## MODELLING CARDIOVASCULAR DISEASE PREVENTION

by

Azadeh Alimadad B.Sc., Azad University, 1997 M.Sc., Carleton University, 2005

a Thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Doctor of Philosophy Program Faculty of Health Sciences

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#### APPROVAL



Examining Committee: Dr. Chair

Dr. Michel Joffres, Senior Supervisor

Dr. Peter Borwein, Supervisor

Dr. Matias Salibian-Barrera, Supervisor

Dr. Scott Venners , Assistant Professor, Faculty of Health Sciences SFU Examiner

Dr. Norman R.C. Campbell, External Examiner, Professor, Department of Medicine University of Calgary

Date Approved:

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## Abstract

According to the World Health Organization (WHO), cardiovascular disease (CVD), which sits under the chronic disease umbrella, is the number one cause of death globally. Over time, we have witnessed different trends that have influenced the prevalence of CVD. One of the ways of decreasing CVD and its social costs and global fatalities is through influencing preventable CVD risk factors. Though many risk factors such as age and gender are not preventable, there are several effective behaviours that reduce the risk of CVD. To estimate the potential impact of various interventions on CVD, such as reducing blood pressure as a result of lowering sodium intake, or increasing awareness regarding healthy eating behaviour, we have used descriptive statistics and modelling.

We estimated the impact of a gradual decrease in sodium intake on CVD mortality and morbidity in Canada (CA), United States (US), and Latin American (LA) countries. Our analysis shows that small changes in sodium intake at the population level can make an important difference in the total number of CVD events that can be prevented.

Using data in Canada and France we also explored the potential role of individual decision making on daily sodium consumption. Our analysis showed that the main obstacle to consumers making healthier choices appears to be neither the availability of products, nor the price. Consumers may be more hampered by the difficulty of comparing food labels than by the availability of lower sodium products. Using Canadian data, we also examined the potential impact of having a positive family history of CVD on CVD mortality. Based on our analysis, father stroke before the age of 60 was a strong predictor for CVD mortality.

Following this analysis, we used mathematical models, to improve our understanding of the impact on CVD of changes in the trend of CVD risk factors such as obesity, social and environmental influences. We investigated each of these risk factors separately, in order to have a clear foundation for more complex models. We also used a Fuzzy Cognitive Map

(FCM) that considered a wide range of interactions and interrelationships between different CVD risk factors.

To my dear Vahid, who pushes me beyond my limitations. Your smile, kind heart, and patience enabled us to overcome the challenging journey we have shared until now. You taught me that it's not about the destination but the journey that matters in life and I couldn't be happier to have you beside me through it all. Thank you for being who you are. With deep gratitude, Azadeh "Drastic action may be costly, but it can be less expensive than continuing inaction" RICHARD E NEUSTADT

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## Chapter 1

## Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, with 80% of all cases occurring in developing countries [1]. In 2008, CVD was responsible for approximately 17 million deaths globally and this number is projected to increase to 25 million in 2030 [2]. In Canada alone, about 27% of all deaths in 2008 were directly related to CVD [3]. In developing nations, CVD is responsible for 11% of the global burden of disease [4]. Middle income countries attribute one third of their deaths to CVD which is a similar problem to many developed countries. Also, developing countries generally face higher rates of disease than developed countries. For example in Tanzania; age-specific stroke rates are three to six times higher than those in the UK [2, 5, 6, 7, 8, 9]. CVD is a major burden on society and account for more death, disability and health care costs than any other class of diseases [10].

#### 1.1 Why CVD is the leading cause of death?

The increase in CVD is attached to several risk factors including tobacco use, hypertension, a lack of physical activity, high lipid levels, excessive weight, excessive use of alcohol, and an unhealthy diet [5, 11]. One must also take into consideration the effects of age, gender, heredity, social and environmental factors, culture, and economic status, which are all wider determinants of health. Approximately 80% of Canadians are exposed to at least one of the above risk factors, and another 11% are exposed to three or more [12]. According to WHO, reduction/avoidance of the modifiable factors can reduce a significant number of cases of premature heart disease and stroke worldwide [13].

Elevated blood pressure has been identified as a major risk factor for developing CVD.

Hypertension has been shown to increase the risk for heart disease and stroke [14, 15], which are the first and third causes of death respectively in the United States [16]. According to the WHO, high blood pressure is the leading risk factor of mortality globally [6], where as many as one billion individuals suffer from hypertension, and approximately 7.1 millions deaths annually are linked to the disease [5]. The advancement of age is also reportedly correlated to the prevalence of hypertension such that more than 50% of people aged 60 to 69 suffer from elevated blood pressure [17]. Reports by Framingham Heart Study investigators demonstrate that approximately 90% of normotensive men and women between the ages of 55 and 65 will develop hypertension in their lifetime (assuming they survive to age 80 to 85) [15].

Nearly one quarter of the world's adult population are facing this issue [18]. The prevalence of hypertension has increased over the recent past decades as much as 28% in North America, roughly 30% in Latin America, and 44% in Europe [19, 20]. A significant proportion of hypertensive patients are unaware that their blood pressure is elevated, and many of those who are aware are either untreated or undertreated. Hypertension awareness varies between 31% and 68% in Latin American countries, 69% in the United States, and 83% in Canada [17, 20, 21].

Approximately 51% of stroke-related deaths and 45% of coronary heart disease-related deaths were attributable to high blood pressure (worldwide) [11]. The increasing prevalence of hypertension has encouraged the WHO to call for enhanced diagnosis and treatment to control hypertension as a serious concern from both as an economic burden on society as well as the factor responsible for a large magnitude of morbidity and mortality [5]. Though the idea of improved control may appear ideal, some critics have claimed that this type of improvement will demand resources and result in increased costs, which in reality may not be affordable in many countries [22].

One possible alternative to the increased cost of the WHO's health initiative could be a focus on prevention instead of treatment. We need to shift our effort from research on the mechanics of dying to social and economic approaches to prevention [23]. The focus on prevention is now more critical than ever due to the prevalence of hypertension, which is significantly increasing because of various factors such as an aging population and a sedentary lifestyle [24, 25]. One of the suggested methods to tackle the complex health consequences of hypertension is through reducing the mean blood pressure of a population [5, 26]. Since higher consumptions of sodium increase blood pressure, and thus the risk of

hypertension, it is recommended to reduce intake levels of sodium [27, 28, 29, 30, 31, 32, 33], which should be easy to implement, rapid, and with an extensive impact on a population. According to Chobanian (2003), sodium reduction could be the first step of intervention for individuals who are prehypertensive and those currently hypertensive [14]. There appears to be a general misunderstanding that salt reduction is only beneficial for certain groups of people and unnecessary for the vast majority of the population [31]. However, the opposite is true as evidence shows that sodium reduction could in fact reduce blood pressure in children and calm the age-related rise in blood pressure [31, 34]. Other evidence also demonstrates that a reduction in sodium intake may reduce the risk of gastric cancer, end-stage kidney disease, left ventricular hypertrophy, congestive heart failure, and osteoporosis [31].

#### 1.2 Different approaches to preventing CVD.

The mentioned statistics in section 1.1 enable us to understand the importance of CVD and how to utilize preventable measures in order to maximize the benefits. Different research has suggested different approaches to the prevention of CVD:

- Some researchers such as Kottke (1985), Burke (1989), and Kannel (1996) suggest the population based approach, which promotes education and health initiatives as instruments to help reduce CVD. A population-wide intervention that is implemented to reduce CVD would require significant government involvement and investment [35, 36, 37]. Few decades ago, the population approach was proposed as the ultimate answer to the problem of mass disease by Rose (1981) [23].
- Other researchers have focused their attention elsewhere. One of them, Oliver (1983), recommends the high risk strategy, which targets intervention at high-risk groups who are already subject to CVD [38].
- Hunt (2003) introduced the family history assessment as an approach that would combine both population and individual approaches by gathering family information with the goal of implementing a prevention program for those with a familial likelihood of developing CVD [39].
- Differing from the above approaches, Bandura (2004) introduced health promotion by social cognitive means. Bandura explained that with increased awareness and societal

efforts, individuals are fully capable of changing their behaviour. He explained that if people lack the knowledge and information, then they will also lack the motivation to change. However, with enhanced public guidance, people are able to change their mindset and, in turn, reduce their risks of CVD [40].

The equation for reducing CVD is not straightforward but if we are able to have a better idea of: the prevalence and incidence of CVD; its relation with other risk factors; environmental and social influences; and an individual's eating habits, behaviors, beliefs, management and decision making, we would be better informed on the dynamics of the disease in the real world. In this work, we have considered mathematical, epidemiological, statistical, behavioral, conceptual and computational models to show the diverse impacts on trend in CVD.

Any model that we are presenting in this work is a simplified representation of a real world situation. It allows us to focus on a specific question or relationship between components or factors. Modelling can be applied to a complex phenomenon with the goal of greater understanding through exploration of the system. In our complex system models we are mainly interested in exploring the importance of each factor that affects other factors and, ultimately, how the interaction of these factors effect CVD. Models are often used as tools to answer our "what if questions" which can help policy makers to shape policy and assess the potential impact of changes or interventions within the system. In general, using different modeling approaches will help us to have a better understanding of our current and future positions in the real world and give us an opportunity to think and take action before it is too late.

#### 1.3 Significance of our Research

The work presented in this thesis is divided in two parts. The first part focuses on descriptive statistics and epidemiological modelling. The second part illustrates the usefulness of mathematical and computational modelling techniques as related to complex social systems. Part One:

• Population level intervention: Using data from different countries, we explored the potential impact of different modelling strategies. More specifically we estimated

the potential impact of gradual sodium reduction on reducing CVD mortality and morbidity in Canada, the United States and Latin American Countries.

- Individual level: Using data in Canada and France we explored the potential role of individual decision making on daily sodium consumption. The existing potential for individuals and industry to decrease the sodium consumption and sodium content is highlighted.
- Family History: Using Canadian data, we examined the potential impact of a CVD related risk factor (positive family history of CVD) on the prevalence of CVD at the population level.

Part Two:

• Mathematical and computational modelling: Through three different mathematical models: Markov, Cellular Automata and FCMs, the potential impact of reducing CVD related risk factors and their influence on trend of CVD mortality as a complex system is explored.

#### 1.4 Thesis Structure

Chapter 2 shows the potential impact of population-level intervention on the prevalence of CVD in Canada, the United States, and Latin American countries, given the gradual decrease in sodium intake. Chapter 3 highlights the importance of individual decision making, environment, and accessibility in terms of choosing healthier (i.e., low-sodium) products at stores, as well as the ability of the industry to decrease the sodium content of some brands. Chapter 4 describes the association between CVD mortality and family history of CVD in the Canadian population. Chapter 5 uses different mathematical and computational models to show the role of social and environmental influences on an individual's eating behavior as one of the risk factors of CVD. It also shows the importance of a fundamental understanding of the progression of CVD related risk factors. Finally, the use of the FCM technique is proposed to look at the problem of CVD as a complex system. FCM has the potential to capture multiple effects and interactions, answer some "what if scenarios" and provide medical decision making support. Chapter 6 concludes the thesis and outlines ongoing and future directions of the research.

## Chapter 2

# Gradual sodium reduction and CVD prevention

The existing relationship between sodium consumption, high blood pressure and CVD is used to estimate the impact of gradual reductions of sodium intake on the prevention of CVD through reduction in blood pressure in Canada, the United States, and Latin American countries.

#### 2.1 Introduction

The average daily intake of salt in both developed and developing countries, is much higher than recommended levels. Research has found that most of the world's population consumes between 2300-4600 mg of sodium daily [41]. An adult in the United States consumes, on average, 4000 mg sodium per 2000 kcal, 80% of which comes from processed foods [42, 43, 44, 45, 46]. The Institute of Medicine recommends a daily intake of less than 5.8 g of salt (2300 mg of sodium), with a lower target of 3.7 g of salt (1500 mg of sodium) per day for individuals over 40 years of age, African Americans, and individuals prone to hypertension [47]. In Canada, a recent survey found that Canadian adults consume on average 3100 mg of sodium per day, excluding the salt added to cooking or at the dinner table [48]. It is estimated that approximately 10 - 20% of dietary sodium is added in cooking and at the table, which makes the total average consumption of sodium approximately 3500 mg/day [43]. According to the Pan American Health Organization (PAHO), the average consumption of salt is between 3500 mg and 4700 mg per day in many countries. For example the average salt intake per day is 3500 mg, 4300 mg, and 4700 mg in Chile, Brazil and Argentina respectively [49].

There is a considerable amount of evidence that links the high consumption of sodium with CVD via high blood pressure [34, 49, 50, 51, 52]. Also, there have been randomized trials showing that a low salt diet reduces blood pressure and the risk of CVD [53, 54, 55]. Further convincing evidence has been illustrated through meta-analysis showing that reductions in blood pressure levels through reductions in sodium intake result in decreased risk of CVD, specifically congestive heart failure (CHF), stroke, and myocardial infarction (MI) [34, 56, 57, 58].

In 2003, in the United Kingdom, it was suggested by the Scientific Advisory Committee on Nutrition that significant evidence has shown that a population reduction in sodium intake to 2400 mg/day is an effective and suitable approach to reduce the large public burden of CVD [59].

Given the seriousness of health-related problems related to sodium intake, it becomes clear that population-level interventions are needed to reduce the level of sodium intake in the United States [60]. These population-level approaches aimed at reducing dietary sodium are described by the WHO as a 'bold policy' for the improvement of global health [5, 28, 59, 61, 62, 63]. Findings by Bibbins-Domingo and colleagues (2010) support this populationwide effort to reduce the level of sodium intake in the United States [32].

There are two common approaches to lowering salt intake including a public health approach and an individual approach. One possible method, using a public health approach, is to require food manufacturers to reduce levels of salt in processed and prepared foods. Given that approximately 75 - 80% of dietary salt comes from processed foods, this populationwide intervention seems to be the most effective approach [43, 56]. However, in the absence of a population approach, the individual approach, which relies on individual decisions to select and prepare foods with little or no salt, is deemed as another effective method of salt reduction, which will be further discussed in the next chapter.

Believing in the public health approach to reducing salt intake, countries like the United Kingdom, Finland, and Ireland have introduced and implemented specific public health programs. Committing to the same approach, some US food manufacturers have taken efforts to reduce salt content in certain foods such as soups, cereals, and breads [30, 36, 37].

The WHO has suggested that government regulation is the most effective method in

reducing sodium amounts added to food because voluntary compliance to reduce salt by food manufacturers has not historically proven to be effective [5]. Illustrating the effectiveness of the population wide approach, Bibbins-Domingo (2010) estimated that the impact of a reduction of 3 g of salt (1200 mg of sodium) per day would decrease the incidence of Coronary Heart Disease (CHD) by 60,000-120,000, stroke by 32,000-66,000 and myocardial infarction by 54,000-99,000 in the US. In addition, using this approach, she has shown the potential cost savings to the healthcare system [32]. Similar results were demonstrated by Danaei and Palar in 2009 [64, 65]. Through a combination of regulations, policies, labelling, health care professionals, public education, and collaboration with the food industry, countries such as the United Kingdom, Japan, Finland, and Portugal have taken advantage of the populationwide salt reduction approach [30, 66]. Using this combination of efforts, Finland reduced consumption of sodium by 2400 mg/day, which paralleled a notable reduction in population blood pressure (10mmHg). This achievement resulted in a large reduction in CVD in the Finish population [67]. Although this approach is highly effective, it is important to consider some barriers that can impede the achievement of sodium reduction at the population level. These include:

- cultural norms
- insufficient attention to health education by health care practitioners
- lack of reimbursement for health education services
- larger food servings in restaurants
- lack of availability of healthy food choices in many schools, worksites, and restaurants
- large amounts of sodium added to foods by the food industry and restaurants
- the higher cost of food products that are lower in sodium and calories.

The above limitations were highlighted by Whelton (2002) [26]. However, the importance of each barrier will vary from population to population.

Over the last two decades, improved treatments for hypertension have been linked with a significant reduction in hospital case-fatality for heart failure. The decline in deaths from CHD has however slowed down compared to after the 1960s and 1970s. Trends in CVD risk factors can impact the prevalence of CVD. For example, decreased tobacco use will slow the

trend in CVD, but on the other hand, the prevalence of CVD is negatively impacted by an increased sedentary lifestyle and poor eating behaviour [68, 69, 70]. The endemic nature of CVD and the potential for controlling the increase of CVD prevalence has encouraged researchers to test different types of models as an attempt to further understand the impact of population-wide reduction in sodium intake. Two different studies by Bibbins-Domingo (2010) and Smith (2010) used computer-simulation models to investigate the impact of sodium reduction on the prevalence of CVD mortality and associated health care costs [32, 71]. Another model by Joffres (2007), studied the impact of a population-wide reduction in dietary sodium by 1840 mg/day on the prevalence of hypertension, improvements in the awareness, treatment and control rates for hypertension, as well as reductions in costs for doctor visits, antihypertensive medications and laboratory services in Canada [72].

Unlike the models described above, we have used strategies that differ from published studies. The significant difference between previous studies and ours is that a sudden fixed reduction in sodium was used in prior studies, whereas our model used a gradual (5 - 10%) decrease in sodium intake. The benefit of our new strategy is that it is more representative of reality and the speed of people's acceptance towards this change. This modeling allows us to show the meaningful impact on mortality and morbidity on CVD as well as hypertension. Another advantage of this gradual aspect is that it allows policymakers to see how the gradual reduction in sodium intake can result in meaningful prevented cases of CVD over time. Since they can examine the effectiveness of this approach after a short period of time (e.g., one year), it will help them to have a better understanding of the impact of sodium reduction on the prevalence of CVD over time. Averages of current sodium intakes from Canada, the US, and Latin America were used to project each country's gradual decrease of sodium intake on hypertension and CVD.

#### 2.2 Method

#### 2.2.1 Description of data

The Pan American Health Organization (PAHO) is a global public health agency with over 100 years experience in health improvement of the nations of the Americas [73]. Using mortality data provided by PAHO, we estimated the impact of a gradual decrease of sodium intake on CVD-related mortality and morbidity in Canada, United States, and Latin American countries. Only 18 out of the 47 countries provided by PAHO, as discussed by experts, were categorized as a representative of Latin American countries and thus were considered in this analysis. These countries include Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela.

The data from the US, Canada, and Latin American countries were analyzed separately. Within each country, we had access to individual data that revealed the cause of death, age of death, and year of death. The reported cause of death by PAHO was compared with the International Classification of Disease (ICD10) to define and categorize the cause of death due to CHD, stroke, and CVD. Since our study attempts to estimate the impact of sodium reduction on blood pressure related cases of CVD, we excluded those subjects whose CVD death was not related to elevated blood pressure. For example, I00-I02 was classified with ICD10 as Acute Rheumatic fever which is categorized as a CVD, however because it is not related to high blood pressure, we did not consider these individual cases as those that have died from CVD in our analysis. The details of the classification of diseases are outlined in Appendix A.

The total number of deaths in each category was separately calculated for males and females over the age of 20. To calculate the age specific death rate, in addition to mortality data from PAHO, we used the United Nations (UN) population estimates from 1995 to 2035. Within each sex, age groups were classified for every 5 years of age: 0-4, 5-9, 10- 14,. . ., 95-99, 100+. Since the UN population estimates were based on 5 year intervals, we used the following formula to calculate the average rate of growth between every 5 year cross-sectional snapshot to estimate the yearly age specific population for each of the four years in between.

$$
\alpha = (\frac{x_t}{x_{t-i}})^{1/i} - 1 \ \ where \ \ x_{t+1} = x_t * (1 + \alpha)
$$

For example the total number of females between the ages of 20-24 in 1995 was 1365000, and 1629000 in 2000. Using the above formula the estimated numbers between 1995 and 2000 are 1365000, 1414000, 1465000, 1518000, 1572000 and 1629000. The total number of years of mortality data for each country varied based on availability of data. For example, Costa Rica had data from 1997 to 2007, and Guatemala only had data from 2005 to 2006. In comparison with other years, a stark difference was observed between the 2006 and 2007 mortality data and thus excluded from our analysis. For this reason, we used the reported total number of deaths due to specified diseases and total population between 1997 and

Country	Available Data	Country	Available Data
Anguilla	$2000 - 2006$	Guyana	$2001 - 2005$
Antigua and Barbuda	$2000 - 2006$	Haiti	1997 - 2004
Argentina	$1997 - 2006$	Martinique	$2000 - 2005$
Aruba	$1999 - 2006$	Mexico	$1998 - 2006$
Bahamas	$1999 - 2005$	Montserrat	1995 - 2006
<b>Barbados</b>	$2000 - 2003$	Netherlands Antilles	$1988 - 2000$
Belize	$1997 - 2005$	Nicaragua	1997 - 2005
Bermuda	$1996 - 2006$	Panama	1998 - 2006
<b>Bolivia</b>	$2002 - 2003$	Paraguay	1996 - 2006
<b>Brazil</b>	$1996 - 2005$	Peru	1999 - 2004
Canada	$2000 - 2004$	Puerto Rico	1999 - 2005
Cayman Islands	1998 - 2004	Saint Kitts and Nevis	1996 - 2006
Chile	1997 - 2005	Saint Lucia	1996 - 2002
Colombia	1997 - 2006	Saint Pierre and Miquelon	2005
Costa Rica	1997 - 2007	Saint Vincent and the Grenadines	$2000 - 2004$
Cuba	$2001 - 2006$	Suriname	1995 - 2005
Dominica	$2001 - 2006$	Trinidad and Tobago	1999 - 2002
Dominican Republic	1996 - 2004	Turks and Caicos Islands	1996 - 2006
Ecuador	$1997 - 2006$	United States of America	1995 - 2005
El Salvador	$1997 - 2006$	Uruguay	1997 - 2004
French Guiana	$2001 - 2005$	Venezuela	1996 - 2005
Grenada	$2000 - 2007$	Virgin Islands (UK)	1996 - 2004
Guadeloupe	$2000 - 2005$	Virgin Islands (US)	1999 - 2005
Guatemala	$2005 - 2006$		

Table 2.1: Available Mortality Data for Latin American Countries

2005 as the reference in our calculation. We calculate the "cause-specific mortality rate" (CMR) of CHD, Stroke, and CVD per year for males and females separately.

$$
CMR = \frac{Number\ of\ deaths\ from\ a\ specific\ cause\ during\ a\ specified\ time\ period}{Mid-interval\ population}
$$

Table 2.1 represents the complete list of countries with available mortality data throughout the years considered.

We calculated the average of the estimated cause-specific mortality rate of each country based on the provided data. If the mortality data was not provided from 1997-2005, then we did our calculation based on available data. For example, Bolivia only has information from 2002-2003, therefore we took the average of two-year-cause-specific mortality rate in this case. The results of our calculation is presented per thousand people in Table 2.2 for all 18 included Latin American countries, Canada and the United States, stratified by gender.

		Male			Female		
Country	Population>	<b>CMR</b>	<b>CMR</b>	<b>CMR</b>	CMR	CMR	<b>CMR</b>
	20 (2012)	(CHD)	(Stroke)	(CVD)	(CHD)	(Stroke)	(CVD)
Argentina	27,852,376	1.08	0.98	3.88	0.66	0.90	3.39
<b>Bolivia</b>	5,648,058	0.11	0.18	0.51	0.07	0.17	0.42
Brazil	133,050,293	0.89	0.85	2.42	0.61	0.76	2.05
Chile	12,218,126	0.93	0.76	2.20	0.65	0.76	2.01
Colombia	29,785,217	1.12	0.54	2.16	0.83	0.59	1.90
Costa Rica	3,163,816	1.07	0.39	1.86	0.78	0.43	1.61
Cuba	8,568,503	2.02	0.98	4.00	1.74	1.04	3.71
Dominican Republic	6,280,801	0.65	0.50	1.63	0.49	0.42	1.39
Ecuador	8,547,081	0.41	0.41	1.70	0.27	0.39	1.52
El Salvador	3,675,750	0.76	0.32	1.66	0.60	0.30	1.47
Guatemala	7,821,191	0.47	0.30	1.56	0.33	0.27	1.35
Mexico	71,855,349	0.92	0.43	1.70	0.71	0.46	1.60
Nicaragua	3,322,998	0.66	0.41	1.42	0.56	0.41	1.31
Panama	2,271,349	0.79	0.72	1.85	0.58	0.67	1.56
Paraguay	3,803,094	1.11	1.20	3.32	0.78	1.30	3.09
Peru	18,481,149	0.24	0.22	0.85	0.19	0.22	0.84
Uruguay	2,381,676	1.61	1.47	4.42	1.13	1.73	4.26
Venezuela	18,534,633	1.37	0.57	2.44	0.93	0.59	2.04
Canada	26,770,251	1.96	0.55	3.06	1.54	0.75	2.94
US	236,203,290	2.45	0.61	3.87	2.21	0.90	3.49

Table 2.2: Population For 20+ and Their Cause-Specific Mortality Rate (per 1000)

The estimated average of cause-specific mortality rate is then multiplied by the population number to approximate the total number of deaths due to these diseases from 2006-2035.

$$
Average = \frac{total\ number\ of\ death\ per\ year}{Estimated\ population}
$$

#### 2.2.2 Design of the model

In general, two different methods have been used to estimate the relationship between sodium reduction and CVD. The direct method estimates the CVD reduction through a decrease in sodium intake. The indirect method, estimates the impact of lowered sodium intake on blood pressure and ultimately its influence on the reduction of CVD. The effect of sodium reduction on CVD, where blood pressure is considered as an intermediary variable, has shown to be a sufficient method [31, 55, 74]. The association between blood pressure and the risk of CVD appears to be independent of other risk factors, showing that the higher the blood pressure, the greater the risk of CVD [75].

	Amount of change	Hypertensive		Normotensive	
Salt	Sodium	Change in Systolic	Change in Diastolic	Change in Systolic	Change in Diastolic
9 grams	3540	$10.7\,$	5.8	5.4	2.5
6 grams	2360		3.9	3.6	
3 grams	1180	3.6	1.9	$^{1.8}$	$0.8\,$
Adapted from He et al (2002)					

Table 2.3: The Magnitude of Change in Blood Pressure Through Sodium Reduction

The goal of our method was to estimate the number of CVD events and deaths that would be reduced each year in the US, Canada and Latin American populations given different scenarios of reduction in sodium intake (5% and 10% reduction) using the indirect method. To estimate the association between sodium intake and blood pressure over time we have used the Meta analysis by He and MacGregor [50, 76]. Through the reduction of 3, 6, and 9 grams of salt, He et al show the magnitude of changes in systolic and diastolic blood pressure for hypertensive and normotensive cases separately. Table 2.3 presents further details.

In this analysis, the magnitude of change in blood pressure was calculated based on the mean arterial pressure  $((2^*$ diastolic $)+$ systolic $)/3$ . Therefore the changes for blood pressure corresponding to a 3, 6, and 9 gram reduction of salt intake is equivalent to 2.47, 4.97, and 7.43 units in hypertensive and 1.13, 2.33, and 3.47 units in normotensive. To be able to estimate the amount of change in blood pressure corresponding to different amounts of sodium reduction, we used a linear regression model to estimate the reduction of blood pressure as a result of reducing sodium intake. We assumed no change in sodium reduction implied no change in blood pressure. Hypertensive and normotensive groups were examined separately due to the varying results of the influence of sodium reduction on blood pressure in these two groups. In the next step, to estimate the relationship between blood pressure and CVD we used the result of a Meta analysis by Psaty et al at 2003 [77]. They have reported the relative risk (RR) of CVD events and CVD mortality, comparing Placebo, Low-Dose Diuretic and several other drugs. We used the relative risk corresponding to the low-dose diuretic versus placebo trials as they best represent the potential impact of sodium reduction on blood pressure and CVD mortality. Their analysis showed the reduction of 13.2 mmHg in systolic blood pressure and 4.9 mmHg in diastolic blood pressure corresponding to the amount of changes of relative risk in CHD, stroke, and CVD. The relative risk and

Outcome	RR(95 percent CI)				
<b>CHD</b>	$0.79$ $(0.69 - 0.92)$				
Stroke	$0.71(0.63 - 0.81)$				
CVD events	$0.76$ $(0.69 - 0.83)$				
<b>CVD</b> Mortality	$0.81$ $(0.73 - 0.92)$				
Adapted from Psaty et al.					

Table 2.4: Association Between Change in Blood Pressure and CVD

its 95% confidence interval for each disease are shown in Table 2.4.

We used previous studies to find the average level of sodium intake for the Unites States, Canada, and 10 Latin American countries. We used the average sodium intake of these 10 Latin American countries in order to estimate the averages of the 8 remaining countries that originally did not have available data on average sodium intake. The ten countries that were used to estimate an average for the remaining 8 included: Argentina, Bolivia, Brazil, Chile, Costa Rica, Cuba, Ecuador, Guatemala, Mexico, and Uruguay. The average sodium intake of mentioned countries was 3880 mg.

We used linear regression analysis and assumed that no change in blood pressure would result in no change in relative risk. The linearity between blood pressure and the risk of CVD has been shown by Lewington et al (2002) and Anderson et al (1991) [75, 78]. Using a regression line, we estimated the effect of gradual changes in blood pressure due to different levels of sodium reduction in the diet on the relative risk of each disease over time.

As we mentioned in the above table, the RR of CVD Mortality and CVD events is available separately. It is worth mentioning that the PAHO data provided to us only considered CVD mortality. Therefore, the RR of CVD mortality became an appropriate measure of effect to use in our analysis. In the case of CHD and stroke, the Psaty study (2003) only provides us RR of combined fatal and non-fatal cases, and unfortunately we did not have access to mortality RR separately. To overcome these challenges, we used two different approaches in our analysis.

#### 2.2.3 Method 1:

Since the RR of CVD mortality was very close to the upper bound of RR of CVD events, we considered the upper bound of relative risk of CHD and stroke events (95% CI) as an appropriate candidate for RR of CHD and stroke mortality. This was used to estimate the number of lives saved for each disease after reducing 5 - 10% sodium intake per year.

To accurately estimate the total number of preventable cases, we treated normotensive and hypertensive cases separately because the change in blood pressure from sodium varies between normotensives and hypertensives. We used the Framingham estimates of the proportion of CHD (70%) and stroke (84%) events that occur in hypertensive patients for each country studied [79, 80, 81]. In the case of total CVD, which is the sum of CHD, stroke and other CVD related diseases, we used the average proportion of CHD and stroke events that occurs in hypertensive as our reference for total CVD. The rest of the population was considered to be normotensive individuals. With these assumptions, the process of our analysis was as follows. For each country, we used the average sodium intake and reduced it by 10% every year. The reduction was then used to estimate the magnitude of change in blood pressure in both normotensive and hypertensive populations separately. Based on the change of blood pressure, we were able to estimate the change in relative risk of CHD, stroke and CVD to estimate the number of lives that could be saved per year. The estimated total number of deaths due to each disease from 2012 was used as our starting point. We used "1-RR" to estimate the total number of preventable cases for each disease. To estimate the RR for the years following the first year, we did the following:

- We assumed the risk at the baseline is equal to A
- After 10\% reduction our risk is equal to B
- If we reduce another  $10\%$  it becomes C
- The relative risk associated to this intervention  $(10\% \text{ reduction in the first year})$ , is equal to  $\frac{B}{A}$
- The relative risk for the second 10% reduction is equal to  $\frac{C}{B}$
- Therefore to estimate the relative risk (after the first and second 10% reduction) we multiplied the relative risk of the first 10% reduction and the second 10% reduction which is equal to ( $\frac{B}{A} * \frac{C}{B}$  $\frac{C}{B}$

Using PAHO and UN data, we had previously estimated the total number of death per year per country without applying any specific intervention. To have an accurate estimate,

Country	Sodium	$1-RR$ Hy-	1-RR Nor-	Prevented	Prevented	Prevented
	(mg/day)	pertensive	motensive	Stroke	<b>CHD</b>	<b>CVD</b>
Argentina	4720	0.024	0.011	537	173	1897
<b>Bolivia</b>	3930	0.020	0.010	17	3	41
<b>Brazil</b>	3930	0.020	0.010	1827	596	4636
Chile	3930	0.020	0.010	158	58	402
Colombia	3880	0.020	0.009	283	171	929
Costa Rica	3930	0.020	0.010	22	18	86
Cuba	3750	0.019	0.009	141	92	492
Dominican Republic	3880	0.020	0.009	49	21	146
Ecuador	3930	0.020	0.010	58	17	215
El Salvador	3880	0.020	0.009	19	15	88
Guatemala	5900	0.030	0.014	53	26	247
Mexico	2800	0.014	0.007	398	217	1278
Nicaragua	3880	0.020	0.009	23	12	70
Panama	3880	0.020	0.009	27	9	60
Paraguay	3880	0.020	0.009	80	21	188
Peru	3880	0.020	0.009	69	23	240
Uruguay	1960	0.010	0.005	33	10	80
Venezuela	3880	0.020	0.009	181	126	640
Canada	3400	0.018	0.008	257	242	1087
US	3370	0.017	0.008	2606	2820	11632

Table 2.5: Number of Lives Saved Following First 10 Percent Sodium Reduction

we had to take into account the total number of prevented cases in our calculations. The preventable cases need to be subtracted from the total number of deaths that was estimated without considering any specific interventions. Table 2.5 shows the number of lives saved due to stroke after the first year of a 10% sodium reduction in the Latin American countries, the US and Canada.

In our analysis, we started with the average sodium intake of each country. In the next step we reduced the sodium intake by 10%, and estimated the total number of lives that can be saved due to this reduction. We repeated this process until the average sodium intake in the population reached the optimal level (1200 mg). The left side of Table 2.6 shows the number of lives that can be saved per year in Canada with a 10% sodium reduction per year and the right side of the table corresponds to the 5% sodium reduction per year. Based on our analysis, if we start the 10% sodium reduction per year from 2012, we will reach the optimal level of sodium intake by 2022 and we can prevent 49,436 CVD related death in Canada during this time. When we reduced the amount of sodium reduction by 5% per year the number of prevented cases after 10 years of reduction dropped to 29,625 cases while

	$10\%$ reduction per year			5% reduction per year				
Years	Sodium level	Stroke	<b>CHD</b>	<b>CVD</b>	Sodium level	Stroke	<b>CHD</b>	<b>CVD</b>
1	3400	280	291	1240	3400	140	146	620
$\overline{2}$	3060	646	555	2329	3230	337	286	1209
3	2754	958	795	3294	3069	522	422	1772
4	2479	1230	1014	4156	2915	697	554	2311
5	2231	1463	1211	4910	2769	859	679	2815
6	2008	1668	1390	5586	2631	1012	800	3297
7	1807	1850	1554	6197	2499	1156	916	3757
8	1626	2014	1706	6754	2374	1293	1030	4200
9	1464	2162	1847	7265	2256	1424	1139	4626
10	1317	2288	1970	7707	2143	1544	1242	5018
11	1186	2403	2084	8112	2036	1658	1341	5395
	Total	16963	14418	57548	Total	10644	8554	35020

Table 2.6: Number of Lives Saved in Canada after 5-10% Sodium Reduction per Year

the level of sodium intake in the population reached 2036 mg per day. The details of the analysis stratified by gender and hypertension status are presented in Appendix B.

We repeated the analysis for United States and all 18 Latin American countries. Table 2.7 presents the summary of our results for United States and Latin American countries. The second column of this table shows the total number of years that each country needs to reach the optimal level of sodium intake. The columns three to five show the total number of lives that can be saved due to stroke, CHD and total CVD for each country. The complete table stratified by gender and hypertension status is presented in appendix B.

The analysis was repeated with UN data for the population over 20 years old and the PAHO mortality data for 2012, but this time, to calculate the total number of preventable cases, we considered a constant number of deaths over time. The total number of deaths in 2012 for each country was considered as our reference. Our results showed that the total number of preventable cases is slightly different when we are using a constant number of deaths compared to a population growth technique. The summary table for the Latin American countries and the complete table for the United States and Canada is included in appendix B.

To check the sensitivity of our results to the average cause-specific mortality rate, we repeated the analysis by using the weighted average cause-specific mortality rates. The weight was spread out over the years with the most recent years having the most weight depending on the availability of data. Our result confirms that the model is not very sensitive

Country	Years	Prevented Stroke	Prevented CHD	Prevented CVD
Argentina	14	48948	15130	141897
<b>Bolivia</b>	12	1373	229	2677
Brazil	12	138831	41591	284672
Chile	12	11864	4000	24455
Colombia	12	22218	12280	58814
Costa Rica	12	1739	1266	5441
Cuba	12	9979	5996	28211
Dominican Republic	12	3799	1507	9201
Ecuador	12	4561	1241	13630
El Salvador	12	1493	1038	5520
Guatemala	16	6800	3359	26516
Mexico	9	20089	9625	51510
Nicaragua	12	1867	891	4616
Panama	12	2099	666	3807
Paraguay	12	6510	1580	12329
Peru	12	5377	1683	15166
Uruguay	5	2577	659	5003
Venezuela	12	14384	9161	40923
US	11	171449	167369	614792

Table 2.7: Number of Years and Lives that Can be Saved to Reach Optimal Level of Sodium (10% yearly reduction)

to the different weighted average cause-specific mortality rates. The details of our findings can be found in appendix B.

As mentioned before, we treated the normotensive and hypertensive cases separately, because the amount of change in their blood pressure due to a specific level of sodium reduction varies from case to case. In the real world, some hypertensive cases are on medication and their level of blood pressure is already controlled. Therefore, those hypertensive people who are treated can be considered the same as normotensive cases. We assume the level of BP reduction in controlled hypertensives to be the same as normotensives. For our own study, we used the exact percentage of controlled hypertensive cases from ten different Latin American countries as reported in the Latin American guidelines on hypertension by Sanchez (2009) [20]. For the remaining eight Latin American countries, we used the average of the reported controlled hypertensive cases to estimate the percentage of hypertensive cases versus normotensive cases. The highest percentage of controlled hypertensive cases was from Argentina at 18%, whereas the lowest percentage came from Paraguay at 7%. The average of the ten countries that was used for the remaining eight was 12.49%. Based on the Framingham study, we know that 84% of strokes occurred in hypertensive and 16% in normotensive groups. For example, in Argentina the percentage of controlled hypertension is 18%. Therefore, we multiplied the percentage of strokes in hypertensive cases (84%) with the percentage of controlled hypertensives (18%) to calculate the percentage of hypertensive cases (15%) which need to move to the normotensive group. As a result, our numbers shift to 69% for hypertensive cases and 31% to normotensive cases. According to the Centers for Disease Control and Prevention (CDC), in 2011 half of the adults with elevated blood pressure have it under control [82]. Therefore the percentage of controlled hypertensive cases in US is considered 50% in this analysis. We considered a hypertension control rate of 66% in Canada [83]. We applied the appropriate percentage of control to all three cases (average rate, weighted average rate, and constant number of deaths) and estimated the total number of lives that can be saved over time. The details of the analysis can be found in appendix B.

#### 2.2.4 Method 2:

As mentioned previously, the relative risk of events is available; however, the relative risk of mortality for CHD and stroke is unavailable. In addition, the total number of fatal cases due to each specific disease in each country per year is available to us, but we are unaware of the total number of non-fatal cases. We used the 2002 Canadian Mortality Database of Statistics Canada, and hospitalization data from the Canadian Institute for health information. These data were unique to our study because, unlike other studies, they provided both total and fatal cases of CHD, stroke, and heart failure. We calculated the proportion of total to fatal CHD, and stroke between the years 1995 to 2002 for males and females separately. In the next step we multiplied these proportions by the total number of fatal cases of each disease per year per country to estimate the total number of events (both fatal and non-fatal cases) of CHD and stroke per year, per country, stratified by gender. To avoid overestimation of number of preventable events, we chose the minimum proportion within the stated years as the reference to apply to our analysis. Table 2.8 presents the minimum of these proportions.

It is important to mention that CVD includes stroke, CHD and other additional diseases. In the case of CVD, to estimate the proportion of total events to fatal cases of CVD, we used the weighted average of proportions of CHD, stroke and heart failure, due to the large difference between the number of heart failure fatal cases versus the fatal cases of CHD or stroke as well as their difference in terms of proportion of total events to fatal cases which

Disease	Male	Female
<b>CHD</b>	3.4	2.6
Stroke	3.4	2.5
<b>CVD</b>	4.4	3.6
Heart failure	13.4	9.6

Table 2.8: Proportion of total CVD events to fatal CVD cases

has been shown in Table 2.8.

We didn't have access to the total number of CHD, Stroke and CVD events for the United States or the Latin American countries. Seemingly, the proportion of non-fatal to fatal CHD and stroke in Canada was close enough to two previous studies [84, 85] to make a confident assumption that Canadian data could be used as our reference to estimate the total number of events of each disease for the United States and Latin American countries as well. The total number of preventable cases of CHD, stroke and CVD as a result of 10% reduction in sodium intake per year for the Latin American countries, the Unites States and Canada are shown in Table 2.9.

Additionally, the different scenarios that were examined in the first approach were repeated using relative risk of events instead of relative risk of mortality. The summary for each scenario is presented in Appendix B.

The result of these analyses can be used further in more complex models to simulate or estimate the cost savings of such an intervention. However, in the absence of such a model we can attain a rough estimate of the potential total costs saved due to an intervention of this kind. Simply, we can multiply the hospital cost of an individual affected by CHD, stroke and CVD with the number of preventable cases due to a specific amount of sodium reduction (5% or 10%). This sum underestimates the total savings as it does not consider medicine costs, post-disease treatment costs, short term employment absence, and other indirect costs.

#### 2.3 Discussion and future work

CVD as the single largest risk factor for mortality worldwide has a major impact on both developed and low/middle income countries. Although resources, capacity, and priorities

Country	Years	Prevented Stroke	prevented CHD	prevented CVD
Argentina	14	156955	109079	687453
Bolivia	12	4453	1701	13188
Brazil	12	449658	306182	1396816
Chile	12	38190	29433	119621
Colombia	12	70796	90069	288091
Costa Rica	12	5578	9340	26787
Cuba	12	32097	43728	138231
Dominican Republic	12	12422	11082	45280
Ecuador	12	14753	9201	66851
El Salvador	12	4758	7503	26823
Guatemala	16	21580	23257	126848
Mexico	9	65719	71736	254313
Nicaragua	12	5995	6489	22583
Panama	12	6817	4918	18756
Paraguay	12	20882	11692	60460
Peru	12	17301	12347	74079
Uruguay	5	8196	5042	24757
Venezuela	12	46295	67832	201559
Canada	11	53718	107148	282893
US	11	538900	1232384	3029447

Table 2.9: Total Number of Prevented Cases in Canada, US and LA Countries

vary across countries, empirical research has suggested that reducing salt consumption as one of the available interventions can be an effective approach in reducing CVD [86]. Most of the studies that have investigated the impact of sodium reduction on CVD or blood pressure as a major risk factor for developing CVD have been conducted in developed countries. In this project, we used available mortality data from PAHO to examine the impact of gradual sodium reduction on CVD mortality and CVD events through the reduction of blood pressure in 18 different Latin American countries as well as Canada and the United States. In addition to the advantage of considering gradual decrease of sodium in our study, we also excluded those subjects whose CVD death was not related to elevated blood pressure to avoid overestimation in our analysis. Subjects over the age of 20 are considered in this analysis, and are stratified by gender and their hypertension status.

Although CVD mortality has shown decreasing trends during the 20th century in developed countries [86], over time the decrease has slowed down and it is not clear whether or not future trends will be sustained, increase or decrease. For this reason, we neither used the regression analysis based on available mortality data from previous years nor did we use the average growth rate of cause specific mortality rate to extrapolate the future trend of CVD. Instead, we have used the average and weighted average cause-specific mortality rate to estimate the total number of preventable cases of CHD, stroke, and CVD. Our analysis confirms that the model is not very sensitive to the specific weight assigned to each year.

Since low-dose diuretics are the most effective first-line treatment, in our analysis we have used the RR of a low-dose diuretic versus a placebo (from Psaty 2003) [77, 87]. It could be argued that we did not use the strongest relative risk between sodium reduction and blood pressure in our analysis [57, 78]. Our reason for not following these studies is that we preferred to be conservative and show the minimum impact of this intervention instead of being in danger of overestimating the association. Our goal was to highlight the massive benefit that we can receive from this action at the population level.

We could attain a rough estimate of the minimum potential total cost savings due to this intervention, which is equal to the total hospital cost per country, multiplied by the number of events. However, rough estimates of the total cost savings due to sodium reduction is presented in several studies [32, 65, 71, 72, 88, 89, 90, 91, 92, 93]. For example, using a simulation model, Bibbins-Domingo et al (2010) estimated reduction in salt intake of 3 g/day saves 10-24 billion in annual medication costs in the United States. Joffres et al (2007) estimated the benefits of sodium reduction on health care costs in Canada when considering a onetime sudden reduction (1840 mg/day) of sodium in the population. Based on their analysis, the direct cost savings are estimated to be approximately \$430 million per year. Rubinstein et al (2009) compared the cost effectiveness of six individual interventions in Argentina. Based on their analysis, lowering salt intake is a strategy considered to be a cost effective approach in Argentina.

There are other studies in the United States that have estimated the benefits of sodium reduction on health care systems. To our knowledge, this is the first study that has considered the gradual impact of sodium reduction on different populations, specifically Latin American countries. Therefore, to have an accurate estimate of the total benefits of population-based reduction in dietary sodium, we need to have access to the cost of hospital, laboratory, and physician office visits, antihypertensive drugs, as well as the relative size of the public and private health sectors in each country, each of which needs further analysis.

Since we did not have the total number of CHD, stroke, and CVD events for countries other than Canada, we used Canadian data to estimate the total number of events in order to project the total number of preventable cases per year for the Latin American countries
		Canada	Unites states		
		Number of lives that can be saved	Number of lives that can be saved		
Method	Uncontrolled Controlled		Uncontrolled	Controlled	
Constant	49,615	34,696	531,287	410,200	
Average rate	49,436	35,181	527,960	412,532	
Weighted average rate	48,541	34,554	510,125	398,709	
		Canada	Unites states		
		Number of events that can be prevented		Number of events that can be prevented	
Method	Uncontrolled	Controlled		Controlled	
Constant	248,562	174,205		2,063,093	
Average rate	243,447	174,439	2,606,176	2,045,960	
Weighted average rate	239,030	171,321	2,519,645	1,978,581	

Table 2.10: Comparing the Results of Three Different Scenarios After 10 Years (10% Yearly Sodium Reduction)

and the United States. However, based on previous studies, it is important to note that both developed and developing countries are similar in terms of high prevalence of CVD in the population.

Furthermore, we did not have the exact distribution of sodium intake for each population so we used the average level of sodium intake in each population based on previous studies, taking into account that results may demonstrate an overestimation or underestimation.

Table 2.10 shows the total number of CVD related deaths that can be prevented after a yearly 10% reduction in sodium intake as well as the total number of CVD events that can be prevented in Canada and the United States after 10 years, considering all three scenarios (Constant number of deaths, average cause-specific mortality rate, and weighted average cause-specific mortality rate) with or without controlling for hypertensive individuals that are on medications.

Although cardiovascular disease is a major public health problem, with a small change, such as sodium reduction, we can see massive differences in population health, as we have seen in our results. Our analysis is an example of an aggregate model. This means that further analysis of individual characteristics are needed to have a better understanding of the impact of sodium reduction on blood pressure, as well as cardiovascular diseases. To increase the level of accuracy in our estimate, we need improved access to certain information such as: the population distribution of sodium intake, blood pressure, and age; as well as the percentage of hypertensives, the percentage of hypertensives on medication, the percentage

of people who are either unaware of their blood pressure, or are aware but untreated. We need to have a better estimates of relationship between sodium intake and blood pressure stratified by age and sex as well as blood pressure and CVD by age and sex. This information can help create a more accurate vision for the future of public health, and can be used in a more complex model to explore the dynamics of CVD trends in the future.

# Chapter 3

# Individual decision making

The previous chapter highlighted the need, importance and impact of a specific intervention at the population level, such as a gradual sodium reduction, and its influence on population health and our society. Since this approach needs strong support from policy makers, governments, and, in particular, the food industry, each of us as an individual does not have much power to make these population level changes. Therefore, the next question is: What can we do in the absence of or in addition to a population level action? How can our awareness and willingness to change affect our regular sodium consumption as an individual?

## 3.1 Introduction

About 5000 years ago, Chinese people discovered salt as a method of food preservation that was also used as a trading commodity in place of money. Salt intake level around the 1870s reached its highest peak but with the invention of deep freezers and refrigerators, salt usage declined as it was no longer required as a preservative. With technology and innovation, processed foods arrived to accommodate the modern lifestyle of the 21st century. As such, salt intake increased due to the need to increase shelf life, but also for the improvement of food taste. One of the many problems with our sodium consuming world is that the more salt we add, the more our palate demands it [50, 94]. In most countries, the demands are returning back to those levels of the 1870s at approximately 3500-4700 mg/day [41, 66, 95]. In reality, our bodies only need about 200 mg/day salt, with a recommended level of 1200- 1500 mg/day and an upper limit of 2300 mg/day [47]. However, based on Statistics Canada,

Canadian consumers are on average exceeding the recommended level and consuming about 3600 mg/day.

It is undeniable that sodium is needed to maintain a healthy body but excess amounts of sodium present challenges to the kidneys, a rise in blood pressure, risk of obesity and CVD, and stomach cancer [41, 96]. Based on results from the 2004 Canadian Community Health Survey (CCHS)-Nutrition (Statistics Canada), we are able to point out that among adults aged 19 to 70, more than 85% of men and 60% of women had sodium intake higher than the recommended upper limit which increases overall health risks [97]. As mentioned above, a rise in high blood pressure is one of the consequences of the excessive intake of salt which leads to CVD. He and Macgregor [66] state that a high level of sodium is a contributor to the high prevalence of hypertension in Western societies. Supporting this statement, the World Health Organization (2002) reports that high blood pressure is estimated to be the leading risk factor for death in the world. In Canada alone, an estimated 15000 people are dying every year due to the excessive consumptions of sodium [98]. With current modern lifestyles, more than 90% of people are likely to develop hypertension, affecting approximately 19% of the adult Canadian population [15, 19, 21].

It has been estimated that a universal reduction in sodium intake close to 1150 mg/day could avoid 22% deaths from strokes and 16% deaths from coronary heart diseases [99]. In particular, using the Canadian Heart Health survey data shows that reducing sodium intake by 1840 mg/day in Canadian population may decrease hypertension prevalence by 30%. The direct cost savings associated to this action is estimated to be approximately 430 million (dollars) per year [72]. The impact of reducing dietary sodium intake is more pronounced in terms of the total number of cases/events that can be prevented compared to deaths. In 2008, Penz et al [10] estimate about 23,000 CVD events per year could be prevented by reducing dietary sodium intake (1800 mg/day) in the Canadian population. Estimates varied from 14,500 to 21,500 events per year when hypertension control rates were considered at 13% to 66%. While targets for a reduction in daily sodium intake have been clearly set, the population appears to be well beyond the guidelines.

Several public health measures have been taken to reduce sodium intake, particularly in processed foods (e.g., Groupe SALT in France), such as regulations to lower the salt content of prepared foods, education campaigns to raise awareness in the population, and clear labelling of the salt content (e.g., 'Pick the Tick' in Australia, traffic light labelling in the UK) [100, 101, 102]. Since 77% of total sodium intake comes from processed and

restaurant foods [43], lowering the sodium content of processed foods has been considered as a key solution to lowering blood pressure [103], along with initiatives such as adopting a healthier behaviour that includes more fresh foods. However, changing our lifestyles is not the only necessary measure, we also need to maintain and sustain these changes in the long term.

Research often recommends a population-wide reduction in sodium intake but little attention has been paid to what is happening at the point of purchase and individuals level. Fortunately a recent study in Australia showed that in the absence of a major change in sodium content of food products, a significant decrease in sodium could be achieved if customers received a basic training regarding food labels [104]. The work in this chapter focuses at what can be done at the individual level and investigates whether a significant decrease in sodium intake can also be met when customers do not change their lifestyle but are able to select healthier products. We examined the potential role of individual decisionmaking on daily sodium consumption by exploring the distribution of sodium content among supermarket foods. We also explored the association between sodium content and product price in three main food categories in both Canada and France. Prices are particularly important, as it was reported that 60% of shoppers would be more likely to buy a product with reduced salt if there was no difference in price [105]. Using our selected data, we computed the lowest, highest and average sodium content that consumers could achieve. We precisely matched products between Canada and France (e.g., canned raviolis, whole wheat slice bread), in order to compare sodium contents between the two countries

### 3.2 Method

The main goal of this study was to analyze the sodium content in the food categories accounting for the largest daily sodium intake in the western population. The sodium content was collected via food labels from January to March 2010 for 825 items in Vancouver (Canada), and 503 items in Nice (France). We focused on processed foods, as it accounts for about 77% of the sodium intake in industrialized countries [106]. The stores chosen for the data collection are representative of the national trends. In Canada, almost half of food purchases are from supermarkets. Data collection in Canada was conducted in Vancouver (British Columbia), which is the third largest Canadian market [107]. The supermarkets chosen in Vancouver and their estimated national market shares are: Safeway (9%), Real Canadian Superstore (35% as part of Loblaw), Save on Food (4% as part of Overwaitea), and Nester's Market [108]. Data collection in France was conducted in Nice, which also holds a significant national market share as the fifth most populous French city. The supermarkets chosen and their estimated national market shares are [109]: Carrefour (12.8%), Auchan  $(8.6\%)$ , Carrefour Market  $(8.5\%)$ , and ED  $(2.5\%)$ .

#### 3.2.1 Definitions of food categories

Food was categorized using the United States Department of Agriculture food coding scheme. Food items were systematically reviewed both in France and Canada for the three food categories that account for the largest daily sodium intake, using a recent report for the United States population [46]: grains (e.g., cereals, breads, canned vegetables and processed food such as corn, lasagna, ravioli, and spaghetti), meat/fish (e.g., bacon, sausages, ham, fish, chicken/beef broth, soups/sauce, and ready meals where meat is the main ingredient), and vegetables (e.g., vegetable soups/sauce, canned/frozen vegetables, vegetable stock/juice, and potato chips). Each food item was classified using a three level hierarchy. First, an item was assigned to grains, meat/fish, or vegetables. Items were further categorized using selected subcategories. Finally, when possible, variations over a same product were gathered in order to compare products between countries (e.g., ready-made lasagnas, light mayonnaise). For each food item, we recorded the price, and the following information from the food label: brand name, product name, weight, quantity, sodium and calories. During the organizing and cleaning process we excluded 163 Canadian items and 75 French items from our analysis due to two possible reasons. First, we eliminated products with unclear labelling, such as freeze dried soups in which the content was based on powder weight or on volume after adding sometimes unknown quantities of water. Secondly, we eliminated products when no equivalent subcategory could be found in the other country. In order to ensure that values were correctly recorded, we compared the sodium content of each food item with the content for items in the most specific category available. For example, the sodium content of lasagna was compared with other lasagnas; if no other lasagnas were available, then the comparison would be made with dishes containing pasta and meat. When the content in the item appeared significantly different from similar food products, the conductors re-checked the labels by returning to the supermarket where the item was originally collected. This additional checking took place from August to September 2010.



Figure 3.1: Sodium content (mg) per kcal (a) and per 100 g (b) in France and Canada for the three main food categories

### 3.2.2 Data analysis

One of the challenges in our analysis was the lack of a standard weight for labels in Canada. For example the contents of BBQ sauces among the items collected were reported using serving sizes such as 15g, 30g, and 37g. The same issue exists regarding the weight of packages. To be able to analyse the relationship between sodium content and price of product accurately, we normalized these quantities and expressed them per 100 g. Labels in France always provide a standard weight of 100g.

Two analyses were conducted using STATA 9. First, we focused on descriptive analysis and explored the distribution of sodium content within and between both countries. Second, we used correlation statistics to investigate the association between sodium content and price of the products in each category. Although the distribution of our data was reasonably normal, we performed both parametric and nonparametric analyses. The result of the nonparametric test (Spearman's and Kendall's correlation) agreed with the parametric test. Since individuals on diet programs (e.g., weight watchers) commonly measure their intake in kcal to control their daily energy intake, we completed the analysis by studying the association between sodium content expressed per kcal, and price. In this situation, we used Pearson's correlation statistic as the data were approximately normal.

### 3.3 Results

The summary statistics of sodium content of processed foods are presented in Figure 3.1 for the three main food categories in each of the countries.



Table 3.1: Average, Minimum and Maximum Sodium Content in Each Categories



Figure 3.2: Sodium content (mg) per kcal (a) and per 100 g (b) in France and Canada in ready to eat breakfast cereals, ready meals, canned vegetables, and soups

Each bar plot describes the minimum, maximum, median, and the two quartiles surrounding the median. Outliers are shown as points, which represent observations that are numerically far away from the rest of the data (i.e., containing very low/high sodium in comparison with the rest of the data).

Table 3.1 presents the average, standard deviation, minimum and maximum sodium content in each category.

Figure 3.2 and 3.3 illustrate the same analysis for the subcategories in which a large enough sample of items was collected in both countries. Our analysis shows that a broad range of sodium content exists in each food category.

Based on previous studies, the cut-off points of 120 mg/100g and 500 mg/100g were used to calculate the percentage of food with low ( $< 120 \text{ mg}/100 \text{g}$ ) and high ( $> 500 \text{ mg}/100 \text{g}$ ) sodium content in each category [104, 110]. In general, more than a third of the products had high sodium content ( $>$  500 mg/100g). Furthermore, more French products than Canadian products have high sodium content ( $> 500 \text{ mg}/100 \text{g}$ ). Indeed, Table 3.2 shows that the



Figure 3.3: Sodium content (mg) per kcal (a) and per 100 g (b) in France and Canada in processed meat, chips, and sauces

			Canada		France		Combined
Category	Subcategory	Low $\%$	$\text{High}\%$	Low $%$	$High\%$	$\text{Low}\%$	High %
Grains	All	10	16	18	13	14	14
Grains	Cereals	41	29	22	11	26	14
Meat and Fish	All		39		60		46
Meat and Fish	Processed Meat	0	94		95		95
Meat and Fish	Ready Meal	$\overline{2}$			2		6
Vegetables	All		32	3	32	6	32
Vegetables	Cans		0	5	3	4	3
Vegetables	Chips		76	5	73	3	74
Vegetables	Sauces	0	100		63		87
	All	5	33	6	38	5	35

Table 3.2: Percentage of selected products with a low and high sodium content

percentage of products with high sodium content is higher in France compared to Canada in our selected sample. However, this trend is reversed for several important categories. For example, our analysis shows that this percentage is higher in Canada for Grains, ready to eat breakfast and ready meals (16%, 29% and 7% respectively) compared to France (13%, 11% and 2% respectively). The percentage of high sodium in processed meat is similar in both countries (94% vs 95%) and much higher in France than Canada for meat and fish (60% vs 39%). Discrepancies were observed between the mean sodium content that we recorded, and the mean sodium content given in the French food composition table (AFFSA). For example, lasagnas are listed with the mean sodium quantity of 333 mg per 100 g in the French food composition table, whereas in our selected products we found a range of sodium varying between 400 mg and 560 mg per 100 g, with a mean of 480 mg per 100 g.

		Canada			France			% Difference	
Category	Subcategory	mg/100	mg/kcal	items	mg/100	mg/kcal	items	$100$ g	100kcal
Grains	Cereals	308	0.87	17	299	0.86	76	$-3$	$-1$
Meat and Fish	Processed Meat	911	4.93	88	1089	5.62	94	20	14
Meat and Fish	Ready Meal	281	2.45	110	365	3.61	53	30	47
Vegetables	$\rm{Cans}$	262	3.82	21	279	9.35	59	6	145
Vegetables	Chips	652	1.24	38	737	1.45	62	13	17
Vegetables	Soups	255	7.36	32	297	8.37	41	16	14

Table 3.3: Average sodium content and percent change for subcategories in Canada and France

Table 3.4: Upper and lower quartiles of sodium density (mg/kcal) by food category and Country

		Canada			France		
Category	Subcategory	Upper Q	Mean	Lower Q	Upper Q	Mean	Lower Q
Grains	All	2.22	1.9	$1.6\,$	1.84	1.43	0.52
Grains	Cereals	1.33	0.87	0.12	1.2	0.86	0.47
Meat and Fish	All	5.77	8.2	2.2	6.1	4.86	3.1
Meat and Fish	Processed Meat	6.3	4.93	2.63	7.11	2.57	3.68
Meat and Fish	Ready Meal	2.86	2.42	1.85	4.23	3.62	2.82
Vegetables	All	7.22	5.61	1.88	8.33	5.97	1.49
Vegetables	$\rm{Cans}$	3.88	3.82	2.18	13.88	8.49	3.05
Vegetables	Chips	1.53	1.24		1.94	0.77	0.85
Vegetables	Sauces	7.33	7.8	3	7.78	2.96	3.46
Vegetables	Sauces	6.94	1.56	4.72	10	$2.5\,$	6.66

We summarize the sodium content for subcategories in which our item count was significant in both countries in Table 3.3. In our sample, we observe that the sodium content per 100 g is significantly higher in France for ready meals (30%), processed meat (20%), soups (16%), and chips (13%) compared to Canada. The comparison in sodium per calorie between France and Canada reveals differences in similar orders of magnitudes, but for canned vegetables this difference becomes more pronounced (about 1.5 times higher in France compared to Canada).

We also investigated the potential impact of consumer choice on his/her daily sodium intake. As shown in Table 3.4, there can be an important difference in sodium content whether one chooses the products with the mean, higher (i.e., in the upper quartile), or lower (i.e., in the lower quartile) sodium density.

To investigate whether the cost of products does not deter consumers from making

	Canada.				France			
		Sodium & Price	Sodium/kcal & Price		Sodium & Price		Sodium/kcal & Price	
Variable	R	P-value		P-value		P-value		P-value
Grains	$-0.158$	0.157	$-0.260$	0.016	$-0.032$	0.748	$-0.127$	0.207
Meat and Fish	0.150	0.008	0.062	0.276	0.610	< 0.001	0.600	${}< 0.001$
Vegetables	$\rm 0.305$	< 0.001	-	-	0.220	0.003	$-0.250$	< 0.001

Table 3.5: Association between sodium content and price, and sodium/kcal and price for Canada and France per category

healthier choices, we analyzed whether there were associations between price and sodium content in the three main categories. Our results are summarized in Table 3.5 and show that there is no significant association between price and sodium content except for meat/fish  $(r=0.15; p = 0.008$  in Canada;  $r=0.6; p < 0.0001$  in France) and for vegetables  $(r=0.31, p = 0.008)$  $p < 0.001$  in Canada; r=0.22, p=0.003 in France).

The association is surprisingly found in the opposite direction. Therefore, a higher price translated to increased sodium content, and particularly more so in French meats  $(r = 0.6)$ .

The association between price and sodium/kcal provides a different picture. In Canada, we found a negative association for grains  $(r=0.26; p=0.016)$  and a positive association for vegetables ( $P < 0.0001$ ). The negative association means that the price decreases as the sodium content increases. In France, the positive association was found for meats and fish  $(r=0.6; p < 0.0001)$  and the negative association for vegetables  $(r=-0.25; p < 0.0001)$ . We also noticed that the price of sodium free products can be significantly lower than similar products with a higher sodium level. For example, Canadian sodium free cereals cost 2/3 of the price of cereals having an average sodium content of 470 mg/100g.

### 3.4 Discussion

The literature on salt reduction strategies has proposed different possible actions to lower the salt content at the industrial level by acting on processed food. However, our data shows that there is also room for improvement at the individual level. In order to demonstrate the extent to which individuals would be able to reach the current sodium consumption guidelines, we collected data about processed food in French and Canadian mainstream supermarkets. Our contribution is twofold. Firstly, we compared the sodium content in France and Canada,

showing a very different picture. In particular, we witnessed a tendency toward larger sodium content in French products. This is particularly worrisome for some commonly eaten products, such as ready meals in which the sodium content is larger in France than in Canada by 30%. However, the total sodium consumption depends on individuals' eating patterns and data suggests that the total sodium consumption in France is slightly lower than the Canadian one. Our analysis showed large variation within categories of products. This has an impact on an individual's sodium intake as exemplified by the following situation. Consider an average U.S. adult, who daily consumes 746 kcal in grains, 410 kcal in meat and 161 kcal in vegetables [46].

Based on our selected data, if this individual was to feed mostly on processed food but chose from amongst the best possible products available, then his or her daily sodium intake would be close to 2400 mg. However, at the other end of the spectrum, the individual could reach 5200 mg. While these are extremes, it highlights that there is a large margin for consumers to lower their sodium consumption, provided that labelling allows efficient comparison of products. Furthermore, one concern possible is that while products with lower sodium content are available to individuals, they might not be purchased due to a difference in cost. We analyzed the relation between sodium content and price in both France and Canada and found that there is no such concern for most food categories. For several categories, the association is surprisingly the opposite: as the food is more expensive, it also contains more salt. Our study demonstrates that the main limitation for consumers toward healthier choices seems to be neither the availability of products, nor the price. Consumers may be more hampered by the difficulty of comparing food labels. We indeed found that if products were to be chosen using sodium per portion, per serving, or percent daily value , then ranking could be difficult for consumers.

In fact, when the ranking was based on portion size, consumers could easily think that the product with a higher level of sodium was the healthier (low sodium content) choice. Our study has several limitations. We focused on mainstream stores and selected products. This was not a random selection of products and therefore should be interpreted with caution. Nevertheless this comparison allowed us to draw some conclusions regarding the main purpose of our study: the comparison of similar products in two different countries, and the ability of individuals to make healthier choices in terms of sodium consumption. We did not survey health stores, which could lead to a different conclusion for the minority of

consumers who use these stores but would unlikely change the overall picture at the population level since the mainstream stores selected in our study account for a large proportion of consumers. Ideally, a study based on the variation in sodium content from food items recorded in food surveys would give a better potential of what could be achieved by choosing labels with lower sodium content. This study points to the importance of the labelling of food products and the potential of individuals to make healthier choices. Despite the fact that more than half of customers read the salt content [105], barriers still prevent them from buying food with lower sodium content. Such barriers include the difficulty of comparing products, since the sodium quantity may only be given per serving and not using a standard unit such as 100g [111]. Indeed, 42% of customers were unable to rank three products based on nutrition labels where only serving sizes were indicated [105].

It is also clear that there is the possibility for the food industry to decrease the sodium content of some of their products, since comparable products are able to achieve this. In Canada, we have among others, a "Health Check Symbol" on the products that are evaluated by the Heart and Stroke Foundation of Canada, "Blue Menu" from President's choice, and different products from various companies with lower sodium than other comparable products. However, we need consistent labelling to achieve the maximum benefit from choices made by individuals, because a product with the health check symbol or any other icon will give a general idea to the consumers about the product, but most of the time individuals would like to be able to count the exact amount of nutrients such as sodium, fat, or calories that they are consuming. While we show that individuals can significantly decrease their sodium intake through comparing similar products, there is still a need to lower the sodium content of processed foods if we want to achieve rapidly healthier sodium intakes at the population level.

# Chapter 4

# Family history

In the previous chapters, we have observed two different approaches: population-wide and individual. The population-wide approach determines the impact of gradual sodium reductions on blood pressure and as a result a decrease in the number of CVD events and CVD mortality per year. We observed that a small amount of change in an individual's sodium intake (5-10%) can make important differences in terms of the number of CVD events at the population level. In the second approach we explored the importance of the role of individual decision making through the availability of products at the supermarket. We then highlighted the specific needs which could benefit an individual's decision making when faced with the abundance of options. Some of these needs vary from enforced education programs to standardized labelling. Both of these approaches are aimed at controlling CVD through the reduction of sodium intake to improve public and population health. In this chapter we focus on a risk factor that to some extent is more complex and harder to control in comparison with other CVD risk factors. We investigate whether or not having a family history of CVD increases the risk of CVD mortality in the Canadian population.

### 4.1 Introduction

Over a century ago, Sir William Osler (1897) was one of the first researchers to point out that angina could recur in families [112]. With time, other significant evidence of increased frequency of CHD for individuals with a family history of the disease was demonstrated by Thomas and Cohen (1955), and Slack and Evans (1966) [113, 114]. Furthermore, in the late 1970s and early 1980s the Western Collaborative Group prospective study involved 3524

male participants showing that participants with a family history of CHD were twice more likely to develop MI and angina than those without a family history of CHD [115]. Since then, there has been considerable progress in this field of research over the last 25 years.

Generally, family history is examined uniquely in each study where first, second, and third degree relatives (e.g., parents, and siblings; grandparents; great-grandparents, etc.) may or may not be included depending on the study. For example, Murabito (2005), when referring to the elderly, showed that a sibling history of CVD has a stronger association with incidence of cardiovascular events in comparison to a parental history of CVD [116, 117]. The Health Family Tree study, which included over 120,000 Utah families, is by far the most impressive study showing the importance of CHD family history at the population level. The study aimed at educating high school students while at the same time identifying high-risk families for preventive medicine programs. It was conducted through take-home health questionnaires and consent forms in order to fill in first degree family history information. The findings showed that 14% of Utah families had a positive family history of CHD. This percentage was responsible for 72% of early CHD cases and 48% of all CHD reported cases [118].

In line with the Health Family Tree Study, the importance of family history for premature CVD has been demonstrated by other researchers [119, 120, 121, 122]. It is important to consider known concerns cited by many authors that the validity of family history information is under question due to recall or reporting bias when individuals are asked for family histories. In response, several researchers have studied the validity of a simple family history assessment. The information provided by the subject is compared with the information provided by a relative of the subject. The sensitivity varied between  $79 - 91\%$  and the specificity ranged between 87 − 99% depending on who was asked (spouse, parent, or sibling). The findings proved that there was strong evidence of the accuracy of a simple family history as an assessment tool for the occurrence of CVD [118, 123].

Due to the importance of family history as a predictive factor of CHD, the New American Heart Association guidelines for primary prevention of CHD and stroke has recommended regular updates of an individual's family history [124].

Today, we know that the interaction between genes, age, nutrition, physical, and cultural environment plays an important role in an individual's health status [125]. Due to genetic variation among individuals, genes are responsible for different degrees of susceptibility of an individual to chronic diseases such as coronary artery disease, hypertension, diabetes,

and obesity [126, 127, 128, 129, 130, 131].

Previous studies indicate that the incidence and prevalence of chronic diseases vary among individuals, families, and nations. Genetic tendency, environmental factors, and quality of care are responsible for these variations [112, 132, 133, 125, 134, 135, 136]. For example, the study by Cusi et al (1997) has suggested the Gl460Trp polymorphism of the alpha-adducin gene is associated with salt sensitivity and primary hypertension. The reduction of sodium intake has greater impact on lowering mean arterial blood pressure in hypertensive patients with a 460Trp allele compared to those homozygous for the wild-type mutation [137]. In contrast, the study by Shin et al examined the same relationship in a Korean population and did not find an association between Gly460Trp polymorphism of the alpha-adducin gene and hypertension [138].

Although both studies have investigated the influence of the same genetic factor on salt sensitivity and hypertension, the cultural and environmental factors were different between these two populations. The family of an individual with a history of coronary artery disease, hypertension, diabetes, cancer, and other chronic diseases is at a higher risk of developing these disease compared to the general population because these families share genes and similar environmental factors [136]. Family history is not a simple risk factor to control; it is an interaction between genes and environment. Genes interact with the environment and it is hard to disentangle these influences, because we only see the result of this interaction which is not the same for all individuals. For some people the genetic background may dominate, and for others it may be the familial lifestyle that dominates. For example, a twin study by Slattery (1988) shows the importance of familial lifestyle such as dietary intake; a factor heavily weighted by cigarette smoking, alcohol and caffeine consumption; fatness; physical activity and physical fitness in relation with blood pressure [139]. In contrast the study by Zeegers (2004), summarized the results of different twin studies on variation in blood pressure that can be attributed to genetic differences. These variation estimated between 30 to 60% [140].

Simopoulos (1999) suggested that changes in environmental factors, including diet, which are matched to an individual's specific genetic susceptibility are the most effective intervention or prevention approach to control chronic diseases. There are specific biomedical tests that can identify susceptibility to chronic diseases such as coronary heart disease and hypertension [136]. In the absence of these tests, family history can be used as an

effective potential screening tool that can identify individuals who are at high risk of developing CVD. Those individuals may then be ideal candidates for enhanced prevention strategies [136, 141, 142].

The fact that the development of CVD in younger patients can be due to a genetic predisposition [21, 143, 144] makes family history different from other CVD risk factors, because it can potentially identify younger individuals who are at high risk of developing CVD even with no signs of an unhealthy life style.

## 4.2 Method

#### 4.2.1 Study population

The Canadian Heart Health Surveys (CHHS) were conducted between 1986 and 1992 to support the development of provincial and national CVD prevention programs. However not all provincial surveys included family history and some provinces did not agree to a recent linkage of the original surveys to mortality files [145, 146].

Since we were interested in the impact of a family history of CVD on CVD mortality, we have used a subset of CHHS data. We have merged the linked cases survey data (LCSD: June 2010), and linked cases survey mortality data (LCSM:July 2010) which restricted our sample to subjects with available demographic information, mortality, clinical measurement, and medical history of their parents. Our final sample contains 2135 male and 2247 female subjects from Saskatchewan and Alberta. We have used this set of data to examine the influence of parental history of CVD as a risk factor on cardiovascular disease mortality in the Canadian population, adjusting for other major risk factors. The total number of records in each database is presented in Table4.1.

#### 4.2.2 Data Analysis

We used ICD 10 to categorize the cause of death due to ischemic heart disease, cerebrovascular disease, congestive heart failure, other CVD, and total CVD. The following information was available to us:

- Father had a Heart attack or Angina
- Attack occured before father was 60

Province	Original CHHD	$_{\rm LCSD}$	Original Family History
РE	2088		
NS	2108	4546	
$_{\rm NB}$	2093	0	
$\rm QC$	2353	0	2353
ON	2538		2538
MΝ	2766	2766	
SК	2158	2147	2158
AL	2237	2235	2237
BC	2394	1424	
ΝF	2394	900	

Table 4.1: Number of Participants

- Father had a Stroke or Cerebral vascular disease
- $\bullet\,$  Stroke occured before father was  $60$
- Mother had a Heart attack or Angina
- Attack occured before mother was 60
- Mother had a Stroke or Cerebral vascular disease
- Stroke occured before mother was 60

We used a combination of the above information to define different variables as representative of positive family history of CVD. Here is the list of abbreviations and acronyms that we have used.

- fha: Father had heart attack
- fha60: Father had heart attack before the age of 60
- $\bullet\,$  fstr: Father had stroke
- fstr60: Father had stroke before the age of 60
- mha: Mother had heart attack
- mha60: Mother had heart attack before the age of 60

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- mstr: Mother had stroke
- mstr60: Mother had stroke before the age of 60
- mhist: Mother had heart attack or stroke
- mhist60: Mother had heart attack or stroke before the age of 60
- fhist: Father had heart attack or stroke
- fhist60: Father had heart attack or stroke before the age of 60
- mfhist: Both parents had a history of heart attack or stroke
- mfhist60: Both parents had a history of heart attack or stroke before the age of 60
- minonephist:At least one of the parents had a history of heart attack or stroke
- minonephist60:At least one of the parents had a history of heart attack or stroke before the age of 60

We limited the CVD risk factors used in this analysis to major risk factors available in our data. The Table 4.2 shows the description of each variable that has been used in our model.

Hypertensive status is based on being either on medication for hypertension, or having a systolic blood pressure of 140 mm Hg or greater or a diastolic blood pressure of 90 mmHg or greater. Since all our inferences are based on our restricted sample, we compared the distribution of selected demographic variables between all three data sets to test the

Variable	Original Survey	Linked Survey	Final Sample
Mean age (yr)	40.8	43.6	40.9
Mean BMI $(kg/m^2)$	25.7	26.1	25.7
Mean LDL	3.1	3.1	3.1
Mean HDL	1.3	1.3	1.3
Mean Cholesterol	5.1	5.1	5
Mean SBP	124.9	125.7	123.3
Mean DBP	77	77	76.6
Diabetes $(\%)$	5.1	5.7	5.4
Regular Smoker $(\%)$	28.5	27.2	25.1
Hypertensives $(\%)$	23.2	25.3	20.9
Sedentary $(\%)$	37.8	36.2	33.4
Male gender $(\%)$	49.2	49.5	48.7

Table 4.3: Distribution of Selected Demographic Variables by Data Sets

similarity between our final sample and the original data set. Table 4.3 shows that our sample is a good representative of the Canadian population.

The proportional hazard model was used to examine the impact of having a family history of CVD on CVD mortality. Unadjusted and adjusted hazard ratios (HRs) were used to summarize this association.

## 4.3 Results and discussion

We had access to parental history of both CHD and stroke. Therefore we used different combinations of this information to define our variables of interest and examine their relationship with our outcome variable such as CHD, stroke, and CVD mortality. However, the number of subjects who have died from CHD, CHF, or stroke is limited in our sample. Therefore we have restricted our outcome variable to total CVD mortality.

#### 4.3.1 Association between CVD mortality and parental history of CVD

Table 4.4 presents unadjusted and adjusted ORs comparing positive with negative parental histories, with regards to their relationship with CVD mortality. In this work, positive parental history means that individual's parents have suffered from heart attack or stroke up to the time of the baseline survey data collection.

Variable	Unadjusted	Adjusted for age	Adjusted for sex	Adjusted for age and sex
fha	$1.59(1.\overline{10,2.17})$	1.17(0.82, 1.68)	1.55(1.10, 2.18)	1.33(0.95, 1.88)
fha60	0.41(0.22, 0.74)	1.29(0.70, 2.23)	0.40(0.22, 0.73)	1.33(0.73, 2.44)
fstr	2.41(1.64, 3.54)	1.44(0.98, 2.12)	2.38(1.62, 3.49)	1.41(0.96, 2.07)
f <sub>str60</sub>	0.70(0.31, 1.60)	2.34(1.04, 5.29)	0.70(0.31, 1.56)	2.45(1.08, 5.57)
fhist	2.16(1.60, 2.93)	1.53(1.13, 2.07)	2.16(1.60, 2.92)	1.54(1.14, 2.09)
fhist60	1.05(0.64, 1.61)	1.87(1.23, 2.90)	1.05(0.69, 1.60)	1.96(1.27,3.01)
mha	2.20(1.52,3.17)	1.22(0.84, 1.76)	2.32(1.60, 3.35)	1.22(0.84, 1.76)
mha60	0.63(0.31, 1.27)	1.61(0.80, 3.25)	0.67(0.33, 1.35)	1.57(0.78, 3.17)
mstr	1.97(1.29, 3.00)	0.73(0.47, 1.11)	2.05(1.34, 3.15)	0.77(0.50, 1.18)
mstr60	0.61(0.23, 1.64)	1.27(0.47, 3.40)	0.62(0.23, 1.65)	1.32(0.49, 3.57)
mhist	2.14(1.55,3.00)	0.92(0.67, 1.27)	2.23(1.60, 3.08)	0.94(0.68, 1.30)
mhist60	1.28(0.77, 2.15)	1.27(0.76, 2.13)	1.34(0.80, 2.24)	1.24(0.74, 2.08)
mfhist	2.84(1.92, 4.22)	1.30(0.87, 1.90)	2.94(1.98, 4.37)	1.32(0.89, 1.96)
$mth$ ist $60$	0.86(0.21, 3.45)	1.65(0.40, 6.64)	0.94(0.23, 3.78)	1.62(0.40, 6.54)
minonephist	2.35(1.73, 3.19)	1.23(0.90, 1.67)	2.38(1.75, 3.24)	1.24(0.91, 1.69)
minonephist60	1.17(0.82, 1.68)	1.66(1.16, 2.38)	1.19(0.83, 1.70)	1.67(1.17, 2.40)

Table 4.4: Adjusted and Unadjusted Odds Ratios with 95% Confidence Intervals

After adjusting for age and gender, a positive family history of stroke and heart attack was associated with a 54% (OR=1.54(1.14,2.09)),  $67\%$  (OR=1.67(1.17,2.40)),  $96\%$  $(OR=1.96(1.27,3.01))$ , and  $145\%$   $(OR=2.45(1.08,5.57))$  increase in the odds of CVD mortality compared to those with negative family history of stroke and heart attack. Father stroke before the age of 60 was a strong predictor for CVD mortality. However, the unadjusted ORs in Table 4.4 showed the odds of CVD mortality in individuals with positive history of heart problem from both mother and father are about three times higher than those without or with just mother or father heart problem history.

Note that of the 4382 subjects in our sample, 447 of them have passed away due to a variety of medical reasons. 170 out of 447 deaths were related to CVD, which may affect the width of our confidence intervals. The next issue that we have to consider is the role of age in our analysis and it's relation with family history of heart problem and CVD mortality. We have to take into account that the role of age in this analysis is more than a specific confounder such as sex.

Age is not just an entity; it is a marker of accumulation of risk factors. For example, the risk of high cholesterol, elevated blood pressure, obesity and many more CVD risk factors increase while people are aging. Further, age is not only related to CVD mortality and CVD risk factors, it is also related to family history of CVD. Age is not an independent

Variable	OR and 95% CI	Adjusted variables
fha.	1.24(0.85, 1.79)	Sex, Cholesterol
fha60	0.96(0.48, 1.92)	Age, Hypertension, Cholesterol
fstr	1.32(0.85, 2.05)	Hypertension, Cholesterol
fstr60	2.57(1.11, 5.92)	Age, Diabetes
fhist	1.41(1.01, 1.96)	Hypertension, Cholesterol
fhist <sub>60</sub>	1.54(0.95, 2.49)	Age, Sex, Hypertension, Cholesterol
mha	1.13(0.78, 1.63)	Age, Hypertension
mha60	1.56(0.76, 3.19)	Age, Hypertension, Smoking
mstr	0.77(0.50, 1.18)	Age, Sex
mstr60	1.04(0.35, 3.08)	Age, Waist
mhist	0.87(0.61, 1.23)	Age, Cholesterol
mhist60	1.08(0.64, 1.80)	Hypertension
mfhist	1.30(0.87, 1.92)	Age
m <sub>thist60</sub>	0.72(0.1, 5.14)	Age, Hypertension, Waist
minonephist	1.08(0.77, 1.5)	Age, Cholesterol
minonephist <sub>60</sub>	1.33(0.90, 1.98)	Age, Hypertension, Cholesterol

Table 4.5: Odds ratios and 95% Confidence Intervals

variable, it is a surrogate for other factors and plays a special role that should be recognized. Generally, older people are more likely to have older parents, and as a result they are more likely to have parents that have died from CVD compared to those with younger parents. The relationship between the age of our subjects and their parent's age was unclear to us. Considering the variety of cultures, norms, socioeconomic status, and lifestyles of people, we couldn't make any assumption in this regard.

The next question that we have to ask is: are we actually controlling for age as a confounding factor or we are over-adjusting when we adjust for age? Table 4.5 presents adjusted odds ratios after controlling for major CVD related confounders listed in Table 4.2. The Cox proportional hazards model was used to examine the relationship between CVD mortality and positive family history of CVD. We used a backward elimination technique with 10% threshold to build our models.

Based on our analysis, a positive father history of stroke before the age of 60 was associated with a 157% increase in the odds of CVD mortality. However, we did not see the same association when we used mother history of stroke before the age of 60. The sensitivity and specificity of CVD deaths as a marker of family risk for CVD will vary with the age of the family. Younger families are more likely to remember correctly that what has happened to their parents compare to older families. Also the accuracy of recalling the details of

an event that has occurred a couple of months/years ago is different with the event that has happened a couple of decades ago. Therefore these factors can introduce some level of information bias to our study.

Family history of CVD has a special role in predicting occurrence of CVD in comparison to other CVD risk factors. It carries information about an individual's genetic disorders, which can help us to identify individuals that are more likely to developed CVD in their lifespan. However, environmental and social factors, such as healthy diet, maintaining a healthy weight, exercising regularly, limiting alcohol use, and not smoking have strong impacts on reducing the risk of cardiovascular disease.

# Chapter 5

# Mathematical modelling

In previous chapters we used descriptive statistics and common epidemiological techniques to show how we can improve the level of health in our population, specifically in terms of reducing the occurrence of CVD. In this chapter we present some techniques that have recently gained importance in the area of health through some examples to highlight the importance of mathematical modeling in this area.

## 5.1 Introduction

In the past centuries, much of the quantitative research in health related problems focused on applying epidemiological and statistical techniques. In order to control the incidence and reduce the prevalence of disease in populations, the mentioned techniques have been used to study the distribution of the disease, conduct an estimation, identify the determinant of health outcome, etc. Their inference is based on a collection of data which mainly focuses on relating a single or multiple exposures to a single or multiple health or disease outcomes.

Simple epidemiological and statistical techniques have been used for a long time to answer these questions. However, in the past decade, multilevel or hierarchical regression models have increasingly been used within the field of epidemiology. While these models allowed epidemiologists to consider the contribution of factors at multiple levels, unfortunately, multilevel methods are fundamentally limited as these models are geared to assessing the relation between 'independent' variables and the 'outcomes' of interest [147]. Therefore, multilevel models fail to present the dynamic relations between outcome and exposure,

and consequently, they are not suitable for complex dynamic systems. In real world problems, when attempting to understand the association between exposure and disease, it is important to consider different components such as the multiple levels, intervening and confounding factors, overlaps, and the interactions between biological, behavioural, social and environmental factors and their influence on each other.

In the attempt to solve and further investigate the complexities of dynamic systems, researchers in recent years have shifted their focus to interdisciplinary research where different approaches collectively have broadened the spectrum of possible future solutions.

The new shift has extended multilevel models, making it suitable approach for both the health care system and health related problems. More specifically, the use of mathematical models such as Markov, cellular automata and network modelling, queuing theory, game theory, differential equations, and system dynamics have proved to be a successful approach in further understanding the complexities of health research. To gain further insight on the usefulness of these models, we use a few examples to illustrate and explain the advantages of mathematical models on: projection of trends, assessing environmental and behavioral changes, and medical decision making support.

# 5.2 A novel algorithm for describing population level trends in body weight

The National Longitudinal Survey of Youth (NLSY79) data set is a representation of 12,686 men and women whom were born in the 1950s and 1960s in the United States and interviewed every year between 1979 and 1994 and then biennially from 1994 to 2006. We calculated the Body Mass Index (BMI) of the subjects biennially between 1986 and 2004 for all individuals who were 21 years or older in 1986. Different categories of BMI were defined as NO: Normal Weight (BMI $\lt 25$ ), OW: Overweight (25  $\leq$ BMI $\lt 30$ ), and OB: Obese (BMI $\geq 30$ ) [148]. We calculated the transition probability between every two time steps (observations) to investigate the dynamics of weight gain and weight loss in our data set. To explore the trends in obesity at the population level, we considered a basic Markov Model with 3 states: Normal weight (NO), Overweight (OW), and Obese (OB). For each state, we calculate the possibility of individuals' movement between these three states. The calculations only reflect the current situation and thus do not consider prior weight class of the individual. If the basic Markovian model holds true, the previous body weight of an individual would have



Figure 5.1: Three and nine state Markov Model

no impact on their future weight class. In order to test the basic Markov assumption, we developed a higher order Markov model and therefore the three-state model becomes a nine state model. The nine state model uses both the current BMI state and the previous BMI state to predict the next BMI state. Our analysis shows that the Markov assumption does not hold true Figure 5.1.

To address this failure, we developed a new model to explain the trend of obesity over time. Our new model, the Maxhist model Figure 5.2, considers an individual's highest historical BMI to determine an individual's most probable weight class in the future. Our results confirmed the importance of weight history, it shows that previous weight of individual matters. For example, based on our estimation, more than 80% of individuals in a



Figure 5.2: Maxhist Model

specific weight category will stay in the same weight category after two years. An exception was for OW females where the probability of staying overweight drops to 65%. An interesting aspect found was that the length of NO stability played an important role in determining the future NO.

To test the capability of the Maxhist model in projecting the prevalence of individual weight class, we compared the result of Maxhist model with that of simple 3 state Markov model. The results confirmed that the Maxhist model is superior to the simple Markov model. Also, the above two models were compared to a regression model as a common modeling technique that has been used in this area to extrapolate the prevalence of overweight and obesity into the future. The validity of the Maxhist model over the other two techniques is displayed in Figure 5.3.

To create the comparison graph, we split the available data of 18 years into the first 10



Figure 5.3: Comparion between Markov, Maxhist and regression models

and the next 8 year period. The first 10 years were used to project the weight status of an individual for the next 8 years. The graph illustrates the deviation of all three models from the actual percentage of normal weight individuals in the second 8-year period. Between the dashed lines, one can see that the Maxhist model provides a significantly better fit to the actual data than the linear regression, and also better than the three-state Markov model. Past the dashed lines, the Maxhist model provides a plausible projection further into the future.

The above example demonstrated that prior body weight of individuals can play an important role in defining an individual's future weight. Since the body weight and physique of an individual is highly associated to the risk of occurrence of CVD, a better knowledge about the progression of obesity or maintaining a healthy body weight in the future will help us to have a better vision regarding the trend of CVD in future.

# 5.3 Social interactions of eating behavior among High School Students: A Cellular Automata Approach

Cellular Automata (CA) modeling has held promise in understanding social dynamics between individuals [149, 150]. It is a mathematical modelling technique that has potential in analyzing non-linear transmissions of human behaviour. To break down the complexity of human behaviour, a CA model make assumptions based on logical possibilities, estimated associations between variables on specific data set, or based on the results of related previous research. We have used Cellular Automata to explore how social interactions among high school students can affect their eating behaviour and their food choice. The underlying premise in our model is based on social interactions among individuals and influences from media, parents, education, environment, and other factors. Students can influence one another and as a result change their eating behaviour over time to have a healthy or unhealthy eating behavior. We assumed that each student belongs to one of the four categories including: 1. bring healthy, 2. bring unhealthy, 3. purchase health and 4. purchase unhealthy.

The interplay of factors such as personal behaviour, social interactions and school food environments makes eating behavior a complex issue. One should consider the school food environment (e.g., cafeteria), as research has shown that eating behaviours in children and, more so in adolescents, are influenced by the physical environment [151, 152]. Further evidence demonstrates that eating behaviour can be influenced by factors such as peers, the amount of food consumption around different people, availability of food, home, and family environment.

In the school environment, the availability of unhealthy snacks plays a major role in the food decision making process when students are socially interacting among peers [151, 152]. Similarly, the influence of peers on one another's decision making is suggested to be a factor in other health-related behaviors, such as alcohol consumption [153] and smoking [154]. Other research has found that overweight people eat less when around normal-weight peers, while still consuming more around overweight peers [152, 155, 156]. Whether making a healthy or unhealthy decision, studies have found that the type of food eaten by peers affects individual decision making [157, 158].

The population in a CA model is represented by a two dimensional square grid where each cell is representative of an entity in the population. In this CA model, each cell



Figure 5.4: Model Structure Illustrating Transition Between Individual States

represents a single student who is surrounded by their eight closest friends or classmates.

Interactions in a social community are dependent on the transition rules integrated in the CA model. The transition rules are used to determine how and to what degree each cell is assumed to interact with surrounding cells.

Over time, cells change as they both receive and give social influence to surrounding neighbours. The core of the model is that students are socially influenced to have healthy or unhealthy eating behaviours. In our CA model, two types of social influences are considered. First, a student can be encouraged or discouraged by his or her classmates to bring or purchase foods. Second, a student can be encouraged or discouraged by his or her classmates to eat healthy or unhealthy foods (Figure 5.4).

For instance, if an individual who normally purchases healthy food spent time with individuals who brings healthy/unhealthy foods on a daily basis, the former may be influenced over time to begin bringing food. Naturally the strength of the social influence of an individual (positive or negative) may cause the individual to transition between states of healthy to unhealthy or vice versa food preferences. In a negative social influence, the individual will be more inclined to bring unhealthy foods.

Since this is a scenario-based model, the variables can be changed according to different



Figure 5.5: Eating Behaviour Patterns When We Change the Positive Influence

scenarios to reflect hypothetical changes in our population of interest. For example, we update the model with one extra external factor. In particular, some students may desire to purchase food, but their parents refuse to give them any money to do so, forcing those students to bring food from home.

The Figure 5.5 represents the impact of social influence on student's healthy eating behaviors. Our assumptions listed as follow

- We have randomly distributed 1600 students in four eating behavior states (25% in each category)
- Social influences are accumulated over time from peers within the defined neighbourhood
- An individual transitions to another state after reaching a specific threshold

Using Matlab we run the simulation for 1000 days when the influence parameters for Healthy or Unhealthy are equal. The population of each group remains similar with approximately 25% each as their initial portion. Then, we increase the positive in influence parameters of healthy/unhealthy by 10%, and as a result we observed a 25% increase in positive eating patterns (i.e., eating healthy).

Conceptualizing the social environment of high school students is important in understanding the progression of obesity and other associated diseases which accompany obesity such as CVD. The results of this exercise shows that students will cluster based on their eating preference. When we increased a positive influence, the population experienced positive effects, resulting in improved healthy eating decisions amongst students (details on [159]).

Calibrating this model by using real data as inputs will increase the potential for investigating the impact of various environmentally related interventions and improve knowledge transfer between research disciplines and public health professionals.

# 5.4 A Fuzzy Cognitive Map based tool to predict CVD mortality in Canadian population

We have used Markov and CA model in previous section to highlight the importance of body weight status, social influences and individuals' eating behavior. In this section we would like to use a mathematical model that recently have been used in the field of health sciences. It can be used as a decision making tool as it has the potential of predicting the impact of different risk factors on specific outcome. In previous chapters, we have discussed the impact of sodium reduction on prevalence of CVD at the population level, the importance of individual decision making on consumer eating behaviour, and we also highlighted the importance of family history and its impact on the development on CVD. Each of these components were studied separately to provide clearer insight on the relationship between CVD and its relevant factors. This failed to capture the comprehensive outcome of the dynamic interplay between all factors affecting CVD. Without taking interaction between system elements and known feedback into consideration, it is difficult to capture all the inter-relationships which occur in reality.

In the following section, we are proposing to use a method which will overcome the above deficiencies. The chosen method is called Fuzzy Cognitive Map (FCM), which is a graphic representation used for modelling interdependence between concepts in the real world [160, 161, 162]. The arrows between the outcome of interest and the various risk factors will be used to assess the causal flow between two components and the corresponding weight  $(-1,1)$ , providing the degree of fuzzy relationship. The factors which have no impact



Figure 5.6: Model structure illustrating Fuzzy Cognitive Map

on one another are not connected through arrows.

#### 5.4.1 Method and discussion

The purpose of our model is to predict death due to CVD, considering an individual's health, behavior and social conditions. Through the proposed methodology, factors such as blood pressure, cholesterol, obesity, triglyceride, physical activity, family history, social influence, alcohol consumption and smoking status were considered. These factors circle around the core of our model outcome (CVD) Figure 5.6. The description of these factors are presented in Table 5.1.

The links between CVD and the surrounding components, or between any two components indicate the weight and direction of the relationship between the two factors. For example, the link and its corresponding weight that directed from cholesterol to CVD encodes that cholesterol has a positive influence on CVD. The positive relationship indicates that an increase in cholesterol results in an increase in CVD.

Commonly, within the process of defining the FCM, the relationship between each two components will be defined through either literature or expert information. The data from

several studies or experts will be gathered to form an educated guess to define the relationship between two components in the range of  $(-1,1)$ . In our model we used the Canadian Heart Health Mortality data to estimate the magnitude of the weight between each two components. Our model has an advantage of access to real data to estimate the association between the studied factors in Canadian population. We calculated the crude odds ratio (OR) between each two factors and used the expert's opinion to specify the direction of association between connected components. For example, the odds of death due to CVD in hypertensive group is 2.1 times the odds of death due to CVD in normotensive group. To re-scale the effect of estimate between -1 and 1, we used the  $log(OR)$  instead of estimated odds ratios [160]. In regards to our previous example, the log of 2.1 is equal to 0.32 which is restricted between (-1,1). The model follows an iterative algorithm for several steps until it converges. Since in each step the model make adjustment, we are using the crude odds ratios instead of adjusted odds ratios to avoid any over adjusting. We also need to mention that because of using the log, the magnitudes of adjusted and unadjusted odds ratios  $(log(QR))$ in our model was very similar to each others.

The Figure 5.6 illustrates our FCM, that have been used to assess the occurrence of CVD death given the surrounding factors. The model allows for each component to be adjusted as an input in order to show its influence on the occurrence of CVD. Therefore, this model has potential to be used as a tool box to answer some "what if" scenario questions.

Unfortunately we did not have suitable information regarding the level of sodium intake of each individual. In the presence of such information we could use the model to show the impact of sodium reduction as our input on CVD mortality as our desired outcome, given the surrounding factors and compared it with our results from chapter two, when we just considered the impact of sodium reduction on CVD mortality through lowering the blood pressure.

The Table 5.1 shows the description of each variable that has been used in this model. Note, to measure the influence of obesity on CVD mortality, we have used the optimal waist circumference ( Table 5.1 ) as an indicator for weight management in our analysis. Also, we have used two variables "Heart prev" and "Stroke prev" (Table 5.1) to show the social influences that people can have on each other. Our data confirmed that an individual's belief in prevention of CVD is associated with the prevalence of smoking. The odds of smoking is lower in those who believed CVD can be prevented in comparison with those who do not believe in prevention of CVD.

	Variable	Description
	CVD.	Death due to cardiovascular disease
$\overline{2}$	<b>BP</b>	Having high blood pressure (Cut point $140/90$ )
3	Chol	Having high cholesterol (Cut point 5.2, fasting only)
4	Waist manage	Having normal waist circumference (Male less than 94cm, Female less than 80cm)
5	Trig	Having high triglyceride (Cut point 2.3, fasting only)
6	Exer	Regularly exercise (1 plus times a week)
7	Exer str	Strength of the exercise (Most of the exercise is strenuous)
8	FH.	Family history of death due to CVD
9	Heart prev	belief on heart disease prevention
10	Stroke prev	belief on stroke prevention
11	Alco	Current drinker
12	Smoke	Regular, occasional, pipe or cigar smoker

Table 5.1: Description of Variables Used in FCM

We constructed an adjacency matrix W which can be understood through the following examples. The increase in blood pressure (being hypertensive) leads to an increase in likelihood of CVD which we defined as a positive relationship between the two components  $W(2, 1) = 0.32$ . The weight of the link represents the magnitude of the association between the two components (restricted between -1 and 1). On the contrary, an increase in weight management lowers the likelihood of CVD  $W(4, 1) = -0.4$ . We defined this relationship as a negative link. When there is no direct link between two components such as drinking alcohol regularly and family history of death due to CVD, it was denoted in our matrix as a neutral (0) relationship  $W(12, 8)$ .



To examine the accuracy of our model, we split our dataset in two different samples. The first sample contains 80% of the data, which was used to explore the relationship between each components. Also in the next step we used this data to tune our model and find an appropriate transformation function. Then we used our model against the second sub sample which was the remaining 20% to measure the accuracy and stability of our proposed model.

- Each individual has their initial values for each components which have been defined in the model (0 or 1 for each component). In other words, we assigned a vector  $A_i$  to each individual, where the vector  $A_i$  contains 12 entries of 0 or 1 and (*i* represents the  $i<sup>th</sup>$  individual in our dataset. For example if the person had normal blood pressure, we assigned 0 to the second entry and if the person was hypertensive we assigned 1 to the second entry of a vector corresponding to that individual.
- In each step we calculated  $A_i(t + 1) = f(A_i(t) + A_i(t) \cdot W)$  where W is the above adjacency matrix that represents the weight of interconnections between each two components, f is our transformation function and t represents the iteration count.

• In this example, 
$$
f(x) = \tanh(x) = \frac{e^{2x} - 1}{e^{2x} + 1}
$$
Function	Sensitivity (80\% data)	Sensitivity $(20\%)$ remaining data
tanh(x)	0.89	0.86
tanh(2x)	0.86	0.86
tanh(3x)	0.72	0.72

Table 5.2: Sensitivity of the FCM Model Based on Different Transformation Function

- The model converges to a steady state when:  $A(t + 1) A(t) \le \epsilon$
- The magnitude of the final vector  $A_i$ , will define the status of each individual for each component. For example, in our model the first entry of vector  $A_i$  is correspond to CVD mortality. In our model if this entry was less than zero in the last iteration, we conclude that the person is in low risk of dying from CVD.

Note, that using this model, our goal was to identify people who are at high risk of dying from CVD , and potentially we were interested in estimating the impact of sodium reduction on CVD mortality while other related factors to CVD as a dynamical system were taken into account. Therefore we were interested in a model with high sensitivity (the probability of someone who has truly died from CVD will be classified as dead due to CVD) and high stability (gave us the same level of sensitivity on different samples), while the level of specificity (probability that someone who truly didn't died from CVD will be classified as didn't die due to CVD) was not an issue in our analysis . The following tables represent the sensitivity of our model in identify those who will die from CVD considering their current health and social conditions, based on different transformation functions that have been used to tune the model.

Based on our analysis, we chose the  $tanh(2x)$  as our appropriate transformation function, because in addition to acceptable levels of sensitivity that provide to identify the high risk individuals, the model performance does not change when we apply it on the second data set to test the accuracy of our model.

It is important to note that our goal in this analysis was not to predict the cause of death in Canadian population, but instead to identify individuals who are at high risk of death due to CVD. In addition, we are highlighting the role and potential of mathematical and computational model in the area of health sciences. It is crucial to remember that there is no universal or perfect model that can answer all of our questions within a complex systems

such as human body's reactions to certain intervention. The answers to our questions and hypothesis however, can lead us to improve the level of health in our population or give us a better vision of what we can anticipate in the near future as well as our long term plans.

There are no specific rules and criteria that can define and check-mark a model as a complete or perfect model. The level of complexity can increase or decrease in our model, but the question that remains unanswered is "How much complexity is necessary?" Although, in complex models we can consider all the interactions and interrelationships between components, but it does not guarantee that the model, as a complex system performs perfectly. Usually we can design a very complex conceptual model that works perfectly on the dataset, where all the relationships derived from. However, they are in the danger of being too sensitive to the other dataset which will limit their practicality in terms of projection in future or using them as a tool to answer our questions. This strategy is similar to over fitting of an specific dataset on regression analysis. Although all the details have been considered in the model, the model per se does not have a value in regards to future prediction.

Considering the above issues, we can see the importance of validation in any proposed model. In our FCM, you can quickly notice the lack of some links between different components, the absence of some important CVD related factors, or the existance of an unusual link in our map. One has to remember that all the factors and links that we include or exclude were based on the effect estimates that we obtained based on our data. Also we should mention that all of the estimates in our model are based on direct (unadjusted) association between each pair components.

Our main interest was to be able to estimate the impact of sodium reduction on CVD mortality, when we are considering all other related factors to CVD and compare it with our results in chapter two, where we only considered the direct impact of sodium reduction on CVD through the reduction in blood pressure. Unfortunately however, we didn't have proper information in our data set that can help us to answer this question. Since the validity of our model was important, we restricted ourselves to a conceptual model that is compatible with our data (80% of the original data).

In our FCM, the conceptual impact of smoking on CVD mortality seems unusual. Because the only significant association that we have found was between smoking and waist management, which in one direction, as shown in Figure 5.6 has a protective impact on CVD mortality. To explore this issue further, we re-run the model without the link between smoking and waist circumference.



Figure 5.7: Manipulated the Original Fuzzy Cognitive Map

When we took the link off, the sensitivity of our model dropped to 74% vs the 86% in our sample (80% of original data) and also dropped to 71% in the remaining data that was used to test the accuracy of our model. Therefore, considering the above social and health condition in Canadian population, we found that our first FCM model works better in terms of identifying the individuals that are at risk of dying from CVD better than the second FCM model. The model can identify these cases at 86% of the time correctly. In our model we have replaced all the missing values with zero's in our dataset.

It is important to note that the mortality data was available to us, not the CVD events. One explanation regarding the unusual impact of smoking on CVD mortality can be related to the impact of smoking on other diseases. Although the number of deaths due to CVD may decrease, the total number of deaths due to lung cancer or other smoking related diseases may increase. To explore this idea, we need a more comprehensive model to capture this phenomena.

### Chapter 6

# Conclusion

#### 6.1 Summary of Contributions

The research presented in this thesis is the combination of six papers that are directly or indirectly related to the issue of CVD prevention. First, using different strategies, we have estimated the impact of a gradual sodium reduction on reducing the number of cardiovascular events in Canada, the United States and 18 Latin American countries. Our study showed that a small change in a dietary measure, such as a decrease in salt intake (5-10% per year) at the population level, was able to lower the blood pressure distribution, and as a result reduce significantly the number of CVD events at the population level.

By reducing in small amounts the sodium intake at the individual level we may observe small changes in the blood pressure of each individual, but this intervention can shift and lower the whole blood pressure distribution of our population and reduce CVD accordingly.

While lowering salt intake is considered by many researchers and physicians as an effective approach to battling the problem of hypertension and CVD, there is some controversy about the magnitude of this relationship. The Meta analysis by Midgley (1996) , Graudal (1998), and Hooper (2002) are examples of studies that have questioned the relationship between sodium intake and hypertension [163, 164, 165]. In 2006, He has highlighted the issues and characteristics of the trials that were used in these studies. Limitations such as a short duration of salt restriction and very small reduction in salt intake were the main reasons that led them to their negative conclusions [34]. However, groups, organizations, and companies, such as the Salt Institute, which are against regulations on reducing the level of salt intake from food products, have used these negative conclusions without further explanation to the public and created major confusion at the consumer level. Examples include the news articles on the Salt Institute's website entitled "Scientific American: Its Time to End the War on Salt", and "New Study Points Finger at Genetics (Not Salt) as Cause of Hypertension".

It is important to remember that approximately 75-80% of dietary sodium comes from processed foods. Therefore, it is important to note that this approach is highly reliable on industry and government policies. In the competitive world that we live in, it seems challenging for companies to voluntarily reduce the sodium content of their products (all products and not just selected items). Since food products are highly dependent on taste, it is unlikely that a company will take such a risk on their own where they are at risk of losing customers to competitors.

Some argue that it is not necessary to decrease the sodium level of the whole population, since some people are already at reasonable or even low levels of sodium intake. However, this argument only focuses on a minority of our population such as very healthy individuals with low sodium intake, or professional athletes who already possess a healthy lifestyle. These individuals will not be at risk due to low sodium intake.

Another argument, which many industries present, is that it is very costly and unreasonable to implement this change. However, this claim is questionable since industry already provides some healthier options with lower sodium. For example, many food brands have a "low-sodium" or "25% less sodium" alternative. If such products are already in place, why cant we continue the shift towards healthier options?

To implement laws and regulations that can help the overall health status of our population, we need the collaboration and accountability of individuals, public education systems, governments, policy makers, and the food industry. For this reason, there is a critical need for a standard, national legislation that forces companies to take action and responsibility toward population health.

In the second paper, we showed that the range of sodium content of similar products varies within and between different brands, and as a result, individuals face options in terms of the product that they choose. Our study demonstrates that although a shift to lower sodium products is feasible, a major obstacle to consumers making healthier choices is the difficulty of comparing food labels. The lack of proper labelling is not limited to supermarket products. Restaurants lack of labelling for the content on their menus, which limits an individual's ability to make informed decisions when dining out. Therefore, although awareness and knowledge about healthy eating can motivate people to take steps toward healthier choices, our society needs encouragement to make the environment ready for those who are willing to change their lifestyle.

In the third paper we showed the influence of positive family history of CVD on the development of an individual's CVD. Using Canadian data, our analysis showed this relationship exists to some degree. We have to note that although the positive association has been observed, we have to be careful in terms of the interpretation of this relationship. Family history plays a special role in predicting the occurrence of CVD. It carries information about the individual's genetic makeup which can help us to identify high risk individuals. At the same time, we have to remember that families often share the same environment and lifestyle. Family history, as measured in this study, is an interaction between genes and environment. Genes interact with the environment and it is hard to disentangle these influences. What we see is the result of this interaction.

The negative impact of excessive sodium in our diet is not limited to raising blood pressure, but is also linked to increase in soft drink consumption. This can influence individuals eating behavior as well as their weight status [166]. Obesity is another factor that influences the development of CVD. In order to explore the complexity of CVD, we need to have a good understanding of the progression of factors that can influence the occurrence and trend of CVD. In this regard, we have used American longitudinal data (NLSY79) to explore the trend in obesity over time. Our results confirmed the importance of an individual's weight history. It shows that previous weight matters, and that people are likely to return to their heaviest historical weight class over time. Therefore, excessive salt intake not only increases the risk of CVD through elevated blood pressure, but it also has an impact on an individual's weight status, and influences the likelihood of developing CVD indirectly.

The eating behaviour of individuals can change through social influence. In the fourth paper we showed how environmental factors, awareness, education and peer influences can impact the eating behaviour and food choice of high school adolescents. They receive positive or negative influences from their friends or classmates, which consciously or unconsciously encourages them to change their behaviour over time. This model highlights the importance of interventions, proper environment, and educational programs in schools.

In the final paper, we used Canadian data to consider all the influences between CVD mortality as our outcome and CVD risk factors such as blood pressure, cholesterol, obesity, triglyceride, physical activity, family history, social influence, alcohol consumption, and smoking status at the same time. In this model, all CVD risk factors are linked to each other. Given individual information such as blood pressure, smoking status, cholesterol level, and family history of CVD, etc., the model can identify those that are likely to die from CVD. The model also has the potential to examine the importance of a specific intervention while we are considering the impact of all other related factors. Using appropriate data we could examine the impact of sodium reduction on CVD mortality while we are taking into account other related factors, and compare the result with our findings in the first paper, where we considered the impact of sodium reduction on CVD mortality through changes in blood pressure .

In general, modelling in the field of health is more than mathematical games. Modelling has been used to simplify a real world phenomenon and help us to have a better understanding of our situation before it is too late. Models can be used as a tool to answer what if scenarios and help policymakers in shaping policy.

### Appendix A

# Appendix A

#### A.1 Hypertensive diseases

#### I10-I15 Hypertensive diseases:

I10 Essential (primary) hypertension I11 Hypertensive heart disease (No data) I11.9 Hypertensive heart disease without (congestive) heart failure I12 Hypertensive renal disease (No data) I12.0 Hypertensive renal disease with renal failure I12.9 Hypertensive renal disease without renal failure I13 Hypertensive heart and renal disease (No data) I13.1 Hypertensive heart and renal disease with renal failure I13.9 Hypertensive heart and renal disease, unspecified I15 Secondary hypertension (No data) I15.0 Renovascular hypertension (No data) I15.1 Hypertension secondary to other renal disorders I15.2 Hypertension secondary to endocrine disorders (No data) I15.8 Other secondary hypertension I15.9 Secondary hypertension, unspecified (No data)

#### A.2 Ischaemic heart diseases

#### I20-I25 Ischaemic heart diseases

I20 Angina pectoris (No data) I20.0 Unstable angina I20.1 Angina pectoris with documented spasm I20.8 Other forms of angina pectoris I20.9 Angina pectoris, unspecified I21 Acute myocardial infarction (No data) I21.0 Acute transmural myocardial infarction of anterior wall I21.1 Acute transmural myocardial infarction of inferior wall I21.2 Acute transmural myocardial infarction of other sites I21.3 Acute transmural myocardial infarction of unspecified site I21.4 Acute subendocardial myocardial infarction I21.9 Acute myocardial infarction, unspecified I22 Subsequent myocardial infarction (No data) I22.0 Subsequent myocardial infarction of anterior wall I22.1 Subsequent myocardial infarction of inferior wall I22.8 Subsequent myocardial infarction of other sites I22.9 Subsequent myocardial infarction of unspecified site I23 Certain current complications following acute myocardial infarction (No data) I23.0 Haemopericardium as current complication following acute myocardial infarction (No data) I23.1 Atrial septal defect as current complication following acute myocardial infarction (No data) I23.2 Ventricular septal defect as current complication following acute myocardial infarction I23.3 Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction (No data) I23.4 Rupture of chordae tendineae as current complication following acute myocardial infarction (No data) I23.5 Rupture of papillary muscle as current complication following acute myocardial infarction (No data) I23.6 Thrombosis of atrium, auricular appendage, and ventricle as current complications

following acute myocardial infarction (No data)

I23.8 Other current complications following acute myocardial infarction (No data)

I24 Other acute ischaemic heart diseases (No data)

I24.0 Coronary thrombosis not resulting in myocardial infarction (No data)

I24.1 Dressler's syndrome

I24.8 Other forms of acute ischaemic heart disease

I24.9 Acute ischaemic heart disease, unspecified

I25 Chronic ischaemic heart disease (No data)

I25.0 Atherosclerotic cardiovascular disease, so described

I25.1 Atherosclerotic heart disease

I25.2 Old myocardial infarction

I25.3 Aneurysm of heart

I25.4 Coronary artery aneurysm

I25.5 Ischaemic cardiomyopathy

I25.6 Silent myocardial ischaemia

I25.8 Other forms of chronic ischaemic heart disease

I25.9 Chronic ischaemic heart disease, unspecified

#### A.3 Cerebrovascular diseases

#### I60-I69 Cerebrovascular diseases:

I60 Subarachnoid haemorrhage (No data)

I60.0 Subarachnoid haemorrhage from carotid siphon and bifurcation

I60.1 Subarachnoid haemorrhage from middle cerebral artery

I60.2 Subarachnoid haemorrhage from anterior communicating artery

I60.3 Subarachnoid haemorrhage from posterior communicating artery

I60.4 Subarachnoid haemorrhage from basilar artery

I60.5 Subarachnoid haemorrhage from vertebral artery

I60.6 Subarachnoid haemorrhage from other intracranial arteries

I60.7 Subarachnoid haemorrhage from intracranial artery, unspecified

I60.8 Other subarachnoid haemorrhage

I60.9 Subarachnoid haemorrhage, unspecified

I61 Intracerebral haemorrhage (No data)

I61.0 Intracerebral haemorrhage in hemisphere, subcortical

I61.1 Intracerebral haemorrhage in hemisphere, cortical

I61.2 Intracerebral haemorrhage in hemisphere, unspecified

I61.3 Intracerebral haemorrhage in brain stem

I61.4 Intracerebral haemorrhage in cerebellum

I61.5 Intracerebral haemorrhage, intraventricular

I61.6 Intracerebral haemorrhage, multiple localized

I61.8 Other intracerebral haemorrhage

I61.9 Intracerebral haemorrhage, unspecified

I62 Other nontraumatic intracranial haemorrhage (No data)

I62.0 Subdural haemorrhage (acute)(nontraumatic)

I62.1 Nontraumatic extradural haemorrhage

I62.9 Intracranial haemorrhage (nontraumatic), unspecified

I63 Cerebral infarction (No data)

I63.0 Cerebral infarction due to thrombosis of precerebral arteries

I63.1 Cerebral infarction due to embolism of precerebral arteries

I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries

I63.3 Cerebral infarction due to thrombosis of cerebral arteries

I63.4 Cerebral infarction due to embolism of cerebral arteries

I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries

I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic

I63.8 Other cerebral infarction

I63.9 Cerebral infarction, unspecified

I64 Stroke, not specified as haemorrhage or infarction

I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction (No data)

I65.0 Occlusion and stenosis of vertebral artery (No data)

I65.1 Occlusion and stenosis of basilar artery (No data)

I65.2 Occlusion and stenosis of carotid artery (No data)

I65.3 Occlusion and stenosis of multiple and bilateral precerebral arteries (No data)

I65.8 Occlusion and stenosis of other precerebral artery (No data)

I65.9 Occlusion and stenosis of unspecified precerebral artery (No data)

I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction (No data)

I66.0 Occlusion and stenosis of middle cerebral artery

I66.1 Occlusion and stenosis of anterior cerebral artery (No data)

I66.2 Occlusion and stenosis of posterior cerebral artery (No data)

- I66.3 Occlusion and stenosis of cerebellar arteries (No data)
- I66.4 Occlusion and stenosis of multiple and bilateral cerebral arteries (No data)
- I66.8 Occlusion and stenosis of other cerebral artery (No data)
- I66.9 Occlusion and stenosis of unspecified cerebral artery (No data)
- I67 Other cerebrovascular diseases (No data)
- I67.0 Dissection of cerebral arteries, nonruptured
- I67.1 Cerebral aneurysm, nonruptured
- I67.2 Cerebral atherosclerosis
- I67.3 Progressive vascular leukoencephalopathy
- I67.4 Hypertensive encephalopathy
- I67.5 Moyamoya disease
- I67.6 Nonpyogenic thrombosis of intracranial venous system
- I67.7 Cerebral arteritis, not elsewhere classified
- I67.8 Other specified cerebrovascular diseases
- I67.9 Cerebrovascular disease, unspecified
- I68\* Cerebrovascular disorders in diseases classified elsewhere (No data)
- I68.0\* Cerebral amyloid angiopathy (No data)
- I68.1\* Cerebral arteritis in infectious and parasitic diseases classified elsewhere (No data)
- I68.2\* Cerebral arteritis in other diseases classified elsewhere (No data)
- I68.8\* Other cerebrovascular disorders in diseases classified elsewhere (No data)
- I69 Sequelae of cerebrovascular disease (No data)
- I69.0 Sequelae of subarachnoid haemorrhage
- I69.1 Sequelae of intracerebral haemorrhage
- I69.2 Sequelae of other nontraumatic intracranial haemorrhage
- I69.3 Sequelae of cerebral infarction
- I69.4 Sequelae of stroke, not specified as haemorrhage or infarction
- I69.8 Sequelae of other and unspecified cerebrovascular diseases

#### A.4 Cardiovascular Diseases (All above plus the followings)

I00-I02 Acute rheumatic fever (Excluded)

I05-I09 Chronic rheumatic heart diseases(Excluded)

I26-I28 Pulmonary heart disease and diseases of pulmonary circulation (Excluded)

I30-I52 Other forms of heart disease( Some of them are excluded)

I30 Acute pericarditis (Excluded)

I30.0 Acute nonspecific idiopathic pericarditis (Excluded)

I30.1 Infective pericarditis (Excluded)

I30.8 Other forms of acute pericarditis (Excluded)

I30.9 Acute pericarditis, unspecified (Excluded)

I31 Other diseases of pericardium (Excluded)

I31.0 Chronic adhesive pericarditis (Excluded)

I31.1 Chronic constrictive pericarditis (Excluded)

I31.2 Haemopericardium, not elsewhere classified (Excluded)

I31.3 Pericardial effusion (noninflammatory) (Excluded)

I31.8 Other specified diseases of pericardium (Excluded)

I31.9 Disease of pericardium, unspecified (Excluded)

I32\* Pericarditis in diseases classified elsewhere (Excluded)

I32.0\* Pericarditis in bacterial diseases classified elsewhere (Excluded)

I32.1\* Pericarditis in other infectious and parasitic diseases classified elsewhere (Excluded)

I32.8\* Pericarditis in other diseases classified elsewhere (Excluded)

I33 Acute and subacute endocarditis (Excluded)

I33.0 Acute and subacute infective endocarditis (Excluded)

I33.9 Acute endocarditis, unspecified (Excluded)

I34 Nonrheumatic mitral valve disorders (Excluded)

I34.0 Mitral (valve) insufficiency (Excluded)

I34.1 Mitral (valve) prolapsed (Excluded)

I34.2 Nonrheumatic mitral (valve) stenosis (Excluded)

I34.8 Other nonrheumatic mitral valve disorders (Excluded)

I34.9 Nonrheumatic mitral valve disorder, unspecified (Excluded)

I35 Nonrheumatic aortic valve disorders (Excluded)

I35.0 Aortic (valve) stenosis (Excluded)

I35.1 Aortic (valve) insufficiency (Excluded)

I35.2 Aortic (valve) stenosis with insufficiency (Excluded)

I35.8 Other aortic valve disorders (Excluded)

I35.9 Aortic valve disorder, unspecified (Excluded)

I36 Nonrheumatic tricuspid valve disorders (Excluded)

I36.0 Nonrheumatic tricuspid (valve) stenosis (Excluded)

I36.1 Nonrheumatic tricuspid (valve) insufficiency (Excluded)

I36.2 Nonrheumatic tricuspid (valve) stenosis with insufficiency (Excluded)

I36.8 Other nonrheumatic tricuspid valve disorders (Excluded)

I36.9 Nonrheumatic tricuspid valve disorder, unspecified (Excluded)

I37 Pulmonary valve disorders (Excluded)

I37.0 Pulmonary valve stenosis (Excluded)

I37.1 Pulmonary valve insufficiency (Excluded)

I37.2 Pulmonary valve stenosis with insufficiency (Excluded)

I37.8 Other pulmonary valve disorders (Excluded)

I37.9 Pulmonary valve disorder, unspecified (Excluded)

I38 Endocarditis, valve unspecified (Excluded)

I39\* Endocarditis and heart valve disorders in diseases classified elsewhere (Excluded)

I39.0\* Mitral valve disorders in diseases classified elsewhere (Excluded)

I39.1\* Aortic valve disorders in diseases classified elsewhere (Excluded)

I39.2\* Tricuspid valve disorders in diseases classified elsewhere (Excluded)

I39.3\* Pulmonary valve disorders in diseases classified elsewhere (Excluded)

I39.4\* Multiple valve disorders in diseases classified elsewhere (Excluded)

I39.8\* Endocarditis, valve unspecified, in diseases classified elsewhere (Excluded)

I40 Acute myocarditis (Excluded)

I40.0 Infective myocarditis (Excluded)

I40.1 Isolated myocarditis (Excluded)

I40.8 Other acute myocarditis (Excluded)

I40.9 Acute myocarditis, unspecified (Excluded)

I41\* Myocarditis in diseases classified elsewhere (Excluded)

I41.0\* Myocarditis in bacterial diseases classified elsewhere (Excluded)

I41.1\* Myocarditis in viral diseases classified elsewhere (Excluded)

- I41.2\* Myocarditis in other infectious and parasitic diseases classified elsewhere (Excluded)
- I41.8\* Myocarditis in other diseases classified elsewhere (Excluded)
- I42 Cardiomyopathy (Excluded)
- I42.0 Dilated cardiomyopathy (Excluded)
- I42.1 Obstructive hypertrophic cardiomyopathy (Excluded)
- I42.2 Other hypertrophic cardiomyopathy (Excluded)
- I42.3 Endomyocardial (eosinophilic) disease (Excluded)
- I42.4 Endocardial fibroelastosis (Excluded)
- I42.5 Other restrictive cardiomyopathy (Excluded)
- I42.6 Alcoholic cardiomyopathy (Excluded)
- I42.7 Cardiomyopathy due to drugs and other external agents (Excluded)
- I42.8 Other cardiomyopathies (Excluded)
- I42.9 Cardiomyopathy, unspecified (Excluded)
- I43\* Cardiomyopathy in diseases classified elsewhere (Excluded)
- I43.0\* Cardiomyopathy in infectious and parasitic diseases classified elsewhere (Excluded)
- I43.1\* Cardiomyopathy in metabolic diseases (Excluded)
- I43.2\* Cardiomyopathy in nutritional diseases (Excluded)
- I43.8\* Cardiomyopathy in other diseases classified elsewhere (Excluded)
- I44 Atrioventricular and left bundle-branch block (Excluded)
- I44.0 Atrioventricular block, first degree (Excluded)
- I44.1 Atrioventricular block, second degree (Excluded)
- I44.2 Atrioventricular block, complete (Excluded)
- I44.3 Other and unspecified atrioventricular block (Excluded)
- I44.4 Left anterior fascicular block (Excluded)
- I44.5 Left posterior fascicular block (Excluded)
- I44.6 Other and unspecified fascicular block (Excluded)
- I44.7 Left bundle-branch block, unspecified (Excluded)
- I45 Other conduction disorders (Excluded)
- I45.0 Right fascicular block (Excluded)
- I45.1 Other and unspecified right bundle-branch block (Excluded)
- I45.2 Bifascicular block (Excluded)
- I45.3 Trifascicular block (Excluded)
- I45.4 Nonspecific intraventricular block (Excluded)
- I45.5 Other specified heart block (Excluded)
- I45.6 Pre-excitation syndrome (Excluded)
- I45.8 Other specified conduction disorders (Excluded)
- I45.9 Conduction disorder, unspecified (Excluded)
- I46 Cardiac arrest (No data)
- I46.0 Cardiac arrest with successful resuscitation (No data)
- I46.1 Sudden cardiac death, so described
- I46.9 Cardiac arrest, unspecified
- I47 Paroxysmal tachycardia (No data)
- I47.0 Re-entry ventricular arrhythmia
- I47.1 Supraventricular tachycardia
- I47.2 Ventricular tachycardia
- I47.9 Paroxysmal tachycardia, unspecified
- I48 Atrial fibrillation and flutter
- I49 Other cardiac arrhythmias (No data)
- I49.0 Ventricular fibrillation and flutter
- I49.1 Atrial premature depolarization
- I49.2 Junctional premature depolarization
- I49.3 Ventricular premature depolarization
- I49.4 Other and unspecified premature depolarization
- I49.5 Sick sinus syndrome
- I49.8 Other specified cardiac arrhythmias
- I49.9 Cardiac arrhythmia, unspecified
- I50 Heart failure (No data)
- I51 Complications and ill-defined descriptions of heart disease (No data)
- I51.0 Cardiac septal defect, acquired
- I51.1 Rupture of chordae tendineae, not elsewhere classified
- I51.2 Rupture of papillary muscle, not elsewhere classified
- I51.3 Intracardiac thrombosis, not elsewhere classified
- I51.4 Myocarditis, unspecified
- I51.5 Myocardial degeneration
- I51.6 Cardiovascular disease, unspecified
- I51.7 Cardiomegaly

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- I51.8 Other ill-defined heart diseases
- I51.9 Heart disease, unspecified
- I52\* Other heart disorders in diseases classified elsewhere (No data)
- I52.0\* Other heart disorders in bacterial diseases classified elsewhere (Excluded)
- I52.1\* Other heart disorders in other infectious and parasitic diseases classified elsewhere (Excluded)
- I52.8\* Other heart disorders in other diseases classified elsewhere (No data)

#### I70-I79 Diseases of arteries, arterioles and capillaries

- I70 Atherosclerosis (No data)
- I70.0 Atherosclerosis of aorta
- I70.1 Atherosclerosis of renal artery
- I70.2 Atherosclerosis of arteries of extremities
- I70.8 Atherosclerosis of other arteries
- I70.9 Generalized and unspecified atherosclerosis
- I71 Aortic aneurysm and dissection (No data)
- I71.0 Dissection of aorta [any part]
- I71.1 Thoracic aortic aneurysm, ruptured
- I71.2 Thoracic aortic aneurysm, without mention of rupture
- I71.3 Abdominal aortic aneurysm, ruptured
- I71.4 Abdominal aortic aneurysm, without mention of rupture
- I71.5 Thoracoabdominal aortic aneurysm, ruptured
- I71.6 Thoracoabdominal aortic aneurysm, without mention of rupture
- I71.8 Aortic aneurysm of unspecified site, ruptured
- I71.9 Aortic aneurysm of unspecified site, without mention of rupture
- I72 Other aneurysm (No data)
- I72.0 Aneurysm of carotid artery
- I72.1 Aneurysm of artery of upper extremity
- I72.2 Aneurysm of renal artery
- I72.3 Aneurysm of iliac artery
- I72.4 Aneurysm of artery of lower extremity
- I72.8 Aneurysm of other specified arteries
- I72.9 Aneurysm of unspecified site
- I73 Other peripheral vascular diseases

I73.0 Raynaud's syndrome (No data)

I73.1 Thromboangiitis obliterans [Buerger]

I73.8 Other specified peripheral vascular diseases

I73.9 Peripheral vascular disease, unspecified

I74 Arterial embolism and thrombosis (No data)

I74.0 Embolism and thrombosis of abdominal aorta

I74.1 Embolism and thrombosis of other and unspecified parts of aorta

I74.2 Embolism and thrombosis of arteries of upper extremities

I74.3 Embolism and thrombosis of arteries of lower extremities

I74.4 Embolism and thrombosis of arteries of extremities, unspecified Peripheral arterial embolism

I74.5 Embolism and thrombosis of iliac artery

I74.8 Embolism and thrombosis of other arteries

I74.9 Embolism and thrombosis of unspecified artery

I77 Other disorders of arteries and arterioles (No data)

I77.0 Arteriovenous fistula, acquired

I77.1 Stricture of artery

I77.2 Rupture of artery

I77.3 Arterial fibromuscular dysplasia

I77.4 Coeliac artery compression syndrome

I77.5 Necrosis of artery

I77.6 Arteritis, unspecified

I77.8 Other specified disorders of arteries and arterioles

I77.9 Disorder of arteries and arterioles, unspecified

I78 Diseases of capillaries (No data)

I78.0 Hereditary haemorrhagic telangiectasia

I78.1 Naevus, non-neoplastic

I78.8 Other diseases of capillaries

I78.9 Disease of capillaries, unspecified

I79\* Disorders of arteries, arterioles and capillaries in diseases classified elsewhere (No data)

I79.0\* Aneurysm of aorta in diseases classified elsewhere (No data)

I79.1\* Aortitis in diseases classified elsewhere (No data)

I79.2\* Peripheral angiopathy in diseases classified elsewhere (No data)

I79.8\* Other disorders of arteries, arterioles and capillaries in diseases classified elsewhere (No data)

I80-I89 Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified (Excluded)

I95-I99 Other and unspecified disorders of the circulatory system (Excluded)

Appendix B

# Appendix B

### **Canada (Average rate & 10% sodium reduction per year)**



#### **Without control**

### **Canada (Average rate & 5% sodium reduction per year)**



#### **Without control**

### **Canada (Average rate & 10% sodium reduction per year)**



### **With control**

# **Canada (Weighted average rate & 10% sodium reduction per year)**



### **Without control**

# **Canada (Weighted average rate & 10% sodium reduction per year) With control**



# **Canada (Constant death/events & 10% sodium reduction per year)**



### **Without control**

# **Canada (Constant death/events & 10% sodium reduction per year) With control**



### **US (Average rate & 10% sodium reduction per year)**

#### **Without control**



### **US (Average rate & 5% sodium reduction per year)**

#### **Without control**



### **US (Average rate & 10% sodium reduction per year)**

### **With control**



## **US (Weighted average rate & 10% sodium reduction per year) Without control**



# **US (Weighted average rate & 10% sodium reduction per year) With control**



## **US (Constant death/events & 10% sodium reduction per year) Without control**



APPENDIX B. APPENDIX B

APPENDIX B. APPENDIX B

# **US (Constant death/events & 10% sodium reduction per year) With control**



### **Summary table for LA countries (without control)**

### **(Average rate & 10% sodium reduction per year)**



### **Summary table for LA countries (without control)**

# **(Average rate & 5% sodium reduction per year)**


## **Summary table for LA countries (with control)**

## **(Average rate & 10% sodium reduction per year)**



## **Summary table for LA countries (without control)**

## **(Weighted average rate & 10% sodium reduction per year)**



## **Summary table for LA countries (with control)**

## **(Weighted average rate & 10% sodium reduction per year)**



## **Summary table for LA countries (without control)**

## **(Constant death/events & 10% sodium reduction per year)**



## **Summary table for LA countries (with control)**

## **(Constant death/events & 10% sodium reduction per year)**



#### Stroke CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 | 4720 | 1399 | 933 | 5437 | 125 | 187 | 762 | 270 | 105 | 978 | 24 | 21 | 137 22 || 4248 || 2551 || 1727 || 10007 || 235 || 354 || 1437 || 624 || 198 || 1818 || 46 || 40 || 260 33 || 3823 || 3514 || 2411 || 13900 || 333 || 504 || 2039 || 918 || 283 || 2547 || 65 || 58 || 370 44 || 3441 || 4330 || 3008 || 17261 || 420 || 639 || 2581 || 1166 || 360 || 3186 || 83 || 74 || 470 55 | 3097 | 5021 | 3525 | 20148 | 497 | 760 | 3064 | 1376 | 429 | 3744 | 99 | 89 | 560 66 | 2787 | 5620 | 3983 | 22684 | 566 | 870 | 3502 | 1558 | 493 | 4240 | 113 | 102 | 641 77 || 2508 || 6147 || 4392 || 24938 || 629 || 970 || 3901 || 1718 || 551 || 4686 || 126 || 115 || 716 88 | 2258 | 6616 | 4762 | 26965 | 687 | 1063 | 4267 | 1860 | 604 | 5089 | 138 | 126 | 785 99 | 2032 | 7040 | 5100 | 28807 | 740 | 1148 | 4606 | 1988 | 654 | 5459 | 150 | 137 | 849 100 | 1829 | 7403 | 5394 | 30402 | 787 | 1224 | 4905 | 2097 | 698 | 5782 | 160 | 147 | 906 111 | 1646 | 7735 | 5664 | 31864 | 830 | 1295 | 5183 | 2197 | 739 | 6079 | 169 | 156 | 959 122 || 1481 || 8042 || 5914 || 33219 || 870 || 1361 || 5442 || 2290 || 777 || 6355 || 178 || 164 || 1008 133 || 1333 || 8329 || 6149 || 34486 || 908 || 1422 || 5684 || 2376 || 813 || 6613 || 186 || 172 || 1054 144 | 1200 | 8600 | 6369 | 35680 | 943 | 1480 | 5912 | 2456 | 847 | 6856 | 193 | 180 | 1097 Stroke CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 | 4720 | 1020 | 470 | 4184 | 91 | 94 | 586 | 267 | 69 | 920 | 24 | 14 | 129 22 || 4248 || 1859 || 870 || 7697 || 172 || 178 || 1105 || 619 || 131 || 1709 || 45 || 26 || 244 33 || 3823 || 2558 || 1214 || 10685 || 242 || 254 || 1568 || 909 || 186 || 2393 || 65 || 38 || 348 44 | 3441 | 3151 | 1514 | 13261 | 306 | 321 | 1983 | 1154 | 237 | 2992 | 82 | 49 | 441 55 | 3097 | 3652 | 1773 | 15472 | 361 | 382 | 2353 | 1362 | 282 | 3514 | 98 | 58 | 525 6 2787 4086 2002 17411 412 437 2688 1541 324 3978 112 67 602 77 | 2508 | 4466 | 2207 | 19132 | 457 | 488 | 2993 | 1698 | 362 | 4394 | 125 | 75 | 672 88 | 2258 | 4805 | 2392 | 20677 | 499 | 534 | 3273 | 1837 | 397 | 4770 | 137 | 83 | 736 99 | 2032 | 5110 | 2560 | 22078 | 537 | 577 | 3530 | 1962 | 429 | 5114 | 148 | 90 | 796 100 | 1829 | 5373 | 2707 | 23297 | 571 | 615 | 3760 | 2070 | 458 | 5416 | 158 | 96 | 849 111 | 1646 | 5613 | 2843 | 24416 | 602 | 650 | 3972 | 2169 | 485 | 5694 | 167 | 102 | 898 12 1481 5835 2968 25450 632 683 4170 2260 510 5951 175 108 944 133 | 1333 | 6043 | 3085 | 26417 | 659 | 714 | 4355 | 2344 | 534 | 6192 | 183 | 113 113 987 144 | 1200 | 6238 | 3195 | 27327 | 685 | 743 | 4529 | 2423 | 556 | 6419 | 191 | 118 | 1027 Number of Sodium Number of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year Number of lives saved by gender and hypertension status per year Number years Normotensive (Female) Sodium IntakeSodium Intake Hypertensive (Male) **Normotensive (Male)** Normotensive (Male) Normotensive (Female) Number of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year Number of Sodium Hypertensive (Male) Normotensive (Male) Hypertensive (Male) Normotensive (Male) Normotensive (Male) years

### **Argentina (Average rate & 10% sodium reduction per year)**

### **Bolivia (Average rate & 10% sodium reduction per year)**





#### **Brazil (Average rate & 10% sodium reduction per year)**

# **Chile (Average rate & 10% sodium reduction per year)**



#### Stroke CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 8880 670 846 2651 60 170 372 129 95 477 12 12 19 67 22 || 3492 || 1243 || 1589 || 4954 || 114 || 324 || 708 || 303 || 182 || 898 || 22 || 37 || 128 33 || 3143 || 1739 || 2248 || 6980 || 163 || 466 || 1015 || 453 || 262 || 1274 || 32 || 53 || 184 44 | 2829 | 2176 | 2840 | 8786 | 208 | 597 | 1298 | 584 | 336 | 1614 | 41 | 69 | 236 55 || 2546 || 2555 || 3364 || 10372 || 248 || 715 || 1553 || 698 || 403 || 1916 || 49 || 83 || 283 6 2291 2894 3839 11806 285 825 1789 800 466 2191 57 96 327 77 | 2062 | 3202 | 4276 | 13115 | 320 | 927 | 2009 | 892 | 525 | 2444 | 64 | 108 | 367 8 1856 3485 4680 14324 352 1023 2214 976 580 2679 70 120 406 99 | 1670 | 3748 | 5058 | 15452 | 382 | 1114 | 2408 | 1054 | 632 | 2899 | 77 | 131 | 442 100 | 1503 | 3978 | 5393 | 16447 | 409 | 1195 | 2582 | 1123 | 678 | 3094 | 82 | 141 | 474 111 | 1353 | 4194 | 5708 | 17382 | 434 | 1272 | 2745 | 1187 | 723 | 3278 | 87 | 151 | 505 122 | 1218 | 4398 | 6006 | 18268 | 458 | 1345 | 2901 | 1248 | 765 | 3452 | 93 | 160 | 534 Stroke CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 1 3880 1 588 | 519 | 2060 1 53 | 104 | 289 | 154 | 76 | 453 | 14 | 15 | 63 22 | 3492 | 1090 | 975 | 3849 | 100 | 199 | 550 | 362 | 146 | 853 | 26 | 29 | 121 33 | 3143 | 1526 | 1379 | 5423 | 143 | 286 | 789 | 540 | 210 | 1210 | 38 | 43 | 175 44 1 2829 1 1909 | 1743 | 6827 1 182 | 366 | 1008 1 697 | 269 | 1533 1 49 | 55 | 224 55 || 2546 || 2241 || 2064 || 8059 || 218 || 439 || 1207 || 833 || 324 || 1819 || 58 || 66 || 269 66 || 2291 || 2539 || 2355 || 9172 || 250 || 506 || 1390 || 954 || 374 || 2080 || 67 || 77 || 310 77 || 2062 || 2809 || 2623 || 10188 || 280 || 569 || 1561 || 1064 || 421 || 2320 || 76 || 87 || 349 88 || 1856 || 3056 || 2871 || 11127 || 308 || 628 || 1720 || 1164 || 465 || 2543 || 84 || 96 || 385 99 || 1670 || 3287 || 3103 || 12004 || 335 || 683 || 1871 || 1258 || 507 || 2752 || 91 || 105 || 419 100 | 1503 | 3489 | 3309 | 12778 | 359 | 733 | 2006 | 1340 | 544 | 2938 | 98 | 113 | 450 111 | 1353 | 3678 | 3502 | 13504 | 381 | 780 | 2133 | 1416 | 580 | 3113 | 104 | 121 | 480 122 | 1218 | 3858 | 3685 | 14193 | 402 | 825 | 2254 | 1488 | 614 | 3278 | 110 | 128 | 507 Hypertensive (Female) Normotensive (Female) Hypertensive (Female) Normotensive (Female) Number of years Number of years Sodium IntakeSodium IntakeNumber of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year Hypertensive (Male) Normotensive (Male) Hypertensive (Male) Normotensive (Male) Number of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year

### **Colombia (Average rate & 10% sodium reduction per year)**

#### Stroke CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 1 3930 1 55 | 91 | 258 1 5 | 18 | 36 | 11 | 10 | 46 | 1 | 2 | 6 22 | 3537 | 102 | 171 | 482 | 9 | 35 | 69 | 25 | 20 | 87 | 2 | 4 | 12 33 | 3183 | 142 | 243 | 680 | 13 | 50 | 99 | 37 | 28 | 124 | 3 | 6 | 18 44 | 2865 | 179 | 307 | 857 | 17 | 65 | 127 | 48 | 36 | 158 | 3 | 7 | 23 55 | 2578 | 210 | 364 | 1012 | 20 | 77 | 152 | 57 | 44 | 187 | 4 | 9 | 28 6 2321 237 415 1151 23 89 175 66 50 214 5 10 32 77 | 2089 | 263 | 462 | 1279 | 26 | 100 | 196 | 73 | 57 | 238 | 5 | 12 | 36 88 | 1880 | 286 | 506 | 1398 | 29 | 111 | 216 | 80 | 63 | 261 | 6 | 13 | 40 99 | 1692 | 308 | 547 | 1509 | 31 | 121 | 235 | 87 | 68 | 283 | 6 | 14 | 43 100 | 1523 | 326 | 582 | 1603 | 34 | 129 | 252 | 92 | 73 | 302 | 7 | 15 | 46 111 1370 1 343 | 616 | 1691 1 36 | 137 | 268 | 97 | 78 | 319 | 7 | 16 | 49 122 | 1233 | 359 | 647 | 1775 | 38 | 145 | 282 | 102 | 83 | 336 | 8 | 17 | 52 **Stroke**  CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 1 3930 1 44 | 50 | 179 1 4 | 10 | 25 | 12 | 7 | 39 | 1 | 1 | 6 22 8337 82 94 335 8 19 19 48 27 14 74 2 3 1 33 | 3183 | 115 | 133 | 472 | 11 | 28 | 69 | 41 | 20 | 105 | 3 | 4 | 15 44 12865 1244 1369 1256 124 135 1268 1262 126 134 14 5 20 55 **1** 2578 **1** 168 1 200 1 703 **1** 16 1 42 1 105 **1** 63 1 31 1 159 **1** 4 1 6 1 23 66 | 2321 | 191 | 228 | 800 | 19 | 49 | 121 | 72 | 36 | 181 | 5 | 7 | 27 77 || 2089 || 211 || 254 || 888 || 21 || 55 || 136 || 80 || 41 || 202 || 6 || 8 || 30 88 | 1880 | 230 | 278 | 971 | 23 | 61 | 150 | 88 | 45 | 222 | 6 | 9 | 34 99 | 1692 | 247 | 300 | 1048 | 25 | 66 | 163 | 95 | 49 | 240 | 7 | 10 | 37 100 | 1523 | 262 | 320 | 1114 | 27 | 71 | 175 | 101 | 53 | 256 | 7 | 11 | 39 111 1 1370 | 276 | 339 | 1178 | 29 | 76 | 186 | 106 | 56 | 272 | 8 | 12 | 42 122 | 1233 | 290 | 356 | 1237 | 30 | 80 | 197 | 112 | 59 | 286 | 8 | 12 | 44 Hypertensive (Female) Normotensive (Female) Hypertensive (Female) Normotensive (Female) Number of years Number of years Sodium IntakeSodium IntakeNumber of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year Hypertensive (Male) Normotensive (Male) Hypertensive (Male) Normotensive (Male) Number of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year

## **Costa Rica (Average rate & 10% sodium reduction per year)**



#### **Cuba (Average rate & 10% sodium reduction per year)**



#### **Dominican Republic (Average rate & 10% sodium reduction per year)**



### **Ecuador (Average rate & 10% sodium reduction per year)**

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#### **El Salvador (Average rate & 10% sodium reduction per year)**





### **Guatemala (Average rate & 10% sodium reduction per year)**

1 | 2057 | 647 | 559 | 3770 | 71 | 130 | 627 | 250 | 98 | 887 | 20 | 21

2 | 1851 | 687 | 595 | 4009 | 76 | 140 | 671 | 266 | 105 | 945 | 21 | 22 | 152

3 | 1666 | 726 | 631 | 4247 | 81 | 149 | 714 | 282 | 112 | 1003 | 23 | 24 | 163

4 | 1500 | 766 | 667 | 4485 | 86 | 158 | 758 | 298 | 118 | 1061 | 24 | 25 | 173

5 | 1350 | 803 | 701 | 4708 | 90 | 166 | 798 | 312 | 125 | 1115 | 25 | 27 | 182

6 | 1215 | 840 | 735 | 4932 | 95 | 175 | 839 | 327 | 131 | 1170 | 27 | 28 | 191

Stroke

Stroke

1

Number of years

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

Number of years

Sodium Intake

Sodium Intake

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

CHD

Hypertensive (Male)

CHD

APPENDIX B. APPENDIX B

 ${\cal APPENDIX}$  B

APPENDIX B.

21 142

#### Stroke CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 | 2800 | 1000 | 938 | 3444 | 90 | 188 | 483 | 193 | 105 | 620 | 17 | 21 | 87 22 || 2520 || 1874 || 1774 || 6492 || 171 || 361 || 923 || 456 || 202 || 1175 || 33 || 41 || 166 33 || 2268 || 2648 || 2526 || 9217 || 245 || 519 || 1327 || 686 || 291 || 1676 || 48 || 59 || 240 44 || 2041 || 3340 || 3210 || 11679 || 313 || 666 || 1700 || 893 || 374 || 2133 || 61 || 76 || 308 55 | 1837 | 3948 | 3817 | 13858 | 375 | 799 | 2037 | 1074 | 449 | 2541 | 74 | 92 | 370 6 1653 4497 4372 15840 432 922 2349 1238 519 2914 85 106 427 7 1488 4999 4884 17661 484 1037 2640 1387 584 3259 96 120 481 88 | 1339 | 5462 | 5359 | 19348 | 533 | 1144 | 2911 | 1524 | 646 | 3580 | 106 | 133 | 531 99 1 1205 1 5894 | 5804 | 20925 | 580 | 1246 | 3167 | 1652 | 703 | 3881 | 115 | 145 | 578 Stroke CHDD | CVD **|** Stroke | CHD | CVD **|** Stroke | CHD | CVD **|** Stroke | CHD | CVD 11 | 2800 | 782 | 763 | 2998 | 70 | 153 | 420 | 205 | 112 | 659 | 18 | 22 | 92 22 | 2520 | 1466 | 1443 | 5651 | 134 | 293 | 803 | 485 | 215 | 1250 | 35 | 43 | 177 33 | 2268 | 2071 | 2055 | 8023 | 192 | 422 | 1155 | 730 | 310 | 1783 | 51 | 63 | 255 44 || 2041 || 2613 || 2611 || 10166 || 245 || 542 || 1480 || 950 || 398 || 2269 || 65 || 81 || 328 55 | 1837 | 3087 | 3105 | 12059 | 293 | 650 | 1773 | 1142 | 478 | 2702 | 78 | 97 | 393 6 1653 3516 3555 13780 337 750 2044 1316 552 3099 90 113 454 77 || 1488 || 3907 || 3970 || 15361 || 379 || 843 || 2296 || 1474 || 621 || 3465 || 102 || 127 || 511 88 || 1339 || 4268 || 4355 || 16825 || 417 || 930 || 2532 || 1620 || 686 || 3805 || 112 || 141 || 564 99 || 1205 || 4605 || 4716 || 18193 || 453 || 1012 || 2754 || 1756 || 748 || 4124 || 122 || 154 || 614 Hypertensive (Female) Normotensive (Female) Hypertensive (Female) Normotensive (Female) Number of years Number of years Sodium IntakeSodium Intake Number of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year Hypertensive (Male) Normotensive (Male) Hypertensive (Male) Normotensive (Male) Number of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year

### **Mexico (Average rate & 10% sodium reduction per year)**

#### Stroke CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 1 3880 1 57 | 56 | 196 1 5 | 11 | 28 | 11 | 6 | 35 | 1 | 1 | 5 22 1 3492 1 106 1 106 369 1 10 22 53 1 26 1 12 67 1 2 2 21 33 | 3143 | 150 | 151 | 524 | 14 | 31 | 76 | 39 | 18 | 96 | 3 | 4 | 14 44 | 2829 | 189 | 192 | 665 | 18 | 40 | 98 | 51 | 23 | 122 | 4 | 5 | 18 5 2546 223 228 789 22 48 118 61 27 146 4 6 22 66 2291 255 262 903 255 56 137 270 32 168 3 5 7 25 77 | 2062 | 283 | 293 | 1009 | 28 | 64 | 154 | 79 | 36 | 188 | 6 | 7 | 28 88 | 1856 | 310 | 323 | 1108 | 31 | 71 | 171 | 87 | 40 | 207 | 6 | 8 | 31 99 | 1670 | 336 | 351 | 1203 | 34 | 77 | 187 | 94 | 44 | 225 | 7 | 9 | 34 100 1 1503 1 357 | 376 | 1285 1 37 | 83 | 201 | 101 | 47 | 241 | 7 | 10 | 37 111 1 1353 1 378 | 399 | 1363 1 39 | 89 | 215 | 107 | 50 | 257 | 8 | 11 | 39 12 1218 398 421 1437 41 94 228 113 53 271 8 11 42 **Stroke**  CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 1 3880 1 45 38 1 158 1 4 1 8 22 1 12 6 35 1 1 1 1 5 22 | 3492 | 84 | 73 | 297 | 8 | 15 | 42 | 28 | 11 | 66 | 2 | 2 | 9 33 | 3143 | 119 | 104 | 422 | 11 | 21 | 61 | 42 | 16 | 94 | 3 | 3 | 14 44 | 2829 | 150 | 132 | 535 | 14 | 28 | 79 | 55 | 20 | 120 | 4 | 4 | 18 525 **1** 2546 **1** 177 1 157 1 635 **1** 17 1 33 1 95 **1** 66 1 25 1 143 **1** 5 1 5 21 66 | 2291 | 201 | 180 | 727 | 20 | 39 | 110 | 76 | 29 | 165 | 5 | 6 | 25 77 || 2062 || 224 || 202 || 812 || 22 || 44 || 124 || 85 || 32 || 185 || 6 || 7 || 28 88 | 1856 | 245 | 222 | 891 | 25 | 49 | 138 | 93 | 36 | 204 | 7 | 7 | 31 99 | 1670 | 265 | 242 | 968 | 27 | 53 | 150 | 101 | 39 | 222 | 7 | 8 | 34 100 | 1503 | 282 | 259 | 1033 | 29 | 57 | 162 | 108 | 42 | 237 | 8 | 9 | 36 111 1 1353 | 299 | 275 | 1095 | 31 | 61 | 173 | 115 | 45 | 252 | 8 | 9 | 39 122 | 1218 | 314 | 290 | 1155 | 33 | 65 | 183 | 121 | 48 | 266 | 9 | 10 | 41 Hypertensive (Female) Normotensive (Female) Hypertensive (Female) Normotensive (Female) Number of years Number of years Sodium IntakeSodium IntakeNumber of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year Hypertensive (Male) Normotensive (Male) Hypertensive (Male) Normotensive (Male) Number of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year

## **Nicaragua (Average rate & 10% sodium reduction per year)**



### **Panama (Average rate & 10% sodium reduction per year)**

## **Paraguay (Average rate & 10% sodium reduction per year)**





#### **Peru (Average rate & 10% sodium reduction per year)**



#### Stroke CHDD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD Stroke CHD CVD 11 1960 1 73 | 48 | 215 1 7 | 10 | 30 | 14 | 5 | 39 | 1 | 1 | 5 22 | 1764 | 136 | 91 | 404 | 12 | 18 | 57 | 33 | 10 | 73 | 2 | 2 | 10 33 | 1588 | 191 | 129 | 572 | 18 | 26 | 82 | 49 | 15 | 104 | 3 | 3 | 15 44 | 1429 | 241 | 163 | 721 | 22 | 33 | 104 | 64 | 19 | 131 | 4 | 4 | 19 55 1 1286 1 284 | 193 | 854 | 27 | 40 | 124 | 77 | 22 | 156 | 5 | 5 | 22 Stroke CHDD | CVD **|** Stroke | CHD | CVD **|** Stroke | CHD | CVD **|** Stroke | CHD | CVD 11 1960 71 29 190 6 6 27 191 4 42 2 1 1 22 | 1764 | 132 | 55 | 357 | 12 | 11 | 51 | 44 | 8 | 79 | 3 | 2 | 11 31588 168 186 | 78 | 504 | 17 | 16 | 72 | 65 | 12 | 112 | 5 | 2 | 16 44 | 1429 | 234 | 98 | 635 | 22 | 20 | 91 | 85 | 15 | 141 | 6 | 3 | 20 Hypertensive (Female) Normotensive (Female) Hypertensive (Female) Normotensive (Female) Number of years Number of years Sodium IntakeSodium IntakeNumber of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year Hypertensive (Male) Normotensive (Male) Hypertensive (Male) Normotensive (Male) Number of events reduced by gender and hypertension status per year Number of lives saved by gender and hypertension status per year

1286 275 116 751 26 24 109 102 18 167 17 4 24

5

## **Uruguay (Average rate & 10% sodium reduction per year)**



### **Venezuela (Average rate & 10% sodium reduction per year)**

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