

Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: a modelling study

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Summary

Background Countries have agreed to reduce premature mortality (defined as the probability of dying between the ages of 30 years and 70 years) from four main non-communicable diseases (NCDs)—cardiovascular diseases, chronic respiratory diseases, cancers, and diabetes—by 25% from 2010 levels by 2025 (referred to as 25×25 target). Targets for selected NCD risk factors have also been agreed on. We estimated the contribution of achieving six risk factor targets towards meeting the 25×25 mortality target.

Methods We estimated the impact of achieving the targets for six risk factors (tobacco and alcohol use, salt intake, obesity, and raised blood pressure and glucose) on NCD mortality between 2010 and 2025. Our methods accounted for multi-causality of NCDs and for the fact that when risk factor exposure increases or decreases, the harmful or beneficial effects on NCDs accumulate gradually. We used data for risk factor and mortality trends from systematic analyses of available country data. Relative risks for the effects of individual and multiple risks, and for change in risk after decreases or increases in exposure, were from re-analyses and meta-analyses of epidemiological studies.

Findings If risk factor targets are achieved, the probability of dying from the four main NCDs between the ages of 30 years and 70 years will decrease by 22% in men and by 19% in women between 2010 and 2025, compared with a decrease of 11% in men and 10% in women under the so-called business-as-usual trends (ie, projections based on current trends with no additional action). Achieving the risk factor targets will delay or prevent more than 37 million deaths (16 million in people aged 30–69 years and 21 million in people aged 70 years or older) from the main NCDs over these 15 years compared with a situation of rising or stagnating risk factor trends. Most of the benefits of achieving the risk factor targets, including 31 million of the delayed or prevented deaths, will be in low-income and middle-income countries, and will help to reduce the global inequality in premature NCD mortality. A more ambitious target on tobacco use (a 50% reduction) will almost reach the target in men (>24% reduction in the probability of death), and enhance the benefits to a 20% reduction in women.

Interpretation If the agreed risk factor targets are met, premature mortality from the four main NCDs will decrease to levels that are close to the 25×25 target, with most of these benefits seen in low-income and middle-income countries. On the basis of mortality benefits and feasibility, a more ambitious target than currently agreed should be adopted for tobacco use.

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Introduction

Non-communicable diseases (NCDs) cause more than 35 million deaths every year and account for more than half of deaths in every region except sub-Saharan Africa.^{1–3} NCD deaths and morbidity pose large—and inequitable—health and economic burdens on individuals, societies, and health systems.^{2,4} In 2011, the UN General Assembly adopted a political declaration that committed member states to the prevention and control of NCDs.⁵ Subsequently, countries agreed to adopt nine global targets, including an overarching target of reducing premature mortality from the four main NCDs (cardiovascular diseases, chronic respiratory diseases, cancers, and diabetes) by 25% relative to their 2010 levels by 2025 (referred to as the 25×25 target). Countries also agreed on targets

for selected NCD risk factors: tobacco use, harmful alcohol use, salt intake, obesity, raised blood pressure, raised blood glucose and diabetes, and physical inactivity. Two additional targets focus on treating people at high risk of heart attack and stroke, and on the availability of drugs to treat NCDs.

The risk factor and mortality targets were chosen independently, based largely on the experiences of countries that had been successful in reducing each of them. To plan and prioritise NCD control and prevention strategies, it is important to know how much achieving the risk factor targets would contribute towards reducing NCD mortality, and whether additional actions are needed to achieve the 25×25 target.⁶ We analysed the potential impacts of reducing six preventable risk factors on future trends in NCD mortality, in aggregate and by

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disease, for high-income and low-income and middle-income countries (LMICs).

Methods

Study design

We estimated the impacts of reducing risk factors according to their global targets on NCD mortality for the years between 2010 and 2025. Consistent with the global target, we defined premature mortality as the probability of dying from one of the four main NCDs between 30 years and 70 years of age in the absence of competing causes. This indicator provides a comparable measure of NCD risk across populations by removing the role of competing causes such as injuries and infectious diseases. We analysed the impacts of six risk factors: tobacco smoking, alcohol use, salt intake, obesity, and raised blood pressure and glucose. Our risk factor scenarios are shown in table 1.

Our analytical approach was based on two epidemiological characteristics of NCDs. First, NCDs have multiple causes, combined effects from which lead to a particular disease rate in the population. Some of these causes can be non-modifiable (eg, genetic determinants), unmeasured or poorly measured (eg, health-care quality or stress), or even unknown. Therefore, trends for a specific NCD can be different from that of any single risk factor or small number of risk factors, depending on how its other determinants and medical treatment are changing. For example, cardiovascular disease mortality in high-income countries has decreased for decades, during which time some of its risk factors (eg, blood pressure, cholesterol, and, in some countries, smoking) have decreased and others (eg, obesity and smoking in other countries) have increased.^{10–12} To account for this characteristic, and

consistent with the vast empirical evidence on proportional effects, we analysed the impacts of risk factors on future NCD mortality as a proportion of projected death rates. The second characteristic of NCDs is that when exposure to one of its risk factors increases or decreases, the harmful or beneficial impacts on disease risk accumulate gradually.^{13–16} We accounted for this characteristic using relative risks (RRs) that were a function of time since exposure change.

These two components of our approach can be incorporated in a time-based, population impact fraction formula,¹⁷ which estimates the proportion of disease-specific deaths for years between 2010 and 2025 that would be avoided if risk factor exposures were reduced according to their targets. For each disease outcome causally associated with a risk factor, we calculated the time-based population impact fraction (PIF) for a given year (20XX) between 2010 and 2025 using the following formula:

$$PIF^{20XX} = \frac{\sum_j P_j^{20XX} RR_j^{20XX} - \sum_j \hat{P}_j^{20XX} RR_j^{20XX}}{\sum_j P_j^{20XX} RR_j^{20XX}}$$

where P^{20XX} and \hat{P}^{20XX} are population distributions (which could be categorical or continuous) of risk factor exposure in year 20XX in the so-called business-as-usual (BAU; ie, projections based on current trends with no additional action) and target scenarios, respectively, and RR^{20XX} is the RR in 20XX (appendix pp 2–3). The first term in the numerator is the weighted (by prevalence) disease risk if risk factors continue their current trend and the second term is the weighted disease risk if risk factor trends are changed according to their target. The risk factor exposure categories, denoted by j , account for both the level of exposure and for time since change in exposure. The RR for each exposure category in this equation depends on time since exposure change. This relation is an extension of the commonly used population attributable or impact fraction in which RRs are a function of exposure level but not of time.

We did all analyses separately by country, sex, 5-year age group for people aged 30 years or older, and for each NCD causally associated with these six risk factors. We calculated global results by aggregating age-and-sex-specific number of deaths and population from all countries. We used age-specific death rates to calculate the probability of dying from the four main NCDs between 30 years and 70 years of age in the absence of competing causes.¹⁸ We defined high-income countries versus low-income and middle-income countries as defined by Di Cesare and colleagues.²

We estimated the proportional reduction in mortality from each NCD if all six risk factor targets are achieved using the formula for the joint effects of multiple risk factors, which accounts for multi-causality and overlap of risk factors.^{19–21} When analysing the combined effects of all six risk factors, we accounted for the fact that some of the effects of body-mass index (BMI) on cardiovascular

See Online for appendix

Scenarios	
Related to risk factor exposure	
Tobacco use	Agreed target: 30% relative reduction in prevalence More ambitious target: 50% relative reduction in prevalence*
Harmful alcohol use	10% reduction in per-person alcohol consumption
Salt intake	30% reduction in mean population intake of salt
Obesity	Halting the rise in the prevalence of obesity
Raised blood pressure	25% relative reduction in the prevalence of raised blood pressure
Raised blood glucose and diabetes	Halting the rise in the prevalence of diabetes
Related to when risk factor exposure is reduced†	
Gradual implementation (main scenario)	Risk factor target is implemented gradually‡
Early action	The risk factor reductions are achieved in the first 5 years, 2010–15‡

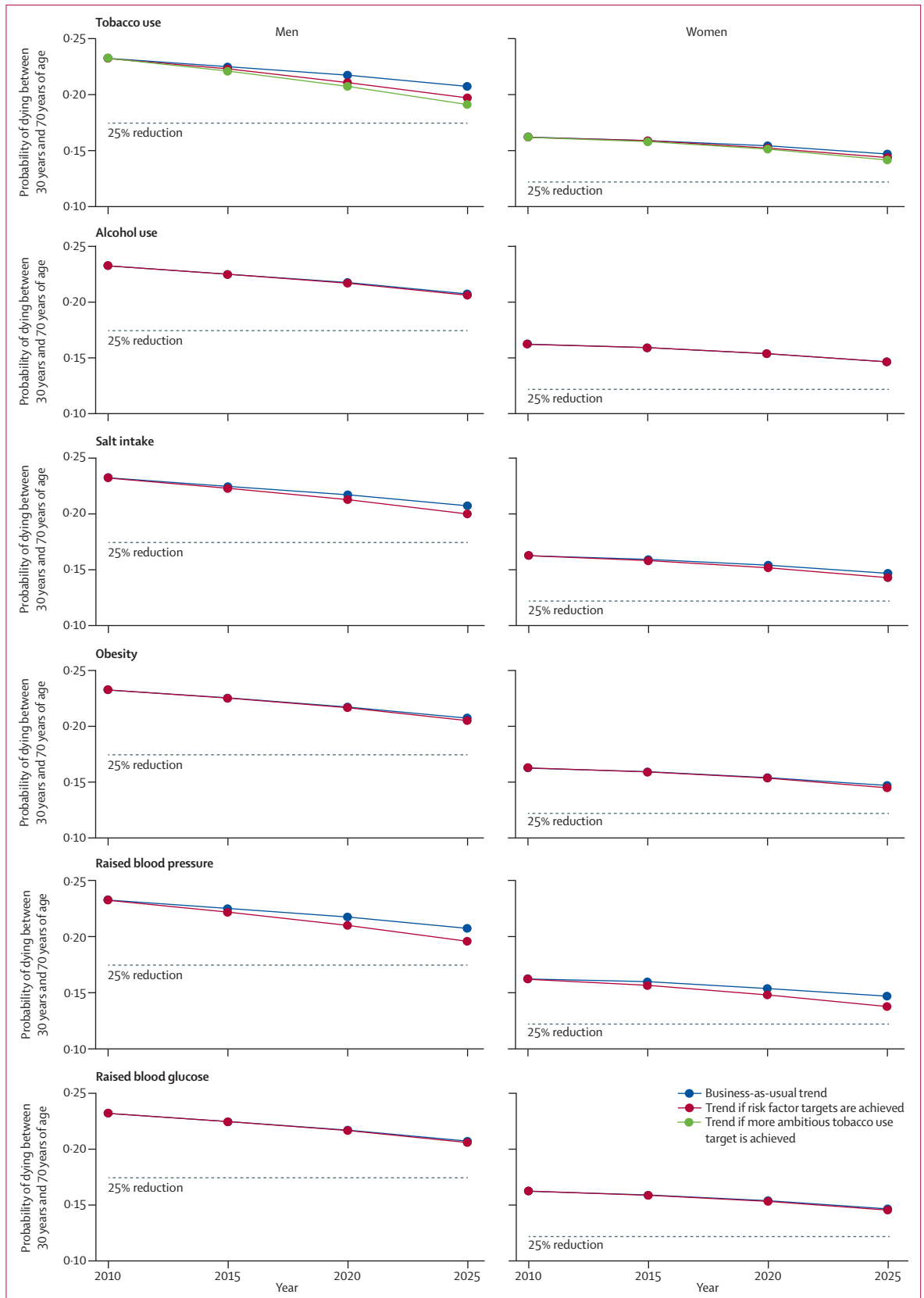
*For tobacco use, we estimated the impacts of meeting the global target as well as a more ambitious scenario, because effective policies for reducing tobacco use have already been successfully implemented in many countries, making a 50% reduction a feasible target.²² †We considered scenarios related to when risk factors are reduced because the benefits of reducing risk factor exposure for non-communicable diseases accumulate gradually over time. ‡Calculations were done in three 5-year intervals for computational efficiency; risk factor exposure reductions were applied at the mid-point of each 5-year interval, which is roughly equivalent to five equal annual reductions (the equivalence is approximate because the change in relative risk over time was non-linear; appendix pp 12–13)

Table 1: Risk factor scenarios used in the analysis

	Exposure metric	Data sources for exposure	Disease outcomes	Data sources for RRs
Tobacco use	Smoking impact ratio, a measure based on excess lung cancer relative to never-smokers that accounts for duration and intensity of smoking ²²	Lung cancer mortality (as described in Methods)	Target NCDs: mouth and oropharynx cancers; oesophagus cancer; stomach cancer; colon and rectum cancers; liver cancer; pancreas cancer; trachea, bronchus, and lung cancers; cervix uteri cancer; bladder cancer; kidney cancer; myeloid leukaemia; diabetes; ischaemic heart disease; stroke; other cardiovascular diseases; chronic obstructive pulmonary disease; other chronic respiratory diseases Other outcomes: tuberculosis; respiratory infections	Re-analysis of American Cancer Society Cancer Prevention Study II (CPS II) cohort data ¹³ (RRs shown in appendix)
Alcohol use	Distribution of alcohol consumption in the population and prevalence of heavy episodic drinking	Official statistics and industry data for national sales, production, imports, and exports for recorded consumption. Government and academic monitoring systems or, when necessary, expert judgments for unrecorded and tourist consumption. Population-based surveys for prevalences of life-long abstainers, former drinkers, and heavy episodic drinkers; for division of consumption by sex and age group; and for the distributions of alcohol consumption among drinkers ²³⁻²⁸	Target NCDs: mouth and oropharynx cancers; oesophagus cancer; colon and rectum cancers; liver cancer; larynx cancer; breast cancer; pancreas cancer; diabetes; hypertensive heart disease; ischaemic heart disease; ischaemic stroke; haemorrhagic and other non-ischaemic stroke; atrial fibrillation and flutter Other NCDs: epilepsy; alcohol use disorders; cirrhosis of the liver; pancreatitis Other outcomes: tuberculosis; lower respiratory infections; HIV/AIDS; transport injuries; poisoning; falls; fires, heat, and hot substances; drowning; other unintentional injuries; self-inflicted injuries; violence	Pooled meta-analytical RR of epidemiological studies for those outcomes with monotonically increasing harmful effects that depended on quantity of alcohol consumed; ²⁹⁻³⁵ Fitting a non-linear dose-response relation to RRs from individual epidemiological studies for diseases with U-shaped or J-shaped dose-response relations; ^{31,36-39} meta-analysis of epidemiological studies with data for episodic heavy drinking for effects of the patterns of drinking; ³⁷ separate RRs from a large retrospective case-control study for Russia and six other countries that were formerly republics of the Soviet Union ⁴⁰
Salt intake	Urinary sodium excretion	Pooled analysis of population-based surveys in a Bayesian hierarchical model ⁴¹	Target NCDs: stomach cancer; rheumatic heart disease; hypertensive heart disease; ischaemic heart disease; ischaemic stroke; haemorrhagic and other non-ischaemic stroke; cardiomyopathy, myocarditis, and endocarditis; other cardiovascular diseases Other NCDs: chronic kidney disease	Meta-analysis of 30 randomised trials of salt reduction for absolute effect on blood pressure; ⁴² World Cancer Research Fund's systematic review and meta-analysis for stomach cancer RR ⁴³
Obesity	Mean body-mass index (BMI)	Pooled analysis of population-based surveys in a Bayesian hierarchical model ^{46,47}	Target NCDs: colon and rectum cancers; pancreas cancer; post-menopausal breast cancer; liver cancer; ovary cancer; corpus uteri cancer; prostate cancer; leukaemia; gallbladder cancer; kidney cancer; non-Hodgkin lymphoma; multiple myeloma; thyroid cancer; diabetes; hypertensive heart disease; ischaemic heart disease; ischaemic stroke; haemorrhagic and other non-ischaemic stroke Other NCDs: chronic kidney disease; osteoarthritis	Meta-analysis of RRs from Asia-Pacific Cohort Studies Collaboration (APCSC), Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE), Emerging Risk Factor Collaboration (ERFC), and the Prospective Studies Collaboration (PSC) for cardiovascular diseases and diabetes; ⁴⁸ systematic review and meta-analysis by Renehan and colleagues ⁴⁹ for the effects of high BMI on liver cancer, prostate cancer, leukaemia, gallbladder cancer, kidney cancer, non-Hodgkin lymphoma, multiple myeloma, and thyroid cancer; systematic review and meta-analysis by the World Cancer Research Fund for colon and rectum cancers, pancreas cancer, post-menopausal breast cancer, ovary cancer, and corpus uteri cancer ⁵⁰⁻⁵⁴
Raised blood pressure	Mean systolic blood pressure	Pooled analysis of population-based surveys in a Bayesian hierarchical model ⁴⁴	Target NCDs: rheumatic heart disease; hypertensive heart disease; ischaemic heart disease; ischaemic stroke; haemorrhagic and other non-ischaemic stroke; cardiomyopathy, myocarditis, and endocarditis; other cardiovascular diseases Other NCDs: chronic kidney disease	Meta-analysis of RRs from APCSC, DECODE, ERFC, and PSC ⁴⁸
Raised blood glucose	Mean fasting plasma glucose	Pooled analysis of population-based surveys in a Bayesian hierarchical model ⁴⁵	Target NCDs: diabetes; ischaemic heart disease; stroke Other NCDs: chronic kidney disease Other outcomes: tuberculosis	Meta-analysis of RRs from APCSC, DECODE, ERFC, and PSC ⁴⁸

Additional details and data sources for exposures and relative risks (RRs) are given in the appendix (pp 4-9). NCD=non-communicable disease.

Table 2: Data sources for risk factor exposures and their associations with non-communicable diseases



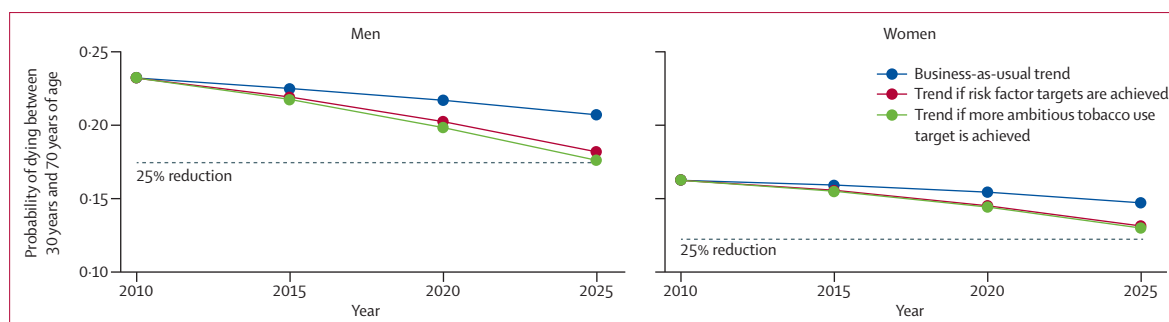


Figure 2: The impact of achieving all of the six risk factor targets on the probability of dying prematurely from the four main non-communicable diseases. See the appendix pp 14–15 for results based on age-standardised death rates and appendix pp 16–17 for results using all non-communicable diseases.

diseases are mediated through raised blood pressure and glucose by separating its mediated and direct effects as described below, and using the direct effect only.

We calculated the contribution of risk factor targets based on how close achieving them would bring premature mortality to the 25×25 mortality target compared with a baseline scenario. We used two types of baseline scenarios. First, when a risk factor had a rising trend in a country (eg, obesity and diabetes in most countries), we compared its target to the baseline of rising trend. Second, when a risk factor already had a decreasing trend (eg, blood pressure and smoking in many high-income countries), we compared its target to a baseline of having kept the risk factor at its 2010 level. We used the second type of baseline because a decreasing risk factor trend means that progress is already being made towards the target in the BAU trend, and hence should be counted towards the estimated benefit of the risk factor target. The contribution of a risk factor towards achieving the mortality target can be greater than 100% when reducing the risk factor leads to a greater than 25% reduction in premature mortality.

Data sources

We measured population exposure to risk factors using metrics related to their targets and with the most comprehensive global data (table 2, appendix pp 4–6). We obtained the NCD disease outcomes associated with each risk factor and the aetiological effect sizes from re-analyses and meta-analyses of epidemiological studies (table 2, appendix pp 7–9)

When exposure to a risk factor decreases or increases, RRs change faster for cardiovascular diseases (with most of the benefits evident within 5–10 years after reducing exposure) than for cancers and chronic obstructive pulmonary disease (COPD), for which it takes two to three decades for RRs to approach their peaks (after initiation) or to return to the levels of those at low exposure (after exposure cessation or reduction).^{13–16} These patterns are quantitatively characterised by the time curves in the appendix (pp 12–13). We used the cardiovascular disease curve for diabetes because findings from randomised trials indicate that the benefits

of behaviour change and pharmacological treatment on diabetes risk occur within a few years,⁵⁵ more similar to cardiovascular diseases than to cancers.

The mediated proportion of the effects of BMI on ischaemic heart disease and stroke was based on a pooled analysis of 97 prospective cohorts with 1.8 million participants.⁵⁶ We calculated RRs for the effects of BMI on ischaemic heart disease and stroke with and without adjustment for mediators, and used them to calculate the proportion of excess relative risk mediated as:

$$\frac{HR_{\text{confounder-adjusted}} - HR_{\text{confounder-and-mediator-adjusted}}}{HR_{\text{confounder-adjusted}} - 1}$$

We assumed that the effect of BMI on hypertensive heart disease is fully mediated through blood pressure. We analysed the effects of salt intake on cardiovascular diseases as mediated through blood pressure to be able to use effect sizes from randomised trials of salt reduction, most of which had blood pressure as an endpoint.

Trends in death rates from NCDs to 2025 under the BAU scenario were from a comprehensive update of the WHO Global Health Estimates, with methods described in detail elsewhere.^{57–59} Briefly, a series of regression equations related age-specific and sex-specific death rates from clusters of diseases to a set of covariates including national income, education, and smoking. The regressions also included a secular time trend above and beyond the trend associated with the covariates. The coefficients of these equations were estimated using historical mortality data, after correction for completeness of death registration and re-distribution of ill-defined and improbable causes of death. These regression equations were then used to estimate death rates by disease cluster, age group, and sex for years 2010–30. A separate model was used for diabetes which additionally accounted for trends in BMI as an important driver of this disease. The diabetes model allowed the so-called background diabetes death rates (ie, death rates expected if BMI had been at optimum levels) to decrease when death rates from other NCDs were decreasing but multiplied this background rate by the increased risk due to the BMI level in the

population. As a result, and consistent with trends over the past two decades, diabetes mortality could increase even if mortality from cardiovascular diseases is decreasing. For this paper, we updated the projections of diabetes death rates to be consistent with BAU trends for BMI. A similar approach was taken for COPD in relation to smoking.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. VK, CDM, GAS, and KDS together

had full access to all data used in this study. ME was responsible for submitting the article for publication.

Results

Under a BAU scenario, the probability of dying between 30 years and 70 years of age from the four main NCDs is expected to decrease by an estimated 0.025 (11%) between 2010 and 2025 for men and by 0.016 (10%) for women at the global level (figures 1, 2). This decrease is largely due to the continuing decline in mortality from cardiovascular diseases and chronic respiratory diseases.^{1,8,10,57} Despite this decrease, the number of deaths

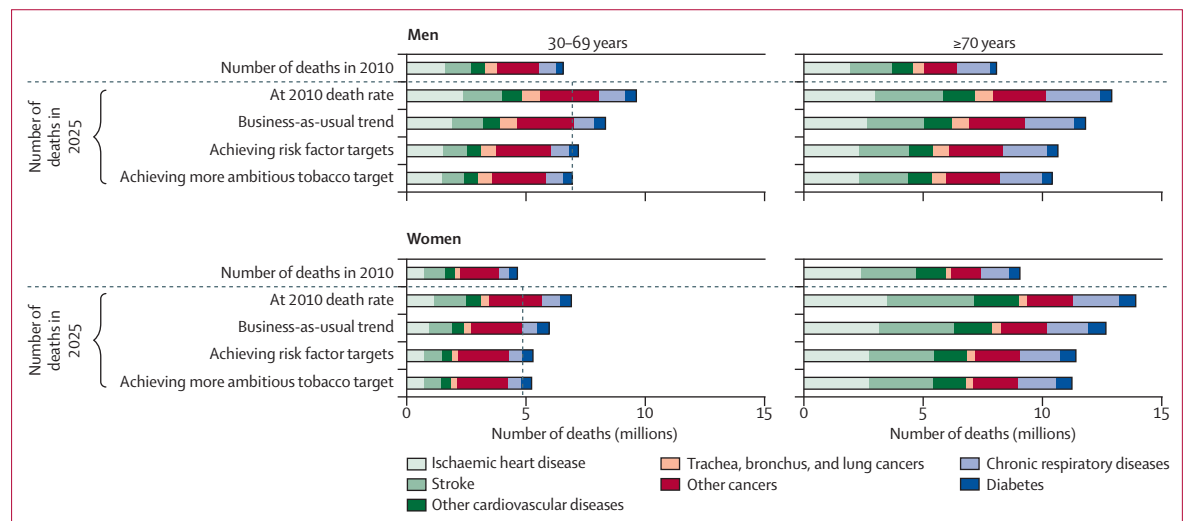


Figure 3: The impact of achieving the six risk factor targets on deaths from the four main non-communicable diseases in men and women
The vertical dotted lines indicate the 25x25 target. The horizontal dotted lines separate data for 2010 from projections for 2025 under different scenarios. See appendix (pp 18–19) for results using all non-communicable diseases.

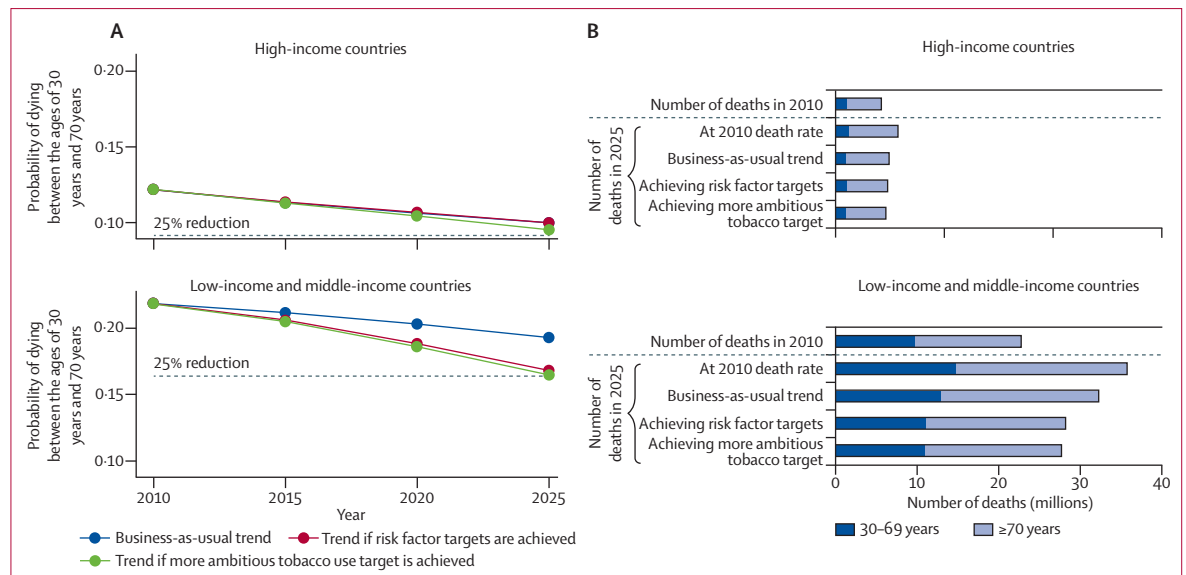


Figure 4: The impact of achieving the six risk factor targets on the probability of dying prematurely (A) and number of deaths (B) from the four main non-communicable diseases in high-income versus low-income and middle-income countries
See appendix (pp 20–21) for results based on age-standardised death rates.

from these four NCDs will rise from 28.3 million in 2010 to 38.8 million in 2025, because of population growth and ageing (figure 3). Of the 10.5 million additional deaths, 3.1 million will occur before 70 years of age and another 7.3 million in older people. The vast majority (9.5 million) of these additional deaths will be in LMICs (figure 4). In people younger than 70 years, the number of deaths is expected to decrease by about 100 000 in high-income countries but increase by 3.2 million in LMICs.

Achieving the six risk factor targets will lead to a further 11% reduction in the probability of death in men and 10% reduction in women, leading to total reductions of 22% in men and 19% in women. Although not sufficient to meet the 25×25 target, achieving the targets for only these six risk factors will close the gap between a situation of rising or stagnating risk factor trends and the 25×25 target by 82% for men and 69% for women. This improvement is equivalent to 5.6 million fewer worldwide deaths from the four main NCDs in 2025 than would have happened if risk factors trends continued to rise (where already increasing) or remained at 2010 level. Of these deaths, 2.3 million will be in people aged 30–69 years and the other 3.3 million in people 70 years or older. Taken over the 15 years, the reduction of risk factors to their targets would result in the delaying of 37 million deaths from the four main NCDs (16 million in people aged 30–69 years and 21 million in those aged 70 years or older; table 3). 85% of men and more than 90%

of women aged 30–69 years whose deaths are averted are not expected to die from the four main NCDs before their 70th birthday.

Action on individual risk factors will have varying impacts and close between 2% and 40% of the gap between a situation of rising or stagnating risk factor trends and the mortality target for men, and between 1% and 42% for women (detailed data not shown). The largest benefits will come from reducing blood pressure and tobacco use. If tobacco use is reduced by a more ambitious 50% relative to its 2010 levels, it will alone close more than half the gap towards the mortality target for men (compared with 39% under the current target) and 24% of the gap for women (compared with 18% under the current target), making it the most important risk factor for preventing premature mortality in men and the second most important in women (second to raised blood pressure). The more ambitious tobacco target would make the combined impact of the six risk factors a more than 24% reduction in probability of dying between the ages of 30 years and 70 years for men, nearly achieving the 25×25 target (figures 2, 3). For women, the combined impact under this more ambitious scenario will be a 20% reduction in the probability of death. The number of deaths prevented or delayed will increase to nearly 43 million if this more ambitious tobacco target is achieved together with targets on the other five risk factors (figure 3).

	Percentage of deaths from the main NCDs in people aged 30–69 years (2010, 2025)	BAU reduction*	Reduction if risk factor targets are achieved*	Risk factor contribution towards the 25×25 mortality target†	Number of deaths delayed or prevented (30–69 years; 70 years or older)†
Ten leading main non-communicable diseases					
Ischaemic heart disease	21.2%, 19.8%	-17%	-33%	>100%	5 000 000; 6 200 000
Stroke	17.3%, 15.9%	-20%	-38%	>100%	4 500 000; 6 000 000
Chronic obstructive pulmonary disease	7.7%, 7.4%	-18%	-27%	>100%	1 000 000; 2 300 000
Lung cancer	6.6%, 7.3%	-3%	-12%	56%	1 200 000; 1 200 000
Diabetes	5.4%, 6.8%	+11%	-5%	51%	1 100 000; 900 000
Liver cancer	4.0%, 4.2%	-2%	-5%	17%	170 000; 100 000
Stomach cancer	3.3%, 3.3%	-10%	-19%	63%	340 000; 350 000
Breast cancer	3.0%, 3.3%	+3%	+3%	1%	9000; 3000
Hypertensive heart disease	2.9%, 2.7%	-19%	-43%	>100%	1 000 000; 2 000 000
Colorectal cancer	2.6%, 2.7%	-9%	-10%	10%	50 000; 60 000
Four main non-communicable diseases					
All cardiovascular diseases	47.7%, 44.0%	-18%	-34%	>100%	11 400 000; 15 900 000
All cancers	36.5%, 39.2%	-3%	-7%	26%	2 400 000; 2 100 000
Chronic respiratory diseases	10.4%, 10.0%	-16%	-24%	92%	1 200 000; 2 500 000
Diabetes	5.4%, 6.8%	+11%	-5%	51%	1 100 000; 900 000
Total	100%	-10%	-21%	77%	16 100 000; 21 400 000

BAU=business as usual. NCD=non-communicable disease. *A negative number shows a decrease and a positive number a rise in mortality. †Contributions of risk factors and number of deaths delayed or prevented are calculated compared with a situation of rising or stagnating risk factor trends. A contribution of 100% implies that achieving the risk factor targets will lead to exactly 25% reduction in the probability of death from that disease; a contribution of more than 100% implies that if risk factor targets are achieved, probability of death decreases by more than 25%.

Table 3: The impact of achieving risk factor targets on premature mortality from non-communicable diseases

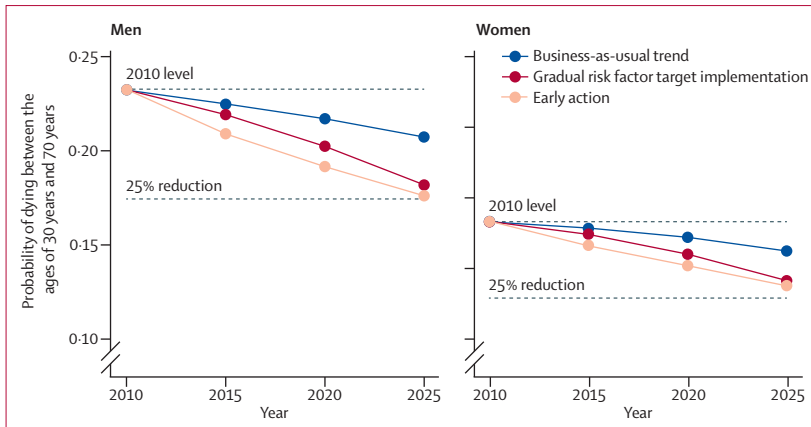


Figure 5: Projected trends in probability of dying prematurely from the four main non-communicable diseases according to speed of action (gradual vs early action)

In 2010, the probability of dying from the four main NCDs was much lower in high-income countries (0.12) than it was in LMICs (0.22; figure 4). Under a BAU scenario, this probability is projected to decrease in both groups about the same in 2025 (0.09) as it was in 2010 (0.10). In high-income countries, meeting the risk factor targets will lead to trends in premature NCD mortality that will be very similar to the BAU trend, because many of the targeted risk factors are already decreasing in these countries.^{10,12} By contrast with the situation in high-income countries, in LMICs, meeting the risk factor targets will noticeably change the course of premature NCD mortality, bringing it much closer to the 25% reduction and delaying or preventing 31 million deaths from the main NCDs. Achieving the risk factor targets will also reduce the inequality in the probability of premature NCD death between the two groups of countries.

Achieving these targets is expected to lead to reductions in probabilities of dying from ischaemic heart disease, stroke, hypertensive heart disease, and COPD that surpass 25% (table 3). Reductions in probabilities of dying from lung and stomach cancers will be 12–19%. Achieving the risk factor targets will also reverse the rising trend in diabetes mortality although the resulting decrease will not be as large as those of cardiovascular diseases and COPD. Among the top ten NCD causes of death, achieving the risk factor targets will have small effects on breast and colorectal cancer trends (as well as on cervical cancer, which is in the top ten for women).

Early action on risk factor targets would further lower mortality, leading to a 24% reduction in probability of death in men (compared with 22% under gradual implementation) and a 21% reduction in women (compared with 19% under gradual implementation; figure 5). The early accumulation of benefits itself helps delay or prevent an additional 18 million deaths over the 15 years of analysis. Late action, however, would leave

little time for the NCD benefits to accrue before 2025, substantially dampening the benefits of reducing risk factors.

Discussion

Achieving just six risk factor targets will contribute substantially to reducing NCD mortality by 2025, closing 77% of the gap between a situation of rising or stagnating risk factor trends and the 25×25 mortality target. High-income countries are already benefiting from mostly favourable risk factor trends, due to decreases in blood pressure and tobacco and alcohol use (as well as cholesterol) although these positive trends are partially offset by rising obesity and glucose.^{7,10,12,44–47,60,61} In LMICs, actions that lower risk factor exposure to their targeted levels will favourably change the projected course of NCD mortality towards the 25×25 target and delay or prevent 31 million deaths from the four main NCDs before 2025. Such actions will also reduce the inequalities in premature NCD mortality between high-income and LMICs, and hence contribute to a global convergence in health.⁶²

Despite the important contribution of risk factors, achievement of the 25×25 mortality target will need additional actions. Examples of such additional actions include the two agreed treatment-related targets (treatment and counselling individuals with a cardiovascular disease risk of $\geq 30\%$ and availability and affordability of quality, safe, and efficacious essential NCD drugs), more ambitious reductions in tobacco use than currently agreed, and immediate implementation of risk factor interventions so that the benefits can accumulate over time.

The strengths of our study include being the first integrated analysis of how targets related to preventable risk factors will contribute towards achieving the 25×25 NCD mortality target, in aggregate as well as for specific diseases (panel). Our findings identify primary prevention as an essential component in efforts to achieve the 25×25 target, and show the need for additional interventions, especially those that can reduce mortality from diabetes and cancers. Our analysis used data for risk factor exposure and mortality trends from systematic analyses that had used up-to-date, comprehensive country-level data. Similarly, RRs for the effects of risk factors were from large epidemiological studies and meta-analyses. We accounted for multi-causality and for the fact that benefits of reducing risk factors for NCDs accumulate gradually. Such gradual accumulation of benefits means that early action can contribute to achieving the 25×25 target and delay millions of additional deaths above and beyond how much risk factor exposure is reduced.

Population-level analyses such as ours have limitations. First, as with all estimations of future trends, is that unexpected factors (eg, new highly effective prevention and treatment interventions or macro-economic shocks) can substantially modify trends in risk factors or mortality, as they did, for example, after the fall of the Soviet Union.⁶⁹

Despite such unpredictable factors, estimates such as ours are needed to plan public health interventions and clinical programmes but should be accompanied by preparedness for unexpected situations. Second, despite improvements in epidemiological surveillance, risk factor exposures and deaths in some countries and regions are affected by data shortage and have relied on prediction models (table 2, appendix pp 4–6). The increased global focus on NCD prevention and control should be accompanied by emphasis on, and resources for, better country-level data for NCD deaths, morbidity, and risk factors. Third, our RRs were from observational studies, and thus could have been affected by residual confounding. To avoid overestimating the impacts of risk factors, we used only those diseases with strong and probable evidence and used RRs from well-adjusted studies only. Fourth, the epidemiological studies that informed the RRs were done in largely western and Asian populations. Although RRs have been shown to be similar between western and Asian cohorts,^{48,56} RRs from other regions would be desirable. Fifth, we did not analyse physical inactivity because how much of its effects are mediated through obesity and raised blood pressure and glucose has not been quantified, and because there are no consistent data for time trends. Although physical inactivity is an important NCD risk factor, mediation and multi-causality mean that its exclusion is unlikely to have greatly changed the combined effect of all risk factors together. Similarly, we did not analyse other forms of tobacco use because of the relative scarcity of data for exposure, which could have led to underestimation of the benefits for some cancers in south Asia, where oral tobacco use is common.

At present, tobacco use is the most policy-responsive of targeted risk factors, with major successes in tobacco control in many countries.^{7–9,61} The Framework Convention on Tobacco Control offers an important vehicle for strengthening and accelerating tobacco control worldwide, but requires rapid and full implementation.^{8,70} Alcohol consumption has decreased in some high-income countries but remains a major public health burden in eastern Europe, Latin America, and sub-Saharan Africa.⁷¹ Reducing the harmful use of alcohol in these regions, and preventing its rise in Asia and elsewhere, should be a priority, and can be achieved by use of policies that limit access, increase prices, and restrict or ban advertising.^{71,72} Lower dietary salt and better diagnosis and treatment have contributed to reducing blood pressure in some high-income countries,^{44,73,74} which is one of the most important determinants of the decrease in cardiovascular disease mortality.^{10–12} Locally applicable salt reduction or substitution strategies are urgently needed in LMICs, where salt intake remains high.^{2,41,75} Higher coverage of blood pressure treatment will need strengthening of the primary care system and the development and implementation of guidelines for use by primary care personnel.^{2,76,77}

Panel: Research in context

Systematic review

We searched PubMed using the search terms “risk factor” AND “modelling” AND “chronic disease” for articles in English published before March 27, 2014. We also identified articles thorough the references accessed for comparative risk assessment studies. We identified no articles that had modelled the role of risk factor targets in achieving the 25×25 mortality target, although this role was discussed by Bonita and colleagues in the *Lancet Series* on non-communicable diseases (NCDs).⁶ We identified articles that attributed past trends or current levels of mortality from specific NCDs to their risk factors, and some articles that had modelled future mortality from a single NCD or multiple NCDs under different scenarios of one or more risk factors.^{17,63–68}

Interpretation

Our findings show that meeting risk factor targets will lower premature mortality from the four main NCDs to levels that are close to the 25×25 target by accelerating the already-decreasing mortality trends in cardiovascular diseases and chronic obstructive pulmonary disease, lowering mortality from lung and stomach cancer, and reversing the rising trend in diabetes mortality. Most of the benefits of achieving the risk factor targets will be in low-income and middle-income countries.

The availability of population-based and personal interventions for tobacco and alcohol use and blood pressure makes rising obesity and diabetes (as well as physical inactivity) the risk factors with the greatest need for new interventions.⁷ Findings from randomised trials of diet change (some combined with exercise) have shown moderate weight loss benefits for up to 2 years,⁷⁸ but long-term and large-scale effectiveness has not been established.⁷⁹ The challenges to scaling up and sustaining such individual-focused interventions show the need for population-based interventions that address diet and physical inactivity.

The Millennium Development Goals included goals and targets related to some health outcomes (but not to NCDs) as well as to risk factors and social determinants of health, but there has been little integration across goals and targets. An opportunity exists to take a more integrated approach to policy formulation and monitoring progress towards targets in the global effort to prevent and control NCDs. In view of our findings, analyses are now needed to assess the benefits of achieving risk factor targets in each region and country and, importantly, by implementing effective policies and programmes to reduce these risks. An integrated approach will not only reduce NCD mortality by 2025, but will also help sustain this reduction beyond 2025, which can, for example, lead to a 30% or larger reduction in mortality from the four main NCDs in 2030 relative to 2010. Such integration will also be essential to efforts to make NCD reduction a part of the post-2015 development agenda and to efforts to achieve a grand convergence in health across the world by 2035.⁶²

Contributors

RBe and ME designed the study with input from other authors. VK and ME developed the analytical strategy, with input from CDM, JR, GAS, and RBe. CDM and GAS analysed mortality data. JR and KS analysed

alcohol data, with input from VK, GAS, LR, VP, and ME. VK, RBo, and ME designed figure graphics. VK analysed the impacts of risk factors on mortality and prepared results. ME wrote the first draft of the paper. Other authors contributed to subsequent drafts. ME oversaw the research.

Declaration of interests

We declare that we have no competing interests. CDM, GAS, LMR, and VP are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of the World Health Organization.

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