Global, regional, and national incidence, prevalence, and YLDs for 301 acute and chronic diseases and injuries for 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013

GBD 2013 Disease and Injury Incidence and Prevalence Collaborators

Introduction

The Global Burden of Diseases, Injuries, and Risk Factors 2013 Study (GBD 2013) is the first of a series of annual updates for the GBD studies that began with estimates for 1990 and were most recently updated to the year 2010. The 2010 update (GBD 2010) systematically quantified prevalence of 1,160 sequelae of 289 diseases and injuries across 21 regions.[1] National estimates for 187 countries were also derived based on the global and regional statistical analysis.[1] Years lived with disability (YLDs), equal to the sum of prevalence times the general public's assessment of the severity of health loss, was extensively used to explore patterns over time, age, sex, and geography.[1] Results for specific diseases and impairments have been extensively published.[2–46] These results have drawn attention to the importance of disability from musculoskeletal disorders, mental and substance abuse disorders, and a variety of other non-communicable diseases.[1] In developing countries, conditions such as anaemia and neglected tropical diseases remained important contributors to health loss.[18,43,47] More generally, the analysis highlighted the global transition towards a rapidly increasing volume of YLDs due to global population growth and aging, combined with little progress in reducing age-specific YLD rates.

Given the ambitious goal of the GBD 2010, to synthesise the global evidence on the country-age-sex-year prevalence of all major conditions, a number of specific estimates have been critiqued. Specific data sources, modeling assumptions, and aspects of the general approach have been challenged and there is widespread recognition that more and higher quality data could improve the estimates.[48–52] Disability weights that were used to calculate YLDs were based on surveys of the general public in five countries (Bangladesh, Indonesia, Peru, Tanzania, and the United States) and an open internet survey. The validity of disability weights has been questioned for selected states including hearing loss, vision loss, drug use, spinal cord lesion, intellectual disability, and musculoskeletal disorders.[53,54] Some authors have questioned whether disability weights should be measuring health or the loss of well-being associated with health states.[53,55] In addition, the YLD uncertainty intervals were large for a number of conditions because of scarce data, the need to statistically adjust for different case definitions, measurement methods, and wide uncertainty intervals for disability weights. Wide uncertainty intervals have limited the number of statistically significant differences for some conditions reported across time and countries. Broad interest and critical discourse on the GBD has also brought to light many unpublished data sources in specific countries that could be used to strengthen the analysis.

Given the prominent role attached to quantification of disease burden for health research and policy nationally and globally, up-to-date estimates reflecting the latest evidence for descriptive epidemiology constitute an essential global public good.[22–27,32,56–60] The GBD 2013 provides an opportunity to incorporate constructive critical commentary on GBD 2010 data sources, model development, methods, and interpretation. Additionally, the GBD 2013 reflects methodological advances and includes new data on disability weights, capturing many new published or unpublished data sources for the conditions included in the GBD. In this paper, we report on the data, methods, and results analysing 188 countries

for the period 1990 to 2013 for 301 diseases and injuries and their 2,337 sequelae. We report incidence for acute sequelae and prevalence for chronic sequelae in addition to YLDs for all causes. Because prevalence and YLDs for the entire period from 1990 to 2013 are re-analysed using consistent data and methods, these results supersede any prior publications on the GBD.

Methods

Overview

Our general approach is similar to the GBD 2010. The analysis of incidence and prevalence for HIV/AIDS, tuberculosis (TB), and malaria for GBD 2013 have already been published in detail.[61] Key changes from GBD 2010 are the inclusion of new data through updated systematic reviews and the contribution of unpublished data sources from many collaborators; elaboration of the sequelae list to include asymptomatic states, such as *Plasmodium falciparum* parasitemia (PfPR) without symptoms; utilisation of more detailed nature of injury codes (N-codes); improvements to the Bayesian meta-regression method; increased simulation size for comorbidity; estimation of the prevalence of injuries by cohort; and use of a novel method to estimate the distribution of mild, moderate, and severe anaemia by aetiology.

Cause and sequelae list changes

Based on feedback from GBD 2010, as well as input from the GBD 2013 collaborators, we expanded the cause and sequelae list (Appendix Table A.1). There are several key changes. First, we have included asymptomatic states as explicit sequelae so that overall disease prevalence estimates are available, which may be useful for disease targeting, health service planning, or mass treatment strategies. Asymptomatic sequelae, by definition, are not associated with ill health and therefore are not assigned disability weights. Second, to deal with the challenge that some of the nature-of-injury categories used in the GBD 2010 were highly heterogeneous, these categories has been expanded from 23 to 47. Third, we added a number of new causes and sequelae. All these additions to the cause list were based on either reducing the size of large residual categories, such as other injuries, or recognition of marked epidemiological heterogeneity within a disease category (Appendix Table A.1). With these changes, the cause list has expanded from 289 to 301 causes and from 1,160 to 2,337 sequelae. The majority of the increase in sequelae is due to the expansion of the nature-of-injury sequelae which apply to each of the external causes of injuries. Appendix Table A.2 provides a list of ICD-10 and ICD-9 codes for all GBD causes and the nature-of-injury categories.

Identification, documentation, and representativeness of data sources

GBD 2010 collaborators undertook systematic reviews for the majority of causes and sequelae. For some sequelae the vast majority of data came from household survey micro-data re-analysis and administrative data such as hospital discharges. For others, the majority of data was extracted from published literature. Documentation of the GBD 2010 systematic reviews, however, was not centralised and only some of these reviews have been published. For this study, we updated systematic reviews through August 2013. In some cases, studies published after August 2013 have been identified and included based on GBD collaborator input; no data or studies were extracted after November 2014. Household surveys including the Demographic and Health Surveys, Multiple Indicator Cluster Surveys, Living Standards Measurement Surveys, Reproductive Health Surveys, and various national health surveys included in the Global Health Data Exchange (ghdx.healthdata.org) were systematically screened for data relevant to sequelae. For

some diseases, case notifications reported to the World Health Organization (WHO) have been used as inputs and have been updated through 2013. Appendix Table A.3 provides a full list of citations for sources organised by country used for this analysis.

We have computed an index of the geographic and temporal representativeness of the data sources available on non-fatal health outcomes for each cause or impairment – the data representativeness index (DRI). The overall DRI simply counts what fraction of countries have any incidence, prevalence, remission, or excess mortality data available for causes that are prevalent in that country. We do not count cause of death data in this measure, even if it is used in the estimation of incidence or prevalence. We compute the same measure for three time periods: prior to 1998, 1998 to 2005, and 2006 onwards. Table 1 provides the overall DRI and period-specific DRI measures for each cause and Table 2 provides the same information for estimation of total impairment prevalence. The DRI has also been computed for Level 1 and Level 2 causes (aggregate causes) by counting data availability for any cause within that aggregate. This metric simply reflects availability of data and does not incorporate any assessment of data quality. The all-cause DRI is 100% overall and for each time period, indicating that there is at least data on one cause for all 188 countries in each time period. At more detailed levels, however, there is wide variation in the DRI across causes and time. DRI ranges from below 2% for 8 causes, including G6PD trait and other mental and substance abuse disorders, to 100% for Chagas, African trypanosomiasis, and food-bourne trematodiases. Causes with required infectious disease case reporting have high DRI values. Other conditions, such as cancers, have DRI values above 70% due to the network of population-based cancer registries. While the time trend varies by condition, many of the highest DRI values are from 1998 to 2005. The lag in data analyses and publications may explain lower DRI values for the period of 2006 to present.

Data representativeness can also be examined at the country level. Figure 1 shows a map of the percent of causes for which there is data available in each of the 188 countries between 1990 and 2013. The DRI values range from 6% in South Sudan to 92% in the USA. Many developed countries have data for more than 65% of causes; Brazil, India, and China have similar levels. Low levels of data availability are seen in a number of sub-Saharan African countries, Central Asia, the Caribbean, and the Balkans. Within regions there is marked variation; for example Kenya has 49%, while Djibouti has less than 10%; Laos has 14%, and Thailand has 54%.

Estimating sequelae incidence and prevalence

Appendix Table A.4 provides a brief description of the modeling strategy used for each sequela and cause. The most extensively used estimation method is the Bayesian meta-regression method DisMod-MR 2.0. For some causes such as HIV or hepatitis B and C, disease-specific natural history models have been used where the underlying three state model in DisMod-MR 2.0 (susceptible, cases, dead) is insufficient to capture the complexity of a disease process. For some diseases with a range of sequelae differentiated by severity, such as chronic obstructive pulmonary disease (COPD) or diabetes mellitus, DisMod-MR 2.0 is used to meta-analyse the data on overall prevalence. Separate DisMod-MR 2.0 models are then used to analyse data on the proportion of cases with different severity levels or sequelae. Likewise, DisMod-MR 2.0 is used to meta-analyse data on the proportions of liver cancer and cirrhosis due to underlying aetiologies such as hepatitis B, hepatitis C, and alcohol use. For acute sequelae, we report incidence (defined by a duration of three months or less) at the cause level in Table 3, as incidence is the preferred measure for conditions of short duration.

DisMod-MR 2.0 represents a major advance in the computational speed, geographic disaggregation of full internally consistent posterior estimation, and display of data results as compared to DisMod-MR 1.0, which was used in GBD 2010. Through cross-validation tests, Flaxman et al. found that the log rates specification of models worked as well or better than the negative binomial specification used in DisMod-MR 1.0.[62] Based on these findings, as well as the substantial improvements in computational speed for log rate models, this specification is the default method for DisMod-MR 2.0. Appendix B provides details of the DisMod-MR 2.0 likelihood estimation. The source code for DisMod-MR 2.0 is available at http://ihmeuw.org/dismod-ode. The DisMod-MR 1.0 sequence of global estimation, regional estimation, and country prediction, which we call an analytical cascade, is illustrated in Appendix Figure B.1. Dismod-MR 2.0 uses a more complete cascade (Appendix Figure B.2). At the global level, a mixed effects non-linear regression using all available country data is used to generate super-region priors. In turn, a super-region specific mixed effects non-linear regression is used to estimate for regions. The same regression method is used for estimating further geographic disaggregation. The analyst can choose, depending on data density, to branch the cascade in terms of time and sex at different levels. In GBD 2010, DisMod-MR 1.0 was used to generate fits for three time periods only: 1990, 2005, and 2010 because of long computational time. For GBD 2013, we generate fits for 1990, 1995, 2000, 2005, 2010, and 2013.

DisMod-MR 2.0 internal validity was assessed using R-Squared for adjusted data. Results for all DisMod-MR 2.0 models are provided in Appendix Table B.1. Adjusted data are the original study data transformed to the reference case definition and measurement method, using the meta-regression component of DisMod-MR 2.0 to make the data from different studies with varying methods comparable. External validity was also evaluated by performing cross-validation on a limited number of sequelae due to the computational time and complexity for this analysis. We selected 10 DisMod-MR 2.0 models representing a range of data densities to evaluate. We held out 30% of data points for incidence and prevalence at random, refit the model, and compared predictions to the held-out data. We assessed model performance using two metrics: the root-mean squared error (RMSE) of the predictions compared to the data held-out, and the coverage of the data prediction with 95% uncertainty intervals. Appendix Table B.2 provides these metrics for the 10 models tested. In all cases, external validity was equal to or only slightly worse than internal validity.

As in GBD 2010, DisMod-MR was not used to model estimates for a short list of causes; custom models were created for many of these. For some of these causes, important improvements in the modeling strategy have been implemented. Changes for HIV and malaria have been described elsewhere.[61] For dengue, the model was modified to use the first component of a principal components analysis of Bhatt et al.'s dengue transmission probability in order to improve estimation of case rates.[63] For lymphatic filariasis (LF), pre-control levels were estimated from data reported in the LF Atlas.[64] Finally, based on critical input from GBD collaborators, we chose to model rheumatic heart disease (RHD) in low- and middle- income countries separately from high-income countries given potential differences in long-term cohort effects of treatment.

Estimation for cancer in GBD 2013 largely followed a similar analytical strategy to GBD 2010, which used a combination of incidence data, survival data, and sequelae durations to estimate cancer prevalence and YLDs.[65,66] The analysis benefited from the inclusion of both the latest edition of Cancer Incidence in Five Continents (Ci5) and a larger number of other cancer registries particularly in China. In GBD 2013,

we also incorporated new data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) and the World Health Organization's International Agency for Research on Cancer's (IARC) Cancer Survival in Africa, Asia, the Caribbean, and Central America (SurvCan) to update best and worst case survival, yearly survival trends, and sequelae durations for all cancers.[67,68] Based on evidence that individuals with most cancers continue to have excess mortality beyond five years as compared to the general population, we now estimate the burden of cancer to ten years after incidence. Estimates for cancer sequelae now represents the burden for all cancer patients in contrast to estimating burden just for cancer survivors (see Appendix C for greater detail on aspects of estimating non-fatal cancer outcomes that were different from the methods used in GBD 2010).

Injuries Analysis

We followed a similar strategy to GBD 2010 for estimating the burden of injuries but for an expanded list of 26 external cause-of-injury categories (from 15) and 47 nature-of-injury categories (from 23) for both short-term outcomes and lasting disability (see Appendix Table A.2 for ICD codes). More detail was added to both external causes and nature of injury categories to reduce epidemiological heterogeneity within each combination of cause and nature-of-injury category. The key analytical steps are explained in greater detail in Appendix D. Here we provide a summary of the methods.

First, for each external cause, DisMod-MR 2.0 was used to analyse incidence based on hospital, emergency department, and survey data. Second, we estimated the distribution of nature of injury for each external cause using data that has been dual E- and N-coded where available. Where individuals were coded with more than one N-code, we used the most severe. Third, we analysed seven studies that provided at least one year follow-up for various natures of injury to estimate long-term disability.[69–75] Fourth, we estimated cohort prevalence of long-term disability from the incident cases of injury for each E-N combination while accounting for excess mortality for the more severe post-injury sequelae. For some injuries, treatment modifies the disability weight. In these cases, we approximated the fraction of injuries receiving treatment as a function of an indicator of health system access.[76]

Short-term disability was estimated for all nature-of-injury by cause-of-injury categories as the product of prevalence (estimated by multiplying incidence by average duration) and the appropriate disability weight. The duration for treated cases of injuries was determined in the Dutch Injury Surveillance System follow-up studies of 2007-2010 and 2001-2004.[71,73] We used expert opinion to estimate a multiplier for the duration of short-term disability from untreated injuries and used the estimates of access to care by country and year as we describe for the long-term disability.

YLDs from 29 residual causes

Despite expanding our list of causes and sequelae in GBD 2013, many diseases remain for which we do not explicitly model disease prevalence and YLDs. The GBD cause list is collectively exhaustive such that all sequelae with an ICD code are mapped to a cause group (Appendix Table A.2). Many less common sequelae are included in 29 of the residual categories. For 14 of these cause groupings, epidemiological data on incidence or prevalence are available so that they can be modeled as other causes have been modeled – this set includes meningitis, cirrhosis, liver cancer, pneumoconiosis, and chronic kidney disease due to other causes; other neoplasms; other cardiovascular and circulatory diseases; other drug use disorders; other mental and substance use disorders; other gynecological diseases; other musculoskeletal disorders; other skin and subcutaneous diseases; age-related and other hearing loss; age-related and other vision loss; other sense organ diseases; and other oral disorders. For 12 residual

categories (other intestinal infectious diseases, other neglected tropical diseases, other maternal disorders, other neonatal disorders, other nutritional deficiencies, other infectious diseases, other chronic respiratory diseases, other digestive diseases, other neurological disorders, other urinary diseases, other hemoglobinopathies and hemolytic anaemias, and other congenital anomalies), epidemiological data on incidence and prevalence were not available for the entire residual cause grouping but sufficient cause of death data allowed for cause of death estimates. For these categories, we estimate YLDs by scaling the YLD age-sex pattern for other diseases in the same Level 2 category by the ratio of YLLs from the residual category to the YLLs from the other diseases, this scaling is undertaken for each country-sex-year. This approach makes the simplifying assumption that on average within a Level 2 disease grouping the experience of disability is proportionate to mortality within a country-sex-year. For an additional three residual categories (other sexually transmitted diseases, other drug use disorders, and other mental and substance use disorders), there were no overall epidemiological data nor sufficient deaths to generate cause of death estimates. For the latter two, we used USA outpatient data or prevalence data from MEPS, NESARC, or the 1997 Australian mental health survey and apply a severity distribution from these surveys in all countries and time periods. These two causes for which USA and Australian data are applied worldwide account for 1.6% of global YLDs.

Impairments

As in GBD 2010, we estimated the country-age-sex-year prevalence of nine impairments: anaemia, epilepsy, hearing loss, heart failure, intellectual disability, infertility, vision loss, Guillain-Barré syndrome, and pelvic inflammatory disease. These were selected because these impairments are sequelae of multiple diseases and data are available to estimate prevalence for the overall impairment. In general, overall impairment prevalence was estimated using DisMod-MR 2.0. Cause-specific estimates of impairments, such as the 19 causes of blindness, are required to sum to the total prevalence estimated for that impairment. Anaemia, epilepsy, hearing loss, heart failure, intellectual disability, and pelvic inflammatory disease are estimated for different levels of severity. Separate estimates were made for primary infertility (in couples who have not been able to conceive) and secondary infertility (in couples having trouble conceiving again) and, for each, if the impairment is affecting men and/or women. The severity distribution of cause-specific prevalence of each impairment was either estimated as explained above or, in the absence of severity-specific data, assumed to be proportionate across all levels of severity. In the case of epilepsy, severity levels were determined by DisMod-MR 2.0 proportion models for primary, severe, and treated epilepsy, and a meta-analysis for seizure-free treated epilepsy, and thus had values that were specific for country, age, sex, and year. Similarly, DisMod-MR 2.0 models produced country-, age-, sex-, and year- specific levels of hearing loss and vision loss. Due to limited information on the severity levels of intellectual disability, we assumed a similar distribution of severity globally based on meta-analysis of IQ-specific data for the overall impairment. This was supplemented by aetiology-specific distributions for chromosomal causes and iodine deficiency, while the severity of intellectual disability included in the long-term sequelae of causes such as meningitis, neonatal tetanus, and malaria was combined with multiple impairments such as motor impairment, blindness, and/or seizures. The severity of heart failure is derived from our MEPS analysis and therefore is not specific for country, year, age, or sex.

Our method for estimating overall anaemia was largely the same as in GBD 2010 but with the addition of new data sources, especially sub-national data for the United Kingdom, China, and Mexico.[43] We adopted different thresholds for defining anaemia during the neonatal period, as the GBD 2010 thresholds did not

account for hematologic realities of early life. The GBD 2013 thresholds match the WHO recommendations[77] with the exception of thresholds for those under one month, as there is no international cutoff for diagnosis at that age.[43,78] In order to disaggregate marginal estimates of anaemia severity and aetiology into a complete set of prevalence estimates for aetiology/severity pairs, we developed a new method for GBD 2013 that employed techniques from Bayesian contingency table modeling.[79,80]

In GBD 2010, hearing loss of more than 35+ db in DisMod-MR 1.0 was estimated and then broken down into six severity levels based on a series of regressions on the proportionate distribution across categories. In GBD 2013, we first estimated the prevalence of normal hearing, hearing loss of 20-34 dB (mild), and greater than 35 dB (moderate and above); these three categories were constrained to add up to 100%. We then ran separate DisMod-MR 2.0 models for five severity levels (i.e., moderate 35-49, moderately severe 50-64, severe 65-79, profound 80-94, and complete 95+ dB), which were then proportionally rescaled to fit in the 35+ dB envelope. In GBD 2010, the same severity distribution was assumed for each cause of hearing loss. In GBD 2013, we customised the prevalence estimation for each aetiology. Hearing loss due to otitis media and age-related hearing loss were estimated by DisMod-MR 2.0 using prevalence data. Hearing loss due to meningitis was estimated as a proportion of meningitis cases from a meta-analysis.[81] Congenital hearing loss was estimated using birth prevalence data in DisMod-MR 2.0, assuming a constant prevalence throughout all ages, as no evidence was found to support an increased mortality risk. We assumed all hearing loss from otitis media is mild or moderate based on reported distribution of hearing loss.[82,83] To account for hearing aids, we assume the use of a hearing aid reduces the severity of hearing loss by one level. The other aetiologies were assumed to cover the full range of severities. More details on impairments are provided in the Appendix E.

Severity distributions

For 190 causes, a range of sequelae are defined in terms of severity. Important changes to the sequelae list with regards to severity include low back pain, alcohol and drug dependence categories, uterine prolapse, and epilepsy. Milder states for low back pain and alcohol and drug dependence categories were added, as these conditions had a large gap between asymptomatic cases and the high value of the disability weight for the least severe symptomatic categories while the epidemiological data on severity indicates a sizeable proportion of cases with milder disability. Stress incontinence was added as a sequela of uterine prolapse with a new disability weight that is distinct from full incontinence. Lastly, epilepsy health states are now better aligned with epidemiological data based on seizure frequency. In cases where severity is related to a particular impairment, such as mild, moderate, and severe anaemia due to malaria, the analysis is driven by the impairment estimation described below. For some outcomes such as COPD or asthma, data have been collected in different locations around the world and these have been modeled using DisMod-MR 2.0 (see Appendix Table A.4 for details). In other cases, published meta-analyses have been used to estimate the allocation of cases by severity level. For the remaining causes, we used the same approach for estimating the distribution of severity as in the GBD 2010; empirical analysis of this model was updated through the addition of two more years from the US Medical Expenditure Panel Survey (MEPS). Appendix Table A.5 lists the GBD causes that can be identified in MEPS and the corresponding ICD-9 CM codes. In total, 203,960 observations were used covering 119,676 individuals. In the cases of dementia, Parkinson's disease, multiple sclerosis, osteoarthritis, schizophrenia, and bipolar disorder, data identified through literature reviews was used to inform the severity distribution. The introduction of a

health state for mild drug dependence required identification of epidemiological data to estimate the proportion of cases with mild versus more severe disability. For cannabis dependence, we used the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) survey in the USA and the Australian National Survey of Mental Health and Wellbeing. For the remaining three drug dependence categories, we only had access to one study on poly-drug users in Australia, which led to about half of dependent cases being assigned to the more severe and mild health states. While this information is derived from a non-representative cohort of drug users, it was considered more appropriate than deriving a severity distribution from a household survey like NESARC in which only a small proportion of those dependent on opioids, cocaine, or amphetamines would be represented.

Revisions to disability weights

The GBD 2010 Disability Weights Measurement study introduced a new method of pairwise comparisons as a means of eliciting weightings for health states in population surveys.[84,85] Data were collected in five countries (Bangladesh, Indonesia, Peru, Tanzania, and the United States) and supplemented with a web survey. In total, responses were collected from 30,230 people in 167 countries. Respondents were presented with a series of randomly selected pairwise comparisons of lay descriptions of health states and asked to state which health state is healthier than the other. Salomon et al. developed a statistical model that yields from these pairwise comparisons disability weights on a scale from 0 (no health loss) to 1 (equivalent to death).[84] Based on critical commentary and review of the GBD 2013 collaborators, we have revised the lay descriptions of 32 states and added 16 new states. The revised lay descriptions were based on identifying inconsistency in the way progression across levels of severity had been handled for some outcomes and the addition of social isolation to the descriptions for complete, profound and severe hearing loss. New states included five milder health states for alcohol and drug dependence; two health states for epilepsy aligning with the epidemiological data defining severe epilepsy in persons who experience on average one or more fits a month and less severe epilepsy in those with between one and eleven fits in the past year; two milder health states for low back pain; and one each for stress incontinence, concussion, hypothyroidism, hyperthyroidism, thrombocytopenic purpura, vertigo, and amputation of one arm without treatment). Appendix Table A.6 provides a complete listing of the lay descriptions of all 235 GBD 2013 health states.

In 2013, we had the opportunity to collaborate with the European Centre for Disease Prevention and Control to collect new data on disability weights in four population-based national surveys (Hungary, Italy, Sweden, and the Netherlands) using the Salomon et al. protocol.[84,86] For reasons of funding and instrument length, the surveys included 140 of the 220 GBD 2010 health states for which the lay descriptions had not been revised, 32 health states with revised lay descriptions, and 42 new health states, 16 of which were included in GBD 2013. These nationally representative samples were comprised of 30,660 respondents. For GBD 2013, the data of GBD 2010 Disability Weights Measurement study and the European Disability Weights Measurement study were pooled in a single analysis of individual responses, thus more than doubling the number of respondents to 60,890 in both studies. For states where the lay description was not previously included, revised, or new, only the European Disability Weights Measurement study data were used. This means that all disability weights in GBD 2013 differ from the GBD 2010 disability weights. Most disability weights have changed only marginally, but some differ more widely (Appendix Table A.7). Some of the more substantial changes were due to the inclusion of incontinence to the lay descriptions for spinal cord injury and the inclusion of the psychological consequences of social isolation in people with more severe hearing loss which led to much higher

disability weights. The statistical analysis generates uncertainty distributions for each disability weight which are propagated into the uncertainty distributions of the estimates of YLDs.

Comorbidity

Disability is experienced by individuals; many individuals experience more than one disease or injury sequela at the same time. To accurately, account for comorbidity and its impact on disability for individuals, we used the GBD 2010 micro-simulation approach. In the micro-simulations, a set of individuals are exposed to the probability of having all the different sequelae included in the GBD to estimate a distribution of the combinations that might be observed in each country-age-sex-year. We model the probabilities within each country-age-sex-year of different sequelae as independent. While there are clear examples where the probability of one sequela changes the probability of other sequelae, such as diabetes and ischemic heart disease, testing reported in Vos et al. suggested that modeling assuming independence was a reasonable approximation.[1] However, for less common sequelae the micro-simulation tends to increase the estimated uncertainty in the number of YLDs substantially; because for example a sequela that is estimated to have a prevalence of less than 1 in 10,000 will not at random appear in many micro-simulations of size 20,000. Two steps have been taken to reduce the inflation of uncertainty for uncommon sequelae. First, the number of simulants in each country-age-sex-year was increased to 40,000; the main limiting factor for the number of simulants is computational resources required to run 62,880 country-age-sex-year simulations each 1000 times to account for uncertainty in each of the input prevalence rates. Second, for sequelae in a country-age-sex-year with a prevalence less than 1 in 20,000, we exclude these from the micro-simulation. YLDs for these sequelae, however, were corrected by the average reduction in YLDs a country-age-sex-year of sequelae included in the micro-simulation compared to a simple calculation of prevalence multiplied by disability weight. The combined disability weight for individuals with multiple sequelae was computed as in the GBD 2010 using a multiplicative model; namely, the individuals' disability weight is equal to one minus the cross product of one minus the disability weight for each sequela that the individual experiences. An output from the comorbidity micro-simulation is counts of the number of sequelae for each simulant in the population. The numbers of simulants with different comorbidities in a country-age-sex-year was adjusted from 40,000 to equal the estimated population in each age-sex-country-year to produce the estimated distribution of individuals in each country with comorbidities. Sequelae with a prevalence of less than one in 20,000 that were not included in the micro-simulation, are also not included in the population pyramids showing individuals by numbers of sequelae (Figures 2a-c). A technical description of the comorbidity simulation is given in Appendix A.

Uncertainty intervals

We report 95% uncertainty intervals for each quantity in this analysis. For disease or sequelae incidence or prevalence rates, age-standardised rates or counts, the models such as DisMod-MR 2.0 provide posterior distributions of each quantity from which 95% uncertainty intervals are computed. For YLDs, we incorporate uncertainty in prevalence and uncertainty in the disability weight into the posterior distribution of YLDs. In practice, we estimate the posterior distribution of YLDs by taking 1000 samples from the posterior distribution of prevalence and 1000 samples of the disability weight to generate 1000 samples of the YLD distribution. We estimate the 95% uncertainty interval by reporting the 25^{th} and 975^{th} values of the distribution. Uncertainty intervals for YLDs at different points in time (1990, 1995, 2000, 2005, 2010, and 2013) for a given disease or sequelae are correlated because of the shared uncertainty in the disability weight.

Results

We begin the presentation of results with population pyramids illustrating number of sequelae, followed by global estimates of the incidence of acute conditions, the prevalence of chronic diseases, and then common impairments such as vision loss, hearing loss, and anemia. We then present the changes in YLDs between 1990 and 2013 globally and by country, decomposing these trends into underlying causes.

Population distribution by number of sequelae

Figures 2a, 2b, and 2c show the population pyramid for developed countries, developing countries excluding sub-Saharan Africa, and sub-Saharan Africa in 1990 and 2013 broken down by the number of sequelae, ranging from very mild to severe, experienced by each individual. The vast majority of the world's population suffers from at least one of the GBD sequelae and most people have multiple. As expected, given the strong relationship between age and disease prevalence for most non-communicable diseases (NCDs) and injuries, the number of individuals with multiple morbidities rapidly increases with age. In developed countries, 35.9% of the age-group 0-4 has no sequela with only 0.03% over age 80 with no sequela. In the age-group over 80, 10.3% have 1-4 sequelae, 64.6% 5-9 sequelae and 25.1% have 10 or more sequelae. The percent of each age-group with multiple morbidities rises progressively with age regardless of the cutoff used to define multiple morbidities. Due to this relationship and the demographic shifts towards older ages in developed countries, the number with more than 10 sequelae increased by 51.6% from 1990 to 2013. In the oldest age-group, 23.6% of women have more than 10 sequelae and 27.8% of men but the large population imbalance at older age favoring women means that there are 1.4 times more women with 10 or more sequelae compared to men.

Figure 2b shows the pyramids for developing countries outside of sub-Saharan Africa and documents that the birth cohorts today are smaller than in 1990. The major demographic change is the large expansion of adults in the age groups 20 to 54 for men and women. Comparing 1990 and 2013, there is little change in the distribution of the population in each age-group by number of sequelae. Rising numbers with multiple morbidities are driven by aging. 20.3% of the age-group 0-4 has no sequela and 0.05% over age 80. In the oldest age group, 12.5% have 1-4 sequelae, 63.9% have 5-9 sequelae, and 23.5% have 10 or more sequelae.

As shown in Figure 2c the dominant result is the massive growth in population from 1990 to 2013 and continued pattern of a population with a low percent of the population at older ages driven by high fertility and comparatively high mortality. Due to a number of very common sequelae that start early in life such as anaemia, soil-transmitted helminths, and schistosomiasis, only 7.8% of the age-group 0-4 in sub-Saharan Africa have no sequelae; by age 80 this is 0.002%. Although there are comparatively few individuals reaching the oldest age-groups, in the population 80 and over, 1.9% have 1-4 sequelae, 42.6% have 5-9, and 55.5% have 10 or more sequelae which is higher than in developed countries. Multiple morbidities are also common in all regions in working age adults: 31.7% with 5 or more sequelae in developed, 37.9% in developing outside of SSA, and 61.6% in sub-Saharan Africa. Of the 2.3 billion individuals in 2013 with more than 5 sequelae, 81.4% of them are under age 65.

Global incidence of acute conditions

The comprehensive and systematic nature of the GBD provides an opportunity to examine the most common acute conditions affecting people around the world and their trends from 1990 to 2013. Table 3

shows the 65 causes of acute (less than 3 months duration) disease and injury incidence with more than 1 million cases per year in 2013. For the causes with more than one acute sequela, such as typhoid fever (acute infection, intestinal perforation and intestinal bleeding), maternal sepsis (puerperal sepsis and other maternal infections), or hypertension in pregnancy (eclampsia, pre-eclampsia and other hypertensive disorders in pregnancy), we aggregate all the acute sequelae for a cause for presentation in this table. Of note, there are two conditions with incidence in 2013 greater than 1 billion: upper respiratory infections (18.8 billion) and diarrheal diseases (2.7 billion). Another twelve diseases and injuries cause from between 100 million to 1 billion incident cases a year: injuries due to other exposure to mechanical force; acute otitis media; tooth pain due to caries of permanent teeth; pyoderma (including impetigo and abscess); falls; lower respiratory infections; clinical episodes of malaria, chlamydia infection; varicella (including chickenpox and herpes zoster episodes); acute hepatitis B; gallbladder and biliary tract disease; and acute hepatitis A. There are 28 diseases and injuries with incident cases between 10 million and 100 million per year including a number of injuries; such as non-venomous animal contact, motor vehicle road injuries, fire, heat and hot substances, motorcycle and pedestrian injuries, and infections such as urinary tract infections, typhoid, hepatitis C and E; dengue; gonorrhea; the initial episodes of genital herpes, trichomoniasis; as well as a number of conditions affecting the digestive system, including gastritis and duodenitis, peptic ulcer disease, pancreatitis, and appendicitis.

Among the most common causes of acute disease incidence, 47 are increasing in absolute numbers of incident cases but only 13 have rising age-standardised rates of which six have statistically significant increases (upper respiratory infections, interstitial nephritis and urinary tract infections, dengue, pancreatitis, paralytic ileus and intestinal obstruction, and unintentional suffocation). Declining numbers are limited to 18 of 65 causes in the table, seven of which are infectious diseases that dominantly affect children. Two are maternal disorders and for one, peptic ulcer disease, the decline is not significant. Some injuries such as non-venomous animal contact, fire, heat and hot substances, collective violence and legal intervention, exposure to forces of nature, venomous animal contact, poisoning, and drowning are declining in absolute incidence numbers. For 52 of 65 causes, age-standardised rates are in fact declining, meaning that for 34 causes, numbers are increasing due to demographic change even though age-standardised rates are declining. In the set of causes causing more than 1 million cases per year, dengue has experienced the most dramatic increase in the age-standardised rates (447.3%).

Global prevalence of chronic diseases

Table 4 summarises the prevalence of chronic disease and injury sequelae (duration of greater than 3 months) aggregated to the cause level. This table provides a high-level view of the leading causes globally of chronic conditions for the 59 causes with a global prevalence greater than 1% in 2013 – note overall prevalence of impairments such as vision or hearing loss are presented in Table 6. Leading causes are a mixture of oral conditions, neurological conditions, skin diseases, musculoskeletal disorders, neglected tropical diseases, gynecological disorders, chronic kidney disease, some causes of anaemia, age-related hearing, other vision loss and injuries. Eight causes affect more than 10% of the world population in 2013: permanent caries without pain, tension-type headaches, iron-deficiency anaemia, G6PD trait, age-related and other hearing loss, genital herpes without symptoms, migraine, and ascariasis. Another 51 causes afflict between 1% and 10% of the world's population. Among this set of conditions are a number that are not prominent causes of YLDs because the average disability weight is comparatively low, but may be important in terms of health system resources or health service planning.

These include G6PD deficiency, genital prolapse, premenstrual syndrome, edentulism, polycystic ovary syndrome, uterine fibroids, and a number of skin diseases.

Rates for only six causes of chronic disease (Table 4) are declining fast enough to lead to declines in the absolute numbers in the world with each condition; these are comprised of micro-nutrient deficiencies, worm infestations, and acute hepatitis B. As noted in Table 3, a number of acute infectious diseases and other acute conditions are also declining in absolute numbers. A further 17 chronic conditions have increasing numbers of cases but statistically significant declines in age-standardised rates: age-related and other hearing loss, genital herpes, uncorrected refractive error, deciduous caries without pain, dermatitis, edentulism and severe tooth loss, osteoarthritis, uterine fibroids, chronic hepatitis C, viral skin diseases, chronic kidney disease due to hypertension, ischemic heart disease (angina, post-MI and heart failure), alcohol use disorders, asthma, chronic kidney disease due to glomerulonephritis, injury due to other exposure to mechanical forces, and endocrine, metabolic, blood, and immune disorders. Five chronic disease and injury states have statistically significant increases in age-standardised rates greater than 5% over the period 1990 to 2013: G6PD deficiency, diabetes mellitus, sickle cell trait, other musculoskeletal disorders, and urolithiasis.

Global impairment prevalence

For five major impairments, Tables 5a-5e shows for each of them the estimated prevalence and the distribution of prevalence by cause and severity in 1990 and 2013 (the remaining four impairments are reported in Appendix E). Tables 5a-5e also provides overall YLDs due to each impairment to provide context on the total burden related to an impairment.

Table 5a shows that we estimated that 1.83 billion had anaemia in 1990 rising to 1.93 billion individuals in 2013. Taking into account the distribution of anaemia across mild, moderate and severe, total anaemia YLDs equaled 62.0 million in 1990 dropping slightly to 61.5 million in 2013. This number of YLDs makes anaemia from all causes larger than the second leading disease contributing to YLDs, MDD – see Table 8b. In addition, to the decrease in overall prevalence, there is a small but notable shift towards more cases of mild anaemia and less severe and moderate anaemia over the period. By 2013, just under half have mild anaemia, 46.9% have moderate anaemia and 3.9% have severe anaemia. Iron-deficiency anaemia accounts for 62.6% of all cases and nearly similar percentages of mild, moderate and severe anaemia. The next five most common causes of anaemia overall are thalassemia trait, malaria, gastritis and duodenitis, other neglected tropical diseases, and other hemoglobinopathies and hemolytic anaemias. Hookworm and schistosomiasis together account for 55.2 million cases and malaria a further 80.6 million cases. Over the period from 1990 to 2013, the number of anaemia cases due to malaria increased by 38.9%. Causes with an increase in cases of more than 50% include chronic kidney disease due to diabetes mellitus, chronic kidney disease due to other causes, and sickle cell disorders.

Table 5b shows that the estimated number of individuals with some form of hearing impairment (20 dB or more) rose from 807.2 million in 1990 to 1.23 billion in 2013. Global hearing loss overall accounted for 25.1 million YLDs in 1990 increasing 51.9% to 36.5 million YLDS in 2013. In 2013, 800.7 million had mild hearing loss (less than 35 db) while 414.5 million had moderate or moderate-severe hearing loss. The number with complete hearing loss (8.0 million) are somewhat higher than in 1990. Just over 90% of hearing loss is classified as age-related and other hearing loss. Otitis media is the next most important cause of overall hearing loss but only causes mild or moderate hearing loss. Congenital anomalies accounted in 2013 for 2.1% of all hearing loss but 21.1% of complete hearing loss.

Table 5c provides a detailed breakdown at the global level of the 61.7 million cases of heart failure (left and right-sided) in the world, more than half of which are categorised as severe. The number of individuals suffering from heart failure in the world increased 96.4% from 1990 to 2013. One third of heart failure is due to ischemic heart disease. Five other causes account for 62.0% of heart failure: hypertensive heart disease, other cardiovascular and circulatory diseases, cardiomyopathy and myocarditis, COPD, and rheumatic heart disease. All other causes each explain less about 5% of heart failure. Notably Chagas disease accounts for 0.6% of heart failure globally but accounts for 11.4% in Brazil. All causes of heart failure cause 8.6 million YLDs in 2013.

Table 5d shows the number of individuals with intellectual impairment increased from 118.2 million in 1990 to 154.0 million in 2013. In 2013, we estimate that borderline (IQ 70-85) and mild (IQ 50-69) accounted for 104.9 million cases and moderate, severe and profound around 49.1 million cases. The most important causes of intellectual impairment in order are idiopathic intellectual disability (61.5%) followed by neonatal causes (mainly preterm birth complications and neonatal encephalopathy), congenital causes (mainly Down's syndrome and chromosomal unbalanced rearrangements), cerebrovascular disease, and infectious causes (mainly meningitis). Comparing levels by cause in 1990 and 2013, idiopathic intellectual disability increased 22.7%, intellectual disability from preterm birth complications 129.6% and intellectual disability from neonatal encephalopathy decreased 5.8%.

Table 5e examines the distribution of visual impairment including presbyopia in 1990 and 2013. The numbers of individuals with visual impairment taking into account the availability of visual aids has increased from 518.6 million in 1990 to 774.1 million in 2013. 72.4% of this total in 2013 was uncorrected presbyopia. Excluding presbyopia, in 1990 there were 137.0 million with moderate or severe vision loss increasing to 178.8 million in 2013. Trends in blindness over the same period were an increase from 23.1 million to 33.1 million. The trend in age-standardised rates for visual impairment overall is 12,702.2 to 11,740.9 per 100,000 and for blindness from 602.5 to 521.3 per 100,000. The most important cause of visual impairment in terms of prevalence and YLDs is uncorrected refractive error accounting for just over 85% of all cases and 56% of YLDs due to vision impairment. In terms of YLDs, the next most important cause is cataract followed by other vision loss, preterm birth complications, glaucoma, macular degeneration and diabetes.

Overall global trends in numbers of YLDs 1990 to 2013

Figure 3 compares the leading causes of global YLDs in 1990 and 2013, using Level 4 of the GBD cause hierarchy which provides detailed cause breakdowns which most relevant to prioritizing specific programs or interventions. The top cause in 1990 and 2013 was low back pain. The second leading cause has changed due to the decline in iron-deficiency anaemia and the rise in MDD. Two more top ten causes are musculoskeletal disorders: neck pain and the large category of other musculoskeletal disorders. Other top ten causes include migraine, age-related hearing loss, COPD, anxiety, and diabetes. Causes that have increased more than 2 ranks over the period 1990 to 2013 include diabetes mellitus, osteoarthritis, dysthymia, medication overuse headache, and Alzheimer's disease and other dementias. Declines of more than two ranks have been observed for dermatitis, diarrheal disease, acne vulgaris, conduct disorder, and war and legal intervention.

Global prevalence and YLDs and age-standardised YLDs 1990 to 2013 for specific causes

Table 6 provide estimates of prevalence and YLDs at the global level for 1990 and 2013 for each cause (the full detail at the level of sequelae is available in Appendix Tables F.1 and F.2; Appendix Table F.3 provides prevalence, YLD, and change by between 1990 and 2013 by cause and age group and Appendix Table F.4 provides prevalence, YLD and change between 1990 and 2013 by cause and country). In the GBD framework, individuals should be assigned to a unique sequela such that the sum of the YLDs or prevalence by sequela should equal the total prevalence and YLDs for a disease or injury. Both because specific sequela are of substantive interest in their own right to help target interventions or needs for new interventions, and to enhance the transparency of computation, we provide the full list of causes and sequelae. Comparison of the percent change in absolute number of YLDs from 1990 to 2013 and the percent change in the age-standardised YLD rate highlights where demographic change, both population increase and rising mean age, have had a major impact. Age-standardised YLDs and prevalence for a number of infectious diseases have statistically significant declines greater than 10% including diarrheal diseases, typhoid, paratyphoid, lower respiratory infections, meningitis, encephalitis, diphtheria, whooping cough, tetanus, measles, Chagas, African trypanosomiasis, cysticercosis, cystic echinococcosis, lymphatic filariasis, onchocerciasis, trachoma, rabies, ascariasis, trichuriasis, and hookworm. In contrast, statistically significant increases in age-standardised rates greater than 10% have been observed for HIV (from 1990 to 2013, but declines since 2005), cutaneous and mucocutaneous leishmaniasis, and dengue. Some other conditions such as malaria, tuberculosis, upper respiratory infections, varicella, visceral leishmaniasis, and schistosomiasis have not had significant changes in either direction greater than 10%.

Age-standardised YLD rates for all maternal causes and sequelae combined are declining significantly. Overall age-standardised YLDs for neonatal disorders increased 80.5% from 1990 to 2013. Large increases in age-standardised rates have been observed for all neonatal causes. Age-standardised YLDs and prevalence of nutritional deficiencies are decreasing as are the absolute numbers of cases. While there is a decline in the age-standardised rates for syphilis, for chlamydia and gonorrhea the trends are either non-significant or small. Hepatitis B and C are declining significantly but hepatitis A and E have non-significant trends. Of note, the number of individuals with chronic hepatitis C infection is increasing.

Age-standardised rates for YLDs from all non-communicable diseases changed by only 1.4% from 1990 to 2013 but YLD numbers increased by 54.2%. Stagnant overall rates mask highly diverse trends for specific causes. Overall neoplasm YLDs are up 82.5% and age-standardised rates increased significantly by 8.5%. However, within neoplasms, significant declines have been observed for stomach cancer, liver cancer due to alcohol, liver cancer due to other causes, larynx cancer, cervical cancer, nasopharynx cancer, gallbladder and biliary tract cancer, and bladder cancer. Significant increases have been seen for liver cancer due to hepatitis C, breast cancer, prostate cancer, colon and rectum cancer, pancreatic cancer, non-melanoma skin cancer, kidney cancer, thyroid cancer, non-Hodgkin's lymphoma, and other neoplasms. Of note, there is no significant change in the age-standardised trachea, bronchus, and lung cancer age-standardised rates. YLDs for cardiovascular diseases overall increased 89.2% but age-standardised rates did not change significantly. Among cardiovascular causes, age-standardised YLD rates declined significantly for atrial fibrillation and flutter and peripheral vascular diseases. In contrast, age-standardised rates increased significantly more than 5% for hypertensive heart disease and cardiomyopathy and myocarditis.

Numbers of YLDs from chronic respiratory diseases are increasing (55.1%) but rates have remained stagnant. Overall cirrhosis age-standardised prevalence and YLD rates are declining although for cirrhosis caused by hepatitis C there is no significant change. Among the digestive diseases, gastritis and duodenitis, appendicitis, inguinal, femoral and abdominal hernia, gallbladder and biliary diseases, and other digestive diseases are increasing in absolute terms but have declining age-standardised rates. In contrast, inflammatory bowel diseases, paralytic ileus and intestinal obstruction, and pancreatitis are increasing in numbers and rates. As a group YLDs from neurological disorders increased 59.6% but age-standardised rates increased only 5.0%. There was no significant change in age-standardised rates for Alzheimer's and other dementias but YLD numbers increased 91.8%. A similar pattern was observed for Parkinson's disease and primary epilepsy which are currently thought to be mainly genetic in origin. YLDs from multiple sclerosis are increasing in rates and numbers. It is not clear if this increase in rates is due to improvements in case ascertainment or reflects a true increase in disease experience. Among the headache disorders, only medication overuse headache had a significant change in rates of 43.3%.

Overall mental and substance use disorders YLDs increased 45.0% from 1990 to 2013 but there was only a 1.0% increase in age-standardised rates. Across all conditions in this group, there were not significant increases or decreases in age-standardised rates greater than 10% including conditions such as autism, and Asperger along with anorexia nervosa and bulimia. Diabetes mellitus YLDs increased by 135.7% but age-standardised rates increased only 43.4%. In contrast, chronic kidney disease increased 49.5% but rates declined 2.8%. Trends in age-standardised rates were different among specific causes of chronic kidney disease (CKD) with CKD due to diabetes increasing but CKD due to hypertension and glomerulonephritis decreasing. Among urinary diseases, the increase in numbers and age-standardised rates for urolithiasis is notable. For most gynecological diseases, numbers are increasing but the significant trend in age-standardised rates is small; uterine fibroids is an exception with declining rates and only a small increase in numbers.

YLDs for the large category of musculoskeletal disorders are increasing by 60.7% but there was no change in age-standardised rates. The only exception to this general pattern is rheumatoid arthritis where age-standardised rates declined significantly by 4.6%. As a group, YLDs due to congenital disorder increased 61.4% and age-standardised rates by 19.7%. These large increases in numbers and age-standardised rates have been observed across the board for congenital causes except for Klinefelter syndrome where rates have not increased significantly. The reason for this large increase in prevalence and YLDs is the improved survival as birth prevalence for congenital disorders remained stable or declined. While skin diseases as a group have had no significant trend for age-standardised YLDs, some causes have declined significantly including cellulitis, pyoderma, and decubitus ulcer. Most causes of vision and hearing loss included in the sense organ category are increasing in absolute number of YLDs but have declining age-standardised rates.

Finally, there is a general pattern where injury YLDs have had substantial decreases in age-standardised YLD rates. There are decreases of more than 30% for road injuries, drowning, fire, heat and hot substances and poisoning, venomous animal contact, non-venomous animal contact, and self-harm.

Changes in YLD rates vary by condition, but the changes in rates generally affect the entire age range across conditions. However, the main conditions that drive change in YLD rates vary with age. In childhood, most infectious diseases and iron-deficiency anemia show decreases in YLD rates while neonatal disorders and congenital conditions show increases, largely due to lower initial case fatality and

better long term survival, and in the case of preterm birth complications, an increase in the birth prevalence. In young adults, large increases from 1990 to 2013 were in disability associated with diabetes, HIV, and medication-overuse headache, while there were large decreases in the YLD rates of iron-deficiency anemia, falls, and collective violence. In adults over the age of 50, reductions in YLD rates for all injuries and increase in diabetes YLD rates stand out.

Leading causes of YLDs for 188 countries

Figure 4 shows the ten leading causes of YLDs for each country. Causes are colour-coded by their global rank to highlight where causes vary substantially in the leading set. There is considerable consistency in the top causes. Low back pain and MDD are among the top ten causes of YLDs in every country. Forty causes appear in the top ten list across all countries but only 16 of these causes appear in the top ten of more than 20 countries. Low back pain is the leading cause in 45 of 50 developed countries and MDD is the leading cause in three countries, with neck pain and diabetes leading in one country each. Across developing country regions, there is more variation in leading causes. Low back pain or MDD is the leading cause in 94 of 138 developing countries. But other conditions such as iron-deficiency anaemia, HIV, and war are leading causes in more than one country. Regional patterns emerge such as the more prominent role of falls in Central Europe where it is ranked second in 11 of 13 countries. The category other musculoskeletal – which includes conditions such as shoulder problems, pathological fractures from osteoporosis, osteomyelitis, and pyogenic arthritis, and systemic lupus erythematous – is prominent in high-income Asia and high-income North America. Anxiety disorders rank more highly in many Caribbean nations and diabetes is prominent in Mexico, Nicaragua, Panama, and Venezuela. In Oceania, some soil-based helminths are highly prevalent, pushing them into the top 5 of the YLD rank list. Onchocerciasis, predominantly the onchocercal skin sequela, is ranked highly in Liberia, Cameroon, and South Sudan. The disability from past war and conflict ranks as the top cause of disability in Cambodia, Nicaragua, and Rwanda, and number two in Vietnam.

Changing YLDs per capita 1990 to 2013 for 188 countries

Figure 5 provides an analysis of the change in the YLDs per person from 1990 to 2013 by country Countries have been ordered by YLDs per person in 1990. YLDs per person in 1990 and 2013 are marked by purple and red lines respectively. Across countries in 1990, YLDs per capita range from 0.072 to more than double at 0.170. In general, developed countries with higher mean age for the population have higher YLDs per capita but there are many exceptions to this general pattern. Change in the YLDs per capita are decomposed into contributing causes shown as coloured bars for cause groups for YLDs – for convenience these cause groups are based on highlighting the major causes of YLDs at the global level. Reductions in YLDs per capita from a cause from 1990 to 2013 are shown as coloured bars to the left of the 1990 starting level (purple line) and increases in YLDs per capita from a cause are shown as bars to the right of the starting line. The figure provides a summary of what causes are contributing to increases or decreases in YLDs per capita for each country.

The majority of countries (139 of 188) saw increases in the YLDs per capita from the period of 1990 to 2013. While the drivers of increased YLDs per capita vary by region and country, in general, musculoskeletal, mental and substance use disorders, neurological disorders, and chronic respiratory conditions play important roles across the majority of regions and countries. In sub-Saharan Africa, increases are largely driven by HIV/AIDS. Declining levels of iron-deficiency anaemia contribute to a decline in YLDs per capita in many countries. In the subset of countries where the overall YLDs per capita declined, specific factors such as long-term disability due to war are an important factor – most

dramatically evident in Lebanon. However, declines due to neglected tropical diseases and malaria, as well as diarrhea and lower respiratory infections (represented as 'other communicable' in Figure 5) also push YLDs per capita lower in some countries. Mostly increasing YLDs per capita mean that by 2013 the range across countries is from 0.076 to 0.153. It is important to note that Figure 5 shows YLDs per capita and not age-standardised YLD rates, therefore changes in YLD rates are influenced by changes in population age structure, as well changes in age-specific disease rates.

YLDs per capita are rising in the majority of countries and YLLs per capita are declining. Both trends are leading to a shift towards greater disability as a share of overall burden. Using the results on YLLs published by Naghavi et al., we show in Figures 6a and 6b the ratio of YLDs to YLDs plus YLLs (namely DALYs).[76] The two panels show the progressive shift from 1990 to 2013 in many parts of the world. Thirty countries now have a majority of DALYs due to YLDs representing a major change from historical patterns where premature mortality was the dominant set of health issues. In 1990, premature mortality still represented more than half of DALYs in every country. By 2013, the lowest YLD to DALY ratio outside of sub-Saharan Africa was in Afghanistan, but the majority of developing countries outside of sub-Saharan Africa have ratios greater than 35%. In sub-Saharan Africa, however, the ratio of YLDs to DALYs ranges from 10.4% in Mali to 38.9% in Cape Verde.

Discussion

We analysed over 30,800 epidemiological sources from 188 countries spanning the last three decades to provide the most up-to-date empirical assessment of the leading causes of acute disease incidence, chronic disease prevalence, and YLDs for six years (1990, 1995, 2000, 2005, 2010, and 2013) for 188 countries using consistent and comparable methods. More importantly, our study provides the first ever comprehensive assessment of the extent, pattern and trend of non-fatal health loss in countries, with attendant implications not only for health policy, but also for the provision and financing of health services.

A wide array of disease and injury sequelae affects the world's population. Disease is ubiquitous and we find that globally in 2013 only 4.3% of the population has no GBD disease or injury sequelae up slightly from 4.2% in 1990. There are 59 diseases and injuries with a global prevalence of greater than 1% but each of which causes comparatively little disability. These conditions including various causes of mild to moderate vision impairment, hearing loss, soil transmitted helminths, mild anaemia, caries, and many others. For many of these common but relatively mild conditions, there are effective interventions.[87–90] The GBD provides multiple insights into the health experience of different populations by quantifying the prevalence of a wide variety of conditions as well as YLDs that take into account the general public's view of severity.

Of the 240 GBD causes that lead to mortality, Naghavi et al. found that global age-standardised death rates were declining in 80%.[76] For YLDs, the distribution of causes where age-standardised rates are declining, stagnant or increasing is different. For 140 causes, distributed across communicable, non-communicable, and injuries, age-standardised rates have declined significantly from 1990 to 2013. For 89 causes, changes in age-standardised rates are statistically indistinguishable from zero over the same period. For 72 causes including epidemic conditions like HIV and dengue but also cancers, diabetes, and COPD age-standardised rates increased significantly. Of 301 causes, the percent change in the age-standardised rate for YLDs is higher than the percent change in the age-standardised YLLs for 213

causes. Divergent rates for diseases and injuries between mortality and morbidity could be occurring because of reductions in case-fatality rates due to treatment or improved background risks such as malnutrition. To the extent that mortality is declining faster than disease prevalence due to treatment, access to care may be a critical driver of trends in health. The mortality-disability temporal disconnect, however, is further evidence of the importance of paying attention to trends in disease incidence, prevalence and YLDs and not simply focusing on mortality. Diabetes is an important example where age-standardised prevalence rates increased 43% while death rates increased only 9%. Stagnant or increasing age-standardised rates combined with rising mean age of the world's population implies substantial future increases in burden from these causes. The documented shift in many developed and developing countries to a larger fraction of DALYs coming from YLDs is another manifestation of this global shift. Despite the evidence on this shift, the majority of global health policy discussion remains focused on premature mortality. For example, in the Sustainable Development Goals Open Working Group proposal[91] with 13 targets for the health goal, only one on narcotic drug abuse and harmful use of alcohol is focused on a disability.

While the general pattern of the last 23 years has been for infectious disease mortality and morbidity measured through incidence or prevalence to decline, there are some very notable exceptions that stress that such trends are not inevitable with rising income per capita and educational attainment. Comparing 1990 and 2013, both HIV and malaria YLDs increased. More careful examination of our estimates for the six time periods shows that malaria and HIV YLDs have been declining since at least 2005. Increases for dengue (nearly 450%), for cutaneous and mucocutaneous leishmaniasis have continued through the period. Increases in dengue have been ascribed to the rise of breeding sites for the mosquito vector in urban and peri-urban areas.[92] Increases for cutaneous leishmaniasis have been related to the expansion of previously non-endemic areas as a result of urbanisation and deforestation with domestic animals as potential reservoirs. Additionally, economic hardship, natural disasters, armed conflict, movement of seasonal workers, development of new projects, and bringing non-immune labor forces into endemic areas are contributing causes. Finally, pressure on populations throughout the world are pushing migration into areas where the infection is endemic, thereby bringing many more humans into contact with the natural vectors and resulting in increased infection rates.[93–96] These counter trends for infectious diseases are a reminder that active surveillance of infectious diseases at a fine-grained geospatial level is essential to detect changes that may run against the general trend towards lower rates.

The GBD 2010 reported that the burden of musculoskeletal disorders were much larger than previously appreciated.[7,8,19,20,37,38] In this analysis, we demonstrate that musculoskeletal disorders range from 9.6% of YLDs to 28.9% of YLDs between 188 countries. Low back pain is the leading cause of YLDs in 86 countries and the second or third leading cause in 67 countries. While the GBD 2010 analysis brought more attention to these disorders, there remains comparatively little policy discussion of the options available to address and prevent these conditions.[1,97] From a health service point of view, it is important to note that there is a connection between the injury analysis of fractures and soft tissue injury and musculoskeletal disorders. We estimate 22 million YLDs from fractures, the vast majority of which is long-term disability. Most of the individuals afflicted would present with a musculoskeletal chief complaint in surveys and therefore to avoid double counting we subtracted the long-term disability from fractures and dislocations out of the estimates of the category of other musculoskeletal conditions. Musculoskeletal disorders combined with fractures and soft tissue injuries reaches a total of 20.8% of

global YLDs in 2013; across countries this total ranges from 10.8% in Mali to 30.0% in South Korea. Our analysis of time trends clearly shows this category of conditions is an important driver of rising YLD rates per capita. Increases are driven by aging of the population in most countries with trends in obesity and physical inactivity likely exacerbating the problem.[98,99] Musculoskeletal disorders are not only an important contributor to the burden of disease but are also a critical component of health expenditure in many high-and middle- income countries.[100–104]

Mental and substance abuse disorders account for 21.2% of YLDs, ranging from 15.4% in Germany to 36.7% in Qatar. MDD is a critical contributor in developed and developing countries alike: it is the leading cause of YLDs in 56 countries, the second leading cause in 56 countries, and the third in 34 countries. While MDD, anxiety disorders, schizophrenia and bipolar disorder are leading causes in nearly all countries, there is much greater country variation in substance use disorders including alcohol. YLDs from alcohol use disorders range from a high of 2.9% in Russia to a low of 0.3% in Iran; YLDs from drug use disorders range from a high of 13.5% in Qatar to a low of 0.6% in Slovenia. New data in the GBD 2013 suggests that Iran and Afghanistan have particular problems with opioid dependence. The GBD 2013 analysis confirms that common mental disorders have well-established sex patterns in most countries: higher rates in women for MDD and anxiety and similar rates for bipolar and schizophrenia for men and women. Treatments if widely and appropriately deployed could lead to substantial reductions in the burden of these disorders; some studies suggest that up to half of YLDs could be averted in some countries.[1,105,106] As new studies accumulate on the role of childhood sexual abuse, intimate partner violence, non-sexual child abuse and bullying, the possibility of prevention programs is growing.[107–111] Systematic quantification of these risks will help establish where prevention programs could be developed and tested.

Advances and gaps in GBD data and methods

For the first time in the GBD studies, we provide a systematic quantification of the geographical and temporal coverage of the input epidemiological data for nearly all sequelae. For a number of diseases with sequelae representing different levels of severity such as MDD (mild, moderate, and severe sequelae), the data representativeness metrics show there are often more data for overall disease prevalence than for determining the distribution of severity for a cause. Sequelae with the highest data representativeness index (DRI) tend to be those where administrative data such as notifiable disease reporting or hospital discharge data can be corrected for completeness and/or selection bias. For some sequelae, such as drug use disorders a single study was available to determine the distribution of cases by level of severity. Despite attempts to quantify uncertainty from various sources in the estimates (see limitations below), it is highly likely that for sequelae with low DRIs uncertainty may be larger than estimated. At the global level, twelve of the top causes of YLDs have a DRI less than 0.25. Priorities for further data collection in a country might usefully be informed by comparing the estimated YLDs and the DRI for the country for each cause. Examining countries, the fraction of sequelae with any data available in a country, shows marked variation across countries within a region or within income group – consider Nigeria with a DRI of 47% and Mauritania at 10% or the United Kingdom at 81%and Greece at 52%. Our computation of the DRI is based on the data available to the GBD through published studies or reports, publicly released datasets, and unpublished data provided. Given our experience in China and Mexico with sub-national burden of disease estimation, it is likely data coverage could be improved through detailed national burden of disease studies which often unearth multiple unpublished sources. Ministries of Health and

national statistical authorities in countries with low coverage should carefully assess which high burden conditions with low data availability would benefit from new data collection efforts.

With each iteration of the GBD, the cause and sequelae list have expanded. Expansion involves taking an existing cause and splitting it into more detailed component causes; for example, eating disorders were broken down into anorexia nervosa and bulimia. Within each Level 2 or Level 3 cause group, there is a category of other such as other mental, musculoskeletal, or neurological disorders. These residual categories contain many rarer causes and some common causes that have very low levels of disability. One of the key values of the GBD is the comprehensive and systematic nature of the analysis; it is likely that in future iterations based on health service utilisation data or new epidemiological studies or policy demand, the cause and sequelae list will be further expanded. The GBD cause list, even in the current expanded form, still has only 301 causes compared to the 11,299 four-digit ICD-10 codes. The GBD cause list provides a more manageable public health and health service planning focused approach to the complexity of disease coding. The sequela list also has many potential applications, such as facilitating the mapping of data collected through different studies and typologies into a common framework.

For GBD 2013, the study has benefited from use of a larger computational cluster compared to GBD 2010 (22 teraflops compared to 8 teraflops). The optimised recoding of DisMod-MR 1.0 to DisMod-MR 2.0, combined with greater computational capacity, has allowed us to generate country-specific posterior estimates for incidence, prevalence, remission, and excess mortality for each of six time periods. We have estimated and reported internal validity of different models and conducted cross-validation studies for 10 of the models. We believe DisMod-MR 2.0 is a substantial improvement over DisMod-MR 1.0 but there remains considerable opportunity to improve these data synthesis tools in the future. In particular, work is underway to develop the next iteration of DisMod-MR that would allow for variation of incidence, remission, excess mortality rates simultaneously over age, geography, and time in contrast to the present approach, where variation in rates over time is captured by independent estimation of the available data for six different time periods. Despite progress in the estimation tools, a fundamental problem in epidemiological synthesis of sparse and heterogeneous data is distinguishing between true variation in the underlying rates and study heterogeneity due to variation in case definitions, assays, instruments, sampling frames etc. DisMod-MR 2.0 allows explicit modeling of these factors but true resolution of this challenge requires more data to be collected with consistent definitions and study design.

The comorbidity micro-simulation for each country-age-sex-year has been used to quantify both co-morbidity and allocate to contributing causes the individual's disability weight. By weighting up each country-age-sex-year micro-simulation by the true population in each age-group, we have created a working model of individual health for all 7.3 billion individuals in the world consistent with the entire GBD non-fatal health outcome results. With future iterations of the GBD, we intend to incorporate data on risk factors into the global micro-simulation providing an even more comprehensive working model of each country's population. This global and national micro-simulation has many potential applications from inequality measurement to comprehensive forecasting of multiple interventions. For example, the GBD micro-simulations provide an ideal environment for modeling the impact of interventions that would reflect the complex interplay between conditions that is often missing in many intervention impact assessments. The distribution of functional health status across individuals in each country for different points in time can also be used to compute measures of individual inequality in functional health. If the correlations between socio-economic indicators within each country-age-sex-year group with health

outcomes and risk factors can be estimated, then the micro-simulation environment could also be used to look at the relationship between health and income inequality.

Disability weights through the inclusion of new data from national surveys in Italy, Hungary, Sweden and the Netherlands and revisions in lay descriptions for selected health states have changed from those used in the GBD 2010. The severe hearing loss disability weight increased from 0.05 to 0.18 with similar increases for profound hearing loss and deafness. Through the inclusion of incontinence in the lay descriptions for spinal cord lesion below the neck, the disability weight increased from 0.047 to 0.296. These findings highlight the critical importance of the exact wording of lay descriptions for use in population surveys. We revised lay descriptions in the latest round of data collection based on critical commentary in the literature and a careful review of all lay descriptions checking for symmetry and consistency. We believe that future iterations of the GBD will benefit from further data collection and vigorous scrutiny and debate by the scientific community of the exact lay descriptions in use – see Appendix Table A.6 for a full listing and Salomon et al. for further detail.[84] In many countries undertaking sub-national burden of disease studies, there may be opportunities to collect further disability weight data using the latest iteration of the GBD lay descriptions and measurement protocol. Such data would help establish if there is any notable national variation in disability weights from the global average and strengthen the global empirical database for disability weight measurement.

The second important component determining average disability weight is the empirical analysis of the distribution of severity controlling for comorbidity. The number of studies or data sources that allow for teasing apart functional health limitations from a particular cause from other comorbid causes remain very limited. Very low DRIs for many sequelae in Table 1 document this limitation. More datasets like the US Medical Expenditure Panel Survey that include both functional health limitation measurement and ICD-coded diagnoses would be extremely helpful in strengthening the empirical assessment of severity controlling for comorbidity. This must be considered one of the most important data gaps for the quantification of many chronic conditions.

GBD 2013 compared to GBD 2010 and other estimates

Because the GBD 2013 has re-estimated prevalence and YLDs for all disease and injury sequelae for 1990, 1995, 2000, 2005, 2010, and 2013, we can compare the results of the GBD 2013 directly with the GBD 2010. The leading global causes of YLDs estimated for the year 2010 in this study (low back pain, MDD, iron-deficiency anaemia, neck pain, and age-related and other hearing loss) are similar to those reported in the GBD 2010 (low back pain, MDD, iron-deficiency anaemia, neck pain, and COPD) for the year 2010. For 97 diseases or injuries, global YLDs from the GBD 2013 for the year 2010 are statistically different from the GBD 2010 estimates for the same year. For 27 diseases and injuries, there were changes in YLDs greater than 30% but these changes were not statistically different than GBD 2010. In general, changes stem from the inclusion of new data, exclusion of studies used in GBD 2010 due to changes of inclusion criteria for each sequela that emerged through the process of replicating many GBD 2010 systematic reviews, the shift to DisMod-MR 2.0 which reduced the impact of large sample size outlier studies, changes in covariates, changes in disability weights, or changes in severity distributions. Appendix Table A.8 provides a more detailed account for each of these cases including changes in inclusion criteria where relevant. At the level of global YLDs, the most notable impact of these changes is the inclusion of age-related and other hearing loss in the top 10 causes of global YLDs; this change is almost exclusively due to the revision of the hearing loss disability weights. The annual updating cycle

for the GBD provides a much more rapid cycle for incorporating new data and critical scientific feedback from GBD collaborators and the broader scientific community. We expect that with each iteration there will be important changes driven by the collection and release of new data but that the number of changes driven by uncovering older studies, exclusion of older studies on quality grounds, or changes in modeling strategy will tend to get smaller with each iteration.

Limitations

A study of this scope has multiple limitations many of which were detailed in the GBD 2010 analysis.[1] Here we focus on selected major limitations that are not specific to the data sources or analysis of a specific sequela. First, For COMO to work effectively, especially with the assumption of independence, individuals with a disease need to be uniquely mapped to a single sequela. For some diseases where there are multiple distinct functional impairments such as motor and cognitive dysfunction for some neonatal disorders, multiple combinations are possible. In some cases, to map all of the possible combinations was infeasible because of increased computational load and the lack of epidemiological data to accurately describe these combinations. In a very limited number of cases, we have not followed the principle of mapping one individual to a unique sequela including schistosomiasis, lymphatic filariasis, and onchocerciasis.

Second, a major limitation that may affect many sequelae is that important unpublished data sources may be missing. The collaborations with investigators in Mexico, China, and England to generate sub-national burden of disease estimates for 2013 has identified multiple unpublished data sources or more detailed age and time breakdowns for published studies. It is highly likely that in other countries there are similar data sources that once identified, could enrich the estimation of the burden of disease for a country.

Third, in this analysis of prevalence and YLDs, we attempt to capture uncertainty from model estimation and available data but 95% UIs may be too narrow because we cannot capture uncertainty that stems from the possibility that countries with data may in some way be different for a given sequela than countries with data. Further, in contrast to the GBD analysis of causes of death, we do not capture uncertainty that stems from model specification. We have undertaken cross-validation studies for a limited number of models but the move to using out of sample validity testing to then create ensembles of good models will require further advances in computational speed of DisMod-MR to make this viable.[76]

Fourth, for the GBD 2013 we have made a substantial effort involving many person-years of effort to enhance the transparency in all aspects of the estimation. In GBD 2010, in some cases contributors who undertook systematic reviews provided results but without study references. For GBD 2013, we have included in the Global Health Data Exchange (GHDx, ghdx.healthdata.org/) 23,653 citations with metadata covering essentially all sources used in any aspect of this analysis. We have provided more detail on modeling strategies and internal validity of model fits. Given the complexity of the GBD analysis spanning so many sequelae, estimation requires a tremendous investment across the network of collaborators measured in person-years. Replication of the entire effort is possible but would require considerable resources and negotiated access to the small number of datasets provided to the GBD through Data Use Agreements that are not in the public domain. With the public release of the Epi Viz tool, everyone will be able to examine the specific studies and data points used for each disease sequela and the model fits. To further satisfy the reasonable scientific curiosity of academics about particular sequelae, the GBD collaborators remain committed to answering detailed questions about all steps of the

analysis and many disease-specific publications will follow in which much greater detail of the modelling assumptions and data for each sequela can be provided.

Fifth, where data for a sequela are collected using different definitions, assays, or instrument items, we have 'cross-walked' between these differences using fixed effects in the meta-regressions. For example, in the DisMod-MR 2.0 model for MDD, the coefficient on symptom scale measures as opposed to a diagnostic interview schedule is 0.83 (0.64-1.04) in log space and 2.30 (1.90-2.83) after exponentiation. By dividing symptom scale prevalence data points by 2.3, we predict the corresponding values for the reference case. Another example of an important cross-walk is between data on opioid dependence from household surveys and the more inclusive estimates from triangulation of data from treatment centres, needle exchange programs and the justice system.[9] DisMoD-MR 2.0 estimates a coefficient of 0.31 (0.15 to 0.74) after exponentiation indicating the household survey prevalence is an underestimate by more than a factor of three. A number of factors could explain this large difference including lack of a steady residence, lower response to surveys and fear of reprisals for admitting to illegal behaviors.[112] We used a similar covariate for triangulated data on cocaine and amphetamine dependence but found no systematic bias compared to household survey data. There is no equivalent approach to address the potential bias from non-response to surveys or the influence of stigma on responses for cannabis and alcohol dependence. In the DisMoD-MR 2.0 model of alcohol dependence we use a number of study characteristics such as the type of survey and the measurement instrument. A review of Chinese studies on alcohol dependence found that variation in prevalence between studies was strongly correlated with such study characteristics.[113] Of particular interest in the Chinese review is their finding that large surveys often rely on proxy reporting for absent household members to improve the response rate and that these surveys tend to underestimate the prevalence of alcohol dependence. While there is a considerable body of evidence describing stigma and alcohol dependence there is no quantification of the magnitude and direction of the bias on population prevalence estimates, probably because it is hard to define a gold standard measurement that would be unaffected by stigma.[114–116] Experience in the GBD 2013 compared to GBD 2010 shows that these fixed effect coefficients for study level characteristics can be substantially influenced by the inclusion of new data sources. Where cross-walks are large, new data in one country can alter results in many other countries. This sensitivity of statistical cross-walks in models with sparse data highlights the value of standardising case definitions, assays and instruments in future data collection. The comprehensive nature of the GBD provides an opportunity to identify what is the reference case approach to measurement given current knowledge for each sequela. We plan to summarise our assessment of best practice for each sequela in a future publication.

Sixth, in models using DisMod-MR 2.0 or natural history models, the relationships between incidence, remission, excess mortality, prevalence, and cause-specific mortality are modeled simultaneously. However, if there are no priors on the age pattern and level of excess mortality across countries, simultaneous estimation does not ensure any correlation in the age-specific rates of prevalence and cause-specific mortality across countries. In this iteration of the GBD, we have devoted much more attention to this estimation challenge by incorporating in many models more direct information on the credible range of excess mortality across age, sex, and country. However, country variation in excess mortality has not been as extensively debated in the literature on burden of disease estimation as for incidence, prevalence, or causes of death. More attention to these relationships and the determinants of excess mortality such as access to care will be beneficial in future iterations of the GBD.

Seventh, COMO, used for quantifying the burden of disease and undertaking intervention analysis, suffers from a major limitation, namely that we assume that within a country-age-sex-year group that prevalence values are independent. For some conditions such as diabetes and ischemic heart disease or anxiety disorders, depression and alcohol dependence, we expect probabilities are dependent. Empirical assessments [117,118] of comorbidity tend to show that age is the dominant driver of comorbidity – ignoring dependent comorbidity, for example in the MEPS data, leads to minimal errors in estimated burden.[1] Incorporating dependent comorbidity into the micro-simulation environment is not technically challenging; the issue is that there are insufficient data to generally estimate the age-specific correlation matrix of all 2,337 sequelae. As compelling and albeit partial evidence on dependence accumulates, we intend to incorporate this into the COMO micro-simulations.

Eighth, in the current version of DisMod-MR 2.0 we were unable to incorporate estimates of the sub-national units for China, Mexico, and the UK as a fifth level in the estimation cascade (Figure 2). Instead, subnational units were modeled as if they were independent countries. If data are sparse, it means that subnational units may borrow strength from the regional estimate rather than the country estimate. In some cases, where only national data were available, we used this data for each sub-national unit after dividing the effective sample size of each data point by the number of sub-national units to avoid over-emphasising the national data used in each unit in the overall estimation. A fifth level of the cascade will be added in the next version of DisMod-MR.

Ninth, there has been a steady drop in the age-standardised rates of YLDs for all injury categories between 1990 and 2013. For the unintentional injury categories apart from falls this is partly driven by a downward trend in case fatality rates accompanied by a drop in incident cases. The larger change affecting the downward trend in YLD rates is related to the difference between disability with and without treatment. In the absence of robust national data on the injury treatment rates, we have assumed that access to treatment scales according to the indicator health system access.[76] The health system access indicator is based on a principal component analysis of coverage of mostly maternal and child health interventions and health system infrastructure. There have been steady global improvements in health system access as captured in this indicator reducing the estimated injury YLDs.

Tenth, substantial efforts have been made in the data preparation and analysis to address issues of ascertainment bias that may affect trends. In another example of dealing with ascertainment bias we cross-walk between diagnostic assays from CK-MB enzymes to troponins for the detection of acute myocardial infarction. Despite these efforts, there are some upward trends that may still relate to residual issues of ascertainment including multiple sclerosis and prostate cancer.

Eleventh, in a study with over half a million YLD estimates generated from sometime sparse and always disparate data sources there remain areas where additional evidence or a change in the modelling strategy could lead to better estimates. Annual updates of GBD allows for a continuing effort to search for new data and improve methods, particularly for conditions with sparse data or inconsistencies between data sources.We are already compiling a list of issues to address in the next iteration. For example, with our collaborators in Qatar, we are searching for data to verify the high YLD estimate for opioid dependence which currently are influenced in the models by studies in in Iran and Afghanistan in the region. In other cases, further data on the clinical severity associated with paragonimiasis would help determine the relevance of the health state used to select the disability weight for this sequelae. In general, we will search for additional evidence on the severity of all conditions for the next iteration of GBD.

Conclusions

Despite these limitations, the implications of our findings are substantial. By extending the GBD analysis to report on commonly understood measures of morbidity and disability in populations, by age, by sex, by country and over time, this study represents an enormous resource for national, regional, and global policy debates about health priorities , not just to keep people alive well into old age, but to also keep them healthy. Without this health intelligence, large, preventable causes of health loss in populations, particularly mental and behavioral disorders and serious musculoskeletal conditions, have hitherto not received the attention that they deserve in national health debates.

The GBD 2013 covers a comprehensive collectively exhaustive and mutually exclusive set of causes and their sequelae at the country level over a period of 23 years. By shifting to a process of annual updating, the GBD provides a relatively rapid mechanism for incorporating new data, methods development, and new insights into old data or disease mechanisms. By steadily increasing the transparency of input sources, documenting in detail the methods used, sharing critical code such as DisMod-MR 2.0, and facilitating on-line exploration of new results using dynamic data visualisations (www.healthdata.org), we believe the GBD can progressively become the vehicle for global health surveillance, not just for mortality, but for reducing health loss among populations everywhere. As a group of investigators, we seek to accommodate within the GBD framework epidemiological debate on each cause, and based on scientific principles, describe the functional health of all individuals in the world. Studies such as this provide the important comprehensive, comparative, and consistent evidence to guide policy and practice, evidence that will become progressively more reliable as more data and information are identified and included as part of the global collaboration.

Table and Figures

Table 1. GBD 2013 data representativeness index by cause (causes aggregated in bold), calculated as fraction of countries with data for each cause and time period

Table 2. GBD 2013 data representativeness index by impairment, calculated as fraction of countries with data for each impairment and time period

Table 3. Global incidence of acute sequelae (duration less than 3 months) by cause where incidence is greater than 1 million cases per year (causes are ordered in terms of overall incidence, 95% uncertainty intervals are shown, statistically significant % change is shown in bold)

Table 4. Global prevalence of chronic sequelae (duration greater than 3 months) by cause where prevalence is greater than 1% (causes are ordered in terms of overall prevalence, 95% uncertainty intervals are shown, statistically significant % change is shown in bold)

Table 5a-5e. Prevalence and YLDs, with percent of total, for 5 impairments (anemia, hearing loss, vision loss, intellectual disability and heart failure) by cause, 1990 and 2013, and prevalence by severity in 2013

Table 6. Prevalent cases and YLDs for 2013, percent change, and percent change of age-standardised rates between 1990 and 2013 for all causes (statistically significant % change shown in bold)

Figure 1. Percent of causes with data available between 1990 and 2013 for 188 countries

Figure 2a. Population pyramid for developed countries with individuals grouped by number of sequelae, 1990 and 2013

Figure 2b. Population pyramid for developing countries (excluding sub-Saharan Africa) with individuals grouped by number of sequelae, 1990 and 2013

Figure 2c. Population pyramid for sub-Saharan African countries with individuals grouped by number of sequelae, 1990 and 2013

Figure 3. Comparison of the rank order of the 25 leading Level 4 causes of YLDs in 1990 to their rank in 2013. DALYs

Figure 4. Ten leading causes of YLDs for 188 countries in 2013 (causes are colour-coded by global rank)

Figure 5. Change in the YLD rate from 1990 to 2013 for 21 regions 188 countries (changes have been decomposed into 21 major cause groups and countries are ordered by the YLD rate in 1990)

Figure 6a. Percentage of DALYs due to YLDs in 1990 for 188 countries

Figure 6b. Percentage of due to YLDs in 2013 for 188 countries

References

1 Vos T, Flaxman AD, Naghavi M, *et al.* Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* 2012; **380**: 2163–96.

2 Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. *Psychol Med* 2014; **45**: 1–13.

3 Blencowe H, Vos T, Lee ACC, *et al.* Estimates of neonatal morbidities and disabilities at regional and global levels for 2010: introduction, methods overview, and relevant findings from the Global Burden of Disease study. *Pediatr Res* 2013; **74**: 4–16.

4 Boyers LN, Karimkhani C, Hilton J, Richheimer W, Dellavalle RP. Global Burden of Eye and Vision Disease as Reflected in the Cochrane Database of Systematic Reviews. *JAMA Ophthalmol* 2014; published online Sept 18. DOI:10.1001/jamaophthalmol.2014.3527.

5 Charlson FJ, Ferrari AJ, Flaxman AD, Whiteford HA. The epidemiological modelling of dysthymia: application for the Global Burden of Disease Study 2010. *J Affect Disord* 2013; **151**: 111–20.

6 Chugh SS, Havmoeller R, Narayanan K, *et al.* Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; **129**: 837–47.

7 Cross M, Smith E, Hoy D, *et al.* The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014; **73**: 1316–22.

8 Cross M, Smith E, Hoy D, *et al.* The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014; **73**: 1323–30.

9 Degenhardt L, Charlson F, Mathers B, *et al.* The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. *Addict Abingdon Engl* 2014; **109**: 1320–33.

10 Degenhardt L, Ferrari AJ, Calabria B, *et al.* The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: results from the GBD 2010 study. *PloS One* 2013; **8**: e76635.

11 Degenhardt L, Whiteford HA, Ferrari AJ, *et al.* Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382**: 1564–74.

12 Driscoll T, Jacklyn G, Orchard J, *et al.* The global burden of occupationally related low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; **73**: 975–81.

13 Erskine HE, Ferrari AJ, Nelson P, *et al.* Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. *J Child Psychol Psychiatry* 2013; **54**: 1263–74.

14 Erskine HE, Ferrari AJ, Polanczyk GV, *et al.* The global burden of conduct disorder and attention-deficit/hyperactivity disorder in 2010. *J Child Psychol Psychiatry* 2014; **55**: 328–36.

15 Feigin VL, Forouzanfar MH, Krishnamurthi R, *et al.* Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; **383**: 245–54.

16 Hay RJ, Johns NE, Williams HC, *et al.* The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 2014; **134**: 1527–34.

17 Higashi H, Barendregt JJ, Kassebaum NJ, Weiser TG, Bickler SW, Vos T. The burden of selected congenital anomalies amenable to surgery in low and middle-income regions: cleft lip and palate, congenital heart anomalies and neural tube defects. *Arch Dis Child* 2014; published online Sept 26. DOI:10.1136/archdischild-2014-306175.

18 Hotez PJ, Alvarado M, Basáñez M-G, *et al.* The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. *PLoS Negl Trop Dis* 2014; **8**: e2865.

19 Hoy D, March L, Brooks P, *et al.* The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; **73**: 968–74.

20 Hoy D, March L, Woolf A, *et al.* The global burden of neck pain: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014; **73**: 1309–15.

21 Hoy DG, Smith E, Cross M, *et al.* The global burden of musculoskeletal conditions for 2010: an overview of methods. *Ann Rheum Dis* 2014; **73**: 982–9.

22 Institute for Health Metrics and Evaluation, Human Development Network, The World Bank. The Global Burden of Disease: Generating Evidence, Guiding Policy – East Asia and Pacific Regional Edition. Seattle, WA: IHME, 2013.

23 Institute for Health Metrics and Evaluation, Human Development Network, The World Bank. The Global Burden of Disease: Generating Evidence, Guiding Policy – Europe and Central Asia Regional Edition. Seattle, WA: IHME, 2013.

24 Institute for Health Metrics and Evaluation, Human Development Network, The World Bank. The Global Burden of Disease: Generating Evidence, Guiding Policy – Latin America and Caribbean Regional Edition. Seattle, WA: IHME, 2013.

25 Institute for Health Metrics and Evaluation, Human Development Network, The World Bank. The Global Burden of Disease: Generating Evidence, Guiding Policy – Middle East and North Africa Regional Edition. Seattle, WA: IHME, 2013.

26 Institute for Health Metrics and Evaluation, Human Development Network, The World Bank. The Global Burden of Disease: Generating Evidence, Guiding Policy – South Asia Regional Edition. Seattle, WA: IHME, 2013.

27 Institute for Health Metrics and Evaluation, Human Development Network, The World Bank. The Global Burden of Disease: Generating Evidence, Guiding Policy – Sub-Saharan Africa Regional Edition. Seattle, WA: IHME, 2013.

28 Leonardi M, Raggi A. Burden of migraine: international perspectives. *Neurol Sci* 2013; **34**: 117–8.

29 Mensah GA, Forouzanfar MH, Naghavi M, *et al.* Comparable estimates of mortality and trends for cardiovascular disease including congenital heart disease in 21 world regions in 1990 and 2010: the Global Burden of Diseases, Injuries and Risk Factors Study. *J Am Coll Cardiol* 2013; **61**. DOI:10.1016/S0735-1097(13)61406-0.

30 Moran AE, Forouzanfar MH, Roth GA, *et al.* Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation* 2014; **129**: 1483–92.

31 Moran AE, Forouzanfar MH, Roth GA, *et al.* The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. *Circulation* 2014; **129**: 1493–501.

32 Murray CJL, Richards MA, Newton JN, *et al.* UK health performance: findings of the Global Burden of Disease Study 2010. *Lancet* 2013; **381**: 997–1020.

33 Pederson H, Okland T, Boyers LN, *et al.* Identifying Otolaryngology Systematic Review Research Gaps: Comparing Global Burden of Disease 2010 Results With Cochrane Database of Systematic Review Content. *JAMA Otolaryngol-- Head Neck Surg* 2014; : E1–6.

34 Powles J, Fahimi S, Micha R, *et al.* Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open* 2013; **3**: e003733.

35 Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. *Parasit Vectors* 2014; **7**: 37.

36 Risal A, Manandhar K, Steiner TJ, Holen A, Koju R, Linde M. Estimating prevalence and burden of major disorders of the brain in Nepal: cultural, geographic, logistic and philosophical issues of methodology. *J Headache Pain* 2014; **15**: 51.

37 Smith E, Hoy D, Cross M, *et al.* The global burden of gout: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; **73**: 1470–6.

38 Smith E, Hoy DG, Cross M, *et al.* The global burden of other musculoskeletal disorders: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; **73**: 1462–9.

39 Whiteford HA, Degenhardt L, Rehm J, *et al.* Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382**: 1575–86.

40 Ferrari AJ, Charlson FJ, Norman RE, *et al.* Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013; **10**: e1001547.

41 Karimkhani C, Boyers LN, Prescott L, *et al.* Global burden of skin disease as reflected in Cochrane Database of Systematic Reviews. *JAMA Dermatol* 2014; **150**: 945–51.

42 Krishnamurthi RV, Feigin VL, Forouzanfar MH, *et al.* Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet Glob Health* 2013; **1**: e259–81.

43 Kassebaum NJ, Jasrasaria R, Naghavi M, *et al.* A systematic analysis of global anemia burden from 1990 to 2010. *Blood* 2014; **123**: 615–24.

44 Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global Burden of Severe Periodontitis in 1990-2010: A Systematic Review and Meta-regression. *J Dent Res* 2014; **93**: 1045–53.

45 Moran A, Forouzanfar M, Sampson U, Chugh S, Feigin V, Mensah G. The epidemiology of cardiovascular diseases in sub-Saharan Africa: the Global Burden of Diseases, Injuries and Risk Factors 2010 Study. *Prog Cardiovasc Dis* 2013; **56**: 234–9.

46 Stovner LJ, Hoff JM, Svalheim S, Gilhus NE. Neurological disorders in the Global Burden of Disease 2010 study. *Acta Neurol Scand Suppl* 2014; **129**: 1–6.

47 Pasricha S-R. Anemia: a comprehensive global estimate. *Blood* 2014; **123**: 611–2.

48 Bittles AH. Genetics and global healthcare. *J R Coll Physicians Edinb* 2013; **43**: 7–10.

49 Byass P, de Courten M, Graham WJ, *et al.* Reflections on the Global Burden of Disease 2010 Estimates. *PLoS Med* 2013; **10**: e1001477.

50 Gabbe BJ, Lyons RA, Harrison JE, *et al.* Validating and Improving Injury Burden Estimates Study: the Injury-VIBES study protocol. *Inj Prev* 2013; published online Aug 6. DOI:10.1136/injuryprev-2013-040936.

51 Spencer S. Global Burden of Disease 2010 Study: A personal reflection. *Glob Cardiol Sci Pract* 2013; **2013**: 115–26.

52 Hser Y-I, Evans E, Grella C. Commentary on Degenhardt et al. (2014): Regional variation in the global burden of disease attributable to opioid dependence—where do the data come from and does population size matter? *Addiction* 2014; **109**: 1334–5.

53 Nord E. Disability weights in the Global Burden of Disease 2010: unclear meaning and overstatement of international agreement. *Health Policy Amst Neth* 2013; **111**: 99–104.

54 Taylor HR, Jonas JB, Keeffe J, *et al.* Disability weights for vision disorders in Global Burden of Disease study. *The Lancet* 2013; **381**: 23.

55 Voigt K, King NB. Disability weights in the global burden of disease 2010 study: two steps forward, one step back? *Bull World Health Organ* 2014; **92**: 226–8.

56 GBD 2010 Country Collaboration. GBD 2010 country results: a global public good. *Lancet* 2013; **381**: 965–70.

57 Gilmour S, Liao Y, Bilano V, Shibuya K. Burden of Disease in Japan: Using National and Subnational Data to Inform Local Health Policy. *J Prev Med Pub Health* 2014; **47**: 136–43.

58 Public Health Policy & Strategy Unit/NHS Commissioning Unit. Living Well for Longer: a call to action to reduce aviodable premature mortality. United Kingdom Department of Health, 2013.

59 The Global Burden of Disease and Its Implication for U.S. Policy. 2013.

60 Yu SC, Tan F, Zhou MG, Liu SW, Zhu XJ, Zhu YL. Global Burden of Disease, Injury and Risk Factor Study 2010: its policy implications for China. *Biomed Environ Sci BES* 2014; **27**: 45–8.

61 Murray CJL, Ortblad KF, Guinovart C, *et al.* Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 1005–70.

62 Flaxman A, Murray C, Vos T, editors. Integrated Meta-Regression Framework for Descriptive Epidemiology. University of Washington Press, 2014.

63 Bhatt S, Gething PW, Brady OJ, *et al.* The global distribution and burden of dengue. *Nature* 2013; **496**: 504–7.

64 London School of Hygiene and Tropical Medicine. GAHI: Global Atlas of Helminth Infections. 2014; published online Oct 25. http://www.thiswormyworld.org/ (accessed Oct 25, 2014).

65 Forouzanfar MH, Foreman KJ, Delossantos AM, *et al.* Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *The Lancet* 2011; **378**: 1461–84.

66 Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095–128.

67 National Cancer Institute (United States). United States - SEER Cancer Statistics Review (CSR) 1975-2011. Bethesda, United States: National Cancer Institute, 2014 http://ghdx.healthdata.org/record/united-states-seer-cancer-statistics-review-csr-1975-2011 (accessed Nov 19, 2014).

68 Sankaranarayanan R, Swaminathan R, Lucas E. Cancer survival in Africa, Asia, the Caribbean and Central America (SurvCan). Lyon, France: International Agency for Research on Cancer: IARC Scientific Publication, 2011.

69 Agency for Healthcare Research and Quality. United States Medical Expenditure Panel Survey 1996-2012. .

70 Centers for Disease Control and Prevention (CDC), Medical University of South Carolina, South Carolina Department of Disabilities and Special Needs, South Carolina Department of Health and Environmental Control. United States - South Carolina Traumatic Brain Injury Follow-up Registry 1999-2013. USA.

71 Haagsma JA. Posttraumatic Stress Disorder Following Injury: Trajectories and Impact on Health-Related Quality of Life. *J Depress Anxiety* 2013. DOI:10.4172/2167-1044.S4-002.

72 Johns Hopkins Bloomberg School of Public Health, University of Washington, Westat, Inc. United States National Study on the Costs and Outcomes of Trauma Care 2001-2003. .

73 Polinder S, van Beeck EF, Essink-Bot ML, *et al.* Functional outcome at 2.5, 5, 9, and 24 months after injury in the Netherlands. *J Trauma* 2007; **62**: 133–41.

74 Ringburg AN, Polinder S, van Ierland MCP, *et al.* Prevalence and prognostic factors of disability after major trauma. *J Trauma* 2011; **70**: 916–22.

75 Van Loey NE, van Beeck EF, Faber BW, van de Schoot R, Bremer M. Health-Related Quality of Life After Burns: A Prospective Multicentre Cohort Study With 18 Months Follow-Up. *J Trauma* 2011; published online Oct 24. DOI:10.1097/TA.0b013e3182199072.

76 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; published online Dec 17. DOI:10.1016/S0140-6736(14)61682-2.

77 Rastogi T, Mathers C. Global burden of iron deficiency anaemia in the year 2000. World Health Organization, 2002.

78 Kates EH, Kates JS. Anemia and polycythemia in the newborn. *Pediatr Rev Am Acad Pediatr* 2007; **28**: 33–4.

79 Bishop YM, Fienberg SE, Holland PW. Discrete Multivariate Analysis - Theory and Practice. MIT Press, 1975.

80 Pearson K. Mathematical contributions to the theory of evolution. Dulau and Co., 1904.

81 Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**: 317–28.

82 Bluestone CD. Epidemiology and pathogenesis of chronic suppurative otitis media: implications for prevention and treatment. *Int J Pediatr Otorhinolaryngol* 1998; **42**: 207–23.

83 Minja BM, Machemba A. Prevalence of otitis media, hearing impairment and cerumen impaction among school children in rural and urban Dar es Salaam, Tanzania. *Int J Pediatr Otorhinolaryngol* 1996; **37**: 29–34.

84 Salomon JA, Vos T, Hogan DR, *et al.* Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2129–43.

85 Salomon J. New disability weights for the global burden of disease. *Bull World Health Organ* 2010; **88**: 879–879.

86 Haagsma JA, Noordhout C, Polinder S, *et al.* The European disability weights study: assessing disability weights based on the responses of 30,660 people from four European countries. *Popul Health Metr* 2015.

87 Aregawi M, Cibulskis RE, Otten M, Williams R. Chapter 3 Interventions to control malaria. In: World malaria report 2009. World Health Organization, 2009.

88 Baltussen R, Knai C, Sharan M. Iron fortification and iron supplementation are cost-effective interventions to reduce iron deficiency in four subregions of the world. *J Nutr* 2004; **134**: 2678–84.

89 Casey GJ, Montresor A, Cavalli-Sforza LT, *et al.* Elimination of iron deficiency anemia and soil transmitted helminth infection: evidence from a fifty-four month iron-folic acid and de-worming program. *PLoS Negl Trop Dis* 2013; **7**: e2146.

90 Yeung CA. A systematic review of the efficacy and safety of fluoridation. *Evid Based Dent* 2008; **9**: 39–43.

91 Proposal for Sustainable Development Goals: Sustainable Development Knowledge Platform. 2014; published online Nov 25. http://sustainabledevelopment.un.org/focussdgs.html (accessed Nov 25, 2014).

92 Llyod LS. Best Practices for Dengue Prevention and Control in the Americas. Washington, D.C.: Environmental Health Project, 2003.

93 Desjeux P. The increase in risk factors for leishmaniasis worldwide. *Trans R Soc Trop Med Hyg* 2001; **95**: 239–43.

94 Desjeux P. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis* 2004; **27**: 305–18.

95 Franke CR, Staubach C, Ziller M, Schlüter H. Trends in the temporal and spatial distribution of visceral and cutaneous leishmaniasis in the state of Bahia, Brazil, from 1985 to 1999. *Trans R Soc Trop Med Hyg* 2002; **96**: 236–41.

96 Reithinger R, Dujardin J-C, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infect Dis* 2007; **7**: 581–96.

97 Hoy D, Geere J, Davatchi F, Meggitt B, Barrero L. A time for action: opportunities for preventing the growing burden and disability from musculoskeletal conditions in low- and middle-income countries. *Best Pr Res Clin Rheumatol* 2014; **28**: 377–93.

98 Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthr Cartil OARS Osteoarthr Res Soc* 2010; **18**: 24–33.

99 Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *J Rheumatol* 1993; **20**: 331–5.

100 Australian Institue of Health and Welfare. Health-care expenditure on arthritis and other musculoskeletal conditions 2008–09. Canberra: AIHW.

101 Statistics Norway. Norway Survey of Living Conditions 2002. Olso, Norway: Statistics Norway.

102 Statistics Norway. Norway Survey of Living Conditions 2005-2006. Olso, Norway: Statistics Norway.

103 Statistics Norway. Norway Survey of Living Conditions 2008-2009. Olso, Norway: Statistics Norway.

104 Statistics Norway. Norway Survey of Living Conditions 2012. Olso, Norway: Statistics Norway.

105 Andrews G, Issakidis C, Sanderson K, Corry J, Lapsley H. Utilising survey data to inform public policy: comparison of the cost-effectiveness of treatment of ten mental disorders. *Br J Psychiatry J Ment Sci* 2004; **184**: 526–33.

106 Vos T, Haby MM, Barendregt JJ, Kruijshaar M, Corry J, Andrews G. The burden of major depression avoidable by longer-term treatment strategies. *Arch Gen Psychiatry* 2004; **61**: 1097–103.

107 Devries KM, Mak JYT, García-Moreno C, *et al.* Global health. The global prevalence of intimate partner violence against women. *Science* 2013; **340**: 1527–8.

108 Forero R, McLellan L, Rissel C, Bauman A. Bullying behaviour and psychosocial health among school students in New South Wales, Australia: cross sectional survey. *BMJ* 1999; **319**: 344–8.

109 Hansen AM, Hogh A, Persson R, Karlson B, Garde AH, Ørbaek P. Bullying at work, health outcomes, and physiological stress response. *J Psychosom Res* 2006; **60**: 63–72.

110 Hillberg T, Hamilton-Giachritsis C, Dixon L. Review of meta-analyses on the association between child sexual abuse and adult mental health difficulties: a systematic approach. *Trauma Violence Abuse* 2011; **12**: 38–49.

111 Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS Med* 2012; **9**: e1001349.

112 Degenhardt L, Bucello C, Calabria B, *et al.* What data are available on the extent of illicit drug use and dependence globally? Results of four systematic reviews. *Drug Alcohol Depend* 2011; **117**: 85–101.

113 Cheng H, Deng F, Xiong W, Phillips MR. Prevalence of alcohol use disorders in mainland China: a systematic review. *Addict Abingdon Engl* 2015; published online Feb 10. DOI:10.1111/add.12876.

114 Pescosolido BA, Martin JK, Long JS, Medina TR, Phelan JC, Link BG. 'A disease like any other'? A decade of change in public reactions to schizophrenia, depression, and alcohol dependence. *Am J Psychiatry* 2010; **167**: 1321–30.

115 Schomerus G, Lucht M, Holzinger A, Matschinger H, Carta MG, Angermeyer MC. The stigma of alcohol dependence compared with other mental disorders: a review of population studies. *Alcohol Alcohol Oxf Oxfs* 2011; **46**: 105–12.

116 Schomerus G, Corrigan PW, Klauer T, Kuwert P, Freyberger HJ, Lucht M. Self-stigma in alcohol dependence: consequences for drinking-refusal self-efficacy. *Drug Alcohol Depend* 2011; **114**: 12–7.

117 Mathers CD, Iburg KM, Begg S. Adjusting for dependent comorbidity in the calculation of healthy life expectancy. *Popul Health Metr* 2006; **4**: 4.

118 Van Baal PH, Hoeymans N, Hoogenveen RT, Wit GA de, Westert GP. Disability weights for comorbidity and their influence on Health-adjusted Life Expectancy. *Popul Health Metr* 2006; **4**: 1.