Population Strategies to Decrease Sodium Intake: A Global Cost-Effectiveness Analysis

by

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Abstract

Excessive sodium consumption is both prevalent and very costly in many countries around the world. Recent research has found that more than 90% of the world's adult population live in countries with mean intakes exceeding the World Health Organization's recommendation, and that more than a million deaths every year may be attributable to excess sodium. This study uses a simulation model to estimate, for the first time, the cost-effectiveness of government interventions to reduce population sodium consumption in every country in the world. It reveals substantial heterogeneity in cost-effectiveness by country that has never before been identified, and illustrates, also for the first time, the sensitivity of intervention efficacy to the theoretical-minimum-risk exposure distribution of sodium intake.

The study makes a number of additional contributions. It offers a comprehensive appraisal of the methodological strengths and limitations of the surveys, imputation models, randomized controlled trials, prospective cohort studies, meta-analyses, and simulation models that together constitute the evidence base for public health recommendations on sodium intake, as well as for this study's own analysis. These methodological issues, some raised for the first time, are evaluated systematically to allow the relative quality of each input to be assessed and to inform prioritization of further research. The study also uses economic theory to ground a discussion of the proper nature and scope of government policies targeting population sodium consumption, and presents an up-to-date survey of sodium reduction initiatives around the world.

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Chapter 1

Introduction

This is a study about salt, and the potential of government action to improve people's health by getting them to eat less of it. Humans have used the substance, a mineral composed primarily of sodium chloride (NaCl), since at least the seventh millennium BC [1]. Since then, it has become a dietary staple, as well as invested with religious significance. The Bible contains the commandment, "With all thine offerings thou shalt offer salt" (*Leviticus* 2:13). Homer calls it "divine" in the *Iliad* (IX:214). Plato has Socrates list salt first among the delicacies people in a "healthy city" will "obviously need" (*Republic* II:372c). Throughout history it has served as currency (Roman soldiers were originally paid in salt, whence our modern word "salary"), influenced the establishment of cities and trade routes, and played an important role in wars, empires, and revolutions [2]. Some amount of sodium is known to be essential to human life: sodium ions are required for the transmission of nerve impulses and the contraction of muscle fibers [3], as well as for the maintenance of the fluid balance in blood cells [4].

Yet, recent evidence suggests many people may be eating too much. Excessive consumption has been linked with hypertension (high blood pressure), among other conditions, and in turn with cardiovascular disease. In particular, eating too much salt seems to lead to retention of sodium by the kidneys, an excess of sodium in the body, and consequently an excess of cellular sodium [5]. This leads to contraction of certain cells in the arteries and reduced vasodilation, so increasing blood pressure. High blood pressure puts strain on the arteries, which can cause them to narrow further, burst, or clog up. Damage to the arteries leading to the heart can cause heart disease, and damage to those leading to the brain can cause stroke. The fact of high salt consumption around the world, together with the burden of cardiovascular disease, has led some public health experts to propose the reduction of population salt intake as a goal of public policy. Governments worldwide have launched initiatives based on these recommendations.

This study does three things. First, it makes an argument for why the adverse health effects of high sodium intake, if they exist, would justify government intervention to reduce population salt consumption. This is despite the fact that such government action may, for example, restrict the freedom of manufacturers to of-

fer products that consumers want to buy and impose costs on some sectors of society. Second, it presents a systematic, comprehensive, and up-to-date survey of current salt reduction initiatives around the world. This illustrates the wide scope of government interest in policy recommendations by researchers in this field, and the willingness of both legislators and bureaucrats to act on them. It also explores the heterogeneity of governments' policy approaches, and the impacts of those policies. Third, it models the cost-effectiveness of population strategies to reduce sodium intake in every country in the world. In doing so, it critically appraises the evidence used to generate such estimates.

This prospective policy evaluation is the chief contribution of this study to the literature. Three aspects of that contribution are worth mentioning. First, no prior work has attempted to estimate the cost-effectiveness of sodium reduction for every country in the world. Previous studies have estimated the effects of sodium reduction for only a single country, or at most a small handful of countries or regions [e.g., 6, 7]. This has left all but a few countries with little information on what they might expect costs or effect sizes to be. It has also masked the substantial heterogeneity in cost-effectiveness between countries, and the causes of that heterogeneity. This study shows, in particular, that some regions have much more to gain than others. Those regions with the most to gain have never previously been identified.

A second contribution of this study is its exploration of the sensitivity of its results to the choice of the theoretical-minimum-risk exposure distribution of sodium intake. The controversy over what the level of sodium intake is below which reductions cease to have any effect on blood pressure is well known, yet no prior cost-effectiveness study has evaluated the relevance of this value to policy. In fact, it matters a great deal in some countries and regions, and not at all in others.

Third, prior studies have tended not to focus on assessing the strength of the evidence for the various causal effects used as inputs to their models. This study takes advantage of new estimates of salt consumption in every country in the world, stratified by age and sex, as well as corresponding estimates of blood pressure and the burden of cardiovascular disease. It uses the results of up-to-date meta-analyses to quantify the various effect sizes and their uncertainties, and a detailed new model developed by the WHO to estimate costs. Yet, there are problems with the methodology used to derive each of these inputs, and strong identifying assumptions are needed for the final estimates to be convincing. This study describes these methodological issues in detail, in some cases for the first time, and presents them systematically to allow the relative quality of each input to be assessed. A comprehensive appraisal of this sort has long been lacking from the literature.

It is hoped, then, that the estimates obtained in this analysis will be practically useful to policymakers and comparable with cost-effectiveness estimates derived for other interventions elsewhere in the literature. It is also hoped they will be interpreted with the appropriate degree of confidence.

The rest of the study proceeds as follows. The argument for government intervention is presented in Chapter 2. Evidence for the existence of imperfect information, negative externalities, and time-inconsistent preferences is evaluated, and the correspondence of each to particular policy prescriptions is defended. Chapter 3 explores the current policy context for salt reduction. The results of a survey of national salt reduction initia-

tives are reported, as are case studies of attempts to pass legislation restricting the salt content of foods, together with examples of successful policies. Building on the previous two chapters, Chapter 4 presents a model to estimate the cost-effectiveness of salt reduction interventions in every country in the world. It explains the inputs to the analysis, derives the statistical model, and presents the results. Chapter 5 is devoted to exploring the limitations of every aspect of the model. Chapter 6 concludes.

Chapter 2

Rationale for government intervention

Excessive salt consumption is both prevalent and very costly in many countries around the world. The World Health Organization (WHO) Global Burden of Disease Nutrition and Chronic Disease Expert Group recently estimated that 181 of 187 countries, representing 99.2% of the world's adult population, had mean sodium intakes exceeding the WHO recommendation [8]. One analysis focused on the United States found that reducing Americans' salt intake by 3g per day would save up to 392,000 quality-adjusted life-years and $10 billion to $24 billion in health care costs annually [9]. Another estimated that, worldwide, 1,648,000 deaths from cardiovascular disease in 2010 were attributable to excess sodium [10]. Assuming high salt consumption does have such effects, there seems a strong case for government intervention in many countries. But two concerns present themselves. The first is whether it is the government's place to intervene. Individuals, it may be argued, should be free to choose what foods they consume: the state should stay out of the kitchen. Second, supposing government action were warranted, it is not obvious what form that action should take. Dietary interventions range from media campaigns and directives on food labeling through to taxation and outright bans.

Economic theory suggests that the answers to these two questions will be related [11]. In diet as in other domains of consumption, individuals are assumed in the baseline case to weigh up the full costs and benefits of the different baskets of goods they can afford, and choose the one they most prefer. Insofar as this is what consumers are doing, there is no good reason for government to intervene to restrict people's choices. First, doing so would not make anyone better off. Every individual is already as well-off as possible, given their preferences and budget constraints. Second, intervention would be authoritarian. In particular, if people choose to consume food that is bad for them, then, as long as they have fully taken into account the costs of doing so, any government intervention would be incompatible with the rights and freedoms that modern states commonly hold their citizens to possess.

There are, however, good reasons to think that individuals do not weigh up the full costs and benefits of the dietary options available to them. They may simply not be aware of the harms of some foods. Even if they are aware of such harms, they may not take into account the costs of these harms that will be borne by others.

Finally, they may fail to consider the preferences they themselves are likely to have in the future. Each of these reasons yields different prescriptions for government intervention, and will be considered in turn.

2.1 Imperfect information

The case in which consumers are unaware of the harms of certain foods is a problem of *imperfect information*. Just as it is often difficult for voters to select which candidate to vote for when they have no idea how the candidates will behave if elected, so too it is difficult for consumers to select which food to buy when they don't know how those choices will affect their health. This may be true in several respects in the case of salt. First, consumers may not be aware that too much salt is bad for them in the first place. Second, they may not know how much they tend to consume and from what sources, nor how much is too much. A recent survey of 1,000 US adults by the American Heart Association (AHA), for example, found that 46% of them believed that salt added to food is the top source of sodium in Americans' diets, when in fact 70-80% of US sodium intake is through consumption of processed foods [12]. Finally, consumers may not be aware of the sodium content of particular foods: either because it is not provided at all, or, if it is provided, because they do not know where to look.

These various information failures each suggest their own remedy. Consumers' lack of knowledge about the health effects of excessive salt consumption may be rectified by a government media campaign on the subject. An awareness campaign by the UK Food Standards Agency launched in 2004, for example, increased public awareness of recommended salt intake limits more than tenfold, from 3% to 34%, within a year [13]. Once consumers are aware of salt intake limits, their ability to manage their intake may be improved by government food labeling directives. These might range from requiring nutritional content labels on all foods, as many governments already do; through to more user-friendly 'traffic light' systems, which grade the levels of sodium and other substances as low, medium, and high; or encouraging or mandating regimes of certification along the lines of the AHA's Heart-Check mark or the Nordic Keyhole (see section 3.1), which require products to meet a range of nutritional standards.

2.2 Externalities

Actions of consumers often impose costs on others. In economic theory, these costs are known as *externalities*. In the same way that individuals often fail to account for the effects on others of the pollution and congestion they cause when they choose to drive rather than using public transportation, so too they often fail to account for the costs on others of their dietary choices. In the case of excess sodium consumption, which is associated with cardiovascular disease, these costs include the costs of healthcare, as well as unemployment and incapacity benefits. In many countries, healthcare and other benefits are provided publicly. One recent analysis found that 75 countries worldwide mandated universal health coverage [14]. In these countries, the medical costs of

any individual's poor health choices are not borne by the individual, but by all taxpayers. Even in countries where people tend to purchase healthcare privately, increases in the cost of insurance resulting from certain individuals' dietary choices are borne by all parties to the scheme in question, since diet is not normally assessed and used to price insurance premia. In this way, individuals make choices based solely on the costs and benefits to them, rather than accounting also for the costs and benefits to society.

Government intervention might then seek to 'internalize' these externalities for consumers. One way of doing this is to alter the prices faced by individuals so that those prices include the costs to society of consumption of the goods in question. This would be achieved via taxation of foods high in salt (or even of salt itself). Such a tax would have the effect both of reducing the consumption of these foods, and also of raising revenue that would offset the costs of healthcare resulting from their consumption. This policy, however, would be ineffective at reducing salt consumption if consumers' preferences for such foods were inelastic (that is, if their demand did not change much in response to changes in price), or if the taxes were not fully passed on by retailers to consumers. A second option is simply to restrict the amount of salt that manufacturers put in food, via either legislation or voluntary agreements, on the grounds that the costs of not doing so outweigh the benefits for society as a whole. This policy imposes most of its costs on manufacturers (ingredient reformulation, etc.), but is a much more certain means of reducing population salt consumption. It is also not even necessarily welfare-reducing for consumers if the reductions are done in such a way and at such a pace as to render the difference in taste unnoticeable. That said, both taxes and quantity restrictions may have unintended side-effects, such as causing consumers to switch to products lower in salt but more unhealthy for other reasons (e.g., higher in sugar, fat, etc.). Policymakers must carefully consider the possibility of these consequences when designing interventions and take steps to mitigate them. They must also pay close attention to them when evaluating the success of existing interventions.

2.3 Time-inconsistent preferences

Finally, individuals may have *time-inconsistent preferences.* This is when someone's preferences over a choice set at one time differ from the same person's preferences over the same choice set at some other time. For example, an individual may prefer to consume all their income during their working life, but, when they reach retirement age, wish that they had saved a proportion of it. Similarly, someone may prefer to eat junk food when they are hungry, but regret doing so when they become obese. Such behavior may be explained as resulting from temporal discounting (feeling or valuing present desires much more than future desires), or a lack of self-control (e.g., having a strong second-order desire to give up junk food, but being overwhelmed by the first-order desire to eat junk food). A more philosophically interesting framework might posit multiple selves. It would thus regard Sheryl at age twenty-five as a quite separate person from Sheryl at age sixty-five. After all, the sixty-five-year-old Sheryl consists of almost entirely different molecules from her younger self, and likely has very different preferences, thoughts, and desires.

In each case, it is reasonable to assume that someone with a preference, earlier in life, for consuming an excessively salty diet might then wish to have eaten more healthily when they find themselves at increased risk of cardiovascular disease later in life. The rationale for government intervention would depend on the explanatory framework. In the case of temporal discounting, intervention would be on the basis of correcting biases in consumers' decision-making: very high temporal discounting is here seen as simply irrational, with government action helping consumers to behave more rationally. In the case of lack of self-control, it could be seen as a commitment device: citizens (through their elected representatives) pass legislation to bind themselves to particular patterns of behavior they regard as desirable but are unable to live up to of their own accord. Finally, in the case of multiple selves, it might be thought that government policy has no good reason to privilege the preferences of Sheryl today over the preferences of Sheryl tomorrow – in the same way it has no good reason to privilege current generations over future generations. It should therefore 'protect' the rights of the sixty-five-year-old Sheryl, potentially at risk of serious health problems, from the harm that would be inflicted by the twenty-five-year-old Sheryl.

These lines of justification, while powerful, nevertheless bring difficulties. First, while there is strong empirical evidence for the presence of imperfect information and large negative externalities, evidence regarding time-inconsistent preferences is lacking. There exist no data on the preferences of older people over the salt consumption of their younger selves; nor, obviously, for any single person today is it possible to predict with much certainty their future preferences. It might well be that, while some proportion of those who do suffer cardiovascular disease and consumed a high-salt diet would wish they had eaten more healthily, the proportion might not be all that high ("better sixty years of indulgence than eighty of abstinence"). Moreover, even if the proportion were high, the policymaker is still left with the salt-favoring preferences of the young, which must somehow be balanced with, rather than simply overridden by, the (potentially) salt-eschewing preferences of the old. Second, government action for the sake of people's future selves, while in the present context well-intentioned, brings with it the potential for much abuse. Once policymakers start claiming the right to take action that may be against the wishes of citizens as they are, there and then, by appealing to those citizens' 'better selves' or 'future selves', they may find themselves tempted to do so in more and more situations with less and less justification: therein lies the road to tyranny.

In summary, economic theory suggests that there may be good grounds for government intervention to prevent ill health resulting from excessive salt consumption, assuming the science is correct. In particular, individuals are likely to be making dietary choices with imperfect information, which suggests there may be a role for government in correcting this: both in terms of educating consumers on the health effects of salt, and making it easy for them to evaluate the salt content of the dietary choices available to them. People are also likely failing to take account of the medical and other costs they may be imposing on the rest of society when they consume a diet excessively high in salt. There is thus a rationale for government to pass legislation that internalizes these costs for consumers via taxation, or simply to restrict the salt content of foods prepared by

manufacturers and the food service industry. The next chapter surveys recent attempts by governments and other organizations around the world to implement such measures.

Chapter 3

Current policy context and previous sodium reduction efforts

Many governments have public health strategies that aim to reduce diet-related disease. A significant number of these seek to reduce population salt consumption. They vary along several dimensions: some merely express a desire to see population salt consumption decrease, while others have concrete strategies, timelines, and policy mechanisms in place; some have much more ambitious salt intake targets than others; in some countries, non-governmental organizations (NGOs) and pressure groups play important roles, but are absent elsewhere; and some governments make all reformulation and labeling measures voluntary, while others pass legislation to make them mandatory.

The rest of this chapter proceeds as follows. First, all country-level salt reduction initiatives currently in place around the world are identified and summarized along the above dimensions. Some notable trends are discussed. Second, three brief case studies of governments that have attempted to pass legislation are presented. Third, the experiences of five countries that have demonstrated success in reducing population salt consumption are detailed.

3.1 Salt reduction initiatives around the world

A study conducted in 2011 by Webster et al. identified thirty-two country salt reduction initiatives worldwide [15]. The results of that analysis are here revised and updated to take account of developments in the past two years. Briefly, the list of national salt reduction programs in Webster et al. was supplemented with information from the World Health Organization Regional Office for Europe [16], the World Action on Salt and Health (WASH) [17], and Google searches using 'salt' or 'sodium', and 'strategy' or 'program' or 'initiative' or 'action plan'. Only strategies that were national in scope were included.

For each strategy, the following information was extracted (definitions reproduced from Webster et al.):

1. Leadership and strategic approach:

   (a) Leadership: the organization leading or coordinating the program (government, NGO or industry).

   (b) Dietary targets: the presence of an agreed national population target for salt consumption with target amount.

   (c) Program specificity: whether the strategy was salt-specific or a part of a broader health program.

   (d) NGO/advocacy action: the presence of consumer/advocacy organizations working on salt (yes/no).

2. Implementation strategies:

   (a) Food reformulation: whether the program included work with the food industry to reformulate foods and whether the approach was voluntary or mandatory (voluntary/mandatory/planned/none).

   (b) Consumer behavior: whether there was a consumer awareness campaign and whether this was led by an NGO or government.

   (c) Labeling: whether any new front-of-pack labeling scheme such as warnings (W), traffic lights (TL), percentage daily intake or Guideline Daily Amount (%DI), or healthy choice scheme (Logo) had been introduced as part of the salt reduction program and whether this was voluntary or mandatory (vol./man.).

Thirty-seven national salt reduction initiatives were found (see table 3.1). Of these, twenty-three were in Europe, six in the Americas, seven in the Western Pacific Region, and one in Africa. Twenty countries had a salt-specific strategy in place. Salt intake targets were identified in all but five countries, ranging from 4g/day in Israel to 8g/day in France and Switzerland. Fifteen countries had a target of 5g; thirteen a target of 6g; Finland set targets of 7g for men and 6g for women.

In thirty-one countries, the government was leading salt reduction efforts, with NGOs doing so in five (all in the Western Pacific Region), and both government and industry in one (the Netherlands). NGOs and advocacy organizations were active in 21 countries in total. In some countries, the influence of advocacy groups was clearly identifiable as being the main spur to government efforts. These groups often act under the umbrella of World Action on Salt and Health (WASH), an advocacy organization whose membership consists mostly of medical and public health professionals [18]. In Australia, for example, the Australian Division of World Action on Salt and Health (AWASH) ran a successful campaign to persuade the government to collaborate with industry to set salt reduction targets [19]. Within Europe, action in many countries has been co-ordinated by the European Commission, which in 2008 established a European Union Framework on voluntary national salt initiatives. In the United States, the impetus has come from the New York City Health Department, which since 2008 has co-ordinated a partnership of more than 90 state and local health authorities and national health organizations under the banner of the National Salt Reduction Initiative (NSRI) [20].

Country	Leadership	Salt intake target (g/day)	Salt-specific program	NGO/advocacy action	Food reformulation	Consumer education	Front-of-pack labeling
Argentina	Government	6	Yes	No	Voluntary	Government	-
Australia	NGO	6	Yes	Yes	Voluntary	NGO	%DI/Logo (vol.)
Barbados	Government	6	No	Yes	Voluntary	Government	-
Belgium	Government	6	No	Yes	Voluntary	Government	-
Brazil	Government	5	Yes	Yes	Voluntary	-	-
Bulgaria	Government	5	No	No	Voluntary	Government	-
Canada	Government	6	Yes	Yes	Voluntary	NGO	Logo (vol.)
Chile	Government	-	Yes	Yes	Planned	Government	W (man.)
China	NGO	6	Yes	Yes	None	Government	-
Cyprus	Government	5	No	No	Voluntary	Government	-
Denmark	Government	5	Yes	No	Voluntary	Government	Logo (man.)
Fiji	Government	5	Yes	Yes	Voluntary	Government	-
Finland	Government	7/6	No	No	Voluntary	NGO	W (man.)
France	Government	8	No	Yes	Voluntary	Government	-
Hungary	Government	5	Yes	No	Voluntary	Planned	-
Ireland	Government	6	Yes	No	Voluntary	Government	% DI (vol.)
Israel	Government	4	No	No	Voluntary	-	-
Italy	Government	-	No	Yes	Voluntary	NGO	-
Japan	NGO	6	Yes	Yes	None	NGO	-
Latvia	Government	5	Yes	No	Voluntary	Planned	-
Lithuania	Government	5	No	No	Voluntary	Planned	-
Malaysia	NGO	-	Yes	Yes	Voluntary	NGO	-
Malta	Government	5	No	No	Voluntary	Government	-
Netherlands	Industry/Government	6	No	Yes	Voluntary	NGO	% DI/logo (vol.)
New Zealand	NGO	-	Yes	Yes	Voluntary	NGO	% DI/logo (vol.)
Norway	Government	5	No	No	Voluntary	Planned	-
Poland	Government	6	No	Yes	Voluntary	Planned	-
Portugal	Government	6	No	No	Mandatory (bread)	Government	-
Singapore	Government	-	Yes	Yes	Voluntary	Government	Logo (vol.)
Slovakia	Government	5	Yes	Yes	Voluntary	NGO	-
Slovenia	Government	5	Yes	No	Voluntary	Government	-
South Africa	Government	5	Yes	No	Mandatory	Planned	-
Spain	Government	5	No	Yes	Voluntary (bread)	Government	-
Switzerland	Government	8	No	Yes	Planned	Planned	-
Turkey	Government	5	Yes	No	Voluntary	Government	Planned
UK	Government	6	No	Yes	Voluntary	Government	TL/%DI (vol.)
USA	Government	6	Yes	Yes	Voluntary	NGO	-

Table 3.1: Salt reduction initiatives around the world

By far the most common implementation strategy was to collaborate with the food manufacturing industry to set voluntary reformulation targets, generally by category of food. Thirty countries have adopted this approach. Many begin by targeting just one food type (most commonly bread: e.g., Cyprus, Italy, Malta, Switzerland); some work with all sectors of the food industry (e.g., Australia, Belgium, Bulgaria, the Netherlands, Norway, UK, US); and some work through trade associations (e.g., Finland, Hungary, Poland, Estonia) [21]. Specific reformulation targets are a common feature, with some countries setting upper limits (e.g., the Czech Republic targets 1.2g of sodium in dried soups and sauces) and others setting percentage reductions (e.g., Slovenia targets 4% reduction per year of salt in baked goods). Portugal has passed legislation to restrict the sodium content of bread, while South Africa has put in place mandatory upper limits for several food categories. Several countries have made additional more minor changes not requiring legislation, such as mandating the removal of salt cellars from school canteens (France).

Consumer education campaigns are also part of most countries' strategies. They are in place in twenty-eight countries, in ten of which they are run by NGOs. They are planned in seven more. In most, they take the form of media campaigns (posters, leaflets, TV ads). Some countries, such as Finland, take a more coordinated approach across government, including imparting information via the education system, labeling, and the healthcare system [21].

Ten countries have implemented labeling initiatives specifically targeting sodium. These include traffic lights (UK), warnings (Finland and Chile), percent daily intake (Australia, Ireland, the Netherlands, New Zealand, and the UK), and logos (Australia, Canada, Denmark, the Netherlands, New Zealand, and Singapore). A good example of international co-operation is the Nordic Keyhole labeling scheme, adopted by Sweden, Denmark, and Norway, and shortly to be joined by Iceland. The scheme was first established by Sweden in 1989, and allows (but does not mandate) food manufacturers to display the keyhole on products that fulfill certain conditions. These include limits on the content of sugar, fat, and other substances as well as salt. Consumer awareness of the label is very high, at 98% in Sweden and Norway and 88% in Denmark [22].

3.2 Case studies of legislation

Efforts to pass legislation to mandate reductions in the sodium content of foods have been made in Canada, South Africa, and Portugal. Each is considered in turn.

In Canada, the proposed legislation was a Private Member's Bill tabled by the Official Opposition's Health Critic, Libby Davies, in January 2013. Her bill claimed to add legal force to the recommendations of the Sodium Working Group, an expert body that had been established in 2007 by the then-Minister of Health, before reporting to and being disbanded by the present Minister of Health in 2010. (Both Ministers are Conservatives in the government of Prime Minister Stephen Harper.)

The working group, whose membership included representatives of food manufacturing and food service groups as well as scientists, policymakers, and health professionals, reached consensus on their recommen-

dations, of which the principal one was voluntary reduction of sodium levels in processed food products and foods sold in food services establishments. It also called for government monitoring and evaluation. The Private Member's Bill sought to mandate a warning label on all prepackaged foods that exceeded the Canadian Ministry of Health's sodium reduction targets, as well as to establish a public registry of the sodium content of all prepackaged foods sold in the country. Davies claimed her bill was supported by almost 40 organizations and experts in Canada, including the Canadian Medical Association, the Canadian Public Health Association, and Hypertension Canada.

In the House of Commons debate on the bill, Colin Carrie, Parliamentary Secretary to the Minister of Health, represented the government in opposing the bill. He argued that the bill would be costly to taxpayers, would "take money out of the pockets of small businesses across the country and add layers of red tape", would carry unintended food health risks in causing consumers to substitute to low-sodium products that may be unhealthy for other reasons, and would anyway be impossible to enforce. Carrie also noted that guidance for the food industry on sodium reduction was only issued very recently, and referenced preliminary monitoring by the government of common high-sodium foods that found "reductions that will have them well-placed to reach the [maximum sodium content] goal by 2016" [23].

The bill was voted down, with 147 nays (all Conservative) and 122 yays (NDP, Liberal, Bloc Québécois, and Green, as well as a single Conservative). It is difficult to infer much from this outcome, since Private Member's Bills are very seldom passed in Canada, especially when opposed by the government as in this case [24]. It does bear remarking that while supporters of the bill claimed that it was "implementing" the working group's strategy, in fact neither of the two main components of the bill (mandatory warning labels and a public registry) were recommended in the group's report.

In South Africa, regulation was backed by the government and did not require approval by the legislature. In July 2012, the Minister of Health set out a draft amendment to the country's Foodstuffs, Cosmetics and Disinfectants Act 1971, which in section 15(1) states that "The Minister may make regulations... prescribing the nature and composition of any foodstuff". The draft amendment set out sodium reduction targets for ten food categories, specifying a maximum total sodium per 100g foodstuff to be achieved by 30 June 2016 and a reduced maximum to be achieved by 30 June 2018. After a period of consultation, the Minister signed a revised amendment into law, the final target date having been delayed a year to 30 June 2019, several maximum limits having been raised a little, and some food categories having been dropped.

In this case, there appears to have been essentially no public debate on the issue. A search of all English-language news sources in South Africa using *LexisNexis*, a full-text newspaper archive, showed that the publication of the draft regulations resulted in just two short pieces [25, 26], followed by four more over the following month. Of these, one concerned claims by the South African Chamber of Baking that the regulations would force up the cost of bread [27]. The final adoption of the amendment occasioned two further pieces, one of which quoted the Consumer Goods Council of South Africa as saying it was "shocked and disappointed" that the law had been passed, as well as manufacturers who called the targets "unrealistic". A government scientist

was quoted as saying that big business in fact chose the legislative policy option during initial engagement sessions as a way to "level the playing field" between large and small companies [28]. There has been no further coverage of the issue in the South African press.

Finally, Portugal's then-ruling Socialist Party in 2009 submitted to Parliament and passed a bill limiting the salt content of bread. It specifies an upper limit of 1.4g salt per 100g bread, and mandates a fine of 5,000 EUR for exceeding this. The limit represented a reduction of about 25% for the salt content of Portuguese bread. The law also requires that labeling on prepackaged bread include information on its salt content. One English-language news article noted that the government was starting to enforce the law in August 2010, and quoted the Portuguese Bread Retailers and Producers Association as saying that bread had become a "scapegoat", when other products contained far more salt [29]. An assessment of the success of this law has not yet been completed, nor do there appear to be any plans to extend the legislation to cover other food categories.

At present, the uses of legislation by governments to achieve salt reduction targets are too few to draw firm conclusions, regarding either the political process or intervention efficacy. That said, two themes are notable. First, industry bodies in each country say they agree with the need to reduce salt, and focus their lobbying efforts on making proposed legislation less stringent (e.g., lesser targets, later deadlines), or more fair (e.g., targeting other food groups besides their own). They tend to emphasize the costs (to themselves) or technical difficulties of reducing salt, but do not dispute the science or overall cost-effectiveness of proposed measures. Second, debates tend to be between public health advocacy organizations (e.g., societies of hypertension) and industry only, with no input from consumer organizations. Industry bodies sometimes complain that consumers will react unfavorably to reduced-salt foods, but consumers themselves do not get involved (except via their purchases). Moreover, journalists do not find private individuals who speak against any salt-reduction measures, including legislation; the only individuals mentioned, quoted, or profiled are those especially keen to reduce their own salt consumption following government guidance. While the substance in question may be one of the most common, the debate is surprisingly rarefied.

3.3 Examples of successful policies

While the majority of countries identified in section 3.1 have only recently started to make sodium reduction a serious object of public policy, and so have not been in a position to evaluate the success of their efforts, a small number have demonstrated some impact. The examples of Finland, France, the UK, Japan, and Turkey are now briefly discussed.

Finland introduced a salt reduction initiative in 1978, at which time average population salt intake was extremely high (12g/d). The initiative was one component of a much broader community-based intervention, the North Karelia project, which was intended to reduce cardiovascular disease mortality in that region. (The project was expanded to include the entire country after three years.) The strategy was led by the Finnish National Nutrition Council, which worked closely with the food industry and media outlets to reduce the

salt content of foods and raise consumer awareness. Legislation was passed in 1993 that required a 'high salt content' warning label on foods containing high levels of sodium, and permitted foods low in sodium to carry a 'low salt' label [30]. A reduced-sodium salt substitute, Pansalt, was also strongly promoted. Surveys using 24-hour urinary sodium excretion found a decrease in average salt intake from 12g to 9g/day between 1978 and 2002, with most of this reduction happening after 1987 [31]. In the same period there was a 60% fall in coronary heart disease and stroke mortality [32]. It is, though, impossible to say how much of this is attributable to the reduction in salt consumption, since the government also implemented antismoking legislation among many other cardiovascular disease-targeted measures in the period, and there was no control group.

In France, the Food Safety Authority (AFSSA) recommended the development of population strategies to reduce salt consumption in 2000, and a working group of scientists and industry was formed in 2001. The group's proposals were adopted by the 'Second National Nutrition and Health Program 2006-10' (Programme National Nutrition Santé 2 [PNNS 2]). The proposals included consumer information campaigns and food reformulation activities. These reformulation efforts focused chiefly on bread, by targeting information at the country's approximately 33,000 bakeries, as well as the flour industry. While no decline in the average salt content of bread has yet been observed, the European Commission reports estimates of a decline in adult population salt intake from 8.1g/day in 1998-9 to 7.7g/day in 2006-7: a reduction of 0.4g/day, or 5.2%. The trend is more pronounced in the highest salt consuming group, with, for example, the proportion of men consuming more than 12g/day decreasing by a third in the same time period. Moreover, the French salt industry has reported a reduction in salt sales to the food industry of 15% from 2001 to 2006, and a reduction in sales of household salt of 5% [33].

The United Kingdom's salt reduction strategy is one of the most vigorous, and has served as a model for many other countries. The country's Food Standards Agency (FSA) began collaborating with the food industry in 2003, inviting various groups to submit formal commitments to reduce salt in their products. Commitments were eventually received from all the major UK retailers, several multinational and national manufacturers and caterers, and trade associations for products making major contributions to salt intakes. The FSA carefully monitored the organizations' progress towards their goals, and supported research and developed guidance to help overcome various technological barriers. For example, it worked with the British Meat Processors Association to develop guidance on reducing salt in meat products while maintaining food safety, and funded significant research into adapting bakery processes to the same end. The FSA in a briefing claims that "industry has indicated that it welcomes this interactive approach with the Agency and is generally positive about the potential for further reductions over time" [34]. Some impressive achievements are also reported there: members of the Association of Cereal Food Manufacturers achieved a 44% reduction in salt in breakfast cereals between 1998 and 2008, for example, while the Food and Drink Federation reduced salt in cooking and pasta sauces by 30% and in soups by a quarter between 2003 and 2005. A recent independent analysis found that the average salt level of UK prepackaged bread was reduced by 20% between 2001 and 2011 [35]. Work on food reformulation has been combined with a large-scale sustained public awareness campaign, with separate

phases launched in 2004, 2005, 2007 and 2009. All focused on women aged 35-65 in social class categories C1C2D (lower middle and working classes), who were regarded as the "gatekeepers" to the highest salt consumers, namely men in those classes. As a result of all these efforts, measured average dietary sodium levels have decreased from 9.5g/day in 2000-1 to 8.6g/day in 2008, or a reduction of 9.5%. An evaluation of the information campaign showed increased awareness of the benefits of reducing salt intake on health, with the proportion of adults claiming to have made a special effort to reduce salt in their diet rising from 34% in 2004 to 43% in 2009 [36].

Japan witnessed an apparently remarkable reduction in population sodium consumption from the 1970s onward, though consumption remains at very high levels and appears now to be increasing again. According to the National Nutrition Survey, which uses a food intake survey rather than urine samples, average daily salt intake decreased from 14.5g in 1973 to 11.4g in 2002: a reduction of 3.1g, or 21.4%. Yoshiike et al. suggest the reduction in sodium levels was due to a nationwide health campaign and the spread of refrigerators [37], though further information on this campaign is hard to come by. Mean blood pressure fell dramatically in the same period, as did morality due to stroke, which was reduced to one-fifth of its 1960s level [38]. These changes, however, coincided with the introduction of universal health coverage, much increased use of antihypertensive drugs, and other interventions, which together appear to have played a bigger role than the reduction of salt consumption [39].

Finally, Turkey has recently reported significant progress in reducing population salt consumption [40]. The government initiated a salt reduction program in 2011, with actions including food reformulation, focusing on bread and tomato pastes, labeling regulations for food products, and significant media campaigns, including this year films on national TV, a salt reduction awareness week, and notices on national lottery tickets. A nationally representative 24-hour urinary excretion study in 2008 found average salt consumption was 18g/day. The study was repeated in 2012, and found consumption had decreased to 15g/day: a 16% reduction. This is a very significant decline to take place in just four years, especially in comparison with the UK experience, and merits further evaluation.

As the preceding examples show, food reformulation and consumer awareness-raising activities have already resulted in significant reductions in population salt consumption in several countries around the world. Moreover, many other countries currently engaged in implementing similar interventions are due to evaluate the effects of their efforts over the coming several years. The common target of 6g/day so far appears to remain elusive for these countries, however, which may motivate a move from a voluntary to a legislative approach. It should also be noted that almost all interventions considered in this section have occurred in high-income countries. High salt intake and CVD mortality are just as prevalent in middle- and low-income countries, as detailed in the next section, and work is needed to investigate alternative intervention strategies that may be more appropriate in these states. Rural areas where most sodium consumed is added during cooking, for example, may benefit more from interventions to encourage salt substitution than the strategies considered above [41].

Chapter 4

Empirical application

The examples in the preceding chapter suggest that salt reduction initiatives can have significant effects on population salt intakes. It is natural to ask what the effect of a given intervention would be on population cardiovascular disease in a particular country, and in turn whether such an intervention would be cost-effective. Salt intakes, blood pressures, and cardiovascular disease prevalence vary greatly around the world, as does the cost of population health interventions. This section attempts to quantify the varying effects and costs of different interventions in every country in the world. Inputs to the analysis, and the methods used to obtain them, are first described in detail. The methods of this analysis follow, and results are presented. Discussion of limitations is reserved for the following chapter.

4.1 Inputs to the analysis

This study uses estimates of global sodium consumption, blood pressure levels, and the burden of cardiovascular disease from the Global Burden of Disease 2010 update. It uses sodium-blood pressure and blood pressure-cardiovascular disease effect sizes from previously published meta-analyses. A population attributable fraction approach is used to obtain the final estimates, with the analysis done at the level of each country-age-sex cohort. Mozaffarian et al. used the same data and a similar approach to estimate the overall impact of excess sodium consumption on cardiovascular mortality worldwide [10]. This study builds on that work by estimating the effect of interventions to reduce sodium consumption by particular amounts in each country, and uses additional data on disability-adjusted life years (DALYs) attributable to cardiovascular disease to calculate the effect according to that metric. This is the first sodium cost-effectiveness analysis to derive estimates for every country in the world, the first to use this new data on exposure levels and effect sizes, and the first to use a new WHO intervention costing tool. Each input is now described.

4.1.1 Global sodium consumption by country, age, and sex

As part of the 2010 Global Burden of Diseases (GBD) project, Powles et al. estimated mean sodium consumption and its uncertainty by age and sex for 187 countries [8]. The authors performed systematic searches between March 2008 and December 2011 for national or subnational data sources on individual-level sodium consumption. Sources that utilized urinary excretion, dietary estimates, or both were admissible. Data were identified and retrieved, by age and sex, from published reports or direct author contacts from 205 surveys. Of these, 142 utilized 24-hour urine collections, 91 dietary estimates, and 28 both. These surveys combined represented 66 countries and 74.1% of the global adult population, with 58% (n=126) from high-income and 42% (n=90) from low- and middle-income nations.

Estimates from dietary surveys have been shown to underestimate those obtained from 24-hour urine collections [42]. For this reason, the authors adjusted the dietary estimates, using 79 data points from 26 surveys that had data on the same individuals in both metrics to estimate the relationship between the two measures. They used a *log-log* linear regression model, and obtained an R^2 of 0.56. (No regression diagnostics were reported.) The final estimates were not adjusted for non-urinary (e.g., sweat) losses, both because urinary excretion represents, on average, about 90% of dietary consumption, and also to maintain comparability with prior regional urinary surveys and with blood pressure trials that measured urinary sodium.

An age-integrating Bayesian hierarchical imputation model (DisMod III) was used to account for differences in missingness, representativeness, and measurement methods, and to quantify sampling and modeling uncertainty. The model incorporated fixed effects for study-specific covariates (whether a study was nationally representative with or without probability sampling, or subnational) and time-varying national-level covariates (lag-distributed national income per capita, and national dietary patterns characterized by scores on 4 factor variables from an analysis of UN Food and Agriculture Organization-compiled food balance sheets). The variance of sub-national-level data was allowed to be different from nationally-representative data. The model also incorporated random effects by super-region, region, and country. The main inputs were sodium consumption data from country-specific age and sex subgroups. The data on age were incorporated using a cubic spline model, to allow for the possibility of sodium intakes being be non-linearly associated with age. This overall structure allowed the model to 'borrow' information across countries and regions as necessary; posterior distributions of mean sodium intake for each country by age and sex subgroups were obtained from an MCMC algorithm with 1,000 iterations, thus incorporating the different sources of uncertainty described. The authors do not report the results of model checks and validation, were any conducted. The final uncertainty intervals published represent the 2.5–97.5 percentiles of the posterior distribution of estimated mean sodium intakes, and these were used as inputs to this study's analysis.

In 2010, which is used as the baseline year in this study's model, mean global sodium consumption was 3.95g/day (10.06g/day salt), with regional means ranging from 2.18 to 5.51g/day. Overall, 181 of 187 countries, representing 99.2% of the world's adult population, had mean intakes exceeding the WHO recommendation of 2g/day sodium (c. 5g/day salt). Of these, 119 countries, representing 88.3% of the world's population, exceeded

this recommended intake by at least 1g/day. All countries except one (Kenya) had mean intakes exceeding the American Heart Association recommended intake of 1.5g/day sodium.

4.1.2 Blood pressure levels by country, age, and sex

Danaei et al. estimated mean systolic blood pressure (SBP) levels and their uncertainties by age and sex for 187 countries, also as part of the 2010 GBP project [43]. First, data were obtained from published and unpublished health examination surveys and epidemiological studies from around the world, including data from 786 country-years and 5.4 million participants. Next, these data were converted to the comparable metric of mean systolic blood pressure. Many published studies reported only hypertension prevalence (the proportion of the population with blood pressure above a certain threshold), not systolic blood pressure. In these cases, the authors developed linear regressions to estimate mean SBP from hypertension prevalence, with each observation in the regressions being one age-sex group for which the authors could calculate both mean SBP and hypertension prevalence. The control variables used were age, sex, year of survey, and whether the country was high income. The uncertainty of these estimates was obtained using a bootstrap procedure, which the authors report validating in a simulation study.

A Bayesian hierarchical model was then developed to obtain estimates for each age-country-year unit. (Years estimated were from 1980 to 2008, though only 2008 estimates were used as inputs to this study's analysis.) As with sodium intakes, such a model was necessary due to the sparse availability of data for many areas of the world: for example, no population-based data at all was available for 64 countries. SBP levels and trends in countries were, as above, nested in subregional, regional, and global levels and trends. Again, similar to the model used for sodium, the model borrowed information across countries, subregions, and regions, according to 'proximity' in geography, time, and country-level covariates (this time also including urbanization), doing so to a greater degree when data were non-existent or non-informative.

Various sources of uncertainty were quantified and propagated through the model. These included the sampling uncertainty of the original data sources, the uncertainty associated with fluctuations between years in national data, additional uncertainty associated with data sources that were not national (due to subgroup variation within each country), uncertainty associated with the estimation of mean SBP from hypertension prevalence, and uncertainty due to use of a model to estimate mean SBP by age group, country, and year when data were missing. The study authors describe extensive model checking, and report that the model did well in both posterior predictive checks and cross-validation, among other tests [43]. The final uncertainty intervals published represent the 2.5–97.5 percentiles of the posterior distribution of estimated mean SBP, and these were used as inputs to this study's analysis.

In 2008, world age-standardized mean SBP was 128.1 mm Hg (95% uncertainty interval: 126.7-129.4) in men, and 124.4 mm Hg (95% UI: 123.0-125.9) in women. The group with the lowest age-standardized mean SBP was women in Australasia (117.6 mm Hg, 95% UI: 112.2-122.7), followed by high-income North America (118.4 mm Hg, 95% UI: 115.1-121.8) and Asia-Pacific (120.5 mm Hg, 95% UI: 117.5-123.3). Men had higher mean

SBP than did women in every subregion apart from west Africa, by up to 9 mm Hg. The highest SBP values in men and women were in central and eastern Europe and sub-Saharan Africa, with mean SBP in these regions ranging 129.2-132.7 mm Hg for women and 132.6-134.8 mm Hg for men.

4.1.3 Cardiovascular disease mortality by country, age, and sex

Lozano et al. estimated cause-specific mortality for 187 countries from 1980 to 2010, again as part of the 2010 Global Burden of Diseases study [44, 45]. The authors obtained data on causes of death from vital registration, verbal autopsy, mortality surveillance, censuses, surveys, hospitals, police records, and mortuaries worldwide. These sources were assessed for completeness, diagnostic accuracy, and missing data, with outliers detected and excluded from subsequent analysis.

Next, each cause of death was modeled individually. This was done by developing a large range of plausible statistical models for each cause, and testing all possible permutations of covariates in each [46]. All models where the sign on the coefficient for a covariate was in the direction expected based on the literature, and the coefficient was statistically significant, were retained. (Example covariates in the case of cardiovascular disease are prevalence of hypertension and prevalence of tobacco smoking.) The four families of models tested were mixed effects linear models of the log of the death rate, mixed effects linear models of the logit of the cause fraction, spatial-temporal Gaussian process regression (ST-GPR) models of the log of the death rate, and ST-GPR of the logit of the cause fraction. Ensemble models were also developed.

The performance of all component models and ensembles was then evaluated using out-of-sample predictive validity tests: 70% of the data were used for initial model fit, 15% for testing, and 15% for validation. In particular, data were held out from the analysis using the pattern of missingness for each cause in the cause of death database. The tests of out-of-sample performance used were the root-mean squared error of the log of the cause-specific death rate, the direction of the trend in the prediction compared to the data, and the validity of the 95% uncertainty interval. Based on these tests, using a rank sum, the best performing model or ensemble was selected for each cause of death. Of all causes of death modeled in this way, cardiovascular diseases had the lowest out-of-sample RMSE.

A final step was to ensure that individual cause estimates summed to the all-cause mortality estimate for every age-sex-country-year group. To do this, a random draw without replacement was taken from the posterior distribution of 1,000 draws for each cause and matched to a draw from the all-cause mortality distribution for that age-sex-country-year. At the level of each of these draws, every cause was proportionately rescaled such that the sum of the cause-specific estimates equalled the number of deaths from all causes generated from a separate demographic analysis [47].

In 2010, according to this analysis, there were 52.8 million deaths worldwide. Ischemic heart disease and stroke collectively killed 12.9 million people, or one in four deaths worldwide. There were 14,669,000 total cardiovascular disease deaths, 6,963,000 coronary heart disease deaths, 5,798,000 stroke deaths, and 1,909,000 other cardiovascular disease deaths. For the present analysis, the following causes of death were utilized for

each country/age/sex group: ischemic heart disease (ICD-10 codes I20-I25), ischemic stroke (I63, I65-I67, I69.3), hemorrhagic and other non-ischemic stroke (I60-I62, I69.0-I69.2, I67.4), hypertensive heart disease (I11-I13), aortic aneurysm (I71), rheumatic heart disease (I01, I02.0, I05-I09), endocarditis (I33), atrial fibrillation and flutter (I48), peripheral vascular disease (I73), myocarditis and cardiomyopathy (I40, I42), and other cardiovascular and circulatory diseases.

4.1.4 Burden of cardiovascular disease in disability-adjusted life years (DALYs) by country, age, and sex

Murray et al. built on the estimates of mortality described above to estimate disability-adjusted life years (DALYs) for 291 causes, 20 ages groups, both sexes, and 187 countries, also for the 2010 Global Burden of Diseases study [48]. DALYs attempt to capture the deficit of a population's health compared with the normative goal of all individuals living the standard life expectancy in full health. For a given population, DALYs are the sum of two components: years of life lost due to premature mortality (YLLs) and years lived with disability (YLDs). The former are computed by multiplying the number of deaths at each age x by a standard life expectancy at age x. The number of deaths are exactly those described in the previous section; the standard life expectancy was computed based on the lowest recorded death rates across countries in 2010. YLDs are computed as the prevalence of different disease-sequelae (a sequela is any pathological condition resulting from a disease) multiplied by the disability weight for that sequela. The prevalence of disease-sequelae was estimated by conducting a systematic analysis of published and available unpublished data sources for prevalence, incidence, remission, and excess mortality, then aggregating this data using a Bayesian meta-regression model, DisMod-MR, very similar to DisMod III described in section 4.1.1 above. The weights were generated using data collected from more than 31,000 respondents via population-based surveys in the USA, Peru, Tanzania, Bangladesh, and Indonesia, and via an open internet survey. The main method used was pairwise comparisons of two randomly selected health states where the respondent selects which health state represents the higher level of health. Results were found to be consistent across levels of educational attainment and cultural groups [49].

In 2010 globally, the total burden of cardiovascular and circulatory diseases was 295,035,800 DALYs, of which ischemic heart disease accounted for 129,819,900 DALYs, stroke 102,232,300 DALYs, and other CVD 62,983,600 DALYs. Cardiovascular and circulatory diseases accounted for 11·8% of global DALYs; the individual diseases within this group with the highest burdens were ischemic heart disease (5·2%), hemorrhagic stroke (2·5%), ischemic stroke (1·6%), and hypertensive heart disease (0·6%). The larger burden of hemorrhagic stroke compared with ischemic stroke, which have roughly equal mortality rates, is mostly due to the younger average age of death for hemorrhagic stroke and so more YLLs per death. Most of the burden of cardiovascular disease is from YLLs, not from YLDs: for example, 93.2% of ischemic heart disease DALYs and 95.7% of stroke DALYs are from YLLs.

4.1.5 Effect of sodium on blood pressure

Two meta-analyses of randomized controlled trials of sodium reduction and blood pressure have recently been published [50, 51]. Neither, however, evaluated whether blood pressure-lowering effects were linear across a range of sodium reduction, nor did they quantify potential heterogeneity owing to age, hypertensive status, race, and duration of intervention. For this reason, a new meta-analysis was conducted for Mozaffarian et al.'s study of the global burden of sodium consumption [10].

First, all randomized trials used in the previous two meta-analyses were identified. Of these, 5 were excluded due to missing data on quantity of sodium reduction, mean age, or duration, and a further 57 excluded due to insufficient duration (<7 days) or mean sodium reduction (<20 mmol/day), or due to the presence of concurrent interventions that were not balanced between groups. This left 103 trials that included 107 group comparisons, with a total of 6,970 subjects. Sodium reductions ranged from 23 to 285 (mean±SD: 99±55) mmol/day, intervention durations from 7 to 1100 (65±160) days, and mean subject age from 13 to 73 (47.4±14.4) years. About two-thirds (64.5%) of comparisons were in hypertensive subjects; and 9.3% in black subjects. In sensitivity analyses, all 160 trials were evaluated. These totaled 9,606 subjects, with sodium reductions ranging from 16 to 341 (119±74) mmol/day, intervention durations from 4 to 1100 (53±136) days, and mean subject age from 13 to 73 (43.6±14.8) years.

Next, the linearity of effects of sodium reduction on blood pressure was evaluated. A semi-parametric restricted cubic spline regression with 4 knots was fitted, adjusting for age (years), hypertensive status (yes/no), and race (black/non-black), with each study weighted by the inverse of its variance. In the primary analysis of 107 randomized group comparisons, a likelihood ratio test comparing the model with a simple linear fit revealed no significant difference (p=0.58), while the first coefficient in the spline was strongly significant (p<0.001). This suggested a purely linear effect. The results were unchanged if all 169 randomized comparisons were included.

For the main meta-regression, a random effects meta-regression was used. This allows for possible heterogeneity in underlying effect sizes between studies, where this heterogeneity may not be explained by study covariates [52]. Trial i is taken to provide an estimate, y_i, of the blood pressure change in mm Hg, standardized to a sodium reduction of 100 mmol/day (2.3g/day sodium, 5.85g/day salt). Each trial also provides a standard error for this estimate, σ_i, which is assumed to be known. (This assumption is common in meta-analysis, though in practice the s.e. will have been estimated from the data in that study). The true effects, θ_i, are assumed to follow a normal distribution around a linear predictor:

$$y_i|\theta_i \sim \mathcal{N}(\theta_i, \sigma_i^2), \text{ where } \theta_i \sim \mathcal{N}(\mathbf{x}_i\beta, \tau^2).$$

τ^2 is the between-study variance, which must be estimated from the data. So,

$$y_i \sim \mathcal{N}(\mathbf{x}_i\beta, \sigma_i^2 + \tau^2)$$

or equivalently

$$y_i = \mathbf{x}_i\beta + u_i + \epsilon_i, \text{ where } u_i \sim \mathcal{N}(0, \tau^2) \text{ and } \epsilon_i \sim \mathcal{N}(0, \sigma_i^2).$$

The vector of covariates $\mathbf{x}_i$ consisted of an intercept, the mean age of subjects in each trial in years, centered at age 50, an indicator for whether the trial was conducted in normotensive or hypertensive subjects, and an indicator for whether the trial was conducted in black subjects. Each study was weighted by the inverse variance of its standardized blood pressure change. Significant effects were found for age, hypertensive status, and race, but not study duration. Coefficients estimated in a regression incorporating these first three covariates were used as inputs to this study. The results were unchanged if all 169 randomized comparisons were included.

4.1.6 Effect of blood pressure on cardiovascular diseases

Singh et al. conducted a pooled analysis of prospective cohort studies to estimate the effect of blood pressure on cardiovascular diseases [53]. The authors combined results from the Prospective Studies Collaborative (61 cohorts, 1 million participants, 120,000 deaths) and the Asia Pacific Cohort Studies Collaborative (37 cohorts, 425,000 participants, 6,900 deaths) [54, 55]. Observational studies were chosen in preference to randomized controlled trials because they estimate the effect of risk factor levels on disease outcome rather than the effect of a particular pharmacological intervention, which may act through other pathways in addition to risk factor reduction; they estimate long-term effects (over years or decades); and they have larger sample sizes and can provide more precise relative risks for more granular age groups and disease categories. The trade-offs of this approach are considered in more detail in the limitations section.

The authors of the Prospective Studies Collaborative study corrected for the attenuation bias caused by blood pressure measurement error. They accounted for time between baseline risk factor measurements and occurrence of events by estimating the "usual" (i.e., long-term average) levels of blood pressure for each age group [56]. These corrections were achieved by estimating two quadratic regressions of mean remeasurements on baseline measurements, one for the 162,000 individuals with a systolic blood pressure (SBP) remeasurement at 1-5 years (average 3.4 years) after the baseline measurement, and the other for the 124,000 individuals with an SBP remeasurement at 6-15 years (average 8.3 years) after baseline. A time-weighted average of the predicted values from the two model fits was then used to correct individual measurements. Justification for the choice of model, model fit, and regression diagnostics were not reported [54]. Singh et al. re-analyzed the results of the Asia Pacific Cohort Studies Collaborative by taking the time-dependent age-specific regression dilution ratios derived from Prospective Studies Collaborative and applying them to the Asia Pacific Cohort Studies Collaborative data.

The authors of the Prospective Studies Collaborative meta-analysis report estimating cause-specific death rates separately for five decades of age at risk (40-49, 50-59, ..., 80-89 years), and each of these for ten categories of baseline blood pressure (<115, 115-124, ..., ≥195 mm Hg). Singh et al. estimated relative risks (RRs), against a theoretical-minimum-risk exposure distribution of 115 mg Hg, for a different set of age groups (25-34, 35-44,

45-54, 55-64, 65-74, 75-84 and 85+ years). These age groups were the ones used in this study. To do this, they interpolated and extrapolated using a linear relationship between ln(RR) and the midpoint of age in each age category. They report that this model had the best fit among a range of models including linear, quadratic, and cubic relationships between age and RR or ln(RR). Again, possible limitations of this procedure are discussed in the limitations section.

Singh et al. estimated overall uncertainty using a simulation approach: for each of 1,000 iterations, they drew a ln(RR) for each age group in one of the original meta-analyses from a normal distribution characterized by the reported ln(RR) and its standard error. They then fitted a linear model to this set of age-specific ln(RR)s, and used the fitted model to estimate a single ln(RR) for each of the age groups used in their final analysis. The distributions of the 1,000 estimated ln(RR)s were used to obtain standard errors for each age group. Age-specific RRs obtained in this way from the different sources were then pooled using a random effects model.

4.1.7 Intervention effects on sodium consumption

The diversity of sodium reduction initiatives in place around the world is surveyed in the previous chapter. While it would be desirable to model the effect of different forms of intervention in different countries, sufficient data do not exist for this to be possible. Instead, this study models a single combined 10-year intervention, along the lines of the UK's salt reduction initiative, consisting of legislation (or voluntary regulation) that reduces the salt content in processed foods, together with a public health campaign designed to encourage consumers to make choices that will reduce their dietary salt consumption. Intervention efficacy is modeled separately for 10% and 30% proportional reductions, and 0.5g and 1.5g absolute reductions, in mean daily salt consumption for each country-age-sex group. In each case, the intervention is assumed to scale up linearly over the implementation period, having 10% of the full effect in the first year, 20% in the second, and so on, reaching full efficacy in the final year.

4.1.8 Intervention costs

Intervention costs were based on data from the WHO NCD Costing Tool, and were not modeled to vary with the differences in intervention efficacy described above [57]. The Costing Tool uses the standard 'ingredients approach' developed by the WHO CHOICE (CHOosing Interventions that are Cost-Effective) project: the units of physical inputs required are assessed for each country and multiplied by the unit price for each input in that country.

The authors of the tool report that quantities were estimated using data obtained from a review of relevant publications and supplemented by primary data from WHO program staff in several countries. In particular, physical inputs were determined according to four stages of policy development: planning (year 1), development (year 2), partial implementation (years 3-5), and full implementation (year 6 onwards). For each stage, quantities were estimated for four categories of resource use: human resources, training, meetings, and mass media. In the planning phase, resource needs were estimated for the preparation of an evidence base and

	Administrative level (Standardised population, in millions)	Planning (year 1) National (50m)	Planning (year 1) Province (5m)	Development (year 2) National (50m)	Development (year 2) Province (5m)	Partial implementation (years 3-5) National (50m)	Partial implementation (years 3-5) Province (5m)	Full implementation (years 6-10) National (50m)	Full implementation (years 6-10) Province (5m)
HUMAN RESOURCES (incl. consultants)	***Roles / responsibilities***	FTE*	FTE	FTE	FTE	FTE	FTE	FTE	FTE
Program management									
Director	*Oversight; Monitoring; Reporting*	0.125	0.0625	0.125	0.0625	0.125	0.0625	0.125	0.0625
Manager	*Oversight; Monitoring; Reporting*	0.25	0.125	0.25	0.125	0.25	0.125	0.25	0.125
Administrative officer	*Data collection; Monitoring*	0.5	0.25	0.5	0.25	0.5	0.25	0.5	0.25
Clerical officer	*Data collection; Monitoring*	1	0.5	1	0.5	1	0.5	1	0.5
Secretary	*Office support*	0.9	0.4	0.9	0.4	0.9	0.4	0.9	0.4
Accountant	*Financial data entry/analysis*	0.25	0.125	0.25	0.125	0.25	0.125	0.25	0.125
I.T. computing manager	*I.T. support*	0.125	0.0625	0.125	0.0625	0.125	0.0625	0.125	0.0625
I.T. computing officer	*I.T. support*	0.25	0.125	0.25	0.125	0.25	0.125	0.25	0.125
Cleaner	*General office maintenance*	0.25	0	0.25	0	0.25	0	0.25	0
Subtotal		3.6	1.7	3.6	1.7	3.6	1.7	3.6	1.7
Promotion / media / advocacy									
Public health specialist	*Advocacy; Dissemination*	0.25	0.125	0.25	0.25	0.25	0.125	0.25	0.125
Public health officer	*Admin / research support*	0.5	0.25	0.5	0.5	0.5	0.25	0.5	0.25
Health educator/trainer	*Advocacy; Dissemination*	0.5	0.25	0.5	0.5	0.5	0.25	0.5	0.25
Public Relations Manager		0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Public Relations Officer		0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Subtotal		2.0	1.4	2.0	2.0	2.0	1.4	2.0	1.4
Law enforcement / inspection									
Superintendent	*Supervision of new (voluntary) code*			0.25	0.25	0.5	0.5	0.5	0.5
Enforcement / health safety officer	*Inspection*			1	1	2	**2**	2	**2**
Lawyer	*Development of new code*	1	0.5	1	0.25	0.25	0.125	0.25	0.125
Legal Officer	*Development of new code*	2	1	2	0.5	0.5	0.25	0.5	0.25
Transport manager	*Transport support*	0.2	0.1	0.3	0.1	0.2	0.1	0.2	0.1
Transport driver	*Transport support*	0.9	0.5	1.1	0.6	0.8	0.6	0.8	0.6
Subtotal		4.2	2.2	5.6	2.7	4.3	3.6	4.3	3.6
National-level technical assistance	*(local planning / implementation)*								
International consultant (No. of 5-day trips p.a.)		2		2		1		1	
TOTAL HUMAN RESOURCES		9.8	5.2	11.2	6.4	9.9	6.7	9.9	6.7

* Full-time equivalent.

Table 4.1: Annual human resource needs at different stages of policy formulation / implementation (standardized population)

	Administrative level (Standardised population, in millions)	Planning (year 1) National (50m)	Planning (year 1) Province (5m)	Development (year 2) National (50m)	Development (year 2) Province (5m)	Partial implementation (years 3-5) National (50m)	Partial implementation (years 3-5) Province (5m)	Full implementation (years 6-10) National (50m)	Full implementation (years 6-10) Province (5m)
TRAINING	***Purpose***								
(for programme staff)									
Training course / workshop (1)	*(salt and public health)*								
Frequency of meetings (expressed per year)		1	1	1	1	1	1	1	1
Number of meetings needed (within the year)		2	1	2	2	1	2	1	2
Length of meetings (days)		2	2	2	2	2	2	2	2
National experts in attendance (No., per diem, travel cost)		2	1	2	1	2	1	4	1
Local experts in attendance (No., per diem, travel cost)		20	15	20	15	20	15	20	15
Local support staff									
Meeting room (rental price per sq. metre; No. of sq m)									
Training course / workshop (2)	*(food inspection)*								
Frequency of meetings (expressed per year)					1		1		1
Number of meetings needed (within the year)					2		1		1
Length of meetings (days)					3		2		2
National experts in attendance (No., per diem, travel cost)					2		1		1
Local experts in attendance (No., per diem, travel cost)					15		15		15
Local support staff									
Meeting room (rental price per sq. metre; No. of sq m)									
MEETINGS	***Purpose***								
(involving external agencies)									
Meetings / workshops (1)	*(planning, + M&E)*								
Frequency of meetings (expressed per year)		1	1	1	1	1	1	1	0.5
Number of meetings needed (within the year)		3	1	2	1	2	1	2	1
Length of meetings (days)		3	3	3	3	2	2	2	2
National experts in attendance (No., per diem, travel cost)		4	3	4	2	4	1	4	1
Local experts in attendance (No., per diem, travel cost)		15	10	15	10	15	10	15	10
Local support staff									
Meeting room (rental price per sq. metre; No. of sq m)									
MASS MEDIA									
Television time (minutes)				150		150		150	
Radio time (minutes)				200	150	150	100	150	100
Newspapers (100 word insert)				60	30	60	30	60	30
Wall posters									
Flyers / leaflets					20000		15000		15000

Table 4.2: Annual other resource needs at different stages of policy formulation / implementation (standardized population)

launch of a public consultation. In the development phase, it was assumed that legislation and regulations would be drafted, enforcement plans and training programs designed, and a media strategy developed. In year 3, it was assumed that the public information campaign would be launched, legislation passed, and inspections initiated. From then on, maintenance of regular inspections, enforcement, and media advocacy was assumed.

Within each category of resource, estimates were made for needs at the central and provincial level. A standardized country of 50 million people was assumed, split into provinces of 5 million each. The resource needs estimated for this population are given in tables 4.1 and 4.2. These standardized estimates were then adjusted to reflect the actual population size and administrative composition of each country, though national-level quantities were not adjusted. The cost of training and meetings was based on the frequency of meetings and workshops each year, their duration, and the number of national and sub-national participants and support staff. For mass media, quantities of TV and radio commercials, newspaper advertisements, wall posters and information leaflets were estimated. The cost of capital items (such as office construction) were not included.

Once quantities were scaled according to the population size and administrative composition of a given country, they were multiplied by country-specific unit costs. These were taken from the WHO-CHOICE database, which contains estimates of salaries, per diem allowances (for training and meetings), media costs, and consumable item prices for each country. These in turn were predicted using linear regression models fitted to a multinational dataset, with GDP per capita, region, and education levels among others used as explanatory variables. Estimates of uncertainty were made neither for prices nor quantities. As such, this study presents the sensitivity of its final results to variations in cost of between 0.25 and 5 times the baseline estimates.

Costs in this study are reported in international dollars, in line with the global cost-effectiveness literature, to enable meaningful comparisons between countries. An international dollar is a hypothetical currency obtained by dividing local currency units by that country's US purchasing power parity (PPP) exchange rate. As such, an international dollar in any given country will purchase the same amounts of goods and services in that country as a US dollar would in the USA. The WHO NCD Costing Tool reports costs in local currency units for 2008. These were converted to 2012 international dollars by first accounting for local inflation, using World Bank GDP deflator figures, then using 2012 PPP exchange rates from the IMF World Economic Outlook Database [58, 59].

4.2 Model

This section describes how the data inputs described above are combined to produce estimates of the cost-effectiveness of different interventions for each country in the world. An outline of the method is as follows. First, an intervention is selected. The intervention is assumed to shift mean salt consumption in every country-age-sex cohort by some fixed amount, either in absolute terms or proportionately. Next, the absolute number of DALYs that would be attributable to sodium in the intervention scenario is calculated by (i) estimating the relative risk of cardiovascular disease death for the blood pressure distribution under the intervention

compared with the blood pressure distribution as it would be under the theoretical-minimum-risk exposure distribution of sodium intake; (ii) using these relative risks to estimate the population attributable fraction (PAF) of cardiovascular disease deaths attributable to sodium under the intervention; and (iii) multiplying the PAF by the absolute number of DALYs attributable to cardiovascular disease in 2010. (Application of the population attributable fraction of disease deaths to DALYs is discussed in section 5.9.) The same procedure is used to calculate the absolute number of DALYs attributable to sodium with no intervention. Finally, the difference between these two numbers is taken to be the effect of the intervention in a given year. The cost-effectiveness of the intervention is calculated by dividing the total cost of the intervention by its total effect over the intervention period, with both cost and effect discounted at 3% per year, and effect scaled up as described in section 4.1.7.

4.2.1 Notation

The annual effect of a given intervention on cardiovascular disease mortality is calculated individually for each country-age-sex cohort. Specify a cohort by $i \in Country$, $j \in Age$, $k \in Sex$, those sets being

$$\begin{aligned} Country &= \{\text{Afghanistan}, \ldots, \text{Zimbabwe}\}, \\ Age &= \{30, 40, 50, 60, 70, 77.5, 85.34\}, \\ Sex &= \{\text{Male}, \text{Female}\}, \end{aligned}$$

with the given ages being the midpoints of the categories {25-34,35-44,45-54,55-64,65-74,75-79,80+}.

For each cohort, the effect on mortality is calculated individually for each of eleven separate cardiovascular disease conditions:

$$\begin{aligned} H = \{&\text{ischemic heart disease} \\ &\text{ischemic stroke} \\ &\text{hemorrhagic and other non-ischemic stroke} \\ &\text{hypertensive heart disease} \\ &\text{aortic aneurysm} \\ &\text{rheumatic heart disease} \\ &\text{endocarditis} \\ &\text{atrial fibrillation and flutter} \\ &\text{peripheral vascular disease} \\ &\text{myocarditis and cardiomyopathy} \\ &\text{other cardiovascular and circulatory diseases}\} \end{aligned}$$

With each country-age-sex cohort is associated a vector of covariates, consisting of mean sodium consumption per day (denoted SDM_{ijk} below) together with its standard deviation (SDM_SE_{ijk}), mean systolic blood pressure (SBP_{ijk}), an indicator for whether the country is high-income ($income_i$), an indicator for whether the country is African ($Africa_i$), and mean, upper and lower confidence intervals for mortality (that is, absolute number of deaths in 2010 in the country/age/sex triad) for each $h \in H$.

In what follows, some letters are used to signify individual draws from distributions, while others are used to denote the distributions themselves. The latter will be distinguished by a tilde, e.g., $\widetilde{X}$.

4.2.2 Estimation of sodium-blood pressure effect

Estimation of the linear effect of changes in sodium intake on systolic blood pressure was described in section 4.1.5. The linear effect, ξ_{ijk}, is modified by age, race, and hypertension. To take account of the uncertainty in the estimates of each modifying coefficient, values for each are drawn from a normal distribution characterized by a mean of the coefficient and a standard deviation of the coefficient's standard error:

$$\begin{aligned}
\beta_0 &\sim \mathcal{N}(B_0, SE_0^2) \\
\beta_1 &\sim \mathcal{N}(B_1, SE_1^2) \\
\beta_2 &\sim \mathcal{N}(B_2, SE_2^2) \\
\beta_3 &\sim \mathcal{N}(B_3, SE_3^2)
\end{aligned}$$

The coefficient on change in sodium intake is then:

$$\xi_{ijk} = (\beta_0 + \beta_1 age_j + \beta_2 Africa_i + \beta_3 hypertension_{ijk}) \cdot \mathbb{1}_{SBP_{ijk}>115}$$

The variable *hypertension*, representing the proportion of individuals in a cohort with hypertension (defined here as systolic blood pressure greater than 140 mm Hg), is estimated using a logit model,

$$hypertension_{ijk} = \frac{e^{\alpha_0+\alpha_1 SBP_{ijk}+\alpha_2 income_i+\alpha_3 age_j+\alpha_4 gender_k}}{1+e^{\alpha_0+\alpha_1 SBP_{ijk}+\alpha_2 income_i+\alpha_3 age_j+\alpha_4 gender_k}}$$

with coefficients taken from Danaei et al. [43] and not subject to uncertainty.

The indicator function is used to account for the fact that there is no evidence for further benefits below the systolic blood pressure theoretical-minimum-risk exposure of 115 mg Hg [45].

4.2.3 Changes in blood pressure resulting from sodium exposure

The theoretical-minimum-risk exposure distribution of daily sodium intake, y, is defined as 2.3g sodium (5.75g salt) and was obtained from observed consumption levels associated with lower disease risk in prospective cohorts. Its derivation is discussed in more detail in section 5.7.

The cohort's sodium exposure distribution under the intervention, $\widetilde{X}_{ijk}$, is estimated by first drawing an estimate for the mean exposure with no intervention,

$$v_{ijk} \sim \mathcal{N}(SDM_{ijk}, SDM\_SE^2_{ijk}),$$

adjusting the draw for the intervention effect (e.g., $\mu_{ijk} = 0.9v_{ijk}$ for a 10% reduction, or $\mu_{ijk} = v_{ijk} - 0.5$ for an absolute reduction of 0.5g), then defining a normal distribution characterized by a mean of the intervention-adjusted draw, μ_{ijk}, and a standard deviation predicted using coefficients from a mean-to-SD regression based on raw data [10]. If the cohort's mean systolic blood pressure is less than its theoretical-minimum-risk exposure of 115 mg Hg, the sodium exposure distribution is specified to be *its* theoretical-minimum-risk exposure distribution, y, to account for the fact that there is no evidence for further benefits below this threshold [45]:

$$\widetilde{X}_{ijk} \sim \mathcal{N}(\mu_{ijk}, (\gamma_0 + \gamma_1\mu_{ijk})^2)$$

Recall that ξ_{ijk} is the linear effect of sodium on BP. The increase in blood pressure caused by the increase in sodium intake to some level, x, of the actual distribution $\widetilde{X}_{ijk}$ from the level of the theoretical-minimum-risk exposure distribution associated with that level is then:

$$\widetilde{\Delta}_{ijk}(x) = \xi_{ijk}(x - y)$$

Note that if the cohort's mean systolic blood pressure is less than 115 mg, ξ_{ijk} will be set equal to 0 and $\widetilde{\Delta}_{ijk}$ will be flat.

4.2.4 Changes in cardiovascular disease risk resulting from changes in blood pressure

With each age group and disease outcome is associated a log relative risk coefficient ($logRR_{jh}$), together with its standard error ($logRR\_SE_{jh}$). The logRR coefficient represents the log risk effect of a 10 mm Hg change in systolic blood pressure. For example, if the logRR coefficient were 0.3, then an increase in blood pressure of 20 mm Hg would result in a log relative risk of $2 \cdot 0.3 = 0.6$, or a relative risk of $e^{0.6} = 1.82$ compared to no increase.

Thus, the age- and sex-specific logRR of $h \in H$ is drawn from a log-normal distribution:

$$LRR_{jh} \sim \mathcal{LN}(logRR_{jh}, logRR\_SE_{jh})$$

The relative risk associated with some level x of the cohort exposure distribution $\widetilde{X}_{ijk}$ compared with the

theoretical-minimum-risk exposure distribution is then:

$$RR_{ijkh}(x) = \begin{cases} \exp((\widetilde{\Delta}_{ijk}(x)/10) \cdot LRR_{jh}) & \text{if } \widetilde{\Delta}_{ijk}(x) \geq 0 \\ 1 & \text{if } \widetilde{\Delta}_{ijk}(x) < 0 \end{cases}$$

Note that the relative risk is set to 1 for any part of the actual cohort sodium exposure that is less than the theoretical-minimum-risk exposure.

4.2.5 Population attributable fraction

The population attributable fraction is then calculated for each $h \in H$ according to the following formula [60]:

$$PAF_{hijk} = \frac{\int_{x \in \widetilde{X}_{ijk}} P_{ijk}(x)(RR_{ijkh}(x) - 1)}{1 + \int_{x \in \widetilde{X}_{ijk}} P_{ijk}(x)(RR_{ijkh}(x) - 1)}$$

where the integrals are over the range of $\widetilde{X}_{ijk}$ and $P_{ijk}(x)$ is the pdf of $\widetilde{X}_{ijk}$.

The number of DALYs in country i attributable to excess sodium consumption under the intervention is calculated by multiplying the PAF by the absolute number of DALYs ($DALYs_{hijk}$) for each disease in that country-age-sex cohort, summing over all diseases, and finally summing over all age-sex cohorts:

$$D_i = \sum_j \sum_k \left[\sum_h (PAF_{hijk} \cdot DALYs_{hijk}) \right]$$

4.2.6 Intervention cost-effectiveness

The intervention effect for each country is simply the difference between D_i and the absolute number of deaths attributable to sodium with no intervention, calculated by setting $\mu_{ijk} = v_{ijk}$ above.

Uncertainty was quantified using Monte Carlo simulation. For each of 1,000 simulations, a draw was made from the distribution of sodium consumption for each country-age-sex cohort, from the distribution of the components of the sodium-blood pressure effect, and from the distribution of the effects of blood pressure on each disease outcome of interest. Each draw produced an estimate of intervention effect for each country, and the draws were combined to derive 95% uncertainty intervals.

The total number of lives saved over the course of the intervention was calculated by summing the annual effects, with the effect being 10% of the total in the first year, 20% in the second, and so on, and discounting at 3% per year. Finally, the intervention cost-effectiveness was calculated by dividing the total cost by the total effect, yielding the cost per DALY for each country, measured in international dollars.

4.3 Results and sensitivity analysis

Table 4.3 gives the results of an intervention to reduce population salt consumption by 10% around the world. For each of four income regions and nine geographic regions, the table shows the total population, average country mean sodium intake and average country mean systolic blood pressure, both weighted by country population size, similarly weighted averages of intervention cost per capita (over the full ten years of the intervention) and GDP per capita, both in international dollars, total DALYs averted per year at full intervention effectiveness for all cardiovascular diseases, coronary heart disease, stroke, and other cardiovascular diseases, and cost-effectiveness of the intervention in international dollars per DALY, weighted by country population size.

Worldwide, at full efficacy, the intervention would avert 5,654,885 DALYs attributable to cardiovascular disease per year (95% UI: 3,729,899, 7,473,522). Of these, 2,366,418 (95% UI: 1,534,283, 3,162,064), or 41.8% of the total, would be attributable to coronary heart disease, 2,278,920 (95% UI: 1,528,584, 2,986,972), or 40.3% of the total, would be attributable to stroke, and 1,009,546 (95% UI: 666,948, 1,332,073), or 17.9% of the total, would be attributable to other cardiovascular diseases. Overall, this represents 1.92% of the total burden of cardiovascular disease worldwide. Per 1,000 people, 1.48 DALYs would be averted per year worldwide (95% UI: 0.98, 1.96); the greatest effect would be in upper-middle income countries (1.73 DALYs per 1,000 people per year, 95% UI: 1.14, 2.27), and the lowest in high income countries (1.01, 95% UI: 0.65, 1.36). The geographic region with by far the greatest effect would be Central Asia/Eastern and Central Europe, at 3.42 DALYs per 1,000 people per year (95% UI: 2.23, 4.52); the region with the least effect would be Australia and New Zealand, at 0.63 DALYs per 1,000 people per year (95% UI: 0.40, 0.86). The former region has the second highest mean sodium intake, at 4.3g/day (95% UI: 3.6, 5.0), and the highest mean systolic blood pressure, at 133 mm Hg (95% UI: 126, 140); the latter has the second lowest mean sodium intake, at 3.4g/day (95% UI: 3.2, 3.7), and the second lowest mean systolic blood pressure, at 124 mm Hg (95% UI: 117, 131).

Intervention cost per capita generally decreases with country income, though not uniformly. The average cost per capita in high income countries (I$2.02) is almost double that in upper-middle income countries (I$1.06); the average cost in lower-middle income countries (I$0.72) is only a little above that in low income countries (I$0.62). Geographically, the cost is highest in Australia and New Zealand (I$2.63), followed closely by Central Asia/Eastern and Central Europe (I$2.59). South Asia (I$0.74), Sub-Saharan Africa (I$0.82), East and Southeast Asia (I$0.82), and Latin America and the Caribbean (I$0.87) all manage costs of less than a dollar per person.

The worldwide weighted average cost per DALY of the 10-year intervention would be 207 international dollars (95% UI: 151, 331). As would be expected given the variation in effects and costs just described, this masks substantial variation by income and region. Lower-middle income countries get the best cost-effectiveness ratio at I$114/DALY (95% UI: 83, 182), followed by upper-middle income countries at I$146/DALY (95% UI: 109, 228). Low income countries face almost double this cost per DALY, at I$236 (95% UI: 159, 424); high-income countries are much higher again, at I$465 (95% UI: 342, 736). Australia and New Zealand, experiencing the

	Population characteristics			Costs (10-year total)		DALYs saved per year				10-year intervention
	Population, millions	Sodium, g/day (95% UI)	SBP, mmHg (95% UI)	Intervention cost/capita, I$	GDP/capita, I$	All CVD (95% UI)	CHD* (95% UI)	Stroke (95% UI)	Other CVD (95% UI)	I$/DALY (95% UI)
	Total	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*	*Total*	*Total*	*Total*	*Total*	*Weighted avg.*
World †	3,818	4.0 (3.5, 4.4)	126 (121, 132)	1.11	13,553	5,654,884 (3,729,899, 7,473,522)	2,366,418 (1,534,283, 3,162,064)	2,278,920 (1,528,584, 2,986,972)	1,009,546 (666,948, 1,332,073)	207 (151, 331)
High income ‡	755	4.0 (3.6, 4.3)	127 (122, 133)	2.02	38,818	763,823 (492,808, 1,024,247)	384,875 (245,046, 518,790)	217,944 (144,509, 289,245)	161,004 (105,264, 216,223)	465 (342, 736)
Upper-middle income	1,528	4.4 (4.0, 4.8)	127 (122, 132)	1.06	11,001	2,640,450 (1,739,462, 3,467,570)	990,194 (640,850, 1,318,975)	1,236,105 (821,166, 1,607,548)	414,152 (277,187, 542,684)	146 (109, 228)
Lower-middle income	1,212	3.7 (3.2, 4.2)	124 (119, 130)	0.72	4,115	1,881,377 (1,234,067, 2,537,980)	875,047 (559,739, 1,178,209)	658,390 (434,301, 875,128)	347,939 (224,808, 466,035)	114 (83, 182)
Low income	323	3.1 (2.3, 3.8)	126 (118, 135)	0.62	1,456	369,234 (245,900, 496,256)	116,302 (78,086, 156,642)	166,481 (112,369, 222,638)	86,451 (56,522, 116,923)	236 (159, 424)
Australia and New Zealand	17	3.4 (3.2, 3.7)	124 (117, 131)	2.63	40,181	10,747 (6,843, 14,568)	6,380 (3,959, 8,751)	2,376 (1,500, 3,213)	1,991 (1,271, 2,692)	922 (680, 1,475)
Canada and U.S.	226	3.6 (3.4, 3.8)	123 (118, 127)	1.67	48,940	230,641 (146,315, 314,482)	132,395 (84,046, 183,531)	46,297 (30,216, 62,602)	51,949 (33,810, 69,542)	362 (265, 567)
Central Asia/ Eastern and Central Europe	273	4.3 (3.6, 5.0)	133 (126, 140)	2.59	14,833	933,646 (607,853, 1,233,348)	523,635 (337,944, 697,005)	304,966 (201,973, 398,907)	105,044 (67,945, 139,124)	206 (153, 319)
East and Southeast Asia	1,354	4.6 (4.2, 5.1)	126 (121, 130)	0.82	10,777	2,134,741 (1,408,243, 2,792,004)	613,648 (402,560, 816,856)	1,177,124 (776,416, 1,532,263)	343,969 (228,482, 452,668)	120 (91, 184)
Latin America and Caribbean	316	3.5 (3.1, 3.9)	126 (120, 133)	0.87	12,505	311,463 (202,025, 415,149)	133,769 (86,151, 179,049)	106,195 (69,067, 142,033)	71,499 (46,012, 95,924)	239 (173, 380)
North Africa and Middle East	225	3.9 (3.2, 4.7)	125 (118, 131)	1.23	12,436	359,124 (229,293, 486,583)	167,361 (106,800, 227,420)	110,465 (71,036, 149,472)	81,297 (51,931, 109,427)	286 (204, 475)
South Asia	786	3.7 (3.4, 4.1)	123 (117, 128)	0.74	3,551	1,105,812 (708,448, 1,489,736)	564,919 (353,267, 774,200)	323,019 (210,581, 431,170)	217,874 (137,759, 295,293)	120 (88, 188)
Sub-Saharan Africa	320	2.5 (2.0, 3.0)	130 (123, 137)	0.82	2,769	294,994 (175,955, 412,589)	83,553 (49,906, 117,749)	138,479 (83,423, 192,882)	72,962 (42,827, 102,902)	290 (194, 524)
Western Europe	301	3.8 (3.5, 4.2)	130 (124, 136)	1.96	35,676	273,716 (174,623, 364,970)	140,757 (88,451, 189,142)	69,999 (45,408, 93,284)	62,960 (40,833, 84,636)	490 (361, 772)

* CHD is coronary heart disease; stroke is ischemic stroke and hemorrhagic and other non-ischemic stroke; other CVD is aortic aneurysm, atrial fibrillation and flutter, cardiomyopathy and myocarditis, endocarditis, hypertensive heart disease, peripheral vascular disease, rheumatic heart disease, and other cardiovascular and circulatory diseases.

† In 2010 globally, the total burden of CVD was 295,035,800 DALYs, of which CHD accounted for 129,819,900 DALYs, stroke 102,232,300 DALYs, and other CVD 62,983,600 DALYs. There were 14,669,000 total CVD deaths, of which 6,963,000 were CHD deaths, 5,798,000 stroke deaths, and 1,909,000 other CVD deaths. The numbers of deaths in each subtype may not exactly sum to the total CVD deaths due to rounding.

‡ Income categorizations based on the World Bank classification system (http://data.worldbank.org/about/country-classifications/country-and-lending-groups).

Table 4.3: Global cost-effectiveness of an intervention to reduction population sodium consumption by 10%

highest costs and smallest effects, face the worst cost-effectiveness ratio at I$922/DALY (95% UI: 680, 1,475). The South Asia and East and Southeast Asia regions tie for the best cost-effectiveness ratio of I$120/DALY (95% UI: 88, 188; 91, 184); the high efficacy of the intervention in Central Asia/Eastern and Central Europe makes up for its high projected cost, generating the next best cost-effectiveness ratio of I$206/DALY (95% UI: 153, 319).

Considering individual countries paints a more nuanced picture. The efficacy of the intervention in terms of DALYs averted per 1,000 people is highest in Kazakhstan (23.2, 95% UI: 15.7, 29.9), Georgia (21.7, 95% UI: 14.5, 28.2), Belarus (19.8, 95% UI: 12.7, 26.7), Mongolia (19.1, 95% UI: 12.5, 25.1), Ukraine (18.8, 95% UI: 12.0, 25.3), and Russia (18.5, 95% UI: 11.9, 24.8), and lowest in Jamaica (1.44, 95% UI: 0.87, 2.07), Qatar (1.34, 95% UI: 0.77, 1.90), Rwanda (1.05, 95% UI: 0.47, 1.83), and Kenya (0.36, 95% UI: 0.20, 0.57). The intervention has 64 times the effect in Kazakhstan as in Kenya, with first and third quartiles 3.6 and 7.9 respectively. The cost per capita is lowest in Moldova (I$0.15), Azerbaijan (I$0.16), Myanmar (I$0.31), and Vietnam (I$0.31). The first and third quartiles are I$0.80 and $3.78 respectively. Eleven countries have costs per capita between I$10 and I$20; eight have costs per capita between I$20 and I$40. The Seychelles faces a figure of I$41.12, and Andorra is an outlier at I$84.51. These high numbers are mostly driven by very small populations coupled with national-level program costs that do not vary by population size. Country-level cost-effectiveness ratios, displayed in figure 4-1, reflect these extremes: Moldova's is best, at I$9.89/DALY (95% UI: 7.36, 15.44), followed by Azerbaijan (I$12.82, 95% UI: 9.69, 20.20), Uzbekistan (I$25.85, 95% UI: 19.85, 38.47), and Myanmar (I$33.31, 95% UI: 25.17, 50.54); the worst are Iceland (I$10,849, 95% UI: 7,914, 17,093), Tonga (I$12,565, 95% UI: 8,587, 20,763), Qatar (I$14,277, 95% UI: 10,034, 24,737), and, predictably, Andorra (I$19,615, 95% UI: 14,468, 31,347). The first and third quartiles are I$150 and I$855 respectively.

It is useful to consider the affordability of interventions in addition to their cost alone. The WHO Commission on Macroeconomics and Health defines interventions that have a cost-effectiveness ratio of less than three times GDP per capita as cost effective, and those with a ratio of less than GDP per capita as very cost effective [61]. By this measure, the 10% intervention is very cost-effective for every country in the world, with the exception of Kenya (1.15xGDP), the Marshall Islands (1.47x), and Tonga (1.68x), for which it is cost-effective. More than 95% of the world's population live in countries where the intervention has a cost-effectiveness ratio of less than 10% of GDP per capita: that is, where it is extremely cost effective. This includes all the world's 20 most populous countries, with the exception of Ethiopia, as shown in figure 4-2. Figure 4-3 displays GDP ratios for all countries.

As well as a 10% intervention, this study also considered the cost-effectiveness of interventions to reduce population salt consumption by 30%, 0.5g, and 1.5g. It estimated these effects given a theoretical-minimum-risk exposure distribution (TMRD) of 2.3g/day sodium, and also for a TMRD of 1g/day. Table 4.4 shows how the cost-effectiveness ratios change for each income and geographic region. In all cases, the 0.5g reduction has an effect between that of 10% and 30%, and 1.5g an effect greater than 30%. Worldwide, with a TMRD of 2.3g/day, the weighted average of country cost-effectiveness ratios for a 10% intervention would be I$207/DALY (95% UI: 151, 331), for a 30% intervention I$74 (95% UI: 53, 118), for a 0.5g intervention I$162 (95% UI: 118, 254), and for a

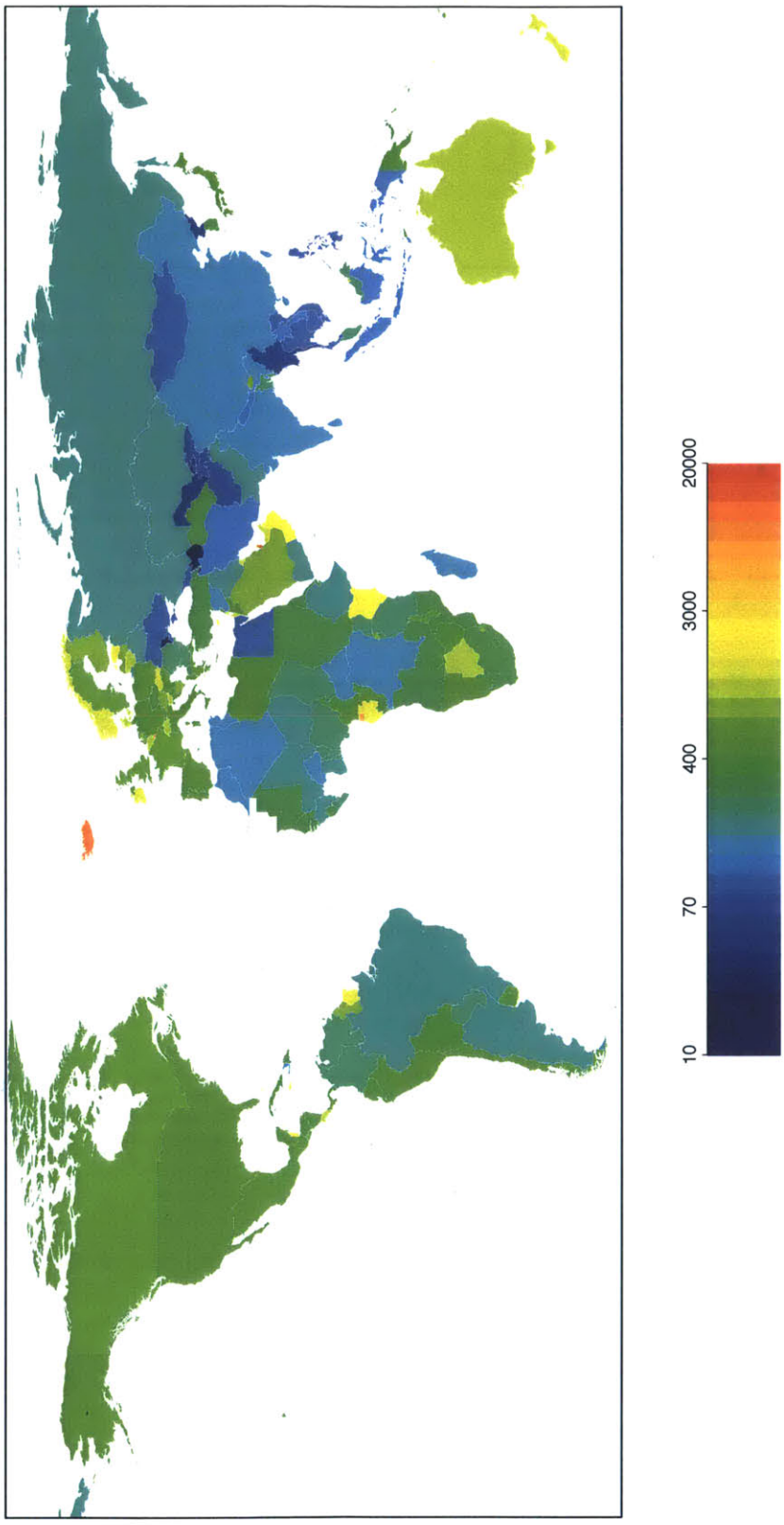

Figure 4-1: Cost-effectiveness of 10% reduction intervention: international dollars per DALY

			Cost-effectiveness (I$/DALY)							
			TMRD = 2.3				TMRD = 1			
	Intervention cost/capita, I$	GDP/capita, I$	10%	30%	0.5g	1.5g	10%	30%	0.5g	1.5g
	Weighted avg.	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*	*Weighted avg.*
World †	1.13	13,553	207 (151, 331)	74 (53, 118)	162 (118, 254)	62 (45, 103)	198 (151, 316)	65 (49, 98)	156 (117, 236)	51 (38, 81)
High income ‡	2.03	38,818	465 (342, 736)	159 (116, 246)	371 (271, 576)	130 (95, 210)	466 (354, 751)	153 (114, 233)	370 (276, 563)	120 (89, 192)
Upper-middle income	1.06	11,001	146 (109, 228)	50 (37, 78)	124 (92, 187)	44 (33, 71)	147 (114, 230)	48 (37, 71)	125 (96, 186)	41 (31, 63)
Lower-middle income	0.72	4,115	114 (83, 182)	40 (29, 63)	84 (61, 131)	32 (23, 53)	111 (85, 180)	37 (27, 56)	82 (61, 125)	27 (20, 43)
Low income	0.80	1,456	236 (159, 424)	112 (72, 208)	146 (97, 265)	101 (65, 194)	130 (96, 212)	43 (32, 69)	76 (56, 120)	28 (20, 47)
Australia and New Zealand	2.63	40,181	922 (680, 1,475)	322 (235, 496)	656 (477, 1,016)	244 (178, 388)	892 (672, 1,432)	294 (219, 450)	629 (464, 969)	206 (150, 331)
Canada and U.S.	1.67	48,940	362 (265, 567)	125 (92, 190)	271 (197, 417)	97 (71, 154)	361 (274, 579)	118 (89, 178)	267 (199, 401)	87 (64, 137)
Central Asia/ Eastern and Central Europe	2.59	14,833	206 (153, 319)	69 (51, 106)	173 (129, 266)	59 (44, 93)	210 (162, 330)	69 (52, 102)	177 (133, 265)	57 (43, 88)
East and Southeast Asia	0.82	10,777	120 (91, 184)	40 (30, 59)	116 (88, 172)	38 (29, 59)	127 (100, 195)	41 (32, 60)	123 (95, 179)	40 (30, 60)
Latin America and Caribbean	0.87	12,505	239 (173, 380)	87 (63, 138)	160 (116, 252)	68 (48, 113)	217 (164, 355)	72 (54, 110)	144 (107, 222)	48 (35, 77)
North Africa and Middle East	1.23	12,436	286 (204, 475)	97 (69, 160)	231 (166, 376)	81 (57, 139)	290 (217, 495)	95 (70, 152)	233 (171, 370)	76 (55, 126)
South Asia	0.74	3,551	120 (88, 188)	41 (30, 63)	92 (67, 142)	32 (23, 53)	121 (92, 196)	40 (30, 60)	92 (68, 142)	30 (22, 48)
Sub-Saharan Africa	1.01	2,769	290 (194, 524)	136 (88, 255)	167 (110, 305)	121 (78, 234)	161 (120, 259)	54 (39, 87)	80 (59, 127)	30 (21, 51)
Western Europe	2.00	35,676	490 (361, 772)	168 (123, 259)	379 (277, 588)	134 (98, 214)	485 (368, 780)	160 (120, 244)	374 (278, 569)	122 (90, 195)

‡ Income categorizations based on the World Bank classification system (http://data.worldbank.org/about/country-classifications/country-and-lending-groups).

Table 4.4: Cost-effectiveness sensitivity analysis

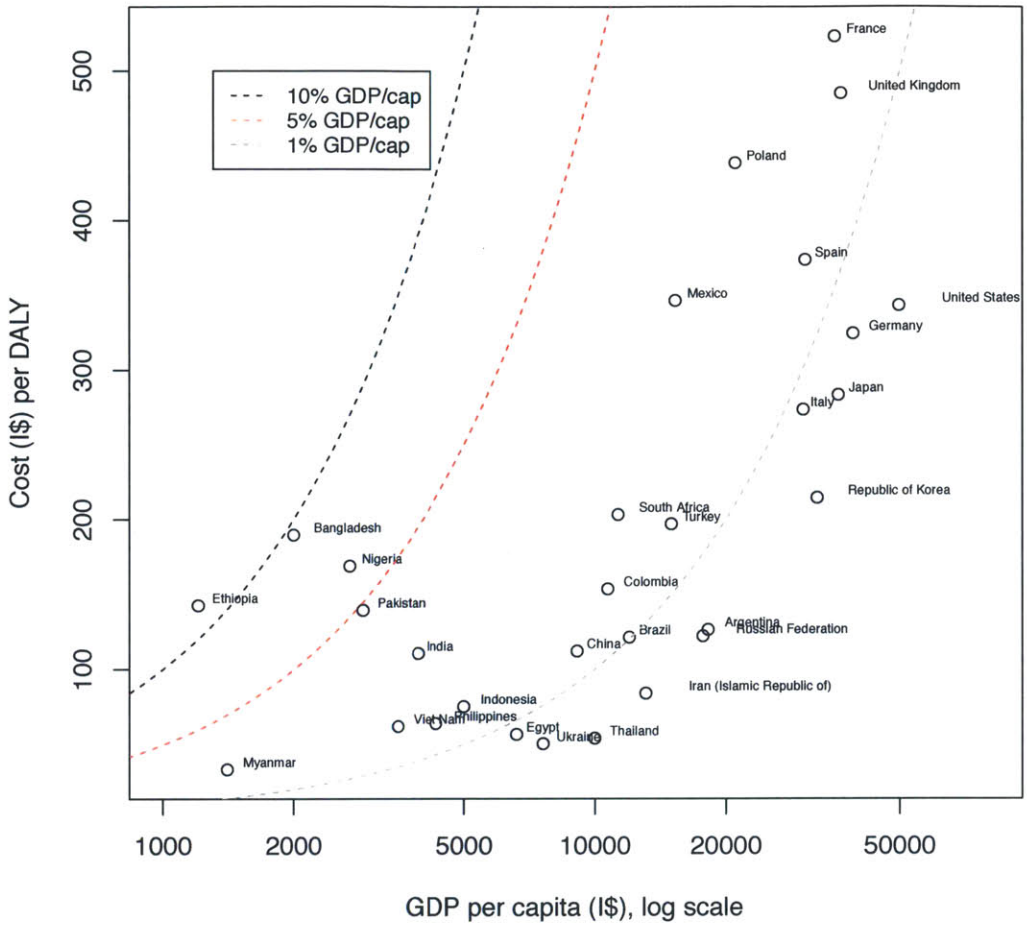

Figure 4-2: Affordability in 20 most populous countries (10% reduction)

1.5g intervention I$62 (95% UI: 45, 103). For the range of interventions considered, the effect is roughly linear: the 30% intervention has between 3.03 (East and Southeast Asia) and 2.57 (Sub-Saharan Africa) times the effect of the 10% intervention when the TMRD is 2.3g/day. The cost-effectiveness of the 10% and 30% interventions is displayed graphically in figure 4-4.

The effect of changing the TMRD from 2.3g/day to 1g/day varies according to the baseline sodium intake in each country. In countries with lower baseline sodium intake, a higher TMRD of sodium intake means there is less opportunity for the intervention to have an effect: intakes are already close to (or at) the theoretical-minimum-risk exposure distribution, so going below it has no effect on the risk of cardiovascular disease. By contrast, if the TMRD is lower, there is more room for the reduction to have an impact. This explains why total DALYs averted worldwide under the 30% intervention increases by 2% when the TMRD is switched from 2.3g/day to 1g/day, whereas it increases by 49% for the Sub-Saharan Africa region, which has very low baseline

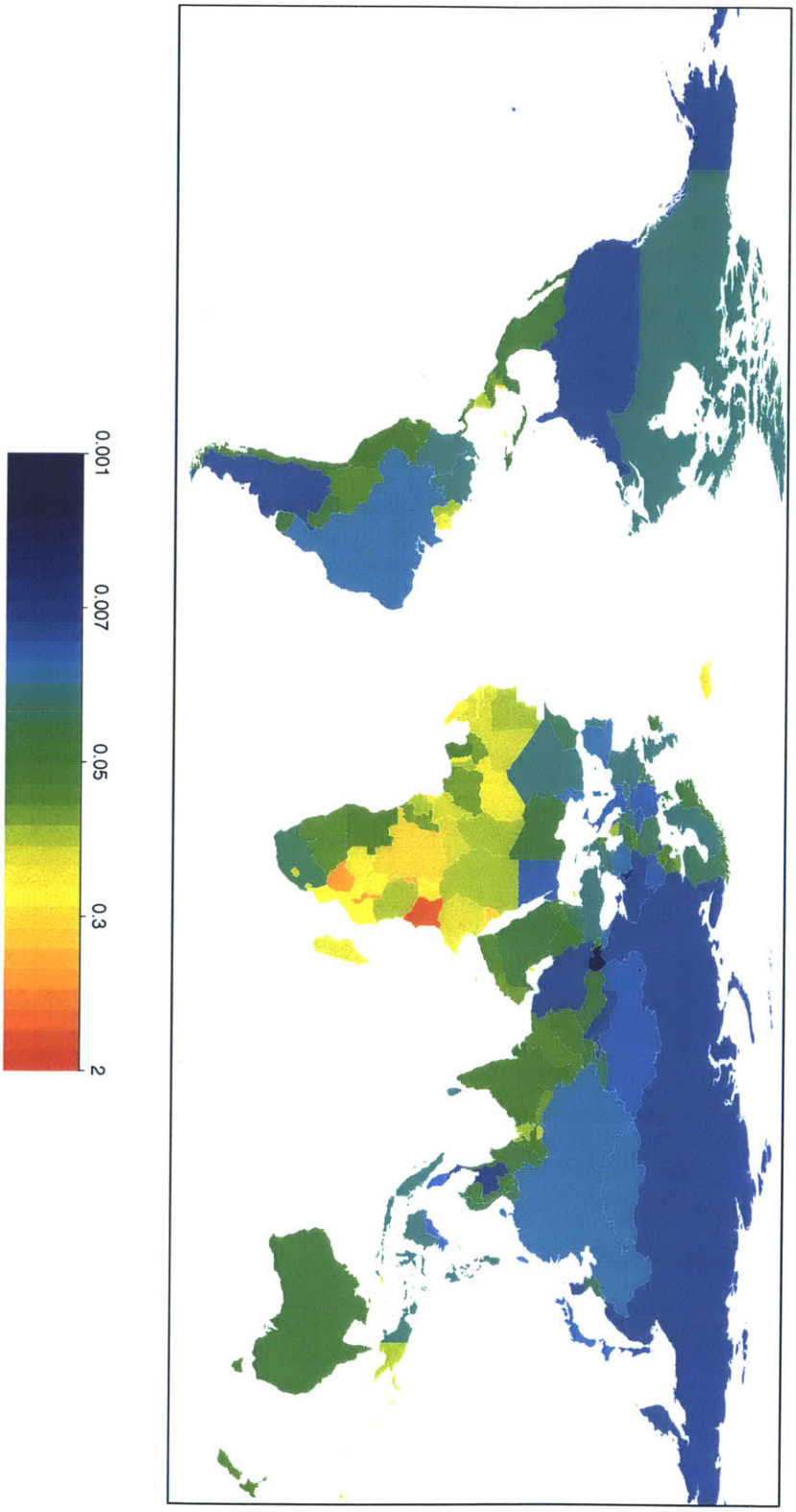

Figure 4-3: Cost-effectiveness of 10% reduction intervention: GDP/capita per DALY

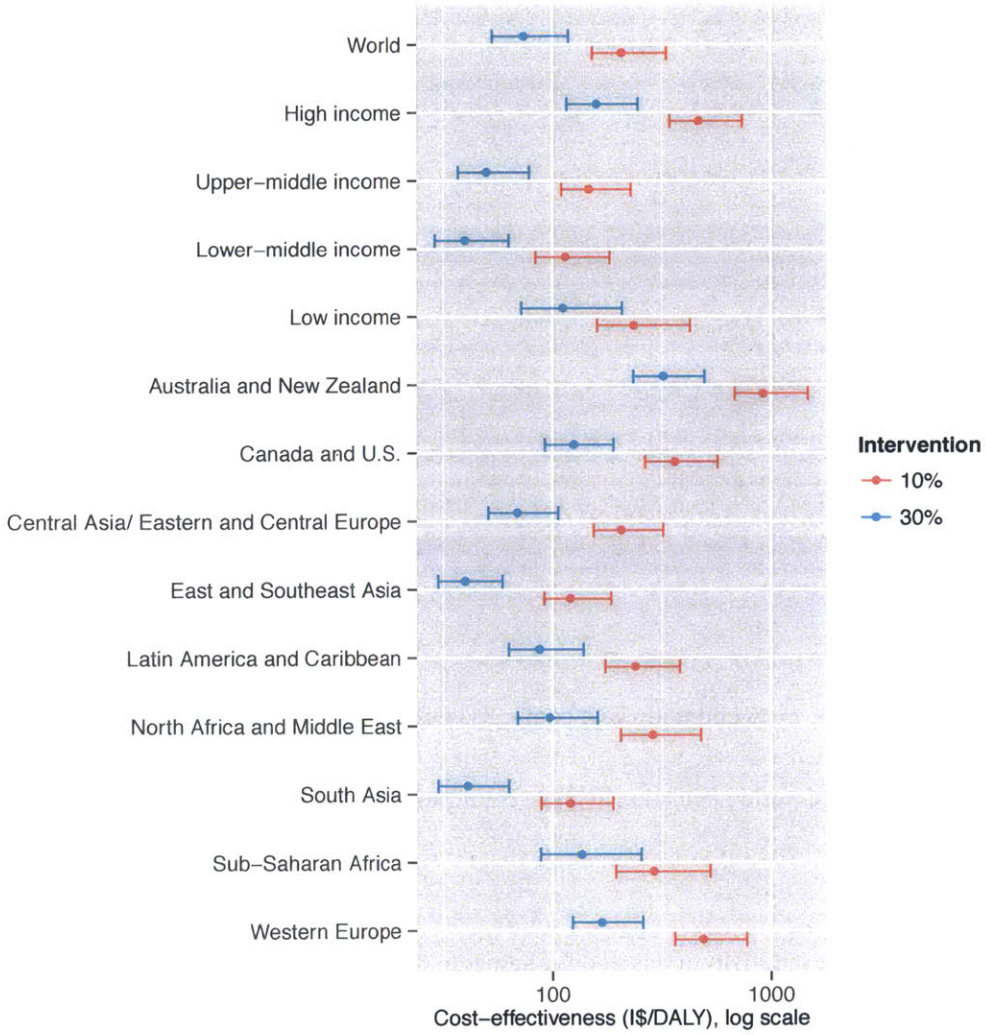

Figure 4-4: Cost-effectiveness of 10% and 30% interventions by income and geographic region

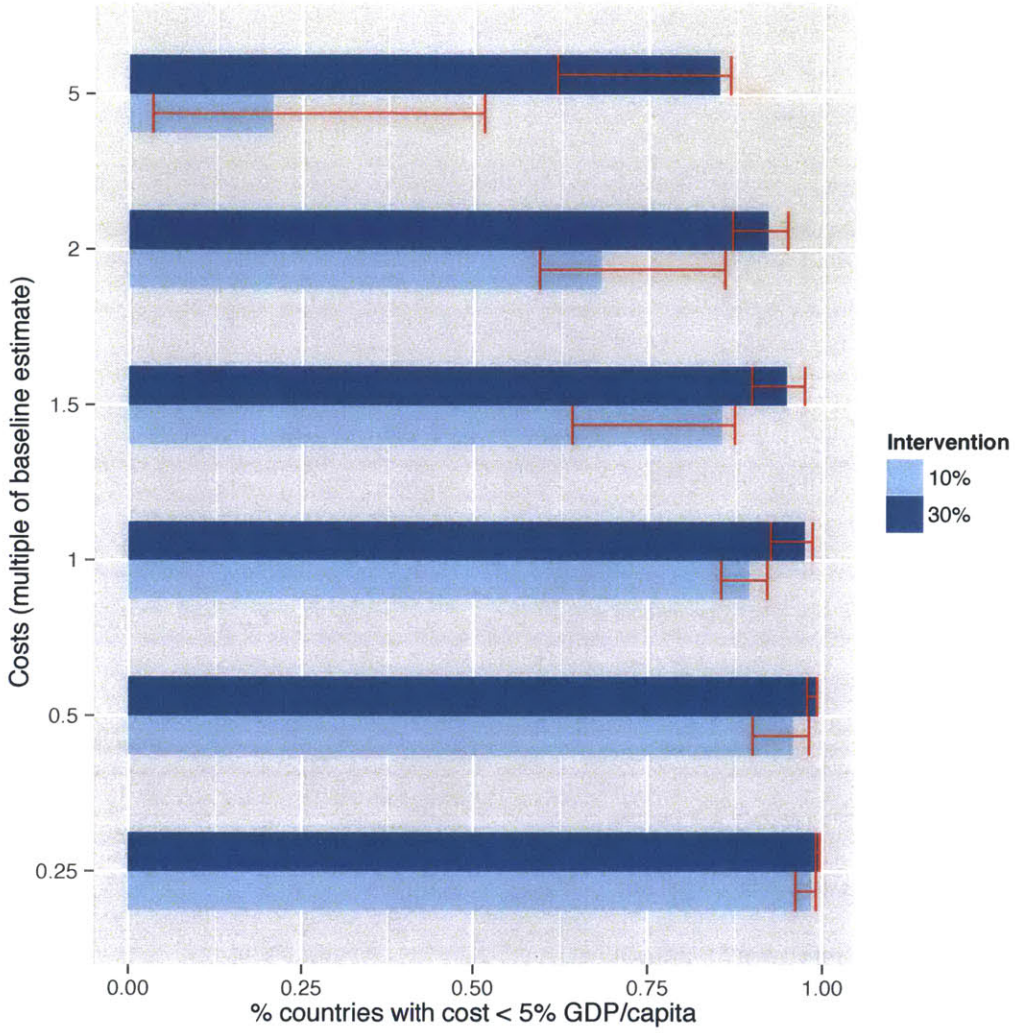

Figure 4-5: Percentage of world population living in countries with cost/DALY less than 5% of GDP per capita

sodium intake.

Figure 4-5 shows the sensitivity of this study's findings to variations in the cost estimates. The percentage of world population living in countries with I$/DALY less than 5% of GDP per capita is displayed for intervention costs of a quarter, half, one, one and a half, two, and five times the baseline estimate. For the 10% intervention, with TMRD 2.3g/day, if the intervention cost were five times baseline then 2% of the world population would live in countries with I$/DALY less than 5% of GDP per capita; 68% would if it were double, 85% would if it were one and a half times, 89% would at baseline, 96% would at half cost, and 98% would at quarter cost. For the 30% intervention, the corresponding figures are 85%, 92%, 95%, 97%, 99.1%, and 99.4%. These numbers should not obscure the fact that the interventions remain highly cost effective even at five times the baseline cost estimate. For the 10% intervention, at five times the baseline cost estimate, 96% of the world's population would live in countries with I$/DALY less than 50% of GDP per capita, and 98% in countries with I$/DALY

less than GDP per capita; for the 30% intervention, the figure is 99% in each case.

A discussion of the limitations of this analysis follows in the next section. At this point, it bears noting that even taking the lower estimate of the 95% uncertainty interval of intervention effectiveness for the 10% intervention for each country, together with an assumption of five times the baseline cost estimates, it is still the case that the intervention cost per DALY would be less than GDP per capita - that is, be very cost-effective - for 96% of the world's population. Moreover, intervention effects are likely to persist long after the intervention itself has ceased to operate, meaning this estimate is likely to be exceptionally conservative in the long run.

Chapter 5

Limitations

This study has attempted to estimate the effect on population cardiovascular disease of interventions to reduce dietary salt in every country in the world, as well as the cost of these interventions. Inputs to the study include estimates of current levels of dietary sodium intake worldwide, current blood pressure, and current cardiovascular mortality, the effect of sodium on blood pressure, the effect of blood pressure on cardiovascular disease, the theoretical-minimum-risk exposure distribution of sodium intake, the effect of interventions on population sodium intake, the program-level resources required to bring about this effect, and the cost of these resources. The limitations of each of these estimations will be discussed in turn. The validity of estimating overall population health effects only via blood pressure-mediated cardiovascular disease will also be assessed.

5.1 Measurement of current levels of dietary sodium intake

As described in the previous section, the mean and 95% uncertainty interval of population sodium intake was estimated for each country in the world using data from existing surveys. The first issue concerns coverage. Survey data were available only for 66 countries: 36.3% of total countries considered in this analysis, and 74.1% of the global adult population. While many of those countries with data had large numbers of high-quality surveys which between them covered nationally representative samples (e.g., 20 for USA, 15 for UK), others had few surveys with low sample sizes that were often significantly out of date. Of the 20 surveys identified for China, for example, 15 were conducted before 1990, the most recent being conducted only in 2002. Estimates for Kenya were based on samples of just two villages, totaling 90 men and 86 women, in 1986. Given the rapid rate of change in consumption habits in many countries around the world in past decades, many of these estimates are now likely to be unreliable.

A second problem concerns measurement methods. Surveys tend to use urinary analysis, dietary recall, or both. Standard protocols for the first involve taking 24-hour or split urine samples (day and night 12-hour periods), refrigerating and then shipping them to a facility where their sodium content is assessed using a sodium

ion selective electrode instrument. This is used to estimate dietary sodium intake on the premise that 90-95% of this intake is excreted in urine. Intake is therefore likely to be under-estimated in populations with increased sodium excreted in sweat. In general, though, urinary assays are considered the 'gold standard' in this research. Dietary recall methods, by contrast, involve either 24-hour dietary recall, food diaries, or food frequency questionnaires. Sodium levels of the reported diets are then estimated by the investigator. This approach can suffer from recall bias, high variation in the sodium content of common food items, missing information on salt added during cooking or at the table, and imprecisely estimated portion sizes [62]. Moreover, analysis of studies using both methods have found that dietary recalls greatly underestimate sodium intake from urine assays: data from the US Trial of Nonpharmacologic Intervention in the Elderly (TONE), for example, found the difference to be 22% on average [42]. Of the 205 surveys used in this analysis, 63 (30.7%) were dietary only, the rest using urine collections or both methods. Half the surveys covering China, the majority covering India, and the only one covering Brazil were dietary only. As such, despite the attempts to correct for underestimation from dietary recall described in the previous section, many of the estimates used in this study are highly uncertain. It is a strength of the analysis that these various sources of uncertainty are quantified and propagated throughout the estimation procedure.

5.2 Measurement of current blood pressure levels

Estimates of blood pressure levels were taken from the 2010 Global Burden of Diseases study [43]. As with the measures of dietary sodium intake, the chief limitation is one of coverage. While data were obtained for 786 country-years and 5.4 million participants, no population-based data at all was available for 64 countries. Community studies provided 65% of all data, national studies only 20%, and subnational studies the remainder. Low study quality is much less of a problem than with estimates of salt intake, though lack of standardization for resting time, position of the arm, and exclusion of the first measurement may have contributed to variability between studies and were not assessed.

Again, the use of a Bayesian hierarchical model is an important strength of the analysis. The model incorporated study coverage offsets and variance components, resulting in larger uncertainty where nationally representative data were not available. This propagated through the model into the uncertainty intervals, so that the figures used in this analysis represent the true availability of information.

5.3 Measurement of current cardiovascular mortality

Data on cardiovascular mortality were also taken from the 2010 Global Burden of Diseases study [44, 45]. Absolute numbers of deaths by age, sex, and cause in each country were obtained from vital registration, verbal autopsy, and mortality surveillance records. There are several sources of inaccuracy. First, data on cause of death, even in settings with medical certification, may not always capture the underlying cause of death. One

recent meta-analysis, for example, found that at least a third of death certificates in European countries and the US are likely to be incorrect, while 50% of autopsies produce findings unsuspected before death [63]. Second, causes of death that should not be identified as underlying causes of death (e.g., senility, cardiopulmonary arrest) are frequently entered as the underlying cause of death on death certificates. These incorrect cause-of-death listings are known as 'garbage codes', and occur in vital registration data at levels as high as 70% (Sri Lanka). The GBD project addresses this problem by redistributing garbage codes proportionately to various causes (called 'target codes') that were the likely underlying causes of death. This redistribution is based on very limited empirical information, and uncertainty distributions were not estimated, so that UIs for some causes may be underestimated. Finally, extensive use was made of verbal autopsy data, especially in low-income settings. Validation studies have shown that such verbal autopsies can be highly unreliable, with physicians performing no better than chance for some cases, including some cardiovascular diseases [64].

5.4 Effect of sodium on blood pressure

The meta-analysis used to estimate the effect of dietary sodium on BP is described in detail in the previous section. Here, two problems with the types of studies used in the meta-analysis are explored, as well as further problems with the meta-regression itself.

First, the protocol used in the randomized controlled trials may not be externally valid for the purposes of this analysis. The standard design begins by moving all experimental participants to a low sodium diet, either by cooking meals for them, or giving participants personalized advice on how to modify their existing diets to reduce sodium, or a combination of these (e.g., providing low-sodium bread only). The treatment group is then given a sodium capsule supplement, and the control group a placebo. The trials incorporate a crossover design, in which the treatment and control groups are then switched, and the average treatment effect is the average of the differences in blood pressure for each individual participant. For external validity, it must be assumed, first, that the effect of removing essentially 'pure' sodium (the capsule supplement) from a diet is the same as removing sodium via food reformulation or other dietary changes. Second, and moreover, it must be assumed that the effect of sodium reduction is not significantly modified by the diet from which it is being removed. There is some evidence to suggest this is false. One study compared the effects of sodium reduction in two diets, one designed to reduce hypertension (rich in vegetables, fruits, and low-fat dairy products) and the other to approximate a typical American diet. The effect on systolic blood pressure of moving from high to low sodium on the standard diet was 6.7 mm Hg (95% C.I. [5.4, 8], $p<0.001$), but only 3 mm Hg (95% C.I. [1.7, 4.3], $p<0.001$) on the hypertension-reduction diet [65]. No meta-analysis has attempted to account for differences in base diet, so this may be a major confounding factor in estimates of the sodium-bp effect.

A second problem concerns measurement error. In studies in which participants are advised how to reduce the sodium content of their existing diets and then left to make the changes themselves, the level of sodium reduction is not controlled but must be measured, often infrequently (e.g., once at the end of each diet phase).

This is done via urinary analysis, as detailed above. There are two potential sources of error. First, studies have shown that intraindividual variability in 24-hour dietary sodium intake can be very large, and significantly exceed interindividual variability. This finding led the authors of one such study to caution that the estimation of mean dietary sodium intake with a single or occasional 24-hour urine collection would be "futile" [66]. Second, trial designs generally specify no protocol to reduce (or evaluate) the possibility of participants, for example, consuming their normal diets for most of the study and only making the effort to follow the prescribed diet on the days they were to submit urine samples. Since it is reasonable to assume, in the absence of evidence to the contrary, that participants were told in advance when they would have to submit samples, and it is also the case that changing one's diet is highly effortful, this possibility should not be discounted. Both of these sources of error are likely to result in the estimation of the effect of sodium on blood pressure being biased downwards: in the first case due to attenuation, and in the second because the effect of a small decrease in sodium would be ascribed to a larger such decrease.

A third issue springs from the nature of the meta-regression itself. Although the inputs to the analysis are randomized trials, it is important to recognize that the relationship described by the meta-regression is merely an observational association [67]. As such, the regression may suffer bias by confounding: an association identified with one trial characteristic may be capturing an association due to other correlated characteristics. For example, whether a study was double blind could be correlated both with blood pressure changes (unblinded reduced-sodium study participants may have become more attentive to other aspects of their diet that affected blood pressure) and with the reduction in sodium intake achieved (unblinded studies may have been less rigorous in general, and so achieved less of a reduction than those which were blinded). Similarly, the participants in studies of older people may have been more diligent in adhering to their prescribed diets than participants in studies of younger people, leading age in the meta-regression to capture that effect rather than the effect of age itself on the dose-response relationship.

Finally, ecological bias is also a possibility. The meta-regression relates the results of the trials to published averages of participant characteristics within trials (e.g., average age, prevalence of hypertension). Yet, the relationship with participant averages across studies may not be the same as the relationship for participants within studies. This phenomenon has been demonstrated in the case of meta-regressions of clinical trials [68]. In the absence of individual-level data for the trials considered, this possibility cannot be investigated. That said, the dose-response relationship and modifiers estimated are consistent with those obtained in a high-quality single trial which evaluated multiple doses among participants with characteristics that varied substantially along the dimensions in question (age, hypertensive status, and black race) [69].

5.5 Effect of blood pressure on cardiovascular diseases

The dose-response relationship between BP and CVD mortality was estimated using data from two pooling projects, the Prospective Studies Collaborative and the Asia Pacific Cohort Studies Collaboration, as described

in the previous section. These pooled data across 61 prospective studies, together totaling 98 cohorts, 1.425 million participants, and 127,000 deaths [70]. The cohorts comprised participants from Europe, North America, Australia, Israel, China, Japan, Taiwan, South Korea, Thailand, Singapore, Australia, and New Zealand. The strength of this evidence base is its size and geographical diversity, as well as the fact that individual-level data were available and used to produce the estimates.

There are two chief limitations. The first is that while, within each age-group of the pooled data, the log risk profile is linear, it does not follow that all 61 populations have a common linear profile. It is possible, for example, to create data such that for every population the data satisfy a spline model (i.e., fit a profile that has a threshold level below which further decreases in blood pressure are not associated with lower risk), yet such that a meta-analysis will produce a linear plot [71]. Moreover, several of the studies used in the meta-analysis do indeed exhibit highly non-linear trends. An analysis of data from the Framingham Heart Study, a large, high-quality study which was included in the meta-regression, found that when logistic-spline models were fitted, estimates of the left and right slopes were significantly different. This finding is sufficient to reject the hypothesis of linearity [72]. Moreover, there was no evidence of a trend up to the 70th percentile of blood pressure for each age group, with risk then increasing sharply for blood pressure higher than the 80th percentile. The linear model would then greatly overestimate risk for more than 70% of the population, and underestimate it for those in the lowest and highest blood pressure ranges. Similar conclusions were reached using data from the large Seven Countries study, also included in the meta-regression [73]. A full re-evaluation of the meta-analysis in light of these findings should be a priority for future research.

The second limitation is that all the data used in the analysis are, anyway, observational. No attempt was made to control for confounding factors such as BMI, alcohol consumption, smoking, stress, physical activity, or medication. Since all of these things could plausibly affect both blood pressure and, independently, cardiovascular disease mortality, the magnitude of the causal link may be different from the size of the association quantified by the meta-analysis. If an intervention existed which only lowered blood pressure and nothing else, randomized controlled trials of this intervention would help to uncover the true effect. Unfortunately, the evidence regarding the range of effects of antihypertensive drugs (which are designed simply to lower blood pressure, and are the only plausible candidate intervention) is inconclusive. A recent meta-analysis sought to determine whether the protective effects of these drugs were explained by blood pressure reduction alone [74]. It concluded that they were – but only because the effect size estimates of the anti-hypertensive trials meta-analysis were similar to the effect size estimates from the prospective cohort study! Clearly, if the results of the prospective cohort study are used to argue that antihypertensive drugs work only through their effects on blood pressure, then the contention that antihypertensive drugs work only through their effects on blood pressure cannot be used to claim identification in the prospective cohort study. Moreover, other studies have shown that antihypertensive drugs that have similar effects on blood pressure can have different effects on outcomes. One meta-analysis found that calcium channel blockers, β-blockers, and lower-dose diuretics all lowered blood pressure by about the same amount, whereas the drugs' effects on health outcomes differed

significantly [75]. This suggests that the protective effects of these drugs is not explained by blood pressure reduction alone. In sum, while the existence of an effect of blood pressure on cardiovascular disease mortality is not in doubt, the magnitude of that effect has not yet been convincingly identified – indeed, may never be.

5.6 Effect of sodium reduction on cardiovascular diseases

An important assumption of this analysis is that the effect of sodium reduction on cardiovascular disease mortality can be identified by 'joining up' the effect of sodium reduction on blood pressure with the effect of blood pressure on cardiovascular disease mortality. For this to be true, several conditions must hold. First, the effect of sodium reduction on blood pressure must be causally identified. Second, so too must the effect of blood pressure on cardiovascular disease mortality. Third, sodium must affect cardiovascular disease only through its effect on blood pressure. Finally, a public health policy analysis such as this one requires that all effects of reducing sodium consumption are captured by the effect on cardiovascular disease: in particular, sodium reduction must not have any adverse effects on other health outcomes.

The first two conditions were explored above. While there was substantial evidence for each effect, tight causal identification was found to be lacking. Additional, direct evidence for the effect of sodium reduction on cardiovascular diseases would therefore be valuable if it existed. In fact, there have been both observational and clinical studies that sought to examine this effect directly, which will now be considered.

Observational studies of this effect have been evaluated in a recent meta-analysis [76]. The review identified 19 independent cohorts from 13 studies published between 1996 and 2008, all of which quantified both salt intake and cardiovascular disease incidence. The studies comprised 177,025 participants from six countries (six studies from the US, two each from Finland and Japan, and one each from the Netherlands, Scotland, and Taiwan), who contributed a total of 10,507 vascular events. Follow-up ranged from 3.5 to 19 years. Estimation of a random effects model found that higher salt intake (an increase of 2.3g sodium per day) was associated with greater risk of stroke (pooled relative risk 1.23, 95% CI [1.06, 1.43], $p<0.01$) and cardiovascular disease (1.14, [0.99, 1.32], $p=0.07$).

Yet, the same problems identified with the meta-analyses in previous sections also afflict this one. Consider, for example, the quality of the data. Salt intake was assessed by 24 hour urine excretion for only four studies, with the rest using 24 hour dietary recall (four studies) and questionnaires (five). Restricting the analysis to 24 hour urine excretion studies only, the pooled risk estimate for cardiovascular disease was 1.10 ([0.92, 1.31], $p=0.32$). Moreover, the estimate of the baseline population salt intake in each study was based on only a single measurement. This makes attenuation bias likely. Most importantly, this was an analysis of observational studies and no attempt was made to account for confounders. People who consume a diet lower in salt are likely also to eat a diet of fresh foods that are lower in fat, are likely to take more exercise, and are less likely to smoke. As such, the lower levels of cardiovascular events observed may not relate to salt intake at all.

Randomized controlled trials designed to identify directly the effect of sodium reduction on cardiovascular

disease have also been undertaken. A recent meta-analysis identified seven that appeared to be well-conducted, reduced sodium intake for the duration of the study, and reported cardiovascular disease and/or all-cause mortality [77]. Three trials were in normotensives (n=3,518), two in hypertensives (n=758), and one in a mixed population (n=1,981). A seventh trial was conducted in participants with heart failure (n=232), and is not considered here. The trials had follow-ups of 6 to 71 months post-randomization, and observational follow-ups of up to 12.7 years. Six of the seven trials reduced salt intake by behavior change programs (counseling sessions, information leaflets, etc.), with participants having food cooked for them in the remaining trial. The reviewers pooled the normotensive and hypertensive studies separately, and found no significant effect for either. For each of all-cause mortality at trial end, all-cause mortality after long-term follow-up, CVD mortality at trial end, and CVD morbidity after long-term follow-up, the reduced salt group fared better but the difference was not significant. The pooled relative risk (RR) for CVD mortality, for example, was consistent with more than a halving of the RR for CVD deaths or a small increase (0.69, [0.45, 1.05], p=0.26).

A follow-up paper re-analyzed the data, but this time pooled the normotensive and hypertensive studies using a random effects model [78]. In this case, the pooled relative risk for cardiovascular disease events for the reduced salt groups at longest follow-up was 0.80, with 95% C.I. [0.63, 1.03], p=0.058. This is a stronger result, but rests on the assumption that the two groups are sufficiently homogenous to be combined legitimately. If normotensives and hypertensives are, instead, regarded as different populations with different effect sizes, which seems highly plausible, such pooling cannot be justified. It should also be noted that urinary sodium was not measured in the long-term follow-ups, nor diet assessed. As such, the effect sizes may be capturing the effect of a one-time reduction in salt consumption, or the intervention groups may have continued on their low-sodium diets after the trial period, in which case the effect sizes would have captured the effect of a long-term reduction. It is also unclear whether the intervention groups switched from high-salt foods to otherwise identical lower-salt foods, or from high-salt foods to lower-salt foods that were altogether different and perhaps much healthier for other reasons. Once more, the evidence is suggestive but not conclusive.

Conflicting evidence exists relating to the third and fourth conditions: namely, that sodium affects cardiovascular disease *only* through its effect on blood pressure, and that sodium reduction has no adverse effects on other health outcomes. A recent meta-analysis of randomized controlled trials of the effect of dietary sodium reduction on outcomes other than blood pressure found that low versus high sodium diets were associated with a significant and persistent increase in plasma renin and plasma aldosterone, as well as plasma cholesterol and plasma triglycerides [51]. The study authors hypothesized that these potentially harmful effects could be enough to cancel out the beneficial effects on blood pressure. A separate meta-analysis of randomized controlled trials found no significant adverse effects of sodium restriction on blood lipids, catecholamine levels, or renal function [79]. Other studies suggest that chronically high dietary sodium may induce blood pressure-independent effects, such as increasing myocardial, arterial, and renal fibrosis and dysfunction [80]. These studies are often very small scale, however, conducted in special populations (e.g., hypertensive blacks [81]) or in animals (generally rats [82]), and few appear to have been replicated.

5.7 Theoretical-minimum-risk exposure distribution of sodium intake

The theoretical-minimum-risk exposure distribution (TMRD) of sodium intake plays an important role in this analysis. In the estimation of intervention effect, the TMRD determines the level of sodium intake further reductions below which cease to have any influence on blood pressure. The TMRD is also what government guidelines on recommended dietary intakes seek to approximate, and informs targets for population sodium reduction programs. It has proven difficult to pin down: while excess sodium consumption causes harm, some amount of it is necessary for the human body to function. There is also evidence that salt sensitivity varies greatly between individuals, on the basis of demographic and genetic factors [83].

A number of methods by which the TMRD might be approximated have been proposed. These include taking the lowest national mean salt intake levels currently observed around the world, and appealing to the lack of salt consumption throughout most of man's evolutionary history [10, 84]. It is unlikely that these would say anything reliable about optimum levels given modern diets and lifestyles, though, as opposed to simply the lowest levels needed to survive. (Indeed, some human societies even today live on essentially zero salt. The Yanomami Indians, a tribe inhabiting the tropical equatorial rain forest of northern Brazil and southern Venezuela, were found to excrete an average of 23mg sodium per day [85]. Yet, evidence of genetic isolation stretching over millennia, and a diet consisting mostly of bananas and insects, calls the external validity of their experience into question.)

The most reliable method of estimating the TMRD would, rather, be to consider the results of the prospective cohort studies and randomized controlled trials mentioned above. Published meta-analyses, however, have not sought to consider the levels to which sodium intakes have been reduced, but only to estimate the effect on blood pressure or cardiovascular outcomes of a standardized reduction (e.g., fall in blood pressure per 100 mmol/day reduction in sodium). Individual studies sometimes display health outcomes by quintile of sodium intake, but not in a consistent way that allows the type of estimation sought here. A recent study by the US Institute of Medicine concluded that the evidence from trials and observational studies was inconsistent and insufficient regarding an association between sodium intake below 2,300mg/day and either an increased or decreased risk of CVD outcomes or all-cause mortality [86]. This figure of 2,300mg/day is therefore the base case used for this analysis. A figure of 1,000mg/day is used in sensitivity checks, and was selected based on the observed intakes associated with lowest blood pressure levels in ecologic studies together with the lowest observed national mean intakes globally [10].

5.8 Intervention effects on sodium consumption

It is impossible to tell in advance, with any degree of certainty, what will be the effect of a given government policy on population sodium intake. Sources of variability include not only the ability of government to influence manufacturers, implement and enforce labeling guidelines, and run effective media campaigns. They also include the ability of manufacturers themselves to change their production processes to use less salt and the

responsiveness of consumers to these various initiatives. Indeed, some populations are more health-conscious than others; some may be more attached to high-salt foods and preparation methods than others; some may be more or less convinced of the benefits to be had from reducing their intake in the first place. Chapter 2 illustrates wide variation in the effectiveness of policies in force around the world. The UK achieved a 9.5% reduction in population salt consumption in 8 years, for example, while Turkey has apparently achieved a 16% reduction in half that time. Given this variability, and the lack of a larger number of case studies from which to infer possible sources of this variability, estimating the likely effectiveness of interventions by country was deemed to be infeasible. Instead, a range of plausible effect sizes were used in calculations for each country.

Policies intended only to influence sodium consumption may have unintended consequences. Manufacturers may replace salt with other substances that are harmful. Consumers may switch to products lower in salt but higher in sugar or fat. The former is perhaps unlikely in policy environments in which government food agencies are collaborating closely with (and so, presumably, watching beadily over) manufacturers as they reformulate their products. But consumer behavior is more difficult to influence. It will be important for governments to monitor the effects of their policies closely, not only on salt intake, but also on wider dietary and health outcomes. The worst case scenario would be if these policies encouraged consumers to think they were optimizing their health simply by cutting down on salt, and caused those who might otherwise be pushed to exercise or focus on other aspects of their diet or lifestyle not to do so. There is no evidence this is likely to happen, but then no studies have been done that seek to assess the effects of sodium intervention policies on anything other than population sodium intake.

5.9 Intervention effects on DALYs attributable to cardiovascular disease

This study's calculation of DALYs averted due to a given intervention effect on population sodium intake rests on a number of assumptions. Recall that the DALY is a measure of disease burden, obtained by summing the years of life lost due to that disease (e.g., 1,000 people each dying 10 years earlier than they would have in the absence of the disease would total 10,000 life years lost) and years lived with disability (e.g., 1,000 people suffering a condition with disability weight 0.3, where 0 is perfect health and 1 is dead, for 10 years each would total 3,000 years lived with disability). This study, however, first estimates just the number of deaths (not years of life lost) attributable to excess sodium intake. As described in the previous section, the population attributable fraction of cardiovascular disease deaths in each cohort under baseline and intervention sodium intakes is calculated by first estimating what cohort blood pressure distributions would be under the two sodium intake distributions. Next, the fraction of cardiovascular disease deaths attributable to these sodium intake distributions is estimated by comparing the corresponding blood pressure levels with what blood pressure levels would be under the TMRD of sodium intake, using relative risks of changes of blood pressure on cardiovascular mortality. Finally, these same fractions are applied to the DALYs calculated as being attributable to cardiovascular diseases in 2010 by the Global Burden of Disease (GBD) project.

A first assumption, then, is that intervention effects on years of life lost and years lived with disability are identical to effects on fatalities *simpliciter*. For example, if it was found that 10% of deaths from a particular cardiovascular disease in a given country-age-sex cohort would be averted as a result of a given reduction in sodium intake, this study assumed that the same reduction in sodium intake would avert 10% of the years of life lost and 10% of the years lived with disability attributable to that disease. A second assumption is that annual benefit is roughly constant. DALYs were calculated by the GBD for 2010 only: i.e., life-years lost were estimated for cardiovascular fatalities that occurred in that year, and years lived with disability were estimated as resulting from non-fatal cardiovascular events that occurred in that year. This study assumed that the absolute effect on these outcomes of a given intervention would be the same in any given year as it would have been in 2010. Third, and moreover, no attempt was made to take account of expected demographic changes over the years considered for the interventions. This is both because creating such projections from GBD data would be an enormous undertaking, and because the improvements in precision, if any, would be marginal when set against the other sources of uncertainty in the analysis.

5.10 Intervention costs

The cost estimates in this study are limited in both accuracy and scope. A standardized template and approach was used to estimate program-level resources, including program management staffing levels, stakeholder meetings, training sessions, and media [57]. It is in fact unlikely that, for example, a media campaign in Canada will take the same form (in terms of types and quantities of advertising per 100,000 population) as in, say, India. Moreover, while the assumption of fixed program costs at the national level (whatever the country size) is plausible for human resource quantities, it is much less plausible for media quantities. The WHO held many consultations with program experts to generate realistic estimates for these resources quantities, but there is no guarantee as to their accuracy. Indeed, there is little reported empirical evidence, and the values used in this study are largely based on expert opinion. Country-level contextualization and validation is thus an important area for future work.

The scope of these estimates is confined to program-level costs only. That is, only the direct cost to government of implementing an intervention is estimated. Costs to other actors, such as food manufacturers, who may incur costs reformulating products, the salt industry, which may suffer reduced demand, and consumers, who may lose utility from having to adapt to potential changes in food taste, were not included. More importantly, health system cost savings were not estimated. If the projected effects on cardiovascular disease events in this analysis are the correct order of magnitude then significant net savings are possible. A recent analysis that considered just the United States, for example, found that an intervention to reduce population salt intake by 3g per day would save $10 billion to $24 billion in health care costs annually [9]. Yet, counting only events prevented seems a little disingenuous. In all cases, death is merely deferred: a heart attack is averted, only, perhaps, to enable a more costly disease to take its place a few years down the line. Moreover, perhaps pensions

that would not have been paid out in the baseline scenario should also be counted as a cost of the policy. These considerations lead to the conclusion that, both technically and philosophically, the restriction in scope of this study's cost estimates may be for the best.

This chapter has illustrated the many challenges involved in this project. Data on current exposures are lacking in coverage; the effect of sodium on cardiovascular diseases is impossible to estimate precisely; and costs are little more than highly educated guesswork. That said, the uncertainty of each input is quantified and propagated throughout the model. The intervention cost-effectiveness figures derived, then, are the most accurate possible given the data available. The further research that will be necessary to improve these estimates is outlined next.

Chapter 6

Conclusion

If the findings of this study are correct, an intervention to reduce population sodium consumption would be highly cost-effective in almost every country in the world. Hundreds of thousands of deaths, and millions of DALYs, would be averted every year at very little cost. These numbers would be strong grounds for government intervention, recalling the arguments in Chapter 2, and would give reason to applaud those states already taking action, as described in Chapter 3. Whether they are correct, however, is only partially certain, and further research is needed to address a number of issues.

First, though, this study's several strengths should be affirmed. It is the first to quantify the cost-effectiveness of sodium reduction interventions for every country in the world. It takes advantage of new estimates of sodium consumption, blood pressure, and the burden of cardiovascular disease. It uses estimates of the sodium-blood pressure effect derived from up-to-date meta-analyses of randomized controlled trials, accounting for heterogeneity by age, race, and hypertension, and estimates of the age-specific blood pressure-cardiovascular disease effect derived from a new analysis of prospective cohorts. Estimates of costs are based on a new costing tool developed by WHO specialists. Uncertainty is quantified wherever possible and propagated throughout the model. Sensitivity analysis demonstrates the robustness of the results to large changes in assumptions of both cost and efficacy.

These strengths are tempered by substantial limitations. The study's model assumes an intervention that will reduce the sodium levels in people's diets and have no other effect. It uses estimates of sodium consumption and blood pressure based on surveys restricted both in scope and methods. It derives sodium-blood pressure and blood pressure-cardiovascular disease effects using models at risk of serious bias. It ignores effects of sodium on cardiovascular disease not mediated by blood pressure, and effects of sodium on other health conditions. Its cost estimates are guesses that have yet to be validated. For every source of uncertainty that was quantified, several others could not be.

As such, this study's final estimates should not be regarded as the last word on the matter. Further research has the potential to strengthen the results substantially. In particular, the use of 24-hour urine collections

to measure sodium intake should be standardized and validated. Associations between sodium intake and health outcomes should be examined so as to adjudicate between the different candidates for the theoretical-minimum-risk exposure distribution. Analyses should be conducted to examine the effects of sodium in combination with other electrolytes, particularly potassium [86]. Studies should be designed to account for potential confounders in prospective cohort analyses, especially those seeking to quantify the effect of blood pressure on cardiovascular disease, as well as the effect of sodium intake on cardiovascular disease. Additional observational research should be conducted to examine associations between sodium intake and other health conditions besides cardiovascular disease. Finally, sodium reduction interventions currently in place around the world should be carefully evaluated, with attention paid to their effects not only on sodium consumption but on diet overall.

In light of this need for further research, three summary remarks are in order. First, the evidence for the benefits of sodium reduction as a population-wide health strategy is strongly suggestive but not conclusive. Section 5.6 considers the direct evidence for the effect of sodium reduction on cardiovascular disease outcomes. It notes that analyses of observational studies do not adjust for confounders, and that correctly pooled analyses of randomized controlled trials do not achieve significance. Serious problems with other sources of evidence for the effect are described elsewhere in the previous chapter. On balance, the data do point to an effect. But it is not beyond reasonable doubt.

Second, much of the literature on this subject is prone to overstating its conclusions. Findings for the harmful effects of salt are said to be "unequivocal" [76], the evidence "robust and strong" [87], even "overwhelming" [88]. Studies with contrary conclusions are vigorously and unfairly attacked. For example, a meta-analysis that found cutting down on salt had "no clear benefits" for reducing the risk of cardiovascular disease was denounced as "[reflecting] poorly on the reputation of the Cochrane Library and the authors" [77, 89]. An observational analysis that found low sodium excretion predicted higher, not lower, cardiovascular mortality was described as "disappointingly weak", with the study's failure to adjust for confounders, and the unreliability of measuring sodium intake from just one 24-hour urinary collection, cited as good reasons to ignore its conclusions [90, 91]. It is unclear why the same flaws in studies that find against salt should be excusable.

Finally, the policy implications are not clear-cut. Were the evidence really overwhelming, there would be little question of the need for action. In reality, substantial uncertainty persists. The number of salt reduction initiatives already in place around the world may be testament as much to the way the evidence has been presented as to its credibility. The findings of the simulation in this study show the great benefits to be obtained if the various identifying assumptions are, indeed, correct. The temptation to believe so is strong, for salt reduction then holds the promise of saving millions of lives easily and cheaply. But this must be set against alternative possibilities: that salt reduction, while reducing blood pressure, may have adverse effects on other aspects of the body's physiology and so increase the risk of other diseases; or that policies to reduce salt consumption may cause people to switch to diets that are less healthy for other reasons. There is also the opportunity cost of focusing on salt rather than other risk factors, such as exercise or consumption of fruit and vegetables.

It is thus the contribution of this study to evaluate honestly and in full the potential of salt reduction policies to improve people's health. The evidence holds great promise: and that promise has here been quantified for every country for the first time. But much investigative work remains to be done. This study has shown what, and why.

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