

# Selected major risk factors and global and regional burden of disease

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## Summary

**Background** Reliable and comparable analysis of risks to health is key for preventing disease and injury. Causal attribution of morbidity and mortality to risk factors has traditionally been in the context of individual risk factors, often in a limited number of settings, restricting comparability. Our aim was to estimate the contributions of selected major risk factors to global and regional burden of disease in a unified framework.

**Methods** For 26 selected risk factors, expert working groups undertook a comprehensive review of published work and other sources—eg, government reports and international databases—to obtain data on the prevalence of risk factor exposure and hazard size for 14 epidemiological regions of the world. Population attributable fractions were estimated by applying the potential impact fraction relation, and applied to the mortality and burden of disease estimates from the global burden of disease (GBD) database.

**Findings** Childhood and maternal underweight (138 million disability adjusted life years [DALY], 9.5%), unsafe sex (92 million DALY, 6.3%), high blood pressure (64 million DALY, 4.4%), tobacco (59 million DALY, 4.1%), and alcohol (58 million DALY, 4.0%) were the leading causes of global burden of disease. In the poorest regions of the world, childhood and maternal underweight, unsafe sex, unsafe water, sanitation, and hygiene, indoor smoke from solid fuels, and various micronutrient deficiencies were major contributors to loss of healthy life. In both developing and developed regions, alcohol, tobacco, high blood pressure, and high cholesterol were major causes of disease burden.

**Interpretation** Substantial proportions of global disease burden are attributable to these major risks, to an extent greater than previously estimated. Developing countries suffer most or all of the burden due to many of the leading risks. Strategies that target these known risks can provide substantial and underestimated public-health gains.

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## Introduction

Detailed descriptions of the magnitude and distribution of diseases and injuries, and their causes are important inputs to strategies for improving population health. Much work has focused on the quantification of mortality patterns and, more recently, on burden of disease.<sup>1,2</sup> Data on disease or injury outcomes alone, such as death or admission to hospital, tend to focus on the need for palliative or curative services. Reliable and comparable analysis of risks to health, however, is key for preventing disease and injury. Analysis of morbidity and mortality due to risk factors has frequently been done in the context of methodological traditions of individual risk factors and in a limited number of settings.<sup>3–10</sup> As a result, most such estimates have been made relative to an arbitrary, constant level of population exposure, without standardisation of the baseline exposure across risk factors. For example, the implicit baseline for much of the estimates of occupational disease and injuries has been “no work”. Furthermore, the criteria for assessment of scientific evidence on prevalence, causality, and hazard size have varied greatly across risk factors, resulting in lack of comparability of estimated population health effects. Finally, the outcome of such estimates has been morbidity or mortality due to specific disease(s), making comparison among different risk factors difficult.

To assess risk factors in a unified framework, while acknowledging risk-factor specific characteristics, the Comparative Risk Assessment module of the global burden of disease (GBD) 2000 study has been set up as a systematic assessment of the changes in population health, which would result from modifying the population distribution of exposure to a risk factor or a group of risk factors.<sup>11</sup> This unified framework for describing population exposure to risk factors and their consequences for population health is an important step in linking the growing interest in the causal determinants of health across various public-health disciplines from natural, physical, and medical sciences to the social sciences and humanities.

In addition to the above disciplinary obstacles and divisions, analysis of population health in a risk-based approach requires a framework for selection of risk factors among distal—eg, poverty or inequality—proximal and environmental—eg, air pollution or diet—and physiological—eg, blood pressure, HIV-1 as risk factor for tuberculosis—determinants of health.<sup>11,12</sup> Our aim was to develop such a framework by selecting risk factors in various levels of causality. Although gaps in epidemiological research on multiple layers of causality and risk-factor interactions would not allow inclusion of all inherently inter-related risk factors of interest, this selected group serves to emphasise the potential for disease prevention as a public-health tool.

The results of this work and additional background material are also presented in *World Health Report 2002*:

*Reducing Risk, Promoting Healthy Life* (available online at <http://www.who.int/whr>). *World Health Report 2002* further addresses interventions and policies to reduce risks.

## Methods

Mathers and colleagues<sup>12</sup> describe two models for causal attribution of health outcomes or states: categorical attribution and counterfactual analysis. In categorical attribution, an event such as death is attributed to a single cause (such as a disease or risk factor) or group of causes, according to a defined set of rules—eg, the International Classification of Disease (ICD) system for attribution of causes of death.<sup>13</sup> In counterfactual analysis, the contribution of one or a group of risk factors to disease or mortality is estimated by comparison of the current or future disease burden with the magnitude that would be expected in some alternative hypothetical scenario (referred to as the counterfactual), including the absence of, or reduction in, the disease(s) or risk factor(s) of interest.<sup>14</sup> In theory, causal attribution of the burden of disease to risk factors can be done with both categorical and counterfactual approaches. For instance, categorical attribution has been used in attribution of diseases and injuries to occupational risk factors in occupational-health registries<sup>4</sup> and attribution of motor vehicle accidents to alcohol consumption. Categorical attribution to risk factors, however, overlooks the fact that many diseases have multiple causes.<sup>15</sup> In the Comparative Risk Assessment project, the estimates of burden of disease and injuries due to risk factors are based on a counterfactual exposure distribution that would result in the lowest population risk, irrespective of whether currently attainable in practice, referred to as the theoretical minimum exposure distribution.<sup>11</sup> Use of theoretical minimum exposure distribution as the counterfactual has the advantage of providing a vision of potential gains in population health by risk reduction from all degrees of suboptimum exposure in a consistent way across risk factors.

Table 1 shows the selected group of risk factors included in the project. The criteria for selection of risk factors included: likely to be among the leading global or regional causes of disease burden; not too specific—eg, every one of the thousands of occupational chemicals—or too broad—eg, environment or food; high likelihood of causality based on scientific knowledge from different disciplines; availability of reasonably complete data on exposure and risk levels or methods for extrapolation when needed; potentially modifiable.

For each risk factor, an expert working group did a comprehensive review of published work and other sources (government reports, international databases, etc) to obtain data on the prevalence of risk-factor exposure and hazard size (relative risk or absolute hazard size when appropriate; table 1). This review included collection of primary data, several re-analyses of original data, systematic reviews, and meta-analyses. The criteria for use of the scientific evidence, to increase comparability while acknowledging the fundamental differences in exposure and hazard quantification across risk factors, included: increasing the equivalence between exposure and hazard measures, population representativeness of prevalence or hazard studies, study design and study quality, and minimising the effects of confounders.

Each expert working group compiled data separately for men and women, eight age groups (0–4, 5–14, 15–29, 30–44, 45–59, 60–69, 70–79, ≥80 years), and 14 epidemiological subregions of GBD 2000, which are

based on a combination of WHO regions and child and adult mortality rates, as described in the annexes of the annual *World Health Report* and summarised in panel 1. Data sources, models, and assumptions used for extrapolation of exposure or relative risk across countries or regions are described in detail for individual risk factors elsewhere.<sup>16</sup> Data and methods for each risk factor were anonymously peer-reviewed by external reviewers (more than 160 peer reviews plus multiple re-reviews as appropriate).

The contribution of a risk factor to disease or mortality (expressed as the fraction of disease or death,  $AF$ , attributable to risk factor in a population) is provided by the generalised potential impact fraction (panel 2; or its discrete version when exposure variable was categorical).<sup>17,18</sup>

Population attributable fractions obtained in this way estimate the percentage reduction in disease or death that would take place if exposure to the risk factor were reduced to the counterfactual distribution, with all other factors remaining the same. Because most diseases are caused by multiple factors, and because some risk factors act through other, more proximal factors, population attributable fractions for multiple risk factors for the same disease can add to more than 100%.<sup>15</sup> For example, some deaths from childhood pneumonia might have been prevented by removal of exposure to indoor smoke from solid fuels, childhood underweight, and zinc deficiency (which itself affects weight-for-age); or some of the cardiovascular disease events might be due to a combination of smoking, physical inactivity, and inadequate intake of fruits and vegetables (both acting partly through obesity, cholesterol, and blood pressure). Such instances would be attributed to all these risk factors. Although lack of additivity can initially seem problematic, multicausality offers opportunities to tailor prevention based on availability and cost of interventions.

For each risk factor-disease pair, population attributable fractions ( $AF$ ) for each of the 224 age, sex, subregion groups were calculated as shown in panel 2, separately for mortality ( $AF_M$ ) and incidence ( $AF_I$ ) when the relative risks for mortality and incidence were different. For each of these 224 groups, the estimates of mortality ( $AM_j$ ) and burden of disease ( $AB_j$ ) from disease  $j$  attributable to risk factor  $i$  were obtained (panel 3). Burden of disease, reported annually in the annexes of the *World Health Report*, was expressed in disability-adjusted-life-years (DALY) with methods and assumptions described elsewhere.<sup>19</sup>

For risk factors for which a relative risk model was not appropriate—eg, occupational or alcohol-caused injuries or effects of lead exposure on blood pressure—disease, injury, or mortality was estimated with existing registers and corresponding hazard relations.

The theoretical minimum exposure distribution was zero in most instances, since zero exposure indicated minimum risk—eg, no smoking. For some risk factors, zero exposure was an inappropriate choice, either because it was physiologically impossible—eg, body-mass index (BMI) and cholesterol—or because there existed physical lower limits to exposure reduction—eg, ambient particulate matter concentration or occupational noise. For these risk factors, the lowest levels observed in specific populations and epidemiological studies were used to choose the theoretical minimum. For example, a theoretical minimum of 115 mm Hg for systolic blood pressure and 3.8 mmol/L for total cholesterol (each with a small SD), are the lowest concentrations at which the dose-response

Risk factor	Exposure variable	Theoretical minimum	Outcomes*	Sources for exposure estimates	Sources for hazard estimates
<b>Childhood and maternal undernutrition</b>					
Under-weight	Children <-1 SD weight-for-age compared with international reference group in 1 SD increments; maternal BMI <20 kg/m <sup>2</sup> ; children aged <5 years	Same fraction of children <-1 SD weight-for-age as international reference group; all women of childbearing age with BMI ≥20 kg/m <sup>2</sup>	Mortality and acute morbidity from diarrhoea, malaria, measles, pneumonia, and selected other group 1 diseases; perinatal conditions from maternal underweight; <i>long-term morbidity from undernutrition</i>	WHO Global Database on Child Growth and Malnutrition—based on systematic analysis of raw data from 310 nationally representative nutritional (anthropometry) surveys in 112 countries	Childhood underweight: re-analysis of 10 cohort studies for mortality to obtain hazard in 1 SD increments, and systematic review and new meta-analysis of existing cohort studies for morbidity; maternal underweight: systematic review and meta-analysis of existing cohort studies
Iron deficiency	Haemoglobin concentrations (g/dL) estimated from prevalence of anaemia	Haemoglobin distributions that halve anaemia prevalence, estimated to occur if all iron deficiency were eliminated†	Anaemia and its sequelae (including cognitive impairment), maternal and perinatal mortality	WHO anaemia database from population-based studies of haemoglobin concentration	Systematic review and new meta-analysis of cohort studies
Vitamin A deficiency	Prevalence of vitamin A deficiency, estimated as low serum retinol concentrations (<0.70 mmol/L) among children aged <5 years and among pregnant women (aged 15–44 years)	No vitamin A deficiency	Mortality due to diarrhoea, measles, malaria, and miscellaneous infectious causes of disease (children <5), morbidity due to malaria (children <5), maternal mortality (pregnant women), vitamin A deficiency and its sequelae (all age groups); <i>maternal morbidity, low birthweight, and other perinatal conditions</i>	Comprehensive review of data from multiple sources, including WHO and Micronutrient Initiative summary reports, journal articles, published and unpublished survey reports (data available for 66 countries for children and 34 for pregnant women; for more than 90 other countries prevalence was zero or negligible based on indirect data)	Systematic review and new meta-analysis as well as re-analysis of randomised trials for childhood and maternal outcomes
Zinc deficiency	Less than the US recommended dietary allowances for zinc	Entire population consuming sufficient dietary zinc to meet physiological needs, taking into account routine and illness-related losses and bioavailability	Diarrhoea, pneumonia, malaria in children aged <5 years; <i>adult and pregnancy outcomes</i>	International Zinc Nutrition Consultative Group (IZINCG) method for estimating the prevalence of inadequate zinc intakes based on the presence and bioavailability of zinc in each country's food supply (from UN-FAO food balance sheets)	Systematic review and new meta-analysis as well as re-analysis of randomised trials
<b>Other nutrition-related risk factors and physical activity</b>					
High blood pressure	Level of systolic blood pressure	115 (SD 6) mm Hg	Ischaemic heart disease (IHD), stroke, hypertensive heart disease and other cardiovascular disease; <i>renal failure</i>	Systematic review of almost 200 studies with over 450 000 participants	Meta-analysis of 37 cohort studies with 425 000 individuals and 23 randomised trials of blood pressure lowering with 70 000 participants
High cholesterol	Concentration of total blood cholesterol	3.8 (SD 1) mmol/L	IHD, stroke; <i>other cardiovascular disease</i>	Review of 150 surveys with more than 630 000 participants	Meta-analysis of 10 cohorts with 490 000 North American and European participants, 29 cohorts with 350 000 participants from the Asia Pacific region, and 49 trials of cholesterol lowering
High BMI (overweight and obesity)	BMI (kg/m <sup>2</sup> )	21 (SD 1) kg/m <sup>2</sup>	IHD, stroke, hypertensive heart disease, diabetes, osteoarthritis, endometrial and colon cancers, post-menopausal breast cancer; <i>gallbladder cancer, kidney cancer, breathlessness, back pain, dermatitis, menstrual disorders and infertility, gallstones</i>	Full or part (ie, some age-sex groups) data from more than 66 countries on mean BMI or prevalence of overweight and obesity from published work, WHO and other reports, and unpublished data	Meta-analysis of 33 cohorts with 310 000 participants for vascular risks, 27 cohorts for cancer risks, and systematic review of other cohort studies for diabetes risks
Low fruit and vegetable intake	Fruit and vegetable intake per day	600 g (SD 50 g) intake per day for adults	IHD, stroke, colorectal cancer, gastric cancer, lung cancer, oesophageal cancer	Country-based food surveys for 26 countries in 9 subregions; for regions without food surveys, UN-FAO food balance sheet data combined with survey information from other regions on the age and sex distribution	Systematic review and new meta-analysis of published cohort studies

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Risk factor	Exposure variable	Theoretical minimum	Outcomes*	Sources for exposure estimates	Sources for hazard estimates
Physical inactivity	Three categories of inactive, insufficiently active (<2.5 h per week of moderate-intensity activity, or <4000 KJ per week), and sufficiently active. Activity in discretionary-time, work, and transport considered	All having at least 2.5 h per week of moderate-intensity activity or equivalent (4000 KJ per week)	IHD, breast cancer, colon cancer, diabetes; <i>falls and osteoporosis, osteoarthritis, lower back pain, prostate and rectal cancer</i>	Systematic review of published work, contacts with national government and non-governmental agencies and cardiovascular disease electronic list-servers to identify data on physical activity levels in three domains (occupation [8 countries], transportation [14 countries], leisure [50 countries]) plus an ecological model for prediction of the activity in the three domains in countries without data (model data from World Bank)	Systematic review of published literature and new meta-analysis of cohort studies
<b>Sexual and reproductive health</b>					
Unsafe sex	Sex with an infected partner without any measure to prevent infection (represented as parameters of an HIV model)	No unsafe sex	HIV/AIDS, sexually transmitted infections, and cervical cancer	UNAID Reference Group Epidemic Projection Model, fit to data from ante-natal clinics for high-HIV prevalence regions; sexual mixing model with surveys of high risk groups for low-HIV prevalence regions; by definition 100% of other STI was attributable to this risk factor	
Lack of contraception	Prevalence of traditional methods or non-use of contraception	Use of modern contraceptives for all women who want to space or limit future pregnancies	Maternal mortality and morbidity; <i>increased perinatal and child mortality</i>	Demographic and health survey (DHS) nationally representative surveys in 58 countries	DHS surveys for contraceptive failure rates and systematic review of published work for conception probabilities among non-users; WHO abortion database
<b>Addictive substances</b>					
Tobacco	Current degree of smoking impact ratio (indirect indicator of accumulated smoking risk based on excess lung cancer mortality); prevalence of oral tobacco use	No tobacco use	Lung cancer, upper aerodigestive cancer, all other cancers, chronic obstructive pulmonary disease (COPD), other respiratory diseases, all vascular diseases, and other medical causes in adults >30; <i>fire injuries, maternal outcomes and perinatal conditions</i>	WHO GBD lung cancer mortality database based on complete (about 70 countries) or partial (about 40 countries) vital registration and IARD estimates	ACS-CPS II prospective study of risk factors for mortality in more than one million Americans and retrospective proportional mortality study of one million deaths in 24 urban centres and 74 rural areas of China
Alcohol	Current alcohol consumption volumes and patterns	No alcohol use‡	IHD, stroke, hypertensive heart disease, diabetes, liver cancer, mouth and oropharynx cancer, breast cancer, oesophagus cancer, selected other cancers, liver-cirrhosis, epilepsy, alcohol use disorders, depression, intentional and unintentional injuries; <i>selected other cardiovascular diseases and cancers, social consequences</i>	WHO Global Status Report (including production and trade data) on average alcohol consumption; systematic review of country surveys on abstinence and levels of alcohol consumption, including contacting researchers for unpublished data; systematic review of published work and multiple regional expert consultation for unrecorded consumption; primary keyinformant questionnaires on patterns of drinking	Published systematic reviews and meta-analyses of health effects plus modelling for role of patterns on IHD and injuries
Illicit drugs	Use of amphetamine, cocaine, heroin, or other opioids and intravenous drug use	No illicit drug use	HIV/AIDS, overdose, drug use disorder, suicide, and trauma; <i>other neuro-psychological diseases, social consequences, hepatitis B and hepatitis C</i>	Systematic review of published work and data-bases of United Nations Drug Control Program and European Monitoring Centre for Drugs and Drug Addiction	Updated systematic review of published work on cause-specific and all-cause standardised mortality ratio; UNAIDS estimates for HIV incidence among drug users (based on prevalence surveys among high-risk groups)
<b>Environmental risks</b>					
Unsafe water, sanitation, and hygiene	6 scenarios, ranging from regulated water and sanitation with hygiene through to no improved water supply and no improved sanitation	Absence of transmission of diarrhoeal disease through water, sanitation, and hygiene	Diarrhoea	Global Water Supply and Sanitation Assessment 2000, based on Demographic Health Surveys (DHS), UNICEF Multiple Indicator Cluster Surveys (MICS), national census reports, other national sample household surveys, together covering countries with 89% of global population	Systematic reviews of multi-country randomised controlled trials and observational studies
Urban outdoor air pollution	Estimated annual average particulate matter concentration for particles with aerodynamic diameters <2.5 microns (PM <sub>2.5</sub> ) or 10 microns (PM <sub>10</sub> )	7.5 µg/m <sup>3</sup> for PM <sub>2.5</sub> , 15 µg/m <sup>3</sup> for PM <sub>10</sub>	Mortality from combined respiratory and selected cardiovascular causes in adults >30, lung cancer, acute respiratory infection mortality in children <5; <i>cardiovascular and respiratory morbidity</i>	PM <sub>10</sub> estimated for 3211 cities with population larger than 100 000 and national capitals based on measured annual average concentrations of PM <sub>10</sub> and total suspended particulates in 304 cities, with a combined population of 559 million with an econometric model of the scale and composition of economic activity, and geoclimatic factors	ACS-CPS II prospective study of risk factors for mortality in more than one million Americans for adult estimates; systematic review and new meta-analysis of time-series studies of mortality in children <5 years

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Risk factor	Exposure variable	Theoretical minimum	Outcomes*	Sources for exposure estimates	Sources for hazard estimates
Indoor smoke from solid fuels	Household use of solid fuels and ventilation	No household solid fuel use	Acute lower respiratory infections in children <5, COPD, lung cancer (coal); <i>cataracts, tuberculosis, asthma, lung cancer from biomass</i>	National censuses, DHS, World Bank Living Standard Measurement Surveys, other surveys and reports by ministries of energy in 52 countries; estimated for other countries from an economic-energy model	Systematic review and new meta-analysis of cross-sectional, cohort and case-control studies
Lead	Current blood lead concentrations	0.016 µg/dL§	Cardiovascular diseases, mild mental retardation; <i>anaemia, gastrointestinal effects; nervous and reproductive system effects; social consequences of IQ loss</i>	Systematic review (more than 700 published sources) on blood lead levels plus data on leaded gasoline use and outphasing	Published systematic reviews and meta-analysis
Global climate change	Climate scenarios based on various carbon emissions and concentrations	1961–1990 concentrations	Diarrhoea, flood injury, malaria, malnutrition; <i>dengue fever, cardiovascular mortality, effects arising from population movement</i>	Climate projection models used by the Intergovernmental Panel on Climate Change (IPCC)	Models for effects of meteorological variables on the incidence of vector-borne and diarrhoeal disease, on flood risk and food production
<b>Occupational risks</b>					
Risk factors for injuries	Current proportions of workers exposed to injury risk factors	Exposure corresponding to lowest rate of work-related fatalities observed: 1 per million per year for 16–17-year-olds employed as service workers in the USA	Unintentional injuries; <i>intentional injuries</i>	International Labour Organization (ILO) Yearbook of Labor Statistics and databases, World Bank World Development Indicators, regional and national databases to estimate employment in various sectors and occupations; exposures assigned based on occupation and sector with review of existing data in a few countries	Occupational mortality statistics from social security, insurance, and other sources from several countries plus correction for under-reporting based on independent studies
Carcinogens	Proportions of workers exposed to background, low, and high concentration of workplace carcinogens	No work-related exposure above background to chemical or physical carcinogens	Leukemia, lung cancer, mesothelioma; <i>cancers of multiple other sites</i>	Same as occupational risk factors for injuries plus European Carcinogen Exposure (CAREX) database	Reviews of published work
Airborne particulates	Proportions of workers with background, low and high levels of exposure	No work-related exposure above background	COPD and asthma; <i>pneumoconiosis, silicosis, asbestosis</i>	Same as occupational risk factors for injuries	Review of published literature
Ergonomic stressors	High, moderate, and low exposure based on occupational categories	Physical workload at the level of managers and professionals (low)	Lower back pain	Same as occupational risk factors for injuries	Review of observational studies and published reviews of literature
Noise	High and moderate exposure categories (>95 dBA and 85-90 dBA)	Less than 85 dBA on average 8 h work	Hearing loss	Same as occupational risk factors for injuries	Published reviews of observational studies
<b>Other selected risks</b>					
Unsafe health-care injections	Exposure ≥1 contaminated injection	No contaminated injections	Acute infection with HBV, HCV and HIV, cirrhosis and liver cancer; <i>selected other infectious diseases</i>	Systematic review of published work, WHO reports, Expanded Programme of Immunization reviews, unpublished reports made available through the Safe Injection Global Network (SIGN) for number of injections and re-use of syringes	Mass action model of infection with hazard modelled on background prevalence of infections (GBD database) and the risk of infection with HBV, HCV, and HIV after a needlestick exposure from an infected source-patient (review of published work)
Childhood sexual abuse	Prevalence of non-contact abuse, contact abuse, and intercourse	No abuse	Depression, panic disorder, alcohol misuse/dependence, drug misuse/dependence, post-traumatic stress disorder and suicide in adulthood; <i>non-mental health outcomes, such as sexually transmitted diseases, unwanted pregnancies, and injuries</i>	Systematic review of 136 published studies in 30 countries	Systematic reviews and new meta-analysis of 48 observational studies from 12 countries

\*Outcomes in italic are those that are likely to be causal but not quantified because of lack of sufficient evidence on prevalence or hazard size, or both. †The resulting haemoglobin concentrations vary across regions and age-sex groups (from 11.66 g/dL in children younger than 5 in SEAR-D to >14.5 g/dL in adult men in developed countries) because the other risks for anaemia (eg, malaria) vary. ‡Theoretical minimum for alcohol is zero, the global theoretical minimum. Specific subgroups might have a non-zero theoretical minimum. §Theoretical minimum for lead is the blood lead concentration expected at background exposure levels. Health effects were quantified for blood lead concentrations above 5 µg/dL where epidemiological studies have quantified hazards.

Table 1: Risk factors, exposure variables, theoretical minima, disease and injury outcome, and data sources for the risk factors assessed

Panel 1: **GBD 2000 subregions**

WHO region	Mortality stratum	Countries
AFR	D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo
	E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
AMR	A	Canada, Cuba, United States of America
	B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
	D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
EMR	B	Bahrain, Cyprus, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
	D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
EUR	A	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
	B	Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan, Yugoslavia
	C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
SEAR	B	Indonesia, Sri Lanka, Thailand
	D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal
WPR	A	Australia, Brunei Darussalam, Japan, New Zealand, Singapore
	B	Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

A=very low child mortality and very low adult mortality; B=low child mortality and low adult mortality; C=low child mortality and high adult mortality; D=high child mortality and high adult mortality; E=high child mortality and very high adult mortality. AFR=Africa. AMR=The Americas. EMR=Eastern Mediterranean. EUR=Europe. SEAR=Southeast Asia. WPR=Western Pacific Region.

relations have been characterised in meta-analyses of cohort studies.<sup>20–22</sup> Alcohol has benefits as well as harms for different diseases, depending on the disease and pattern of alcohol consumption.<sup>23,24</sup> A theoretical minimum of zero was chosen for alcohol, because, despite benefits for vascular diseases in some populations, the global and regional burden of disease due to alcohol was dominated by its effects on neuropsychological diseases and injuries, which are considerably larger than the benefits to vascular diseases. Finally, for factors with protective effects—ie, fruit and vegetable intake and physical activity—a counterfactual

exposure distribution was chosen based on high-intake populations and the level to which the benefits could continue in view of current scientific evidence. The theoretical minimum for the risk factors are reported in table 1. With theoretical minimum as the baseline, this work is distinct from intervention analysis, the purpose of which is to estimate the benefits of a particular intervention or group of interventions. In addition to information on risk exposure, interventional analysis would require data on effectiveness of interventions.

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The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Panel 2: **Potential impact fraction equation used to estimate population attributable fraction (AF)**

$$PIF = \frac{\int_{x=0}^m RR(x)P(x) - \int_{x=0}^m RR(x)P'(x)}{\int_{x=0}^m RR(x)P(x)}$$

RR(x)=relative risk at exposure level x. P(x)=population distribution of exposure. P'(x)=counterfactual distribution of exposure. m=maximum exposure level.

Panel 3: **Equations used to calculate attributable mortality and incidence**

$$\begin{aligned} AM_{ij} &= AF_{M_{ij}} \times M_{ij} \\ A-YLL_{ij} &= AF_{M_{ij}} \times YLL_{ij} \\ A-YLD_{ij} &= AF_{I_{ij}} \times YLD_{ij} \\ AB_{ij} &= A-YLL_{ij} + A-YLD_{ij} \end{aligned}$$

YLL=years of life lost to premature mortality. YLD=years of life lived with disability due to disease incidence.

	Africa		The Americas		Eastern Mediterranean		Europe		Southeast Asia		Western Pacific		World			
	High child, high adult	High child, very high adult	Very low child, very low adult	Low child, low adult	High child, high adult	Low child, low adult	Very low child, very low adult	Low child, low adult	High child, high adult	Low child, low adult	High child, high adult	Very low child, very low adult	Low child, low adult	Very low child, very low adult	Total	
<b>Total population</b>	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	Total	
<b>Total mortality</b>	147/133/ 146/945	171/600/ 173/915	160/494/ 164/689	213/309/ 217/623	35/471/ 35/759	72/156/ 66/903	174/275/ 168/301	201/514/ 210/376	108/182/ 110/277	114/051/ 129/133	147/173/ 146/646	75/796/ 78/558	785/055/ 747/878	616/519 5483/4944	29/232/26629 55/861	6045017
<b>Childhood and maternal undernutrition</b>	2206/2050	3154/3001	1342/1392	1459/1120	290/237	409/287	1750/1602	2020/2054	1034/916	1878/1721	1234/1022	6358/5764	616/519	5483/4944	29/232/26629	55/861
<b>Other nutrition related risks and physical inactivity</b>	438/402	487/441	0/0	14/11	14/11	8/8	223/229	0/0	9/8	0/0	40/29	573/614	0/0	95/94	3748	
Underweight	59/67	65/80	2/3	3/4	3/4	3/4	36/44	2/3	3/3	2/2	15/19	139/185	0/0	34/39	841	
Iron deficiency	90/112	120/151	0/0	2/2	2/2	0/0	34/53	0/0	0/0	0/0	10/13	68/101	0/0	7/9	778	
Vitamin A deficiency	74/68	128/116	0/0	3/2	5/4	2/2	44/45	0/0	2/2	0/0	5/4	132/141	0/0	6/6	789	
Zinc deficiency	87/128	79/116	179/191	170/162	20/20	76/57	164/171	325/354	281/289	514/671	133/139	668/519	85/76	711/758	7141	
High blood pressure	34/52	36/53	161/189	88/79	10/9	51/31	114/101	265/282	144/136	387/518	72/40	488/507	39/39	222/265	4415	
High cholesterol	14/19	21/35	135/137	117/144	15/18	36/28	58/67	183/197	117/141	202/265	44/58	42/110	21/20	163/184	2591	
High BMI	21/31	33/41	92/79	81/58	7/7	27/15	51/48	95/75	80/67	234/247	55/48	378/311	26/19	269/232	2726	
Low fruit and vegetable intake	20/25	21/27	74/81	52/55	6/6	21/13	47/43	103/103	64/62	147/175	34/34	218/185	23/19	132/134	1922	
Physical inactivity																
<b>Sexual and reproductive health risks</b>	198/234	805/923	8/8	22/27	17/11	0/4	33/39	3/9	1/8	3/13	30/25	231/177	0/3	18/36	2886	
Unsafe sex	..16	..33	..0	..5	..4	..1	..23	..0	..0	..0	..7	..56	..0	..3	149	
Lack of contraception																
<b>Addictive substances</b>	43/7	84/26	352/294	163/58	5/1	43/10	114/19	531/145	255/53	548/73	181/12	785/132	128/49	661/137	4907	
Tobacco	53/15	125/30	27/-22	207/39	22/6	6/1	8/1	65/-85	100/25	338/88	51/9	148/21	23/-28	465/66	1804	
Alcohol	5/1	1/0	10/7	7/4	1/0	5/1	18/4	11/6	3/1	18/5	13/1	40/8	2/1	28/2	204	
Illicit drugs																
<b>Environmental risks</b>	129/103	207/169	0/1	16/15	13/10	9/9	117/135	0/1	8/7	1/1	25/21	326/327	0/0	42/35	1730	
Unsafe water, sanitation, and hygiene	11/11	5/5	14/14	16/14	3/2	5/3	28/23	12/11	20/18	22/24	17/15	72/60	10/8	176/179	799	
Urban outdoor air pollution	93/80	118/101	0/0	7/9	5/5	1/1	56/60	0/0	8/9	1/3	15/22	218/304	0/0	137/366	1619	
Indoor smoke from solid fuels	5/4	4/3	2/1	14/7	2/1	5/2	12/6	4/2	15/8	26/13	6/3	38/19	0/0	21/10	234	
Lead	18/18	18/18	0/0	0/0	0/0	0/0	10/11	0/0	0/0	0/0	1/0	35/38	0/0	2/1	154	
Global climate change																
<b>Occupational risks</b>	14/1	18/1	3/0	17/1	2/0	8/0	27/2	4/0	5/0	15/1	19/1	79/5	2/0	78/5	310	
Risk factors for injuries	1/0	1/0	7/2	4/1	0/0	1/0	2/0	12/2	6/1	13/2	4/0	13/2	4/1	30/9	118	
Carcinogens	5/2	7/3	12/2	9/1	1/0	1/0	9/2	17/2	7/2	15/3	10/3	54/17	4/1	113/54	356	
Airborne particulates	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	
Ergonomic stressors	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0	
Noise																
<b>Other selected risks to health</b>	27/23	0/0	1/0	1/0	1/1	0/0	24/20	0/0	1/0	6/4	19/9	92/62	0/0	137/58	501	
Unsafe health-care injections	0/0	2/1	1/1	1/0	0/0	0/0	1/1	1/1	1/1	3/2	1/0	16/18	1/1	10/14	79	
Childhood sexual abuse																

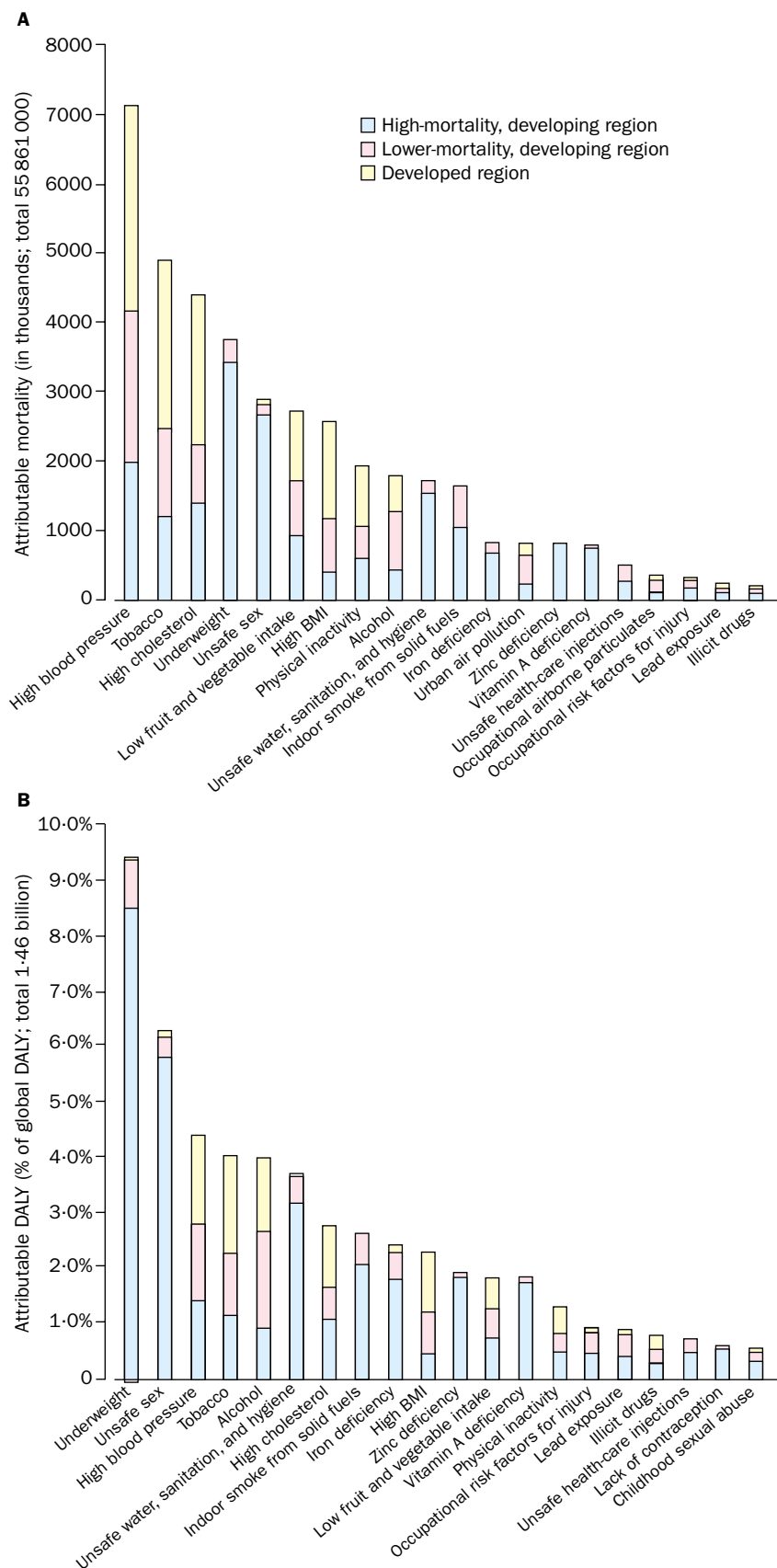
The table shows the estimated mortality for each risk factor considered individually. These risks act in part through other risks and act jointly with other risks. Consequently, the mortality due to groups of risk factors will usually be less than the sum of individual risks.

**Table 2: Mortality (thousands of deaths) by sex due to risk factors in 14 GBD subregions**

	Africa		The Americas		Eastern Mediterranean		Europe mortality		Southeast Asia		Western Pacific		World			
	High child, high adult	High child, very high adult	Very low child, low adult	Low child, low adult	High child, high adult	Low child, high adult	Very low child, very low adult	Low child, high adult	Low child, high adult	High child, high adult	Very low child, very low adult	Low child, high adult	Very low child, very low adult	World		
	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F	M/F		
<b>Total population</b>	147 133/ 146 945	171 600/ 173 915	160 494/ 164 689	213 309/ 217 623	35 471/ 35 759	72 156/ 66 903	201 514/ 210 376	108 182/ 110 277	147 173/ 146 646	639 087/ 602 719	75 796/ 78 558	785 055/ 747 878	3 045 295/ 2 999 722	6 045 017		
<b>Total DALY</b>	73 650/ 70 695	103 191/ 101 977	24 480/ 21 804	45 372/ 35 065	91 58/ 78 95	12 590/ 10 131	28 006/ 25 314	21 304/ 17 689	33 585/ 29 302	178 923/ 177 345	8780/ 7591	131 634/ 110 818	761 562/ 693 911	1 455 473		
<b>Childhood and maternal undernutrition</b>	15 530/ 14 375	17 189/ 15 710	12/11	570/498	512/410	324/312	8203/8407	10/9	1634/ 1239	21 297/ 22 766	6/6	4048/3972	69 733/68 067	137 801		
Iron deficiency	2263/2521	2451/2905	223/255	446/465	121/217	239/277	1449/1746	87/211	681/847	5614/6883	31/81	1876/2462	15 756/19 301	35 057		
Vitamin A deficiency	3178/3856	4208/5167	0/0	79/103	53/68	9/8	1159/1758	0/0	347/406	2321/3368	0/0	241/306	11 596/15 042	26 638		
Zinc deficiency	2625/2414	4563/4150	1/1	115/99	174/138	66/63	1547/1574	0/0	65/56	4635/4961	0/0	208/219	14 201/13 833	28 034		
<b>Other nutrition-related risks and physical inactivity</b>	980/1295	984/1177	1642/1141	1807/1438	208/178	840/570	1781/1698	2624/1828	2699/2180	5386/4632	1394/1402	7010/5316	781/451	6783/6044	34 920/29 350	64 270
High blood pressure	395/563	456/578	1451/1012	1070/803	109/87	605/320	1273/1051	2062/1317	1461/996	4109/3211	828/412	5562/5528	380/227	2376/2195	22 136/18 301	40 437
High cholesterol	246/318	341/546	1825/1654	1505/1918	189/234	534/456	882/1027	1922/1735	1420/1445	2578/2684	650/818	686/1939	334/295	2430/2804	15 543/17 872	33 415
Low fruit and vegetable intake	253/354	434/471	833/536	896/581	72/67	322/172	607/550	785/413	2431/1684	614/524	4139/3521	237/118	2718/2042	15 117/11 544	26 662	
Physical inactivity	225/280	262/309	691/576	582/585	61/68	265/164	559/492	852/654	1461/1236	414/409	2489/2186	228/160	1436/1318	10 159/8933	19 092	
<b>Sexual and reproductive health risks</b>	6205/7753	24 059/ 29 664	281/235	843/912	521/310	30/162	1125/1508	114/202	134/295	1009/925	7413/6004	12/65	804/995	42 600/49 269	91 869	
Unsafe sex	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
Lack of contraception	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
<b>Addictive substances</b>	591/97	1311/367	3567/2606	2190/813	51/14	593/197	1780/379	4991/1464	3381/715	7230/832	2712/180	10 474/1621	994/325	8313/1296	48 177/10 904	59 081
Tobacco	1441/393	3621/785	2925/702	7854/1443	789/170	162/22	328/36	3103/416	2183/446	7543/1570	1793/284	4927/675	708/43	12 020/1941	49 397/8926	58 323
Alcohol	543/156	495/163	808/379	791/310	200/71	449/78	620/453	786/344	181/81	762/223	406/421	1386/282	231/101	1110/259	8769/2719	11 488
Illicit drugs																
<b>Environmental risks</b>	3797/3119	6365/5355	31/30	686/603	436/320	314/315	3797/4506	33/33	64/57	734/506	8762/9725	14/13	2112/1879	27 432/26 726	54 158	
Unsafe water, sanitation, and hygiene	153/132	80/67	87/65	133/99	24/20	47/30	305/253	73/44	170/118	154/128	718/594	53/31	1343/1161	3533/2871	6404	
Urban outdoor air pollution	3036/2358	3865/3059	2/4	193/251	175/154	32/32	1817/1691	0/0	233/244	458/532	6641/7596	0/0	2569/3528	19 040/19 499	38 539	
Indoor smoke from solid fuels	512/488	460/433	68/49	907/789	140/125	238/187	606/504	75/43	424/211	379/337	1489/1198	15/10	1496/1251	7112/5814	12 926	
Lead	321/305	631/636	1/2	35/36	13/10	10/10	357/391	1/2	2/2	19/15	1213/1325	/1	92/77	2700/2816	5517	
Global climate change																
<b>Occupational risks</b>	662/55	773/68	116/14	745/74	92/9	287/25	1224/96	180/22	495/41	715/63	3517/258	85/10	2939/301	12 071/1054	13 125	
Risk factors for injuries	11/4	16/6	58/16	42/9	4/1	13/2	21/4	97/14	134/19	38/7	134/22	25/4	303/103	962/220	1183	
Carcinogens	106/37	141/69	184/36	213/44	21/4	37/4	148/39	216/43	167/43	135/47	862/315	68/18	1726/493	4130/1224	5354	
Airborne particulates	21/16	25/20	17/10	32/15	4/2	9/3	25/16	21/11	21/14	26/19	111/78	9/5	146/110	485/333	818	
Ergonomic stressors	109/49	127/60	92/31	122/43	15/6	60/21	142/88	117/47	136/92	219/185	799/303	26/22	735/365	2788/1362	4151	
Noise																
<b>Other selected risks to health</b>	804/742	0/0	0/0	13/5	20/12	0/0	437/390	0/0	106/59	356/456	2341/1759	0/0	2028/791	6356/4105	10 461	
Unsafe health-care injections	244/187	167/238	98/320	147/118	46/27	41/83	85/225	61/175	132/205	42/56	1079/2340	29/96	888/1158	2934/5302	8235	
Childhood sexual abuse																

The table shows the estimated disease burden for each risk factor considered individually. These risks act in part through other risks and act jointly with other risks. Consequently, the burden due to groups of risk factors will usually be less than the sum of individual risks.

Table 3: Burden of disease (thousands of DALYs) by sex due to risk factors in 14 GBD subregions



**Figure 1: Mortality (A) and burden of disease (B) due to leading global risk factors**

High-mortality, developing regions=subregions in D and E mortality strata. Lower-mortality, developing regions=AMR-B, EMR-B, SEAR-B, and WPR-B subregions. Developed regions=AMRA, EUR, and WPR-A. The figure shows the estimated mortality and disease burden for each risk factor considered individually. These risks act in part through other risks and act jointly with other risks. Consequently, the burden due to groups of risk factors will usually be less than the sum of individual risks.

## Results

The mortality and burden of disease for men and women attributable to risk factors included in the Comparative Risk Assessment project in the 14 GBD subregions are presented in tables 2 and 3. Figure 1 shows the contribution of the 20 leading global risk factors to mortality and burden of disease for the world and for three broad combinations of regions—demographically and economically developed, lower-mortality developing, and high-mortality developing. Figure 2 presents the burden of disease due to the leading ten risk factors for each of these regional groups, also showing the disease composition, divided into broad groups of disease and injury. The different ordering of risk factors in their contributions to mortality and disease burden reflect the age profile of mortality—eg, mortality from underweight results in larger loss of healthy life years because it is concentrated in children aged younger than 5—and the non-fatal effects—eg, neuropsychological outcomes of alcohol.

Despite disaggregation into underweight and micronutrient deficiency (which are not additive) and methodological changes, undernutrition has remained the single leading global cause of health loss (figure 1), with comparable contributions in 1990 (220 million DALY, 16% for malnutrition)<sup>2</sup> and 2000 (140 million DALY, 9.5%, for underweight; 2.4%, 1.8%, and 1.9% for iron, vitamin A, and zinc deficiency, respectively; 0.1% for iodine-deficiency disorders). This pattern exists because although prevalence of underweight has decreased in most regions of the world in the past decade, it has increased in sub-Saharan Africa,<sup>25</sup> where its effects are disproportionately large because of simultaneous exposure to other childhood disease risk factors. A part of the decrease in the burden of disease due to poor water, sanitation, and hygiene (from 6.8% in 1990 to 3.7% in 2000) is due to a decline in mortality associated with global diarrhoeal disease (from 2.9 million deaths in 1990 to 2.1 million in 2000); a result of improved case-management interventions, particularly oral rehydration therapy.

Leading causes of burden of disease in all high-mortality, developing regions were childhood and maternal undernutrition—including underweight (14.9%),

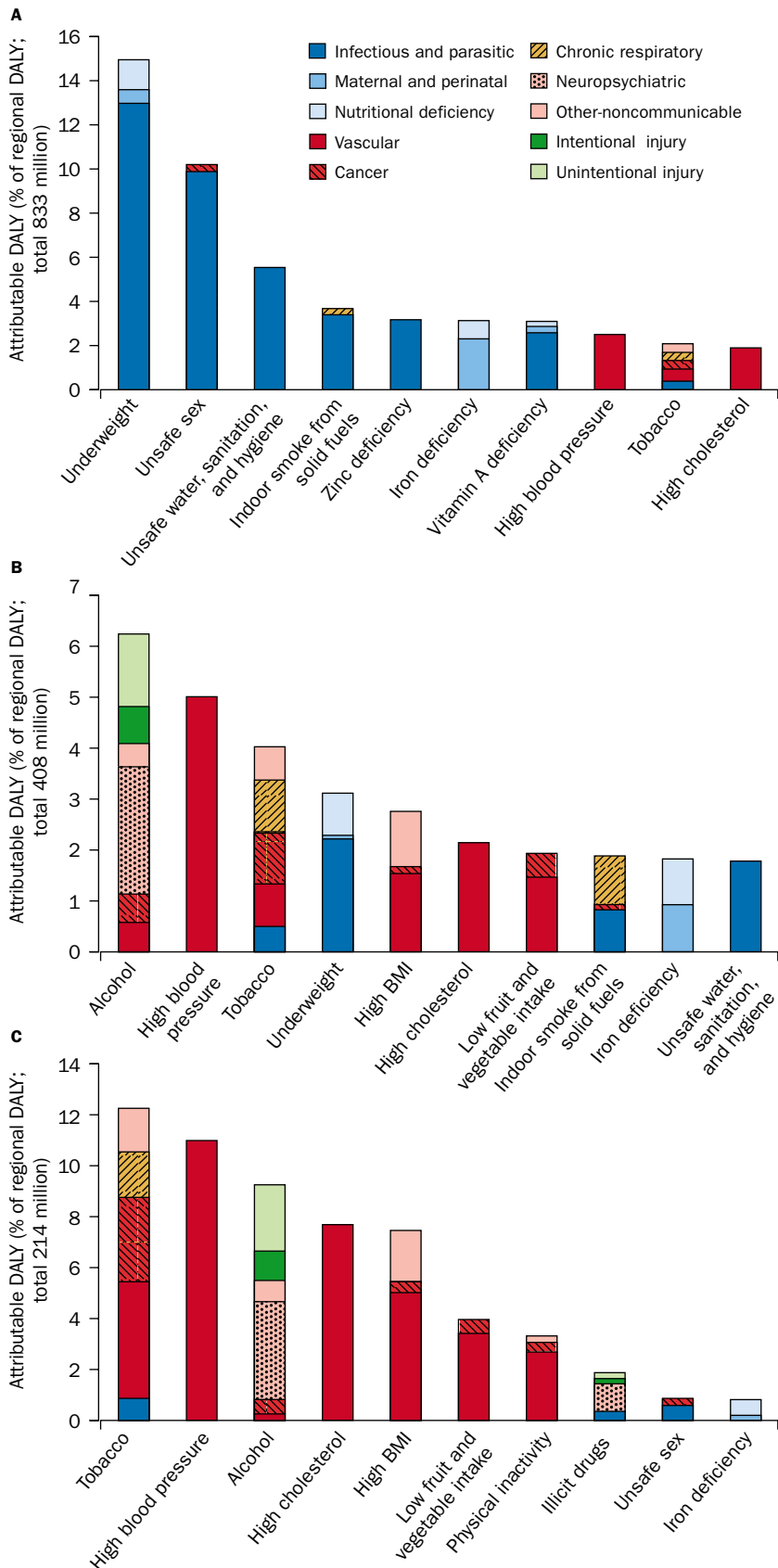


Figure 2: Burden of disease due to leading regional risk factors divided by disease type in high-mortality developing regions (A), lower-mortality developing regions (B), and developed regions (C)

Attribution of disease burden to specific disease categories (versus risk factors) is an example of categorical attribution, according to the *International Classification of Disease* (ICD) system.

micronutrient deficiencies (3.1% for iron deficiency, 3.0% for vitamin A deficiency, and 3.2% for zinc deficiency)—unsafe sex (10.2%), poor water, sanitation, and hygiene (5.5%), and indoor smoke from solid fuels (3.6%). The relative contribution of unsafe sex was disproportionately large (26.2%) in GBD subregion AFR-E (panel 1), where prevalence of HIV-1 is the highest, making it a leading cause of burden of disease in this region. The outcomes of these risk factors were mostly communicable, maternal, perinatal, and nutritional conditions (figure 2), which dominate the disease burden in high-mortality developing regions. Despite the large contribution of these diseases and their underlying risk factors, tobacco, blood pressure, and cholesterol already resulted in significant loss of healthy life years in these regions. For example, in GBD subregion SEAR-D (panel 1; dominated by India in terms of population) the burden of disease attributable to tobacco, blood pressure, and cholesterol had comparable magnitude to micronutrient deficiencies and is only marginally smaller than that attributable to indoor smoke from solid fuels and poor water, sanitation, and hygiene.

In addition to their relative magnitude within these regions, the absolute size of the loss of healthy life years attributed to risk factors in high mortality, developing regions is enormous. Childhood and maternal underweight and unsafe sex in these regions alone (with 38% of global population) contribute as much (>200 million DALY) to loss of healthy life as do all diseases and injuries combined in developed countries (with 22% of global population).

Across developed regions, tobacco (12.2%), high blood pressure (10.9%), alcohol (9.2%), high cholesterol (7.6%), and high BMI (7.4%) were consistently the leading causes of loss of healthy life, contributing mainly to non-communicable diseases and injuries. Tobacco was the leading cause of disease burden in all developed-country regions, except EUR-C (panel 1; dominated by Russia) where alcohol resulted in a slightly larger loss of healthy life. The increase in the disease burden due to high blood pressure compared with 1990<sup>2</sup> (from 3.9% in the established market economies and 5.9% in the formerly-socialist economies) mainly reflects new evidence on hazard size

after correction for regression dilution bias.<sup>26</sup> The contributions of these risk factors to disease burden are consistently larger than those of leading diseases in these regions—eg, ischaemic heart disease (9·1%), unipolar depressive disorders (7·1%), cerebrovascular disease (6·2%)—emphasising the potential health gains by risk reduction.

The lower-mortality, developing regions present possibly the most striking mixture of leading risk factors and diseases. The leading risk factors in these regions (40% of global population) include those from both developed regions and high-mortality, developing regions with comparable magnitudes—eg, underweight (3·1%) and high BMI (2·7%) had comparable contributions to the burden of disease.<sup>27</sup> Furthermore, the decline in the share of burden of disease due to the risk factors—eg, the ratio of 1st and 10th leading risk factors—in lower-mortality, developing regions was slower than those in the other two groups of countries—ie, less clustering of risk-factor burden—further emphasising the role of a more extended and mixed group of risk factors.

Alcohol led the causes of burden of diseases in lower-mortality, developing regions as a whole (6·2%) and in GBD subregions AMR-B and WPR-B (table 3), but had relatively low contribution to the burden of disease in GBD subregion EMR-B (table 3). In general, regions AMR-B and EMR-B had risk-factor profiles similar to the developed regions (tobacco, blood pressure, cholesterol, BMI, and alcohol) whereas regions SEAR-B and WPR-B (table 3) had a more mixed risk-factor profile (with the leading five of these selected risks being underweight, blood pressure, tobacco, unsafe sex, and alcohol in SEAR-B; and alcohol, blood pressure, tobacco, underweight, and indoor smoke from solid fuels in WPR-B).

An important finding of this analysis is the key role of nutrition in health worldwide. About 15% of the global disease burden can be attributed to the joint effects of childhood and maternal underweight or micronutrient deficiencies. Additionally, almost as much can be attributed to risk factors that have substantial dietary determinants—high blood pressure, high cholesterol, high BMI, and low fruit and vegetable intake. These patterns are not uniform within regions and in some countries nutritional transition has been healthier than in others.<sup>28,29</sup> Furthermore, the major nutritional and related risk factors show inter-regional heterogeneity—eg, the relative contributions of blood pressure, cholesterol, and BMI were different in regions AMR-A, SEAR-D, and WPR-B. This heterogeneity further indicates the importance of concurrent and comparable quantification of distal and proximal risk factors to provide a more complete picture of the role of various distal and proximal risk factors.

The analysis also provides quantitative evidence on the public-health importance of several previously unquantified risk factors, including indoor smoke from solid fuels (2·6% of global disease burden), high BMI (2·3%), and zinc deficiency (1·9%). The burden of disease due to other risks—eg, physical inactivity—was lower than expected if methodology and results from the limited number of industrialised countries had been extrapolated.<sup>30</sup> The finding that the contribution of physical inactivity to burden of disease is less than expected could arise partly because of difficulties in measuring exposure to this risk factor, which resulted in the use of a categorical exposure variable with a conservative baseline of sufficient (versus vigorous) activity. But this finding also reflects the inclusion of occupational and transportation domains of activity (that

are common among rural populations of developing countries) in addition to usual leisure-time activity, which is more relevant to developed countries and urban populations.<sup>31,32</sup>

For those risk factors that solely or primarily affected children (except childhood sexual abuse), there was little difference in health loss between the sexes. By contrast, the risk factors that affect adults, generally differed between the sexes. Unsafe sex, lack of contraception, and iron and vitamin A deficiency, which affect maternal conditions, and childhood sexual abuse contributed to larger burden of disease among women. The effects of diet and exercise are comparable in magnitude, although in general slightly larger for men. The burden of disease due to smoking, alcohol, and illicit drugs was much greater among men, especially in developing countries, indicating the social and economic forces that have so far made addictive substances more accessible to men. The burden of disease due to occupational risks was also concentrated more among men than women, partly because of the inclusion of only formal employment in the analysis, and partly because of differences in jobs held by men and women, with men having a greater presence in heavy industrial jobs and formal agriculture.

## Discussion

Quantitative risk assessment is always affected by uncertainty of exposure, and of both the existence and magnitude of hazard. In one classification, risk assessment uncertainty can be divided into parameter uncertainty and model uncertainty.<sup>33</sup> Parameter uncertainty is often quantifiable with random-variable methods—eg, uncertainty due to sample size or measurement error. Model uncertainty is due to gaps in scientific theory, measurement technology, and data. It includes uncertainty in causal relations or the form of the exposure-response relation (threshold versus continuous, linear versus non-linear, etc), the degree of bias in measurement, etc. Defined broadly, model uncertainty also includes extrapolation of exposure or hazard from one population to another. Uncertainty in international risk assessment is dominated by the model uncertainty, which is a result of lack of and difficulty of direct studies on exposure, hazard, and background disease burden. This difficulty has motivated innovative assumptions and extrapolations even in the best-studied risk factors in a limited number of countries.<sup>3</sup>

Uncertainty in disease causation<sup>34,35</sup> in practice was secondary to uncertainty on hazard size, because when causality was uncertain, estimates of hazard needed for risk assessment were also unknown or uncertain. For example, whether climate change or inequality would increase disease, or whether the relations between occupational factors or physical inactivity and lower back pain are causal, each have equivalent questions on hazard magnitude. The collectivity of scientific knowledge from a diverse group of scientific disciplines would confirm the possibility of a causal relation in the above instances, but would shift the debate to hazard size. As a result, for some risk factors, only the contribution to a subset of disease outcomes could be quantified in our analysis, because epidemiological studies did not provide enough information for hazard quantification for all risk factor-disease pairs, even when the causal relation is believed or suspected (table 1).

In this analysis, estimates of hazard size in individual studies were as much as possible adjusted for confounding. Extrapolation of hazard from a limited number of studies to other populations has, however,

received less attention in epidemiological research. Although the robustness of relative measures risk has been confirmed for more proximal factors in studies across populations,<sup>21,22,36</sup> their extrapolation is an important source of uncertainty for more distal risks—eg, childhood sexual abuse—or for those whose effects are heterogeneous—eg, alcohol and injuries versus alcohol and cancer. Because multiple risks and disease are often correlated—eg, concentrated among certain socio-economic groups—estimating population attributable fraction would require stratified—eg, by other risk factors—prevalence and disease data. Lack of stratified data is another source of uncertainty, leading to underestimation of effects in the presence of positive risk factor correlation.

Direct exposure data for many risk factors were limited because of difficulties in their measurement and because of underinvestment in risk-factor surveillance, especially in developing countries. To allow maximum use of available data, such risk factors were represented with indirect or aggregate indicators—eg, smoking impact ratio for accumulated hazards of smoking, weight-for-age for childhood undernutrition, and use of solid fuels for indoor air pollution. Furthermore, for some risks, multiple data sources allowed limiting the range of exposure estimates. For example, in the absence of alcohol surveys, total alcohol production, trade, and unrecorded consumption, provided upper bounds on the fraction of the population that would be in the highest consumption category. Finally, some of the risk factors in table 1 are represented with continuous exposure variables—eg, high blood pressure. Others have used categorical variables—eg, indoor smoke from solid fuels, underweight, and physical inactivity—even though the health effects occur along a continuum. This choice reflected the availability of exposure data and hazard estimates in categories. In such instances, the contribution to disease within the baseline category would not be captured.

Our findings should, therefore, be considered within the context of limited available data, and subject to uncertainty. The uncertainty varies across risk factors and geographical regions. Further discussion and quantification of sources and quantification of uncertainty with respect to the analysis is provided elsewhere.<sup>16</sup> The analysis itself indicates the need for better data and monitoring methods for better quantification and intervention of important risk factors, especially more detailed data on exposure. Health research has often focused on questions that, although scientifically intriguing, have not taken into account population health,<sup>10,37,38</sup> resulting in underinvestment in research on some important global risk factors—eg, indoor smoke from solid fuels<sup>39</sup> and alcohol drinking patterns<sup>23</sup>—and lack of empirical evidence for the interactions of multiple risk factors, such as nutrition and tobacco. To inform interventions and policies, similar analyses to this one should take place on smaller scales—eg, national—and include microlevel data and a more comprehensive list of both distal and proximal risk factors—eg, poverty, life events and stress, risk factors for injuries, salt and fat intake, and diabetes.

Despite inherent uncertainties, the quantification of the burden of disease attributable to selected risk factors shows that the loss of health in the world is on the one hand dominated by those risk factors that affect the poorest regions and populations, such as undernutrition, poor water, sanitation, and hygiene, and indoor smoke from solid fuels, and on the other hand by hazards such as alcohol, tobacco, high blood pressure, and high

cholesterol, that in 2000—even compared with a decade earlier<sup>2</sup>—are widespread or have large estimated health impacts. Nowhere is this picture more apparent than in the lower-mortality, developing regions, where 38% of the global population live, and where individuals are affected by both groups of risk factors.

Comparison of the disease burden attributable to risk factors across the three regional groups (figures 1 and 2) provides a cross-sectional picture of a risk-factor transition, in which the relative contribution of adult or non-communicable disease risk factors increases as childhood and communicable disease risk factors decrease with economic and demographic development. Analyses of previous development-based transitions have shown the role of policy in inducing or delaying, and in shaping the dynamics of the transition.<sup>40</sup> Examples in public health include rapid control of vector-borne diseases,<sup>41</sup> high maternal mortality where contraception and abortions are not accessible for non-economic reasons, and potential HIV/AIDS epidemics in some developed countries.<sup>42</sup> At the same time, at least some risk-factor transitions are confirmed by the increasing role of hazards such as tobacco and obesity both in relative and absolute terms over time.<sup>43,44</sup> The increase in the global burden of disease due to tobacco, from 2.6% in 1990 to 4.1% in 2000, although partly due to new evidence on hazard size after correction for confounding,<sup>45</sup> mostly indicates the increased accumulated hazards, and is most noticeable in developing countries. The cross-sectional comparison shows that risk factors such as alcohol and high blood pressure and cholesterol, if not increasing in absolute terms,<sup>46,47</sup> are important contributors to diseases in all regions.

The large remaining disease burden due to childhood mortality risks shows the continued need to develop and deliver effective interventions, including lowering technology cost for interventions. At the same time, four of the five leading causes of burden of disease affect adults (figure 1). Risk factors for adult communicable and non-communicable diseases make substantial contributions even in regions that include some of the countries with low income and high infant mortality. The public-health community should, therefore, continually reassess the appropriate balance between interventions to address childhood disease risk factors and those that affect adult health. Dynamic and systematic policy responses—eg, healthier nutritional or environmental transitions—can largely mitigate the spread of such risk factors and their more distal causes to a large extent throughout the development process.<sup>28,48</sup> Furthermore, as shown by the persistence of diseases such as malaria or by the large increase in the disease burden due to HIV/AIDS and its risk factors since 1990—eg, unsafe sex from 3.5% in 1990 to 6.3% in 2000—as well as the potential for HIV/AIDS epidemics in some Eastern European countries<sup>42</sup> or China,<sup>49</sup> important communicable disease risk factors also need dynamic monitoring and policy responses.

There are several reasons why risk factors that were not among the leading global causes of disease burden in this study should not be neglected. Most obviously, this analysis could be expanded with other risk factors that are both prevalent and hazardous. Second, many comparatively smaller risk factors make important contributions to burden of disease in various populations. For example in GBD subregion WPR-B (dominated by China), affected by large industrial activity based on coal, ambient air pollution and lead exposure have health effects comparable to poor water, sanitation, and hygiene, and larger than some micronutrient deficiencies.

Similarly, lack of contraception was among the ten leading risk factors for female burden of disease in several regions.

Some risk factors with comparably low global disease burden are highly concentrated among sectors of society—eg, occupational exposure among mine workers—and have implications for health inequalities. This concentration might also imply that risks can be targeted more easily. For other risk factors, such as childhood sexual abuse, ethical considerations can outweigh direct contributions to disease burden in policy debate. Finally, although the burden of disease due to a risk factor might be comparatively small, effective or cost-effective interventions might exist. Examples include reducing the number of unnecessary medical injections coupled with the use of sterile syringes, and reduction in exposure to lead or ambient air pollution in industrialised countries in the second half of the 20th century, which often also led to benefits such as energy saving.

A few risk factors account for a large contribution to global loss of healthy life. Furthermore, several risk factors have relative prominence in regions at all stages of development. This pattern shows that disease prevention by addressing known distal and proximal risk factors can provide substantial and underestimated public-health gains. Treatment of established disease will always have a role in public health, especially in the instances of diseases such as tuberculosis, where treatment contributes to prevention. At the same time, the current devotion of a disproportionately small share of resources to disease prevention by reducing known risk factors should be reconsidered in a more systematic way in view of this evidence.

#### Contributors

C J L Murray and A D Lopez developed the initial Comparative Risk Assessment framework. M Ezzati, A D Lopez, A Rodgers, and C J L Murray developed methods and criteria for assessment and use of evidence and data analysis, did peer review, and coordinated revisions of the manuscript. Risk factor working groups reviewed scientific evidence and data sources for each risk factor and selected and summarised data on exposure, outcomes, and hazard. S Vander Hoorn designed and did statistical analyses. M Ezzati, A D Lopez, A Rodgers, C J L Murray, and S Vander Hoorn wrote the report.

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#### Conflict of interest statement

None declared.

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