Global and regional mortality from 235 causes of death for 20 age-groups in 1990 and 2010: A systematic analysis.

Rafael Lozano, Mohsen Naghavi, Kyle Foreman, Stephen Lim, Kenji Shibuya, Victor Aboyans*, Tim Adair*, Rakesh Aggarwal*, Stephanie Ahn*, Miriam Alvarado*, Kathryn Andrews*, H. Ross Anderson*, Charles Atkinson*, Derrick Bennett*, Robert J. Berry*, Kavi Bhalla*, Boris Bikbov*, Ian Bolliger*, Chiara Bucello*, Christine Budke*, Peter Burney*, Charles Canter*, Jonathan Carapetis*, Honglei Chen*, David Chou*, Salim Chowdhury*, Sumeet Chugh*, Luc Coffeng*, Samantha Colquhoun*, Katherine Colson*, Leslie Cooper*, Matthew Corriere*, Monica Cotrinovis*, Karen Courville de Vaccaro*, William Couser*, Benjamin Cowie*, Michael Criqui*, Kaustubh Dabhadkar*, Nabila Dahodwala*, Diego De Leo*, Louisa Degenhardt*, Allyne Delossantos*, Herbert Duber*, Don Des Jarlais*, E. Ray Dorsey*, Patricia Espindola*, Patricia Erwin*, Majid Ezzati*, Abraham D. Flaxman*, Mohammad H. Forouzanfar*, Richard Franklin*, Michael K. Freeman*, Emmanuela Gakidou*, Flavio Gaspari*, Diego Gonzalez-Medina*, Yara Halasa*, Diana Haring*, James Harrison*, Rasmus Havmoeller*, Roderick Hay*, Peter Hotez*, Damian Hoy*, Kathryn Jacosben*, Spencer L. James*, Rashmi Jasrasaria*, Rachel Jenkins*, Nicole Johns*, Ganesan Karthikeyan*, Nicholas Kassebaum*, Andre Keren*, Rita Krishnamurthi*, Steven Lipshultz*, Michael F. MacIntyre*, Leslie Mallinger*, Lyn March*, Guy Marks*, Robin Marks*, Akira Matsumori*, Richard Matzopoulos*, Bongani Mayosi*, Mary McDermott*, John McGrath*, George Mensah*, Tony Merriman*, Catherine Michaud*, Matthew Miller*, Ali A. Mokdad*, Andrew Moran*, Luigi Naldi*, K.M. Venkat Narayan*, Kiumarss Nasseri*, Paul Norman*, Summer Lockett Ohno*, Saad B. Omer*, Katrina Ortblad*, Richard Osborne*, Doruk Ozgediz*, Bishnu Pahari*, Andrea Panozo Rivero*, Rogelio Perez Padilla*, Fernando Perez-Ruiz*, Norberto Perico*, David Phillips*, Kelsey Pierce*, C. Arden Pope III*, Esteban Porrini*, Murugesan Raju*, Dharani Ranganathan*, Juergen Rehm*, David Rein*, Guiseppe Remuzzi*, Fred Rivara*, Thomas Roberts*, Felipe Rodriguez De Leòn*, Lisa Rosenfeld*, Joshua Salomon*, Uchechukwu Sampson*, Ella Sanman*, David Schwebel*, Donald Shepard*, Jessica Singleton*, Andrew Steer*, Bernadette Thomas*, Imad Tleyjeh*, Thomas Truelsen*, Jaakko Tuomilehto*, Eduardo Undurraga*, Lakshmi Vijayakumar*, Theo Vos*, Gregory Wagner*, Mengru Wang*, Kerrianne Watt*, Martin Weinstock*, Robert Weintraub*, James Wilkinson*, Anthony Woolf*, Sarah Wulf*, Paul Yip*, Azadeh Zabtian*, Alan D. Lopez†, Christopher JL Murray†,§

*Listed alphabetically
†Senior authors
§ Corresponding author

Abstract

Background

Reliable and timely information on the leading causes of death in populations, and how these are changing, is a critical input into health policy debates. We aimed to estimate annual deaths for the world and 21 regions over the period 1980-2010 for 235 causes, with uncertainty intervals, 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. Data quality was assessed for completeness, diagnostic accuracy, missing data, stochastic variations and probable causes of death. We applied six different modeling strategies to estimate cause-specific mortality trends depending on the strength of the data. For 133 causes and three special aggregates we utilized the Cause of Death Ensemble model (CODEm) approach, which utilizes 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. Model performance was assessed using rigorous out-of-sample testing of prediction error and the validity of 95% uncertainty intervals. For nine causes with low observed numbers of deaths, we developed negative binomial models with plausible covariates. For 28 causes where death is rare, we modeled the higher level cause in the GBD cause hierarchy 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 and HIV) we used natural history models based on information on incidence, prevalence, and case-fatality. We separately estimated etiological fractions for diarrhea, lower respiratory infections, meningitis, chronic kidney disease, maternal conditions, cirrhosis, and liver cancer. For deaths due to collective violence and natural disasters, we used mortality shock regressions. For every cause, we estimated 95% uncertainty intervals that capture both parameter estimation uncertainty and uncertainty due to model specification where CODEm has been used. We constrained cause-specific fractions within each age-sex group to sum to total mortality based on draws from the uncertainty distributions.

Findings

In 2010 there were a total of 52·8 million deaths globally. At the most aggregate level, communicable, maternal, neonatal, and nutritional causes (CMNN) were 24·8% of deaths worldwide in 2010, down from 34% in 1990. This was largely due to declines in mortality from diarrheal disease (2·5 to 1·4 million), lower respiratory infections (3·4 to 2·8 million), neonatal conditions (3·1 to 2·2 million), measles (0·63 to 0·13 million), and tetanus (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 has also risen by an estimated 19·9% since 1990 to 1·17 million deaths in 2010. Tuberculosis killed 1·2 million people in 2010. Deaths from noncommunicable diseases (NCDs) rose by just under eight million deaths between 1990 and 2010, accounting for two out of every three deaths (34·5 million) worldwide by 2010. Eight 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. Ischemic heart disease (IHD) 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. IHD, stroke, chronic obstructive pulmonary disease (COPD), lower respiratory infections (LRI), lung cancer, and HIV/AIDS were the leading causes of death in 2010. IHD, LRI, stroke, diarrheal disease, malaria, and HIV/AIDS being the leading causes of years of life lost due to premature mortality (YLLs) in 2010, similar to what was estimated for 1990 (HIV/AIDS added, preterm conditions dropped). YLLs from LRI and diarrhea have declined by 45-54% since 1990; IHD and stroke YLLs increased by 17-28%. Regional variations in leading causes of death are substantial. Communicable, maternal, and neonatal causes still accounted for 50% of premature mortality in sub-Saharan Africa in 2010. Age standardized death rates from some key condition have risen (HIV/AIDS, Alzheimer's disease, diabetes mellitus, and chronic kidney disease in particular), but for the vast majority of diseases, death rates have fallen over the past two decades; including major vascular diseases, COPD, all forms of cancer, liver cirrhosis, and maternal conditions. For others, notably malaria, prostate cancer, and injuries, there has been little change.

Interpretation

Population growth, increased average age of the world's population, and largely declining age, sex, and cause-specific death rates combine to drive a broad shift from communicable, maternal, neonatal and nutritional causes towards noncommunicable 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 there is marked regional variation in many causes including 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.

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 critical input into policy debates and planning current interventions, as well as prioritizing 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 required. 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 standardizing 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 approximately 18·8 million deaths out of an as estimated annual total of 51·7 million deaths in 2005, which is the latest year for which the largest number of countries reported deaths by 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 which 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 in part 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 under-five mortality by cause consistent with all-cause mortality data in 1983. The 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 has been 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 has been paid to priority diseases such as malaria, HIV/AIDS, and tuberculosis. The Child Health Epidemiology Reference Group (CHERG) has also produced estimates of under-five mortality from 16 causes that sum to estimates of under-five deaths for 2000-2003, 2008, and 2010[18–20] partially 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. In addition 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 last five years, for example, papers 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 rigor, and moreover are not constrained to sum to estimates of all-cause mortality from demographic sources.

Global cause of death assessments can be characterized in four dimensions: the universe of raw data identified and examined, efforts to evaluate and enhance quality and comparability of data, the statistical modeling strategy, and whether causes of death are constrained to sum to all-cause mortality. In terms of the universe of data, the various iterations of the GBD and CHERG analysis of under-five deaths 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 data on case-fatality rates combined in a natural history progression model. 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, over the last 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; noncommunicable diseases; and injuries. More recently, the array of modeling 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 modeling options, an important innovation has been the reporting of out-of-sample predictive validity to document the performance of complex models. [22,38]

Given the developments in the field of mortality and cause of death estimation, for the GBD 2010 we have 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 modeling strategy in order to generate more realistic uncertainty intervals and more accurate predictions.[38] These innovations have been used in estimating mortality for an expanded GBD cause list of 291 causes compared with 134 in the GBD 1990 Study; of the 291 causes, 235 are causes of mortality, while 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 et al[40] and results by cause presented here. In this paper, 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.

Data and 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 International Classification of Diseases and Injuries (ICD) to the GBD cause list are reported elsewhere.[39] While results are reported in this paper 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. Using longer time series improves the performance of many types of estimation models; data prior to 1980, however, are much sparser for developing countries so we have restricted the analysis to 1980-2010.

Database development

Over the five year duration of the GBD 2010 study, we have 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, multiple sources of data have been used. We briefly outline below the main types of data identified and how they have been used. **Web Table 1a** provides a summary of the site-years of data identified by broad type of data system and, similarly, **Web Table 1b** illustrates the number of site-years by GBD region. The data presented in this table 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, sub-Saharan Africa Central has the most limited evidence base with data on only 27 causes from at least one country.

Vital registration with medical certification of causes of death

We have identified 2,798 site-years of vital registration (VR) data from 130 countries over the period 1980 to 2010. 3% of the site-years were coded using ICD8, 44% using ICD9, 40% using ICD10, 12% use country-specific tabulations of ICD8, ICD9 and ICD10, and 1% use non-ICD tabulations. In addition, 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 ICD9, the ICD10 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.

Verbal autopsy data collected through sample registration systems, demographic surveillance systems, or surveys

Verbal autopsy (VA) 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 VA data across 66 countries, of which 10% were nationally representative. VA 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 VA, different recall periods, and different age groups, quite apart from cultural differences in the interpretation of specific questions. **Web Table 2** provides a full listing of the sources used for all VA and non-VR data organized by country.

Population-based cancer registries

Population-based cancer registries provide an important source of data on incidence of cancers in various countries. We identified 2,715 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 et al,[31] we have developed estimated mortality to incidence (MI) ratios for all major cancers by age, sex, and country. The log of the MI ratio has been estimated as a function of national income per capita with random effects for country, year, and age. The estimated mortality to incidence ratios have been used to map cancer registry data on incidence to expected deaths which have been incorporated into the database. MI ratios by country, age, and sex are available on request.

Police reports

In most countries, police and crime reports are an important source of information for some types of injuries, notably road injuries and inter-personal violence. The police reports used in this analysis were collected from published studies, national agencies, and institutional surveys such as the United Nations Crime Trends survey and the WHO Global Status Report on Road Safety Survey.[30,41] By comparing to other sources such as VR data, we have evaluated whether police reports are likely to be complete and cover the entire country. In total, we included in the analysis 1,129 site-years of police reports from 122 countries from 1980 to 2010 that met our criteria.

Burial site and mortuary data

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 use information on the fraction of injuries due to specific sub-causes from these sources. These proportionate fractions of injury deaths due to specific causes are transformed into fractions of all causes by multiplying by the fraction of all deaths due to injuries estimated from a model for all injuries (see CODEm modeling description below).

Survey and census data on pregnancy related deaths and on injury mortality

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 1,557 surveys years with sibling history data, and a further 52 household survey/census years of data covering 61 countries. We also identified 52 surveys/censuses covering injury mortality across 65 survey/census years.

Maternal mortality surveillance systems

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.

Health facility data

We included in addition 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. Data were adjusted 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 et al. 2007.[42] This method attempts to correct for selection bias in the deaths that occur in hospital. Finally, we use only the fraction of injury deaths due to specific injuries from these sources and convert them to fractions of deaths from all causes following the method described for burial and mortuary data.

Assessing and enhancing data quality and comparability

Data quality was assessed and enhanced following six steps which are outlined in more detail below.

Step 1. Assessing 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 may be different than those that are not. Murray and Lopez[43] hypothesized in the GBD 1990 study that deaths recorded in countries with incomplete vital registration would more likely originate from wealthier sectors of populations where the cause of death structure was skewed towards noncommunicable rather than communicable diseases, the latter being more common among 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 has been 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 may 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 et al[42] showed that the fraction of deaths in hospital is higher for acute causes where death is not immediate but occurs over a matter of days such as for some maternal causes. Further, evidence on sub-national mortality patterns[45] clearly indicates 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 have assessed the completeness of vital registration or sample registration data over age five using the most accurate variants of death distribution methods: synthetic extinct generations, the generalized growth balance method, and a hybrid of the two.[46] Under age five completeness has been assessed by comparing registration data to survey and census data on child mortality. More details on how the synthesis of these methods is carried out are provided in Wang et al (2012).[47] 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 may be high but coverage is not.

For adults, there are few vital registration or sample registration data points with completeness below 70% in the database. Because completeness is often lower for deaths under age five compared to over age five, we have investigated the impact of including data on causes of death with completeness below 70%. We have rerun cause of death models for the major causes of under-five death five different ways: excluding all data with completeness below 30%, below 40%, below 50%, below 60%, and below 70%. At the global level, the number of deaths estimated in 2010 for ARI and diarrhea for example differ by 0·9% and 1·2%, respectively, between models that include all data and those that exclude data where under-five death registration is below 70% complete. The difference is slightly larger in 1980 where 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 have chosen to use all available data. These sensitivity analyses suggest that at least for major causes of child death, there is no consistent evidence of selection bias towards causes of death in richer populations.

Assessing completeness is feasible for vital registration and sample registration data but not for small – scale studies on verbal autopsy, which may not detect all deaths through household recall. In fact, household recall often yields a substantial undercount of deaths.[48,49] 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. Mapping revisions and variants of the ICD

Vital registration data and some verbal autopsy data for the period 1980 to 2010 are reported using multiple variants of the ICD8, ICD9 and ICD10. We have mapped these revisions to the GBD cause list in **Web Table 3**. This mapping provides the codes for the detailed list for ICD9 and ICD10, as well as the basic tabulation list for ICD9 (BTL). We identified three national variants of ICD9 BTL that we have also mapped to the GBD cause list. Of note, there were 119 GBD causes not available in the BTL, such as the pneumonia and diarrhea etiologies, some of the cancers, hepatitis by type, some of the cardiovascular causes, many of the mental and behavioral disorders, some musculoskeletal conditions, and certain injury subtypes.

Step 3. Garbage Codes

Murray and Lopez[43] introduced the concept of "garbage codes" in the GBD 1990 and proposed methods to redistribute deaths assigned to garbage codes to likely 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 simple algorithms proposed to redistribute these proportionately to various causes (called "target codes") that were the likely underlying causes of death.[50] A similar approach was applied for the GBD 2000 and subsequent WHO updates. For the GBD 2010, we have identified causes that should not be assigned as underlying cause of death at a much more detailed level.[51] In total, we have identified 2,759 garbage codes in ICD10 detailed data, 3,382 garbage codes in ICD9 detailed data, and 85 garbage codes in the ICD9 BTL ranging from abdominal rigidity to yellow nail syndrome. Garbage codes have been identified at the most detailed level possible (e.g. the fourth digit level for ICD9 and ICD10). For each garbage code, the potential underlying causes of death have been identified based on pathophysiology. For example, the target codes for peritonitis include acute gastric ulcers with perforation and acute tubulointerstitial nephritis; the target codes for disseminated intravascular coagulation include other septicemia and premature separation of placenta. Moreover, redistribution proportionate to the number of deaths observed in the target codes cannot be reliably applied; for example, while there are many injuries, 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 based on the limited published literature, expert judgment, statistical analysis[52] and in some cases, proportionate allocation across target causes. **Web Tables 4 a-g** provide a complete listing of the redistribution algorithms used, organized by garbage code. The extent of garbage coding in VR data varies widely across countries from a low of 5·5% in Finland to a high of 69·6% in Sri Lanka.

Step 4. Age splitting and age-sex splitting

Sources report data using varying age groups; for consistency in the analysis, the GBD project defined and utilized a standardized 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 have been computed for each cause using the entire pooled dataset on medically certified causes of death. In the few cases where studies report deaths for both sexes combined, a similar approach is used to allocate these deaths to age-sex groups. The webappendix provides more detail on the development of the age splitting model and the age-sex splitting model.

Step 5. Smoothing

For some causes in some countries, the number of deaths observed in a year is very low; zero, one, or two deaths may be observed in some years due to stochastic fluctuation. For models using the log of the death rate, observations that record zero deaths are either dropped or an arbitrary small number is substituted for zero observations; both approaches can lead to bias. This problem is exacerbated in modeling strategies that attempt to capture spatial and temporal correlation structure. In cases where multiple years for a country-cause-age group are observed with zero deaths, we have used a standardized smoothing algorithm, essentially a type of moving average, as described in the webappendix.

Step 6. Outlier detection

Despite these efforts to enhance quality and comparability, the data from some sources appear 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 have identified outliers that meet 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 has been excluded from subsequent analysis. The interpretation of large inconsistency or disproportionate effect varies by cause and has been based on the consensus of the investigators.

Modeling individual causes of death

We have used six different modeling strategies for causes of death depending on the strength of the available data. **Web Table 5** indicates the modeling 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 more detail on the different modeling strategies used. All of the strategies, however, have been designed to generate uncertainty distributions for the cause-specific death rate by age, sex, country, and year. We have attempted to capture uncertainty due to model parameter estimation, model specification, and fundamental uncertainty. For Cause of Death Ensemble Modeling (CODEm), the validity of uncertainty distributions has been assessed. The uncertainty distribution for a cause for a given country, year, age and sex group from the modeling process is propagated into computation of years of life lost due to premature mortality (YLLs) and various geographic and age-sex aggregates by sampling 1,000 draws from the posterior distribution.

Cause of Death Ensemble modeling (CODEm)

For all major causes of death except for HIV/AIDS and measles, we have used cause of death ensemble modeling (CODEm) – 133 causes in the cause list and three other special aggregates. CODEm has been used to analyze 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.

1) 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. In addition, 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.

2) The performance of all component models and ensembles is evaluated using out-of-sample predictive validity tests. Thirty percent 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 results in terms of model results have been obtained. Tests of out-of-sample performance include both 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 uncertainty interval.

3) Based on out-of-sample predictive validity, the best performing model or ensemble is selected. The rigorous evaluation of out-of-sample performance means that for each CODEm model, we generate objective data on the validity of the resulting uncertainty intervals.

Web Table 6 summarizes 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 have been run for different age ranges when there is reason to believe that the relationship between covariates and death rates may be different in in different age ranges for example in children compared to adults. For each 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 leukemia with the smallest. Out-of-sample performance also varies substantially across causes; kidney cancer has the largest RMSE in females (2·039) and the smallest RMSE is for cardiovascular and circulatory disease in males (0·555). Over 50% of the models in **Web Table 6** 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. Due to 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 uncertainty intervals; ideally, the 95% uncertainty interval for a model would capture 95% of the data out-of-sample. Higher coverage suggests that uncertainty intervals are too large and lower than 95% suggest uncertainty intervals are too narrow. Coverage across the CODEm models ranges from 99·0% for "other neurological conditions" to a low of 84·2% for pneumoconiosis.

Negative binomial models

For 13 causes, the number of deaths observed in the database is 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 **Web Table 5**. 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 28 cases where death is a rare event, we have first modeled the parent cause in the GBD hierarchy using CODEm and then allocated deaths to specific causes using a fixed proportion. Proportions have been computed using all available data in the database and are 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 females. Lower respiratory infections, upper respiratory infections, meningitis, and encephalitis varied by region and age. Thalassemia, sickle cell, G6PD, and other hemoglobinopathies and hemolytic anemias 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.

Diarrhea, lower respiratory infection, meningitis, cirrhosis, maternal, liver cancer, and chronic kidney disease etiologies

The GBD 2010 cause list includes 10 etiologies for diarrhea, five etiologies for lower respiratory infections (LRI), and four etiologies for meningitis. In addition, we have included a breakdown of maternal causes, cirrhosis, liver cancer, and chronic kidney disease by specific primary etiologies. In most of these cases, published data are available on the etiology or primary diagnosis for community,

hospital, or registered cases, but not for deaths. For these etiologies, systematic reviews of the published data and careful review of statistical annuals such as renal registries have been undertaken. These studies or data points on etiology have been meta-analyzed using the GBD Bayesian meta-regression tool described elsewhere.[53] The meta-regression have generated region-age-sex estimates with uncertainty of etiological fractions for diarrhea, LRI, meningitis, chronic kidney disease, maternal conditions, cirrhosis, and liver cancer – see the webappendix for more details. These fractions are then applied to estimates of the parent cause, which have been estimated using CODEm. In the cases of cirrhosis, liver cancer, maternal conditions, and chronic kidney disease, the studies or datasets on etiology identify primary cause as assessed clinically; for diarrhea, LRI, and meningitis, etiology is 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, there are almost no deaths recorded in vital registration or verbal autopsy studies, most likely because data have not been collected in focal populations with substantial disease present. Second, there are reasons to believe that there is systematic misclassification of deaths in cause of death data sources, particularly for congenital syphilis,[54,55] whooping cough,[56] measles,[57] and HIV/AIDS.[58] For these causes, natural history models have been used that begin with data on incidence or prevalence of disease and case-fatality rates – see the webappendix for brief descriptions. In the case of HIV/AIDS, a hybrid approach has been used. For 36 countries, with complete and high quality vital registration systems, we have used CODEm, in consultation with UNAIDS. For the remaining countries, we have 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 dramatically higher than 2010 estimates and are inconsistent with the all-cause mortality evidence. For these two countries, we have used the 2010 UNAIDS revision.

Mortality Shock Regressions

To estimate deaths directly due to natural disasters or collective violence, we use a different approach. First, we develop a variable for reported battle and disaster deaths per 10 thousand using various databases for both disasters and collective violence; next, we estimate the empirical relationship between under-five mortality and adult mortality (45q15) and this variable in settings where data were collected during these mortality shocks. As a final step, we use this empirical relationship 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 in Murray et al.[59]

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 VR systems. In country-years where estimates are available from more than one source, priority is given to VR data if it gives higher estimated deaths. When VR data are not available, priority is given to the Uppsala Conflict Data Program (UCDP)/PRIO Armed Conflict Dataset as 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).[60–62]

The relationships between under-five mortality and adult mortality and the disaster and collective violence covariates are estimated using 43 empirical observations for disasters and 206 empirical observations for collective violence (only years with over 1 per 10,000 crude death rate from shocks are kept in this analysis). The relationship is estimated for excess mortality from these data sources by first subtracting from observed mortality rates the expected death rates in shock years using the methods outlined in Murray et al.[59] The coefficients from these regressions and the disaster and collective violence covariates are used to predict excess deaths from these two causes. Because these models take into account competing causes by estimating the relationship between excess mortality and these covariates, we do not subject estimates for these two causes to the CoDCorrect algorithm described below. 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

Given that we develop single cause models, it is imperative as a final step to ensure that individual cause estimates sum to the all-cause mortality estimate for each age-sex-country-year group. This must be done taking into account uncertainty in each cause of death model outcome, where some causes are known with much greater precision than others. We use a simple algorithm called CoDCorrect; at the level of each draw from the posterior distribution of each cause, we proportionately rescale each cause such that the sum of the cause-specific estimates equals the number of deaths from all causes generated from the demographic analysis.[47]

In practice, a random draw without replacement is taken from the posterior distribution of 1,000 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 is 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 each cause in countries where there is substantial uncertainty in the level of all-cause mortality.

Repeated simulation studies demonstrate that the two-stage approach used here, namely modeling each cause individually and then applying the CoDCorrect algorithm, gives high levels of cause-specific mortality fraction accuracy (see the webappendix for details). These simulation studies also demonstrate that under all circumstances tested the two-stage approach to cause of death modeling is as good as or better than a single-stage approach as proposed by Salomon and Murray.[36]

We apply CoDCorrect in a hierarchical fashion. **Web Table 5** identifies three levels of application of CoDCorrect. We first apply the algorithm for level 1 causes. We then apply CoDCorrect for level 2 causes such that the sum of level 2 causes for a country-year-age-sex group equals the draws of the level 1 cause. This cascade is repeated for level 3 causes. We have chosen levels for each cause based on

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consideration of the amount and quality of available data. For example, because there are substantially more data on all cardiovascular causes from verbal autopsy studies than for specific cardiovascular causes, we have designated "all cardiovascular" as a level 1 cause for CoDCorrect. Another example of this approach is for the category "chronic respiratory diseases" where there is substantially more data for the aggregate cause than for COPD, asthma, pneumoconiosis, and interstitial lung disease. Since we only want to group causes at level 2 or level 3 that are strongly related with common determinants, we do not use higher level aggregates such as "all noncommunicable diseases" as level 1 causes because it is difficult to develop plausible models for these groups that include some causes that are increasing and others that are decreasing over the same time period.

Web Table 23 shows the percentage change in each 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 is applied to all causes, the net effect of CoDCorrect is 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, multiple options are possible such as all cancers versus site-specific cancers. We have opted to produce tables of rankings using the level of disaggregation that seems most relevant for public health decision-making. Although we report more disaggregated causes, because of considerations related to public health programs, we have chosen to include diarrheal 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 years of life lost due to premature mortality (YLLs)

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 five million (see Murray et al[39] for details). In practice, for deaths in a given age-interval such as 20-24, we use country-specific estimates from the demographic analysis of the mean age of death in that interval.[47] In the GBD 2010, the terminal age-group for the analysis of causes of death and years lived with disability (YLDs) is 80 years and older because of the scarcity and quality of data for older age groups. Because the all-cause mortality analysis is undertaken, however, for more detailed age-groups up to age 110, we are able to take into account the mean age of death over 80 in each country-year-sex group in computing YLLs.

Decomposing Changes in Cause of Death Numbers into Demographic and Epidemiological Factors

To help understand the drivers of change in the numbers of deaths by cause or region, we have decomposed change from 1990 to 2010 into growth in total population, change in population age- and sex-structure, and change in age- and sex-specific rates. We compute 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 aging scenario computed as the number of deaths expected in 2010, using 1990 age-sex specific rates and 2010 age 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 aging scenario is the number of deaths due to aging of the population. The difference between 2010 deaths and the population growth and aging scenario is the difference in death numbers due to epidemiological change in age- and sex-specific death rates. Each of these three differences is also presented as a percent change with reference to the 1990 observed death number.

We have calculated change in the risk of death, by cause, directly using age standardized death rates, based on the WHO world population standard age structure.[63]

Further details on the data and methods used for specific causes of death is available on request.

Results

Global Causes of Death

The GBD cause list divides causes into three broad groups. At the most aggregate level, communicable, maternal, neonatal, and nutritional (CMNN) causes account for 13·2 million of 52·8 million total deaths at all ages or 24·8% in 2010. Noncommunicable causes account for 34·5 million or 65·4%. The third category, injuries, accounts for 5·1 million or 9·6%.The continued decline in deaths from communicable, maternal, neonatal, and nutritional conditions is striking, if not surprising. By 2010, these largely preventable conditions accounted for one-quarter (13·2 million) of the 52·8 million deaths estimated to have occurred worldwide in that year, down from 15·9 million (34%) in 1990. The annual number of deaths from noncommunicable diseases, by contrast, rose by just under 8 million, to 34·5 million, or two out of every three deaths in 2010. The global fraction of deaths due to injuries increased slightly between 1990 and 2010 (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, aging of the population, and changes in age- 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 CMNN causes, population growth alone would have increased this category by 46·8%, noncommunicable diseases by 22·9%, and injuries by 31·1%. Aging of the world's population such that the mean age of the world has increased from 26·1 to 29·5 years contributed to an 11·2% decrease in CMNN conditions, a 39·2% increase in noncommunicable disease deaths, and a 9·2% increase in injuries. Declines in age- and sex-specific death rates have contributed to 52·6% decrease in CMNN deaths, a 32·1% decrease in noncommunicable disease deaths, and a 15·9% decrease in injury deaths. With declining age-specific death rates from all three groups of causes, including noncommunicable diseases, the global shift

towards noncommunicable diseases and injuries as leading causes of death is being driven by population growth and aging, and not by increases in age-sex-cause specific death rates.

At the second level of the GBD cause hierarchy, there are 21 major cause groups. **Figure 1** (a-d) summarizes the composition of causes of death for each age-sex group for males and females separately in 1990 and 2010 at this second level of cause disaggregation. The structure of causes of death changes systematically with age. In the neonatal age groups, conditions arising during the neonatal period dominate, but with important contributions from the category of diarrheal disease, lower respiratory infections, and other infectious diseases and other noncommunicable diseases, including congenital causes. By the post-neonatal period, causes of death are dominated by diarrhea, LRI, and other infectious diseases such as measles, among others. At ages 1-4, the category neglected tropical diseases and malaria are also an important contributor to global mortality. In the age group 5-14, infectious diseases, HIV/TB, injuries, and some cancers predominate, although overall mortality at these ages is low. Important sex differences are evident from ages 15-34; among males, injuries, HIV/TB, and some noncommunicable diseases predominate. Among women of the same age group, injuries are 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, ranging from 0·9% in Australasia to 16·8% in Sub-Saharan Africa, West. By age 40, more than 50% of global deaths in 1990 were from noncommunicable diseases – this transition age shifts to 45 in 2010 because of the HIV epidemic. Beginning at age 50, circulatory causes begin a steady rise to become the largest cause of death.

Comparison of the 1990 and 2010 plots in **Figure 1** reveals a number of shifts in the cause structure by age and sex. At younger age groups, neonatal conditions and other noncommunicable 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 younger adult males and females. By 2010, for example, HIV/TB and injuries accounted for over half of all deaths in the age group 20-39 in males. Other important shifts, with age, are evident: a rising fraction of deaths in many age groups from diabetes, chronic kidney diseases, blood and endocrine disorders, and cancers, along with a decline 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 due to maternal causes has notably declined.

At a more disaggregated cause level, there is interest in a broad global overview of who dies of what, and how this is changing. **Table 2** provides total death numbers and age-standardized death rates for each cause in 1990 and 2010.   Because there is substantial interest in causes of death for different age-groups, **Web Tables 25 and 26** provide global deaths for the 20 GBD age groups, by sex, and including 95% uncertainty for 2010 and 1990, respectively. In addition to the death numbers, we present the death rates by age for 2010 and 1990 in **Web Tables 27 and 28**, respectively, for those readers interested in comparing change in age-sex-specific death rates. There are numerous features of the tables that warrant discussion: we limit ourselves here to some general observations which we believe characterize the principle epidemiological trends around the turn of the millennium. Much of the decline in the communicable, maternal, neonatal, and nutritional causes was due to the substantial reductions in diarrheal disease (2·5 to 1·4 million), lower respiratory infections (3·4 to 2·8 million), neonatal conditions (3·1 to 2·2 million), measles (0·63 to 0·13 million), and tetanus (0·27 to 0·06 million),

reflecting the scaling up of effective treatments and technologies to combat these conditions generally associated with poverty. Not all diseases in this category declined, however. The table shows the massive increase in deaths between 1990 and 2010 from HIV/AIDS (0·3 to 1·5 million), despite the decline 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 (1·0 to 1·5 million), 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 (0·34 million), with smaller fractions due to hepatitis C and alcohol. The largest cause fraction (13·3%) among all causes of death in 2010 was due to IHD, closely followed by stroke (11·1%), being roughly split equally between ischemic (2·8 million) and hemorrhagic and other (3·0 million). Together, IHD and all forms of stroke killed an estimated 12·9 million people in 2010, one quarter of the global total, compared to 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, from 0·66 to 1·3 million, as did deaths from chronic kidney disease (0·40 to 0·74 million). Deaths from Alzheimer's disease and other dementias rose more than three-fold to 0·49 million in 2010, while deaths from Parkinson's disease doubled to 0·11 million. One of the few causes in this group to decline was COPD, falling from 3·1 to 2·9 million. This is consistent with the declines observed with development in countries such as the UK in the first part of the 20th century, only to be reversed as the impact of tobacco use becomes evident.[64,65] The massive increases in tobacco use since the 1970s, particularly among men in less developed countries, will likely reverse this trend over the next decade or so.[66]

One million more deaths from injuries occurred in 2010 (5·1 million) than two decades earlier, a 24% increase. This was driven primarily by a 421·2 thousand increase in road traffic deaths, which claimed 1·3 million lives in 2010. Falls also claimed an additional 191,700 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 (0·67 to 0·89 million) and interpersonal violence (0·34 to 0·46 million). Deaths from forces of nature, war, and legal intervention were over twice as common (227 thousand) 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-standardized mortality rates, we effectively control for demographic changes across populations over time. Changes in age-standardized 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 conditions have declined by a quarter since 1990, a much greater reduction than suggested from numbers of deaths alone. The age-standardized death rate from diarrheal diseases fell by 44%, whereas LRI declined by 27%. Interestingly, age-standardized 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 declines in mortality in developed countries and more modest increases in less developed countries where the full impact of smoking , particularly among men, has yet to occur. Breast cancer mortality rates fell by 15%, even though numbers of deaths from the disease increased by over one-third.

Our findings suggest important declines (20% or more) in age-standardized death rates from major vascular diseases, particularly heart disease and strokes, for the world as whole, even though numbers of vascular disease deaths increased by one-third to 15·6 million in 2010. Death rates have also declined from COPD (43%) and liver cirrhosis(16%), but almost doubled from Alzheimer's, and rose by 15-20% from diabetes and chronic kidney disease. These represent important global health challenges that may, or may not, be evident from an assessment of trends in numbers of deaths alone. Globally, while the number of injury deaths has risen by 24% since 1990, death rates have declined modestly (8%), although this masks variable trends for different injuries, with death rates from drownings and poisonings falling by about one third, less dramatically for self harm (10%) and violence (1%), and rising for transport injuries(6%) and, interestingly, from adverse effects of medical treatment (44%). There was also a massive rise in death rates from forces of nature (369%) comparing 1990 to 2010 due to the Haiti earthquake in 2010.

Causes of death under age 5 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 in recent years. **Web Tables 25 and 26** provide a breakdown of deaths under 5 into the early neonatal, late neonatal, post-neonatal, and 1-4 age groups in 2010 and 1990 respectively. To facilitate an understanding of the leading causes at different ages under 5, we show in **Figure 2a, 2b and 2c** the distribution of deaths in the neonatal periods, the post-neonatal period and ages 1-4, respectively. Of 2·8 million early and late neonatal deaths, we estimate that 2·1 million are from neonatal conditions including preterm birth complications, neonatal sepsis, and neonatal encephalopathy, among others. A further 137 thousand deaths are also due to conditions that arise in the neonatal period but which lead to death after the first month of life. Among the important neonatal conditions, preterm accounts for 29% of global neonatal deaths, with nearly equal shares for neonatal sepsis and neonatal encephalopathy - 17% each. Of the remaining 741 thousand neonatal deaths, congenital anomalies account for 183 thousand deaths, although the majority of congenital deaths occur after the first month of life. Injuries account for 28 thousand neonatal deaths, other noncommunicable causes including hemoglobinopathies and hemolytic anemias, some rare cancers, sudden infant death syndrome (SIDS), and other rare causes account for 46 thousand deaths. Among communicable diseases, notably lower respiratory infections (194 thousand), diarrhea (77 thousand) and meningitis (46 thousand) account for the remaining neonatal deaths.

In the post-neonatal period, (**Figure 2b**) we have estimated 2·0 million deaths. Nearly half of these deaths are due to three diseases: lower respiratory infections, diarrheal diseases, and malaria. Other important causes of death during the post-neonatal period include nutritional deficiencies, meningitis and encephalitis, injuries, whooping cough, measles, and HIV/AIDS. Causes that primarily cause death in the neonatal period also contribute to 14·1% of deaths between one month and 11 months including neonatal conditions, congenital anomalies, and congenital syphilis. Our analysis of etiologies suggests

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that the most important identified causes of post-neonatal lower respiratory infections are respiratory syncytial virus (RSV), Haemophilus Influenzae Type b (HiB) and pneumococcus. For diarrheal diseases, the most important cause is rotavirus followed by similar shares for cryptosporidium and enteropathogenic E. Coli (EPEC). In the age-group 1-4 (**Figure 2c**), we find 2·0 million deaths distributed across a wider array of causes. The most important cause globally in this age group is malaria, followed by lower respiratory infections, diarrheal diseases, and nutritional deficiencies. These four causes account for 52·3% of deaths in this age group. Four causes account for between three and five percent of deaths each: HIV/AIDS, meningitis/encephalitis, measles, and drowning. Etiologies for LRI substantially shift in this age group compared to the under-one age groups with a much more substantial role played by pneumococcal deaths. Just under 14% of deaths in this age group are from a long list of noncommunicable causes, each of which accounts for a relatively small number of deaths.

Because of the focus of MDG 5 on maternal mortality, it is of particular interest to examine the composition of causes of death in reproductive aged women (and men). While deaths related to pregnancy and child birth have been given special priority in the MDGs, arguably any death in these young adult age groups is a major cause for concern. For women aged 15-49 years, we have estimated 3·5 million deaths from all causes in 2010. **Figure 3a** shows that the leading cause was HIV/AIDS (14·4%), followed by cardiovascular disease (10·7%), maternal conditions (7·3%), suicide (4·8%), tuberculosis (4·6%), breast and cervix cancer (4·2%), and road injury (4·0%). The top seven causes account for half of the deaths of women in these age groups. While there is no MDG related specifically to male deaths in the reproductive age-groups, conditions targeted by MDG 6 take an important toll on men in the age-groups 15-49. The leading causes of death for males in this age-group, however, are cardiovascular diseases (12·8%), and road traffic injures and HIV/AIDS (10·7% each), with other major causes including suicide (5·7%) and interpersonal violence (5·2%).

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 time periods. Communicable, maternal, neonatal, and nutritional causes are in red. Noncommunicable causes are in blue. Injuries causes are in green. The mean and 95% uncertainty intervals of cause rankings are also shown, as is the percentage change in the number of deaths, by cause, between 1990 and 2010. While the top four causes of death in 1990 remain the top four in 2010, the change in numbers of deaths is noteworthy, with IHD and stroke increasing by 26-35% over the interval, while LRI and COPD are declining by 7-18%. Lung cancer increased from the 8th cause to the 5th cause over the two decades due to 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. Diarrheal, 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.

While 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 equal weight to a death at age 90 compared, for example, to a death at age 25 or age 5. Consequently, the predominance of noncommunicable causes

may be misleading. In the GBD, the computation of years of life lost based on the standard expectation of life at the age of each death quantifies the amount of life lost due to premature mortality (YLLs) due to each cause. By computing YLLs, we can aggregate information on deaths across all ages in order to summarize overall patterns of premature mortality. The demographic and epidemiological transition is illustrated in **Figure 5**, which shows the change in the composition of YLLs by single year from 1990 to 2010 for both sexes combined. The impact of major mortality shocks including the Rwanda genocide (1994) and the famine in the Democratic People's Republic of Korea (covering most of the 1990s with a peak in 1995), are evident even at the global scale. The fraction of YLLs due to infectious diseases predominantly in children has declined 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 noncommunicable diseases, particularly cardiovascular diseases. The share of YLLs from noncommunicable diseases expanded from 33·3% in 1990 to 42·8% in 2010. **Web Tables 29 and 30** show the global YLLs with 95% uncertainty intervals for 2010 and 1990, respectively.

Figure 6 provides a comparison of the top 25 causes of YLLs for both sexes combined. This provides 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 ischemic heart disease in 2010; over this period, the total number of YLLs from LRI decreased by 45% but increased 28% for ischemic 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 noncommunicable diseases increased in importance over the two decades: ischemic heart disease, stroke, lung cancer, cirrhosis, diabetes, liver cancer, and chronic kidney disease in particular, although COPD and congenital causes have declined in rankings of YLLs. Among injuries, road traffic, self harm, and interpersonal violence have increased substantially in both absolute and relative terms, while drowning has declined.

An important innovation in this study has been the quantification of uncertainty by cause. Uncertainty intervals vary widely across causes. **Figure 7** shows the 95% uncertainty interval for YLLs for each cause in 2010, ordered by the mean rank of each cause. The two leading causes - ischemic heart disease and LRI - have nearly overlapping uncertainty intervals. There is quite a gap between these two causes and the next highest ranked cause, stroke. The 12th ranked cause, neonatal sepsis, has an uncertainty interval that is nearly three times wider than the 11th ranked cause, COPD. A number of causes have much larger uncertainty intervals than adjacent causes in the rank list. Natural history models for whooping cough, measles, and syphilis have large uncertainty intervals. This stems from considerable empirical uncertainty on the estimation of incidence and case-fatality rates. In contrast, the HIV/AIDS natural history model developed by UNAIDS has remarkably narrow uncertainty in many countries with large epidemics. Across the causes analyzed using CODEm, where the validity of uncertainty intervals have been evaluated using out-of-sample performance, there is also substantial variation across causes reflecting both the coherence of the underlying data, and whether powerful explanatory covariates have been identified.

Regional Variation

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 have been ordered by the mean age at death, a crude but informative measure of the demographic and epidemiological transition.[40] At both time periods, there is 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 had been achieved, even in Africa, in reducing YLLs from communicable, maternal, neonatal, and nutritional causes in particular, 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**, particularly compared with other developed regions, where cancer causes as much, if not more, premature death. In 1990 the impact of the civil violence in Papua New Guinea in 1990 and the 2010 Haiti earthquake lead 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 Latin America Central to a low of 6% in the Caribbean, nearly a four-fold variation.

Table 3 shows the rank for each cause that is either in the global top 25 causes of YLLs in 2010 or which appears in the top 25 causes of YLLs for any region. **Web Table 31** presents the same information for 1990. Different colors represent different bands of ranks, with the top ranked causes shown in red, progressing through orange, yellow, green, and finally causes ranked lowest being shown in blue. These "heat maps" help to visualize important variations in ranking of YLLs across regions. In both 1990 and 2010, a similar number of causes (60 or so) appear in the rankings, but with very substantial regional variations. At the top of the table, listing causes highest in global rankings of YLLs, causes such as lower respiratory diseases, ischemic heart disease, and stroke are top 10 causes of premature death in almost all regions in 2010, as was preterm birth complications in all regions except Europe, Asia Pacific High Income, and East Asia. The massive impact of HIV/AIDS on mortality in most developing regions by 2010 is also clear with North Africa / Middle East, East Asia, Central Asia, and Latin America Southern being notable exceptions. Malaria is a leading global cause but a minor cause in most regions outside sub-Saharan Africa and Oceania. Road injury is a remarkably consistent cause of YLLs; its lowest regional ranking is 19th in Oceania and it is in the top five causes in eight regions. All the neonatal causes and tuberculosis are important causes in some developing regions but relatively minor causes in the more epidemiologically and demographically advanced regions. This table also highlights causes that are not in the top 25 global rankings but are important in selected regions. In some cases, these regional patterns give a glimpse of future patterns and trends. Suicide is a top ten cause in the eight regions with the most advanced health transition. Other causes that seem to be strongly related to the epidemiological and demographic transition include colorectal cancer, breast cancer, pancreas cancer, brain cancer, non-Hodgkin's lymphoma, Alzheimer's disease, kidney cancer, and prostate cancer. Other diseases have a more focal regional pattern that is not directly related to the broad health transition. More notable examples highlighted by multi-colored rows in the table include: cirrhosis, diabetes, interpersonal violence, sickle cell, whooping cough, poisonings, esophageal cancer, drug use, gallbladder cancer, malignant melanoma, and African trypanosomiasis. In general, the distribution of ranks by cause

for YLLs is much more heterogeneous than for YLDs.[53] This is true for both time periods and suggests marked regional variation in disease and injury control priorities in order to improve survival.

There is marked variation in cancer rates by site and overall across regions in 2010 (**Figure 9).** The figure shows crude death rates to highlight the mixture of cancers seen in health systems of each 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 population age-structure. In general, crude cancer death rates are higher in the regions with a more advanced demographic transition. But regions such as Asia-Pacific High-Income have a substantially different cancer profile than Europe Western 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 Africa regions are the lowest. Latin America Central, Latin America Tropical, and Latin America Andean have relatively low cancer rates overall whereas the Caribbean has higher rates than expected for its demographic transition.

Discussion

The GBD 2010 is the most comprehensive and systematic analysis of causes of death undertaken to date. The addition of time trends over the period 1980-2010 and quantification of uncertainty increases both the utility and the methodological rigor 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% uncertainty intervals to aid interpretation. These cause of death estimates at the regional level are constructed from separate cause of death estimates at the country level for 187 countries. No such resource for policymakers, donors, or scholars currently exists. At the most aggregate level, we have documented dramatic changes in cause of death structure in regions such Latin America Central and Latin America Tropical. We have also identified regions, such as Eastern Europe and Central Asia, where levels of mortality have increased profoundly over the last 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 due to population growth alone is reversed by population aging and declines in age-sex-specific death rates.   In contrast, both population growth and aging are driving up death numbers from noncommunicable diseases and injuries more than the declines expected due to 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 LRI, diarrhea, malaria, and meningitis, and tuberculosis and maternal causes in younger adults, to one dominated by the noncommunicable causes over age 40. Quite different regional stories are overlaid on this broad pattern. Injuries have very distinct regional patterns with violent death much more common in selected regions. The HIV epidemic has had massive effects in sub-Saharan Africa East and Southern. Diabetes has a major impact in Latin America Central, 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 certain age groups or for specific causes; these differences warrant careful discussion.

The HIV epidemic has dramatically changed the pattern of causes of death over the period 1990 to 2010 in sub-Saharan Africa East and Southern. In 2010, we estimate 1·46 million deaths due to HIV/AIDS compared to UNAIDS estimates of 1·77 million. This is a 21% difference at the global level. For specific countries and regions, the differences are much larger. Given that we use UNAIDS estimates as the input to CoDCorrect for the majority of countries, 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 this is an important strength of the burden of disease approach. Some differences in results also stem from Thailand, where the 2012 UNAIDS assessment increased mortality compared to their 2010 assessment by a factor of two. Even the 2010 UNAIDS assessment was twice the magnitude recorded in two national verbal autopsy studies and vital registration data. [67,68] We have chosen 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 significant portion of the global UNAIDS and GBD differences. Since Nigeria is a country with a large population, a significant 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 significantly lower (27·9% in 2010) than UNAIDS and this large death difference 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 uncertainty interval for deaths at all ages provided by UNAIDS varies by plus 8·5% or minus 8·1%. Our uncertainty intervals based on the UNAIDS figures are 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 time course of the HIV epidemic by UNAIDS as well as further data on the levels of adult mortality in some key countries such as Nigeria.

Based on a single-cause analysis, Murray et al (2012)[25] reported 1.24 million malaria deaths in 2010 of which 42% were over age 5. These estimates had very large uncertainty intervals; for example, the number of deaths over age 5 in sub-Saharan Africa was estimated to range from 307 thousand to 658 thousand. Large uncertainty in the results reflected both the relatively 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 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 is estimated to be about 5% less or about 1.17 million. For deaths under 5, the change is from 714 thousand to 676 thousand. For deaths over 5, the change is from 524 thousand to 494 thousand. Our finding of substantial deaths due to malaria in populations over age 5 is driven by the evidence from verbal autopsy studies in endemic areas.[25] Validation studies suggest that VA studies may overestimate adult deaths at low malaria cause fractions and underestimate adult malaria deaths when malaria deaths are common.[69] The findings of adult deaths from malaria are consistent with hospital discharge and death data in endemic areas but remain controversial.[70–73] Our uncertainty interval for global

deaths over age 5 from malaria is 365,356 to 643,977 in part reflecting 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 diarrhea and lower respiratory infection (LRI) pathogens. These are important both for the prioritization of existing treatments, such as rotavirus or pneumococcal vaccines, but also for the development of future technologies. Making sense of the data on etiology is extremely challenging. For diarrhea, many pathogens can be cultured from the stool of individuals without diarrhea. Studies such as the Global Enterics Multi-Center Study (GEMS)[74] are trying to estimate relative risks of diarrhea in the presence of different pathogens. In the available observational data that do not use this relative risk approach, there is a strong relationship between the prevalence of a given pathogen and the number of pathogens tested. Studies testing only one pathogen effectively report higher fractions due to a pathogen than studies that test for multiple pathogens. This is likely due to the frequency of multiple pathogens in the same stool sample and rules for allocating shares of diarrhea to pathogens such that the sum of the pathogen cause fractions total to 100%. In our analysis, we have adjusted study results to be equivalent to studies reporting two to eight pathogens. Given 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 diarrhea etiologies. When large multi-center studies such as GEMS publish their results this will be an important addition to the analysis; future revisions of the GBD should make use of these results as they become available. Nevertheless, our results are notably different than widely cited findings. For example, we find 173 thousand deaths due to rotavirus under age 5 and 78 thousand deaths over age 5 in 2010; this contrasts with claims from WHO of 453 thousand rotavirus deaths under age 5 alone in 2008.[75] Higher numbers were likely reported by WHO for three reasons: higher all-cause under-five global deaths than currently estimated by UNICEF or the GBD; a much higher fraction of under-five deaths attributed at the time to diarrhea; and a higher fraction of diarrhea attributed to rotavirus. Because rotavirus remains an important cause of death in many countries, the GBD estimates by country will be an important tool to assist in understanding where its burden is greatest.

For respiratory pathogens, there are even greater challenges. In many observational studies, no pathogen is identified in a substantial fraction of cases. Even in severe cases that lead to hospitalization there is likely to be considerable variation in the case-fatality rate by pathogen, which confounds the analysis. The substantial differences in our results from published assessments by O'Brien et al[35] for pneumococcal LRI, Nair et al for RSV and Watt et al for Hib deserve exploration.   Our findings of 168 thousand pneumococcal LRI deaths under age 5 in 2010 and 381 thousand in 1990 under age 5 contrast sharply with the 826 thousand for the year 2000 published by O'Brien et al.[35] in 2009. O'Brien used an estimate of 10·6 million under-five deaths from all causes for the year 2000 which contrasts with our estimate of 9·4 million and UNICEF's of 9.6 million. They used a higher estimated fraction of under-five deaths due to LRI than here, 27% and 18% respectively. The fraction of under-five LRI deaths due to pneumococcal pneumonia was 35·8 % (16·0-50·9 % UI) in 2000 compared with 19·9% (16·1%-24·8% UI) in the GBD 2010 for 2010. The 95% uncertainty intervals for these cause fractions substantially overlap. Differences in the mean estimate stem largely from the exclusive use by O'Brien et al of the results of four vaccine trials in the Gambia, the Philippines, the United States, and South Africa to estimate an

average fraction of pneumonia under five. Although they reviewed the literature, they chose to not use the published observational studies. These observational data suggest substantial variation across regions; for example, pneumococcus may be less common in South Asia. We have used both the trials and observational data to generate different etiological fractions by region giving extra weight to the trials; our findings, however, still show variation by region and age. For RSV LRI, our findings of 234 thousand deaths under age 5 in 2010 and 521 thousand in 1990 are notably higher than the 66 thousand to 199 thousand deaths for the year 2005 reported by Nair et al.[76] in 2010. Nair et al. reviewed the published studies on RSV but chose, based on expert opinion, to assume no RSV deaths over the age of 2; the published literature, however, records deaths over age 2.[77,78] Hospitalization data in the US, for example, suggests considerable burden of severe RSV at least in the ages 3-5. Other studies (refs)[79,80] argue that RSV is an important and often missed pathogen causing severe LRI in the elderly. Studies, however, vary markedly in their sampling, culturing, and identification protocols which may also account for some heterogeneity. Given that most studies show high fractions of neonatal LRI deaths due to RSV, the area that needs the most attention is the extent to which RSV is a major cause of post-neonatal LRI deaths. For HiB LRI, Watt et al published in 2009 for the year 2000, an estimate of 292 thousand deaths which compares well with our finding of 184 thousand (154,053 – 219,456 95% UI) in 2010 and 447 thousand (385,717 – 506, 594 95% UI) in 1990. The similarity of the result, however, is somewhat misleading. They used a much higher estimate of all-cause under-five mortality and a higher cause fraction due to LRI than we use here. In other words, we estimate a large fraction of LRI deaths under five due to HiB than Watt et al. The primary reason is that they assumed that over age two HiB does not cause LRI death; the available observational data, however, demonstrate HiB mortality at all ages.[81–84] For example, the study in Japan found severe cases of hospital-acquired and community-acquired pneumonia related with HiB, the differences in these assessments for all the respiratory pathogens is even more marked. New multi-center studies like PERCH[85] will hopefully provide much needed data to strengthen the analysis of etiology by region.

In 2010, we estimate that there were 1·20 million deaths due to tuberculosis, about 14% more than the WHO estimate of 1·05 million (2011 WHO TB Report). Our analysis and WHO's 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 each country is estimated; WHO uses locally informed expert consultation to assess both under-diagnosis and under-reporting while we have used a statistical model to try and estimate the case detection rate. Our models also capture more of the temporal and spatial correlation structure in the cause of death data yielding quite different estimates than the WHO where data are strong (e.g. Japan and Thailand). These differences result in significant variations between our estimates and those from WHO at the country and regional levels that deserve further investigation. Despite these variations, there are also countries, such as Ecuador, where our estimates, WHO estimates, and the cause of death data are in close alignment. Both 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 multiple studies[86,87] in the peer-reviewed literature and UN reports.[88] These studies, however, have focused on the maternal mortality ratio. ICD10 rules recommend that pregnancy-related deaths due to HIV should be included in the computation of the MMR but reported in cause of death tabulations for HIV. The GBD 2010 follows this convention so that our 255 thousand maternal deaths in 2010 do not include 18,970 HIV-related deaths in pregnancy included in the HIV totals. We have also revised the method used to estimate the fraction of maternal deaths related to HIV/AIDS in this study compared to Lozano et al. 2011.[23] In this study, 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 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 hemorrhage accounting for 23% of deaths in 2010, followed by hypertensive disorders causing 19%, abortion causing 15%, sepsis causing 9%, and obstructed labor causing 4%. These results contrast with various estimates reported by WHO; one for 2005, which are based in 35,197 deaths reported in various published studies[89] and one largely based on VR data for 2008.[16] The 2005 WHO report estimated that abortion caused only 8% of maternal deaths but 14% in the 2008 study. There are also substantial differences for other maternal causes as well. Our findings are based both 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 under-five deaths, our results differ from those published by CHERG[20] for the same year in several key ways: CHERG estimates 1.40 million LRI deaths compared to 848 thousand in this study; CHERG estimates 801 thousand for diarrheal diseases versus 666 thousand in the GBD; for malaria CHERG estimates 564 thousand versus 676 thousand here. Within the neonatal causes, there are also marked 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 critical 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. Understanding the source of the differences for neonatal causes, however, is challenging. Differences must stem from any or all of the following: the datasets used, the adjustments to the data, and the modeling strategies. In their analysis of post-neonatal child mortality (1-59 months), CHERG reports using VR data for 578 country years between 1998-2009, while we use 1,125 country years for that period. They use 113 study years between 1980-2008; in contrast, we use 294. The reduced number of studies used by CHERG is due to 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 modeling strategy. For a single cause such as diarrheal diseases or lower respiratory infections, we develop one ensemble model using all the data. The one ensemble model includes component models with a wide variety of functional forms but all include age group fixed effects. CHERG tests and develops four different models with no relationship between them: for under five mortality rates (UFMR) below

35 for under 1 month, for above 35 UFMR under 1 month, for 1-59 months under 35 UFMR, and for 1-59 months above 1-59 above 35 UFMR. The relationships between covariates in these different models are estimated as completely independent. Covariate selection is performed for each cause of death independently for each of the four models. They use multinomial logistic models to make estimates for six causes of death simultaneously, a method found to perform worse than modeling causes individually and then scaling to all-cause mortality (see webappendix Section 4). Their model structure does not allow for spatial or temporal patterns in the residuals, likely substantially reducing model performance.[22] Model performance is difficult to assess and compare with ours: they report undertaking a cross-validation study but no metrics of model performance are reported such as the coverage of their uncertainty intervals or a measure of prediction error. Further, in their cross-validation study they leave out 10% of the data at random; as demonstrated in previous studies,[23] this is the easiest task for prediction. A much harder task, which is used in this study, is to leave out long sequences or all data for some countries and see how well the models perform. In addition, 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 they use. The high levels of mortality for lower respiratory infections may be related to the demonstrated bias in rigorous validation studies of physician-certified verbal autopsy to over report the LRI cause fraction.[69] While this study uses physician-certified verbal autopsy data on LRI, by separating the data into four components and not including country random effects in their models, the bias towards higher LRI in VA studies may be having a larger impact 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 modeling strategy may also cause distortions in the results. Interestingly, given the substantial difference in modeling approaches, the results for 2010 between the two approaches are actually surprisingly close.

The health-related MDGs place special priority on reducing under-five mortality, maternal mortality, and deaths from HIV, tuberculosis, and malaria. These causes collectively accounted for 42·4% of YLLs in 2010. Despite the fact that the computation of YLLs heavily weights deaths under five, over half (57·6%) of global years of life lost in 2010 were due to non-MDG diseases and injuries. Important global causes that are not included in the MDGs include ischemic heart disease, stroke, and road traffic injuries. 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 indicates that the MDG-related YLLs are declining at 2·0% per year, whereas the non-MDG related YLLs are increasing at 0·8% per year. Population aging, 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 over 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 noncommunicable diseases

argues strongly for inclusion of these conditions, and their principle causes, in this agenda, particularly given their close relationship to poverty reduction goals.[91–96] It also stresses the need to understand the effective and affordable options for prevention of noncommunicable 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. It is important to note that 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 2-4 are associated with increased risk of death. It is likely that the directly coded deaths due to chronic kidney disease estimated here capture only those deaths due to end-stage renal disease. There are other diseases such as diabetes that are also associated with an elevated risk of death from other causes. In the case of diabetes, the risk factor analysis[99] provides an assessment of all mortality associated with hyperglycemia. 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 number of direct conflict-related deaths estimated for 2010: 17,670. One needs to interpret this number with great caution. First, in the ICD cause list only direct deaths are assigned to this cause; this is not the total number of deaths related to conflict which would include indirect deaths mediated through multiple mechanisms such as the destruction of healthcare infrastructure.[100] Second, the number of direct deaths varies substantially from year to year. During the period 1990 to 2010, direct deaths peaked at 496·4 thousand in 1994 with a low in 2001 of 14·7 thousand and a low figure of 17.7 thousand in 2010. In the following year 2011, because of the conflict in Libya, for example, direct deaths were likely to have been much higher, closer to 61 thousand. 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 impact on human populations.

For the first time in the GBD enterprise, we have included deaths that are primarily related to hepatitis B, hepatitis C, alcohol, and other causes as sub-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. There are interactions between hepatitis and alcohol consumption such that assessing 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 thousand and due to hepatitis C is 499 thousand. If all deaths related to these diseases were directly counted in the main GBD 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 dramatically 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 Asia Central, Oceania, sub-Saharan Africa East and West, Europe Eastern, and Latin America Central. Not all of this regional and country variation can be explained by hepatitis B, hepatitis C, or total alcohol consumption. For example, high rates in Europe Eastern may 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 may 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 has increased from 908 thousand 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 thousand in 1990 to 461 thousand in 2010. Road deaths of occupants in motorized vehicles with three or more wheels and road deaths of riders of motorized vehicles with two wheels each have also increased by about 200 thousand over the past two decades. Regional detail shows road deaths in Asia East, Asia South, sub-Saharan Africa East and sub-Saharan Africa West rapidly escalating over the past two decades, while in high-income areas with a history of road safety programs such as Europe Western and North America High Income, 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 Asia Pacific High Income at 1 per 100 thousand. The rate in 2010 in North America High-Income dominated by the United States of 7 per 100 thousand was nearly seven times higher than Asia Pacific High Income, Western Europe, or Australasia. But in Latin America Tropical the rates are substantially greater still, at 30 per 100 thousand, and even higher in Latin America Central and sub-Saharan Africa Southern, 33 per 100 thousand. The massive 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 Latin America Tropical males, violence is the number one cause of YLLs. In 2010, males in the 20 to 24 age group alone suffered 653·6 thousand YLLs, three quarters the size of the 824·0 thousand YLLs suffered by North America High-Income males 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 **Web Table 23** the effect is to reduce the number of deaths estimated for many causes compared to 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 where the magnitude of these corrections is comparatively large, future research should be targeted to trying 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 where the data are the most inconsistent and our knowledge the most uncertain. The considerable difference between single cause model estimates and those presented here raises questions about the value of publishing single cause assessments. Some organizations 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 problems or stimulate

methods innovation or new data collection will need to be balanced against the greater robustness of more comprehensive assessments such as presented here.

A study of this size and scope undoubtedly 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 modeling strategies had to be made. We highlight some key limitations. First, cause of death data even in settings with medical certification may not always accurately capture the underlying cause of death. Autopsy studies[104–106] have demonstrated that medically certified causes of death may be incorrect.   Second, our approach to garbage code redistribution, while an improvement over past efforts, could benefit strongly from more empirical information on misclassification collected in places where gold standard cause of death assignment is possible. We have not been able to develop uncertainty distributions around garbage code redistribution algorithms; to the extent that this is poorly known, our uncertainty intervals for some causes may be underestimated. Third, we have made extensive use of verbal autopsy data especially in low-income settings.   Verbal autopsy validation studies suggest VA is quite accurate for some causes such as breast cancer, drowning, or road injuries but for other causes may be less accurate.[69]   VA performance for some key causes of child death such as LRI 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 where VA 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 uncertainty intervals.   The use of negative binomial models and fixed proportion models where data are extremely weak is another area where better data and improved methods could strengthen the overall findings.   Fifth, where natural history models have been used, it is at present extremely difficult to validate these. Natural history models are in principle used when there are concerns that direct cause of death data are potentially biased. Improvements in cause of death data for some causes such as HIV/AIDS may allow in the future opportunities to validate natural history models in selected countries. Where natural history models have been used, there is a potential that these approaches will tend to yield higher estimates than using more empirical strategies such as CODEm.   Sixth, our use of CODEm for most major causes of death means that our uncertainty intervals have in most cases been demonstrated 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 uncertainty intervals 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 cause of death data itself. Eighth, in cases where expert opinion and the available data diverge, we have tended to follow the available data. Examples of this practice include estimating deaths from malaria over age 5 or deaths from Hib over age 2. Subsequent more detailed studies may affirm that expert opinion was correct and the available data substantially biased. Nevertheless, we believe it is important to follow the balance of the available data that meet our quality criteria.

Improving cause of death data collection in the future is the most direct and obvious pathway to better global, regional, and national cause of death estimation with narrower uncertainty intervals. Improved verbal autopsy tools[108–111] mean that it may soon be feasible to apply them routinely to generate comparable cause of death data cost effectively in populations where 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 this case is to improve cause of death certification and coding. Other countries such as Saudi Arabia have functioning civil registration run by Ministries of the Interior that are not fully utilized by Ministries of Health. Collectively, the global health community would benefit enormously by placing much greater priority on strengthening vital registration systems to improve cause of death measurement. This is now the key focus of the Health Metrics Network and it is reasonable to expect that significant 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 tools have been developed and applied. These tools 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 endeavor, 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 massive 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. There can be no doubt that 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.

Author Contributions

CJLM, ADL, and RL prepared the first draft. RL, MN, KF, SL, KS, ADL, and CJLM finalized the draft based on comments from other authors and reviewer feedback. ADL and CJLM conceived of 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 manuscript.

Conflicts of Interest

We declare no conflicts of interest.

Acknowledgements

Figures and Tables

Table 1. Decomposition analysis of the change of global death numbers by broad cause groups from 1990 to 2010 into total population growth, population aging and changes in age-,sex-and cause-specific death rates.

Table 2. Global death numbers for 235 causes in 1990 and 2010 for all ages and both sexes combined (thousands) and age-standardized death rates (per 100 thousand) with 95% uncertainty intervals and percent change.

Table 3. Ranking of YLLs for top 25 global causes in 2010 and additional causes appearing within the top 25 causes for any region across 21 geographic regions ordered by overall global ranking. Red indicates the causes with the highest ranking (1-10), followed by those in dark orange (11-20), orange (21-30), yellow (31-50), green (51-90), and, finally, blue (91-171) showing the lowest ranked causes.

Figure 1a, 1b, 1c, 1d. Percentage of global deaths for females and males in 1990 and 2010 by cause and age. The causes include war and natural disaster; intentional injuries ("Intent Inj"); accidents; transport accidents; other non-communicable diseases ("Oth NCD"); musculoskeletal diseases ("MSK"); diabetes, urinary, blood, and endocrine ("DUBE"); mental and behavioral disorders ("Mental"), neurological disorders ("Neuro"), digestive diseases; cirrhosis; chronic respiratory diseases ("Chronic Resp"); cardiovascular and circulatory diseases ("Cardio & Circ"); cancer; other communicable diseases ("Other Comm"); nutritional deficiencies ("Nutr Def"); neonatal; maternal; parasitic; child infectious diseases; and HIV + TB.

Figure 2a, 2b, 2c. Pie chart of global deaths in 2010 for both sexes combined and ages 0-27 days (neonatal), 28-365 days (post-neonatal), and 1-4 years by cause. Some cause abbreviations used in the figures are lower respiratory infections ("LRI"); pneumonia ("Pneum"); *Haemophilus influenzae* type b ("HIB"); respiratory syncytial virus (RSV); enterotoxigenic E. coli ("ETEC"); cryptosporidiosis ("Crypto"); enteropathogenic E. coli ("EPEC"); campylobacter ("Campylo"); diabetes, urinary, blood, and endocrine ("DUBE"); and other non-communicable diseases ("Other NCD").

Figure 3a, 3b. Pie chart of global deaths in 2010 for males and females ages 15-49. Some cause abbreviations used in the figures are lower respiratory infections ("LRI"); cardiovascular disease ("CVD"); and chronic kidney disease ("CKD") .

Figure 4. Global death ranks for all ages and both sexes combined with 95 % UI for the top 25 causes and the percent change with 95 % UI from 1990 and 2010. The colors represent the various level one

causes; blue is for non-communicable diseases, red is for communicable, maternal, neonatal and nutritional conditions, and green is for injuries. The dashed lines signify descending order in rank, while the solid lines signify ascending order in rank. Some cause abbreviations used in the figure are ischemic heart disease ("IHD"); lower respiratory infections ("LRI"); chronic obstructive pulmonary disorder ("COPD"); tuberculosis ("TB"); cancer ("CA"); road injuries ("Road Inj"); protein energy malnutrition ("PEM"); neonatal encephalopathy ("N Enceph"); hypertensive heart disease ("HTN Heart"); neonatal sepsis ("N Sepsis"); other circulatory ("Oth Circ"); rheumatic heart disease ("Rheum HD"); and chronic kidney disease ("CKD").

Figure 5. Percentage of global YLLs from 1990 to 2010 for all ages and both sexes combined by cause and year. The causes include war and natural disaster; intentional injuries ("Intent Inj"); accidents; transport accidents; other non-communicable diseases ("Oth NCD"); musculoskeletal diseases ("MSK"); diabetes, urinary, blood, and endocrine ("DUBE"); mental and behavioral disorders ("Mental"), neurological disorders ("Neuro"), digestive diseases; cirrhosis; chronic respiratory diseases ("Chronic Resp"); cardiovascular and circulatory diseases ("Cardio & Circ"); cancer; other communicable diseases ("Other Comm"); nutritional deficiencies ("Nutr Def"); neonatal; maternal; parasitic; child infectious diseases; and HIV + TB.

Figure 6. Global YLL ranks for all ages and both sexes combined with 95 % UI for the top 25 causes and the percent change with 95 % UI from 1990 and 2010. The colors represent the various level one causes; blue is for non-communicable diseases, red is for communicable, maternal, neonatal and nutritional conditions, and green is for injuries. The dashed lines signify descending order in rank, while the solid lines signify ascending order in rank. Some cause abbreviations used in the figure are lower respiratory infections ("LRI"); ischemic heart disease ("IHD"); chronic obstructive pulmonary disorder ("COPD"); protein energy malnutrition ("PEM"); tuberculosis ("TB"); neonatal encephalopathy ("N Enceph"); neonatal sepsis ("N Sepsis"); road injuries ("Road Inj"); cancer ("CA"); and chronic kidney disease ("CKD").

Figure 7. Global YLL 95 % UI (millions) vs rank by cause in 2010.

Figure 8a, 8b. Percentage of YLLs for all ages and both sexes combined by cause and region in 1990 and 2010. The causes include war and natural disaster; intentional injuries ("Intent Inj"); accidents; transport accidents; other non-communicable diseases ("Oth NCD"); musculoskeletal diseases ("MSK"); diabetes, urinary, blood, and endocrine ("DUBE"); mental and behavioral disorders ("Mental"), neurological disorders ("Neuro"), digestive diseases; cirrhosis; chronic respiratory diseases ("Chronic Resp"); cardiovascular and circulatory diseases ("Cardio & Circ"); cancer; other communicable diseases ("Other Comm"); nutritional deficiencies ("Nutr Def"); neonatal; maternal; parasitic; child infectious diseases; and HIV + TB.

Figure 9. Cancer death rates (per 100 thousand) in 2010 for all ages and both sexes combined by cause and region.

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