

Chapter 19

Costs and Cost-Effectiveness of Interventions and Policies to Prevent and Treat Cardiovascular and Respiratory Diseases

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INTRODUCTION

The risk factors and disease conditions covered in this volume of *Disease Control Priorities* constitute the majority of the health burden facing middle- and high-income countries (MICs and HICs, respectively) today and are fast approaching a majority of the burden in low-income countries (LICs). Previous editions of *Disease Control Priorities*, published in 1993 and 2006, acknowledged the importance of cardiovascular and related diseases (CVRDs) to the future health and economic well-being of populations in low- and middle-income countries (LMICs) and singled out tobacco taxes and treatment of heart disease with low-cost generics as high-priority, cost-effective interventions. With some exceptions, most of the conclusions about cost-effectiveness were extrapolated from analyses done in HICs (Rodgers and others 2006) and from modeling, because of the paucity of economic analysis of interventions for CVRDs using LMIC data. In 2012, the World Health Organization (WHO) reviewed the cost-effectiveness of noncommunicable disease (NCD) interventions, based on a limited number of modeled studies. The results were used to develop the WHO Best Buys for interventions recommended in the NCD Global Action Plan (WHO 2011).

By 2016, when the WHO updated its review of cost-effectiveness evidence, considerably more LMIC data were available. This chapter also benefits from a larger universe of economic analyses on the conditions and risk factors covered in the chapters in this volume—both from models and from experience. Some recent systematic reviews have examined evidence on the cost-effectiveness of interventions to tackle CVRDs in LMICs (for example, Shroufi and others 2013; Suhrcke, Boluarte, and Niessen 2012; Wiseman and others 2016). These reviews found modest, but growing, evidence of the cost-effectiveness of CVRD interventions in these settings and noted a bias in favor of research on personal medical interventions over population-level interventions.

The chapter catalogues the results of dozens of high-quality, cost-effectiveness analyses for cardiovascular disease (CVD), diabetes, respiratory, and kidney-related conditions and risk factors (hereafter termed CVRDs)—much of it with country-specific data. It begins by summarizing the available literature on population-level health and intersectoral policies to address the major risks in LMICs and discusses some methodological issues in these analyses. It then assesses and discusses the cost-effectiveness of personal services

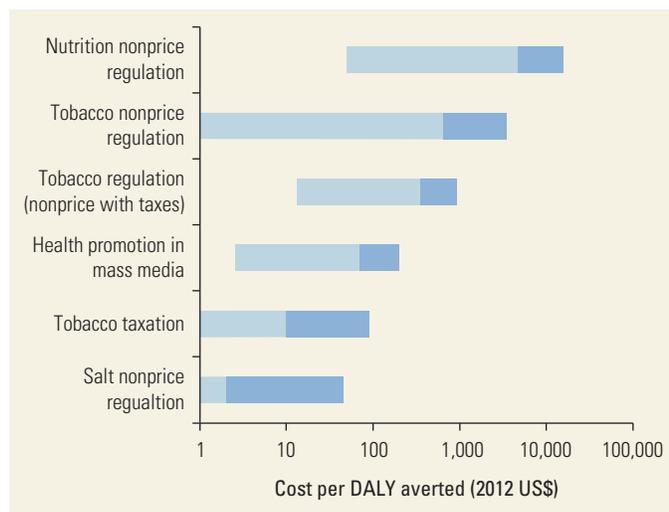
delivered through various levels of the health system. It is intended to complement the reviews of effective policies and interventions in other chapters with cost-effectiveness results useful for informing decisions about policies, packages, and delivery platforms. The methodology used for the review is described in online annex 19A, along with the detailed results.

POPULATION-LEVEL INTERVENTIONS AND POLICY

This section reviews the cost-effectiveness of fiscal and regulatory policies used to change behavior and address the external costs associated with tobacco consumption, dietary issues such as obesity (Cawley 2015; Suhrcke and others 2006), and physical activity. Overall, the evidence in favor of fiscal and regulatory policies to curb tobacco consumption is, beyond doubt, more convincing than the evidence for diet. Although mass media campaigns show some promise in HICs, at least when focused on specific dietary targets, evidence of their cost-effectiveness is more nuanced. There is little cost-effectiveness data from LMICs on population-level physical activity interventions.

Figure 19.1 summarizes the evidence on cost-effectiveness for population-level interventions. The figure

Figure 19.1 Average Cost-Effectiveness of Population-Level Interventions for CVRD Risk Factors, 2000–14



Sources: Based on a systematic literature review of cost-effectiveness ratios for LMICs from 2000 to 2014, including Cecchini and others 2010; Chow, Darley, and Laxminarayan 2007; Higashi and others 2011; Murray and others 2003; Ortegón and others 2012; Ranson and others 2002; Rubinstein and others 2009; Rubenstein and others 2010; Salomon and others 2012.

Note: CVRD = cardiovascular and related disease; DALY = disability-adjusted life year. The bars capture the range of estimated costs per DALY averted from the set of studies reviewed. From each study, the mean estimate is taken as the relevant estimate. The average is the space where the light blue and dark blue bars meet. Light blue represents the range below the average; dark blue represents the range above the average. Negative numbers are not plotted because the x-axis is on a logarithmic scale. Any bars that touch the y-axis have at least one source that found the intervention to be cost saving.

only captures cost-effectiveness studies that have expressed outcomes in cost per disability-adjusted life years (DALYs) averted. Table 19A.2 in annex 19A provides more detailed results.

Keeping these reservations in mind, figure 19.1 suggests the following conclusions:

- Overall, population-level interventions to address the risk factors for CVRDs appear to have favorable cost-effectiveness ratios. Several—price and nonprice tobacco interventions and nonprice salt regulation—have the potential to be cost saving.
- Of the population-level interventions examined, tobacco taxation and nonprice salt regulation are, on average, considerably more attractive from a cost-effectiveness standpoint than other, often less intrusive, interventions. However, the seeming superiority of nonprice salt regulation is likely to be driven by the extraordinarily positive results of one study (Rubinstein and others 2009).
- A particularly large range of cost-effectiveness ratios is found across the many types of tobacco regulation, due to diversity in policies and variation in costs.

A summary of the cost-effectiveness literature for CVRD risk factors, specifically tobacco and diet, follows. The cost-effectiveness of interventions to deter excess alcohol use is discussed in volume 4, chapter 7 (Medina-Mora and others 2015).

Tobacco Use

Fiscal policies to tackle tobacco-related harm have typically ranked among the most preferred options for addressing CVRDs. In its NCD Best Buys, the WHO ranked the taxation of tobacco as one of the most cost-effective ways to tackle NCDs in LMICs (WHO 2011). This recommendation rests on a considerable body of research regarding effectiveness, but few studies have directly examined the cost-effectiveness of the policy. Ortegón and others (2012) applied the WHO's Choosing Interventions That Are Cost-Effective (CHOICE) model (Tan-Torres Edejer and others 2003) to estimate the cost-effectiveness of 123 single or combined interventions, including tobacco taxation, in two WHO regions with high adult and child mortality—South-East Asia and Sub-Saharan Africa. They found that increasing tobacco taxation to 40 percent to 60 percent of the retail price was among the most favorable of the interventions considered. Previously, Ranson and others (2002) estimated highly favorable cost-effectiveness ratios for increasing tobacco taxation by 10 percent at global and regional levels.

In low- and middle-income regions, they found that such tobacco taxation would cost about US\$4–US\$91 per DALY averted.

Chow, Darley, and Laxminarayan (2007) compared a 10 percent increase in the price of tobacco in India to nicotine replacement therapy and other nonprice interventions, including bans on advertising and promotion of tobacco, dissemination of information on the health consequences of using tobacco, and restrictions on smoking in public and work spaces. The tax increase was estimated to cost US\$13 per DALY averted—a very favorable cost-effectiveness outcome compared with the other interventions analyzed. Similarly, in a modeling exercise for Mexico, Salomon and others (2012) found that increasing the tobacco tax from 60 percent of the retail price of cigarettes to 80 percent had a cost-effectiveness ratio of about US\$22 per DALY averted, which compared very favorably with a ban on advertising, at US\$435 per DALY averted. Higashi and others (2011) obtained similar results for Vietnam.

Modeled evidence suggests that policies regulating tobacco through smoking bans, graphic warning labels, mass media campaigns, advertising bans, and others are generally more cost-effective than personal interventions to reduce tobacco consumption in LMIC settings. However, as with taxation, studies that model regulatory interventions are sensitive to assumptions about the quality of enforcement, the prevalence or intensity of smoking habits, and purchasing patterns.

Two studies modeled tobacco regulation across countries, compared with tobacco taxation. Using a static model, Ranson and others (2002) compared a tobacco tax to nicotine replacement therapy and a combination of other nonprice interventions. A later study (Navarro and others 2014) compared a tobacco tax with a ban on advertising and promotion, dissemination of information on the health consequences of smoking, and restrictions on smoking in public places and workplaces. Results from both of these studies show that nonprice interventions cost between US\$47 and US\$921 per DALY averted in LMICs, which is a less favorable cost-effectiveness result than tobacco taxation (US\$3.9–US\$90.8 per DALY averted), but more attractive than nicotine replacement therapy for individual treatment (US\$363–US\$1,128 per DALY averted).

Ortegon and others (2012) modeled the cost-effectiveness of a set of nonprice population-level interventions for South-East Asia and Sub-Saharan Africa. The population-level tobacco control interventions included restrictions on smoking in public places, advertising bans, warning labels, and consumer information campaigns. The personal interventions included nicotine replacement therapy and physician advice. Of all

of the tobacco and other interventions considered in their analysis, combinations of population-level tobacco interventions were found to be highly cost-effective in both regions. Moreover, the overall set of population-level interventions was more cost-effective than adding individual treatment options (nicotine replacement therapy and physician advice) to the entire package.

Several studies have compared the cost-effectiveness of various tobacco policies in specific countries (or regions of countries), often using similar modeling strategies. Salomon and others (2012) applied the CHOICE model to Mexico to estimate cost-effectiveness of tobacco policies such as excise taxes, advertising bans, indoor air quality laws, and nicotine replacement therapy, as well as combinations of these. A comprehensive advertising ban and enforcement of the air quality law showed favorable cost-effectiveness, whereas nicotine replacement therapy did not. In the incremental analysis, tobacco taxation dominated most other single and combined strategies, with the exception of the “taxation plus ban on advertising” set (which cost US\$435 per DALYs averted).

Higashi and others (2011) modeled the cost-effectiveness of four population-level tobacco interventions in Vietnam: an excise tax increase, graphic warning labels on cigarette packs, mass media campaigns including educational messages for different media, and smoking bans in public or in workplaces. Graphic warning labels on cigarette packs showed the most favorable cost-effectiveness ratios, followed closely by excise tax increases (except for a large tax increase, in which case taxation was the most cost-effective), mass media campaigns, public smoking bans, and workplace smoking bans (table 19.1). The analysis concluded that all

Table 19.1 Costs per Disability-Adjusted Life Year Averted of Population-Level Tobacco Interventions in Vietnam, Exclusive of Potential Cost Offsets (Compared with Status Quo Interventions in Place)

Intervention	Cost per Disability-Adjusted Life Year Averted	
	2007 Vietnamese dong	2012 US\$
Graphic pack warning label	500	0.05
Tax increase maximum (from 55 to 85%)	290	0.03
Tax increase minimum (from 55 to 75%)	4,200	0.41
Tax increase minimum (from 55 to 65%)	8,600	0.83
Smoking ban (public)	67,900	6.56
Smoking ban (work)	336,800	32.53
Mass media campaign	78,300	7.56

Source: Higashi and others 2011.

Note: Cost offset is the savings expected from lower health care costs.

interventions would be cost saving by preventing or reducing spending on future treatment of tobacco-related illness. This study method is unusual, and there is no consensus on whether and how to account for the costs of future unrelated health care (van Baal and others 2011).

Rubinstein and others (2010) modeled the costs and effects of a mass media campaign to promote tobacco cessation among smokers, in addition to population-level salt reduction and four individual, clinical treatment interventions. The mass media campaign produced a cost-effectiveness ratio of US\$3,583 per DALY averted, which, while not cost saving (which would require a cost-effectiveness ratio of US\$1,582), was still considered good value for money.

Donaldson and others (2011) modeled the cost-effectiveness of an effective prohibition on smoking in public places in Gujharat State in India compared with the current, poorly enforced prohibition of smoking in public places in some districts of the state. The results are expressed in life years (LYs) saved and in heart attacks averted rather than in DALYs averted. A complete ban is highly cost-effective when key variables, including legislation effectiveness, are varied in the sensitivity analyses. Without including medical treatment costs averted, the cost-effectiveness ratio ranges from US\$2.4 to US\$135.0 per LY saved and US\$44.5 to US\$464.0 per acute myocardial infarction averted. When including potential future savings in tobacco-related health care costs, the ban becomes cost saving.

In summary, cost-effective policies to reduce tobacco consumption are available. The most favorable policy appears to be a large tax increase on tobacco. Regulatory approaches, including bans on smoking in public places, warning labels, advertising and promotion restrictions, and mass media campaigns, are also attractive from a cost-effectiveness standpoint. All fiscal and regulatory approaches are superior to individual approaches to tobacco reduction.

Diet

Interest has recently increased in the potential use of fiscal policy in many HICs and increasingly in some MICs to improve diets. In addition to changing eating behaviors and reducing obesity, fiscal policies have been justified as a way to eliminate externalities. The argument is made that, whether through health insurance or tax-funded public payment, healthy-weight individuals will subsidize the medical care costs of obese individuals. The higher medical care costs may be passed on to the public in the form of higher payroll or income taxes (Cawley 2015).

For this and other reasons, real-world implementation of fiscal policies to influence dietary behavior is

expanding rapidly,¹ yet a considerable amount of research has not yet settled a vigorous debate on the subject. Several recent systematic and nonsystematic reviews of the effectiveness of dietary pricing policies have been published, each with a somewhat different focus (Cabrera Escobar and others 2013; Epstein and others 2012; Eyles and others 2012; Powell and others 2013; Thow, Downs, and Jan 2014). Reflecting wide recognition that diet-related taxation is far more nuanced than tobacco taxation, existing reviews reach varying conclusions regarding the use of fiscal policy to improve diet. For example, according to Thow and others (2010, 1), “Taxes and subsidies on food have the potential to influence consumption considerably and improve health, particularly when they are large,” while, according to Cornelsen and others (2015, 18), “There is a very real possibility that [taxes on unhealthy foods and beverages] may not be beneficial after all.” The magnitude of the tax or subsidy needed to influence consumption and health, as well as the optimal design of such fiscal policies (that is, what precisely should be taxed or subsidized), is also unclear.² In a recent series in *The Lancet* on obesity, Popkin and Hawkes (2015) concluded that taxes on unhealthy food and beverages can reduce obesity by altering preferences.

Some of the variation in the conclusions may be attributed to differences in the scope of each review, given that they tend to differ in regional focus, the precise outcome indicator used, and the type of estimation methodologies used. Part of the problem in developing conclusive evidence is the relatively short real-world experiences with implementing significant fiscal policy measures. Inevitably, most studies rely on analysis of empirical relationships between food prices and food purchases, on analysis of consumption- or diet-related health (for which it is difficult to establish true causal evidence as a proxy for the effect of a policy), or on hypothetical modeling studies (which depend on the assumptions in the model).

Early evidence is mixed. In a short-term evaluation of the first city-level tax on sugar-sweetened beverages (SSBs) in Berkeley, California, Cawley and Frisvold (2015) found relatively little pass-through of the SSB tax to consumers, in that retail prices rose by less than half of the amount of the tax. The direct effect on consumption and obesity is likely to be smaller than expected given that much of the previous literature found or assumed full or even overshifting of taxes.

In contrast, the Mexican SSB tax appears to have had a greater effect on prices and hence on sales and consumption. Grogger (2015) found that the price of SSBs increased by more than the amount of the tax shortly after the policy was implemented. Evaluating the same

policy, Colchero and others (2016) concluded that the policy resulted in a 6 percent reduction in purchases (9 percent among low-income groups) and a shift away from SSBs to water and diet drinks.

In light of uncertainty about the effectiveness of diet-related fiscal policies, it is perhaps not surprising that only a few studies have examined their cost-effectiveness, particularly in LMICs. Cecchini and others (2010) modeled obesity prevention policies in LMICs, covering Brazil, China, India, Mexico, and South Africa. Their results indicate that fiscal measures (including increasing the price of food with unhealthy content or reducing the cost of healthy foods rich in fiber) are less expensive per capita than regulatory or individual interventions and are the only measures that were cost saving for all LMICs at both 20- and 50-year time horizons. Additionally, they were cost saving by a magnitude of twice the other interventions considered. Price interventions and regulation appear to produce the largest health gains in the shortest timeframe.

Using a simulation model (relying, in part, on the results of Cabrera Escobar and others 2013), Manyema and others (2014) estimated the effect of a 20 percent tax on SSBs on the prevalence of obesity among adults in South Africa. A 20 percent tax was predicted to reduce energy intake by about 36 kilojoules per day. Obesity was projected to decline 3.8 percent in men and 2.4 percent in women. The number of obese adults was projected to decrease by more than 220,000.

Regulatory and Mass Media Policies

Reducing salt content in manufactured foods through mandatory government regulations or voluntary action from industry is recommended in the WHO Global NCD Action Plan (WHO 2011). In addition to cost-effectiveness of salt regulation, economic analyses have been performed on mass media campaigns and regulation of other undesirable food content, such as trans fatty acids (trans fats) in processed foods. This section reviews those studies.

Salt Consumption

In a wide-ranging application of the CHOICE modeling approach, Murray and others (2003) modeled salt reduction, mass media health education, and individual treatment, as well as various combinations of interventions, in two LMIC regions (South-East Asia, with high rates of adult and child mortality, and Latin America and the Caribbean, with low rates of adult and child mortality) and one high-income region (Europe, with very low rates of adult and child mortality). They found that population-based interventions had more favorable

cost-effectiveness ratios than personalized health service interventions. Voluntary agreements to reduce salt were less cost-effective than legislative measures, with salt reduction legislation estimated to avert one DALY for as little as US\$3.74 in South-East Asia and US\$2.6 in Latin America and the Caribbean. Combining salt legislation with mass media programs could improve the cost-effectiveness ratio even further. The most cost-effective set of interventions is, however, a mix of population-level preventive interventions and personalized treatments.

Two follow-up studies using the WHO CHOICE model provide multiregional estimates of the cost-effectiveness of salt regulation and other interventions. Asaria and others (2007) modeled the cost and effects of shifting the distribution of risk factors associated with salt intake and tobacco use on chronic disease mortality for 23 countries with 80 percent of the chronic disease burden in LMICs. They showed that, over 10 years (2006–15), implementing these interventions could avert 13.8 million deaths at a cost of less than US\$0.40 per person per year in low-income and lower-middle-income countries, and US\$0.50–US\$1.00 per person per year in upper-middle-income countries (as of 2005). Ortegón and others (2012) provided updated evidence on broadly similar interventions in two WHO regions: South-East Asia and Africa. They modeled the cost-effectiveness of reducing the amount of salt in processed foods via voluntary agreement with industry and via regulation. They concluded that supply-side interventions to reduce salt had less favorable cost-effectiveness ratios than interventions to reduce demand; provide combination drug therapy, either alone or in a multidrug regimen, for high-risk CVD patients (25 percent or more absolute risk of experiencing a cardiovascular event over the next decade); or provide retinopathy screening and glycemic control for patients with diabetes.

The CHOICE model was again used to model salt reduction in Buenos Aires (Rubinstein and others 2009) and in Argentina (Rubinstein and others 2010). The studies modeled similar interventions: reducing the amount of salt in bread via voluntary industry agreements and mass education programs as well as individual treatment options (for example, Murray and others 2003). While broadly similar, the findings for Argentina were more favorable for salt reduction, finding that any approach would be cost saving, while the findings for Buenos Aires showed that voluntary industry salt reduction would cost very little and would have a more favorable cost-effectiveness ratio than a mass media campaign.

Ferrante and others (2012) also assessed the cost-effectiveness of salt reduction in Argentina. They simulated

the effects of an intervention that reduced salt content by 5 percent to 25 percent in a wide range of food groups, including bread, bread products, meat products, canned foods, soups, and dressings. This intervention was found to be cost saving while producing substantial improvements in population-wide, diet-related health outcomes. In a study of four countries in the eastern Mediterranean region, Mason and others (2014) evaluated three policies to reduce dietary salt intake—a health promotion campaign, labeling of food packaging, and mandatory reformulation of salt content in processed food—and found that salt reduction may be cost saving, either applied on its own or in combination with other interventions.

Trans Fats Consumption

Several policy guidelines and recommendations, internationally and nationally, have recommended the elimination of trans fatty acids to reduce coronary heart disease worldwide (see chapter 6 in this volume, Afshin and others 2016). The WHO has called for their elimination in its global strategy on diet, physical activity, and health (WHO 2004). Several types of measures to reduce consumption of trans fats have also been implemented, including total bans, mandatory labeling, restaurant bans, and voluntary reformulation (Downs, Thow, and Leeder 2013). So far, very little empirical evaluation of the effectiveness, let alone cost-effectiveness, of these policies has been undertaken. However, some research has used a modeling framework to evaluate some of them.

To the best of our knowledge, the only economic evaluation in an LMIC context is by Chow, Darley, and Laxminarayan (2007), who analyzed the costs and health effects of legislation mandating the replacement of trans fats produced from partial hydrogenation with polyunsaturated fats. This analysis estimated that substituting 2 percent of the energy from trans fats with polyunsaturated fats would cost US\$0.50 per adult per year and reduce coronary artery disease by 7 percent over 10 years.

A recent example from an HIC is a modeling study by Allen and others (2015) that simulated costs and effects of three options for restricting the consumption of trans fats in England: a ban on trans fatty acids in processed foods, improved labeling of trans fatty acids, and a ban on trans fats in restaurant foods. The research sought to examine the effects of various approaches across different socioeconomic groups. The expected health effects of a total ban, as well as policies to improve labeling or remove trans fatty acids from restaurant and fast foods, would lead to a considerable reduction in coronary heart disease mortality. The benefits would be larger among lower socioeconomic groups. In addition, the study predicted large cost savings from these policies. Going beyond the

usual economic costs, this study included the costs of informal care and lost productivity, among others.

Physical Activity

Increasing physical activity can reduce mortality and improve population health. Governments in many countries have recognized this opportunity, but the evidence on what works best to promote physical activity and what is best value for money is scarce and concentrated largely on HICs. One exception is a study about a comprehensive, school-based intervention program for childhood obesity in China, based on a two-year multiple-center randomized controlled trial. Nutrition-only and physical activity-only interventions were compared with a combined nutritional plus physical activity program (Meng and others 2013). The combined intervention was found to be more cost-effective than either of the single interventions, preventing a case of obesity or overweight for a cost of US\$1,519.

Laine and others (2014) reviewed 10 studies from HICs on population-, community-, and individual-level physical activity interventions. Expressing the cost-effectiveness of these studies in dollars per metabolic equivalent of task-hours (MET-h) gained (making comparisons to nonphysical activity interventions impossible), they found that the most efficient interventions to increase physical activity were community rail trails (US\$0.006 per MET-h), pedometers (US\$0.014 per MET-h), and school health education programs (US\$0.056 per MET-h). It is not clear how generalizable these findings are to an LMIC context.

A more encompassing cost-effectiveness review of physical activity by Müller-Riemenschneider, Reinhold, and Willich (2009) identified only eight studies covering 11 intervention strategies, again from HICs only, including, for instance, advice from general practitioners, trail development, promotion of worksite physical activity, and phone delivery of intervention messages. To the extent that any broader patterns could be observed, the more environmental interventions (trail development) and interventions targeted at general practitioners seemed to be the most cost-effective when measured by costs per person becoming physically active.

Lehnert and others (2012) also concluded that environmental approaches have particular promise. They reviewed the long-term cost-effectiveness of obesity prevention interventions, some of which focus on physical activity. Their review focused exclusively on cost-utility analyses, estimating the value for money of interventions as measured by their costs per DALYs averted or quality-adjusted life years (QALYs) gained. Doing so increased the comparability of the results across interventions. The potential downside of relying

on such decision-analytic modeling results, however, is that they may be based on a set of assumptions that are not readily appreciated and the point estimate of each cost-utility ratio will be highly uncertain.³

Issues in Economic Analysis of Population-Level Health Policies

Research on the cost-effectiveness of population-level preventive interventions is still limited, even in HICs (Schwappach, Boluarte, and Suhrcke 2007), as a result of the methodological challenges of conducting economic evaluations in the public health field (Pitt, Goodman, and Hanson 2016; Weatherly and others 2009). The most binding challenge may be that of attributing potential health effects directly to an intervention, especially when the change is targeted to entire populations or communities, randomized controlled trials are difficult to undertake, and the impact of the intervention takes a long time to emerge. In addition, because many population-level and community-level interventions may be located outside of health care settings, at least part of their costs and consequences are incurred by sectors other than health. These intersectoral costs and consequences may not be taken into account, and how to do so is not obvious (Claxton, Sculpher, and Culyer 2007; Greco, Lorgelly, and Yamabhai 2016). For instance, the cost-effectiveness of tobacco taxation is an unsatisfying concept. First, many of the costs are likely to be incurred by administrative units outside of the health care system, such as the Finance Ministry. Second, while economists agree that the revenues raised by taxes on tobacco are a transfer from consumers to government and thus should not be included in the benefit ledger, it is difficult to measure the efficiency effects of taxation (deadweight loss), and thus tobacco revenues are not usually included in analyses. As such, societal cost-effectiveness or cost-benefit analysis may better capture the full effects of tobacco taxation rather than a purely health system perspective. Results of these different types of economic evaluations are not directly comparable (Claxton and others 2010). Examples of cost-benefit analyses for water, sanitation, and hygiene are reviewed in volume 7, chapter 9 (Hutton and Chase 2017). The chapter by Chang, Jamison, and Horton (2018) in volume 9 discusses cost-benefit methods.

Assessing the impact—effectiveness and cost-effectiveness—of population-level interventions is fraught with challenges that often go beyond those faced in the evaluation of clinical interventions. A major difficulty is that researchers usually need to rely on observational data and modeling studies rather than on randomized studies. Economic modeling is the basis for

cost-effectiveness conclusions in earlier editions of *Disease Control Priorities* and the WHO's CHOICE project.⁴

Moreover, comparability across studies is limited for several reasons. First, the relevant cost-effectiveness threshold for a given intervention in any given country is not clear.⁵ Adhering strictly to the widely used rule of thumb of one (or three) times gross domestic product per capita poses the risk that, if the threshold is too high, interventions could displace services and forgo more health than they generate. If the threshold is too low, new interventions could be rejected that would offer a health gain (Revill and Sculpher 2012). Second, because of the limited number of studies for each type of intervention, a single outlier may well tilt the relative ranking one way or another. Third, some types of interventions, such as nonprice regulation of tobacco or salt, may still encompass a wide range of specific interventions and hence widely different cost-effectiveness ratios. Even for more narrowly defined interventions, such as tobacco taxation, the exact magnitude of the tax treatment may differ.

INDIVIDUAL-LEVEL CARE AND MANAGEMENT OF CHRONIC DISEASE

The large reductions in age-adjusted CVD mortality rates in HICs have resulted from three complementary types of interventions. One targets persons with acute or established CVD. A second assesses risk and targets persons with multiple risk factors before their first CVD event. The third uses mass education or policy interventions directed at the entire population to reduce the overall level of risk factors. This section highlights the variety of cost-effective interventions aimed at individuals in different settings, including the community, primary health centers, and hospitals. Much work remains to be done in LMICs to determine the best strategies given limited resources; if implemented, these interventions could help reduce the burden of CVD mortality. Table 19A.3 in online annex 19A lists the cost-effectiveness ratios for many of the most promising interventions used either in the community or at primary health centers that could be or have been adopted in low- and middle-income regions. Table 19A.4 lists the ratios for interventions that occur at primary health centers, first-level hospitals, or advanced-level hospitals and are focused on individuals with established disease.

Community-Based Care

Screening

Primary prevention is paramount for the large number of individuals who are at high risk for CVD. In particular, a significant amount of the reduction in CVD

mortality has come from the control of risk factors (Ford and Capewell 2011). Globally, the major risk factors are poorly controlled. Control rates for hypertension are less than 5 percent. Control rates for lipids are likely even worse, given that many countries do not have the facilities to measure lipids, and statins have become available only recently in low-income regions. For example, several Western European countries have hypertension control rates (blood pressure below 140/90) of less than 10 percent, with Spain having a control rate of less than 5 percent (Wolf-Maier and others 2004). Low control rates reflect low detection rates in addition to lack of drug availability.

Although preventive treatment is available in many LMICs, Mendis and others (2005) found that fewer than 10 percent of members of the community received the recommended care. Awareness, treatment, and control rates of major cardiovascular risk factors such as hypertension must be improved to prevent significant disease. Improved mortality rates require improved awareness of risk, appropriate initiation of treatment when available, and control of risk factors through appropriate follow-up. Major barriers to improving care include crowded primary health centers with long wait times, scarcity of professional health staff, and high costs of traditional screening programs.

Given limited resources, finding low-cost prevention strategies is a top priority. Using prediction rules or risk scores to identify persons at higher risk so as to target specific behavioral or drug interventions is a well-established primary prevention strategy and has proved to be cost-effective in LMICs (Gaziano, Opie, and Weinstein 2006; Gaziano and others 2005). Most methods have included age, sex, hypertension, smoking status, diabetes mellitus, and lipid values; some have included family history (Assmann, Cullen, and Schulte 2002; Conroy and others 2003; Ferrario and others 2005; Wilson and others 1998). See chapter 22 in this volume (Jeemon and others 2017) for a discussion of absolute risk measurement.

More attention is now focused on developing risk scores that would be easy to use without losing predictive discrimination in resource-poor countries. In LICs, a prediction rule that requires a lab test may be too expensive for widespread screening or for any use. In response to this real concern, the WHO released risk prediction charts with and without cholesterol for different regions of the world (Mendis, Lindholm, and others 2007). Pandya, Weinstein, and Gaziano (2011) demonstrated that a risk tool using nonbiometric information (age, systolic blood pressure, body mass index) can screen as effectively as one that uses lab results. Furthermore, the results of the risk tool have been validated in other cohorts in LMICs (Gaziano and

others 2013; Gaziano and others 2016), and the method of assessing absolute risk has proved to be more cost-effective than relying on blood pressure alone (Gaziano and others 2005).

Community Health Workers

Shifting the responsibility for screening to community health workers (CHWs) was shown to be as effective as having nurses or physicians screen for CVD risk in a community study in Bangladesh, Guatemala, Mexico, and South Africa (Gaziano, Abrahams-Gessel, Denman, and others 2015). CHWs using a mobile phone app was found to be life saving in Guatemala (34 lives), Mexico (281 lives), and South Africa (471 lives) per 210,000 adults screened at very cost-effective ratios. Having CHWs conduct screening using a simple tool was much more cost-effective when the primary health system was prepared and equipped to treat persons identified as high risk (Gaziano, Abrahams-Gessel, Surka, and others 2015). In countries like South Africa, where at least half of persons identified as being high risk received medications, the screening intervention was cost saving.

Even in settings such as Guatemala, where fewer than 5 percent of eligible patients received statins, the intervention was still attractive at US\$565 per QALY gained. In Mexico, where 36 percent of eligible patients were started on hypertension medications and 18 percent were started on statins, the incremental cost-effectiveness ratio for screening by CHWs was less than US\$4 per QALY gained.

CHWs can help improve adherence once individuals are on treatment. Twice yearly visits by a CHW for hypertension and adherence education have a cost-effectiveness ratio of US\$320 per QALY gained compared with usual care in South Africa; the cost can be as low as US\$17 per QALY gained in an urban setting with shorter distances between homes and as much as US\$1,500 per QALY gained in a deep rural setting with greater distances between dwellings (Gaziano and others 2014).

Primary Health Center Care

Much of the screening for cardiometabolic conditions that does not happen in the community can occur in primary health centers, particularly opportunistic hypertension screening. Regardless of the location of the screening, once identified, the bulk of primary prevention for ischemic heart disease and stroke will occur in primary health centers. Furthermore, great overlap occurs in many of the medications used. While many of the interventions for secondary prevention may be initiated in primary care hospitals, once patients are stabilized, they generally receive care at a primary health center.

Much of the management is centered on control of hypertension, blood lipids, and diabetes.

Hypertension and Cholesterol

Control of risk factors is paramount to primary prevention of CVD and a major focus of primary health centers. Blood pressure control has been a cornerstone of the prevention of stroke, ischemic heart disease, and peripheral vascular disease for more than 50 years and is cost-effective in all regions of the world (Rubinstein and others 2010; Wang and others 2011).

Issues regarding the cost-effectiveness of such interventions have recently focused on finding ways to improve the efficiency of identifying who most benefits from treatment, how to improve access to medications, how to improve adherence to medications, and how best to deliver medications. One trend has been to evaluate the overall risk of a patient rather than a single risk factor such as blood pressure. Several studies have shown that it is more cost-effective to identify potential risks based on overall CVD risk than on blood pressure or cholesterol levels alone (Gaziano and others 2005; Lim and others 2007; Rubinstein and others 2010). Similar analyses have been done for cholesterol treatment, and guidelines have been set in both Europe and the United States, while the WHO has moved to global risk-based assessments for initiating statin-based medications. Murray and others (2003) showed that lowering cholesterol for persons at high cardiovascular risk (absolute risk greater than 35 percent) was cost-effective.

Diabetes

The costs associated with mortality and morbidity from diabetes worldwide are staggering. People with diabetes consume two to three times the health care resources of persons without diabetes, and diabetes consumes up to 15 percent of national health care budgets (Zhang and others 2010). Management of persons with diabetes includes control of glucose levels through medications as well as screening for and managing the secondary microvascular complications of diabetes, including retinopathy, nephropathy, and peripheral neuropathy. Although diabetes is associated with increased risk of macrovascular complications, such as strokes and myocardial infarctions, randomized trials have not shown consistent reductions in macrovascular endpoints, and most of the cost-effectiveness literature has focused on microvascular complications.

One study in India found that conducting a telemedicine retinopathy screening program for diabetics in rural areas either once or twice in a lifetime and providing photocoagulation for persons screening positive were cost-effective at US\$1,320 and US\$1,343 per QALY

gained, respectively (Rachapelle and others 2013). Some interventions, although not studied in LMICs, should receive strong consideration, given the overwhelmingly positive results in HICs.

Intensive treatment of blood pressure in diabetics through the use of generic statins is cost saving, especially for persons older than age 60 years (Li and others 2010). Screening for microalbuminuria five years after the onset of diabetes and treatment with angiotensin-converting enzyme inhibitors (ACEi) is also cost saving for the prevention of end-stage renal disease. Use of angiotensin receptor blockers is cost saving and highly cost-effective in HICs. Other potentially cost-saving interventions include comprehensive foot care to prevent ulcers.

Rheumatic Heart Disease

Acute rheumatic fever remains the most important cause of acquired heart disease in children and young adults in the world (Carapetis, McDonald, and Wilson 2005). Although it is rarely fatal, each case is responsible for the loss of up to 16 years of life and 3 QALYs due to disability (Michaud and Narula 1999). For this reason, the World Heart Federation made the elimination of acute rheumatic fever and control of rheumatic heart disease one of the six main goals in its strategic plan through 2015. In most LMICs, prevention has focused on secondary prevention among persons who have had a previous episode of rheumatic fever. This approach includes life-long treatment with penicillin, either orally or through intramuscular injections.

Secondary prevention in persons without a previous episode of acute rheumatic fever, through screening with echocardiography, was also found to be cost-effective at less than US\$100 per QALY gained (Tian and others 2015). In the absence of a vaccine against group A streptococcal infection, primary prevention depends on short-term oral or intramuscular penicillin treatment of patients presenting with acute sore throat (pharyngitis) caused by the infection.

Yet, primary prevention has not been widely adopted in LMICs because of barriers to implementation and cost-effectiveness (Karthikeyan and Mayosi 2009). More recently, investigators have found that using a clinical scoring mechanism not based on lab results followed by intramuscular injection with penicillin for persons judged to be positive would be cost-effective at US\$150 per QALY gained for children ages 3–15 years presenting with sore throat in South Africa (Irlam and others 2013).

First-Level Hospital Care

Treatment with aspirin, blood pressure medications, and statins is the cost-effective mainstay for managing

the care of persons with a previous stroke or ischemic heart disease event. Unfortunately, use of appropriately recommended medications is extremely low in many countries. Medications such as aspirin, ACEi, beta blockers, and statins have been shown to be cost-effective, with costs less than US\$1,000 per DALY averted in all LMIC regions (Gaziano, Opie, and Weinstein 2006; Lim and others 2007). Unfortunately, costs to individuals and access to medications may be limiting the full benefit of life-saving medications. This section discusses methods for improving access and availability as well as adherence. Overcoming these challenges is critical to the primary and secondary prevention that occurs at primary health centers and outpatient care facilities in first-level hospitals.

Drug Availability and Adherence

Several factors are responsible for the low use of medications, including inadequate availability and access to affordable medications, scarcity of health care providers, and complicated medication regimens. In many LMICs, the cost of a month's supply of generic secondary prevention medications ranges from 1.5 to 18.4 times the daily wage of government workers (Mendis, Fukino, and others 2007), and the availability of cardiovascular medications ranges from 25 percent in the public sector to 60 percent in the private sector (Cameron and others 2011; van Mourik and others 2010).

The availability of generic medications was influenced by the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) in 1995; the agreement obliged World Trade Organization members to protect pharmaceutical patents for 20 years from their filing (Smith, Lee, and Drager 2009). The subsequent Doha Declaration in 2003 granted nations compulsory licenses to manufacture essential medications domestically without permission of the patent holder, a trend that increased until 2006 (Beall and Kuhn 2012; Correa 2006; Lybecker and Fowler 2009). Canada is the only country to have issued a compulsory license to export generic medications to poorer nations, helping increase the availability of generic medications (Lybecker and Fowler 2009). Other studies have shown that, from 2001 to 2011, generic medications in the private sectors of 19 countries in Latin America, the Middle East, and South Africa accounted for approximately 70 percent to 80 percent of market share, which is larger than in most European countries (Kaplan, Wirtz, and Stephens 2013).

The literature on interventions to improve medication adherence is sparse. Recent reports suggest that lower out-of-pocket expenses, case management, patient education with behavioral support, and mobile phone

messaging, supported by broader guidelines and regulatory and communication-based policies, may improve adherence (De Jongh and others 2012; Laba and others 2013; Tajouri, Driver, and Holmes 2014; Viswanathan and others 2012). In this context, the Post-Myocardial Infarction Free Rx Event and Economic Evaluation trial in the United States has shown that eliminating copayments for drugs after a myocardial infarction increases medication adherence to 49.0 percent from 35.9 percent (Choudhry and others 2011). Furthermore, insurance plans that were generous, targeted high-risk patients, offered wellness programs, did not offer disease management programs, and covered medications ordered by mail were associated with a 4 to 5 percentage point higher rate of medication adherence (Choudhry and others 2014). While these studies are promising, future research is needed to determine whether the models could be replicated successfully in LMICs.

One way to address availability and affordability is to give a combination of generic CVD medications (polypill) to all adults with significant risk for CVD (Wald and Law 2003). This single intervention could reduce ischemic heart disease by as much as 50 percent.

The use of a polypill in primary prevention reduces the need for dose titrations, improves adherence, and increases the use of cheap generics in a single formulation (Lonn and others 2010). Several studies have shown reductions in risk factors, such as blood pressure and cholesterol levels (Yusuf and others 2009), and improvements in adherence. The most promising study to date included persons with established heart disease and persons at high risk for CVD. In the UMPIRE (Use of a Multi-drug Pill in Reducing Cardiovascular Events) study, patients who received the fixed-dose combination pill had increased adherence of more than 20 percent and reductions in both cholesterol and blood pressure levels (Thom and others 2013). However, no study has yet been published with reductions in ischemic heart disease or stroke endpoints, although several are underway (Eguzo and Camazine 2013; Lonn and others 2010; Yusuf and others 2009).

The use of a polypill in secondary prevention is less controversial because, even though no trial has proved its efficacy in secondary prevention, multiple trials have shown that the individual component medications (aspirin, statins, beta blockers, and angiotensin II receptor blockers) improve outcomes in patients with known CVD or high levels of risk factors (Lonn and others 2010). A large case-control analysis of 13,029 patients with ischemic heart disease in the United Kingdom indicated that combinations of medications (statin, aspirin, and beta blockers) decrease mortality in patients with known CVD better than single medications (Hippisley-Cox and

Coupland 2005). Finally, the use of combination therapy was shown to be cost-effective in LMICs for both primary and secondary prevention, with the best cost-effectiveness ratio for secondary prevention (Gaziano and others 2005; Lim and others 2007).

Heart Failure

Diuretics are the mainstay treatment for heart failure. They have been shown to be cost-effective for managing hypertension in HICs (Tran and others 2007) and LMICs (Alean and others 2009), but their cost-effectiveness has not been evaluated for the treatment of heart failure. However, congestive heart failure (CHF) is associated with much higher risks and costs than hypertension, and the relative risk reduction for CHF is similar to that for hypertension, making it safe to infer that diuretics are cost-effective. All other agents for CHF have been compared with a baseline of diuretic therapy. ACEi are an integral part of the treatment of patients with CHF, both reducing costly admissions and prolonging life. Cost-effectiveness studies dating back to the 1990s have shown them to be either highly cost-effective or cost saving in HICs (Butler and Fletcher 1996; Paul and others 1994; Tsevat and others 1995). Their use was found to be cost saving when added to diuretics in all six LMIC regions or to be extremely cost-effective (US\$50 per DALY averted) in areas with limited access to hospitals (Gaziano 2005).

Beta blockers are equally integral for managing patients with CHF with reduced ejection fraction. Similar cost-effectiveness results were seen in HICs in the late 1990s for carvedilol and in the early 2000s for metoprolol of less than US\$30,000 per QALY gained to as low as US\$4,000 per QALY gained (Delea and others 1999; Levy and others 2001). However, these agents cost up to US\$500–US\$1,000 per year. When analysis was repeated using generic pricing in all six LMIC regions, the incremental cost-effectiveness ratios were extremely favorable, ranging from US\$124 to US\$219 per DALY averted (Gaziano 2005). Mineralocorticoid agents have a favorable health profile in patients with reduced-systolic-function CHF, reducing both all-cause mortality and hospitalizations. Although eplerenone has proved to be cost-effective in HICs (Weintraub and others 2005), its cost-effectiveness has not been evaluated in LMICs (McKenna and others 2010). One limitation to its use is the need for blood tests to monitor renal function and electrolytes.

Devices such as implantable cardioverter defibrillators for persons with advanced heart failure have been found to be cost-effective in HICs. In LMICs, they have been evaluated in Brazil, with an incremental cost-effectiveness ratio of US\$50,000 per QALY gained

(Ribeiro and others 2010). When compared with medical therapy in Brazil, implantable cardiac resynchronization therapy was even more cost-effective, at US\$17,700 per QALY gained in 2012 U.S. dollars. When both capabilities were combined in the same device, the incremental cost-effectiveness ratio was nearly US\$33,000 per QALY gained (Bertoldi and others 2013). Similar values were found in Argentina (Poggio and others 2012).

Respiratory Conditions

There is relatively little information about the costs of treating and managing respiratory conditions in LMICs. One economic modeling study indicated that chronic obstructive pulmonary disease (COPD) and asthma interventions had poor cost-effectiveness compared with interventions for other chronic conditions because they relied on expensive imported drugs and, in the case of COPD, had relatively few health gains. Only one inhaled corticosteroid was available in the Colombian health insurance plan, and it was the most cost-effective therapy for treating pediatric asthma patients. The next best option cost more than US\$55,000 per QALY gained (Rodriguez-Martinez, Sossa-Briceno, and Castro-Rodriguez 2013). Using low-dose inhaled corticosteroids for mild asthma was relatively inexpensive and averted a sizable number of DALYs. Using low-dose inhaled corticosteroids for mild persistent asthma cost about US\$2,321 per DALY averted in Sub-Saharan African countries and about US\$1,133 per DALY averted in South-East Asian countries. Using low-dose inhaled corticosteroids plus long-acting beta agonists for moderate to persistent asthma cost about US\$4,763 per DALY averted in Sub-Saharan Africa and US\$1,878 per DALY averted in South-East Asia. Prescription treatment of COPD stage II (inhaled bronchodilator) cost about US\$11,000 and US\$5,000 in Sub-Saharan Africa and South-East Asia, respectively. While all three interventions had about the same costs per DALY averted in each region, they were much more expensive in Sub-Saharan Africa than in South-East Asia (Stanciole and others 2012).

Acute and Hospital-Based Care

Acute Ischemic Heart Disease

Management of persons with acute myocardial infarction has been shown to be cost-effective in all six LMIC regions. Using aspirin in the acute setting for ST elevation myocardial infarction (STEMI) costs between US\$10 and US\$20 per QALY gained (Gaziano 2005). Using generic beta blockers costs only US\$2 per QALY gained more than using aspirin alone (Gaziano 2005). Using a combination of aspirin, beta blockers, ACEi, and

statins in the acute phase was cost-effective in China for acute myocardial infarction, at US\$3,100 per QALY gained. Additional treatment of patients with the anti-platelet agent clopidogrel had a higher incremental cost-effectiveness ratio of nearly US\$18,000 per QALY gained. Use of unfractionated heparin for patients with acute coronary syndrome was found to be quite cost-effective at US\$2,800 per QALY gained.

Generic thrombolytics such as streptokinase can be added for approximately US\$700 per QALY gained in an emergency ward capable of administering intravenous medications with physician supervision (Gaziano 2005). Thrombolysis was not evaluated separately in China, but the use of streptokinase in secondary hospitals or percutaneous coronary interventions in hospitals had a combined ratio of approximately US\$9,000 per QALY gained (Wang and others 2014). Using primary percutaneous coronary interventions alone for persons with STEMI was US\$10,700 per QALY gained in China. In Brazil, delivering thrombolysis with tenecteplase within 60 minutes of an event by paramedics in a prehospital environment was shown to be cost saving (Araujo and others 2008). This intervention requires a highly developed emergency response team with educated paramedics and physicians able to diagnose and rule out contraindications to thrombolysis. Although patients with chest pain should ideally go to an emergency department capable of treating both STEMI and non-STEMI, in areas where advanced emergency transport systems are lacking and where patients seek treatment from their primary doctors, such as in rural India, it is more cost-effective, at US\$13 per QALY gained, to use a prehospital electrocardiogram machine than to do nothing (Schulman-Marcus, Prabhakaran, and Gaziano 2010).

Kidney Disease

Like diabetes, patients with chronic kidney disease can gain significant benefits from aggressive blood pressure and lipid control. However, no studies of these interventions have been conducted in LMICs. In particular, patients with chronic kidney disease would benefit particularly from the use of ACEi and statins as well as from screening for proteinuria.

COSTS OF PREVENTION AND TREATMENT OF CVRDs IN LMICs

To complement this review of cost-effectiveness, a systematic literature review was conducted of intervention costs for CVRDs in LMICs from the provider's perspective, given that these costs are poorly understood (Brouwer and Levin 2015). The review focuses on

diabetes, chronic kidney disease, hypertension, stroke, ischemic heart disease, and nonischemic heart disease because of their interrelated risk factors, prevention strategies, and interventions, such as tobacco cessation or hypertension control. Total costs of prevention or treatment per person or per year were inflated to 2012 U.S. dollars for comparability across geographic settings and time periods. The methodology for the review is provided in annex 19A.

The review found that prevention of CVD and related diseases is much less expensive than treatment, although many treatments are cost-effective using standard income thresholds. Most current treatment costs are very high in LMICs, and little is known about the costs of scaling up prevention and early treatment to avoid more catastrophic expenditures. The least expensive interventions were prevention strategies to reduce tobacco use and salt consumption at the population level, while the treatment of chronic kidney disease was the most expensive, followed by surgical interventions for ischemic heart disease. Promotion policies for salt, tobacco, and cholesterol control were inexpensive, at less than US\$1.00 per person per year, ranging from about US\$0.15 per person per year for mass media campaigns to US\$0.80 per person per year for cholesterol control (Ha and Chisholm 2011). The costs of tobacco cessation programs varied, depending on whether individual- or population-based platforms were used. For example, average unit costs ranged from less than US\$0.01 per person per year for package warnings in Vietnam (Salomon and others 2012) to US\$10,000 per person per year for school-based smoking cessation programs in India (Brown and others 2013). These cost estimates are useful when considering whether to scale up national prevention programs because low per capita costs can quickly translate into high overall program costs depending on the country's population and its geographic distribution.

Treating CVD and its risk factors is complex, in part because of the interrelationship between hypertension, diabetes, and ischemic heart disease and the fact that multiple shared risk factors affect CVD health outcomes. The clinical heterogeneity of CVD can make treatment costs for a single condition much more variable than for infectious or some other chronic diseases. For example, CVD encompasses different types of heart and related diseases, such as hypertension, stroke, and heart failure, with different levels of severity, associated care, and management. Nonetheless, age-adjusted CVD mortality has continued to decline in both HICs and LMICs as a result of an abundance of both policy- and individual-level interventions reviewed in this chapter. As indicated, numerous clinical protocols are available for treating

complicated conditions, including different combinations of medications, different diagnostics and imaging technologies, different surgeries, and different requirements for inpatient care and follow-up visits, making cost comparisons between studies all but impossible. Additionally, clinical characteristics, capabilities, and practices vary widely among and within countries; the distribution of costs can vary widely even within a hospital offering different levels of care, such as general, specialty, and intensive care (Khealani and others 2003).

Primary prevention and early management of care can occur at primary care levels with less sophisticated human resource and equipment needs, making local health delivery platforms an attractive option in low-resource settings. There is currently a small but growing body of evidence for CVD treatment and prevention costs in MICs, with fewer in LICs.

CRITICAL RESEARCH GAPS

The lack of data on costs and effectiveness, particularly data from or focused on LMICs, limits the ability of decision makers to plan and allocate resources efficiently and may also result in the underuse of cost-effective interventions (Bloom and others 2014).

Limited evidence of the cost-effectiveness of interventions for cardiometabolic diseases in LMICs largely reflects the limited evidence of intervention effectiveness. The lack of such information makes undertaking cost-effectiveness studies in LMICs very difficult, leading to the use of modeling approaches. It also limits the ability of decision makers to assess whether interventions with demonstrated cost-effectiveness in other countries are likely to be replicable with similar results in a particular country.

Population- and community-level interventions that appear to be the most cost-effective are inherently difficult to evaluate, further complicating assessment. Unlike individual-level interventions, attributing health outcomes to specific interventions is generally difficult, if not impossible. For instance, because interventions can take place outside the health system (for example, through fiscal policy changes or urban planning), assessing their costs can be more difficult than for interventions made through the health system. Nonetheless, the studies discussed in this chapter demonstrate the possibility of producing valuable data.

Additional research is needed on fiscal and regulatory policy changes and other population-level interventions to address the risk factors and burden of cardiometabolic disease. The lack of data on interventions to improve diets and increase physical activity in LMICs is a particular concern.

Comparability is also a concern. Cost data on clinical treatments often reflect experiences in urban areas (more often from middle-income than from low-income countries). Such costs may not be transferable to rural areas and may not be appropriate for making regional or national assessments. Cost comparability would benefit from a more consistent methodology and clear presentation of data on the elements and drivers of cost. Using established, accepted intervention protocols to guide economic evaluations and enable comparability of cost reporting has the potential to improve comparability across studies.

A related issue is the limited availability of longitudinal studies in LMICs, particularly studies concerned with population- and community-level interventions. Without such studies, decision makers will have difficulty both assessing trends, including cost-scale and cost-quality relationships, and prioritizing interventions. This issue is particularly relevant given the significance of generational and age differences for CVD risk factors and intervention strategies in LMICs.

Also needed is research on the costs of scaling up prevention and early treatment in LMICs and the systematic capture of successful experiences and transferable practices in designing and embedding such programs in LMICs, particularly in low-resource settings. In sum, targeted studies focused on LMICs are critical to tailoring responses to CVDs that have actual impacts and are cost-effective. Particularly needed is research on the costs of population-level prevention interventions; low-cost, community-based prevention strategies; strategies for individual-level interventions and platforms to reach low-resource populations; comparable treatment and prevention costs in lower-resource settings; evidence and experience on the design, replicability, scale-up, and implementation costs of interventions in LMICs; and quality data on costs to inform the design, implementation, and scale-up of evidence-based interventions in these countries.

CONCLUSIONS

Many interventions are available for managing cardiovascular, kidney, and respiratory diseases, which account for a large portion of NCDs globally. HICs as well as some LMICs have seen dramatic declines in age-adjusted mortality related to these conditions as a result of many clinical and policy-based interventions. Some interventions have been shown to be cost-effective in both HICs and LMICs, while others need further evaluation.

The burden of CVD is growing in many LMICs, and future research should put greater emphasis on nonclinical interventions. Significant differences in outcome

measures and methodologies preclude the ranking of interventions by their degree of cost-effectiveness. Appropriate calibrations should be used when transferring effectiveness estimates from HICs for the purpose of modeling cost-effectiveness in LMICs. In rare instances, studies of CVD risk factors and intervention follow-up are needed. Some pharmaceutical strategies are cost-effective.

Clarification is needed on the diagnostic approach to targeting a single high-risk factor versus absolute risk, the role of patient compliance, and the potential consequences of large-scale medicalization for public health.

ANNEX

The annex to this chapter is as follows. It is available at <http://www.dcp-3.org/CVRD>.

- Annex 19A. Methods, Framework, and Results

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - (a) lower-middle-income = US\$1,046 to US\$4,125
 - (b) upper-middle-income (UMICs) = US\$4,126 to US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

1. As of September 2016, several jurisdictions, including France, Mexico, Berkeley in California, St. Helena, and some islands in the South Pacific, have introduced taxation on SSBs. Hungary has introduced taxes on SSBs, salty condiments, and some snack foods. Finland has introduced taxes on sweets, ice cream, and soft drinks. Norway has introduced taxes on SSBs, chocolate, and sugar. Denmark is the only country that has explicitly introduced (and subsequently withdrawn) a tax on foods high in saturated fat for health purposes (Wareham and Jebb 2015).
2. Two related meta-analyses also provide relevant information on food price elasticities in low, middle-, and high-income countries. While Green and others (2013) focused on own-price elasticities of a range of aggregate food groups, Cornelsen and others (2014) undertook a meta-analysis of cross-price elasticities worldwide. Both studies concluded that changes in food prices have the largest own-price effects in LICs, while cross-price effects are more varied and depend on country income level, reinforcing, undermining, or alleviating own-price effects.
3. For a review of the cost-effectiveness of brief interventions to promote physical activity predominantly in a primary care context, see Vijay and others (2015).

4. For additional examples of economic modeling to inform health priorities, see Vos and others (2010) or various background reports to the United Kingdom's National Institute for Health and Care Excellence public health guidance (Morgovan and others 2010), available for a wide and growing range of topics (<https://www.nice.org.uk/guidance/published?type=ph>).
5. Countries vary in the opportunity costs they face when using resources for new interventions, with opportunity costs defined as the health gains forgone because resources are not available to deliver interventions elsewhere in the health system. Opportunity costs should—in principle—be reflected in the cost-effectiveness threshold (Revell and others 2015).

REFERENCES

- Afshin, A., R. Micha, M. Webb, S. Capewell, L. Whitsel, and others. 2017. "Effectiveness of Dietary Policies to Reduce Noncommunicable Diseases." In *Disease Control Priorities* (third edition): Volume 5, *Cardiovascular, Respiratory, and Related Disorders*, edited by D. Prabhakaran, S. Anand, T. A. Gaziano, J.-C. Mbanya, Y. Wu, and R. Nugent. Washington, DC: World Bank.
- Alefan, Q., M. I. M. Ibrahim, T. A. Razak, and A. Ayub. 2009. "Cost-Effectiveness of Antihypertensive Treatment in Malaysia." *Malaysian Journal of Pharmaceutical Sciences* 7 (2): 137–52.
- Allen, K., J. Pearson-Stuttard, W. Hooton, P. Diggle, S. Capewell, and others. 2015. "Potential of Trans Fats Policies to Reduce Socioeconomic Inequalities in Mortality from Coronary Heart Disease in England: Cost-Effectiveness Modelling Study." *BMJ* 351 (September 15): h4583.
- Araujo, D. V., B. R. Tura, A. L. Brasileiro, H. L. Neto, A. L. Pavao, and others. 2008. "Cost-Effectiveness of Prehospital versus Inhospital Thrombolysis in Acute Myocardial Infarction (Structured Abstract)." *Arquivos Brasileiros de Cardiologia* 90 (2): 91–98.
- Asaria, P., D. Chisholm, C. Mathers, M. Ezzati, and R. Beaglehole. 2007. "Chronic Disease Prevention: Health Effects and Financial Costs of Strategies to Reduce Salt Intake and Control Tobacco Use." *The Lancet* 370 (9604): 2044–53.
- Assmann, G., P. Cullen, and H. Schulte. 2002. "Simple Scoring Scheme for Calculating the Risk of Acute Coronary Events Based on the 10-Year Follow-Up of the Prospective Cardiovascular Munster (PROCAM) Study." *Circulation* 105 (3): 310–15.
- Beall, R., and R. Kuhn. 2012. "Trends in Compulsory Licensing of Pharmaceuticals since the Doha Declaration: A Database Analysis." *PLoS Medicine* 9 (1): e100115.
- Bertoldi, E. G., L. E. Rohde, L. I. Zimmerman, M. Pimentel, and C. A. Polanczyk. 2013. "Cost-Effectiveness of Cardiac Resynchronization Therapy in Patients with Heart Failure: The Perspective of a Middle-Income Country's Public Health System." *International Journal of Cardiology* 163 (3): 309–15.
- Bloom, D. E., E. T. Cafiero-Fonseca, V. Candeias, E. Adashi, L. Bloom, and others. 2014. *Economics of Non-Communicable*

- Diseases in India: The Costs and Returns on Investment of Interventions to Promote Healthy Living and Prevent, Treat, and Manage NCDs.* Geneva: World Economic Forum; Cambridge, MA: Harvard School of Public Health.
- Brouwer, E., and C. Levin. 2015. "Provider Costs for Prevention and Treatment of Cardiovascular and Related Conditions in Low- and Middle-Income Countries: A Systematic Review." *BMC Public Health* 15 (November 26): 1183.
- Brown, H. S., III, M. Stigler, C. Perry, P. Dhavan, M. Arora, and others. 2013. "The Cost-Effectiveness of a School-Based Smoking Prevention Program in India." *Health Promotion International* 28 (2): 178–86.
- Butler, J. R., and P. J. Fletcher. 1996. "A Cost-Effectiveness Analysis of Enalapril Maleate in the Management of Congestive Heart Failure in Australia." *Australian and New Zealand Journal of Medicine* 26 (1): 89–95.
- Cabrera Escobar, M. A., J. L. Veerman, S. M. Tollman, M. Y. Bertram, and K. J. Hofman. 2013. "Evidence That a Tax on Sugar Sweetened Beverages Reduces the Obesity Rate: A Meta-Analysis." *BMC Public Health* 13 (November 13): 1072.
- Cameron, A., I. Roubos, M. Ewen, A. K. Mantel-Teeuwisse, H. G. Leufkens, and others. 2011. "Differences in the Availability of Medicines for Chronic and Acute Conditions in the Public and Private Sectors of Developing Countries." *Bulletin of the World Health Organization* 89 (6): 412–21.
- Carapetis, J. R., M. McDonald, and N. J. Wilson. 2005. "Acute Rheumatic Fever." *The Lancet* 366 (9480): 155–68.
- Cawley, J. 2015. "An Economy of Scales: A Selective Review of Obesity's Economic Causes, Consequences, and Solutions." *Journal of Health Economics* 43 (September): 244–68.
- Cawley, J., and D. Frisvold. 2015. "The Incidence of Taxes on Sugar-Sweetened Beverages: The Case of Berkeley, California." Working Paper 21465, National Bureau of Economic Research, Cambridge, MA.
- Cecchini, M., F. Sassi, J. A. Lauer, Y. Y. Lee, V. Guajardo-Barron, and others. 2010. "Tackling of Unhealthy Diets, Physical Inactivity, and Obesity: Health Effects and Cost-Effectiveness." *The Lancet* 376 (9754): 1775–84.
- Chang, A., D. T. Jamison, and S. Horton. 2018. "Benefit-Cost Analysis." In *Disease Control Priorities* (third edition): Volume 9, *Disease Control Priorities: Improving Health and Reducing Poverty*, edited by D. T. Jamison, R. Nugent, H. Gelband, S. Horton, P. Jha, R. Laxminarayan, and C. N. Mock. Washington, DC: World Bank.
- Choudhry, N. K., J. Avorn, R. J. Glynn, E. M. Antman, S. Schneeweiss, and others. 2011. "Full Coverage for Preventive Medications after Myocardial Infarction." *New England Journal of Medicine* 365 (22): 2088–97.
- Choudhry, N. K., S. Dugani, W. H. Shrank, J. M. Polinski, C. E. Stark, and others. 2014. "Despite Increased Use and Sales of Statins in India, per Capita Prescription Rates Remain Far below High-Income Countries." *Health Affairs* 33 (2): 273–82.
- Chow, J., S. R. Darley, and R. Laxminarayan. 2007. "Cost-Effectiveness of Disease Interventions in India." Discussion Paper dp-07-53, Resources for the Future, Washington, DC.
- Claxton, K., M. Sculpher, and A. Culyer. 2007. "Appropriate Methods for the Evaluation of Public Health Interventions." CHE Research Paper 31, Centre for Health Economics, York.
- Claxton, K., S. Walker, S. Palmer, and M. Sculpher. 2010. "Appropriate Perspectives for Health Care Decisions." CHE Research Paper 54, Centre for Health Economics, York.
- Colchero, M. A., B. M. Popkin, J. A. Rivea, and S. W. Ng. 2016. "Beverage Purchases from Stores in Mexico under the Excise Tax on Sugar-Sweetened Beverages: Observational Study." *BMJ* 352 (January 6): h6704.
- Conroy, R. M., K. Pyorala, A. P. Fitzgerald, S. Sans, A. Menotti, and others. 2003. "Estimation of Ten-Year Risk of Fatal Cardiovascular Disease in Europe: The SCORE Project." *European Heart Journal* 24 (11): 987–1003.
- Cornelsen, L., R. Green, A. Dangour, and R. Smith. 2015. "Why Fat Taxes Won't Make Us Thin." *Journal of Public Health* 37 (1): 18–23.
- Cornelsen, L., R. Green, R. Turner, A. Dangour, B. Shankar, and others. 2014. "What Happens to Patterns of Food Consumption When Food Prices Change? Evidence from a Systematic Review and Meta-Analysis of Food Price Elasticities Globally." *Health Economics* 24 (12): 1548–59.
- Correa, C. M. 2006. "Implications of Bilateral Free Trade Agreements on Access to Medicines." *Bulletin of the World Health Organization* 84 (5): 399–404.
- De Jongh, T., I. Gurol-Urganci, V. Vodopivec-Jamsek, J. Car, and R. Atun. 2012. "Mobile Phone Messaging for Facilitating Self-Management of Long-Term Illnesses." *Cochrane Database of Systematic Reviews* 12 (December 12): CD007459.
- Delea, T. E., M. Vera-Llonch, R. E. Richner, M. B. Fowler, and G. Oster. 1999. "Cost-Effectiveness of Carvedilol for Heart Failure." *American Journal of Cardiology* 83 (6): 890–96.
- Donaldson, E. A., H. R. Waters, M. Arora, B. Varghese, P. Dave, and others. 2011. "A Cost-Effectiveness Analysis of India's 2008 Prohibition of Smoking in Public Places in Gujarat." *International Journal of Environmental Research and Public Health* 8 (5): 1271–86.
- Downs, S., A. M. Thow, and S. R. Leeder. 2013. "The Effectiveness of Policies for Reducing Dietary Trans Fat: A Systematic Review of the Evidence." *Bulletin of the World Health Organization* 91 (4): 262–69H.
- Eguzo, K., and B. Camazine. 2013. "Beyond Limitations: Practical Strategies for Improving Cancer Care in Nigeria." *Asian Pacific Journal of Cancer Prevention* 14 (5): 3363–68.
- Epstein, L. H., N. Jankowiak, C. Nederkoorn, H. A. Raynor, S. A. French, and E. Finkelstein. 2012. "Experimental Research on the Relation between Food Price Changes and Food-Purchasing Patterns: A Targeted Review." *American Journal of Clinical Nutrition* 95 (4): 789–809.
- Eyles, H., C. Ni Mhurchu, N. Nghiem, and T. Blakely. 2012. "Food Pricing Strategies, Population Diets, and Non-communicable Disease: A Systematic Review of Simulation Studies." *PLoS Medicine* 9 (12): e1001353.
- Ferrante, D., J. Konfino, R. Mejia, P. Coxson, A. Moran, and others. 2012. "The Cost-Utility Ratio of Reducing Salt Intake and Its Impact on the Incidence of Cardiovascular Disease in Argentina." *Revista Panamericana de Salud Pública* 32 (4): 274–80.
- Ferrario, M., P. Chiadini, L. E. Chambless, G. Cesana, D. Vanuzzo, and others. 2005. "Prediction of Coronary

- Events in a Low-Incidence Population: Assessing Accuracy of the CUORE Cohort Study Prediction Equation.” *International Journal of Epidemiology* 34 (2): 413–21.
- Ford, E. S., and S. Capewell. 2011. “Proportion of the Decline in Cardiovascular Mortality Disease due to Prevention versus Treatment: Public Health versus Clinical Care.” *Annual Review of Public Health* 32 (April): 5–22.
- Gaziano, T. A. 2005. “Cardiovascular Disease in the Developing World and Its Cost-Effective Management.” *Circulation* 112 (23): 3547–53.
- Gaziano, T. A., S. Abrahams-Gessel, S. Alam, D. Alam, M. Ali, and others. 2016. “Comparison of Nonblood-Based and Blood-Based Total CV Risk Scores in Global Populations.” *Global Heart* 11 (1): 37–46.
- Gaziano, T. A., S. Abrahams-Gessel, C. A. Denman, C. M. Montano, M. Khanam, and others. 2015. “An Assessment of Community Health Workers’ Ability to Screen for Cardiovascular Disease Risk with a Simple, Non-Invasive Risk Assessment Instrument in Bangladesh, Guatemala, Mexico, and South Africa: An Observational Study.” *The Lancet Global Health* 3 (9): e556–63.
- Gaziano, T. A., S. Abrahams-Gessel, S. Surka, S. Sy, A. Pandya, and others. 2015. “Cardiovascular Disease Screening by Community Health Workers Can Be Cost-Effective in Low-Resource Countries.” *Health Affairs* 34 (9): 1538–45.
- Gaziano, T. A., M. Bertram, S. M. Tollman, and K. J. Hofman. 2014. “Hypertension Education and Adherence in South Africa: A Cost-Effectiveness Analysis of Community Health Workers.” *BMC Public Health* 14 (March 10): 240.
- Gaziano, T. A., L. H. Opie, and M. C. Weinstein. 2006. “Cardiovascular Disease Prevention with a Multidrug Regimen in the Developing World: A Cost-Effectiveness Analysis.” *The Lancet* 368 (9536): 679–86.
- Gaziano, T. A., A. Pandya, K. Steyn, N. Levitt, W. Mollentze, and others. 2013. “Comparative Assessment of Absolute Cardiovascular Disease Risk Characterization from Non-Laboratory-Based Risk Assessment in South African Populations.” *BMC Medicine* 11 (July 24): 170.
- Gaziano, T. A., K. Steyn, D. J. Cohen, M. C. Weinstein, and L. H. Opie. 2005. “Cost-Effectiveness Analysis of Hypertension Guidelines in South Africa: Absolute Risk versus Blood Pressure Level.” *Circulation* 112 (23): 3569–76.
- Greco, G., P. Lorgelly, and I. Yamabhai. 2016. “Outcomes in Economic Evaluations of Public Health Interventions in Low- and Middle-Income Countries: Health, Capabilities, and Subjective Wellbeing.” *Health Economics* 25 (1): 83–94.
- Green, R., L. Cornelsen, A. D. Dangour, R. Turner, B. Shankar, and others. 2013. “The Effect of Rising Food Prices on Food Consumption: Systematic Review with Meta-Regression.” *BMJ* 346 (June 17): f3703.
- Grogger, J. 2015. “Soda Taxes and the Prices of Sodas and Other Drinks: Evidence from Mexico.” Working Paper 21197, National Bureau of Economic Research, Cambridge, MA.
- Ha, D. A., and D. Chisholm. 2011. “Cost-Effectiveness Analysis of Interventions to Prevent Cardiovascular Disease in Vietnam.” *Health Policy and Planning* 26 (3): 210–22.
- Higashi, H., K. D. Truong, J. J. Barendregt, P. K. Nguyen, M. L. Vuong, and others. 2011. “Cost-Effectiveness of Tobacco Control Policies in Vietnam: The Case of Population-Level Interventions.” *Applied Health Economics and Health Policy* 9 (3): 183–96.
- Hippisley-Cox, J., and C. Coupland. 2005. “Effect of Combinations of Drugs on All Cause Mortality in Patients with Ischaemic Heart Disease: Nested Case-Control Analysis.” *BMJ* 330 (7499): 1059–63.
- Hutton, G., and C. Chase. 2017. “Water Supply, Sanitation, and Hygiene.” In *Disease Control Priorities* (third edition): Volume 7, *Injury Prevention and Environmental Health*, edited by C. N. Mock, O. Kobusingye, R. Nugent, and K. Smith. Washington, DC: World Bank.
- Irlam, J., B. M. Mayosi, M. Engel, and T. A. Gaziano. 2013. “Primary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease with Penicillin in South African Children with Pharyngitis: A Cost-Effectiveness Analysis.” *Circulation. Cardiovascular Quality and Outcomes* 6 (3): 343–51.
- Jeemon, P., R. Gupta, C. Onen, A. Adler, T. A. Gaziano, and others. 2017. “Management of Hypertension and Dyslipidemia for Primary Prevention of Cardiovascular Disease.” In *Disease Control Priorities* (third edition): Volume 5, *Cardiovascular, Respiratory, and Related Disorders*, edited by D. Prabhakaran, S. Anand, T. A. Gaziano, J.-C. Mbanya, Y. Wu, and R. Nugent. Washington, DC: World Bank.
- Kaplan, W. A., V. J. Wirtz, and P. Stephens. 2013. “The Market Dynamics of Generic Medicines in the Private Sector of 19 Low- and Middle-Income Countries between 2001 and 2011: A Descriptive Time Series Analysis.” *PLoS One* 8 (9): e74399.
- Karthikeyan, G., and B. M. Mayosi. 2009. “Is Primary Prevention of Rheumatic Fever the Missing Link in the Control of Rheumatic Heart Disease in Africa?” *Circulation* 120 (8): 709–13.
- Khealani, B., Z. F. Javed, N. Syed, S. Shafqat, and M. Wasay. 2003. “Cost of Acute Stroke Care at a Tertiary Care Hospital in Karachi, Pakistan.” *Journal of Pakistan Medical Association* 53 (11): 552–55.
- Laba, T. L., J. Bleasel, J. A. Brien, A. Cass, K. Howard, and others. 2013. “Strategies to Improve Adherence to Medications for Cardiovascular Diseases in Socioeconomically Disadvantaged Populations: A Systematic Review.” *International Journal of Cardiology* 167 (6): 2430–40.
- Laine, J., V. Kuvaia-Köllner, E. Pietilä, M. Koivuneva, H. Valtonen, and others. 2014. “Cost-Effectiveness of Population-Level Physical Activity Interventions: A Systematic Review.” *American Journal of Health Promotion* 29 (2): 71–80.
- Lehnert, T., D. Sonntag, A. Konnopka, S. Riedel-Heller, and H. König. 2012. “The Long-Term Cost-Effectiveness of Obesity Prevention Interventions: Systematic Literature Review.” *Obesity Reviews* 13 (June): 537–53.
- Levy, A. R., A. H. Briggs, C. Demers, and B. J. O’Brien. 2001. “Cost-Effectiveness of Beta-Blocker Therapy with Metoprolol or with Carvedilol for Treatment of Heart Failure in Canada.” *American Heart Journal* 142 (3): 537–43.
- Li, R., P. Zhang, L. E. Barker, F. M. Chowdhury, and Z. Zhang. 2010. “Cost-Effectiveness of Interventions to Prevent and

- Control Diabetes Mellitus: A Systematic Review.” *Diabetes Care* 33 (8): 1872–94.
- Lim, S. S., T. A. Gaziano, E. Gakidou, K. S. Reddy, F. Farzadfar, and others. 2007. “Prevention of Cardiovascular Disease in High-Risk Individuals in Low-Income and Middle-Income Countries: Health Effects and Costs.” *The Lancet* 370 (December 15): 2054–62.
- Lonn, E., J. Bosch, K. K. Teo, P. Pais, D. Xavier, and others. 2010. “The Polypill in the Prevention of Cardiovascular Diseases: Key Concepts, Current Status, Challenges, and Future Directions.” *Circulation* 122 (2): 2078–88.
- Lybecker, K. M., and E. Fowler. 2009. “Compulsory Licensing in Canada and Thailand: Comparing Regimes to Ensure Legitimate Use of the WTO Rules.” *Journal of Law and Medical Ethics* 37 (2): 222–39.
- Manyema, M., L. Veerman, L. Chola, A. Tugendhaft, B. Sartorius, and others. 2014. “The Potential Impact of a 20% Tax on Sugar-Sweetened Beverages on Obesity in South African Adults: A Mathematical Model.” *PLoS One* 9 (8): e105287.
- Mason, H., A. Shoaibi, R. Ghandour, M. O’Flaherty, S. Capewell, and others. 2014. “A Cost-Effectiveness Analysis of Salt Reduction Policies to Reduce Coronary Heart Disease in Four Eastern Mediterranean Countries.” *PLoS One* 9 (1): e84445.
- McKenna, C., J. Burch, S. Suekarran, S. Walker, A. Bakhai, and others. 2010. “A Systematic Review and Economic Evaluation of the Clinical Effectiveness and Cost-Effectiveness of Aldosterone Antagonists for Postmyocardial Infarction Heart Failure.” *Health Technology Assessment* 14 (24): 1–162.
- Medina-Mora, M. E., M. Monteiro, R. Room, J. Rehm, D. Jernigan, and others. 2015. “Alcohol Use and Alcohol Use Disorders.” In *Disease Control Priorities* (third edition): Volume 4, *Mental, Neurological, and Substance Use Disorders*, edited by V. Patel, D. Chisholm, T. Dua, R. Laxminarayan, and M. E. Medina-Mora. Washington, DC: World Bank.
- Mendis, S., D. Abegunde, S. Yusuf, S. Ebrahim, G. Shaper, and others. 2005. “WHO Study on Prevention of Recurrences of Myocardial Infarction and Stroke (WHO-PREMISE).” *Bulletin of the World Health Organization* 83 (11): 820–29.
- Mendis, S., K. Fukino, A. Cameron, R. Laing, A. Filipe Jr., and others. 2007. “The Availability and Affordability of Selected Essential Medicines for Chronic Diseases in Six Low- and Middle-Income Countries.” *Bulletin of the World Health Organization* 85 (4): 279–88.
- Mendis, S., L. Lindholm, G. Mancia, J. Whitworth, M. Alderman, and others. 2007. “World Health Organization (WHO) and International Society of Hypertension (ISH) Risk Prediction Charts: Assessment of Cardiovascular Risk for Prevention and Control of Cardiovascular Disease in Low- and Middle-Income Countries.” *Journal of Hypertension* 25 (8): 1578–82.
- Meng, L., H. Xu, A. Liu, J. van Raaij, W. Bemelmans, and others. 2013. “The Costs and Cost-Effectiveness of a School-Based Comprehensive Intervention Study on Childhood Obesity in China.” *PLoS One* 8 (10): e77971.
- Michaud, C. R. R., and J. Narula. 1999. “Cost-Effectiveness Analysis of Intervention Strategies for Reduction of the Burden of Rheumatic Heart Disease.” In *Rheumatic Fever*, edited by J. Narula, R. Virmani, K. Srinath Reddy, and R. Tandon, 485–97. Washington, DC: American Registry of Pathology.
- Morgovan, C., S. Cosma, S. Ghibu, C. Burta, M. Bota, and others. 2010. “Study of Diabetes Mellitus Care Cost in Romania during 2000–2008.” *Fundamental and Clinical Pharmacology* 24 (1): 92.
- Müller-Riemenschneider, F., T. Reinhold, and S. Willich. 2009. “Cost-Effectiveness of Interventions Promoting Physical Activity.” *British Journal of Sports Medicine* 43 (1): 70–76.
- Murray, C. J. L., J. A. Lauer, R. C. W. Hutubessy, L. Niessen, N. Tomijima, and others. 2003. “Effectiveness and Costs of Interventions to Lower Systolic Blood Pressure and Cholesterol: A Global and Regional Analysis on Reduction of Cardiovascular-Disease Risk.” *The Lancet* 361 (9359): 717–25.
- Navarro, J. C., A. C. Baroque II, J. K. Lokin, and N. Venketasubramanian. 2014. “The Real Stroke Burden in the Philippines.” *International Journal of Stroke* 9 (5): 640–41.
- Ortegon, M., S. Lim, D. Chisholm, and S. Mendis. 2012. “Cost-Effectiveness of Strategies to Combat Cardiovascular Disease, Diabetes, and Tobacco Use in Sub-Saharan Africa and South East Asia: Mathematical Modelling Study.” *BMJ* 344 (March 2): e607.
- Pandya, A., M. C. Weinstein, and T. A. Gaziano. 2011. “A Comparative Assessment of Non-Laboratory-Based versus Commonly Used Laboratory-Based Cardiovascular Disease Risk Scores in the NHANES III Population.” *PLoS One* 6 (5): e20416.
- Paul, S. D., K. M. Kuntz, K. A. Eagle, and M. C. Weinstein. 1994. “Costs and Effectiveness of Angiotensin Converting Enzyme Inhibition in Patients with Congestive Heart Failure.” *Archives of Internal Medicine* 154 (10): 1143–49.
- Pitt, C., C. Goodman, and K. Hanson. 2016. “Economic Evaluation in Global Perspective: A Bibliometric Analysis of the Recent Literature.” *Health Economics* 25 (Suppl 1): 9–28.
- Poggio, R., F. Augustovsky, J. Caporale, V. Irazola, and S. Miriuka. 2012. “Cost-Effectiveness of Cardiac Resynchronization Therapy: Perspective from Argentina.” *International Journal of Technology Assessment in Health Care* 28 (4): 429–35.
- Popkin, B. M., and C. Hawkes. 2015. “Sweetening of the Global Diet, Particularly Beverages: Patterns, Trends, and Policy Responses.” *The Lancet Diabetes and Endocrinology* 4 (2): 174–86.
- Powell, L. M., J. F. Chriqui, T. Khan, R. Wada, and F. J. Chaloupka. 2013. “Assessing the Potential Effectiveness of Food and Beverage Taxes and Subsidies for Improving Public Health: A Systematic Review of Prices, Demand and Body Weight Outcomes.” *Obesity Reviews* 14 (2): 110–28.
- Rachapelle, S., R. Legood, Y. Alavi, R. Lindfield, T. Sharma, and others. 2013. “The Cost-Utility of Telemedicine to Screen for Diabetic Retinopathy in India.” *Ophthalmology* 120 (3): 566–73.
- Ranson, M. K., P. Jha, F. J. Chaloupka, and S. N. Nguyen. 2002. “Global and Regional Estimates of the Effectiveness and Cost-Effectiveness of Price Increases and Other Tobacco

- Control Policies (Structured Abstract).” *Nicotine and Tobacco Research* 4 (3): 311–19.
- Revill, P., J. Ochalek, J. Lomas, R. Nakamura, B. Woods, and others. 2015. “Cost-Effectiveness Thresholds: Guiding Health Care Spending for Population Health Improvement.” Centre for Health Economics, University of York. <http://www.idshealth.org/wp-content/uploads/2015/01/CE-Thresholds-iDSI-Working-Group-Final-Report.pdf>.
- Revill, P., and M. Sculpher. 2012. “Cost-Effectiveness of Interventions to Tackle Non-Communicable Diseases.” *BMJ* 344 (March): d7883.
- Ribeiro, R. A., S. F. Stella, S. A. Comey, L. I. Zimmerman, M. Pimentel, and others. 2010. “Cost-Effectiveness of Implantable Cardioverter-Defibrillators in Brazil: Primary Prevention Analysis in the Public Sector.” *Value in Health* 13 (2): 160–68.
- Rodgers, A. L., C. Lawes, T. A. Gaziano, and T. Vos. 2006. “The Growing Burden of Risk from High Blood Pressure, Cholesterol, and Bodyweight.” In *Disease Control Priorities in Developing Countries*, second edition, edited by D. T. Jamison, J. G. Breman, A. R. Measham, G. Alleyne, M. Claeson, D. B. Evans, P. Jha, A. Mills, and P. Musgrove. Washington, DC: World Bank and Oxford University Press.
- Rodriguez-Martinez, C. E., M. P. Sossa-Briceno, and J. A. Castro-Rodriguez. 2013. “Cost-Utility Analysis of the Inhaled Steroids Available in a Developing Country for the Management of Pediatric Patients with Persistent Asthma.” *Journal of Asthma* 50 (4): 410–18.
- Rubinstein, A., L. Colantonio, A. Bardach, J. Caporale, S. G. Marti, and others. 2010. “Estimation of the Burden of Cardiovascular Disease Attributable to Modifiable Risk Factors and Cost-Effectiveness Analysis of Preventative Interventions to Reduce This Burden in Argentina.” *BMC Public Health* 10 (October 20): 627.
- Rubinstein, A., S. Garcia Marti, A. Souto, D. Ferrante, and F. Augustovski. 2009. “Generalized Cost-Effectiveness Analysis of a Package of Interventions to Reduce Cardiovascular Disease in Buenos Aires, Argentina.” *Cost Effectiveness and Resource Allocation* 7 (May 6): 10.
- Salomon, J. A., N. Carvalho, C. Gutierrez-Delgado, R. Orozco, A. Mancuso, and others. 2012. “Intervention Strategies to Reduce the Burden of Non-Communicable Diseases in Mexico: Cost-Effectiveness Analysis.” *BMJ* 344 (March 2): e355.
- Schulman-Marcus, J., D. Prabhakaran, and T. A. Gaziano. 2010. “Pre-Hospital ECG for Acute Coronary Syndrome in Urban India: A Cost-Effectiveness Analysis.” *BMC Cardiovascular Disorders* 10 (March 12): 13.
- Schwappach, D., T. Boluarte, and M. Suhrcke. 2007. “The Economics of Primary Prevention of Cardiovascular Disease: A Systematic Review of Economic Evaluations.” *Cost Effectiveness and Resource Allocation* 5 (1): 5.
- Shroufi, A., R. Chowdhury, R. Anchala, S. Stevens, P. Blanco, and others. 2013. “Cost-Effective Interventions for the Prevention of Cardiovascular Disease in Low- and Middle-Income Countries: A Systematic Review.” *BMC Public Health* 13 (March 28): 285.
- Smith, R. D., K. Lee, and N. Drager. 2009. “Trade and Health: An Agenda for Action.” *The Lancet* 373 (9665): 768–73.
- Stanciole, A. E., M. Ortegon, D. Chisholm, and J. A. Lauer. 2012. “Cost-Effectiveness of Strategies to Combat Chronic Obstructive Pulmonary Disease and Asthma in Sub-Saharan Africa and South East Asia: Mathematical Modelling Study.” *BMJ* 344 (March 2): e608.
- Suhrcke, M., T. A. Boluarte, and L. Niessen. 2012. “A Systematic Review of Economic Evaluations of Interventions to Tackle Cardiovascular Disease in Low- and Middle-Income Countries.” *BMC Public Health* 12 (January 3): 2.
- Suhrcke, M., R. Nugent, D. Stuckler, and L. Rocco. 2006. “Chronic Disease: An Economic Perspective.” Oxford Health Alliance, London.
- Tajouri, T. H., S. L. Driver, and D. R. Holmes Jr. 2014. “‘Take as Directed’: Strategies to Improve Adherence to Cardiac Medication.” *Nature Reviews Cardiology* 11 (5): 304–7.
- Tan-Torres Edejer, T., R. Balthussen, T. Adam, R. Hutubessy, A. Acharya, and others. 2003. *Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis*. Geneva: WHO.
- Thom, S., N. Poulter, J. Field, A. Patel, D. Prabhakaran, and others. 2013. “Effects of a Fixed-Dose Combination Strategy on Adherence and Risk Factors in Patients with or at High Risk of CVD: The UMPIRE Randomized Clinical Trial.” *JAMA* 310 (9): 918–29.
- Thow, A. M., S. Downs, and S. Jan. 2014. “A Systematic Review of the Effectiveness of Food Taxes and Subsidies to Improve Diets: Understanding the Recent Evidence.” *Nutrition Reviews* 72 (9): 551–65.
- Thow, A. M., S. Jan, S. Leeder, and B. Swinburn. 2010. “The Effect of Fiscal Policy on Diet, Obesity, and Chronic Disease: A Systematic Review.” *Bulletin of the World Health Organization* 88 (8): 609–14.
- Tian, M. P., V. S. Ajay, D. B. M. Dunzhu, S. S. Hameed, X. Li, and others. 2015. “A Cluster-Randomized, Controlled Trial of a Simplified Multifaceted Management Program for Individuals at High Cardiovascular Risk (SimCard Trial) in Rural Tibet, China, and Haryana, India.” *Circulation* 132 (9): 815–24.
- Tran, K., C. Ho, H. Noorani, K. Cimon, A. Hodgson, and others. 2007. *Thiazide Diuretics as First-Line Treatment for Hypertension: Meta-Analysis and Economic Evaluation*. Technology Report 95. Ottawa: Canadian Agency for Drugs and Technologies in Health.
- Tsevat, J., D. Duke, L. Goldman, M. A. Pfeffer, G. A. Lamas, and others. 1995. “Cost-Effectiveness of Captopril Therapy after Myocardial Infarction.” *Journal of the American College of Cardiology* 26 (4): 914–19.
- van Baal, P., T. Feenstra, J. Polder, R. Hoogenveen, and W. Brouwer. 2011. “Economic Evaluation and the Postponement of Health Care Costs.” *Health Economics* 20 (4): 432–45.
- van Mourik, M. S., A. Cameron, M. Ewen, and R. O. Laing. 2010. “Availability, Price, and Affordability of Cardiovascular Medicines: A Comparison across 36 Countries Using WHO/HAI Data.” *BMC Cardiovascular Disorders* 10 (June 9): 25.
- Vijay, G. C., E. C. Wilson, M. Suhrcke, W. Hardeman, and S. Sutton. 2015. “Are Brief Interventions to Increase Physical

- Activity Cost-Effective? A Systematic Review.” *British Journal of Sports Medicine* 50 (7): 408–17.
- Viswanathan, M., C. E. Golin, C. D. Jones, M. Ashok, S. J. Blalock, and others. 2012. “Interventions to Improve Adherence to Self-Administered Medications for Chronic Diseases in the United States: A Systematic Review.” *Annals of Internal Medicine* 157 (11): 785–95.
- Vos, T., R. Carter, J. Barendregt, C. Mihalopoulos, J. Veerman, and others. 2010. *Assessing Cost-Effectiveness in Prevention (ACE-Prevention): Final Report*. Melbourne: University of Queensland; Brisbane: Deakin University.
- Wald, N. J., and M. R. Law. 2003. “A Strategy to Reduce Cardiovascular Disease by More Than 80%.” *BMJ* 326 (7404): 1419.
- Wang, M., A. E. Moran, J. Liu, P. G. Coxson, P. A. Heidenreich, and others. 2014. “Cost-Effectiveness of Optimal Use of Acute Myocardial Infarction Treatments and Impact on Coronary Heart Disease Mortality in China.” *Circulation: Cardiovascular Quality and Outcomes* 7 (1): 78–85.
- Wang, Y. C., A. M. Cheung, K. Bibbins-Domingo, L. A. Prosser, N. R. Cook, and others. 2011. “Effectiveness and Cost-Effectiveness of Blood Pressure Screening in Adolescents in the United States.” *Journal of Pediatrics* 158 (2): 257–64.e7.
- Wareham, N., and S. Jebb. 2015. “What Is the Evidence Base for Various Fiscal Measures?” Report on behalf of the MRC Epidemiology Unit and Centre for Diet and Activity Research, University of Cambridge.
- Weatherly, H., M. Drummond, K. Claxton, R. Cookson, B. Ferguson, and others. 2009. “Methods for Assessing the Cost-Effectiveness of Public Health Interventions: Key Challenges and Recommendations.” *Health Policy* 93 (2–3): 85–92.
- Weintraub, W. S., Z. Zhang, E. M. Mahoney, P. Kolm, J. A. Spertus, and others. 2005. “Cost-Effectiveness of Eplerenone Compared with Placebo in Patients with Myocardial Infarction Complicated by Left Ventricular Dysfunction and Heart Failure.” *Circulation* 111 (9): 1106–13.
- WHO (World Health Organization). 2004. “Global Strategy on Diet, Physical Activity, and Health.” WHO, Geneva.
- . 2011. “Scaling up Action against Noncommunicable Diseases: How Much Will It Cost?” WHO, Geneva.
- Wilson, P. W., R. B. D’Agostino, D. Levy, A. M. Belanger, H. Silbershatz, and others. 1998. “Prediction of Coronary Heart Disease Using Risk Factor Categories.” *Circulation* 97 (18): 1837–47.
- Wiseman, V., C. Mitton, M. M. Doyle-Waters, T. Drake, L. Conteh, and others. 2016. “Using Economic Evidence to Set Healthcare Priorities in Low-Income and Lower-Middle-Income Countries: A Systematic Review of Methodological Frameworks.” *Health Economics* 25 (Suppl 1): 140–61.
- Wolf-Maier, K., R. S. Cooper, H. Kramer, J. R. Banegas, S. Giampaoli, and others. 2004. “Hypertension Treatment and Control in Five European Countries, Canada, and the United States.” *Hypertension* 43 (1): 10–17.
- Yusuf, S., P. Pais, R. Afzal, D. Xavier, K. Teo, and others. 2009. “Effects of a Polypill (Polycap) on Risk Factors in Middle-Aged Individuals without Cardiovascular Disease (TIPS): A Phase II, Double-Blind, Randomised Trial.” *The Lancet* 373 (9672): 1341–51.
- Zhang, P., X. Zhang, J. Brown, D. N. R. Vistisen, R. Sicree, and others. 2010. “Global Healthcare Expenditure on Diabetes for 2010 and 2030.” *Diabetes Research and Clinical Practice* 87 (3): 293–301.