Published in final edited form as:

Curr Cardiol Rep. 2016 January ; 18(1): 10. doi:10.1007/s11886-015-0679-4.

25 by 25: Achieving Global Reduction in Cardiovascular Mortality

Sagar Dugani^{1,3} and Thomas A. Gaziano²

Sagar Dugani: sagar.dugani@utoronto.ca; Thomas A. Gaziano: tgaziano@partners.org

¹Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston 02115, USA

²Division of Cardiology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston 02115, USA

Abstract

Four non-communicable diseases—cardiovascular disease, chronic respiratory disease, diabetes mellitus, and cancer—account for over 60 % of all deaths globally. In recognition of this significant epidemic, the United Nations set forth a target of reducing the four major NCDs by 25 % by 2025. Cardiovascular disease alone represents half of these deaths and is the leading cause of death globally, representing as much as 60 % of all deaths in regions such as Eastern Europe. In response, the WHO set specific targets on conditions and risk factors and changes in the health systems structure in order to achieve the goals. The focus was set on lifestyle risk factors—physical activity, salt-intake, and tobacco—and established conditions—obesity, hypertension, and diabetes mellitus. Health system efforts to improve medical treatment of high risk are encouraged. Efforts to achieve the goal are being promoted by leading international CVD organizations.

Keywords

Ischemic heart disease; Prevention; Cardiovascular; Global; Mortality

Introduction

Non-communicable diseases (NCDs)—which comprise cardiovascular disease (CVD), cancer, chronic respiratory diseases, and diabetes—are responsible for a significant proportion of global morbidity and mortality. In 1990, NCDs were responsible for 57 % of global mortality, and by 2010, this increased to 65 % of global mortality. In 2008, of the 57 million deaths globally, 36 million were due to NCDs [1], with up to 80 % of those

Correspondence to: Thomas A. Gaziano, tgaziano@partners.org.

³Present address: Division of General Internal Medicine, St. Michael's Hospital, 30 Bond Street, Toronto, ON M5B 1W8, Canada

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Sagar Dugani and Thomas A. Gaziano declare that they have no conflict of interest.

occurring in low- and middle-income countries (LMICs). Surprisingly, a significant number of deaths in LMICs occur before the age of 60 years, resulting in substantial loss of human, economic, and financial resources, the latter of which is projected to reach US\$21 trillion over the next 15 years [2]. In health care costs alone, four conditions, chronic obstructive lung disease, cancer, CVD, and mental health will cost nearly US\$47 trillion of which 40 % of that will be attributed to CVD [3].

The growing epidemic of NCDs has been recognized for several years but the efforts to coalesce international attention to the problem have been more recent. Approximately 15 years ago, the World Health Organization (WHO) released a global strategy for the prevention and control of NCDs [4]. Despite this, targets to curb the rise in NCDs were not explicitly outlined in the United Nations Millennium Development Goals [5]. Instead, over the next decade, several regional initiatives were launched to tackle the NCD epidemic locally [6]. In 2008, in a major step forward, 160 parties worldwide ratified the WHO Framework Convention on Tobacco Control [7], making it one of the most successful treaties in the United Nations' history to tackle a major risk factor for all NCDs. In the same year, the WHO released their 2008–2013 Action Plan on the prevention and control of NCDs [8]. These initiatives from the UN, WHO, and regional organizations culminated in a high-level meeting of the UN General Assembly in September 2011 where the prevention and control of NCDs were discussed. Of the previous 23 meetings convened by the United Nations, this was only the second health-related meeting, with the first one, almost a decade prior, focused on the human immunodeficiency virus (HIV) epidemic. In quick succession 8 months later, the 65th World Health Assembly adopted a resolution to reach a '*global target of 25 % reduction in premature mortality from noncommunicable diseases such as cardiovascular disease, cancer, diabetes and chronic respiratory diseases by 2025*' [9]. This historic resolution was adopted by all 194 member countries, highlighting the shared burden faced by all nations. A month later, the Rio+20 UN Conference on Sustainable Development acknowledged that the global burden of NCDs is one of the major challenges of the twenty-first century [10, 11]. These major initiatives have led to the widespread adoption of the slogan '25 by 25', reflecting a commitment to a 25 % reduction in NCD mortality by the year 2025 and reminiscent of the '3 by 5' AIDS initiative that aimed to treat 3 million people by the year 2005. Several groups have advocated for the inclusion of NCDs in the 2015 Sustainable Development Goals (SDGs), which describe the post-MDG development agenda [11, 12, 13].

In recognition of the rising burden of NCDs faced largely by LMICs, the UN SDGs, scheduled to be ratified in the fall of 2015, have included targets towards reducing the number of deaths due to NCDs. In parallel, in 2013, the Global CVD Taskforce brought together leading organizations to address the goals including the World Heart Federation, the American Heart Association, the American College of Cardiology, the European Society of Cardiology, and European Heart Network, which has committed to a 25 % reduction in cardiovascular mortality by the year 2025.

Ultimately, the WHO set voluntary targets for six risk factors and two health services goals in order to achieve the 25% reduction in NCD premature mortality. The six risk factor goals for reduction are as follows: hypertension prevalence by 25 %, tobacco use by 30 %, sodium

intake by 30 %, physical inactivity by 10 %, and harmful alcohol use by 10 %. The two health systems based goals include essential medicines and technologies coverage of 80 %, and drug therapy and counseling for 50 % of the population.

Of all the non-communicable diseases, CVD accounts for the largest fraction of deaths and will be the focus of this review. Specifically, we will describe strategies that have resulted in reducing CVD deaths in high-income countries (HICs) and how these strategies might be implemented in LMICs to achieve similar success. We will conclude with describing the unfinished agenda in reducing CVD mortality in LMICs.

Global Burden of Cardiovascular Disease

The World Bank has divided the world into seven regions: one region consisting of HICs and six geographic regions consisting of LMICs. Data on cardiovascular mortality comes largely from the Global Burden of Disease study, which analyzed trends in morbidity and mortality from 187 countries. In 2013, there were more than 17.3 million CVD-related deaths, which represented a 41 % increase over the prior 3 decades, despite a 39% decrease in age-specific death rates [14•]. This increase in CVD deaths has been attributed to a 55 % increase in mortality due to aging populations and a 25 % increase in mortality due to population growth [14•]. A significant proportion of global CVD is driven by deaths among 85 % of the global population residing in LMICs. The burden of deaths due to CVD is shared unequally; while many HIC and Latin American countries have shown age-adjusted declines, only Western Europe and Central Europe have demonstrated an actual decline in the number of CVD deaths whereas the rest of the world has shown an increase [14•].

Success in reducing the number of cardiovascular deaths relies on effective interventions for primary and secondary prevention of cardiovascular disease. Primary prevention depends on the optimal management of cardiovascular risk factors, notably tobacco use, excessive alcohol use, diet and salt intake, and physical activity. Secondary prevention depends on several factors including access to hospital and appropriate therapies, prescription of established secondary prevention medications, and continued medical care. Interventions to improve primary and secondary prevention have focused on the individual—and population—levels, as described below. Success of each of these strategies both in HIC and LMIC have been described in detail before [15•] and briefly reviewed below.

Reduction in CVD Mortality in High-Income Countries

The HICs are divided into four subregions—Australasia, Asia-Pacific, Western Europe, and North America—and have a combined population of 1 billion. As described above, CVD-related deaths have shown different trends in different high-income countries. To understand the trend of cardiovascular deaths in the USA, Ford and colleagues used a statistical model to assess the relative contribution of cardiac treatments and changes in risk factors in reducing the burden of CVD [16]. Compared to deaths 2 decades prior, in 2000, there were approximately 340,000 fewer deaths, of which 44 % were attributed to reduction in management of risk factors (reduction in total cholesterol, systolic blood pressure, smoking prevalence, and physical inactivity) and 47 % were attributed to acute management and secondary prevention (improved revascularization, treatment for acute myocardial infarction

and heart failure, and other treatments) [17]. In addition to improved therapies, the development of coronary care units, where patients with high cardiovascular acuity could be monitored and managed also contributed to the reduction in cardiovascular mortality [18]. Similarly, there has been a 50–80% decline in CVD mortality in most high-income countries including Canada, UK, Scotland, Sweden, and New Zealand [19]. As seen in the USA, the 40–75 % of the reduction in mortality in other high-income countries can be attributed to changes in risk factors and 25–50 % can be attributed to more effective treatments [19].

Reduction in CVD Mortality in Low- and Middle-Income Countries

The major burden of cardiovascular morbidity and mortality is concentrated in LMICs. Therefore, efforts to reduce the global burden of CVD will likely require efforts that address root causes of CVD and its risk factors, particularly the lifestyle interventions that affect major risk factors. However, the management of those with current high levels of risk, including those with established CVD will need equal attention. Given the relatively short time frame to meet the 2025 goal, efforts will have to include both population-based strategies as well as strengthening health services for the delivery of primary and secondary prevention as well as acute management.

The World Bank has established six regions of LMICs: East Asia and the Pacific, Central and Eastern Europe and Central Asia, Latin America and the Caribbean, Middle East and North Africa, South Asia Region, and Sub-Saharan Africa. The GBD study showed that over the past 3 decades, the South Asia Region has had the largest increase in CVD deaths with 1.7 million more deaths in 2013 than in 1990, representing a 97 % increase. East Asia registered a 47 % increase over the same time period [14••].

Risk Factors

As seen in HICs, several interventions in LMICs have aimed to reduce the burden of CVD risk factors and to improve CVD treatments. Approximately 82 % of the 1.1 billion smokers reside in LMICs [20] and by 2030, approximately 10 million deaths annually will be attributed to smoking. Mortality among cigarette smokers is 2–3-fold higher than similarly aged non-smokers [21]. Further, other forms of tobacco including bidis, kreteks, and second-hand smoke are associated with increased CVD mortality [22–27]. To curb the use of tobacco products, tobacco taxation remains the most cost-effective anti-smoking intervention [28, 29]; however, strong political opposition has remained a major barrier to wider implementation. In addition to increasing taxes on tobacco, other strategies that may be successful in reducing tobacco use include public advertisements, legislation to ban smoking in public places [30, 31], and pictorial warnings on tobacco products, which has been successful in both high-income and middle-income countries [32, 33].

In addition to smoking, regulation of dietary salt and fat remains an important target to manage deaths due to cardiovascular disease. The association between salt intake and cardiovascular mortality is conflicting [34, 35]. The World Health Organization recommends sodium consumption of less than 2 g per day or salt consumption of less than 5 g per day [36]. Analysis of sodium intake in 187 countries shows that from 1990 to 2010, the average intake was 3.95 g per day [37]. In addition to salt intake, dietary fat is associated

with increased coronary heart disease risk in women [38] and a 2 % increase in energy intake from trans-fatty acids is associated with a 23 % increase in incidence of cardiovascular disease [39]. In general, efforts to reduce dietary salt involve collaboration with the food industry, implementation of government policies, and increase in salt-taxes. There are relatively few studies on this topic in LMICs, and most data comes from HICs. In the UK, industries voluntarily reduced the salt content of food and the average daily salt consumption decreased from 9.6 to 8.6 g (www.food.gov.uk) [40]. Modeling work across 23 countries shows that reducing salt content by 15 % and smoking prevalence by 20 % over a 10-year period could avert 8.5 million and 3.1 million cardiovascular deaths, respectively [41]. This supports other work that reducing salt intake could result in a significant decline in cardiovascular events and medical costs [42, 43].

Many middle-income countries have adopted interventions to reduce physical inactivity as well. Most countries follow the recommendation of the 1996 US Surgeon General to perform at least 30 min of moderate-intensity physical activity on most days of the week [44]. However, to date, fewer interventions have been implemented in low-income countries and very few middle- or low-income countries have actually evaluated the outcomes of their physical activity interventions. This is clearly an area where additional study is needed. Regardless, adopting physical activity interventions is likely to be a cost-effective intervention: a voluntary program to increase walking in the USA in which 25 % of the sedentary population complies with the program would generate US\$6.8 billion in savings (in 2001 US dollars) [45].

Efforts to prevent diabetes have centered on lifestyle interventions. Most of these interventions involve both changes in diet and physical activity. Four of the largest trials in this area have shown that such interventions can delay or even prevent diabetes in a high-risk population [46–49]. Trials have also been conducted to assess the efficacy of pharmacologic treatments in the prevention of diabetes; while many of these have shown a decreased incidence of diabetes, the cost, side effects, and other logistical concerns of implementing such interventions on a large scale are significant [50].

In terms of treatment of people with established diabetes, Venkat Narayan et al. assessed three interventions to be both cost-saving and feasible: glycemic control in people with HbA1c greater than 9 %, blood pressure control in people with blood pressure greater than 160/95 mmHg, and foot care in people with high risk of foot ulcers [50]. All of these, however, require a health infrastructure in which diabetics has affordable access to care as well as availability of effective, inexpensive drugs.

The risk factor that was missing from the WHO targets that is most glaring is an effort to address lipid levels. There will certainly be some change in lipid levels if there are improvements in physical activity and reductions in obesity levels. Certainly, some of the reductions in cholesterol levels that have occurred in both HIC and LMICs over the last 30 years [51] is a result of some of the lifestyle changes that have occurred. However, much of the reductions particularly over the last 20 years have been since the introduction of the statin medications. While this may be addressed in part with the attention placed on increasing coverage for essential medications, by not addressing it directly there may be

some loss of opportunity, particularly since simvastatin was only recently added to the WHO essential medication list and several other statins remain off the list.

Health System Challenges

A clear barrier to the prevention and treatment of cardiovascular disease in developing countries is the lack of essential medications. Investigators from the WHO conducted a survey of 32 medications used to treat chronic diseases in six LMICs (Bangladesh, Malawi, Nepal, Brazil, Pakistan, and Sri Lanka) [52]. The study found that availability of cardiovascular medications was poor in the public sector, forcing patients to either purchase medicines in the more costly private sector or to forgo treatment altogether. Cameron et al. found that in 40 LMICs, generic medications for communicable diseases were significantly more available than those for non-communicable diseases in both the public sector (53.5 % availability vs. 36.0 %) and the private sector (66.2 % availability vs. 54.7 %) [53].

Equally as striking is the low level of affordability of these drugs in developing countries. The study by Mendis et al. found that 1 month of combination therapy with the lowest-priced generic version of aspirin, a statin, a beta-blocker, and an ACEI cost 1.5 days' wages of the lowest-level government worker in Sri Lanka; more than 5 days' wages in Brazil, Nepal, and Pakistan; and more than 18 days' wages in Malawi [52]. The lack of availability and affordability of cardiovascular medicines was confirmed in a 2010 study. Investigators conducted a survey of five anti-hypertensive medications in 36 countries with different socioeconomic status [54]. They showed that the overall availability of cardiovascular medicines was poor (mean 26.3 % in public sector for lowest-priced generic, 57.3 % in private sector) and that buying a brand product cost 4.2 times as much as buying the lowest-priced generic. This finding highlights the important role that generic drugs play in treating illness in poorer nations.

Acute Management

The use of the CCU is cost-effective when triage to the highest-risk patients is appropriately applied [55, 56]. Aspirin and beta-blocker usage for ACS ranges from 75–95 % in middle-income countries [57]. Further, it has been shown to be highly cost-effective in this setting, costing less than \$25/QALY gained [58]. The use of thrombolytic therapy for AMI varies by LMIC region. Though this therapy is used more commonly than PCI in countries with low GNI, the time to initiation of thrombolytic therapy is longer than in their high GNI counterparts (4.3 vs. 2.8 h) [57] leading to a reduction in its effectiveness. Nonetheless, thrombolysis with streptokinase (the most commonly used and least expensive agent) [59] has been shown to be cost-effective in developing nations according to WHO's standards [58, 60].

As of 2002, the majority of patients with acute coronary syndromes in multiple regions of the world did not undergo any type of revascularization procedure. Rates of PCI were highest in the USA and were particularly low in Eastern Europe [61, 62]. Unsurprisingly, PCI use was significantly associated with GNI, as only 1.3 % of ACS patients in low GNI countries received PCI compared with 22.7% of ACS patients in high GNI countries [57]. As

with CABG, efforts to implement PCI can be cost-effective in HI countries, but less is known about whether the same holds true for LMIC.

Conclusions

High-income countries have seen on average 2–5 % reductions in age-adjusted CVD mortality over the last 40 years fairly consistently. Therefore, a goal of 25 % reduction for the next 10 years is achievable provided appropriate attention and resources are focused on the challenge. The targets set by the WHO regarding risk factors are reasonable in most cases and serve as an appropriate starting point. Certainly targeting tobacco control and hypertension through reduced salt intake, increased physical activity and improved diet will be important key features of the global effort. However, additional focus on management of lipids with the use of statins should be more clearly targeted as well. Efforts to improve acute management of those with acute ischemic heart disease should parallel the great preventive efforts ongoing at the policy level as well. To mirror the success of the prior 50 years will require efforts focused at the national or international level as well as at the individual patient.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. World Health Organization (WHO). Global Health Observatory Database [database on the Internet]. 2008. Available from: <http://www.who.int/gho/database/en/>
2. Bloom, DE.; Cafiero, E.; Jané-Llopis, E.; Abrahams-Gessel, S.; Bloom, LR.; Fathima, S., et al. The global economic burden of noncommunicable diseases. Cambridge: Program on the Global Demography of Aging, Harvard TH Chan School of Public Health; 2012.
3. Bloom, DE.; Chisholm, D.; Jané-Llopis, E.; Prettner, K.; Stein, A.; Feigl, A. Cambridge: Program on the Global Demography of Aging, Harvard TH Chan School of Public Health; 2011. From burden to "best buys": reducing the economic impact of non-communicable disease in low-and middle-income countries.
4. World Health Organization. Global Strategy for the prevention and Control of Noncommunicable Diseases. 2000 Mar. Available from: http://apps.who.int/gb/archive/pdf_files/WHA53/ea14.pdf?ua=1
5. World Health Organization. United Nations Millennium Declaration 55/2. 2000 Sep. Available from: http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/55/2
6. World Health Organization. Political declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases. RESOLUTION/66/2. 2011 Sep. Available from: http://www.who.int/nmh/events/un_ncd_summit2011/political_declaration_enpdf
7. World Health Organization. Geneva: World Health Organization; 2003. WHO framework convention on tobacco control. Available from: <http://apps.who.int/iris/bitstream/10665/42811/1/9241591013.pdf>
8. World Health Organization. World Health Organization; 2008–2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases. Available from: <http://www.who.int/nmh/publications/9789241597418/en/index.html>

9. World Health Organization. Sixty-Fifth World Health Assembly Resolutions, Decisions, Annexes. 2012 May 21–26. Available from: <http://www.who.int/mediacentre/events/2012/wha65/en/>. WHA65/2012/REC/1
10. United Nations Assembly General (UNAG). The future we want. New York: United Nations; 2012. Available from: <http://www.uncsd2012.org/content/documents/727The%20Future%20We%20Want%2019%20June%201230pm.pdf>
11. Haines A, Alleyne G, Kickbusch I, Dora C. From the earth summit to Rio+20: integration of health and sustainable development. *Lancet*. 2012; 379(9832):2189–2197. [PubMed: 22682465]
12. Alleyne G, Binagwaho A, Haines A, Jahan S, Nugent R, Rojhani A, et al. Embedding non-communicable diseases in the post-2015 development agenda. *Lancet*. 2013; 381(9866):566–574. [PubMed: 23410606] This article explains the importance of having the goals for controlling non-communicable diseases in the UN development goals for success in reducing the CVD burden.
13. Sachs JD. From millennium development goals to sustainable development goals. *Lancet*. 2012; 379(9832):2206–2211. [PubMed: 22682467]
14. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med*. 2015; 372(14):1333–1341. [PubMed: 25830423] This article explains the driving forces for increasing overall CVD mortality including population growth and aging of the population despite declines in age-adjusted death rates due to improvements in care or risk factors.
15. Gaziano TA, Pagidipati N. Scaling up chronic disease prevention interventions in lower- and middle-income countries. *Annu Rev Public Health*. 2013; 34:317–335. [PubMed: 23297660] Reviews the interventions both at the individual level and at the population or policy level that can contribute to the reduction in cardiovascular disease mortality and the potential challenges implementing them.
16. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol*. 2007; 50(22):2128–2132. [PubMed: 18036449]
17. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007; 356(23):2388–2398. [PubMed: 17554120]
18. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med*. 2012; 366(1):54–63. [PubMed: 22216842]
19. O'Flaherty M, Buchan I, Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s? *Heart*. 2013; 99(3):159–162. [PubMed: 22962283]
20. Jha P, Ranson MK, Nguyen SN, Yach D. Estimates of global and regional smoking prevalence in 1995, by age and sex. *Am J Public Health*. 2002; 92(6):1002–1006. [PubMed: 12036796]
21. Jha P, Peto R. Global effects of smoking, of quitting, and of taxing tobacco. *N Engl J Med*. 2014; 370(1):60–68. [PubMed: 24382066]
22. Balbinotto Neto G, Silva EN. The costs of cardiovascular disease in Brazil: a brief economic comment. *Arq Bras Cardiol*. 2008; 91(4):198–199. 217–218. [PubMed: 19009169]
23. Piano MR, Benowitz NL, Fitzgerald GA, Corbridge S, Heath J, Hahn E, et al. Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment: a policy statement from the American Heart Association. *Circulation*. 2010; 122(15):1520–1544. [PubMed: 20837898]
24. Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet*. 2011; 377(9760):139–146. [PubMed: 21112082]

25. Pell JP, Haw S, Cobbe S, Newby DE, Pell ACH, Fischbacher C, et al. Smoke-free legislation and hospitalizations for acute coronary syndrome. *N Engl J Med*. 2008; 359(5):482–491. [PubMed: 18669427]
26. Cronin EM, Kearney PM, Kearney PP, Sullivan P, Perry IJ. Impact of a national smoking ban on hospital admission for acute coronary syndromes: a longitudinal study. *Clin Cardiol*. 2012; 35(4): 205–209. [PubMed: 22278857]
27. Gupta R, Gupta N, Khedar R. Smokeless tobacco and cardiovascular disease in low and middle income countries. *Indian Heart J*. 2013; 65(4):369–377. [PubMed: 23992997]
28. Jha, PCF.; Moore, J.; Gajalakshmi, V.; Gupta, PC.; Peck, R.; Asma, S.; Zatonski, W. Chapter 46: Tobacco Addiction, Disease Control Priorities in Developing Countries. 2nd. Jamison, DTBJ.; Measham, AR.; Alleyne, G.; Claeson, M.; Evans, D.; Jha, P.; Mills, A.; Musgrove, P., editors. Washington DC: Oxford University Press and The World Bank; 2006.
29. Pagidipati NJ, Gaziano TA. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. *Circulation*. 2013; 127(6):749–756. [PubMed: 23401116]
30. Blecher E. The impact of tobacco advertising bans on consumption in developing countries. *J Health Econ*. 2008; 27(4):930–942. [PubMed: 18440661]
31. Higashi MH, Truong KD, Barendregt JJ, Nguyen PK, Vuong ML, Nguyen TT, et al. Cost effectiveness of tobacco control policies in Vietnam. *Appl Health Econ Health Policy*. 2011; 9(3): 183–196. [PubMed: 21506624]
32. Moodie C, MacKintosh AM, Hammond D. Adolescents' response to text-only tobacco health warnings: results from the 2008 UK youth tobacco policy survey. *Eur J Pub Health*. 2009;ckp199.
33. Wakefield MA, Hayes L, Durkin S, Borland R. Introduction effects of the Australian plain packaging policy on adult smokers: a cross-sectional study. *BMJ open*. 2013; 3(7):e003175.
34. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, Tikhonoff V, Seidlerová J, Richart T, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA*. 2011; 305(17):1777–1785. [PubMed: 21540421]
35. O'Donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA*. 2011; 306(20):2229–2238. [PubMed: 22110105]
36. World Health Organization. Sodium intake for adults and children: Guideline, 2012. Available from: http://apps.who.int/iris/bitstream/10665/77985/1/9789241504836_eng.pdf?ua=1&ua=1
37. Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, et al. Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ open*. 2013; 3(12):e003733.
38. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med*. 1997; 337(21):1491–1499. [PubMed: 9366580]
39. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N Engl J Med*. 2006; 354(15):1601–1613. [PubMed: 16611951]
40. Wyness LA, Buttriss JL, Stanner SA. Reducing the population's sodium intake: the UK food standards Agency's salt reduction programme. *Public Health Nutr*. 2012; 15(02):254–261. [PubMed: 21729460]
41. Asaria P, Chisholm D, Mathers C, Ezzati M, Beaglehole R. Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. *Lancet*. 2007; 370(9604):2044–2053. [PubMed: 18063027]
42. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, et al. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*. 2010; 362(7):590–599. [PubMed: 20089957]
43. Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. *Ann Intern Med*. 2010; 152(8):481–487. W170–W173. [PubMed: 20194225]

44. World Health Organization. Background document prepared for the WHO Workshop on Physical Activity and Public Health. Geneva: 2005. Review of best practice interventions to promote physical activity in developing countries.
45. Willett, WC.; Koplan, JP.; Nugent, R.; Dusenbury, C.; Puska, P.; Gaziano, TA. Chapter 44. Prevention of chronic disease by means of diet and lifestyle changes (Table 44.2). In: Jamison, DTBJ.; Measham, AR.; Alleyne, G.; Claeson, M.; Evans, DB.; Jha, P.; Mills, A.; Musgrove, P., editors. Disease control priorities in developing countries. New York and Washington DC: Oxford University Press and the World Bank; 2006.
46. Eriksson KF, Lindgarde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia*. 1991; 34(12):891–898. [PubMed: 1778354]
47. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346(6):393–403. [PubMed: 11832527]
48. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997; 20(4):537–544. [PubMed: 9096977]
49. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001; 344(18):1343–1350. [PubMed: 11333990]
50. Venkat Narayan, KMZP.; Kanaya, AM.; Williams, DE.; Engelgau, MM.; Imperatore, G.; Ramachandran, A. Chapter 30. Diabetes: the pandemic and potential solutions. In: Jamison, DTBJ.; Measham, AR.; Alleyne, G.; Claeson, M.; Evans, DB.; Jha, P.; Mills, A.; Musgrove, P., editors. Disease control priorities in developing countries. 2nd. New York, NY and Washington DC: Oxford University Press and The World Bank; 2006.
51. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3 · 0 million participants. *Lancet*. 2011; 377(9765):578–586. [PubMed: 21295847]
52. Mendis S, Fukino K, Cameron A, Laing R, Filipe A Jr, Khatib O, et al. The availability and affordability of selected essential medicines for chronic diseases in six low- and middle-income countries. *Bull World Health Organ*. 2007; 85(4):279–288. [PubMed: 17546309]
53. Cameron A, Roubos I, Ewen M, Mantel-Teeuwisse AK, Leufkens HG, Laing RO. Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries. *Bull World Health Organ*. 2011; 89(6):412–421. [PubMed: 21673857]
54. van Mourik MS, Cameron A, Ewen M, Laing RO. Availability, price and affordability of cardiovascular medicines: a comparison across 36 countries using WHO/HAI data. *BMC Cardiovasc Disord*. 2010; 10:25. [PubMed: 20534118]
55. Masoudi FA, Bonow RO, Brindis RG, Cannon CP, Debuhr J, Fitzgerald S, et al. ACC/AHA 2008 statement on performance measurement and reperfusion therapy: a report of the ACC/AHA task force on performance measures (work group to address the challenges of performance measurement and reperfusion therapy). *J Am Coll Cardiol*. 2008; 52(24):2100–2112. [PubMed: 19056001]
56. Weinstein MC, Stason WB. Cost-effectiveness of interventions to prevent or treat coronary heart disease. *Annu Rev Public Health*. 1985; 6(1):41–63. [PubMed: 2859868]
57. Orlandini A, Diaz R, Wojdyla D, Pieper K, Van deWerf F, Granger CB, et al. Outcomes of patients in clinical trials with ST-segment elevation myocardial infarction among countries with different gross national incomes. *Eur Heart J*. 2006; 27(5):527–533. [PubMed: 16410369]
58. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl JMed*. 1977; 296(13):716–721. [PubMed: 402576]
59. Sikri N, Bardia A. A history of streptokinase use in acute myocardial infarction. *Tex Heart Inst J*. 2007; 34(3):318–327. [PubMed: 17948083]
60. Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. *Circulation*. 2005; 112(23):3547–3553. [PubMed: 16330695]

61. Giugliano RP, Llevadot J, Wilcox RG, Gurfinkel EP, McCabe CH, Charlesworth A, et al. Geographic variation in patient and hospital characteristics, management, and clinical outcomes in ST-elevation myocardial infarction treated with fibrinolysis. Results from InTIME-II. *Eur Heart J*. 2001; 22(18):1702–1715. [PubMed: 11511120]
62. Kramer JM, Newby LK, Chang WC, Simes RJ, Van de Werf F, Granger CB, et al. International variation in the use of evidence-based medicines for acute coronary syndromes. *Eur Heart J*. 2003; 24(23):2133–2141. [PubMed: 14643274]