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Measuring health at a global level with a unified tool: A review of institutional and methodological milestones of the Global Burden of Disease project

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Foreword

This publication is part of a broader project on the quantification of work- and environment related-cancer focusing on the use of health impact measurements and mostly on Population attributable fractions (PAFs), a tool used in epidemiology to evaluate the burden of disease attributed to known risk factors in a population. The aim of the overall project is first to analyze the development and circulation of the concept of PAF as one of the tools contributing to revealing the burden of work- and environment- related cancer, and at the same time hiding their unequal distribution; and then to identify potential avenues to quantify this burden in different social groups and according to gender (Counil & Henry, 2019). It was funded by the Fondation de France and is conducted jointly at the French Institute for Demographic Studies (Ined) and Paris-Dauphine University.

As the Global Burden of Disease (GBD) project uses attributable risk estimates in the course of its Comparative Risk Assessment (CRA) module, with estimates split by risk factors such as occupational carcinogens, it seemed important to document the trajectory of this specific tool within a large, international and highly influential global health quantification enterprise.

A complete review of the published methodology of the GBD and CRA, which spans over thousands of pages of technical explanations, was out of the scope of this work. Therefore, while the analysis is thorough in its conception, it is inevitably incomplete and subject to the author's own selection of specific dimensions to look into in order to feed the broader project. These choices were made on the grounds of the most widely discussed aspects of the GBD and CRA, the most cited papers, and through a grey literature review of the estimates published.

Summary (English)

The Global Burden of Disease (GBD) project represents one of the most comprehensive initiatives of health quantification to date. The Institute of Health Metrics and Evaluations (IHME), its hosting organization, produces estimates that have become increasingly influential in global health, with a clear ambition to inform policies. The following working paper, first of two volumes included in this research, provides a thorough examination of the historical development of the GBD by looking at its conceptual, methodological, and organizational evolutions. In this first volume, we will focus on the main measurement of the study, the disability-adjusted life years (DALY), and its two components: years of life lost (YLL) and years lost to disability (YLD). The work will then explore some of the most prominent critiques of the project and will try to understand how the GBD has addressed these issues methodologically. Finally, the work ponders on the institutional influences that could have affected the project, while trying to trace the most important actors in the development of its estimates. The research relies on a literature review (non-structured) of published studies and commentaries. It follows a chronological development of the GBD estimates since their first publication in 1993 to the version released in 2019.

Key words: GBD, IHME, DALY, YLD, YLL, global health, health metrics, epidemiology, public health, Gates Foundation, health policy

Résumé (français)

Le projet Global Burden of Disease (GBD) représente l'une des entreprises de quantification de la santé les plus complètes à ce jour. L'Institute of Health Metrics and Evaluations (IHME), son organisation hôte, produit des estimations de plus en plus influentes en matière de santé globale et d'orientation des politiques. Le présent document de travail, premier de deux volumes issus d'une recherche en cours, propose un examen détaillé du développement du GBD en se penchant sur ses évolutions historiques conceptuelles, méthodologiques et organisationnelles. Dans ce premier volume, nous nous concentrerons sur le principal instrument de mesure mobilisé, les années de vie corrigées de l'incapacité (DALY), et ses deux composantes : les années de vie perdues (YLL) et les années perdues en raison de l'incapacité (YLD). Le travail explorera ensuite les critiques les plus importantes du projet et tentera de comprendre comment le GBD a abordé ces questions sur le plan méthodologique. Enfin, le travail s'interroge sur les influences institutionnelles qui ont pu affecter cette entreprise de quantification, tout en essayant de retracer les acteurs les plus importants dans le développement de ses estimations. La recherche s'appuie sur une analyse documentaire (non structurée) des études et commentaires publiés. Elle suit un développement chronologique des différentes étapes et estimations du GBD, depuis leur première publication en 1993 jusqu'à l'édition publiée en 2019.

Mots-Clés : GBD, IHME, DALY, YLD, YLL, santé globale, indicateurs de santé, épidémiologie, santé publique, Fondation Gates, politiques de santé

Table of Contents

Introduction

The Global Burden of Disease (GBD) project has polarized the discussion in global population health over the last thirty years. From its introduction in 1993, it has greatly reshaped the approach with which international organizations, donors, and people see, understand, and are involved with health. This review has tried to trace a historical evolution of the most important methodological and institutional changes that the GBD project and studies have gone through in order to understand their purpose, scope and influence.

Since the famous "*Investing in Health"* World Development Report published by the World Bank in 1993 outlined the first effort to estimate the burden of all diseases, sequela and injuries at a global level, enumerating what affects people's health has radically changed in its conception. Its changes can also be observed through the eyes of the critiques it received, as the GBD tried to establish itself as an accepted measurement in its scientific community.

In this first working paper, this review tries to take a wholesome approach to this method of estimation of population health, originally developed by Christopher Murray and Alan Lopez, by looking at its main analytical components and understanding the choices made in relation to the use of its estimates.

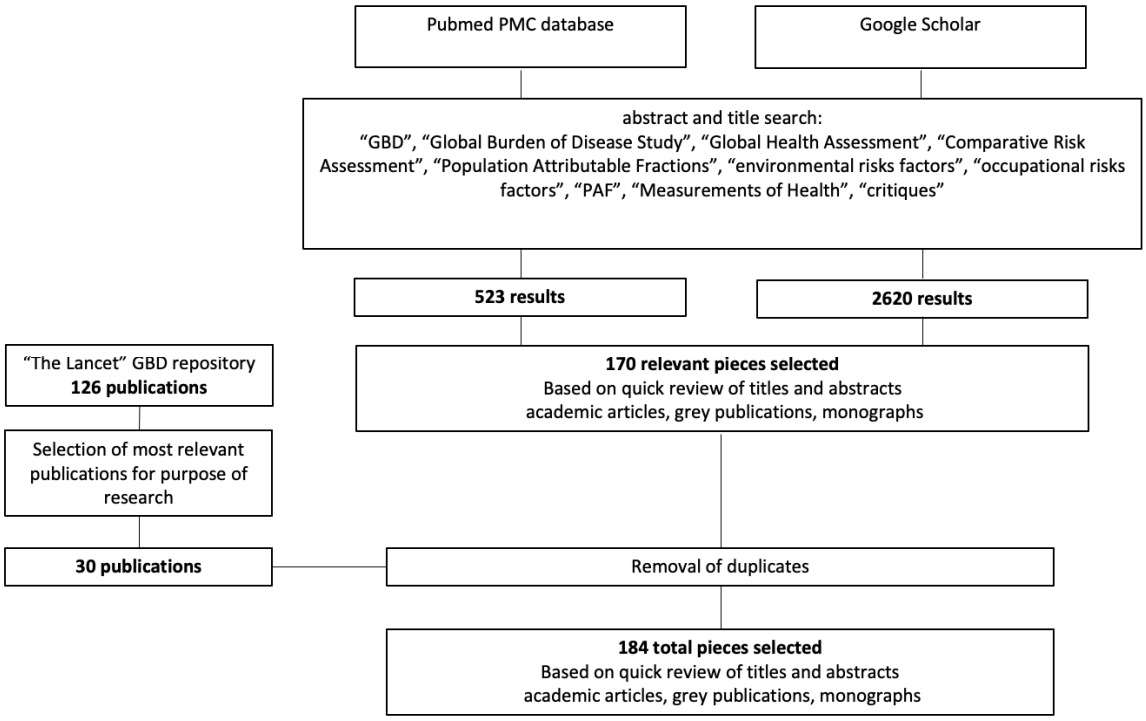
A second working paper gives particular attention to the development of the comparative risk assessment (CRA) study, which analyzes the contribution of various risk factors to the global burden of diseases and injuries by using attributable risks. This second paper is published separately (Document de Travail n° 266).

Methods and limitation

This literature review was un-structured for time constraints, but nonetheless followed an analytical methodology to be as unbiased and as accurate as possible. The main scientific search engines used for researching relevant documents were PubMed (PMC database) and Google Scholar advanced researches. Papers were selected and searched based on their abstract and title, with the following terms used in varied combinations: "GBD", "Global Burden of Disease Study", "Global Health Assessment", "Comparative Risk Assessment", "Population Attributable Fractions", "environmental risks factors", "occupational risks factors", "PAF", "Measurements of Health", "critiques".

The aim of the research was to identify all relevant academic literature, grey literature, and monographs which could help in the development of the storyline. After a first review, 523 results were identified on PubMed and 2620 results on Google Scholar, starting in year 1991. "The Lancet" dedicated GBD page was considered the main point of departure in order to identify the principal publications of the methodology, this included 126 indexed articles at the end of the research period (June 18th 2019). After a quick scanning, 170 articles indexed in Pubmed or Google Scholar were considered as relevant for the study, and 30 more articles were selected from "The Lancet" index of GBD studies. A Zotero library was then created and shared between co-authors of the research. Duplicate studies and non-relevant material were filtered. In total, 184 articles were selected and reviewed. A methodological mapping is shown in the flow-chart below.

Flow-chart of article selection process



Only a sub-set of articles are cited in this report, as this does not stand as a systematic literature review; the aim of the study was to understand the main features of the GBD methodology and review its evolutions throughout time. The authors, however, followed some imposed parameters in order to have a somewhat reproducible and traceable methodology. While thorough, the work presents several limitations. First of all, due to its limited time, it could not possibly analyze all materials relevant to the Global Burden of Diseases project. Therefore, literature was selected based on the authors' own judgement on relevance. Inevitably, this selection is partial and could have missed out on some aspects.

Additionally, the scope of the work was particularly interested in looking at the GBD's comparative risk assessment modules, and more specifically focusing on environmental and occupational risks. Therefore, the research was veered toward these topics. Lastly, it was developed with the aim of aiding a larger research, its aim was not to evaluate the GBD methodology, but rather to trace it and understand its changes through history. Regardless of these limitations, this is the first effort of this kind to the authors' knowledge and serves as a good overview of the GBD method and its CRA module, highlighting some of its most prominent praises and critiques over the years. It stands as a solid introduction to an incredibly vast database, and we hope it can lead to further studies and discussions which we deem necessary in the field of global population health and global health metrics.

A Timeline of the Global Burden of Diseases Publications and Updates

The Global Burden of Diseases (GBD) method has a complicated structure, released through various publications, opinion pieces, and reports all seemingly disconnected from one another. Because each of its components are so complex and require significant effort in study and design, they are often published as separate entities. Importantly, the GBD is a *method* which details different *measurements, metrics, and studies.* Therefore, all parts of the GBD method are stand-alone entities, part of a conglomeration which looks at depicting the status of global health in its entirety. Quite confusingly, while some sort of "update" on estimates were published yearly, not all yearly updates are considered "GBD updates"–that is, only a few updates are presented as complete reviews of the methodology, others just report updates in numbers. To make it easier to follow along the text, Figure i sets a timeline of publications mentioned in this report which defines years of publication along with titles of GBD updates.

The GBD in the 1990s' – DALYs and their moral conundrum

The Global Burden of Diseases (GBD) stands as one of the most comprehensive enumerations of global health burdens and causes in modern public health and epidemiology. It was formally introduced in 1993 in a joint work of the World Bank and the World Health Organization in the "*World Development Report: investing in health"* (The World Bank, 1993). The World Development Report, an annual review of the World Bank on the global status of economic and social development, for the first time introduced a comprehensive analysis on the importance of health in determining economic prosperity. The 1987 Report had previously looked at the imbalances of costs and benefits of healthcare sector in developing countries, citing it as a major source of economic stagnation. However, the analysis overlooked the value of wellbeing, focusing on a cost-benefit analysis of healthcare (The World Bank, 1988).

The 1993 Report took a different perspective by focusing on the role of disease burden in furthering the gap in health inequalities – the World Bank was now monitoring global health, and proposed an important tool to tackle health inequalities by devising a measurement which could quantify health while also aiding economic policy (Kenny, 2017). In the public health section, Christopher J.L. Murray and Alan Lopez presented a new population health summary metric, the Disability-Adjusted Life Years (DALYs), which took into consideration the effects on the complete health status of diseases, injuries, and sequalae which either disabled or killed people (The World Bank, 1993). DALYs immediately distinguished themselves as a revolutionary unit of measurement not only for their grandiose feat (to enumerate the complete global burden of all diseases and sequalae suffered by every country), but also because of their relatively easy computation: DALYs combined the years lived with disability (YLD) and years of life lost (YLL) tied to any given health problem (Murray & Lopez, 1997a). DALYs represent also a very easy unit of measurement to understand, as it simply equates to one lost year of healthy life (Murray, 1996).

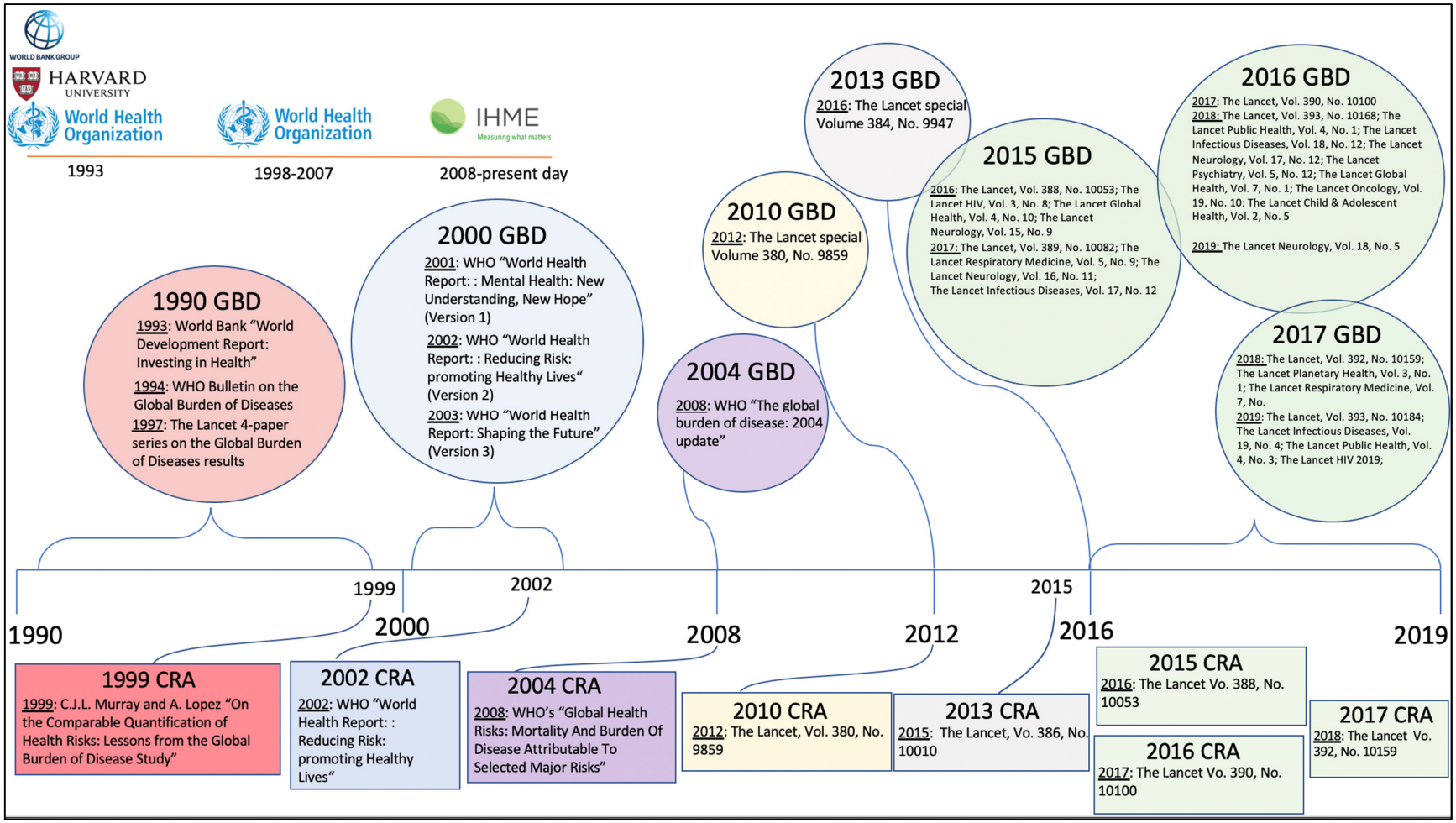


Figure i. A Precise Timeline of the GBD method publications with respective CRA (as of June 2019)
Source: Graphical representation made by author, information retrieved from all GBD publications, IHME website, and The Lancet dedicated webpage on the GBD method – See the full references list in Annex1.

This universal interpretation allows people, policymakers, and experts to speak a common language, giving enormous potential to this new dimension of health. Murray and Lopez, two international experts in health statistics (Keating, 2018), developed a complete, collaborative methodology, which was explained in a series of 4 papers in the WHO Bulletin in 1994, then again following the same format in 1997 in *The Lancet*.

The 8 seminal papers of the GBD methodology

Murray C. J., 1994, « Quantifying the burden of disease: the technical basis for disability-adjusted life years. », *Bulletin of the World Health Organization*, 72(3), p. 429‑445.
Murray C. J., **Lopez** A. D., 1994, « Global and regional cause-of-death patterns in 1990. », *Bulletin of the World Health Organization*, 72(3), p. 447‑480.
Murray C. J., **Lopez** A. D., 1994, « Quantifying disability: data, methods and results », *Bulletin of the World Health Organization*, 72(3), p. 481‑494.
Murray C. J., **Lopez** A. D., **Jamison** D. T., 1994, « The global burden of disease in 1990: summary results, sensitivity analysis and future directions. », *Bulletin of the World Health Organization*, 72(3), p. 495‑509.
Murray C. J., **Lopez** A. D., 1997, « Mortality by cause for eight regions of the world: Global Burden of Disease Study », *The Lancet*, 349, p. 8.
Murray C. J., **Lopez** A. D., 1997, « Regional patterns of disability-free life expectancy and disability-adjusted life expectancy: Global Burden of Disease Study », *The Lancet*, 349(9062), p. 1347‑1352.
Murray C. J., **Lopez** A. D., 1997, « Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study », *The Lancet*, 349(9063), p. 1436‑1442.
Murray C. J., **Lopez** A. D., 1997, « Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study », *The Lancet*, 349(9064), p. 1498‑1504.

These 8 papers would form the base of the conceptual and philosophical approach behind the GBD method, almost unchanged for nearly two decades (Institute for Health Metrics and Evaluation, 2014b).

The first necessary development to quantifying the global burden of all diseases, injuries, and sequelae is establishing a structural order of analysis. Murray and Lopez initially simply disaggregated poor health in three broad groups following the WHO's International Classification of Diseases (ICD) approach: (1) communicable, maternal, perinatal, and nutritional disorders; (2) non-communicable and chronic diseases; (3) road-traffic accidents and injuries. This division allowed for a separate computation of different health problems which affected different parts of the population in different ways (Murray, 1994). In their original conception, DALYs required four overarching assumptions which greatly affected the measurement of the burden of diseases: 1) the standard duration of a life, and therefore the years of life lost due to premature death at each age; 2) the value of a healthy year of life lived at every age; 3) the discount rate on the value of future time in respect to the present; and 4) the weight of each disability measured. Consequentially, it also required to define what *disability* meant, and how such affected the quality of life of a person. YLDs and YYLs were created in order to capture these four dimensions of the health metric.

Years of Life Lost

Years of life lost were defined as the difference between life expectancy in low mortality countries and age of actual death of a given individual. The life expectancy of Japan – at the time the highest in the world – was used for this calculation. This decision dealt with the definition of the standard duration of a life, asymmetrical due to the natural differences

observed between men and women, at 80 and 82.5 respectively (Murray, 1994). The guiding principle of the GBD was to "treat like health outcomes as like", meaning that no loss of life anywhere had to be considered differently in any way; this principle was critical for cross-national comparability and for creating a meaningful, universal metric (Murray & Lopez, 1994a). For this reason, any socioeconomic or educational gradient was also excluded from the calculations as deemed too selective in the development of a measurement that needed global application–the only stratifications taken into analysis, therefore, were age and sex (Murray, 1994). Regarding the former, the authors defined a "weight" for each age, so as to value differently the life lost according to years lived at the time of death.

The weighting valued years lived as young adults (10-35y) more than those at an older age or of newborns, creating a slightly left-skewed curve, which steeply raised after birth and leveled off toward later life (Murray, 1994). The choice was justified based on the social value given to life according to the "productive" role in society an individual has at each age, as well as their caring cost as age goes by. This was further supported by, as justified by the author, a general public idea which "believes that the time lived in the middle age groups should be weighted as more important than the extremes." (Murray, 1994). Age weighting gave an economic aspect to DALYs, valuing life as social capital rather than life *per se.* This approach would later be heavily criticized, deemed as unfit in the evaluation of global wellbeing that the project aspired to do, or in its role of advising policy makers around the world (Anand & Hanson, 1997). If health outcomes had to be treated all alike, then people's health–no matter the age–should not be valued differently. The consideration of a lost life at 20 to be more important than one lost at 70 implied that people have a monetary contribution and cost to their society, and that this last should be a prime factor in the decision of allocation of health interventions:

> *The line of thought from the first question to the application in cost effectiveness analyses seems to be that the healthier the person, the more valuable their life is to themselves and to society and the greater their claim on restricted healthcare resources to have their life extended. This makes sense only if the value of life is not seen as a dimension distinct from health, but rather as a direct positive function of health. (Arnesen & Nord, 1999)*

This seemed in stark contrast with the measures taken to value all individuals equally: "a principle of universalism of life" as claimed by Murray and Lopez, "would argue strongly for a common intrinsic valuation of human life, regardless of the age at (or time period in) which it is lived" (Anand & Hanson, 1997).

Years Lived with Disability

Years lived with disability had a more complex formulation. First, the choice between defining "disability" and "handicap" required designating what the inquiry wanted to observe. Certainly, not all diseases incur handicaps, but nonetheless disable a person. Conversely, handicaps can have more of a social stratification, as the same sequela can cause two different handicaps to two different people and, consequently, affect their quality of life differently. Therefore, a measurement of disability which includes in its broader scope even the handicapping effect of a disease or an injury, was chosen (Murray, 1994). Then, sequelae, injuries, and diseases needed to be subdivided into some form of hierarchy, as the burden of

very different health conditions (say, near-sightedness and an amputated leg) bring different disabilities, even if both persist for the rest of an individual's life (Murray, 1994).

To assess severity, a "disability scale", ranging from 0 (perfect health) to 1 (a health status comparable to death) was created. This was achieved by convening focus groups of experts for every disability, then grouping disabilities as alike in gravity–that is, events which incur the same "level of disability" were given a communal weight, so as to have 6 disability weights applicable to the calculation rather than a different weight for each of the 108 considered disease, injurie, and sequelae. This created a 6-rank system ranging from the smallest disability having a weight of .096 (that is, almost perfect health) to the biggest of .920 (Murray, 1994). Due to the complicated aspects of disability, and how these affect individuals, co-morbidity was left out of the analysis, and two disabilities happening from the same sequela to the same person were weighted singularly within the calculation of YLDs (Murray, 1994).

The method of disability weights derivation was heavily criticized, specifically for having such a utility-oriented method of estimation (Anand & Hanson, 1997). The medical experts' evaluation, assessed as a 2 step person-tradeoff questions[1], inherently considered the life of a disabled person worth less than the one of a healthy individual (Arnesen & Nord, 1999). It also posed a budget-allocation dilemma: designing a health intervention would incur deciding whether to allocate money to save the lives of a group of disabled individuals, or increase the life of a healthy population (The World Bank, 1993). This methodology was deemed flawed in light of the scope of the GBD–to assess the health of individuals, rather than creating a comparison of diseases from a health economics perspective. In other word, "A valuation of human beings according to their functional capacity is in sharp contrast to the humanistic values laid down in the Declaration of Human Rights" (Arnesen & Nord, 1999). It was also judged too simplistic and narrow to rely on the opinion of a small poll of experts for establishing a universal scale for disability weights, specifically because of the complex cultural aspect tied to disabilities. A major limitation of an economic evaluation of disabilities, such as this one, is that it lacks the depth of "cross-cultural differences in the interpretation of disability [which] show that the lives of individuals with disability are limited not so much by their specific type of disability as by the social interpretation of that disability." (Groce, 1999). In summary, it was deemed ethically questionable and incomplete to develop a measurement for the experience of a disability by not taking into consideration the opinion of those that experience it, or their perception at the general population level (Østerdal, 2009; Ütün et al., 1999).

The GBD study foresaw a dimension of health action, so as to ultimately create an agenda of critical areas where to invest for the health of a population. A choice on investment priorities was then necessary to include in both dimensions of health (YLD and YLL): should the GBD propose long-term investments on health systems, or quick action with shorter to medium-term implications? The aspect of time preference required deciding how to "discount" future

[1] In person trade-offs, individuals are asked to choose between curing a certain number of individuals in one disability class versus another number in a different class. When the individual grader is indifferent, the two outcomes are then equivalent, and a weight is derived. Each participant is asked two versions of the person trade-off question, one about extending life for people in a given health state *versus* extending life for healthy people, the second about giving health back to people in a given health state versus extending life for healthy people. Two questions are asked because people's answers to each one are invariably inconsistent with the other, and the process of making them consistent forces the participant to think through the implications of their decision in greater depth (Murray, 1994; Murray, 1996).

time, so as to regard as more or less valuable to act now rather than later. A discount rate values the health of the future at a "reduced" rate to that of today (the opposite of an interest rate in monetary terms) (Ganiats, 1992). This argument is closely related to economic investment theory and gives the measurement of DALYs a cost-benefit analysis dimension similar to that of QALYs (Sassi, 2006). The discount rate on costs and benefits of health interventions had been a debated issue in public health policy well before the wake of the GBD, mainly centered on the correct value to be used and the ethical dilemma of using different discount rates for costs and benefits. Critics of the idea of using equal discount rates for costs and benefits of health interventions prominently argued that the practice valued economic return on investments the same as human lives. The use of a lower rate for discounting the future value of benefits than that of costs would suggest an increased importance on the returns in terms of lives saved rather than monetary investments (Keeler & Cretin, 1983).

The use of no discount rate in the calculation of DALYs, according to the authors, would over-value short-term interventions by yielding high returns in the present and the future. Similarly, using a discount rate of benefits lower than that of the costs would solicit a continued postponement, as costs for any intervention would seem to be always lower in the future and therefore more convenient (Murray, 1994). This dilemma, known as the time paradox of investment, was resolved by applying a mild future discount rate of 3% yearly, so as to give some balanced value to the future, but keeping in mind the usual assumption that if people could choose between the value of healthier life today rather than tomorrow, most would choose today even if the future gains in health could potentially be greater.

This decision was based upon some contemporary conventions, including the chance that one might not be alive in the future (Murray, 1994). However, the time discount within the cost-benefit analysis disregards the health of future generations, as well as valuing life with decreasing marginal returns[2] (Anand & Hanson, 1997; Ganiats, 1992). From a budgeting point of view, "attaching lower weight to future health makes preventive health care seem less cost effective because such interventions typically involve current costs and future effects" (Brouwer et al., 2005), making present investments seem obsolete and justifying the postponement of taking action. Finally, the introduction of discounting also influences the decision on whether DALYs should be calculated from an incidence or prevalence perspective. With a discounting multiplier in the formula, future incidence is less important than the current one, yielding a lower number of DALYs in the future (Schroeder, 2012). Because the GBD aimed at measuring DALYs as a stream of healthy years of life lost to a disability in the future, it was constructed as an incidence-based measurement rather than prevalence-based, on the basis that this choice would bring internal consistency (due to the fact that disability can be calculated from both a prevalence and an incidence perspective, while death only as incidence) and more sensitivity to epidemiological trends (Murray, 1994).

Projections of the future burden

Another important set of estimates presented in the 1997 papers, all published in The Lancet, proposed alternative projections of the burden of disease from 1990 to 2020. This last exercise saw the development of global mortality and disability by cause in three scenarios (optimistic,

[2] The term *decreasing marginal returns* means that additional years will increase in weight up until a certain peak. After that peak is reached, an additional year will yield a lower weight. A graphical representation of the curve created can be found in the summary table 1 at the end of this chapter.

baseline, and pessimistic) (Murray & Lopez, 1997d). The 1997 projections of health made separate projection models for both sexes, 7 age groups, and 9 causes-of-death-clusters[3]. Future patterns were predicted based on 4 independent variables: 1. per capita income; 2. average years of schooling per adult; 3. smoking intensity; and 4. time. Nine linear equations, all in the same form, were then developed based on these 4 factors and applied to the 9 causes of death clusters. A scale, derived from the observed death rates for 1990 divided by the predicted values of the same year was created for age, sex, causes, and region–these were then kept constant to make predictions to 2020. The relationship between age-sex-specific morality of a disorder and the age-sex-specific mortality of causes-of-death clusters to which it belonged was used to generate the projections, which were done for eight regions and all age-sex groups from 1990 in 5-year intervals until 2020. This generated 10,976 total different iterations, with variations of the four independent variables observed. DALYs were executed for the three scenarios intended (optimistic, baseline, and pessimistic) taking also into consideration demographic changes likely to happen, the natural development of the epidemiologic transition, and growth in the life expectancy of the world (Murray & Lopez, 1997d).

Gaps and limitations of the first Global Burden of Disease Methodology

Many population health scientists pointed that the methodology fell short on the biased choices which it required in its calculation, presenting some important lacunae in the exercise of evaluating health in its whole. A too narrowly-generalized understanding of health and wellbeing around the world (Arnesen & Nord, 1999; Groce, 1999; Ütün et al., 1999) and its insensitivity to the gender and social aspects of health (Bastian, 2000) made it an unfit global measurement; far too inaccurate given the mediatic impact which its results would have on global health policies (Anand & Hanson, 1997; Paalman et al., 1998; Ugalde & Jackson, 1995). The influence of the World Bank, at its core a lending institution, raised some concerns on the scope of the study–the original results, in fact, focused particularly on galvanizing change in the developing South, where the World Bank was heavily involved (The World Bank, 1993). Evaluating global health and the creation of development priorities from an institution governed by the United States and that issued international loans at interest rates for the sake of economic growth raised some concerns regarding its role in the health development panorama (Paalman et al., 1998). This was also in light of the extended data interpolation which the method depended on for countries which lacked enough data for a detailed analysis:

> *Estimates based on poor data are then aggregated-for example, the countries of sub-Saharan Africa with their wide variations in costs and in disease burden, are lumped together. Despite their limitations, the estimates are valuable if only as a starting-point for discussions-and as an incentive, if one were needed, to improve the data. Health is worth investing in and that investment should be bigger. The World Bank tells us where that investment would best be placed. But there is a risk that a report from such an*

[3] Communicable, maternal and perinatal disorders (1) ; nutritional disorders (2) (representing all group 1 disorders from the previously stated diseases and injuries subdivision used in DALYs calculation); (3) malignant neoplasms, (4) cardiovascular diseases, (5) digestive diseases, (6) chronic respiratory diseases (group 2, non-communicable); (7) road-traffic accidents, (8) other unintentional injuries, and (9) intentional injuries (group 3, injuries)– to establish total mortality for all age groups and each sex.

influential and well-funded organization will be used uncritically as the basis for decisions on policy and resource allocation. (The Lancet, 1993)

Interpolation between countries following a clustering based on similar demographic and socioeconomic factors seemed like an oversimplification, especially because the countries missing the epidemiological data necessary for correct estimations were likely going to rely the most on the results published by the GBD. This conundrum exposed an important limitation, not only of the method, but of the institution which presented it to the international community as well–the GBD resembled the imposition of the World Banks' neo-colonialist development model, reliant on a "one-size-fit-all" formula of growth, and that had failed the international efforts of global development under the Bretton Woods economic system (Ugalde & Jackson, 1995). Imprecision and insensitivity–to gender, burden of disease at different ages, and the experience of disability of different populations–were the central topic of critique of the first GBD itineration. Nevertheless, the work done for the 1993 World Development Report was a catalyst in population health metrics, which galvanized the scientific community and international organizations to challenge the GBD's estimates, opening the doors to a new era in the field of global population health.

The GBD at the turn of the Century

After the 1993 World Development Report (henceforth, the 1990 GBD[4]), Murray and Lopez moved the GBD project to the WHO, and established a disease burden unit in 1998 which updated the global burden of disease numbers, reporting it first in its 1999 World Health Report (WHR) with 1,382,564 DALYs in all WHO Regions–importantly, no methodological changes were made (World Health Organization, 1999a).

In 2002, the 2000 GBD, an official update of the 1990 estimates, was released in three versions. Small changes were made to the original methodology, but they are worth noting; the regions of analysis were changed from those of the World Bank to those of the WHO: 6 global regions, subdivided in 14 epidemiological sub-regions based on levels of child and adult mortality rates of Member States, a proxy variable of development[5]. The GBD 2000 also updated the list of diseases from 108 to 135, and relied more on national mortality estimates, as well as expanded databases, improved (according to the author's own account) in the years elapsed between the two publications. The approach, however, remained largely the same to that originally presented in 1993, with a better detailed explanation of steps taken for internal consistency and statistical methods used (World Health Assembly, 2000). The GBD 2000 addressed the controversial issue of disability weights, pledging it had "initiated a two-tiered data collection strategy involving general population surveys, combined with more detailed surveys among respondents with high levels of educational attainment in the same sites." (Murray et al., 2002). This would later make up the disability weight evaluation used in the 2010 GBD.

[4] Annex 2 summarizes the main measurements and findings of the 1990 GBD.

[5] The regions are (World Health Organization, 1999b): African Region (AFR) with two sub regions: AFRO D and AFRO E / Eastern Mediterranean Region (EMR) with two sub regions: EMR B and EMD D / European Region (EUR) with three sub regions: EUR A, EUR B, and EUR C / Region of the Americas (AMR) with three sub regions: AMR A, AMR B, AMR D / South East Asian Region (SEAR) with two sub regions : SEAR B and SEAR D / Western Pacific Region (WPR) wit two sub regions: WPR A and WPR B / This represent 191 WHO Member States of the world.

The Global Burden of Disease methodology in the 21st Century

With the Bill and Melinda Gates Foundation (BMGF) getting involved in the creation of the 2010 Global Burden of Disease update, the methodology has radically changed its approach to population health. As all of the elements of the measurement are rooted within one another, the construction of the new estimates required an almost complete redesign (Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012a). The BMGF announced their official commitment to the project in 2005, and the Institute of Health Metrics and Evaluation (IHME) was founded at the University of Washington two years later, with Murray as the chief coordinator of the GBD. The project prioritized the establishment of a large network of 500 experts in 50 countries in order to begin to assess the burden of disease for the population of 187 nations (TEDMED, 2013). In 2012, 5 years later, *The Lancet* published over 1000 pages reporting the global burden of diseases and injuries from 1990 to 2010, a detailed analysis of comparative risk factors affecting and contributing to the health loss of people worldwide, along with an online visualization tool giving the possibility to compare the burden of different diseases and contrasting the impact of different risk factors on global health. Truly unprecedented in its computation, the method compiled a database of over 800 million deaths worldwide derived from 291 diseases and over 1000 sequalae (Das & Samarasekera, 2012; Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012a). It established teams of statisticians and modelling experts who devised unique predicting and projecting models with the claimed concern of ensuring validity, consistency and accountability of estimates. The GBD 2010 was much more concerned with establishing a reproducible methodology, as well as setting the foundations of a powerful tool for current and future development in the field of population health metrics, both for estimating disease burden and burden attributed to known risk factors, that is performing comparative risk assessment (CRA)[6]. Since the 2010 publication, the GBD study has been updated subsequently in 2013, and has planned yearly updates since 2015. The IHME in the 21st century aimed to establish itself as a new entity in global health, one independent from any international organization or government and devoted to mapping the disease burden of different populations. Throughout the next chapter, a detailed evaluation of the changes in methodology and their justifications will be presented, to then compare it to the 1993 GBD itineration, and the further adjustments made in the 2013 and 2015 updates.

Designing a classification of diseases and sequelae

It is important, first and foremost, to understand that the method behind the estimation of the GBD is one made of various analytical components, which are all inevitably interconnected with one another – this means, for example, that changes in the estimation method of age-specific mortality rates will necessarily induce changes in the estimation of healthy life expectancy; changing the methods in codifying causes of death, will inevitably lead to changes in the estimation of diseases prevalence. Figure 1 allows for a clear visualization of the GBD's 18 independent parts. Analyzing all 18 in detail would be outside the scope of this research; this review will instead focus on some specific but significant amendments from the original methodology.

[6] For a more detailed explanation of the CRA methodology, please see *"Ranking the burden of disease attributed to known risk factors: A review of the GBD Comparative Risk Assessment approach through the lens of occupational and environmental health" (Document de travail n° 266).*

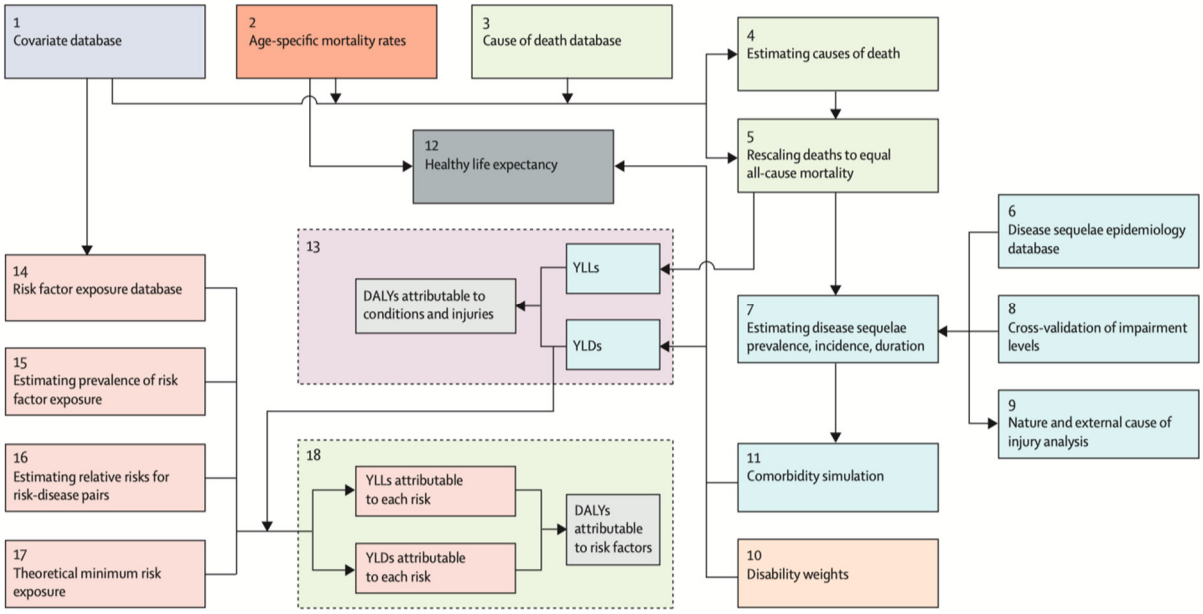


Figure 1. 18 analytical components of the global burden of diseases study, 2010
Source: Reproduced from Murray et al. 2012. GBD 2010: design, definition, and metrics. 2012, The Lancet 380: 2063-66.

Some basic structural changes are important to point out right away; the GBD 2010 changed its global regional subdivision which, since the World Health Reports (WHR), had used the WHO's regions grouped by general demographic similarities (mortality and fertility rates). Now, it took into account epidemiological homogeneity and geographic contiguity, developing a 21-region system with seven super-regions[7]. The GBD 2010 also adopted much more precise age-groups sub-division, which increased to 21 from the previously defined 8, with a more detailed subdivision at younger and older ages given the rise in burden of non-communicable diseases and the desire for more detailed stratification of diseases affecting various different stages of early childhood development.

Disease disaggregation remained at the three basic groups as in the 1990 evaluation: 1) communicable, maternal, neonatal and nutritional disorders; 2) non-communicable diseases; and 3) injuries. However a new hierarchical structure for health status, based on three levels of possible aggregation, was developed in order to cluster different diseases in the same medical causal groups. This hierarchical list subdivides medical causes with similar attributes under the same categories. Importantly, hierarchy is not of importance, but rather specificity – the higher the level, the more specifically the medical cause is defined. For example, two diseases like stomach and liver cancer would both be categorized under Level 1 as non-communicable diseases and under Level 2 as neoplasms. Liver cancer due to an underlying

[7] The 21 regions, subdivided by the seven super-regions are: **High Income**: Southern Latin America, Western Europe, High-income North America, Australasia, High-income Asian Pacific / **Latin America and Caribbean**: Caribbean, Central Latin America, Tropical Latin America, Andean Latin America / **Sub-Saharan Africa**: Southern sub-Saharan Africa, Western sub-Saharan Africa, Central sub-Saharan Africa, Eastern sub-Saharan Africa / **North Africa and Middle East**: North Africa and Middle East / **South Asia**: South Asia / **Southeast Asia, East Asia, and Oceania**: East Asia, Southeast Asia, Oceania / **Central Europe, Eastern Europe, and Central Asia**: Central Asia, Central Europe, Eastern Europe

condition, such as hepatitis B or C, would also be categorized under Level 4, as hepatitis is the specific causal agent of the cancer. A visual representation of this hierarchical structure can be found in Figure 2 below.

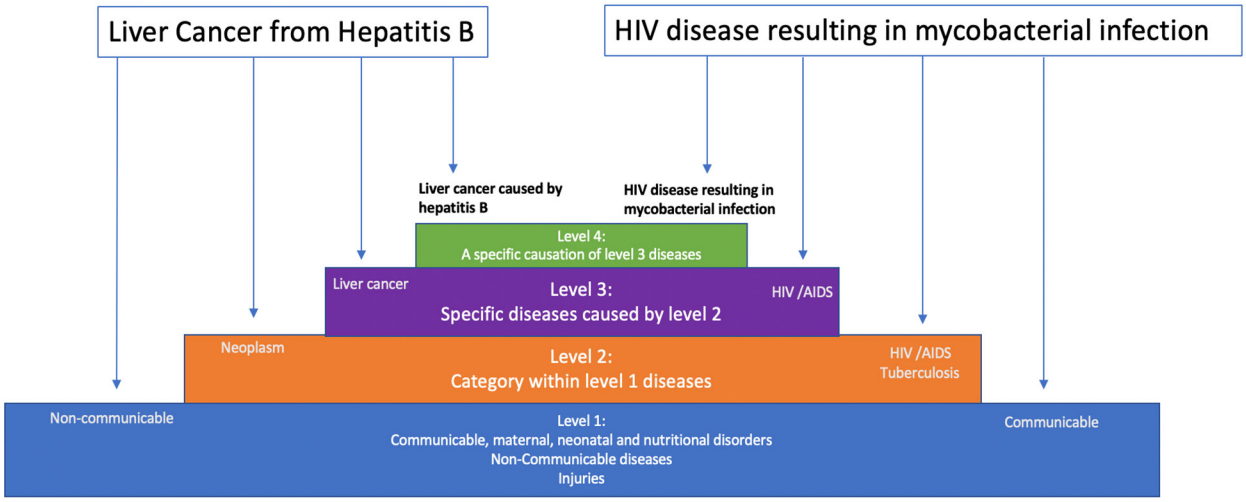


Figure 2. Visual representation of 4 level GBD hierarchical (medical) cause disaggregation for two diseases
Source: graph made by the authors, data gathered from Murray et al. 2012. Supplement to GBD 2010: design, definitions, and metrics. Lancet 2012, 280:2063-66.

Not all diseases or injuries have all 4 levels of explanation: for example, tuberculosis, would fall under Level 2 (HIV/AIDS and tuberculosis) but not also under Level 4, as no further causation is found other than contracting tuberculosis itself; the same can be said about traffic injuries.

The choice of calculating prevalence rather than incidence is a good point of departure to look at more specific analytical changes. The 1990 estimates calculated incidence primarily for two reasons: one, the authors found more consistency in estimating years lived with disability (YLDs) and years of life lost (YLLs) by using incidence, since death can only be estimated as an incidence, therefore treating fatal and non-fatal outcomes alike in calculations; second, as incidence is a reflection of current epidemiological trends, the authors found incidence to be more relevant to the public health questions they were interested in addressing and more useful for policymakers (Murray, Ezzati, Flaxman, Lim, Lozano, Naghavi, et al., 2012). However, this approach had some notable disadvantages. First, it underestimated the burden of people living with prolonged life impairments due to diseases for which incidence is easier to curb than prevalence, such as HIV/AIDS. Second, it required the decision, in part arbitrary, on when a disease or a sequalae could be deemed to start, adding an additional level of bias.

The 2010 estimates aimed to increase reproducibility by eliminating as many subjective decisions made in the estimation process as possible, the authors said, as well as to provide an analysis of comorbidity - which was lacking before. For these reasons, a prevalence approach was deemed more objective[8], as it also allowed for an easier calculation of

[8] More specifically, in an analysis of a prevalence vs. an incidence approach, the prevalence approach was favoured because of the possible insensibility to people living with prolonged disability in an incidence approach; the arbitrary choice of establishing when a disease process starts is not present in a prevalence perspective, so less biased; for planning and decision-making purposes, assigning the burden to the age at which health loss is

comorbidity (Murray, Ezzati, Flaxman, Lim, Lozano, Naghavi, et al., 2012). This change required a complete re-design of the databases used, and a significant update of the 2010 itineration was the extensive covariate database constructed, with 84 topics and 174 variants (Box 1 found in Figure 1). The covariate database represented an aggregation of independent variables for estimation of diseases and risk factors (it included, for example, alcohol consumption in liters per capita, live births, and total mean cholesterol per capita) (Murray, Ezzati, Flaxman, Lim, Lozano, Naghavi, et al., 2012). This in turn created the new list of 291 causes of death, injury, and sequela which the GBD estimated. The resulting list is a complex aggregation of many different types of data sources from all over the world, tracing the history of deaths from 1950 to 2010 for all countries.

In past estimations, this aspect had been the biggest limitation to the value of the GBD's results, especially when looking at causes of death in countries lacking proper epidemiological data, for which missing data was either extrapolated by Region, or deemed as missing and ignored (Anand & Hanson, 1997; Paalman et al., 1998; The Lancet, 1993). To solve this problem, the 2010 GBD aimed instead at modelling more accurate estimates in order to fill those gaps. Causes of death were estimated by developing the Cause of Death Ensemble Model algorithm (CODEm), a complex model ensemble approach which averages the results of four different models–two linear mixed models, and two spatial-temporal Gaussian Process Regression models–in order to create a best-case scenario of possible trends in causes of death. CODEm creates country-specific estimates rather than regional ones, and in the case of countries completely missing data for some causes of death, regional or super-regional estimates were used (Foreman et al., 2012).

Detailing the extremely complex method of estimation used by CODEm would be out of the scope of this review, but it is important to highlight that, while the algorithm was trained by being fed six different plausible scenarios of missing data (such as completely missing data, yearly gaps, or missing data only for some age cohorts) and then tested through 3 steps in its predictive validity based on its estimation on data which was already observed, it still presented *modelled*, rather than *observed* events. As the model runs through half a million of possible scenarios and almost 2 thousand models for each medical cause selected, requiring days of computational work and extensive data storage, results still seem quite hard to replicate anywhere outside the IHME. CODEm was instrumental in developing a database of causes of death, and necessary for shaping the new estimation of prevalence, incidence, and all-cause mortality used for calculating YLLs, YLDs, and DALYs–all which radically changed in this method of estimation.

New methods for estimating healthy life and death

The measures of life, death and disability went under extensive analytical revision in order to become as reproducible and as objective as possible:

> *We tended to make lots of not so replicable ad-hoc decisions and few people knew what we were doing anyway. This exercise has deliberately tried to minimize the ad-hoc decisions and instead aimed to maximize what information we can get from the data. We also have much more closely involved hundreds of experts and young*

experienced is more useful; finally, incorporation of comorbidity is more straightforward in a prevalence approach than an incidence approach (Murray, Ezzati, Flaxman, Lim, Lozano, Naghavi, et al., 2012).

> *researchers who are very capable of looking over our shoulders and are much more articulate at picking apart the estimates.–Theo Vos* (Das & Samarasekera, 2012)

While the addition of YLDs and YLLs to derive DALYs did not change, the GBD method dropped both heterogeneous age-weights and the yearly 3% discount rate on future life years, two defining attributes in the construct of the metrics in 1990 and 2000. The practice had strongly been criticized in the years since the first publication of estimates in the late 1990s, largely seen as placing a differential worth on lives, as well as significantly affecting the reported burden of disease–the measurement, in short, "favored" the burden suffered by young adults and working-age groups, while significantly discounting the burden of diseases of young children and at older age (Anand & Hanson, 1997; Arnesen & Nord, 1999; Kenny, 2017; Paalman et al., 1998).

Years of Life Lost: enhanced accuracy and comparability

Years of life lost remained unchanged in their calculation, but significant work went into increasing their accuracy. To control for comparability between different causes of death, for which data has to be equally reliable even if differently reported, the methodology developed a six-step assessment for data quality and comparability, shown in Figure 3 (Lozano et al., 2012). To ensure consistency in findings of single-cause models to all-cause mortality, the CoDCorrect algorithm which "proportionately rescaled every cause such that the sum of the cause-specific estimates equaled the number of deaths from all causes generated from the demographic analysis" (Lozano et al., 2012) was used for each cause. In other words, CoDCorrect ensured that the sum of singularly-estimated mortalities matched the observed all-cause mortality. Finally, the reference life tables used for estimating the normal length of a life also changed. In 1990, the GBD used the life expectancy of Japan, and different ages for men and women (80 and 82.5 years respectively). The new approach estimated life expectancy to be 86 years given recent significant improvements in longevity, and was also standardized for both sexes as this reference duration was "meant to represent the aspiration for healthy lifespan for all individuals" (Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012a).

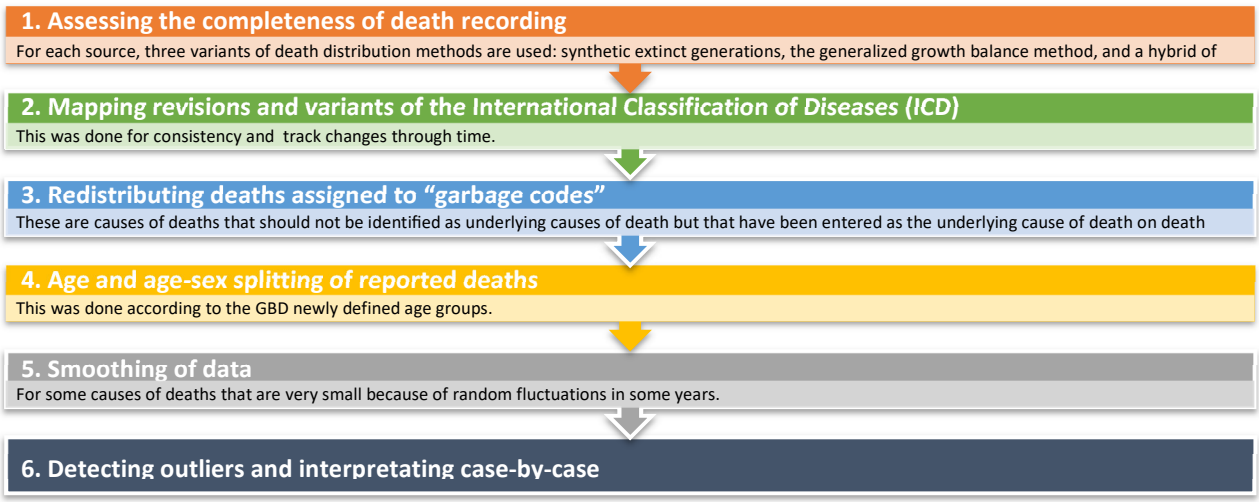


Figure 3. GBD 2010 6-step assessment for causes of death data quality and comparability
Source: Lozano et al. 2012

Assessing disability: a new approach

Years lived with disability were particularly criticized for their insensitivity to the widely different experience of disabilities and sequelae around the world. As previously discussed, the 1990 methodology accounted for disability by assigning disability weights to six generalized groups of disabilities and sequelae. The weights were established by small focus groups of experts which were posed a two person-trade-off questions, inherently defining the burden of disability strictly from a clinical and academical reference point–for a population health measurement, this method was highly restrictive, and insensitive to the wide spectrum of disability experience (Arnesen & Nord, 1999; Bastian, 2000; Groce, 1999; Ütün et al., 1999)[9]. When the GBD was transferred to the WHO, a population survey was crafted in order to capture a more realistic perception of disabilities around the world, which took into consideration differences in culture, sex, and economic development (Murray & Lopez, 2000). This new definition of disabilities took a long time to be implemented, being announced for the 2000 GBD update, but officially used only in the 2010 methodology. A population survey between 2009 and 2010 was carried out by phone call in the United States and by home visit in Bangladesh, Indonesia, Peru, and Tanzania; 14 thousand households were asked paired comparison questions, which exposed to participants two hypothetical individuals with randomly-assigned health states, asking which they considered healthier. An open-access web survey was also issued a year later which specifically targeted individuals interested in global health by advertising it on online publications, blogs, and news items in health journals. Over 16 thousand people responded to the online survey, for a total of over 30 thousand individual respondents to the overall survey (Salomon, Vos, et al., 2012).

The way in which people perceive the health states presented to them will inevitably affect their judgement of severity. The description used by the study, then, is of particular importance within the design of the disability weights. Salomon et al. used a disease-specific health state description, which, unlike other models–such as the multi-attribute utility instrument (MAUI) which favors a description of the health state only through generic attributes–include disability scenarios (the disability as a consequence of a health complication), illustrations of specific symptoms, and possible treatments (Haagsma et al., 2014). There is extensive debate on how to properly calibrate weights and whether it is appropriate to include all the details presented in the disease-specific model, as it tends to frame the impact of a disability with relations to a particular disease, as this might create bias of evaluation. Reviews of the method have shown that it seems to be more sensitive in identifying and quantifying small changes (Haagsma et al., 2014; Patrick & Deyo, 1989).

The surveys were designed to provide the largest and most heterogeneous pool of opinions possible. Based on respondents' answers, a numerical integration was used to obtain mean estimates of disability weights which ranged from 0 to 1[10]. A finding worth pointing out is the comparison analysis, which found a close correlation (0.7) with the previously estimated weights –suggesting that previously surveyed experts understood fairly well how a severe sequela affected people around the world. However, importantly, mild outcomes, which are also the most diffused, had substantially different weights, perhaps indicating that sequelae

[9] Please refer to the chapter *The GBD in the 1990s'–DALYs and their moral conundrum* for a more detailed discussion on this issue.

[10] For a thorough explanation of the methodology, please see Vos et al. 2012 *"Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010*" The Lancet Vol 380, 2012: page 2131-2134.

affecting people's lives in a prolonged, yet less acute way were much less well-understood at the clinical level. Lower back pain for example had a previous weight of 0.06, but was then re-calibrated to 0.27. In contrast, infertility had a disability weight of 0.18 according to experts, but lowered to 0.01 based on the survey (Salomon, Vos, et al., 2012).

Years Lived with Disability: more comprehensive and less biased

The 1990 GBD lacked epidemiological, clinical, and general evidence on the experience of sequelae and their relation to diseases and injuries. Moreover, as stated by the authors, the methodology was limited in its use because it included no uncertainty intervals and comorbidity could not be accounted for (Vos et al., 2012). While the arithmetic of YLDs became much simpler, now multiplying only sequelae prevalence and disability weight, their computation grew significantly more intricate and complex as a new set of modelling approaches were implemented. The 2010 revision sought first and foremost to collect much more detailed account for sequelae burden; the previous two GBD estimates included 483 (1990) and 474 (2000) sequelae respectively (some were dropped in the second revision because of duplicates or lack of valid evidence) (Murray et al., 2002). In comparison, the 2010 study included a list of 1160 sequelae derived by 291 diseases, outsourced from 9 different epidemiological sources of data[11].

Text box 1: What are sequelae, diseases, and disabilities?

Sequelae: disease, condition, or injury. This generic term represents all diseases, injuries, and problems enumerated in the GBD and the CRA. Sequelae are consequences of diseases or injuries– for example, losing a limb due to diabetes, or developing asthma due to exposure to pollution.

Disease: represent a disorder caused by a secondary factor. This includes all communicable (for example influenza, HIV, and hepatitis) and non-communicable diseases (cancer, myocardial infarction, or cerebrovascular accident). Diseases, in the GBD, do not represent their disabling factors, only their incidence and prevalence around the world.

Disabilities: any condition which disables or handicaps a person. These include short-slightness, leg paralysis, or amputation of a limb, as well as infertility, or deafness.

Comorbidities: two or more sequelae happening simultaneously in the global population. This includes both diseases and disabilities listed above. For example, suffering from two diseases, two disabilities, or a disability and a disease at the same time would represent a comorbidity. Importantly, comorbidity does not take into account the disability caused by a disease, and vice-versa.

[11] These are: 1) systematic reviews for disease sequelae; 2) reports of governments for tropical diseases; 3) population-based disease registry data for many non-communicable and chronic diseases; 4) networks of antenatal clinics for HIV and other sexually-transmitted disorders; 5) hospital discharge data coded to ICD9 or ICD10 for 43 countries; 6) ambulatory data for skin diseases and other mental and behavioral disorders; 7) interview questions, direct measurements (eg, hearing, vision, and lung function testing), serological measurements, and anthropometry from the re-analysis of multiple household surveys; 8) re-analysis of cohort or follow-up studies for some impairments due to injuries; 9) indirect prevalence studies as an input to estimate the total number of drug users. (Vos et al., 2012)

The greatest challenge in enumerating the burden of disability on the global population is to encompass the different experiences entailed to every sequelae equally, even where data is scarce and for countries which might not necessarily record disabilities in the same way. Moreover, databases are often not standardized and so are often differently formatted, requiring the GBD to compile and coherently organize all the information in order for it to all fit the same format (Vos et al., 2012).

DISMOD had been previously introduced in the 1990 methodology (Murray & Lopez, 1997b); however the method was revised to include a Bayesian meta-regression model, creating the DisMod-MR algorithm[12]. The algorithm was designed with the purpose of addressing "key limitations in descriptive epidemiological data, including missing data, inconsistency, and large methodological variation between data sources" (Vos et al., 2012). Importantly, DisMod-MR was able to compensate for the previous shortcoming of uncertainty intervals for all estimates of YLDs, providing a maximum likelihood estimate for all age groups and by sex for 187 countries through the variation of 179 selected covariates (not specified in the text). Comorbidity, previously disregarded, was now taken into account by running micro-simulations of co-occurrence through a Monte Carlo simulation (in other words, a model which estimates thousands of possible outcomes by small variations in the interaction between variables) of 20 thousand hypothetical individuals–this was done for each age, sex, country, and year. Co-occurrence was, in practice, modelled as a function of the prevalence of each sequelae and their probability of being independent or dependent on each other. A combined disability weight was then calculated for the individuals with every combination of disorders (Vos et al., 2012). Co-occurrence was completely modelled, with the observations only based on clinical studies of known possible co-morbidities.

Disability-Adjusted Life Years

The combination of YLLs and YLDs produces as their main output DALYs, a central summary metric of the GBD method. Most of the analytical changes to DALYs are inevitably summarized in the changes described above of its two main components. DALYs now took the value of a measure - in fact, a quantification tool - of absolute health loss, strictly tied to epidemiological and demographic changes observed, or rather modelled based on available observations and a range of assumptions.

YLLs, YLDs and DALYs were also assessed as projections from 1990, 2005, and 2010 and all computed in 2 counter factual scenarios in order to grasp changes which were attributable to epidemiological transitions and those attributable to demographic shifts. The first scenario (scenario 1) looked at estimates in 2010 if only total population numbers increased to 2010 levels while the age-sex structure, age-specific, and sex-specific rates remained constant since 1990. The second scenario (scenario 2) computed the number of YLLs, YLDs and DALYs expected in 2010 using 1990 age and sex-specific rates but with 2010 age and sex-specific population numbers (Murray, Vos, Lozano, Naghavi, Lopez, et al., 2012). These two alternative scenarios could help disentangle three sources of variation in the modelled trends:

– Differences between scenario 1 and 1990 estimates could be attributed strictly to the growth in the population (population growth component).

[12] The model includes the following combinations: covariates that predict variation in true rates; covariates that predict variation across studies because of measurement bias; super-region, region, and country random intercepts; and age-specific fixed effects. (Vos et al., 2012)

– Change from scenario 1 to scenario 2 reflect deaths which can be attributed to population aging (aging component).
– The differences between 2010 estimates and scenario 2 indicate the variation explained by epidemiological changes in age-specific and sex-specific death rates (health transition component).

The 2010 GBD computed DALYs also for 1990, in order to capture the shift in the population's wellbeing over the span of the two decades elapsed due to general social improvements. The GBD had introduced a ranking system for the top diseases, sequelae, and injuries affecting people's health in order to visually communicate this change–Figure 4 shows the change in ranking from 1990 to 2010 grouped by level 1 (See Figure 2 for details on the level grouping)[13]. Ranking is based on diseases and injuries contributing most DALYs in the world.

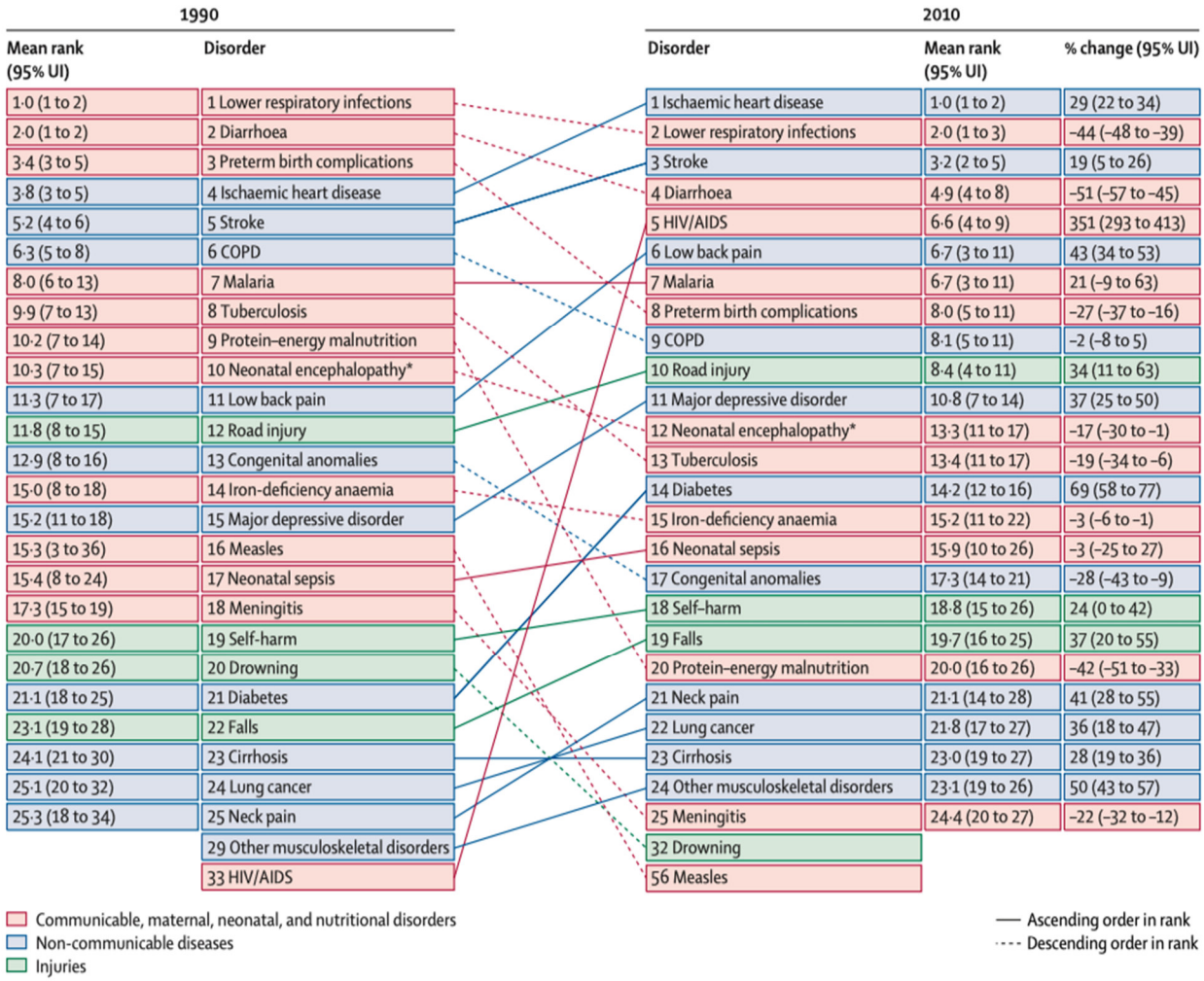


Figure 4. GBD 2010 ranking of top 25 causes of DALYs worldwide: 1990-2010 change.
Source: Reproduced from Murray et al. 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012 380: 2197-223.

[13] Annex 4 shows that a similar comparison was already made in GBD 1990, but by contrasting the estimated burden in 1990 with the expected (projected) burden in 2020.

The ranking system introduced by the methodology echoed its function as a tool for policymakers by providing an assessment of the progress made in global health between the 1990 and 2010 evaluations: malnutrition and many diseases for which tough immunization campaigns were carried out were successfully repressed, losing many places in the ranking. The list also showed the advancement of non-communicable diseases as the next principal causes of death and disability, prompting countries still not ready to face this burden to develop programs of prevention and management (Murray, Vos, Lozano, Naghavi, Lopez, et al., 2012). The advantage of identifying priorities through a burden ranking in global health is hard to understate, but the practice inevitably raises questions about the influence of its financial supporters. The BMGF, one of the founding donors of the GBD, also uses the rankings to establish program priorities and develop interventions (Tichenor & Sridhar, 2019).

Conceptual Evolution of the Method

The complete re-design of its databases, the meticulous work behind creating estimates and predictions which accounted for their uncertainties, and the detailed methodology laid out in the 12 papers that made up the study allowed for the establishment of a more robust methodology. Moreover, the wide array of open access webtools which accompanied the publications of results made global health a topic seemingly more approachable by the public and institutions alike. However, the complexity of the research, as well as the immense human capital which it required for its completion made it an exercise almost impossible to reproduce anywhere else outside of the IHME. While the thousands of pages of manuscripts and published appendices made it accessible and transparent, it also made it extremely hard to navigate, and this design largely hides some fundamental aspects in its methodology–namely, exactly how it derived its data, the completeness of its databases, or the way in which uncertainty was dealt with. Annex 3 summarizes main analytical and technical aspects of GBD 1990, 2000 and 2010.

Contemporary critiques

Some authors criticized the new GBD for relying on inaccurate estimations (Byass et al., 2013), and on its role in assisting the budget allocation of health programs. Voigt and King (2017) considered that many prevention and eradication programs were not addressing the problems causing the most DALYs–would the GBD affect a re-distribution of resources based on projections?

> *A distribution of resources that, from the outside, may look like a 'misalignment', could reflect different, but entirely reasonable, normative decisions about which objectives to prioritize. Moreover, different communities may differ in their priorities, and a distribution of resources—including one that 'aligns' with the burden of disease—that reflects the priorities of one country may not be appropriate for another (Voigt & King, 2017).*

The guidance of health policy and action may indeed be simplified with the implementation of a catch-all metric; however, this inherently has to generalize health states across different populations. This issue had been raised in the earlier versions of the GBD, but more concerned with the insensitivity to different cultural aspects of disability, which the DALY measurement was not taking into account (Hausman, 2012a). Focusing more on the actual evaluation of different health states on the same ground: "no single number can measure how good a health

state is, because the same health state may have a different value in a different context."(Hausman, 2012b). By comparing health outcomes, the GBD inevitably categorized one state worse than another–some authors found this unfit to assist the evaluation of health programs or for defining global health priorities:

> *There is no way to quantify the magnitudes of health of those suffering from different kinds of pathologies, because it is often the case that one health state contains neither more nor less nor the same amount of health as another. (Hausman, 2012b)*

Some concerns were also raised on methodological issues, particularly in the development of estimates focused on interpolation, necessary in countries with unreliable data. Uncertainty intervals, it was argued, grasped the precision of the *measurement*, or the models, rather than of the source of data (Byass et al., 2013). Methodological discrepancies with the WHO, which was still assessing its own burden of disease study at the time of the publishing of the GBD results, found differences so significant that the organization withheld its acceptance "pending the availability of more detailed information on the data and methods used" (World Health Organization, 2013b).

The Global Health Estimates study (GHE) produced by the WHO used the same methodological approach as the GBD in 2010. It published its own official results in 2013 (World Health Organization, 2013a) detailing some analytical differences in data sources used, life tables, and estimates of certain burdens of disease–assuming some diseases were more prevalent than the GBD. These differences represented the beginning of a competition between the two international institutions in estimating the global burden of disease (Atun, 2014).

The GBD method from 2013 until today

In order to understand the evolution of the methodology of the Comparative Risk Assessment – CRA being most relevant to the overall purpose of our research (see Document de travail n°266) –, it is necessary to trace the evolution of the GBD project in its whole. While this chapter will not delve into details of the GBD method from 2013 onwards, it is worth explaining some of the innovations that the 2013, 2015, 2016 and 2017 updates brought to the method for completeness.

The 2013 GBD study was presented differently, e.g. as individual studies by specific teams of researchers which focused on key public health issues: smoking; maternal mortality; child mortality; overweight; child mortality; overweight and obesity; HIV/AIDS, malaria, and tuberculosis; causes of death, and nonfatal outcomes (Institute for Health Metrics and Evaluation, 2014a). No particular methodological differences were introduced from the 2010 update.

The 2015 GBD was the first of an ambitious goal of updating results yearly–a goal actually reached in 2016 and 2017 at the time of review. Of particular importance was the introduction of the Socio-Demographic Index (SDI), or a measurement for classifying the social and economic development of countries and regions (Institute for Health Metrics and Evaluation, 2014a). This created a global subdivision based upon a GBD metric, which has two important implications. First, it established a new method of extrapolation in the case of incomplete data, based on the socio-demographic profile and similarity of two countries. Second, it re-distributed the regional analysis by a subdivision defined only within the GBD project, abandoning the methodology of the WHO World Regions. With a consistently growing list of

observed diseases within the study, the 2015 update also committed to closely following the recommendations of the Guidelines for Accurate and Transparent Health Estimates Reporting (Institute for Health Metrics and Evaluation, 2014b). This was likely prompted by the critiques of estimates being simply too complicated to reproduce (Li, 2014; Voigt & King, 2017). An interesting structural change of the 2015 update is how it was published. While previous updates were presented mainly through a special GBD issue, the 2015 studies were scattered in a number of specific issues within *The Lancet*. This choice cannot be undermined as casual, especially in a period in which the study was inevitably trying to gain scientific consensus and cement itself as an authority in observational epidemiology (Figure i at the beginning of this manuscript details all The Lancet numbers where the various GBD results can be found) . It was then key to present specific results to the people most interested. While the 2013 GBD was published through 3 topic-specific issues of *The Lancet,* the 2015 results (published in 2016 & 2017) appeared in at least 10.

The 2016 GBD, published between 2017, 2018 and 2019 had roughly the same dispersion, and focused on specific topics of analyses that now included alcohol use, United States' disease burden at state level, and global mortality to firearms. Microanalysis such as the one carried out at state level in the United States holds particular importance in the future possibilities which the GBD project most likely will wish to provide with its growing international audience. The 2016 methodology remained the same–the only claimed changes, as in all GBD updates since 2013, have been mainly in data sources. The specificity of which sources have changed, or what has actually changed from one year to the other, remains unclear and realistically hard to check manually. While this aspect is understandable given the incredibly vast amount of information gathered and produced by the project, it makes it very difficult to interpret trends in published estimates and rankings of health problems and their risk factors.

At time of review, the 2017 update stands as the latest of the project, which for the first time relied on its own population estimations and projections – demographic analysis hence also finds itself as a central theme in this latest publication. "A Fragile World", the heading title of the Lancet editorial, reflects on the contemporary problems of an ageing society and more socially-determined diseases, providing estimates for deaths from opioids around the world and depressive disorder due to bullying. Particularly interesting for the scope of the GBD project is the inclusion of health worker's density estimates (Lancet, 2018). This hints at an analysis which aims at identifying failures of the health labor market, pinpointing the shortcomings of healthcare systems.

> *GBD 2017 is a reminder that, without vigilance and constant effort, progress can easily be reversed. But the GBD is also an encouragement to think differently in this time of crisis. By cataloguing inequalities in health-care delivery and patterns of disease geography, this iteration of the GBD presents an opportunity to move away from the generic application of UHC [Universal Health Coverage] and towards a more tailored precision approach to UHC… GBD 2017 should be an electric shock, galvanizing national governments and international agencies not only to redouble their efforts to avoid the imminent loss of hard-won gains but also to adopt a fresh approach to growing threats. (Lancet, 2018)*

This call to action is a clear change of tone of the project which in its debut in 1993, was more focused on establishing its function as a measurement (whose aim was to assist policy, but

not directly advocate for specific policies), than in giving policy suggestions. In the years elapsed, the GBD has established itself as the primary source of epidemiological intelligence for international institutions at the forefront of global health. In 2013, the IHME developed regional reports for the World Bank aimed at landscaping the health progress done in the 6 global regions which it had analyzed two decades earlier. In the 2015 and 2016 GBD updates, a Sustainable Development Goals (SDGs) analysis[14] was specifically focused on the targets which the WHO set as necessary to achieve its Health 2020 agenda. This institutional reconciliation, in a period of particular bureaucratization of international organizations due to their important political influence around the world, gives the estimates of the project strong agenda-setter potential in international health policy. Future developments will tell us whether the project aims at becoming a tool to describe health, or a watchdog for health policy progress.

Understanding the influences of the first enumeration of the GBD

To trace the change of the philosophy, methodology, and approach of the GBD method, it is important to understand the institutions that influenced it. The 1993 World Development Report was a landmark moment in the redefinition of global health, linking directly health issues to economic development objectives in the agendas of international organizations and governments (Kenny, 2017). Unlike more classical epidemiological indicators of health status, the DALYs metric bridged the gap between estimating the burden of specific diseases and offering a comparable economic measure value at a global scale, with the aim to advise international health action in terms of economic priorities. Some of its critics pointed out the implications of the World Bank influencing global health policy, an institution which had traditionally been interested in economic development programs, rather than health (Anand & Hanson, 1997; Norheim, 2014). It is worth looking at some of the GBD technical aspects mentioned before in order to understand the radical changes which the methodology went through in the following decade.

A quantification tool of health, in order to be universal, must value all lives the same. While DALYs were conceived to make “health outcomes as alike” (Murray, 1994) their original computation seemed tied to economic productivity and cost of care. Age-weights placed the most burden of lost healthy life in the working age-group, discounting the burden of lost life of the oldest and youngest age cohorts. While this choice is thoroughly explained, it is hard to justify: an indicator of health status should not be concerned with the ethical dilemma of deciding which loss of life has less value, but merely enumerate the total. It is hard to understand this choice even from an epidemiological point of view, as an abundance of evidence already existed at the end of the 20th century highlighting the growing burden of disease due to aging in developed countries, and due to children’s health in developing countries. We can find, however, a reasonable rationale behind this choice if seen related to the influence of the institution sponsoring the study (Kenny, 2015).

The first GBD was commissioned by the World Bank, an international organization which, prior to the 1993 World Development Report, had primarily been concerned with healthcare systems. Given its function of issuing loans for development, the World Bank constantly faced

[14] The project aimed at providing projections and estimates for the health-related Sustainable Development Goals. “The GBD created a set of 37 health-related SDG indicators for 188 countries from 1990 to 2016… which were used to construct the health-related SDG index, a summary measure of overall performance across the health-related SDGs.” (Institute for Health Metrics and Evaluation, 2019)

the dilemma of deciding how to allocate very limited resources: an investment, even if in sake of development, has to be well placed in order to not be wasted. In one of the seminal papers laying the founding principles of the GBD method, Murray (1994) claims the metric is needed in order to develop "a single indicator of the burden of disease for use in planning and evaluating the health sector", also acknowledging the complex ethical choice left to decision makers in assessing the relative value of life in light of a healthcare sector which is faced with scarce, diminishing resources. However, it seems odd for a global indicator of disease burden to take this decision, first and foremost because its universal use will necessarily entail different choices in different health systems. While Murray claimed that the social preference entrenched in DALYs was not firmly identified into any intellectual tradition (Murray, 1994), it is hard to overlook the utilitarian influence in the value of a healthy life tied to age-weights. Taking into consideration the World Bank's interest in having a metric which could help in understanding how to lend money for strengthening healthcare systems, then a population's workforce would plausibly be within the priorities of the organization. Heterogeneous age weights can be seen to reflect that line of reasoning. So does the yearly discount rate established at 3% in the original DALYs formula. Both factors contributed to devalue healthy years of life lost to death or disability for newborns and as age progresses.

Health here is part of a productivity formula–giving the possibility to understand how to increase health providers' efficiency by improving health particularly among the working age population:

> *The DALY metric was designed for the purposes of carrying out cost-benefit analyses of potential health interventions so as to design economically rational health systems. But more than just facilitating cost-benefit analyses, the DALY metric accomplishes an economization of health by imagining health as a form of human capital*. (Kenny, 2017)

This view of the GBD frames it as a tool for economic analysis, and we can further understand the economic influences of the World Development Report by looking at its main author and editor. Dean Jamison (pupil of economist and Nobel laureate K.J. Arrow) economist at the World Bank, mainly focused his research on cost-benefit and cost-effectiveness analysis in educational and healthcare reforms. Prior to the 1993 Report, Jamison co-authored "Disease Control Priorities in Developing Countries" (1993), "the cost effectiveness of immunization" (1993) and "Education and productivity in developing countries: An aggregate production function approach" (1991). In a similar fashion to the above-mentioned publications, the first GBD results had a prescriptive aim, with an outlook on optimizing the performance of the health system:

> *Adoption of the main policy recommendations of this Report by developing country governments would enormously improve the health status of their people, especially poor households, and would also help to control health care spending. Millions of lives and billions of dollars could be saved. Implementation of the public health and essential clinical care packages, pursuit of economic growth strategies that reduce poverty, and increased investment in schooling for girls would have the largest payoffs in averting deaths and reducing disability. Scaling back public spending for tertiary care facilities, specialist training, and clinical care with lower cost-effectiveness would help to increase the effectiveness of health spending. So would encouragement of competition*

in delivery of health services and regulation of insurance and of provider payment systems (The World Bank, 1993).

The World Bank's involvement within the realm of global health quickly moved it at the forefront of health development programs: by the end of the 1990, its lending in health had surpassed the whole WHO budget, becoming the dominant institution in the field's progress (Fair, 2008). This also marked a gradual loss in relevance of the WHO in health agenda-setting (Kenny, 2017), which only briefly hosted the project before the foundation of the Institute of Health Metrics and Evaluation (IHME) at the University of Washington.

In part because of its substantial funding power provided by the Bill and Melinda Gates Foundation, the IHME's signaled a radical change in approach to the enumeration of population health, centering on its role as a methodology to track changes in population health rather than carrying out a socioeconomic analysis from a health sector perspective. The 2010 Global Burden of Disease, the first estimations published independently from any international institution, proved and established the immense computational power which the IHME was capable of: the list of diseases observed more than doubled (from 136 in 2004 to 291), the comparative risk assessment analysis went from 24 to 67 risk factors, the list of contributing partners soared to more than 500 experts with 7 global leading institutions directly involved, and perhaps most importantly the DALYs formula was completely revisited.

DALYs dropped its principle of heterogeneous weighting, standardizing the burden of disease as equal through all age groups. Future years of life were no longer discounted at a rate of 3%, therefore not depicting health as a "future investment" with different returns. The "simplified" (called as such by the authors) DALYs formula also used a new method for evaluating disability weights, now based on population surveys rather than experts' opinion, an important step toward better interpreting disabilities from a population health perspective. The new design was also now based on 20 age groups, providing a more detailed demographic analysis than previously. Instead of decomposing its observations through the socioeconomic division of the World Bank, the simplified DALYs followed a mortality and demographic-based global partition, which was intended to represent better the health experience of similar countries for extrapolation (Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012b).

Published through a series of 12 papers and editorials on a special *The Lancet* issue, the 2010 GBD focused on detailing the extensive work behind the database collection, parameters of estimation, and complex modelling which went behind the creation of the most comprehensive assessment of world health to date (Das & Samarasekera, 2012). Looking at the main contributing authors again can give us a sense of the measurement and whole project development. Majid Ezzati, chair in global and environmental health at the School of Public Health at Imperial College London (UK) lead many of the comparative risk assessment publications. Theo Vos, of the School of Public Health in Queensland (Australia), was the lead author in the research on years lived with disabilities. The method seemed poised to establishing itself as the leader in the field, developing a targeted universal metric, much more precise and aimed at providing a more complete, less biased picture of health status.

From the 1993 World Development Report, where the GBD represented a tool of analysis with an economic purpose, reliant on its implications on socioeconomic conditions and primarily used by the World Bank (Kenny, 2017), the updated GBD methodology worked towards

closing the gap between policy and epidemiological estimates, by providing a comprehensive and robust database on observational and evidence-based health. One of the first assertions made in one of many papers compiling the methodology and design of the 2010 estimates is that "the GBD construct of the burden of disease is health loss, not income or productivity loss" (Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012a). While the aim of the study remained to aid and guide policymakers in the field of health prevention and response, it now approached health status differently. The original DALYs formula required far too many ethical decisions, rendering it subject to personal bias and giving it scarce reproducibility. In its original conception, it was aimed at providing a priority list of health interventions, with the precision of estimates seeming secondary to the value of actually creating them. Now established as a standard of health quantification globally, its purpose goes far beyond its own reports: the IHME to this day trains its own developers, statisticians, and epidemiologists, propagating the GBD method and expanding its influence everywhere in the field of population health metrics.

The GBD project to measure health at a global level: Final reflections

The review carried out in this report has tried to pinpoint the pivotal moments in the development of one of the most talked about enterprises of measurement of health in the last three decades. While inevitably incomplete, this report hopes to shine light on the evolution and relevance of the first effort of its kind to wholesomely quantify the burden of disease, injuries, disability and premature death affecting the world population. The GBD was instrumental in the galvanization of institutions to put global health at the center of discussion for development, as well as in the development of an agenda for action to curb health inequalities worldwide. It is indeed impossible to downplay the pivotal role which the 1993 World Development Report played in highlighting the importance of health at international level, even if it did so in a specific way linking it to economic objectives of development policies. It was also influential in defining the complexity behind the concept of health, as well as its innumerable different interpretations. The GBD, in this sense, has also opened an important debate about inclusion and sensitivity to the wide experiences of health that individuals have.

Its pitfalls are in part inevitable due to the nature of the exercise *per se*: in order to completely quantify every aspect of health of the world, a collective rather than individualistic point of view is needed. It is crucial to understand this aspect while critically analyzing the evolution of the GBD, as a measurement necessarily needs generalization in order to be as applicable as possible. Tracing the evolution of the GBD allows to also understand the genealogy of a changing landscape of actors of global health, in which the results were and still are arguably amongst the most influential published every year. Of course, some analytical questions come to mind about the computation, value, and significance behind these results. While it would be out the scope of this report to critically analyze the methodology laid out in the various GBD reports, the current reflection aims at raising some questions for future analysis.

The comprehensiveness of the GBD project sometimes seems to come at the cost of reproducibility and accuracy. While undoubtedly meticulous in its well-defined estimation process, delving into the densely-written appendices in order to comprehend the growth and evolution of the statistical methods, as well as trying to confirm the findings through the same methodology becomes virtually impossible by any other entity outside of the IHME. Reproducibility was one of the GBD's founding pillars (Das & Samarasekera, 2012; Lopez,

2005; Murray & Lopez, 1999, 2017; Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012b). It came with the transferring of the method to the University of Washington. While the steps taken for estimation are well traced, the availability of raw data, as well as of the algorithms employed in order to construct their estimates, projections, and uncertainty intervals, is unclear (Byass et al., 2013; Li, 2014; Polinder et al., 2012; Voigt & King, 2017; Watts & Cairncross, 2012). Moreover, the complexity of the study, which relies mainly on its self-defined datasets and methods of analysis, would make previously published results the only point of comparison worth pursuing–this last exercise is however often impossible, as well as discouraged by the institution.

This has important policy implications, especially as results becomes more readily available and the analysis more widespread: if the GBD is the biggest, most comprehensive assessment of global health, involving thousands of academics and scientists worldwide, but also virtually the only study of its size, does it mean that it holds institutional or academic hegemony? Of course, the GBD is not the only assessment of population health, but few other exercises can compare in dimension. In countries with scarce epidemiological data, the GBD study can at times be a critical tool for policy-makers in order to calibrate decisions (Anand & Hanson, 1997; Arnesen & Nord, 1999). However, its heavy reliance on extrapolation and statistical projections for countries which lack the observational data to properly estimate an accurate burden of disease raises some concerns about the value of using the study as a guidance.

It is clear that the GBD's philosophy is based on the principle of producing estimates even in the absence of evidence, rather than producing no number at all. This choice should be based upon clearly detailed and easily accessible methodologies–at times, this seems impossible with hundreds of annex pages. A nexus between a clearly complex estimation method that must be explained in detail, but ease of access in some key aspects of the estimates must be made for the sake of the study's principles. It seems generally hard to navigate the amount of evidence provided–which, while it might be important to document for transparency, tends to overshadow some necessary information, for example how uncertainty intervals are developed, what they represent, and their relevance within the results (Byass et al., 2013; Hausman, 2012b).

The yearly update of estimates is, surely, a grandiose feat and an ambitious goal for the project, and one that could truly sediment it as a standard of health evaluation in the coming years, making it the most up-to-date digital epidemiology database of diseases, injuries, and sequalae available. However, the publishing process tied to the numerous papers which make up every GBD update still remains unclear. Surely, by being published on one of the most prestigious medical journals available in academia, *The Lancet*, the expectation is for every paper, with every annex and supplementary issue, to be rigorously peer-reviewed at the same standard of every other scientific publication. While the scientific reviewing process is not publicly explained, simply looking at the amount of evidence that needs to be reviewed at every itineration makes it hard to believe that it is plausible within the timeframe of a single year. The preoccupation is that, for the sake of publishing, the studies could be put under a different scrutiny than other scientific articles, giving it not only an unfair advantage at academic level, but also risking to not be at the highest standard of scientific accuracy.

This, in turn, can have two chained effects: the GBD would be unfairly advantaged in its publication process, and consequentially making it the most widespread published study of its kind. Moreover, the possibility that the GBD becomes a "yardstick" for other population health estimates because of its spread as a consequence of the platform provided by *The Lancet* is

worrisome for the rigor of health metrics–the GBD must stand as an option for scientists and policymakers amongst many other tools, not the only solution. Surely, the GBD has galvanized organizations and scientists to develop alternative methods to enumerate people's health; this healthy prolific effect has created different projections which try to compensate on some of the GBD methodological shortcomings, while at the same time producing an array of different estimates which can be compared, discussed, and used for different reasons (Atun, 2014). With this in mind, it is of vital importance that the GBD estimates do not become the standard to which every other projection must adhere to because of the study's prolific academic presence–especially if this is facilitated by a different review process to that of other scientific studies.

To conclude, a word should be spent on the traceability of the history of the project, which is at times hard to follow[15]. Robustness is in part derived by a well-defined timeline of the methodological evolution of a measurement. The IHME's website provides a short, simplistic description of this history, without detailing where to find the exact papers that explain the methodology of each itineration. While looking for evidence, it was particularly complicated to find, trace, and organize an already difficult history. Only the publications since 2010 are all easily available in one place, leaving behind a significant part of the method's history. It is unclear whether this choice is made in light of the idea that yearly results are expected to supersede the previous ones, therefore invalidating the work before, because the method has fundamentally changed in its enumeration since 1993, or simply because of poor institutional arrangements. Regardless, if the measurements are intended to be understood and used by anyone interested in population health, then navigating its past should be made much more fluent.

The Global Burden of Disease will inevitably continue to grow in the future–as our knowledge of what affects our health and measuring our progress in health becomes more precise, so will the scope and purpose of a measurement trying to enumerate all of it. Maintaining the principle of reproducibility and accuracy is necessary for a project of its magnitude. While it is important for the study to continuously expand its list of diseases and risk factors to be as comprehensive as possible, it is just as important to focus on increasing the observational evidence for every country analyzed–the GBD is in the unique position to promote better data gathering and guide countries through their lacunae. Lastly, it is still unclear how much the method is actually accepted within the wider academic and scientific community, and needless to say that its future success and legacy is dependent on the scientific traction which the methods gain outside of the selected, albeit large, body of people who directly work on it.

[15] At the time of writing, the only available timeline for the GBD was through the IHME's website, with little traceability provided for the earliest updates of the exercise. On the 24th of August, 2020 Colin Mathers published a paper detailing the history of GBD, found in the bibliography. (Mathers, 2020).

Annex

Annex 1: Reference list corresponding to Figure i. A Precise Timeline of the GBD method publications with respective CRA (as of June 2019)

1990 GBD: review of the global burden of diseases, injuries, and sequelae of the year 1990, presented through the following papers:

- **1993:** World Development Report (World Bank) **published in 1993 as a monograph**.
- **1994**: Bulletin of the World Health Organization on the Global Burden of Disease study, **published as 4 papers in 1994**.
- **1997:** Four-part papers series detailing the results of the Global Burden of Disease study, **published in The Lancet in 1997**.
- **1997:** The *"GLOBAL BURDEN OF DISEASE AND INJURY–A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020"*, a book published by Harvard University Press as a collaboration of the World Bank, the WHO, and Harvard University School of Public Health **in 1997**.
- **1999: Not officially part of the 1990 GBD**, C.J.L. Murray and A. Lopez paper *"On the Comparable Quantification of Health Risks: Lessons from the Global Burden of Disease Study"* published in Epidemiology Vol. 10, No. 5 in 1999. This paper introduced the methodology of for the Comparative Risk Assessment (CRA) which would be officially first published in 2002.

2000 GBD: review of the global burden of diseases, injuries, and sequelae of the year 2000, presented through the following papers:

- **2001:** WHO's "*World Health Report 2001: Mental Health: New Understanding, New Hope"* **published as a monograph in 2001** and is considered "Version 1" of the results of the new GBD updates.
- **2002:** WHO's "*World Health Report: Reducing Risk, Promoting Healthy Life"* **published as a monograph in 2002** and is considered "Version 2" of the results of the new GBD updates. Moreover, the 2002 WHR is the first *official* itineration of the Comparative Risk Assessment (CRA), and establishes as the methodology used in later exercises.
- **2003:** WHO's "*World Health Report: Shaping the Future"* **published as a monograph in 2003** and is considered "Version 3" of the results of the new GBD updates.
- **All of the data published for this GBD update are also available online, downloadable as raw files for analysis.**

2004 GBD: review of the global burden of diseases, injuries, and sequelae of the year 2004, and last official itineration of the GBD method coordinated by the WHO, presented through the following papers:

- **2008:** WHO's *"The global burden of disease: 2004 update"* **published as a monograph in 2008**.
- **2008:** WHO's *"Global Health Risks: Mortality And Burden Of Disease Attributable To Selected Major Risks"* **published as a monograph in 2008**, this is considered the second updated of the CRA part of the methodology

2010 GBD: a substantial, complete review of the global burden of diseases, injuries, and sequelae of the year 2010, coordinated by the newly-created (in 2007) Institute of Health Metrics and Evaluation (IHME) at the University of Washington. **All results from the 2010 GBD supersede previous GBD results.** Published through the following papers:

- **2012:** *The Lancet* special Volume 380, No. 9859 as 15 articles, commentaries, and opinion pieces **published in 2012** detailing:
    - The new GBD design, ethical decisions, and methodological approach
    - Updates on YLLs, YLDs, HALE, and DALYs estimates from 1990 to 2010, with their related databases
    - Newly-estimated disability weights and their methodology

- Updates on the CRA introduced in the 2002 WHR's "*Reducing Risk, Promoting Healthy Life*"

- **2012:** publishing of website with webtools that allow for comparison of various risk factors, diseases, and countries. Data on website updated with every GBD itineration.

2013 GBD: review of the global burden of diseases, injuries, and sequelae of the year 2013. **All results from the 2013 GBD supersede previous GBD results.** Published through the following papers:

- **2016:** *The Lancet* special Volume 384, No. 9947 as 15 articles, commentaries, and opinion pieces **published in 2016** detailing:
  - Specific analysis of the burden of some diseases
  - Updates on databases and methods of estimation

2015, 2016, and 2017 GBD: review of the global burden of diseases, injuries, and sequelae of the year 2015. **All results from the 2015, 2016, and 2017 GBD supersede previous GBD results.** The 2015 GBD also introduced the production of annual updates, still in practice today. Published through the following papers:

- **2015 GBD:** detailing the global burden of diseases, injuries and sequelae in 2015
  - **2016-17:** *The Lancet* Vol. 388, No. 10053 and Vol. 389, No. 10082*; The Lancet Infectious Diseases* Vol. 17 No. 12; *The Lancet Neurology* Vol. 16, No. 11*; The Lancet Respiratory Medicine* Vol. 5 No. 9 as 36 articles, commentaries, and opinion pieces of **published in 2016 and 2017** detailing:
    - Specific analysis of the burden of some diseases
    - Updates on databases and methods of estimation
    - The introduction of a new summary measurement of development: The Socio-demographic Index (SDI)
- **2016 GBD:** detailing the global burden of diseases, injuries and sequelae in 2016
  - **2017-19:** *The Lancet* Vol. 390, No. 10100 and Vol. 392, No. 10152; *The Lancet Global Health* Vol. 6, No. 10; *The Lancet Oncology* Vol. 19, No. 10; *The Lancet Infectious Diseases* Vol. 18, No. 11*; The Lancet Neurology* Vol. 17, No. 11 and Vol. 18, No. 4; *The Lancet Psychiatry* Vol. 5, No. 12 as a series of 44 articles, commentaries, editorials, and opinion pieces **published between 2017 and 2019** detailing:
    - A new report on the Sustainable Development Goals (SDGs) indicators
- **2017 GBD:** detailing the global burden of diseases, injuries and sequelae in 2017
  - **2018-19:** *The Lancet* Vol. 392, No. 10159 and Vol. 393, No. 10184; *The Lancet Public Health* Vol. 4, No. 3; *The Lancet Infectious Diseases* Vol. 19, No. 4; *The Lancet Respiratory Medicine* Vol. 7, No. 1; *The Lancet Planetary Health* Vol. 3, No. 1 as a series of 16 articles, commentaries, editorials, and opinion pieces **published (and still being published) between 2018 and 2019** detailing:
    - An independent estimation of population for all 195 countries analysed

Annex 2: THE GLOBAL BUDREN OF DISEASE 1990 - Summary of measurements, findings, and decisions

<table>
<tr>
<td>Years of Life Lost (YLL)
(Murray & Lopez, 1994a; Murray & Lopez, 1997a)</td>
<td>Group 1 diseases: 17.2 million deaths
Group 2 diseases: 28.1 million deaths
Group 3 diseases: 5.1 million deaths
Total YLL not directly assessed by authors (1990)</td>
</tr>
<tr>
<td>Years Lived with Disability (YLD)
(Murray, 1994; Murray & Lopez, 1994b; The World Bank, 1993)</td>
<td>By disease group:
Group 1 diseases: 26% of all YLD
Group 2 diseases: 61.1% of all YLD
Group 3 diseases: 12.6% of all YLD

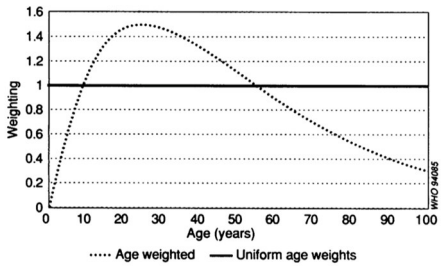
By age group:
0-4: 22.8% of all YLD / 5-14: 13.4% of all YLD / 15-44: 36.2% of all YLD / 45-49: 12.6% of all YLD / 60+: 15% of all YLD

472. 2 million YLDs globally (1990)
Group 1 diseases: communicable, maternal, perinatal, and nutritional disorders
Group 2 diseases: non-communicable and chronic diseases
Group 3 diseases: road-traffic accidents and injuries</td>
</tr>
<tr>
<td>Disability-Adjusted Life Years (DALYs)
(Murray, 1996; Murray & Lopez, 1997b; The World Bank, 1993)</td>
<td>1.36 billion DALYs lost worldwide (1990)

Life expectancy at birth with and without disability-adjustment:

<table>
<tr><th rowspan="2">WB region</th><th colspan="2">Life-expectancy at birth (LE)</th><th colspan="2">Disability-adjusted life expectancy (DALE)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>EME</td><td>73.4</td><td>80.5</td><td>67.4</td><td>73.9</td></tr>
<tr><td>FSE</td><td>65.7</td><td>74.8</td><td>59.4</td><td>67.8</td></tr>
<tr><td>CHN</td><td>66.2</td><td>69.8</td><td>59.5</td><td>62.2</td></tr>
<tr><td>LAC</td><td>65.8</td><td>70.3</td><td>57.6</td><td>61.9</td></tr>
<tr><td>OAI</td><td>60.8</td><td>64.9</td><td>53.7</td><td>56.9</td></tr>
<tr><td>MEC</td><td>60.3</td><td>63.4</td><td>53.6</td><td>55.8</td></tr>
<tr><td>IND</td><td>57.9</td><td>59.1</td><td>51.0</td><td>51.5</td></tr>
<tr><td>SSA</td><td>48.4</td><td>51.0</td><td>41.0</td><td>43.4</td></tr>
</table>

The World Bank’s World Regional Division:
EME= Established Market Economies / FSE= Former Socialist Economies of Europe / CHN= China / LAC= Latin America and Caribbean / OAI= Other Asia and islands / MEC= Middle-eastern crescent / IND= India / SSA= Sub-Saharan Africa</td>
</tr>
</table>

Age-weighting (Murray, 1994; Murray & Lopez, 1994b)	Derived from a modified Delphi method: polls from experts, as well as general social perception of value of life from a tuberculosis program attended by an author.  Continuous age-weighting function: $Cxe^{-\beta x}$ Where: C= Constant. So that unequal age-weights do not change the global estimated burden of disease from the total that would be estimated with uniform age weights. β= Constant. Assumes general form of age-weight distribution as figure above. e= life expectancy at each age. x= age.
Time-discounting (Murray, 1994)	In order to address the time paradox of investment, a 3% discount rate is applied to the calculation of DALYs yearly, making future time "lose" 3% of value every year.
Disability-weights (Murray, 1994; Murray, 1996; Murray & Lopez, 1994b)	Assessed through panel of experts and small focus groups (10-12 people). For each 108 disease, experts gave opinion on disabling effect on people. Two separate groups decided disease weights through 2 step person-tradeoff questions. Weights were established by mean of value given by panel of experts. 22 indicative disabling conditions subdivided in 6 classes. 0= perfect health, 1= comparable to death **Class I:** 0.096 **Class II:** 0.220 **Class III:** 0.400 **Class IV:** 0.600 **Class V:** 0.810 **Class VI:** 0.920
Comparative risk assessment (Leigh et al., 1996; Murray & Lopez, 1997c; The World Bank, 1993)	10 risk factors recognized: tobacco, alcohol, drugs, occupation, air pollution, poor water & hygiene, hypertension, physical inactivity, malnutrition, unsafe sex. Occupational risks established through the analysis of Leigh et al. (1996) based on direct and indirect observations of occupational diseases and injuries where possible, and extrapolation through similar socioeconomic and demographic development per country. Air pollution risk established through the analysis of Hong (1996)[16] based on exposure to suspended particles & Sulphur dioxide in air. Exposure levels available everywhere but SSA.

[16] Hong CJ. Air pollution. In: Murray CJL, Lopez AD, eds. Quantifying global burden health risks: the burden of disease attributable to selected risk factors. Cambridge: Harvard University Press, 1996. Cited in Murray, Lopez (1996), original report not found.

1990-2020 projections (Murray & Lopez, 1997d)	**DALYs lost in 1990: 1.38 billion** **DALYs projected for 2020: 1.39 billion (1.30–1.69)** Deaths: Group 1: 15.2 million 1990 – 10.3 (8.2-16.9) million 2020 Group 2: 28.1 million 1990 – 49.7 (48-53) million 2020 Group 3: 5.1 million 1990 – 8.4 (8.2-8.4) million 2020 Linear formula for 4 different independent variables: $LnM_{a,k,i} = C_{a,k,i} + \beta_1 LnY + \beta_2 LnHC + \beta_3 T$ Where: a,k,i= age-group, sex, and medical cause M= mortality rate. C= Constant Y,HC,T= income per capita, human capital (education) , time. Smoking prevalence was added only to age-groups <30.

Annex 3: Summary Table - Comparison of main analytical and technical aspects of GBD 1990,2000, and 2010.

Source: Table made by authors, direct sources of information and data available in right-most column

Analytical component	**GBD 1990**	**GBD 2000***	**GBD 2010**	Source
Population Health Summary measurements				
DALYs	DALYs= YLL + YLD • Heterogenous age-weights • Yearly 3% discount rate **Total DALYs estimated worldwide: 1,362,100,000**	DALYs= YLL + YLD • Heterogenous age-weights • Yearly 3% discount rate **Total DALYs estimated worldwide: 1,472,392,000**	DALYs= YLL + YLD • No age weights • No discount rate **Total DALYs estimated worldwide:** **In 1990:** 2.503 billion **In 2010:** 2.490 billion	GBD 1990 GBD 2000 (Murray, Vos, Lozano, Naghavi, Flaxman, Lopez, et al., 2012) ***this GBD was published in 3 versions through WHR 2001, 2002, and 2003. Numbers in this table are reported from Version 1 in WHR 2001** GBD 2010 (The World Bank, 1993)
YLD	• YLD= I x DW x A I = Incident cases in population DW= disability weight of condition A= average duration of case until remission or death (discounted at 3% every additional year of life) **In 1990**: 472.7 million YLDs globally	• YLD= I x DW x A **In 2000:** 546.3 million YLDs globally	• YLD= P x DW • No discounting or age-weights P = prevalence of sequela • No discounting or age-weights **In 1990:** 583 million YLDs globally **In 2010:** 777 million YLDs globally	GBD 1990 (Murray et al., 2002 ; World Health Organization, 2002a) GBD 2000 (Vos et al., 2012) GBD 2010 (Murray et Lopez, 1997a)

<table>
<tr><th>Analytical component</th><th>GBD 1990</th><th>GBD 2000*</th><th>GBD 2010</th><th>Source</th></tr>
<tr><td>YLL</td><td>• YLL= N x L

N= number of deaths due to a condition at each age
L= standard life expectancy at age of death (with age weighting and yearly 3% discount rate applied)

YLL not directly enumerated
Total estimated death in 1990: 50.4 million worldwide</td><td>• YLL= N x L

In 2000: 926 million YLLs globally

Total estimated deaths in 2000:
55.6 million</td><td>• YLL= N x L
• No discounting or age-weights

YLL not directly enumerated

Total estimated deaths worldwide:
In 1990: 46.5 million
In 2010: 52.8 million</td><td>GBD 1990 (Murray et al., 2002 ; World Health Organization, 2002a)
GBD 2000 (Murray et Lopez, 1997b)</td></tr>
<tr><td>HALE</td><td>
<table>
<tr><td>World Bank Region</td><td colspan="2">Disability-adjusted life expectancy (DALE) Global</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td></tr>
<tr><td>EME</td><td>67.4</td><td>73.9</td></tr>
<tr><td>FSE</td><td>59.4</td><td>67.8</td></tr>
<tr><td>CHN</td><td>59.5</td><td>62.2</td></tr>
<tr><td>LAC</td><td>57.6</td><td>61.9</td></tr>
<tr><td>OAI</td><td>53.7</td><td>56.9</td></tr>
<tr><td>MEC</td><td>53.6</td><td>55.8</td></tr>
<tr><td>IND</td><td>51.0</td><td>51.5</td></tr>
<tr><td>SSA</td><td>41.0</td><td>43.4</td></tr>
</table>
</td><td>
<table>
<tr><td colspan="2">Disability-adjusted life expectancy (DALE) of top and bottom 3 countries*</td></tr>
<tr><td>Japan</td><td>74.5</td></tr>
<tr><td>Australia</td><td>73.2</td></tr>
<tr><td>France</td><td>73.1</td></tr>
<tr><td>Malawi</td><td>29.4</td></tr>
<tr><td>Niger</td><td>29.1</td></tr>
<tr><td>Sierra Leone</td><td>25.9</td></tr>
</table>
* DALE estimates available for 191 countries, selected countries only for comparison purpose</td><td>Global male Healthy-life expectancy (HALE) at birth in 2010: 59 years (UI 57.3–60.6)
Global female HALE at birth in 2010: 63.2 years (UI 61.4–65.0)
• Measurement switched from DALE to HALE, however the two names are seemingly used interchangeably, as if they were the same.
• Calculated HALE with life table methods, incorporating estimates of average health over each age interval.
• Computed estimates of average overall health for each age group, adjusting for comorbidity with a Monte Carlo simulation method to capture how multiple morbidities can combine in an individual.
• Global disaggregation by sex and age groups available at source, p. 2147 and p.2145-52</td><td>GBD 1990 (Mathers et al., 2001)
GBD 2000 (Salomon, Wang, et al., 2012)
GBD 2010 (Murray et Lopez, 1999)</td></tr>
</table>

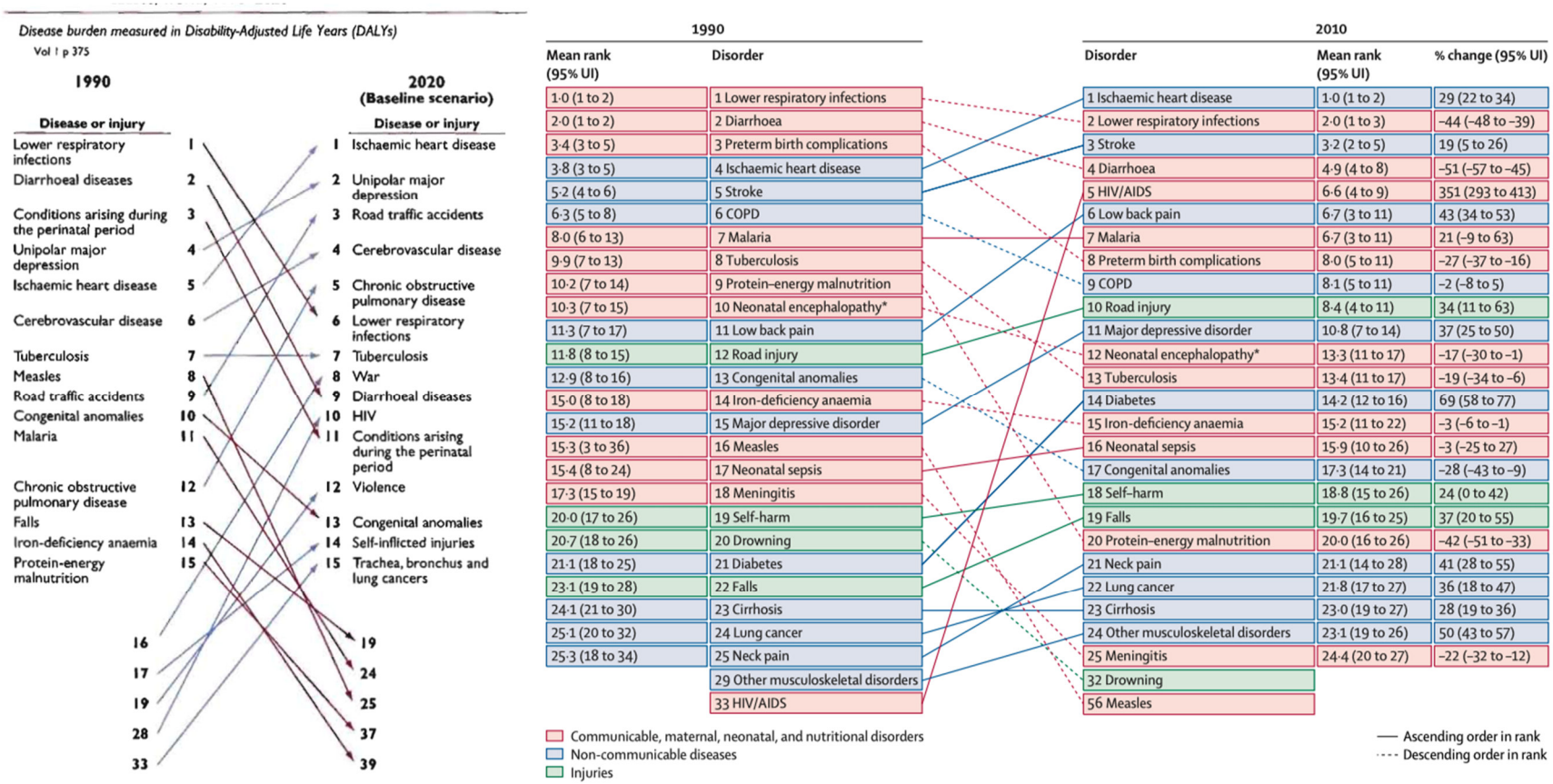
Analytical component	GBD 1990	GBD 2000*	GBD 2010	Source
Comparative Risk Assessment	• DALYs lost attributable to 10 risk factors through PIF (analysis not included in GBD 1990) Leading risk factors contributing to lost DALYs in 1990: Malnutrition: 219.6 million DALYs Poor water & sanitation: 93.4 million DALYs Unsafe Sex: 48.7 million DALYs Alcohol: 47.7 million DALYs Occupation: 37.9 million DALYs Tobacco: 36.2 million DALYs Hypertension: 19 million DALYs Physical inactivity: 13.6 million DALYs	• 26 risk factors traced • First CRA methodology introduced with WHR 2002 using PIFs for estimating the proportional reduction in disease burden resulting from a specific change in the distribution of a risk factor, and PAFs for converting risk factor to disease burden. • Introduced analysis on theoretical minimum exposure Leading 10 risk factors contributing to lost DALYs in 2000: Underweight: 138 million DALYs Unsafe sex: 92 million DALYs Blood pressure: 64 million DALYs Tobacco: 59 million DALYs Alcohol: 58 million DALYs Unsafe water, sanitation and hygiene: 54 million DALYs Cholesterol: 40 million DALYs Indoor smoke from solid fuels: 39 million DALYs Iron deficiency: 35 million DALYs Overweight: 33 million DALYs	• 64 risk factors traced • Same methodology as WHR 2002 but with improved data, new epidemiological evidence, and statistical methods aiming at more accurate estimation. •Uncertainty Intervals included in all analysis • CRA computed for 1990 and 2010 Report top 10 as in 1990? Attributable DALYs to risk factor clusters in 2010: Dietary risk factors and physical inactivity: 245.3 million DALYs Air Pollution: 186.7 million DALYs Child and Maternal Undernutrition: 166 million DALYs Tobacco smoking (including second-hand smoke): 156.8 million DALYs Alcohol & drug use: 120.6 million DALYs Occupational risks: 62.4 million DALYs Physiological risk factors: 40.2 million DALYs Sexual abuse & violence: 23.5 million DALYs Unimproved water & sanitation: 21.1 million DALYs Other environmental risks: 16 million DALYs	GBD 1990 (World Health Organization, 2002b) GBD 2000 (Lim et al., 2012b) GBD 2010 (Lim et al., 2012)

Analytical component	**GBD 1990**	**GBD 2000***	**GBD 2010**	Source
Technical aspects				
Age-weighting	Heterogeneous age-weights which value differently how much a disease or sequela affects people at different stages of life. Heaviest "weight of burden" in working-age groups (15-44), decrease importance to younger and older cohorts.	Same as GBD 1990 methodology	No age-weighting applied to any calculation	GBD 1990 (Murray, 1994) GBD 2000 (Murray et al., 2002) GBD 2010 (Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012a)
Future value of life discount rate	3% discount rate applied yearly based on the assumption that people value more a year in healthy life today rather than in the future. Method particularly increases magnitude of DALYs lost in working age group.	Same as GBD 1990	No discount rate applied to any calculation	GBD 1990 (Murray, 1994) GBD 2000 (Murray et al., 2002) GBD 2010 (Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012a)

Analytical component	GBD 1990	GBD 2000*	GBD 2010	Source
Disability-Weights	Based on expert's consultation through small focus-groups for every sequela analyzed. Subdivided into 6 classes grouped by general impairment of sequalae. **Class I (0.096**): Limited ability to perform at least one activity in one of the following areas: recreation, education, procreation or occupation. **Class II (0.220):** Limited ability to perform most activities in one of the above-mentioned areas. **Class III (0.400):** Limited ability to perform activities in two or more of the above-mentioned areas. **Class IV (0.600):** Limited ability to perform most activities in all of the above-mentioned areas. **Class V (0.810):** Needs assistance with instrumental activities of daily living such as meal preparation, shopping or housework. **Class VI (0.920):** Needs assistance with activities of daily living such as eating, personal hygiene or toilet use.	Same as GBD 1990	Population survey of over a period of two years through 5 countries with 2 surveys: – A face-to-face interview with 11.320 selected respondents in Bangladesh, Indonesia, Peru, and Tanzania. – A web-based open survey with 13.391 respondents in the United States Assigned unique disability weight for 220 sequelae through linear logit regression and numerical integration. Unique disability weights available at source, p.2135-37.	GBD 1990 (Murray, 1994) GBD 2000 (Murray et al., 2002) GBD 2010 (Salomon, Vos, et al., 2012)
Uncertainty Intervals	No uncertainty intervals included in analysis.	No uncertainty intervals included in analysis.	Computed Uncertainty levels with various statistical methods in all calculations and for all above-mentioned estimates.	GBD 1990 (Murray & Lopez, 1997b, 1997d) GBD 2000 (Murray et al., 2002) GBD 2010 (Murray, Ezzati, Flaxman, Lim, Lozano, Michaud, et al., 2012a)

Annex 4 - Comparison of biggest disease burden ranking of GBD 1990 (left) and GBD 2010 (right) with proposed projections of change in burden in two different reference periods.

Source: Reproduced from The World Bank. "World Development Report: investing in health" 1993, The World Bank. Murray C.J.L. et al. "Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010" 2012, The Lancet 380: 2197–223



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