
Chapter 27

POTENTIAL HEALTH GAINS FROM REDUCING MULTIPLE RISK FACTORS

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1. INTRODUCTION

Estimates of the burden of disease attributable to selected individual risk factors were presented in chapter 26. Diseases and injuries are, however, almost always caused by multiple risk factors (Rothman 1976; Walter 1980), motivating analysis of the health benefits of simultaneous reductions in multiple risks. Estimating the joint effects of multiple distal and proximal risks is particularly important because many factors act through other, intermediate, factors (Murray and Lopez 1999; Yerushalmy and Palmer 1959), or in combination with other factors, as we described in chapter 1 of this book. For example, education, occupation and income may affect smoking, physical activity and diet, which are risk factors for cardiovascular diseases, both directly and through further layers of intermediate factors such as body mass index (BMI), blood pressure and cholesterol. Multi-causality also means that a range of interventions can be used for disease prevention, with the specific choice determined by factors such as cost, technology availability, infrastructure and preferences.

A number of works have estimated the joint effects of two or more risk factors in specific cohorts (Hirayama 1990; Neaton and Wentworth 1992; Rothman and Keller 1972; Stampfer et al. 2000; Willet 2002), or for specific groups of diseases and risks (Doll and Peto 1981; Smith et al. 1999). Innovative models and methods have also been developed to quantify the complexity of multiple risk factor effects, especially as they interact over time (Manton et al. 1993; Robins 1999). Estimating joint risk factor effects beyond specific diseases or cohorts, however, remains relatively unexplored in epidemiology and population health. Using comprehensive reviews of data on selected major risk factors in various levels of causality, this chapter is an attempt to do so.

We further used the joint effects of multiple risk factors to estimate the potential gain in healthy life expectancy (HALE) from reducing these risks. Analysis of multiple risk factors, with heterogeneous contributions to disease burden in different populations, would also allow estimating how much of the cross-population health differentials (e.g. differences in HALE) are due to the selected risk factors. By estimating gains in HALE based on causes of disease, this work also contributes in a systematic way to the continued debate on the potential limits to life expectancy (Oeppen and Vaupel 2002; Riley 2001).

2. METHODS

2.1 ESTIMATING JOINT POPULATION ATTRIBUTABLE FRACTIONS

Methods and data sources for estimating the burden of disease attributable to individual risk factors were described in chapter 2.5. The contribution of a risk factor to disease or mortality relative to some alternative exposure scenario (i.e. population attributable fraction, PAF, defined as the proportional reduction in population disease or mortality that would occur if exposure to the risk factor were reduced to an alternative exposure scenario [Eide and Heuch 2001; Miettinen 1974]) is given by the generalized “potential impact fraction” in Equation 1.

$$PIF = \frac{\int_{x=0}^m RR(x)P(x)dx - \int_{x=0}^m RR(x)P'(x)dx}{\int_{x=0}^m RR(x)P(x)dx} \quad (1)$$

where

$RR(x)$: relative risk at exposure level x

$P(x)$: population distribution of exposure

$P'(x)$: alternative or counterfactual distribution of exposure, and

m : maximum exposure level

In equation 1, RR , P , and P' may represent joint relative risks and exposure distributions for multiple risk factors (i.e. x may be a vector of risk factors), with RR for each risk factor estimated at the appropriate level of the remaining ones (Eide and Heuch 2001). Alternatively, for n biologically independent and uncorrelated risk factors, the joint PAF is given by equation 2 (Miettinen 1974; Walter 1976). If risk factors are independent and uncorrelated, the proportion of the remaining disease which is attributed to the i th additional risk factor equals PAF_i (and hence $1 - PAF_i$ not attributable to this factor). Therefore, the second term in the right hand side of equation 2 (i.e. the product of all

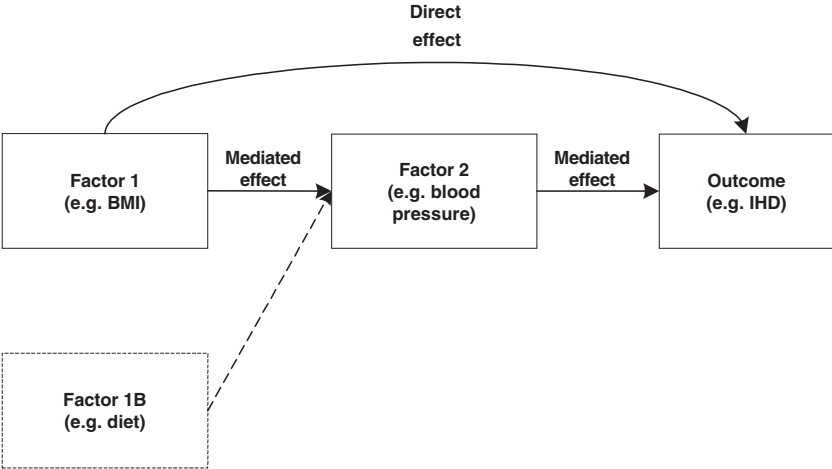
[1 - PAF_i] terms) is the fraction of disease not attributable to any of the *n* risk factors. One minus this term is the fraction attributable to the combined effects of the *n* risk factors:

$$PAF = 1 - \prod_{i=1}^n (1 - PAF_i) \tag{2}$$

where PAF_i is the PAF of individual risk factors

Estimating the joint effects of multiple risk factors is in practice complex for several reasons. First, some of the effects of the more distal factors (e.g. physical inactivity) are mediated through intermediate factors (e.g. high BMI itself through blood pressure) (Figure 27.1). Estimating the joint effects of distal and intermediate factors requires knowledge of independent hazards of the distal ones (vs individual risk factor effects, which are based on total hazard) (Figure 27.1). Second, the hazard due to a risk factor may depend on the presence of other risk factors (effect modification) (Koopman 1981; Rothman and Greenland 1998). Third, there may be correlation between exposure to various risk factors, because they are affected by the same distal factors and policies.

Figure 27.1 Mediated and direct effects



Note: Some of the effects of a risk factor (e.g. BMI) may be mediated through other factors (e.g. blood pressure). When estimating the total effects of individual distal factor on disease, both mediated and direct effects should be considered. This is because in the presence of mediated effects, controlling for the intermediated factor would attenuate the effects of the more distal one (Greenland 1987). When estimating the joint effects of the more distal factor (e.g. BMI) and the intermediate one (e.g. blood pressure), the direct and mediated effects must be separated, especially if the intermediate factor is affected by other distal factors (e.g. diet).

For example, undernutrition, poor water and sanitation and the use of solid fuels are more common among poor rural households in developing countries, or smokers generally have higher and more harmful patterns of alcohol consumption and worse diet than non-smokers.

While the current literature refers to scenarios 1 and 2 as biological interaction and to scenario 3 as statistical interaction (Miettinen 1974; Rothman and Greenland 1998; Rothman et al. 1980), this distinction is somewhat arbitrary and the three scenarios may occur simultaneously. For example, zinc deficiency affects mortality from diarrhoea directly as well as through lowering growth (weight-for-age) (scenario 1) (Brown et al. 2002; Zinc Investigators' Collaborative Group 1999), and may also be correlated with underweight, other micronutrient deficiencies, and poor water and sanitation (scenario 3). Similarly alcohol and smoking may not only be correlated (scenario 3), but also affect each other's hazard for some diseases (scenario 2) (Rothman and Keller 1972). Although the epidemiological literature has placed much emphasis on removing or minimizing the effects of confounding covariates, mediated and stratified hazards have received disproportionately little empirical attention. Therefore, we used reviews of extant literature and re-analysed existing cohort data to strengthen the empirical basis for considering interactions in sensitivity analyses.

In one set of estimates (referred to as the unadjusted scenario), we assumed no mediated effects or interactions among risk factors. We then included the mediated effects and interactions described above in a second scenario (referred to as the adjusted scenario).

JOINT EFFECTS OF CARDIOVASCULAR DISEASE RISK FACTORS

Epidemiological studies on the effects of high BMI, physical inactivity, and low fruit and vegetable intake on cardiovascular disease risk have illustrated some attenuation of the effects after adjustment for intermediate factors (e.g. blood pressure or cholesterol) (Berlin and Colditz 1990; Blair et al. 2001; Eaton 1992; Gaziano et al. 1995; Jarrett et al. 1982; Jousilahti et al. 1999; Khaw and Barrett-Connor 1987; Liu et al. 2001, 2000; Manson et al. 1990, 2002; Rosengren et al. 1999; Tate et al. 1998). This attenuation confirms that some of the hazard of the more distal factors is mediated through the intermediate ones (Figure 27.1). The attenuation has varied among studies but has consistently been less than one half of the excess risk of the distal factors. We used an upper bound of 50% as the proportion of the excess risk from these risk factors mediated through intermediate factors that are themselves among the selected risks.

To include effect modification, deviations from the multiplicative model of 10% for ischaemic heart disease (IHD) and 30% for ischaemic stroke were used based on existing studies (both sub-multiplicative) (Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998; Neaton and Wentworth 1992).

JOINT EFFECTS OF SMOKING AND OTHER RISK FACTORS

Liu et al. (1998) found that in China, the relative risks for mortality from lung and other cancers, respiratory diseases and cardiovascular diseases were approximately constant in different cities whose non-smoker mortality rates from these diseases varied by a factor of 4–10 (see Figures 4 and 6 in Liu et al. 1998). This finding has also been confirmed in studies which stratified hazards for serum cholesterol (Jee et al. 1999).

JOINT EFFECTS OF CHILDHOOD UNDERNUTRITION FOR INFECTIOUS DISEASES

Zinc affects child growth (Brown et al. 2002) and some of its effects on infectious diseases may be mediated through growth (e.g. underweight). As no published source for these mediated effects existed, data from some of the available zinc trials (Zinc Investigators' Collaborative Group 1999) were re-analysed and an upper bound of 50% on the proportion of zinc deficiency risk mediated through underweight was used. Vitamin A deficiency, which affects some of the same diseases as underweight and zinc deficiency, has been found not to change the hazard size for the other two risk factors based on stratified results from clinical trials and recent reviews of micronutrient deficiency literature (Christian and West Jr. 1998; Ramakrishnan and Martorell 1998; Ramakrishnan et al. 1995; West et al. 1991).

JOINT EFFECTS OF UNDERNUTRITION AND ENVIRONMENTAL RISK FACTORS IN CHILDHOOD DISEASES

Anthropometric (growth) indicators of childhood nutrition (e.g. weight-for-age) are aggregate measures of multiple factors which include nutrition (e.g. protein-energy intake) and previous infection (Pelletier et al. 1993; Scrimshaw et al. 1968; UNICEF 1990). Therefore, some of the risks for indoor smoke from solid fuels and poor water, sanitation and hygiene (which result in acute lower respiratory infections [ALRI] and diarrhoea, respectively) may be mediated through underweight. In a review of existing literature, Briend (1990) concluded that attempts to disentangle direct and mediated contributions, especially over long time periods needed to affect population-level anthropometry, have not established diarrhoea as a significant cause of underweight. Other works, however, have found evidence that infection (especially diarrhoea) could result in reduced growth and increased the prevalence of underweight (Black 1991; Guerrant et al. 1992; Lutter et al. 1989, 1992; Martorell et al. 1975a, 1975b; Stephensen 1999). To account for potential mediated effects, we chose an upper bound of 50% for the proportion of the excess risks for indoor smoke from solid fuels and for poor water, sanitation and hygiene mediated through underweight in subregions¹ where underweight was a cause of disease burden.

RISK FACTOR CORRELATION

To estimate the joint effects of risk factors with a continuous exposure variable (e.g. blood pressure and cholesterol), each integral in the *PIF* relationship may be replaced with

$$\int_{x_1=0}^{m_1} \int_{x_2=0}^{m_2} RR_1(x_1)RR_2(x_2)P(x_1,x_2)dx_1dx_2,$$

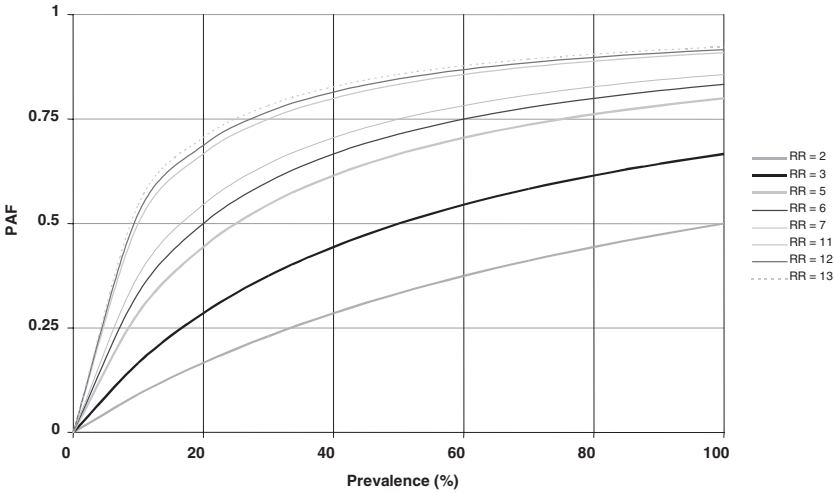
where subscripts 1 and 2 denote the two risk factors and *P* is the joint distribution of the two exposures. If the joint *RR* were a linear function of exposure levels (x_1 and x_2), then correlation between the two risk factors would not affect total hazard. Because individual *RR*s are non-linear functions of exposure (e.g. in a logistic or Cox proportional hazard model) and joint *RR*s are the product of such terms, positive correlation between risk factors would, in general, imply a larger *PAF* than zero correlation, which in turn would be larger than negative correlation (sub-multiplicative effect modification could result in smaller *PAF* even with positive correlation for some *RR* values). Similarly, for categorical risk factors, positive correlation would in general result in larger *PAF* (see also Greenland 1984).

For the range of exposures and relative risks observed here, this secondary effect of risk factor correlation would be considerably smaller than the joint attributable fraction, which may be confirmed by micro-simulation of exposure distributions and relative risks. This is because the *PAF* relationship is an increasing concave function of individual or joint *RR* (i.e. rate of increase declines with increasing *RR* or prevalence) (Figure 27.2). Because the risk factors considered in this analysis individually accounted for large fractions of the diseases affected by them in populations where these diseases are important components of disease burden, the joint effects approached 100% asymptotically, limiting the overestimation potential (e.g. individually, underweight accounted for 60–70% of under-five diarrhoea in AFR-D, AFR-E and SEAR-D; poor water, sanitation and hygiene for approximately 90%; vitamin A deficiency for 20%-30%; and zinc deficiency for 10–17%; similarly, in various developed subregions, individually, high blood pressure accounted for 44–64% of IHD; high cholesterol for 51–68%; high BMI for 17–36%; low fruit and vegetable intake for 19–35%; and physical inactivity for 15–16%).

2.2 GAINS IN HEALTHY LIFE EXPECTANCY (HALE)

The incidence of many conditions (e.g. neuropsychiatric conditions or long-term effects of injuries) may cause ill health but not death. It is therefore important to capture both fatal and non-fatal health outcomes in describing population health. Healthy life expectancy or health-adjusted life expectancy (HALE) reduces total life expectancy into equivalent years of “full health” by taking into account the distribution and severity of health states in the population (Mathers 2002). Inputs to the calculation of HALE include the period life table (or age-sex-specific

Figure 27.2 PAF relationship as a function of prevalence and relative risk



Note: PAF relationship is an increasing concave function of both prevalence (seen in the shape of each curve) and RR (seen in the declining distance between each adjacent pair of curves). As a result, for joint risk factor PAF, errors due to deviations from a simple uncorrelated multiplicative model (due to risk factor correlation or effect modification) are secondary to the joint PAF. For example, for two risk factors with RR = 2 and RR = 3, a multiplicative model would result in a joint RR of 6. The PAF would be approximately correct even if the true joint RR were 5 or 7, as the PAF curves are close for these RR values. This phenomenon becomes increasingly dominant with increasing number of risk factors (i.e. the curves for RR = 11, 12, and 13 are even closer than those for RR = 5, 6 and 7). Further, the flattening of PAF curves at high exposures limits the error due to risk factor correlation.

mortality rates) and prevalences of health states (resulting from diseases, their sequelae, and their combinations) for each country. Methods for estimating HALE have been described in detail elsewhere (Mathers et al. 2001). Unlike estimates of the burden of disease which compare current mortality and disability to a normative survivorship function (Murray and Lopez 1996), estimates of the gain in HALE account for competing risks.

The estimates in this chapter show the improvements in HALE for the year 2000, that would have been observed if exposure to the selected risk factors had been reduced to the theoretical-minimum-risk counterfactual distribution, as described in each of the risk factor chapters. In each of the 14 subregions, joint disease-specific PAFs were estimated for all diseases affected by the 20 leading global risk factors (chapter 26; see also individual risk factor chapters), for all age and sex groups.

Mortality and incidence in the counterfactual scenario are $(1 - PAF_M)$ and $(1 - PAF_I)$ times their original values where PAF_M and PAF_I are the PAF of mortality and incidence attributable to the joint effects of the risk

factors. The age-sex-specific mortality and age-sex-cause-specific prevalence of diseases and their sequelae were adjusted to these levels to estimate the HALE gain as a result of multiple risk factor removal. Reduction in prevalence was obtained from reduction in incidence under equilibrium conditions (Kruijshaar et al. 2002). Cause-specific estimates were necessary for non-fatal conditions because of different disability weights (Murray and Lopez 1996) but not for fatal conditions.

3. RESULTS

Table 27.1 shows the individual and joint contributions of the 20 selected risk factors for the 10 leading diseases in the world and in three broad combinations of subregions—high-mortality developing (38% of global population), lower-mortality developing (40% of global population) and demographically and economically developed (22% of global population).² For most diseases, the joint effects of these risk factors were substantially less than the crude sum of the individual effects (e.g. globally four separate risk factors were each responsible for 10%, 18%, 45% and 88% of diarrhoeal disease, but with a joint PAF of 92–94%), confirming that a large number of cases are caused by the joint actions of more than one of these risk factors acting as sufficient causes (Rothman 1976), or through other factors.

Globally, large fractions of diarrhoea (92–94%), ALRI (55–62%), lung cancer (72%), upper aerodigestive cancer (60%), chronic obstructive pulmonary disease (COPD) (60%), IHD (83–89%) and stroke (70–76%) were attributable to the joint effects of the risk factors considered here (see Willet 2002 and Stampfer et al. 2000 for consistent vascular disease examples from specific cohorts). The joint PAFs for cancers other than lung and upper aerodigestive (23%), perinatal conditions (23%), maternal conditions (42%), and intentional (29%) and unintentional (20%) injuries, which have more diverse risk factors, were smaller but non-negligible. Although the fraction of total malaria burden attributable to childhood undernutrition was relatively large (56–59%), this was because of the contribution of mortality at younger ages to disease burden. No adult malaria was attributed to the above risk factors because the epidemiological literature has focused on quantifying increased risk of malaria as a result of childhood undernutrition only. Finally, with the exception of alcohol and drug dependence, which were fully attributable to their specific risk factors, very small fractions or none of neuropsychiatric conditions, tuberculosis, congenital anomalies, and a number of other diseases were attributed to the risk factors considered in this book.

Figure 27.3 shows the individual and joint contributions (including overlap) of selected major risk factors to each of the following disease categories in the three subregional groups described above: I. communicable, maternal, perinatal and nutritional conditions;

Table 27.1 Individual and joint contributions of 20 selected risks to 10 leading diseases and total burden of disease in the world and different subregional groupings^a

		(a) World			
Disease/condition	% global disease burden (total 1.46 billion DALYs)	% global mortality (total 55.9 million deaths)	Contributing risk factors (individual PAF for disease burden)	Joint PAF ^b (disease burden)	Joint PAF ^b (mortality)
Lower respiratory infections	6.1	6.8	Underweight (childhood) (40%); zinc deficiency (16%); indoor smoke from solid fuels (36%); tobacco (2%) ^c	55–62%	40–45%
HIV/AIDS	5.5	4.6	Unsafe sex (94%); unsafe health care injections (5%); illicit drugs (3%)	96%	96%
Unipolar depressive disorders	4.5	0.0	Alcohol (2%); childhood sexual abuse (6%)	7%	NA ^d
Diarrhoeal diseases	4.2	3.5	Underweight (childhood) (45%); vitamin A deficiency (18%); zinc deficiency (10%); unsafe water, sanitation and hygiene (88%)	92–94%	92–94%
Ischaemic heart disease	4.0	12.6	High blood pressure (49%); high cholesterol (56%); high BMI (21%); low fruit and vegetable intake (31%); physical inactivity (22%); tobacco (12%); alcohol (2%)	83–89%	78–85%
Low birth weight	3.5	2.5	Underweight (maternal) (10%); iron deficiency (19%); alcohol (0.2%)	29%	31%
Stroke	3.1	9.6	High blood pressure (62%); high cholesterol (18%); high BMI (13%); low fruit and vegetable intake (11%); physical inactivity (7%); tobacco (12%); alcohol (4%)	70–76%	65–73%

continued

Table 27.1 Individual and joint contributions of 20 selected risks to 10 leading diseases and total burden of disease in the world and different subregional groupings^a (continued)

Disease/condition	(a) World (continued)				Joint PAF ^b (disease burden)	Joint PAF ^b (mortality)
	% global disease burden (total 1.46 billion DALYs)	% global mortality (total 55.9 million deaths)	Contributing risk factors (individual PAF for disease burden)			
Malaria	2.9	2.0	Underweight (childhood) (45%); vitamin A deficiency (16%); zinc deficiency (18%)		56–59%	60–62%
Road traffic accidents	2.6	2.2	Alcohol (20%); illicit drugs (2%); occupational risk factors for injuries (6%)		28%	29%
Tuberculosis	2.5	2.9	Tobacco (10%) ^c		10%	12%
Communicable, maternal, perinatal, and nutritional conditions	42.0	32.6	Multiple risks (see chapter 26)		49–50%	50–51%
Noncommunicable diseases	45.7	58.3	Multiple risks (see chapter 26)		35–36%	49–52%
Injuries	12.3	9.1	Multiple risks (see chapter 26)		22%	25%
All causes	100	100	All 20 selected risks (see chapter 26)		39–40%	47–49%

<i>(b) High-mortality developing subregions</i>					
Disease/condition	% regional disease burden (total 830 million DALYs)	% regional mortality (total 26.4 million deaths)	Contributing risk factors (individual PAF for disease burden)	Joint PAF ^a (disease burden)	Joint PAF ^b (mortality)
HIV/AIDS	9.0	9.2	Unsafe sex (97%); unsafe health care injections (5%); illicit drugs (0.3%)	97%	97%
Lower respiratory infections	8.2	9.8	Underweight (childhood) (46%); zinc deficiency (19%); indoor smoke from solid fuels (41%); tobacco (1%) ^c	62–69%	49–54%
Diarrhoeal diseases	6.3	6.6	Underweight (childhood) (49%); vitamin A deficiency (19%); zinc deficiency (11%); unsafe water, sanitation and hygiene (88%)	93–95%	93–94%
Low birth weight	5.0	4.4	Underweight (maternal) (12%); iron deficiency (22%); alcohol (0.2%)	32%	34%
Malaria	4.9	4.2	Underweight (childhood) (45%); vitamin A deficiency (17%); zinc deficiency (19%)	57–60%	60–63%
Unipolar depressive disorders	3.1	0.0	Alcohol (1%); childhood sexual abuse (8%)	9%	NA ^d
Measles	3.0	2.7	Underweight (childhood) (34%); vitamin A deficiency (15%)	42%	43%
Ischaemic heart disease	3.0	9.1	High blood pressure (44%); high cholesterol (54%); high BMI (11%); low fruit and vegetable intake (33%); physical inactivity (21%); tobacco (8%); alcohol (4%)	80–87%	77–84%
Tuberculosis	2.9	3.8	Tobacco (8%) ^c	8%	10%
Birth asphyxia and birth trauma	2.7	1.9	Iron deficiency (20%)	20%	27%

continued

Table 27.1 Individual and joint contributions of 20 selected risks to 10 leading diseases and total burden of disease in the world and different subregional groupings^a (continued)

(b) High-mortality developing subregions (continued)					
Disease/condition	% regional disease burden (total 830 million DALYs)	% regional mortality (total 26.4 million deaths)	Contributing risk factors (individual PAF for disease burden)	Joint PAF ^b (disease burden)	Joint PAF ^b (mortality)
Communicable, maternal, perinatal, and nutritional conditions	58.9	54.5	Multiple risks (see chapter 26)	54–56%	56–57%
Noncommunicable diseases	30.5	37.0	Multiple risks (see chapter 26)	33–34%	47–50%
Injuries	10.6	8.4	Multiple risks (see chapter 26)	17%	19%
All causes	100	100	All 20 selected risks (see chapter 26)	44–45%	50–51%
(c) Low-mortality developing subregions					
Disease/condition	% regional disease burden (total 408 million DALYs)	% regional mortality (total 16.0 million deaths)	Contributing risk factors (individual PAF for disease burden)	Joint PAF ^b (disease burden)	Joint PAF ^b (mortality)
Unipolar depressive disorders	5.9	0.0	Alcohol (1%); childhood sexual abuse (4%)	5%	NA ^d
Stroke	4.7	13.8	High blood pressure (58%); high cholesterol (13%); high BMI (11%); low fruit and vegetable intake (10%); physical inactivity (5%); tobacco (8%); alcohol (7%)	67–74%	62–69%

Lower respiratory infections	4.1	4.6	Underweight (childhood) (24%); zinc deficiency (5%); indoor smoke from solid fuels (20%); tobacco (3%) ^c	35–42%	25–29%
Road traffic accidents	4.1	3.4	Alcohol (20%); illicit drugs (1%); occupational risk factors for injuries (6%)	27%	27%
Chronic obstructive pulmonary disease	3.8	9.2	Indoor smoke from solid fuels (26%); tobacco (26%)	52%	55%
Ischaemic heart disease	3.2	9.3	High blood pressure (45%); high cholesterol (48%); high BMI (22%); low fruit and vegetable intake (31%); physical inactivity (22%); tobacco (8%); alcohol (3%)	79–87%	73–82%
Birth asphyxia and birth trauma	2.6	1.1	Iron deficiency (10%)	10%	17%
Tuberculosis	2.4	3.3	Tobacco (10%)	12%	13%
Alcohol use disorders	2.3	0.2	Alcohol (100%); childhood sexual abuse (5%)	100%	100%
Hearing loss	2.2	0.0	Tobacco (5%) ^c	5%	NA ^d
Communicable, maternal, perinatal, and nutritional conditions	25.0	18.1	Multiple risks (see chapter 26)	28–29%	27–28%
Noncommunicable diseases	59.8	70.5	Multiple risks (see chapter 26)	33–34%	46–48%
Injuries	15.3	11.5	Multiple risks (see chapter 26)	24%	25%
All causes	100	100	All 20 selected risks (see chapter 26)	30–31%	40–42%

continued

Table 27.1 Individual and joint contributions of 20 selected risks to 10 leading diseases and total burden of disease in the world and different subregional groupings^a (continued)

Disease/condition	(d) Developed subregions				
	% regional disease burden (total 21.4 million DALYs)	% regional mortality (total 13.5 million deaths)	Contributing risk factors (individual PAF for disease burden)	Joint PAF ^b (disease burden)	Joint PAF ^b (mortality)
Ischaemic heart disease	9.4	23.3	High blood pressure (58%); high cholesterol (63%); high BMI (33%); low fruit and vegetable intake (28%); physical inactivity (22%); tobacco (22%); alcohol (-0.2%)	89–93%	82–87%
Unipolar depressive disorders	7.2	0.0	Alcohol (3%); childhood sexual abuse (4%)	7%	NA ^d
Stroke	6.0	13.4	High blood pressure (72%); high cholesterol (27%); high BMI (23%); low fruit and vegetable intake (12%); physical inactivity (9%); tobacco (22%); alcohol (0%)	81–86%	71–79%
Alcohol use disorders	3.5	0.2	Alcohol (100%); childhood sexual abuse (3%)	100%	100%
Alzheimer and other dementias	3.0	1.4	None of the selected risks	0%	NA ^d
Hearing loss	2.8	0.0	Tobacco (10%) ^c	10%	NA ^d
Chronic obstructive pulmonary disease	2.6	3.2	Indoor: smoke from solid fuels (2%); tobacco (69%)	71%	74%

Road traffic accidents	2.5	1.4	Alcohol (38%); illicit drugs (4%); occupational risk factors for injuries (4%)	45%	44%
Osteoarthritis	2.5	0.0	High BMI (21%); Tobacco (10%) ^c	28%	NA ^d
Trachea, bronchus and lung cancers	2.4	4.5	Indoor smoke from solid fuels (coal only) (0%); tobacco (85%); low fruit and vegetable intake (11%)	86%	87%
Communicable, maternal, perinatal, and nutritional conditions	9.0	6.7	Multiple risks (see chapter 26)	24–25%	20–21%
Noncommunicable diseases	78.2	85.7	Multiple risks (see chapter 26)	41–42%	54–57%
Injuries	12.8	7.6	Multiple risks (see chapter 26)	36%	37%
All causes	100	100	All 20 selected risks (see chapter 26)	39–40%	51–53%

NA Not applicable.

^a The risk factors also contribute to other diseases in each subregion which are not among the leading 10.

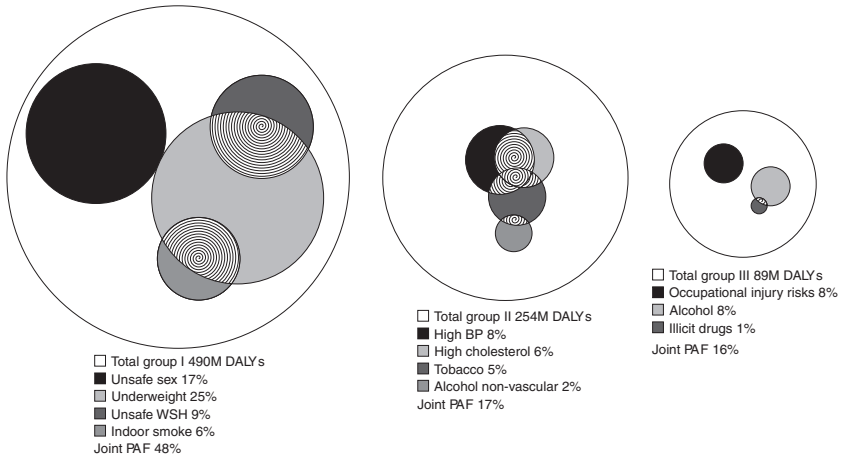
^b The first number is the PAF for adjusted scenario and the second for the unadjusted scenario in cases where adjustment for mediated effects and effect modification applied (see methods).

^c Affected by tobacco in the category "other respiratory diseases" or "selected other medical causes" (Peto et al. 1992). The PAF has large uncertainty.

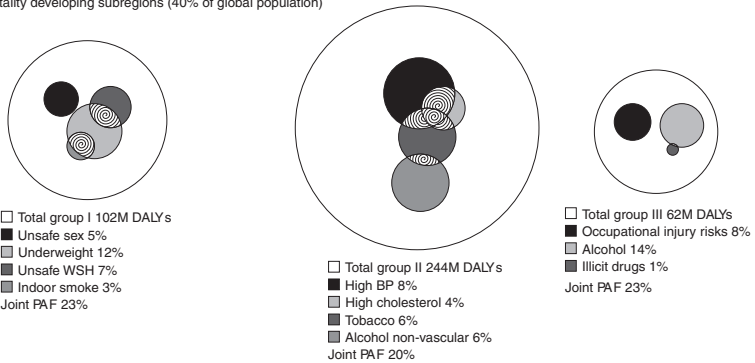
^d The number of deaths coded to "hearing loss", "unipolar depressive disorders", "osteoarthritis", and "alzheimer and other dementias" is zero or very small in the GBD database, making the mortality PAF for these diseases undefined or unstable.

Figure 27.3 Individual and joint contributions (adjusted scenario as described in methods) of selected risk factors to different disease groups

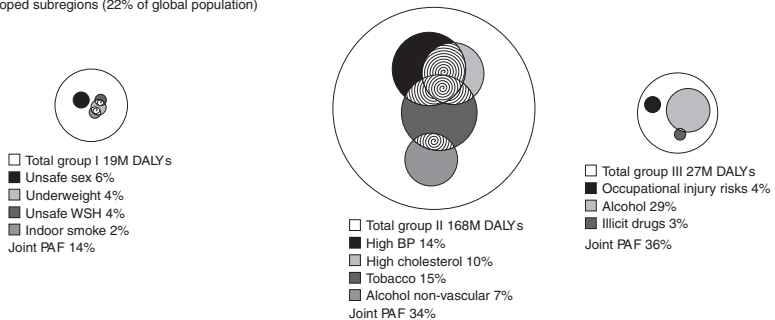
(a) High-mortality developing subregions (38% of global population)



(b) Low-mortality developing subregions (40% of global population)



(c) Developed subregions (22% of global population)



continued

Notes for Figure 27.3

Key: High-mortality developing subregions: AFR, AMR-D, EMR-D and SEAR-D. Low-mortality developing subregions: AMR-B, EMR-B, SEAR-B and WPR-B. Developed subregions: AMR-A, EUR and WPR-A. Group I: communicable, maternal, perinatal and nutritional conditions; Group II: noncommunicable diseases; Group III: injuries; WSH, water, sanitation and hygiene; BP, blood pressure.

Note: The size of each circle shows the absolute size of the burden (in millions of DALYs). Numbers for individual risk factors show the total burden including those overlapping with the remaining factors shown in lined pattern. Note that each risk factor may also have contributions to other disease groups (e.g. indoor smoke also causes COPD, which is in Group II and alcohol also causes injuries, which are in Group III). In reality, there is a small overlap between underweight and unsafe sex since underweight children with HIV/AIDS are likely to survive for a shorter period (not estimated in this work).

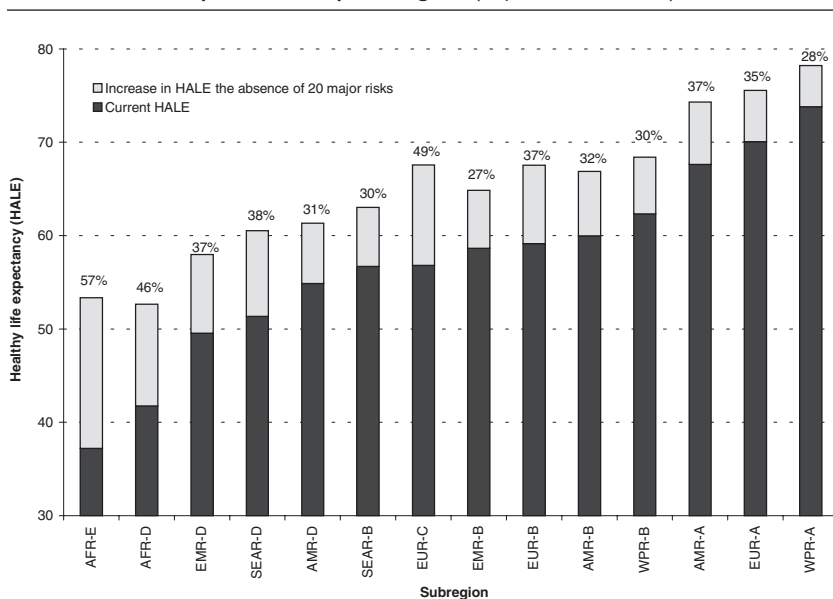
II. noncommunicable diseases; III. injuries. Communicable, maternal, perinatal and nutritional conditions, and their underlying risk factors, in high-mortality developing subregions contributed disproportionately to global loss of healthy life (i.e. large Group I disease burden and large fraction (54–56%) attributable to the selected risk factors). Noncommunicable diseases and their risk factors (54–57% attributable to the selected risk factors) dominated the burden of disease in developed subregions, although, by comparison, this was considerably smaller than total disease burden in high-mortality developing subregions. Both disease groups and their risk factors, with intermediate levels, affected low-mortality developing subregions.

Table 27.1 and Figure 27.3 also show that the selected risk factors for each disease group exhibited heterogeneous contributions to disease burden across clusters of countries and subregions. For Group I diseases, unsafe sex had the lowest proportional contribution in low-mortality developing countries but made a very large contribution in high-mortality developing countries. For Group II diseases, the relative contributions of high cholesterol and tobacco varied across the three subregional groupings, with their relative contributions reversing from one to another. Similarly, for Group III, the relative contributions of alcohol and occupational factors showed considerable heterogeneity across subregional groups.

Gains in HALE from removing these 20 selected risk factors are shown in Figure 27.4. Globally, in the year 2000, an estimated 47% of mortality and 39% of disease burden were attributable to the joint effects of 20 selected risk factors. Global HALE would increase from 56.2 to 65.5 years in the absence of these risks (adjusted scenario). The corresponding results for the unadjusted scenario were nearly identical with HALE increasing to 66.0 years.

Figure 27.4 shows that the removal of major risk factors would not only have resulted in improvements in each subregion, but also, in general, reduced the health differentials across subregions (i.e. larger gains in subregions with lower HALE) with the largest gain in health in

Figure 27.4 The joint effects of leading 20 global risk factors on HALE in year 2000, by subregion (adjusted scenario)



Note: The numbers show the fraction of the total burden of disease in each subregion attributable to the selected risk factors.

AFR-E (16.1 years) and the smallest in WPR-A (4.4 years). Important exceptions to the monotonic decreasing relationship between HALE gain and initial HALE were EUR-C and EUR-B (mainly consisting of the countries of eastern and central Europe and the former Soviet Union). In these subregions, the leading global risk factors jointly account for a disproportionately larger share of disease burden (49% in EUR-C and 37% in EUR-B) and led to substantial loss of healthy life years (10.7 in EUR-C and 8.3 in EUR-B), emphasizing the concentration of disease burden among a few important risk factors (alcohol, tobacco, high blood pressure and high cholesterol) in these two subregions.

4. DISCUSSION

The estimates of the joint contributions of 20 selected leading global risk factors showed that these risks together were responsible for a considerable loss of healthy life in different regions of the world. In particular, for some of the leading global diseases (e.g. ALRI, diarrhoea, lung cancer, IHD and stroke), substantial proportions were attributable to these selected risk factors. Removing these 20 risk factors would not only have resulted in a 9.3-year (17%) gain in global HALE, but also would have

accounted for some of the interregional HALE differences. In fact, the analysis showed that even populations with currently high HALE (e.g. developed regions of the western Pacific and Europe) could further benefit from risk reduction. These results provide a guide to the potential gains in (healthy) life expectancy (estimated statistically from past trends [Oeppen and Vaupel 2002; Riley 2001]) through disease prevention by reducing known risks. Similar analyses for the leading 10 selected global risks suggest a gain of 8.1 years in HALE (vs 9.3 years for the leading 20). This concentration of disease burden further emphasizes the contribution of leading risks such as undernutrition, unsafe sex, high blood pressure, tobacco and alcohol to global loss of healthy life.

At the same time, the estimated joint contributions of these risk factors left an important part of the global disease burden unexplained and did not fully explain interregional HALE differentials. This was because only a small fraction of some important diseases was attributable to the selected risk factors considered here. These include diseases whose determinants: i) are diffuse among environmental and behavioural factors (e.g. some cancers, perinatal conditions, and neuropsychiatric diseases) (see Doll and Peto 1981 for examples from cancers); ii) have more complex, multi-factor etiology and often heterogeneous determinants in different populations and therefore difficult to quantify without data at very small scale (e.g. tuberculosis and injuries); iii) involve long delays; or iv) have limited quantitative research at the population level (e.g. neuropsychiatric diseases), often as a result of the above three factors as well as difficulties in measuring exposure or outcome (Evans 1978). Mitigation of many such diseases (e.g. malaria, tuberculosis or injuries) may be better guided by analyses of the effects of interventions tailored to individual settings than by risk factor analysis.

The results of this analysis changed little with plausible assumptions about mediated risks or effect modification among risk factors. An important reason for this is the concave shape of the PAF relationship (Figure 27.2). Because risk factors considered in the analysis individually accounted for large fractions of the diseases affected by them (e.g. diarrhoea and IHD), the joint effects approached 100% asymptotically limiting the sensitivity of results to assumptions about interaction. We emphasize that this does not include the considerably larger uncertainty in each of the individual PAF estimates discussed in detail in chapters 1 and 26 of this book. At the same time, since for many of the important causes of global disease burden (e.g. childhood infectious and vascular diseases), multiple important risk factors were included, the joint effects would likely remain large regardless of uncertainties in the individual PAF.

An additional important source of uncertainty, affecting both individual and joint risk factor estimates, is the concentration of *both* risks and diseases in specific subgroups (vs correlations of risks alone, discussed above). For many risk factors and diseases, exposure and outcome

are simultaneously higher in some groups (e.g. higher malnutrition, unsafe water, sanitation and hygiene, and indoor smoke in poor rural households in developing countries; unhealthy diet, and higher smoking and BMI in some groups in developed countries). In these circumstances, PAFs based on population averages would in general underestimate the effects compared to group-specific analysis, even if the relative risks are constant across groups (Greenland 1984) (also confirmed by micro-simulation). Higher concentration of disease and mortality (e.g. childhood mortality and vascular diseases) in the same groups due to factors such as limited access to health services would magnify this effect, becoming an important contributor to underestimation of the benefits of risk reduction when population level exposure and mortality data are used. In addition to risk factor analysis, estimates of HALE include large uncertainty, especially in countries with poor mortality and disease registration systems as estimated and discussed elsewhere (Mathers et al. 2001). Further implications of these findings for research, and for policies and programmes aimed at improving population health, are discussed in chapter 29.

ACKNOWLEDGEMENTS

We thank T. Armstrong, R.E. Black, F. Bull, G. Colditz (with E. Rimm and M. Stampfer), C. Lawes, K. Lock, V. Parag, J. Powles, A.J. Rice, K.P. West Jr., G. Whitlock, W. Willet and M. Woodward for discussion and references on independent and mediated effects.

NOTES

- 1 See preface for an explanation of this term.
- 2 High-mortality developing subregions: AFR, AMR-D, EMR-D and SEAR-D. Low-mortality developing subregions: AMR-B, EMR-B, SEAR-B and WPR-B. Developed subregions: AMR-A, EUR and WPR-A.

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