The Applicability, Usefulness, and Limitations of the PREVENT Model, as Demonstrated by Modeling the Effects of Alcohol Consumption Interventions on Coronary Heart Disease Mortality: Canada, 1992-2040

by

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Abstract

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Coronary heart disease is a major cause of death in Canada. For health care planning, it is important to be able to anticipate future trends in CHD mortality and assess the potential effect of interventions. PREVENT is a population disease model designed to project the effect of interventions in terms of future morbidity and mortality. This paper seeks to provide some evidence for the validity of PREVENT projections by performing sensitivity analyses in the context of estimating the potential effect of interventions on alcohol consumption for projected CHD mortality in Canada. Variables examined are relative risk values, lowest risk category, time spread of the intervention, age group versus cohort analysis, and starting year of the intervention. The results of the analysis do not refute the validity of the model and suggest that PREVENT has the potential to be a useful population disease modeling tool. Suggestions for further refinements are offered.

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1. Introduction

1.1 Rationale

A new imperative for the effective management of scarce health care resources has emerged in this age of fiscal restraint. Called upon to make do with less, health care providers are restructuring in an attempt to maintain the quality of service. For those in primary care, this means amalgamating and downsizing where possible in an effort to reduce redundancy. For many in primary prevention, however, the true measure of success, both in terms of cost-efficient operation and the public good, is maximizing the health of the population such that the demand for scarce health care resources is reduced. As the main provider of health care in Canada, governments have an interest in carefully devising health policies based on the analysis of relevant data such that the impact on the health of the population is beneficial.

Epidemiology, the study of the occurrence and distribution of disease in human populations, should have an important role in the development of these policies. Epidemiologic studies are most commonly designed to determine the aetiology of disease, but as Kelsey et al. [1] observe, epidemiologic studies also play an important role in setting priorities for investigation and control, and deciding where preventive efforts should be focused.

If health care planning means anticipating future population health outcomes and needs, and identifying opportunities for maximizing population health, then epidemiology, in concert with demography, should provide the tools for health policy analysts to achieve these aims. PREVENT, a model developed by Louise Gunning-

Schepers [2], attempts to fill at least part of this need for planning tools. By combining demographic modeling with disease modeling and making use of available data such as relative risks and exposure prevalence estimates, PREVENT provides population estimates of absolute measures, such as, future mortality, future mortality reduction, and potential years of life gained (PYLG). These measures can be useful in allocating resources and identifying opportunities for intervention.

Prevalence of disease, relative risks and odds ratio estimates from epidemiological investigations offer the basic information about diseases and risk factors and are sometimes used in health care planning to justify focusing attention on a particular disease or risk factor. For example, diseases with a high population prevalence are often the focus of attention. Diseases with high relative risks for dramatic outcomes, like death, also garner much attention.

Some diseases fall into these categories, but many do not. There are diseases that individually are not high prevalence or high incidence diseases, but as a group are all strongly related to a specific exposure. If exposure to this risk factor is reduced, the incidence of the entire group of diseases could be reduced. Other diseases are highly prevalent but only weakly associated with known risk factors, meaning that opportunities for intervention may not be great. Still others produce significant morbidity in a large proportion of the population but almost no mortality. For some diseases, the impact on a population is not static. Changing demographics, exposures to risk factors, and treatments over time mean that the population impact of a disease today may not be indicative of the future.

Clearly, disease prevalence and relative risk estimates alone do not provide the entire picture. With such variation in the impact of diseases on a population, and in the state of knowledge about risk factors for diseases, it is important for health care planners to carefully analyze available data before investing in treatment and prevention programs. More specifically, the health care planner with an interest in the general health of the population must be able to:

(1) anticipate the impact each disease will have on the population, and

(2) identify opportunities for intervention to reduce the impact of each disease.

This type of knowledge will help health care planners manage their resources to meet anticipated tertiary care needs and where possible fund primary prevention programs to ultimately reduce the demand for tertiary care services.

This is where the PREVENT mathematical model may be of use. Implemented as a microcomputer program, it was designed to use epidemiologic and demographic data to provide projections that can inform health care planning. It is an attributable-risk based model that transforms epidemiological data such as exposure prevalences and relative risks into absolute population health measures like mortality, PYLG, or morbidity. It is designed to be neither disease nor risk factor specific, but is a general tool that theoretically may be used for any set of disease and risk factor combinations.

The research findings presented in this paper are the results of a PREVENT analysis assessing the effect of theoretical alcohol consumption interventions on projected population mortality from coronary heart disease (CHD) in Canada. The weight of evidence from epidemiological studies conducted over the past twenty years generally supports the idea that a J-shaped or U-shaped curve best describes the relationship

between alcohol consumption and mortality from CHD. Non-drinkers and drinkers at the higher end of the alcohol consumption spectrum have a higher mortality from CHD than drinkers in middle categories. The theoretical interventions examined in this paper attempt to reduce CHD mortality by moving non-drinkers or abstainers and drinkers at the higher end of the spectrum (the cut-off point is varied) to intermediate levels of alcohol consumption.

This should not be interpreted to mean that the above intervention is advocated as good health care planning. Alcohol has consequences for diseases other than CHD (e.g., breast cancer) and it may be that the adverse consequences of intermediate levels of alcohol consumption outweigh the benefits (at least in terms of the mortality). A comparison of the intervention effect on different diseases is needed before the adoption of such an intervention can be justified. However, such a comparison has itself an important prerequisite: evidence for the validity of the model used in the comparison. This paper will present the results of a sensitivity analysis designed to provide some information about the validity of PREVENT as a modeling tool.

The question of validity is important for all population models. The validity of the results depends on the credibility of the data used as input to the model and the methodology used in the model [2]. The literature review in the Background section examines the alcohol/CHD relationship and specific criteria are applied for selecting studies for use in this analysis in an effort to use the most credible data available.

The Background section also provides a description of the methodology which PREVENT uses, in comparison with other models, and the Discussion section delves into the strengths and weaknesses of PREVENT's methodology. The sensitivity analysis tests

whether the model produces results that are congruent with expectations, i.e.., does projected mortality reduction per year change in the expected direction when the relative risks used as input data are changed?

It should be noted, however, that the sensitivity analysis alone cannot confirm the validity of the PREVENT model. In her original publication, Gunning-Schepers [2] explored the validity of the PREVENT model through both historical testing and sensitivity analyses. Historical testing can be used for testing models that simulate future developments. Historical exposure data is used as input into the model, and the outcome projections produced by the model are compared with historical outcomes. Gunning-Schepers explored the development of smoking-related lung cancer mortality in the Netherlands between 1970 and 1984. Unfortunately, in most countries the detailed historical prevalence data available for smoking are not available for most other risk factors (including alcohol consumption), making historical testing impractical for many risk factor/disease combinations.

Gunning-Schepers also performed some sensitivity analyses for various risk factor/disease combinations. A sensitivity run simply examines how sensitive the model is to variations in the initial input data. "Input data" can take the form of epidemiological or demographic data or they can be various analysis options. Gunning-Schepers examined the effect of varying relative risk values, prevalence values, and time dimension variables. This study will examine some of the variables examined by Gunning-Schepers and others which she did not examine. In her paper, Gunning-Schepers reported that the model responded as expected to changes in input data. This paper will also present the results of sensitivity analyses, but in the context of alcohol consumption and CHD mortality.

1.2 Objectives

This paper presents the results of sensitivity analyses on CHD mortality reduction. Variables examined are relative risk values, lowest risk category, time spread of the intervention, age group vs. cohort analysis, and starting year of the intervention. Values for some of these variables are not derived from the literature, either because little information is available about them or because they are analysis options in PREVENT rather than population estimates. They are nonetheless included in the sensitivity analyses because the purpose of the analyses is to confirm that CHD mortality reduction varies in the expected direction with variation in input. This test can be performed for both analysis options and population estimate input data. Examining the model in the context of alcohol and CHD serves a dual purpose. First, it provides an opportunity to test the effect of a theoretical intervention on alcohol consumption, and second, it provides information about the performance of the model in a context other than smoking/lung cancer. For a model which is ideally applicable to any set of risk factors and diseases, it is important to test its performance in different risk factor/disease scenarios.

Specifically, the objectives of this research are:

(1) to use the PREVENT model to estimate the potential effect of interventions on alcohol consumption for projected CHD mortality and related measures in Canada, and

(2) to provide some evidence for the validity of the results in (1) by performing sensitivity analyses with PREVENT.

The results of the sensitivity analyses detail both the direction in which the results move in response to variation in input data, and the magnitude of the sensitivity of the results to variation in input data. The former is necessary for establishing the validity of the model (the model should respond in a way that one would expect based on the change in input data) and the latter quantifies uncertainty in the results, if the methodology used by the model is valid. As mentioned above, another important part of establishing validity is comparing the model's output with historical data or with prospectively collected data. This analysis does not involve a historical run because historical data for the alcohol consumption/CHD combination is not available at the required level of detail (in fact, a historical run is only practical for a very small number of risk factor/disease combinations). This means that further work on the validity of the PREVENT model will depend on comparisons with prospectively collected data. Such a comparison is beyond the scope of this study; only the results of a sensitivity analysis are presented here.

If the sensitivity analysis fails to produce changes in results that would be expected based on changes in initial input, the validity of the model is thrown into question and it may be that some of the problems or issues raised in the Discussion section may need to be addressed before valid results can be produced. If support for the validity of the results is found as a result of the sensitivity analysis, and further research establishes the validity of the model through comparisons with prospectively collected data, then it may be possible to have greater confidence in PREVENT runs which compare the effect of interventions on a risk factor for different diseases (e.g., alcohol, and breast cancer vs. CHD) -- a necessary step before anything can be said about the overall health benefits or disadvantages of intervening on exposure.

2. Background

There are a number of components involved in projecting the effect of a risk factor intervention on a related health outcome. First, it is necessary to be clear about the health outcome(s) of interest. Health outcomes commonly used in health research include mortality, potential years of life lost (PYLL), and morbidity measures. Yet, there is no theoretical reason why other outcomes, such as sick days, lost wages, and hospital length of stay cannot be used. Many risk factors are associated with multiple health outcomes, and it is possible that an analysis using one outcome will produce results that contradict an analysis using another outcome. Section 2.1 will present justification for the choice of CHD mortality as the outcome of interest in this analysis.

Second, it is necessary to collect as much information as possible concerning the relationship of the risk factor to the health outcome of interest. Section 2.2 provides a brief review of the literature on the relationship of alcohol consumption and CHD mortality, a subject of considerable debate over the past decade. This analysis will necessarily take one point of view in this debate.

Finally, a method of producing projections must be explicitly chosen. A survey of different models that have been used for CHD mortality projections in Section 2.3 will make it clear that there are a number of different ways of approaching the same problem. Each of these approaches has strengths and weaknesses. An explanation for the choice of PREVENT as the model for this analysis is presented.

2.1 Selection of the Health Outcome of Interest

Alcohol consumption is associated with many outcomes. Some are accident-related injuries due to the physical impairment induced by alcohol, such as falls and motor vehicle (car, snowmobile, and boat) accidents [3]. Others are diseases, such as CHD, liver cirrhosis, and breast cancer [4], which can vary in severity and mortality rate. And still others are social consequences of alcohol consumption -- inability to hold employment, family dysfunction, and engaging in fights.

This analysis will focus on the effect of alcohol on CHD mortality, CHD mortality reduction, and potential years of life gained. There are a few reasons behind the choice of CHD mortality as the principal outcome of interest. First, CHD is one of the most important causes of death in the Canadian population. Thus, a study that examines CHD mortality is relevant and likely of interest. Second, it is an outcome for which data are available because most CHD deaths are recorded on the death certificate (data quality is always an issue but difficult to address at a national level). Other outcomes, e.g., family dysfunction, may be just as interesting, but their prevalence at a national level is difficult to determine because data collection is not mandated by law in a way that the cause of death must be ascertained and recorded. Thus, while it may be possible for a cohort or case-control study to collect information on family dysfunction, there are no national databases with this type of information that can be readily used for population projections. Third, while it is possible to use CHD morbidity rather than CHD mortality as an outcome, there is a greater chance that CHD events that do not result in death are not recorded because an individual may not go to hospital. Finally, population-based case registries do exist for CHD mortality.

It should be clear that while narrowing the focus to mortality turns this analysis into a more practical undertaking, it also precludes any general conclusions about the benefits or disadvantages of alcohol consumption. The conclusions reached will necessarily address only the relationship between alcohol and CHD mortality.

2.2 Alcohol and CHD

2.2.1 Health Effects of Alcohol Consumption

Liver cirrhosis is perhaps the disease most widely recognized as being associated with alcohol consumption [5], but evidence has accumulated over the years for a relationship with primary liver cancer, cancer of the oropharynx (in men), cancer of the larynx (in men), cancer of the esophagus (in men), rectal cancer (in beer drinkers), and breast cancer (in women) [4]. Anderson et al. [4] reviewed 156 papers in an effort to summarize findings on the risk for disease from alcohol consumption; nineteen of the 24 papers (80%) examining the relationship between alcohol and hypertension found a significant dose-response relationship in men. Heavy drinking has been found to be a risk for atrial arrhythmia [81 82], and alcohol is a risk factor for cardiomyopathy [82].

Some evidence for a J-shaped relationship between alcohol consumption and ischemic stroke exists [6 7], and a minority of researchers assert that the relationship between alcohol and hypertension is J-shaped [8 9]. However, the most commonly found J-shaped relationship is the one that appears to exist between alcohol consumption and CHD mortality (a J-shaped relationship exists between alcohol consumption and overall mortality [10 11] but this appears to be driven primarily by CHD mortality). The literature describing the relationship between alcohol consumption and CHD mortality is reviewed in Section 2.2.3.

2.2.2 Risk Factors for CHD

There is a large body of literature describing prospective studies designed to elucidate the aetiology of CHD at a population level. About 30 such studies have been conducted in Europe and the Mediterranean area, 25 in North America, and another five in other parts of the world over the past 25 years [12].

Despite the diversity of methodologies used and populations considered in these studies, a generally well accepted group of risk factors has emerged for CHD. Of primary importance are smoking, physical inactivity [78 79], elevated blood pressure, and above-optimal levels of total serum cholesterol, all of which exhibit direct relationships. Diabetes, male gender, and older age are also risk factors but the low prevalence of diabetes, the static nature of gender, and the inevitability of aging diminishes the potential of these risk factors [13] for public health interventions. Other potential risk factors, still debated in the literature, include physical height (negative association), body mass index (U-shaped relationship), and alcohol consumption (U- or J-shaped relationship).

Few studies have examined whether there is a difference in risk factors for CHD incidence and CHD mortality. Håheim et al. found that although the strength of the association differed for some risk factors (blood pressure and daily cigarette smoking), all of the variables they examined were risk factors for both CHD and death from CHD [14].

2.2.3 Relation between Alcohol Consumption and CHD

A number of investigators have found a J-shaped curve for the relation between alcohol consumption and CHD mortality, such that abstainers and excessive drinkers are at higher risk of death than those who consume intermediate amounts of alcohol [11 15 16]. Indeed, most have found a protective effect associated with moderate alcohol consumption [17].

This finding has been controversial, because others suggest that the apparent protective effect of alcohol for abstainers is confounded by previous health status [10 18 19 20].

Previous health status is an issue because, in some studies, abstainers include those who were formerly drinkers, but gave up alcohol for reasons of poor health, or who have never drunk for reasons of poor health [10]. It is also possible that some abstainers are previous excessive drinkers with a higher risk for health problems [18 20]. There is a great deal of variation among studies in the degree to which possible confounders like smoking, diet, previous health status, and previous drinking status have been controlled.

Most epidemiologic investigations of alcohol and CHD have been based on samples of western, middle-aged men. Fuchs et al. explore the question of the relationship between alcohol and CHD mortality for women and find that the excess risk for female drinkers begins a lower volumes of alcohol consumption [21].

Examining the question of whether different types of alcohol (i.e. wine, beer, spirits) have differential effects on CHD incidence, Rimm et al.[80] reviewed 12 ecological, three case-control, and 10 separate prospective cohort studies. They concluded that there was evidence for a reduced risk of CHD with all types of alcohol consumption and that a substantial part of the cardioprotective effect is derived from alcohol rather than other components of each type of drink.

Two hypotheses concerning the biologic mechanism for the protective effect of alcohol on CHD have garnered attention [22 23]. First is the idea that the cardioprotective effect of moderate alcohol consumption could be mediated by its effects on HDL-cholesterol. It is thought that alcohol consumption results in higher levels of HDL-cholesterol which has been associated with reduced risk for CHD. Support for this view

has been found in analysis of data from the Multiple Risk Factor Intervention Trial (MRFIT) [24]. In a review of the literature, Srivastava et al. conclude that there are two plausible hypotheses for the exact molecular mechanisms [25]. First is the theory that alcohol may raise HDL levels by direct stimulation of liver lipoprotein synthesis and secretion, secondary to ethanol's induction of microsomal enzyme activity. Second, is the idea that alcohol may raise HDL levels by enhancing lipoprotein lipase activity in tissues outside the liver, thus promoting transfer of surface components from VLDL and chylomicrons to nascent HDL particles. It has been suggested that alcohol-modified LDL is cleared from the circulation at a faster rate than native-LDL and that alcohol-induced HDL particles are cleared at a slower rate than the native particles.

The second hypothesis concerns alcohol's inhibitory effect on platelet aggregation and thus on blood clot formation, an important element in myocardial infarction [26]. The exact mechanisms by which alcohol achieves this anti-clotting effect are unclear.

It is worth noting that behind the scenes of some epidemiologic investigations is the vested interest of the large wine, beer, and hard liquor industries. The alcohol industry does fund and promote research that confirms a protective effect of moderate alcohol consumption, and this may skew the literature in favour of the cardioprotective effect of alcohol. There are also a few researchers not funded by industry who challenge a public health policy that discourages alcohol use. Nonetheless, such potential conflicts of interest should be noted.

The purpose of this paper is not to delve into the debate surrounding the U- or J-shaped curve, but to produce estimates of the effect of interventions on alcohol consumption for future CHD mortality, assuming the U- or J-shaped curve is correct. If

the U- or J-shaped curve is not correct, a similar analysis could be done, but the intervention in question would encourage reducing alcohol consumption for all individuals in the population.

2.3 Modeling CHD Mortality and the Effect of Interventions

Projecting the evolution of a given population and assessing the effect of interventions on the population involves developing an underlying model. Most population models are computation intensive and thus typically implemented as computer programs. Over the years, a number of computer models aimed at estimating the impact of risk factor prevalences on disease incidence and mortality have appeared. Most of these models can be classified as one of three types:

- logistic models
- microsimulation models
- attributable risk models

This section reviews some of the models in these three general categories, finishing with a brief description of the PREVENT model and an explanation for the choice of PREVENT over other models for this analysis. A table summarizing all of the models reviewed is provided at the end of Section 2.3.

2.3.1 Logistic Models

McGill Cholesterol Model

In an effort to evaluate the lifetime benefits of reducing total serum cholesterol levels to prevent CHD, Grover and colleagues developed a logistic regression model using Framingham data [27]. The primary model estimates the probability of dying from CHD and the probability of a CHD event as a function of age, diastolic blood pressure, total

serum cholesterol level, the presence of glucose intolerance, and smoking status. For men, the model for the annual risk of all CHD events (myocardial infarction, uncomplicated angina pectoris or coronary insufficiency, CHD death, all CHD events, and non-fatal CHD) was as follows:

$$Risk = \alpha + \beta_1 Age + \beta_2 Age^2 + \beta_3 CHL + \beta_4 DBP + \beta_5 SMOK + \beta_6 LVH + \beta_7 GLU + \beta_8 (CHL)(AGE)$$

This risk was adjusted for the level of high-density lipoprotein (HDL) using a gender specific modifier (HDL_{mod}) to produce an annual probability of a CHD event:

$$\text{Prob} = HDL_{\text{mod}} \times \frac{e^{RISK}}{1 + e^{RISK}}$$

The model was validated using data from three primary prevention clinical trials: the Helsinki Heart Study, The Lipid Research Clinics Coronary Primary Prevention Trial, and The Multiple Risk Factor Intervention Trial (MRFIT). The authors conclude that the model accurately predicts the results of these trials.

The model has been validated using clinical trials that involved middle-aged men, and it is uncertain how the model performs with other populations such as women and the very old. Also, since this model does not have a separate demographic modeling component, population structure changes (e.g., immigration) are not taken into account. It would be premature to use this model as a population model of the effect of cholesterol level modification on CHD incidence although further modifications may produce a model that can be used for this purpose.

2.3.2 Microsimulation Models

POHEM

POHEM is a population health model based on microsimulation modeling [28]. In contrast to many other models which simulate changes at a population or cohort level, POHEM simulates at the level of the individual. The model first generates a population of individuals based on starting parameters describing the population. This population can then be followed forward in time with adjustments made according to the probability of individual life events (i.e., mortality, morbidity) occurring. Population survey data are used to estimate these probabilities of life events, and Monte Carlo techniques are used to assign life events to specific individuals. Population health outcomes can be obtained by aggregating across individuals in the population.

The state variables used in the modeling are socioeconomic status variables (e.g., education, marital status, labour force participation, income), risks (e.g., smoking cholesterol, blood pressure, obesity), diseases (e.g., CHD, cancers, dementia, arthritis), and functional status, costs, and health (e.g., utility scales).

POHEM is able to model multiple disease and risk factors and report multiple outcomes such as mortality, morbidity, and costs. The theoretical framework on which POHEM is based is comprehensive in design because POHEM takes a broader view of health than many other models. Unfortunately, this also increases the complexity of the model. More importantly, perhaps, the input data required to implement a model of a more comprehensive view of health are often not available at a population level and thus, in practical terms, POHEM is not able to offer anything more than models based on available data.

CRISPERS

The Chronic Disease Risk Intervention Simulation Program for Epidemiologic Research Studies (CRISPERS) is a generalized Monte Carlo simulation system for chronic disease [29]. Like POHEM, simulation begins with a population of individuals that are synthetically generated using Monte Carlo techniques to assign risk probabilities of health events. An 'event' occurs for an individual if the assigned random number for an individual falls within a set range determined by the overall event probability. Health outcomes at the population level (e.g., morbidity, mortality) are obtained by summing individual health status across all individuals in the population.

CRISPERS has been used to model CHD, but is limited by its inability to model more than one disease at a time. It is able to model multiple risk factors, adjust for demographic changes in a population, and account for the latency period between disease incidence and mortality. It was not originally designed to assess the impact of interventions, but a sub-program called CRISPERT has been developed to support intervention modeling [30]. CRISPERS is a mainframe based program.

2.3.3 Attributable Risk Models

SAMMEC and ARDI

Two programs developed for the Center for Disease Control, SAMMEC II and ARDI, are implementations of an attributable risk based model on a microcomputer to calculate deaths, PYLL, health-care costs, indirect mortality costs, and disability costs associated with cigarette smoking and alcohol use.[31 32]

SAMMEC II and ARDI use diagnosis-, sex-, and age-specific (0-34, 35-64, 65

plus) relative risk estimates for exposure-related diseases. Estimates of current and former smoker or drinker prevalence must also be available. The user enters the number of deaths in the population by five-year age groups and sex for each exposure-related diagnosis. For each age group and sex, the exposure-attributable mortality is then calculated by multiplying the number of deaths by the population attributable risk.

Exposure-attributable mortality = Deaths x PAR

Exposure-attributable PYLL is calculated by adding a $PYLL_a$ term which is the number of potential years of life lost for that age of death:

Exposure-attributable PYLL = Deaths x PAR x $PYLL_a$

Exposure-attributable indirect mortality costs are calculated in a similar manner to the exposure-attributable PYLL. A measure called the present value of future earnings (PVFE) for the age at death is substituted in the equation:

Exposure-attributable mortality costs = Deaths x PAR x PVFE

Both SAMMEC II and ARDI are static models, in that the population of interest is not modeled into the future using birth, life expectancy, and population mortality estimates. For most risk factor/disease combinations, there is a *latency* period between disease incidence and death and a *lag* time between cessation of exposure (if it occurs) and a reduction in risk to the lowest possible risk for a formerly exposed individual. This means that the SAMMEC II and ARDI attributable mortality calculations make the simplifying assumptions that mortality occurs in the same year disease does and that formerly exposed individuals are the same as never exposed individuals in terms of risk of disease.

*CAN*TROL*

Cancer strategy planners have recognized the need for quantitative methods to estimate the effectiveness, cost and yield of different cancer control activities. CAN*TROL is a computer based program for modeling the impact of cancer control activities year by year. [33] It has been used to evaluate the value of mammography screening in women under 50 years of age and to estimate the cost effectiveness of particular treatments for stage III colon cancer. [34 35]

CAN*TROL has several components: a population model, a cancer incidence component, a "screening and detection" component, a treatment and support component, and a total mortality component. The population model uses the births and deaths for each year to model the population by sex and five-year age group for each year in the future. The incidence component provides estimates of the number of cases of each cancer occurring in the population by sex and five-year age group. The "screening and detection" component further stratifies these estimates by stage of disease. Information on the cost of new cancer cases and the quality of life for new cases can also be obtained from this component. The treatment and support component calculates patient survival for various stages of treatment as a function of time after diagnosis and treatment. Also provided are quality of life measures for cancer patients and costs associated with treatment, support, and terminal care. The total mortality component calculates the mortality from causes other than cancer and the cost of terminal care for other causes of death.

CAN*TROL has the ability to partition the population into any number of subpopulations which may be targets of different interventions. These subpopulations

can vary by size, relative risks, proportion of cases in each stage, and stage-specific survival rates. This partitioning ability enables the analyst to take into account different geographic regions, populations with access to different levels of care, programs aimed at people with particular exposures, and subpopulations that are expected to respond differently to cancer control activities.

The intervention modeled can be designated to have an effect over a defined time period, and interventions can be specific to subpopulations. The program can calculate the maximum potential change that would occur if exposure to the risk factor were eliminated and the proportion of the maximum change that is expected to occur as a result of an intervention. The delay in the expression of this change can also be quantified. CAN*TROL has the ability to consider the simultaneous effects of an intervention on multiple diseases.

PREVENT

PREVENT is a model developed in the Netherlands by Gunning-Schepers to simulate the effect of an intervention on risk factors on diseases.[2] The model has been used to simulate interventions on numerous risk factors for various diseases in the Dutch population.

The model is based a modified-version of the population attributable risk called the *potential impact fraction (PIF)*. It uses life-table methods to simulate the evolution of the population and assesses the impact of an intervention by translating the PIF into absolute measures like mortality and PYLL. A more detailed description of the methodology is provided in the Section 2.4.

PREVENT is able to model multiple risk factors, multiple diseases, and accounts for the latency period between disease incidence and death (if applicable), and the lag time between cessation of exposure to a risk factor and the point in time at which the formerly exposed individual achieves lowest possible risk for disease. Users can specify trends for risk factor prevalence, the level of stratification of input data, and different interventions for sub-populations defined by the stratification variables.

Table 2-1 summarizes the characteristics of the population health models reviewed in this paper. Of the models reviewed, PREVENT and CAN*TROL are the most usable for disease modeling at a population level because the data requirements most closely match data that are typically available at a national level e.g., prevalences by five year age group, sex, and exposure category. Either model could have been used for this analysis although PREVENT is offered as a general disease modeling tool and CAN*TROL is described as a cancer modeling tool. Perhaps the strongest reason for choosing PREVENT is that the model was specifically designed with *intervention* modeling in mind. CAN*TROL is capable of modeling interventions but was not designed with this as its primary goal. PREVENT also has the advantage of being able to perform a cohort analysis (treats exposure prevalences as characteristic of a cohort) or an age-group (treats exposure prevalences as a characteristic of an age-group) analysis. Some other models, like POHEM, are more sophisticated in design but less practical because population data is not available at the level of detail required. CHD may be best described by logistic models [36] but to date no logistic model has been combined with a demographic model to produce a seamless population disease model. PREVENT appears to provide the best balance of sophistication in design, availability of input data, and

intervention modeling capabilities from among the models reviewed. For these reasons, PREVENT is the model of choice for this analysis.

Table 2-1 Comparison of Different Models

Model	PREVENT	CAN*TROL	SAMMEC II / ARDI	CRISPERS	POHEM	Cholesterol
Methods						
PAR	√	√	√			
Monte Carlo				√	√	
Logistic						√
Times						
Latency	√	√	X	√	√	√
Lag	√	X	X	√	√	X
Lead	X	√	X	√	√	X
Multiples Diseases	√	√	√	X	√	X
Multiple Risks	√	√	X	√	√	√
Cost/Benefit Analysis	X	√	√		√	X
Automatic Trend Adjustment						
Population	√	√	X	√	X	X
Risk Factor	√	X	X	X	√	X
Outcome Measures						
Morbidity	√	√	√	√	√	√
Mortality	√	√	√	√	√	√
PYLG/PYLL	√	√	√	√	√	X
Others	X	√	√	√	√	X
Models Interventions	√	√	X	√	X	X
Model Flexibility						
Intervention Types	√	√	X	√	X	X
Intervention Periods	√	√	X	√	X	X
Populations	√	√	√	√	√	X
Models forward 10 yrs.	√	√	X	√	√	√
Cohort Analysis option	√	X	X	X	X	X

Blanks boxes indicate insufficient information or not applicable to model. This table is a modified version of one presented in Herbert (1992). [37]

2.4 The PREVENT Model

2.4.1 Underlying Attributable Risk and Potential Impact Fraction Calculations

As indicated above, PREVENT falls in the general class of attributable risk-based models, but is perhaps more correctly described as a potential impact fraction-based model. In this section, I will describe how the attributable risk is related to the potential impact fraction and in the following section, some of the additional modifications

PREVENT has made to permit more realistic modeling.

There are two general classes of attributable risk definitions [38]:

- attributable risk in the exposed group
- attributable risk in the total population

In quantifying the impact of a risk factor on a population, as is the case here, it is the attributable risk in the total population that is of interest. This population attributable risk (PAR) may be defined as the number of incident cases due to association with the risk factor divided by the total number of incident cases in the population. If R is the incidence of disease in the total population and R_0 is the incidence of disease for those not exposed to the risk factor, then:

$$PAR = \frac{R - R_0}{R} = \frac{RR - 1}{RR}$$, where RR is the relative risk of disease (1)

This definition reflects the traditional etiologic view of PAR as the proportion of incident cases in a population that is attributable to the risk factor. Common formulae for the calculation of the PAR are based on an estimate of the relative risk associated with exposure to the risk factor and an estimate of the prevalence of exposure to the risk factor in the population [39]:

$$PAR = \frac{p(\hat{RR} - 1)}{1 + p(\hat{RR} - 1)} \Leftrightarrow \frac{\hat{RR} - 1}{\hat{RR} + \frac{1}{p} - 1}$$

These formulae are used because relative risk data are often readily available from etiologic investigations and prevalence data may be obtained from population surveys.

Morgenstern and Bursic [40] present an alternative formulation that makes use of relative risk and prevalence data which are stratified by k + 1 ordered categories of the risk factor (i = 0, 1....,k) . If f_i is the fraction of the population in each risk factor category

and R_i is the incidence of disease in the ith category then the total incidence R can be expressed as:

$$R = \sum_{i=0}^{k} f_i R_i \text{, where } \sum_{i=0}^{k} f_i = 1 \qquad (2)$$

Substituting (2) into (1) we get:

$$PAR = \frac{\sum_{i=0}^{k} f_i R_i - R_0}{\sum_{i=0}^{k} f_i R_i} \qquad (3)$$

Dividing by R_0, (3) becomes:

$$PAR = \frac{\sum_{i=0}^{k} f_i RR_i - 1}{\sum_{i=0}^{k} f_i RR_i} \text{ , where } RR_i \text{ is the relative risk in the ith category} \qquad (4)$$

The PAR is undefined for preventive exposures, i.e., RR < 1, but an analogous measure, the *prevented fraction (PF)*, may be defined. It is the fraction of the potential cases of disease in the absence of exposure that are prevented by exposure to the risk factor [41] [39] and may be calculated using:

$$PF = \frac{R_0 - R}{R_0} = 1 - RR \qquad (5)$$

PREVENT calculations are based on (4) which in turn are based on the definition of attributable risk in (1). This means that RR values less than 1 cannot be used in analyses using PREVENT. Fortunately, this doesn't mean that preventive exposures cannot be studied using PREVENT. Redefining the exposure categories such that the lowest risk category is the referent category will produce RR values that are greater than or equal to

one in all categories.

The *potential impact fraction* (*PIF*) is a useful concept for describing the impact of a risk factor intervention on disease incidence. The attributable risk is conceptually equivalent to a maximum PIF -- if an intervention were to reduce the prevalence of the risk factor to zero the PIF would equal the attributable risk. In practice, complete elimination of a risk factor is rarely achieved so a modified attributable risk measure is necessary to quantify the potential impact of an intervention on disease incidence. If R and R' are the pre-intervention and post-intervention incidences in the total population respectively then:

$$PIF = \frac{R - R'}{R} \tag{6}$$

Note that R' = R_0 if the maximum potential impact is achieved. If g_i is the fraction of the post-intervention population in the i-th risk factor category, then the total post-intervention risk can be expressed as:

$$R' = \sum_{i=0}^{k} g_i R_i \text{, where } \sum_{i=0}^{k} g_i = 1 \tag{7}$$

Substituting (2) and (7) into (6) gives:

$$PIF = \frac{\sum_{i=0}^{k} f_i R_i - \sum_{i=0}^{k} g_i R_i}{\sum_{i=0}^{k} f_i R_i}$$

Dividing by R_0 gives:

$$PIF = \frac{\sum_{i=0}^{k} (f_i - g_i) RR_i}{\sum_{i=0}^{k} f_i RR_i} \tag{8}$$

PREVENT uses equation 8 as the basis for its potential impact fraction (*PIF*) calculations. The ordered categories i = 0...k are defined as the subgrouping created by the simultaneous stratification by age and sex [2]. This enables PREVENT to use information on the relationship between risk factor exposure and disease incidence as effectively as possible. If separate estimates are available in the literature by sex or age category, then this information can be used in the model. If the information is unavailable, then each category can be given identical relative risk and prevalence estimates.

In doing an analysis with PREVENT, the prevalence of exposure and the *RR* associated with various levels of exposure are obtained from previously conducted descriptive and analytic studies, respectively. The intervention effect used as input data may be obtained from previous intervention studies but, since such studies are rare, it is also possible to use hypothetical data.

The actual *PIF* that PREVENT calculates is a modified version of the formula described above. To provide more realistic modeling, PREVENT adjusts the PAR and PIF calculations to address two issues:

- the effect of time
- the effect of other risk factors

2.4.2 Time Adjustments in PREVENT

The expression for *PIF* in equation 8 is static in that an intervention is assumed to have an instantaneous effect on prevalence (*f* to *g*) and on the relative risk of the formerly exposed (the formerly exposed are assigned the same relative risk as the unexposed). Indexing for time means that an intervention can have an associated time spread, i.e.,

amount of time it takes for the intervention to have full effect on prevalence. It also means that those who are no longer exposed can be assigned residual relative risks that are different from those given to the never exposed. These values are usually intermediate between exposed relative risk and unexposed relative risk values. In PREVENT, these formerly exposed relative risk values are assumed to decrease linearly with time to some lowest possible risk level [2].

The actual modifications to the calculations are indexing prevalence by time and the creation of a LAG variable which quantifies the amount of time it takes to reach the lowest possible risk level for the formerly exposed after cessation of exposure.

A consequence of the introduction of LAG is that not only will interventions have a slow reduction in risk over time but that past interventions (and thus past changes in prevalences) will have an effect on future incidence. Thus, it is necessary to quantify autonomous trends that are separate from the intervention under study. If f_0 and RR_0 are the proportion and relative risk at time 0 and f_t and RR_t take trends into account at time t, we can define the trend impact fraction TIF, the incident cases prevented at a certain moment in time t, by:

$$TIF_t = \frac{\sum f_0 RR_0 - \sum f_t RR_t}{\sum f_0 RR_0}$$

PIF is modified to account for the fact that the reference incidence is not static but evolves over time as a consequence of risk factor trends. If f_t and RR_t take only trends into account and f'_t and RR'_t take trends and intervention into account then:

$$PIF_i = \frac{\sum f_i RR_i - \sum f_i' RR_i'}{\sum f_i RR_i}$$

2.4.3 Assumptions for Modeling Multiple Risk Factors in PREVENT

Since most diseases have multiple risk factors, it is important to clearly state what the expected impact of multiple risk factors is on disease incidence. Data on the effect of joint exposure data are rare in the literature, and even if available, it cannot be assumed that the nature of the relationship between two risk factors will hold for two other risk factors. It was thus necessary for Gunning-Schepers to assume that the risk for a disease associated with any one risk factor is independent of other risk factors.

PREVENT was thus designed as a multiplicative model as opposed to an additive model. It assumes independence of the effect of risk factors and enables EFs and PIFs to be calculated sequentially for each risk factor without knowledge of the joint effect [2]. If the mortality rate associated with risk factor A is independent of the mortality rate associated with risk factor B, then the mortality rate when both risk factors are present is the sum of the two independent mortality rates. In an additive model, the mortality rate when both risk factors are present would be the sum of the two independent mortality rates plus a third term representing the effect of the interaction [38].

The implication of a multiplicative model for this particular analysis is that risk factors like alcohol can be investigated independently of other risk factors. Information on the relationship between alcohol and CHD mortality is used for intervention effect estimation without reference to relationships between other exposures and CHD mortality, e.g., tobacco use and CHD mortality.

More difficult to address is the case where interaction exists. In this case, the model's assumption of the independence of risk factors is incorrect and the relative risk estimates for the risk factors of interest may be skewed depending on the values of interacting risk factors in the population.

It should be noted that PREVENT assumes confounding factors are controlled for in the studies from which relative risks are taken. This means that the estimate of the relative risk associated with a risk factor is valid and not entangled with the effect of another risk factor. The possibility of unknown confounders always exists, however, and these may affect the relative risk estimates and therefore alter the effect of the risk factor in the simulation.

3. Method

This section describes the data sources used in this analysis and outlines the rationale for choosing each data source over alternative sources. PREVENT requires the following population and risk factor data:

- Base Year of Simulation
- Population Data: structure by age and sex
  total mortality
  birth projections
  life expectancy
  disease specific mortality
- Risk Factor Data: relative risks for disease specific mortality
  prevalence of exposure to risk factor in population
  effect of intervention on prevalence

3.1 Base Year of Simulation

PREVENT projections begin the year after the selected base year of simulation. The base year chosen is dependent on the overall aim of the analysis. If the goal is to determine whether the model is accurate, historical testing may be done. The base year of simulation for historical testing would likely be twenty or thirty years in the past in order to compare simulation results with actual data collected over the past few decades. If the aim of the researcher is to predict future health patterns, then a more recent base year may be chosen. In this analysis, selection of the base year of simulation involves balancing the desire to use the most current data and selecting a base year of simulation for which all the required types of data are available.

Since this paper aims to provide a sensitivity analysis rather than historical testing, it makes sense to choose a base year which is fairly recent and for which all the required data are available at a national level. At the time that this analysis was started,

1992 was the most recent year for which data was available and it was thus chosen as the base year.

3.2 Population Data

A PREVENT run produces outcome measures like mortality and PYLL for a specific population. For this analysis, the Canadian population was chosen, and the data sources were selected to produce input data that were representative of the Canadian population.

3.2.1 Structure

Data Required: PREVENT requires sex-specific population structure data in one-year age groups from under 1 to 95 plus years old.

Data Source: The 1991 Census conducted by Statistics Canada produced estimates of the Canadian population distribution by sex and age in one-year age groups from under 1 to 90 years old. Statistics Canada produces annual postcensal estimates of the population of Canada in noncensus years. Thus, the postcensal estimate for 1992 represents the best data source for this analysis with a base year of simulation of 1992. The 1995 final revised postcensal estimates for the 1992 population, obtained by special request from the Demography Division of Statistics Canada, are presented in Table 3-1 and Figure 3-1.

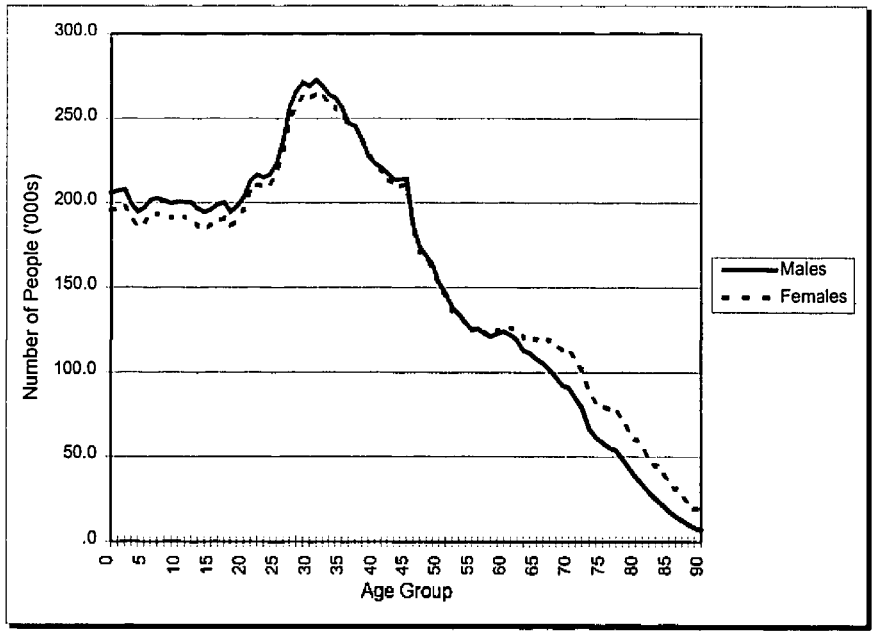
Issues: Clearly, some estimate must be made of the population distribution by sex in one-year age groups for those 91 to 95+ years of age. As Figure 3-1 shows, after approximately age 70, the national population of both males and females appear to decline linearly. Of course, this does not provide sufficient reason to believe that the population will continue to decline linearly above age 90 because age is not the only

Table 3-1 Population Structure, Canada, 1992

Age	Population ('000s)		Age	Population ('000s)		Age	Population ('000s)	
	Male	Female		Male	Female		Male	Female
Under 1	206.0	195.7	32	268.9	262.6	64	111.4	120.7
1	207.3	196.5	33	263.8	258.3	65	107.8	119.1
2	207.8	197.6	34	262.2	256.6	66	105.2	120.4
3	199.4	189.9	35	256.4	253.4	67	101.5	118.4
4	194.8	186.2	36	247.1	244.5	68	97.2	116.3
5	197.4	189.1	37	245.4	244.5	69	92.6	113.1
6	201.8	193.3	38	237.0	237.8	70	90.7	112.8
7	202.6	193.6	39	227.8	229.0	71	85.0	107.7
8	201.0	192.2	40	223.1	221.6	72	79.1	101.8
9	199.9	191.1	41	220.3	218.3	73	66.5	88.3
10	200.5	191.3	42	217.3	213.9	74	61.8	82.9
11	200.7	191.8	43	213.7	211.6	75	58.4	80.3
12	200.3	190.0	44	213.8	210.1	76	55.5	78.1
13	196.6	186.3	45	214.1	211.0	77	53.8	77.2
14	194.5	184.4	46	186.2	182.9	78	48.6	72.3
15	196.1	187.2	47	173.8	170.6	79	43.6	65.9
16	199.1	189.5	48	168.3	166.1	80	38.2	60.1
17	200.1	190.6	49	163.3	161.1	81	33.9	55.6
18	194.7	186.4	50	152.5	150.5	82	29.6	49.8
19	198.1	189.4	51	146.3	145.2	83	25.3	44.7
20	203.5	195.7	52	137.9	136.5	84	21.7	40.1
21	213.1	207.6	53	133.9	133.1	85	18.0	35.3
22	216.3	210.5	54	129.0	128.1	86	15.0	31.0
23	214.9	210.2	55	124.7	125.0	87	12.6	27.1
24	216.5	211.8	56	125.5	125.9	88	10.4	23.1
25	223.1	218.4	57	123.1	123.8	89	8.4	19.5
26	237.3	231.1	58	120.9	121.2	90	6.8	19.4
27	256.8	249.4	59	122.9	124.6	91	5.1	16.5
28	266.0	257.4	60	123.7	125.4	92	3.5	13.8
29	270.9	262.6	61	121.7	126.0	93	2.2	11.2
30	269.3	261.5	62	118.8	124.1	94	1.1	8.8
31	272.5	265.2	63	112.9	120.2	95plus	8.0	14.5

predictor of population. If a baby boom occurred between 1887 and 1902, it could have the effect of producing a nonlinear decrease in population in the upper age groups in the current decade. It may also be the case that those who survive to age 90 are blessed with a hardiness which gives them a longevity beyond that predicted by linear extrapolation. The opposite scenarios of a baby bust or a rapid decrease in health are also possible.

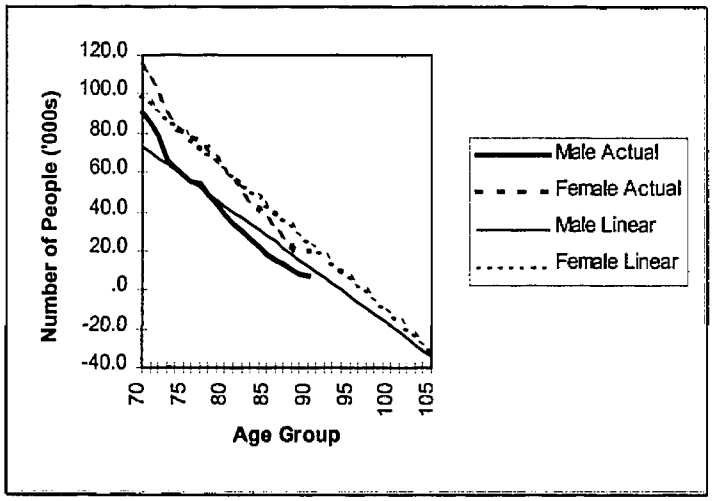
Figure 3-1 Population Structure, Canada, 1992

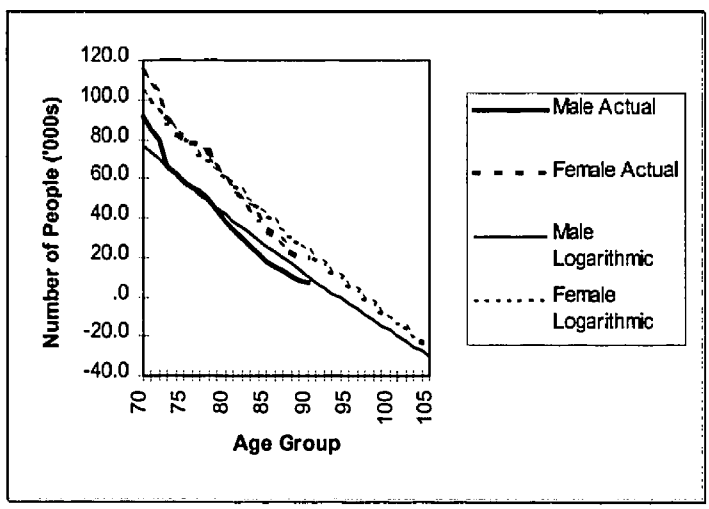


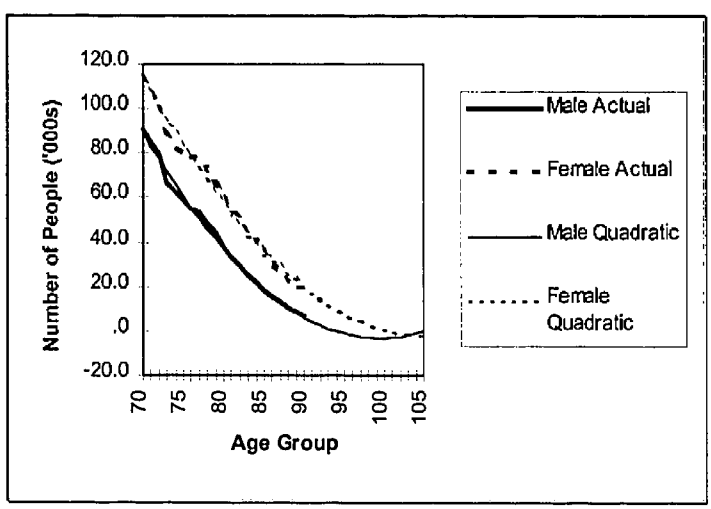
Data available for turn of the century are not detailed enough to determine whether there had been a small baby boom or baby bust; however, inspection of the 1986 census data shows that the numbers aged 84 to 89 (who would be 90 to 95 years old in 1992) are consistent with a linear decreasing trend between ages 70 and 90 for both males and females.

Three different models were applied to the data points between 70 and 90 years of age: a linear model, a logarithmic model, and a quadratic model The resulting lines fit reasonably well; however, extrapolation produced zero population for males before age 90 and for females before age 95. Imputing zero values for ages 96 to 100 for males and age 100 for females improved the expected values but not sufficiently. A quadratic line was then fit with the imputed zeros and this produced the best results. Zero population was still reached before it should have been, but the results were close enough that the

Figure 3-2 Linear, Logarithmic, and Quadratic Curve Estimations







few remaining conflicting data points were manually imputed with reasonable values. The results of the line fitting are given in Figure 3-2 and the expected values are in Table 3-1.

3.2.2 All-Cause Mortality

Data Required: PREVENT requires population mortality data to be sex and age specific. Numbers must be input as rates (per 100,000) for each one-year age group between under one and 95 plus.

Data Source: The total mortality rates used in this analysis were calculated using the number of deaths in Canada [42] (see Table 3-2) and the population structure data from section 3.2.1. The calculated rates used as input data for the PREVENT analysis are given in Table 3-3. The calculated rates were all reasonable, with the exception of the rate for males in the 95 plus age category. The quadratic function used for extrapolation of the population in the age category predicts a population of 200 males; however, it is known that there were 1607 deaths in this age category in 1992.[42] The quadratic function thus underestimates the population of 95 plus males in 1992, and it was necessary to 'guesstimate' a mortality rate of 60,000 per 100,000 for this group and from this calculate a 1992 population of 2678 males aged 95 and over.

3.2.3 Birth Projections

Data Required: PREVENT requires 51 years of birth projections by sex in absolute numbers.

Data Source: A 1994 Statistics Canada publication provides 48 years of birth projections for Canada [43]. For the purpose of this analysis, the projections for 1993 and 1994 are

Table 3-2 Number of Deaths, Canada, 1992

Age	Deaths		Age	Deaths		Age	Deaths	
	Male	Female		Male	Female		Male	Female
Under 1	1389	1042	32	337	140	64	2068	1203
1	81	89	33	386	122	65	2076	1193
2	75	57	34	370	140	66	2350	1366
3	72	40	35	405	190	67	2451	1520
4	41	29	36	418	178	68	2482	1590
5	48	45	37	398	188	69	2699	1663
6	54	47	38	415	200	70	2872	1804
7	38	26	39	407	224	71	3004	2028
8	40	23	40	452	210	72	3022	2085
9	38	32	41	435	236	73	2784	1928
10	36	22	42	434	262	74	2894	2014
11	35	24	43	529	254	75	3000	2324
12	53	31	44	524	277	76	3107	2339
13	47	34	45	559	349	77	3218	2617
14	66	31	46	531	325	78	3282	2730
15	83	49	47	533	383	79	3312	2905
16	142	74	48	607	396	80	3164	2841
17	139	72	49	651	395	81	2976	3004
18	209	65	50	649	434	82	2889	2941
19	257	63	51	698	407	83	2754	2881
20	225	79	52	731	452	84	2518	2952
21	227	85	53	825	501	85	2341	2937
22	227	77	54	832	484	86	2122	2861
23	229	73	55	927	525	87	1981	2799
24	235	81	56	1057	602	88	1789	2666
25	251	81	57	1190	635	89	1580	2553
26	260	88	58	1209	711	90	1311	2207
27	298	105	59	1355	719	91	1086	2111
28	309	113	60	1533	879	92	912	1876
29	343	109	61	1692	931	93	660	1574
30	337	127	62	1856	1006	94	533	1381
31	342	106	63	1842	1036	95+	2678	4964

replaced by actual count data from another Statistics Canada publication [44] leaving 46 years of birth projections. These data are presented in Table 3-4 and Figure 3-3.

Issues: Birth projections for the remaining two years (2041-42 and 2042-43) are not given in the Statistics Canada publication. PREVENT requires 50 years of birth projections for it to calculate complete projections through to 2043. The alternatives

Table 3-3 Mortality Rates, Canada, 1992 (per 100,000)

Age	Mortality Rate		Age	Mortality Rate		Age	Mortality Rate	
	Male	Female		Male	Female		Male	Female
Under 1	674.27	532.45	32	125.33	53.31	64	1856.37	996.69
1	39.07	45.29	33	146.32	47.23	65	1925.79	1001.68
2	36.09	28.85	34	141.11	54.56	66	2233.84	1134.55
3	36.11	21.06	35	157.96	74.98	67	2414.78	1283.78
4	21.05	15.57	36	169.16	72.80	68	2553.50	1367.15
5	24.32	23.80	37	162.18	76.89	69	2914.69	1470.38
6	26.76	24.31	38	175.11	84.10	70	3166.48	1599.29
7	18.76	13.43	39	178.67	97.82	71	3534.12	1883.01
8	19.90	11.97	40	202.60	94.77	72	3820.48	2048.13
9	19.01	16.75	41	197.46	108.11	73	4186.47	2183.47
10	17.96	11.50	42	199.72	122.49	74	4682.85	2429.43
11	17.44	12.51	43	247.54	120.04	75	5136.99	2894.15
12	26.46	16.32	44	245.09	131.84	76	5598.20	2994.88
13	23.91	18.25	45	261.09	165.40	77	5981.41	3389.90
14	33.93	16.81	46	285.18	177.69	78	6753.09	3775.93
15	42.33	26.18	47	306.67	224.50	79	7596.33	4408.19
16	71.32	39.05	48	360.67	238.41	80	8282.72	4727.12
17	69.47	37.78	49	398.65	245.19	81	8778.76	5402.88
18	107.34	34.87	50	425.57	288.37	82	9760.14	5905.62
19	129.73	33.26	51	477.10	280.30	83	10885.38	6445.19
20	110.57	40.37	52	530.09	331.14	84	11603.69	7361.60
21	106.52	40.94	53	616.13	376.41	85	13005.56	8320.11
22	104.95	36.58	54	644.96	377.83	86	14146.67	9229.03
23	106.56	34.73	55	743.38	420.00	87	15722.22	10328.41
24	108.55	38.24	56	842.23	478.16	88	17201.92	11541.13
25	112.51	37.09	57	966.69	512.92	89	18809.52	13092.31
26	109.57	38.08	58	1000.00	586.63	90	19279.41	11376.29
27	116.04	42.10	59	1102.52	577.05	91	21294.12	12793.94
28	116.17	43.90	60	1239.29	700.96	92	26057.14	13594.20
29	126.61	41.51	61	1390.30	738.89	93	30000.00	14053.57
30	125.14	48.57	62	1562.29	810.64	94	48454.55	15693.18
31	125.50	39.97	63	1631.53	861.90	95+	60000.00	34234.48

were to extrapolate the birth projections curve or to drop the final two years from the analysis and ignore projections provided by PREVENT for those two years.

Figure 3-3 presents total birth projections for Canada from 1996 to 2041. It is not obvious that extrapolation of a fitted line will produce acceptable results. In contrast to the extrapolation done for the population structure -- a situation in which the population

is known to ultimately reach zero -- there is no 'ultimate' number of births. Births in any given year depend on many factors including the population structure for women in their fertile years, levels of female employment, knowledge and use of effective contraception, sterilization and other means of birth control, economic factors, and postponed childbearing.[43] Each of these factors follows different patterns. For example, economic factors may apply a downward pressure on fertility rates while postponed childbearing may only have a temporary downward effect on fertility rates. Given the complexity of projecting births and the questionable nature of the necessary assumptions, the final two years were dropped from the analysis.

A second issue arose from the fact that available birth projections are not given separately by sex as required by PREVENT. Data from Statistics Canada [44] show that the male-female ratio of live births in Canada has not varied greatly since 1974. Assuming that this ratio will remain constant over the simulation period, an average of the male-female ratios for the twenty year period 1974 to 1994 (1.055144) was applied to the birth projection figures for 1995 to 2039 to obtain the separate male and female birth projections figures given in Table 3-4 (1993 and 1994 figures, for both males and females, are actual numbers of births).

3.2.4 Life Expectancy

Data Required: PREVENT needs the life expectancy for a 95 years old male and a 95 year old female to generate a life expectancy table for the population in the base year.

Data Source: A Statistics Canada publication provides life expectancies for Canadians

Table 3-4 **Projected Births, Canada, 1992-2040**

Year	Births			Year	Births		
	Male	Female	Total		Male	Female	Total
1992	200.2	189.8	390.0	2017	213.0	201.9	414.9
1993	199.4	189.0	388.4	2018	213.7	202.5	416.2
1994	197.7	187.4	385.1	2019	214.1	203.0	417.1
1995	197.2	186.8	384.0	2020	214.4	203.2	417.6
1996	196.6	186.4	383.0	2021	214.5	203.3	417.8
1997	196.3	186.0	382.3	2022	214.5	203.3	417.8
1998	195.4	185.2	380.6	2023	214.4	203.1	417.5
1999	194.8	184.6	379.4	2024	214.2	203.0	417.2
2000	194.4	184.3	378.7	2025	214.0	202.8	416.8
2001	194.4	184.3	378.7	2026	213.8	202.7	416.5
2002	194.7	184.5	379.2	2027	213.7	202.6	416.3
2003	195.2	185.0	380.2	2028	213.7	202.5	416.2
2004	196.0	185.8	381.8	2029	213.8	202.6	416.4
2005	197.0	186.8	383.8	2030	214.0	202.8	416.8
2006	198.2	187.9	386.1	2031	214.3	203.1	417.4
2007	199.6	189.1	388.7	2032	214.8	203.5	418.3
2008	201.0	190.5	391.5	2033	215.3	204.0	419.3
2009	202.5	191.9	394.4	2034	215.9	204.7	420.6
2010	204.0	193.4	397.4	2035	216.7	205.3	422.0
2011	205.6	194.8	400.4	2036	217.4	206.1	423.5
2012	207.1	196.2	403.3	2037	218.3	206.9	425.2
2013	208.5	197.6	406.1	2038	219.2	207.7	426.9
2014	209.8	198.9	408.7	2039	220.1	208.5	428.6
2015	211.1	200.0	411.1	2040	220.9	209.4	430.3
2016	212.1	201.1	413.2				

Figure 3-3 **Projected Births, Canada, 1992-2040**

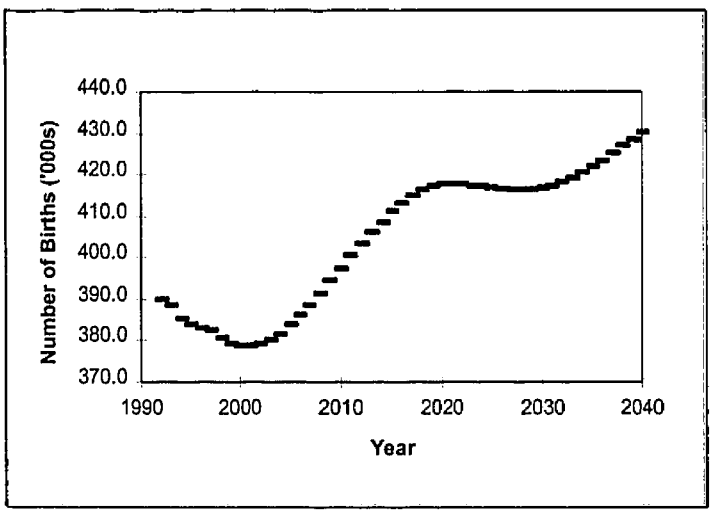
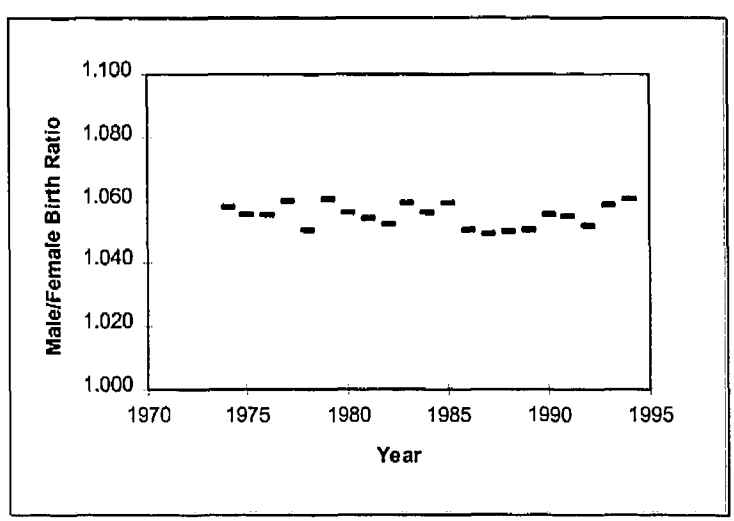


Table 3-5 **Male/Female Birth Ratio, Canada, 1974-1994**

Year	Number of Males	Number of Females	M/F Ratio
1974	180250	170400	1.057805
1975	184534	174789	1.055753
1976	184832	175155	1.055248
1977	185923	175477	1.059529
1978	183879	174973	1.050899
1979	188382	177682	1.060220
1980	190395	180314	1.055908
1981	190603	180743	1.054553
1982	191307	181775	1.052438
1983	192236	181453	1.059426
1984	193678	183353	1.056312
1985	193247	182480	1.059004
1986	191043	181870	1.050437
1987	189314	180428	1.049250
1988	192989	183806	1.049960
1989	201152	191509	1.050353
1990	208205	197281	1.055373
1991	206612	195916	1.054595
1992	204378	194264	1.052063
1993	199744	188650	1.058807
1994	198173	186939	1.060094
		Average	1.055144

Figure 3-4 **Male/Female Birth Ratio, Canada, 1974-1994**



by single years of age [45] but since PREVENT generates its own life table, the only required data are the life expectancies of 95 year old males and females. These are 2.86 years and 3.35 years, respectively.

3.2.5 Mortality from CHD

Data Required: For disease-specific mortality, PREVENT requires that data be input as mortality rates (per 100,000) for 20 five-year age groups by sex.

Data Source: CHD mortality data, as classified using the International Classification of Diseases v. IX code (ICD 410-414), were obtained by special request from the Health Statistics Division of Statistics Canada. Table 3-6 presents the mortality data, both absolute numbers of deaths and rates.

Issues: The data from Statistics Canada are available in five year age categories up to 85 plus years old. PREVENT requires the disease-specific mortality rates to be further stratified in the upper age category (85 plus) into 85 to 89 years, 90 to 94 years, and 95 plus years old. Some estimate of the distribution of CHD mortality over these three age categories must be made. CHD is an age-related disease, but since age is not the only predictor of CHD, it is not clear what kind of relationship exists between the two variables. Attempts at fitting linear, logarithmic, and quadratic lines all produced large deviations from the observed values and were thus considered unacceptable for extrapolation. Following a methodology used by Herbert,[37] CHD mortality rates, as a proportion of all-cause mortality rates, were examined separately by sex for possible trends.

Table 3-6 CHD Mortality Rate, Canada, 1992

Age Group	Deaths		Mortality Rate per 100,000	
	Male	Female	Male	Female
0 to 4	1	0	0.10	0.00
5 to 9	0	0	0.00	0.00
10 to 14	1	0	0.10	0.00
15 to 19	1	0	0.10	0.00
20 to24	4	5	0.38	0.49
25 to 29	5	3	0.40	0.25
30 to 34	34	7	2.57	0.54
35 to 39	98	9	8.14	0.75
40 to 44	235	30	21.68	2.80
45 to 49	384	71	42.52	7.98
50 to 54	548	117	78.50	16.90
55 to 59	899	241	146.21	38.94
60 to 64	1392	457	237.17	74.28
65 to 69	1889	848	375.64	144.56
70 to 74	2223	1266	580.60	256.79
75 to 79	2349	1827	904.48	488.43
80 to 84	1995	1954	1340.24	779.70
85 to 89	814	1345	1263.97	988.97
90 to 95	543	897	2903.74	1286.94
95plus	271	448	3387.50	3089.65

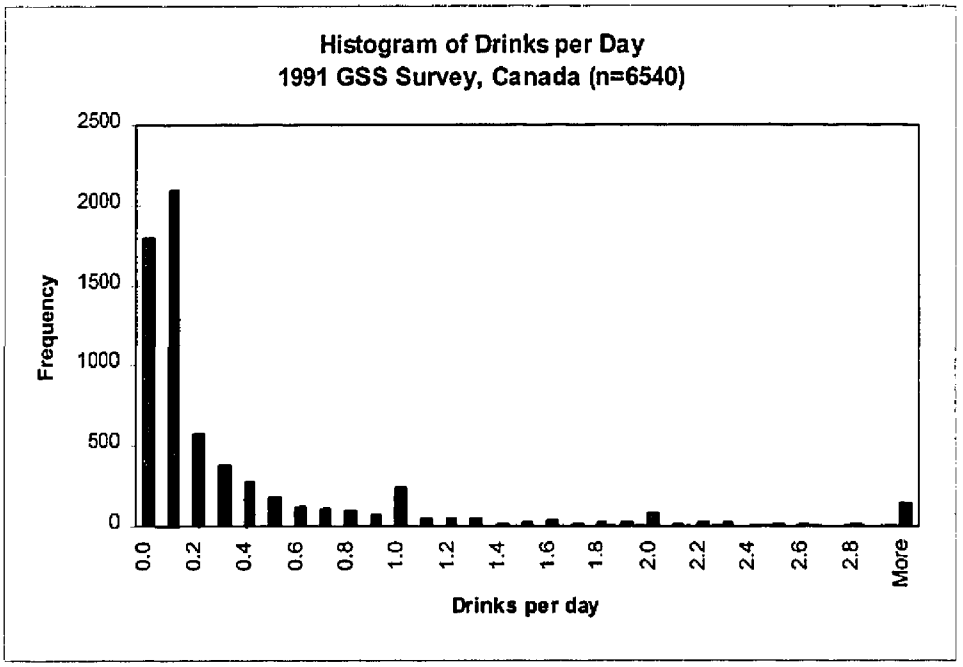
3.3 Risk Factor Data

3.3.1 Prevalence Estimates

Data Required: Estimates of the prevalence of alcohol consumption for 1992 in Canada by age and sex are required by PREVENT.

Data Source: Statistics Canada conducts a telephone survey of Canadians on a regular basis to solicit information concerning social patterns. In the 1991 Cycle 6 of the General Social Survey (GSS) are questions concerning the frequency of alcohol consumption and the quantity of alcohol consumed on drinking occasions. For this analysis, estimates of alcohol consumption were obtained by multiplying frequency of drinking by the average quantity drunk on each occasion. Below is a histogram of the calculated drinks per day:

Figure 3-5



The histogram suggests that one-third of Canadians are abstainers, one-third drink less than 0.2 drinks a day on average, and the remaining third drink 0.2 or more drinks per day on average. The proportion of Canadians who drink 1.5 drinks a day or more on average is relatively small (6.7% of the population).

PREVENT requires that the exposure variable be categorized into six or fewer categories. For the purposes of this analysis, five categories have been defined: *abstainer (those who have not had any alcohol in the past twelve months)*, *> 0 to 0.5 drinks/day*, *>0.5 to 1.0 drinks/day*, *> 1.0 to 1.5 drinks/day*, and *> 1.5 drinks/day*. A crosstabulation by age category, sex, and drinking category produced the prevalence estimates shown in Table 3-7.

Issues: The GSS is conducted using a sample of the national population. It will be assumed that the alcohol consumption calculations approximate the drinking patterns of

the national population, even though the survey is cross-sectional in design and respondents are thus required to recall their drinking patterns over the previous year.

Table 3-7 Prevalence of Alcohol Consumption In Canada, 1991 by sex and age group (drinks per day)

		Drinking Categories									
		abstainer		> 0 to 0.5		> 0.5 to 1.0		> 1.0 to 1.5		> 1.5	
		Count	Row %	Count	Row %	Count	Row %	Count	Row %	Count	Row
Male	under 40	138	9.5%	907	62.6%	201	13.9%	91	6.3%	113	7.8%
	40 to 49	61	13.1%	285	61.0%	56	12.0%	19	4.1%	46	9.9%
	50 to 59	93	26.6%	145	41.4%	42	12.0%	19	5.4%	51	14.6%
	60 plus	369	36.6%	347	34.4%	139	13.8%	23	2.3%	131	13.0%
Female	under 40	280	21.3%	940	71.4%	60	4.6%	19	1.4%	18	1.4%
	40 to 49	95	22.7%	274	65.6%	32	7.7%	7	1.7%	10	2.4%
	50 to 59	109	34.0%	174	54.2%	22	6.9%	4	1.2%	12	3.7%
	60 plus	607	54.8%	381	34.4%	85	7.7%	9	0.8%	26	2.3%

From Table 3-7, it is clear that in some drinking categories the validity of the prevalence estimates can be challenged because of the small number of individuals in these categories, e.g., females drinking more than one drink per day on average. These small numbers do not come as a surprise because it is well known that there are relatively few women who drink large amounts of alcohol. Since the GSS Survey is one of the larger national surveys, it would be difficult to obtain better estimates stratified by sex and age group.

As discussed earlier, the evidence to date supports the idea that all types of drinks confer some cardioprotective effect [80]. Thus, this analysis does not distinguish between different types of drinks.

3.3.2 Relative Risk Estimates

Data Required: Relative risk data are needed separately by sex, age group, and exposure level. Residual risk data, defined as the minimum relative risk which is experienced after

the cessation of exposure, is also needed by sex, age group and exposure level.

Data Source: Although studies suggest a J-shaped curve for the relationship between alcohol consumption and CHD mortality, the reported relative risks vary widely. This inconsistency in the published literature presents an opportunity for a sensitivity analysis.

Since there are an infinite number of possibilities for the exact shape of the J-shaped curve, a sensitivity analysis must make some assumptions about how the J-shaped curves in the different scenarios will differ from each other. For this analysis, the J-shaped curves vary along three dimensions:

- the relative risk at the low-point of the curve
- the level of alcohol consumption at the low-point of the curve

Rather than designating one study as having the correct relative risk value or level of alcohol consumption at the low-point of the curve, ranges of values are derived from the literature. Since the literature in the area of alcohol and CHD is extensive, it is important to first choose from among the many studies examining the relation between alcohol consumption and CHD. For the purpose of this analysis, the reviewed studies were measured against the following criteria:

1. Studies which examine CHD mortality

Some studies look at coronary artery disease (CAD) or cardiovascular disease (CVD) which includes events such as stroke. These studies are excluded because the relationship between alcohol and stroke may differ from that for alcohol and CHD. Since myocardial infarction (MI) forms the bulk of CHD deaths, studies examining MI specifically are considered. Although the risk factors for CHD mortality and CHD incidence appear to be similar,[14] the magnitude of relative risk is different. Thus studies which examine only

CHD incidence are excluded for the purposes of establishing the range of relative risks.

2. Prospective studies with a reasonably long follow-up period

A case-control study design in a study of mortality presents problems. Retrospective designs have potential problems in terms of recall bias. Since enough studies have been conducted in this domain, it is reasonable to restrict this analysis to prospective studies which generally provide better estimates of relative risk.

3. Studies which control for possible confounders

Given the controversy over the effect of former drinkers becoming abstainers, it is desirable that the relative risks examined be based on studies which controlled for this confounder. Other obvious confounders, such as age and smoking status, must be controlled for.

Some other criteria were also considered that did not necessarily result in exclusion if a study did not meet the criterion. These included sample size (a prospective study should have a fairly large sample size for enough cases to occur), location of sample (studies that were conducted in areas of the world that were similar to a Canadian population were favoured), and date of publication (recent results are more likely to be applicable to current populations than earlier results).

The studies that could be quickly dismissed because they fell short of the criteria in too many areas are listed in Table 3-8 along with the reasons they were dropped. Table 3-9 outlines the characteristics of the studies that were used to obtain the range of values for the low point of the curve. It should be evident that if a meta-analysis with sample

size as the primary weighting criterion had been performed, the American Cancer Society [11] and Nurses Cohort Study [21] would overwhelm the other studies because of their large sample sizes. This would amount to assuming that these two studies had the correct relative risk values. The alternative approach, used in this analysis, is to view all the studies in Table 3-9 as useful and use a range of values obtained from the studies as the basis for constructing different scenarios. This partly acknowledges that the advantage of sample size is often offset by the logistical difficulties of conducting larger studies (potentially resulting in more errors in the data).

The low-point relative risk values for the four theoretical J-shaped or U-shaped curves used in this analysis are presented in Table 3-10. The choice of values used for the low-point of the curve in these scenarios is informed by the studies in Table 3-9. The values for the complete curve are not taken from any one particular study because no one particular study has a perfect J-shaped or U-shaped curve. Also, the cut-points used for the drinking categories differ from study to study. Rather, relative risk values for the category with lowest risk are compared and used to inform the choice of values for the scenarios in Table 3-10. Some assumptions were necessary, for example, neither Fuchs nor Garfinkel have results for women at the high end of the drinking spectrum because so few women drink more than two or three drinks a day. For this analysis, it is assumed the risk for women increases at higher consumption levels as it does for men.

Among the studies selected, Colditz[70], Suh[24], and Fuchs[21] appear to be on the low end of the spectrum, suggesting that the cardioprotective effect of alcohol is in the range of 0.3 to 0.5 relative risk (those who do not drink as referent category). Boffetta[11] and Garfinkel[72] suggest that the protective effect may only be in the range of 0.7 to 0.8 at its

Table 3-8 Excluded Studies

Study	Not a prospective cohort	Not CHD or MI	CHD incidence not mortality	Lacked basic control of confounders	Follow-up period too short	Sample size too small
Bianchi (1993) [46]	X		X		n.a.	
de-Labry (1992) [47]				X		X
Farchi (1992) [48]						
Garg (1993) [49]			X		n.a.	
Gordon (1987) [50]			X	X	n.a.	
Gordon (1981) [51]				X		
Jackson (1991) [52]	X		X		n.a.	
Kaufman (1985) [53]	X	X	X		n.a.	
Kittner (1983) [54]			X		n.a.	
Kivela (1989) [55]						X
Klatsky (1990) [56]		X				
Klatsky (1981) [57]			X		n.a.	
Klatsky (1981)		X		X		
Kono (1986) [58]						
Lazarus (1991) [59]						
Marmot (1981) [60]		X				
Miller (1990) [61]			X		n.a.	
Rimm (1991) [62]		X		X	X	
Rimm (1991)			X		n.a.	
Rosenberg (1981) [63]	X	X	X		n.a.	
Scragg (1987) [64]	X	X	X	X	n.a.	
Shaper (1987) [65]			X		n.a.	
Suhonen (1987) [66]					X	X
Wannamethee (1992) [67]					?	
Yano (1977) [68 69]			X	X		

Table 3-9 Selected Studies

	Population	Sample Size	Follow-up Period	Adjusted For
Colditz (1985)[70]	American M & F	1,184	4.75 yrs.	Sex, age, smoking, cholesterol
Camacho (1987) [71]	American M & F	4,590	15 yrs.	Age
Boffetta (1990)[11]	American M	276,802	12 yrs.	Age, smoking
Garfinkel (1988)[72]	American F	581,321	12 yrs.	Smoking
Gordon (1983)[73]	American M	9,532		Age, smoking
Suh (1992)[24]	American M	11,688	<=12 yrs.	Age, smoking
Fuchs (1995)[21]	American F	85,709	12 yrs.	Age, smoking

greatest. In the four scenarios in Table 3-10, the relative risk is varied between 0.5 and 0.7 (0.3 was not used because only Colditz reported this value and it was for those who drink ~0.5 drinks/day or less -- he found a relative risk of 0.6 for those drinking between 0.5 drinks/day and 3.0/drinks a day). The values for the entire curve in the different scenarios are presented in Section 4.2.

These scenarios are designed to test the effect of varying the relative risk and level of alcohol consumption at the low point of the J-shaped curve on CHD mortality. Other factors, such as whether the intervention is modeled with the assumption that alcohol consumption is an age group characteristic or a cohort characteristic are also explored (see the Results section).

What little information there is on residual relative risk after cessation of exposure suggests that the cardioprotective effect is lost once drinking stops. For this analysis, I assume that former drinkers have no more protection than abstainers. This assumption is consistent with at least one of the hypotheses (platelet aggregation) relating to the biological mechanism of the cardioprotective effect of alcohol (See Section 2.2.3).

Table 3-10 **Four Curve Low Points**

Scenario	Alcohol consumption at lowest relative risk (avg. drinks/day)	Relative Risk at lowest point
1	>1.0 to 1.5	0.5
2	> 1.0 to 1.5	0.7
3	> 0.5 to 1.0	0.5
4	> 0.5 to 1.0	0.7

3.3.3 Intervention Estimates

Data Required: In order for PREVENT to compute the projected impact of an intervention on the CHD mortality in a population, data on the impact of an intervention on the prevalence of exposure to alcohol consumption at a population level are required.

Data Source: There is very little in the literature concerning the effect of interventions to change alcohol consumption at a population level (historically, prohibition is perhaps the most significant population level intervention) and nothing of a form that could be used in the PREVENT analysis. In one of the few community based studies in the literature, van Assema et al.[76] were unable to show that intervention methods such as mass media messages, self-help materials, lectures, and small group activities had any effect on excessive alcohol use. The disappointing results may be related to the time limitation of the study. Interventions on smaller populations, e.g. general practitioner settings, have been reported in the literature[77], however, these populations are not likely to be representative of the Canadian population. Theoretical estimates of intervention effects are therefore used in this analysis.

Intervention data entered into PREVENT should ideally be stratified by the same variables (sex and age-group) that the prevalence and relative risk input data are stratified by. For simplication, in this analysis, the theoretical intervention estimates used are assumed to be the same for all age and sex categories in higher risk drinking categories.

The intervention estimates are expressed as the *percent reduction in the proportion of the population in higher risk drinking categories* (stratified by age and sex) -- not a percent reduction in quantity consumed. For example, Table 3-11 depicts the prevalence estimates in the population after a 50% intervention with > *0.5 to 1.0* drinks

per day as the category with lowest risk. Since the intervention moves individuals from higher risk to lower risk, the lowest risk category does not have a reduction but rather an increase in the proportion of the population it contains. In the base scenario (see table in Section 4.2), the intervention estimates used are 10%, 20%, 30%, 40%, and 50%. In the sensitivity analyses, the intervention estimate in all scenarios is 50%.

Table 3-11 Prevalence Estimates Before and After 50% Intervention, Canada

Before Intervention:

		Drinking Categories									
		abstainer		> 0 to 0.5		> 0.5 to 1.0		> 1.0 to 1.5		> 1.5	
		Count	Row %	Count	Row %	Count	Row %	Count	Row %	Count	Row
Male	under 40	138	9.5%	907	62.6%	201	13.9%	91	6.3%	113	7.8%
	40 to 49	61	13.1%	285	61.0%	56	12.0%	19	4.1%	46	9.9%
	50 to 59	93	26.6%	145	41.4%	42	12.0%	19	5.4%	51	14.6%
	60 plus	369	36.6%	347	34.4%	139	13.8%	23	2.3%	131	13.0%
Female	under 40	280	21.3%	940	71.4%	60	4.6%	19	1.4%	18	1.4%
	40 to 49	95	22.7%	274	65.6%	32	7.7%	7	1.7%	10	2.4%
	50 to 59	109	34.0%	174	54.2%	22	6.9%	4	1.2%	12	3.7%
	60 plus	607	54.8%	381	34.4%	85	7.7%	9	0.8%	26	2.3%

After Intervention:

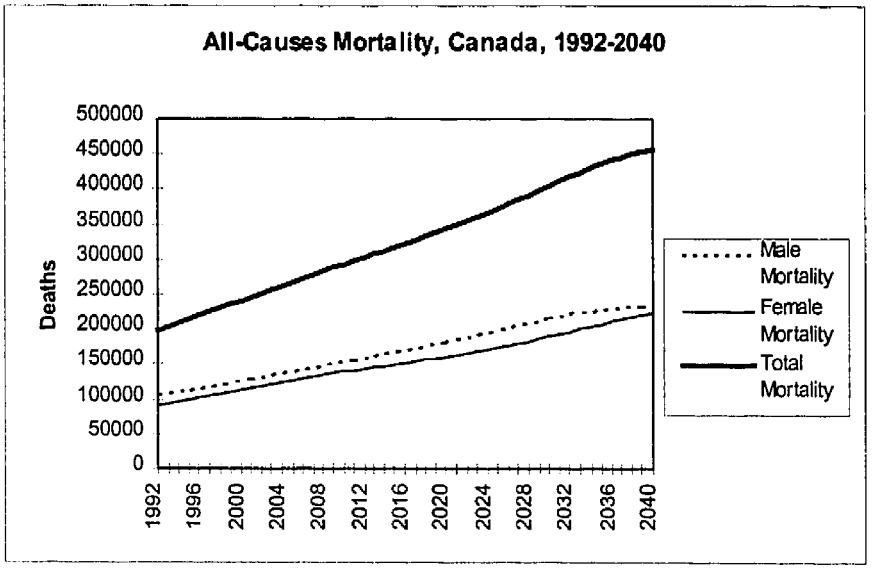
		Drinking Categories (in drinks per day)									
		abstainer		> 0 to 0.5		> 0.5 to 1.0		> 1.0 to 1.5		> 1.5	
		Count	Row %	Count	Row %	Count	Row %	Count	Row %	Count	Row
Male	under 40	69	4.8%	454	31.3%	825	56.9%	46	3.2%	57	3.9%
	40 to 49	95	6.6%	442	30.5%	811	56.0%	30	2.1%	72	5.0%
	50 to 59	193	13.3%	300	20.7%	812	56.0%	39	2.7%	106	7.3%
	60 plus	265	18.3%	249	17.2%	824	56.9%	17	1.2%	94	6.5%
Female	under 40	154	10.7%	518	35.7%	758	52.3%	10	0.7%	10	0.7%
	40 to 49	165	11.4%	476	32.8%	780	53.8%	12	0.9%	17	1.2%
	50 to 59	247	17.0%	393	27.1%	775	53.5%	9	0.6%	27	1.9%
	60 plus	397	27.4%	249	17.2%	781	53.9%	6	0.4%	17	1.2%

4.1 PREVENT Projections

PREVENT provides results for both the entire population and for specific disease subpopulations. This subsection will present results for the entire Canadian population using a base intervention scenario which has been assigned intermediate values of various input variables where possible (see section 4.2 for specific values). For example, relative risk values in the literature vary from 0.7 to 0.5 for the protective effect of alcohol at the low point of the J-shaped curve, and the relative risk used for the low point of the J-shaped curve in the base scenario is 0.6. Note that 0.7 to 0.5 relative risk, in the lowest risk category with abstainers as referent category, is equivalent to 1.4 to 2.0 relative risk among abstainers if the lowest risk category is the referent category.

To provide some context for examining CHD deaths, it is useful to look at all-cause mortality projections for Canada. All-cause mortality is calculated in PREVENT

Figure 4-1

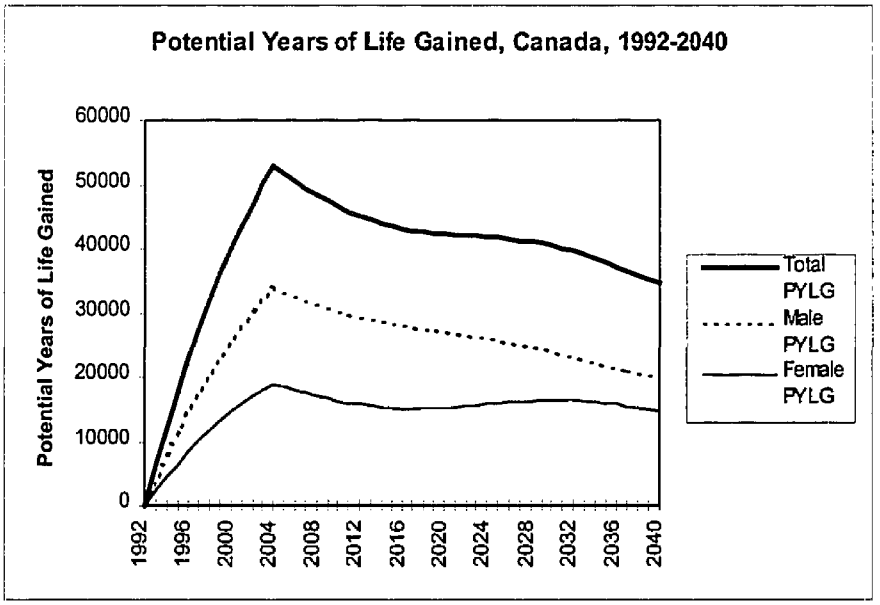


using the overall mortality rate. PREVENT projects all-cause mortality in Canada to increase steadily over the next 48 years. Male deaths are just over 100,000 and female deaths just under 100,000 in 1992. By 2040, this is projected to reach 230,000 deaths for males and 220,000 deaths for females, a combined total of 450,000 deaths per year. This steady increase in deaths is not due to an increase in mortality rate but probably due to a shift in the population pyramid to upper age categories.

In mortality studies, potential years of life lost (PYLL) is sometimes used as an outcome measure. Since this intervention analysis examines deaths prevented, it is possible to look at the analogous potential years of life gained (PYLG) as a result of an intervention. To calculate PYLG, every prevented death is multiplied with its age specific life expectancy and the result is summed over ages. The life expectancies are derived from overall mortality.

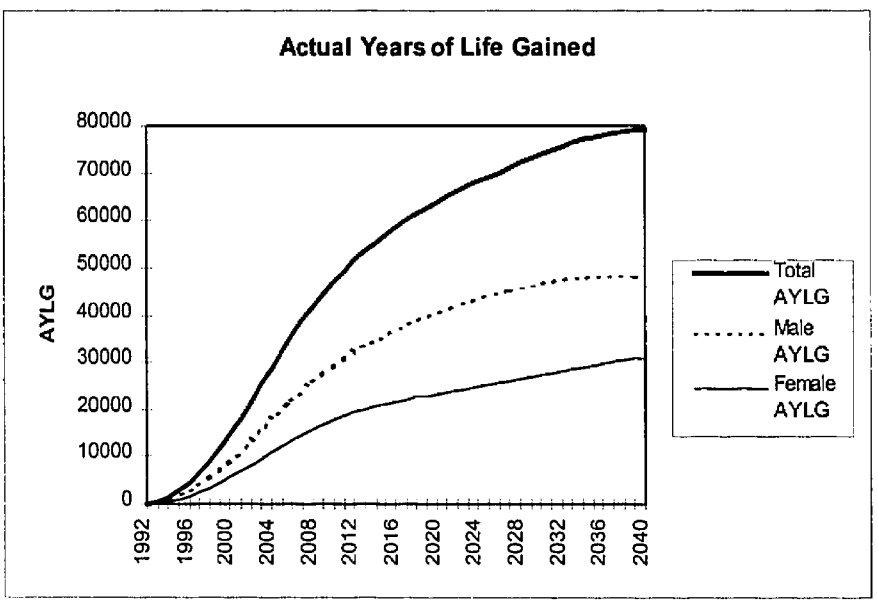
Looking at a 50% intervention (see Section 3.3.3 for a definition of a 50% intervention) using the base scenario, PREVENT calculates that the PYLG peaks at about 53,000 years. The shape of the curve bears some resemblance to the total mortality reduction curve, but after the 12 year intervention, the decline in PYLG is much slower than the decline in deaths prevented. This is because most CHD deaths occur in upper age categories which leads to a smaller PYLL than deaths in lower age categories. Not shown on the graph are the PYLG for the other interventions of 40%, 30%, 20%, and 10%. The results are in proportion to the magnitude of the intervention, i.e., the PYLG with a 10% intervention is one-fifth of the PYLG in the 50% intervention graphed below. PREVENT also calculates the actual years of life gained (AYLG) which is the difference between the reference and the intervention population. The rate of increase in actual

Figure 4-2



years of life gained increases during the 12 year span of the intervention. After the intervention, the number of AYLG continues to increase but the rate of increase declines. The AYLG for the other interventions of 40%, 30%, 20%, and 10% are in proportion to the magnitude of the intervention.

Figure 4-3



Potentially of interest is whether the life expectancy of men and women changes as a result of the intervention. PREVENT generates its own life expectancy table and calculates that the life expectancy of men and women is 74.5 years and 81.0 years respectively under the 50% intervention scenario. Over the course of the simulation, there is a greater increase in life expectancy for men (74.5 to 74.9 years old) than women (81.0 to 81.2 years old).

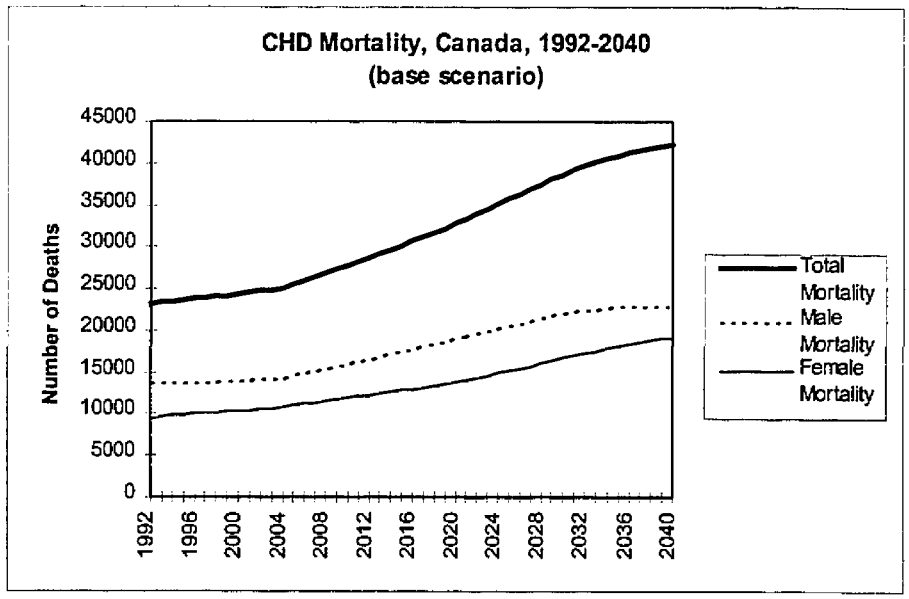
Finally, it is also important to examine the effect of the intervention in terms of CHD-specific mortality. In 1992, there are 14,000 male CHD deaths and 10,000 female CHD deaths. Under the 50% intervention scenario, the effect of the intervention appears

Table 4-1 Life Expectancy, Canada, 1992-2040

	Men	Women		Men	Women
1992	74.53	80.96	2018	74.86	81.16
1994	74.59	81.00	2020	74.87	81.17
1996	74.65	81.03	2022	74.87	81.17
1998	74.70	81.07	2024	74.88	81.17
2000	74.75	81.10	2026	74.88	81.17
2002	74.79	81.12	2028	74.88	81.18
2004	74.83	81.14	2030	74.89	81.18
2006	74.83	81.15	2032	74.89	81.18
2008	74.84	81.15	2034	74.89	81.18
2010	74.84	81.15	2036	74.89	81.18
2012	74.85	81.15	2038	74.89	81.18
2014	74.85	81.16	2040	74.89	81.18
2016	74.86	81.16			

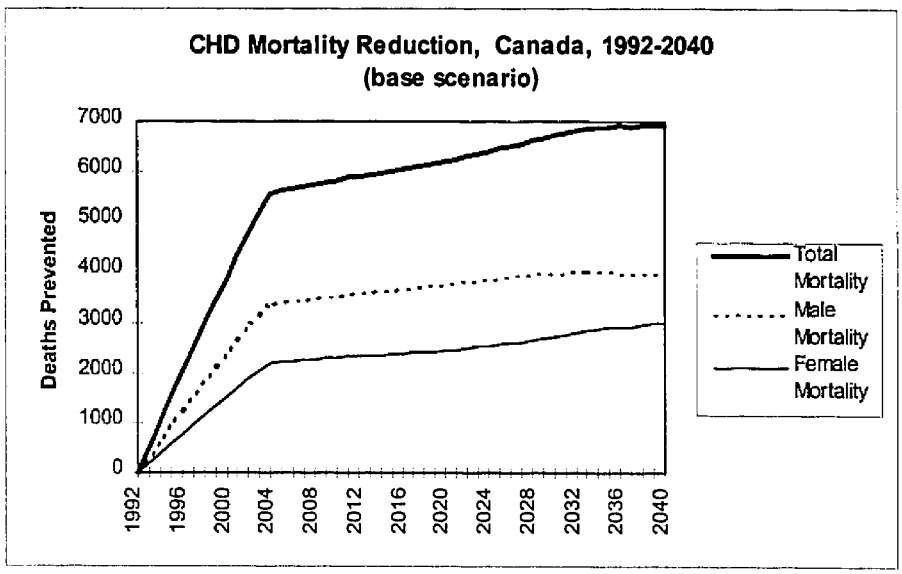
to balance population pressures for the span of the 12 year intervention such that the number of CHD deaths remains fairly steady (slight increase). Once the intervention ends in 2004, population pressures take hold and the numbers of deaths start to climb reaching 42,000 per year by 2040. Without the intervention, PREVENT projects that 49,000 per year would die because of CHD (not shown).

Figure 4-4



The graph of CHD mortality reduction makes this clearer. The intervention results in a rapid increase in the number of CHD deaths prevented. At the end of the 12 year intervention, PREVENT assumes that the effect of the intervention on alcohol consumption continues and so deaths continue to be prevented.

Figure 4-5



The results presented thus far are that total mortality is projected to increase, mortality reduction is anticipated to be greater for males than females, mortality reduction is proportional to the intervention effect, PYLG increases during the intervention and gradually drops off afterwards, the increase in life expectancy is greater for men than women, CHD mortality holds steady during the intervention and increases afterwards, and CHD mortality reduction increases during the intervention and is stable afterwards.

This type of information, in the context of a valid model and realistic interventions, is useful for population health planning. The next subsection presents the results of a sensitivity analyses, in the context of alcohol and CHD, aimed at providing some information about the validity of the model. As previously mentioned, comparisons with historical data or prospectively collected data are also necessary to establish the validity of the model; the following sensitivity analyses are a first step. Following the example of Gunning-Schepers, CHD mortality reduction is used as the outcome of interest.

It is important to note that the interventions modeled in this paper are theoretical interventions. An intervention which moves non-drinkers to become drinkers, at the same time as it moves excessive drinkers to drink at more moderate levels, may have a maximal impact on CHD deaths but is not necessarily a realistic intervention for implementation. The more common type of intervention, which tries to shift exposure levels in an entire population in one direction or another, is arguably difficult enough to implement.

4.2 Sensitivity Analyses

Outcome estimates are only as good as the methods used to produce the estimates and the quality of the input data. As discussed in the Background section, the PREVENT methodology is one of a number of different approaches to population modeling and intervention simulation. It is arguably the most practical method for population level estimation because it makes use of data that are typically available. However, data availability does not mean that there won't be variation in the reported values, e.g., published relative risks. Other input data, mostly analysis parameters, are not found in the literature, so there is uncertainty about the values most appropriately used.

The sensitivity analyses done in this section involve establishing a range of values for each variable and performing a PREVENT run using the extreme values in the range. The range of values chosen may be derived from the literature or may simply be based on an assessment of what are realistic parameters for an intervention. Both approaches are used in the sensitivity analyses in this paper. Table 4-2, following, outlines the different scenarios in the sensitivity analyses. Note that the base scenario was used in Section 4.1.

4.2.1 Varying Relative Risk and the Lowest Risk Category

This analysis assumes that the relationship between alcohol consumption and CHD mortality is correctly described by a U-shaped or J-shaped curve. However, the exact location of the low point of the curve is uncertain. Thus, this subsection will report results of a sensitivity run on location of the low point of the curve.

As described in the Method section, two different relative risk scenarios have been constructed for this analysis. These are theoretical scenarios because they are not

Table 4-2 **Base and Sensitivity Analysis Scenarios for Data Input to PREVENT**

Variable	Scenarios										
	Base	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Relative Risk											
abstainers	1.7	2.0	1.4	2.0	1.4	2.0	1.4	2.0	1.4	2.0	1.4
> 0 to 0.5	1.3	1.5	1.2	1.4	1.2	1.5	1.2	1.4	1.2	1.5	1.2
> 0.5 to 1.0	1.2	1.2	1.1	1.0	1.0	1.2	1.1	1.0	1.0	1.2	1.1
> 1.0 to 1.5	1.0	1.0	1.0	1.7	1.3	1.0	1.0	1.7	1.3	1.0	1.0
> 1.5	2.4	2.9	1.8	2.9	1.8	2.9	1.8	2.9	1.8	2.9	1.8
Cohort or age group analysis	cohort	age	age	age	age	cohort	cohort	cohort	cohort	age	age
Time spread of intervention	12 year	1 year	1 year	1 year	1 year	1 year	1 year	1 year	1 year	24 year	24 year
First year of intervention	1992	1992	1992	1992	1992	1992	1992	1992	1992	1992	1992
Intervention effect on alcohol	10-50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%

Variable	Scenarios										
	11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Relative Risk											
abstainers	2.0	1.4	2.0	1.4	2.0	1.4	2.0	1.4	2.0	1.4	2.0
> 0 to 0.5	1.4	1.2	1.5	1.2	1.4	1.2	1.5	1.2	1.4	1.2	1.5
> 0.5 to 1.0	1.0	1.0	1.2	1.1	1.0	1.0	1.2	1.1	1.0	1.0	1.2
> 1.0 to 1.5	1.7	1.3	1.0	1.0	1.7	1.3	1.0	1.0	1.7	1.3	1.0
> 1.5	2.9	1.8	2.9	1.8	2.9	1.8	2.9	1.8	2.9	1.8	2.9
Cohort or age group analysis	age	age	cohort	cohort	cohort	cohort	age	age	age	age	cohort
Time spread of intervention	24 year	24 year	24 year	24 year	24 year	24 year	1 year	1 year	1 year	1 year	1 year
First year of intervention	1992	1992	1992	1992	1992	1992	2002	2002	2002	2002	2002
Intervention effect on alcohol	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%

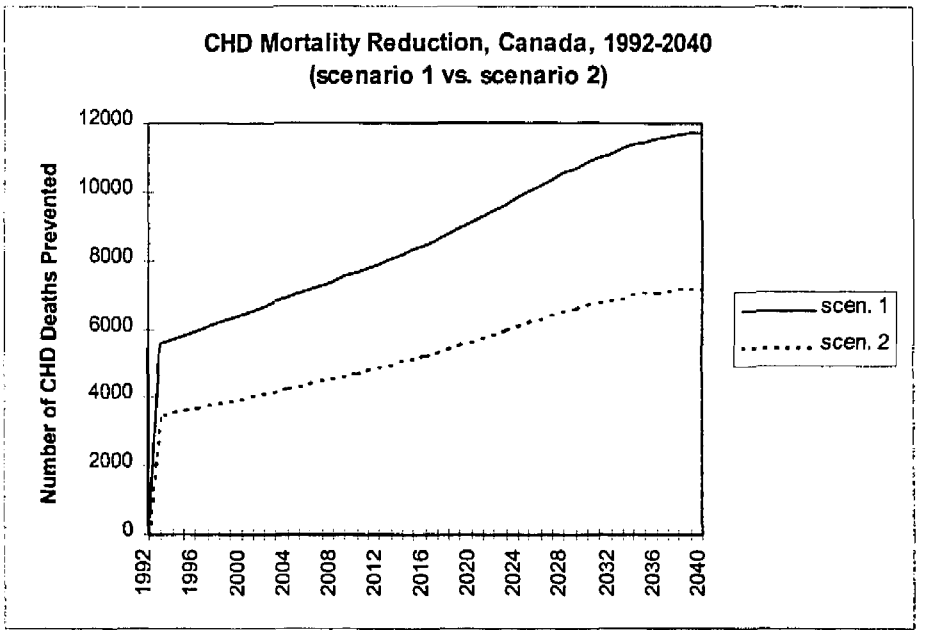
Variable	Scenarios										
	22	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**
Relative Risk											
abstainers	1.4	2.0	1.4	2.0	1.4	2.0	1.4	2.0	1.4	2.0	1.4
> 0 to 0.5	1.2	1.4	1.2	1.5	1.2	1.4	1.2	1.5	1.2	1.4	1.2
> 0.5 to 1.0	1.1	1.0	1.0	1.2	1.1	1.0	1.0	1.2	1.1	1.0	1.0
> 1.0 to 1.5	1.0	1.7	1.3	1.0	1.0	1.7	1.3	1.0	1.0	1.7	1.3
> 1.5	1.8	2.9	1.8	2.9	1.8	2.9	1.8	2.9	1.8	2.9	1.8
Cohort or age group analysis	cohort	cohort	cohort	age	age	cohort	cohort	age	age	cohort	cohort
Time spread of intervention	1 year	1 year	1 year	24 year	24 year	24 year	24 year	24 year	24 year	24 year	24 year
First year of intervention	2002	2002	2002	2002	2002	2002	2002	2002	2002	2002	2002
Intervention effect on alcohol	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%

taken directly from any one study but are designed to reflect the relative risk magnitudes reported in the literature. In the first scenario, the relative risk values are 2.0, 1.5, 1.2, 1.0, and 2.9 for the drinking categories *abstainer*, *> 0 to 0.5 drinks/day, >0.5 to 1.0 drinks/day*, *> 1.0 to 1.5 drinks/day*, and *> 1.5 drinks/day,* respectively (equivalent to a 0.5 relative risk for protective effect of alcohol at the low-point of a J-shaped curve). The second scenario relative risk values are 1.4, 1.2, 1.1, 1.0, 1.8 for the same categories respectively (equivalent to a 0.7 relative risk for the protective effect of alcohol at the low-point of a J-shaped curve). An intervention effect of 50% in the first year of the simulation is assumed in both scenarios.

In Figure 4-6, scenario 1 projects the number of CHD deaths prevented to be about 5600 in 1993 and to rise to almost 12,000 by 2040. In comparison, scenario 2 begins around 3500 and peaks at 7200 CHD deaths prevented in the year 2040. This suggests that the number of deaths prevented varies in the direction expected. One would expect that a scenario with a greater assumed protective effect of alcohol, hence lower relative risk for the intermediate drinking categories, would produce larger numbers of deaths prevented. The lower relative risk implies that the mortality rate is lower, and everything else being equal, the number of deaths should be lower. Scenario 1, with an assumed protective effect of alcohol greater than that in scenario 2, projects larger numbers of CHD deaths prevented.

The area under each of the curves is the total number of CHD deaths prevented over the 48 year span of the simulation. Table 4-3 below presents these numbers separately by sex. The "percentage difference from base" column provides the percentage difference in the projected number of CHD deaths prevented from *the*

Figure 4-6



projected number of CHD deaths prevented in the base scenario. This is not meant to imply that the base scenario is the correct scenario. The base scenario is used simply as a reference point against which the other scenarios can be compared and the percentage difference can be positive or negative. A large gap in the "percentage difference from base" between Scenario 1 and Scenario 2 would suggest that the varying the relative risk has a substantial effect on results, whereas a small gap suggests that varying relative risk has little consequence for the results of this analysis. It should be evident that the gap of

Table 4-3 Effect of Relative Risk on Number of Deaths Prevented

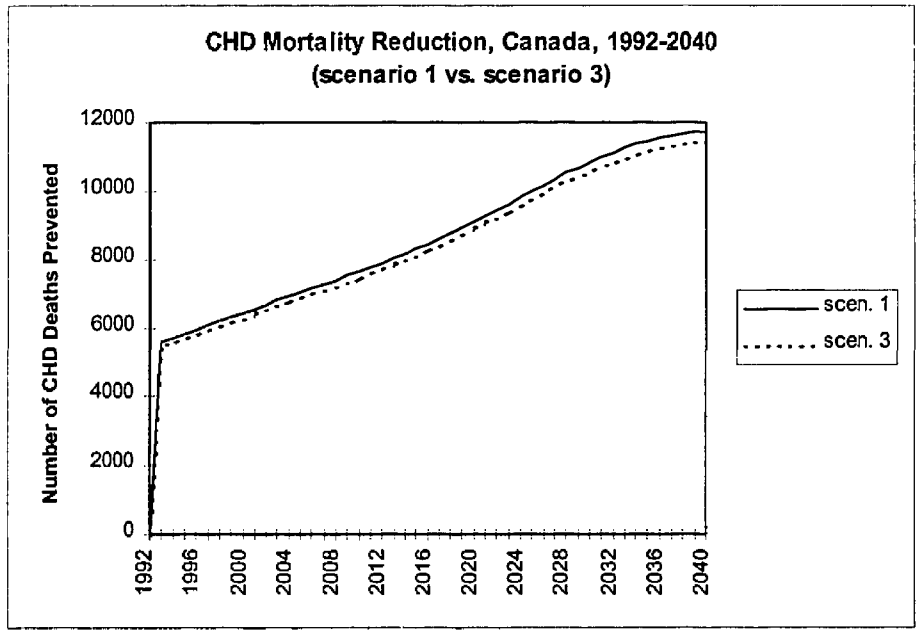
		Number of Deaths Prevented	Percentage Difference from Base
Scenario 1	Male	251000	+58%
	Female	167000	+56%
	Total	418000	+58%
Scenario 2	Male	164000	+3%
	Female	94000	-12%
	Total	259000	-3%

61 (58% + 3%) suggests that the uncertainty in relative risk values has a substantial effect on projections. Note that the gap is greater for females (68) than males (55).

A recent review of research suggests that the cardioprotective effect of alcohol exists in a dose range of 10 to 20 grams of alcohol per day.[26] This is equivalent to "five-sixths" to "one and two-thirds" standard drinks per day. In this analysis, the categories close to "five-sixths" to "one and two-thirds" drinks per day are the > *0.5 to 1.0 drinks/day* category and the > *1.0 to 1.5 drinks/day* category. In scenarios 1 and 2, the lowest risk category is the > *1.0 to 1.5 drinks/day* category. To permit a sensitivity analysis on the category with lowest risk, scenarios 3 and 4 use the > *0.5 to 1.0 drinks/day* category as the lowest risk category.

Figure 4-7 suggests that mortality reduction varies in the direction expected. If two scenarios differ by the category chosen as lowest risk category, then whether mortality reduction differs between the two should depend on the prevalence estimates for each of the categories (everything else being equal). The scenario with the lower prevalence of exposure in the lowest risk category should have the greater reduction in mortality. The lower prevalence of exposure implies that, compared to the other scenario, the other exposure categories have higher prevalences. A 50% intervention, for example, on higher prevalences moves more individuals to the lowest risk category than a 50% intervention on lower prevalences. From Section 3.3.1 we know that scenario 1 has lower prevalence estimates in the lowest risk category than scenario 3. Figure 4-7, below, suggests that CHD mortality reduction is greater in scenario 1 than in scenario 3. The choice of lowest risk category appears to have a much smaller impact on PREVENT projections for CHD mortality reduction than do the relative risk values. In fact, the

Figure 4-7



number of CHD deaths prevented over the 48 year simulation period (418000) in scenario 1 is only 10,000 deaths greater than the number of deaths prevented in scenario 3. Scenarios 2 and 4 also differ little in the projected number of death prevented (not shown).

Table 4-4 Effect of Lowest Risk Category on Number of Deaths Prevented

		Number of Deaths Prevented	Percentage Difference from Base
Scenario 1	Male	251000	+58%
	Female	167000	+56%
	Total	418000	+58%
Scenario 3	Male	245000	+54%
	Female	162000	+51%
	Total	408000	+53%

4.2.1 Cohort vs. Age-Group Analysis

PREVENT provides a number of different analysis options which can have an important effect on the outcome. Significant among these is the option to treat the exposure of

interest as a cohort characteristic or as an age-group characteristic. If alcohol consumption is treated as a cohort characteristic, then, as the population ages, the proportions within an age group that fall into the different alcohol consumption categories are assumed to move with the aging individuals. If alcohol consumption is treated as an age-group characteristic, then, the proportions for a specific age group are assumed to be static and apply to each new wave of individuals passing through the age group.

Scenarios 1 through 4, described in the previous section, all assume that alcohol consumption is an age-group characteristic. All four scenarios have been repeated (as scenarios 5 through 8) assuming that alcohol consumption is a cohort characteristic.

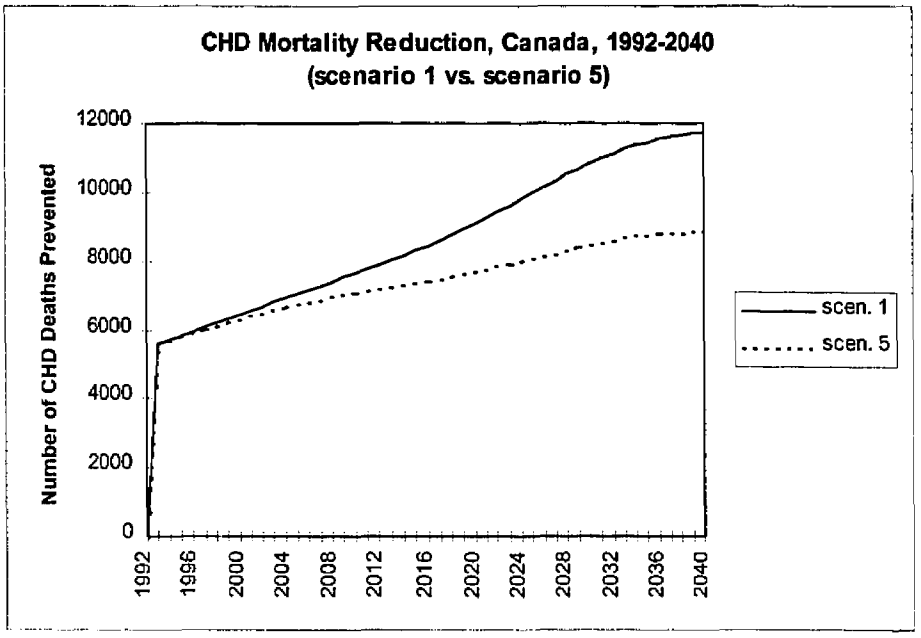
Table 4-5 Age-Group vs. Cohort Analysis Comparisons

Relative Risk at Low Point of J-Curve	Category with Lowest Relative Risk	Age-Group Analysis	Cohort Analysis
0.5	> 1.0 to 1.5	scenario 1	scenario 5
0.7	> 1.0 to 1.5	scenario 2	scenario 6
0.5	> 0.5 to 1.0	scenario 3	scenario 7
0.7	> 0.5 to 1.0	scenario 4	scenario 8

Figure 4-8 suggests that the age group vs. cohort analysis option has the expected impact on mortality reduction. Since the age group simulation and the cohort simulation both begin with the same exposure prevalences in the each age category, once would expect mortality reduction to be similar in the early years of the simulation. As time passes, individuals in one age group move into the next age group. In the cohort simulation, these individuals take their exposure level with them. This differs from the age-group simulation where these individuals adopt the exposure level of the age-group they enter.

From Section 3.3.3, we know that the younger age categories tend to have lower prevalences in the higher risk exposure categories. This means that in the cohort analysis, as the simulation progresses, the impact of the intervention will diminish as smaller and smaller proportions of the population are moved from higher risk exposure categories to the lowest risk exposure category. Thus we would expect the age-group simulation to project higher mortality reduction than the cohort simulation. Figure 4-8 shows that scenario 1, an age-group simulation, begins with a similar mortality reduction to scenario 5, a cohort simulation, but diverges as the simulation progresses. By 2040, the age-group analysis scenario is projected to reduce CHD mortality by 11,700 deaths per year compared with only 8,900 deaths per year for the cohort analysis scenario.

Figure 4-8



Comparing the total number of deaths prevented over the 48 year simulation period, it is apparent that the choice of age-group vs. cohort analysis has a sizable effect on the projected number of CHD deaths prevented. The gap in percentage difference (23%) is

larger than that for the sensitivity run on choice of lowest risk category (gap of 5%) but smaller than that for the sensitivity run on relative risk (gap of 61%). Unlike relative risk, however, the gap due to the variation of analysis type is smaller for females (18%) than males (26%).

Table 4-6 Effect of Analysis Type on Number of Deaths Prevented

		Number of Deaths Prevented	Percentage Difference from Base
Scenario 1	Male	251000	+58%
	Female	167000	+56%
	Total	418000	+58%
Scenario 5	Male	210000	+32%
	Female	148000	+38%
	Total	358000	+35%

The other three comparisons (scenario 2 vs. scenario 6, scenario 3 vs. scenario 7, and scenario 4 vs. scenario 8) may be used to explore the possibility that the above gaps are dependent on the relative risk values and the choice of lowest risk category. Table 4-7 shows that there may be interaction, although without confidence limits, it is impossible to tell whether these results are due to chance or not.

The greatest gaps in the "percentage difference from base" belong to the scenario 3 vs. scenario 7 comparison and the scenario 1 vs. scenario 5 comparison (53% - 30% = 23% and 58% - 35% = 23%, respectively). The driving force behind these large gaps is the greater assumed cardioprotective effect of alcohol (0.5 relative risk for lowest risk category). These two comparisons differ, however, when gender is taken into account. The scenario 1 vs. scenario 5 comparison has a gap of 26% for males and 18% for females, but the scenario 3 vs. scenario 7 comparison has a gap of 24% for males and a gap of 21% for females. This is primarily due to the effect of the choice of lowest risk

category which lowers the number of deaths prevented in scenario 7 in comparison to scenario 5.

Note that in scenario 7, the number of deaths prevented is lower than in scenario 5, but in scenario 8, the number of deaths prevented is about the same as in scenario 6. The effect of the choice of lowest risk category noted above is balanced by a decreased cardioprotective effect of alcohol.

Table 4-7 Effect of Analysis Type on Number of Deaths Prevented

		Number of Deaths Prevented	Percentage Difference from Base
Scenario 2	Male	164000	+3%
	Female	94000	-12%
	Total	259000	-3%
Scenario 6	Male	136000	-14%
	Female	84000	-21%
	Total	220000	-17%
Scenario 3	Male	245000	+54%
	Female	162000	+51%
	Total	408000	+53%
Scenario 7	Male	206000	+30%
	Female	139000	+30%
	Total	345000	+30%
Scenario 4	Male	165000	+3%
	Female	94000	-12%
	Total	259000	-3%
Scenario 8	Male	142000	-11%
	Female	84000	-21%
	Total	225000	-15%

4.2.3 Varying the Time Spread of the Intervention

An intervention can have a fairly swift impact on exposure levels in a population or it may take years for the intervention effect to reach its maximal level. This section will examine the impact of varying the time spread of the intervention (i.e., the time between

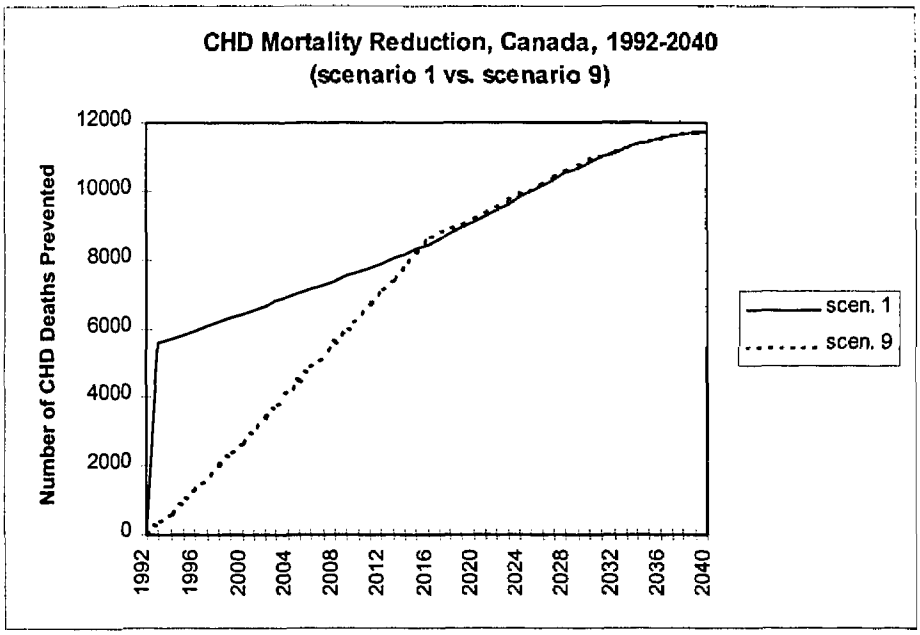
the beginning of the intervention and the point of maximal intervention effect) on CHD mortality reduction. Table 4-8 shows that the two basic scenarios compared in this analysis are a one year time spread and a 24 year time spread. A 48 year time spread is not used because the simulation period is 48 years and the intervention starting date is a variable that will be explored in the subsection 4.4.2 (an intervention with a 48 year time spread and a start date after 1992, the simulation start date, would go beyond the simulation period).

Table 4-8 Intervention Time Spread Comparisons

Relative Risk at Low-Point	Category with Lowest Relative Risk	Analysis Type	One Year Time Spread	24 Year Time Spread
0.5	> 1.0 to 1.5	age-group	scenario 1	scenario 9
0.7	> 1.0 to 1.5	age-group	scenario 2	scenario 10
0.5	> 0.5 to 1.0	age-group	scenario 3	scenario 11
0.7	> 0.5 to 1.0	age-group	scenario 4	scenario 12
0.5	> 1.0 to 1.5	cohort	scenario 5	scenario 13
0.7	> 1.0 to 1.5	cohort	scenario 6	scenario 14
0.5	> 0.5 to 1.0	cohort	scenario 7	scenario 15
0.7	> 0.5 to 1.0	cohort	scenario 8	scenario 16

Since a longer time spread of the intervention implies that population has less time to be affected by the intervention at its maximal level, one would expect mortality reduction to be lower for scenarios with longer time spreads (everything else being equal). Figure 4-9 shows that scenario 9, the 24 year time spread scenario, doesn't reach its maximal intervention effect until the year 2016, at which time its effect is the same as scenario 1, the one year time spread scenario. Thus mortality reduction is lower for the scenario with a longer intervention time spread. Note that PREVENT assumes that the effect of an intervention on prevalences of exposure lasts after the actual intervention has ceased.

Figure 4-9



The number of CHD deaths prevented per year clearly differs the most in the early years of the intervention. The implication for the total number of deaths prevented over the simulation period is that scenario 1 can be expected to be more effective than scenario 9 (as suggested by the area under the curves). The table below shows that PREVENT projects 418,000 prevented deaths in scenario 1 but only 357,000 prevented deaths in scenario 9.

Table 4-9 Effect of Intervention Time Spread on Number of Deaths Prevented

		Number of Deaths Prevented	Percentage Difference from Base
Scenario 1	Male	251000	+58%
	Female	167000	+56%
	Total	418000	+58%
Scenario 9	Male	214000	+35%
	Female	143000	+34%
	Total	357000	+34%

Figure 4-10, below, shows that for all the one year vs. 24 year comparisons, the number of CHD deaths prevented is reduced when the intervention is spread over 24 years (it is likely that the decrease in deaths prevented follows a straight line as shown). For ease of interpretation, those scenarios which assume the > *0.5 to 1.0* category is the lowest risk category are not graphed (i.e., scenarios 3, 4, 7, 8, 11, 12, 15, and 16). Varying the category with lowest risk has already been shown to produce little variation in the number of CHD deaths prevented. Figure 4-12 suggests that the fall in deaths prevented is greater for the "scenario 1 vs. scenario 9" and "scenario 5 vs. scenario 13" comparisons than the other two comparisons.

Figure 4-10

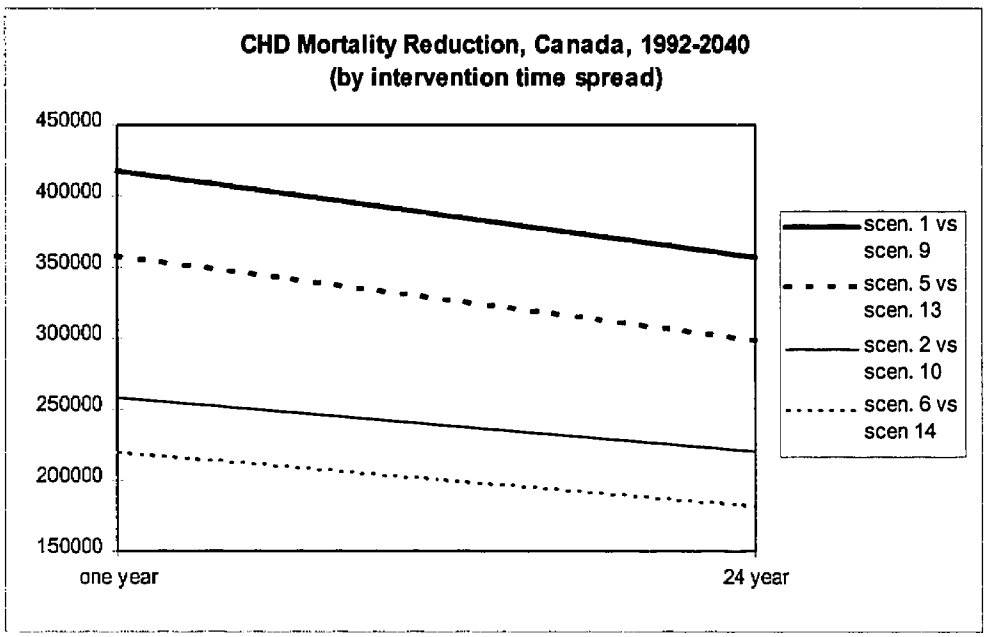


Table 4-10 confirms that the slopes of the lines do appear to differ. The driving force behind the difference of 20,000 deaths appears to be the relative risk values.

Table 4-10 **Difference in Deaths Prevented by Intervention Time Spread Comparison**

	Difference in Number of Deaths Prevented
Scenario 1 vs. Scenario 9	61000
Scenario 5 vs. Scenario 13	60000
Scenario 2 vs. Scenario 10	38000
Scenario 6 vs. Scenario 14	37000

4.2.4 Varying the Starting Year of the Intervention

The last variable to be examined in this paper is the starting year of the intervention. This variable may have an impact on the number of CHD deaths prevented because the proportion of individuals in each age category can differ at different points in time, i.e., due to population evolution. As the simulation progresses, individuals pass from one age category to the next, with some individuals dying (the number depends on the total mortality rate for the previous age category). This implies that the population affected by the intervention varies over time. This will probably mean differences in absolute outcome measures like the number of CHD deaths prevented. In this particular case, the number of CHD deaths prevented in Canada will be compared for two different intervention start dates: 1992 and 2002.

Note that the lower boundary for the starting year of the intervention is the start year of the simulation, but that strictly speaking there is no upper boundary because the starting year of the intervention is determined by the initiator of the intervention. Thus the sensitivity run reported in this subsection is not based on uncertainty in the values for the starting year of the intervention. Rather, it is a test of whether variation in the starting year of the intervention produces the expected results in CHD mortality reduction. As in

previous subsections, a 50% intervention is used.

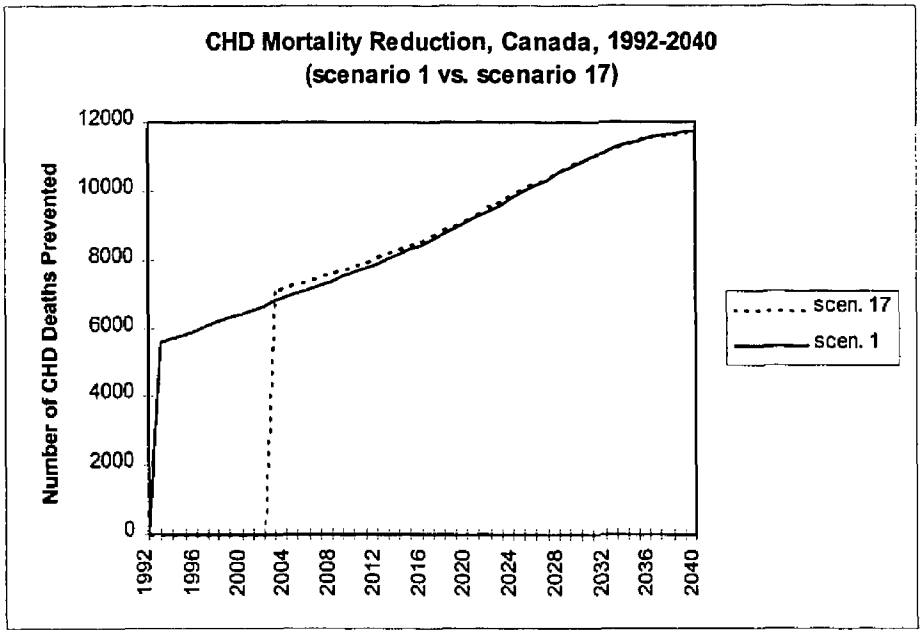
Table 4-11 Intervention Starting Year Comparisons

Relative Risk at Low-Point of J-shaped Curve	Analysis Type	Time Spread of the Intervention	1992 Intervention Start Date	2002 Intervention Start Date
0.5	age group	one year	scenario 1	scenario 17
0.7	age group	one year	scenario 2	scenario 18
0.5	cohort	one year	scenario 5	scenario 21
0.7	cohort	one year	scenario 6	scenario 22
0.5	age group	24 year	scenario 9	scenario 25
0.7	age group	24 year	scenario 10	scenario 26
0.5	cohort	24 year	scenario 13	scenario 29
0.7	cohort	24 year	scenario 14	scenario 30

The expected results depend on how the population structure for 1992 (see subsection 3.2.1) differs from the projected population structure for 2002. This largely depends on the mortality rates in each age category (and birth rate for the two youngest age categories). It is not obvious from the material presented in this paper how the population structure will differ. Fortunately, others have worked to provide these type of projections; George et al. [43] project that the "christmas tree with a thick trunk" population pyramid for Canada in 1993 will evolve into "pot with lid" population pyramid in 2016 and an "urn" population pyramid by 2041 (see following page). Delaying the starting year of the intervention will obviously reduce the total number of deaths prevented in the 48 year simulation period. However, the population pyramids suggest that the number of deaths prevented in the first year of the intervention should be greater in the scenario with a intervention starting year of 2002 than in the scenario with an intervention starting year of 1992, because there are larger numbers of individuals in the upper age categories in the

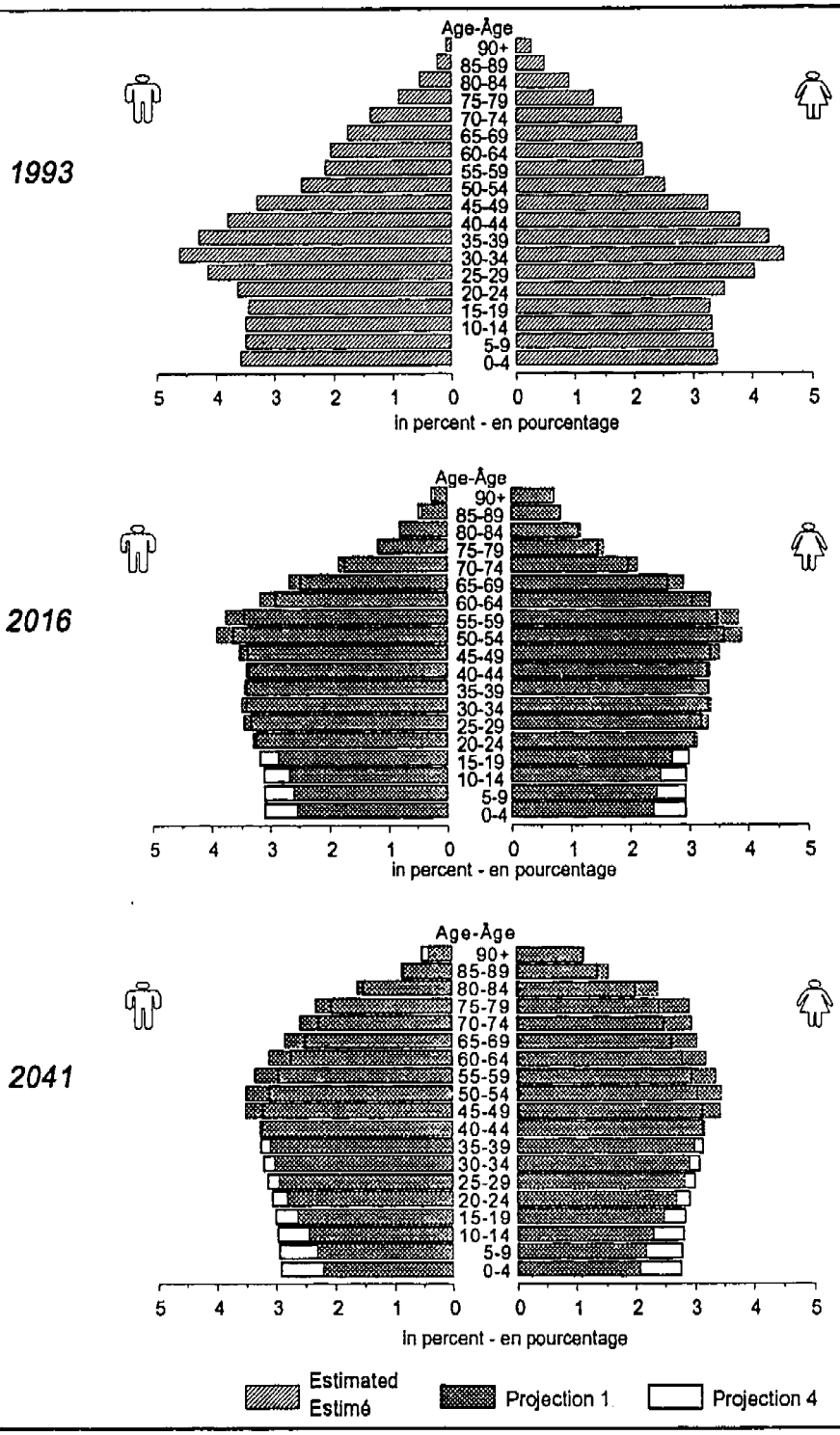
former case. Figure 4-11 shows that scenario 17, with a intervention starting year of 2002, begins with a mortality reduction in excess of that for the first year of scenario 1 which has an intervention starting year of 1992.

Figure 4-11



As would be expected, there is an impact in terms of the number of CHD deaths prevented because delaying the start of the intervention means there is less time within the simulation to change exposure in the population. In this particular case, Table 4-12 shows that a 1992 vs. 2002 intervention starting date results in a projected 57,000 difference in CHD deaths prevented. Of course, if the simulation is extended beyond 48 years, one would expect the difference in the number of CHD deaths prevented to be much smaller. In this particular analysis, the simulation cannot be extended because birth projections are not available beyond 2040.

Figure 4-12 Population by Age Group and Sex, Canada, 1993, 2016, and 2041



Source: George MV, Norris MJ, Nault F, Loh S, Dai SY. Population Projections for Canada, Provinces and Territories 1993-2016. Ottawa: Statistics Canada, 1994.

Table 4-12 Effect of Starting Year of Intervention on Number of Deaths Prevented

		Number of Deaths Prevented	Percentage Difference from Base
Scenario 1	Male	251000	+58%
	Female	167000	+56%
	Total	418000	+58%
Scenario 17	Male	216000	+36%
	Female	144000	+35%
	Total	361000	+36%

Plotting the projected number of CHD deaths prevented reveals that there appear to be some small differences in the effect of varying the starting date of the intervention, depending on which two scenarios are compared (note that the lines are used for clarity and not to imply that CHD mortality reduction follows a straight line from a 1992 intervention starting date through to a 2002 intervention starting date). The slopes of the "scenario 1 vs. scenario 9" comparison and the "scenario 5 vs. scenario 13" comparison are similar, as are the slopes of the "scenario 9 vs. scenario 25" comparison and the "scenario 13 vs. scenario 29" comparison, suggesting that the analysis type (age-group vs. cohort) does not modify the effect of intervention starting date. However, the slope of the "scenario 1 vs. scenario 9" comparison differs from both the "scenario 2 vs. scenario 10" comparison and the "scenario 9 vs. scenario 25" comparison suggesting that the relative risk values and the time spread of the intervention both independently modify the impact of the starting date of the intervention (but in opposite directions).

An examination of the actual projected number of deaths appears to support these conclusions (although, without confidence limits, it can't be concluded that the observed differences aren't within the boundaries of error).

Figure 4-13

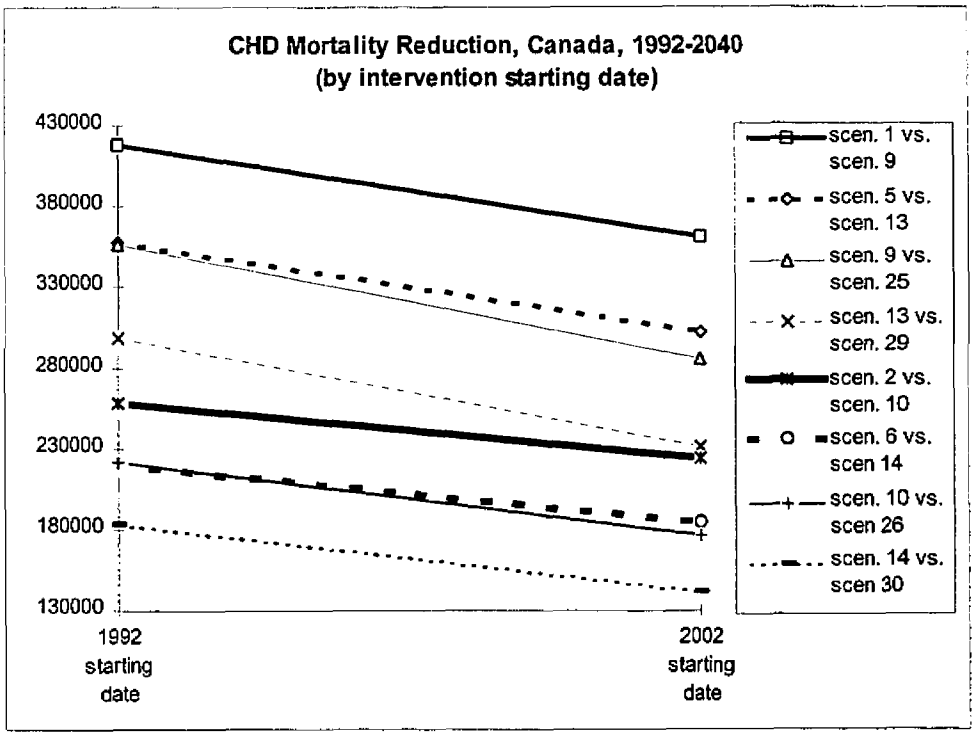


Table 4-13 **Difference in Deaths Prevented by Intervention Starting Year Comparison**

	Difference in Number of Deaths Prevented
Scenario 1 vs. Scenario 9	61000
Scenario 5 vs. Scenario 13	60000
Scenario 9 vs. Scenario 25	72000
Scenario 13 vs. Scenario 29	67000
Scenario 2 vs. Scenario 10	38000
Scenario 6 vs. Scenario 14	37000
Scenario 10 vs. Scenario 26	44000
Scenario 14 vs. Scenario 30	41000

5. Discussion

The results of the analyses suggests that PREVENT has the potential to be a useful tool for population health planning. While other models oversimplify population modeling or make unrealistic demands for input data, PREVENT balances data availability and level of data stratification in such a way as to make projections possible but potentially still useful. The option to provide greater detail in input data is often available in PREVENT, but is usually not a requirement for projections. This flexibility means that projections can usually be done with the best available data.

The sensitivity analysis in the context of alcohol and CHD mortality revealed that PREVENT responds to the values of the input variables in a way that is anticipated based on variation of the input data. Variation in some input variables produces greater variances in CHD mortality reduction than others (e.g., variation in the relative risk produced a difference of about 60% in CHD mortality reduction projections but other variables, such as the category with lowest risk, age group versus cohort analysis, and the time spread of the intervention produced mortality reduction ranges that were notable but not as large) but the direction in which mortality reduction changed was always consistent with expectations.

As has been previously mentioned, the sensitivity analysis only partially addresses the question of validity. A valid model should produce changes in output (e.g. mortality reduction) in the direction expected with changes in input data. However, a model can change its projections in the right direction but still produce invalid results because the magnitude of the change is too small or large. Ascertainment of this aspect of validity

must be done by comparing projections with actual data (either historical or prospectively collected). Since historical testing is impossible for many risk factor/disease combinations and prospective follow up impractical except in the long term, we are forced to make assumptions about the validity of the model.

If the results are valid, it is apparent that the relative risk sensitivity analysis produced the largest variation in mortality reduction. This may be attributable to the large degree of uncertainty surrounding relative risk in the context of alcohol and CHD mortality. The U-shaped or J-shaped curve is controversial partly because the results published by various investigators differ so widely. This makes alcohol/CHD mortality an ideal context in which to test PREVENT because if PREVENT produces useful results even with fairly large variation in relative risk values then it can potentially handle most risk factor/disease combinations where the range in relative risks may not be as large. The definition of "usefulness" depends on the health planner, but it might be that variations in mortality reduction projections that are an order of magnitude smaller than total projected CHD mortality are useful for planning purposes. Section 4.1 showed that annual CHD mortality would increase from about 25,000 deaths to 40,000 deaths over the simulation period. Subsection 4.2.1 showed that the difference in projected mortality reduction between the relative risk scenarios would increase from about 2,000 deaths to 5,000 deaths over the simulation period (some of the input variables differ between the base scenario CHD mortality projection and the relative risk sensitivity analysis projection, but this example is for illustration). These figures suggest that the variation in mortality reduction is an order of magnitude less than the projected CHD mortality.

The methodological basis for PREVENT described in the Background section

suggests that PREVENT is designed in a sound manner, and for this reason one might assume that the results are valid, even though only prospective data collection will truly reveal whether PREVENT produces valid results for some risk factor/disease combinations. If the results are valid, this analysis suggests that an intervention on alcohol can have a clear impact on both overall and CHD mortality, at least theoretically. A 50% intervention is projected to produce a yearly mortality reduction in the low thousands per year. Even a 10% intervention could prevent almost a thousand deaths a year. Part of the reason for the large numbers is, of course, the fact that CHD is a major cause of mortality in Canada. A PREVENT analysis on another cause of death might not provide nearly as dramatic an intervention effect on mortality.

The sensitivity analyses done in this paper suggests that the general shape of the mortality reduction curve does not depend on relative risk values used as input data but the magnitude of the reduction does depend on these values. PREVENT calculates that for alcohol/CHD mortality, the extremes of the relative risk range produce as much as a 60% difference in projected mortality reduction. With annual mortality reduction projected to be in the low thousands, this kind of variation translates into substantial numbers of deaths and can have significant implications for resource planning.

The sensitivity analyses also project variation on the order of about 60,000 prevented CHD deaths over the simulation period for both the choice of analysis type (age-group or cohort) and the starting year of the intervention. The choice of analysis type is more important as the length of the simulation increases. The choice of the category with lowest relative risk, subject to much speculation in the literature, appears to have a minimal effect on the projected number of prevented CHD deaths. This

information on the magnitude of the change in projections may be useful for prioritizing further efforts. If uncertainty in relative risk values causes greater variation in results than the issue of age-group vs. cohort analysis, then perhaps further research should concentrate on narrowing the range of relative risk values before establishing whether the risk factor is best modeled in a cohort model or an age-group model.

The rest of this section is mostly a discussion of the implications for the projections of the model's assumptions and limitations. Some of the issues are raised for the sake of completeness but others are problems which could potentially be resolved in a future release of PREVENT.

The final subsection is a discussion of the substantive consequences of this analysis.

5.1 Assumptions and Limitations of PREVENT

Although there is overlap between the two categories of issues, the order of presentation in this subsection will roughly be to first address issues surrounding the input data and then tackle issues surrounding the methodology PREVENT uses for projections.

Data availability and quality issues are not unique to PREVENT. Much of the input data needed by PREVENT must be taken from the international literature. While some publications might be classified as reports on surveillance, much of the epidemiologic literature is oriented toward testing aetiologic hypotheses and not with population disease modeling in mind. Considerations of power and sample size mean that data may not be stratified by the needed variables. Or data may be stratified but the

cut-points may differ from publication to publication. These types of problems suggest the need for easy access to data warehouses. Just as peers should be able to access data on which journal articles are based to satisfy their own curiosity about published results, those interested in disease modeling should be able to access potential input data as required by any population model. Some funding institutions, particularly in the U.S., have made it mandatory for investigators to archive data in order to receive financial support. This is a step in the right direction.

One might also argue that the problem of variable cut-points can be lessened by adopting non-categorical models, e.g., logistic models. This might help for some variables like age, but for other variables (e.g., alcohol consumption), the value of a continuous variable may be minimal. Most surveys of alcohol consumption are crude estimates of drinking behaviour at best because they rely on respondent recall (of quantity and frequency of drinking) and depend on the respondent's ability to correctly estimate an average or "usual" value for number of drinks consumed on an occasion or the frequency of drinking over a given time period. Volume of alcohol consumed is then calculated by combining quantity and frequency information, but since this is a calculated value, the uncertainty about the value is even greater than that about each of the components. Perhaps the best population model isn't one that forces a choice between continuous or categorical input forms but one that presents the option of analyzing the input data either way for comparison.

In this paper, prevalence estimates were stratified by sex and age group. It should be noted, however, that these are not the only variables on which stratification can be done. Socioeconomic status (SES) and race/ethnicity has been shown to be

independently associated with risk for some diseases. Unfortunately, there is no standard definition for SES, making comparison of different studies extremely difficult. Race/ethnicity also suffers from problems of definition although not to the same extent. Relative risks for diseases like sickle cell anemia are probably adequately stratified with race/ethnicity values like African, European, Oriental, and South Asian, but it is not clear whether this holds for other risk factors/diseases.

The variation in values for input data in the literature presents problems. Confidence limits on the input data (e.g., relative risk, prevalence estimates) that could be translated into confidence limits on the output (i.e., number of deaths prevented) would provide the ability to distinguish between factors that have a statistically significant impact. However, the number of studies with sample sizes large enough to provide narrow confidence limits on mortality reduction estimates is likely very small because of the numerous calculations with estimated quantities that are made in moving from prevalence and relative risk estimates to mortality reduction estimates.

Finally, there is the issue of the length of the simulation period. Ideally, one would like projections for as long a simulation period as possible because the more information one has about future developments, the more opportunity there is to plan or intervene. In this analysis, a 48 year simulation period was used because birth projections were available up to 2040. However, some of the modeling assumptions are stronger early in the simulation and much weaker towards the end of the simulation period. Changes in all-cause mortality rates and the effects of immigration (discussed below) fall into this category of assumptions. There is no simple way of determining a "'cut-off" point for projections because the model assumptions can differ in when they become

weaker.

Aside from input data issues, there are also a number of methodological issues surrounding PREVENT projections. As described in the Background section, the disease modeling aspect of PREVENT falls under the classification of attributable risk models. These types of models necessarily require exposure or risk factor prevalence information and relative risks associated with different levels of exposure for an outcome such as mortality. In modeling diseases for which risk factor prevalence data is readily available, an attributable risk model may be adequate, but for others, where exposure prevalences may change rapidly, it quickly becomes apparent that an attributable risk based model can present problems.

For example, measuring the prevalence of exposure to risk factors for HIV infection is virtually impossible. Even if information about the sexual behaviours or drug use of individuals can be measured, and this is difficult in a general population because of the sensitivity of the topic, it does not necessarily follow that the information about exposure to risk factors has been obtained. It is impossible to tell from the respondent alone whether a sexual encounter or IV drug use exposed them to a risk factor like HIV. It might be possible to estimate the prevalence of exposure by working backwards from the number of deaths and various rates (i.e. case fatality rate, rate of infection upon exposure) but this approach has flaws (e.g. some rates will be based on clinical trials, treatments are constantly changing). Considering these problems, it may be that other disease modeling approaches are more appropriate for some risk factor/disease combinations.

The demographic component of PREVENT is based on the commonly used life

table methodology for population projections. However, PREVENT provides little in the way of direct output from its population modeling component. Not only does it make certain comparisons impossible (for example, it would be useful to compare the internally generated life expectancy table with similar tables produced by Statistics Canada) but interpretation of results is hampered. An updated version of PREVENT which provides these projections should be straightforward since PREVENT must generate these figures internally anyway in order to provide intervention effect estimates.

One shortcoming of the population modeling component of PREVENT is evident even without access to the output: PREVENT does not take into account immigration patterns in its population modeling. In the Netherlands, where population immigration accounts for a relatively small proportion of changes in population structure from year to year, this simplification does not present a problem. In Canada, however, immigration accounts for a substantial proportion of population structure changes from year to year. Badets [74] reports that 1,238,455 immigrants came to Canada between 1981 and 1991 . If the annual immigration numbers can be approximated as 120,000/year, it is clear that immigration accounts for one-seventh (14%) of population structure change from year to year (there are about 400,000 births a year and 200,000 deaths a year in Canada -- see Sections 3.2.2 and 3.2.3). Obviously, immigrants arrive in Canada at various ages, so it is not possible to add immigration projections to yearly birth projections. However, the impact for this particular analysis of alcohol-CHD may not be that great since almost all immigrants to Canada are under 45 years of age (37% of immigrants were aged 25 to 44 when they came to Canada, 27% were 15 to 24, and 28% were under 15[74]). Since the high CHD mortality rates do not begin until about age 55 for males and age 65 for

females (see Sections 3.2.5 and 3.2.2), it is likely that the first twenty or so years of projections in this paper for number of CHD deaths prevented are not substantially different from what would have been projected had immigration been taken into account.

As discussed in the Background section, PREVENT makes some assumptions about the interaction of the effect of risk factors on diseases. There is general uncertainty in biological models whether the risk associated with exposures combines additively or multiplicatively. Gunning-Schepers opted to assume a multiplicative model. The obvious advantage of this assumption is that the effect of one risk factor on outcome is assumed to be independent of the effect of other risk factors. This makes the use of data from aetiologic investigations possible since relative risks for the joint effect of exposures are rarely published. Indeed, in this analysis, only the effect of alcohol was considered, and this exclusive type of analysis was possible only because PREVENT is a multiplicative model. Had an additive model been assumed, it would have been necessary to consider the combined effect of alcohol with other significant risk factors for CHD like tobacco use and diet. Some researchers who have explored the issue of additive models versus multiplicative models have concluded that the use of multiplicative models is reasonable in situations where specific data are lacking [75] or for specific groups of diseases.[36]

Another issue has to do with the assumption PREVENT makes about exposure prevalences after the end of the intervention (but before the end of the simulation). PREVENT assumes that once an intervention ends, the adjusted exposure prevalences remain as they are for the remainder of the simulation period. This is separate from modeling the effect of trends in exposure prevalences. Trends are assumed to be

independent of the intervention and apply throughout the simulation period. PREVENT is capable of modeling trends in addition to the intervention although this has not been done in this analysis because unlike some exposures, e.g. smoking, alcohol consumption prevalences have been fairly stable in Canada. However, PREVENT is not capable of modeling "elastic" risk factors. It is typical for some interventions to affect prevalence of exposure as long as they are being implemented but once they cease, the tendency is toward an 'undoing' of the intervention effect. Interventions to promote condom use among adolescents might be an example of this kind of elastic risk factor. There is a wealth of information on the temporary effect of interventions like media programs, and legal changes surrounding impaired driving, unless there is reinforcement. Tax changes are perhaps one of the few interventions which have a long-term effect (but even there a proportion of the population will find ways to get around the tax).

The issue of cohort versus age-group analysis noted above must also be considered. That PREVENT provides this option at all is evidence of the sophistication of the model compared to other models (see Table 2-1 in subsection 2.3.3), but this choice in analysis also brings with it some new problems. It is reasonably clear which of the two types defined by PREVENT (age-group or cohort) some risk factors fall under, e.g., hypertension is strongly associated with age and can thus be considered an age-group characteristic. Many risk factors and exposures, however, do not fit neatly into either category. Tobacco use and alcohol consumption are of this latter type. It is likely that alcohol use has both cohort and age-group aspects. PREVENT only provides the option to choose one or the other. It would be desirable to be able to define a mix of cohort characteristic and age-group characteristic for a risk factor exposure.

The mortality rates which are input for the base year of the simulation are used for every year of the simulation. Over a ten year period, the mortality rates may not vary too greatly (although for certain subpopulations, advances in treatment have had a marked effect on mortality rates, e.g., infants and advances in cardiovascular surgical procedures). However, over a fifty year period, the mortality rates can fluctuate notably, especially considering that mortality rates are input into PREVENT stratified by sex and five-year age group. Among adults, improved diet, healthier lifestyles, and advances in health care exert a downward pressure on mortality rates in all but the uppermost age categories. The advent of new diseases with high case fatality rates, e.g., AIDS, exert an upward pressure on mortality rates. In sum, mortality rates can change (and have changed in the past) and the simplification PREVENT makes in assuming static mortality rates can lead to error in projected prevented deaths.

PREVENT is fairly sophisticated in that it incorporates time dimension concepts like latency period (time between disease incidence and death) and lag time (time between cessation of exposure, if it occurs, and a reduction in risk to the lowest possible risk for a formerly exposed individual). However, PREVENT does not include adjustments for lead time (time between beginning of exposure and the upward movement of risk to the point of maximum risk for the category). In practice, lead time data are rarely available in the literature. Nonetheless, it may be of interest to explore the effect of lead time on projected prevented deaths through a sensitivity analysis. It should also be noted that for lag time, the reduction in risk is assumed to occur in a linear (straight line) fashion, which may be a reasonable assumption for some diseases but not for others.

5.2 Consequences of this Analysis

The two objectives of this paper were:

(1) to use the PREVENT model to estimate the potential effect of interventions on alcohol consumption for projected CHD mortality and related measures in Canada

(2) to provide some evidence for the validity of the results in (1) by performing sensitivity analyses with PREVENT

The sensitivity analyses has provided evidence for the validity of the results, although not to the exclusion of the possibility that the magnitude of changes in mortality reduction are incorrect. Comparisons with historical or prospectively collected data are needed to confirm the validity of the model.

With regard to the first objective, the results suggest that the theoretical intervention modeled can have a significant impact on CHD mortality. A 50% intervention is projected to prevent between 200,000 and 400,000 deaths over the length of the simulation. Even a 10% intervention could prevent almost a thousand deaths a year. These are not numbers to be ignored, but do the results then suggest that the intervention modeled in this paper should be seriously considered as a public health intervention? Unfortunately not.

First, the benefits achieved in this analysis were largely achieved by moving the bulk of the population in the abstainer category to the drinking category with lowest risk (either > *0.5 to 1.0 drinks/day*, or >*1.0 to 1.5 drinks/day*). Such an intervention may be of theoretical interest, but there is no evidence to support the idea that such an intervention would actually work. In fact, some research has shown that this type of intervention is likely to fail. There is the added complication that this theoretical

intervention moves different alcohol consumption subpopulations in different directions, i.e., it moves abstainers to drink and drinkers at the high end of the spectrum to lower consumption levels.

Second, as mentioned in the Introduction, no general conclusion can be made about the benefits or advantages of alcohol consumption as a result of the analyses in this paper, and such a general conclusion is necessary before any intervention on alcohol consumption can be advocated. The primary outcome in this analysis has been CHD mortality and CHD mortality reduction. As discussed in the Background section, there are many other diseases related to alcohol consumption. Any analysis aimed at making a general statement about the benefits or advantages of alcohol consumption must take into consideration all of these other diseases, and preferably look at multiple outcomes, such as mortality, mortality reduction, morbidity, PYLL, sick days, income lost, etc..

6. Conclusion

The PREVENT analysis done in this paper has been an interesting exercise in population disease modeling. It has served both as a test of the validity of the PREVENT model and an exploration of the effect of theoretical alcohol consumption interventions on CHD mortality.

The sensitivity analyses have provided some support for the validity of the model, and the projected mortality reduction is of an order of magnitude which suggests that the relationship between alcohol and CHD mortality and the distribution of the population in alcohol consumption categories provides ample opportunity for interventions, at least theoretically.

It appears that Gunning-Schepers has succeeded in developing a model which combines demography and epidemiology to produce a useful tool for population health planning. Issues as to how the projections will compare to actual data remain, but these issues are no different from the questions of validity that can be asked of all population projection models. The results in this paper at least do not refute the validity of the model, and suggest that PREVENT is useful at demonstrating for which risk factors and diseases one can expect interventions to produce substantial results.

Further work on the model should focus on accumulating evidence for the validity of the model, expanding the scope of its use to other domains, modifying the model to address some of the issues raised in the Discussion, and finally, performing analyses which compare the beneficial and harmful effects of exposures for a particular outcome measure, e.g., the effect of alcohol on CHD mortality compared to the effect of alcohol

on breast cancer and other disease mortality.

Further modifications, together with the potential prospective validation of the model in various of areas of inquiry, would transform this model from one with potentially useful results to one with great utility. In any case, it appears that PREVENT advances the state of the art in population disease modeling and provides a solid foundation for future work.

Glossary

abstainer - the alcohol consumption category label for those who don't drink alcohol. In the General Social Survey, it is specifically those who haven't consumed any alcohol in the past 12 months. In some early studies reporting a J-shaped curve, former heavy drinkers were included in the abstainer category. More recent analyses have excluded fromer heavy drinkers from the abstainer category.

attributable risk - the number of incident cases due to association with the risk factor divided by the total number of incident cases in the population

base scenario - an intervention scenario which has been assigned intermediate values of various input variables where possible

gap in percentage difference from base - the difference between two scenarios in the percentage difference from base value calculated for each scenario.

intervention estimate - expressed as the percent reduction in the proportion of the population in higher risk drinking categories e.g. a 50% intervention could reduce the 5% of the population who are heavy drinkers to 2.5% by moving them to the lowest risk category.

J-shaped curve - is the shape of the curve describing the relationship between average daily alcohol consumption for an individual and CHD incidence/mortality. Some feel it is more appropriately described as a U-shaped curve.

lowest risk category - the alcohol consumption category containing the low-point of the J-shaped curve.

low-point of the J-shaped curve - the point of the J-shaped curve which has lowest risk for death from CHD.

mortality reduction - the number of CHD deaths prevented over the simulation period

percentage difference from base -- the percentage difference in the projected number of CHD deaths prevented in a scenario from the projected number of CHD deaths prevented in the base scenario

PIF (potential impact fraction) - describes the impact of an risk factor intervention on disease incidence. The attributable risk is conceptually equivalent to a maximum PIF -- if an intervention were to reduce the prevalence of the risk factor to zero the PIF would equal the attributable risk.

PYLG - potential years of life lost, calculated by multiplying every prevented death with its age specific life expectancy and the result is summed over ages

referent category - the alcohol consumption category with the risk of CHD death

scenario - an individual PREVENT run with set values for input variables.

sensitivity analysis - the comparison of PREVENT output (e.g. CHD deaths prevented) under different scenarios, i.e. different values for input variables.

TIF (trend impact fraction) - describes the impact of autonomous trends in risk factor prevalence, e.g. decreasing cigarette smoking in the population on disease incidence.

References

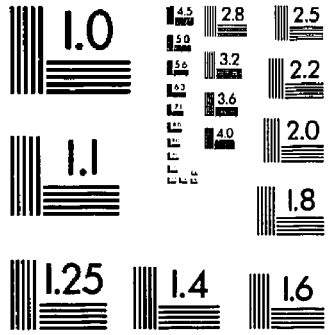
1. Kelsey JL, Thompson WD, Evans AS. Methods in Observational Epidemiology. Monographs in Epidemiology and Biostatistics. Vol. 10. New York: Oxford University Press, 1986.
2. Gunning-Schepers L. The Health Benefits of Prevention: A Simulation Approach. Amsterdam: Elsevier, 1989.
3. Klingemann H, Holder H, Gutzwiller F. Alcohol-related accidents and injuries. Addiction 1993;88:861-1027.
4. Anderson P, Cremona A, Paton A, Turner C, Wallace P. The risk of alcohol. Addiction 1993;88(11):1493-508.
5. Smart R, Mann R. Alcohol and the epidemiology of liver cirrhosis. Alcohol Health and Research World 1992;16:217-222.
6. Camargo CA. Moderate alcohol consumption and stroke: the epidemiologic evidence. Stroke 1989;20:1611-1626.
7. Klatsky AL, Armstrong MA, Friedman GD. Alcohol use and subsequent cerebrovascular disease hospitalizations. Stroke 1989;20:741-746.
8. Moore RD, Levine DM, Southard J, Entwistle G, Shapiro s. Alcohol consumption and blood pressure in the 1982 Maryland Hypertension Survey. American Journal of Hypertension 1990;3:1-7.
9. MacMahon S. Alcohol consumption and hypertension. Hypertension 1987;9:111-112.
10. Shaper AG. Alcohol and mortality: a review of prospective studies. British Journal of Addiction 1990;85:837-847.
11. Boffetta P, Garfinkel L. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. Epidemiology 1990;1(5):342-8.
12. Epstein FH. Contribution of epidemiology to understanding coronary heart disease. In: Marmot M, Elliott P, eds. Coronary Heart Disease Epidemiology. Oxford: Oxford University Press, 1992.
13. Stamler J. Established major coronary risk factors. In: Marmot M, Elliot P, eds. Coronary heart disease epidemiology. Oxford: Oxford University Press, 1992.
14. Håheim LL, Holme I, Hyermann I, Leren P. The predictability of risk factors with respect to incidence and mortality of myocardial infarction and total mortality. A 12-year follow-up of the Oslo Study, Norway. Journal of Internal Medicine 1993;234:17-24.
15. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. New England Journal of Medicine 1988;319(5):267-73.
16. Marmot MG. Alcohol and coronary heart disease. International Journal of Epidemiology 1984;13(2):160-7.
17. Ashley MJ, Ferrence R, Room R, Rankin J, Single E. Moderate drinking and health: report of an international symposium. Canadian Medical Association Journal 1994;151(6):809-28.
18. Ferrence R, Bondy S. Limitations of data and design in studies on moderate drinking and health. Contemporary Drug Problems 1994;21:59-70.
19. Colsher PL, Wallace RB. Is modest alcohol consumption better than none at all? An

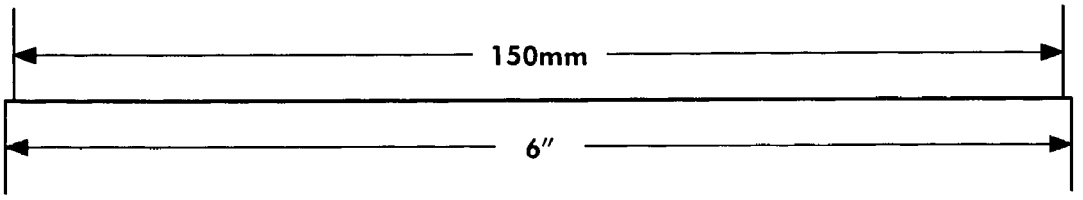
epidemiological assessment. Annual Review of Public Health 1989;10:201-219.
20. Ferrence RG, Truscott S, Whitehead PC. Drinking and the prevention of coronary heart disease: findings, issues and public health policy. Journal of Studies on Alcohol 1986;47(5):394-408.
21. Fuchs CS, Stampfer MJ, Colditz GA, Giovannuci EL, Manson JE, Kawachi I, Hunter DJ, Hankinson SE, Hennekens CH, Rosner B, Speizer FE, Willett WC. Alcohol consumption and mortality among women. New England Journal of Medicine 1995;332(19):1245-150.
22. Rankin JG. Biological mechanisms at moderate levels of alcohol consumption that may affect the development, course and/or outcome of coronary heart disease. Contemporary Drug Problems 1994;21(1):45-58.
23. Arria AM, Van Thiel DH. The epidemiology of alcohol-related chronic disease. Alcohol Health and Research World 1992;16:209-216.
24. Suh I, Shaten BJ, Cutler JA, Kuller LH. Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. The Multiple Risk Factor Intervention Trial Research Group. Annals of Internal Medicine 1992;116(11):881-7.
25. Srivastava LM, Vasisht S, Agarwal DP, Goedde HW. Relation between alcohol intake, lipoproteins and coronary heart disease: the interest continues. Alcohol & Alcoholism 1994;29(1):11-24.
26. Renaud S, Criqui MH, Farchi G, Veenstra J. Alcohol drinking and coronary heart disease. In: Vershuren PM, ed. Health Issues Related to Alcohol Consumption. Brussels: ILSI Europe, 1993;81-123.
27. Grover SA, Abrahamowicz M, Joseph L, Brewer C, Coupal L, Suissa S. The benefits of treating hyperlipdemia to prevent coronary heart disease: Estimating changes in life expectancy and morbidity. Journal of the American Medical Association 1992;267(6):816-822.
28. Wolfson MC. POHEM -- a framework for understanding and modeling the health of human populations. World Health Organization Statistical Quarterly 1994;47:157-176.
29. Zhuo Z, Gatewood L, Ackerman E. A Monte Carlo simulations program for coronary heart disease. . Fourteenth Symposium on Computer Applications in Medical Care: IEEE Computer Society Press, 1990;303-307.
30. Zhuo A, Ackerman E, Gatewood L. An expert system for simulation of coronary heart disease risk factor intervention. . The Annual Symposium on Computer Application in Health Care, 1991;674-678.
31. Shultz JM, Novotny TE, Rice DP. Quantifying the disease impact of cigarette smoking with SAMMEC II software. Public Health Reports 1991;106(3):326-333.
32. Shultz JM, Rice DP, Parker DL, Goodman RA, Stroh G, Chalmers N. Quantifying the Disease Impact of Alcohol with ARDI Software. Public Health Reports 1991;106(4):443-450.
33. Eddy DM. CAN*TROL: A computer model for designing national cancer control strategies. Bulletin de Cancer 1987;74(April):323-332.
34. Eddy DM, Hasselblad V, McGivney W, Hendee W. The value of mammography screening in women under age 50 years. JAMA 1988;259(10):1512-1519.
35. Brown ML, Nayfield SG, Shibley LM. Adjuvant therapy for stage III colon cancer:

Economics returns to research and cost-effectiveness of treatment. Journal of the National Cancer Institute 1994;86(6):424-430.
36. Spasoff RA, McDowell IW. Estimating the combined effect of several disease precursors in health risk appraisal. American Journal of Preventive Medicine 1987;3:182-189.
37. Herbert M. Modelling Future Mortality in Ontario: Extension of the Prevent Model and Development of an Ontario Database [M.Sc.]. University of Ottawa, 1992.
38. Kahn HA, Sempos CT. Statistical methods in epidemiology. Monographs in epidemiology and biostatistics. Vol. 12. New York: Oxford University Press, 1989.
39. Rothman KJ. Modern Epidemiology. 1st ed. Boston: Little, Brown, 1986.
40. Morgenstern H, Bursic E. A method for using epidemiologic data to estimate the potential impact of an intervention on the health status of a target population. Journal of Community Health 1982;7(4):292-309.
41. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. American Journal of Epidemiology 1974;99:325-332.
42. Canadian Centre for Health Information. Deaths, 1992. . Ottawa: Statistics Canada, Canadian Centre for Health Information, 1994.
43. George MV, Norris MJ, Nault F, Loh S, Dai SY. Population Projections for Canada, Provinces and Territories 1993-2016. . Ottawa: Statistics Canada, 1994.
44. Statistics Canada. Health Statistics Division. Births and Deaths, 1994. . Ottawa: Statistics Canada, 1996.
45. Millar WJ, David P, Statistics Canada. Health Statistics Division. Life Tables, Canada and Provinces, 1990-1992. . Ottawa: Statistics Canada, Health Statistics Division, 1995.
46. Bianchi C, Negri E, La Vecchia C, Franceschi S. Alcohol consumption and the risk of acute myocardial infarction in women. Journal of Epidemiology and Community Health 1993;47(4):308-311.
47. de Labry LO, Glynn RJ, Levenson MR, Hermos JA, LoCastro JS, Vokonas PS. Alcohol consumption and mortality in an American male population: recovering the U-shaped curve--findings from the normative Aging Study. Journal of Studies on Alcohol 1992;53(1):25-32.
48. Farchi G, Fidanza F, Mariotti S, Menotti A. Alcohol and mortality in the Italian rural cohorts of the Seven Countries Study. International Journal of Epidemiology 1992;21(1):74-81.
49. Garg R, Wagener DK, Madans JH. Alcohol consumption and risk of ischemic heart disease in women. Archives of Internal Medicine 1993;153(10):1211-1216.
50. Gordon T, Doyle JT. Drinking and mortality. The Albany Study. American Journal of Epidemiology 1987;125(2):263-270.
51. Gordon T, Kagan A, Garcia-Palmieri M, Kannel WB, Zukel WJ, Tillotson J, Sorlie P, Hjortland M. Diet and its relation to coronary heart disease and death in three populations. Circulation 1981;63(3):500-515.
52. Jackson R, Scragg R, Beaglehole R. Alcohol consumption and risk of coronary heart disease. British Medical Journal 1991;303(6796):211-6.
53. Kaufman DW, Rosenberg L, Helmrich SP, Shapiro S. Alcoholic beverages and myocardial infarction in young men. American Journal of Epidemiology 1985;121(4):548-554.

54. Kittner SJ, Garcia-Palmieri MR, Costas RJ, Cruz-Vidal M, Abbott RD, Havlik RJ. Alcohol and coronary heart disease in Puerto Rico. American Journal of Epidemiology 1983;117(5):538-550.
55. Kivela SL, Nissinen A, Ketola A, Punsar S, Puska P, Karvonen M. Alcohol consumption and mortality in aging or aged Finnish men. Journal of Clinical Epidemiology 1989;42(1):61-68.
56. Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and nondrinkers. American Journal of Cardiology 1990;66(17):1237-42.
57. Klatsky AL, Friedman GD, Siegelaub AB. Alcohol and mortality. A ten-year Kaiser-Permanente experience. Annals of Internal Medicine 1981;95(2):139-145.
58. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Alcohol and mortality: a cohort study of male Japanese physicians. International Journal of Epidemiology 1986;15(4):52732.
59. Lazarus NB, Kaplan GA, Cohen RD, Leu DJ. Change in alcohol consumption and risk of death from all causes and from ischaemic heart disease. British Medical Journal 1991;303(6802):553-6.
60. Marmot MG, Rose G, Shipley MJ, Thomas BJ. Alcohol and mortality: a U-shaped curve. Lancet 1981;1(8220 Pt. 1):580-583.
61. Miller GJ, Beckles GL, Maude GH, Carson DC. Alcohol consumption: protection against coronary heart disease and risks to health. International Journal of Epidemiology 1990;19(4):923-30.
62. Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, Stampfer MJ. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet 1991;338(8765):464-8.
63. Rosenberg L, Slone D, Shapiro S, Kaufman DW, Miettinnen OS, Stolley PD. Alcoholic beverages and myocardial infarction in young women. American Journal of Public Health 1981;71(1):82-85.
64. Scragg R, Stewart A, Jackson R, Beaglehole R. Alcohol and exercise in myocardial infarction and sudden coronary death in men and women. American Journal of Epidemiology 1987;126(1):77-85.
65. Shaper AG, Phillips AN, Pocock SJ, Walker M. Alcohol and ischaemic heart disease in middle aged British men. British Medical Journal Clinical Research Ed. 1987;294(6574):733-7.
66. Suhonen O, Aromaa A, Reunanen A, Knekt P. Alcohol consumption and sudden coronary death in middle-aged Finnish men. Acta Medica Scandinavica 1987;221(4):335-41.
67. Wannamethee G, Shaper AG. Alcohol and sudden cardiac death. British Heart Journal 1992;68(5):443-448.
68. Yano K, Rhoads GG, Kagan A. Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. New England Journal of Medicine 1977;297(8):405-409.
69. Yano K, MacLean CJ, Reed DM, Shimizu Y, Sasaki H, Kodama K, Kato H, Kagan A. A comparison of the 12-year mortality and predictive factors of coronary heart disease among Japanese men in Japan and Hawaii. American Journal of Epidemiology 1988;127(3):476-87.

70. Colditz GA, Branch LG, Lipnick RJ, Willett WC, Rosner B, Posner B, Hennekens CH. Moderate alcohol and decreased cardiovascular mortality in an elderly cohort. American Heart Journal 1985;109(4):886-9.
71. Camacho TC, Kaplan GA, Cohen RD. Alcohol consumption and mortality in Alameda County. Journal of Chronic Diseases 1987;40(3):229-36.
72. Garfinkel L, Boffetta P, Stellman SD. Alcohol and breast cancer: A cohort study. Preventive Medicine 1988;17:686-693.
73. Gordon T, Kannel WB. Drinking habits and cardiovascular disease: the Framingham Study. American Heart Journal 1983;105(4):667-673.
74. Badets J. Canada's Changing Immigrant Population. . Ottawa: Statistics Canada, 1994.
75. Walter SD, Holford TR. Additive, multiplicative, and other models for disease risks. American Journal of Epidemiology 1978;108(5):341-346.
76. Van Assema P., Steenbakkers M., Kok G., Eriksen M., de Vris H. Results of the Dutch Community Project "Healthy Bergeyk". Preventive Medicine 1994; 23(3):394-401.
77. Gibbins RL, Riley M, Brimble P. Effectiveness of programme for reducing cardiovascular risk for men in one general practice. British Medical Journal 1993; 306(6893):1652-6.
78. Montano L. Ischemic Heart Disease Mortality Attributable to Physical Inactivity in Ontario. Public Health and Epidemiology Report Ontario 1994; 5(6):135-8.
79. Powell, Kenneth E. Physical Activity and the Incidence of Coronary Heart Disease. Ann. Rev. Public Health 1987; 8:253-287.
80. Rimm EB. Klatsky A. Grobbee D. Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits. British Medical Journal 1996; 312(7033):731-6.
81. Cohen E.J., Klastsky A.L., Armstrong M.A. Alcohol use and supraventricular arryhthmia. American Journal of Cardiology 1988; 62:971-973.
82. Klatsky A.L., Friedman G.D., Siegelaub A.B. Alcohol use and cardiovascular disease: the Kaiser-Permanente experience. Circulation 1981; 64(Suppl. III): 32-41.





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