verbal autopsy data for 1980–2010 are reported using several variants of the ICD 8, ICD 9, and ICD 10. We mapped these revisions to the GBD cause list in the appendix. This mapping provides the codes for the detailed list for ICD 9 and ICD 10, as well as the basic tabulation list for ICD 9 (BTL). We identified three national variants of ICD 9 BTL that we also mapped to the GBD cause list. Of note, there were 119 GBD causes not available in the BTL, such as pneumonia and diarrhoea aetiologies, some of the cancers, hepatitis by type, some of the cardiovascular causes, many of the mental and behavioural disorders, some musculoskeletal disorders, and some injury subtypes.

Step 3 relates to the redistribution of deaths assigned to garbage codes. Murray and Lopez[43] introduced the notion of "garbage codes" in the GBD 1990 and proposed methods to redistribute deaths assigned to garbage codes to probable underlying causes of death. Garbage codes are causes of death that should not be identified as underlying causes of death but have been entered as the underlying cause of death on death certificates. Classic examples of garbage codes include senility or cardiopulmonary arrest. In the GBD 1990, major garbage codes were identified and

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simple algorithms proposed to redistribute these proportionately to various causes (called "target codes") that were the likely underlying causes of death.[49] A similar approach was applied for the GBD 2000 and subsequent WHO updates. For the GBD 2010, we identified causes that should not be assigned as underlying cause of death at a much more detailed level.[50] In total, we identified 2759 garbage codes in ICD 10 detailed data, 3382 garbage codes in ICD 9 detailed data, and 85 garbage codes in the ICD 9 BTL, ranging from abdominal rigidity to yellow nail syndrome. Garbage codes have been identified at the most detailed level possible (eg, the fourth digit level for ICD 9 and ICD 10). For every garbage code, the potential underlying causes of death were identified on the basis of pathophysiology. For example, the target codes for peritonitis included acute gastric ulcers with perforation and acute tubulointerstitial nephritis; the target codes for disseminated intravascular coagulation included other septicaemia and premature separation of placenta. Moreover, redistribution proportionate to the number of deaths noted in the target codes cannot be reliably applied; for example, although many injuries exist, not all peritonitis deaths are likely due to injuries. Similarly, the probability of deaths due to a target cause being misclassified on death certificates as a garbage code is not equal. We have developed allocations of the garbage codes on the basis of the little published scientific literature, expert judgment, statistical analysis,[51] and in some cases proportionate allocation across target causes. The appendix (pp 71–103) provides a complete listing of the redistribution algorithms used, organised by garbage code. The extent of garbage coding in vital registration data varies widely across countries from a low of 5·5% in Finland to a high of 69·6% in Sri Lanka.

Step 4 consists of age splitting and age-sex splitting. Sources report data according to varying age groups; for consistency in the analysis, the GBD project defined and used a standardised set of 20 age groups throughout. Data reported for more aggregate age groups are split into estimates of age-specific deaths using the global observed pattern of relative risks of death for a cause by age and the local distribution of the population by age. Relative risks of death by age were computed for each cause using the entire pooled dataset on medically certified causes of death. In the few cases in which studies reported deaths for both sexes combined, a similar approach was used to allocate these deaths to age-sex groups. The appendix (p 104) provides more detail on the development of the age splitting model and the age-sex splitting model.

Step 5 consists of smoothing. For some causes in some countries, the number of deaths observed in a year is very low; zero, one, or two deaths might be noted in some years because of stochastic fluctuation. For models using the log of the death rate, either observations that record zero deaths are dropped or an arbitrary small number is substituted for zero observations; both approaches can lead to bias. This issue is exacerbated in modelling strategies that attempt to capture spatial and temporal correlation structure. In cases for which many years for a country-cause-age group did not report any deaths, we used a standardised smoothing algorithm, essentially a type of moving average, as described in the appendix (p 104).

Step 6 consists of outlier detection. Despite these efforts to enhance quality and comparability, the data from some sources seem completely implausible. Where these sources are one of many in a country for a given cause, they have little effect on the results. In some cases, however, time series estimation can be substantially affected by these outliers. We identified outliers that met the following criteria: large inconsistency with other data for the same cause in the same country at the same time; large inconsistency with other data for similar countries; or disproportionate effect on time series estimation. In these cases, the observation was excluded from subsequent analysis. The interpretation of large inconsistency or disproportionate effect varies by cause and was based on the consensus of the investigators.

Modelling of individual causes of death

We used six different modelling strategies for causes of death depending on the strength of the available data. The appendix (p 105) shows the modelling strategy used for each cause; in the table, "aggregation" means that the parent cause in the hierarchy is simply the sum of the causes under that rubric. In the following section, we provide additional detail on the different modelling strategies used. All of the strategies, however, were designed to generate uncertainty distributions for the cause-specific death rate by age, sex, country, and year. We attempted to capture uncertainty due to model parameter estimation, model specification, and fundamental uncertainty. For Cause of Death Ensemble Modelling (CODEm), the validity of uncertainty distributions were assessed. The uncertainty distribution for a cause for a given country, year, age, and sex group from the modelling process is propagated into computation of years of life lost because of premature mortality (YLLs) and various geographic and age-sex aggregates by sampling 1000 draws from the posterior distribution.

CODEm

For all major causes of death except for HIV/AIDS and measles, we used CODEm—133 causes in the cause list and three other special aggregates. CODEm was used to analyse maternal mortality, breast and cervical cancer mortality, and malaria mortality in published studies.[22,25,31] The logic and development of CODEm is reported in detail elsewhere.[38] In brief, CODEm develops models following three steps:

First, a large range of plausible statistical models are developed for each cause. Based on published studies, plausible relationships between covariates and the relevant cause are identified. Essentially all possible permutations of these selected covariates are tested. All models where the sign on the coefficient for a covariate is

in the direction expected based on the literature and the coefficient is statistically significant are retained. Where there are n covariates, this means testing 2^n models. Additionally, four families of statistical models are developed using covariates: mixed effects linear models of the log of the death rate, mixed effects linear models of the logit of the cause fraction, spatial-temporal Gaussian process regression (ST-GPR) models of the log of the death rate, and ST-GPR of the logit of the cause fraction. Finally, ensemble models, or blends of these various component models, are developed.

Second, the performance of all component models and ensembles is evaluated using out-of-sample predictive validity tests. 30% of the data is excluded from the initial model fits; half of that (15% of total) is used to evaluate component models and build ensembles. Out-of-sample predictive validity tests are based on comparing predictions for the remaining 15% of the data withheld from the model-building exercise with the actual observed data. Data are held out from the analysis using the pattern of missingness for each cause in the cause of death database. For example, if there are countries with no data, then the algorithm will exclude all data for some countries; if some countries only have data for children, then the algorithm will exclude all adult data for some countries. In this way, the out-of-sample predictive validity testing mimics the task required of a good cause of death model. The out-of-sample predictive validity testing is repeated until stable model results have been obtained. Tests of out-of-sample performance include the root-mean squared error of the log of the cause-specific death rate, the direction of the trend in the prediction compared to the data, and the validity of the 95% UI.

Third, on the basis of out-of-sample predictive validity, the best performing model or ensemble is selected. The rigorous evaluation of out-of-sample performance means that for every CODEm model, we generate objective data on the validity of the resulting UIs.

The appendix (p 112) summarises the performance of the CODEm models developed for 133 causes in the cause list for which we exclusively use CODEm and three special aggregates in the GBD 2010. For some causes, separate models were run for different age ranges when there was reason to believe that the relation between covariates and death rates might be different in different age ranges, for example, in children compared with adults. For every model, we show the in-sample root mean squared error of the log death rates (RMSE) and the out-of-sample performance in the 15% of data not used in the model building process. In all cases, the out-of-sample performance is worse (larger RMSE) than the in-sample performance. Of note, the gap between in-sample and out-of-sample performance varies substantially across causes—from mechanical forces (firearm) with the largest difference to leukaemia with the smallest. Out-of-sample performance also varies substantially across causes; kidney cancer has the largest RMSE in female individuals (2·039) and the smallest RMSE is for cardiovascular and circulatory disease in male individuals (0·555). More than 50% of the models the appendix (p 112) have an out-of-sample RMSE of less than 1. The next columns provide the assessment of how often the model predicts the trend from year to year observed in the data. Because of stochastic fluctuation in death rates, we do not expect a good model to predict the trend observed in the data 100% of the time. The gap between in-sample and out-of-sample trend test is less notable than the gap for the RMSE. The final assessment of model performance is the validity of the UIs; ideally, the 95% UI for a model would capture 95% of the data out-of-sample. Higher coverage suggests that UIs are too large and lower than 95% suggest UIs are too narrow. Coverage across the CODEm models ranges from 99·0% for "other neurological disorders" to a low of 84·2% for pneumoconiosis.

Negative binomial models

For 27 causes, the number of deaths recorded in the database was too low to generate stable estimates of out-of-sample predictive validity. For these causes, we developed negative binomial models using plausible covariates. These causes are identified in the appendix (p 105). For these negative binomial models, standard model building practice was followed, where plausible covariates were included in the model development and reverse stepwise procedures followed for covariate inclusion. Uncertainty distributions were estimated using both uncertainty in the regression betas for the covariates and from the gamma distribution of the negative binomial.

Fixed proportion models

In 27 causes where death is a rare event, we first modelled the parent cause in the GBD hierarchy using CODEm and then allocated deaths to specific causes using a fixed proportion. Proportions were computed using all available data in the database and were fixed over time, but, depending on data density, allowed to vary by region, age, or sex. Specifically, uterine fibroids, polycystic ovarian syndrome, endometriosis, genital prolapse, and other gynecological disorders varied by region and age for female individuals. Lower respiratory infections, upper respiratory infections, meningitis, and encephalitis varied by region and age. Thalassaemia, sickle-cell disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and other haemoglobinopathies and haemolytic anaemias vary in proportion by country, age, and sex. Opioid, cocaine, amphetamine, and other drug use disorders varied by region and year. Finally, cellulitis, decubitus ulcer, other skin and subcutaneous diseases, abscess, impetigo, and other bacterial skin diseases all varied by age and sex.

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Diarrhoea, lower respiratory infection, meningitis, cirrhosis, maternal disorders, liver cancer, and chronic kidney disease disaggregated by subcause

The GBD 2010 cause list includes ten aetiologies for diarrhoea, five for lower respiratory infections, and four for meningitis. Additionally, we included a breakdown of maternal causes, cirrhosis, liver cancer, and chronic kidney disease by subcause. In most of these cases, published data are available on the cause or primary diagnosis for community, hospital, or registered cases, but not for deaths. For these causes, systematic reviews of the published data and careful review of statistical annuals such as renal registries have been undertaken. These studies or datapoints on aetiology were meta-analysed using the GBD Bayesian meta-regression method described elsewhere.[52] The meta-regression generated region-age-sex estimates with uncertainty of causal fractions for diarrhoea, lower respiratory infections, meningitis, chronic kidney disease, maternal disorders, cirrhosis, and liver cancer (appendix pp 121–129). These fractions were then applied to estimates of the parent cause, which were estimated using CODEm. In the cases of cirrhosis, liver cancer, maternal disorders, and chronic kidney disease, the studies or datasets on cause identified primary cause as assessed clinically; for diarrhoea, lower respiratory infections, and meningitis, cause was based on laboratory findings.

Natural history models

For a few selected causes, there is evidence that cause of death data systems do not capture sufficient information for one of two reasons. First, for some causes such as African trypanosomiasis, almost no deaths are recorded in vital registration or verbal autopsy studies, most likely because data have not been obtained in focal populations with substantial disease present. Second, there is systematic misclassification of deaths in cause of death data sources, particularly for congenital syphilis,[53,54] whooping cough,[55] measles,[56] and HIV/AIDS.[57] For these causes, natural history models have been used that begin with data on incidence or prevalence of disease and case-fatality rates (appendix pp 129–141). In the case of HIV/AIDS, a hybrid approach was used. For 36 countries, with complete and high quality vital registration systems, we used CODEm, in consultation with UNAIDS. For the remaining countries, we used the estimates with uncertainty by age and sex provided directly by UNAIDS based on their 2012 revision. In the case of Thailand and Panama, however, UNAIDS 2012 revision estimates are considerably higher than 2010 estimates and are inconsistent with the all-cause mortality evidence. For these two countries, we used the 2010 UNAIDS revision.

Mortality shock regressions

To estimate deaths directly due to natural disasters or collective violence, we used a different approach. First, we developed a variable for reported battle and disaster deaths per 10 000 using various databases for both disasters and collective violence; next, we estimated the empirical relation between under-5 mortality and mortality in adults ($_{45}q_{15}$) and this variable in settings where data were collected during these mortality shocks. As a final step, we used this empirical relation observed in periods of mortality shocks along with detailed data by age to allocate deaths due to natural disasters and collective violence by age. Details of this approach are outlined by Murray and colleagues.[58]

To develop the covariate on battle deaths during collective violence, we used data from the Armed Conflict Database from the International Institute for Strategic Studies (1997–2011), the Uppsala Conflict Data Program (UCDP)/PRIO Armed Conflict Dataset (1946–present), and available data from complete vital registration systems. In country-years where estimates are available from more than one source, priority is given to vital registration data if it gives higher estimated deaths. When vital registration data are not available, priority is given to the Uppsala Conflict Data Program (UCDP)/PRIO Armed Conflict Dataset since it has much longer and more consistent time series of estimates. The covariate for deaths due to natural disaster is based on the International Disaster Database (Centre for Research on the Epidemiology of Disasters).[59–61]

The relations between under-5 mortality and adult mortality and the disaster and collective violence

	All causes	Communicable, maternal, neonatal, and nutritional disorders	Non-communicable diseases	Injuries
1990 deaths (thousands)	46 511	15 859	26 560	4092
Deaths expected with 2010 population, 1990 population age structure, 1990 death rates (thousands)	61 307	23 295	32 647	5365
Deaths expected with 2010 population, 2010 population age structure, 1990 death rates (thousands)	70 316	21 513	43 062	5741
2010 deaths (thousands)	52 770	13 156	34 540	5073
Percentage change from 1990 due to population growth	31·8%	46·9%	22·9%	31·1%
Percentage change from 1990 due to population ageing	19·4%	–11·2%	39·2%	9·2%
Percentage change from 1990 due to change in death rates	–37·7%	–52·7%	–32·1%	–16·3%
Percentage change from 1990 to 2010	13·5%	–17·0%	30·0%	24·0%

Table 1: **Decomposition analysis of the change of global death numbers (thousands) by level 1 causes from 1990 to 2010 into total population growth, population ageing, and changes in age-specific, sex-specific, and cause-specific death rates**

covariates were estimated using 43 empirical observations for disasters and 206 empirical observations for collective violence (only years with crude death rates from shocks of more than one per 10 000 were kept in this analysis). The relation was estimated for excess mortality from these data sources by first subtracting from observed mortality rates the expected death rates in shock years with the methods outlined by Murray and colleagues.[58] The coefficients from these regressions and the disaster and collective violence covariates were used to predict excess deaths from these two causes. Because these models take into account competing causes by estimating

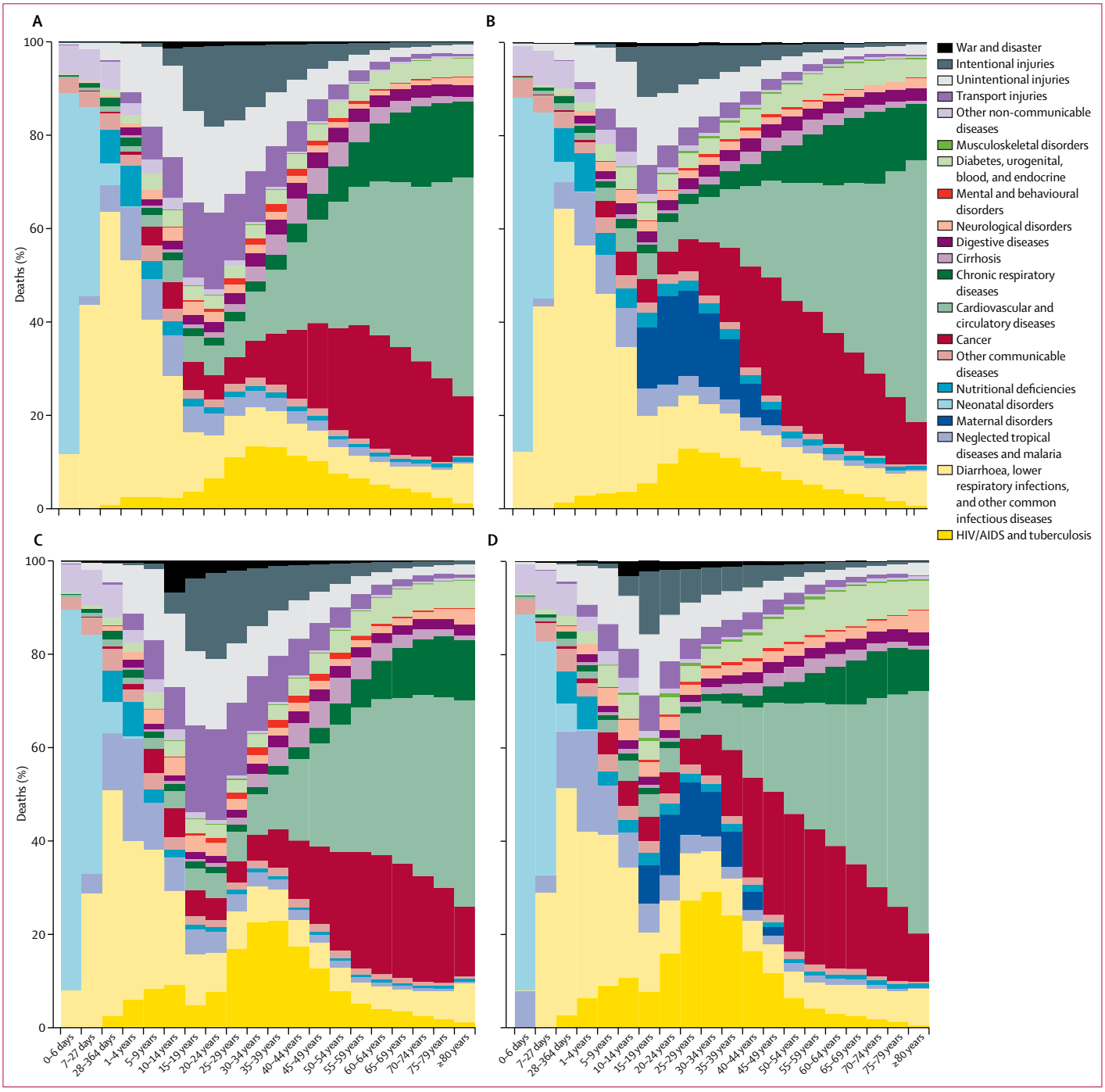

Figure 1: **Percentage of global deaths for female and male individuals in 1990 and 2010 by cause and age**
(A) Male individuals, 1990. (B) Female individuals, 1990. (C) Male individuals, 2010. (D) Female individuals, 2010. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

the relation between excess mortality and these covariates, we did not subject estimates for these two causes to the CoDCorrect algorithm described in the following text. The age pattern of mortality from these mortality shocks is based on the relative age pattern of mortality observed in the empirical data from functioning vital registration systems.

Combining results for individual causes of death to generate final estimates—CoDCorrect algorithm

Because we had developed single-cause models, it was imperative as a final step to ensure that individual cause estimates summed to the all-cause mortality estimate for every age-sex-country-year group. This had to be done taking into account uncertainty in every cause of death model outcome, where some causes were known with much greater precision than others. We used a simple algorithm called CoDCorrect; at the level of each draw from the posterior distribution of each cause, we proportionately rescaled every cause such that the sum of the cause-specific estimates equalled the number of deaths from all causes generated from the demographic analysis.[40]

In practice, a random draw without replacement was taken from the posterior distribution of 1000 draws for each cause and matched to a draw from the all-cause mortality distribution for that age-sex-country-year. We assumed that if the sum of deaths from each individual cause was large, it was more likely to be associated with a higher draw of the all-cause mortality level. To reflect this, we induced a rank order correlation of 1·0 between the sum of the random draws across causes and the all-cause mortality level. The effect of this rank order correlation was to increase the uncertainty in the final estimates for every cause in countries where substantial uncertainty existed in the level of all-cause mortality.

Repeated simulation studies show that the two-stage approach used here—namely, modelling each cause individually and then applying the CoDCorrect algorithm, gives high levels of cause-specific mortality fraction accuracy (appendix pp 146–148). These simulation studies also show that, under all circumstances tested, the two-stage approach to cause of death modelling is as good as or better than a single-stage approach as proposed by Salomon and Murray.[36]

We applied CoDCorrect in a hierarchical way. The appendix (pp 106–110) identifies three levels of application of CoDCorrect. We first applied the algorithm for level 1 causes. We then applied CoDCorrect for level 2 causes such that the sum of level 2 causes for a country-year-age-sex group equalled the draws of the level 1 cause. This cascade was repeated for level 3 causes. We chose levels for each cause based on consideration of the amount and quality of available data. For example, because there were substantially more data on all cardiovascular causes from verbal autopsy studies than for specific cardiovascular causes, we designated "all cardiovascular" as a level 1 cause for CoDCorrect. Another example of this approach is for the category "chronic respiratory diseases" where there was substantially more data for the aggregate cause than for chronic obstructive pulmonary disease (COPD), asthma, pneumoconiosis, and interstitial lung disease. Since we only wanted to group causes at level 2 or level 3 that were strongly related with common determinants, we did not use higher level aggregates such as "all non-communicable diseases" as level 1 causes because it was difficult to develop plausible models for these groups that included some causes that were increasing and others that were decreasing in the same time period.

The appendix (p 144) shows the percentage change in every cause of death for 2010 due to the application of CoDCorrect to level 1 causes at the global level. This provides a rough metric of how much inconsistency there is between models for specific causes of death and the demographic analysis. Although at the draw level the same scalar was applied to all causes, the net effect of CoDCorrect was to change the size of more uncertain causes by more than is done for more certain causes, a desirable property.

Ranking lists

For the presentation of leading causes of death, the level at which one ranks causes is subject to debate. Given the GBD cause list tree structure, many options are possible, such as all cancers versus site-specific cancers. We opted to produce tables of rankings using the level of disaggregation that seemed most relevant for public health decision making. Although we report more disaggregated causes, because of considerations related to public health programmes, we chose to include diarrhoeal diseases, lower respiratory infections, maternal causes, cerebrovascular disease, liver cancer, cirrhosis, drug use, road injury, exposure to mechanical forces, animal contact, homicide, and congenital causes in the ranking list.

Computation of YLLs due to premature mortality

YLLs are computed by multiplying deaths at each age by the reference standard life expectancy at that age. The reference standard has been constructed using the lowest observed death rate in each age group across countries with a population greater than 5 million (see Murray and colleagues[39] for details). In practice, for deaths in a given age-interval such as 20–24 years, we used country-specific estimates from the demographic analysis of the mean age of death in that interval.[40] In the GBD 2010, the terminal age group for the analysis of causes of death and YLDs is 80 years and older because of the scarcity and quality of data for older age groups. Because the all-cause mortality analysis was undertaken, however, for more detailed age groups up to age 110 years, we were able to take into account the mean age of death over 80 years in every country-year-sex group in computing YLLs.

	All ages deaths (thousands)			Age-standardised death rates (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
All causes	**46 511·2 (45 497·4–47 726·2)**	**52 769·7 (50 877·7–53 917·2)**	**13·5%**	**999·1 (979·2–1022·0)**	**784·5 (756·3–801·6)**	**–21·5**
Communicable, maternal, neonatal, and nutritional disorders	15 859·2 (15 065·8–16 842·5)	13 156·4 (12 377·2–13 807·6)	–17·0%	271·1 (258·4–287·2)	189·8 (178·6–199·2)	–30·0
HIV/AIDS and tuberculosis	1770·3 (1600·2–2032·7)	2661·4 (2358·1–2895·7)	50·3%	39·3 (35·4–45·2)	39·4 (34·8–42·9)	0·2
Tuberculosis	1471·5 (1318·5–1716·1)	1196·0 (923·7–1376·8)	–18·7%	33·3 (29·8–38·7)	18·0 (13·9–20·7)	–46·0
HIV/AIDS	298·8 (242·0–378·5)	1465·4 (1334·2–1606·0)	390·4%	6·0 (4·8–7·7)	21·4 (19·4–23·5)	258·4
HIV disease resulting in mycobacterial infection	53·8 (42·4–70·0)	256·9 (231·9–284·1)	377·2%	1·1 (0·8–1·4)	3·7 (3·4–4·2)	254·4
HIV disease resulting in other specified or unspecified diseases	245·0 (197·7–312·6)	1208·4 (1091·6–1333·9)	393·3%	4·9 (3·9–6·3)	17·6 (15·9–19·5)	259·3
Diarrhoea, lower respiratory infections, meningitis, and other common infectious diseases	7772·1 (7136·0–8769·2)	5276·9 (4742·2–5790·4)	–32·1%	131·9 (122·4–146·5)	76·4 (68·6–83·7)	–42·1
Diarrhoeal diseases	2487·4 (2306·8–2661·9)	1445·8 (1278·9–1607·0)	–41·9%	41·0 (38·3–43·6)	20·9 (18·5–23·3)	–49·0
Cholera	120·9 (96·7–149·1)	58·1 (44·2–74·3)	–52·0%	1·8 (1·4–2·2)	0·8 (0·6–1·0)	–54·5
Other salmonella infections	134·7 (107·5–162·4)	81·3 (61·8–101·7)	–39·6%	2·3 (1·8–2·7)	1·2 (0·9–1·5)	–48·2
Shigellosis	194·0 (161·5–227·4)	122·8 (97·4–149·6)	–36·7%	3·3 (2·8–3·9)	1·8 (1·4–2·2)	–46·5
Enteropathogenic *E coli* infection	205·5 (163·0–250·2)	88·7 (66·8–112·8)	–56·8%	3·0 (2·4–3·6)	1·2 (0·9–1·6)	–58·2
Enterotoxigenic *E coli* infection	184·0 (155·6–218·2)	120·8 (95·7–147·6)	–34·4%	3·3 (2·7–3·9)	1·8 (1·4–2·2)	–45·8
Campylobacter enteritis	210·8 (171·2–253·6)	109·7 (81·8–137·2)	–48·0%	3·3 (2·7–4·0)	1·6 (1·2–2·0)	–52·5
Amoebiasis	67·7 (53·2–82·8)	55·5 (40·6–73·8)	–18·1%	1·4 (1·1–1·7)	0·8 (0·6–1·1)	–39·0
Cryptosporidiosis	222·6 (181·5–264·7)	99·8 (76·1–125·0)	–55·2%	3·2 (2·6–3·8)	1·4 (1·1–1·8)	–56·6
Rotaviral enteritis	523·3 (433·5–605·7)	250·9 (191·5–308·2)	–52·1%	7·9 (6·5–9·2)	3·6 (2·7–4·4)	–54·9
Other diarrhoeal diseases	623·9 (466·5–814·3)	458·3 (339·1–603·9)	–26·5%	11·6 (8·8–14·8)	6·8 (5·0–8·9)	–41·6
Typhoid and paratyphoid fevers	136·5 (16·5–254·7)	190·2 (23·8–359·1)	39·4%	2·4 (0·3–4·4)	2·7 (0·3–5·1)	15·5
Lower respiratory infections	3415·4 (3109·5–3650·9)	2814·4 (2487·8–3033·0)	–17·6%	62·3 (57·0–67·2)	41·0 (36·3–44·2)	–34·1
Influenza	574·6 (519·3–625·8)	507·9 (444·2–553·8)	–11·6%	10·9 (10·0–11·8)	7·5 (6·5–8·1)	–31·8
Pneumococcal pneumonia	858·4 (778·5–932·3)	827·3 (718·4–899·5)	–3·6%	17·0 (15·5–18·6)	12·1 (10·5–13·2)	–28·7
H influenzae type B pneumonia	606·9 (541·5–669·6)	379·9 (337·1–420·5)	–37·4%	9·8 (8·9–10·8)	5·5 (4·8–6·0)	–44·4
Respiratory syncytial virus pneumonia	534·8 (463·4–608·4)	253·5 (215·0–296·6)	–52·6%	7·6 (6·6–8·6)	3·5 (3·0–4·1)	–53·3
Other lower respiratory infections	840·6 (747·9–926·9)	845·8 (734·1–927·6)	0·6%	16·9 (15·1–18·6)	12·4 (10·8–13·6)	–26·5
Upper respiratory infections	4·0 (3·6–4·2)	3·0 (2·7–3·4)	–23·6%	0·1 (0·1–0·1)	<0·05 (0·0–0·05)	–36·2
Otitis media	5·2 (0·0–61·0)	3·5 (0·0–39·8)	–33·5%	0·1 (0·0–1·0)	<0·05 (0·0–0·6)	–42·3
Meningitis	492·2 (444·1–583·3)	422·9 (360·2–471·7)	–14·1%	8·1 (7·4–9·4)	6·1 (5·1–6·7)	–25·0
Pneumococcal meningitis	124·9 (111·8–149·3)	118·4 (98·4–132·0)	–5·2%	2·1 (1·9–2·5)	1·7 (1·4–1·9)	–19·5
H influenzae type B meningitis	118·9 (103·2–148·5)	83·0 (70·6–97·0)	–30·2%	1·8 (1·5–2·2)	1·2 (1·0–1·4)	–33·9
Meningococcal infection	77·1 (68·8–92·7)	75·0 (61·8–85·0)	–2·6%	1·3 (1·2–1·5)	1·1 (0·9–1·2)	–16·5
Other meningitis	171·3 (153·2–199·2)	146·4 (119·8–164·4)	–14·6%	2·9 (2·6–3·3)	2·1 (1·7–2·4)	–27·4
Encephalitis	143·5 (126·7–168·1)	119·3 (98·0–137·1)	–16·9%	2·4 (2·1–2·8)	1·7 (1·4–2·0)	–28·3
Diphtheria	6·3 (0·0–53·0)	2·9 (0·0–24·9)	–53·5%	0·1 (0·0–0·8)	<0·05 (0·0–0·3)	–55·2
Whooping cough	166·5 (0·6–815·7)	81·4 (0·3–399·0)	–51·1%	2·3 (0·0–11·4)	1·1 (0·0–5·5)	–51·6
Tetanus	272·8 (163·4–456·1)	61·3 (31·0–114·0)	–77·5%	4·1 (2·4–7·6)	0·9 (0·4–1·6)	–78·8
Measles	631·2 (188·2–1492·6)	125·4 (41·3–295·5)	–80·1%	9·0 (2·7–21·3)	1·7 (0·6–4·1)	–80·6
Varicella	11·2 (0·0–75·0)	6·8 (0·0–46·4)	–38·9%	0·2 (0·0–1·3)	0·1 (0·0–0·7)	–50·8
Neglected tropical diseases and malaria	1210·6 (1014·1–1485·4)	1321·8 (1055·6–1677·6)	9·2%	21·0 (17·5–25·9)	18·9 (15·1–23·9)	–10·0
Malaria	975·7 (781·2–1239·5)	1169·5 (916·5–1526·9)	19·9%	16·6 (13·4–21·3)	16·7 (13·0–21·7)	0·5
Chagas disease	9·3 (4·6–19·9)	10·3 (5·1–28·6)	10·8%	0·2 (0·1–0·5)	0·2 (0·1–0·4)	–30·4
Leishmaniasis	87·2 (50·6–138·4)	51·6 (33·2–76·1)	–40·9%	1·5 (0·9–2·4)	0·7 (0·5–1·1)	–51·3
African trypanosomiasis	33·5 (9·9–72·7)	9·1 (1·1–29·0)	–72·8%	0·6 (0·2–1·4)	0·1 (0·0–0·4)	–79·2
Schistosomiasis	10·5 (0·0–62·9)	11·7 (0·0–69·8)	10·9%	0·2 (0·0–1·5)	0·2 (0·0–1·1)	–28·6
Cysticercosis	0·7 (0·0–2·8)	1·2 (0·0–4·3)	58·5%	<0·05 (0·0–0·1)	<0·05 (0·0–0·1)	7·3
Echinococcosis	2·0 (0·0–7·7)	1·2 (0·0–4·7)	–41·2%	<0·05 (0·0–0·2)	<0·05 (0·0–0·1)	–62·2
Dengue	11·4 (3·7–23·5)	14·7 (6·1–24·3)	28·9%	0·2 (0·1–0·4)	0·2 (0·1–0·4)	3·2
Rabies	54·1 (32·4–103·4)	26·4 (15·2–45·2)	–51·2%	1·0 (0·6–1·9)	0·4 (0·2–0·7)	–61·7

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	All ages deaths (thousands)			Age-standardised death rates (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
(Continued from previous page)						
Intestinal nematode infections	3·4 (0·0–16·4)	2·7 (0·0–13·0)	–21·7%	0·1 (0·0–0·2)	<0·05 (0·0–0·2)	–27·3
Ascariasis	3·4 (0·0–16·4)	2·7 (0·0–13·0)	–21·7%	0·1 (0·0–0·2)	<0·05 (0·0–0·2)	–27·3
Other neglected tropical diseases	22·9 (14·3–29·5)	23·7 (16·6–30·9)	3·4%	0·5 (0·3–0·6)	0·3 (0·2–0·5)	–23·6
Maternal disorders	358·6 (297·7–429·4)	254·7 (203·8–303·3)	–29·0%	6·9 (5·7–8·3)	3·7 (2·9–4·4)	–47·2
Maternal haemorrhage	84·8 (69·0–101·7)	58·3 (46·2–68·7)	–31·2%	1·7 (1·4–2·0)	0·8 (0·7–1·0)	–49·8
Maternal sepsis	33·8 (28·0–41·6)	21·9 (17·6–26·7)	–35·3%	0·6 (0·5–0·8)	0·3 (0·2–0·4)	–50·8
Hypertensive disorders of pregnancy	69·8 (57·6–85·0)	47·1 (37·7–57·2)	–32·5%	1·3 (1·1–1·6)	0·7 (0·5–0·8)	–48·8
Obstructed labour	19·1 (15·6–23·8)	10·9 (8·6–13·5)	–43·0%	0·4 (0·3–0·5)	0·2 (0·1–0·2)	–57·3
Abortion	56·1 (46·4–68·7)	37·1 (29·8–45·1)	–33·8%	1·1 (0·9–1·3)	0·5 (0·4–0·6)	–50·3
Other maternal disorders	95·1 (78·4–112·8)	79·4 (63·0–92·4)	–16·6%	1·9 (1·5–2·2)	1·1 (0·9–1·3)	–38·7
Neonatal disorders	3081·1 (2684·2–3393·8)	2236·4 (2014·6–2470·1)	–27·4%	42·4 (36·9–46·7)	31·0 (27·9–34·3)	–26·8
Preterm birth complications	1204·1 (998·1–1376·8)	859·7 (731·6–990·1)	–28·6%	16·6 (13·7–18·9)	11·9 (10·1–13·7)	–28·0
Neonatal encephalopathy (birth asphyxia/trauma)	638·1 (516·7–798·1)	511·4 (402·2–619·4)	–19·9%	8·8 (7·1–11·0)	7·1 (5·6–8·6)	–19·2
Sepsis and other infectious disorders of the newborn baby	534·6 (292·0–817·1)	513·7 (317·6–841·0)	–3·9%	7·4 (4·0–11·2)	7·1 (4·4–11·7)	–3·1
Other neonatal disorders	704·3 (529·1–860·3)	351·7 (293·5–429·8)	–50·1%	9·7 (7·3–11·8)	4·9 (4·1–6·0)	–49·7
Nutritional deficiencies	976·9 (854·4–1155·7)	684·1 (546·0–790·1)	–30·0%	17·3 (15·1–20·4)	9·9 (7·9–11·5)	–42·8
Protein–energy malnutrition	883·0 (726·7–1052·6)	599·8 (459·4–701·9)	–32·1%	15·4 (12·6–18·3)	8·7 (6·6–10·1)	–43·7
Iodine deficiency	2·0 (1·7–2·4)	3·4 (2·4–3·8)	67·7%	<0·05 (0·0–0·1)	<0·05 (0·0–0·1)	17·5
Iron-deficiency anaemia	80·8 (66·5–97·8)	69·4 (51·6–78·9)	–14·1%	1·6 (1·3–2·0)	1·0 (0·8–1·2)	–37·3
Other nutritional deficiencies	11·1 (9·6–14·0)	11·5 (8·0–12·8)	3·4%	0·2 (0·2–0·3)	0·2 (0·1–0·2)	–31·4
Other communicable, maternal, neonatal, and nutritional disorders	689·5 (569·9–815·1)	721·2 (626·8–830·4)	4·6%	12·3 (10·4–14·2)	10·6 (9·2–12·1)	–14·3
Sexually transmitted diseases excluding HIV	209·4 (130·0–324·3)	118·3 (71·6–187·7)	–43·5%	3·0 (1·9–4·6)	1·6 (1·0–2·6)	–45·6
Syphilis	202·9 (121·9–315·8)	113·3 (66·9–181·7)	–44·1%	2·9 (1·8–4·4)	1·6 (0·9–2·5)	–45·4
Sexually transmitted chlamydial diseases	1·5 (0·8–2·0)	1·2 (0·8–1·8)	–23·7%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	–49·1
Gonococcal infection	1·1 (0·6–1·5)	0·9 (0·6–1·3)	–23·6%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	–49·0
Other sexually transmitted diseases	3·8 (2·0–5·0)	2·9 (2·0–4·5)	–23·6%	0·1 (0·0–0·1)	<0·05 (0·0–0·01)	–49·0
Hepatitis	210·2 (200·3–221·1)	307·7 (268·2–356·5)	46·4%	4·4 (4·2–4·6)	4·6 (4·0–5·3)	4·6
Acute hepatitis A	99·0 (56·5–154·2)	102·8 (51·2–228·1)	3·9%	2·1 (1·1–3·3)	1·5 (0·8–3·4)	–25·1
Acute hepatitis B	68·6 (46·7–84·4)	132·2 (91·1–169·7)	92·7%	1·5 (1·1–1·9)	2·0 (1·4–2·6)	29·2
Acute hepatitis C	8·1 (4·9–11·6)	16·0 (11·6–21·4)	97·1%	0·2 (0·1–0·3)	0·2 (0·2–0·3)	25·6
Acute hepatitis E	34·5 (19·6–55·0)	56·6 (23·3–113·3)	64·2%	0·6 (0·3–0·9)	0·8 (0·3–1·6)	36·1
Other infectious diseases	269·9 (192·2–320·5)	295·2 (205·6–362·1)	9·4%	4·9 (3·5–5·7)	4·3 (3·0–5·3)	–11·8
Non-communicable diseases	26 560·3 (25 843·4–27 249·3)	34 539·9 (33 164·7–35 313·0)	30·0%	645·9 (629·9–662·9)	520·4 (499·5–532·0)	–19·4
Neoplasms	5779·1 (5415·9–6201·9)	7977·9 (7337·1–8403·8)	38·0%	140·8 (131·9–151·4)	121·4 (111·6–127·9)	–13·8
Oesophageal cancer	344·7 (279·7–428·8)	395·2 (298·4–482·1)	14·7%	8·5 (6·9–10·6)	6·1 (4·6–7·4)	–28·7
Stomach cancer	774·1 (602·8–1014·2)	754·9 (571·9–990·4)	–2·5%	19·0 (14·8–25·0)	11·5 (8·7–15·1)	–39·5
Liver cancer	463·0 (386·5–526·8)	752·1 (643·6–880·3)	62·4%	11·2 (9·4–12·8)	11·5 (9·8–13·4)	2·3
Liver cancer secondary to hepatitis B	210·2 (176·9–239·4)	341·4 (290·1–402·6)	62·4%	5·1 (4·3–5·8)	5·2 (4·4–6·1)	2·6
Liver cancer secondary to hepatitis C	113·0 (96·6–129·3)	195·7 (165·2–222·0)	73·3%	2·8 (2·4–3·2)	3·0 (2·5–3·4)	7·6
Liver cancer secondary to alcohol use	93·4 (78·6–106·4)	149·0 (127·3–172·6)	59·5%	2·3 (1·9–2·6)	2·3 (1·9–2·6)	–0·1
Other liver cancer	46·5 (38·2–52·6)	66·0 (57·2–77·3)	42·0%	1·1 (0·9–1·2)	1·0 (0·9–1·2)	–7·7
Larynx cancer	81·9 (43·5–133·4)	98·3 (52·8–159·2)	20·1%	2·0 (1·1–3·3)	1·5 (0·8–2·4)	–25·1
Trachea, bronchus, and lung cancers	1036·3 (825·8–1314·3)	1527·1 (1126·3–1779·4)	47·4%	25·5 (20·4–32·4)	23·4 (17·3–27·3)	–8·3
Breast cancer	319·1 (310·1–337·0)	438·7 (420·1–461·9)	37·5%	7·8 (7·6–8·3)	6·6 (6·4–7·0)	–15·3
Cervical cancer	192·3 (120·5–264·4)	225·4 (145·2–311·5)	17·3%	4·7 (2·9–6·4)	3·4 (2·2–4·7)	–26·9
Uterine cancer	45·2 (25·3–79·4)	58·6 (27·5–87·8)	29·7%	1·1 (0·6–2·0)	0·9 (0·4–1·3)	–20·2
Prostate cancer	155·6 (88·8–239·6)	256·0 (141·1–404·4)	64·5%	4·0 (2·3–6·1)	3·8 (2·1–6·1)	–3·1
Colon and rectum cancers	490·5 (417·2–547·3)	714·6 (627·9–822·6)	45·7%	12·2 (10·4–13·6)	10·8 (9·5–12·5)	–10·9

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	All ages deaths (thousands)			Age-standardised death rates (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
(Continued from previous page)						
Mouth cancer	81·9 (68·6–88·3)	123·9 (104·2–136·3)	51·2%	2·0 (1·7–2·2)	1·9 (1·6–2·1)	–5·9
Nasopharynx cancer	45·2 (29·9–59·6)	64·9 (42·3–83·3)	43·6%	1·1 (0·7–1·4)	1·0 (0·6–1·3)	–8·2
Cancer of other part of pharynx and oropharynx	74·0 (43·8–90·9)	102·4 (59·5–128·5)	38·3%	1·8 (1·1–2·2)	1·6 (0·9–2·0)	–12·9
Gallbladder and biliary tract cancer	97·4 (66·1–136·0)	151·7 (100·4–206·8)	55·7%	2·4 (1·6–3·4)	2·3 (1·5–3·1)	–4·7
Pancreatic cancer	200·0 (154·1–261·5)	310·2 (231·7–393·1)	55·1%	5·0 (3·8–6·5)	4·7 (3·5–6·0)	–4·8
Malignant melanoma of skin	31·0 (20·3–46·6)	49·1 (29·9–69·5)	58·4%	0·8 (0·5–1·1)	0·7 (0·5–1·1)	–1·5
Non-melanoma skin cancer	20·5 (12·5–32·7)	30·6 (17·5–46·3)	49·6%	0·5 (0·3–0·8)	0·5 (0·3–0·7)	–10·7
Ovarian cancer	113·6 (82·9–138·8)	160·5 (115·9–200·6)	41·2%	2·8 (2·0–3·4)	2·4 (1·8–3·1)	–12·1
Testicular cancer	6·5 (3·8–8·3)	7·7 (4·8–10·0)	18·6%	0·1 (0·1–0·2)	0·1 (0·1–0·1)	–18·9
Kidney and other urinary organ cancers	85·1 (62·0–112·9)	162·1 (125·5–219·8)	90·6%	2·1 (1·5–2·7)	2·5 (1·9–3·3)	19·4
Bladder cancer	123·4 (100·2–148·5)	170·7 (131·1–201·2)	38·3%	3·1 (2·5–3·7)	2·6 (2·0–3·0)	–16·3
Brain and nervous system cancers	131·5 (88·7–188·3)	195·5 (115·1–239·3)	48·7%	3·0 (2·1–4·4)	3·0 (1·7–3·6)	–2·5
Thyroid cancer	24·0 (18·0–29·9)	36·0 (26·4–43·2)	50·2%	0·6 (0·4–0·7)	0·5 (0·4–0·7)	–6·7
Hodgkin's disease	18·9 (11·8–26·2)	17·7 (11·6–25·5)	–6·0%	0·4 (0·3–0·6)	0·3 (0·2–0·4)	–36·7
Non-Hodgkin lymphoma	143·2 (119·4–158·9)	210·0 (166·0–228·5)	46·7%	3·3 (2·8–3·7)	3·2 (2·5–3·4)	–5·0
Multiple myeloma	49·3 (34·5–71·2)	74·1 (48·9–102·2)	50·4%	1·2 (0·9–1·8)	1·1 (0·7–1·6)	–7·5
Leukaemia	218·3 (175·7–269·2)	281·3 (219·6–328·0)	28·9%	4·7 (3·8–5·9)	4·2 (3·3–4·9)	–11·5
Other neoplasms	412·7 (319·5–521·9)	608·4 (441·2–737·3)	47·4%	9·8 (7·6–12·4)	9·2 (6·7–11·2)	–5·7
Cardiovascular and circulatory diseases	11 903·7 (11 329·4–12 589·3)	15 616·1 (14 542·2–16 315·1)	31·2%	298·1 (283·9–314·9)	234·8 (218·7–245·2)	–21·2
Rheumatic heart disease	462·6 (431·5–517·7)	345·1 (305·8–374·3)	–25·4%	11·1 (10·3–12·4)	5·2 (4·6–5·6)	–53·1
Ischaemic heart disease	5211·8 (5014·5–5643·9)	7029·3 (6577·2–7431·1)	34·9%	131·3 (126·4–142·2)	105·7 (98·8–111·9)	–19·5
Cerebrovascular disease	4660·4 (4436·1–5154·9)	5874·2 (5304·7–6280·1)	26·0%	105·7 (98·8–111·9)	88·4 (79·8–94·4)	–24·6
Ischaemic stroke	2241·1 (2088·0–2494·9)	2835·4 (2657·0–3262·8)	26·5%	57·6 (53·7–64·0)	42·3 (39·6–48·7)	–26·6
Haemorrhagic and other non-ischaemic stroke	2419·4 (2050·9–2827·9)	3038·8 (2643·4–3496·9)	25·6%	59·7 (50·6–69·7)	46·1 (40·1–53·1)	–22·7
Hypertensive heart disease	590·7 (481·0–740·6)	873·2 (715·5–1074·1)	47·8%	14·9 (12·1–18·6)	13·1 (10·8–16·2)	–11·5
Cardiomyopathy and myocarditis	286·8 (250·5–316·8)	403·9 (361·5–450·4)	40·8%	6·7 (5·9–7·4)	6·1 (5·4–6·8)	–9·8
Atrial fibrillation and flutter	34·4 (27·9–43·1)	114·7 (92·7–144·7)	233·9%	0·9 (0·7–1·1)	1·7 (1·4–2·1)	89·6
Aortic aneurysm	131·9 (94·6–173·3)	191·7 (140·3–249·2)	45·3%	3·3 (2·4–4·3)	2·9 (2·1–3·8)	–12·7
Peripheral vascular disease	18·6 (12·2–28·7)	49·8 (32·9–74·8)	167·0%	0·5 (0·3–0·7)	0·7 (0·5–1·1)	53·3
Endocarditis	35·8 (30·0–44·4)	48·3 (39·3–55·4)	34·8%	0·8 (0·7–1·0)	0·7 (0·6–0·8)	–8·0
Other cardiovascular and circulatory diseases	470·6 (446·3–489·9)	685·9 (664·0–705·3)	45·7%	11·5 (11·0–11·9)	10·3 (9·9–10·5)	–10·9
Chronic respiratory diseases	3986·3 (3914·3–4063·8)	3776·3 (3648·2–3934·1)	–5·3%	98·2 (96·4–100·1)	57·0 (55·1–59·4)	–41·9
Chronic obstructive pulmonary disease	3099·0 (2914·2–3338·6)	2899·9 (2669·3–3245·8)	–6·4%	77·4 (72·8–83·3)	43·8 (40·4–49·1)	–43·3
Pneumoconiosis	167·0 (86·3–295·2)	124·7 (78·3–196·9)	–25·3%	4·2 (2·2–7·3)	1·9 (1·2–3·0)	–54·8
Asthma	380·2 (273·8–589·6)	345·7 (282·6–529·1)	–9·1%	9·0 (6·6–13·9)	5·2 (4·3–8·0)	–42·1
Interstitial lung disease and pulmonary sarcoidosis	65·0 (44·5–89·8)	115·1 (76·7–152·0)	77·2%	1·6 (1·1–2·2)	1·7 (1·2–2·3)	9·1
Other chronic respiratory diseases	275·2 (200·8–375·8)	290·8 (226·8–356·5)	5·7%	6·0 (4·4–8·1)	4·3 (3·4–5·3)	–28·3
Cirrhosis of the liver	777·8 (663·1–867·9)	1030·8 (868·8–1160·5)	32·5%	18·6 (15·8–20·7)	15·6 (13·2–17·6)	–15·8
Cirrhosis of the liver secondary to hepatitis B	241·7 (198·5–270·5)	312·4 (270·8–378·3)	29·3%	5·8 (4·8–6·5)	4·8 (4·1–5·8)	–18·5
Cirrhosis of the liver secondary to hepatitis C	211·9 (181·1–240·7)	287·4 (245·4–330·5)	35·6%	5·2 (4·4–5·9)	4·4 (3·7–5·0)	–15·3
Cirrhosis of the liver secondary to alcohol use	206·1 (168·6–245·3)	282·8 (225·6–335·0)	37·2%	5·0 (4·1–5·9)	4·3 (3·4–5·1)	–13·9
Other cirrhosis of the liver	118·2 (101·4–136·7)	148·2 (126·6–173·0)	25·4%	2·6 (2·2–3·0)	2·2 (1·9–2·6)	–14·4
Digestive diseases (except cirrhosis)	973·1 (877·1–1063·5)	1111·7 (999·5–1210·0)	14·2%	22·9 (20·7–25·0)	16·7 (15·0–18·1)	–27·2
Peptic ulcer disease	319·3 (265·9–338·8)	246·3 (215·0–282·2)	–22·9%	7·5 (6·3–8·0)	3·7 (3·2–4·2)	–50·9
Gastritis and duodenitis	15·6 (11·3–21·1)	14·3 (11·0–18·2)	–8·7%	0·4 (0·3–0·5)	0·2 (0·2–0·3)	–42·1
Appendicitis	39·5 (27·2–57·0)	34·8 (22·0–46·9)	–12·0%	0·8 (0·6–1·2)	0·5 (0·3–0·7)	–38·1
Paralytic ileus and intestinal obstruction without hernia	121·0 (78·7–141·1)	148·1 (112·1–192·2)	22·4%	2·8 (1·8–3·2)	2·2 (1·7–2·9)	–20·9
Inguinal or femoral hernia	23·3 (22·8–23·7)	17·1 (16·7–17·3)	–26·7%	0·5 (0·5–0·6)	0·3 (0·2–0·3)	–53·4
Non-infective inflammatory bowel disease	29·5 (16·8–37·7)	34·0 (23·6–39·7)	15·1%	0·6 (0·4–0·8)	0·5 (0·3–0·6)	–20·3
Vascular disorders of intestine	51·4 (28·9–104·6)	73·4 (41·2–150·0)	42·9%	1·3 (0·7–2·6)	1·1 (0·6–2·3)	–15·2

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	All ages deaths (thousands)			Age-standardised death rates (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
(Continued from previous page)						
Gallbladder and bile duct disease	74·0 (63·6–93·6)	89·1 (72·1–105·0)	20·4%	1·8 (1·5–2·2)	1·3 (1·1–1·6)	–25·5
Pancreatitis	51·6 (37·7–64·6)	76·6 (57·4–95·5)	48·5%	1·2 (0·9–1·5)	1·2 (0·9–1·4)	–6·0
Other digestive diseases	247·9 (194·2–296·2)	378·1 (301·6–500·4)	52·5%	5·9 (4·6–7·0)	5·7 (4·5–7·5)	–3·1
Neurological disorders	594·5 (468·3–703·0)	1273·8 (980·9–1466·9)	114·3%	13·7 (10·8–16·1)	18·8 (14·5–21·8)	37·8
Alzheimer's disease and other dementias	141·2 (110·8–208·5)	485·7 (307·8–590·5)	244·0%	3·6 (2·8–5·4)	7·1 (4·5–8·6)	95·4
Parkinson's disease	53·5 (42·4–70·1)	111·1 (81·2–138·6)	107·7%	1·4 (1·1–1·8)	1·7 (1·2–2·1)	20·8
Epilepsy	130·2 (86·4–167·7)	177·6 (119·7–222·3)	36·4%	2·6 (1·8–3·1)	2·6 (1·7–3·2)	1·0
Multiple sclerosis	15·4 (11·4–18·8)	18·2 (14·1–21·8)	17·8%	0·4 (0·3–0·4)	0·3 (0·2–0·3)	–25·0
Other neurological disorders	254·2 (154·1–343·1)	481·1 (317·9–690·7)	89·3%	5·7 (3·5–7·7)	7·2 (4·8–10·4)	25·9
Mental and behavioural disorders	138·1 (95·2–188·0)	231·9 (176·3–329·1)	68·0%	3·2 (2·2–4·3)	3·5 (2·6–4·9)	9·3
Schizophrenia	20·0 (13·1–24·6)	19·8 (16·6–25·0)	–1·3%	0·5 (0·3–0·6)	0·3 (0·2–0·4)	–36·7
Alcohol use disorders	74·6 (40·1–119·2)	111·1 (64·0–186·3)	48·9%	1·8 (1·0–2·8)	1·7 (1·0–2·8)	–5·0
Drug use disorders	26·6 (15·5–56·4)	77·6 (48·8–124·4)	191·7%	0·5 (0·3–1·2)	1·1 (0·7–1·8)	112·5
Opioid use disorders	8·9 (5·0–18·7)	43·0 (26·9–68·4)	385·8%	0·2 (0·1–0·4)	0·6 (0·4–1·0)	257·5
Cocaine use disorders	1·2 (0·7–2·7)	0·5 (0·2–0·5)	–55·1%	<0·05 (0·0–0·1)	<0·05 (0·0–0·05)	–67·7
Amphetamine use disorders	0·3 (0·1–0·5)	0·5 (0·1–0·3)	40·1%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	1·5
Other drug use disorders	16·2 (9·6–34·2)	33·6 (21·9–55·9)	107·3%	0·3 (0·2–0·7)	0·5 (0·3–0·8)	50·3
Eating disorders	5·4 (2·4–8·3)	7·3 (4·5–9·9)	35·0%	0·1 (0·1–0·2)	0·1 (0·1–0·1)	–12·8
Other mental and behavioural disorders	11·4 (5·2–17·0)	16·1 (9·8–22·1)	41·7%	0·3 (0·1–0·4)	0·2 (0·1–0·3)	–11·4
Diabetes, urogenital, blood, and endocrine diseases	1544·3 (1420·0–1804·0)	2726·2 (2447·1–2999·1)	76·5%	36·1 (33·4–41·6)	41·0 (36·8–45·1)	13·8
Diabetes mellitus	665·0 (593·3–757·5)	1281·3 (1065·2–1347·9)	92·7%	16·3 (14·5–18·6)	19·5 (16·2–20·5)	19·7
Acute glomerulonephritis	135·2 (57·4–357·3)	84·2 (41·4–191·8)	–37·7%	2·7 (1·2–7·4)	1·2 (0·6–2·8)	–54·5
Chronic kidney diseases	403·5 (354·5–468·9)	735·6 (612·1–810·4)	82·3%	9·6 (8·4–11·2)	11·1 (9·2–12·2)	15·4
Chronic kidney disease due to diabetes mellitus	91·9 (79·7–109·9)	178·3 (147·7–198·4)	94·1%	2·3 (2·0–2·7)	2·7 (2·3–3·0)	19·2
Chronic kidney disease due to hypertension	91·5 (80·1–106·9)	175·3 (147·0–193·3)	91·5%	2·2 (2·0–2·6)	2·6 (2·2–2·9)	18·5
Chronic kidney disease unspecified	220·2 (191·9–252·9)	382·0 (317·9–422·3)	73·5%	5·1 (4·5–5·9)	5·7 (4·8–6·3)	12·3
Urinary diseases and male infertility	140·1 (102·5–172·6)	267·1 (204·5–343·4)	90·7%	3·4 (2·5–4·2)	4·0 (3·0–5·1)	18·0
Tubulointerstitial nephritis, pyelonephritis, and urinary tract infections	83·0 (61·4–107·2)	163·3 (109·1–199·8)	96·7%	2·0 (1·5–2·6)	2·4 (1·6–3·0)	20·0
Urolithiasis	18·4 (12·4–27·8)	19·0 (11·0–26·0)	3·1%	0·5 (0·3–0·7)	0·3 (0·2–0·4)	–36·8
Other urinary diseases	38·6 (26·2–49·3)	84·9 (63·5–114·1)	119·6%	0·9 (0·6–1·1)	1·3 (1·0–1·7)	40·8
Gynaecological diseases	5·1 (3·7–6·4)	7·0 (5·9–8·0)	39·0%	0·1 (0·1–0·1)	0·1 (0·1–0·1)	–9·0
Uterine fibroids	0·4 (0·3–0·5)	0·8 (0·6–0·9)	85·7%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	16·5
Endometriosis	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	91·5%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	28·6
Genital prolapse	0·2 (0·1–0·2)	0·4 (0·3–0·4)	118·5%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	32·5
Other gynaecological diseases	4·5 (3·2–5·7)	5·9 (4·9–6·7)	31·5%	0·1 (0·1–0·1)	0·1 (0·1–0·1)	–13·4
Haemoglobinopathies and haemolytic anaemias	111·4 (72·8–160·4)	114·8 (86·2–151·1)	3·1%	2·1 (1·4–3·0)	1·7 (1·3–2·2)	–22·2
Thalassaemias	25·1 (17·0–34·4)	17·9 (15·1–20·4)	–28·9%	0·4 (0·3–0·6)	0·3 (0·2–0·3)	–41·3
Sickle-cell disorders	23·8 (15·1–32·7)	28·6 (16·8–40·9)	20·5%	0·4 (0·3–0·5)	0·4 (0·2–0·6)	3·6
G6PD deficiency	4·3 (3·4–5·3)	4·0 (3·5–4·6)	–5·6%	0·1 (0·1–0·1)	0·1 (0·1–0·1)	–31·8
Other haemoglobinopathies and haemolytic anaemias	58·3 (36·2–91·2)	64·3 (40·9–89·2)	10·3%	1·2 (0·8–1·8)	0·9 (0·6–1·3)	–23·0
Other endocrine, nutritional, blood, and immune disorders	84·0 (42·3–115·5)	236·1 (148·8–417·9)	181·2%	1·8 (0·9–2·5)	3·5 (2·2–6·2)	91·8
Musculoskeletal disorders	69·5 (46·2–89·6)	153·5 (110·7–214·8)	121·0%	1·7 (1·1–2·2)	2·3 (1·7–3·2)	37·8
Rheumatoid arthritis	33·5 (23·5–43·5)	48·9 (37·9–68·6)	45·8%	0·8 (0·6–1·1)	0·7 (0·6–1·0)	–9·9
Other musculoskeletal disorders	36·0 (25·0–42·8)	104·7 (83·8–143·7)	191·0%	0·8 (0·6–1·0)	1·6 (1·2–2·1)	84·0
Other non-communicable diseases	793·9 (670·6–970·4)	641·7 (524·8–721·4)	–19·2%	12·7 (10·8–15·3)	9·2 (7·5–10·3)	–28·0
Congenital anomalies	663·2 (551·7–843·4)	510·4 (404·7–596·3)	–23·0%	10·1 (8·4–12·7)	7·2 (5·7–8·4)	–28·3
Neural tube defects	118·5 (70·5–173·3)	70·8 (39·8–104·6)	–40·3%	1·7 (1·0–2·5)	1·0 (0·6–1·5)	–42·2
Congenital heart anomalies	278·9 (234·9–355·9)	223·6 (199·5–246·7)	–19·8%	4·3 (3·7–5·3)	3·2 (2·8–3·5)	–26·4
Cleft lip and cleft palate	8·4 (3·3–16·6)	3·7 (2·1–5·5)	–56·2%	0·1 (0·0–0·2)	0·1 (0·0–0·1)	–56·2

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	All ages deaths (thousands)			Age-standardised death rates (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
(Continued from previous page)						
Down's syndrome	22·0 (9·8–37·5)	17·4 (11·1–25·4)	–21·0%	0·3 (0·2–0·6)	0·2 (0·2–0·4)	–28·3
Other chromosomal abnormalities	34·6 (11·9–80·3)	18·9 (9·7–33·8)	–45·4%	0·5 (0·2–1·1)	0·3 (0·1–0·5)	–46·8
Other congenital anomalies	200·8 (115·8–298·9)	176·0 (118·9–218·7)	–12·3%	3·1 (1·9–4·5)	2·5 (1·7–3·1)	–19·3
Skin and subcutaneous diseases	100·6 (77·5–118·3)	109·2 (84·9–124·0)	8·5%	2·2 (1·7–2·6)	1·6 (1·3–1·8)	–26·5
Cellulitis	26·1 (19·9–30·8)	26·6 (20·4–30·2)	2·0%	0·6 (0·4–0·7)	0·4 (0·3–0·5)	–28·9
Abscess, impetigo, and other bacterial skin diseases	42·1 (31·2–51·0)	39·7 (31·1–45·1)	–5·7%	0·8 (0·6–1·0)	0·6 (0·5–0·7)	–30·6
Decubitus ulcer	32·1 (26·0–38·5)	42·6 (32·9–48·7)	32·5%	0·8 (0·6–1·0)	0·6 (0·5–0·7)	–20·6
Other skin and subcutaneous diseases	0·3 (0·1–0·1)	0·4 (0·1–0·1)	4·4%	<0·05 (0·0–0·05)	<0·05 (0·0–0·05)	–28·7
Sudden infant death syndrome	30·0 (15·4–56·7)	22·0 (13·1–36·5)	–26·7%	0·4 (0·2–0·8)	0·3 (0·2–0·5)	–26·7
Injuries	4091·7 (3851·9–4489·7)	5073·3 (4556·7–5548·1)	24·0%	82·0 (77·2–90·3)	74·3 (66·8–81·3)	–9·3
Transport injuries	958·2 (770·4–1175·0)	1396·8 (1101·4–1850·1)	45·8%	19·4 (15·4–23·6)	20·5 (16·1–27·1)	5·9
Road injury	907·9 (764·1–1123·4)	1328·5 (1050·9–1747·0)	46·3%	18·4 (15·4–22·7)	19·5 (15·4–25·6)	6·2
Pedestrian injury by road vehicle	284·1 (210·6–333·9)	461·0 (337·1–617·3)	62·3%	5·8 (4·2–6·7)	6·8 (5·0–9·1)	17·6
Pedal cycle vehicle	54·9 (41·7–66·7)	83·3 (62·3–101·4)	51·7%	1·1 (0·9–1·4)	1·2 (0·9–1·5)	7·8
Motorised vehicle with two wheels	131·7 (99·4–163·4)	206·4 (159·7–233·8)	56·7%	2·6 (2·0–3·3)	3·0 (2·3–3·4)	14·4
Motorised vehicle with three or more wheels	336·9 (268·8–420·5)	474·5 (379·3–581·4)	40·9%	6·8 (5·5–8·4)	7·0 (5·6–8·5)	2·4
Road injury other	100·3 (49·0–182·3)	103·3 (50·7–202·2)	3·0%	2·0 (1·0–3·7)	1·5 (0·7–3·0)	–25·2
Other transport injury	50·2 (41·7–65·1)	68·3 (58·0–82·7)	35·9%	1·0 (0·8–1·3)	1·0 (0·8–1·2)	–0·0
Unintentional injuries other than transport injuries	2030·1 (1896·0–2266·8)	2122·8 (1867·5–2283·8)	4·6%	39·6 (37·1–44·3)	31·0 (27·3–33·4)	–21·6
Falls	348·6 (311·2–415·3)	540·5 (415·2–611·9)	55·0%	7·8 (7·0–9·4)	8·0 (6·1–9·1)	2·0
Drowning	432·9 (353·3–516·1)	349·1 (299·9–437·8)	–19·4%	7·5 (6·3–9·0)	5·1 (4·3–6·3)	–33·1
Fire, heat, and hot substances	280·1 (233·6–330·1)	337·6 (234·7–433·8)	20·5%	5·3 (4·5–6·3)	4·9 (3·4–6·3)	–7·3
Poisonings	202·9 (157·3–326·8)	180·4 (130·1–239·9)	–11·1%	4·0 (3·2–6·5)	2·6 (1·9–3·5)	–34·4
Exposure to mechanical forces	276·0 (199·6–417·1)	215·6 (154·6–255·3)	–21·9%	5·5 (4·0–8·1)	3·2 (2·3–3·7)	–42·2
Mechanical forces (firearm)	127·5 (76·8–206·0)	79·8 (52·0–127·1)	–37·4%	2·5 (1·5–4·1)	1·2 (0·8–1·8)	–53·2
Mechanical forces (other)	148·5 (103·0–197·4)	135·7 (83·5–161·0)	–8·6%	3·0 (2·1–3·9)	2·0 (1·2–2·4)	–33·1
Adverse effects of medical treatment	42·0 (32·7–49·3)	83·7 (64·6–96·2)	99·1%	0·9 (0·7–1·0)	1·2 (1·0–1·4)	41·0
Animal contact	75·0 (50·7–97·5)	64·3 (41·0–88·4)	–14·3%	1·4 (1·0–1·9)	0·9 (0·6–1·3)	–34·4
Animal contact (venomous)	54·9 (30·1–89·3)	47·0 (25·6–84·7)	–14·3%	1·0 (0·6–1·7)	0·7 (0·4–1·2)	–34·4
Animal contact (non-venomous)	20·1 (10·7–30·8)	17·3 (10·0–24·6)	–14·2%	0·4 (0·2–0·6)	0·3 (0·1–0·4)	–34·5
Unintentional injuries not classified elsewhere	372·5 (311·9–403·8)	351·6 (301·4–387·8)	–5·6%	7·1 (6·0–7·7)	5·1 (4·4–5·7)	–27·9
Self-harm and interpersonal violence	1008·5 (838·8–1201·9)	1340·0 (1108·2–1616·9)	32·9%	21·1 (17·5–25·4)	19·7 (16·2–23·8)	–6·9
Self-harm	669·8 (519·5–853·4)	883·7 (655·6–1105·2)	31·9%	14·5 (11·3–18·4)	13·1 (9·7–16·3)	–9·6
Interpersonal violence	338·7 (245·8–416·6)	456·3 (354·9–610·9)	34·7%	6·7 (4·8–8·3)	6·6 (5·1–8·9)	–1·0
Assault by firearm	141·8 (107·4–175·7)	196·2 (153·9–233·6)	38·4%	2·8 (2·1–3·5)	2·8 (2·2–3·4)	1·9
Assault by sharp object	83·1 (55·4–119·8)	126·7 (82·2–188·2)	52·5%	1·7 (1·1–2·4)	1·8 (1·2–2·7)	10·9
Assault by other means	113·8 (85·2–129·3)	133·4 (107·3–159·0)	17·2%	2·2 (1·7–2·5)	1·9 (1·6–2·3)	–13·5
Forces of nature, war, and legal intervention	94·9 (65·0–162·3)	213·7 (119·2–433·5)	125·2%	1·9 (1·3–3·4)	3·1 (1·7–6·3)	62·0
Exposure to forces of nature	31·4 (18·2–60·0)	196·0 (106·9–401·9)	523·5%	0·7 (0·4–1·3)	2·9 (1·6–5·8)	336·4
Collective violence and legal intervention	63·5 (44·3–101·8)	17·7 (12·2–29·6)	–72·2%	1·3 (0·9–2·1)	0·3 (0·2–0·4)	–79·5

Data are deaths (95% uncertainty interval) or % change. %Δ=percentage change. *E coli=Escherichia coli. H influenzae=Haemophilus influenzae*. G6PD=glucose-6-phosphate dehydrogenase. *For these causes the mean value is outside of the 95% uncertainty interval; this occurs because the full distribution of 1000 draws is asymmetric with a long tail. A small number of high values in the uncertainty distribution raises the mean above the 97·5 percentile of the distribution.

Table 2: **Global deaths for 235 causes in 1990 and 2010 for all ages and both sexes combined (thousands) and age-standardised rates (per 100 000) with 95% UI and percentage change**

Decomposition of changes in numbers of causes of death into demographic and epidemiological factors

To help understand the drivers of change in the numbers of deaths by cause or region, we decomposed change from 1990 to 2010 into growth in total population, change in population age and sex structure, and change in age-specific and sex-specific rates. We computed two counterfactual sets of cause of death numbers: (1) a population growth scenario computed as the number of deaths expected in 2010 if only total population numbers increased to the level of 2010 but the age-sex structure of population stayed the same as in 1990 and age-sex

specific rates remained at 1990 levels; and, (2) a population growth and population ageing scenario computed as the number of deaths expected in 2010, using 1990 age-sex specific rates and 2010 age-specific and sex-specific population numbers. The difference between 1990 numbers and the population growth scenario is the change in death numbers due strictly to the growth in total population. The change from the population growth scenario to the population growth and ageing scenario is the number of deaths due to ageing of the population. The difference between 2010 deaths and the population growth and ageing scenario is the difference in death numbers due to epidemiological change in age-specific and sex-specific death rates. Each of these three differences is also presented as a percentage change with reference to the 1990 death number.

We calculated change in the risk of death, by cause, directly using age standardised death rates, based on the WHO world population standard age structure.[62] Further details on the data and methods used for specific causes of death are available on request.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and the final responsibility to submit for publication.

Results

The GBD 2010 cause list divides causes into three broad groups. At the most aggregate level, communicable, maternal, neonatal, and nutritional causes account for 13·2 million (24·9%) of 52·8 million total deaths at all ages in 2010. Non-communicable causes account for 34·5 million or 65·5%. The third category, injuries, accounts for 5·1 million or 9·6%. The continued decrease in deaths from communicable, maternal, neonatal, and nutritional disorders is striking, if not surprising. The number of deaths from these disorders decreased by 2·7 million from 15·9 million in 1990 to 13·2 million in 2010, representing a 17% decrease from 1990 to 2010. The annual number of deaths from non-communicable diseases, by contrast, rose by just under 8 million, to 34·5 million, or two of every three deaths in 2010. The global fraction of deaths due to injuries increased slightly between 1990 and 2010 (from 8·8% to 9·6%), but this masks some important trends in mortality from these causes.

Table 1 decomposes these global trends into the contribution of total increase in population size, ageing of the population, and changes in age-specific and sex-specific rates. Global population growth alone would have been expected to increase deaths from all causes by 31·8% from 1990 to 2010. Because of the correlation between population growth rates and mortality rates from communicable, maternal, neonatal, and nutritional causes, population growth alone would have increased this category by 46·9%, non-communicable diseases by 22·9%, and injuries by 31·1% (table 1). Ageing of the world's population such that the mean age of the world increased from 26·1 years to 29·5 years contributed to an 11·2% decrease in communicable, maternal, neonatal, and nutritional disorders, a 39·2% increase in non-communicable disease deaths, and a 9·2% increase in injuries (table 1). Declines in age-specific and sex-specific death rates have contributed to a 52·7% decrease in communicable, maternal, neonatal, and nutritional deaths, a 32·1% decrease in non-communicable disease deaths, and a 16·3% decrease in injury deaths. With decreasing age-specific death rates from all three groups of causes, including non-communicable diseases, the global shift towards non-communicable diseases and injuries as leading causes of death is being driven by population growth and ageing, and not by increases in age-sex-cause specific death rates.

At the second level of the GBD 2010 cause hierarchy, there are 21 major cause groups. Figure 1 (A–D) summarises the composition of causes of death for every age-sex group for male and female individuals separately in 1990 and 2010 at this second level of cause disaggregation. The structure of causes of death changed systematically with age. In the neonatal age groups, disorders arising during the neonatal period dominated, but with important contributions from the category of diarrhoeal disease, lower respiratory infections, and other infectious and non-communicable diseases, including congenital causes. By the post-neonatal period, causes of death were dominated by diarrhoea, lower respiratory infections, and other infectious diseases such as measles, among others. At ages 1–4 years, the category neglected tropical diseases and malaria were also an important contributor to global mortality. In the age group 5–14 years, infectious diseases, HIV/tuberculosis (HIV/TB), injuries, and some cancers predominated, although overall mortality at these ages was low. Important sex differences were evident from ages 15–34 years; among male individuals, injuries, HIV/TB, and some non-communicable diseases predominate. Among female individuals of the same age group, injuries were a smaller cause of death with maternal causes making an important contribution. In 2010, maternal causes accounted for 10·7% of deaths of women in this age group. By age 40 years, more than 50% of global deaths in 1990 were from non-communicable diseases—this transition age shifts to 45 years in 2010 because of the HIV epidemic. Beginning at age 50 years, circulatory causes begin a steady rise to become the largest cause of death.

The comparison of the 1990 and 2010 plots shows various shifts in the cause structure by age and sex (figure 1). At younger age groups, neonatal disorders and other non-communicable causes, including congenital anomalies, predominate. The unfolding HIV/AIDS epidemic at the global level is clearly evident from the huge increase in the contribution of HIV/TB to cause of death patterns among young adult men and women. By 2010, for example, HIV/TB and injuries accounted for more than half of all

deaths in the age group 20–39 years in men. Other important shifts, with age, are evident—namely, a rising fraction of deaths in many age groups from diabetes, chronic kidney diseases, blood and endocrine disorders, and cancers, along with a decrease in the fraction due to chronic respiratory deaths in the middle-aged and older groups. For women, the share of deaths at ages 20–39 years due to maternal causes notably decreased.

At a more disaggregated cause level, there is interest in a broad global overview of who dies of what, and how this is

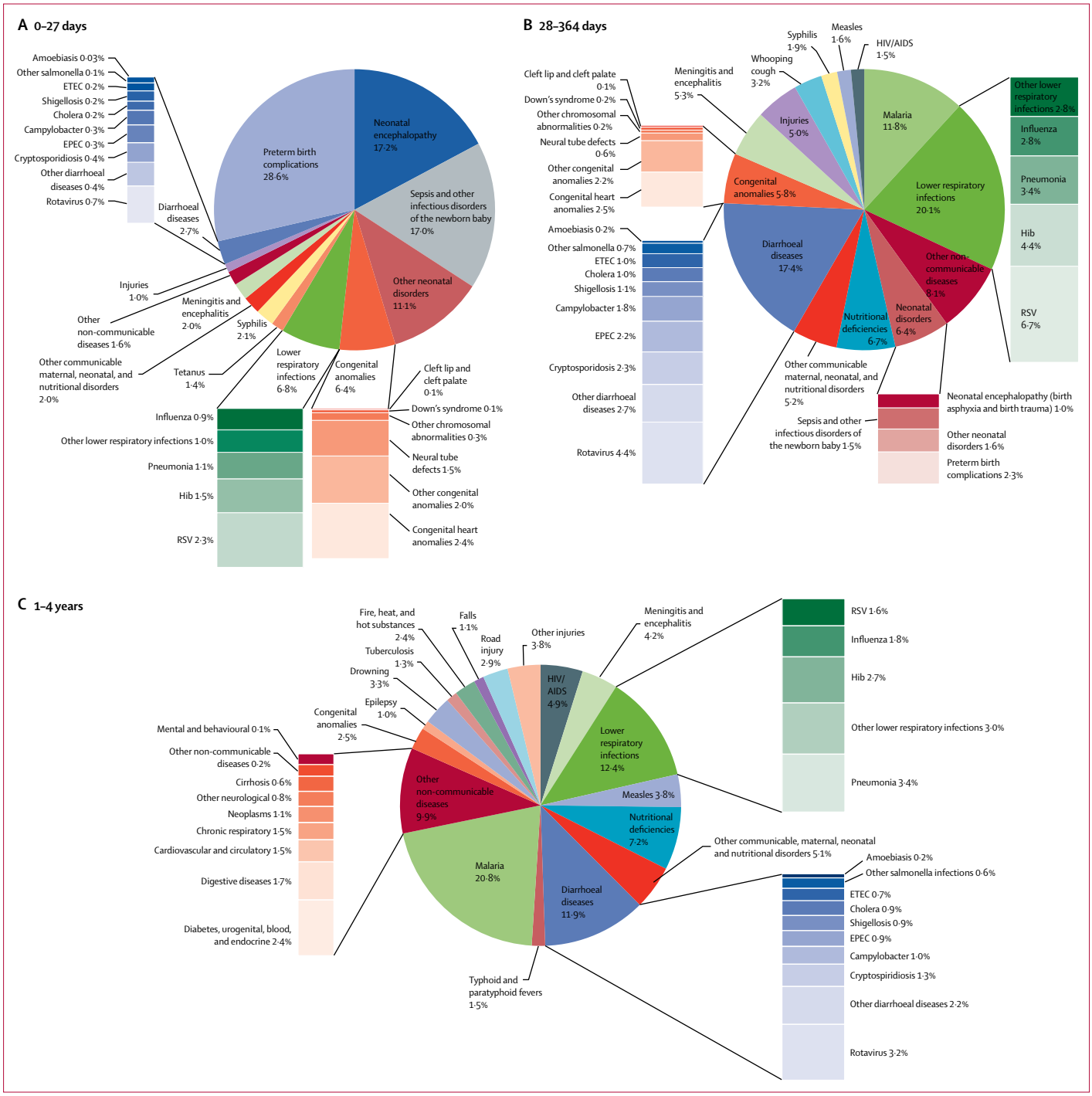

Figure 2: **Pie chart of global neonatal, post-neonatal, and child deaths in 2010 for children of both sexes combined by cause**
(A) Age 0–27 days (neonatal); 2 840 157 total deaths. (B) Age 28–364 days (post-neonatal); 2 031 474 total deaths. (C) Age 1–4 years; 1 969 567 total deaths. ETEC=enterotoxigenic *Escherichia coli*. EPEC=enteropathogenic *E coli*. Hib=*Haemophilus influenzae* type B. RSV=respiratory syncytial virus.

changing. Table 2 provides total numbers of deaths and age-standardised death rates for each cause in 1990 and 2010. Because there is substantial interest in causes of death for different age groups, we provide global deaths for the 20 GBD age groups, by sex, and including 95% UI for 2010 and 1990 (appendix pp 149–340). In addition to the numbers of deaths, we present the death rates by age for 2010 and 1990 in for those readers interested in comparing change in age-sex-specific death rates (appendix pp 341–533). There are many features of the tables that warrant discussion: we limit ourselves here to some general observations that we believe characterise the principal epidemiological trends around the turn of the millennium. Much of the decrease in the communicable, maternal, neonatal, and nutritional causes was due to the substantial reductions in diarrhoeal disease (from 2·5 to 1·4 million), lower respiratory infections (from 3·4 to 2·8 million), neonatal disorders (from 3·1 to 2·2 million), measles (from 0·63 to 0·13 million), and tetanus (from 0·27 to 0·06 million), reflecting the scaling up of effective treatments and technologies to combat these disorders generally associated with poverty (table 2). Not all diseases in this category decreased, however. Table 2 shows the massive increase in deaths between 1990 and 2010 from HIV/AIDS (from 0·3 to 1·5 million), despite the decrease after 2006, as well as a 19·9% rise in malaria mortality over the two decades.

Cancers claimed 8·0 million lives in 2010, 15·1% of all deaths worldwide, with large increases in deaths from trachea, bronchus, and lung cancers, twice the number of deaths from the next two most common sites for mortality (liver and stomach). Roughly half of the total liver cancer mortality was attributed to hepatitis B infection, with smaller fractions due to hepatitis C and alcohol (table 2). The largest cause fraction (13·3%) among all causes of death in 2010 was due to ischaemic heart disease, closely followed by stroke (11·1%), being roughly split equally between ischaemic stroke and haemorrhagic and other non-ischaemic stroke (table 2). Together, ischaemic heart disease and all forms of stroke killed an estimated 12·9 million people in 2010, a quarter of the global total, compared with one in five deaths worldwide 20 years earlier. Cirrhosis of the liver was the cause of a million deaths in 2010, 33% more than in 1990, roughly equally attributable to hepatitis B, hepatitis C, and alcohol. Diabetes deaths worldwide almost doubled, as did deaths from chronic kidney disease. Deaths from Alzheimer's disease and other dementias rose more than three-fold, and deaths from Parkinson's disease doubled. One of the few causes in this group to decrease was COPD, falling from 3·1 to 2·9 million. This is consistent with the decreases observed with development in countries such as the UK in the first part of the 20th century, only to be reversed as the effect of tobacco use becomes evident.[63,64]

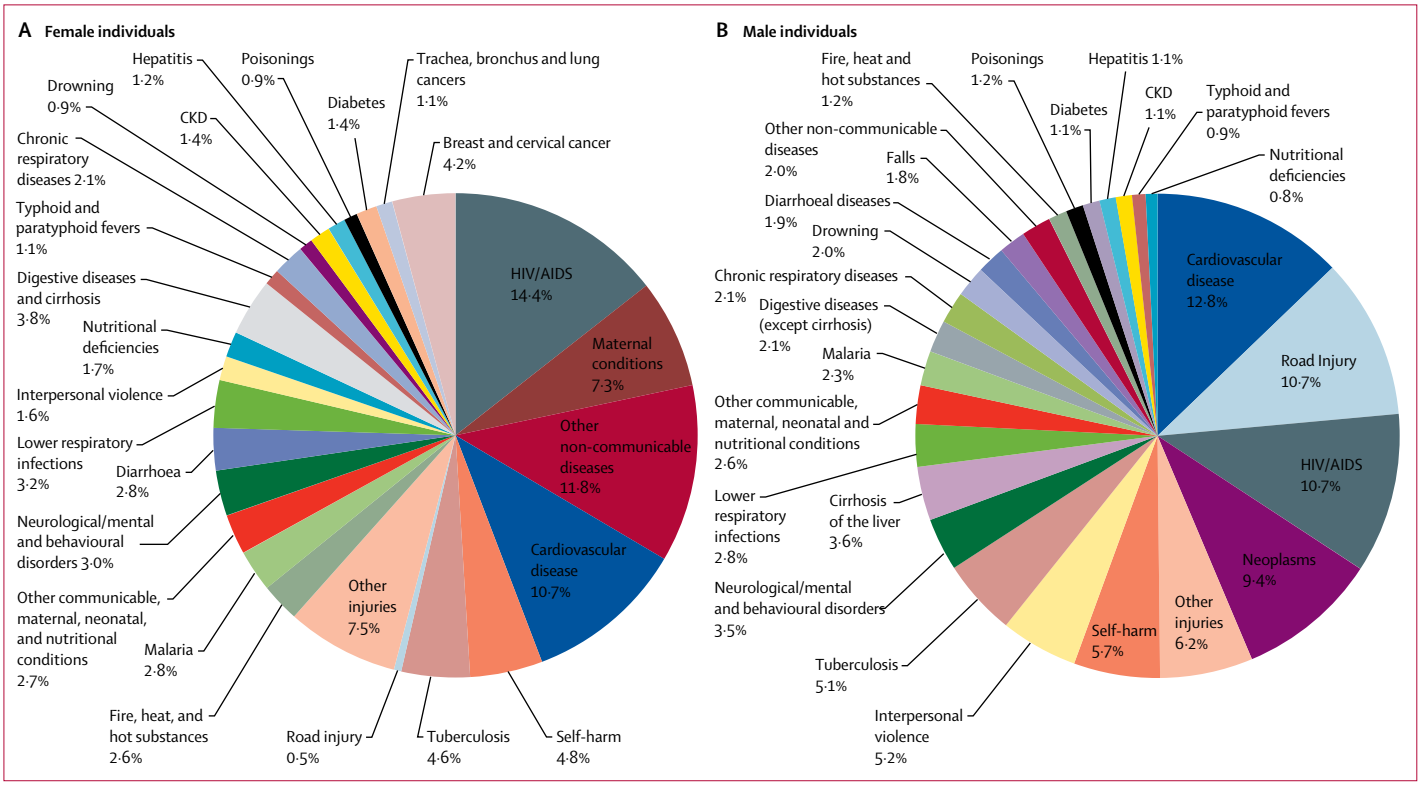

Figure 3: **Global deaths in 2010 for individuals aged 15–49 years**
(A) Female individuals, 3 496 480 total deaths. (B) Male individuals, 5 741 344 total deaths. CKD=chronic kidney disease.

The massive increases in tobacco use since the 1970s, especially in men in less developed countries, might reverse this trend over the next decade or so.[65]

One million more deaths from injuries occurred in 2010 (5·1 million) than two decades earlier, a 24% increase (table 2). This was driven primarily by a 420 600 increase in road traffic deaths, which claimed 1·3 million lives in 2010. Falls also claimed an additional 191 900 lives compared with 1990, with most other accidental causes being relatively constant, or decreasing, especially drowning. Deaths from intentional injuries increased for both self-harm and interpersonal violence. Deaths from forces of nature, war, and legal intervention were more than twice as common than two decades earlier. Given the huge annual fluctuation in deaths from forces of nature and war, trends must be interpreted with caution. The fact that deaths from injuries are rising, and account for one in ten deaths worldwide, argues for far greater policy action to prevent them.

Trends in numbers of deaths are of interest and importance for health services and health policies that are designed to reduce premature mortality from various causes. Yet numbers of deaths alone do not provide a clear indication of whether disease control strategies are working since they are heavily dependent on changes in population size and age structure. By computing age-standardised mortality rates, we effectively controlled for demographic changes across populations over time; however, age-standardised death rates are sensitive to the population standard used. Changes in age-standardised mortality rates between 1990 and 2010 are shown in the right hand panels of table 2. Death rates from all communicable, maternal, neonatal, and nutritional disorders have decreased by 30% since 1990, a much greater reduction than suggested from numbers of deaths alone (table 2). The age-standardised death rate from diarrhoeal diseases fell by 49%, whereas lower respiratory infections decreased by 34%. Interestingly, age-standardised death rates from trachea, bronchus, and lung cancers fell by 8% between 1990 and 2010, despite a 47% increase in numbers of deaths, due to continued decreases in mortality in developed countries and more modest increases in less developed countries where the full impact of smoking, especially in men, has yet to occur. Breast cancer mortality

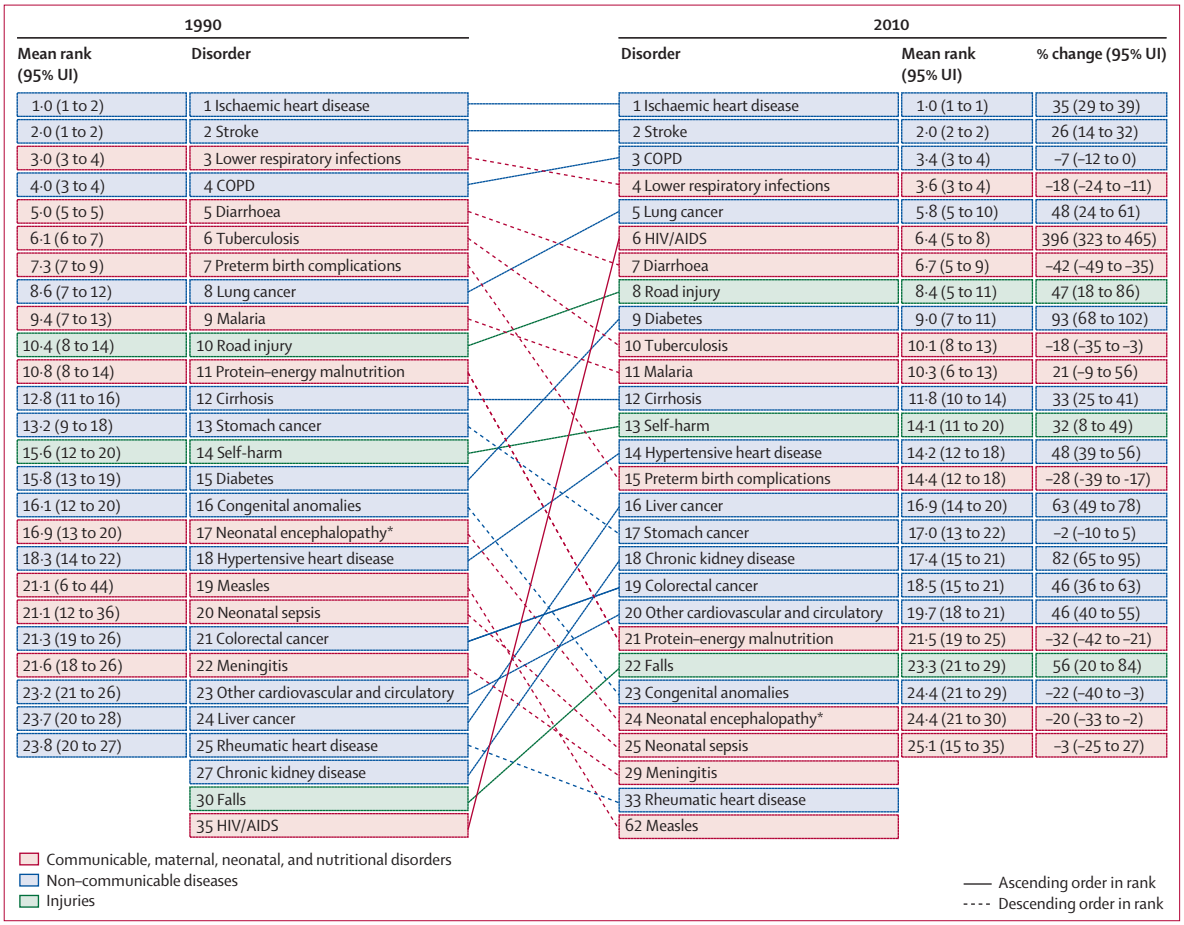

Figure 4: **Global death ranks with 95% UIs for the top 25 causes in 1990 and 2010, and the percentage change with 95% UIs between 1990 and 2010**
UI=uncertainty interval. COPD=chronic obstructive pulmonary disease. *Includes birth asphyxia/trauma. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

rates fell by 15%, even though numbers of deaths from the disease increased by more than a third.

Our findings suggest important decreases (20% or more) in age-standardised death rates from major vascular diseases, especially heart disease and strokes, for the world as whole, even though numbers of vascular disease deaths increased by a third to 15·6 million in 2010 (table 2). Death rates for COPD and liver cirrhosis also decreased, but almost doubled for Alzheimer's disease, and rose for diabetes and chronic kidney disease. These represent important global health challenges that might, or might not, be evident from an assessment of trends in numbers of deaths alone. Globally, although the number of deaths from injury rose by 24% since 1990, death rates decreased modestly, although this masks variable trends for different injuries, with death rates from drownings and poisonings falling by about a third, less dramatically for self-harm and violence, and rising for transport injuries and, interestingly, from adverse effects of medical treatment. Death rates from forces of nature also massively increased (by 336%) comparing 1990 to 2010 because of the earthquake in Haiti in 2010.

Causes of death in children younger than 5 years are of particular interest because of the global focus on improving child survival over the past few decades that has been reinforced by the push to achieve Millennium Development Goal (MDG) 4 (to reduce by two thirds, between 1990 and 2015, the under-5 mortality rate) in recent years. The appendix (pp 149–340) provides a breakdown of deaths in children younger than 5 years into the early neonatal, late neonatal, post-neonatal, and 1–4 years age groups in 2010 and 1990. To facilitate an understanding of the leading causes at different ages under 5 years, we show in figure 2A, B, and C the distribution of deaths in the neonatal periods, the post-neonatal period, and ages 1–4 years, respectively. Of 2·8 million early and late neonatal deaths, we estimate that 2·1 million were from neonatal disorders including preterm birth complications, neonatal sepsis, and neonatal encephalopathy, among others. A further 137000 deaths were also due to disorders that arise in the neonatal period but which lead to death after the first month of life. Among the important neonatal disorders, preterm events accounted for 29% of global neonatal deaths, with nearly equal shares for neonatal sepsis and neonatal encephalopathy—17% each. Of the remaining 741000 neonatal deaths, congenital anomalies accounted for 183000 deaths, although most congenital deaths occured after the first month of life. Injuries accounted for 28000 neonatal deaths; other non-communicable causes including haemoglobinopathies and haemolytic anaemias, some rare cancers, sudden infant death syndrome (SIDS), and other rare causes accounted for 45000 deaths. Among communicable diseases, notably lower respiratory infections (194000), diarrhoea (77000), and meningitis (46000) accounted for the remaining neonatal deaths.

In the post-neonatal period (figure 2B), we estimated 2·0 million deaths. Nearly half of these deaths were due to three diseases: lower respiratory infections, diarrhoeal diseases, and malaria. Other important causes of death during the post-neonatal period included nutritional deficiencies, meningitis and encephalitis, injuries, whooping cough, measles, and HIV/AIDS. Causes that primarily lead to death in the neonatal period also contributed to 14·0% of deaths between 1 month and 11 months including neonatal disorders, congenital anomalies, and congenital syphilis. Our analysis of lower respiratory infections disaggregated by pathogen suggested that the most important identified causes of post-neonatal lower respiratory infections were respiratory syncytial virus (RSV), *Haemophilus influenzae* type B (Hib), and pneumococcus. For diarrhoeal diseases, the most important pathogen was rotavirus followed by cryptosporidium. In the age group 1–4 years (figure 2C), we noted 2·0 million deaths distributed across a wider array of causes. The most important cause globally in this age group was malaria, followed by lower respiratory infections, diarrhoeal diseases, and nutritional deficiencies. These four causes accounted for 52·4% of deaths in this age group. Four causes account for between 3% and 5% of deaths each: HIV/AIDS, meningitis or encephalitis, measles, and drowning. The specific pathogens causing lower respiratory infections substantially shifted in this age group compared with the age groups of under 1 year with a much more substantial part played by pneumococcal deaths. Just under 14% of deaths in this age group were from a long list of non-communicable causes, each of which accounted for a relatively small number of deaths.

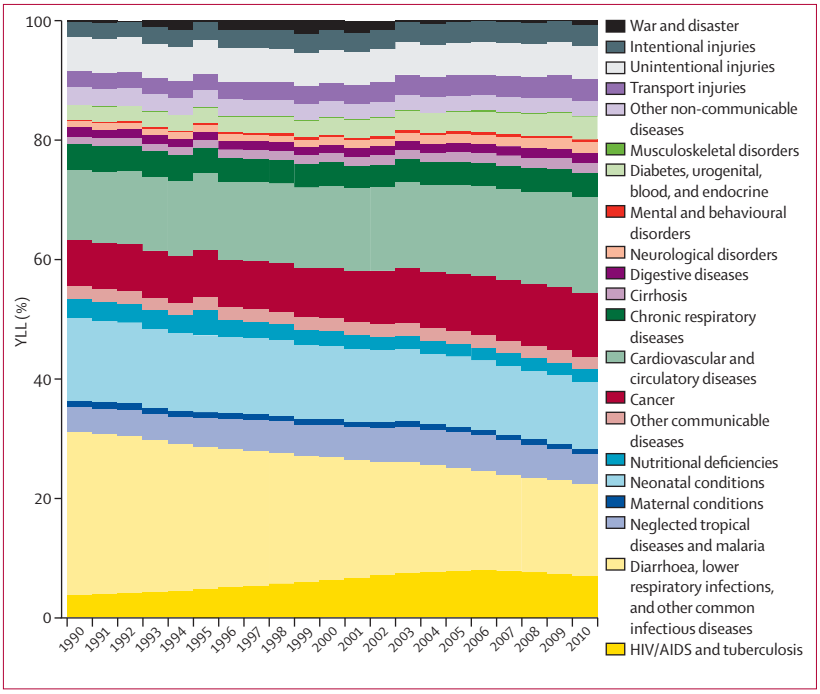

Figure 5: **Percentage of global years of life lost (YLLs) from 1990 to 2010 for all ages and both sexes combined by cause and year**

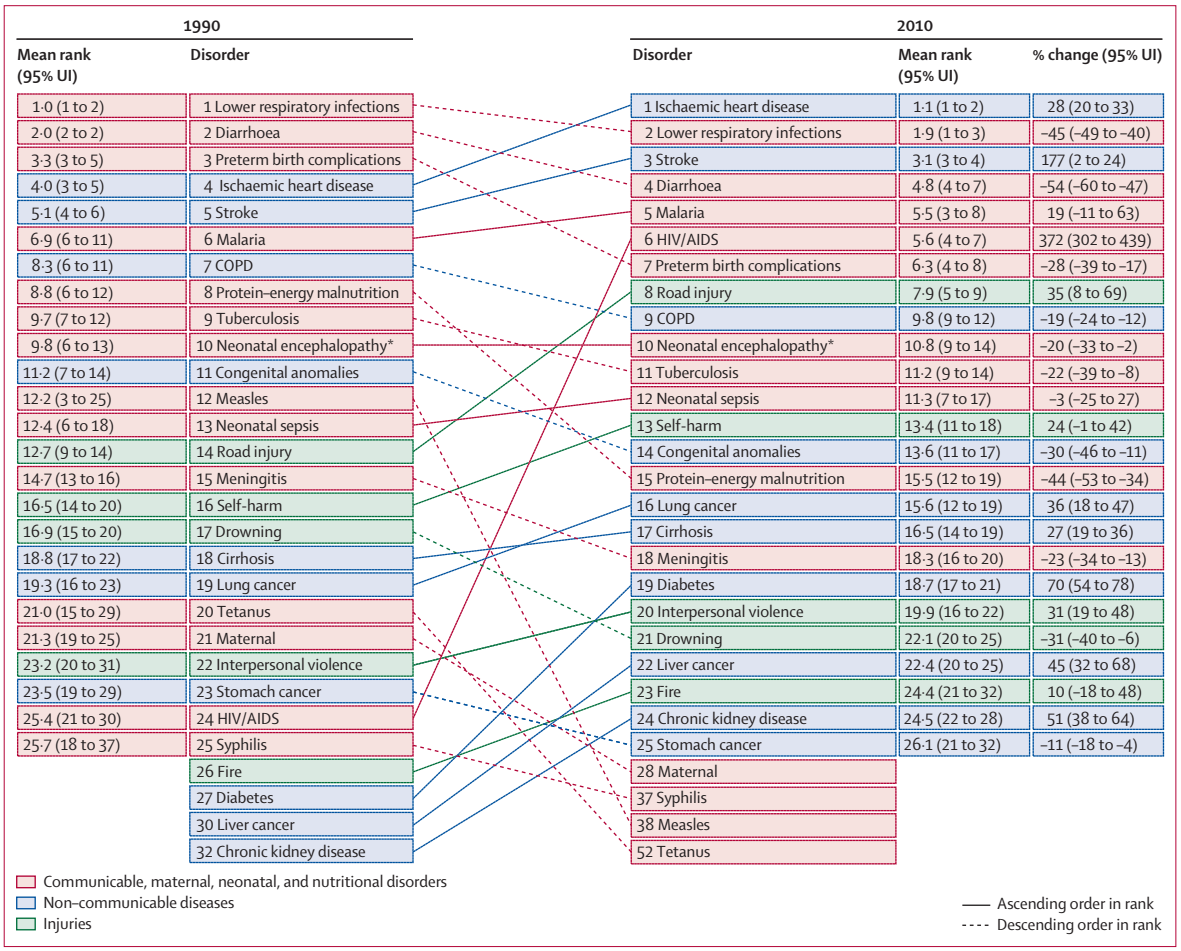

Figure 6: **Global years of life lost (YLLs) ranks with 95% UIs for the top 25 causes in 1990 and 2010, and the percentage change with 95% UIs between 1990 and 2010**

YLLs=years of life lost. UI=uncertainty interval. COPD=chronic obstructive pulmonary disease. *Includes birth asphyxia/trauma. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

Because of the focus of MDG 5 on maternal mortality, the composition of causes of death in women and men of reproductive age is of particular interest. Although deaths related to pregnancy and childbirth have been given special priority in the MDGs, any death in these young adult age groups is a major cause for concern. For women aged 15–49 years, we estimated 3·5 million deaths from all causes in 2010. Figure 3A shows that the leading cause was HIV/AIDS, followed by cardiovascular disease, maternal disorders, suicide, tuberculosis, breast and cervical cancer, and digestive diseases and cirrhosis. The top seven causes accounted for half of the deaths of women in these age groups. Although there is no MDG related specifically to male deaths in the reproductive age groups, disorders targeted by MDG 6 take an important toll on men in the age groups 15–49 years. The leading causes of death for men in this age group, however, were cardiovascular diseases, road traffic injuries, and HIV/AIDS, with other major causes including suicide and interpersonal violence.

Identification of more detailed causes is perhaps more important for priority setting and planning, since interventions are generally cause-specific. Figure 4 shows the top 25 causes of death in the world ranked in 1990 and 2010 with arrows connecting the causes between the two periods. Although the top four causes of death in 1990 remain the top four in 2010, the change in numbers of deaths is noteworthy, with ischaemic heart disease and stroke increasing by 26–35% over the interval, but lower respiratory infections and COPD declining by 7–18%. Lung cancer increased from the 8th cause to the 5th cause in the two decades because of a 48% increase in absolute number of deaths. The largest change was for HIV/AIDS, rising from the 35th cause to the 6th leading cause of death. Diarrhoea, tuberculosis, and malaria all dropped in the global league table. Large increases in absolute number of deaths and their relative importance can be seen for diabetes, liver cancer, falls, and chronic kidney disease. Each of these causes has increased by more than 50% over the two decades.

Whereas the number of deaths from a given cause is a widely understood measure, its utility as a metric for informing public health priorities is limited since it gives

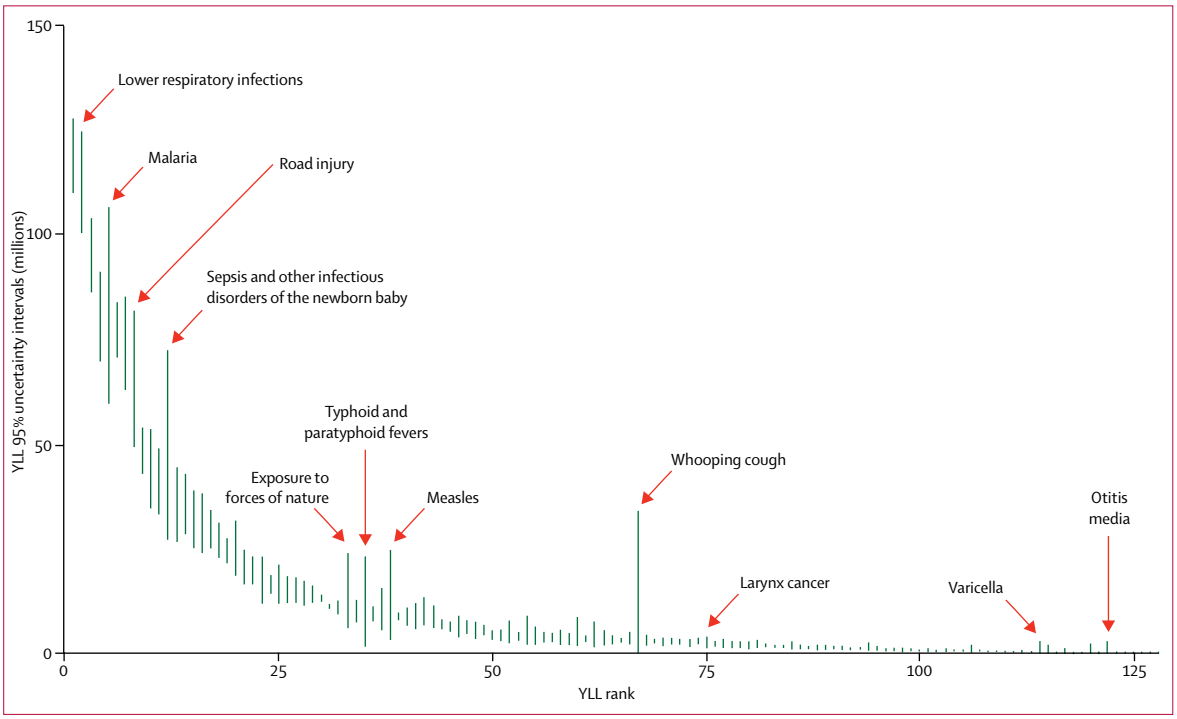

Figure 7: **Global YLLs (millions) with 95 % uncertainty intervals versus rank by cause in 2010**
YLLs=years of life lost. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

equal weight to a death at age 90 years compared, for example, with a death at age 25 years or 5 years. Consequently, the predominance of non-communicable causes might be misleading. In the Global Burden of Disease studies, the computation of years of life lost based on the standard expectation of life at the age of each death quantified the amount of life lost due to premature mortality (YLLs) from each cause. By computing YLLs, we could aggregate information on deaths across all ages to summarise overall patterns of premature mortality. Figure 5 shows the demographic and epidemiological transition, with the change in the composition of YLLs by single year from 1990 to 2010 for both sexes combined. The effect of major mortality shocks such as the Rwanda genocide (1994) and the famine in North Korea (covering most of the 1990s with a peak in 1995), were evident even at the global scale. The fraction of YLLs due to diarrhoea, lower respiratory infections, meningitis, and other common infectious diseases decreased substantially from 27·3% in 1990 to 15·4% in 2010. The percentage due to HIV/TB has increased due to the HIV epidemic. There is a concomitant expansion of YLLs due to non-communicable diseases, particularly cardiovascular diseases. The share of YLLs from non-communicable diseases increased from 33·3% in 1990 to 42·8% in 2010. The appendix (pp 534–725) shows the global YLLs with 95% UIs for 2010 and 1990.

Figure 6 provides a comparison of the top 25 causes of YLLs for both sexes combined, which gives an even more meaningful perspective on priorities for disease control than a simple ranking of causes of death according to the numbers of deaths from each cause. The leading cause of YLLs globally was lower respiratory infections in 1990 and ischaemic heart disease in 2010; in this period, the total number of YLLs from lower respiratory infections decreased by 45% but increased 28% for ischaemic heart disease. More generally, a number of communicable, maternal, neonatal, and nutritional causes declined in both absolute terms and in relative importance as causes of YLLs—most notably measles, tetanus, preterm birth complications, tuberculosis, meningitis, and protein-energy malnutrition. Conversely, several non-communicable diseases increased in importance over the two decades: ischaemic heart disease, stroke, lung cancer, cirrhosis, diabetes, liver cancer, and chronic kidney disease particularly, although COPD and congenital causes have declined in rankings of YLLs. Among injuries, road traffic, self-harm, and interpersonal violence increased substantially in both absolute and relative terms, whereas drowning decreased.

An important innovation in this study was the quantification of uncertainty by cause. UIs varied widely across causes. Figure 7 shows the 95% UIs for YLLs for each cause in 2010, ordered by the mean rank of every cause. The two leading causes—ischaemic heart disease and lower respiratory infections—have nearly overlapping UIs. These two causes are separated by a substantial gap with the next highest ranked cause, stroke. The 12th ranked

cause, neonatal sepsis, has a UI that is nearly three times wider than the 11th ranked cause, COPD. Several causes have much larger UIs than adjacent causes in the rank list. Natural history models for whooping cough, measles, and syphilis have large UIs. This originates from considerable empirical uncertainty on the estimation of incidence and case-fatality rates. By contrast, the HIV/AIDS natural history model developed by UNAIDS has remarkably narrow uncertainty in many countries with large epidemics. Across the causes analysed with CODEm, where the validity of UIs were evaluated using out-of-sample performance, there was also substantial variation across causes reflecting both the coherence of the underlying data, and whether powerful explanatory covariates were identified.

Figure 8 shows the composition of causes of death at the second level of aggregation (21 cause groups) for the 21 GBD regions in 1990 and 2010 for both sexes combined. The regions were ordered by the mean age at death, a crude but informative measure of the demographic and epidemiological transition.[40] At both time periods, there was substantial variation across regions in the relative importance of different causes, with communicable diseases and related causes being much more important in parts of sub-Saharan Africa and parts of Asia than in north Africa, and vascular diseases and cancer predominating in most other regions. By 2010, substantial progress was achieved, even in Africa, in reducing YLLs from communicable, maternal, neonatal, and nutritional causes particularly, although these still accounted for three out of four premature deaths in Africa. The predominance of vascular diseases as a cause of premature mortality in eastern Europe is clear from figure 8, especially compared with other developed regions, where cancer causes as much, if not more, premature death. The impact of the civil violence in Papua New Guinea in 1990 and the 2010 earthquake in Haiti led to notable shifts due to war and disaster. The combination of road injuries, other unintentional injuries, and intentional injuries ranges from a high of 23% of YLLs in 2010 in central Latin America to a low of 6% in the Caribbean, nearly a four-fold variation.

Figure 9 shows the rank for every cause that was either in the global top 25 causes of YLLs in 2010 or appeared in the top 25 causes of YLLs for any region. The appendix (p 726) presents the same information for 1990. Different colours represent different bands of ranks (figure 9). Such heat maps help to visualise important variations in ranking of YLLs across regions. In both 1990 and 2010, a similar number of causes (60 or so) appeared in the rankings, but with very substantial regional variations. At the top of figure 9, causes highest in global rankings of YLLs, such as lower respiratory diseases, ischaemic heart

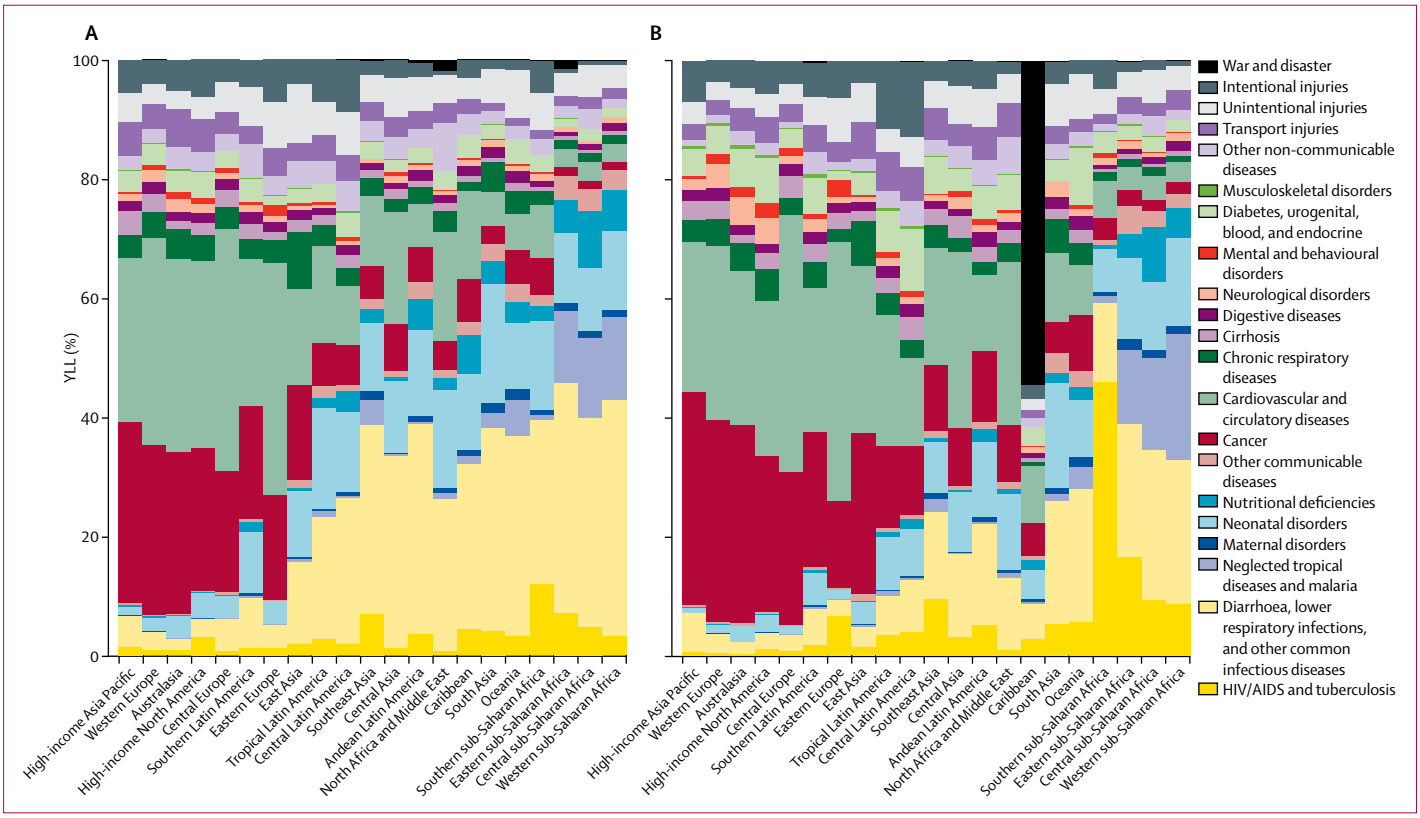

Figure 8: **Percentage of YLLs for all ages and both sexes combined by cause and region in 1990 and 2010**
YLLs=years of life lost. (A) 1990. (B) 2010. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

Ranking Legend 1–10 11–20 21–30 31–50 51–90 91–176

Cause	Global	High-income Asia Pacific	Western Europe	Australasia	High-income North America	Central Europe	Southern Latin America	Eastern Europe	East Asia	Tropical Latin America	Central Latin America	Southeast Asia	Central Asia	Andean Latin America	North Africa and Middle East	Caribbean	South Asia	Oceania	Southern sub-Saharan Africa	Eastern sub-Saharan Africa	Central sub-Saharan Africa	Western sub-Saharan Africa
Ischaemic heart disease	1	2	1	1	1	1	1	1	2	2	2	4	1	3	1	2	4	5	11	17	16	17
Lower respiratory infections	2	5	9	14	11	8	3	9	9	5	4	3	2	1	3	4	1	1	2	3	4	2
Cerebrovascular disease	3	1	2	3	3	2	2	2	1	3	10	1	3	5	2	3	9	8	7	14	13	12
Diarrhoeal diseases	4	57	61	76	54	80	55	44	61	23	12	6	14	8	7	7	3	3	3	4	2	3
Malaria	5	119	120	117	120	119	122	119	119	109	108	19	116	98	41	39	36	4	14	2	1	1
HIV/AIDS	6	65	40	56	26	44	20	3	23	8	11	9	20	9	38	5	13	10	1	1	5	4
Preterm birth complications	7	38	30	17	14	24	6	26	18	6	7	7	5	4	4	6	2	7	6	5	6	7
Road injury	8	10	11	6	5	7	4	5	4	4	3	5	7	2	6	11	11	19	12	11	11	9
Chronic obstructive pulmonary disease	9	12	5	7	4	10	11	13	3	11	14	17	11	23	17	27	5	27	27	29	25	32
Neonatal encephalopathy*	10	63	51	32	41	54	28	29	20	12	13	10	4	7	12	13	7	17	9	9	10	10
Tuberculosis	11	32	73	82	82	40	47	15	29	33	31	2	10	14	34	14	8	6	5	8	8	11
Sepsis	12	71	74	68	62	68	29	55	79	13	16	24	35	11	10	10	6	20	18	7	12	5
Self-harm	13	3	6	5	6	5	5	4	8	15	15	20	9	18	22	21	10	22	16	24	30	50
Congenital anomalies	14	24	23	13	19	20	8	17	11	9	9	12	8	6	5	12	12	14	13	15	7	15
Protein–energy malnutrition	15	67	76	79	73	82	52	84	59	38	19	38	50	19	25	19	16	16	29	6	3	6
Trachea, bronchus, and lung cancers	16	4	3	2	2	3	7	6	5	17	21	15	15	27	14	16	34	45	33	66	54	64
Cirrhosis of the liver	17	9	7	18	9	4	9	7	14	10	8	11	6	12	9	20	15	12	28	23	21	20
Meningitis	18	69	69	67	67	61	39	61	51	36	30	26	23	24	19	18	17	9	19	10	9	8
Diabetes mellitus	19	14	13	10	7	14	10	33	15	7	5	8	17	16	11	9	19	2	8	26	26	24
Interpersonal violence	20	49	50	38	12	31	12	8	31	1	1	16	13	10	20	8	27	24	4	18	17	23
Drowning	21	25	54	34	40	29	26	18	12	19	17	22	12	17	24	31	18	28	26	22	18	29
Liver cancer	22	7	20	28	30	21	33	37	6	34	26	18	29	31	29	30	57	21	41	45	47	30
Fire, heat, and hot substances	23	47	66	63	46	53	36	25	52	51	44	40	30	39	28	33	14	26	23	16	19	13
Chronic kidney diseases	24	13	22	21	16	22	16	31	22	16	6	14	16	13	16	22	25	11	17	32	36	31
Stomach cancer	25	6	15	25	34	13	18	12	7	24	18	33	19	15	27	34	43	31	50	52	56	60
Falls	26	21	21	29	29	17	40	21	16	28	27	29	33	33	32	36	23	42	55	27	31	19
Hypertensive heart disease	27	20	18	40	21	9	17	24	17	14	22	21	21	25	13	17	30	52	15	38	39	46
Maternal disorders	28	85	89	88	78	85	61	75	55	48	41	27	51	26	39	29	24	18	20	13	15	14
Colon and rectum cancers	29	8	4	4	10	6	13	14	13	21	28	31	31	34	33	25	55	50	40	56	63	63
Other cardiovascular and circulatory diseases	30	17	10	19	17	11	15	52	21	20	24	23	26	21	8	23	45	39	30	37	35	39
Breast cancer	31	16	8	8	13	12	14	19	24	22	25	30	28	32	26	28	47	35	38	46	55	59
Cardiomyopathy and myocarditis	32	28	24	26	20	15	19	16	34	18	38	37	22	28	15	32	38	40	22	35	32	38
Exposure to forces of nature	33	122	120	117	120	119	58	119	124	125	90	123	124	123	124	1	125	120	126	127	126	124
Exposure to mechanical forces	34	50	64	53	48	50	38	11	35	50	35	36	18	29	21	41	28	32	10	28	22	40
Typhoid and paratyphoid fevers	35	95	110	102	102	113	49	111	39	62	50	13	119	53	36	69	21	76	21	25	37	27
Leukaemia	36	19	19	15	22	23	22	28	19	29	20	32	27	20	23	38	48	23	49	68	62	66
Syphilis	37	102	101	83	101	87	82	98	74	61	57	48	66	30	47	24	41	41	31	12	14	18
Measles	38	106	105	101	108	105	103	110	103	106	93	34	83	58	94	106	20	54	35	19	38	22
Oesophageal cancer	39	18	28	30	33	39	30	41	10	35	61	52	32	66	58	55	46	61	36	44	57	78
Rheumatic heart disease	40	36	41	49	60	36	34	36	28	41	51	28	24	48	18	48	32	36	37	43	44	49
Epilepsy	41	56	48	43	63	48	57	49	43	44	33	39	25	36	42	46	53	30	25	20	24	16
Asthma	42	42	60	50	57	59	65	50	49	54	46	25	41	62	30	45	26	13	32	40	34	33
Poisonings	43	64	65	42	25	47	68	20	25	95	58	57	34	60	40	85	31	15	43	30	28	43
Encephalitis	44	82	96	103	90	84	109	66	99	75	97	69	48	105	45	96	22	91	46	41	42	42
Cervical cancer	46	34	44	48	45	25	24	34	38	27	23	35	40	22	67	35	52	29	34	31	43	41
Pancreatic cancer	47	11	14	12	18	16	21	22	27	37	39	50	43	47	50	40	73	78	53	83	80	87
Brain and nervous system cancers	48	30	17	20	28	19	37	32	26	26	32	42	38	43	31	44	64	88	54	87	70	104
Non-Hodgkin lymphoma	49	23	26	16	24	33	31	51	37	40	40	43	45	35	46	42	51	47	45	48	58	54
Alzheimer's disease and other dementias	50	26	12	9	8	43	27	53	41	45	66	82	79	76	68	37	81	66	58	80	86	75
Tetanus	52	112	113	113	114	110	118	114	86	108	109	64	121	103	79	59	40	51	104	33	45	25
Acute hepatitis A	54	100	103	104	104	99	108	92	78	101	94	91	91	92	54	104	33	25	98	53	64	44
Alcohol use disorders	55	55	31	47	32	18	41	10	73	25	29	59	39	49	108	54	76	72	61	103	99	117
Kidney and other urinary organ cancers	57	29	25	24	23	27	32	27	36	57	47	75	49	63	57	58	85	80	76	84	85	79
Drug use disorders	58	72	34	22	15	57	69	23	64	71	52	70	37	40	35	52	93	56	24	59	72	69
Prostate cancer	63	31	16	11	27	26	23	42	72	30	34	77	59	42	56	26	100	68	47	75	79	74
Whooping cough	67	99	95	84	87	94	87	95	93	105	65	44	63	37	59	43	37	33	56	21	29	21
Gallbladder and biliary tract cancer	68	15	39	51	58	37	25	59	40	49	45	60	60	44	71	67	63	67	89	113	98	84
Iron-deficiency anaemia	72	77	83	90	81	90	74	89	90	63	43	85	73	38	114	15	75	55	44	54	27	26
Interstitial lung disease and pulmonary sarcoidosis	78	22	47	46	38	70	54	76	71	72	59	100	75	46	65	101	62	81	70	77	77	85
Sickle-cell disorders	80	109	94	107	86	104	105	107	120	80	88	122	117	102	64	51	108	115	100	67	20	28
Malignant melanoma of skin	91	73	38	23	44	45	71	56	77	70	77	106	72	84	103	94	117	48	88	116	113	111
African trypanosomiasis	106	122	120	117	120	119	125	119	124	125	127	123	124	123	124	123	125	120	124	76	23	68

Figure 9: **Regional ranking of leading causes of years of life lost (YLLs), 2010**
Causes in the figure are ordered according to global ranks for causes. The figure shows all causes that are in the 25 leading causes in at least one region. Ranks are also colour-shaded to indicate rank intervals. *Includes birth asphyxia/trauma. An interactive version of this figure is available online at http://healthmetricsandevaluation.org/gbd/visualizations/regional.

disease, and stroke were the top ten causes of premature death in almost all regions in 2010, as were complications of preterm birth in all regions except Europe, high-income Asia Pacific, and east Asia. The massive effect of HIV/AIDS on mortality in most developing regions by 2010 was also clear, with north Africa and Middle East, east Asia, central Asia, and southern Latin America being notable exceptions. Malaria was a leading global cause but a minor cause in most regions outside sub-Saharan Africa and Oceania. Road injury was a remarkably consistent cause of YLLs; its lowest regional ranking is 19th in Oceania and it was in the top five causes in eight regions. All the neonatal causes and tuberculosis were important causes in some developing regions but minor causes in the more epidemiologically and demographically advanced regions. Figure 9 also highlights causes that were not in the top 25 global rankings but were important in selected regions. In some cases, these regional patterns gave a glimpse of future patterns and trends. Suicide was a top ten cause in the eight regions with the most advanced health transition. Other causes that seemed to be strongly related to the epidemiological and demographic transition included colon and rectum cancer, breast cancer, pancreatic cancer, brain cancer, non-Hodgkin lymphoma, Alzheimer's disease, kidney cancer, and prostate cancer. Other diseases had a more focal regional pattern that was not directly related to the broad health transition. More notable examples highlighted by multicoloured rows include: cirrhosis, diabetes, interpersonal violence, sickle-cell disease, whooping cough, poisonings, oesophageal cancer, drug use, gallbladder cancer, malignant melanoma, and African trypanosomiasis. Generally, the distribution of ranks by cause for YLLs was much more heterogeneous than for YLDs.[52] This was true for both time periods and suggests marked regional variation in disease and injury control priorities to improve survival.

Marked variation was noted in cancer rates by site and overall across regions in 2010 (figure 10). Figure 10 shows crude death rates to highlight the mixture of cancers recorded in health systems of every region but to remove the effect of variation in population size across regions. Crude rates are affected both by variation in age-specific and site-specific death rates and by population age-structure. In general, crude cancer death rates were higher in the regions with a more advanced demographic transition. But regions such as high-income Asia Pacific had a substantially different cancer profile from that in western Europe due to breast cancer, liver cancer, and stomach cancer along with a number of smaller cancers. At the other end of the epidemiological spectrum, crude cancer rates in three of the sub-Saharan African regions were the lowest. Central Latin America, tropical Latin America, and Andean Latin America have low cancer rates overall, whereas the Caribbean had higher rates than expected for its demographic transition.

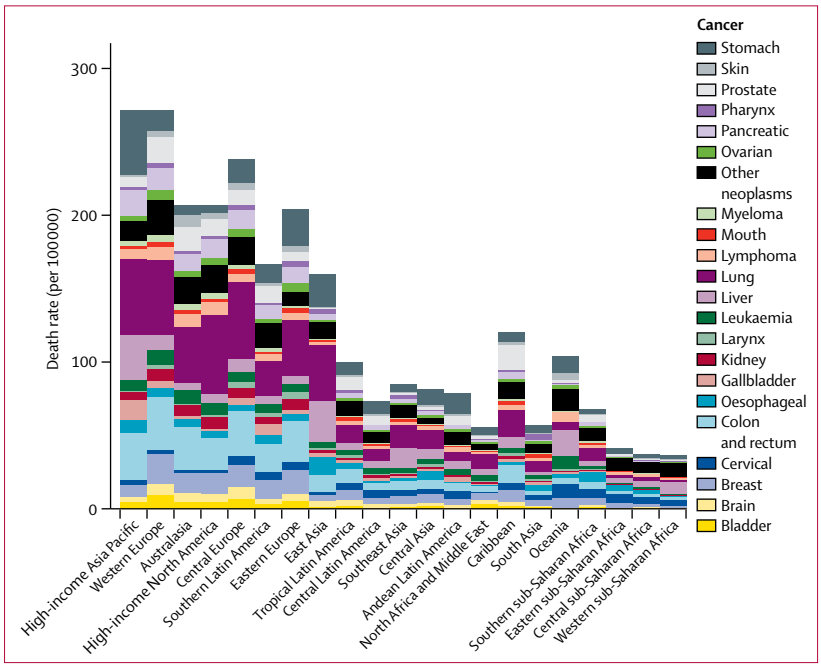

Figure 10: **Cancer death rates in 2010 for all ages and both sexes combined by cause and region**

Discussion

The GBD 2010 is the most comprehensive and systematic analysis of causes of death undertaken to date. The addition of time trends over 1980–2010 and quantification of uncertainty increases both the utility and the methodological rigour of the results. The global health community can now draw on annual estimates of mortality, by age and sex, for 21 regions of the world, for each year from 1980 to 2010, for 235 separate causes, each with 95% UIs to aid interpretation. These estimates of cause of death at the regional level are constructed from separate estimates of cause of death at the country level for 187 countries. No such resource for policy makers, donors, or scholars currently exists. At the most aggregate level, we have documented great changes in cause of death structure in regions such as central Latin America and tropical Latin America. We have also identified regions, such as eastern Europe and central Asia, where mortality has increased profoundly over the past two decades but the cause of death structure has not changed dramatically, at least for leading causes.

The shifting pattern of the number of deaths by cause across time, regions, and age groups is consistent with the three key drivers of change: rising total population, rising average age of the world's population, and the broad epidemiological transition. For communicable, maternal, neonatal, and nutritional causes, the increase expected because of population growth alone is reversed by population ageing and decreases in age-sex-specific death rates. By contrast, both population growth and ageing are driving up the number of deaths from non-communicable diseases and injuries more than the decreases expected

because of lower age and sex-specific rates. Overall, these factors are leading to a shift from a pattern dominated by the main infectious disease killers of children (such as lower respiratory infections, diarrhoea, malaria, and meningitis), and tuberculosis and maternal causes in younger adults, to one dominated by the non-communicable causes over age 40 years. Quite different regional stories are overlaid on this broad pattern. Injuries have very distinct regional patterns, with violent death being much more common in selected regions. The HIV epidemic has had massive effects in eastern and southern sub-Saharan Africa. Diabetes has a major effect in central Latin America, the Caribbean, north Africa the Middle-East, and Oceania. Theories of the epidemiological transition need to be nuanced to capture these distinct trends and patterns that suggest different health trajectories in different regions in the coming decades. Our findings are also different from many published studies on causes of death in some age groups or for specific causes; these differences warrant careful discussion.

The HIV epidemic has greatly changed the pattern of causes of death between 1990 and 2010 in eastern and southern sub-Saharan Africa. We estimated that, in 2010, 1·47 million deaths were due to HIV/AIDS compared with UNAIDS estimates of 1·77 million, which is a 21% difference at the global level. For specific countries and regions, the differences are much larger. We used UNAIDS estimates as the input to CoDCorrect for most countries, so the difference is almost entirely due to the juxtaposition of evidence on levels of all-cause mortality and natural history model estimates of HIV/AIDS deaths. We believe that this is an important strength of the burden of disease approach. Some differences are also due to the data from Thailand, where in the 2012 UNAIDS assessment mortality doubled compared with their 2010 assessment. Even the 2010 UNAIDS assessment was twice the magnitude recorded in two studies of national verbal autopsy and vital registration data.[66,67] We chose to use the 2010 UNAIDS revision estimates for Thailand because of the implausible nature of the 2012 revision estimates. Nigeria is another example of a country whose estimates contribute to a substantial part of the differences between global data from UNAIDS and GBD 2010. Since Nigeria is a country with a large population, a major HIV/AIDS epidemic, and poor data quality, when we fit our HIV/AIDS estimates for Nigeria into the country's all-cause mortality levels our estimates are much lower (27·9% in 2010) than those of UNAIDS and this large difference in death is reflected at the global level. The uncertainty distributions for UNAIDS estimates of mortality in some countries in sub-Saharan Africa are implausibly narrow; for example, at the peak of the epidemic in Malawi, the UI for deaths at all ages provided by UNAIDS varied by plus 8·5% or minus 8·1%. Our UIs based on the UNAIDS figures were also implausibly narrow. Improved estimation of mortality from HIV/AIDS including uncertainty in the future will come both from continued progress in the estimation of the timecourse of the HIV epidemic by UNAIDS and from further data on the levels of adult mortality in some key countries such as Nigeria.

On the basis of a single-cause analysis, Murray and colleagues[25] reported 1·24 million malaria deaths in 2010 of which 42% were in individuals older than 5 years. These estimates had very large UIs; for example, the number of deaths in those older than 5 years in sub-Saharan Africa was estimated to range from 307 000 to 658 000. Large uncertainty in the results reflected both the sparse data available on causes of death in adults and the large variation in results across different models included in the final ensemble model. In these GBD 2010 results, where the sum of cause-specific estimates must equal the number of deaths from the demographic analysis for each country-age-sex-year, the number of malaria deaths in 2010 was estimated to be about 5% less or about 1·17 million. For deaths in children younger than 5 years, the change was from 714 000 to 676 000. For deaths in individuals older than 5 years, the change was from 524 000 to 494 000. Our finding of substantial deaths due to malaria in populations older than 5 years is driven by the evidence from verbal autopsy studies in endemic areas.[25] Validation studies suggest that verbal autopsy studies overestimate adult deaths at low malaria cause fractions and underestimate adult malaria deaths when malaria deaths are common.[68] The findings of adult deaths from malaria are consistent with data of hospital discharge and death in endemic areas but remain controversial.[69–72] Our UI for global deaths in individuals older than 5 years from malaria was 365 356 to 643 977, partly depicting the uncertainty in the underlying data sources.

An innovative dimension of the GBD 2010 has been the addition of estimates of deaths due to different diarrhoea and lower respiratory infection pathogens. These are important both for the prioritisation of existing treatments, such as rotavirus or pneumococcal vaccines, and for the development of future technologies. Making sense of the data by aetiology is extremely challenging. For diarrhoea, many pathogens can be cultured from the stool of individuals without diarrhoea. Studies such as the Global Enterics Multi-Center Study (GEMS)[73] are trying to estimate relative risks of diarrhoea in the presence of different pathogens. In the available observational data that do not use this relative risk approach, the relation between the prevalence of a given pathogen and the number of pathogens tested is strong. Studies testing only one pathogen effectively report higher fractions due to a pathogen than do studies that test for multiple pathogens. This finding is probably caused by the frequency of various pathogens in the same stool sample and rules for allocating shares of diarrhoea to pathogens such that the sum of the pathogen cause fractions total to 100%. In our analysis, we adjusted study results to be equivalent to studies reporting two to eight pathogens. Because of both the huge heterogeneity of results and the variation in the number of

pathogens tested across studies, great caution should be used in interpreting our findings on the diarrhoea aetiologies. When large multicentre studies such as GEMS publish their results, their findings will be an important addition to this analysis; future revisions of the GBD should make use of these results as they become available. Nevertheless, our results are notably different from widely cited findings. For example, we reported 173 000 deaths due to rotavirus in children younger than 5 years and 78 000 deaths in individuals older than 5 years in 2010; these findings contrast with claims from WHO of 453 000 rotavirus deaths in children younger than 5 years alone in 2008.[74] Higher numbers were probably reported by WHO for three reasons: higher all-cause global deaths in children younger than 5 years than currently estimated by UNICEF or the GBD 2010; a much higher fraction of deaths in children younger than 5 years attributed at the time to diarrhoea; and a higher fraction of diarrhoea attributed to rotavirus. Because rotavirus remains an important cause of death in many countries, the GBD estimates by country, when released, will be an important method to assist in understanding where its burden is greatest.

For respiratory pathogens, even greater challenges exist. In many observational studies, no pathogen is identified in a substantial fraction of cases. Even in severe cases that lead to hospital admission, the case-fatality rate is likely to vary substantially by pathogen, which confounds the analysis. The substantial differences in our results from published assessments by O'Brien and colleagues[35] for pneumococcal lower respiratory infections, Nair and colleagues[75] for RSV, and Watt and colleagues[76] for Hib deserve exploration. Our findings of 168 000 deaths due to pneumococcal lower respiratory infection in children younger than 5 years in 2010 and 381 000 in 1990 contrast sharply with the 826 000 for the year 2000 published by O'Brien and colleagues.[35] in 2009, these investigators used an estimate of 10·6 million deaths in children younger than 5 years from all causes for the year 2000, which contrasts with our estimate of 9·4 million and UNICEF's estimate of 9·6 million. They used a higher estimated fraction of deaths in children younger than 5 years due to lower respiratory infections than in our study, 27% and 18%, respectively. The fraction of lower respiratory deaths in children younger than 5 years due to pneumococcal pneumonia was 35·8% (UI 16·0–50·9) in 2000 compared with 19·8% (16·1–24·8) in the GBD 2010 for 2010. The 95% UIs for these cause fractions substantially overlap. Differences in the mean estimate result largely from the exclusive use by O'Brien and colleagues of the results of four vaccine trials in the Gambia, the Philippines, the USA, and South Africa to estimate an average fraction of pneumonia in children younger than 5 years. Although they reviewed the literature, they chose not to use the published observational studies. These observational data suggest substantial variation across regions; for example, pneumococcus might be less common in south Asia. We used both the trials and observational data to generate different breakdowns by pathogen by region giving extra weight to the trials; our findings, however, still showed variation by region and age. For RSV lower respiratory infections, our findings of 234 000 deaths in children younger than 5 years in 2010 and 520 000 in 1990 are notably higher than the 66 000 to 199 000 deaths for the year 2005 reported by Nair and colleagues[75] in 2010. They reviewed the published studies on RSV but chose, on the basis of expert opinion, to assume no RSV deaths in individuals older than 2 years;[75] the scientific literature, however, records deaths in those older than 2 years.[77,78] Data on hospital admission in the USA, for example, suggests substantial burden of severe RSV at least in the ages 3–5 years. Other investigators[79,80] argue that RSV is an important and often missed pathogen causing severe lower respiratory infections in elderly people. Studies, however, vary markedly in their sampling, culturing, and identification protocols, which might also account for some heterogeneity. Most studies show high fractions of neonatal lower respiratory deaths due to RSV, so the extent to which RSV is a major cause of post-neonatal lower respiratory deaths needs the most attention. For deaths due to Hib lower respiratory infection, Watt and colleagues[76] published in 2009 for the year 2000, an estimate of 292 000 deaths that compares well with our finding of 184 000 (95% UI 154 053–219 456) in 2010 and 447 000 (385 717–506 594) in 1990. The similarity of the result, however, is somewhat misleading. They used a much higher estimate of all-cause under-5 mortality and a higher cause fraction due to lower respiratory infection than we used. In other words, we estimated a larger fraction of lower respiratory infection deaths in children younger than 5 years due to Hib than did Watt and colleagues. The main reason for this difference is that Watt and colleagues assumed that Hib in individuals older than 2 years does not cause death; the available observational data,[81–84] however, show Hib mortality at all ages. For example, results from the study in Japan[84] showed severe cases of hospital-acquired and community-acquired pneumonia related to Hib, the differences in these assessments for all the respiratory pathogens is even more striking. New multicentre studies such as PERCH[85] will hopefully provide much needed data to strengthen the analysis of pathogens by region.

We estimate that in 2010 1·20 million deaths were due to tuberculosis, about 14% more than the WHO estimate of 1·05 million (2011 WHO TB Report). Our analysis and that of WHO use fundamentally different methods but do not yield, at the aggregate level, substantially different conclusions. The key difference lies in how the case-detection rate in every country was estimated; WHO used locally informed expert consultation to assess both under-diagnosis and under-reporting whereas we used a statistical model to try and estimate the case detection rate. Our models also captured more of the temporal and spatial correlation structure in the cause of death data yielding quite different estimates than did the WHO

where data were strong (eg, Japan and Thailand). These differences result in important variations between our estimates and those from WHO at the country and regional levels that deserve further investigation. Despite these variations, for some countries, such as Ecuador, our estimates, WHO estimates, and the cause of death data were in close alignment. Assessments at the global and regional level point to substantial continued and sustained progress in reducing tuberculosis mortality. Our higher levels of mortality for tuberculosis in 2010 suggest that tuberculosis should remain a major priority.

Deaths due to maternal causes have been reported in various studies[86,87] in the peer-reviewed scientific literature and UN reports.[88] These studies, however, focused on the maternal mortality ratio. ICD 10 rules recommend that pregnancy-related deaths due to HIV should be included in the computation of the maternal mortality ratio but reported in cause of death tabulations for HIV. The GBD 2010 follows this convention so that our 255 000 maternal deaths in 2010 do not include 18 970 HIV-related deaths in pregnancy included in the HIV totals. We also revised the method used to estimate the fraction of maternal deaths related to HIV/AIDS in this study compared with Lozano and colleagues.[23] In GBD 2010, our estimates of the fraction of maternal deaths related to HIV/AIDS come from a review and statistical analysis of available data that provide a detailed breakdown of maternal deaths. Further, the deaths due to maternal causes reported here are after the application of the CoDCorrect algorithm, which is a strength of the comprehensive burden of disease approach. The global number of deaths due to maternal causes was reduced by 9·8% through the application of CoDCorrect. The revised approach for maternal mortality presented here also highlights the major causes of maternal death. The largest specific cause of maternal death is maternal haemorrhage accounting for 23% of deaths in 2010, followed by hypertensive disorders causing 18%, abortion causing 15%, sepsis causing 9%, and obstructed labour causing 4%. These results contrast with various estimates reported by WHO—one estimate for 2005, which is based on 35 197 deaths reported in various published studies[89] and one largely based on vital registration data for 2008.[16] The 2005 WHO report estimated that abortion caused only 8% of maternal deaths but 14% in the 2008 study.[16] There are also substantial differences for other maternal causes as well. Our findings are based on a larger set of published studies, including reports from 18 countries such as India, South Africa, Bangladesh, Ghana, and Pakistan, which contribute 22 943 additional maternal deaths on the detailed causes of maternal death.

For deaths in children younger than 5 years, our results differ from those published by CHERG[20] for the same year in several key ways: CHERG estimated 1·40 million deaths due to lower respiratory infection compared with 847 000 in our study; CHERG estimated 801 000 for diarrhoeal diseases versus 666 000 in the GBD 2010; for malaria CHERG estimated 564 000 versus 676 000 here. Within the neonatal causes, there are also striking differences in the composition of specific neonatal causes, with CHERG estimating much higher fractions due to preterm birth complications and lower fractions due to sepsis and other disorders. In exploring these differences, it is crucial to distinguish between the neonatal age group (under 28 days) and causes arising during the neonatal period that can cause mortality both under 28 days and in the post-neonatal period and less commonly over age 1 year. Understanding the source of the differences for neonatal causes, however, is challenging. Differences must arise from any or all of the following: the datasets used, the adjustments to the data, and the modelling strategies. In their analysis of post-neonatal child mortality (1–59 months), CHERG reported using vital registration data for 578 country-years between 1998 and 2009, whereas we used 1125 country-years for that period. They used 113 study years between 1980 and 2008; by contrast, we used 294 years. CHERG used a reduced number of studies because of their decision to use only studies that report on six major causes. The largest differences and the ones likely to explain the differing results lie in the modelling strategy. For a single cause such as diarrhoeal diseases or lower respiratory infections, we developed one ensemble model using all the data. The one ensemble model included component models with a wide variety of functional forms but all included age group fixed effects. CHERG tested and developed four different models with no relation between them: for under-5 mortality rates (UFMR) lower than 35 for babies younger than 1 month, for UFMR higher than 35 for babies younger than 1 month, for UFMR lower than 35 for children aged 1–59 months, and for UFMR higher than 35 for children aged 1–59 months. The relations between covariates in these different models were estimated as completely independent. Covariate selection was done for every cause of death independently for each of the four models. They used multinomial logistic models to make estimates for six causes of death simultaneously, a method found to perform worse than modelling causes individually and then scaling to all-cause mortality (appendix pp 146–148). Their model structure does not allow for spatial or temporal patterns in the residuals, probably substantially reducing model performance.[22] Model performance is difficult to assess and compare with ours: they reported undertaking a cross-validation study but no metrics of model performance were reported such as the coverage of their UIs or a measure of prediction error. Further, in their cross-validation study they left out 10% of the data at random; as shown in previous studies,[23] this is the easiest task for prediction. A much harder task, which was used in the GBD 2010, is to leave out long sequences or all data for some countries and see how well the models perform. Additionally, leaving out data for one cause without also dropping it for the other causes in that country-year makes for an even simpler task in a multinomial logistic model

such as the one CHERG used. The high levels of mortality for lower respiratory infections might be related to the bias in physician diagnosis of verbal autopsies, which was demonstrated in a rigorous validation study.[68] Although this study[68] used physician-certified verbal autopsy data on lower respiratory infections, by separating the data into four components and not including country random effects in their models, the bias towards higher such infections in verbal autopsy studies might have had a larger effect on their estimation procedure. Finally, the CHERG estimation strategy uses multinomial models for a subset of models and then adds on estimates for selected causes in selected countries such as HIV/AIDS, measles, tetanus, and malaria. The differential treatment of some causes and not others in the modelling strategy might also have caused distortions in the results. Interestingly, given the substantial difference in modelling approaches, the results for 2010 between the two approaches were actually surprisingly close.

The health-related MDGs place special priority on reducing under-5 mortality, maternal mortality, and deaths from HIV, tuberculosis, and malaria. These causes collectively accounted for 42·4% of YLLs in 2010. Even though the computation of YLLs heavily weights deaths in children younger than 5 years, more than half (57·6%) of global YLLs in 2010 were due to non-MDG diseases and injuries. Important global causes that are not included in the MDGs include ischaemic heart disease, stroke, COPD, road traffic injuries, and self-harm. The predominance of these causes in YLL rankings is not merely a volume issue: many of those who die from these causes do so at young adult ages. A more holistic view of preventable mortality within the MDG platform would argue that these causes ought to be included in any evidence-based framework for reducing avoidable deaths. Examination of the trends from 1990 to 2010 indicated that the MDG-related YLLs were declining at 2·0% per year, whereas the non-MDG related YLLs were increasing at 0·8% per year. Population ageing and the substantial if incomplete progress in reducing age-specific death rates from the MDG related causes all suggest that these trends will continue. Indeed, if they do, then non-MDG related causes are likely to account for more than two-thirds (67·6%) of YLLs by 2025. These findings highlight the importance of looking more critically and comprehensively at what are the leading causes of death and YLLs worldwide, and how these are changing. Our analyses, for the first time, allow such comparative assessments and are important inputs into discussions about goals and targets for the post-MDG era.[90] The rapid and global rise in premature death from leading non-communicable diseases argues strongly for inclusion of these disorders, and their principal causes, in this agenda, particularly in view of their close relation to poverty reduction goals.[91–96] It also stresses the need to understand the effective and affordable options for prevention of non-communicable diseases and injuries and treatment including both medical and surgical interventions.[97]

Our study suggests that the number of deaths where chronic kidney disease is the ICD underlying cause of death increased by 82% from 1990 to 2010. In addition to these deaths, a reduced glomerular filtration rate (GFR) has been associated with an increased risk of death.[98] Even chronic kidney disease stages II–IV are associated with increased risk of death. The directly coded deaths due to chronic kidney disease that we estimated probably capture only those deaths due to end-stage renal disease. Other diseases such as diabetes are also associated with an increased risk of death from other causes. For diabetes, the risk factor analysis[99] provides an assessment of all mortality associated with hyperglycaemia. This number is substantially larger than the number of deaths directly coded to diabetes estimated here.

Those who study the health effects of war will be surprised by the 17 670 deaths related to direct conflict estimated for 2010. This number should be interpreted with great caution. First, in the ICD cause list, only direct deaths are assigned to this cause; 17 670 is not the total number of deaths related to conflict, which would include indirect deaths mediated through various mechanisms such as the destruction of health-care infrastructure.[100] Second, the number of direct deaths varies substantially from year to year. During 1990–2010, direct deaths peaked at 496 400 in 1994 with a low in 2001 of 14 700 and 17 700 in 2010. In 2011, because of the conflict in Libya, for example, direct deaths were likely to have been much higher, closer to 61 000. For episodic events such as wars or natural disasters, it is important to consider the burden of disease over longer periods of time to fully appreciate their effect on human populations.

For the first time in the GBD enterprise, we included deaths that were mainly related to hepatitis B, hepatitis C, alcohol, and other causes as disaggregated causes for cirrhosis and liver cancer. These categorical breakdowns are not counterfactual assessments but rather an attempt to assign deaths to the primary or dominant cause. Interactions exist between hepatitis and alcohol consumption, such that assessment of these conditions as a risk factor would give different results. Nevertheless, this categorical attribution provides a useful assessment of the magnitude of direct burden, particularly for guiding intervention priorities. The total number of deaths due to hepatitis B in 2010 was estimated to be 786 000 and those due to hepatitis C 499 000. If all deaths related to these diseases were directly counted in the main GBD 2010 cause list, hepatitis B would be the 15th ranked cause of death and hepatitis C would be the 25th ranked cause of death. Cirrhosis rates vary greatly across countries, with Egypt having the highest level related to an iatrogenic epidemic of hepatitis C that began as early as the 1920s.[101] Some regions have high rates such as central Asia, Oceania, eastern and western sub-Saharan Africa, eastern Europe, and central Latin America. Not all this regional and country variation can be explained by hepatitis B, hepatitis C, or total alcohol consumption. For

example, high rates in eastern Europe might be related to the content rather than volume of alcohol consumed. Theories on this distinction include hepatotoxic alcohol constituents in homemade poor quality alcohol, which is common in these regions.[102] Given that much of the burden of cirrhosis can be preventable, its substantial global mortality deserves more policy attention.

The much more detailed categories of causes of death for injuries in the GBD 2010 provide some important insights into the global epidemic of road injuries. The number of deaths increased from 908 000 in 1990 to 1·329 million in 2010. These results are similar to the 1·237 million reported for 2007 by WHO.[103] The composition of this increase in road injuries, however, has differed by sub-cause. Road deaths to pedestrians were the major cause, rising from 284 000 in 1990 to 461 000 in 2010. Road deaths of occupants in motorised vehicles with three or more wheels and road deaths of riders of motorised vehicles with two wheels each have also increased by about 200 000 in the past two decades. Regional detail shows road deaths in east Asia, south Asia, and eastern and western sub-Saharan Africa rapidly escalating over the past two decades, whereas in high-income areas with a history of road safety programmes such as western Europe and high-income North America, road deaths have decreased.

Violence as a cause of death is one of the most heterogeneous across different regions. Crude death rates for violence are lowest in high-income Asia Pacific at one per 100 000. The rate in 2010 in high-income North America dominated by the USA of seven per 100 000 was nearly seven times higher than high-income Asia Pacific, western Europe, or Australasia. But in tropical Latin America, the rates are substantially greater still, at 30 per 100 000, and even higher in central Latin America and southern sub-Saharan Africa, at 33 per 100 000. The huge variation in violence raises important questions about the origins and sociopolitical context of violence, the drivers of change in violence-related mortality, and the effectiveness of public health strategies in reducing deaths from violence. In men from tropical Latin America, violence is the number one cause of YLLs. In 2010, men in the 20–24 years age group alone had 653 600 YLLs, three quarters the size of the 824 000 YLLs in men in high-income North America of all ages combined.

An important dimension to the GBD is the requirement that estimates of causes of death sum to estimates of all-cause mortality. The discipline of requiring this internal consistency has been a hallmark of burden of disease analysis since the GBD 1990. As quantified in the appendix (p 144) the effect is to reduce the number of deaths estimated for many causes compared with single-cause analyses. The correction factor is an indication of inconsistency at the country-age-sex-year level between demographic analysis and the cause-specific analyses. We believe that for causes for which the magnitude of these corrections is comparatively large, future research should be targeted to try to build a better understanding of the strengths and weaknesses of the various data sources, whether epidemiological or demographic. In some sense, the CoDCorrect ratios can help direct attention to settings in which the data are the most inconsistent and our knowledge the most uncertain. The substantial difference between single-cause-model estimates and those presented here raises questions about the value of publishing single-cause assessments. Some organisations such as WHO have in recent years been producing both types of assessments: WHO with CHERG produces estimates for 16 major causes of child death but also publishes single-cause estimates for tuberculosis, HIV/AIDS, malaria, maternal mortality, and other causes. Should leading scientific journals continue to review and publish studies on single-causes of death? Due consideration of the value of single-cause models to bring attention to neglected issues or stimulate innovation in methods or new data collection will need to be balanced against the greater robustness of more comprehensive assessments such as those presented here.

A study of this size and scope has many limitations. The ambition to estimate mortality from 235 causes with uncertainty for 187 countries over time from 1980 to 2010 means that many choices about data sources, quality adjustments to data, and modelling strategies had to be made. We highlight some key limitations. First, data on cause of death, even in settings with medical certification, might not always accurately capture the underlying cause of death. Results from autopsy studies[104–106] have shown that medically certified causes of death might be incorrect. Second, our approach to garbage code redistribution, although an improvement over past efforts, could benefit strongly from more empirical information on misclassification obtained in places where gold standard cause of death assignment is possible. We were not able to develop uncertainty distributions around garbage code redistribution algorithms; to the extent that this is poorly known, our UIs for some causes might be underestimated. Third, we made extensive use of verbal autopsy data, especially in low-income settings. Verbal autopsy validation studies[68] suggest that verbal autopsy is accurate for some causes such as breast cancer, drowning, or road injury, but less accurate for other causes. Verbal autopsy performance for some key causes of child death such as lower respiratory infections is particularly poor. Much could be learned about causes of death in countries where death certification is poor through the more widespread testing and application of recent advances in verbal autopsy methods, which greatly reduce heterogeneity in diagnostic practices across populations in which verbal autopsy is currently used.[107] Fourth, for some causes of death such as kidney cancer, poisonings, or paralytic ileus, only weak covariates have been identified that explain the spatial or temporal variation in the cause. Inevitably, model estimates for these causes will have wide UIs. The use of negative binomial models and fixed proportion models where data are extremely weak is another area for

which better data and improved methods could strengthen the overall findings. Fifth, where natural history models have been used, their validation is extremely difficult at present. Natural history models are in principle used when concerns exist that data on direct cause of death are potentially biased. Improvements in data on cause of death for some causes such as HIV/AIDS might allow in the future opportunities to validate natural history models in selected countries. Where natural history models have been used, these approaches potentially will tend to yield higher estimates than those using more empirical strategies such as CODEm. Sixth, our use of CODEm for most major causes of death means that our UIs have in most cases been shown to be valid, but for causes where we have had to use other methods such as negative binomial, fixed proportion, or natural history models, the UIs have not been independently validated. Seventh, CODEm can be improved in the future by including an even broader set of model families. Ultimately, the greatest limitation is the availability of data on cause of death itself. Finally, in cases where expert opinion and the available data diverge, we tended to follow the available data. Examples of this practice include estimating deaths from malaria in individuals older than 5 years or deaths from Hib in those older than 2 years. Subsequent more detailed studies might affirm that expert opinion was correct and the available data substantially biased. Nevertheless, we believe that to follow the balance of the available data that meet our quality criteria is important.

Improving data collection on cause of death in the future is the most direct and obvious pathway to improved estimation of global, regional, and national causes of death with narrower UIs. Improved verbal autopsy methods[108–111] mean that it might soon be feasible to apply them routinely to generate comparable data on cause of death cost effectively in populations in which we are still substantially ignorant about the leading causes of death. Opportunities for strengthening death registration, cause of death certification, and the more widespread use of verbal autopsy exist. Some countries have civil registration systems that capture less than 70% of deaths; the priority in such cases is to improve certification and coding of cause of death. Other countries such as Saudi Arabia have functioning civil registration run by Ministries of the Interior that are not fully used by Ministries of Health. Collectively, the global health community would benefit enormously by placing much greater priority on strengthening vital registration systems to improve measurement of cause of death. This is now the key focus of the Health Metrics Network and it is reasonable to expect that substantial progress can be made with appropriate leadership, attention, and collaboration among global development partners.[112]

In the GBD 2010, a substantially new set of analytical approaches and methods have been developed and applied. These methods range from improved diagnostic redistribution methods to CODEm and CoDCorrect, drawing on information for almost a billion deaths and time series for hundreds of covariates that affect mortality. This is a massive endeavour, but, with appropriate investment and leadership, updating results as new data on causes of death or alternative covariates become available will be much more feasible than hitherto. Rather than huge periodic revisions of the GBD every decade, it is now feasible to conduct annual updates so that the consumers of health intelligence have the most recent and comprehensive information on comparative causes of disease burden available where and when it is required to help guide public health decision making. Public health priorities everywhere are changing, or soon will be, as large and avoidable causes of disease burden become more common with development. To not have strategically important and comparable health information available and used to inform the new health dialogue and disease control priorities, as we have shown here it can be, would be a massive missed opportunity for global health.

Contributors

CJLM, ADL, and RL prepared the first draft. RL, MN, KF, SL, KS, ADL, and CJLM finalised the draft on the basis of comments from other authors and reviewer feedback. ADL and CJLM conceived the study and provided overall guidance. All other authors developed cause-specific models, reviewed results, provided guidance on the selection of key covariates, and reviewed the report.

Conflicts of interest

E R Dorsey has received consulting fees from Medtronic and Lundbeck and research support from Lundbeck and Prana Biotechnology. M Ezzati chaired a session and gave a talk at the World Cardiology Congress (WCC), with travel cost reimbursed by the World Heart Federation. At the WCC, he also gave a talk at a session organised by PepsiCo with no financial or other renumeration. P J Hotez reports holding several positions: Dean, National School of Tropical Medicine, Baylor College of Medicine; Director, Sabin Vaccine Institute Texas Children's Hospital Center for Vaccine Development; and President, Sabin Vaccine Institute. He also is an inventor on several patents: 5,527,937 "Hookworm Anticoagulant"; 5,753,787 "Nucleic Acids for Ancylostoma Secreted Proteins"; 7,303,752 B2 "Hookworm vaccine"; 12/492,734 "Human Hookworm Vaccine"; 61/077,256 "Multivalent Anthelminthic Vaccine"; and PCT-20100701/0.20.5.18 "Malaria Transmission blocking vaccine". G A Mensah is a former employee of PepsiCo. F Perez-Ruiz was an adviser for Ardea, Menarini, Novartis, and Metabolex; was a member of the Speaker's Bureau for Menarini, Novartis; an adviser for educational issues for Savient; led an investigation grants for the Spanish Health Ministry, Hospital de Cruces Rheumatology Association; and was principal investigator in clinical trials for Ardea.

Acknowledgments

We would like to thank the countless individuals who have contributed to the Global Burden of Disease 2010 Study in various capacities. We would also like to specifically acknowledge the important contribution to this work from multiple staff members of the WHO. We also wish to thank the following organisations that hosted consultations during the final stages of the analytic process, providing valuable feedback about the results and the data to improve the study's findings overall: Pan American Health Organisation; Eastern Mediterranean Regional Office of WHO; UNAIDS; Ministry of Health, Brazil; China Centers for Disease Control; and the University of Zambia. We would like to thank Cynthia Boschi Pinto for her input into the analyses and estimates. Finally, we would like to acknowledge the extensive support from all staff members at the Institute for Health Metrics and Evaluation and specifically thank: James Bullard, Andrew Ernst, and Serkan Yalcin for their tireless support of the computational infrastructure required to produce the results; Linda A Ettinger for her expert administrative support and facilitating communication and coordination among the authors; Peter Speyer, Abigail McLain, Katherine Leach-Kemon, and Eden Stork for their

persistent and invaluable work to gain access to and catalogue as much data as possible to inform the estimates; and Erin C Mullany for her systematic efforts in organising drafts of papers, formatting correspondence with expert groups, and preparing the final manuscript. The following individuals would like to acknowledge various forms of institutional support. J P Abraham acknowledges the World Bank Global Road Safety Facility and Department of Global Health & Population, Harvard School of Public Health, and the WHO Violence and Injury Prevention. K Bhalla was supported by the World Bank Global Road Safety Facility for researcher salaries, to pay for many small projects in Africa to digitise secondary data sources, and supporting several gatherings of the injury expert group over the past 6 years. B Bikbov acknowledges the Moscow State University of Medicine and Dentistry, Moscow, Russia; Academician V I Shumakov Federal Research Centre of Transplantology and Artificial Organs, Moscow, Russia; and International Society of Nephrology. G L Birbeck has received research funding from the US NIH, the Dana Foundation, and the Doris Duke Charitable Foundation; she has also received travel grants from the WHO for related work. H Chen acknowledges his participation in this study was in part supported by the intramural research program of the NIH, the National Institute of Environmental Health Sciences. L E Coffeng received financial support from the African Programme for Onchocerciasis Control (WHO/APOC) for work on onchocerciasis. M Cortinovis, F Gaspari, and N Perico acknowledge the International Society of Nephrology (ISN) on the behalf of the entire Genitourinary Expert Group. M Cross and L March acknowledge the University of Sydney (USYD); Institute of Bone and Joint Research, University of Sydney, Department of Rheumatology, Royal North Shore Hospital, St Leonards NSW 2065 Australia. N Dahodwala was supported by NIH grant K23 AG034236 and the Parkinson Council while working on this project. L Degenhardt is supported by an Australian NHMRC Senior Research Fellowship and funding to support work on illicit drug dependence was provided by the Australian National Drug and Alcohol Research Centre of the University of New South Wales, NSW, Australia. R Havmoeller is supported by a grant from the Swedish Research Council (#2011-1071). D Hoy was supported by the Bill & Melinda Gates Foundation and the Australian National Health and Medical Research Council. P J Hotez acknowledges grant support from several sources: the Bill & Melinda Gates Foundation regarding human hookworm vaccine through the Sabin Institute (Human Hookworm Vaccine Initiative 1 Human Hookworm Vaccine Initiative; Human Hookworm Vaccine Initiative 3 Clinical Development and Evaluation of the Na-GST-1 and Na-APR-1 Hookworm Vaccine Antigen); the National Institutes of Health (Product development of a membrane tetraspanin vaccine against schistosomiasis; RBD Recombinant Protein-based SARS Vaccine for Biodefense); and the Dutch Government (Product Development Support of the Human Hookworm Vaccine). K H Jacobsen was supported by the WHO for her work on Hepatitis A. B M Mayosi was funded by the Lily and Ernst Hausmann Research Trust. T R Merriman acknowledges the Health Research Council of New Zealand. D Ozgediz is grateful for the collaboration colleagues at Mulago Hospital and Makerere University in Kampala, Uganda. B Pahari would like to thank the Mario Negri Institute. U Sampson was funded in part by The Harold Amos Medical Faculty Development Award of the Robert Wood Johnson Foundation and The Vanderbilt Clinical and Translational Scholars Award. M Segui-Gomez's participation was partly supported by funds of the European Center for Injury Prevention, Universidad de Navarra. E Smith acknowledges Department of Health and Ageing, Commonwealth Government of Australia, Institute of Bone and Joint Research (IBJR), University of Sydney (USYD), Department of Rheumatology, Royal North Shore Hospital, St Leonards NSW 2065 Australia. L Rushton was supported by honorarium for board membership of the European Centre for Ecotoxicology and Toxicology of Chemicals; research grants to Imperial College London (as PI) from the European Chemical Industry Council (CEFIC) and CONCAWE (Conservation of Clean Air and Water Europe). P Yip was supported by a General Research Grant at the University of Hong Kong.

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