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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

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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's (GBD) comparative risk assessment analysis (CRA) is a quantitative estimation of the contribution of known risk factors to the injuries and sequelae enumerated by the study each year. The CRA was introduced in 2002 and has a complex methodology that builds on the epidemiologic concept of attributable risk, or population attributable fractions (PAFs). This work, second of two volumes on the GBD's evolution, is focused on explaining and tracing the methodological choices of its risk assessment component, with a specific focus on environmental and occupational risk factors. We explore the estimates provided by the Institute of Health Metrics and Evaluation (IHME) and understand how they were calculated. Then, we assess some of the most pressing critiques, and conclude by reflecting on its influence, methodological choices, and future outlook as the IHME sets itself a leading institution in health estimates. This work is part of a broader research analyzing the role of population health metrics, in particular PAFs, on the definition of public health problems and influencing their agendas. The research relies on a literature review (non-structured) of published studies and commentaries. It follows a chronological development of the CRA estimates since their first publication in 2002 to the version released in 2019.

Key words: GBD, CRA, risk assessment, risk factors, IHME, DALY, YLD, YLL, attributable fraction, PAF, global health, health metrics, epidemiology, public health, Gates Foundation, health policy

Résumé (français)

L'évaluation comparative des risques (CRA) consiste en une estimation quantitative de la contribution des facteurs de risque connus aux lésions et séquelles recensées chaque année par l'étude du Global Burden of Disease (GBD). Introduit en 2002, ce module repose sur une méthodologie complexe qui s'appuie sur le concept épidémiologique de risque attribuable, ou fractions attribuables à la population (FAP). Ce travail, second de deux volumes retraçant l'histoire du GBD, s'attache à présenter les choix et évolutions méthodologiques du CRA, avec un accent particulier sur les facteurs de risque environnementaux et professionnels. Nous explorons les estimations fournies par l'Institute of Health Metrics and Evaluation (IHME) et analysons leurs modalités de calcul. Nous évaluons ensuite certaines des principales critiques et concluons en nous interrogeant sur l'influence et les perspectives induites par cet exercice, l'IHME s'imposant comme une institution de premier plan en matière d'estimations sanitaires. Ce travail fait partie d'une recherche plus large analysant le rôle des mesures d'impact en santé, en particulier les FAP, sur la définition des problèmes de santé publique et leur mise à l'agenda politique. La recherche s'appuie sur une revue de la littérature (non structurée) des études et commentaires publiés. Elle suit une évolution chronologique des estimations du CRA depuis leur première publication en 2002 jusqu'à la version publiée en 2019.

Mots-Clés : GBD, CRA, évaluation des risques, facteur de risque, IHME, DALY, YLD, YLL, fraction attribuable, FAP, santé globale, indicateurs de santé, épidémiologie, santé publique, Fondation Gates, politiques de santé

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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.

A first working paper, published separately (Lionello, Counil, Henry, 2021), tried 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.

This 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. The CRA has used, since its conception, relative risks published in the literature and population attributable fractions (PAF) in order to measure the attributable and avoidable risks in the population.

Specific attention has been placed on the study of environmental and occupational risks, two fields that have significantly evolved throughout the years. The report will try to understand the importance that these two sets of risk factors have gained in the different updates of the study.

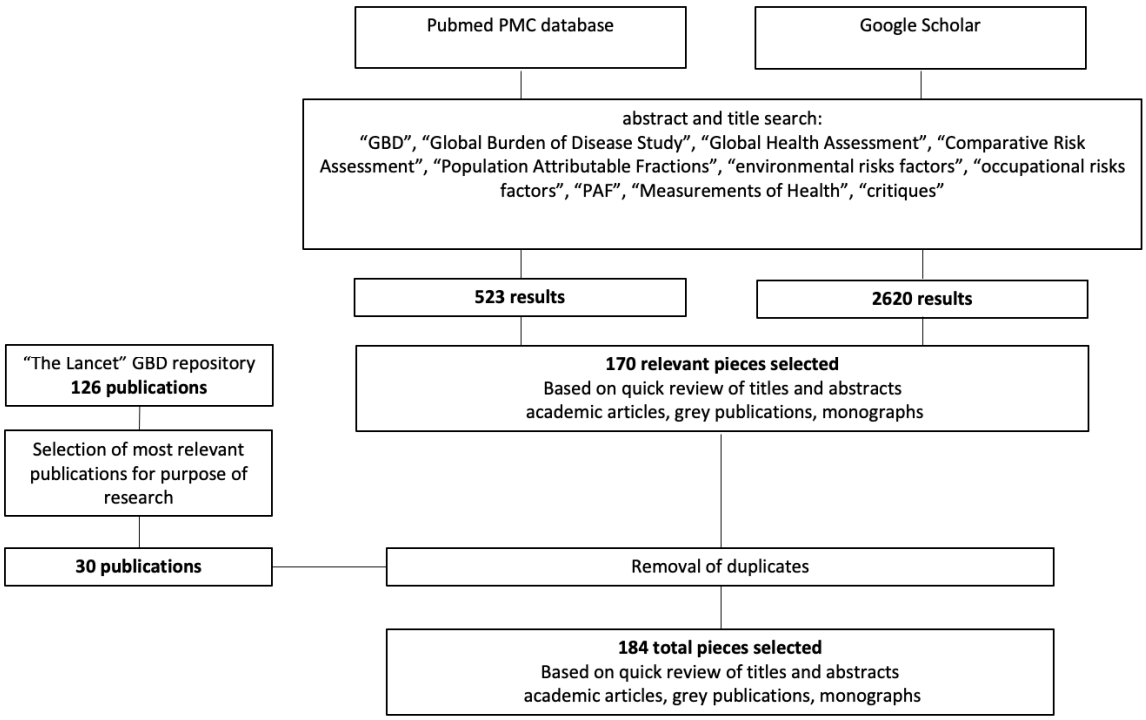
Methods and limitation

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.

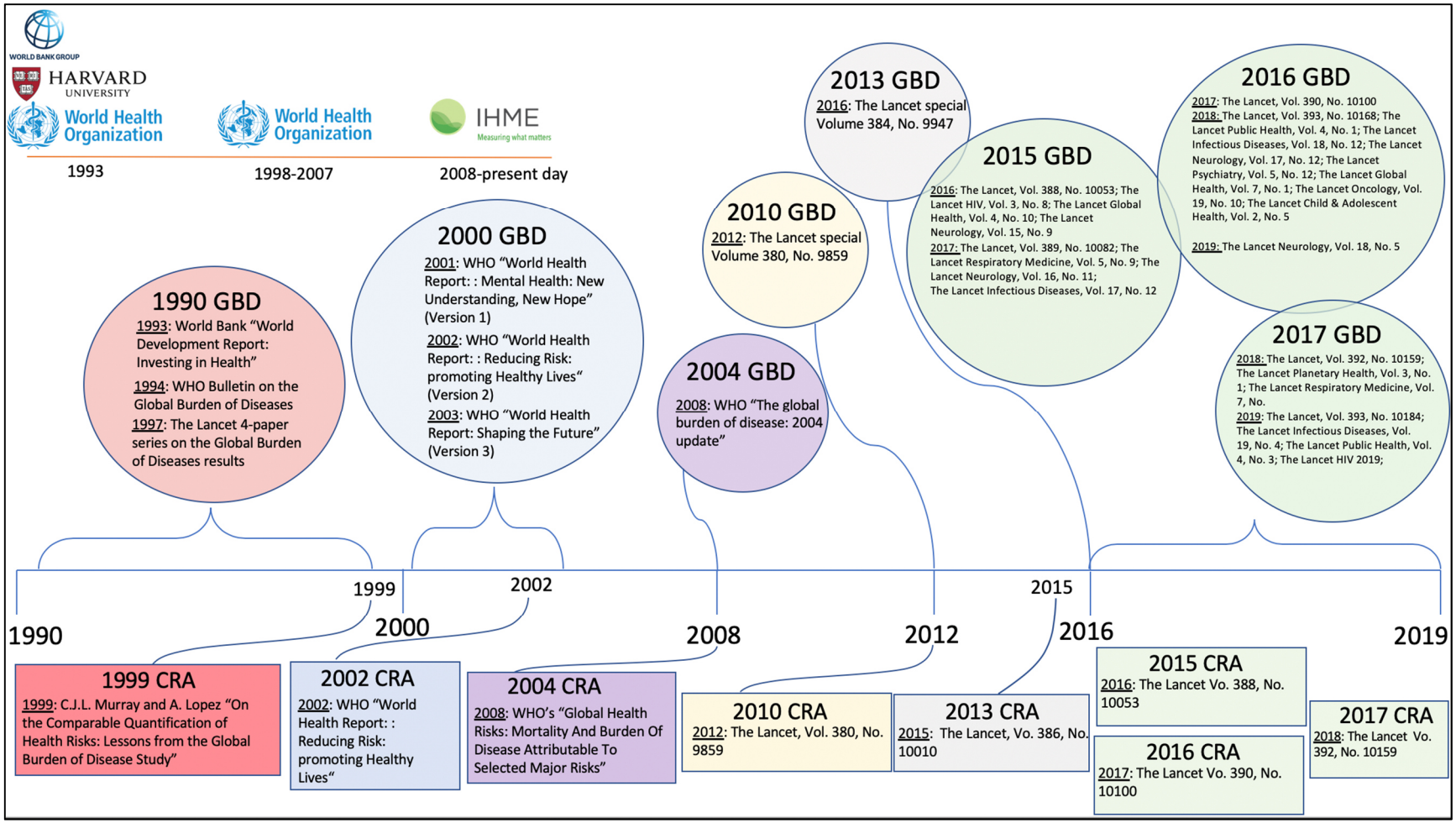


Figure i. A Precise Timeline of the GBD method publications with respective CRA (as of June 2019)

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.

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 1997 GBD: a prototype of Comparative Risk Assessment

The 1997 GBD - summarized in a first working paper (Documents de Travail n° 264) - presented for the first time a risk assessment for 10 "risk factors" (tobacco; alcohol; illicit drugs; occupation; air pollution; poor water supply, sanitation and personal & domestic hygiene; hypertension; physical inactivity; malnutrition; and unsafe sex) each individually assessed by a separate study by experts in the field, with specific risk-outcome pairs analyzed and researched singularly (Murray & Lopez, 1997a). The risk assessment tried to link a specific risk factor with the 108 diseases and injuries taken under investigation. Importantly, not all DALYs lost observed in the GBD could be traced to one of the risk factors chosen; the risk assessment, rather, showed behavioral and environmental elements which increased the possibility of developing some diseases, sequelae, or dying. Attributable burden was defined as: "the difference between currently observed burden and the burden that would be observed if past levels of exposure had been equal to a specified reference distribution of exposure" (Murray & Lopez, 1997a). Of particular interest in the risk assessment analysis was the handling of missing epidemiological data, which in some cases needed to be interpolated from other observations deemed robust. This was a decision made on the grounds that not every country could possibly have specific epidemiologic studies analyzing the effects of a risk factor on its own population, and that some countries lacked the exposure databases needed. This meant that for some countries, estimation of risk factors was not (only) based on direct observations.

For example, two methods were used in the study of occupational risk factors:

– **a direct approach** which based itself on occupational data where they were available for each country, and extrapolated such observations to countries with similar demographic, developmental, and socioeconomic features within the same World Bank Region of the

world[1] in cases of missing observational data. The direct approach was different for occupational injuries and occupational diseases. The ILO report on global incidence of occupational injuries was the main source of data for the former, using the most recent data available for each country based on compulsory reporting systems and compensation schemes. Work-related diseases, on the other hand, had much less reliable data, with only Scandinavian countries reporting incidence of different occupational diseases by age and sex at the time of the study, based on compensated cases. Data for specific diseases attributed to occupational risk factors were used when available at the national level. Disease-specific rates were not extrapolated in countries which lacked the observational data; instead, national estimates of overall rates of occupational diseases were deemed as more stable and reliable to extrapolate in countries with no data (Leigh et al., 1999).

– **an indirect approach** which made approximate global estimates of work-related diseases and injuries based on age and sex specific rates adjusted from the Finnish Registry of Occupational Diseases, corresponding to the more comprehensive compensation system at that time (1993). To then obtain absolute numbers for every country, the derived rates were applied to the specific population distribution of each World Bank Region based on the assumed economic developmental level; for example, the rates were applied normally for Established Market Economies, but incidence rate were doubled for Sub-Saharan Africa. This approach was used for: specific pneumoconioses, musculoskeletal conditions, accidental injury, cancer, neuropsychiatric disorders, pesticide & other poisoning, skin conditions, and noise-induced hearing loss (Leigh et al., 1999).

This was perhaps the only plausible estimation methods available to the authors, given the incredibly complex task of attributing a disease or injury to a certain occupational exposure or circumstance in light of the scarce occupational and health statistics of the time, even in the most industrialized countries under investigation (Leigh et al., 1996).

This first 1997 risk factor investigation (published in 1999) introduced the foundations of risk assessment, however the analysis remained simple, unable to give much more than a comparison of DALYs attributable to the 10 broad risk factors introduced in the 1990 GBD. “Occupation” accounted for 37.9 million DALYs, with no specification of disease outcomes (Murray & Lopez, 1999). The method derived its DALYs estimation from a WHO Report by Leigh et al. which estimated globally for 1990 28.9 million non-fatal and 97 500 fatal occupational injuries, and between 585 000 – 705 000 deaths due to occupational disease (an estimated 1.17-1.41% interval of 50 million total worldwide deaths is reported in the study) derived from the direct approach mentioned above (Leigh et al., 1996, pp. 9–12). The 1997 risk assessment can be considered the predecessor to the comparative risk assessment (CRA), which in 2010 developed a completely different structure with a much more robust theoretical framework and a richer database, becoming a pioneering backbone of the methodology.

[1] The regions are subdivided in the following 8 groups: Established Market Economies, Former Socialist Economies of Europe, India, China, Other Asian Islands, Sub-Saharan Africa, Latin America & the Caribbean, and Middle Eastern Crescent

The 2002 World Health Report: comparative assessment of risk factors

While from 1998 to 2001 the WHO World Health Report generally focused on simply updating the observations of the 1990 GBD project, it is worth analysing the 2002 report "*Reducing Risks, Promoting Healthy Life"* which introduced important updates for risk factors assessment[2] (World Health Organization, 2002). The 1997 risk-factor analysis (part of the 1990 GBD methodology) had several methodological limitations: it accounted only for 10 general risk factors with little explanation on their choice (see above), relied heavily on extrapolation by similar economic development due to the lack of data in most of the countries investigated, did not allow for comparison between different estimates, and did not take into account the variation in time-lags between exposures and health outcomes (Murray & Lopez, 1997b). This was largely due to the fact that certain risk factors were much better documented than others, consequentially making comparison hard and extrapolation necessary. In 1999, Murray and Lopez published, separate from the GBD series of paper, a methodological approach to comparative risks assessment which involved using a single method of evaluation – the potential impact fraction (PIF). PIFs could be used to show the proportional reduction, in the total number of new cases of a certain disease, resulting from the specific change in the distribution of a risk factor in population – they however acknowledged the implementation of this approach was then out of reach:

> *We propose the following conceptual approach be used when evaluating the burden attributable to a particular risk factor in future work. In the short term, it is not realistic to expect that the following standardization can be achieved. Progress, however, toward greater standardization should be encouraged. (Murray & Lopez, 1999)*

The 2002 WHR, focused on assessing risk, advanced the above-mentioned methodology and developed a system "to increase comparability between the estimates of the impact of different risk factors and characterize the timing of these impacts" significantly changing the assessment by developing a common method for evaluation and standardization (World Health Organization, 2002). The list was expanded to 26 selected risk factors[3] broadly divided in 7 categories:

- Childhood and maternal undernutrition
- Other diet-related risks and physical inactivity
- Sexual and reproductive health risks
- Addictive substances
- Environmental risks

[2] For clarity, the 1990 GBD refers to the work completed between the World Bank's 1993 WDR and The Lancet 4 paper series published in 1997. The 2002 CRA described in this chapter is part of the 2000 GBD, published by the WHO between 2001 and 2003 through three World Health Reports. For clarity, please refer to the provided timeline at the beginning of the report.

[3] Total list of risk factors included: Underweight, Iron deficiency, Vitamin A deficiency, Zinc deficiency, Blood pressure, Cholesterol, Overweight, Low fruit and vegetable intake, Physical inactivity, Unsafe sex, Lack of contraception ,Tobacco, Alcohol, Illicit drugs, Unsafe water, sanitation and hygiene, Urban air pollution, Indoor smoke from solid fuels, Lead exposure, Climate change, Risk factors for injury, Carcinogens, Airborne particulates Ergonomic stressors, Noise, Unsafe health care injections, Childhood sexual abuse.

- Occupational risks
- Other selected risks to health

Risk factors were chosen following 5 principles: 1) potential global impact; 2) high likelihood of causality; 3) potential modifiability; 4) neither too specific nor too broad; and 5) availability of data on risk factor distribution and risk factor-disease associations (World Health Organization, 2002). These selection criteria had some degree of arbitrariness and were inevitably subject to the authors' personal choice, but nevertheless introduced a consistent rationale of selection which was missing in the 1997 analysis. Of critical importance in risk assessment and risk factors selection is the issue of establishing causality. The 2002 WHR followed a methodology of risk assessment (World Health Organization, 2002) that relied on a subset of the classical points of discussion of causality brought by A.B Hill (Hill, 1965; World Health Organization, 2002); the selected standards were:

Temporality: Causes must precede the effects in time.
Strength: The stronger the association, the most likely causal.
Consistency: Different observations under different circumstances yield the same results.
Biological Gradient: Dose-response curve suggests causality.
Plausibility: The risk-outcome pair shall be biologically plausible.
Experimental Evidence: Evidence of causation under experimental circumstances is present for the risk factor of interest.

These six standards increase the confidence of the causal relationship between a risk factor and an outcome (Hill, 1965), and help in the selection process of risk factors to analyse. Risk assessment was defined as "a systematic approach to estimating the burden of disease and injury due to different risks[4]" (World Health Organization, 2002).

An instrumental concept used in CRA: Population attributable fraction

While the 1997 CRA looked at separate risk factors with independently-developed methodologies – all derived differently from analysis in their respective fields – the 2002 WHR introduced the use of population attributable fractions (PAFs)[5] as a single evaluation metric of disease burden due to exposure to risk factors –-although the provided formula was instead for population impact fraction (PIF), referred to by the authors of the report as the preferred metric where multi-level (of exposure) data are available (see formula 1 & 2). The measurement, which represents the proportional reduction in DALYs if exposures to a risk factor were to be reduced to an established lower level (Figure 1) allowed analysis from two critical aspects: the *attributable* burden of diseases due to a certain risk factor exposure, and the *avoidable* burden in the future due to changes in such exposure. This approach aimed at providing a cost-benefit analysis to policy-makers when evaluating possible health interventions (World Health Organization, 2002). In fact, the report tracked the "distributional

[4] In the cited report, "the word "risk", it is defined in this report as "a probability of an adverse outcome, or a factor that raises this probability"".

[5] The methodological references on PAF that are cited are: King G, Tomz M, Wittenberg J. Making the most of statistical analysis: improving interpretation and presentation. *American Journal of Political Science* 2000; 44:341-55.Robins JM. A new approach to causal inference in mortality studies with a sustained exposure period: applications to control of the healthy workers survivor effect. *Mathematical Modeling* 1986; 7:1393-512. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *American Journal of Public Health* 1998; 88:15-9. Rothman KJ, Greenland S. *Modern epidemiology.* 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1998.

transition" of risk factors selecting "plausible, feasible, and cost-effective scenarios" in the reduction of exposure between current levels and an established "unavoidable" minimum threshold of exposure in the population. Impact fractions such as PAFs allowed to quantify both attributable and avoidable burden by using only one metric and, most importantly, could be equally calculated for all risk factors analysed, enhancing comparability.

Population Attributable Fraction (PAF) and Population Impact Fraction (PIF) formula

(Formula 1)

$$PAF = \frac{P(RR-1)}{P(RR-1)+1}$$

*Where **RR** is the relative risk for the exposed group as compared to a reference group (typically non exposed) and **P** is the fraction of the population with this exposure.*

(Formula 2)

$$PIF = \frac{\sum_{i=1}^{n} P_i\,(RR_i - 1)}{\sum_{i=1}^{n} P_i\,(RR_i - 1) + 1}$$

*Where **RR i** is the RR for exposure category i as compared to a reference category, **P i** is the fraction of the population in exposure category i, and **n** is the number of exposure categories.*

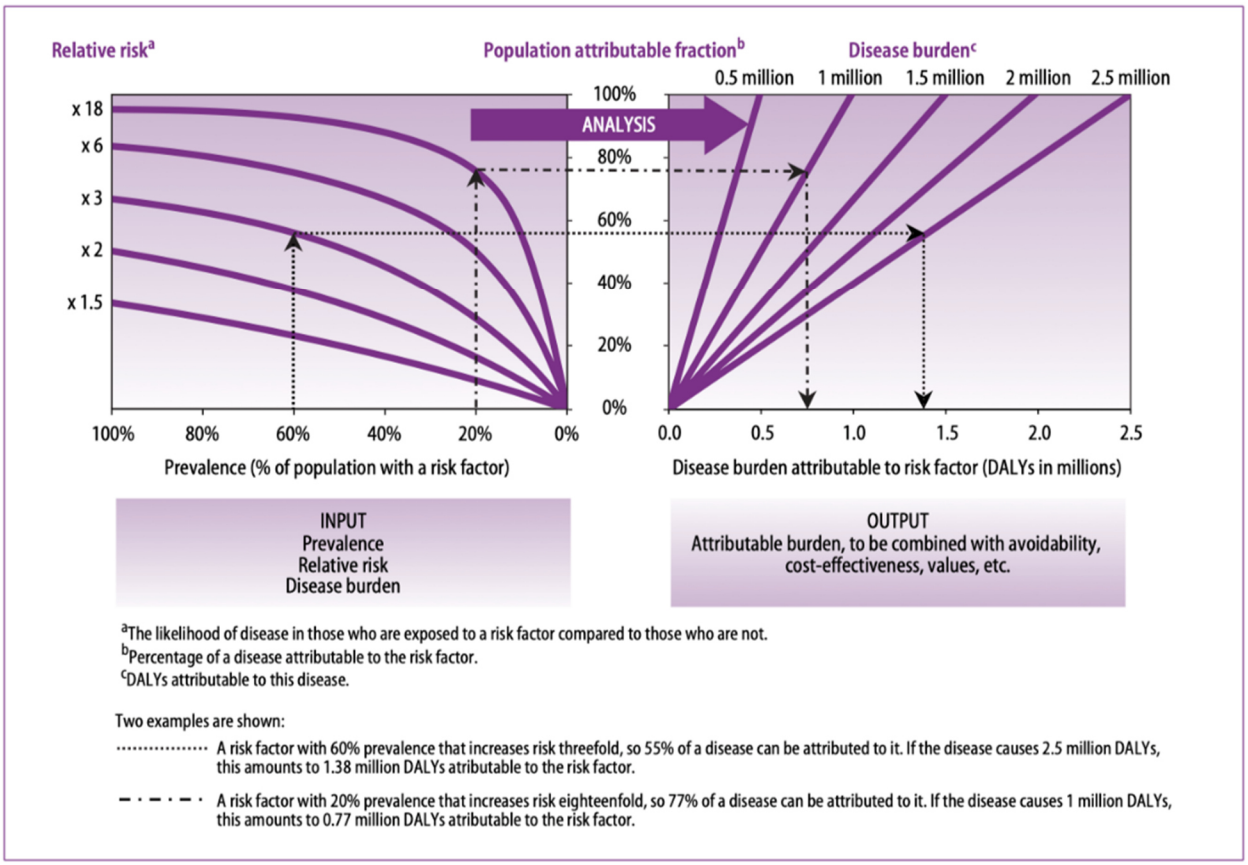


Figure 1. Determination of attributable burden in DALYs with prevalence of risk factor and relative risk.
Source: Reproduced from WHO 2002 World Health Report: Reducing Risks, Promoting Health Life.

Risk assessment computation: avoidable and attributable burden

Attributable Burden

Attributable burden was assessed for all WHO Regions for the year 2000. The current risk factor exposure was contrasted with an established theoretical minimum counterfactual exposure as a benchmark – this represented the level of exposure which pertained the least risk of developing a disease or injury. The theoretical minimum (which represents the counterfactual exposure used) was introduced for the first time with this WHR report and has since become a foundation of the GBD Comparative Risk Assessment. This threshold varied specifically for each risk factor and was not simply generalized to zero exposure: while abstention from smoking can be considered a realistic theoretical minimum (the authors argue), zero blood cholesterol level would be quite impossible to observe, as well as no air pollution, for different reasons. The level considered as the least detrimental for health in the outcomes observed was selected. Theoretical minimums were kept consistent throughout all regions within a single risk factor, in order to enhance comparability between populations. Attributable risk assessed the *current burden* of disease due to the exposure of populations for the selected behavioural, physiological, and environmental factors. It did not retain only detrimental risk factors – exposure to "protective risks" was also taken into analysis, such as the protective benefits of a balanced diet by determining its effect on people with low "exposure" to it (World Health Organization, 2002).

Rather than focusing on targeting high-risk individuals and exposures (that is, the extremities on the yardstick measuring risk), the report advocated for eliminating the biggest portion of risk, even if this meant tackling the population with the lowest risk level:

> *Population-based strategies that seek to shift the whole distribution of risk factors have the potential to control population incidence. Such strategies aim to make healthy behaviours and reduced exposures into social norms and thus lower the risk in the entire population (World Health Organization, 2002).*

Exposure to risk factors, then, was taken to be on a continuum rather than fixed in one moment in time. Therefore, policies focused on lowering the widest prevalence of exposure possible (even if this is low), may have a much bigger impact on present and future health than ones aimed at lowering the exposures which seem to be most detrimental (Rose, 2001).

Avoidable Burden

Avoidable burden, defined as "the fraction of total disease burden in a particular year that could be avoided *in the future* with a specific reduction in current and future exposure compared to predicted current trends" (World Health Organization, 2002) was calculated for 2010, 2020, and 2030 by looking at the distributional transition, with a 10 to 30% reduction in population exposure to risk factor, from the year 2000 levels towards the theoretical minimum of each of the 26 risk factors defined. Small to moderate risk reductions were favoured in order to propose feasible options for policy makers looking to tackle the burden of diseases.

Gains in healthy life expectancy[6] with the theoretical removal of selected risk factors were also calculated.

The research acknowledged that, while not all the burden of disease for the three groups of diseases of the GBD could be attributed to the selected risk factors, they still played a substantial role. The exact enumeration of how much can be attributed to the risk factors, along with a ranking transition of different risk factors between 2000, 2010, and 2020 (the only available enumeration of attributable risk for each selected risk factor) is reported below (Figure 2).

Rank	Estimated attributable burden in 2000		Estimated avoidable burden after 25% distributional transition from 2001 in 2010		in 2020	
		DALYs (millions)	% total		DALYs (millions)	% total		DALYs (millions)	% total
1	Underweight	138	9.5	Unsafe sex	42	3.0	Unsafe sex	71	4.8
2	Unsafe sex	92	6.3	Blood pressure	25	1.7	Blood pressure	27	1.9
3	Blood pressure	64	4.4	Underweight	23	1.6	Tobacco	22	1.5
4	Tobacco	59	4.1	Tobacco	17	1.2	Cholesterol	17	1.2
5	Alcohol	58	4.0	Cholesterol	15	1.1	Underweight	16	1.1
6	Unsafe water, sanitation and hygiene	54	3.7	Alcohol	15	1.1	Alcohol	16	1.1
7	Cholesterol	40	2.8	Overweight	13	0.9	Overweight	15	1.0
8	Indoor smoke from solid fuels	39	2.6	Iron deficiency	9	0.6	Low fruit and vegetable intake	9	0.6
9	Iron deficiency	35	2.4	Low fruit and vegetable intake	9	0.6	Iron deficiency	7	0.5
10	Overweight	33	2.3	Unsafe water, sanitation and hygiene	8	0.6	Physical inactivity	6	0.4
Total DALYs		*1 455*			*1 417*			*1 459*	

Figure 2. Ranking of estimated attributable (in 2000) and avoidable (in 2010 & 2020) burdens of 10 leading selected risk factors after a 25% distributional transition from 2001 onward.
Source: Reproduced from WHO 2002 World Health Report: Reducing Risks, Promoting Health Life.

Use of population attributable fractions

Attributable and future avoidable burden are calculated by computing the population attributable fractions for each of the 26 risk factors identified and based upon the input of three types of data (summarized in Figure 3). The first is the current distribution of exposure to the risk factor in each population, for the seven clusters of risks, by age and sex, also establishing a theoretical minimum counterfactual exposure, kept constant for all populations. While data sources improved significantly since the first 1997 study – as risk factors were, for the 2002 analysis, in part also selected on the criteria of availability of evidence – some data extrapolation was still needed, and was based on generalizations of particular WHO regional subgroups based on health, demographic, and socioeconomic indicators (World Health Organization, 2002).

The second variable necessary in the calculations was the established relationship between exposure to risk factor and disease risk. This process in particular relied heavily on extrapolated data, as direct information on dose-response relationships remained, as in the 1997 analysis, mainly available only for selected developed countries.

[6] The World Health Organization (WHO) defines Healthy life expectancy (HALE) as "a form of health expectancy that applies disability weights to health states to compute the equivalent number of years of good health that a new born can expect".

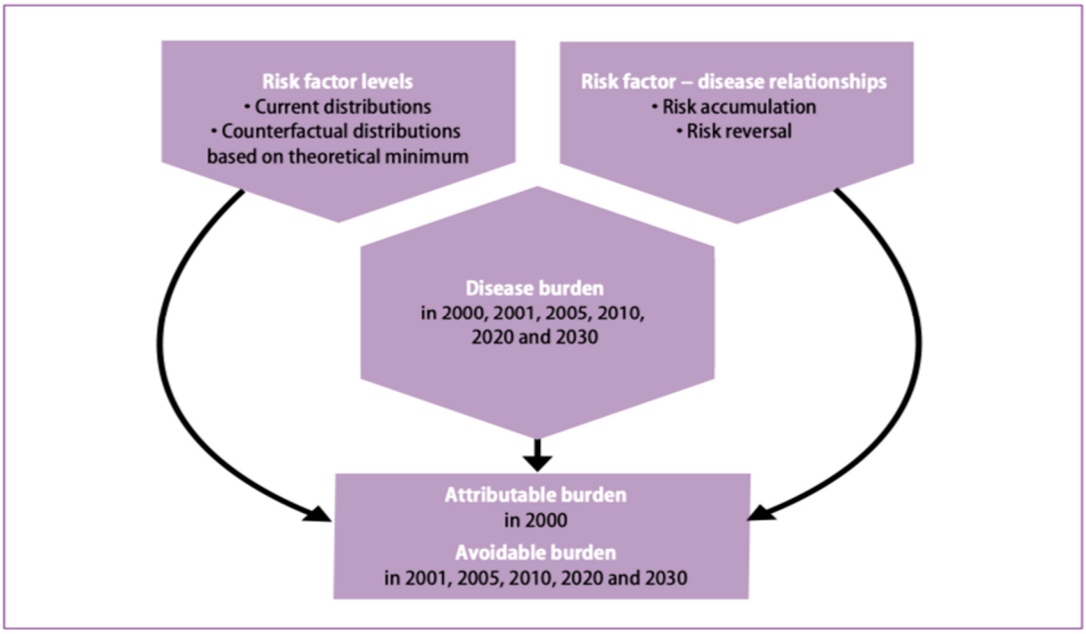


Figure 3. The three main data inputs for risk assessment–risk factor distributions, risk-disease relationship, and the burden of disease. *Source: Reproduced from WHO 2002 World Health Report: Reducing Risks, Promoting Health Life.*

In the light of this, it was decided to use data that was as generalizable as possible without colluding results in the need of extrapolating data. While population representativeness is important in assessing risk factor distributions, it was generally assumed that the intrinsic biological foundation of *risk factors-diseases* relationships makes them generalizable across different population groups. The reliability and comparability of epidemiological studies used to establish the exposure-disease relationship, typically through Relative risk (RR) estimates, were used as the main indicators of consistency in establishing those relationships (World Health Organization, 2002).

The last necessary data input were the estimates of current and future disease burden, or the DALYs estimated and projected by GBD. Estimates of risks burden were taken singularly, assuming all other risks factors were held constant–this decision was done on the grounds of a lack of data for assessing joint risks effects.

The 2002 risk assessment reported 95% confidence intervals obtained by running 500 statistical simulations of all parameters within the exposure-risk distributions and re-estimated all PAFs–a significant step forward on reliability of results from the 1997 estimates. In its 2010 and 2020 projections, it predicted a similar risk rank to that of 2002, with little change on the total burden in DALYs which the 10 leading risk factors caused. The two tables at the end of this report summarize, by type of risk factor, theoretical minimum level, health outcome observed, and the burden of risk for the environmental (Annex 2) and occupational (Annex 3) subgroups.

In a further exercise, malnutrition, water sanitation, breastfeeding, unsafe sex, alcohol, tobacco, overweight, and air pollution (indoor and urban) were mapped by socioeconomic status (occupational risks factors were not), using as absolute poverty levels living under US$1, between 1 and 2, or living on more than US$2 per day. The comparison of healthy life expectancy by absolute level of poverty was made between countries and was not concerned on countries' internal economic differences. Rather than regional characteristics, the

socioeconomic analyses used individual-level data - not clearly defined though as referring to individual-country-data or observations on individuals within national populations; nor was the source of this data (World Health Organization, 2002).

While acknowledging the lack of reliable data for an accurate analysis of absolute poverty, the Report estimated one-fifth of the total population to live on less than US$1, and nearly 50% under US$2. Only 11 subregions (AFR-D,AFR-E,AMR-D,AMR-D,EMR-B,EMR-D,EUR-B,EUR-C,SEAR-B,SEAR-D,WPR-B) were included in the analysis – the remaining three were assessed to have "negligible levels of absolute poverty". Absolute poverty was found to have a particularly strong association (although the analysis did not report confidence or plausibility intervals) with child underweight, unsafe water and sanitation, and indoor air pollution; however, the Report lacks a clear explanation of the calculations undertaken in order to define said prevalence. Similarly, a shift in population impact fractions is also presented by subregion and risk factor, reporting potential reductions in case of a shift in exposure prevalence between poverty groups. The findings present the following claim:

> *If people living on less than $2 per day had the same risk factor prevalence as people living on more than $2 per day, then protein–energy malnutrition, indoor air pollution and unimproved water and sanitation would be reduced by approximately 37%, 50% and 51%, respectively (see Table 4.1). These total population impact fractions would be reduced to 23%, 21% and 36% if the impoverished had the same risk factor prevalence as people living on exactly $2 per day. (World Health Organization, 2002)*

Cost-effectiveness analyses

A substantial part of the report was devoted to the importance of cost-effectiveness analyses of different interventions, with an evaluation of existing programs and their effect on alleviating the burden of disease related to some risk factors. The cost-effectiveness analysis was designed by projecting a plausible scenario if a set of interventions taken into consideration had not been implemented, compared to results achieved through their implementation. Healthy life years gained were estimated by running a 4-state population model over a period of 100 years in the absence of the set of interventions analysed, portraying a "natural" development of diseases due to the exposure of the population to a certain risk factor. Costs included expenses for training and preparation of personnel, and the interventions reported were chosen on the basis of showing achievable solutions for policymakers. The cost-effective analysis provided a prioritization system for policy action given resource availability and feasibility of tackling certain risk factors (World Health Organization, 2002). The analysis was independently done for each of the WHO epidemiological subregions.

Occupational risks were not fully evaluated, citing a lack of programs and data as main justification. Only a brief mention on the effectiveness of seat-belts for motor vehicle accidents –although they were part of environmental hazards in another section–and some observational studies on efforts for reducing occupational back pain is included. No successful program nor intervention is analysed (World Health Organization, 2002, pp. 127–129).

The only cost-effective intervention evaluated in the environmental risk group was for curbing unsafe water, sanitation, and hygiene – no rationale was stated on the type of grouping done for different risk factors likely because of the intended audience of the WHR, less focused on

these methodological details and more on results. The elimination of diarrhoea tied to this risk factor group was the metric of evaluation of gains in DALYs; 5 possible interventions were investigated: 1) reaching the Millennium Development Goal of halving the number of people with no access to safe water; 2) achieving disinfection of drinking sources of water at point of use; 3) the same improvements of the Millennium Development Goals, but with a higher level of coverage; 4) a mix of the 2nd and 3rd interventions just described; and 5) the provision of: piped water to houses, water treatment for pathogens, quality monitoring programs, water pollution control, and sewage connection with treatment of wastewaters. Cost effectiveness was evaluated by moving from the level of coverage of each sub-region to 98% of coverage. No intervention was analysed for the EUR-A and AMR-A subregions, as all their populations were considered to have access to safe water.

The *2002 World Health Report: Reducing Risks, Promoting Health Life* can be defined as the first Comparative Risk Assessment of the GBD project, laying the philosophical and methodological groundwork in concomitance with an article in The Lancet on the same evaluation (Ezzati et al., 2002). This new method of risk assessment introduced a powerful analysis tool for policymakers and allowed for an interpretation of risk factors in terms of cost-effectiveness of interventions aiming at improving health outcomes. However, the substantial data needed for a deeper analysis was clearly lacking – the incompleteness of the investigation for occupational and environmental risk factor showed that the burden of disease by these two were still deeply under-estimated. It is obvious that the research also suffered from a lack of epidemiological evidence, with some exposure-outcome relationships described with small and relatively old studies, raising doubts about the robustness of conclusions. Still, the report clearly aimed at stimulating action for better data reporting and monitoring of health hazards, and the publication of these results – through the WHO – was instrumental in building stronger evidence for the future. As a consequence of the 2002 WHR, 6 national comparative risk assessments were done prior to the 2010 GBD for the United States, Australia, Iran, Japan, South Africa, and Mexico (Begg et al., 2008; Danaei et al., 2009; Farzadfar et al., 2011; Ikeda et al., 2012; Norman et al., 2007; Stevens et al., 2008).

Comparative Risk Assessment: A tool for policy

Assessing the role of risk factors in the development of health outcomes has always been a central part of the GBD. As mentioned earlier, the first risk factor analysis was done in 1990, with the definition of 10 risk factors accounting for almost 40% of the world's total DALYs (Murray & Lopez, 1997a). The analysis, however, lacked the fundamental comparative component of the GBD method, as contribution of risk factors were assessed as singular studies investigating the role of each defined risk. The poor availability of epidemiological data, as well as the heterogeneity of the quality of risk factors' analysis at the beginning of the 21st century made the feat complicated:

> *Comparability of risk factor contributions is hindered by the lack of standardization of methods and by the differences in reliability of the underlying epidemiological studies of relative risk and population exposure levels. (Murray & Lopez, 1999)*

The GBD set out to develop a common method of enumeration in order to create a comparable assessment of health risk factors. Introduced by Murray and Lopez in 1999, the computation of population attributable fractions (PAFs) seemed like a good solution because

of their use of generalizable terms. PAFs are calculated through relative risks (RR), which are considered to be relatively consistent through different populations because tied to the biological relationship between the disease and the risk. They yet also depend on the prevalence of exposure, which is specific to each population; and on a counterfactual lower exposure, which allows to maintain the point of contrast (or reference group) constant across populations, increasing comparability. PAFs, importantly, aim at quantifying the proportional reduction in DALYs (or death or morbidity) if exposure to a risk factor were to be brought down to a theoretical minimum. The same metric may therefore portray either the attributable burden (when the minimum is set to zero) or the avoidable burden (when the minimum is set to a theoretical achievable lower level) of disease for each risk factor. Attributable burden is estimated with the following equation:

$$AB_{jasct} = \sum^{w} DALY_{oasct} PAF_{joasct}$$

Where AB ***jasct*** is the attributable burden for risk factor ***j*** in age group ***a***, sex ***s***, country ***c*** and year ***t***. DALY ***oasct*** is disability-adjusted life-years for cause ***o*** (of ***w*** relevant outcomes for risk factor **j**) in age group **a**, sex **s**, country ***c*** and year ***t***. PAF ***joasct*** is the population attributable fraction for cause **o** due to risk factor ***j*** in age group ***a***, sex ***s***, country ***c*** and year ***t*****.**

Equation 1. Formula for establishing attributable burden (AB).
Source: Forouzanfar et al., 2015, « Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013 », The Lancet, 386(10010), p. 2287-2323

The first official comparative risk assessment (CRA) was published for the 2000 GBD estimates as the 2002 World Health Report[7]. These estimates calculated attributable fractions (World Health Organization, 2002, pp. 220, Statistical Annex) for 26 defined risk factors – an analysis which saw significant improvements from its predecessor, but also exposed the lacunae in some areas of risk assessment, most notably for occupational and environmental risks factors, whose contribution to health outcomes was poorly reported (World Health Organization, 2002, pp. 67–77). The CRA was specifically introduced as a tool for policy analysis, with an evaluation of cost-benefits in relation to potential interventions aiming at diminishing risk factor exposure. The work became a staple GBD practice, the second being published in 2008 as part of the 2004 GBD study. Unlike other metrics included in the study, the methodology using PAFs has remained fairly similar to the one introduced in 2002. Most of the work done in subsequent CRAs is focused on refining and improving relative risks' estimates, and reviewing literature which might identify new risk-disease relationships (World Health Organization, 2009). As its analytical and technical aspects have been already thoroughly discussed in a previous dedicated chapter, this section will primarily look at the specific evolution in estimation of the contribution of occupational and environmental risk factors.

[7] For a more detailed analysis of this work, please refer to the chapter "The *2002 World Health Report: comparative assessment of risk factors".*

The Importance of occupational and environmental risk factors

The analysis of occupational and environmental risks factors performed in 1990, which focused primarily on "injuries and diseases" for the former and "air pollution" for the latter, lacked epidemiological data and evidence for causation. The analysis on occupational injuries and diseases was based on observations in developed countries, then extrapolated to the majority of countries with missing data:

> *For occupational diseases, data from reporting systems were available for the USA, Canada, Australia, Sweden, Denmark, the UK, Switzerland, Luxembourg, Hungary, Mexico, and China (selected causes only). For most of the working population in countries without registration systems, the reported rates from Canada and Australia were used to estimate occupational-disease death rates (Murray & Lopez, 1997a).*

To the same extent, environmental risk factors were reduced to the exposure to suspended particulates and Sulphur dioxide. Importantly, no specific exposure-disease relationships were detailed within the report, giving little context to the observations and their impact at population health levels, making the effort more of an observation of potential causes impacting ill-health, rather than a proper risk-factor analysis. The introduction of the CRA with the 2000 update changed the perspective of analysis. Environmental and occupational risks, now subdivided into five specific major risk factors affecting health, focused on specific measurable health outcomes, using pairs of exposure-outcome relationships instead of using indirect methods (as for occupational risk factors) or simply all-cause mortality (for environmental risk factors).

However, the results of the first CRA were largely inconclusive for these two groups of risk factors, detailing a lack of relevant data, rather than providing a meaningful analysis of their impact on health. The 2002 World Health Report included a reflection on realistic risk reductions in order to lead to better health. No interventions were proposed for the adverse health outcomes attributed to environmental and occupational causes. For the former, only water access and hygiene were reviewed, and for the latter none of the described risk factors–work-related injuries, carcinogens, airborne particulates, ergonomic stressors, and noise–had evaluated interventions (World Health Organization, 2002). The underrepresentation of these two areas of health risks in the report necessarily highlights both the missing evidence as well as their underrated effect on health. Few academic references are cited in support to the claims drawn by the report, leaving a substantial gap in the 2002 approach. The 2004 CRA did not significantly update the findings from 2002, and can be mostly seen as one of the midst of an institutional transition of the GBD project from the WHO to the IHME. Just over 5 million and 300 thousand deaths were attributed to environmental risks factors worldwide in the 2004 CRA, compared to 4 million 530 thousand in 2002; 987 thousand deaths by occupational injuries and diseases were calculated in 2004, quite a significant increase from the 699 thousand enumerated in 2002 (World Health Organization, 2009, 2002). This discrepancy can largely be described by an almost doubled increase in attributable deaths by airborne particulates (Timothy Driscoll et al., 2005; World Health Organization, 2009).

The substantial breakthroughs in analysis and estimates came with the 2010 GBD and related CRA, which, as mentioned elsewhere[8], completely revisited the method of risk factor assessment, granularity of specific risks, and estimation methods. The 2010 GBD envisioned a complete redesign of all of its 18 analytical components. The CRA presents a hierarchical clustering of risks, with three degrees of specificity. Level 1 groups risk factors by mechanisms, biology, or potential policy intervention. The first level generally mirrors the original risk grouping found in previous CRA, which grew from 7 to 10, adding "additional environmental risks factors", "sex abuse and violence", and "physiological risk factors" as groups. Level 2, where most risk factors could be found, indexes the specific risk factors analyzed (high cholesterol, tobacco smoking, or lead exposure for example). Level 3 is present only for occupational carcinogens and specifies the type of carcinogen based on specific agents. As in the case of the hierarchical structure of diseases found in the GBD, it does not represent magnitude, but rather specificity. This allowed for three types of analysis (based on three different equations, provided below) (Lim et al., 2012):

1. Continuous exposures: For which PAFs were calculated by comparing the present distribution of exposure to the theoretical-minimum-risk exposure distribution for each age group, sex, year and cause for all of the 64 individual risk factors.

$$PAF = \frac{\int_{x=0}^{m} RR(x)P1(x)dx - \int_{x=0}^{m} RR(x)P2(x)dx}{\int_{m=0}^{m} RR(x)P1(x)dx} \quad (\mathbf{a})$$

Where PAF is the population attributable fraction (burden attributable to risk factor), RR(x) is the RR at exposure level x, P1(x) is the (measured or estimated) population distribution of exposure, P2(x) is the counterfactual distribution of exposure and m the maximum exposure level.

2. Categorical exposures: by comparing exposure categories to a reference category for each age, sex, year, and cause.

$$PAF = \frac{\sum_{i=1}^{n} P_i(RR_i - 1)}{\sum_{i=1}^{n} P_i(RR_i - 1) + 1} \quad (\mathbf{b})$$

Where RR i is the RR for exposure category i, P i is the fraction of the population in exposure category i, and n is the number of exposure categories.

3. Cluster exposures: For each of the level 1 categories (which are clusters of specific risk factors), generating combined PAFs for risk factors for each age, sex, year, and cause.

$$PAF = 1 - \prod_{r=1}^{R}(1 - PAF_r) \quad (\mathbf{c})$$

Where r is each individual risk factor, and R is the number of risk factors in a cluster. This approach assumes that risk factors are independent—it does not account for mediation, exposure correlation, or effect modification that might exist between risk factors in a cluster.

[8] For a more detailed account on the analytical and structural changes to the methodology of the 2010 GBD, please see the "*The Global Burden of Disease methodology in the 21st Century"* Chapter in the GBD analysis (Document de travail n° 264).

Equation 2. PAF for: (1) continuous exposures, (2) categorical exposures, and (3) cluster exposures
Source: Lim.S et al. 2012. "A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010". The Lancet, 2012, 380: 2240-60.

Relative risks (RR) used in the 2010 CRA were all derived singularly from published studies in the field–a significant improvement in transparency is the clear availability of each source (Lim et al., 2012, specific sources: p.2227 for environmental RRs, p.2231-2233 for occupational RRs). The increased granularity in data developed a more specific subdivision in major risk factors. In line with the whole 2010 GBD shift toward estimation through computation, exposure estimation was strongly reliant on a vast array of complex statistical methods and algorithms. Occupational risk factors were modelled only through Spatiotemporal Gaussian process regression, while environmental risks used a variety of available methods specific to the risk factors analyzed on top of Spatiotemporal Gaussian process regression[9]. The level 3 risk factors for work carcinogens include 13 mutually exclusive risk factors, all singularly measured according to a specific pair of risk factor-health outcome.

The granularity of the estimates shows a notable growth in the field of occupational risks factors' analysis which was clearly lacking before. While in the previous CRA estimates of occupational diseases and injuries were peripheral, in 2010 they ranked amongst the top 20 risks in terms of attributable DALYs (Lim et al., 2012). This is due likely to the development of a broader understanding of how populations perceive chronic pain, which occupational risks greatly contribute to in DALYs calculations (cf. low back pain). Occupational risk factors were estimated to cause over 811 thousand deaths in 1990, growing to over 850 in 2010. Environmental risks, on the other hand (adding the level 1 categories of "air pollution" and "other environmental risks") contributed to 7.6 million deaths in 2010, slightly decreased from the 7.7 million estimated in 1990 (the decrease largely led by a million deaths less by indoor pollution, but a significant increase in estimated deaths by ambient particulate matter).

Methodologies compared

A comparison between the four sets of estimates is unfortunately hard and likely inaccurate for several reasons. First, the estimation techniques from the first two CRAs (2002 and 2004) to the third one in 2010 significantly changed, now relying heavily on algorithms. Second, the whole 2010 GBD study specifies that its results are intended to supersede previous ones, therefore not offering comparisons with previous estimates and making it difficult to track how much of the differences are related to changes in methods rather than temporal trends. Third, the different level of specificity between the three studies, as well as different groupings used to present results, make it hard to understand where discrepancies might be and what they could be attributable to. Lastly, comparing DALYs, with their calculation completely changing between 2002 (the first CRA publication year) and 2012 (the 2010 publication year), would be like comparing two completely different measurements. Hence the choice we made to report attributed deaths only in Figure 4.

[9] Every single model used, subdivided by each specific risk factor analyzed, can be found at (Lim et al., 2012, Environmental risks p.2227; Occupational risks p.2231-2233).

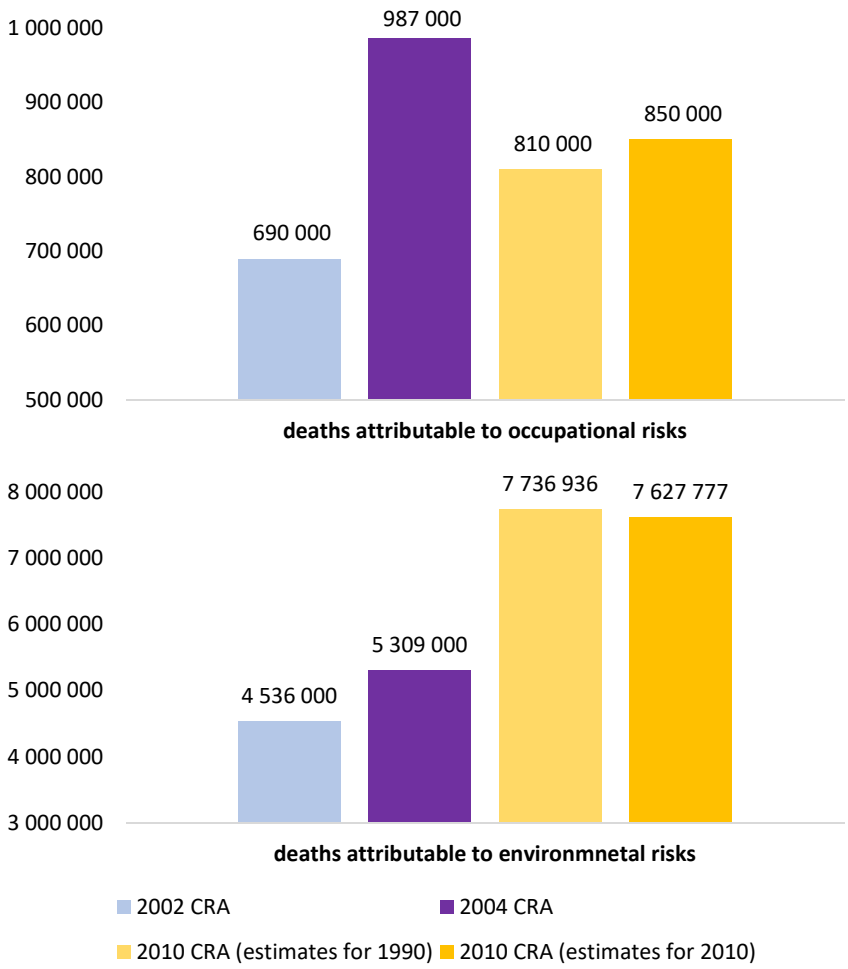


Figure 4. Comparison of attributable deaths by environmental and occupational risk factors of the 2002, 2004, and 2010 CRA studies.
Source: Authors' own graph. Data aggregated from: WHO. 2002. "World Health Report: reducing risk, improving lives" WHO, Geneva, 2002; WHO. 2008. "Global Health Risks: Mortality and burden of disease attributable to selected major risks" WHO, Geneva, 2008; Lim.S et al. 2012. "A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010". The Lancet, 2012, 380: 2240-60.

The methodology for enumerating total deaths has not significantly changed in the GBD (unlike disabilities, whose weighting changed between the three updates). Just a glance at Figure 4 shows that, at least by the numbers, reasonable differences exist between the three studies. Part of the explanation of these differences is given by the change in accuracy of the contribution of the risk factors to total death. For environmental risk factors, estimates for the year 1990 are still much higher than for 2002 and 2004–since the 1990 estimates were done with the latest 2010 methodology, this could be explained by a better understanding of the impact of the environment on health. The differences between estimates for occupational risks factors, on the other hand, are harder to understand. With more granularity in observed occupational risks and their outcomes, we could expect an increase in observed deaths due to occupational risks. At the same time, with increased awareness of the dangers posed by occupational exposures, improvements in treatments, and preventive measures at work, we could also expect a decrease in deaths. It is unclear what defines the stark differences in deaths attributed to occupational risk factors recorded in 2004, but it raises attention to the

results produced. The section discussing occupational risks in the 2009 report shows, as in the case of the 2002 World Health Report, a lack of cited evidence, as well as a relatively scarce range of studies reported for such a wide variety of possible health problems related to work (World Health Organization, 2009).

The consequential 2013, 2015, 2016, and 2017 CRA give us the possibility to understand the importance of environmental and occupational risks retained in later updates. For simplicity, the analysis on changes between these four updates will focus only on these two categories of risk factors, without delving too much in the complex explanations of the changing methods on estimation technique. This choice was made for two reasons. First, estimation methods for occupational and environmental risks have remained largely the same from 2010 to 2017. Second, while it might be an incomplete picture to not analyze in detail the specific changes which happened within each category, it is indicative to look at the staggering differences in numbers between 2013 and 2017, especially since all analysis present a re-assessment of the burden of disease for the whole period since 1990.

The 2013 CRA update (published in 2015) uses the same estimation methodology of 2010, with improvements in seven specific fields:

> (*1) addition of six new risk factors*[10]*; (2) new data for exposure; (3) assumption of a lognormal rather than a normal distribution for most of the continuous risk factors to better represent the observed population distributions; (4) updates to the systematic reviews and meta-analyses of relative risks; (5) aggregation of the burden at multiple levels of risk factors, including the combined effect of all GBD risk factors and aggregates of three large classes*[11]*—i.e., behavioral, environmental and occupational, and metabolic risk factors; (6) systematic inclusion of mediation between major risk factors in the quantification of the burden associated with joint risks*[12]*; and (7) quantification of the risk burden for 188 individual countries. (Forouzanfar et al., 2015)*

A further innovation is also the inclusion, in the meta-data, of a data representativeness index (DRI), reported as a percentage and indicating the fraction of countries for which the study has found any data for each risk factor analyzed over specific periods. For example, occupational asthmagens report a 52.7% DRI, meaning that the CRA found data on exposure to occupational asthmagens in 52.7% of the countries; conversely, for almost half of the countries, exposures were estimated through either extrapolation or statistical modelling. The DRI tells us that the data for some environmental risks was relatively well available worldwide: fractioned between unsafe water & sanitation (80.3% in the total time period analyzed), air pollution (100%) and other environmental risks (49.5%). Occupational risks, on the other hand, had much scarcer global representation, showing 72.3% in the whole period analyzed, but 56.4% in data prior to 1998, 64.4% in the period between 1998-2005, and 55.3% in the

[10] Broader classes of each additional risk factor were: handwashing (unsafe water, sanitation, and handwashing class) and exposure to trichloroethylene (occupational risks); childhood wasting, childhood stunting (dietary risks), unsafe sex (unsafe sex), and low glomerular filtration rate (metabolic risks) in behavioural risks.

[11] Cluster of risks in the 2013 GBD are: **Under Environmental and Occupational risks**: Unsafe water, sanitation, and handwashing; Air pollution; Other environmental risks; Occupational risks; **Under Behavioural risks**: Child and maternal malnutrition; Tobacco smoke; Alcohol and drug use; Dietary risks; Sexual abuse and violence; Unsafe sex; Low physical activity; **Under Metabolic risks**: High fasting plasma glucose; High total cholesterol; High systolic blood pressure; High body-mass index; Low bone mineral density; Low glomerular filtration rate

[12] List of mediation factors can be found in the Supplementary Appendix of the 2013 GBD, pp. 710-11.

2006-13 period. Explanation for this gap is not available, but this is indicative of the results reported and of the (still under-represented) global exposure to these risks being largely based on "labor force surveys and censuses on the economically active population available from the International Labour Organization" (Forouzanfar et al., 2015) even in a high-income country like France. This means that estimates relied heavily on extrapolation for the burden of occupational risks largely based on exposure of a subgroup of higher-income countries. Furthermore, the granularity of DRI was in fact highly variable, from single risk factors to sub-groups only, as for occupational carcinogens for which no single factor had a DRI reported.

As the previous GBD study, the results in 2013 are meant to supersede all previous estimations, as the analysis also re-evaluates data from: before 1998, between 1998 and 2005, and between 2006 and 2013 (reason for the series chosen, however, is not specified).

Since the method of DALYs estimation remained the same between 2010 and 2013, a direct comparison of estimates is possible. The 2013 report states that "At the global level, the correlation of the number of DALYs attributable to the same risks for the year 2010 across GBD 2010 and GBD 2013 is 0.97" (Forouzanfar et al., 2015). However, environmental risks have a discrepancy of almost 100 million DALYs between the 2010 and 2013 estimates for the year 1990 (see Table 1). Whether this difference can be attributed to more scientific evidence of diseases related to the environment is hard to understand. DALYs related to occupational diseases seem to have been revised downward in the 2013 estimates, with an almost 10 million DALYs difference in the estimates for 1990, and an almost 7 million DALYs reduction between 2010 and 2013 estimates for 2010/13 –which, given the differences in previous years' estimates, makes it impossible to understand whether this can be attributable to improvement in prevention or not. Yet as both studies provide uncertainty intervals, the range of reported values partly overlap.

DALYs attributable to occupational and environmental risk factors				
CRA itineration	Occupational risks		Environmental risks	
	1990	**2010/13**	**1990**	**2010/13**
2010 CRA	55 141 000 (45 312 000-66 718 000)*	62 488 000 (2010) (49 471 000-76 240 000)	312 460 000**	223 491 000** (2010)
2013 CRA	43 879 000 (35 819 000-52 859 000)	55 352 000 (2013) (44 589 000-67 890 000)	400 345 000 (374 489 000-424 432 000)	289 517 000 (2013) (265 778 000-312 094 000)

* U.I.: Uncertainty Interval ** Number composed by authors following 2013 methodology, no U.I. available[13]

Table 1. DALYs attributable to occupational and environmental risk factors in the 2010 and 2013 CRA. *Source: Lim.S et al. 2012. "A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010". The Lancet, 2012, 380: 2240-60; Forouzanfar et al. 2015. "Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013" The Lancet, 2015, 386: 2287-2323.*

The 2015 CRA (published in 2016) introduced yearly updates on the estimates of burden of disease attributable to risk factors. The 2015, 2016, and 2017 CRA updates will be analyzed

[13] Environmental Risks clustered as a larger class were introduced in the 2013 methodology. For comparison purpose, the DALYs from the sub-classes that are clustered under "environmental risks" in the 2013 CRA were added together to obtain the numbers for environmental risks reported above.

together, as their structure of analysis and development remained similar. Moreover, they retain some structural difference between the above-analyzed 2010 and 2013 CRAs: these "new generation" of CRA did not report changes in DALYs since 1990, but instead in 10-year periods (so 2005-15, 2006-16, and 2007-17 respectively). A Summary Exposure Value (SEV) was introduced which allowed "comparisons over time and across place for dichotomous, polytomous, and continuous risks" (Forouzanfar et al., 2016). SEVs are calculated for each risk factor and for each age, sex, location, year, and outcome. It is presented as a value from 0 to 100%, indicating the "relative risk-weighted prevalence of exposure" for a given population – 0% being "no excess risk for a population", and 100% indicating "when the population is at the highest level of risk".

$$SEV = \frac{\sum_{i=1}^{n} Pr_i RR_i - 1}{RR_{max} - 1}$$

Where Pr i is prevalence of category i exposure, RR i is relative risk of the category i, and RR max is the maximum relative risk observed (between categories).

Equation 3. General form of Summary Exposure Value (SEV) equation
Source: Forouzanfar et al. 2016. "Global, regional, and national comparative risk assessment of 79 behavioral, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015". The Lancet, 2016, 388: 1659–724.

Annex 4 compares the summary exposure value (SEV) for each of the reports where the measurement is available. It is still unclear how much it adds to the interpretation of the attributable deaths and DALYs described below, as well as their important changes over time. Annex 5 further compares the difference CRAs considered in our report in terms of risk factors analyzed, attributable DALYs, and sources of data.

Table 2 presents an overview of the changes in estimates which happened between these three yearly updates on all possible comparable grounds regarding occupational and environmental risks. It notably shows a drastic drop in deaths attributed to occupational carcinogens between the 2016 and 2017 CRA (falling from 746 540 to 334 000). Tracing a common thread between these and the previous CRA analysis is rather complicated–most likely by design, which specifically imposes the impossibility of comparison with preceding studies. Little can be said in light of comparison between the three estimation, which in some cases present notable differences between subsequent years–no clear explanation can be given for these changes, as estimates are not supposed to be compared. The complex, and computationally intensive estimation method through which these numbers are derived makes it increasingly difficult in these last three exercises to pinpoint the differences which might have created different results.

For instance, Table 3 suggests an important progression in data representation for occupational risks, especially looking at the DRI and related meta-analysis for carcinogens. The DRI specifies that the 2017 CRA was allegedly able to collect at least some data for almost every country analyzed. DRI however should be interpreted in the light of the actual data chosen as proxy to exposure. For example, the GBD 2015, authors acknowledge that they used "the proportion of the population in coarse occupational categories as a proxy for exposure to specific carcinogens". The 2015 analysis also included a report on the available

epidemiological evidence for the analyzed risk factors[14]. A total of 270 studies were considered for all occupational risk factors observed in 2015, and 315 for 2016 (Forouzanfar et al., 2016; Gakidou et al., 2017). The same number is not available for the 2017 CRA. Differently from the 2010 GBD, while the studies above represent the prospective observational studies explaining the association between the risk factor and the health outcome, no exact study was cited from which relative risks were derived or extracted. The appendix of 2015 CRA report states that "Details and citation information for the data sources used for relative risks are provided in searchable form through a new web-tool (http://ghdx.healthdata.org/)". This tool is still available but as for other searchable database, it provides only data used for the last GBD update (currently the 2019 itineration) so that the lists of specific studies inputted in the course of previous itineration are not readily available anymore.

The effort to update estimates yearly is justified by authors by the ambition to feed future policy-making. However, the CRA still remains a complex report, where information on availability, completeness and fitness-for-purpose of input data is difficult to untangle, when it comes to examine specific risk factors that make up the larger clusters. Based on the metrics tailored for the purpose of the study - typically DRI – and considering its results in isolation would give the impression that the analysis paints an almost complete picture of health burden due to occupational and environmental risks. Its strength stands in the seemingly extensive analysis which the CRA is able to achieve at a global scale, however making it impossible to compare to other studies.

[14] The table with the number of studies considered for occupational and environmental risks can be found at (Forouzanfar et al., 2016, pp. 1666–1667) for the 2015 CRA and (Gakidou et al., 2017, pp. 1349–1350) for the 2016 CRA No table is available for 2017.

Deaths and DALYs attributable to occupational and environmental risk factors						
	2015 CRA		**2016 CRA**		**2017 CRA**	
Period specific to CRA	**2005**	**2015**	**2006**	**2016**	**2007**	**2017**
Deaths						
By all environmental risks						
Unsafe water, sanitation, and handwashing	2 179 000	1 466 000	2 213 210	1 660 770	1 990 000	1 610 000
Air pollution (all causes)	6 466 000	6 485 000	6 219 850	6 116 400	4 630 00	4 900 000
Other environmental risks (residential radon & lead exposure)	514 000	558 000	518 270	597 740	929 000	1 140 000
By all occupational risks						
All occupational risks	951 000	1 086 000	1 409 600	1 528 020	1 090 000	1 160 000
Occupational carcinogens	391 000	489 000	628 390	746 540	217 000	334 000
Occupational Injuries	189 000	204 000	352 960	335 710	348 000	304 00
DALYs						
By all environmental risks						
Unsafe water, sanitation, and handwashing	129 221 000	95 305 000	118 178 240	75 769 040	120 000 000	84 400 000
Air pollution (all causes)	186 850 000	167 290 000	188 446 120	162 795 900	158 000 000	147 000 000
Other environmental risks (residential radon & lead exposure)	10 400 000	10 673 000	14 319 520	15 128 920	23 500 000	26 400 000
By all occupational risks						
All occupational risks	55 835 000	63 615 000	68 543 890	75 925 430	58 800 000	63 700 000
Occupational carcinogens	8 109 000	9 832 000	17 462 680	20 682 730	5 600 000	6 750 000
Occupational Injuries	12 212 000	13 492 000	21 906 210	21 774 600	22 700 000	21 100 000

Table 2. Deaths and DALYs attributable to occupational and environmental risks for 2015, 2016, and 2017 CRAs.
Source: table made by the authors, data obtained from respective 2015, 2016, and 2017 Comparative Risk Assessment publications cited above.

Data Representative Index for environmental and occupational risks (DRI reported for level 2 risk groups, and level 3 for occupational risks)												
DRI (the period is specific to each CRA)	**CRA 2013**			**CRA 2015**			**CRA 2016**			**CRA 2017**		
	<1998	**2006-2013**	**Total**	**<2005**	**2005-2015**	**Total**	**<2006**	**2006-2016**	**Total**	**<2007**	**2007-2017**	**Total**
Unsafe water, sanitation, and handwashing	59%	60.6%	80.3%	73.2%	60.6%	78.8%	58%	75.4%	70%	80.3%	63.7%	82.4%
Air pollution (all causes)	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Other environmental risks (residential radon & lead exposure)	34%	26.6%	49.5%	44.9%	40.9%	47%	48.7%	26.2%	51.8%	47.2%	30.1%	48.7%
Occupational Risks	56.4%	55.3%	72.3%	94.4%	93.4%	94.4%	92.3%	90.8%	100%	100%	100%	100%
Occupational carcinogens	34%	51.6%	62.8%	94.4%	93.4%	94.4%	86.7%	85.6%	92.8%	100%	100%	100%
Occupational injuries	5.3%	18.6%	20.7%	24.2%	32.3%	35.4%	82.6%	75.4%	87.2%	88.1%	82.9%	92.2%

Table 3. Data Representative Index (DRI) for environmental and occupational risks for 2013, 2015, 2016, and 2017 CRAs.
Source: table made by the authors, data obtained from respective 2015, 2016, and 2017 Comparative Risk Assessment publications cited above.

The CRA as a policy assessment tool: shortcomings and reflections on future developments

In the conclusion of the volume dedicated to the GBD of this same review, the reproductibility and comprehensiveness of the study are highlighted–the same observations remain true for the CRA methodology, which relies heavily on modelling and the interpolation of missing data. Rather than focusing on these critiques, we will focus these concluding remarks on the significance of these findings on global public health policy and address the CRA's lacunae in being an effective tool for guiding it.

The Comparative Risk Assessment's seems at times overlooked within the GBD study even if its implications and significance are central to the findings of the project. The development of a measurement which estimates the risk factors of every disease and sequelae could arguably be seen as even more meaningful for health policy than the actual estimation of DALYs, possibly giving policymaker precise factors to target in order to reduce health risks. Moreover, looking at the detailed geographical granularity (e.g. country level) which the latest publications delve into could give the possibility of developing very targeted solutions.

While trying to understand the findings detailed in each CRA, the non-comparative nature of the work does let to wonder how improvements from the previous enumeration can be precisely quantified. If both the estimation method and estimates change at every update, it becomes hard to understand whether these fluctuations are due to the methodology or a change in risk factors' impact. Every new edition of the study re-calculates the risks and numbers for the whole (10-year) period, making it hard to understand health progress due to successful public policies. Summary tables presented in this working paper try to put in comparison some numbers from all CRAs; this last exercise is precisely unrecommended by the GBD authors (as the findings of every new publication are meant to replace former ones); but considering the relatively frequent publication of these results, it seems right to ponder what the effects of constantly changing values might mean for policymakers. For example, the estimated DALYs for occupational risk factors (Table 2) were 68 543 890 (60 461 380 to 77 147 090) in 2006 and 75 925 430 (66 060 970 to 86 257 100) ten years later, according to the 2016 CRA (Gakidou et al., 2017). The 2017 CRA estimates re-calibrated their numbers, now attributing to the same risk 59 800 000 DALYs (52 300 000 to 68 100 000) in 2007 and 63 700 000 (54 900 000 to 73 200 000) in 2017 (Stanaway et al., 2018). The magnitude of change is actually quite substantial, surpassing in both cases the uncertainty intervals of the previous estimates. Risk factor analysis can have incredibly important implications for understanding health priorities, especially since the study has started to also look at mental health issues: these estimates could guide policymakers in areas which remain underestimated in their impact on population's health. However, the purpose of the work as it is, with continuously changing estimates, seems to be restricted to the IHME's own endeavour. It could be argued that the studies' main purpose is precisely to put under the limelight health risks and burdens neglected by public health policy, however this is in contradiction with the GBD's actually observed influence, where findings of the IHME are often taken as a point of departure in the development of policy agendas, especially in North America (Devin, 2019; Leach-Kemon & Redford, 2018; McKee, 2019a, 2019b). This has proven to be especially true even during the COVID-19 crisis, when the IHME's pandemic models were often used for policy development and Cristopher Murray appeared often weighting in for future possible solutions (Achenbach & Cha, 2020; Brennan, 2020; Mandavilli, 2020; Murray, 2020).

In the latest estimates published (2017) 1.21 billion (uncertainty interval 1.14–1.28) DALYs were attributable to risk the factors included (Stanaway et al., 2018). It is hard to understand the actual impact which these findings might have had in the past years in the development of policies, as the study drives away from giving any type of recommendations. If the GBD intends to influence future health policy, however, the continuous changing nature of each estimate must be given some better explanation, and this still remains a major weakness of the work. With particular attention to occupational risks, for which estimated DALYs could significantly change occupational health policies, policymakers need clear explanation for such significant gaps between years. At the 2019 International Society for Environmental Epidemiology congress (ISEE 2019) staggeringly different numbers (10 times higher than those defined by the GBD of the same year) in the estimation of lead-related cardio-vascular diseases (CVD) deaths in the US were presented (Lanphear et al., 2018). This example, while perhaps specific, illustrates that there still remains uncertainty within the scientific community in the validity of the GBD. It remains unclear whether the IHME regards these differences as either simple methodological discrepancies, or as red flags of the heavy use of statistical modelling in order to produce estimates. Either way, such gaps cannot pass unaddressed, both from the IHME and the institutions which sponsor their results.

Finally, the continuous introduction of new metrics makes it difficult to track or properly understand their validity, especially as they are usually developed *ad hoc*. Establishing the validity of the conclusion which these indices suggest proves to be hard with no precedent evidence available. Most importantly, extracting methodological information from the CRA reports is an incredibly complex task, and while the research is thorough in its analysis, even understanding some critical conclusions such as the representativeness of data within the observed results is hard. Given the intrinsically long policy process of tackling these risk factors, it seems complicated to keep up with the publication of these results while understanding the pace of progress when values constantly change. Certainly, more insight would be needed into the rationale for putting so much effort in providing yearly updates. It is also to be questioned if this comes at the cost of leaving behind improvements of some computational modules (and their related assumption) in order to provide more robust figures even if more spaced in time. The amount of evidence which needs to be revised yearly in order for the studies to go through the usual process of peer-reviewing, especially given the very short period of time available, still remains an issue when considering results, and it is still unclear how the GBD project plans to update its estimates yearly on statistics that most national agencies do not provide with the same cadence–making the GBD and CRA necessarily always more reliant on modelling for creating estimates.

The CRA endeavour is still relatively young, and the IHME's commitment to update estimates every year remains in its establishing phase. It could be that, as evidence builds up and the sources of information stabilize, that estimates too will tend to fluctuate less. The CRA then has an opportunity to develop a quantification of risks that is analysable for policy, offers reflections on improvements made by public health campaigns, and allows for a clearer understanding of changes in methodological approach.

But even in this best-case scenario, several difficulties will remain. First of all, as this report has shown, the quality of the data varies according to the selected risks and geographical areas, and there is a great risk of forgetting these weaknesses when using these global figures on a worldwide scale. Secondly, the figures are constructed in a totally different way from one year to another. This makes it difficult to carry out public policy evaluations over a long period

of time based on this instrument. Finally, IHME is increasingly in a monopoly situation to produce data of this scope and is itself largely controlled by a major player in global health policies (the BMGF). This raises a series of questions, beyond CRA, about its role in setting the global health agenda (Tichenor and Sridhar, 2019) that will need to be explored in greater depth in future work.

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

Environmental risks			
Risk Factors	Theoretical Minimum	Measured health outcome	Evidence (risk factor level, risk-disease relationship, and diseases burden)
Unsafe water, sanitation, and hygiene	No diarrhoea transmitted through water, sanitation or hygiene.	• Diarrhoea	• Risk factor level: 6 broad scenarios characterized from populations with water access which range from: no access to water & sanitation, full access to clean water & sanitation services, ideal scenario where no diseases burden is associated with risk factor. • Risk-disease relationship[15]: 88% of diarrhoeal diseases in the world attributable to unsafe water & sanitation. • Disease burden: 1.7 million deaths, 54.2 million DALYs worldwide. •Source: (World Health Organization et al., 2000)
Urban air pollution	7.5 µg/m^3 for PM 2.5 (presence of small particles that are smaller than 2.5 micrometres)	• Cardiovascular mortality • Respiratory mortality • Lung cancer • Mortality from acute respiratory infections in children	• Risk factor level: recent epidemiological studies identified severe health effects of combustion-derived health pollution in North America, Europe, Asia, Africa, and Latin America as cities expand. Association of air pollution from small particles is well documented to be independently related to lung cancer and other cardiopulmonary mortality. • Risk-disease relationship: Ambient air pollution causes: 5% of trachea, bronchus and lung cancer; 2% of cardiorespiratory mortality, and 1% of respiratory infections globally. • Disease burden: 0.8 million deaths, 7.8 million DALYs worldwide. • Source: (Health Effects Institute, 2001; Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society, 1996; Arden Pope & Dockery, 1999; Cohen & Pope, 1995; Krzyzanowsk & Schwela, 1999)
Indoor smoke from solid fuels	No solid fuel use	• Acute respiratory infections in children • Chronic obstructive pulmonary disease • Lung cancer	• Risk factor level: Human exposure to air pollutants is mostly driven by indoor environmental degradation. Cooking and heating are still dominated by burning of solid fuel, with 75% of people in India and between 50-75% of people in Latin American and Africa using it with limited ventilation. Exposure to indoor fossil fuel recorded globally regularly exceed WHO standard guidelines, being often a much bigger burden on health than outdoor air pollution. Studies consistently show a strong relationship between indoor solid fuel use and diseases. • Risk-disease relationship: indoor smoke from solid fuels causes: 35.7% of lower respiratory infections, 22% of chronic obstructive pulmonary diseases, 1.5% of trachea, bronchus and lung cancer. • Disease burden: 2.7% of DALYs worldwide (no total number of deaths reported in report). • Source: (Bornehag et al., 2001; Bruce et al., 2000; Smith, 2000; Smith et al., 2000; Spengler & Chen, 2000; Wargocki et al., 2002)
Lead exposure	0.016 µg/dl blood lead levels	• Cardiovascular disease • Mild mental retardation	• Risk factor level: Lead is present in air, soil, and water due to its vast use in the past and still today even after significant evidence of its adverse health effects. Industrial development has led to an increase in in environmental contamination worldwide, but substantial regulations have controlled its use everywhere. However, 120 million people worldwide are estimated to have levels of lead in their body that substantially surpass the theoretical minimum threshold. • Risk-disease relationship: Lead poisoning affects almost all body functions and systems, however the wide range of large health effects was newly observed at time of analysis–no direct relationships are reported or estimated. • Disease burden: 234 thousand deaths, 12.9 million DALYs worldwide. •Source: (Centers for Disease Control and Prevention (CDC), 2000; Kaiser et al., 2001; Ostrowski et al., 1999; Schwartz, 1994)
Climate change	1961–1990 concentrations (not specified)	• Diarrhoea • Flood injury • Malaria • Malnutrition	• Risk factor level: The 2001 IPCC estimated that global average land and sea level rises had increased at unprecedented speed, declaring climate change a worldwide health threat. 1990s were at the time the warmest decade on record, with warming observed in every continent,

[15] Definition of the risk-disease relationship refers to PAFs rather than RR.

			along with substantial changes in patterns of precipitation and extreme weather conditions. The IPCC had concluded that most of the excessive warming happened since the industrial revolution was likely due to human activities, and that every person would be affected in some way by climate change. Climate change models were used to simulate past, present, and future greenhouse gasses emissions, concluding that the likely rise of temperatures between 1990 and 2100 could be between 1.4-5.8 °C if not action were to be taken. • Risk-disease relationship: climate change was estimated to be responsible for: 2.4% of diarrhoea, 6% of malaria cases, 7% of dengue fever cases (no number reported on malnutrition). • Disease burden: 154 thousand deaths, 5.5 million DALYs worldwide. • Source: (International Panel on Climate Change, 2001; Parry et al., 1999)

Annex 2 - Summary of environmental risk factors analysis with reference studies.
Source: WHO 2002 World Health Report: Reducing Risks, Promoting Health Life.

Occupational risks			
Risk Factors	Theoretical Minimum	Measured health Outcome	Evidence (risk factor level, risk-disease relationship, and diseases burden)
Work-related risk factors for injuries	Lowest rate of work-related fatalities observed: 1 per million per year for 16–17-year-olds employed as service workers in the United States	• Injury	• Risk factor level: Every workplace presents risk of injuries, with industrial and agricultural workers exposed to the highest levels. Falls, accidents, motor vehicle, and contact with machinery all fall under this category. Number of works at risk of injury were estimated by employment using broad occupational categories, subdivided by region, sex, and age. Literature survey allowed to obtain injury rates. Both intentional and unintentional injuries and deaths were taken in review. • Risk-disease relationship: no direct numbers reported due to the nature of analysis. • Disease burden: 310 thousand deaths, 13.1 million DALYs worldwide (population age 15-69). • Source: (T. Driscoll et al., 2001; R. Loewenson, 1999; National Institute for Occupational Safety and Health, 2000; *Work, Health and Safety*, 1995)
Work-related carcinogens	No work-related exposure to chemical or physical agents that cause cancer above background	• Leukaemia • Lung Cancer	• Risk factor level: More than 150 chemical or biological agents encountered in occupational settings were classified as carcinogen. Potency, dose received, other prevalent exposures (e.g. tobacco consumption), and individual susceptibility were all taken into consideration in the influence analysis. • Risk-disease relationship: Occupational exposure accounts for: 10.3% of lung, trachea, and bronchus cancer; 2.4% of leukaemia cases. • Disease-burden: 146 thousand deaths, 1.4 million DALYs worldwide. Source: (World Health Organization, 2001)
Selected airborne particulates	No work-related exposure	• Chronic respiratory disease	• Risk factor level: Mining, construction and other manufacturing jobs are highly exposed to microparticles of asbestos, silica, and coal dust. Inhalation of these particles is now well known to cause a variety of respiratory diseases and disorders. Development of diseases and their severity is influenced by the amount of exposure, with diseases characterized by long latency periods–this means that disease rates decline gradually slowly. • Risk-disease relationship: occupational exposure could account for: 5-18% of asthma, 14% of chronic obstructive pulmonary disease. • Disease burden: 243 thousand deaths, 3 million DALYs worldwide. • Sources: (Center for Disease Control and Prevention (CDC), 2000; Chen et al., 2001; Rene Loewenson, 2001; National Institute for Occupational Safety and Health, 2002)
Work-related ergonomic stressors	Physical workload at the level of that of managers and professionals	• Lower-back pain	• Risk factor level: ergonomic stressors in work-related environment are virtually present in all professions. Lower-back pain, while rarely fatal, is a major cause of loss of quality of life, and are reported not only in particularly physically demanding jobs (such as farming, or heavy equipment operators) but in nurses as well. Occurs similarly in industrialized and developing countries. • Risk-disease relationship: work-related ergonomic stressors could account for 37% of reported back pain worldwide. • Disease burden: lower-back pain is rarely fatal but caused 0.8 million DALYs worldwide. • Sources: (Bernard, 1997; Force, 1989; Jin et al., 2000; Leigh & Sheetz, 1989; Nachemson, 1985; National Research Council (US) and Institute of Medicine (US) Panel on Musculoskeletal Disorders and the Workplace, 2001)
Work-related noise	Less than 85 dB over eight working hours	• Hearing loss	• Risk factor level: Excess noise is one of the most common occupational hazards found, with exposure to noises over 85 dB considered to alter workers' hearing at the frequency of human voices, significantly impairing spoken communication. Hearing loss is defined at 41dB for 500,1000, 2000, and 4000 Hz. • Risk-disease relationship: based on this definition of hearing loss, 16% of it is attributable to work-related noise worldwide.

			• Disability burden: while hearing loss rarely induces death, it accounted for 415 thousand DALYs. Occupational noise was responsible for 4.2 million DALYs worldwide. • Sources: (European Agency for Safety and Health at Work, 2000; Goelzer et al., 2001; National Institute for Occupational Safety and Health (NIOSH), 2001).

Annex 3 - Summary of occupational risk factors analysis with reference studies.
Source: WHO 2002 World Health Report: Reducing Risks, Promoting Health Life.

Summary Exposure Value (SEV, %) for each environmental and occupational risks (Uncertainty Intervals not included)												
CRA itineration	**GBD2015**				**GBD2016**				**GBD2017**			
Sex	**Male**		**Female**		**Male**		**Female**		**Male**		**Female**	
Period	**1990**	**2015**	**1990**	**2015**	**1990**	**2016**	**1990**	**2016**	**1990**	**2017**	**1990**	**2017**
Environmental risks												
Unsafe sanitation	55%	33.7%	54.2%	33.7%	56.46%	33.26%	55.13%	33.34%	58.1%	29.88%	57.19%	30.28%
Lead exposure	19.4%	15.7%	17.5%	14.5%	20%	15%	10.27%	8.37%	15.65%	11.14%	9.56%	7.15%
Residential radon	14.7%	15.6%	14.8%	15.8%	26.12%	26.17%	26.27%	26.34%	23.73%	23.68%	23.72%	23.66%
Unsafe water source	62.1%	56%	61.1%	55.7%	23.27%	20.08%	22.94%	20.04%	43.22%	33.57%	42.46%	33.87%
No handwashing with soap	84.3%	77.1%	83.9%	76.9%	36.22%	33.13%	35.82%	33.34%	37.81%	31.51%	37.33%	33.05%
Ambient particulate matter pollution	46.4%	48.9%	45.5%	48%	44.42%	49.56%	43.79%	48.87%	30.08%	41.9%	26.83%	38.48%
Ambient ozone pollution	38.5%	48.2%	38.2%	47.4%	38.49%	48.75%	38.22%	47.94%	41.72%	42.89%	41.25%	42.58%
Household air pollution from solid fuels	23.2%	16%	29.3%	20.6%	34.05%	18.95%	35.67%	20.69%	45.57%	31.57%	46%	25.67%
Occupational risks												
CRA itineration	**GBD2015**				**GBD2016**				**GBD2017**			
Sex	**Male**		**Female**		**Male**		**Female**		**Male**		**Female**	
Period	1990	2015	1990	2015	1990	2016	1990	2016	1990	2017	1990	2017
Exposure to asbestos	2.5%	2.4%	0.9%	0.8%	4.11%	3.9%	1.47%	1.19%	2.67%	2.36%	0.98%	0.74%
Exposure to arsenic	0.3%	0.3%	0.1%	0.1%	0.91%	1.02%	0.72%	0.88%	0.32%	0.34%	0.29%	0.31%
Exposure to benzene	1.3%	1.9%	0.6%	1.2%	0.77%	0.96%	0.65%	0.94%	0.54%	0.65%	0.51%	0.68%
Exposure to beryllium	0.1%	0.1%	0.1%	0.1%	0.09%	0.11%	0.07%	0.09%	0.06%	0.07%	0.05%	0.07%

Occupational risks												
CRA itineration	**GBD2015**				**GBD2016**				**GBD2017**			
Sex	**Male**		**Female**		**Male**		**Female**		**Male**		**Female**	
Period	**1990**	**2015**	**1990**	**2015**	**1990**	**2016**	**Period**	**1990**	**2015**	**1990**	**2015**	**1990**
Exposure to cadmium	0.3%	0.4%	0.1%	0.1%	0.18%	0.22%	0.13%	0.19%	0.13%	0.15%	0.11%	0.14%
Exposure to chromium	1.3%	1.4%	0.6%	0.6%	0.38%	0.50%	0.28%	0.42%	0.27%	0.34%	0.23%	0.30%
Exposure to diesel engine exhaust	6.7%	11.5%	1.5%	3.5%	2.29%	3.11%	1.22%	1.86%	1.51%	2.07%	0.94%	1.25%
Exposure to formaldehyde	1.1%	1.1%	0.6%	0.6%	0.79%	1.01%	0.57%	0.80%	0.59%	0.71%	0.49%	0.60%
Exposure nickel	0.9%	1%	0.4%	0.4%	1.60%	1.75%	1.07%	1.27%	0.35%	0.36%	0.28%	0.28%
Exposure to hydrocarbons	1.6%	2.2%	0.6%	0.8%	0.80%	1.05%	0.58%	0.86%	0.55%	0.70%	0.48%	0.62%
Exposure to silica	6.6%	11.3%	1.3%	1.8%	5.76%	6.21%	3.11%	3.29%	3.71%	4.05%	2.50%	2.32%
Exposure to sulphuric acid	1.4%	1.6%	0.5%	0.6%	0.93%	1.03%	0.68%	0.83%	0.65%	0.69%	0.58%	0.61%
Exposure to trichloro-ethylene	0.5%	0.5%	0.2%	0.2%	0.22%	0.30%	0.16%	0.24%	0.16%	0.20%	0.13%	0.17%
Exposure to asthamgens	30.2%	23.6%	17.3%	17.1%	23.14%	23.97%	10.7%	13.39%	16.13%	15.39%	8.50%	8.04%
Exposure to particulate matter	23.4%	23.2%	13.3%	13%	12.28%	12.60%	5.59%	6.49%	8.45%	8.48%	5%	5.20%
Exposure to occupational noise	42.5%	40.5%	25.2%	24.4%	16.38%	16.21%	7.11%	8.45%	8.6%	8.91%	5.21%	5.74%
Occupational injuries	-	-	-	-	-	-	-	-	-	-	-	-
Occupational ergonomic factors	30.2%	23.6%	17.3%	17.1%	24.56%	23.44%	12.46%	15.15%	17.09%	14.71%	11.25%	9.65%

Annex 4 - Summary Exposure Values (SEV) for occupational and environmental risks analyzed in 2015, 2016, and 2017 CRA.
Table made by authors. Sources: Forouzanfar al.., 2016. Gakidou et al., 2017. Stanaway et al., 2018.

Complete summary of Comparative Risk Assessment from 1999 to 2017				
	1999 CRA	**2002 CRA**	**2004 CRA**	**2010 CRA**
Risks analyzed	10 risk factors: • Malnutrition • Poor water and hygiene • Unsafe sex • Occupation • Alcohol • Hypertension • Physical inactivity • Illicit drugs • Air pollution • Tobacco	26 risk factors, divided in 7 categories: 1. Childhood and maternal undernutrition 2. Other diet-related risks and physical inactivity 3. Sexual and reproductive health risks 4. Addictive substances 5. Environmental risks • Unsafe water, sanitation and hygiene • Urban air pollution • Indoor smoke from solid fuels • Lead exposure • Climate change 6. Occupational risks Risk factors for • Injury • Carcinogens • Airborne particulates • Ergonomic stressors • Noise 7. Other selected risks to health	24 risk factors divided in 7 categories (same as 2002 CRA)	67 risk factors subdivided into 10 categories: 8. Unimproved water and sanitation 9. Air Pollution 10. Other environmental risks 11. Child and maternal undernutrition 12. Tobacco smoking, including second-hand smoke 13. Alcohol and drug use 14. Physiological risk factors 15. Dietary risk factors and physical inactivity 16. Occupational risk factors (18 separate risks, 13 separate carcinogens exposures analysed[16]) 17. Sexual and abusive violence
DALYs lost due to occupational and environmental risks	Occupation 37 900 000 (occupation)	Occupational risk 22 553 000	Occupational risks 26 667 000	Occupational risks 55 414 000 (1990 estimates) 62 488 000 (2010 estimates)
	Poor water and hygiene 93 400 000 (air pollution not enumerated in DALYs)	Environmental risks 119 005 000	Environmental risks 128 377 000	Air pollution (aggregated by author) 254 926 000 (1990) 186 703 000 (2010)
				Unimproved water and sanitation 52 169 000 (1990 estimates) 21 187 000 (2010 estimates)
				Other environmental risks 5 365 000 (1990) 16 051 000 (2010)
Sources	(Murray & Lopez, 1999, p. 603)	(World Health Organization, 2002, p. 228,229)	(World Health Organization, 2009, p. 52 (Annex A))	(Lim et al., 2012, pp. 2241–2242) For specific relative risks (Lim et al., 2012, pp. 2231-2233 (occupational risks) 2227 (environmental risks))

[16] For simplicity and space, they are not enumerated in the table. For a complete enumeration of all carcinogens and occupational risks analysed, consult (Lim et al., 2012, pp. 2232–2233)

	2013 CRA	2015 CRA	2016 CRA	2017 CRA
Risks analyzed	79 different risks divided in 3 level hierarchy Level 1: behavioural, environmental and occupational, and metabolic risks levels 2: 13 sgroups Unsafe water, sanitation, and handwashing Air pollution Occupational risks (14 level 3 risks) Child and maternal malnutrition Tobacco smoke Alcohol and drug use Dietary risks Sexual abuse and violence Unsafe sex Low physical activity	79 different risks (same hierarchy as 2013 CRA)	84 different risks (same hierarchy as 2013 CRA)	84 different risks (same hierarchy as 2013 CRA)
DALYs lost due to occupational and environmental risks (UI in parentheses)	Occupational risks 43 879 000 (35 819 to 52 859) (1990) 55 352 000 (44 589 to 67 890) (2013)	Occupational risks 55 835 000 (40 024 000 to 65 679 000) (2005) 63 615 000 (53 616 000 to 75 415 000) (2015)	Occupational risks 68 543 890 (60 461 380 to 77 147 090) (2006) 75 925 430 (66 060 970 to 86 257 100) (2016)	Occupational risks 59 800 000 (52 300 000 to 68 100 000) (2007) 63 700 000 (54 900 000 to 73 200 000) (2017)
	Air pollution: all causes 157 831 000 (145 269 000 to 171 007 000) (1990) 141 456 000 (130 071 000 to 153 652 000) (2013)	Air pollution: all causes 186 850 000 (164 716 000 to 209 142 000) (2005) 167 290 000 (148 167 000 to 185 780 000) (2015)	Air pollution: all causes 186 446 120 (170 917 710 to 200 934 770) (2006) 162 795 900 (150 578 260 to 175 615 700) (2016)	Air pollution: all causes 158 000 000 (142 000 000 to 172 000 000) (2007) 147 000 000 (132 000 000 to 162 000 000) (2017)
	Unsafe water, sanitation, and handwashing 190 423 000 (174 685 000 to 208 033 000) (1990) 83 867 000 (72 879 000 to 95 568 000) (2013)	Unsafe water, sanitation, and handwashing 129 221 000 (116 430 to 142 602) (2005) 95 305 000 (85 818 to 105 821) (2015)	Unsafe water, sanitation, and handwashing 118 178 240 (99 042 42 to 141 176 50) (2006) 75 796 040 (61 906 38 to 93 460 54) (2016)	Unsafe water, sanitation, and handwashing 120 000 000 (103 000 000 to 138 000 000) (2007) 84 400 000 (71 800 000 to 102 000 000) (2017)
	Other environmental risk factors 17 015 000 (12ì 567 000 to 22 173 000) (1990) 18 822 000 (13 300 000 to 25 407 000) (2013)	Other environmental risk factors 10 400 000 (5 470 000 to 16 412 000) (2005) 10 673 000 (55 160 000 to 16 975 000) (2015)	Other environmental risk factors 14 319 520 (84 961 800 to 21 426 170) (2006) 15 128 920 (88 91 770 to 22 939 090) (2016)	Other environmental risk factors 23 500 000 (16 500 000 to 30 600 000) (2007) 26 400 000 (18 400 000 to 34 800 000) (2017)
Sources	(Forouzanfar et al., 2015, pp. 2302–2303)	(Forouzanfar et al., 2016, pp. 1677–1681)	(Gakidou et al., 2017, pp. 1374–1380)	(Stanaway et al., 2018, pp. 1940–1945)

Annex 5 - Risk factors analyzed, attributable DALYs, and sources of data for all CRA analyzed in the working paper.
Table made by authors. Specific sources for data cited in the table.

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