On the Comparable Quantification of Health Risks: Lessons from the Global Burden of Disease Study

Christopher J. L. Murray[1] and *Alan D. Lopez*[2]

Extensive discussion and comments on the Global Burden of Disease Study findings have suggested the need to examine more carefully the basis for comparing the magnitude of different health risks. *Attributable burden* can be defined as the difference between burden currently observed and burden that would have been observed under an alternative population distribution of exposure. Population distributions of exposure may be defined over many different levels and intensities of exposure (such as systolic or diastolic blood pressure on a continuous scale), and the comparison distribution of exposure need not be zero. *Avoidable burden is* defined as the reduction in the future burden of disease if the current levels of exposure to a risk factor were reduced to those specified by the counterfactual distribution of exposure. Choosing the alternative population distribution for a variable, *the counterfactural distribution of exposure, is* the critical step in developing a more general and standardized concept of comparable, attributable, or avoidable burden. We have identified four types of distributions of exposure that could be used as the counterfactual distributions: *theoretical minimum risk, plausible minimum risk, feasible minimum risk,* and *cost-effective minimum risk.* Using tobacco and alcohol as examples, we explore the implications of using these different types of counterfactual distributions to define attributable and avoidable burden. The ten risk factor assessments included in the Global Burden of Disease Study reflect a range of methods and counterfactual distributions. We recommend that future assessments should focus on avoidable and attributable burden based on the *plausible minimum risk* counterfactual distribution of exposure. (Epidemiology *1999; 10:594-605)*

Keywords: attributable burden, counterfactural distributions of exposure, Global Burden of Disease, risk factors.

The Global Burden of Disease Study

The Global Burden of Disease Study (GBD) is one of the first attempts to evaluate premature mortality and disability from a large number of diseases and injuries and from a variety of population exposures[1-6] The study had the following four specific objectives: (1) to develop internally consistent estimates of mortality from 107 major causes of death, disaggregated by age and sex, for the world and for eight geographic regions (Established Market Economies, Former Socialist Economies of Europe, India, China, Other Asia and islands, Middle Eastern Crescent, Latin America and the Caribbean, and Sub-Saharan Africa); (2) to develop internally consistent estimates of the incidence, prevalence, duration, and case fatality for 483 disabling sequelae resulting from the above causes, disaggregated by age, sex, and region; (3) to estimate the fraction of mortality and disability attributable to ten major risk factors, disaggregated by age, sex, and region; and (4) to develop projection scenarios of mortality and disability, disaggregated by age, sex, and region. The study was based on the collaboration of more than 100 scientists from more than 20 countries. In this paper, we revisit the conceptual and methodological issues that have emerged when attempting comparable assessments of the burden of disease attributable to exposures, behaviors, and states on the basis of the experience of the GBD. Extensive discussion and comments on the GBD findings have suggested the need to examine more carefully the basis for comparing risk factor assessments and to develop a standardized approach for similar efforts in the future.

The methods used in the G131) are extensively presented elsewhere.[1] For convenience, a very brief discussion is provided in the following paragraphs. To estimate mortality for the 107 causes of death, vital registration data with medical certification of cause were obtained for approximately 14 million deaths. Various methods were developed and applied to correct for miscoding of cardiovascular diseases. The cause was estimated for the remaining deaths using a combination of sample registration systems, such as the Diseases Surveillance Points operated by the Chinese Academy of Preventive Medicine, population laboratories such as Morogore, (Tanzania) or Matlab (Bangladesh), and disease-specific epidemiological studies.

Internally consistent epidemiological assessments of incidence, prevalence, case fatality, and mortality were

From the [1]Harvard School of Public Health, Harvard University, Cambridge, MA, and the [2]World Health Organization, Geneva, Switzerland.

Address correspondence to: Christopher J. L. Murray, Center for Population and Development Studies, Harvard School of Public Health, 9 Bow Street, Cam. bridge, MA 02138.

The views expressed in this article are those of the authors and do not necessarily reflect the position of the World Health Organization.

developed by identifying a network of experts from the World Health Organization, World Bank, the U.S. Centers for Disease Control and various academic institutions. For each of the 107 diseases and injuries, the major disabling sequelae were identified (483 in all); for example, for diabetes mellitus, the health outcomes evaluated were the metabolic disorder itself, diabetic foot, neuropathy, blindness caused by retinopathy, and ampu tations. Experts reviewed published and unpublished surveys and studies to estimate age and sex-specific incidence, prevalence, duration, and case-fatality rates by region for each of the 483 disabling sequelae. Computer software, DisMod, was developed and used to test whether estimates of incidence, prevalence, duration, and case-fatality rates were internally consistent. Through an iterative process using DisMod and reassessmerits of the available data, the experts working on the study developed internally consistent estimates of incidence, prevalence, average duration, and case-fatality rates that have been published in *Global Health Statistics.*[2]

Information on mortality by cause and the descriptive epidemiology of disability were used to calculate a variety of measures, such as disability-adjusted life expectancy and disability-adjusted life years (DALYs), which are a composite of years of life lost because of premature mortality and years lived with disability, adjusted for the severity of the disability. Time spent in health states worse than perfect health is weighted in the calculation of DALYs by health state preferences that have been measured using a combination of ordinal rankings, visual analogues, and person trade-off techniques. The sensitivity of the estimated DALYs for each disease and injury for alternative value choices has been investigated.

Collaborating experts were identified to work on estimating the burden of disease and injury attributable to ten selected risk factors. Risk factor estimates were in most cases based on reviews of regional data on the prevalence of exposure and international data on relative risks. Age, sex, and region-specific estimates of the prevalence of exposure and relative risks were used to estimate attributable fractions for relevant causes of disease and injury. Finally, a distal socioeconomic determinants health projection model was developed using econometric analysis of a panel of cause-of-death data for 47 countries from 1950 to 1990. In this model, the independent variables included were income per capita, average years of schooling, time (capturing technology change), and smoking intensity. This model has been supplemented with disease-specific models for tuberculosis and human immunodeficiency virus. Baseline, optimistic, and pessimistic projection scenarios were developed using the models and alternative assumptions about the evolution of the independent variables.

In the first section of this paper, we address a series of conceptual issues that emerge in trying to develop meaningful comparisons of various health risks at the global and regional levels. We propose a typology of attributable and avoidable burden assessments that may provide a basis for future efforts to standardize the quantification of health risks. Several special measurement issues related to attributable burden are discussed, followed by a review of the G131) risk factor results and their limitations. The paper concludes with a tentative proposal for a more standardized approach to future global and regional efforts.

Defining Attributable and Avoidable Burden

Investigators from disciplines such as epidemiology, demography, environmental sciences, public health, economics, and sociology increasingly address similar questions of the relation between different types of causal factors and human health. Many epidemiologists are familiar with the framework of necessary, sufficient, and component causes.[7] This framework emphasizes the possibility that several component causes may be acting together to cause disease. The causes analyzed by epidemiologists are usually biological, physiological, or behavioral factors. In contrast, social scientists are often interested in investigating the relation between social, cultural, and economic factors and health. For example, income is statistically related to health but must act through a variety of causal pathways such as diet, tobacco use, access to health services, poor water supplies, etc. Mosley and Chen[8] attempted to link the epidemiologic and social science approaches by providing a multilayer causal framework for child mortality. In the following section, we attempt to provide an extension of the Mosley and Chen[8] framework to all causes of mortality and disability.

Figure 1 provides a simplified schema of the complex causal web between various types of causes and health outcomes. In this schematic, three layers of causal factors are distinguished. At the most distal level are the social, cultural, and economic factors that influence health outcomes. These variables operate through other proximal determinants and physiological and pathophysiological pathways. At the next level in the causal hierarchy are individual behaviors or exposures, such as tobacco use, alcohol use, physical activity, diet, use of health care interventions, water supply contamination, and many others. All of these proximal determinants ultimately influence health outcomes through physiological or pathophysiological mechanisms. These physiological or pathophysiological factors can also be observed; body mass index (BMI), weight for height, blood pressure, serum cholesterol, and human leukocyte antigen types are examples of measures of these pathways. For heuristic purposes, this causal web shows only three layers of causes, but one could usefully subdivide and categorize each of these different layers of determinants.

In the nomenclature of Rothman and Greenland[7] combinations of component causes can be sufficient and/or necessary. Although this terminology is useful in emphasizing that combinations of exposures or factors may be required to observe an outcome, it is ill suited to the hierarchical nature of causation presented in Figure 1. Income per capita is strongly related to health, but it

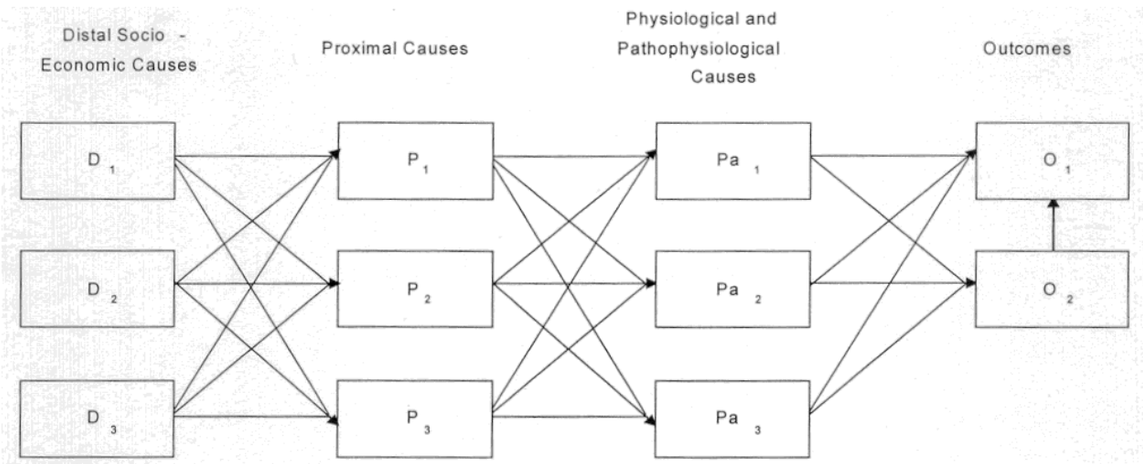

FIGURE 1. Simplified causal web linking exposures and outcomes.

operates through many pathways. Because of the large number of pathways and their complexity, it is difficult to apply usefully the terminology of component, sufficient, and necessary causes in the assessment of the burden of risk factors.

What is an exposure, a behavior, or, more generally, a risk factor? The language of risk factors can be applied to any part of the causal chain illustrated in Figure 1, regardless of the level of the causal factor. Given the construction of the term, risk factors are often dichotomous transformations of the underlying continuous causal variables shown in the schematic. For example, poverty is generally defined as income below some threshold value, and hypertension is blood pressure over some threshold. In this broad sense, the term risk factor can be thought of as synonymous with some distal, proximal, or causal variable related causally to health outcomes.

If the functional form and parameter values for the relation between all the links in the causal web are known (which is never likely to be true given the current state of knowledge), how do we summarize the direction and intensity of the relationship between a given causal variable and health outcomes? There are two basic approaches: characterizing the relation between change in one variable and change in the health outcome, and comparing the magnitude of health outcomes to some counterfactual state where the level of the risk factor or factors has been changed.

If all of the links in the causal web shown in Figure 1 were known, we could evaluate the partial derivative of a change in the expected value of a variable (V) with respect to the health outcome (H), *ie*, $\delta V/\delta H$. As the distal and proximal causal variables in Figure 1 must operate through a set of physiological variables to influence health outcomes, by definition the partial derivative of changes in the distal variables while all other variables were held constant would be 0. We would, in fact, be more interested in the total derivative dV/dH, which allows the other variables related to V to change as a function of V. Although a set of total derivatives for each of the causal variables related to a health outcome might be extremely interesting, for many it would be difficult to interpret. Both partial and total derivatives suffer from the problem that they are entirely context specific. Any change in any other variable, or a change in the level of the variable of interest, could change the derivative. Moreover, total or partial derivatives would capture the relation between a change in the expectation of the distribution of exposure and the health outcome, assuming that the form of the population distribution of exposure remained unchanged. As the expectation of the distribution of exposure rarely changes without some change in the form of the distribution of exposure, these measures of the relation between a risk factor and health outcomes would be less informative.

The main alternative is to estimate the health outcomes that would be observed if some variable or variables took on an alternative population distribution of exposure. In epidemiology, the classical approach is to define an attributable fraction, which is the proportion of the disease in the specific population that would be eliminated in the absence of the exposure.' This definition is based on a simple dichotomous exposure variable and a particular comparison distribution of exposure, namely zero exposure. For many of the risk factors or health determinants of interest, this approach is either too restrictive or inappropriate. We can generalize the attributable fraction concept by defining *attributable burden* to be the difference between burden currently observed and burden that would have been observed under an alternative population distribution of exposure. In this case, the population distribution may be defined over many different levels and intensities of exposure (such as systolic or diastolic blood pressure on a continuous scale), and the comparison distribution of exposure need not be zero. Choosing the alternative population

stribution for a variable, which we will call (borrowing om the social science literature) *the counterfactual distribution of exposure, is* the critical step in developing a ore general concept of comparable attributable burden.

If there are time lags between the value of a variable or sk factor and the effect on health outcome, then the unterfactual must be defined with respect to time as ell. Much of the literature on attributable risk, such as the timates of smoking-attributable mortality by Peto *et al*,[10] *is* based on estimating current burden attributable to ast exposure. We propose first to make a distinction etween attributable burden and avoidable burden. *Attributable burden is* the reduction in current burden that ould have been observed if past levels of exposure to a sk factor had been equal to some counterfactual distribution of exposure. For example, the attributable burden of bacco use might be defined as the reduction in the urrent burden of disease that would have been observed no one had smoked in the past. *Avoidable burden is* efined as the reduction in the future burden of disease that ould be observed if the current levels of exposure to a sk factor were reduced to those specified by the unterfactual distribution of exposure. With these definitions, the avoidable burden of tobacco, for example, ould be the reduction in future burden of disease if no ne smoked in the current year. When there is only a brief ne lag between exposure to a risk factor and outcome, e difference conceptually and empirically between tributable and avoidable burden will be minimal. When ere are considerable time lags between exposure and utcome, there will be a major difference between tributable and avoidable burden.

The way in which time is incorporated into causal tribution frameworks can greatly affect the meaning and mparability of attributable burden. For example, reenland and Robins[11] have argued that traditional finitions of the attributable fraction of disease due to an posure capture only excess cases and not all cases that e etiologically caused by the exposure in question. As reenland and Rothman[7], p54 and Greenland and Robins[11] oint out, the terms "attributable risk" and "attributable action" have been used to refer variously to the risk fference, the rate fraction, the etiologic fraction, and the cess fraction. In this paper we will follow the practice of reenland and Rothman[7] and use the term attributable action to encompass this family of fractional measures. obins and Greenland" have specified statistical ocedures for estimation of these epidemiologic fractions.

Excess cases are generally treated as being time dependent, with only those cases occurring by some time t ter exposure being counted as attributable. Etiologic ses (and thus the calculation of the etiologic fraction) ould also include cases that would have occurred anyway time t in the absence of exposure, but because of the posure, the case occurred much earlier in the interval (t). Whether or not these cases are counted as attributable exposure will clearly affect the calculation of the tributable fraction. Many of these problems related to ne can be resolved if the outcome used is not an event such as death or disease but is a time-based unit such as year of healthy life.

Calculating future burden due to current exposure is inherently more uncertain, given secular trends in diseases, possible changes in the exposure-outcome relationship, expected socioeconomic changes, and likely advances in technology. On the other hand, the future burden of disease and injury caused by current exposure is more important for public health planning and prevention than are estimates of current burden due to past exposures, because the latter cannot be altered. Nevertheless, attributable burden may be interesting, because it is likely to be a good predictor of avoidable burden.

How should we choose the counterfactual distribution of exposure? We have identified four types of distributions of exposure that could be used as the counterfactual distributions: *theoretical minimum risk, plausible minimum risk, feasible minimum risk,* and *cost-effective minimum risk.* The *theoretical minimum risk* distribution would be the distribution of exposure that would have the lowest associated population risk, or in other words, would generate the largest estimate of attributable or avoidable burden. In the case of tobacco, the *theoretical minimum risk* distribution is zero exposure to tobacco for the entire population (because any tobacco use is hazardous), whereas the *theoretical minimum risk* distribution for alcohol (at least in rich countries) would be that where the entire middle- and old-age population had one to two drinks a day, the point at which the relative risk of death from alcohol is the lowest.[13-15] The theoretical minimum risk distributions for both alcohol and tobacco assume that the entire adult population would receive exactly the same level of exposure.

Many theoretical minimum risk distributions (including the two cited above) are implausible; we cannot ever imagine a world where such a distribution of exposure would occur. Thus, the theoretical minimum risk distribution for occupational hazards would be one in which no one worked, for sexually transmitted diseases and the risks of reproduction it would be one in which no one had sex, and for alcohol it would be one in which no one abstained. Calculations of attributable or avoidable burden based on *theoretical minimum risk* counterfactuals may therefore not be that useful for informing debates on health priorities and policies. An alternative approach to defining a counterfactual distribution of exposure would be *plausible minimum risk, ie,* that distribution of exposure among the set of plausible distributions that would minimize population risk. Plausible in this context does not mean that it is likely or feasible in the near future, rather that it is possible to imagine a society with such a distribution of risk. For example, once tobacco addiction is present in a population, it is not plausible to imagine a society in which no one smokes. Nor is it plausible to imagine a society in which no one works or in which no one has sex. Plausibility also implies that the shape of the distribution is one that could be found in some real population. The implied counterfactual distribution of blood pressure for the burden of hypertension as calculated in the GBD using a

classic dichotomous variable approach would be a population in which the blood pressure of everyone with a systolic blood pressure (SBP) greater than 110 min was reduced to 110 min, but the distribution of SBP for the rest of the population that started with an S13P less than 110 min did not change. By using a threshold definition of *at risk,* in this case an SBP greater than 110 ram, the implied counterfactual has an implausible shape.

Given that some *plausible* minimum *risk* distributions could not be achieved in the near future or perhaps even in the distant future, planners may be interested in calculating attributable and avoidable burden using a counterfactual distribution of exposure based on the principle of *feasible* minimum *risk.* The distinction between plausible and feasible is important to appreciate. Feasible implies that there exists or has existed a population with this distribution of exposure. Plausible means that the distribution is imaginable or possible, whereas feasible means that is has actually been achieved. Feasible minimum risk has been widely used in the literature on poor water supply, domestic hygiene, and sanitation[16] A specific example of such *feasible* minimum risk calculations is provided in the 1993 World Development Report for poor household environments.[17]

A fourth approach to defining the counterfactual distribution of exposure is the minimum risk distribution that could be achieved cost effectively through the implementation of interventions. In other words, the counterfactual distribution of exposure is defined by what the distribution of exposure would be if all feasible interventions costing less than some value per healthy year of life saved were implemented. The threshold cost per year of healthy life saved that is deemed cost effective will vary across communities, as will the degree to which feasible interventions can shift the distribution of exposure. Because of this, a specific *cost-effective* minimum *risk* distribution, unlike the other three counterfactuals described, will be context dependent and not applicable to all communities.

The four counterfactual distributions are illustrated for tobacco and alcohol in Figure 2; these are intended to be only illustrative. We hope that by proposing various counterfactual distributions, we might also stimulate a more extensive debate on what is plausible, feasible, and cost effective for tobacco and alcohol. The *theoretical* minimum *risk* distribution for tobacco is zero consumption for all members of the population, and for alcohol it is one to two drinks per day for both males and females, middle aged or older.[10,13-15] In the second row of graphs in Figure 2, the *plausible* minimum *risk* distributions are shown. For tobacco it is based on progress observed in the more educated population groups in the United Kingdom,[18] as well as what might be plausible minimum levels of addiction among adults. The *plausible* minimum *risk* distribution for alcohol is based on the drinking trends of Australian females.[15] It includes a fraction of the population who are abstainers and the observation that in any society in which most individuals have one to two drinks a day there will be members of society who consume more than two drinks per day.[13-15] The *feasible* minimum *risk* distribution for tobacco is based on prevalence levels actually achieved for males and females in Sweden[19] and on the consumption distribution of older female smokers in the United States in the early 1990s.[20] Although there may be societies in Sub-Saharan Africa with lower rates of consumption, we should distinguish *feasible* minimum *risk* distributions in societies before and after tobacco addiction has been common. For alcohol, the *feasible* minimum *risk* distribution is based on observed drinking patterns in the United States and the United Kingdom in the early 1990s.[13,14] In the fourth row, we illustrate both the typical current distribution of consumption in a specific population and the likely shift in consumption that is possible with cost-effective intervention. For tobacco, this is based on the estimated effectiveness of policies to reduce smoking deaths reported in Townsend.[21] For alcohol, the redistribution of drinkers is based on evidence about the likely effects of prices and taxes as reported in Edwards *et al.*[22] Figure 2 clearly illustrates that estimates of attributable or avoidable burden of tobacco and alcohol would be heavily influenced by the principle used to select the counterfactual distribution of exposure.

Measurement Issues

It is critical to keep in mind that the sum of attributable burden is unbounded. As is clearly illustrated in Figure 1, death and disability from many diseases and injuries can be caused by multiple factors acting simultaneously, and the same event can legitimately be attributed to many underlying causes. For example, imagine a model of disease causation that requires the coincidence of three factors such as hypertension, alcohol, and smoking. If any one of the three is not present, a death will be averted. Using a variety of counterfactual distributions of exposure for each of these risk factors, that death is fully attributable to all three risk factors. Because attributable burden is theoretically unbounded, the plausibility of an estimate is its only constraint. The sum of attributable fractions can exceed 100% for a given cause or for all-cause mortality. Because there are no bounds on the sum of attributable fractions, there is also no limiting factor to temper the claims of advocates or analysts. For this reason one must interpret the estimates of attributable burden of any given exposure with great caution.

A related problem exists when at a given level in the causal hierarchy, there are complex interactions between different risk factors. For example, consider the cluster of diet, BMI, diabetes, physical activity, cholesterol, and hypertension in relation to mortality from cardiovascular diseases. Changes in the distribution of BMI and its effect on mortality may be mediated through changes in diabetes brought about by a reduction in BMI. The health effects of a change in BMI should include both the direct effects on mortality as well as those mediated through changes in other related risk factors. Analogous to the distinction between partial and total derivatives discussed above, the attributable

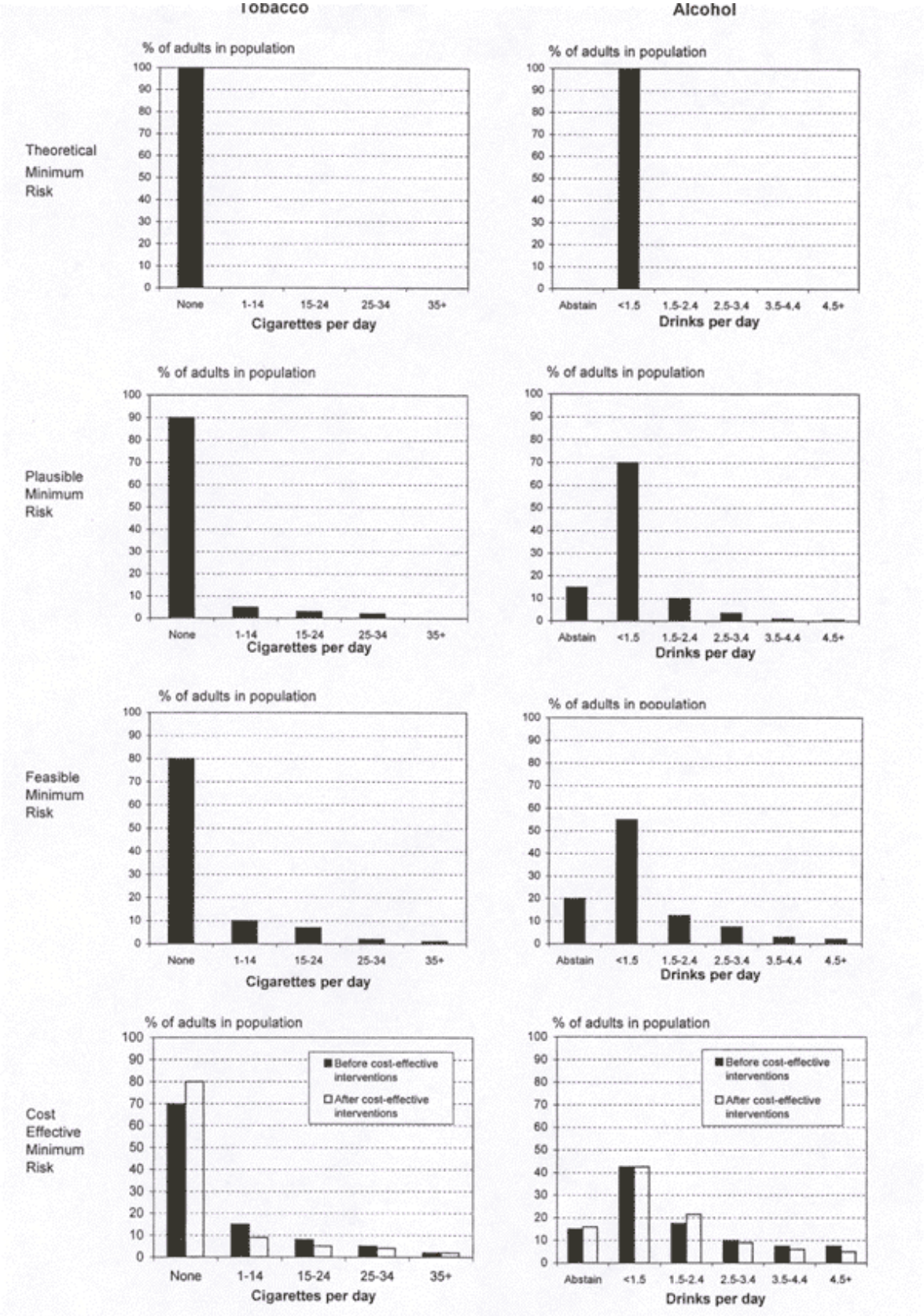

FIGURE 2. Counterfactual distribution of exposures for tobacco and alcohol. In the case of tobacco, we have assumed, for the sake of convenience, that all tobacco is hazardous. For some conditions, however, such as endometrial cancer, ulcerative colitis, and Parkinson disease, smoking appears to be protective and might well be so for Alzheimer disease, although this remains unproven.` The contribution of these causes is far outweighed by the established risks of smoking for major vascular, neoplastic, and respiratory diseases. For alcohol, the hazard function is not only determined by average consumption, but also by the pattern of drinking. The balance of risks and benefits from alcohol consumption is also strongly age dependent. [13]

burden from changes in exposures should include all effects regardless of the pathway through which they occur. When clusters of risk factors have several multidirectional causal links, the unbounded nature of the sum of attributable risk becomes clear. Unfortunately, many published relative risks for various exposures are based on multiplicative risk models that essentially control for the effects of a variable mediated through other variables included in the risk equation. The result is that, frequently, the estimated effects reported are partial and not total.

Estimates of attributable burden can be divided into four categories defined by the methods used: event categorization and three variants of the attributable fraction approach. An example of the event categorization method is the assessment of burden attributable to occupational exposures and hazards. For the assessment of occupation-related injuries in the G131), Leigh *et al*[23] used a legally mandated registration system to categorize events as injuries due to occupational risks. The event categorization method is problematic for two reasons. First, events are either 100% attributable to an exposure factor or not at all. This approach does not accord with any realistic representation of risks. Second, the event categorization method forces the counterfactual distribution of exposure to be the zero distribution. Indeed, there is no obvious way to incorporate any other counterfactual distribution. For occupational injuries, assuming the counterfactual distribution to be the zero distribution is highly implausible, as there will always be some occupational risks as long as people work.

In theory, the attributable burden from a risk factor is defined by the following equations:

$$AB = \sum AF_j B_j,$$

where

$$AF_j = \frac{\int_{x=0}^{m} R_j(x)\,P(x) - \int_{x=0}^{m} R_j(x)\,P'(x)}{\int_{x=0}^{m} R_j(x)\,P(x)}$$

and where *AB* is the attributable burden from a variable or risk factor, AF_j is the attributable fraction of disease burden for cause j, B_j is the burden from cause j, *Rj(X) is* the relative risk of burden (death or disability) from cause j for exposure level x, PM is the distribution of the population by exposure level [for lagged exposures, P(x) would be an index of weighted cumulative exposure], P'(x) is the counterfactual distribution of exposure for the population, and m is the maximum level of exposure. Where the relative risk functions for death and disability from a cause are different, separate attributable fractions would need to be calculated.

This equation is in fact the continuous analogue of the potential impact fraction (PIF), defined as "the proportional reduction in the total number of new (incident) cases of a certain disease, resulting from a specific change in the distribution of a risk factor in the population at risk."[24] Given a number (m) of exposure categories, the PIF can be written as follows:

where P^i and P'^i are, respectively, the proportions of the population in exposure category i before and after intervention, and R^i is the relative risk.

To estimate attributable burden, it is necessary to know the relative risks for each cause of death and disability as a function of exposure level, the current (and past for time lagged variables) levels of exposure, the counterfactual distribution of exposure, and the burden of disease due to each cause of death and disability in a given population. Relative risk functions are usually estimated from case-control or prospective studies. The usual practice in the literature on attributable burden is to assume that relative risks are universal; *ie,* those studied in one population can be applied to many other populations, albeit with caution. However, there is clear evidence from the two large American Cancer Society Cancer Prevention Study (CPS) prospective studies[20](CPS 1 and CPS 11) on the risks of smoking in the United States that relative risks can change. Between CPS 1 (1959-1965) and CPS 11 (1982-1988), the relative risk of lung cancer for current smokers compared with lifelong nonsmokers increased from 11.4 to 22.4 for males and from 2.7 to 11.9 for females, reflecting rising hazards with longer exposure (in this case, duration ofsmoking).[20] In fact, the impact of an exposure on mortality risk is not simply multiplicative; therefore, we would expect relative risks to change depending (m other risk factors and on levels of exposure.

Despite these concerns, the major determinant of variation (among different populations) in the attributable burdens due to a particular risk factor is not differences in relative risk functions, but rather differences in the population distribution of exposure levels. Once this population distribution is determined, the population attributable burden is calculated by estimating what the level of mortality or disability would be if the distribution of the population by exposure level were shifted to the counterfactual distribution of exposure. Estimating the population distribution of exposure for particular risk factors, therefore, is the major challenge in deriving attributable burden, at least for those exposures for which the relative risk does not change dramatically over time.

Another important consideration in estimating attributable burden is the suitability of the available measures of exposure. For many exposures, such as cigarette smok-

ing, relative risk is a function of the duration, intensity, and type of exposure. Frequently, survey or consumption data are available only for current exposure status, such as the proportion of the population who are current smokers, the proportion who drank a certain number of drinks in the last 2 weeks, etc. Current exposure status measures are then used as proxies for cumulative past exposures. However, for most risk factors, current exposure, as summarized by a single index, is likely to be a very poor indicator of cumulative exposure over an individual's lifetime. Creative methods have been used to overcome the difficulties of measuring past exposure. For example, Peto *et al*[10] estimate cumulative past exposure to smoking based on observed lung cancer rates, because in most developed countries lung cancer in excess of some standard such as the CPS 11 nonsmoker lung cancer rates is due almost entirely to the cumulative effects of smoking. Unfortunately, for many of the risk factors in the G131), the measures of exposure are current-status measures and are often quite poor. For others, it is virtually impossible to measure the population distribution by exposure status at one moment in time or even over a period of time; an example of this problem is the measurement of blood-alcohol levels used to estimate the impact of alcohol consumption on road traffic accidents. Individuals can move quite rapidly between exposure states (for example, various blood alcohol levels), creating enormous difficulties in estimating the average population distribution of exposure.

When data on the population distribution of exposure are completely lacking, as is often the case, some have estimated the burden of a risk factor by taking the fraction of current burden attributable to a risk factor in one population and applying it to other populations. Implicitly, this practice is based on the assumption that both the relative risks and the population distributions of exposure are identical across the populations studied, which is unlikely to be the case. An example of this type of approach is the regional estimates of DALYs attributable to alcohol, published in the *World Development Report 1993.*[17] This indiscriminate use of attributable fractions is difficult to justify, because it is highly unlikely that the population distributions of exposure for most risk factors are identical across all communities. Even cruder variants of this approach have been used, not even taking into consideration the structure of burden by cause, *ie,* using estimates of the overall attributable fraction of burden from all causes calculated for one population and simply applying them to another.

The more plausible approach, which involves measuring relative risks and population distribution of exposure, is certainly the preferred method for many risk factors. This framework assumes that the harm from exposure occurs only in the exposed, ie, the harm is internalized. However, for. selected risk factors, such as alcohol and illicit drug use, exposure may indirectly affect individuals who are not exposed. A road traffic accident caused by a drunk driver who collides with another person or vehicle is an obvious example. An individual under the influence of drugs or alcohol may commit violent acts against other individuals. The resulting attributable burden will not be captured in the relative risk and exposure framework outlined earlier. When externalities such as these exist, the relative risk and exposure method needs to be extended. The estimates for the burden of alcohol and illicit drugs included in the GBD do not take externalities into account explicitly, as no reliable data were available to do so.

In evaluating claims on attributable burden for various risk factors, a critical question is whether a causal relation has been established. Various criteria for demonstrating causality have been proposed, including strength of the association, consistency of effect, specificity, temporal relationship, biological gradient, biological plausibility, coherence of evidence, experimental evidence, and reasoning by analogy.[25] For some risk factor-disease interactions, such as smoking and lung cancer, all of the relevant criteria for causality have been met. For other risk factors, such as air pollution, malnutrition, and some occupational injuries, this is not the case. Consequently, the degree of confidence in attributable burden estimates for different risk factors will vary, being greatest for those exposures for which causality has been reliably demonstrated, notably tobacco and alcohol. However, even when strict causality criteria have not been established, the weight of evidence regarding the impact of risk factors may still be substantial. In these cases, the estimates of attributable burden are at least interesting from a public health point of view.

GBD Attributable Burden Assessment

As an illustration of the difficulties and issues that emerge in undertaking comparable assessments of risk factors, in this section we review the methods and results of the risk factor component of the GBI). Table 1 provides a summary of various methodological aspects of the analyses of burden attributable to the ten major risk factors. Two of the ten risk factors are physiological variables, and the remaining eight variables can probably best be classified as proximal causes. Table 1 indicates that levels of exposure have been measured in very different ways for each risk factor. In fact, this type of comparative assessment demonstrates quite clearly that the approaches to measuring and estimating the population distribution of exposure have been developed in an *ad hoc* manner within the literature on each of the major risk factors. The counterfactual distributions of exposure are *theoretical* minimum *risk* distributions for water supply and sanitation, tobacco, occupation, physical activity, and illicit drugs. The distributions used for hypertension, malnutrition, air pollution, and unsafe sex do not correspond to either *theoretical* minimum *risk* or *plausible* minimum *risk* counterfactuals. In part, this is because dichotomous exposure variables have been used for blood pressure, nutritional status, and air pollution.

Table 2 provides a comparison of the attributable DALYs for each of ten major risk factors that were evaluated in the GBD and the number of DALYs esti-

TABLE 1. Summary of Methodological Differences in Approaches Used to Estimate Attributable Burden from Ten Major Risk Factors, Global Burden of Disease Study, 1990*

Risk Factor	Type of Risk Factor: Exposure	Type of Risk Factor: Physiological State	Relative Risk Controlled for Confounding	Measure of Exposure	Reference Distribution of Exposure	Time Lag from Exposure to Burden
Malnutrition		0		Population less than 2 SDs weight-for-age based on extensive national surveys	Population weight-for-age higher than minus 2 SDs	Intermediate
Poor water, sanitation, and hygiene	0			Based on the theoretical fecal-oral route of transmission	Zero	Short
Unsafe sex	0			Based on theoretical model of transmission of STDs and on contraceptive demand surveys for maternal conditions	Zero	Short to long
Alcohol (disease)†	0		0	Indexed on alcohol consumption, non-hepatitis B cirrhosis, and alcohol dependence syndrome	Zero	Long
Alcohol (injury)†	0			Indexed on estimate of consumption patterns based on small,scale studies	Zero	Short
Occupation (disease)†	0			Registration data for EME, FSE, and LAC and constant rates for all other regions	Zero	Long
Occupation (injury)†	0			Registration data for EME and co~stant rates for all other regions	Zero	Short
Tobacco	0		0	Indexed on lung cancer	Zero	Long
Hypertension		0		Population surveys of blood pressure	Systolic blood pressure of 110 mmHg	Long
Physical inactivity	0		0	Population surveys of activity patterns	Regular physical activity	Long
Illicit drugs	0			Small-scale studies	Zero	Short to intermediate
Air pollution	0			Monitoring systems in urban areas for most regions	WHO guidelines	Short to long

EME = Established Market Economies; FSE = Formerly Socialist Economies of Europe; LAC = Latin America and the Caribbean. * Source: Murray and Lopez.' t For alcohol use and occupational exposures, different methods and characteristics apply depending on whether the burden arises from a disease or injury. These characteristics are, therefore, listed separately in the table.

mated for leading disease and injury categories. Six of the ten risk factors analyzed in the GBD are comparable in magnitude with the diseases or injuries in the list of ten leading causes of DALYs. Globally, hypertension causes slightly more burden than self-inflicted injuries, and physical inactivity causes as much burden as pertussis and bipolar disorder. The risk factor of the set of ten that is estimated to cause the smallest burden is air pollution, which is nevertheless equivalent in magnitude to cataract.

Comparability of risk factor contributions is hindered by the lack of standardization of methods and by the differences in the reliability of the underlying epidemiological studies of relative risk and population exposure levels. Yet the estimates do suggest that some exposures are major contributors to disease burden, either regionally or globally (Tables 3 and 4). Large populations in the developing world are malnourished and have little access to safe water and sanitation. These two exposures cause a large amount of disease burden in some regions, most notably Sub-Saharan Africa and India, where collectively they account for 30-40% of the entire disease and injury burden as measured by DALYs. Even allowing for the fact that these two exposures are negligible causes of burden in developed regions, the global contribution is about 16% for malnutrition and 8% for unsafe water and sanitation.

Unsafe sex, tobacco, alcohol, and occupational hazards each cause an estimated 2-4% of the entire annual burden of disease and injury. Moreover, there are marked regional variations in the amount of disease and injury burden attributable to various exposures. In both the Established Market Economies and the Former Socialist Economies of Europe, where men have been smoking for decades, the full effects of the enormous hazards of tobacco use are now being felt, with 10-12% of the entire burden of disease currently attributable to tobacco. Conversely, in less developed regions, where men have not been smoking long enough to incur significant risks and where women by and large do not smoke at all, the proportionate contribution of tobacco to disease burden is currently much smaller (typically 1-4%). However, on the basis of current smoking patterns, this burden is predicted to rise dramatically within the next three decades.[5] Alcohol, too, displays marked regional variations, causing only marginally less disease and injury burden than tobacco in rich countries, but causing a higher proportion of the burden than tobacco in poorer regions. This proportion is particularly marked in Latin America and the Caribbean, where almost one

TABLE 2. Comparative Magnitude of Global Disability-Adjusted Life Years (DALYs) for the 25 Leading Diseases and Injuries and 8 Major Risk Factors

Diseases or Injuries	DALYs (millions)	Risk Factors
	219.6	Malnutrition
1 Lower respiratory infections	112.9	
2 Diarrheal diseases	99.6	
	93.4	Poor water sanitation/ personal hygiene
3 Conditions arising during perinatal period	92.3	
4 Unipolat major depression	50.8	
	48.7	Unsafe sex
	47.7	Alcohol
5 Ischemic heart disease	46.7	
6 Cerebrovascular disease	38.5	
7 Tuberculosis	38.4	
	37.9	Occupation
8 Measles	36.5	
	36.2	Tobacco
9 Road traffic accidents	34.3	
10 Congenital anomalies	32.9	
11 Malaria	31.7	
12 Chronic obstructive pulmonary disease	29.1	
13 Falls	26.7	
14 Iron-deficiency anemia	24.6	
15 Protein-energy malnutrition	20.9	
16 War	20.0	
	19.0	Hypertension
17 Self-inflicted injuries	18.9	
18 Tetanus	17.5	
19 Violence	17.4	
20 Alcohol use	16.6	
21 Drownings	15.7	
22 Bipolar disorder	14.2	
	13.6	Physical inactivity
23 Pertussis	13.4	
24 Ostcoarthritis	13.3	
25 Cirrhosis of the liver	13.2	

Source: Murray and Lopez.[1]

in ten DALYs in 1990 were attributed to alcohol,[5] but much less so in the Middle Eastern Crescent, where alcohol consumption is not socially acceptable.

Discussion

There are major obstacles to reliably quantifying the burden of disease due to risk factors. However, to ensure that these exposures are given the same consideration as disease and injury in the public health policy debate, it is essential that estimates of their current and future public health impact be made. In this paper, we have summarized the first results of a comparative assessment of the impact of ten major health hazards in 1990. We have done so fully aware of the uncertainties around both the science and the information base required to estimate attributable burden. These results must be seen as approximate, but they are nonetheless provocative. What they suggest is that some exposures, particularly malnutrition, poor water, and other hygiene-related factors, remain a major cause of disease burden, accounting for as much, if not more, of the global burden of disease as more widely publicized health problems, such as malaria, measles, tuberculosis, and maternal conditions. Other risk factors, particularly occupational exposures, alcohol, unsafe sex, and tobacco, also accounted for a significant number of DALYs globally in 1990 and deserve a commensurate response from the global public-health community. In particular, DALYs attributable to tobacco use are projected to triple between 1990 and 2020.[5] The epidemic of tobacco-induced disease has become a global public health emergency, requiring concerted action at all levels of the health system.

The GBD assessment of the magnitude of risk factors illustrates the power of comparing risk factor burden with the burden of specific diseases and injuries. Such comparisons are an effective means of drawing the attention of decision makers to the magnitude of health problems caused by various distal socioeconomic, proximal, or physiological variables. In future efforts at comparative risk factor assessment, the number of variables examined needs to be expanded to include distal determinants. One clear manner to improve future revisions of the GBD is to standardize the methods for risk factor assessment. We propose that the following conceptual approach be used

TABLE 3. Percentage of Deaths Attributed to 10 Major Risk Factors in the Global Burden of Disease Study, 1990

	Regions										
Risk Factors	**EME**	**FSE**	**IND**	CHN	**OAI**	**SSA**	**LAC**	MEC	World	Developed	Developing
Malnutrition	0.0	0.0	18.4	3.1	12.3	31.9	4.5	9.8	11.7	0.0	14.9
Poor water/sanitation	0.0	0.1	9.0	0.9	6.4	10.7	4.5	8.3	5.3	0.0	6.7
Unsafe sex	0.8	0.9	2.4	0.5	2.4	5.9	2.5	1.1	2.2	0.8	2.5
Tobacco	14.9	13.6	1.4	9.2	4.0	0.9	3.3	2.4	6.0	14.5	3.7
Alcohol	1.2	1.4	1.2	1.3	1.8	3.2	4.5	0.5	1.5	1.3	1.6
Occupation	2.Z	2.0	2.0	2.8	2.7	1.4	3.2	2.4	2.2	2.1	2.3
Hypertension	11.1	16.3	3.9	3.2	1.0	2.5	8.1	7.7	5.8	12.9	3.8
Physical inactivity	11.7	7.0	3.6	2.6	1.1	0.1	3.9	3.1	3.9	10.1	2.3
Illicit drugs	0.4	0.2	0.1	0.2	0.2	0.1	0.5	0.1	0.2	0.3	0.2
Air pollution	0.9	5.5	0.9	0.8	0.7	0.3	1.1	1.0	1.1	2.5	0.7

EME = Established Market Economies; FSE = Formerly Socialist Economics of Europe; IND = India; CHN = China; OAI = Other Asia and Islands; SSA = Sub-Saharan Africa; LAC = Latin America and the Caribbean; MEC = Middle Eastern Crescent.

TABLE 4. Percentage of **DALYs Attributable** to 10 **Major Risk Factors in the Global Burden** of Disease Study

	Regions										
Risk Factors	EME	FSE	IND	CHN	OAI	SSA	LAC	MEC	World	Developed	Developing
Malnutrition	0.0	0.0	22.4	5.3	14.5	32.7	5.1	11.0	15.9	0.0	18.0
Poor water/sanitation	0.1	0.2	9.5	2.0	7.4	10.1	5.3	8.8	6.8	0.1	7.6
Unsafe sex	2.0	2.2	4.0	0.4	4.4	6.5	3.7	1.5	3.5	2.1	3.7
Tobacco	11.7	12.5	0.6	3.9	1.5	0.4	1.4	1.2	2.6	12.1	1.4
Alcohol	10.3	8.3	1.6	2.3	2.8	2.6	9.7	0.4	3.5	9.6	2.7
Occupation	5.0	3.8	2.0	3.9	2.8	1.3	3.7	2.6	2.7	4.6	2.5
Hypertension	3.9	5.9	0.9	1.0	0.3	0.6	1.8	1.7	1.4	4.7	0.9
Physical inactivity	4.8	2.8	1.0	0.8	0.3	0.0	1.0	0.8	1.0	4.0	0.6
Illicit drugs	2.3	1.3	0.1	0.3	0.7	0.2	1.6	0.7	0.6	1.9	0.4
Air pollution	0.5	3.1	0.5	0.4	0.4	0.2	0.5	0.5	0.5	1.5	0.4

EME = Established Market Economies; FSE = Formerly Socialist Economies of Europe; IND = India; CHN = China; OAI = Other Asia and Islands; SSA Sub-Saharan Africa; LAC = Latin America and the Caribbean; MEC = Middle Eastern Crescent.

Sources: Mason *et al.*,[26] Huttly,[16] Berkley,[27] Murray and Lopez,[1] Leigh *et al.*,[23] Nichols and Elliot,[28] Koplan and Pratt,[29] Donoghoe *et al.*[30] and Hong *et al.*[31]

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, as follows.

(1) Where possible, avoidable burden should be estimated. As a second alternative, attributable burden should be calculated.

(2) Assessments of avoidable and attributable burden should be based on all pathways through which a variable is causally related to a health outcome. Total assessments rather than partial assessments are particularly important when applying this approach to distal socioeconomic variables.

(3) The counterfactual distribution of exposure should be based on the principle of *plausible minimal risk* rather than the *theoretical minimal risk* distribution that will generate the lowest level of the health outcome of interest. The qualification of plausibility is meant to exclude counterfactual distributions that are not reasonable. Currently, what is considered plausible is clearly ambiguous or at the very least imprecise for many risk factors. Nevertheless, it may be reasonable to hope that a consensus could be created for most risk factors on plausible minimal risk.

(4) Global and regional risk factor assessments should be based on the relative risk-exposure model. Efforts should be made to measure or develop plausible estimates of regional population distributions of exposure. Relative risks based on epidemiological studies in one context applied to another should be carefully reviewed. Guidelines for extrapolating or generalizing relative risks from one population to another should be developed and promulgated by an authoritative organization such as the World Health Organization. Efforts should be made to assess, even if qualitatively, the uncertainty introduced by generalizing relative risks from selected populations to other populations.

Despite the substantial methodological problems in calculating comparable and reliable estimates of burden attributable to various exposures, we remain convinced that such quantification must be attempted if epidemiology is to contribute effectively to the improvement of public health. Effective advocacy, health promotion, and disease prevention require plausible information about the causes of disease and injury. Public health will be better served if we know not only that a particular exposure is hazardous, but also the comparative magnitude of that hazard compared with other health concerns. Having said this, in reporting and interpreting such risk factor assessments, we would strongly argue for clarity in defining the reference used to determine what is and is not avoidable burden, and in each case, the extent to which causality criteria have been met. This clarity will greatly increase the comparative value of risk factor quantification and thereby enhance their usefulness for stimulating public policy responses.

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