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The Economic Impact of Dietary Sodium Reduction in Canada

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by

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Abstract

OBJECTIVES: To determine the cost-utility of dietary sodium reduction in the Canadian population, given on the anticipated effect on incident cardiovascular disease (CVD).

METHODS: The Canadian Cardiovascular Disease Policy Model is a state transition model, which simulates CVD events, healthcare costs and consequences from the perspective of a publically funded healthcare system for the Canadian population. We evaluated the economic impact of reducing the dietary sodium intake of Canadian adults.

RESULTS: Over a 50-year time horizon, reducing dietary sodium by 1800 mg/day is projected to reduce the cumulative incidence of coronary heart disease and stroke by 2.66% and 4.45% respectively, while decreasing the total number of myocardial infarctions and strokes by 2.23% and 4.45% respectively. The model predicted a decrease in overall mortality of 0.47%, a gain of 1.22 million QALYs, and a savings of $20.7 billion in healthcare costs.

CONCLUSION: Reducing dietary sodium intake at the population level has the potenital to substantially decrease healthcare costs and improve health outcomes.

Keywords: Cardiovascular disease, Cardiovascular Disease Policy Model, High blood pressure, Dietary sodium reduction

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List of Symbols, Abbreviations and Nomenclature

BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
CVDPM	Cardiovascular disease policy model
DALY	Disability adjusted life year
DSP	Diastolic Blood Pressure
ICUR	Incremental cost-utility ratio
GBD	Global Burden of Disease
HC	Hypertension Canada
MI	Myocardial Infarction
POHEM	Program in Occupational Health and Environmental Medicine
QALY	Quality adjusted life year
RR	Relative risk
SBP	Systolic Blood Pressure
SWG	Sodium working group
UK	United Kingdom
US	United States
WHO	World Health Organization

Chapter 1: Background

1.1: Hypertension

Elevated blood pressure (BP) leads to a range of vascular diseases with hypertension being the most prevalent (1). In adults, hypertension is most often defined by a systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg (2); however, BP greater than 120 mmHg systolic or 80 mmHg diastolic is considered elevated (2). Hypertension is the leading attributable risk factor for premature mortality globally (1). In Canada, the prevalence of hypertension has gradually increased over time, and in 2012-2013 it was 23% in adults aged ≥ 20 years (3). Hypertension is the most common reason to visit a primary healthcare physician in Canada, and over four million prescriptions are written for antihypertensive medications every month (4). The cost attributable to hypertension was estimated to be 13.9 billion dollars in 2010 (5), and is expected to rise to 20.5 billion dollars by 2020 (5). Hypertension is also known to be a risk factor for dementia, cardiovascular disease (CVD) and kidney disease (6, 7). Of these chronic conditions, CVD specifically is associated with significant morbidity and mortality (8). Increased BP has been shown to account for 62% of strokes, and 49% of coronary heart disease (CHD) (9). Globally, stroke and CHD accounted for a combined 15 million deaths in 2015 (8).

In Canada, CVD is one of the leading causes of death and hospitalization (10). More than 64 thousand Canadians died from cardiovascular causes in 2014, with CHD and stroke accounting for 26% and 7% of all deaths, respectively (11). The risk of CVD morbidity and mortality increases with rising BP, and doubles with each 20/10 mm Hg increase in BP (12).

1.2: Dietary Sodium

A significant proportion of the prevalence of hypertension is attributed to poor lifestyle choices; therefore, hypertension is highly preventable (13). Some of these lifestyle factors include a diet high in sodium and saturated fats, inadequate physical activity, and excessive alcohol consumption (14). Of these modifiable risk factors, dietary sodium has been recognized as an important factor in the prevention and treatment of elevated BP (13, 15-17). Numerous leading public health organizations established recommendations for dietary sodium intake levels, based on scientific evidence, to help prevent further rise in BP.

Hypertension Canada (HC) recommends a dietary sodium intake of no more than 2000 mg/day (2). Evidence for this target is supported by a Cochrane meta-analysis of randomized controlled trials that found a substantial BP lowering effect by reducing dietary sodium intake from a mean of 3800 mg/day to a mean of 2000 mg/day (18). While 2000 mg/day is the evidence based target, 2300 mg/day is the interim target both federally and provincially (19). Currently, the average Canadian dietary sodium consumption is approximately 3800 mg/day, which is almost double the amount recommended (20). Reducing dietary sodium intake in the population has been recognized as a potentially important strategy in the prevention and treatment of hypertension and CVD (13, 15-17).

1.3: Review of the Literature

1.3.1: Effectiveness of sodium reduction

Sodium is an essential nutrient for maintenance of plasma volume, acid-base balance, transmission of nerve impulses and normal cell function (21, 22); however, excess dietary sodium increases BP, and can lead to negative health consequences (23). The necessary physiological requirement of sodium for adults is approximately 500 mg/day (24) with a recommended adequate intake of 1500 mg/day (19); however, the average sodium consumption in Canada is about 3800 mg/day (20).

Excess dietary sodium has been directly linked to elevated BP, in turn, increasing the risk of hypertension and CVD (17, 18, 25). The World Health Organization found high blood pressure accounted for 62% of strokes and 49% of CHD cases (9). Reducing dietary sodium intake by approximately 1100 mg/day has been estimated to decrease stroke and CHD mortality by 22% and 16%, respectively (26). Since BP is a risk factor for the development of CVD, we would expect that reducing sodium intake levels should improve CVD health indirectly. A literature review was conducted to examine the evidence supporting this relationship.

1.3.2: The effect of dietary sodium intake on blood pressure

The role of dietary salt (largest source of dietary sodium) restriction in lowering BP in humans dates back to the early 20th century, where Ambard and Beaujard were the first to demonstrate this connection (27). In the 1960s, the relationship between BP and salt intake was extensively studied by Dahl. He was the first to report a positive association between salt intake and the prevalence of hypertension across populations (28). In the 1980s, the well-known

INTERSALT study supported the findings of Dahl (29-31). This was an observational study in about 10 000 subjects from 52 communities with varying salt intake levels. The study demonstrated high salt intake was associated with an increased risk of blood pressure. In the 1990s, Frost and colleagues collected data on 47, 000 non-African subjects across 24 communities and confirmed the findings from Dahl and the INTERSALT study (32). Since the 1990's, the body of evidence has grown substantially with the addition of new epidemiological and experimental studies. Many systematic reviews and meta-analyses of these studies have been conducted to determine the overall effect of dietary sodium on BP. Two high-level systematic reviews and meta-analyses from the literature review were key to examining the association between dietary sodium intake and BP, which were by He et al (18), and Aburto et al. (21).

A Cochrane systematic review by He et al. (18) of randomized controlled trials (RCTs) examined studies published in and before 2012. They quantified the effects of a modest reduction in dietary salt of 4.4 g/day (1733 mg/day of sodium). Most trials had participants achieve dietary salt reduction through some combination of dietary advice, education, counseling or provision of key foods with reduced sodium content. The mean study duration was 4 weeks. They found a significant fall in average BP in both hypertensive and normotensive individuals, regardless of sex or ethnic group. Across all individuals, regardless of hypertension status, pooled estimates in mean changes in SBP and DBP across 34 studies (3230 participants) were -4.18 mmHg (95% confidence interval (CI): -5.18 to -3.18 mmHg) and -2.06 mmHg (95% CI: -2.67 to -1.45 mmHg), respectively. Among hypertensive individuals, pooled estimates of mean changes in SBP and DBP across 22 studies (999 participants) were -5.39 mmHg (95% CI: -6.62 to -4.15 mmHg) and -2.82 mmHg (95% CI: -3.54 to -2.11 mmHg), respectively. In normotensive

individuals, pooled estimates of mean changes in SBP and DBP across 12 studies (2240 participants) were -2.42 mmHg (95% CI: -3.56 to -1.29 mm Hg) and -1.00 mmHg (95% CI: -1.85 to -0.15 mm Hg), respectively. He et al. (18) also examined the dose-dependent effect of salt/sodium on BP, and found that the greater the reduction in salt/sodium, the greater the fall in SBP.

Aburto et al. (21) synthesized the health impacts of lower sodium intake compared to higher sodium intake across RCTs published between 2011 and 2012 . The minimum sodium reduction across the studies was 40 mmol/day (approximately 920 mg/day) with a duration ranging from four weeks to 36 months. In the meta-analysis of 36 studies, representing 5508 participants, dietary sodium reduction was found to significantly reduce SBP and DBP, by 3.39 mmHg (95% CI: 2.46 mmHg to 4.31 mmHg) and 1.54 mmHg (95% CI: 0.98 mm Hg to 2.11 mmHg), respectively. The SBP reduction was greater in studies of participants with hypertension (4.06 mmHg, 95% CI: 2.96 mmHg to 5.15 mmHg) than in those that included participants without hypertension (1.38 mmHg, 95% CI: 0.02 mmHg to 2.74 mmHg). Evidence from this meta-analysis of more recent RCTs supported the findings found by He et al. (18).

Evidence from these systematic reviews also suggests that the relationship between sodium reduction and BP is dose-dependent (i.e., a larger reduction in sodium intake leads to a larger reduction in BP) (18, 21). The variation in effect sizes (mean changes in BP) across the systematic reviews, and meta-analyses are largely due to differences in inclusion and exclusion criteria related to study design, study duration, and methods to measure sodium intake.

A review of the literature found an additional meta-analysis, and an observational study supporting a BP lowering effect due to a reduction in dietary sodium consumption (33, 34). A more conservative meta-analysis of RCTs restricted to a duration of greater than six months and <2300mg/day of sodium also found a benefit in BP reduction (35) . The observational study, using health survey data collected in England, found salt intake decreased by 1400 mg/day (approximately 551 mg/day of sodium) from 2003-2011. This salt decrease was associated with a fall in mean SBP and DBP of 3.0 ± 0.33 mmHg and 1.4 ± 0.20 mmHg (33). Strong evidence supports that dietary sodium reduction, if sustained and applied to the general population, will lead to a substantial reduction in blood pressure.

1.3.3: Effect of dietary sodium intake on CVD and mortality

Increased sodium intake has also been linked to CVD (18, 36). The Trials of Hypertension Prevention (TOHP), phase I (744 participants) and phase II (2382 participants) were the first RCTs that examined the relationship between dietary sodium reduction and CVD in humans (37). The trials lasted for 18 months (phase I) and 26-48 months (phase II) with a follow up period of 15 and 10 years, respectively. Net sodium reductions were 44 mmol/day (approximately 1112 mg/day) and 33 mmol/day (approximately 760 mg/day), respectively for phase I and phase II. Overall, participants in the sodium reduction groups, compared with the control groups experienced a 20% non-significant reduction in all-cause mortality (hazard ratio: 0.80; 95% CI: 0.51-1.26) (32), and a statistically significant 30% lower incidence of CVD (hazard ratio: 0.70; 95%CI: 0.53-0.94). Since TOHP, additional studies examining the relationship between dietary sodium reduction and risk of CVD have been added to the literature.

A 2009 meta-analysis of 13 cohort studies (including the TOHP trials) found a direct association between dietary sodium intake, and subsequent risk of CVD (38).

Some cohort studies published after 2009 found a curved (J or U shape) association or no association between dietary sodium and CVD disease outcomes (39-42). This has ultimately led to controversy, and the positive association between sodium intake and CVD risk has been highly debated. However, it is argued that these new cohort studies have methodological flaws, and the findings should be interpreted with caution (43). Many of the methodological flaws pertain to the accuracy in the measurement of dietary sodium intake (44). Some of the methods of measurement for dietary sodium intake range from 24-hour urine collection, dietary surveys, and spot urine collection.

The 24-hour urine collection method is where an individual's urine is collected over a 24-hour period to measure urinary sodium excretion (45). This method captures approximately >90% of sodium excretion, and is considered the gold standard method for estimating sodium intake (44). However, a major disadvantage of this method is the high level of participant compliance needed, as well as education on the collection method (45). This places a high burden on participants; therefore, many studies end up estimating dietary sodium intake through dietary surveys or spot urine collections (44). Dietary surveys tend to have incomplete food composition databases to assess sodium content, difficulty measuring discretionary sodium use (cooking), and underreporting (44, 46). This leads to dietary surveys generally underestimating sodium intake by 30-50% (44, 46). The spot urine collection method is where a single sample of urine is collected, and equations are applied to calculate the 24-hour urinary sodium excretion;

however, this method has not been sufficiently validated (44, 47). This method also does not account for the intra-individual variability of urinary excretions in a single 24-hour period; thus, resulting in either an overestimation or underestimation of 24-hour urinary sodium excretion (45). Studies using spot urine or dietary survey, as a measurement collection, may not be adequate to refute the scientific consensus that sodium intake is associated with CVD risk.

In addition to the type of measurement used to estimate dietary sodium intake, the inconsistency in results could also be attributed to limitations of study design, and conflicts of interest. Many of the studies examining the effect of sodium intake on CVD outcomes are observational studies. Observational studies are susceptible to confounders and reverse causation; which can distort the association between the exposure and outcome in the study (48, 49). Financial conflicts of interest are also another concern. Several of the dissenting scientists have had long-term associations with the food/salt industry, and some of these were not publically disclosed. This could represent potential conflicts of interests, which can in turn impact the interpretation and reporting of nutritional evidence (50, 51).

In addition to the controversial observational studies, Taylor et al. (52) conducted a meta-analysis (2011) of seven RCTs, and detected no relationship between sodium intake and CVD risk. However, the results were underpowered, and there were methodological limitations in the included studies (53-55). Aburto and colleagues (21) responded with another systematic review that included both RCTs and cohort studies to increase the power of the meta-analysis. They applied filters to exclude low quality studies. They found that increased sodium intake was

associated with an increased risk of stroke (RR 1.24, 95% CI: 1.08-1.43), stroke mortality (RR 1.63, 95% CI: 1.27-2.10) and CHD (RR 1.32, 95% CI: 1.13-1.53) (21).

A more recent Cochrane systematic review and meta-analysis of RCTs studied the effects of reducing dietary salt, via advice and sodium substitutes, on cardiovascular events and mortality (16). The meta-analysis quantified the health impacts across 8 studies (3518 participants) in normotensive individuals, and across 5 studies (3766 participants) in hypertensive individuals. There was weak evidence of association between dietary sodium reduction, and either all-cause mortality or CVD-specific mortality in both hypertensive and normotensive groups. However, pooled relative risk (RR) estimates for cardiovascular events across studies combining both hypertensive and normotensive participants (6 studies, n=5912) found a significant association between dietary sodium reduction and CVD events (RR = 0.77, 95% CI: 0.63-0.95). Further, a systematic review of the literature was conducted in the period June 2013 to May 2015 to determine the effect of dietary sodium consumption on CVD disease outcomes (56, 57). There were 564 studies reviewed, but only 14 studies were of high quality. All fourteen of these studies supported dietary sodium reduction improving CVD disease outcomes.

1.3.4: Summary of effect of dietary sodium on BP and CVD

Table 1 summarizes the body of evidence found on the effectiveness of dietary sodium reduction in decreasing BP, CVD outcomes, and mortality. There is well-documented evidence that supports the association between dietary sodium reduction and a drop in BP in both the general and hypertensive populations. On the other hand, there are mixed findings regarding the

association of sodium intake and CVD risk, CVD mortality, and all-cause mortality. However, studies finding an adverse or no impact of lowering dietary sodium were found to have methodological limitations, and were not designed to evaluate the relationship between dietary sodium and CVD risk (43). When quality filters are applied to exclude studies of low quality, nearly all studies support the benefit on CVD risk from dietary sodium reduction (56, 57). Based on this, it is reasonable to assume that decreasing sodium intake decreases BP, which in turn decreases the risk of CVD.

Table 1: Association between sodium and health outcomes

Health Outcome	Direction of relationship with sodium	Strength of Evidence
High Blood Pressure or hypertension	↑	****
CHD events	↑	****
Stroke events	↑	****
Cardiovascular disease and stroke mortality	↑	***
Overall mortality	↑	**

**** Strong evidence (multiple RCTs, observational studies)

*** Convincing evidence (other experimental data other than RCTs)

** Moderate evidence (limited experimental data, some observational studies only)

1.4: Strategies to Reduce Dietary Sodium

Currently, there is considerable variation in strategies and policy options to reduce dietary sodium. These strategies can be categorized as follows: 1) Individual level interventions, 2) Structural interventions at the population level, and 3) Intermediate level interventions. An individual level intervention focuses on changing consumer responses using behavior change approaches, such as dietary counseling, medical advice, or leaflets (58, 59). A structural

intervention focuses on the development of policies at the population level, such as regulatory change, taxes or subsidies. Lastly, intermediate interventions focus on targeting specific subgroups within the population either at worksites, schools or communities (58-60).

Evidence from public health programs for tobacco control and alcohol policies support structural interventions achieving consistently larger improvements in population health, compared to individual and intermediate level interventions (61-63). This indicated the existence of a public health 'effectiveness hierarchy', and structural interventions were the best approach to consider in the implementation of a public health program (58, 61-63). A recent systematic review assessed the effectiveness of different intervention programs to reduce sodium intake. It found that a public health 'effectiveness hierarchy' did exist with structural interventions consistently achieving better health outcomes than individual level interventions (58, 61-64). Hence, in the implementation of a public health program aiming to reduce dietary sodium consumption, a structural intervention should be considered in order to achieve the largest population health improvements.

Over recent years, there has been a significant growth in the number of structural intervention strategies, with national salt reduction programs identified in 75 countries (61-63). Finland, Japan and the United Kingdom (UK) have been recognized for their successful policy approaches for population-wide dietary salt reduction (65). The Japanese governments implemented a public education program in the 1960s, and over the following decade the mean sodium consumption fell by 550 mg/day (66). Stroke mortality was estimated to fall by 80% (66). Finland was one of the first countries to systematically approach dietary sodium reduction

through media campaigns, co-operation with the food industry, and implementing sodium labeling legislation (65, 67). From 1978 to 2007, the Finnish population achieved an average reduction of 1573 mg/day (58, 61-63). Stroke and CHD mortality fell by 52% and 15%, respectively over 30 years (68, 69). The UK was one of the first countries to have a coherent systematic ongoing reduction of the salt content in food products. The UK salt reduction strategy included voluntary reformulation, a consumer awareness campaign, food labeling, target settings, population monitoring (70). From 2003-2011, the population average dietary salt reduction was 1400 mg/day (551 mg/day of sodium) (33), and stroke and ischemic heart disease mortality decreased by approximately 42% and 40%, respectively. Having a multi-component dietary sodium reduction strategy was found to be the most effective in reducing dietary sodium (58, 61-64).

1.5: Economic Evaluation

Economic evaluation has been defined as the "comparative analysis of alternative courses of action in terms of their costs and consequences" (71). Economic evaluations enhance decision-making and help set health policy. In this study, an economic evaluation will be used to explore the potential health and economic impacts of a population level reduction in dietary sodium in Canada.

1.5.1: Types of economic evaluations

There are four main types of economic evaluations used to study the costs and benefits of alternative programs; cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis (71). These types of economic evaluations vary in the data

required, and how they use information on costs and effectiveness. Klarenbach and colleagues summarized the characteristics of the four types of economic evaluations (Table 2) (72) .

Cost-minimization analysis compares the costs of alternative intervention programs or policies where the consequences (effectiveness) of two or more treatments are assumed to be equal (71). Programs are ranked by cost, and the program with the lowest costs is deemed the optimal program. Cost-minimization analysis is the least common among the four types of economic evaluations, as most intervention programs do not have equivalent effectiveness.

Cost-effectiveness analysis compares the costs and consequences (effectiveness) of two or more intervention programs or policies (71). Effectiveness (health benefits) is measured in either units of improved functional status (e.g., units of BP or cholesterol) or natural units such as life years saved (71). The measurement for costs and effectiveness are non-comparable units; therefore, their ratio, the incremental cost-effectiveness ratio (ICER) is used to assess health intervention programs. The ICER is defined as the difference between costs of two intervention programs divided by the difference in their effectiveness (73). This type of analysis is used when trying to determine the intervention that will maximize specific benefits given a fixed budget (18).

Cost-utility analysis is an adaptation of cost-effectiveness analysis. It compares the costs and consequences (effectiveness) of two or more intervention programs or policies; however, effectiveness is quantified using utility-based measures (74). Utility-based measures can be either quality-adjusted life years (QALY) or disability adjusted life years (DALYs). QALYs

measure disease burden in terms of morbidity and mortality reduction (quality and quantity of life lived) (74, 75). QALYs are calculated by determining the years of life remaining for a patient, weighted by their utility (on a 0 to 1 scale). A utility of 1 is used to represent perfect health, and a utility of 0 represents death. DALYs, on the other hand, are the sum of years of life lost due to premature mortality and disability (76). A utility-based measure allows comparisons across interventions with different types of health effects. The incremental cost utility ratio (ICUR) summarizes the incremental cost associated with the gain of one QALY (74). A lower ICUR indicates higher value. In Canada, QALY thresholds are generally accepted to determine best value programs; an intervention costing less than $20,000/QALY indicates good value, between $20,000-$100,000/QALY indicates moderate value, and over $100,000/QALY indicates low value (77).

A cost-benefit analysis (CBA) compares the costs and consequences (effectiveness) of two or more intervention programs or policies (71, 77) by summing all costs and consequences for an intervention or policy represented by a monetary unit. The summary measures for CBA are net benefits and benefit-cost ratios (74). Generally, if the net benefit is greater than zero the program is considered to provide positive economic benefits, and if it is less than zero the program is considered not to be of benefit. By valuing all costs and benefits in the same monetary units, CBA allows the comparison of diverse interventions or policies.

In all types of economic evaluations different perspectives may be used. Perspectives are the viewpoints from which the studies are conducted and determine which costs to include in the analysis (78). Common perspectives are societal, employer, client, government, or insurer (78).

Table 2: Klarenbach et al. Characteristics of Economic Evaluations

Type of evaluation	Costs considered	Health considerations	Strengths	Important issues
Cost-minimization	All present and future health-care costs relevant to the patient and the disease state are compared for each therapeutic strategy	No difference in health status attributable to disease or treatment strategies is assumed	Requires minimal data (on costs only) Enables assessment of the technical efficiency of each strategy	Assumption of identical outcomes of disease and the treatments compared should be robust
Cost-effectiveness	All present and future health-care costs relevant to the patient and the disease state are compared for each therapeutic strategy	Uses commonly evaluated health outcomes, including clinical or surrogate outcomes, such as blood pressure, renal function (eGFR), and serum LDL levels	Relates costs of treatment with therapeutic effectiveness based on health outcomes that are readily available from clinical trials	The 'cost per unit of health' values obtained in cost-effectiveness analyses can be difficult to interpret; comparisons between populations and diseases are not possible Effectiveness outcome may not capture all relevant health outcomes
Cost-utility	All present and future health-care costs relevant to the patient and the disease state are compared for each therapeutic strategy	Health status is transformed into a quality-adjusted life-year score anchored between 0 (death) and 1 (perfect health) All aspects of disease and its treatment are captured in one metric	The metric comprehensively measures health, enabling benchmarking and comparisons of outcomes among disparate populations and diseases	Cost–utility analyses require the greatest amount of data of all these types of economic evaluation Assumptions might be required when estimating health-related quality of life
Cost-benefit	All present and future health-care costs relevant to the patient and the disease state are compared for each therapeutic strategy	Health benefits and costs can be attributed to a monetary value All aspects of disease and its treatment are captured in one metric	Values all costs and benefits in the same enabling a comparison of diverse interventions using net benefit criteria (71)	Measurement difficulties and objections to valuing health benefits in monetary terms (71)

Source: (72)

1.6: Cardiovascular Disease (CVD) Models

Mathematical modeling is used extensively in economic evaluations of pharmaceuticals and healthcare technologies. Mathematical modeling is defined as "a logical mathematical framework that accounts for events over time, and across populations based on data drawn from primary or secondary sources", in order to estimate outcomes of interest to clinicians and decision makers (75). Mathematical modeling is important for developing and guiding public health initiatives. Model development can be complex and all models must be internally and externally validated to ensure the model can make accurate predictions of future events (75). Models can be used to simulate different scenarios in the population and estimate their impact on CVD health consequences and costs. In order to explore the potential health and economic impacts of a population level reduction in dietary sodium, we required a mathematical model that includes the following inputs: costs, effectiveness, risk factors and considers CVD disease specific categories, such as myocardial infraction, angina, heart attack etc.

A systematic review by Unal et al. (2006) found 42 published CHD models with 6 principal policy models that generated more than one publication (79). Based on this systematic review and a review of more current literature, we identified the following principal CVD/CHD population models: Cardiovascular Disease Policy Model (CVDPM), PREVENT Model, Cardiovascular Life Expectancy Model (CVD Life Expectancy Model), CHD Policy Analysis Model, Impact Coronary Heart Disease Mortality Model (IMPACT), Global Burden of disease (GBD) Model, Dynamic Modeling for Health Impact Assessment (DYNAMO-HIA), Rijksinstituut voor Volksgezondheid en Milieu Cardiovascular Disease Model (RIVM CDM)

and Program in Occupational Health and Environmental Medicine (POHEM). A description of each of these models follows, and Table 3 and 4 summarizes their important features.

Table 3: Summary of CVD models

Model	Type of model	Model setting & study population	Purpose
CHD (CVD) Policy Model (Weinstein and Goldman)	State transition Markov model	USA, Men and women aged 35-94	Examine trends in CVD mortality and expected gain in life expectancy from risk factor modification; also used to evaluate interventions for primary and secondary prevention of CVD and health promotion activities
PREVENT (Gunning-Scheppers)	Cell based	Netherlands, Denmark, England depending on the purpose aged <65	Estimates the health benefits of changes in population risk factor prevalence by comparing continuation of existing trends with alteration of the proportions of population with given risk factor levels; recent upgrades include the addition of disease-specific and total morbidity and healthcare costs
CVD Life Expectancy Model (Grover et al.)	Life table analysis – Markov model from 1998 onward	Canada, adult men and women, age group not clear	Calculates the annual probability of dying from CHD and the annual risk of CHD events; also calculates the risk of dying during the 12 months following a non-fatal MI
CHD Policy Analysis (Sanderson and Davies)	Microsimulation	England and Wales, men and women up to 85 years	Simulates the impact of different primary prevention strategies on benefits and costs and evaluates the impact of different treatments given to two different groups for CHD patients, stable angina, or AMI
IMPACT (Capewell, Critchley and Unal)	Spread-sheet	Scotland, England & Wales, New Zealand. Initially men and women aged 45-84. IMPACT Model for England and Wales includes 25-84.	Combines data sources to find deaths prevented/postponed for a specific time period; currently upgrading to IMPACT2
Global Burden of Disease (Murray and Lopez)	Population attributable risk method	World divided into eight geographic regions M-F all ages	Estimates attributable burden of a disease for a specific risk factor, population, and time

DYNAMO-HIA (Hendrikson et al.)	Dynamic, Markov-type model based on a multi-state model	Finland, France, Ireland, Italy, the Netherlands, Poland, Spain, Sweden and UK population	Quantifies the effect of health policies (on user specified risk factor changes) on mortality and multiple disease incident rates
RIVM CDM (Saha et al.)	Markov state transition model based off of life table	Netherlands Population	A chronic disease model that estimates cardiovascular morbidity and mortality effects due to changes in cardiovascular risk factors vs. changes in rate of uptake of cardiovascular therapies
POHEM (Hennessy et al.)	Dynamic microsimulation	Two approaches: synthetic population of Canadians or a population from a cross sectional survey of Canadians over 20 years	Simulates individuals' disease states, risk factors, and health determinants in order to estimate health outcomes such as disease incidence, prevalence, life expectancy, health-adjusted life expectancy, quality of life, and healthcare costs

Table 4: Inputs and Outcomes of CVD models

Model	Risk factors included	Disease groups & treatments included	Outcomes	Sensitivity analysis	Validation/ Calibration
CVDPM (Weinstein and Goldman)	Smoking, total cholesterol, DBP and weight to estimate CHD risk using Framingham Equations	Angina, AMI, sudden death, post MI, CABG, PTCA and stroke Specific treatments considered in different studies (ie. statins, aspirin, beta blockers)	Number of deaths prevented, LYG, CHD incidence (number of arrests, angina, AMI), CHD mortality, cost per life year	one-way sensitivity analysis and Monte Carlo simulation	Calibrated using 1986 mortality data.
PREVENT (Gunning-Scheppers)	Smoking, cholesterol, hypertension, obesity,	Ischemic heart disease (IHD), stroke	Number of deaths prevented, life years gained	One-way, different scenarios	Not checked

	physical activity, alcohol				
CVD Life Expectancy Model (Grover et al.)	Smoking, total cholesterol, DBP, glucose intolerance, age	Did not consider CHD disease categories but treatments can be considered for primary prevention	Years of life saved, cost per life year saved, years of life without CHD symptoms	One-way	Calibrated
CHD Policy Analysis (Sanderson and Davies)	Smoking, cholesterol, systolic blood pressure	Angina (stable and unstable), AMI, post-MI, CABG, PTCA	Deaths prevented, morbidity prevented, CHD & non-cardiac deaths, unstable angina admissions, angiograms, PTCA, CABG		No validation reported
IMPACT (Capewell, Critchley and Unal)	Initially smoking, cholesterol, blood pressure – then also obesity, diabetes and physical activity and deprivation	Considers all principal CHD categories and over 20 specific CHD treatments	Deaths prevented or postponed, life years gained	Multi-way sensitivity analysis using analysis of extremes method	Estimated falls in CHD mortality were compared with observed falls over specific time period stratified by age and sex
Global Burden of Disease (Murray and Lopez)	Malnutrition, poor water, unsafe sex, alcohol, tobacco occupation, hypertension, physical activity, illicit drugs, and air pollution	None	DALYs	Multi-way sensitivity analysis- discounting and age weighting	None

DYNAMO-HIA (Hendrikson et al.)	Smoking, BMI, Blood pressure	None	Prevalence of stroke, IHD, all-cause mortality, life expectancy and disability-adjusted life expectancy		
RIVM CDM (Saha et al.)	Smoking, blood glucose level, obesity, cholesterol, hypertension	Acute myocardial infarct, angina pectoris, chronic heart failure, stroke	Number of new CVD cases, prevalence, mortality, health life expectancy (QALY), Costs of illness		
POHEM (Hennessy et al.)	Blood pressure, total cholesterol & HDL, obesity, diabetes, smoking	Heart disease risk factor prevalence, stroke, AMI hospitalizations, primary interventions such as cholesterol medications, reducing BMI	Disease incidence, life expectancy, health-adjusted life expectancy, health-related quality of life, projected costs of disease and treatment	Probabilistic sensitivity analysis	Validated internally and (where possible) externally, also calibrated

The CVDPM examines the effect of CVD risk factors on CVD morbidity, mortality, quality adjusted life years, and costs (80). It can also be used to evaluate primary and secondary prevention interventions for CVD. This model was originally built to simulate CHD only, but has been revised to include stroke. PREVENT estimates the health benefits of changes in population risk factor prevalence over long periods of time by comparing: 1) continuation of existing trends with, 2) changes in risk factor levels (81). The model has gone through several updates. Updates include the addition of disease-specific and total morbidity, and healthcare costs as outputs. Risk factors now have the option of being categorical or continuous. The Cardiovascular Life Expectancy Model includes two components: primary and secondary prevention (82). The primary prevention component calculates the annual probability of dying from CHD and the annual risk of CHD events. The secondary prevention component calculates the risk of dying during the 12 months following a non-fatal myocardial infarction. This model is used to measure the cost-effectiveness of interventions. The CHD Policy Analysis Model is divided into two components. The primary prevention component of the model simulates the impact of different primary prevention strategies on benefits and costs. The treatment component evaluates the impact of different treatments given to two different groups of CHD patients: stable angina or acute myocardial infarction. IMPACT is a cell-based model for coronary heart disease with modules in primary prevention, and disease treatment at the individual or population level (83). Building on the original model, IMPACT2 is being developed to simulate individual coronary heart disease patients using event driven software. The model has been designed to allow subsequent extension into other cardiovascular and chronic diseases, but still does not consider costs. The Global Burden of Disease Model uses population attributable risk methods. The GBD can estimate the attributable burden of disease for a specific risk factor, population and time (76,

84). DYNAMO-HIA is a tool used to determine the impact of health policies influencing health determinants of CVD, and quantifies mortality and incidence rates (67). RIVM CDM describes cardiovascular morbidity and mortality effects due to changes in cardiovascular risk factors, and changes in uptake of cardiovascular therapies (85). POHEM is a continuous time longitudinal model of CVD. Using data from Statistics Canada, the model simulates the Canadian population and allows for a comparison of competing health intervention alternatives. The model incorporates demographic changes, and non-coronary heart disease mortality.

All nine CVD models are population level models, and consider most major risk factors for CVD (smoking, obesity/BMI, blood pressure, and cholesterol). Only the CVDPM, POHEM, PREVENT are inclusive of both CHD and stroke; all the other models only look at CHD. All models except the GBD Model, PREVENT and DYNAMO-HIA consider most CHD disease groups (i.e., angina, AMI) and individual treatments (i.e., statins, beta-blockers). The CHD Life Expectancy Model does not consider CHD disease categories, but treatments can be considered for primary prevention.

The outcomes of the CVD models are health impact, costs or both. All nine models report the health outcome "deaths prevented/gained" except GBD, which reports only DALYs. Along with GBD, CVDPM, PREVENT, RIVM CDM, DYNAMO-HIA and POHEM consider health effectiveness (include CVD utility data as a input parameter in the model) and report quality of life either as QALY or DALY. The models that can report both costs and health outcomes are CVDPM, POHEM, CVD Life Expectancy, RIVM CDM and PREVENT Model.

The models that included input parameters of cost, effectiveness, CVD risk factors, and which considered CVD disease categories and individual treatments were only CVDPM and POHEM. Although POHEM seemed a good fit for our study objectives, studies using this model did not report any cost outcomes; other POHEM disease versions reported cost outcomes. The CVDPM was found to be the most comprehensive model in addressing economic evaluations for CVD outcomes from the literature review. The model assessed both cost-effectiveness of interventions and future disease trends. The CVDPM also included comprehensive information on disease categories and risk factors. The CVDPM is based on the U.S. population and was easily adapted to the Canadian population. More details about the CVDPM can be found in the methods section.

1.7: Economic Evaluation of Sodium Reduction

Two studies have examined the impact of population dietary sodium reduction on risk of CVD in Canada using mathematical modeling. Penz et al. (86) used a linear regression model to estimate changes in cardiovascular events from a dietary sodium reduction of 1840 mg/day. It was found that 11,500 CVD events per year would be prevented. Dietary sodium reductions of 2400 mg/day and 1200 mg/day were estimated to reduce CVD events by 16,776 and 8313 per year, respectively. Belanger et al. (87) examined the changes in CVD, and cancer mortality associated with changing dietary sodium using a scenario model for 2004. They modeled the effect of decreasing salt intake to 5.8 g/day (approximately 2300 mg/day of sodium) from current salt intake levels. They found that 3,166 deaths could be averted with dietary sodium reduction; however, the study did not stratify the averted deaths by disease type. Both studies came to the

conclusion that a population level sodium reduction strategy would be effective in reducing CVD events and saving lives; however, neither study assessed the impact on costs.

Only one Canadian study examined the impact on future costs associated with population dietary sodium reduction; however, it was related to hypertension management, not CVD events. Joffres et al. (88) estimated the change in prevalence of hypertension, and the impact on direct healthcare costs of hypertension management from a reduction in dietary sodium additives in food. For hypertensive subjects, a sodium reduction of 1840 mg/day was estimated to decrease SBP and DBP by 5.06 mmHg and 2.7 mmHg, respectively. The prevalence of hypertension was estimated to decrease by 30% leading to one million fewer cases of hypertension in Canada. Direct cost savings from fewer physician visits, laboratory tests and lower medication use were estimated at $430 million per year. However, hypertensive prevalence data was based on the Canadian Heart Health Survey conducted between 1986 and 1992 (89), which has a lower prevalence estimate than current estimates (90). The number of hypertensive individuals in the study was less than half of today's estimates; however, it should be noted that the age adjusted prevalence was similar.

The Cardiovascular Disease Policy Model (CVDPM) has been used in the United States, China and Argentina to determine the cost-effectiveness of population level sodium reduction (91-93). In the United States dietary salt reduction of 3 g/day (1200 mg/day sodium) was estimated to save 194,000 to 392,000 QALYs and $10 billion to $24 billion dollars annually (91-93). In Argentina, dietary sodium reduction of 319-387 mg/day would avert 1900 deaths, 13,000 myocardial infractions, and 10 000 total strokes. In China, reducing the mean salt intake to 9

g/day (3540 mg/day) would lead to a gain of 303,000 QALYs per a year, and save 1.4 billion international dollars (91-93). All three of these studies reported cost savings, and supported a population sodium reduction strategy. Although these studies were successful in determining the cost-effectiveness of population sodium reduction in these countries, Canada's population estimates and risk factor distributions are different. Therefore, it is important to determine accurate estimates of the cost-effectiveness of sodium reduction for the Canadian population.

1.8: Thesis Overview

Evidence supports that rising BP is a risk factor for CVD. The rise in BP can be attributed in part to excess consumption of dietary sodium. A population-wide dietary sodium reduction can improve CVD outcomes and healthcare costs, however the magnitude of the impact is currently unknown for the Canadian context. **Therefore, the primary objective of this thesis was to determine the cost-utility of a reduction in dietary sodium in the Canadian population based on the anticipated reduction in incident cardiovascular disease.** The secondary objective was to examine the cost impact of changes in management of hypertension treatment in the Canadian population, resulting from a dietary sodium reduction.

Chapter 2: Methods

2.1: Overview of Analyses

The primary analysis was a cost-utility analysis, from the perspective of the publically funded healthcare system, comparing dietary sodium reduction with no change in dietary sodium, and its effect on CVD in the Canadian adult population. The primary outcomes were incremental cost, and quality adjusted life years (QALYs) gained. Secondary outcomes included CVD events and CVD mortality.

The CVDPM, adapted to the Canadian population, was used to perform the analysis, and the effect of sodium reduction was assumed to act through blood pressure. Model parameters, including costs, risk factor levels, baseline CVD prevalence, and population demographics were derived from Canadian data. Blood pressure distributions, and hypertension prevalence were estimated from Statistics Canada population surveys. Effectiveness of dietary sodium reduction on BP was extracted from published literature.

The secondary analysis examined the cost impact of changes in management of hypertension treatment in the Canadian population resulting from dietary sodium reduction. The primary outcome was cumulative cost. Blood pressure distributions and hypertension prevalence were estimated from Statistics Canada population surveys. Cost estimates, and effectiveness of dietary sodium reduction on BP were extracted from the literature.

2.2: Primary Objective

To determine the cost-utility of dietary sodium reduction in the Canadian population based on the anticipated reduction in incident cardiovascular disease.

2.2.1: Target population

The target population for this analysis was adult Canadians, 35 to 94 years of age. Population size and demographic characteristics used in the CVDPM were determined from the Canadian Census of Population, which is conducted every five years (most recent in 2011) (94). Excluded from the survey's coverage are: persons living in the three territories; persons living on reserves, and other Aboriginal settlements in the provinces; full-time members of the Canadian Forces; the institutionalized population and residents of certain remote regions. These exclusions represent 4% of Canadians. The base year for the model was 2012; each year people can exit the model through death, or enter the model as 35 year olds. The size of the 2012 population, by sex and ten-year age groups (34-44, 45-54, 55-64, 65-74, 75-84, 85-94), was estimated by Statistics Canada based on expected population growth from the 2011 Census data (94). The number of 35-year-olds entering the model each year was also taken from Statistic Canada's population projections.

2.2.2: Comparators

This economic analysis compared a strategy of population-level dietary sodium reduction to a strategy of maintaining current levels of sodium intake (base case). The dietary sodium intake target levels considered were 2300 mg/day (upper limit and interim federal target) and 2000 mg/day (HC recommended target), which correspond to mean reductions in dietary sodium

of 1800 mg/day and 1500 mg/day, respectively. We also estimated the effect of increasing mean dietary sodium intake by 500 mg/day.

2.2.3: Perspective

The perspective of the publically funded healthcare system was adopted for this economic evaluation. All costs were borne by a government payer, and included direct health care costs. This economic evaluation did not include indirect costs incurred by individuals, such as cost of travel or productivity losses. By adopting a publically funded healthcare system perspective, the results of this study will inform government decision makers considering policy changes regarding dietary sodium consumption.

2.2.4: Sodium reduction intervention

To estimate the cost of a population-wide sodium reduction intervention, we relied on previously published estimates. After conducting a literature review, we found one article with published cost estimates relevant to the Canadian context. A population-wide sodium reduction intervention was estimated to cost $2.02 per person annually for Canada (95). Intervention costs were based on a government 'soft regulation policy', modeled on the UK's program, and included government supported industry agreements to reduce sodium in processed foods, government monitoring of industry compliance, and public health campaigns (95). The WHO-CHOICE database (96) was used to determine country specific resource needs, and costs for Canada. The cost estimate was reported in international dollars and was converted to 2014 CAD dollars using purchasing power parity exchange rates from the International Monetary Fund Economic Outlook Database (97).

2.2.5: Analytical approach and modeling

2.2.5.1: Overview of the cardiovascular disease policy model

The CVDPM is a computer simulation state transition (Markov cohort) model that has been calibrated with Canadian input data. The model was first developed in 1987 for the U.S. population, and has been updated to reflect current CVD management (92). The model estimates population incidence, prevalence, mortality, and health care costs of CVD in adults aged 35-94 years (93). CVD is defined as CHD and stroke, and events captured in the model include angina, myocardial infarction, percutaneous coronary interventions (i.e., angioplasty, stent placements), coronary artery bypass surgery, and stroke. The model summarizes outcomes by 10-year age group and sex.

The model is based on three submodels: the demographic-epidemiologic model, the bridge model and the disease-history model. The demographic-epidemiologic models predicts the probabilities that individuals will have their first CVD event and then pass to the bridge model. This first CVD event can be either a CHD event or a stroke, and the probability of having each is based on an individual's age, sex, and CVD risk factors (Body Mass Index [BMI], cholesterol, BP, smoking status, diabetes status), with equations derived from the Framingham Heart Study (98). The bridge model characterizes initial CVD events, and their sequelae for 30 days. The disease-history model predicts subsequent CVD events, and deaths in a population with CVD. The model can be used to estimate the effect of changes in model inputs, including population demographics and risk factor levels. Figure 1 displays the conceptual diagram of sodium reduction on CVD prevention.

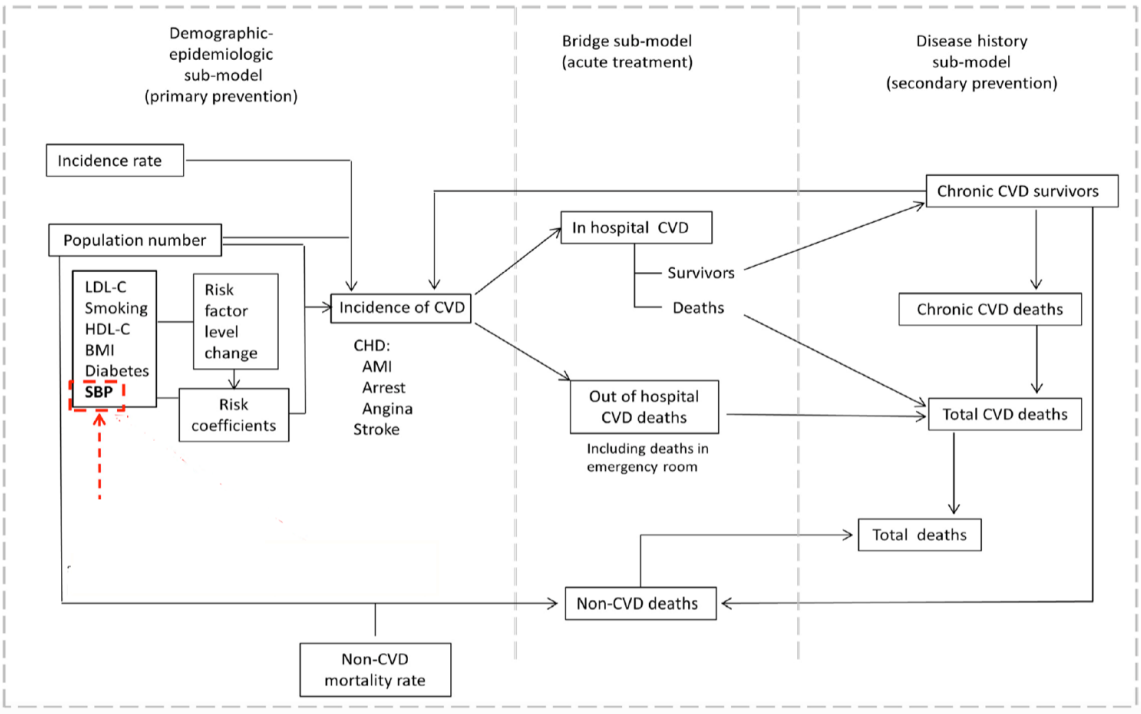


Figure 1: CVDPM Conceptual diagram of the effect of sodium reduction on the CVD prevention. AMI, acute myocardial infarction; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure. (98).

The model has been adapted to the Canadian context, by modifying population estimates, CVD risk factors distributions, CVD event rates and mortality rates, and costs available from pre-existing national sources (Statistics Canada and the Canadian Institute for Health Information [CIHI]). These data are representative of the vast majority of the Canadian adult population (>96% in the case of Statistics Canada surveys, and >97% in the case of CIHI data) (99). Table 5 summarizes the primary input variables and data sources used in the Canadian CVDPM. For more details about the model please see Appendix A.

Table 5: Inputs and Data Sources for CVDPM

Variable	Source
Demographics	The Canadian Census, Canadian Socio-Economic Information Management System (CANSIM), Statistics Canada (100)
CVD Risk Factors and Prevalence of CVD	The Canadian Health Measures Survey (CHMS) (101) and the Canadian Community Health Survey (CCHS) (102), 2007-2013, Statistics Canada
Incidence of CVD	Incidence of coronary heart disease: Risk coefficients from the Framingham Heart Studies and the burden of CVD risk factors in Canada (above) Incidence of stroke: Discharge Abstract Database (DAD)/Hospital Morbidity Database (HMDB) (103), 2005/2006-2014/2015, the Canadian Institute for Health Information (CIHI)
Effects of Risk Factors on Incidence of CVD and non-CVD death (Risk Coefficients)	Framingham Heart Study (104, 105)
CVD Events and Procedures	DAD/HMDB (103) and the National Ambulatory Care Reporting System (NACRS) (106), 2005/2006-2014/2015, the Canadian Institute for Health Information (CIHI)
Mortality Rates	In-hospital CVD-related deaths: DAD/HMDB (103) and NACRS (106), 2005/2006-2014/2015, CIHI All other deaths: Vital Statistics Death Database, 2012, Statistics Canada (107)
Health Care Costs	The Interdisciplinary Chronic Disease Collaboration, 2010/2011-2012/2013, Alberta Health Administrative data (CVD costs) (108, 109); National Health Expenditure Database, 2015 update, CIHI (CVD and non-CVD costs) (110)
Health State Utilities	2010 Global Burden of Disease disability weights study (76, 84, 111)

2.2.5.2: Estimating the effect of sodium reduction

Research supports a direct relationship between sodium intake and BP (18, 21). For this study, we assumed a reduction in dietary sodium would exert its effects by decreasing SBP. The SBP was the primary modifiable input in the CVDPM. SBP is a risk factor in the CVDPM, and is categorized into three levels (SBP <130 mmHg, SBP 130-139 mmHg, SBP ≥140 mmHg), stratified by age and sex, and a mean SBP for each age-sex-BP category is used by the model to derive age-sex-SBP risks of incident CVD. These SBP cutoffs reflect current clinical guidelines for categorization of blood pressure (normal, high-normal, or high (2). The proportion of individuals distributed across the SBP levels (SBP <130, SBP 130-139, SBP ≥140) was determined by age, and sex group for input into the CVDPM, using data from the Canadian Health Measures Survey (101). The initial baseline mean SBP in each SBP category was also determined. All 3 cycles of the Canadian Health Measure Survey (2007-2013) were used to increase the sample size, and limit the effect of sampling error.

Next, we quantified the mean SBP change in each SBP category for each age and sex group, according to the amount of dietary sodium reduced. Pooled mean changes in SBP from dietary sodium reduction, for both normotensive and hypertensive individuals, were taken from a recently updated Cochrane review meta-analyses (Table 6) (18). The relationship between reduction in sodium, and the mean change in SBP was assumed to be linear; therefore, the relative pooled mean change in SBP for one mg of dietary sodium reduction was used to determine the expected change in SBP associated with the different sodium reduction levels (Table 7).

To determine the SBPs associated with sodium reduction for each SBP category, we subtracted the expected reduction in SBP from the baseline mean SBP, by age and sex group. The mean SBP change for hypertensive individuals was applied to everyone with a SBP ≥ 140 mm Hg in the CVDPM; however, we recognized that a proportion of individuals with a SBP ≤ 139 mm Hg could be taking an anti-hypertensive medication to control their SBP, and thus would be classified as hypertensive. To account for this, we determined the proportion of individuals taking an anti-hypertensive medication for SBP categories <130 mm Hg and SBP 130-139 mm Hg in each age and sex category from the Canadian Health Measures Survey (101). Then using the mean SBP change for normotensive and hypertensive individuals, and the proportion taking an anti-hypertensive medication, we determined the expected weighted SBP change for all individuals, in each age-sex-SBP category (Appendix B). The expected weighted SBP changes were applied to all individuals in each age-sex-SBP category in the CVDPM. We repeated this analysis for all sodium targets found in Table 7. Data analysis was performed using STATA 14 (StataCorp LP, College Station, USA).

2.2.5.3: Estimating the effect of sodium increase

To determine the mean SBP change from increased sodium consumption, we assumed a linear relationship between dietary sodium intake and SBP. We assumed an increase in dietary sodium would exert its effects by increasing SBP, which was the reverse effect we assumed for a reduction in dietary sodium. Similar to our analysis in the dietary sodium reduction strategy, we quantified the mean SBP change in each age-sex-SBP category, according to a 500 mg/day increase in dietary sodium intake.

Table 6: Population estimates of mean changes in SBP from sodium reduction from He *et al.*

Sodium reduction (mg/day)	Population target	95% CI of sodium reduction (mg/day)	Design of trails	Number of trials	Sample size	Study duration (median)	Mean SBP Change (mmHg) [95% CI]	Source
1724	Hypertensive	1221-2678	RCTs	22	999	5 weeks	-5.39 [-6.62 to -4.15]	(18)
	Normotensive		RCTs	12	2240	4 weeks	-2.42 [-3.56 to -1.29]	

RCTs, randomized control trials; SBP, systolic blood pressure

Table 7: Population estimates of expected mean changes in SBP from sodium reduction

Change in dietary sodium intake	Population target (based on SBP)	BP Mean Change (mmHg) [95% CI]
1800 mg/day decrease	Hypertensive	-5.63 (-6.91 to -4.33)
	Normotensive	-2.53 (-3.70 to -2.20)
1500 mg/day decrease	Hypertensive	-4.70 (-5.76 to -3.61)
	Normotensive	-2.10 (-3.08 to -1.84)
500 mg/day increase	Hypertensive	1.57 (1.2 to 1.92)
	Normotensive	0.70 (0.61 to 1.03)

2.2.5.4: Modeling the effect of change in SBP

We used the Canadian CVDPM to estimate the incremental change in cost, CVD events, deaths, and QALYs, resulting from the changes in SBP across age and sex categories. We used a time horizon of 50, 10 and 5 years. We intended to apply a 1.5% annual discount to future costs, and health utilities in accordance with current Canadian guidelines (112); however, due to a technical issue with the CVDPM, a fraction could not be entered. To be conservative, we used a 2% annual discount rate. We assumed that a population wide sodium reduction intervention would cost $2.02 per person annually (95). Subgroup analyses by age, and sex category were performed.

2.2.6: Outcome measures

Model outcomes were cumulative total cost in 2014 CAD dollars, total number of fatal (in hospital death only) and non-fatal MI events, total number of fatal and non-fatal stroke events, total number of CVD and all cause deaths, CVD incidence (new fatal and non-fatal cases of CHD and stroke), and cumulative QALYs. We determined total costs, QALYs, and CVD outcomes for each strategy, as well as the absolute differences in outcomes between strategies. We planned to assess the cost-utility of treatment with dietary sodium reduction relative to comparator treatment of no dietary sodium reduction, and reporting the incremental cost-utility ratios (ICURs). For example,

$$\text{ICUR} = \frac{Cost_{Na\ reduction} - Cost_{comparator\ treatment}}{Effectiveness_{Na\ reduction} - Effectiveness_{comparator\ treatment}}$$

However, our strategy of dietary sodium reduction was cost saving; thus, we present absolute differences in costs and CVD outcomes.

2.2.7: Uncertainty analysis

Sensitivity analysis examined the impact of uncertainty in input parameters on the estimates of cost-effectiveness. We performed one-way deterministic sensitivity analysis for key parameters, by varying one input parameter at a time while holding all other parameters constant. We examined uncertainty ranges from the lower, and upper 95% confidence bounds surrounding the mean change in SBP. We also assessed the effect of both a 25% increase and 25% decrease in annual healthcare costs and intervention costs.

2.3: Secondary Objective

To examine the cost impact of changes in management of hypertension treatment in the Canadian population, resulting from a reduction in dietary sodium.

2.3.1: Estimating change in hypertension management costs secondary to dietary sodium reduction

The cost impact of changes in management of hypertension was sub-divided into two components. The first part examined the potential healthcare savings resulting from individuals substituting their treatment with anti-hypertensive medication with dietary sodium reduction. The second part examined the potential healthcare savings of people with uncontrolled hypertension who would otherwise start on an anti-hypertensive medication unless they decreased their sodium intake. The target population for both analyses was adult Canadians, 35 to 94 years of age. Population size was determined from the Canadian Census of Population (100).

In the first analysis, we determined the potential healthcare savings of people who could manage their hypertension using dietary sodium reduction instead of anti-hypertensive medication. Using data from the Canadian Health Measures Survey (101), we first identified any individual taking an anti-hypertensive medication. We assumed anyone taking an anti-hypertensive medication, with a SBP < 140 mm Hg, was on a either a single (60%) or a combination of two (40%) anti-hypertensive medications with a weighted average reduction of 11.3 mmHg in SBP (113). We added the weighted average of 11.3 mm Hg to the SBP of all individuals taking an anti-hypertensive medication with a SBP < 140 mm Hg, and then applied the corresponding mean SBP decrease associated with dietary sodium reduction of 1800 mg/day (Table 7).

Next, we determined the proportion of individuals in this group who continued to have a controlled SBP <140 mm Hg and assumed that these individuals could come off their medication, if they were able to reduce their sodium intake. Using this proportion and Statistics Canada population data (100), we extrapolated to the total number in the population who could substitute their anti-hypertensive medication with dietary sodium reduction. To estimate the reduction in hypertension management costs, we applied cost inputs from Table 8. Cost estimates were determined from published and unpublished literature, and included laboratory costs, primary care physician (PCP) costs, and anti-hypertensive medication costs. We varied the definition of controlled SBP to ≤120 and ≤130, and repeated the same analysis. We determined the first year costs, and applied a 2% annual discount to future costs for 50, 10 and 5 years.

The second analysis determined the potential healthcare savings for untreated people with an uncontrolled SBP ≥140, who could theoretically achieve controlled SBP <140 with the addition of dietary sodium reduction. We applied the mean change in SBP associated with dietary sodium reduction of 1800 mg/day (Table 7) to individuals with uncontrolled SBP. We then determined the proportion of individuals with controlled SBP who were previously not being treated with an anti-hypertensive medication, but were now being controlled after dietary sodium reduction. Using these proportions and Statistics Canada population data (100), we quantified the total number in the population who could control their high SBP with dietary sodium reduction. To estimate the reduction in hypertension management costs, we applied cost inputs from Table 8. We estimated future hypertension management cost savings for the first year, and applied a 2% annual discount to future costs for 50, 10 and 5 years.

Table 8: Input costs for hypertension management treatment

Input	Cost (CDN$ per person)	Source
Annual mean PCP cost related to hypertension[¶]	74.67	(114)
Annual mean cost of laboratory tests*	33.26	(115)
Annual cost of antihypertensive medication[§] (60% 1 drug 40% two drugs)	299.60	(116)

*, Annual cost of medication was assumed to be $214 and $428 for one and two medications, respectively. Calculation is based on a weighted average of 60% and 40% of the population taking one medication and two medications, respectively.
[¶], Calculation based on an annual hypertension related PCP visit of 2.08 multiplied by cost of PCP per visit ($35.90)
[§], Calculation based on an annual hypertension related laboratory tests of 1 multiplied by cost of a lab test ($33.26)

Chapter 3: Results

3.1: Mean Changes in SBP

Table 9 displays the mean changes in SBP for the three SBP categories (SBP ≥140 mmHg, SBP 130-139 mmHg, and SBP <130 mmHg), according to age and sex for each of the pre-specified reductions in dietary sodium. For both sodium reduction levels (1800 mg/day and 1500 mg/day) the mean change in SBP varied across groups, depending on the proportion within each group defined as hypertensive (i.e., with either SBP ≥ 140 mmHg or on anti-hypertensive medication). All individuals in the SBP ≥ 140 mmHg category, regardless of diagnosis or treatment status, were subject to the maximal reduction in SBP, i.e., that associated with sodium reduction in hypertensive individuals. Those in the 130-140 mmHg or ≤130 mmHg groups with a higher proportion of individuals taking BP lowering medication had a larger mean change in SBP; therefore, benefitting more from sodium reduction. The higher reductions in SBP with older age groups reflect a higher proportion of individuals with diagnosed hypertension (i.e., those whose SBP is < 140 mmHg, but who are taking anti-hypertensive medication) at older ages. Males also had a higher reduction in SBP in the SBP categories <130 mmHg and 130-139 mmHg, in comparison to females, which also reflects the higher prevalence of treated hypertension in males.

Table 9: Mean changes in SBP for dietary sodium reduction levels of 1800 and 1500 mg/day stratified by SBP, sex and age group

Sex	Age	Mean SBP change from sodium reduction by SBP category*					
		1800 mg/day sodium reduction			1500 mg/day sodium reduction		
		SBP <130 (mmHg)	SBP 130-139 (mmHg)	SBP ≥140 (mmHg)	SBP <130 (mmHg)	SBP 130-139 (mmHg)	SBP ≥140 (mmHg)
Male	35-44	-2.72	-2.71	-5.63	-2.26	-2.25	-4.70
	45-54	-3.00	-3.64	-5.63	-2.49	-3.03	-4.70
	55-64	-3.28	-4.03	-5.63	-2.73	-3.36	-4.70
	65-74	-4.06	-3.97	-5.63	-3.38	-3.30	-4.70
	75-84	-4.23	-4.74	-5.63	-3.52	-3.95	-4.70
	85-94	-4.23	-4.74	-5.63	-3.52	-3.95	-4.70
Female	35-44	-2.60	-2.68	-5.63	-2.16	-2.23	-4.70
	45-54	-3.02	-3.21	-5.63	-2.51	-2.67	-4.70
	55-64	-3.24	-3.77	-5.63	-2.69	-3.14	-4.70
	65-74	-3.74	-4.46	-5.63	-3.11	-3.71	-4.70
	75-84	-4.09	-3.84	-5.63	-3.41	-3.20	-4.70
	85-94	-4.09	-3.84	-5.63	-3.41	-3.20	-4.70

*, SBP category refers to the three SBP categories used in the Canadian CVDPM model (SBP ≥140, SBP 130-139, and SBP <130)
SBP, systolic blood pressure

3.2: Model Validity

We established face and internal validity consistent with published guidelines (112). We examined the effect of a change in mean SBP on predicted CVD outcomes and compared this to the expected effect from published studies. A 10% decrease in SBP resulted in a decrease in incidence of CHD and stroke, a decrease in the number of MI and stroke events, and a decrease in CVD related deaths. These effects are consistent with those seen in observational cohort studies (33); however, the magnitude of the decrease was lower than that found in studies that tested BP lowering drug therapies (65, 117)

3.3: Primary Analysis

The model estimated that a population-wide reduction in dietary sodium of 1800 mg/day would result in a gain of 1,224,235 QALYs and a decrease of $20.7 billion in healthcare costs, over a lifetime horizon of 50 years (Table 10). The model did not specifically account for hypertension management costs. The associated decreases in new fatal and non-fatal cases of CHD and stroke were 199,808 and 120,381, respectively over 50 years (Table 11). The decreases in total fatal and non-fatal stroke and MI events were 134,119 and 115,528, respectively. The model also predicted 89,734 fewer deaths from any cause, including CVD.

When the time horizon was changed to five and 10 years, the model predicted that dietary sodium reduction would lead to a gain of 29,226 and 101,774 QALYs, and estimated savings of $2.7 and $5.2 billion in healthcare costs, respectively. The associated decreases in new fatal and non-fatal cases of CHD, and stroke for five years were 28,098 and 11,645, respectively. The decreases in total fatal and non-fatal CVD events were 12,233 for stroke and 12,187 for MI. The

associated decrease in new fatal and non-fatal cases of CHD, and stroke for 10 years were 50,900 and 22,222, respectively. The decreases in total fatal and non-fatal CVD events were 23,660 for stroke and 23,398 for MI. The predicted deaths from any cause, including CVD, were 10,363 and 20,069 lower, for five and 10 years respectively (Table 12).

The average annual healthcare savings associated with a daily reduction in sodium of 1800 mg/day was estimated by dividing the total cost savings for each time horizon by the associated number of years. This resulted in $54.6 million annually over five years, $105 million annually over 10 years, and $414 million annually over 50 years.

With a population-wide reduction in dietary sodium of 1500 mg/day, the model estimated a gain of 1,021,458 QALYs and an estimated decrease of $16.8 billion in healthcare costs, over a lifetime horizon of 50 years (Table 10). The associated decreases in new fatal and non-fatal cases of CHD, and stroke were 166,689 and 100,654, respectively over 50 years (Table 11). The decreases in total fatal and non-fatal CVD events were 112,144 for stroke and 96,377 for MI. The model also predicted 74,870 fewer deaths from any cause, including CVD.

When the time horizon was changed to five and 10 years, the model predicted that a dietary sodium reduction of 1500 mg/day would lead to a gain of 24,409 and 84,982 QALYs, and estimated savings of $2.2 and $4.2 billion in healthcare costs, respectively. The associated decreases in new fatal and non-fatal cases of CHD, and stroke for five years were 23,473 and 9,753, respectively. The decreases in total fatal and non-fatal CVD events were 10,246 for stroke and 10,182 for MI. The associated decreases in new fatal and non-fatal cases of CHD, and stroke

for 10 years were 42,511 and 18, 607, respectively. The decreases in total fatal and non-fatal CVD events were 19,811 for stroke and 19,543 for MI. The predicted deaths from any cause, including CVD, were 8,651 and 16,753 lower for five and 10 years, respectively.

The average annual healthcare savings associated with a daily reduction in sodium of 1500 mg/day was estimated by dividing the total cost savings for each time horizon by the associated number of years. This resulted in $44.1 million annually over five years, $84.6 million annually over 10 years, and $336 million annually over 50 years.

Table 10: Projected QALYs gained and healthcare savings for different sodium reduction levels and time horizons

Sodium reduction	Mean SBP change within category *	Time horizon (years)	Total QALYs gained	Total cost savings (CDN$)	Annual cost savings (CDN$)
1800 mg/day	SBP ≥140: -5.63 mmHg SBP 130-139: -4.74 to -2.68 mmHg SBP <130: -4.09 to -2.60 mmHg	50 years	1,224,235	20,688,275,720	413,765,514
		10 years	101,774	5,226,000,750	104,520,015
		5 years	29,226	2,731,554,943	54,631,099
1500 mg/day	SBP ≥140: -4.76 mm Hg SBP 130-139: -3.95 to -2.23 mmHg SBP <130: -3.52 to -2.16 mmHg	50 years	1,021,458	16,804,875,575	336,097,512
		10 years	84,982	4,232,097,127	84,641,943
		5 years	24,409	2,207,059,043	44,141,181

*, range of mean SBP within each category varies according to the estimated proportion with hypertension among age and sex groups
SBP, systolic blood pressure, QALY, quality adjusted life year; CDN, Canadian

Table 11: Health outcomes and costs for a decrease in dietary sodium over 50-year time horizon

Outcome	Sodium reduction				
	No sodium reduction (base case)*	1800 mg/day		1500 mg/day	
	Total number	Total number	Change from base case	Total number	Change from base case
Prevalence of CVD	136,409,236	132,174,405	-4,234,831	132,872,651	-3,536,585
Number of CHD deaths	3,093,057	3,028,681	-64,376	3,039,326	-53,731
Number of stroke deaths	634,817	609,061	-25,756	613,285	-21,532
Number of deaths from any cause	18,920,611	18,830,877	-89,734	18,845,741	-74,870
New fatal and non-fatal cases of CHD	7,497,864	7,298,056	-199,808	7,331,175	-166,689
New fatal and non-fatal cases of stroke	2,707,168	2,586,787	-120,381	2,606,514	-100,654
Number of fatal and non-fatal MI events	5,177,161	5,061,633	-115,528	5,080,784	-96,377
Number of fatal and non-fatal stroke events	3,018,867	2,884,748	-134,119	2,906,723	-112,144
Cost of intervention (CDN$)	n/a	$1,375,188,019	$1,375,188,019	$1,374,028,841	$1,374,028,841

Total Healthcare cost (CDN$)	$3,494,716,865,875	$3,472,653,402,136	$-22,063,463,739	$3,476,537,961,459	$-18,178,904,416
QALYs gained	755,909,413	757,133,648	1,224,235	756,930,871	1,021,458

*, Base case results refer to sodium consumption being maintained at current levels (about 3800 mg/day) with no sodium reduction intervention
SBP, systolic blood pressure, QALY; quality adjusted life year; CDN, Canada; CHD, coronary heart disease; MI, myocardial infarction

Table 12: Total health outcomes and costs for different sodium reduction levels over 5 and 10 years

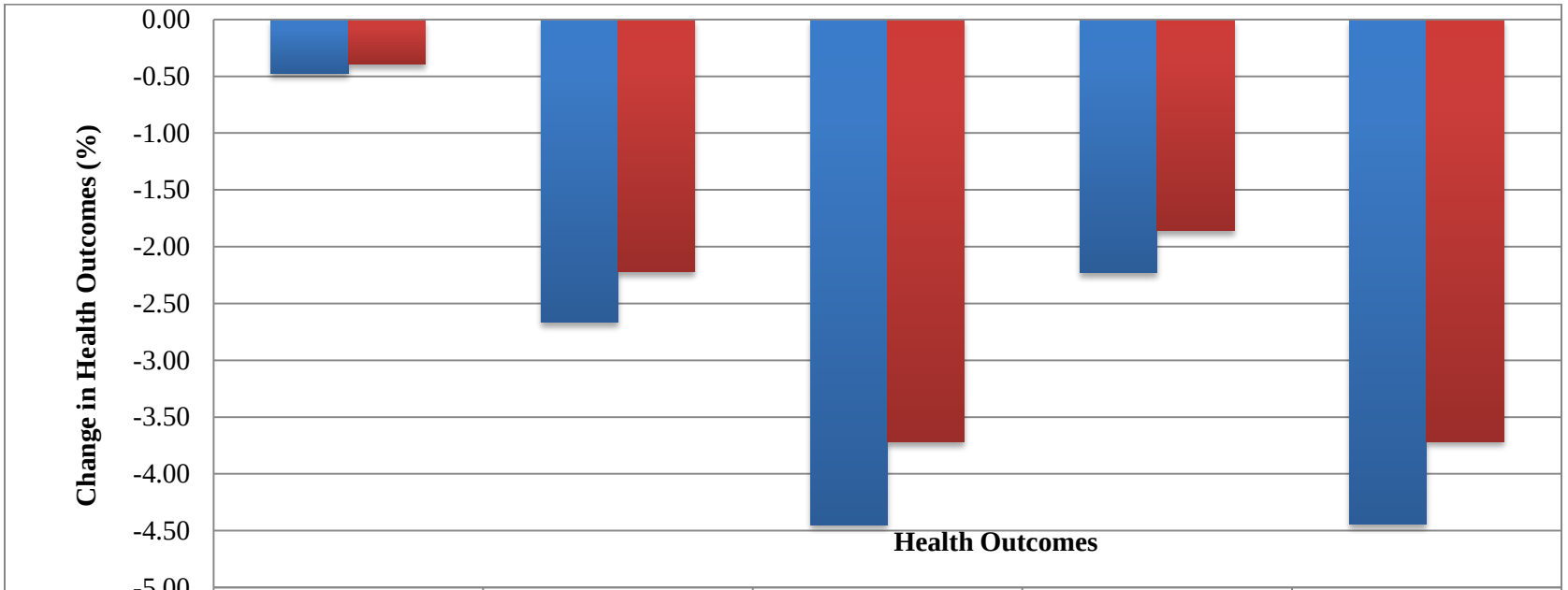
Outcome	Sodium reduction									
	No sodium reduction (Base case)*		1800 mg/day				1500 mg/day			
	5 years	10 years	5 years		10 years		5 years		10 years	
	Total number	Total number	Total number	Change from base case	Total number	Change from base case	Total number	Change from base case	Total number	Change from base case
Prevalence of CVD (per 10,000)	1,102	2,169	1,094	-9	2,139	-30	1,095	-7	2,144	-25
Number of CHD deaths	227,436	448,328	224,605	-2,831	441,756	-6,572	225,070	-2,366	442,837	-5,491
Number of stroke deaths	47,887	93,767	45,645	-2,242	89,429	-4,338	46,009	-1,878	90,135	-3,632
Number of deaths from any cause	1,449,013	2,836,044	1,438,650	-10,363	2,815,975	-20,069	1,440,362	-8,651	2,819,291	-16,753
New fatal and non-fatal cases of CHD	708,885	1,353,139	680,787	-28,098	1,302,239	-50,900	685,412	-23,473	1,310,628	-42,511
New fatal and non-fatal cases of stroke	221,416	431,286	209,771	-11,645	409,064	-22,222	211,663	-9,753	412,679	-18,607
Number of fatal and non-fatal MI events	441,235	857,521	429,048	-12,187	834,123	-23,398	431,053	-10,182	837,978	-19,543
Number of fatal and non-fatal stroke events	244,920	477,792	232,687	-12,233	454,132	-23,660	234,674	-10,246	457,981	-19,811

Cost of sodium reduction intervention (CDN$, Millions)	$-	$-	$216.77	$216.77	$387.25	$387.25	$216.74	$216.74	$387.13	$387.13
Reduction in total healthcare costs (CDN$, Billions)	$481.76	$881.30	$478.81	$-2.95	$875.69	$-5.61	$479.33	$-2.42	$876.68	$-4.62
QALYs gained (thousands)	117,154	209,939	117,183	29	210,040	102	117,178	24	210,024	85

*, Base case results refer to sodium consumption being maintained at current levels (about 3800 mg/day) with no sodium reduction intervention
SBP, systolic blood pressure, QALY; quality adjusted life year; CDN, Canada; CHD, coronary heart disease; MI, myocardial infarction

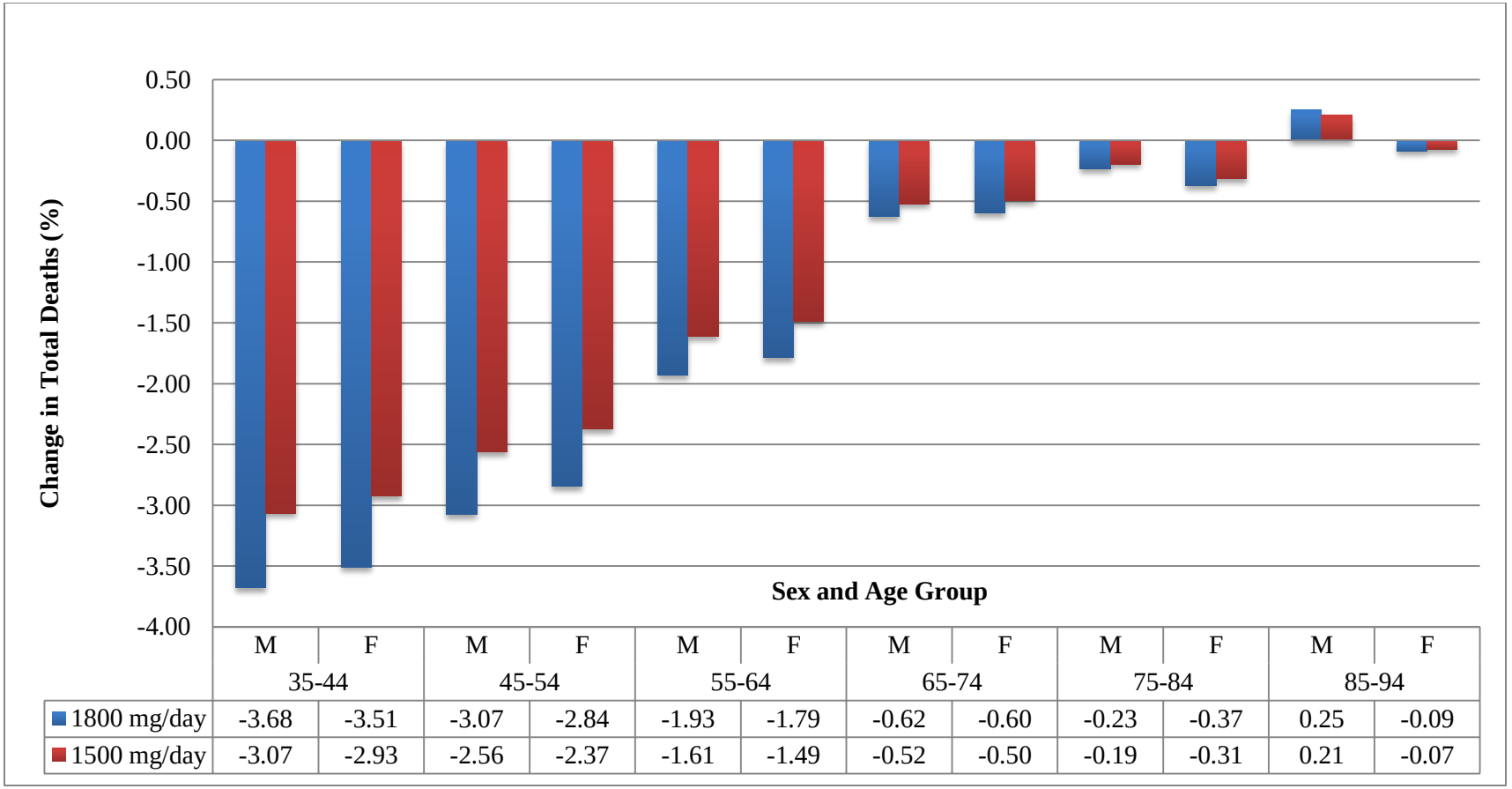
Figure 2 depicts the relative change in CVD outcomes (incidence of CHD and stroke, total MI and stroke events, and total deaths) from the base case for both the 1800 mg/day, and 1500 mg/day dietary sodium reductions. All age and sex categories experienced a larger change in reduction of total health outcomes with a sodium reduction of 1800 mg/day, in comparison to a 1500 mg/day dietary sodium reduction.

Figures 3, 4 and 5 depict how the epidemiological distribution of CVD health outcomes (50-year incidence of CHD and stroke, number of total MI and stroke events, and total deaths) across age and sex groups would be expected to shift with dietary sodium reduction. The incidence of CVD events is predicted to decrease in all age groups less than 85, with a compensatory increase in the oldest age group. The young and middle-aged populations are projected to have a larger relative reduction in 50-year incidence of CHD and stroke, number of total MI and stroke events, and total deaths from any cause, compared to older age groups. The oldest age group, 85-94, is expected to have an increase in incidence of CHD, total MI events and total deaths from any cause, after dietary sodium reduction. This increase is hypothesized to be secondary to delaying adverse health events to an older age. While the total number of events across all ages decreases, there are more events in this oldest age group because events that would have been expected to occur at younger ages are occurring later in life.



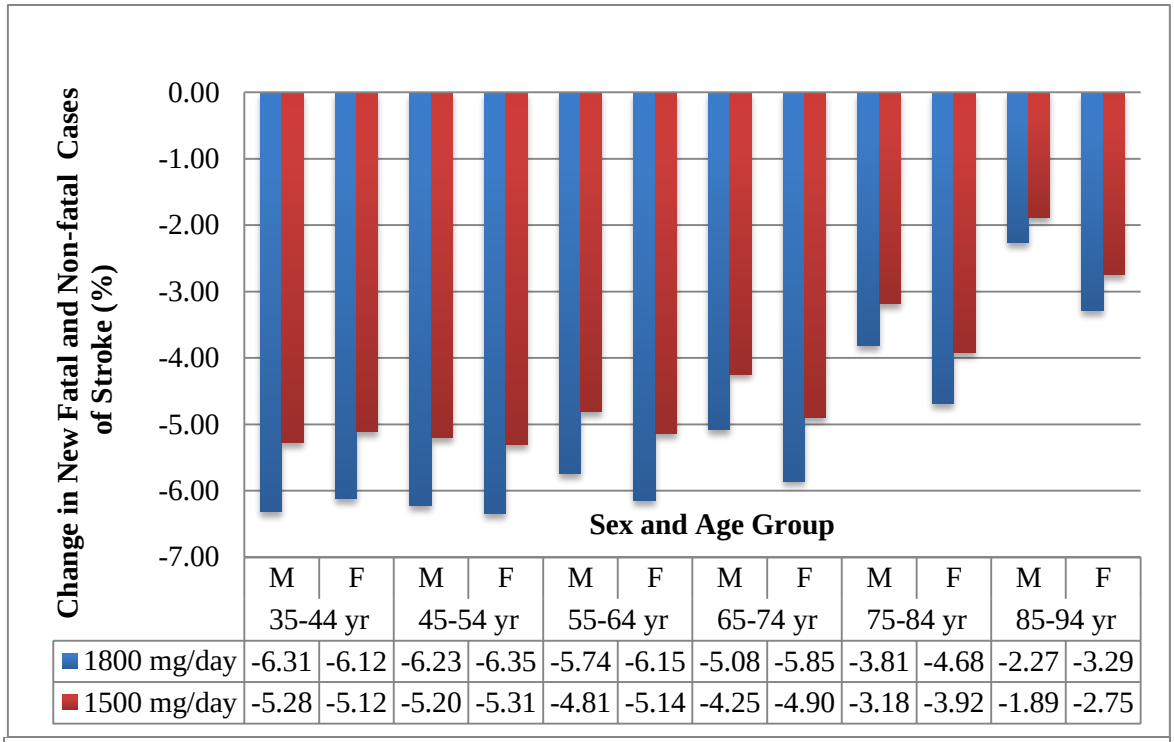
	Change in total deaths	Change in new fatal and non-fatal cases of CHD	Change in new fatal and non-fatal cases of stroke	Change in tota fatal and non-fatal MI events	Change in total fatal and non-fatal stroke events
1800 mg/day	-0.47	-2.66	-4.45	-2.23	-4.44
1500 mg/day	-0.40	-2.22	-3.72	-1.86	-3.71

Figure 2: Change in health outcomes for CHD, stroke, & MI over 50 years from reductions in dietary sodium of 1800mg/day and 1500 mg/day

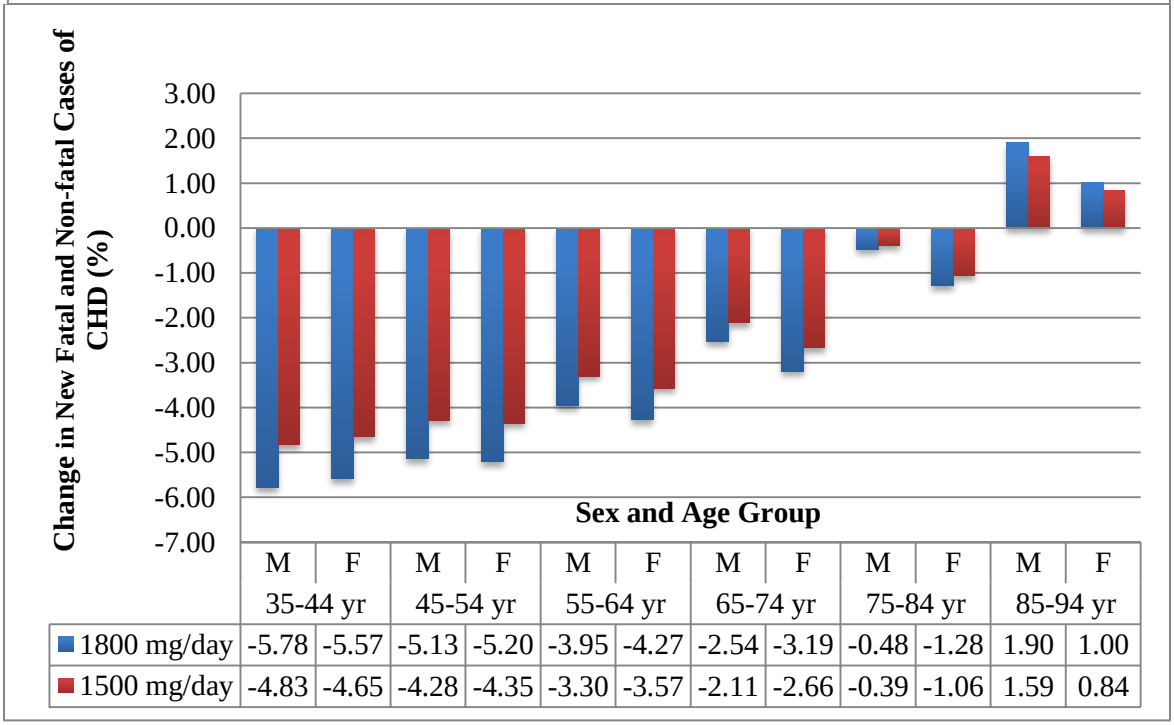


	M	F	M	F	M	F	M	F	M	F	M	F
	35-44		45-54		55-64		65-74		75-84		85-94	
1800 mg/day	-3.68	-3.51	-3.07	-2.84	-1.93	-1.79	-0.62	-0.60	-0.23	-0.37	0.25	-0.09
1500 mg/day	-3.07	-2.93	-2.56	-2.37	-1.61	-1.49	-0.52	-0.50	-0.19	-0.31	0.21	-0.07

Figure 3: Projected change in total deaths occurring in a given age and sex group over 50 years due to a sodium dietary reduction of 1800mg/day and 1500 mg/day

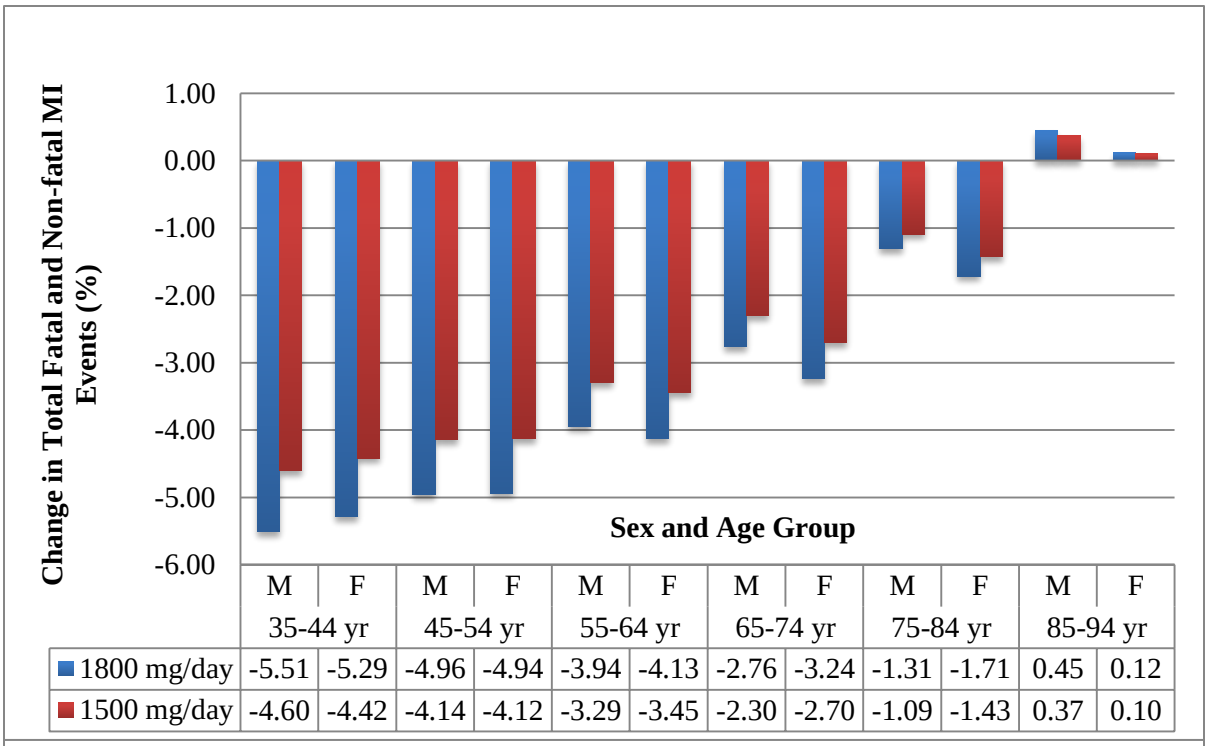


	M	F	M	F	M	F	M	F	M	F	M	F
	35-44 yr		45-54 yr		55-64 yr		65-74 yr		75-84 yr		85-94 yr	
1800 mg/day	-6.31	-6.12	-6.23	-6.35	-5.74	-6.15	-5.08	-5.85	-3.81	-4.68	-2.27	-3.29
1500 mg/day	-5.28	-5.12	-5.20	-5.31	-4.81	-5.14	-4.25	-4.90	-3.18	-3.92	-1.89	-2.75

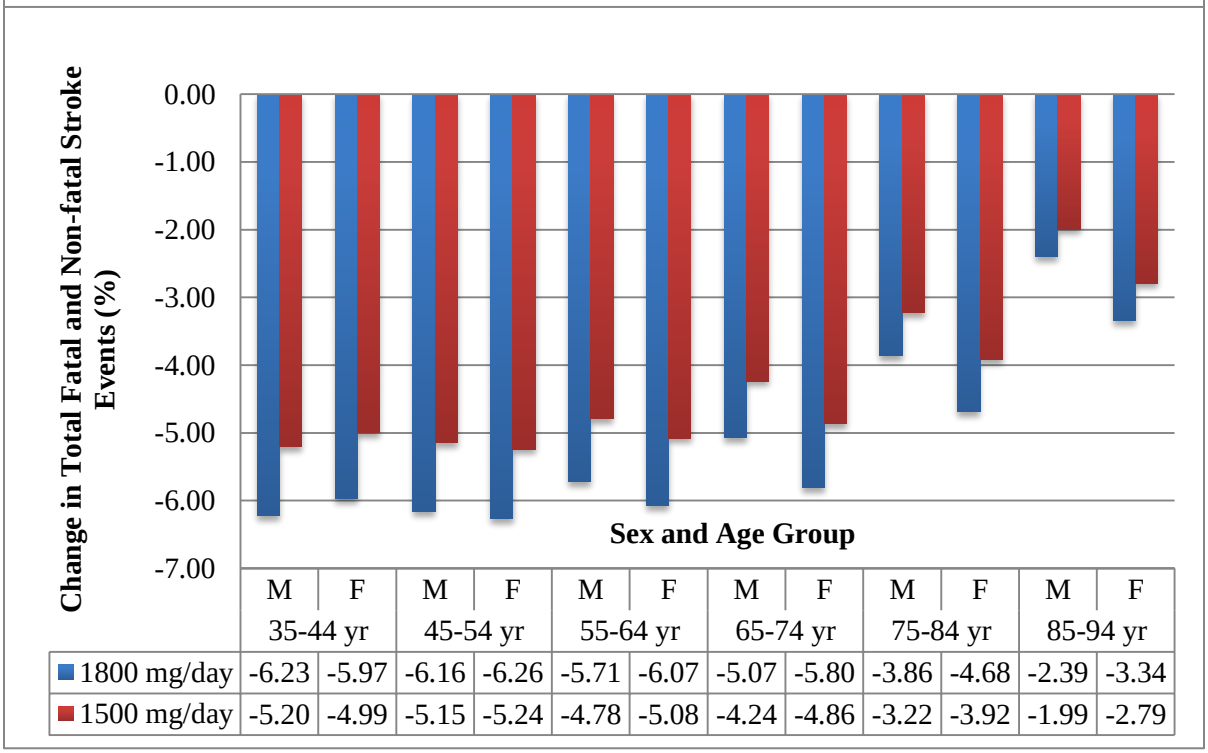


	M	F	M	F	M	F	M	F	M	F	M	F
	35-44 yr		45-54 yr		55-64 yr		65-74 yr		75-84 yr		85-94 yr	
1800 mg/day	-5.78	-5.57	-5.13	-5.20	-3.95	-4.27	-2.54	-3.19	-0.48	-1.28	1.90	1.00
1500 mg/day	-4.83	-4.65	-4.28	-4.35	-3.30	-3.57	-2.11	-2.66	-0.39	-1.06	1.59	0.84

Figure 4: Projected change in new fatal and non-fatal cases of coronary heart disease and stroke occurring in a given age and sex group over 50 years due to a sodium dietary reduction of 1800mg/day and 1500 mg/day



	M	F	M	F	M	F	M	F	M	F	M	F
	35-44 yr		45-54 yr		55-64 yr		65-74 yr		75-84 yr		85-94 yr	
1800 mg/day	-5.51	-5.29	-4.96	-4.94	-3.94	-4.13	-2.76	-3.24	-1.31	-1.71	0.45	0.12
1500 mg/day	-4.60	-4.42	-4.14	-4.12	-3.29	-3.45	-2.30	-2.70	-1.09	-1.43	0.37	0.10



	M	F	M	F	M	F	M	F	M	F	M	F
	35-44 yr		45-54 yr		55-64 yr		65-74 yr		75-84 yr		85-94 yr	
1800 mg/day	-6.23	-5.97	-6.16	-6.26	-5.71	-6.07	-5.07	-5.80	-3.86	-4.68	-2.39	-3.34
1500 mg/day	-5.20	-4.99	-5.15	-5.24	-4.78	-5.08	-4.24	-4.86	-3.22	-3.92	-1.99	-2.79

Figure 5: Projected change in number of fatal and non-fatal myocardial infarctions and strokes occurring in a given age and sex group over 50 years, due to a dietary sodium reduction of 1800mg/day and 1500 mg/day

3.4: Increased Sodium Consumption

We estimated the effect of increasing dietary sodium consumption by 500 mg/day. The model estimated a loss of 615,707 QALYs, and an increase of $8.2 billion in healthcare costs, over a lifetime horizon of 50 years (Table 13). The associated increase in new cases of CHD and stroke were 56,078 and 33,994, respectively over 50 years. The increases in CVD events were 37,882 for stroke and 32,374 for MI (Table 14). The model predicted 25,166 more deaths from any cause, including CVD, and an increase in the number of deaths from CHD (18,072) and stroke (7,260).

With a time horizon of five and 10 years, the model predicted that an increase in dietary sodium would lead to a loss of 8,240 and 28,677 QALYs, and an increase in healthcare costs of $672 million and $1.3 billion, respectively (Table 14). The associated increases in new cases of CHD, and stroke for five years were 7,939 and 3,317, respectively. The increases in CVD events were 3,484 for stroke, and 3,441 for MI. The associated increases in new cases of CHD and stroke for 10 years were 14,362 and 6,321, respectively. The increases in CVD events were 6,730 for stroke, and 6,597. The predicted deaths from any cause, including CVD, were 2,918 and 5,646 higher, for five and 10 years respectively.

The average annual healthcare cost associated with a daily increase in sodium of 500 mg/day was estimated by dividing the total cost for each time horizon by the associated number of years. This resulted in $13.4 million annually over five years, $26 million annually over 10 years, and $165 million annually over 50 years.

Table 13: Projected loss in QALYs and increase in healthcare costs for an increase in sodium consumption

Level of sodium increase	Mean SBP change within category*	Time horizon	Total loss of QALYs	Total cost increase (CDN$)	Annual cost increase (CDN$)
500 mg/day	SBP ≥140 mm Hg: 1.57 mmHg SBP 130-139: 0.74 to 1.32 mmHg SBP <130: 0.75 to 1.17 mmHg	50 years	615,707	8,242,090,491	164,841,809
		10 years	28,677	1,298,998,536	25,979,970
		5 years	8,240	672,492,780	13,449,855

*, range of mean SBP range within each category varies according to the estimated proportion with hypertension among sex, age and SBP groups
SBP, systolic blood pressure; QALY, quality adjusted life year; CDN, Canadian

Table 14: Total health outcomes and costs for an increase in sodium consumption over time horizons of 50, 10 and 5 years

Outcome	Sodium reduction								
	No change in sodium (base case)*			500 mg/day increase					
	50 years	10 years	5 years	50 years		10 years		5 years	
	Total Number	Total Number	Total Number	Total Number	Change from base case	Total Number	Change from base case	Total Number	Change from base case
Prevalence of CVD (per 10,000 persons)	13,521	2,161	1,100	13,641	119	2,169	8	1,102	2
Number of CHD deaths	3,075,279	446,496	226,641	3,093,351	18,072	448,349	1,853	227,441	800
Number of stroke deaths	627,469	92,531	47,248	634,729	7,260	93,764	1,233	47,886	638
Number of deaths from any cause	18,894,805	2,830,413	1,446,100	18,919,971	25,166	2,836,059	5,646	1,449,018	2,918
New fatal and non-fatal cases of CHD	7,442,629	1,338,890	700,986	7,498,707	56,078	1,353,252	14,362	708,925	7,939
New fatal and non-fatal cases of stroke	2,672,794	424,950	218,093	2,706,788	33,994	431,271	6,321	221,410	3,317
Number of fatal and non-fatal MI events	5,144,889	850,975	437,810	5,177,263	32,374	857,572	6,597	441,251	3,441

Number of fatal and non-fatal stroke events	2,980,563	471,046	241,429	3,018,445	37,882	477,776	6,730	244,913	3,484
Total Healthcare cost (CDN$, Billions)	$5,578	$880	$481	$3,495	$8	$881	$1	$482	$0.672
QALYs gained (thousands)	1,190,611	209,967	117,162	755,914	-616	209,939	-29	117,154	-8

*, Base case results refer to sodium consumption being maintained at current levels (about 3800 mg/day)
SBP, systolic blood pressure, QALY; quality adjusted life year; CDN, Canada; CHD, coronary heart disease; MI, myocardial infarction

3.5: Sensitivity Analysis

Our results were sensitive to deviations in the mean change in SBP associated with dietary sodium reduction. Assuming the mean SBP change associated with a dietary sodium reduction of 1800 mg/day is equal to the lower bound of its 95% confidence interval (i.e., maximum blood pressure reduction for a given reduction in dietary sodium), healthcare savings were 31% higher ($27,138,534,257 vs. $20,688,275,720), and QALYS gained were 27% higher (1,557,898 QALYs vs. 1,224,235) (Table 15). In contrast, assuming a SBP mean change equal to the upper bound of the 95% CI (i.e., minimum blood pressure change for a given reduction in dietary sodium), healthcare savings were 24% lower ($15,647,939,203 vs. $20,688,275,720), and QALYs gained were 22% lower (959,815 QALYs vs. 1,224,235). A similar pattern of results was noted when the upper and lower bounds of the 95% CI were used for the 1500 mg/day reduction in sodium.

Varying the baseline annual intervention or CVD healthcare costs by +/- 25% did not substantively alter the results. A 25% increase in annual intervention costs for a dietary sodium reduction of 1800 mg/day leads to a decrease in healthcare cost savings to $ 20.3 billion over 50 years. A 25% decrease in annual intervention costs for a dietary sodium reduction of 1800 mg/day leads to an increase of healthcare cost savings to $ 21 billion over 50 years. A similar pattern was seen for 1500 mg/day dietary sodium reduction. A 25% decrease in annual CVD healthcare costs resulted in an increase of healthcare cost savings to $25 billion for a dietary sodium reduction of 1800 mg/day over 50 years. In contrast, a 25% increase in annual CVD healthcare costs resulted in a decrease in healthcare cost savings to $15 billion over 50 years. A similar pattern was seen for 1500 mg/day dietary sodium reduction.

Table 15: Results of scenario and deterministic sensitivity analyses for time horizon of 50 years

Sensitivity Analysis	Total QALYs gained (% Change)	Total savings (CDN$) (% Change)	Annual savings (CDN$)
Base case**			
Sodium reduction of 1800 mg/day	1,224,235	20,688,275,720	413,765,514
Sodium reduction of 1500 mg/day	1,021,458	16,804,875,575	336,097,512
Scenario Analysis			
Lower bound of 95% CI for mean change in SBP* (1800 mg/day) SBP ≥140: -6.62 mmHg SBP 130-139: -5.74 to -3.69 mmHg SBP <130: -5.09 to -3.61 mmHg ¶	1,557,898 (27)	27,138,534,257 (31)	542,770,685
Lower bounds of 95% CI for mean change in SBP* (1500 mg/day) SBP ≥140: -5.76 mmHg SBP 130-139: -4.75 to -3.21 mmHg SBP <130: -4.55 to -3.14 mmHg ¶	1,359,302 (33)	23,324,414,661 (39)	466,488,293
Upper bounds of 95% CI for mean change in SBP* (1800 mg/day) SBP ≥140: -4.15 mmHg SBP 130-139: -3.56 to -2.21 mmHg SBP <130: -3.23 to -2.15 mmHg ¶	959,815 (22)	15,647,939,203 (24)	312,958,784

Lower bounds of 95% CI for mean change in SBP* (1500 mg/day) SBP ≥140: -3.61 mmHg SBP 130-139: -3.10 to -1.93 mmHg SBP <130: -2.81 to -1.884 mmHg ¶	837,290 (18)	13,300,297,231 (21)	266,005,945
-25% minimum and +25% maximum value change of costs			
Annual intervention cost for 1800 mg/day dietary sodium reduction	n/a	Min result= 21,029,541,047	Min result= 420,590,821
		Max result= 20,342,526,626	Max result= 406,850,532
Annual intervention cost for 1500 mg/day dietary sodium reduction	n/a	Min result= 17,144,981,724	Min result= 342,899,634
		Min result= 16,457,967,303	Min result= 329,159,346
Annual healthcare costs of cardiovascular disease for 1800 mg/day dietary sodium reduction	n/a	Min result= 24,982,720,359	Min result= 499,654,407
		Max result= 15,426,221,761	Max result= 308,524,435
Annual costs of cardiovascular disease for 1500 mg/day dietary sodium reduction	n/a	Min result= 20,279,169,622	Min result= 405,583,392
		Max result= 12,519,130,218	Max result= 250,382,604

SBP, systolic blood pressure; BP, blood pressure

*, range of mean SBP range within each category varies according to the estimated proportion with hypertension among sex, age and SBP groups

**, Base case refers to main sodium reduction analyses found in Table 1

¶, Mean SBP changes vary according to sex and age groups and ranges are only displayed. All values can be found in Appendix A.

3.6: Estimating Change in Hypertension Management Costs Secondary to Dietary Sodium Reduction

Table 16 displays the potential healthcare savings resulting from individuals substituting their BP lowering medication, i.e., anti-hypertensive medication, with dietary sodium reduction. If controlled SBP is defined as <140 mmHg, we estimated that 13% of CHMS respondents, extrapolated to 2,616,376 Canadians, would be able to substitute their BP lowering medication with dietary sodium reduction. Given our estimated annual cost of hypertension management of $1.4 billion, this would result in an estimated annual healthcare savings of $1.1 billion. If this annual savings remained consistent over 50 years, the discounted estimated healthcare savings would be $33.1 billion. For a short time period of five and 10 years, the near term healthcare savings were $4.1 and $8.7 billion, respectively.

If controlled SBP is defined as ≤130 mmHg, we estimated that 9% of CHMS respondents, extrapolated to 1,859,575 Canadians, would be able to substitute their treatment of a BP lowering medication strategy with a dietary sodium reduction. This would result in an estimated annual healthcare savings of $758 million. If this annual savings remained consistent over 50 years, the discounted estimated healthcare savings would be $23.5 billion. For a short time period of five and 10 years, the healthcare savings were $2.9 and $6.2 billion, respectively.

If controlled SBP is defined as ≤120 mmHg, we estimated that 5% of CHMS respondents, extrapolated to 967,771 Canadians, would be able to substitute their treatment of a BP lowering medication strategy with a dietary sodium reduction. This would result in an estimated annual healthcare savings of $394 million. If this annual savings remained consistent over 50 years, the discounted estimated healthcare savings would be $12.2 billion. For a short time period of five and 10 years, the healthcare savings were $1.5 and $ 3.2 billion, respectively.

Table 17 displays the potential savings in hypertension management costs associated with controlling BP using sodium reduction in those with uncontrolled hypertension (SBP ≥140 mm Hg). These individuals are either untreated or undiagnosed (and untreated) and currently not incurring hypertension management costs, but represent potential costs to the healthcare system if they were to be managed according to guidelines. We estimated that 242,430 Canadians with untreated and uncontrolled SBP could achieve controlled SBP with dietary sodium reduction and this represents a potential for averted future spending of $99 million annually. Over 50 years this would amount to $ 3.1 billion. For a short time period of five and 10 years, the potential for avoided costs was determined to be $376 million and $806 million, respectively.

Table 16: Savings in hypertension management costs associated with dietary sodium reduction of 1800mg/day, due to estimated number of individuals able to maintain BP control by substituting sodium reduction for medications

SBP target	Proportion of 35-94 year olds with hypertension controlled with sodium reduction¶	Extrapolated number of Canadians**	First year*		5 years		10 years		50 years	
			Total savings (CDN$)	Savings per person (CDN$)	Total savings (CDN$, Billions)	Savings per person (CDN$)	Total savings (CDN$, Billions)	Savings per person (CDN$)	Total savings (CDN$, Billions)	Savings per person (CDN$)
<140 mmHg	0.13	2,616,376	1,066,257,048	54	4.1	206	8.7	442	33.1	1,683
≤130 mmHg	0.09	1,859,575	757,836,431	385	2.9	147	6.2	314	23.5	1,196
≤120 mmHg	0.05	967,770	394,397,494	20	1.5	76	3.2	164	12.2	623

SBP, systolic blood pressure

*, Healthcare savings determined from the first year only, i.e. no discounting

**, Extrapolation based on a total Canadian population of 19,670,040 aged 35-94

¶, Proportion of CHMS respondents

Table 17: Savings in hypertension management costs for uncontrolled hypertension associated with 1800 mg/day dietary sodium reduction, due to estimated number of individuals able to maintain BP control with the addition of dietary sodium reduction

BP target	Proportion of 35-94 year olds with hypertension controlled with sodium reduction¶	Extrapolated number of Canadians**	First year*		5 years		10 years		50 years	
			Total savings (CDN$, Millions)	Savings per person (CDN$)	Total savings (CDN$, Millions)	Savings per person (CDN$)	Total savings (CDN$, Millions)	Savings per person (CDN$)	Total savings (CDN$, Billions)	Savings per person (CDN$)
<140 mmHg	0.01	242,430	99	5	376	19	806	41	3.1	156

SBP, systolic blood pressure

*, Healthcare savings determined from the first year only, i.e. no discounting

**, Extrapolation based on a total Canadian population of 19,670,040 aged 35-94

¶, Proportion of CHMS respondents

Chapter 4: Discussion

4.1: Overview of Primary Analyses

Our study demonstrated that a reduction in the risk of CVD could be achieved through the blood pressure lowering effects of reduced dietary sodium, leading to significant economic benefits to the healthcare system, and the Canadian population. We found that, compared to no dietary sodium reduction, reducing population dietary sodium intake by 1500 mg/day and 1800 mg/day, over a 50 year time horizon, is predicted to increase health by 1,021,458 and 1,224,235 QALYs, and decrease healthcare costs by $16.8 and 20.7 billion, respectively. Reducing dietary sodium consumption to 2300 mg/day (the upper limit and 2016 interim target for government (19), and corresponding to a mean reduction in dietary sodium of 1500 mg/day) and 2000 mg/day (recommended target by HC and He et al. (18), and corresponding to a mean reduction in dietary sodium of 1800 mg/day) is projected to benefit the Canadian population, and yield substantial reductions in morbidity, mortality and healthcare costs. If no change in sodium consumption occurs in the Canadian population resulting from consumer behavior, national policies or food reformulation, there could be high costs to the healthcare system, and detrimental healthcare outcomes. With just a small increase in dietary sodium consumption of 500 mg/day, over a lifetime horizon, the Canadian population would experience an estimated increase in healthcare costs of $8.2 billion, and a loss of 615,707 QALYs. The cost savings and improved health outcomes from dietary sodium reduction support the implementation of intervention programs and policies to achieve better outcomes.

Our primary analyses were robust to sensitivity analyses. When assessing the uncertainty of the mean change in SBP due to a reduction in dietary sodium of 1800 mg/day, the QALYs

gained varied by 22% on the lower end and 27% on the upper end, and the cost savings varied by 24% on the lower end and 31% on the upper end. Similar results were seen with 1500 mg/day dietary sodium. In all cases, the results favor a dietary sodium reduction strategy. Our model was sensitive to variations in CVD healthcare costs, and dietary sodium reduction intervention costs; however, dietary sodium reduction remained dominant in all scenarios.

Our findings are consistent with previous modeling studies supporting the cost-effectiveness of population-wide sodium reduction programs and policies, all of which predicted significant savings for the healthcare system, and reduction in morbidity and mortality (91, 92, 118). In the United States, the CVDPM predicted that dietary sodium reduction of 1180 mg/day would save 194,000 to 392,000 QALYs and $10 to $24 billion in healthcare costs annually (92). There were greater health benefits for black people overall; women experienced the lowest number of stroke events, younger adults experienced the lowest mortality rates, and older adults experienced the greatest reduction in CHD events. The study also predicted that a modest reduction of just 394 mg/day would save costs and improve CVD health outcomes. Our results are also consistent with studies that used different CVD models. United Kingdom and Australian models with the same dietary sodium targets as Canada predicted similar results to our study (70, 119).

Our results are also consistent with a Canadian study examining the impact of dietary sodium reduction on CVD events. Penz et al. (86) estimated that reducing dietary sodium by 1840 mg/day would prevent 11.5 thousand CVD events (MI, stroke and heart failure) annually in their primary analysis. In their study, the average Canadian dietary sodium consumption was

considered to be approximately 3500 mg/day; therefore, the study modeled dietary sodium reduction of 1840 mg/day to meet the recommended dietary intake level of <2300 mg/day. In our study, we modeled different dietary sodium reduction levels, due to updated data available on the average Canadian dietary sodium consumption (3800 mg/day) (20). Hence, we examined the changes in CVD outcomes from a dietary sodium reduction of 1800 mg/day and 1500 mg/day to correspond to the recommended dietary sodium intake of 2000 mg/day and 2300 mg/day, respectively. Penz et al. (86) also used an older Cochrane review meta-analysis to determine the mean change in SBP associated with dietary sodium reduction. The mean change in SBP was lower in the Penz et al. (86) study, in comparison to ours. This could result in an underestimation of the number of cardiovascular events reduced from dietary sodium reduction. A linear regression model was used in the Penz et al. (86) study to examine the impact of dietary sodium reduction on cardiovascular outcomes. In comparison to the CVDPM, a linear regression model does not take into account competing health states; therefore, this could impact final reported outcomes. The estimated number of CVD events prevented in our study is likely a more accurate representation of the impact of dietary sodium reduction on CVD outcomes.

Savings from the impact of dietary sodium reduction on hypertension management costs was also updated in our study. Joffres et al. (88) predicted that an 1840 mg/day reduction in dietary sodium would save $430 million annually from drugs, physician visits, and laboratory visits. Joffres et al. (88) defined controlled SBP to be <140 mm Hg. Using the same SBP target, our study estimated healthcare savings of $1.1 billion for a dietary reduction of 1800 mg/day. Higher cost savings from our study could be potentially due to our study using more recent Canadian cost data, updated hypertension prevalence data from CHMS, and an updated

Cochrane review meta-analysis of mean changes in SBP associated with dietary sodium reduction. In the Joffres et. al (88) study, Canadian cost data for laboratory costs, physician visits, and anti-hypertensive medications were all derived from data between 2001 and 2003. Joffres et. al (88); therefore, used lower costs estimates for physician visits ($27.30 per visit vs. $35.90 per visit) and annual laboratory tests ($24.40 per hypertensive person vs. $33.26 per hypertensive person). These would result in lower estimate of the cost savings of hypertension management associated with dietary sodium reduction. In the Joffres et al. (88) study, hypertensive prevalence was based on the Canadian Heart Health Survey conducted between 1986 and 1992 (89), which is lower than current estimates used in our study (90). This would also result in an underestimation of the impact of dietary sodium reduction on the number of cases of hypertension that could be reduced in the present day, and subsequently underestimate the associated cost savings. Lastly, the Cochrane review meta-analysis used to determine the mean change in SBP associated with dietary sodium reduction was based on an older meta-analysis, which had a lower reduction in SBP associated with dietary sodium reduction, in comparison to our study. This would result in an underestimation of the number of individuals able to maintain their SBP control by substituting dietary sodium reduction for medications. Subsequently, this would lead to an underestimation of cost savings of hypertension management.

4.2 Dietary Sodium Consumption for Hypertension Management

There is an extensive amount of literature supporting the association between dietary sodium consumption, and both increased blood pressure and increased CVD risk (18, 23). Over 27 national and international organizations, including Hypertension Canada, the World Health

Organization, Canadian Heart and Stroke Foundation, and the American Heart Association have reviewed the literature, and all support population-wide efforts to reduce dietary sodium consumption (92, 120, 121). However, concerns still exist among a small group of people who believe that the level of dietary sodium consumption has no impact on the risk of CVD (43). Even so, we still see a benefit in terms of lower hypertension management costs if we are able to take people off their BP medications by substituting dietary sodium reduction.

Our findings are supported by previous studies (91, 92, 118). Projections from Finland, Japan, and the UK suggest substantial health gains from dietary salt/sodium reduction that requires a relatively small investment in resources, compared with that required to support a clinical hypertension control strategy (92, 118, 122). Clinical management of high BP is resource intensive with large healthcare expenditure on healthcare practitioner time and drug therapies (122). Even a low-intensity salt reduction program conducted in Australia was predicted to deliver approximately the same health benefits as a clinical hypertension control program at just 1%-2% of the cost (123). BP lowering drugs are an effective therapy for hypertension management, but dietary sodium reduction strategies are lower-cost, and more accessible. Regardless of long-term CVD effects, dietary sodium reduction would still lead to near-term cost savings, due to the decrease in hypertension management costs.

4.3 Health Policy Implications

The results of this study, reinforced by other studies, argue very strongly for national programs to reduce sodium consumption (123). Experience from countries like Japan, Finland, and the United Kingdom suggest that sustained reductions in population dietary sodium intake of

1700-1800mg/day are possible (65), and lead to large health gains for resource investments that are a fraction of the cost required for clinical hypertension control strategies (58, 61-63). Our findings support a call to action for a national regulatory program to reduce dietary sodium consumption.

Currently, there is considerable variation in strategies, and policy options to reduce dietary sodium consumption; however, evidence from a recent systematic review supports comprehensive strategies involving multiple components (product reformulation, food labeling and media campaigns/consumer awareness) to achieve larger reductions in population-wide sodium consumption (58, 120). The review concludes that a combination of the three components is needed. Evidence from Finland, Japan and the UK support a combination program encompassing product reformulation, food labeling and media campaigns/consumer awareness as well (58, 120). The Finnish population implemented a multi-prong approach in the 1970s, and achieved an average reduction in dietary sodium of 1573 mg/day (58, 61-63). Stroke and CHD mortality fell by 52% and 15%, respectively over 30 years (68, 69). The Japanese government implemented a public education program in the 1960s and over the following decade the mean sodium consumption fell by 550 mg/day (66). Stroke mortality was estimated to fall by 43% over 20 years (124). In the UK, from 2004 to 2011, the population experienced a mean dietary sodium reduction of 551 mg/day (33). This reduction in population sodium intake was associated with a reduction in stroke and CHD mortality by 42% and 40%, respectively. The parallel change in mean SBP and DBP was -3.0 ± 0.33 and -1.4 ± 0.20. The successes experienced in these countries set an example for other countries to follow.

Canada was one of the countries to follow the example set by the UK, and started working towards creating a national effort to reduce dietary sodium consumption; however, it has not been as successful as the UK's program. The expert Sodium Working Group (SWG) in Canada was formed in 2008, and was responsible for creating a population health strategy to reduce dietary sodium intake in Canadians. After the SWG released their report in 2010, the Canadian Health Ministers met and agreed to lower the average Canadian sodium intake to an interim target of 2300mg/day by 2016 (125). This was the same target recommended by the UK. To achieve this target goal, the SWG suggested the following strategies: 1) creating voluntary sodium reduction targets in the food supply; 2) public educational awareness campaign; 3) food science and health research related to sodium; and 4) monitoring of sodium consumption levels and program evaluation. This multi-pronged approach was similar to the UK approach.

Similar to the UK, the majority of the sodium content in the Canadian diet is found in processed and commercialized foods (restaurants, fast-food chains etc.) (123, 126). In Canada, of the estimated average sodium consumption of 3800 mg/day, 77% is from processed food, 12% is naturally occurring, 6% is added at the table, and 5% is added during cooking. The main source of dietary sodium is processed food, fast food, restaurants and takeaways (121). The consumer has little control over the amount of sodium that is added in this food type. Canada would need the food industry to reduce the sodium content in their food products by about 40% to achieve the target sodium consumption of 2300 mg/day (127). The SWG determined the major dietary sources of sodium, and how to reduce sodium additives in various food categories to achieve dietary sodium intake targets. The Federal Minister disbanded the SWG in 2011, and there was no longer a group that could monitor whether companies reduced the level of sodium in their

food products (121). Provincial and Territorial governments released a "Reducing the Sodium Intake of Canadians: A Provincial and Territorial Report on Progress and Recommendations for Future Action" (19) in response to Health Canada not moving forward with the recommendations of the SWG. In 2012, the Canadian government responded by releasing sodium benchmarks for food products; and the food industry was to voluntarily reach these benchmarks by December 2016. However, without monitoring and evalaution, and federal leadership, the voluntary approach was not as successful as it has been for other countries, such as the UK.

Reducing sodium content in processed food is complex and there has been resistance from the food industry (127). Changes in sodium additives are often detectable and alter the taste of the food product, which could result in consumers changing their preferences to another food product. There is also no single replacement for sodium additives, and food manufacturers face technical challenges, and extra cost in making modifications to the sodium content of foods. A recent study found that only 16% of food categories showed a statistically significant reduction in sodium content from 2010 to 2013 in Canada (128). While some effort has been made by the food industry to reduce sodium content in food products, much progress still needs to be made. The voluntary approach lacks substantive and timely progress; thus, raising questions about the effectiveness, and sustainability of a voluntary approach to reduce sodium levels in processed and packaged foods.

A mandatory reformulation strategy would help drive the food industry to make changes in the sodium content of their food products. Mandatory reformulation strategies are being

recommended to achieve larger reductions in dietary sodium intake vs. voluntary reformulation (127). A successful example of this was in Denmark. Denmark moved from voluntary agreements on trans-fatty acid reduction to a legislative ban of trans-fatty acids. This mandatory regulation has led to rapid and large reductions in the trans-fatty acid content in processed food (119). Although the UK salt reduction program had been carried out successfully on a voluntary basis, sustained media pressure, and direct pressure from a quasi-government agency and non-governmental organizations was also used to ensure food manufacturers reduced salt and met the targets. This led to nearly all food manufacturers, retailers and trade associations, along with several catering companies agreeing to start reformulation. The UK also implemented a monitoring strategy, which was essential to ensure the food industry was meeting targets. To improve the success of population-wide dietary sodium reduction in Canada, the federal government may need to either introduce a mandatory regulatory approach or place higher pressure on the food industry to meet sodium reduction benchmarks for the different food categories. A sodium-monitoring program is also needed to ensure the food industry is staying on track to meet the federal interim target.

Another key component for Canada to be successful in the implementation of a population-wide sodium reduction strategy is to improve the food labeling system. Evidence from the UK and other countries supports that a clear labeling of food products is necessary for consumers to understand how much sodium they are consuming. The UK implemented a "traffic light" labeling system (65, 129). This is a color code on food packages of Green, Amber or Red for low, medium and high amounts of salt, fat, sugar and calories. This labeling system has already been shown to affect food purchases, especially when it is the Red category (65). Until

recently, Canada has largely focused on teaching consumers how to read food nutritional labels. In October 2016, Health Canada announced a multi-year Healthy Eating Strategy, in which the government is updating the nutritional tables found on food labels to help consumers make informed decisions about which food products are healthy options (130). To complement this strategy and aid in its success an effective public health campaign may be beneficial.

A public health education campaign implemented in UK that aimed to increase awareness of the detrimental health effects of excess sodium consumption, encouraged reduction of sodium additives in cooking, and taught how to read food product labels was successful in helping reduce population dietary sodium intake (70). This led to an additional 20 million people in the UK saying they would cut dietary sodium consumption, and half of them said they now check food labels (120). Similar to the goals of the consumer awareness campaign in the UK, Canada created a small task force to develop and array of tools to disseminate information to the public, healthcare professionals, and policy makers (127, 131). Canada implemented a sodium awareness public health campaign between 2012 and 2014. The availability of data assessing the effectiveness of the awareness campaign is limited. Provincial governments and non-governmental organizations were primarily responsible for conducting these consumer awareness campaigns, and there remains a lack of a standard campaign strategy that cuts across all provinces and territories, and limited participation of the federal government to provide resources to support these programs.

In summary, while Canada has begun to enact dietary sodium reduction policies, progress has been limited. The Provincial governments cannot mandate/regulate sodium, and need the

Federal government to either introduce a mandatory regulatory approach or place a higher pressure on the food industry to meet sodium reduction benchmarks. With Health Canada's recent implementation of Healthy Eating Strategy, the government seems to be applying pressure to the food industry to make changes. Recently, the Prime Minister mandated to the Minister of Health to implement strategies aimed at reducing dietary sodium. A stronger sodium-monitoring and evaluation program would also be needed to ensure food industry is staying on track to meet dietary sodium target goals, and analyze if current strategies are effective. Lastly, an educational campaign to bring awareness to the detrimental health effects of excess dietary sodium consumption would be needed to help change consumer behavior. There would also be the need to educate consumers on how to read nutritional food tables, which can be confusing, to help them make informed choices about healthy food options. By improving the above components, Canada could achieve a more successful national population-wide dietary sodium reduction strategy.

4.4: Population Models in Decision Making

CVD is a leading cause of death in Canada, and a burden on the healthcare system with substantial financial and societal costs. There is great emphasis to implement public health programs that can help reduce the prevalence of CVD and its costs, and to improve health outcomes (132). In Canada, there is an increasing reliance on simulation models to project future incidence and prevalence of risk factors and diseases, and future demands of healthcare resources (133, 134). The population modeling from this study can play an important role in helping inform decision makers about the effectiveness of a population-wide sodium reduction strategy.

The Canadian CVDPM simulates individuals' disease states and risk factors to describe and project health outcomes, allowing policy makers to have an understanding of population health benefits, and implications of resource allocation, when making decisions regarding the comparative benefits of a range of health interventions (135). This is incredibly important in a public healthcare system, where resources are limited. CVD is also a complex disease process with multiple contributing risk factors, adding to the complexity of evaluating CVD health intervention programs with only an observational study or a simple regression model (136).

The Canadian CVDPM integrates various Canadian data sources, allowing the evaluation of health intervention programs to determine the impact of policy/public health programs in the Canadian context. Further, the US CVDPM has been validated in multiple studies (80, 91, 92); therefore, the model outcomes are reliable estimates of a real life situation. Strengths of our study include its reliance on the best available evidence for the effect of sodium reduction on SBP. We based our effect estimates on a meta-analysis of RCTs. Further, the adaption of CVDPM to the Canadian context permits generalizability to Canadians. Most importantly, we performed a set of robust sensitivity analyses allowing for the consideration of realistic possibilities and interpretations of the data.

Traditionally, policy and program evaluation has typically been undertaken after implementation in population health. This approach can be very costly in terms of failing or encountering unforeseen consequences from a policy/program (136). Using a population mathematical model like the Canadian CVDPM allows a policymaker to examine the expected

outcomes, consequences, and benefits of a policy/program in advance of implementation; therefore, playing an important role in public health planning (136).

4.5: Limitations

Our analysis has some limitations. Models are subject to the limitations of the data sources used to determine model inputs, though we did our best to use the best available and most representative data, including Statistics Canada health surveys and national administrative health data from CIHI, as well as effect estimates from a large Cochrane meta-analysis. Assumptions were made in order for the model to be usable and manageable. We assumed that a reduction in dietary sodium would lead to a drop in mean SBP. We also assumed the inverse relationship with an increase in dietary sodium consumption. This study did not include indirect costs, or long-term care costs, which would have led to an underestimation of overall costs. When we were identifying high BP individuals from the CHMS data, we did not adjust for comorbidities such as diabetes, which would have redefined the SBP range of someone being considered hypertensive; therefore, our outcomes would be underestimates because the mean change in SBP applied to these individuals would be based on the normotensive mean change. We also only considered mean changes in SBP not diastolic blood pressure from a dietary sodium reduction; therefore, our overall drop in BP could potentially be more significant resulting in an underestimation of our outcomes. The Canadian data sources also have limitations. All administrative health data sources are prone to miscoding, including diagnostic codes, procedure codes and causes of death. Surveys (i.e., the CHMS) are prone to sampling error as well as recall bias. The Canadian Census is also not fully representative of the Canadian population. Extensive sensitivity analyses were conducted to test the effect of these potential

limitations. In the hypertension management cost analysis, individuals taking a BP lowering medication, who maintained controlled SBP <140 mmHg even after BP medication adjustment and before dietary sodium reduction, were not excluded from the cost analysis. This could have resulted in an overestimation of costs savings; however, controlled SBP thresholds of ≤120 mmHg and ≤130 mmHg were also applied and these provide more conservative savings estimates. Finally, we did not attempt to account for the association between dietary sodium and/or BP, and other conditions (e.g., kidney disease, dementia, gastric cancer, etc.), and any reduction in risk associated with a decrease in dietary sodium. Our analysis therefore likely underestimates the benefit of decreasing dietary sodium.

Chapter 5: Conclusion

An extensive amount of literature links higher dietary sodium consumption with increased blood pressure, and increased CVD risk. Our study demonstrated that the risk of CVD and its subsequent costs and adverse health effects could be decreased by reducing dietary sodium; therefore, leading to significant benefits to the healthcare system and the Canadian population. Canada has begun the implementation of a population-wide dietary reduction strategy modeled after that of the UK. For the strategy to be more successful in Canada, the Federal government should apply continued pressure on the food industry to meet sodium reduction benchmarks. Implementation of a sodium-monitoring program would also help to ensure the food industry is staying on track to meet the sodium benchmark targets, and monitor the population to further understand dietary sodium consumption patterns. A population-wide reduction in dietary sodium could substantially decrease healthcare costs and improve health outcomes. The results of this work may be useful to policy makers in revising Canadian sodium regulation and policy.

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Supplementary Appendix

Appendix A: More Details of the CVDPM

CVD Risk Factors

Risk factor variables included in the model are systolic blood pressure, cholesterol levels (high and low density lipoprotein concentrations), BMI, cigarette smoking status and presence of diabetes mellitus. The CHMS and the CCHS 2007-2013 surveys were used to estimate these risk factors for the Canadian adult population. Prevalence of CVD by age and sex was determined by self-report of a history of heart disease or stroke. The quantitative risk factors the proportion of Canadians that fall into each cutoff group were estimated and the mean value in each group was determined.

CVD Events and Procedures

The 2012 CIHI Discharge Abstract Database was used to collect number of cardiovascular events (myocardial infarctions, cardiac arrests, cases of stable/unstable angina, congestive heart failures, and strokes) and number of coronary artery revascularizations (coronary artery bypass grafts and percutaneous coronary interventions).

Mortality Rates

The Discharge Abstract Database and National Ambulatory Care Reporting System were used to collect in-hospital related CVD deaths (myocardial infarction, stroke and coronary artery revascularization). Vital Statistics Canada was used to determine all other remaining (non-CVD) deaths.

Utility

In the model, the population was assigned a QALY weight for each health state based off of utility and disutility weights for CVD history and CVD events, respectively. The condition-specific health-related quality-of-life weights were based on the 2010 Global Burden of Disease (GBD) disability weights study (76, 84, 111). The study was also used to estimate short-term disutility values for experiencing CVD events. The GBD study is an epidemiological study examining the trends, injury incidence, prevalence and years lived with disability for 188 countries between 1990-2013 for 291 major diseases and injuries (29). Murray and colleagues provide more details of the study (76). The GBD study uses disability adjusted life years (DALYs), which are the sum of years of life lost due to premature morality and years lived with disability. The term disutility in this study refers to loss of any short or long term functioning, other than death, in terms of mobility, pain, affect and cognition. All utilities besides the short-term disutility of a stroke event were assumed to be the same by age and sex.

Costs

The model includes four types of health care costs, which are the following:

- CVD event and procedure costs (0-29 days following an event or procedure)
- Post-event CVD-attributable costs (30-364 days following an event or procedure)
- Health care costs not attributable to CVD
- The health care costs of 95-year-old survivors who exit the model

All costs were inflated to 2014 Canadian dollars using Statistics Canada's consumer price index (137). Costs were also stratified by age group, sex and are fixed in the model. Consistent with Canadian guidelines, costs will be discounted 5% annually (40).

Every CVD event and procedure in the model has an associated cost for the day the event occurred and the proceeding 29 days. Post-event CVD attributable costs are assigned to all individuals every year who have had a CVD event or procedure previously. The data source for these two types of costs were taken from Alberta administrative health care usage data from Alberta Health and via the Alberta Kidney Disease Network for 2010/11-2012/13 (108, 109). This administrative data source includes health care encounters for all residents with public health insurance, accounting for >99% of the population. These health administrative data include CVD-related and non-CVD-related encounters for hospitalizations, physician claims, and ambulatory care (emergency room, day surgery costs, diagnostic imaging). They also include prescription medication costs for residents aged 65 years of age and older because only these individuals have a universal publicly funded drug plan. These data do not include drug costs for those less than 65 years of age, long-term care use, rehabilitation, capital costs, and costs for other health professionals and their services (dentists, optometrists, physiotherapists, home care nurses). Hospitalization costs were calculated using the Canadian Institute for Health Information's case mix grouper system (138). All the costs of a hospitalization were assumed to be accrued on the start date of the hospitalization. Ambulatory care usage was costed in a similar way using Alberta's Ambulatory Care Classification System groupers (139). Physician claims costs are the total amount paid by the government, and total prescription drug costs were available for dispensed medications.

Healthcare costs not attributable to CVD are assigned every year to individuals in the model with and without CVD. The Canadian Institute for Health Information's publically available National Health Expenditure Database (the 1975 to 2015 expenditure report) (110) was

used to calculate the average annual non-CVD healthcare. These costs include spending on hospitals, other institutions, physicians, other professionals, drugs, capital, public health, administration, and other health spending (spending on capital, public health, administration, and other health spending was distributed evenly among the ages and sexes, regardless of utilization). They exclude federal and municipal government spending on health, as well as individual and private sector healthcare spending.

The costs of 95-year-old survivors who exit the model are assigned a healthcare cost for their remaining lifetime. Alberta Health administrative data is used again to estimate mean costs after their 95^{th} birthday to their death. This cost is dependent on sex but not on CVD status or CVD risk factors.

Appendix B: Results

Table 18: Percentage of Canadian population taking an anti-hypertensive medication stratified by age and sex

Sex	Age	Percentage of population (%) taking an anti-hypertensive medication for each SBP		
		<130 mm Hg	130-139 mm Hg	140+ mm Hg
Male	25-34	1.1	3.0	6.5
	35-44	6.2	5.9	12.4
	45-54	15.2	35.8	53.2
	55-64	24.2	48.4	26.1
	65-74	49.2	46.3	44.9
	75-84	54.8	71.3	65.5
	85-94	54.8	71.3	65.5
Female	25-34	0.9	7.3	26.7
	35-44	2.2	5.0	19.4
	45-54	15.8	21.9	31.1
	55-64	22.8	40.1	37.0
	65-74	39.1	62.2	65.9
	75-84	50.3	42.3	65.5
	85-94	50.3	42.3	65.5

Table 19: Upper and lower bound confidence interval mean changes in SBP for dietary sodium reduction levels of 1800 and 1500 mg/day stratified by sex and age group

Sex	Age group	SBP change from sodium reduction in respective SBP categories (mm Hg)											
		1800 mg/day sodium reduction LCL			1800 mg/day sodium reduction UCL			1500 mg/day sodium reduction LCL			1500 mg/day sodium reduction UCL		
		<130 mm Hg	130-139 mm Hg	140+ mm Hg	<130 mm Hg	130-139 mm Hg	140+ mm Hg	<130 mm Hg	130-139 mm Hg	140+ mm Hg	<130 mm Hg	130-139 mm Hg	140+ mm Hg
Male	35-44	-3.73	-3.72	-6.62	-2.24	-2.23	-4.15	-3.25	-3.24	-5.76	-1.95	-1.94	-3.61
	45-54	-4.01	-4.64	-6.62	-2.42	-2.84	-4.15	-3.49	-4.04	-5.76	-2.11	-2.47	-3.61
	55-64	-4.28	-5.03	-6.62	-2.60	-3.10	-4.15	-3.73	-4.38	-5.76	-2.27	-2.70	-3.61
	65-74	-5.06	-4.97	-6.62	-3.11	-3.05	-4.15	-4.40	-4.32	-5.76	-2.71	-2.66	-3.61
	75-84	-5.23	-5.74	-6.62	-3.23	-3.56	-4.15	-4.55	-4.99	-5.76	-2.81	-3.10	-3.61
	85-94	-5.23	-5.74	-6.62	-3.23	-3.56	-4.15	-4.55	-4.99	-5.76	-2.81	-3.10	-3.61
Female	35-44	-3.61	-3.69	-6.62	-2.15	-2.21	-4.15	-3.14	-3.21	-5.76	-1.88	-1.93	-3.61
	45-54	-4.03	-4.21	-6.62	-2.43	-2.56	-4.15	-3.50	-3.67	-5.76	-2.12	-2.23	-3.61
	55-64	-4.24	-4.78	-6.62	-2.58	-2.93	-4.15	-3.69	-4.16	-5.76	-2.24	-2.55	-3.61
	65-74	-4.74	-5.45	-6.62	-2.91	-3.38	-4.15	-4.13	-4.75	-5.76	-2.53	-2.94	-3.61
	75-84	-5.09	-4.84	-6.62	-3.14	-2.97	-4.15	-4.43	-4.21	-5.76	-2.73	-2.59	-3.61
	85-94	-5.09	-4.84	-6.62	-3.14	-2.97	-4.15	-4.43	-4.21	-5.76	-2.73	-2.59	-3.61

Table 20: SBP change associated with an increase in sodium consumption for SBP categories stratified by age and sex

Sex	Age	SBP Categories					
		SBP change from 500 mg/day sodium increase			Mean SBP from 500 mg/day sodium increase		
		<130 mm Hg	130-139 mm Hg	140+ mm Hg	<130 mm Hg	130-139 mm Hg	140+ mm Hg
Male	35-44	0.75	0.75	1.57	110.85	135.15	152.07
	45-54	0.83	1.01	1.57	113.63	134.61	149.97
	55-64	0.91	1.12	1.57	114.81	135.22	149.17
	65-74	1.13	1.10	1.57	116.63	135.10	152.97
	75-84	1.17	1.32	1.57	115.07	135.42	153.27
	85-94	1.17	1.32	1.57	112.77	135.92	154.17
Female	35-44	0.72	0.74	1.57	102.82	134.54	148.27
	45-54	0.84	0.89	1.57	109.24	135.29	153.87
	55-64	0.90	1.05	1.57	112.70	134.95	156.47
	65-74	1.04	1.24	1.57	117.34	135.54	154.87
	75-84	1.14	1.07	1.57	118.14	135.17	155.17
	85-94	1.14	1.07	1.57	114.94	135.97	159.67