The mortality and morbidity of alcohol-attributable injury

How new dimensions of exposure and relative risk lead to novel calculations of total lifetime risk, alcohol attributable fractions, and a new analytical framework for the burden of disease in Canada.

by

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Abstract

Alcohol is a recognized cause of over 60 injuries and diseases and is consistently in the top 5 most important risk factors for global burden of disease. It is important to be able to measure how drinking alcohol affects our health, and how our risk of getting injured or acquiring diseases caused by alcohol is dependent on how much alcohol we drink. This type of information allows us to make personal choices about our health and is an integral piece of public health evidence to inform how alcohol policy is informed, implemented, or monitored. This analysis will, for the first time, model the effects of alcohol for injury outcomes over the entire drinking lifetime for men and women separately using a new method that aims to improve upon existing calculations by accounting for different patterns of drinking – both acute consumption and average daily drinking. In both cases, both the amount consumed and the number of times it is consumed is taken into account. Within acute consumption, the number of occasions and the amount

consumed at each occasion was counted. What's more, for the first time in this field, a lifetime approach was adopted – risks will no longer be seen as discrete, individual events that occur independently of each other. In this study, risks are combined much like other exposures to environmental substances or contaminants – in a cumulative manner over a lifetime of drinking. The method combines data sources from experimental data, from meta-analyses, Canadian mortality and hospital data, and survey data, making this a rich, yet complicated analysis. Its products were dose-response risk curves for each injury outcome, by sex, and age group, and alcohol-attributable fractions and their variance estimation for mortality and morbidity for injury. This study has important implications for forming and planning health policy, represents advancements in absolute risk calculation, and will result in important consumer-level information that will enable development of limits around healthy drinking.

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1 Literature Review

1.1 The health burden of alcohol consumption

Alcohol consumption is causally associated with over 60 causes of death and disability (1-3) (for details see (4-7)). It has been identified as one of the top 3 leading risk factors for mortality and morbidity from injury and chronic disease globally (2-4), with 3.7% of all deaths worldwide (6.1% of all deaths in men and 1.1% of all deaths in women) in 2002 attributable to this risk factor. Globally, unintentional injuries (e.g. motor vehicle collisions, falls, and drowning) account for 28% of the alcohol-attributable global burden of disease as measured in disability-adjusted life-years with intentional injuries (e.g. suicides, homicides) making up another 12 percent of this burden (4, 7). It is important to recognize that injury outcomes make up the bulk of premature death (under 70 years of age) due to alcohol internationally, with men and those under 30 disproportionately affected (8, 9). Alcohol is recognized as being the cause of a significant death and disability burden in Canada (10) - fatal injury is the leading cause of alcohol-attributable mortality and morbidity in this country (11). This accounts for approximately 75% of the net deaths-attributable and 40% of all premature deaths attributable to alcohol (12). The cost to Canadians is not only measured in shortening our lives – approximately $3.3 billion was spent in direct health care costs due to alcohol-caused health outcomes, with the overall cost due to alcohol consumption in 2002 totaling $14.5 billion, about $463 dollars per person (11, 13).

1.2 Variable mechanisms of harm for injury outcomes

Ethanol is a controlled substance in Canada (14). It is considered a psychoactive drug and is able to cross the blood brain barrier and act upon the central nervous system by affecting cognition, perception, mood, behaviour, and psychomotor abilities (15). The effects of alcohol are mediated via three main mechanisms that can result in harm to the consumer (15, 16):

Toxicity: this refers to the direct biological action on cells, influencing chronic disease in both negative (5, 17-19) and beneficial ways, as in the case of ischemic heart disease and stroke (20).

Intoxication: this reflects the action of ethanol on the central nervous system, resulting in mainly acute outcomes, such as motor vehicle crashes (21-23), falls (24, 25), suicide (26, 27), and violence (15, 28-31).

Dependence: this is a clinical disorder as well, but dependence on alcohol is also implicated in both chronic and acute outcomes (32).

Figure 1 shows how these mechanisms are inter-related to cause a myriad of social and physical harms, including injury outcomes, but also illustrate how drinking patterns greatly influence these three mediators (33). On the one hand, injury risk is an effect of a drinking pattern characterized by acute alcohol consumption, where alcohol-attributable injury risk is due to short-term intoxication from a single drinking episode and the risk and severity of injury follow a dose-response relationship with the amount of alcohol in the body at the time of injury (34-36). On the other though, average consumption over a long period of time has traditionally been more important for determining the risk of chronic disease death, where cumulative cell damage over years of daily consumption of alcohol is important in the development of scar tissue or organ cell death (36).

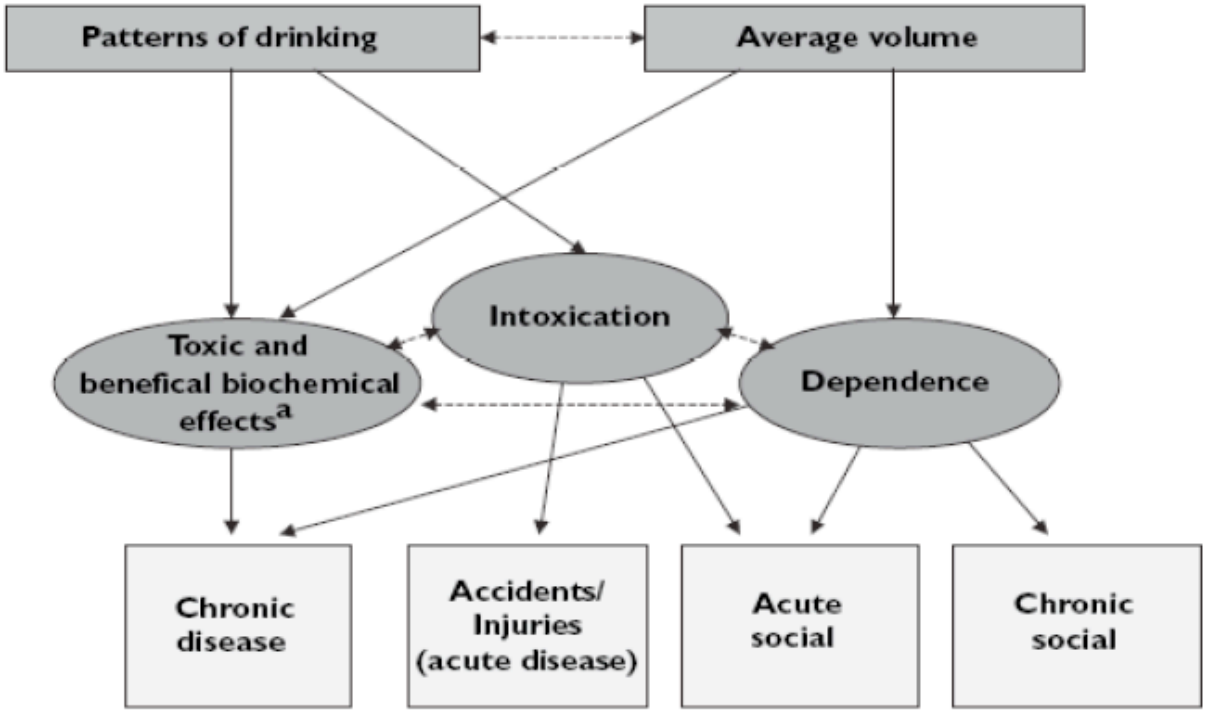

Figure 1-1. Conceptual model of alcohol consumption showing relationships among consumption types, three main mediating factors, and various types of harm (used with permission from (36)).
a = independent of intoxication or dependence

It is important to note the differences traditionally associated between patterns of drinking and average volume. Consider the case of a man who drinks, on average, 14 drinks per week. His risk of injury or other negative outcome *as a direct cause of his drinking* will be significantly different if he drinks 2 drinks each night of the week with his meal, or if he chooses to drink all of those drinks in one evening on a weekend (14 drinks in one sitting). Each carries a different risk for injury and chronic disease, and this is what is meant when we recognize that patterns of drinking themselves are deterministic of negative alcohol-attributable outcomes (33). Both average daily consumption and irregular heavy drinking are related to alcohol-attributable injury via intoxication and toxic effects (37-42), so we will focus the next section of the discussion on these two mediator's relationships to acute injury outcomes, with special mention of the biochemical action of ethanol in the brain and central nervous system that potentiate the effects.

1.2.1 Toxic effects

Toxic effects of alcohol have traditionally been the domain of chronic heavy drinking styles, where sustained, regular heavy consumption causes tissue damage in the liver (43, 44), cardiovascular system (20, 45, 46), and other organs and organ systems (47). With respect to injury outcomes, though, toxic effects of alcohol consumption are mainly related to patterns of consumption (specifically irregular drinking episodes where a high number of drinks are consumed in one sitting), resulting in acute toxicity such as overdose and/or poisoning. Ethanol and its metabolites have been associated with a number of different neurotransmitter systems in the brain, including dopamine, serotonin, Gamma Amino-Butyric Acid (GABA), glutamate, and endogenous opioids (15). High doses of ethanol thus interacts with all of these systems after crossing the blood brain barrier to exert its toxic effects (48). With respect to acute toxicity, however, it appears ethanol mainly interferes with the action of GABA-A receptors (49-51), which are neurons throughout the brain responsible for controlling alertness, muscle tension, anxiety, and some voluntary and involuntary movement in an inhibitory fashion – that is, their function is to relax systems, and GABA has been shown to be a precursor to sleep (52). Ethanol increases inhibitory GABA-A function, resulting in reduced anxiety and relaxation upon the introduction of ethanol, which are the normal effects of drinking alcohol at moderate consumption levels (15). Overdose of ethanol resulting in acute alcohol toxicity, though, results in a considerable loss of GABA-A control and function, and can lead to sedation or cessation of breathing altogether (53, 54). The lethal dose of alcohol occurs at a blood alcohol concentration (BAC) range between approximately 0.22 - 0.5%, with the usual lethal dose approximately 0.36% (55, 56).

1.2.2 Intoxication

The main cause of alcohol-attributable injury in the population at large is due to alcohol intoxication (57), which can be attributed not only to irregular heavy, or binge, drinking, but also to average daily consumption, since the effects of alcohol can be felt and measured at low and moderate doses (15). The link between intoxication and injury outcomes is strong, and this link is seen in experimental and epidemiologic studies alike. The effects of ethanol in the central nervous system bring about 4 main changes in the drinker, all of which increase the risk of an acute outcome while under the influence of alcohol (16):

1. Psychomotor impairment;
2. Lengthened reaction time;
3. Impairment of judgment;
4. Emotional changes and decreased responsiveness to social expectations.

The glutamate-controlled N-methyl-D-aspartate (NMDA) receptor appears to be the chief target responsible for the effects of intoxication, although the effects on the GABA, dopamine, serotonin, and opioid systems are all affected, even at low and moderate doses of alcohol (2 or less drinks) (15). The NMDA receptors are responsible for a host of neural function, including spatial learning and memory, information processing, reaction time, proprioceptive ability (tracking), vigilance (ability to focus in the presence of distraction), balance, as well as some subjective reactions, such as the perceived degree of intoxication, pleasant affect, and overall mood (58, 59). As a result, there is interplay between all of these factors that can lead to a combination of factors that result in injury – a loss of inhibition and impulsivity (60-62), poor decision making (63, 64), psychomotor ability, and slower reaction time (65) all combine to put the drinker at a much higher risk of an injury (66). When severe enough, this injury outcome can result in death and/or an emergency room visit (66).

1.3 Acute injury risk based on single-occasion drinking

Emergency room studies are the best evidence to date of the relationship of single-occasion drinking on the risk of being injured as a direct result of drinking. The Emergency Room Collaborative Alcohol Analysis Project (ERCCAP), a 16-country study of emergency departments (ED), has provided much of the recent evidence on alcohol and injury and has shown there to be a dose-response relationship between single-occasion BAC and the risk of injury across multiple countries and continents, reporting an overall odds ratio of between 4.93 – 5.93 after consumption of any alcohol for all injury combined (67-71). What's more, injury is also associated with usual consumption in a dose-dependent fashion i.e. average daily consumption, not just binge drinking patterns of consumption (70). There are other country-level factors that have been shown to be important modifiers in the relationship between alcohol and injury as well, including gross national product and purchasing power parity (e.g. poorer countries experience more harm for a given BAC level) (71, 72), and for traffic collisions, policy

such as seatbelt laws, the availability of public transport, conditions of roads, and legal drinking age are important (36). Lastly, the cultural role of alcohol and the context within which people people consume alcohol also has important implications for alcohol-attributable injury (73-75). The threshold for negative effects of alcohol on psychomotor tasks has been reported to be approximately 0.04% blood alcohol concentration (BAC), although for completion of complex tasks, this level may be much lower (76).

1.4 The alcohol-attributable fraction

The proportion of a disease or outcome that is due to the influence of some external causal factor is called the attributable fraction (77). In alcohol epidemiology, this fraction is termed the alcohol-attributable fraction (AAF) and is defined as that proportion of disease that would theoretically disappear if alcohol consumption went to zero. In the categorical case (78), it has been calculated using the formula (77-79):

Equation 1

$$AAF = \frac{\sum_{i=1}^{k} p_i(RR_i - 1)}{\sum_{i=0}^{k} p_i(RR_i - 1) + 1}$$

where P_i is equal to the proportion of the population exposed in group $_i$ and RR_i is the relative risk of mortality in exposed group i compared with the reference group (in alcohol often non-drinkers or lifetime abstainers). This is computed for as many drinking categories exist, from i = 0 to k, where i = 0 represents the reference group. This framework has been used extensively by the World Health Organization (WHO) to estimate burden of disease as a part of its Comparative Quantification of Risk analysis (2, 4, 80), and has been used by colleagues in other countries to establish the alcohol-attributable burden of disease (5, 12, 81) to provide evidence for local and national alcohol policy and planning (82).

However, these calculations have used methods developed for chronic disease outcomes and have only considered average alcohol intake and also using opnly three categories of average alcohol consumption after periods of time. More recently, a more differentiated consideration of average alcohol consumption has been introduced (83). As we will see later on in this document, shifting patterns of drinking with age and sex may also be important in this calculation as well.

The calculation of AAF for injuries is conceptually different than for chronic disease, since the acute effects of alcohol become very important and reliance on average consumption alone would considerably bias the results towards lower attributable fraction estimates (39, 84).

Current Canadian AAFs were adapted based on prior estimates by the WHO that were developed for the whole of the Americas A region (which includes the United States and Cuba) (1). The calculation of new AAFs allows for the calculation of age- and sex-specific attributable fractions using a range of new, higher quality data inputs, and hence a more valid and reliable means of estimating alcohol-attributable mortality and morbidity in Canada based on its alcohol-drinking population.

1.5 Re-thinking alcohol exposure and risk over the life course

Relative risks for alcohol-attributable injury have historically been reported on a per-occasion basis due to the nature of the way much of the epidemiology has been studied– typically ED studies, as described previously (e.g. (67-69), and BAC-based roadside collision tests (see (85, 86). However, this typical risk presentation can be problematic for risk assessment since it does not reflect the underlying, baseline risk of injury (87). A fourfold relative risk (RR) for a given drinking occasion, for instance, may still represent a low absolute risk over a lifetime, but a drinker may repeat the same pattern many times, thereby raising their cumulative risk over a period of time based on repeated occasions. Thus, although the acute risk immediately following consumption is still a very important scenario, and one that needs to be accounted for in any study of alcohol-attributable injury, it does not tell the whole story of alcohol's risk profile. What's more, as patterns of drinking (occasions and amounts) change with age, lifetime risk calculations must accordingly account for these changes. Likewise, daily alcohol exposure and its variation with age and gender over a lifetime are also vitally important in the alcohol-injury risk profile (88-90). It is intuitively obvious that a man or woman who drinks to get drunk 100 times per year has a different annual risk profile than someone who gets drunk only once per year, however this has not been empirically tested or studied in the alcohol field. A person who drinks 5 drinks per day for 50 years intuitively has a different cumulative risk profile from someone who, on average, drinks less (or more) alcohol per day over his or her lifetime, or has a fluctuating daily drinking amount.

From a policy perspective, or from the perspective of a consumer, it is important to know the absolute risk of injury associated with a particular pattern as cumulated over time – for instance, over an adult lifetime (87, 91). Favouring presentation of the absolute lifetime risk over the single – occasion relative risk is not at all common in alcohol-injury literature, though, probably due to the acute nature of the outcome.

The lifetime-exposure model is very common with respect to other environmental exposures such as contaminants or foodstuffs, both of which also carry acute consequences. For instance, in terms of exposure to carcinogenic compounds in drinking water, the World Health Organization sets a general upper guideline ‘‘at the concentration which would give rise to a risk of 1 additional cancer per 100,000 people’’ on a lifetime basis (92). A study of regulation of risky substances in the United States and Canada mentions risk thresholds set at 1 in 22,000 and 1 in 10,000 (93). Additionally, for behaviors that are seen as voluntary, such as driving an automobile, higher risks are routinely accepted. For example, in the United States, the lifetime risk of dying in a traffic collision associated with driving 10,000 miles per year (16,000 km/year) has been calculated to be approximately 1 in 60 (94). What’s more, it may be more useful in terms of risk communication to express risk as probabilities with common denominators instead of relative risks (91). Research into the use and interpretability of RR versus absolute risk is equivocal - although the absolute risk may be clearer and more understandable, the RR may have a larger impact due to its larger size, with the caveat that the patient may not understand the underlying risk is different (87).

1.6 Risk communication: a primer on relative versus absolute risk

In this study, explicit distinctions are made between the absolute risk (also called attributable risk) (AR) and the relative risk (RR), but it is necessary to explain the context of this distinction with respect to the body of literature around the subject. Previous research has found that the presentation of statistical information, specifically risks, in different but equivalent formats can lead to different decisions (95, 96). A number, or a probability, or a percentage, it seems, can be interpreted differently depending on the way it is presented, by whom it is presented, and to whom it is presented (91, 97-100). What’s more, the framing of this risk has also shown to be important (87). For example, certain cancer therapies have been found to be preferred by patients

if the probability of their outcome was framed as the risk of surviving compared to the risk of dying (101).

Much of the intervention and epidemiological research, including in alcohol, has focused on the presentation of relative risk, but more recent research has shown that this may exaggerate certain effects, both negative and positive, and may be coercive in their effect for both patients and clinicians (102-106). Let us consider the following example to illustrate the difference:

> Disease A occurs in a certain population at an incidence of 2.5 per 1000 (0.0025).
> Risk Factor A increases the incidence of Disease A to 5 per 1000 (0.005).
> In relative terms, the RR increases by 100% due to Risk Factor A
> In absolute terms, the AR increases by 0.25% due to Risk Factor A.

This example shows how relative risk may inflate the effect and thus the interpretation of the danger. Even though the two are logically equivalent when the underlying risk of disease is also presented, the interpretation has shown to favour the RR in decision-making because of its larger magnitude (87, 100). Two recent meta-analyses comparing the two risk presentations consistently found that the RR is frequently interpreted as larger and more persuasive by medical professionals, medical students, and patients, thereby leading to misinterpretation (99, 100), with the latter recommending the use of AR over RR. The decision-making literature is thus seeing a shift in choices for risk communication, with an increasing majority arguing for the preferential use of absolute risk over the relative risk, since it provides a clearer picture of true risk since the underlying baseline risk is also presented (87, 91).

This difference in framing and interpretation of risk may lead to a vital decision in the context of public health and this thesis. Risk communication is one of the key foundations of epidemiology and the utility of research findings depends on it. For this reason, and based on the most recent findings from meta-analyses on AR vs RR, the AR was used exclusively as the risk metric for communication in this thesis. Understanding the baseline risk and increases due to certain risk factors is a cornerstone of this work and represents one of the major advances in the alcohol-injury field.

1.7 Summary

The majority of alcohol-injury literature to date has presented injury risk as a single, independent event (e.g. (68)), has assumed a constant drinking level by an entire population reliant on baseline measures (e.g. (107)), and/or fixed or proxy levels of alcohol consumption across genders and age groups (e.g. (18, 108)). Since we already know that both the pattern of drinking and average consumption is crucial to the risk-injury profile, we need to assess and account for both binge and average daily volume in our analysis of this risk factor and injury. Importantly as well, drinking patterns and average alcohol consumption levels change over a lifetime (88, 90), usually increasing in younger adulthood and tapering off through midlife and old age (109) but injury risk estimation has never reflected changing patterns of consumption over a lifetime within the same population. It should be stressed that the per-occasion risk is still important – it is required to assess the dose-response risk for alcohol on injury, but requires further refinement by treating injury as a collection of different outcomes instead of only one. Both injury type and severity are important and often overlooked facets of the alcohol-injury relationship (18) - while some ED-based studies to date suggests that there should be no reason for either the type of injury (110-112) or severity (113, 114) incurred after drinking to be addressed in alcohol-risk analysis, there is some new evidence pointing to different risk profiles of severe versus non severe injuries, particularly for motor-vehicle collisions where head injuries occurred (115-117) and for different risk profiles for different types of injuries (113, 118). This study aims to fill in a number of methodological and analytical gaps in the alcohol-attributable injury arena by accounting for different modes of consumption, changing consumption patterns with age and gender, and by treating injury as a heterogeneous outcome that is defined by both type and severity.

1.8 The current study

Specifically, this study will incorporate absolute lifetime risk modeling to determine estimates of risks of mortality and morbidity from alcohol- attributable injury and chronic disease in the Canadian population for 2005. This analysis, although rooted in burden of disease analysis in terms of its approach (2, 5, 7, 119, 120), represents an extension in terms of conceptualization, data sources, and complexity. Analyses of this breadth have not been done before in the alcohol-injury field and are important in both presenting absolute risk from drinking alcohol to the Canadian population and as drivers for public health policy and decision-making. A novel

methodology was developed to calculate lifetime risks and accompanying AAFs using Canadian mortality and morbidity data.

1.8.1 Advancements this study brings to the existing literature

This analysis will build upon past estimation of alcohol-attributable risk in five specific ways:

1. Move away from traditional per-occasion/average daily volume risks to lifetime risks so comparison with environmental exposures is possible and meaningful.

2. Incorporate patterns of drinking and average daily consumption into the same model of lifetime risk. This has a benefit of including three risk scenarios in a cumulative fashion instead of only one (see Figure 1-2)

3. Account for changes in average daily drinking and binge occasions over a lifetime to present an adaptive lifetime risk model that better approximates a "drinking lifetime". This will require measuring daily average drinking and binge occasions/amounts for each age and sex in Canada for the year 2005.

4. Address the possibility of differential per-occasion risk profiles for both injury type and severity where possible through meta-analysis and incorporate these into the lifetime risk approach.

5. Incorporate a variance estimate into the risk estimation strategy and providing confidence intervals for estimates of lifetime risk. This will require measuring and combining random error in alcohol measurement, liver metabolism data, and the error in relative risk estimation.

This study will present results for lifetime alcohol-attributable risks for mortality and morbidity separately for injury in Canada for the year 2005, confidence limits surrounding these estimates, new alcohol-attributable fractions, and implications of the findings for the Canadian population in the context of current drinking guidelines and Canadian alcohol policy, with an overall aim to improve the health of Canadians via risk modification and harm reduction through subsequent development of low-risk drinking guidelines.

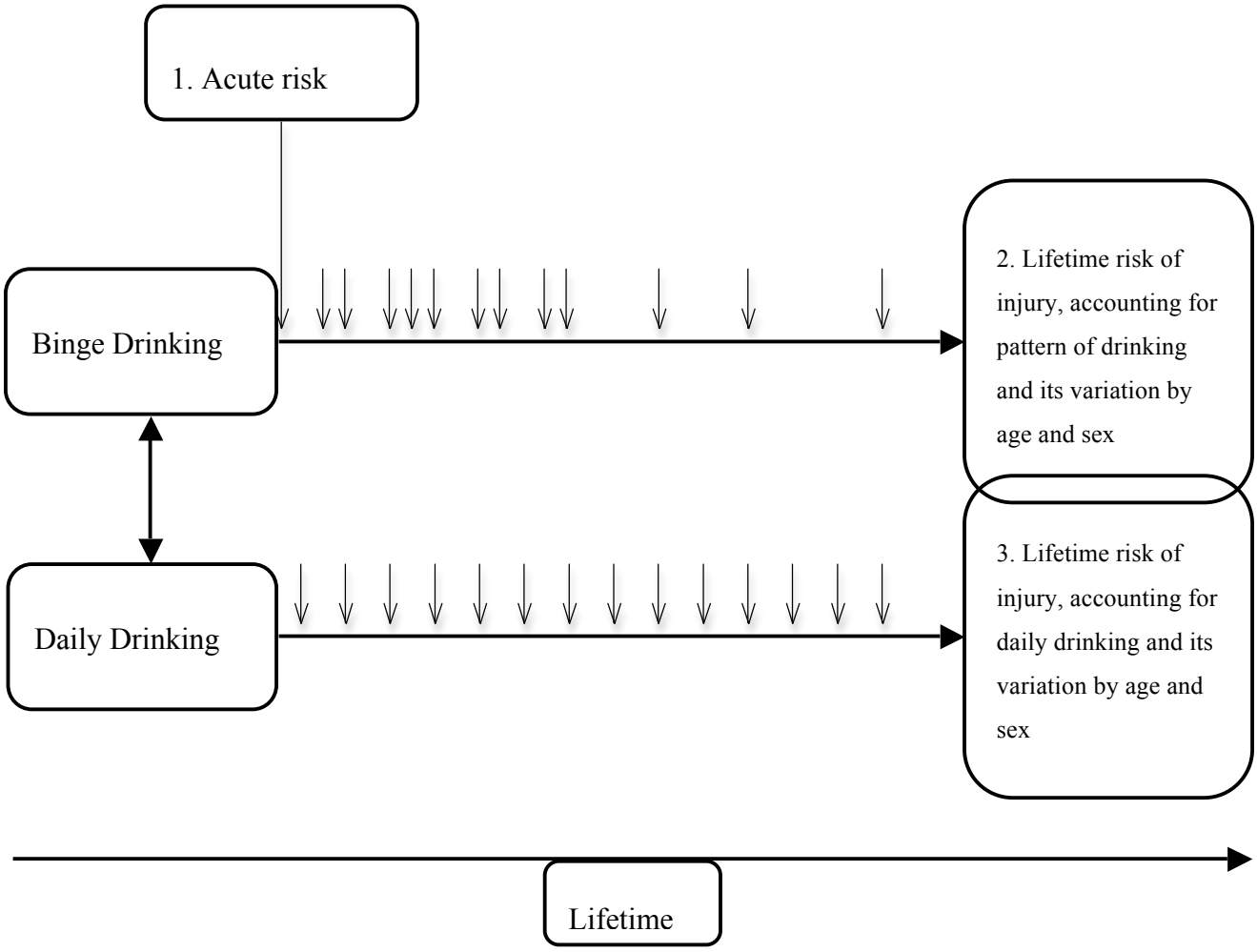

Figure 1-2. Conceptual model of three risk scenarios of alcohol-attributable injury due to (1) single-occasion risky drinking, (2) lifetime risk of repeated single occasions over time and their changing pattern with age and sex, and (3) lifetime risk of injury due to daily drinking and it variation with age and sex.

2 Overview of Methods

2.1 The Iterative Approach

The methods, and the subsequent organization of manuscripts in this thesis show an iterative, scientific approach. First, the crux of the method (Chapter 3) is presented, followed by iterative improvements to the original inputs via the following 3 chapters. Thus, although the methods are summarized below, this work is a 4-year iterative process of defining, obtaining (at times, synthesizing), and manipulating the best available data for this analysis.

2.2 Brief Summary

The method to calculate the absolute lifetime-attributable risk of injury from alcohol consumption has 5 main information inputs. Alcohol consumption data (both average daily volume and drinking patterns, respectively) for the Canadian population will come from Canadian survey data, rates of liver metabolism of ethanol will come from experimental data, relative risk for single-occasion drinking will come from meta-analysis, mortality data was obtained Statistics Canada, and morbidity statistics from the Canadian Institute for Health Information (CIHI), a repository for injury and related statistics. These data are searchable via International Classification of Disease, 10th Revision (ICD-10) diagnosis codes (121), and information was obtained by injury types based on ICD-10 code. The International Classification of Diseases is a World Health Organization initiative that classifies morbidity and mortality information for statistical purposes, for the indexing of hospital records by disease and operations, and for the appropriate storage and retrieval of data (122). These data are combined in a number of calculations to obtain the lifetime alcohol-attributable risk. The calculation is the same for morbidity, although the risk-per-occasion data and the underlying baseline risk will differ compared to the mortality calculation. All calculations were completed by age, sex, and injury type for mortality and morbidity separately.

2.3 Injury conditions for which alcohol is causal

There is a large body of work showing that alcohol is associated with the risk of intentional and unintentional injury in cross-sectional (24, 27, 110, 123, 124), case–crossover (125-127), and case–control analyses (23, 128). What's more, these general relationships have persisted

throughout the last 40–50 years of research (85, 129), across countries and cultural boundaries (130-134) and without major distinctions by age or gender (18), although absolute values of risk tend to be higher for young males involved in fatal motor vehicle crashes (135). The categories of alcohol-attributable injury for this thesis have been selected based on the usual causal criteria (136), with alcohol as a component or sufficient (i.e. strong and consistent relationships across studies, biological plausibility, temporality, dose-response, specificity etc), based on (137). Please see Table 2-1 for a summary of injury categories by ICD-10 code.

Table 2-1 Injury categories and the source of the relative risk relationship with alcohol consumption

Condition	ICD-10 Code
Unintentional injuries	
Motor vehicle collisions	§
Poisonings	X40-X49
Falls	W00-W19
Fires	X00-X09
Accidental Poisonings and exposure to alcohol	X45
Drowning	W65-W74
Other Unintentional injuries	†Rest of V-series and W20-W64, W 75-W99, X10-X39, X50-X59, Y40-Y86, Y88, and Y89
Intentional injuries	
Self-inflicted injuries	X60-X84 and Y87.0
Intentional self-poisoning by and exposure to alcohol	X65
Homicide	X85-Y09, Y87.1
Other intentional injuries	Y35

§ V021–V029, V031–V039, V041–V049, V092, V093, V123–V129, V133–V139, V143–V149, V194–V196, V203–V209, V213–V219, V223–V229, V233–V239, V243–V249,V253–V259, V263–V269, V273– V279, V283–V289, V294–V299, V304–V309, V314–V319, V324–V329, V334–V339, V344–V349, V354–V359, V364–V369, V374–V379, V384–V389, V394–V399, V404–V409, V414–V419, V424–V429, V434–V439, V444–V449, V454–V459, V464– V469, V474–V479, V484–V489, V494–V499, V504–V509, V514–V519, V524–V529, V534–V539, V544–V549, V554–V559, V564–V569, V574–V579, V584–V589, V594–V599, V604–V609, V614–V619, V624–V629, V634–V639, V644–V649, V654– V659, V664–V669, V674–V679, V684–V689, V694–V699, V704–V709, V714–V719, V724–V729, V734–V739, V744–V749, V754–V759, V764–V769, V774–V779, V784–V789, V794–V799, V803–V805, V811, V821, V830–V833, V840–V843, V850– V853, V860–V863, V870–V878, V892.

†Rest of V = V-series MINUS §.

2.3.1 Data sources

There are a number of sources of data that are required for the calculation of lifetime alcohol-attributable risk of injury for the Canadian population. These are:

Alcohol Exposure data: Both patterns of alcohol consumption and average daily volume were needed for the alcohol-exposure measure. Both measures were calculated by age and sex categories. The age categories were 15-29, 30-44, 45-59, 60-69, 70-79, and 80+. All alcohol consumption data used in the calculations come from the most recent survey of Canada's alcohol consumption habits - the Canadian Alcohol and Drug Use Monitoring Survey (CADUMS) 2008 (138). It is a nationally representative survey of alcohol consumption in Canada and is representative of alcohol drinking in 2005. The precise methods used in the CADUMS are available elsewhere (139). In brief, though, it was an 8-month long telephone survey that used random-digit dialing to identify respondents. The survey reported a response rate of 36.5%, with 15, 801 individuals in the final dataset. These individuals provided the mean binge drinking estimates (number of occasions and amount of alcohol consumed per occasion) and average daily consumption data by age group and sex. Binge episodes and amounts per occasion are determined via 2 questions, and average volume is based on extrapolation of beverage-specific quantity-frequency questions over the past 30 days. Estimates of average volume are required to be upshifted to match per-capita consumption based on (83) (more below on this adjustment).

Original alcohol-attributable fraction: The alcohol-attributable fraction (AAF) was applied to separate the total risk of injury into a baseline-risk of injury (excluding the alcohol-attributable portion), which is the starting point for the lifetime-attributable risk calculation. All AAFs were supplied by age, sex, and injury type for mortality and morbidity separately. AAFs are calculated by the WHO by region, which are categorizations of countries based on similar geographic, economic, and development indicators. These regions are classified as: A (very low child mortality and very low adult mortality), B (low child mortality and low adult mortality), C (low child mortality and high adult mortality), D (high child mortality and high adult mortality) and E (high child mortality and very high adult mortality) (1). The AAFs for Americas Region A (of which Canada is a part) were applied to Canadian mortality and morbidity data, respectively, for each age group, sex, and injury type.

Mortality Data: The mortality data for the year 2005 (to match alcohol consumption data) was obtained by selected ICD-10 code from Statistics Canada Vital Statistics database via their E-STAT program, which makes these data available at no cost to students (140). It is an administrative survey that collects medical causes of death information annually for all provinces and territories in Canada. Reporting of death by cause is virtually complete. Late or missing

registration of deaths may occur with Canadians living outside of the country or with unidentified bodies, but this number is typically less than 10 deaths per year. The direct, antecedent and underlying cause of death, other significant conditions (homicide, suicide etc) and further information where required is identified by a medical doctor or coroner. For more additional information, including more information on data accuracy and methodology please see (141).

Average human liver ethanol metabolism rate: The per-occasion risk must account in some way for the metabolism of alcohol. This was modeled based on experimental data recommended by the National Institute for Alcoholism (142). After the consumption of 1 standard drink, BAC reaches its peak approximately 30–45 minutes after ingestion. Rapid consumption of multiple drinks results in a higher BAC during the period following ingestion, because the liver has a relatively fixed rate of metabolism. In general, in the ensuing 0.5–1.5 hours, the consumption of 1 Canadian standard drink results in a BAC of about 0.02 mg/mL; having 2 drinks in succession leads to a BAC of about 0.05 mg/mL; approximately 3 drinks results in a BAC of 0.07–0.08 mg/mL; and approximately 4 drinks results in a BAC of about 0.09 mg/mL (142).

Relative Risk for per-occasion alcohol exposure: These data are vitally important for the per-occasion risk of drinking and its dose-dependent relationship with alcohol consumption. These data will come from meta-analysis, which is a key analytical component of this thesis since per-occasion risk quantification used previously in this field has not presented changing risks by injury type or severity (18, 143) and thus are insufficient for the current proposed analysis. The meta-analysis that will form part of this thesis is outlined below.

2.3.2 Meta-analysis to model dose-response, per-occasion risk

This study was completed in three main phases: the systematic review, data abstraction, and the meta-analysis. A systematic review of the literature published between 1st January 1980 and 1st January 2010 was completed. Databases queried were Medline, EMBASE, CINAHL, PubMED, CABS (BIDS), WHOLIS, SIGLE, ETOH, Alcohol in Moderation (Alcohol Industry Database), and Web of Science using a pre-defined Keyword algorithm.. It combined the search terms “alcohol” AND “case–control” OR “case–crossover” AND “risk” AND “injury” OR specific outcomes: “motor vehicle collisions”; “poisonings”; “falls”; “suicide”; “homicide”; “drowning”;

"fire"; "poisoning"; and was restricted to full articles (excluding reviews; editorials; and letters) of human studies only. Abstracts were selected from the total pool of identified citations and were excluded from further investigation if at least one of the following criteria is met:

- No indication of any information pertaining to an association between alcohol and injury morbidity/mortality.
- The study was NOT a case–control or case–crossover.
- Inappropriate exposure data: no dose–response information presented (e.g., "yes" versus "no" alcohol consumption was unacceptable in this case).
- The article did not have an appropriate endpoint measure (e.g., improper case definition).
- Acute consumption was not presented e.g., average weekly consumption was used.

From the pool of abstracts selected from this first phase, full-length articles were reviewed and assessed for their inclusion based on the same five criteria. Data abstraction of articles selected for inclusion was the next phase of the meta-analysis. Information about the level of alcohol exposures in each study, the number of cases at each exposure level, the total population at risk at each exposure level, the adjusted estimates of relative risk (RR), and the corresponding upper and lower 95% confidence intervals of the adjusted RR were recorded. When ranges of alcohol are given, the midpoint was taken. In cases where no upper bound for the highest category existed, 50% of the length of the previous category range was added to the low bound and this measure was used. In cases where BAC is measured instead of actual consumption, BAC was converted to grams of pure ethanol consumption by using a modified Widmark formula (144). The following formula was used, solving for the number of beverages consumed and then converting to grams of pure alcohol (see Equation 1, taken from: (145)):

(Equation 1)

$$BAC = \frac{((0.01882816 \times \text{no. of beverages consumed} \times \text{concentration}))}{(\text{weight kg} \times \text{gender fraction})} - (\text{liver clearance rate})$$

where **0.01882816** = concentration of alcohol in blood (g/L), **concentration** = alcohol by volume of the specific beverage type. For this analysis we assume 40% (spirits), 12.5% (wine), 5% (beer). **Weight kg** =weight in kilograms. The average weights of men and women in different countries corresponding to each study were based on published data and was country-specific. **Gender fraction** = percentage of water in the human body: this is assumed to be 58% for men and 49% for women. **Liver clearance rate** = the rate at which liver metabolized alcohol per hour. This is assumed to be 0.017 per hour. All drinking was assumed to have taken place in the 6 h prior to the BAC level being taken, corresponding to how many ED-based injury studies measure alcohol consumption upon presentation (refer to Background section of this document. A sensitivity analysis assuming a 3 h drinking window prior to injury presentation will also be done.

To determine dose-specific relative risk relationships via meta-analysis, the data were inverse-variance weighted (146) and first-order and second-order fractional polynomial regression based on either a random effects or fixed effects (based on heterogeneity test between risk estimates of different studies (147, 148) was run. The best-fit curves were chosen based on the usual fit criteria (149), using the linear curve as the referent model for first-order models and the quadratic as the referent for all second-order models. Based on the number of studies identified in the main search, the abstracted data was separated by injury type and severity (mortality or morbidity) to generate individual, per-occasion risk estimates by injury type and severity separately. The dose-response curves will form the RR input for the determination of injury mortality/morbidity for both binge and daily consumption estimation, albeit using a different overall method for each.

2.4 Calculation of absolute lifetime risk due to drinking patterns

2.4.1 Step 1: Calculation of alcohol-attributable risk

The gender-specific, population-level absolute risk of injury mortality was calculated by dividing the sex- and age-specific number of injury deaths (by injury category) by the total population at risk in each age and sex category for males and females, respectively, for Canada in 2005. The age categories that were used were 15-29, 30-44, 45-59, 60-69, 70-79, and 80+. The injury-, age-

and gender-specific AAF was applied to this total risk to calculate the portion of the overall risk in each injury category that was alcohol-attributable.

2.4.2 Step 2: The baseline risk

This alcohol-attributable rate will then be subtracted from the corresponding overall age- and gender-specific risk to estimate the baseline risk. The baseline risk can be defined as the injury mortality risk that would have occurred in Canada without any involvement of alcohol in the year 2005. In other words: this injury mortality risk is not due to alcohol, but to other environmental or personal factors. This baseline injury mortality risk was used for all subsequent calculations.

2.4.3 Step 3: Determination of relative risk for per-occasion drinking

This baseline injury risk was multiplied by the relative risk associated with alcohol consumption, as determined by the results of the meta-analysis completed as part of this work. This calculation will result in the dose-specific, per-occasion risk for one occasion, by age and gender for each injury type and severity (mortality versus morbidity).

2.4.4 Step 4: Combination of absolute risk data and relative risk data

Multiplying the absolute risk for injury mortality per day by the dose-specific, per-occasion risk of having had a specific number of drinks prior to the injury will yield the absolute risk of dying from injury mortality after the consumption of a specific number of drinks. For instance, if the risk of one person dying in a road traffic collision is 3/1,000, and the relative risk due to drinking two drinks before the event is 2.00, then the resulting conditional probability is 0.003x2.00 = 0.006 or 6/1,000). However, this step only accounts for one lifetime drinking occasion, whereas in fact, the probability of injury mortality increases with the frequency with which a person drinks in addition to how much he/she consumes (see Equation 2).

(Equation 2) $$\Pr(\text{Death} \mid N) = 1 - (1 - (\Pr(\text{death})_d / i_d)^N)$$

Where **N** = the number of binge drinking occasions per year by age and sex according to the survey data from the CADUMS 2008. These will change by age and sex group based on the outputs of the survey,

Pr(Death | N): = the risk of injury death (per 1,000) given N yearly drinking occasions,

$Pr(death)_d$ = the risk of injury death for one drinking occasion per year, depending on the number of drinks per occasion. For the morbidity analysis, mortality risk will of course be risk of hospitalization.

i_d = the adjustment of the yearly risk to reflect the actual risk period, which is the measured time period over which alcohol exerts its effects. i_d varies with numbers of drinks consumed in the drinking occasion, based on the liver metabolism data outlined previously. The adjustment is necessary because the relative risks reflect a single drinking occasion, with 1 drinking occasion is assumed to be 24 hours. However, the risk over 24 hours is substantially smaller than the risk during the active period of alcohol's effects since the body clears alcohol in a shorter period of time than 24 hours. Thus, the risk period (i_d) adjustment for the period of time in which alcohol's action is most apparent. The method used decreases the risk function substantially compared to an assumed risk period of 24 hours and is thus a conservative estimate. For example, for three drinks per occasion we assumed a risk period of three hours during the 24-hour period of that day. So, i_d becomes 365*(24/3), as it is based on the probability of one year.

This risk scenario, i.e. the relative risks associated with each drinking event, obviously changes as the amount of consumption increases for each drinking occasion. The BAC concentration after drinking was modeled based on (142), the liver metabolism data previously identified. The resulting BAC levels obviously differ among individuals and with respect to the context of drinking, but the following risk periods (that time following consumption where risk is significantly higher) can be assumed: one drink -> 30 minutes; three drinks -> two hours; five drinks -> three hours; seven or more drinks -> 4.8 hours. These risks will then be aggregated across all age groups and injury categories to obtain different alcohol-attributable risk scenarios for men and women, respectively.

2.5 Calculation of absolute lifetime risk due to average volume

2.5.1 Step 1: Calculating average volume

Average volume by sex and age was a required input, as for the calculations for drinking pattern. However, there is one main problem with the characterization of the volume of alcohol exposure

in populations: the best indicator, adult per capita consumption (150) is not available by sex and age. This results in the finding that, while surveys such as the CADUMS 2008 do measure alcohol consumption by sex and age, although tend to severely underestimate true adult consumption (150, 151). For example, in the Canadian Addiction Survey of 2004 (152), survey estimates of average drinking were found to underestimate per capita consumption by 60-70% (12). Thus, survey estimates of average volume need to be up-shifted to match per-capita consumption based on sales import and export data, widely considered to be the most accurate measure of consumption (153). The up-shifted alcohol consumption distribution over the whole population has recently been calculated by Rehm et al. (83), where total volume is taken from sales data and fitted to the distribution of exposure in the survey by age and sex.

2.5.2 Step 2: Calculating the consumption-specific AAF for average volume

This method will calculate the lifetime-attributable risk of injury mortality/morbidity due to average daily drinking, independent of binge consumption. The same RR scenarios (based on meta-analysis) were used as in the previous calculation, but in this step, the AAF must be calculated based on distributions of average drinking prevalent in the Canadian population, based on CADUMS 2008. The formula to compute the alcohol-attributable injury for average consumption is:

Equation 3

$$AAF = \frac{P_{abs+former} + \int_0^{150} P(x)RR(x)dx - 1}{P_{abs+former} + \int_0^{150} P(x)RR(x)dx}$$

where **P(x) =** the prevalence of drinking at level x (in grams per day, modeled by the gamma function). The **RR(x)** = the relative risk at this level compared to lifetime abstainers and former drinkers, corrected for time at risk. To adjust the RR(x) for time at which a person is at risk for an injury, we computed the time at risk through the modeling alcohol metabolism rates, namely, the rate at which alcohol is metabolized by the liver using the following formula:

(Equation 4) $RR(x) = P_{dayatrisk}*(RR_{Crude}(x)-1)+1$

where $\mathbf{P_{dayatrisk}}$ (calculated here based on the drinking level x) = the proportion of a day at risk per drinking occasion (see previous section for the description of i_d), and $\mathbf{RR_{Crude}(x)}$ = the relative risk at drinking level x compared to being sober, not adjusted for the time at risk per occasion.

2.5.3 Step 3: Combination of total risk and AAF

The AAF for each injury category, age, and sex group was based on the average daily consumption for each age and sex group, respectively. This AAF was applied to the total risk to get the one-year, alcohol-attributable risk for average daily consumption. This risk, as for the binge drinking calculation, was subtracted from the total one-year risk to obtain the baseline risk of injury for each injury type, age, and sex group.

2.5.4 Step 4: Calculation of lifetime risk for average volume

To get the lifetime risk, a similar approach to the patterns of consumption injury was used, although the number of drinking days was 365 to get an average volume measure (using Equation 1). Age-sex-disease one-year risks were multiplied by the time spent in each age category; e.g. for women 30-39, their one-year alcohol-attributable risk of death would be multiplied by 10, since they would have spent 10 years in this "risk-block" that is specific to the mean daily volume consumed. For those in the oldest age category, their risks were attenuated for life expectancy in 2005 (men: 78.0, women: 82.7) (154). Finally, the risks were added up across age groups and disease categories to obtain gender-specific risks as for the binge calculation.

2.5.5 Step 5: Calculation of absolute risk from total consumption

This step is a simple addition of the absolute lifetime risk from binge consumption and the absolute lifetime risk from average volume.

2.6 Calculation of the alcohol-attributable fraction

The alcohol-attributable fraction is computed in much the same way as the absolute risk, separately for binge consumption and average consumption. For average volume, the estimate from Step 2, using Equation 3 and Equation 4. For binge occasions the AAF was estimated by Equation 5:

(Equation 5)
$$AAF = \frac{P_{abs+former} + P_{current(Non-Binge)} + P_{Current(Binge)}RR(x) - 1}{P_{abs+former} + P_{current(Non-Binge)} + P_{Current(Binge)}RR(x)}$$

where $\mathbf{P_{abs+former}}$ = the proportion of lifetime abstainers and former drinkers, and $\mathbf{P_{current(Binge)}}$ and $\mathbf{P_{Current(Non-Binge)}}$ are the prevalences of current drinkers who engage and who do not engage in binge drinking, respectively. $\mathbf{RR_{binge}(x)}$ is equal to the risk ratio for binge drinkers given a binge amount of alcohol consumed corrected for both time at risk and number of drinking occasions. $RR_{binge}(x)$ was calculated as follows:

(Equation 6) $$RR_{binge}(x) = P_{dayatrisk} * P_{daysatrisk} * (RR_{Crude}(x)-1)+1$$

where $\mathbf{P_{dayatrisk}}$ (calculated based on the average binge consumption x) and $\mathbf{P_{daysatrisk}}$ are the proportion of a given day during which a person binge drinks and is at risk, and the percentage of days the person undertakes binge drinking, respectively.

2.7 Methods to calculate the uncertainty estimates

Calculations to estimate the uncertainty around absolute risk estimates and the AAF were identical and require computer simulation, requiring a bootstrapping-like approach to generate 95% confidence intervals around the risk and AAF estimates (155, 156). For the 2005 Canadian population, 10,000 randomly generated datasets were computed based on random samples of the distributions of average volume, binge occasions, relative risk (by injury type), and prevalence estimates of current drinking and abstention. 10,000 AAFs (pr absolute risks) (for each and sex group) were generated based on the above methods to create a distribution of the AAF per age and sex group, from which the mean (point estimate) and variance was taken.

3 Manuscript 1: Determination of lifetime injury mortality risk in Canada in 2002 by drinking amount per occasion and number of occasions

Citation:

Taylor B, Rehm J, Room, R, Patra J, Bondy S. Determination of lifetime injury mortality risk in Canada in 2002 by drinking amount per occasion and number of occasions. American Journal of Epidemiology 2008;168(10):1119-25.

3.1 Abstract

Injury is the leading cause of alcohol-attributable mortality in Canada. Risk is determined by amount consumed per occasion and accumulates across drinking episodes. This study estimated the alcohol-attributable injury mortality in Canada in 2002 by combining absolute risk of injury unrelated to alcohol with gender- and consumption per occasion-specific relative risks, while taking into account the number of lifetime drinking occasions. The absolute risk increased as drinking occasions and number of drinks per occasion increased. The absolute risk remained relatively low at less than two drinking occasions per month regardless of number of drinks. Absolute risk levels reached one in 1,000 at five or more drinks once per month for men, and between 5 and 7 drinks once per month for women, and reached one in 100 for all levels above three drinks per occasion for men and 5 drinks per occasion for women at or above three drinking sessions per week for both genders. No safe level of consumption is recommended based on these results, although the risk is much lower for drinking three or less standard drinks less than three times weekly. Absolute risk reflects long-term effects of drinking patterns and is important for risk-communication and alcohol-control policy.

3.2 Background

Fatal injury is the leading cause of alcohol-attributable mortality in Canada (12). Globally, unintentional injuries account for 28 percent of alcohol-attributable global burden of disease as measured in disability-adjusted life-years and intentional injuries make up another 12 percent of this burden (4, 7). Numerous studies have found positive associations between alcohol and many different types of injury and injury-related death in various settings (25, 38-42, 86, 130, 157-160). Moreover, most reviews have concluded that alcohol consumption is causally associated with both intentional and unintentional injury based on accepted, standard epidemiological criteria (e.g., (5, 36, 161, 162). Likewise, both the risk and severity of injury follow a dose-response relationship with the amount of alcohol present in the body at the time of injury (e.g. (19, 34, 35).

The risks of injury associated with alcohol consumption are normally expressed in terms of relative risk (RR) for the amount drunk on a particular occasion. However, such calculations do not reveal much about the absolute risk of alcohol-attributable injury. From a policy perspective, or for that matter from the perspective of a consumer, it is important to know also the absolute risk associated with a particular pattern as cumulated over time – for instance, over a lifetime. This is a conventional calculation with respect to some other hazards to human life such as environmental contaminants or hazardous foodstuffs. For instance, in terms of exposure to carcinogenic compounds in drinking water, the World Health Organization sets a general upper guideline "at the concentration which would give rise to a risk of one additional cancer per 100,000 people" on a lifetime basis (92). However, it is clear that thresholds have been set at more risky levels in particular instances. A study of regulation of risky substances in the U.S. and Canada mentions risk thresholds set at 1:22,000 and 1:10,000 (93). For behaviors that are seen as voluntarily taken on, such as driving an automobile, higher risks are routinely accepted. For example, the lifetime risk of dying in a traffic collision associated with driving 10,000 miles a year in the U.S. has been calculated to be about one in 60 (94).

While the relationship between alcohol and injury is well established, there is a lack of studies giving the level of absolute risk of alcohol-attributable injury. The aim of the current study is to fill this gap by estimating the absolute lifetime risk of alcohol-attributable injury mortality for Canadians at different amounts of alcohol consumed during a drinking occasion and different

frequencies of such occasions. This work will allow for quantification of risk for different levels of consumption per occasion and different frequencies of drinking such an amount on a lifetime basis for the Canadian population.

3.3 Materials and Methods

Estimation of alcohol-attributable injury mortality in Canada required combining absolute yearly risk of injury with gender- and consumption-specific RRs, while taking into account the number of lifetime drinking occasions at a particular level, and then calculating the risk per drinking. This required three main steps:

1. Determination of injury mortality risk without the impact of alcohol, i.e., the amount of risk on any specific day to die of injury. This risk was derived from the 2002 Canadian mortality data specified for sex and age. First, the overall sex-and age-specific injury risk was determined, and then the alcohol-attributable portion was subtracted.

2. Determination of relative risk for drinking different quantities of alcohol before the event.

3. Combination of 1 and 2 for estimation of risk per drinking day by alcohol consumption level and total number of lifetime drinking occasions at the level.

Mortality data in Canada for the year 2002, with the underlying cause coded according to the International Classification of Diseases version 10 (ICD 10), were obtained from Statistics Canada.

3.3.1 Determination of injury mortality risk

First, based on usual epidemiological criteria (5, 136, 163), we identified all injury categories on which alcohol has a causal effect and included them in the analyses. These conditions are listed in Table 3-1 as well as the sources of the alcohol-attributable fraction (AAF). AAF is defined as the proportion of disease that would not have occurred if the risk factor (in our case, alcohol) was not present. In other words, it is the fraction of total disease directly caused by alcohol. AAFs for injuries were based on direct estimates of alcohol involvement where available for Canada (traffic collisions; fire); for other types of injury were based on results from the America

A region derived by the comparative risk analysis of the Global Burden of Disease study (4) (for details of calculation see below).

Table 3-1 Alcohol-related disease categories and sources for determining alcohol-attributable fractions (AAF).

Cause of death	ICD-10 codes	WHO GBD Codes	Source
Unintentional injuries			
Motor vehicle collisions	*	W 150	Traffic Injury Research Foundation of Canada, 2004 (164); Transport Canada, 2004 (165)
Poisonings	X40 - X49	W 151	Rehm et al., 2004 (4); adjusted to Canada by AAF for traffic collisions
Falls	W00 - W19	W 152	Rehm et al., 2004 (4); adjusted to Canada by AAF for traffic collisions
Fires	X00 - X09	W 153	Council of Canadian Fire Marshals and Fire Commissioners, 2003 (166)
Drowning	W65-W74	W 154	Rehm et al., 2004 (4); adjusted to Canada by AAF for traffic collisions
Other unintentional injuries	† Rest of V & W20 - W64, W75 - W99, X10 -X39, X50 - X59, Y40 -Y86, Y88, Y89	W 155	Rehm et al., 2004 (4); adjusted to Canada by AAF for traffic collisions
Intentional injuries			
Self-inflicted injuries	X60 - X84, Y87.0	W 157	Rehm et al., 2004 (4); adjusted to Canada by AAF for traffic collisions
Homicide	X85 -Y09, Y87.1	W 158	Rehm et al., 2004 (4); adjusted to Canada by AAF for traffic collisions
Other intentional injuries	Y35	W 160	Rehm et al., 2004 (4); adjusted to Canada by AAF

* V021-V029, V031-V039, V041-V049, V092, V093, V123-V129, V133-V139, V143-V149, V194-V196, V203-V209, V213-V219, V223-V229, V233-V239, V243-V249,V253-V259, V263-V269, V273-V279, V283-V289, V294-V299, V304-V309, V314-V319, V324-V329, V334-V339, V344-V349, V354-V359, V364-V369, V374-V379, V384-V389, V394-V399, V404-V409, V414-V419, V424-V429, V434-V439, V444-V449, V454-V459, V464-V469, V474-V479, V484-V489, V494-V499, V504-V509, V514-V519, V524-V529, V534-V539, V544-V549, V554-V559, V564-V569, V574-V579, V584-V589, V594-V599, V604-V609, V614-V619, V624-V629, V634-V639, V644-V649, V654-V659, V664-V669, V674-V679, V684-V689, V694-V699, V704-V709, V714-V719, V724-V729, V734-V739, V744-V749, V754-V759, V764-V769, V774-V779, V784-V789, V794-V799, V803-V805, V811, V821, V830-V833, V840-V843, V850-V853, V860-V863, V870-V878, V892.

† Rest of V = V-series MINUS *.

The gender-specific, population-level absolute risk of injury mortality was calculated by dividing the sex- and age-specific number of injury deaths (by injury category) by the total population at risk in each age and sex category for males and females, respectively, for Canada in 2002. The age categories used were 15-29, 30-44, 45-59, 60-69, 70-79, and 80+. This risk was then multiplied by the age- and gender-specific AAF to obtain that portion of the overall risk in each injury category that was alcohol-attributable.

This alcohol-attributable rate was then subtracted from the corresponding overall age- and gender-specific risk to estimate the baseline risk. The baseline risk can be defined as the injury mortality risk that would have occurred in Canada without any involvement of alcohol in the year 2002. In other words: this injury mortality risk was not due to alcohol, but to other environmental or personal factors. This baseline injury mortality risk was used for all subsequent calculations.

3.3.2 Determination of relative risk for different alcohol quantities

This injury risk was then multiplied by the relative risk associated with alcohol consumption, as measured in Canadian standard drinks (13.6 grams of pure alcohol (167)). Estimation of this risk required a number of steps. First, relative risks corresponding to consumption of standard drinks were identified in a recent World Health Organization (WHO)-sponsored case-crossover study of hospital emergency rooms in 10 different countries (N = 4,320, 91 percent response rate), where patients presenting with injury were given a questionnaire that asked about drinking prior to the collision which caused the injury (160). These yielded volume-specific RRs corresponding to specific numbers of standard drinks. However, since the standard drink size in this study (16 ml of pure alcohol) did not equal the standard drink size of Canada (13.6 grams), the Borges et

al. (2006) (160) data was modeled and linearly approximated for consumption up to five drinks and then converted to Canadian standard drinks based on the linear equation. Beyond five standard drinks, the Borges et al. (2006) (160) risk data were used. Please see Table 3-2 for the raw risk data in 16ml standard drinks and the corresponding relative risks after conversion to Canadian standard drinks.

Table 3-2 Conversion of alcohol intake volumes from Emergency Room studies (Borges et al. 2006 (160))

Before conversion ("Drinks" in international settings, approximately 12.5grams)		After conversion (Canadian 13.6 gram standard drinks)	
Number of drinks	**RR**	**Number of drinks**	**RR**
0	1	0	1.00
1	3.3	1	2.31
2.5	3.9	3	4.92
4.5	6.5	5	6.54
>6	10.1	7+	10.10

3.3.3 Combination of absolute risk data and relative risk data

Multiplying the absolute risk for injury mortality per day by the relative risk of having had a specific number of drinks prior to the injury will yield the absolute risk of dying from injury mortality after a specific number of drinks. For instance, if the risk of one person dying in a road traffic collision is 3/1,000, and the relative risk due to drinking two drinks before the event is 2.00, then the resulting conditional probability is 0.003x2.00 = 0.006 or 6/1,000). However, this step only accounts for one lifetime drinking occasion, whereas in fact, the probability of injury mortality increases with the frequency with which a person drinks in addition to how much he/she consumes (see Equation 1).

(Equation 1) $$Pr(Death \mid N) = 1 - (1- (Pr(death)_d/i_d)^N)$$

Where

N = the number of drinking occasions per year (1, 12, 24, 52, 156, 260, 365). These equate to 1/year, 1 per month, twice per month, once per week, three times per week, 5 times per week, and every day, respectively)

Pr(Death | N) = the risk of injury death (per 1,000) given N yearly drinking occasions

$Pr(death)_d$ = the risk of injury death for one drinking occasion per year, depending on the number of drinks per occasion

i_d = adjustment to the yearly risk to reflect the actual risk period, which is the measured time period over which alcohol exerts its effects. i_d varies also with numbers of drinks consumed in the drinking occasion. For example, for three drinks per occasion we assumed a risk period of three hours during the 24-hour period of that day. So, i_d becomes 365*(24/3), as it is based on the probability of one year.

This risk scenario, i.e. the relative risks associated with each drinking event, obviously changes as the amount of consumption increases for each drinking occasion. After the consumption of one standard drink, the blood alcohol concentration reaches its peak roughly 30-45 minutes after ingestion. Rapid consumption of multiple drinks results in higher blood alcohol in the period following ingestion because the liver has a relatively fixed rate of metabolism. In general, the consumption of one Canadian standard drink results in a blood alcohol concentration (BAC) of approximately 0.02 mg/ml, two drinks in succession lead to a BAC of about 0.05, roughly three drinks results in 0.07-0.08 mg/ml, and approximately four drinks results in a BAC of roughly 0.09 mg/ml in the 0.5-1.5 hours following consumption (142). These levels obviously differ among individuals and with respect to the context of drinking, but the following risk periods (that time following consumption where risk is significantly higher) can be assumed: one drink -> 30 minutes; three drinks -> two hours; five drinks -> three hours; seven or more drinks -> 4.8 hours. These were the time periods modeled in the above formula.

3.4 Results

Figures 3-1 and 3-2 show the results for overall risk of injury per 1,000 population by the number of lifetime drinking occasions and number of standard drinks consumed prior to the injury for men and women, respectively. Comparing the two graphs, for all numbers of drinking occasions and number of standard drinks, men are at a roughly two-fold higher risk than women. Injury mortality per se is higher among men than among women. However, both men and women show similar patterns of increasing risk of injury mortality as both the lifetime drinking occasions and number of drinks consumed increases. In addition, for both men and women, lifetime drinking occasions at or under twice per month results in relatively similar risk profiles, with a major jump in risk seen at two drinking occasions per week. For men, the injury mortality risk reaches one in a level of five or more standard drinks once per month and for women, the risk achieves one in 1,000 per day at consumption of between 5 and 7 standard drinks about once per month. Drinking seven or more standard drinks about every day, men reach a maximum risk of about 66/1,000 and women reach a maximum mortality risk of approximately 32/1,000. For both men and women, drinking more than 3 drinks 3 or more times per week resulted in a lifetime injury mortality risk of one in 100, or 1%, although this risk is also achieved at different combinations of more drinks/less occasions or less drinks/more occasions.

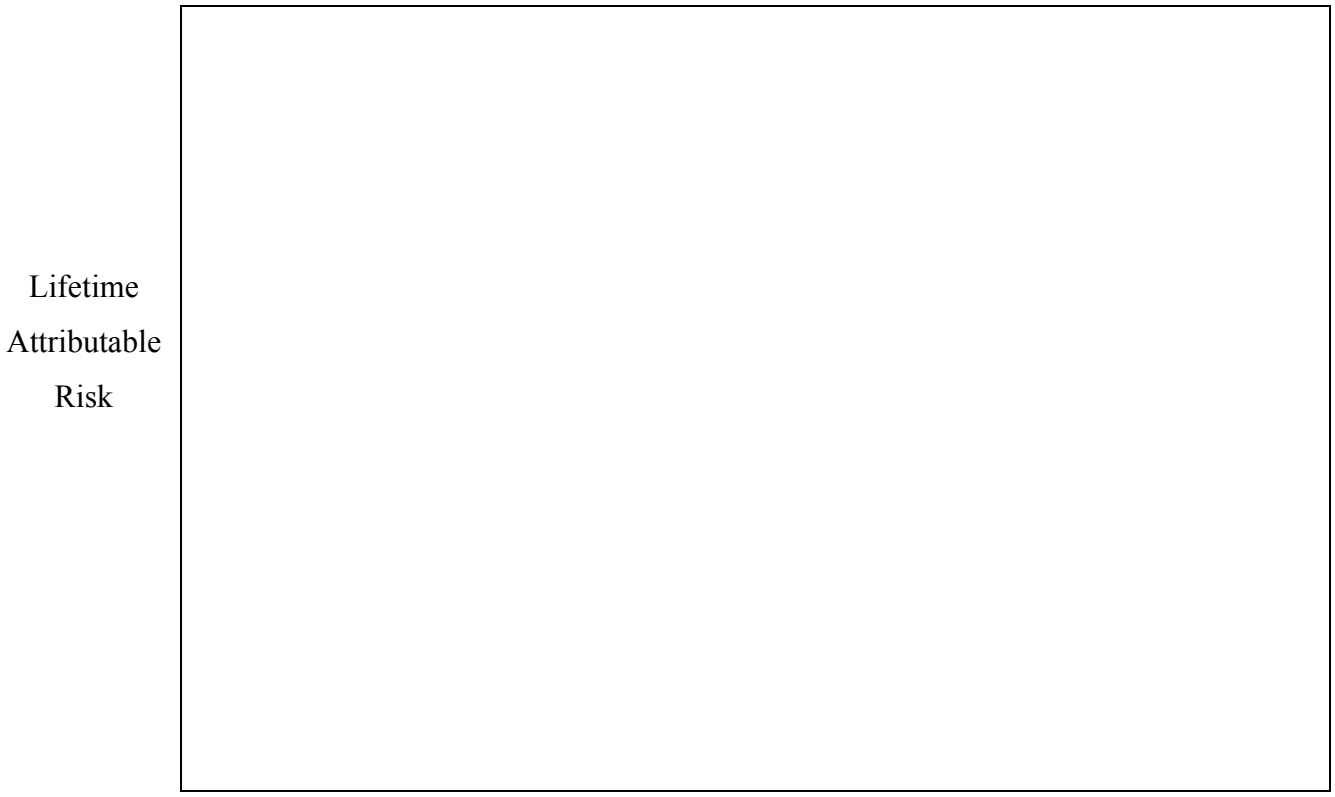

Figure 3-1 Risk per 1,000 of lifetime injury mortality by number of standard drinks consumed on an occasion and lifetime number of such occasions among men in Canada, 2002.

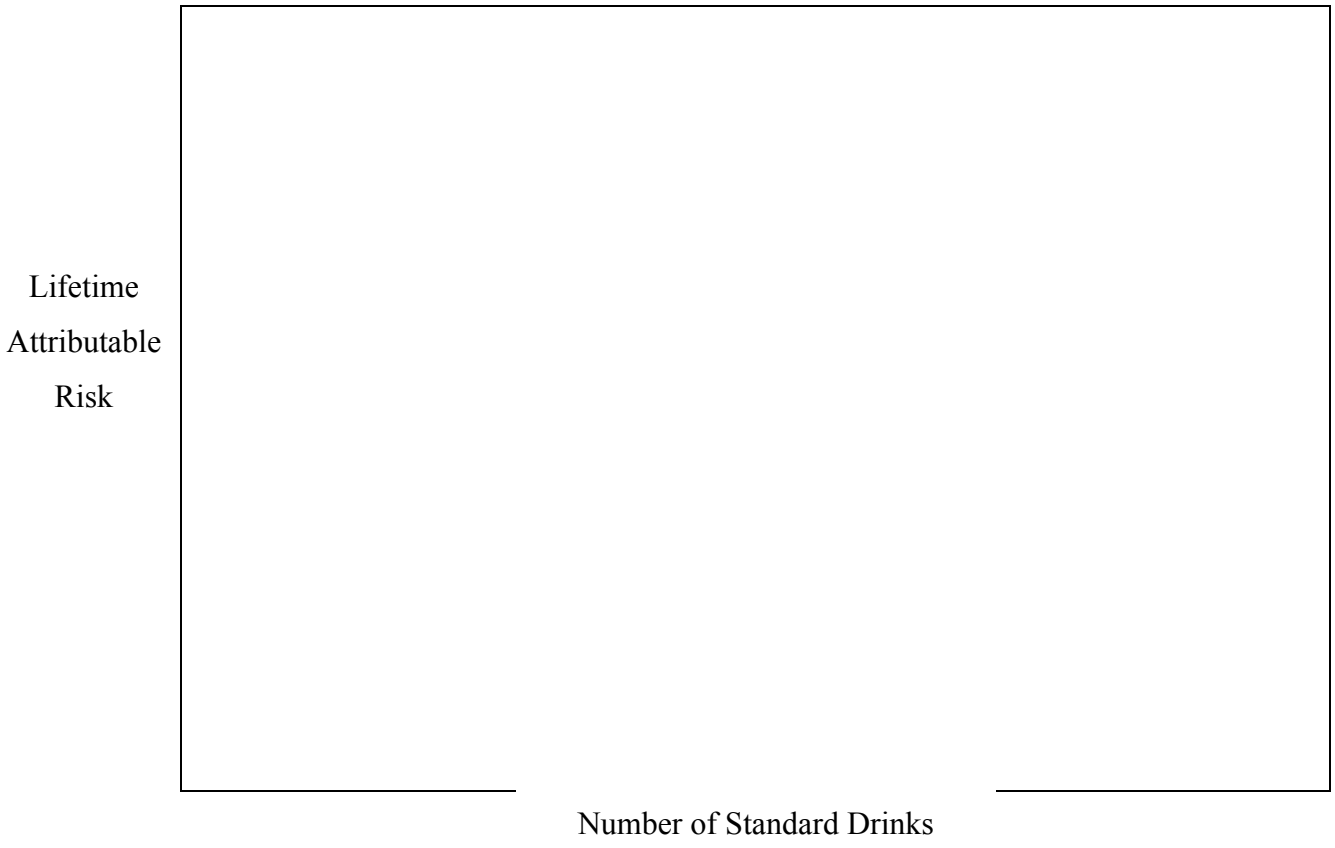

Figure 3-2. Risk per 1,000 of lifetime injury mortality per day by number of standard drinks consumed on an occasion and lifetime number of such occasions among women in Canada, 2002

3.5 Discussion

For both men and women, the risk of injury death increased as both the number of drinking occasions and the number of drinks consumed per drinking occasion increased. The risk was higher for men than women, particularly at higher numbers of drinks and occasions. Also, there was a "risk threshold" effect seen between drinking once a month and twice a month – below this marker the risk of injury was low and relatively equal for all alcohol volumes for men and women, respectively, but above this level the risk was significantly higher for both men and women.

These estimates are conservative in the sense that they are based on emergency room (ER) studies, i.e. on studies where the injured person survived. The relevant literature indicates that

injuries tend to be more severe when alcohol is involved, and thus the relative risk and alcohol-attributable fraction are larger for mortality compared to morbidity (4). On the other hand, having ER studies as the basis may also have led to an overestimate of the effects. Clearly, the attendees of ERs are not representative of the general population. They may be characterized as higher risk-taking, and thus the RR for alcohol in this population may be higher than in the general population. Unfortunately, we do not have much knowledge to test or quantify this potential effect. Our findings are different from accepted norms of alcohol-attributable risk for men as compared to women, which warrants some brief discussion. It is generally well-accepted that women have a lower tolerance for alcohol for gender-based genetic and metabolic reasons (142), including a lower average body weight (142). As a result, everyday wisdom dictates that women *ceteris paribus* should have higher risks of alcohol-attributable injury given that they, on average, get more intoxicated for the same amount of alcohol. The problem in applying this lies in the *ceteris paribus* clause. Lifetime risk of injury is not equal for men and women. Instead, men have a higher risk of lifetime injury in all cultures, presumably related to a higher propensity of risk taking. Only if we hold this variable (i.e. risk-taking) constant, do we get the expected results, that for a given number of drinks or blood alcohol concentration, women have higher risks of incurring injury (see (85) for an example with motor vehicle collisions).

As well, the issue of predisposing personality and behavioral factors also play a role i.e. that if one simply chooses *not* to drive a car or enter a potential risky situation after consuming alcohol, his or her risk of alcohol-attributable motor vehicle or other injury death goes to zero. In theory, this is true, but in practice, it assumes that alcohol consumption and risk-taking behavior are independent of each other, whereas the literature clearly shows they are not, both in terms of risk perception and behavior, even at moderate doses (61, 62, 168).

The authors also recognize that drinking patterns – frequency and quantity consumed per occasion, may change significantly over the life course. While these formulae can be applied to assess risk for changing consumption patterns over a lifetime, for the purposes of presenting the method and its interpretation, combinations of number of occasions and number of drinks consumed per occasion (of which there are a huge number) are impractical. Figures 1 and 2 are population-based estimations and thus are not based on one individual's behavior, but rather the behavior of Canadian men and women as a whole, respectively, in 2002. The Canadian population does not have individual risk profiles, but rather overall risk profiles, and as a group,

have been found to have drunk alcohol in about one-third of their motor vehicle collisions in each year from 1999-2004 (164, 169-173), showing a stable trend. So, regardless of risk-behavior, alcohol has been shown to play a major causal role in motor vehicle collisions in an individual and, more importantly in the context of this article, a population level. Further work, however, may lead to presentation of calculations for individual risk scenarios based on usual lifetime drinking patterns.

The results of this analysis are important clinically and for population guidelines, as well as for the research community. It is important to disentangle frequency of drinking and amount consumed per occasion. Epidemiologic literature on injury prevention is not well-served by looking merely at volume of consumption. Injury risk is an acute phenomenon and amount consumed per occasion has to be considered. This study also complements and extends emergency room studies in presenting cumulative risk across episodes for the individual. Absolute risks also tend to be more interpretable and more useful for personal risk communication. They also reflect the public health impact of alcohol consumption and drinking patterns better than relative risks or statistics of correlation. Correspondingly, this method and results are very important from a public health perspective. These methods were recently adopted to develop low-risk drinking guidelines for Australia, recommending that relatively high risk (compared to accepted risk of other risk factors) is achieved at a level of 3 standard drinks of pure alcohol three times or more per week (1 Australian standard drink = 10 grams of pure alcohol). This result was one of the factors leading to a proposed revision of the current guidelines for drinking in Australia. Thus, it is important to be able to communicate risk in a palatable and understandable form for the public. For example, how does one's individual risk of dying due to drinking 3 drinks three times per week compare with the mortality risk posed by asbestos, or eating fruit that has been grown with toxic pesticides? In fact, alcohol poses a much higher risk than all three of these substances. It turns out that asbestos poses a mortality risk of between one in 1,000 and one in 10,000 lifetime risk, and eating pesticide-grown fruit carries a lifetime risk of one in 22,000 (93), both of which are orders of magnitude lower than the risk of injury death due to drinking alcohol. As well, the absolute mortality risk will increase when long-term effects of drinking alcohol are also taken into account by accounting for alcohol-attributable chronic disease deaths from disease such as liver cirrhosis, heart disease, and some cancers (4, 12, 36).

Risk communication to the public will enable them to understand their own risk profile and risk tolerance level to enable healthy decision-making based on sound analysis and comparison. From a public health standpoint, developing lifetime risk data are important for construction of low risk drinking guidelines, both for Canadians and elsewhere, in order to communicate the risk of harmful and hazardous drinking behaviors.

3.6 Invited Commentary: Is Alcohol a Risk Factor for Trauma and Chronic Disease Mortality? Narrowing the Gap Between Evidence and Action

The following is a reprint of an invited commentary in the American Journal of Epidemiology by Dr. Norman Giesbrecht, to which a response follows. This can be found at:
American Journal of Epidemiology. 2008;168 (10): 1126-1129 and the response at
American Journal of Epidemiology. 2008;168 (10): 1130-1131. The commentary by Dr. Giesbrecht also concerns another paper published in the same issue of the Journal (174). References to this article have no bearing on this thesis or the response, but for the sake of completeness and not wanting to paraphrase or cut certain sections out of Dr. Giesbrecht's response, the commentary is reprinted in its entirety here.

3.6.1 Abstract

Alcohol has been linked with over 60 chronic diseases and types of trauma, and in developed countries alcohol consumption is ranked third in terms of disability-adjusted life years (of 26 risk factors considered). In this issue of the Journal, two papers from Finland and Canada provide new evidence of the negative effects of alcohol consumption on trauma and mortality. Herttua et al. (Am J Epidemiol. 2008;168(10):1110–1118) used data from a natural experiment involving an increase in access to alcohol and its links to mortality; they offer provocative findings on differential impacts by gender, age, and socioeconomic level. Taylor et al. (Am J Epidemiol. 2008;168(10):1119–1125) focused on lifetime risk of alcohol-related injury mortality, exploring the implications for high-risk drinking patterns. These authors offer agendas for future research on the differential impacts of policy changes according to demographic dimensions, and they highlight the need for a refined measurement of alcohol intake—since the amount of alcohol in a "standard drink" consumed by heavier drinkers is probably not the same as it is for other consumers. There is still a substantial gap between alcohol's position as a significant contributor to mortality and disability and the implementation of effective interventions

3.6.2 Commentary

These two papers (174, 175) provide important new insights into the impacts of alcohol consumption on chronic disease and trauma. By implication they highlight the gap between evidence of alcohol's damage and the need for higher profile, better resourced and more potent interventions and policies.

While these relationships have been known for many years (176, 177), it is in this decade that the relative impact of alcohol on death, disease and disability (DALYs) has been shown to be not dissimilar from that of tobacco. In developed countries such as Canada, Finland and the United States, alcohol ranked 3rd (at 9.2 % of total DALYs) of 26 risk factors considered, behind tobacco and high blood pressure, and ahead of cholesterol, body mass index, low fruit and vegetable intake, physical inactivity, and illicit drugs (178). Alcohol has been linked with over 60 diseases and types of trauma (7).

As indicated by Kimmo Herttua and colleagues (174), an increase in access to alcohol, through a policy change, can have a measurable negative impact by stimulating a rise in alcohol-related mortality. The publication by Benjamin Taylor and colleagues (175) signals that even at relatively low levels of consumption absolute risk is greater than for other dangers that currently receive more attention in public debate and discussion.

Herttua and colleagues (174) conclude that a decline in taxes on alcoholic beverages - which impacted retail prices of alcohol - contributed to an increase in chronic disease mortality related to alcohol consumption, with not much impact on trauma, and greater impact among women, older adults, and those with lower socio-economic advantages.

The relationship between real price of alcohol and damage from alcohol has been demonstrated in numerous studies (179, 180). Thomas Babor and colleagues (181) concluded that price/taxation policies was one of most -- if not the most -- potent policy lever, given the strength of the evidence, cross-cultural range of the studies and number extent of research. This paper (174) provides a recent high quality natural experiment, which allows for an exploration of the impacts by social status, age and gender, and a comparison by type of mortality.

The rationale for the decline in taxes was the lifting of personal import restrictions that appear to have contributed to an increased volume of imports from Estonia, for example. I would have welcomed a brief presentation of annual data on the per capita ethanol volume of official sales of alcohol in Finland for domestic consumption during the 5-year period under study, and also an estimate of population level ethanol volume of personal imports during this period. A tax reduction as indicated by Herttua et al. analyze is likely the main factor for the changes in mortality that they present, but they have not ruled out, it seems, the possibly modest contribution of imports for personal consumption, or controlled for changes in real price during the period under study.

During the time period the increase in trauma mortality is modest compared to that from chronic disease. And there is substantial variation in impact by age. Also, as indicated in Tables 1 and 2 the % change in mortality is greater among women than men, although there is little discussion of the results by gender. It appears that further research is warranted on impacts of policy changes and changes in drinking behavior and drinking patterns among women, youth and young adults.

In this study alcohol-related mortality has been organized into two groups: acute and chronic. Since alcohol may be a more potent contributing cause to some types of mortality than others, future work might explore an approach where mortality data are 'weighted' according to strength of the epidemiologically accessed relationship with alcohol.

The policy implications of this paper are clear and line with previous research (181). Reducing access to alcohol is likely to reduce alcohol-related damage including alcohol-related mortality. However, in the European context where there is substantial international pressure to increase access combined with an erosion of long-standing control on alcohol, it is particularly challenging to implement these prevention measures.

The paper by Taylor and colleagues breaks new ground by offering estimates of population level absolute risks of alcohol-related trauma. They also imply that risks of alcohol consumption above a modest amounts/occasions are greater than other behaviors or contexts that receive substantial greater attention in the media and among policy makers.

As the authors imply, future work will benefit from developing more accurate estimates of the

number of drinking occasions and amount consumed per occasion. An operational definition of a standard drink is not likely to be accurate for all types of drinkers and may also vary by age and gender. For example, emerging data from an ongoing U.S.-based study indicates that heavy drinkers tend to pour larger drinks (or have larger drinks poured for them). Furthermore, regular customers, likely to be heavier drinkers, are likely to receive more liberal servings of poured drinks in licensed establishments (182). It is feasible that in countries or regions where most of the alcohol consumption involves self-service or informally provision in private settings there will be greater deviation from a conventional standard drink volume, especially among heavier drinkers.

A theme of this paper is that high risk drinking is fairly common behavior. This can be illustrated from a 2007 survey of Ontario students in grades 7 to 12 (183): overall 61.2% reported drinking in the past 12 months before the survey (representing 616,300 students in Ontario), 26.3% (262,400) reported drinking 5 or more drinks on a single occasion at least once in the 4 weeks before the survey; and 18.6% (193,000) scored 8 or more on the Alcohol Use Disorders Identification Test considered to represent hazardous or harmful drinking.

This paper has important implications for specifying the content of low risk levels and the text for risk reduction guidelines for alcohol consumption. It may be tempting to conclude that population level risks of alcohol-related trauma will be reduced through the promotion of such guidelines. However, rigorous investigations of the impact of national or regional guidelines remain to be undertaken. Low risk drinking guidelines have been developed and promoted in many countries, and are currently under review in Australia and Canada. One can imagine a multi-year experiment where matching jurisdictions are randomly assigned to ‘no special intervention’, ‘low risk guidelines promotion’, and ‘low risk guidelines plus community-based prevention’. However, governments typically don’t take this type social experimental approach to alcohol policy-making. -- with significant exceptions in the Nordic countries (e.g., (184)).

In the absence of convincing evidence that low risk drinking guidelines have any impact and the political will to facilitate the type of experiment noted above, we are left with extrapolating from studies where information dissemination and education are the primary prevention tools. Warning labels on alcoholic beverage containers introduced in the United States in 1988 have been shown to among the most popular alcohol policy interventions (185), and growing in public

support for a number of years since their implementation (186). There is evidence of an impact on perceptions, attitudes and behavioral intentions (187), but beyond that their impact on drinking behavior, high-risk drinking and drinking-related problems remains to be demonstrated (181).

Similarly, school-based programs to educate youth about the risks of alcohol continue to have great popularity, and impacts on attitudes, intentions and perceptions have been noted (188). However, their impacts on drinking behavior, high-risk drinking and drinking-related problems are either not evident or short-lived (189-191).

Warning labels are required on every alcoholic beverage container in the U.S. and thus, potentially, occasional drinkers will see them at least once, and heavy drinkers regularly. Evaluations of school-based alcohol education programs are based on those who participated in them. In both cases there is an absence of evidence of their impacts on behavior. Given these circumstances, can we expect that low risk drinking guidelines, even if they were printed on every bottle or can of alcohol, would have any measurable impact?

Nevertheless there are several justifications for drinking guidelines. The public has the right to know the content of products that are sold and risks associated with it's use, especially with governments involvement in licensing or retailing, the latter in control states in the United States or via liquor boards in Canadian and Finnish jurisdictions.

Secondly, guidelines are potentially a useful complement to interventions shown to be effective, such as server interventions at package stores or licensed premises (192), controls on overall access to alcohol (increase in real price, and ceiling on density) (181, 193), and community-based prevention (194). Third, they can be an important political resource in raising the profile of alcohol by pointing to the risks associated with its use and pointing to levels that while not necessarily safe, are less risky.

Drinking guidelines also serve as markers for tracking and documenting social behavior, and a tool for policy advocates or policy managers. In Ontario, the current low risk drinking guidelines of no more than 2 standard per day (13.6 grams of ethanol) and no more than 9 standard drinks per week for men and 14 for men (195). Between 2003 and 2005 there has been a significant increase in the percent drinking above this level, from 21% to 25%, and it is particularly elevated

among younger adults aged 18-29 (38%) (183). The percentage of adults aged 18+ who report drinking 5+ per occasion at least weekly has also increased and was 11% in 2005 (183). Overall alcohol sales in the province has risen from 7.1 to 7.9 litres of absolute alcohol per person aged 15 and older since 1996 (196, 197).

Have these developments stimulated markedly greater activities among policy makers at the national and provincial levels? An optimistic conclusion is 'not yet'.

Alcohol policy advocates may have to wait for some time for an alcohol strategy that promotes the most effective population level interventions combined with resources that are required to achieve a marked reduction in alcohol-related damage (181, 198).

Alcohol is a substantial risk factor for trauma and chronic disease, as shown in these papers (174, 175), and evidence of its contribution is growing (e.g. (199, 200). However, the inadequate responses to date in developed countries such as Canada would suggest that in the policy-making circles it's perceived risk is much lower than is the actually the case (178) and is illustrated by the new data presented in these two papers (174, 175).

The recent experiences in the United Kingdom provide a timely public health warning of how inadequate policies can stimulate increased damage from alcohol. These experiences also offer a positive lesson showing the willingness of the medical community and other sectors to mobilize to address the fall-out from misguided policies (201-204). The recent experiences in both Canada and Finland analyzed in these papers offer agenda for further research and additional empirical support for more effective population level interventions.

3.7 Taylor et al. Respond to ‘‘Alcohol and Trauma and Chronic Disease Mortality’’

The authors would like to thank our colleague Dr. Giesbrecht for his commentary on our method to calculate lifetime risk of alcohol-attributable injury and its wider applications, specifically as part of an evidence-based tool in the construction of guidelines on low risk drinking. Guidelines have often taken on a normative, indeed moral, cast, alongside the framing in terms of science and risk -- particularly when industry influence is strong. Setting a guideline inherently involves drawing arbitrary lines on multiple risk curves between alcohol and various disease and injury outcomes and there have previously been no explicit standards for how that line should be drawn (with the exception of a guideline oriented only to chronic disease (205). The work we did was stimulated by a wish to put guidelines on the risk of drinking into the frame of lifetime risks, which is more generally used in the estimation of health risks such as risks of water contamination or radon, and to make explicit and transparent the basis on which any line was to be drawn in adopting guidelines. This can be seen as a positive first step in establishing an evidence base on which governments or consumers can make necessary judgments of risk from alcohol, or for that matter, from any other potentially harmful exposures. The method we have proposed is the first systematic analysis based on drinking pattern and volume per occasion to be applied to a lifetime risk approach and the first ever to be applied to low risk drinking guidelines, despite the existence of such guidelines in over 30 countries (206). It is of course subject to continued scrutiny and improvement, but is the first step towards rigorous risk estimation of this nature for alcohol specifically. What’s more, this first step points to a much higher risk than previously estimated for Canadians and Australians (207), indicating that personal judgment, even by experts in the alcohol field, may be more sympathetic to an extra pint than rigorous evaluation may indicate.

We share some of Dr. Giesbrecht’s skepticism about the previous development and impact of low-risk drinking guidelines in the past (see also (208)). Although there are certainly older antecedents (209), national guidelines on drinking are primarily a product of the last 30 years. The guidelines have often come from sources which are authoritative but not specifically concerned with alcohol policy, such as medical associations; those with a specific interest in

alcohol and public health have often treated them with some skepticism (e.g., (210)). All of the guidelines are about risk, usually the risk to the drinker him- or herself; no guideline yet has been based specifically on the risk of drinking to others than the drinker, though this is presumably the strongest rationale for government action. Instead, risks to others have been covered by legislation one risk at a time, e.g., by blood-alcohol limits for driving or operating a boat. Some of the guidelines also include a semi-explicit normative element; something called "sensible drinking" obviously involves more than just a calculus of risk.

In our view, if there continues to be a demand for guidelines, there should be an explicit separation of the scientific from the normative judgments. Science can specify the degree of risk – to the drinker, and also to others around the drinker – with increasing accuracy. Such calculations of risk should be periodically repeated, and the risk estimates updated. The schedule of every 5 years specified by the Australian National Health and Medical Research Council seems sensible. What is to be done with these calculations in terms of normative advice about drinking is then a matter that involves more than research technicalities. How much risk it is appropriate to take, on any drinking occasion and in cumulative terms over time, is part of a discussion about how social life should be conducted and what is the place of drinking in society. Making the cumulative risks explicit is a basis for this discussion, but it does not settle the answer.

4 Manuscript 2: The more you drink, the harder you fall: A systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together.

Citation:

Taylor B, Irving, HM, Kanteres F, Room R, Borges G, Cherpitel C, Greenfield T, Rehm J. The more you drink, the harder you fall: a systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together. Drug and Alcohol Dependence. 2010; 110: 108-116.

4.1 Abstract

Alcohol consumption causes injury in a dose-response manner. The most common mode of sustaining an alcohol-attributable injury is from a single occasion of acute alcohol consumption, but much of the injury literature employs usual consumption habits to assess risk instead. An analysis of the acute dose-response relationship between alcohol and injury is warranted to generate single occasion- and dose-specific relative risks. A systematic literature review and meta-analysis was conducted to fill this gap. Linear and best-fit first-order model were used to model the data. Usual tests of heterogeneity and publication bias were run. Separate meta-analyses were run for motor vehicle and non motor vehicle injuries, as well as case-control and case-crossover studies. The risk of injury increases non-linearly with increasing alcohol consumption. For motor vehicle collisions, the odds ratio increases by 1.24 (95% CI: 1.18-1.31) per 10-gram in pure alcohol increase to 52.0 (95% CI: 34.50 – 78.28) at 120 grams. For non-motor vehicle injury, the OR increases by 1.30 (95% CI: 1.26-1.34) to an OR of 24.2 at 140 grams (95% CI: 16.2 – 36.2). Case-crossover studies of non-MVC injury result in overall higher risks than case-control studies and the per-drink increase in odds of injury was highest for intentional injury, at 1.38 (95% CI: 1.22 - 1.55). Efforts to reduce drinking both on an individual level and a population level are important. No level of consumption is safe when driving and less than 2 drinks per occasion should be encouraged to reduce the risk of injury.

Keywords: alcohol, injury, epidemiology, risk, meta-analysis

4.2 Introduction

There is little doubt that alcohol consumption causes injury (4). Although the risk of alcohol-attributable injury from motor vehicle collisions (MVC) is the most visible connection in the research literature and popular media, a large body of work has shown that alcohol consumption is broadly associated with the risk of both intentional and unintentional injury in cross-sectional (24, 27, 110, 123, 124), case-crossover (125, 160), and case-control analyses (23, 128). The most common mode of sustaining an alcohol-attributable injury is from a single occasion of acute alcohol consumption, most commonly leading to intoxication and/or drunkenness and thus impairment. Recent work has shown that engaging in such occasions of acute consumption repeatedly results in high cumulative risks of injury over the life course (175, 207). In previous work, measures of association have tended to show linear, dose-response relationships with risk compared to zero alcohol consumption (112, 160, 211, 212). What's more, these general relationships have persisted throughout the last 40-50 years of research (85, 129), across countries and cultural boundaries (131-134) and without major distinctions by age or gender (18), although absolute values of risk tend to be higher for young males involved in fatal motor-vehicle crashes (135). Overall, the disease burden attributable to alcohol consumption is high, particularly with respect to premature death and disability (213).

There are two particular problem areas in the literature of alcohol and injury. The first is varying and/or unusable exposure measurements and the second is the inclusion of lab-based studies to generate risk estimates. In the first case, injury risks have tended to be based on two drinking models – usual consumption patterns or acute exposure. Information on usual consumption patterns does not capture the influence of alcohol on a particular episode of injury. It does not give information on whether alcohol was even consumed nor at what level prior to a specific injury event. For acute exposure measures, even though we can be certain the alcohol consumption occurred prior to the injury, many studies only report a dichotomous (YES/NO) measure of alcohol consumption. This precludes the construction of dose-response curves that have been informative in other areas of alcohol epidemiology, even though we are certain that risk increases with number of drinks consumed. Tightly controlled lab-based studies do exist and provide dose-response risk curves, but this is also problematic since tightly controlled situations may not represent real world scenarios. Thus, case-control and case-crossover in emergency

room settings represent the best available evidence for measuring the real association between acute alcohol consumption and injury outcomes. The only previous meta-analysis for injury and alcohol consumption is Corrao et al. (18), but this study suffered from the same problem in exposure definition by only presenting risk estimates as a function of usual consumption (18).

This systematic review and meta-analysis thus aims to fill two gaps in this research at once– (1) to calculate a dose-response curve between alcohol and injury (2) by using only high-quality, real world epidemiological studies. Specifically, it will systematically seek out and locate those articles that present risk estimates of injury by specific alcohol consumption categories during the 6 hours immediately preceding the injury or report the blood alcohol level at the time of presentation/reporting of the injury. This will enable this analysis to pool acute alcohol dose-response data to capture an overall estimate of drinking during the period immediately before the outcome, and thus try to capture the true, real-world risk more accurately.

4.3 Methods

This study was completed in three main phases: the systematic review, data abstraction, and the meta-analysis.

4.3.1 Case Definition

The definition of injury was relatively broad in the sense that no strict adherence to ICD codes or strict diagnostic criteria was followed, since some studies only used qualitative descriptions of injury (e.g. “hit”, “cut”, “fall” etc.) and others used the more traditional ICD-9 or ICD-10-based definitions. Most studies were either emergency room studies (e.g. (160)) in which the patient presented with an injury, was admitted and recruited, or were MVC studies based on collision data, (e.g. (214)).

4.3.2 Systematic Review

A systematic review of the literature published between 1 January, 1980 and 21 November, 2008 was completed. Databases queried were Medline, EMBASE, CINAHL, PubMED, CABS (BIDS), WHOKIST, SIGLE, ETOH, Alcohol in Moderation (Alcohol Industry Database), and Web of Science using a pre-defined key word algorithm. Initially, the search used the bare minimum in search criteria in order to cast the widest net (and therefore the most conservative strategy) to identify articles. It combined the search terms “alcohol” AND “case control” OR

"case crossover" AND "risk" AND "injury" OR specific outcomes: "motor vehicle collisions", "poisonings", "falls", "suicide", "homicide", "drowning", and was restricted to full articles (excluded reviews, editorials, and letters) of human studies only. This resulted in 323 articles, from which 182 were selected for closer inspection. For this analysis, only case-control or case-crossover articles were selected since these represent the best available evidence on alcohol-injury. Abstracts were selected from the total pool of identified citations and were excluded from further investigation if at least one of the following criteria were met:

1. No indication of any information pertaining to an association between alcohol and injury morbidity/mortality
2. The study was NOT a case-control or case-crossover
3. Inappropriate exposure data: No dose-response information presented (e.g., "yes" versus "no" alcohol consumption was unacceptable in this case)
4. The article did not have an appropriate endpoint measure (e.g. improper case definition)
5. Acute consumption was not presented e.g., average weekly consumption was used

In the event no abstract was available or existed, the full journal article was obtained and the abstract was reviewed and assessed for exclusion based on the same criteria. For non-English articles, a native speaker of the language in which the article was written completed the translation. For those abstracts selected for further investigation, the full article was obtained and judged based on the same five criteria. Only those articles NOT meeting any of the five exclusion criteria were selected for data abstraction. Full reference lists of selected articles and reviews were hand-searched to identify any studies that may have been missed in the systematic search.

4.3.3 Data abstraction

Information about the level of alcohol exposures in each study, the number of cases at each exposure level, the total population at risk at each exposure level, the adjusted estimates of relative risk (RR), and the corresponding upper and lower 95% confidence intervals of the adjusted RR were all recorded. When ranges of alcohol were given, the midpoint was taken. In cases where no upper bound for the highest category existed, 50% of the length of the previous

category range was added to the low bound and this measure was used. In some cases, risks for increasing blood alcohol concentrations (BAC) were reported instead of consumption in grams of pure ethanol prior to the event. In these cases, BAC was converted to grams of consumption by using a modified Widmark formula (144). The following formula was used, solving for the number of beverages consumed and then converting to grams of pure alcohol (taken from (145)):

BAC = [(0.01882816 × no. of beverages_consumed × concentration) / (weight_kg × gender_fraction)] – (liver clearance rate)

Where:

0.01882816 = concentration of alcohol in blood (g/L)

concentration = alcohol by volume of the specific beverage type. For this analysis we assumed 40% (spirits), 12.5% (wine), 5% (beer).

weight_kg = weight in kilograms. For this analysis, average weights of men and women in different countries were based on published data and were country specific.

gender fraction = percentage of water in the human body: this was assumed to be 58% for men and 49% for women.

liver clearance rate = the rate at which liver metabolized alcohol per hour. This was assumed to be 0.017 per hour. All drinking was assumed to have taken place in the three hours prior to the BAC level being taken, corresponding to how many of the injury studies had measured alcohol consumption.

To convert the number of drinks to grams, we assumed different standard drink sizes for different countries in which the individual studies took place (US: 14g; Australia/New Zealand: 10g; Europe: 12g).

If the study did not include a measure of association but enough information existed for the reviewer to calculate an odds ratio (OR) or RR, this was done. If the study only reported combined (male + female) measures, the one measure was applied to both males and female datasets.

4.3.4 Meta-analysis

Step 1: Quantifying the heterogeneity of risk estimates across all studies was important given the diversity of study methods, effect sizes, and controlled variables (147). Heterogeneity was quantitatively assessed among studies by using both the Q statistic and the I^2 statistic (148). To assess publication bias, two independent tests were used - Begg's and Egger's regression asymmetry test for publication (215, 216). This was done to investigate whether the existing literature was reflective of all studies, including negative or null associations, as well as those reporting positive associations and high-risk estimates. If the studies were found to be highly heterogeneous and a large amount of between-study variation existed, it would be important to account for this variation by using a random effects model. If the opposite were true, a fixed effects model was justified (217, 218). All analysis was completed using STATA software version 10.1 (Stata Corporation, College Station, TX).

Step 2: The meta-analysis step was the curve-generating step, using linear and first-order fractional polynomial regression of the inverse-variance weighted data to estimate a best fitting curve to the data according to Royston (146). The first order fractional polynomials take the general form shown in Equation 1:

$$\text{Log}\,(RR \mid x) = \beta_1 x^{P1} \qquad \text{(Equation 1)}$$

Where x is the alcohol exposure level (in grams per day, P^1 is the polynomial power and β_1 is the corresponding coefficient. No intercept term exists since all models have a start point of Log RR = 0 (RR = 1 at zero consumption). For first-order models, P^1 takes values from -2 to +3. For model fitting, models were tested systematically from least to most complicated (linear, first order, second order) using the GLST command in STATA.

Best-fit curves or lines were assessed using standard goodness-of-fit statistics, with an emphasis on decreased deviance (gain) compared to the quadratic model. Comparisons of curves to determine the best fit were made using a Chi-square distribution, as recommended by Royston and Altman (149), using the linear (P = 1) as the referent for all first-order polynomials.

In addition to abstracting the number of cases, controls, sex, measures of association, and 95% confidence intervals, dummy variables for each study were created to differentiate between

studies of general injury or motor-vehicle collisions (0 or 1, respectively), and case-crossover or case-control design (0 or 1, respectively).

4.4 Results

Figure 4-1 illustrates the search and article selection process, with numbers of articles retrieved and discarded at the abstract selection and the article selection phases.

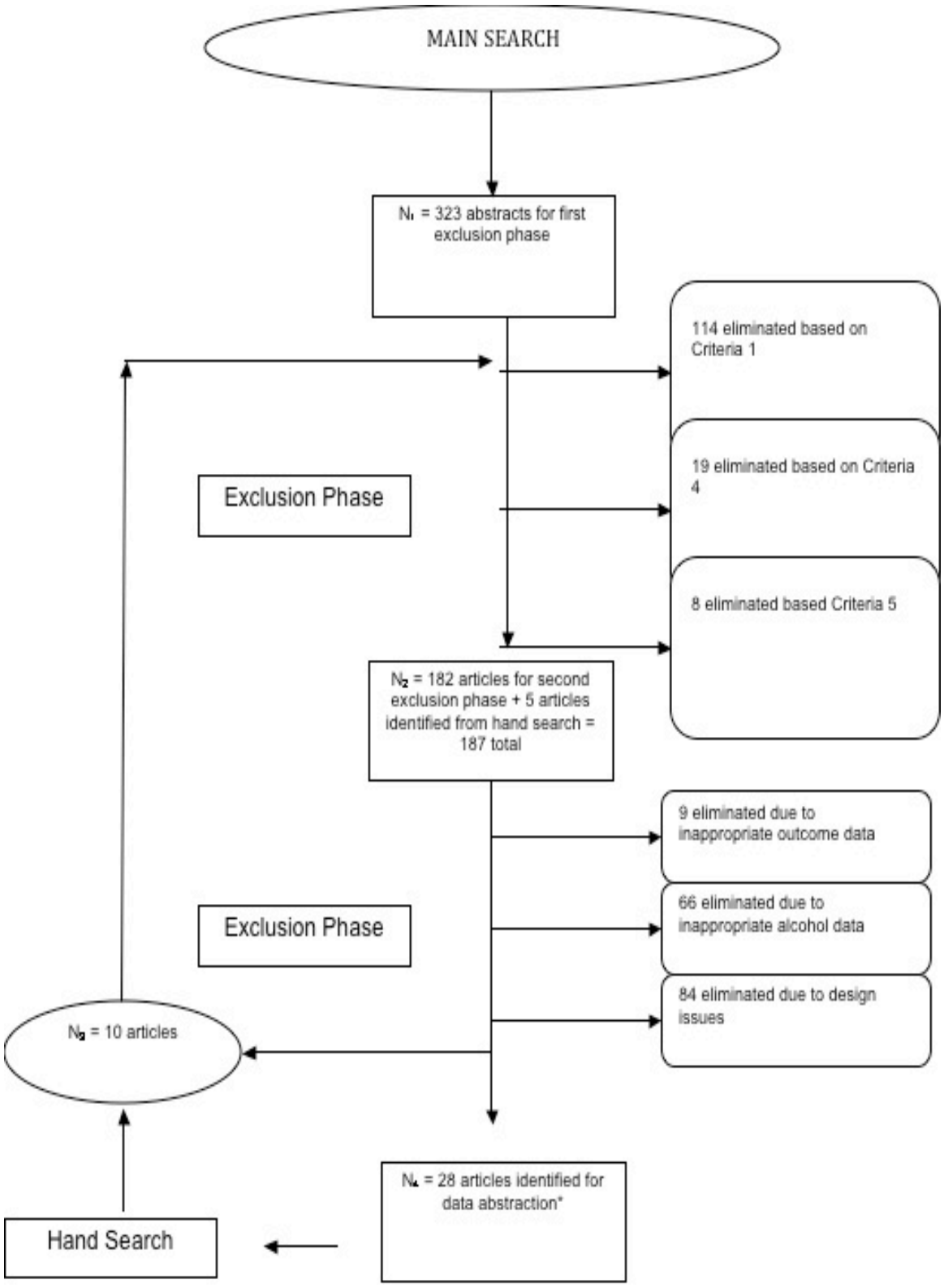

Figure 4-1. Results of the systematic review of the relationship between alcohol and injury.

4.4.1 Systematic Review

The systematic review identified 28 articles assessing the relationship between acute alcohol and injury. 9 of the articles presented multiple separate analyses and thus it was possible to present data from the same article on different groups. Overall, 39 datasets from the 28 articles were included in this meta-analysis (see Table 4-1). The search identified 14 datasets (8 articles) of MVC only (all case-control studies) and 25 datasets of other types of injury (23 articles). A total of 6 studies used a case-crossover design and all studies except for 3 investigated only injury morbidity as an outcome. Most studies reported combined estimates for males and females, so it was not possible for this study to separate gender effects either.

Table 4-1 Description of studies selected for meta-analysis, with selected characteristics.

Author	Year	Study Type	Data Type	Endpoint	N Cases	Covariates included*	Country
Haworth		case-control	Roadside testing	Both	214	1, 2, 3, 4	Australia
(Honkanen et al., 1983) (219)	1983	case-control	Emergency room	Morbidity	278	1, 2, 3, 5, 6, 7, 8, 9, 10, 11	Finland
(Olkkonen & Honkanen 1990) (220)	1990	case-control	Emergency room	Morbidity	140	3, 9, 12, 13	Finland
(Borges et al., 1994)(221)	1994	case-control	Emergency room	Morbidity	274	1, 2, 3, 4, 5, 14, 15	Mexico
(Hurst et al., 1994) (86)	1994	case-control	Roadside testing	Morbidity	4878	--	USA
(Vinson et al., 1995) (222)	1995	case-crossover	Emergency room	Morbidity	350	10, 14, 15, 17, 18	USA
(Borges & Rosovsky 1996) (223)	1996	case-control	Emergency room	Morbidity	40	1, 2, 5, 6, 10, 14, 15	Mexico
(Borges et al., 1998)	1998	case-control	Emergency room	Morbidity	445	1, 2, 5, 6, 14, 15	Mexico
(Cherpitel et al., 1999) (224)	1999	case-control	Emergency room	Morbidity	725	1, 2, 6, 14, 15, 18, 19, 28, 33	Canada
(Li et al., 2001) (211)	2001	case-control	Emergency room	Morbidity	124	1, 2, 19	USA
(Smith et al., 2001) (128)	2001	case-control	Death record review/population controls	Mortality	221	1, 2, 3, 4, 5, 19, 20, 21	USA
(Stockwell et al., 2002) (212)	2002	case-control	Population-based	Morbidity	797	1, 2, 4, 6, 10, 14, 15, 19, 22, 23	Australia
(Keall et al., 2004) (225)	2004	case-control	Roadside testing	Mortality	85	1, 2, 3, 24	New Zealand
(Mura et al., 2003) (226)	2003	case-control	Emergency room	Morbidity	900	--	France
(Vinson et al., 2003a) (125)	2003	case-control	Emergency room/population controls	Morbidity	102	1, 6, 4, 14, 25	Australia

(Connor et al., 2004) (227)	2004	case-control	Emergency room	Morbidity	571	1, 2, 3, 14, 26, 27	New Zealand
(Krüger & Vollrath 2004) (214)	2004	case-control	Roadside testing	Morbidity	1451	1, 2, 3, 5, 24	Germany
(Watt et al., 2004) (228)	2004	case-control	Emergency room	Morbidity	488	10, 15, 22, 24, 25, 28, 29, 30	Australia
(Borges et al., 2004) (126)	2004	case-crossover	Emergency room	Morbidity	705	1, 2, 6, 22, 28, 31, 32	Mexico
(Cherpitel et al., 2004) (229)	2004	case-crossover	Emergency room	Morbidity	218	2	Poland
(Spurling & Vinson 2005) (230)	2005	both	Emergency room/population controls	Morbidity	2517	1, 2, 16, 32	USA
(Borges et al., 2006) (160)	2006	case-crossover	Emergency room	Morbidity	4290	--	Argentina, Belarus, Brazil, Canada, China, Czech Republic, India, Mexico, Mozambique, New Zealand, South Africa, Sweden
(Borges et al., 2008b) (231)	2008b	case-crossover	Emergency room	Morbidity	188	--	Argentina, Mexico, Brazil
(Borges et al., 2008a) (232)	2008a	case-crossover	Emergency room	Morbidity	530	1, 2	Argentina, Mexico, Brazil
(Kool et al., 2008) (233)	2008	case-control	Hospital/Death record review	Morbidity	335	1, 2, 15, 19, 22	New Zealand
(Kuendig et al., 2008) (112)	2008	case-control	Emergency room	Morbidity	3682	1, 2, 28	Switzerland
(Peck et al., 2008) (23)	2008	case-control	Roadside testing	Morbidity	3791	1, 2	USA
(Gmel et al., 2008) (234)	2009	case-crossover	Emergency room	Morbidity	486	2	Switzerland

*NOTE: 1: Age 2: Sex 3: Hour of day 4: Location 5: Day of week 6: Marital status 7: Road Conditions 8: Socioeconomic Status 9: Health condition 10: Drug use 11: Shoe type 12: Impaired vision 13: Hour of day 14: Education 15: Employment 16: Place of residence 17: Body weight 18: Weather conditions 19: Race 20: Driver/passenger 21: Vehicle type 22: Income 23: Drinking pattern 24: # of passengers/accompanying people 25: Health insurance coverage 26: Seatbelt use 27: Tiredness/fatigue 28: Usual alcohol use 29: Risk-taking behaviour 30: Risk perception 31: Cause/weapon used 32: Alcohol abuse 33: Previous ER visit

Figure 4-2 shows the results of the heterogeneity assessment for non-motor vehicle collisions, which indicated significant heterogeneity between these studies (Q-statistic = 136.74, df = 67 I^2 = 51, $p < 0.0001$). The meta-analysis was run as a random effects model in order to account for this variability. Publication bias was detected by the Begg's ($p = 0.023$) and Egger's ($p = 0.004$) tests, with scarcity seen at the bottom right of the funnel plot (not shown). The forest plot shows the relative contributions of each study to the pooled estimate, which shows the odds of a non-MVC injury increase by 1.30 (95% CI: 1.26-1.34) for every 10-gram increase in alcohol consumption.

Among non-motor vehicle collision studies, comparisons between case-control and case-crossover studies were made. This analysis (not shown) indicated that case-control studies presented lower overall risks than case-crossover studies (p = 0.02), reinforcing the substantial heterogeneity seen in this group of studies.

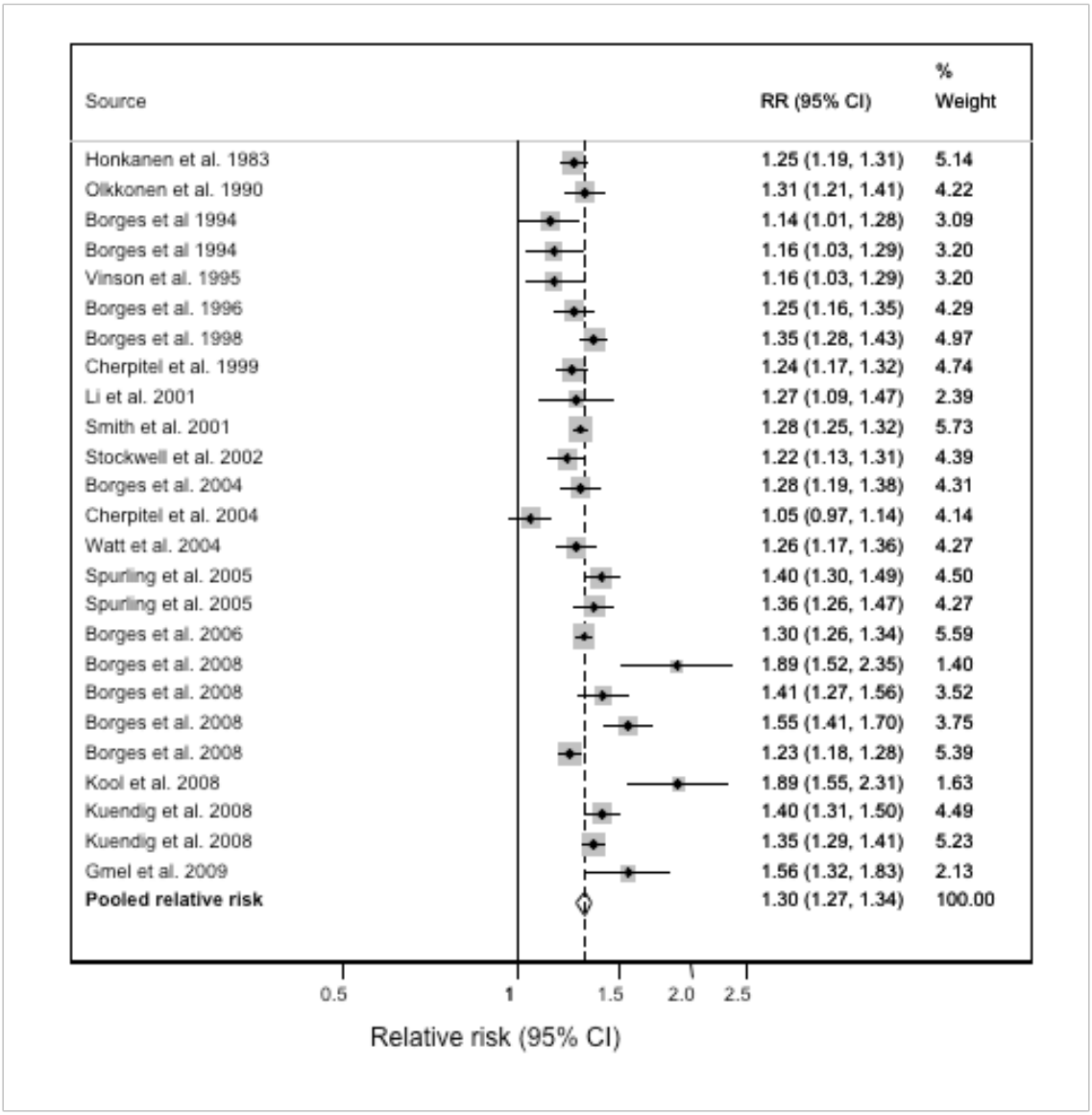

Figure 4-2. Forest plot for studies of non-motor vehicle collisions only and estimated relative risks associated with a 10 g/day increase in alcohol consumption: Estimates were derived from a random effects linear model.

The results of the heterogeneity assessment studies reporting motor vehicle collisions are shown in Figure 4-3. A large degree of variation between study estimators was seen for this group of

injuries as well (Q-statistic = 485.11 df = 43, I^2 = 91, p < 0.0001), indicating that a random effects model would be appropriate for curve-fitting steps. No publication bias was detected by either the Begg's test (p= 0.732) or the Egger's test (p=0.494). The forest plot in Figure 3 shows the odds of an MVC injury increase by 1.24 (95% CI: 1.18-1.31) for every 10-gram increase in alcohol consumption.

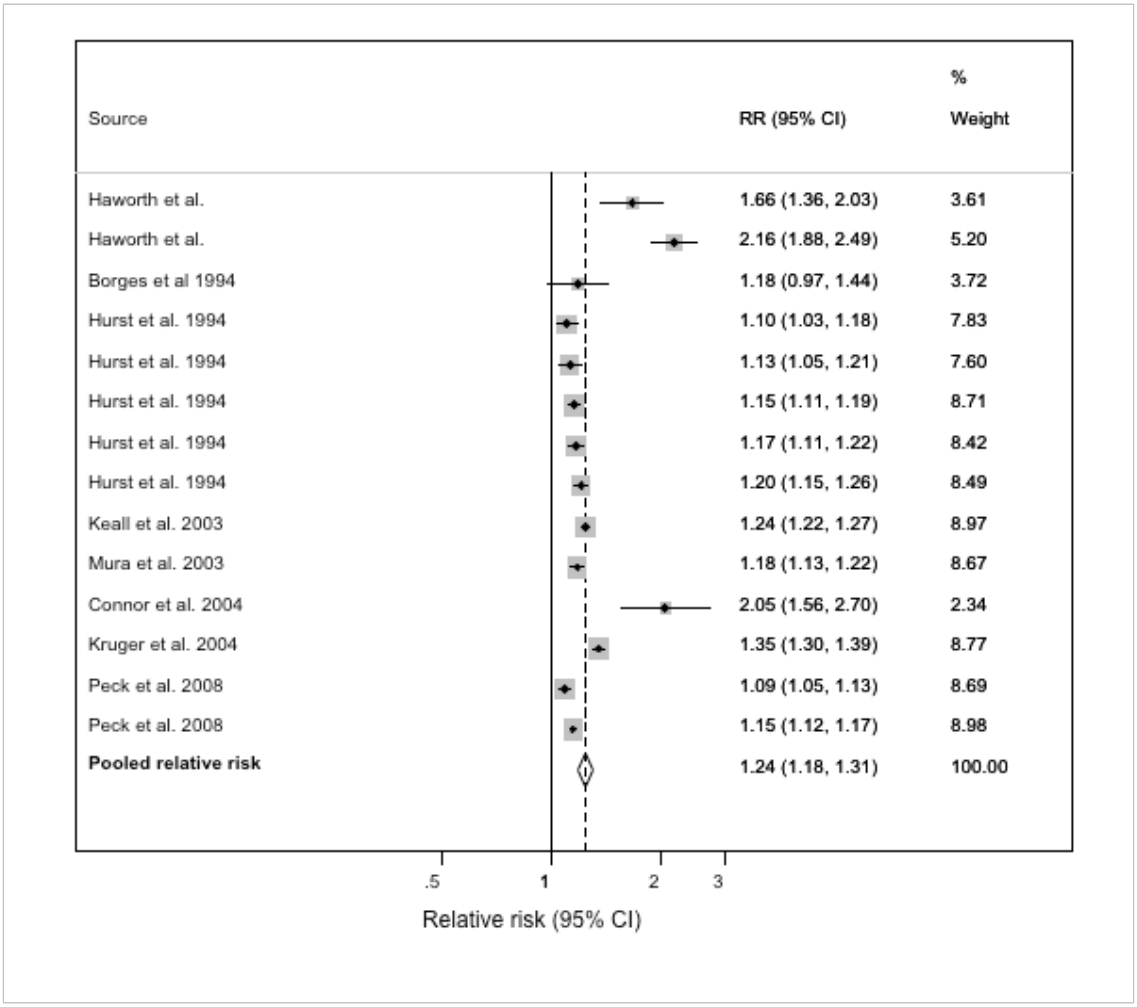

Figure 4-3. Forest plot for studies of motor vehicle collisions only and estimated relative risks associated with a 10 g/day increase in alcohol consumption: Estimates were derived from a random effects linear model.

4.4.2 Meta-analysis

The results of the meta-analysis (Figures 4-4 and 4-5) showed a strong dose-response relationship of alcohol consumption and both MVC and non-MVC injury. Initially, the linear

model for both MVC and non-MVC curves was fit to the pooled data, and then a first-order best-fit curve was attempted to try and improve the fit of the line to the data. For both MVC and non-MVC, the best-fit line was not the linear model but was $P^1 = 2$ (squared) and $P^1 = 0.5$ (square root), respectively.

At 140 grams of pure alcohol consumption prior to injury, a maximum odds ratio of 24.2 (95% CI: 16.2 – 36.2) for non-MVC injury was calculated. The curve for MVC went up much quicker, with an odds of about 52.0 (95% CI: 34.50 – 78.28) at 120 grams of alcohol consumed in the three hours prior. Even at generally accepted moderate doses (24 grams per day, or 2 standard drinks), the odds ratios for non-MVC and MVC injuries were 1.79 (1.59 – 2.00) and 2.20 (2.03 – 2.09), respectively.

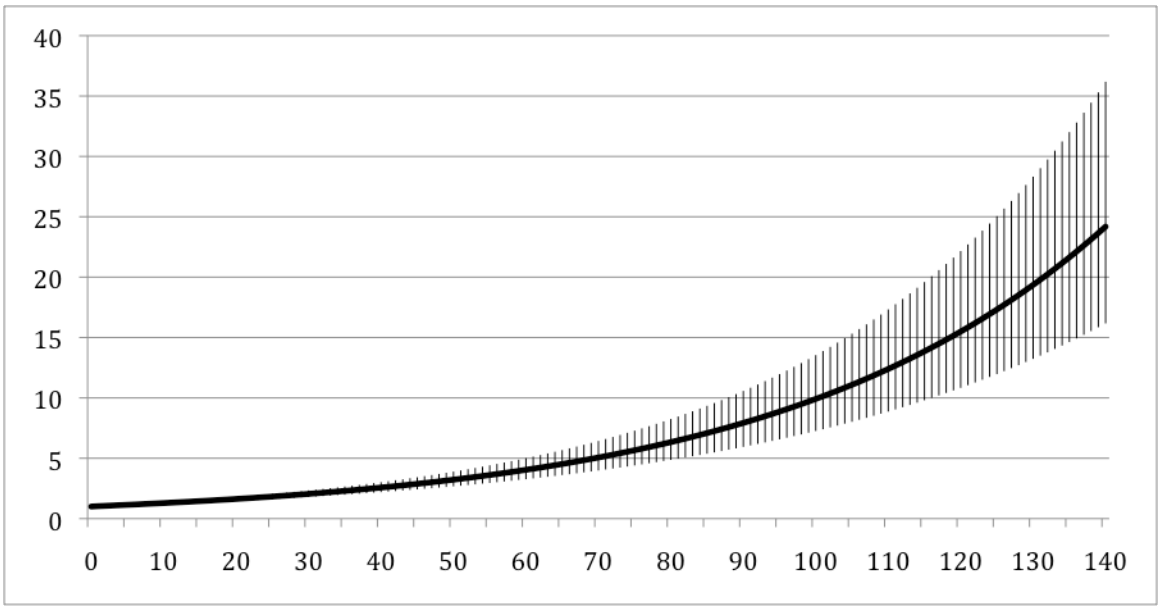

Figure 4-4. Dose-response curve for the amount of alcohol consumed 3 hours prior and the odds of non-motor vehicle collision injury.

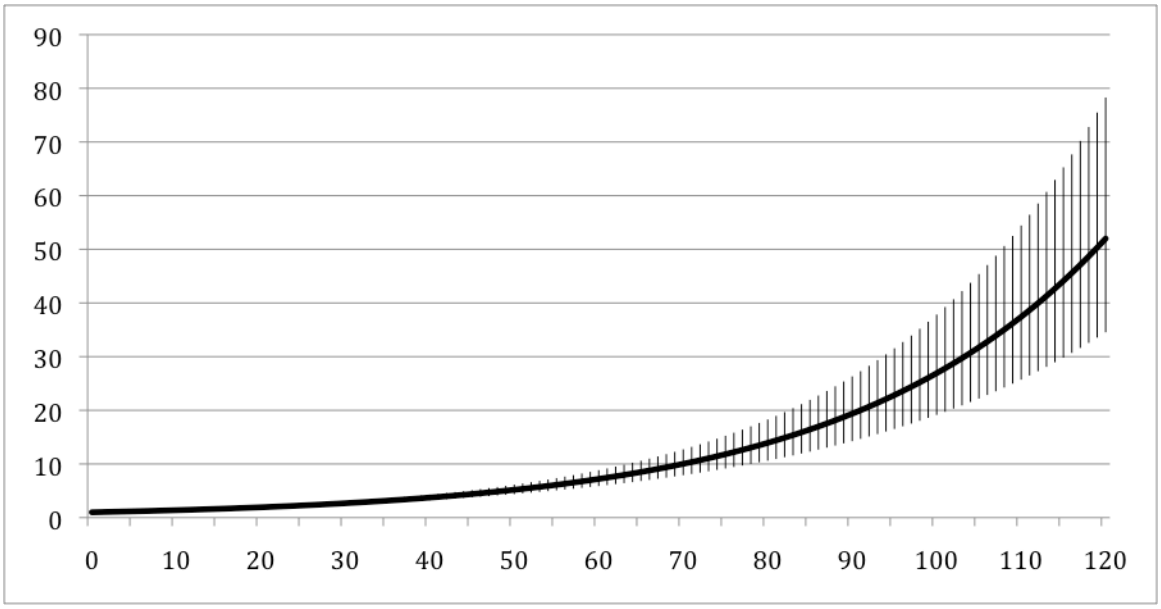

Figure 4-5. Dose-response curve for the amount of alcohol consumed 3 hours prior and the odds of motor vehicle collision injury.

A second analysis was run that separated out different injury types, with the stipulation that each injury-specific meta-analysis must have had at least 3 datasets included. This resulted in 4 distinct injury groups: violence (including one study on suicide), falls, MVC, and other unintentional injury. Identical meta-analyses were run on each of these injury subtypes and are shown in Table 4-2. Deviations from the non-MVC group were seen with falls, for which the data fit best to a linear line. The two unintentional injury categories (falls and other unintentional) had statistically similar pooled odds ratios, indicated by overlapping of confidence intervals. Intentional injury had the highest odds ratio point estimate of all injury categories and was significantly larger than the odds ratio of MVC, but not significantly different from the ratios for either falls or other unintentional injury. Separation of studies of falls and intentional injury from the non-MVC category resulted in a small decrease in heterogeneity of the other unintentional injury category, but the difference was non-significant (not shown).

Table 4-2 Selected results of separate meta-analyses for specific injury types

Injury Type	No. of studies *	Number of datasets	Best fit line	Increase in odds per 10-gram increase in consumption
Intentional Injury	5	5	non-linear	1.38 (95% CI: 1.22 - 1.55)
Falls	5	5	linear	1.25 (95% CI 1.14 - 1.36)
MVC	8	14	non-linear	1.24 (95% CI: 1.18 - 1.31)
Other unintentional	13	15	non-linear	1.32 (95% CI: 1.27 - 1.36)

* Note: 9 studies presented data on more than one injury category

4.5 Discussion

This is the first meta-analysis to quantify the overall relationship between episodic alcohol consumption and the risk of acute injury. It confirmed that the risk of injury rises monotonically with increasing alcohol consumption, consistent with previous individual studies. Comparison to the only other meta-analysis investigating alcohol and injury (18) is difficult since that analysis used average daily consumption as the exposure measure and not acute drinking. The present study is the first meta-analysis to separate motor vehicle from non-motor vehicle crashes and also the first to separate case-control from case-crossover studies. Non-linear, positive relationships between alcohol consumption and the risk of injury were found for both MVC and non-MVC injuries, with non-MVC injuries having a greater proportional per-drink increase in risk, although confidence intervals overlapped slightly. As well, the risk profile for intentional injury was found to be higher than other types of injury when analysis by injury type was done, confirming previous, single studies (126, 127).

There are a number of limitations that provide context to the risk estimates provided in this article. Some of these are inherent to meta-analyses generally and some are specific to the alcohol-injury field. Of the former, the first is the value of pooled risk estimates when the heterogeneity between individual study risks is high (as in this analysis). Some have argued that if heterogeneity is found to be significant, the merit of the pooled estimate is lowered. However, tests of heterogeneity are generally underpowered and it is more important, and may be of more use, to identify the sources of heterogeneity through more thoughtful consideration rather than by the statistic alone (147, 235).

In this and all meta-analyses, differences between single studies in additional independent variables, sample size, and statistical technique were apparent despite efforts to separate out injury types as much as possible. When this was done, the heterogeneity dropped significantly for each type of non-MVC crash, reinforcing the differences in risk estimates and methods between them and the need for this kind of separation in future. As well, including observation level data on confounding factors was not possible given the aggregate nature of the data and data-sharing policy. Among individual studies, experimental design differed mainly with variations between case-control and case-crossover designs. There are a number of differences in these study types that can affect heterogeneity, the most important of which is obviously the control group and the biases that result from this difference. In a case-crossover study, between-person confounding is well controlled compared to case-control studies, but recall biases still exist (160, 236). Since the respondent is his own control, the differences in cases and controls do not lie between people, but rather within people, specifically, the time between case and control periods. The control period is farther away (e.g. the week previous) from the case interview and therefore self-reported alcohol consumption is more likely to be estimated or misreported by the respondent when interviewed at the case period (current time). It is important, as well, that investigations of single-occasion drinking and injury risk may be particularly susceptible to this type of recall bias - previous research has reported that 7-day recall bias is higher in sporadic drinkers than regular drinkers, the majority of whom are young men (234), a group in which injury constitutes the highest alcohol-attributable mortality (237). Analysis of this 7-day recall bias compared to 1 day prior found that respondents underestimated their consumption by almost 1 standard drink, meaning the injury risk estimates may be inflated in case-crossover studies using 7-day recall methods (236).

A second important source of uncertainty in this analysis may be a result of differences in how alcohol consumption is measured. Some studies used a breathalyzer or other blood-alcohol measures while others use self-reported drinking in the time preceding the injury. This creates the problem of determining the actual level of alcohol in the blood at the time of injury. The Widmark formulas used to estimate numbers of standard drinks from BAC measures require estimations of weight, time spent drinking, and liver clearance rates, all of which may combine to cause considerable uncertainty in consumption estimates and thus the OR/RR. The literature estimates the uncertainty (standard deviation) of Widmark methods between 1.2 and 2.1 drinks

per 10 standard drinks (coefficient of variation: 12.3% to 21.2% (238). In addition, the correlation between objective and subjective measures is limited, showing a high degree of uncertainty in the measurement of exposure (e.g., (239)).

Many of the studies presented here used data from emergency room studies, which may not reflect all alcohol-attributable injuries, nor the general population. However, the relative risks for alcohol-attributable death are considerably higher than for morbidity (4), so this study can be seen as a conservative estimate in this regard.

Lastly, previous work has shown that the relationship between alcohol and injury may be confounded by usual drinking patterns, risk-taking behaviour and substance use (228). Many of the studies included in this meta-analysis did not control for these factors, or only controlled just one or two of them. This means the overall pooled estimate may be biased with respect to these confounders. On the other side of this argument, though, is that explicitly controlling for some of these types of confounders may lead to biased risk estimates due to the fact that alcohol and risk-taking behaviour, for example, are on the causal path from alcohol consumption and injury. Decisions to engage in activities that are likely to lead to an injury are positively influenced to a large degree by the consumption of alcohol, so over-controlling by including these confounders would result in incorrect RR as well (61, 62, 168).

Future work in this field, particularly in the areas of what variables to control for and why, is necessary. Over-controlling for variables that are on the causal pathway biases risk estimates towards a null finding, which is dangerous in terms of public health policy and risk communication. Additionally, research in this field must strive to adopt standard exposure assessment tools. This is one of the most challenging aspects of this field, considering that study participants may provide unreliable information themselves either from fear of legal implications or social factors, and may not be examined for alcohol use until a significant amount of time has passed from the time of initial injury. Efforts to improve in these areas will result in making different studies more comparable and result in more reliable relative risks.

With consistent risk estimates comes responsibility to reduce well-established harms, and the alcohol-injury association is no different. Strategies to reduce binge drinking and injury should be high on the public agenda, and there are a number of policy measures that have prove to be effective in this area. These include policies that affect price, such as increased taxation, setting

limits on alcohol retail outlet density and operating hours, raising the legal age of purchase of alcohol, and random, roadside breath testing of drivers (16).

4.6 Conclusion

The risk of injury increases non-linearly with increasing alcohol consumption, so efforts to reduce drinking both on an individual level and a population level are important. No level of consumption is safe and even for 2 standard drinks, the odds of injury are almost double for most types of injury. Obviously abstinence is related to the lowest risk, but policy measures such as taxation, raising legal drinking ages, and efforts to reduce acute alcohol consumption and associated injury, are to be encouraged and implemented given the high risks associated with acute alcohol consumption.

5 Manuscript 3: Combining best evidence: a novel method to calculate the alcohol-attributable fraction and its variance for injury mortality

Citation:

Taylor B, Shield K, Rehm J. Combining best evidence: a novel method to calculate the alcohol-attributable fraction and its variance for injury mortality. BMC Public Health 2011, 11:265.

5.1 Abstract

Background: The alcohol-attributable fraction for injury mortality is defined as the proportion of fatal injury that would disappear if consumption went to zero. Estimating this fraction has previously been based on a simplistic view of drinking and associated risk. This paper develops a new way to calculate the alcohol-attributable fraction for injury based on different dimensions of drinking, mortality data, experimental data, survey research, new risk scenarios, and by incorporating different distributions of consumption within populations. For this analysis, the Canadian population in 2005 was used as the reference population.

Methods: Binge drinking and average daily consumption were modeled separately with respect to the calculation of the AAF. The acute consumption risk was calculated with a probability-based method that accounted for both the number of binge drinking occasions and the amount of alcohol consumed per occasion. The average daily consumption was computed based on the prevalence of daily drinking at various levels. These were both combined to get an overall estimate. 3 sensitivity analyses were performed using different alcohol consumption parameters to test the robustness of the model. Calculation of the variance to generate confidence limits around the point estimates was accomplished via Monte Carlo resampling methods on randomly generated AAFs that were based on the distribution and prevalence of drinking in the Canadian population.

Results: Overall, the AAFs decrease with age and are significantly lower for women than men across all ages. As binge drinking increases, the injury mortality AAF also increases. Motor vehicle collisions show the largest relative increases in AAF as alcohol consumption is increased, with over a 100% increase in AAF from the lowest to highest consumption category. Among non-motor vehicle collisions, the largest change in total AAF occurred both for homicide and other intentional injuries at about a 15% increase in the AAF from the lowest to the highest binge consumption scenarios.

Conclusions: This method combines the best available evidence to generate new alcohol-attributable fractions for alcohol-attributable injury mortality. Future research is needed to refine the risk function for non-motor vehicle injury types and to investigate potential interactions between binge drinking and average volume of alcohol consumption.

5.2 Background

The proportion of a disease or outcome that is due to the influence of some external causal factor is called the attributable fraction (77). In alcohol epidemiology, this fraction is termed the alcohol-attributable fraction (AAF) and is defined as that proportion of disease that would disappear if alcohol consumption went to zero. In the categorical case (78), it has been calculated using the formula (77, 79):

(Formula 1)

$$AAF = \frac{\sum_{i=1}^{k} p_i (RR_i - 1)}{\sum_{i=0}^{k} p_i (RR_i - 1) + 1}$$

where P_i represents the proportion of the population exposed in group i and RR_i is the relative risk of mortality in exposed group i compared with the reference group (in alcohol often non-drinkers or lifetime abstainers). This is computed for as many drinking categories exist, from i = 0 to k, where i = 0 represents the reference group. This framework has been used extensively by the World Health Organization to estimate the burden of disease as a part of its Comparative Quantification of Risk analysis (2, 4, 80), and has been used by colleagues in other countries to establish the alcohol-attributable burden of disease (5, 12, 240).

However, these calculations have historically been relatively simplistic, with calculations usually being performed for three categories of average consumption only. More recently, a more differentiated consideration of average alcohol consumption has been introduced (83).

The calculation of AAF for injuries is a conceptually different than for chronic disease, since the acute effects of alcohol become very important and reliance on average consumption alone would considerably bias the results towards lower fraction estimates (39, 84).

Recent work by this group has attempted to improve on the calculation of the AAF for injury by trying to account multiple drinking scenarios and by including other alcohol-drinking variables to better assess fatal injury risk (175, 207).

This has meant incorporating 2 different dimensions of alcohol consumption for computing injury AAF: (1) drinking pattern measures such as binge drinking (both number of weekly occasions and the amount consumed per occasion) and (2) by additionally accounting for mean daily consumption of alcohol by modeling the specific distribution of drinkers and their daily drinking habits within a given population. What's more, we have tried to include alcohol metabolism rates in the liver to better assess time at risk of injury during intoxication, and, even more recently, attempting to account for the discrepancy between per capita consumption versus actual consumption in average daily alcohol drinking levels (241, 242).

The end result of these attempts has been the incorporation of data from many different sources, making this AAF calculation a veritable "data melting pot" – it combines survey data, meta-analyses of relative risk, mortality data, and experimental lab data. While this is not problematic for the calculation of the AAF point estimate, it is very complicated for the calculation of the variance around each point estimate, as each source of data has its own distribution and variance, making combining their different errors complex.

This paper attempts a novel method (the distributional approach) developed by our group to more accurately calculate the AAF and its variance for injury mortality. The main objectives of this paper are four-fold:

- Present the method to calculate alcohol-attributable fractions for fatal injury, its inherent sources and assumptions, and its data sources.
- Present the point estimate and uncertainty estimates
- Provide sensitivity analyses to provide context and alternative scenarios for the above
- Discuss future improvements that will help in more accurate calculation of the AAF for mortality

5.3 Methods

The approach we used to develop AAFs for injury mortality is presented below following a brief description of the underlying survey, as it was the source of the alcohol consumption data, one of the most important driving factors behind both the AAF point estimate and the corresponding confidence interval.

5.3.1 Description of underlying survey

For all alcohol consumption data used in the calculations (except for one of the sensitivity analyses), the Canadian Alcohol and Drug Use Monitoring Survey (CADUMS) 2008 (138) was used. It is a nationally representative survey of alcohol consumption in Canada and is representative of alcohol drinking in 2005. The precise methods used in the CADUMS are available elsewhere (139). In brief, though, it was an 8-month long telephone survey that used random-digit dialing to identify respondents. The survey reported a response rate of 36.5%, with 15, 801 individuals in the final dataset. It was these individuals that provided binge drinking estimates and average daily consumption data for the distributional method.

5.3.2 Computing the probability of alcohol-attributable injury for a given drinking scenario

The method described here builds on earlier work by Taylor et al. (175) and Rehm et al. (207). Briefly, it calculated the probability of dying from an alcohol-attributable injury from binge drinking and daily consumption separately, and then added each together to get a final probability of death for each injury as a function of total alcohol consumption (binge + average daily drinking). This resulting probability was then converted to numbers of deaths due to both binge and daily drinking, and finally divided by the total number of deaths from all causes to estimate the AAF for each injury subtype. All calculations calculated consumption variables using the Canadian standard drink definition (13.6 grams of pure alcohol). The method describes here uses the following inputs:

1. Mortality data for Canada for the year 2005 by age and sex for each injury subtype. Please see Table 5-1 for a list of the injuries considered in this analysis.

Table 5-1 Injury categories and the source of the relative risk relationship with alcohol consumption.

Condition	ICD 10 Code	Source for AAF Calculation
Unintentional injuries		
Motor vehicle collisions	§	(175, 207, 243)
Poisonings	X40-X49	(175, 207, 243)
Falls	W00-W19	(175, 207, 243)
Fires	X00-X09	(175, 207, 243)
Accidental Poisonings and exposure to alcohol	X45	(175)
Drowning	W65-W74	(175, 207, 243)
Other Unintentional injuries	†Rest of V-series and W20-W64, W 75-W99, X10-X39, X50-X59, Y40-Y86, Y88, and Y89	(175, 207, 243)
Intentional injuries		
Self-inflicted injuries	X60-X84 and Y87.0	(175, 207, 243)
Intentional self-poisoning by and exposure to alcohol	X65	(175)
Homicide	X85-Y09, Y87.1	(175, 207, 243)
Other intentional injuries		(175, 207, 243)

§ V021–V029, V031–V039, V041–V049, V092, V093, V123–V129, V133–V139, V143–V149, V194–V196, V203–V209, V213–V219, V223–V229, V233–V239, V243–V249,V253–V259, V263–V269, V273– V279, V283–V289, V294–V299, V304–V309, V314–V319, V324–V329, V334–V339, V344–V349, V354–V359, V364–V369, V374–V379, V384–V389, V394–V399, V404–V409, V414–V419, V424–V429, V434–V439, V444–V449, V454–V459, V464– V469, V474–V479, V484–V489, V494–V499, V504–V509, V514–V519, V524–V529, V534–V539, V544–V549, V554–V559, V564–V569, V574–V579, V584–V589, V594–V599, V604–V609, V614–V619, V624–V629, V634–V639, V644–V649, V654– V659, V664–V669, V674–V679, V684–V689, V694–V699, V704–V709, V714–V719, V724–V729, V734–V739, V744–V749, V754–V759, V764–V769, V774–V779, V784–V789, V794–V799, V803–V805, V811, V821, V830–V833, V840–V843, V850– V853, V860–V863, V870–V878, V892. †Rest of V = V-series MINUS §.

2. The mean frequency of binge drinking (5+ drinks per occasion for men, 4+ drinks per occasion for women) occasions in the past year, by age and sex. This was calculated using the CADUMS database previously described. For average daily consumption, frequency was set to 365 (=every day).

3. The amount of alcohol consumed per occasion in grams of pure alcohol. For average daily consumption, this was the consumption by age and sex. Please see section B of these methods for the calculation of average daily consumption using the CADUMS 2008 data. For binge drinking, this quantity was estimated from the CADUMS data, which used 4+ and 5+ drinks per occasion. For the main analysis, 4 and 5 drinks for men

and women, respectively, was used. Three different quantities were used for the sensitivity analysis.

4. Alcohol metabolism rates: the rate at which alcohol is metabolized by the liver must be accounted for in the adjustment of risk, since injury risk is only apparent as long as alcohol is exerting its effects. Therefore, the rate of alcohol clearance by the liver was modelled based on (142) (http://pubs.niaaa.nih.gov/publications/aa35.htm) and then converted into a risk period for a given number of drinks in a 24-hour time period. It corrects for the fact that, for one drinking occasion, the individual consuming a drink is not at risk for an entire 24-hour period on the day in which consumption occurs and varies by numbers of drinks consumed in one drinking occasion. As a result, higher numbers of drinks result in fewer (but longer) individual risk periods. For example, for three drinks consumed in one occasion, which carries a risk period of approximately 3 hours, there would be 8 (24/3) possible individual risk periods in a 24 hour period. On the other hand, for consumption of 1 drink, which carries a risk period of 30 minutes, there are consequently 48 separate possible risk period in 24 hours. Please see Figure 5-1 for the results of this modeling.

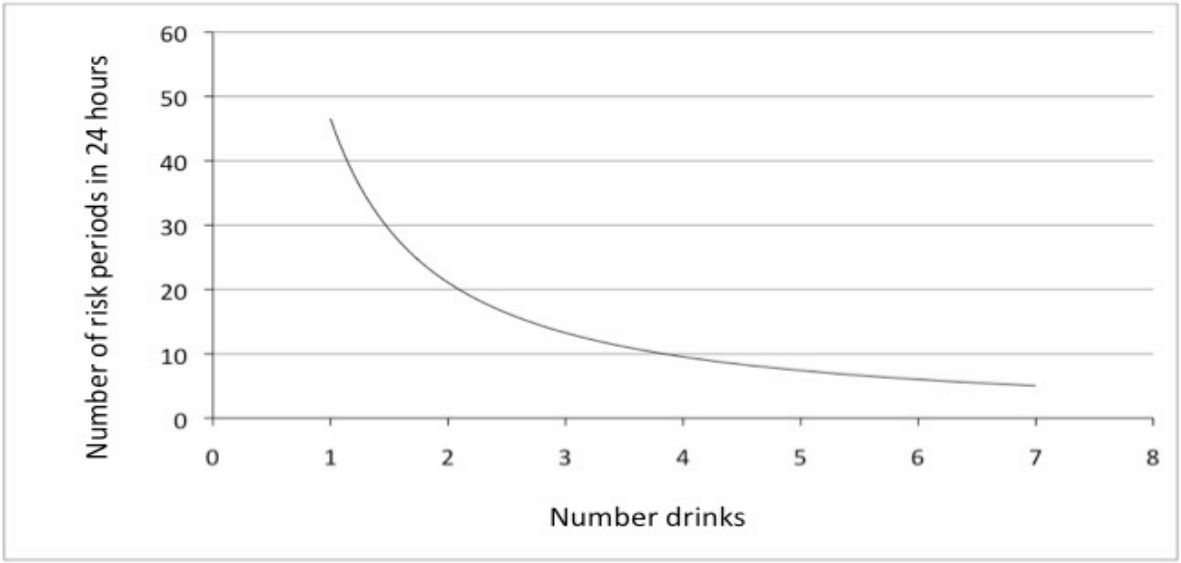

Figure 5-1. Number of risk periods in a 24-hour period based on alcohol liver clearance rates, based on [19].

5. RR function: The relationship between the amount of alcohol consumed for one drinking occasion was determined via meta-analysis (243). Fractional polynomial meta-regression was used to determine the best-fit line for each of motor-vehicle injury and non-motor-vehicle injury mortality (includes falls, fires, violence, drowning, poisoning, suicides, other intentional injury, and non-intentional injury combined), respectively. The final results of this meta-analysis were the following risk functions:

(Formula 2a): RR_{MVC}: $LN(RR) = 3.292589*x^2$

(Formula 2b) $RR_{NON-MVC}$: $LN(RR) = 2.189702*x^{0.5}$

Where x = dose of pure ethanol (in grams) in one drinking occasion

The curves become relatively unstable at levels beyond approximately 100 grams of pure alcohol per occasion due to a scarcity of data points beyond this level in any of the studies include in the original meta-analysis. Accordingly, if alcohol consumption per occasion was indicated as greater than 108 grams per day, the RR function was calculated based on exactly 108 grams per occasion.

5.3.3 Calculating average daily consumption

It is well known that population surveys underestimate adult per capita consumption (151). This discrepancy between the estimated alcohol consumption of Canadians from surveys and adult per capita consumption data arise from the fact that those excluded from the CADUMS 2008 consume more alcohol than the general population, such as the homeless, respondents not answering truthfully or having problems recalling the amount of alcohol consumed in the week prior to when they participated in the survey, and people who don't participate in surveys consuming more alcohol on average than people who do participate in surveys (242). For the CADUMS 2008 we estimated undercoverage to be 27% (calculated by dividing the alcohol consumption estimated from per capita data by the alcohol consumed estimated from the CADUMS 2008) . Thus, data on consumption from population surveys need to be triangulated with estimates of adult per capita consumption. Adult per capita consumption is based on sales import and export data and is generally considered to be the most accurate measure of consumption. To calculate the up-shifted mean daily consumption, we multiplied the sex and age specific means by the estimated under coverage of the CADUMS 2008; to be conservative, under coverage was calculated assuming that 10% of adult per capita consumption was not consumed.

The up-shifted daily alcohol consumption distribution was then calculated based on methods outlined by Kehoe and colleagues (244), who found that average daily alcohol consumption could be modeled using a gamma distribution, and later found it to be the best overall fit for population-level alcohol consumption globally (245). Furthermore, using regression analysis they found that the standard deviation of this distribution could be expressed empirically as a function of the mean. Based on this function, we were able to calculate the shape (θ) and scale (κ) parameters of the gamma distribution.

5.3.4 Calculation of the AAF

The formula to compute the alcohol-attributable injury for binge consumption is presented below:

(Formula 3)
$$AAF = \frac{P_{abs+former} + P_{current(Non-Binge)} + P_{Current(Binge)}RR(x) - 1}{P_{abs+former} + P_{current(Non-Binge)} + P_{Current(Binge)}RR(x)}$$

where $P_{abs+former}$ is the proportion of lifetime abstainers and former drinkers, and $P_{current(Binge)}$ and $P_{Current(Non-Binge)}$ are the prevalences of current drinkers who engage and who do not engage in binge drinking, respectively. $RR_{binge}(x)$ represents the risk ratio for binge drinkers given a binge amount of alcohol consumed corrected for both time at risk and number of drinking occasions. $RR_{binge}(x)$ was calculated as follows:

(Formula 4)
$$RR_{binge}(x) = P_{dayatrisk} * P_{daysatrisk} * (RR_{Crude}(x)-1)+1$$

where $P_{dayatrisk}$ (calculated based on the average binge consumption x) and $P_{daysatrisk}$ represent the proportion of a given day during which a person binge drinks and is at risk, and the percentage of days the person undertakes binge drinking, respectively.

The formula to compute the alcohol-attributable injury for average consumption is below:

(Formula 5)
$$AAF = \frac{P_{abs+former} + \int_0^{150} P(x)RR(x)dx - 1}{P_{abs+former} + \int_0^{150} P(x)RR(x)dx}$$

where P (x) represents the prevalence of drinking at level x (in grams per day, modeled by the gamma function. The RR(x) is the relative risk at this level compared to lifetime abstainers and former drinkers, corrected for time at risk. As average consumption is a daily intake estimate, no correction for the number of drinking occasions was needed. To adjust the

RR(x) for time at which a person is at risk for an injury, we computed the time at risk through the modeling alcohol metabolism rates, namely, the rate at which alcohol is metabolized by the liver using the following formula:

(Formula 6) $$RR(x) = P_{dayatrisk}*(RR_{Crude}(x)-1)+1$$

where $P_{dayatrisk}$ (calculated here based on the drinking level x) represents the proportion of a day at risk per drinking occasion, and $RR_{Crude}(x)$ is the relative risk at drinking level x compared to being sober, not adjusted for the time at risk per occasion.

5.3.5 Methods to calculate the uncertainty estimates

A Monte Carlo-like approach was used to calculate the 95% confidence intervals (CIs) of the AAFs for average and binge consumption (155). First, we estimated the variance of the AAF from 10,000 randomly generated AAFs that were calculated from 10,000 random sets of the lowest level parameters (the parameters from which all other values are derived) for each age, sex and injury type. Parameters were generated based on their distribution, mean and variance. These parameters were then used to calculate the risk ratio functions, prevalence of drinkers, number of drinking occasions per year, time at which a person is at risk, and the amount consumed per occasion (expressed as a consumption prevalence distribution for average consumption and a point estimate for binge consumption). Please see Appendix 1 for an example of the code used in R to compute these uncertainty estimates.

5.3.5.1 Generating average consumption for AAF parameters

For the average consumption AAF, we generated estimates of under coverage by first generating the prevalence of current drinkers for each age and sex group. The average daily alcohol consumption among current drinkers for the population mean was then calculated based on the weighted average derived from group and sex specific prevalences and means. Age and sex specific means were then up-shifted based on the under coverage calculated from the general overall population mean.

The κ parameter of the gamma distribution was generated in accordance with Rehm and colleagues (83), while the θ parameter was calculated by dividing the generated up-shifted mean daily alcohol consumption by the generated κ parameter.

5.3.5.2 Generating binge consumption AAF parameters

Prevalence of binge drinkers was generated based on estimates derived from the CADUMS 2008. The numbers of binge drinking occasions were generated based on estimates derived from the National Epidemiologic Survey on Alcohol and Related Conditions data (2001 – 2002).

Risk ratio estimates for both binge and average consumption AAFs were generated based on the variance of the beta estimate from the fractional polynomial meta-regression.

5.3.6 Sensitivity Analysis

Sensitivity analyses were planned *a priori* to test the robustness of the methods to theoretical increases in binge drinking since this is a major driver, if not *the* major driver of alcohol-attributable injury and of this AAF estimation method. There are 3 sensitivity analyses planned, each showing increases in binge drinking quantity. This meant from the original 4/5 drinks (54.4 and 68 grams per drinking occasion) per occasion for men and women, respectively, this consumption level was increased to 5/6 drinks per occasion (Sensitivity Analysis I), and 6/7 drinks per occasion (Sensitivity Analysis II). Lastly, the average number of drinks per drinking occasion, by age and sex, was computed from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) 2001 and 2002 was used to simulate a "real life" scenario for Canadians, assuming, of course, that Canadians consumed approximately equally amounts to white Americans (Sensitivity Analysis III). Details of the NESARC and its methods, sampling frame, and questions can be found elsewhere (246, 247).

All calculations and simulations were performed using R (version: 2.11.1).

5.4 Results

Table 5-2 shows the consumption data, by age and sex, used for this method. Note that Table 5-2 shows both the prevalence of alcohol consumption groups on the top and then the raw estimates and the corrected, up-shifted estimates for daily drinking on the lower half of the table, in addition to binge drinking variables. Also note that for binge drinking, the mean quantity was the value inputted for Sensitivity Analysis III. This table shows that the majority of men and women

in all age groups drink, but that consumption generally decreases with age. More men drink compared to women, and drink more on average. What's interesting on this table also is the dramatic increases in mean alcohol consumption following the up-shift to correct for per capita consumption, at times approximately a 3-fold increase.

Table 5-2 Average daily alcohol consumption estimates for Canada, 2008.

Gender	Age group	Raw estimates (current drinkers)		Corrected estimates (current drinkers)		Number of drinking occasions per week	
		Mean (g/day)	95% CI	Mean (g/day)	95% CI	Mean number	95% CI
Women	15 - 29	9.0	(3.7-14.4)	27.9	(23.6-32.2)	0.81	(0.64-0.98)
	30 - 44	3.6	(3.1-4.1)	11.2	(10.5-11.9)	0.77	(0.67-0.87)
	45 - 59	4.9	(4.2-5.6)	15.2	(14.1-16.3)	1.07	(0.95-1.18)
	60 - 69	4.6	(3.8-5.5)	14.3	(13.0-15.6)	1.04	(0.84-1.23)
	70 - 79	4.4	(3.1-5.6)	13.5	(11.8-15.1)	0.91	(0.66-1.17)
	80+	4.1	(2.5-5.6)	12.6	(10.8-14.3)	0.86	(0.51-1.21)
Men	15 - 29	12.8	(10.1-15.6)	39.7	(36.0-43.4)	1.13	(0.94-1.31)
	30 - 44	9.7	(8.1-11.4)	30.1	(27.8-32.5)	1.35	(1.19-1.52)
	45 - 59	11.7	(9.3-14.2)	36.3	(33.9-38.8)	1.66	(1.47-1.84)
	60 - 69	11.1	(8.2-13.9)	34.3	(29.9-38.7)	1.65	(1.35-1.95)
	70 - 79	9.9	(7.0-12.7)	30.6	(25.9-35.2)	1.69	(1.24-2.14)
	80+	5.9	(3.2-8.6)	18.2	(15.0-21.3)	1.41	(0.83-1.99)

Table 5-3 shows how the RR value changes with the quantity consumed per binge occasion for the main analysis and each of the three sensitivity analyses. As alcohol consumption increases, the RR also increases. However, of particular note in this table is that for lower alcohol consumption values (4/5 drinks per occasion) the RR for MVC injury is lower than for non-MVC injury, but as alcohol consumption increases, the risk of an MVC injury surpasses that of a non-MVC injury due to the steeper dose-response curve of MVC injury, also highlighted by the steep increase in risk with modest increases in per-occasion consumption.

Table 5-3 Description of the relative risk of injury mortality by age and sex for the main analysis (4/5 drinks per occasion) and for each of the sensitivity analyses for motor vehicle injury and non-motor vehicle injury mortality.

	15-29		30-44		45-59		60-69		70-79		80+	
	M	**W**	**M**	**W**	**M**	**W**	**M**	**W**	**M**	**W**	**M**	**W**
Motor Vehicle Injury												
Main Analysis	4.58	2.65	4.58	2.65	4.58	2.65	4.58	2.65	4.58	2.65	4.58	2.65
Sensitivity Analysis I	8.96	4.58	8.96	4.58	8.96	4.58	8.96	4.58	8.96	4.58	8.96	4.58
Sensitivity Analysis II	19.77	8.96	19.77	8.96	19.77	8.96	19.77	8.96	19.77	8.96	19.77	8.96
Sensitivity Analysis III	43.57	8.75	19.30	7.84	19.30	7.84	10.61	6.85	10.61	6.85	10.61	6.85
Non-Motor Vehicle Injury												
Main Analysis	6.08	5.03	6.08	5.03	6.08	5.03	6.08	5.03	6.08	5.03	6.08	5.03
Sensitivity Analysis I	7.23	6.08	7.23	6.08	7.23	6.08	7.23	6.08	7.23	6.08	7.23	6.08
Sensitivity Analysis II	8.47	7.23	8.47	7.23	8.47	7.23	8.47	7.23	8.47	7.23	8.47	7.23
Sensitivity Analysis III	9.64	7.19	8.43	7.01	8.43	7.01	7.50	6.78	7.50	6.78	7.50	6.78

The results of the main analysis (including 95% confidence intervals) and side-by-side comparisons to each of the sensitivity analyses for motor vehicles and non-motor vehicle collisions by age and sex is shown in Table 5-4. Since the RR for each of non-motor vehicle injuries is the same, they were grouped together for brevity in this table. Overall, the AAFs decrease with age and are significantly lower for women than men across all ages. Additionally, we can see that as binge drinking increases, the injury AAF also increases. For men and women, the sequential increase from 4 to 6 drinks per occasion showed relatively small corresponding increases in the AAF. However, when the NESARC data was used in the third sensitivity analysis, the jump to 8 or more drinks (seen in men aged 15-29) had a significant impact on the RR, resulting in a doubling of the AAF for motor vehicle collisions. Smaller relative increases were seen for non-motor vehicle collision AAFs at this age level, as well as overall for women and older age groups This is mirrored in Table 5-5, which shows the AAF increases within each injury subtype, but the amount of increase is augmented by the type of injury itself within non-motor vehicle collisions.

Motor vehicle collisions show the largest relative increases in AAF as alcohol consumption is increased, with the largest jump occurring for the third sensitivity analysis at over a 100%

increase. Among non-motor vehicle collisions, the largest change in total AAF occurred both for homicide and other intentional injuries at about a 15% increase in the AAF from the lowest to the highest binge consumption scenarios.

Table 5-4 Alcohol-attributable fractions and 95% confidence intervals for motor vehicle and non-motor vehicle collisions - main analysis and each of the three sensitivity analyses.

	15-29				30-44				45-59				60-69				70-79				80+			
	M		W		M		W		M		W		M		W		M		W		M		W	
	AAF	±	AAF	±	AAF	±	AAF	±	AAF	±	AAF	±	AAF	±	AAF	±	AAF	±	AAF	±	AAF	±	AAF	±
Main Analysis: Binge 4/5																								
MVC	0.22	0.14	0.13	0.17	0.16	0.11	0.02	0.06	0.15	0.10	0.03	0.05	0.16	0.13	0.03	0.07	0.16	0.17	0.03	0.10	0.09	0.14	0.04	0.11
Non_MVC	0.43	0.21	0.26	0.22	0.30	0.15	0.01	0.00	0.32	0.16	0.03	0.01	0.34	0.20	0.04	0.01	0.32	0.25	0.03	0.02	0.12	0.15	0.03	0.01
Sensitivity Analysis I: Binge 5/6																								
MVC	0.23	0.14	0.13	0.12	0.16	0.10	0.02	0.01	0.15	0.10	0.03	0.01	0.16	0.13	0.03	0.02	0.16	0.15	0.03	0.01	0.09	0.14	0.04	0.02
Non_MVC	0.45	0.20	0.27	0.22	0.32	0.15	0.02	0.01	0.33	0.15	0.03	0.01	0.35	0.21	0.04	0.01	0.33	0.23	0.03	0.02	0.12	0.15	0.03	0.01
Sensitivity Analysis I: Binge 6/7																								
MVC	0.28	0.14	0.13	0.12	0.19	0.10	0.03	0.01	0.16	0.10	0.03	0.01	0.17	0.13	0.03	0.02	0.17	0.17	0.03	0.01	0.09	0.15	0.04	0.02
Non_MVC	0.47	0.21	0.27	0.23	0.33	0.15	0.02	0.01	0.33	0.15	0.03	0.01	0.35	0.21	0.04	0.01	0.33	0.25	0.03	0.02	0.12	0.17	0.03	0.01
Sensitivity Analysis III: NESARC data																								
MVC	0.57	0.19	0.18	0.14	0.37	0.13	0.04	0.03	0.22	0.10	0.03	0.02	0.19	0.13	0.03	0.02	0.19	0.16	0.03	0.01	0.10	0.14	0.04	0.02
Non_MVC	0.52	0.22	0.28	0.23	0.35	0.15	0.02	0.01	0.34	0.15	0.04	0.01	0.35	0.21	0.04	0.01	0.33	0.23	0.03	0.02	0.12	0.15	0.03	0.01

Table 5-5 Alcohol-attributable fractions by injury subtype, men and women c for the main analysis and each of the sensitivity analyses.

Cause	Main Analysis			SA I			SA II			T
	Total AAF	LB	UB	Total AAF	LB	UB	Total AAF	LB	UB	
Unintentional injuries										
Motor vehicle collisions	0.14	0.03	0.25	0.14	0.05	0.24	0.17	0.07	0.26	
Poisonings	0.24	0.12	0.37	0.25	0.13	0.38	0.26	0.13	0.38	
Falls	0.13	0.03	0.23	0.14	0.04	0.23	0.14	0.03	0.24	
Fires	0.20	0.08	0.32	0.20	0.09	0.32	0.21	0.09	0.33	
Accidental poisonings and exposure to alcohol	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
Drowning	0.22	0.10	0.35	0.23	0.11	0.35	0.24	0.12	0.36	
Other Unintentional injuries	0.27	0.13	0.40	0.27	0.14	0.41	0.28	0.15	0.42	
Intentional injuries										
Self-inflicted injuries	0.27	0.13	0.41	0.28	0.14	0.42	0.29	0.14	0.43	
Intentional self-poisoning by and exposure to alcohol	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
Homicide	0.28	0.14	0.43	0.29	0.15	0.44	0.30	0.16	0.45	
Other intentional injuries	0.37	0.18	0.55	0.38	0.20	0.56	0.39	0.21	0.57	

5.5 Discussion

The highest impact factor in this calculation was the alcohol consumption variables, which in turn drive the relative risk function. However, the consumption variables in this analysis came from surveys (CADUMS for the main analysis, NESARC for the sensitivity analysis), which carry limitations with respect to reaching certain populations, and inherent biases in self-reported data that are common to survey instruments. Usual surveys are based on households, and populations such as institutionalized and homeless are not part of the sampling frame, particularly in telephone surveys. This has an effect for both methods since drinking distributions tend to be characterized by a "concentration of consumption". This means that a small portion of the population is likely to be responsible for a large proportion of the alcohol drinking. For instance, in the NESARC sample, the 6.7% of the heaviest White male drinkers consume 33% of the overall consumption, so excluding or undersampling relatively small groups may result in relatively large proportions of under coverage (see also (248)). Underreporting of consumption will also result in underestimation of the AAF since lower alcohol consumption would result in significantly lower relative risks, meaning that the computed AAF would be significantly reduced. Data around this topic is difficult to collect and the literature on this area is relatively sparse but tends to support the hypotheses that self-reports on alcohol consumption in medical epidemiology and in surveys are relatively valid overall (249-251). However, some evidence shows that few questions about frequency of alcohol consumption embedded in health questionnaires yield higher levels of consumption compared to surveys where alcohol is the main topic (252). Thus, for this analysis, the CADUMS data may be less reliable than for the NESARC data, but the discrepancy is difficult to quantify. Thus, more research is needed before one can further generalize on procedures on how to select the level of true consumption to be taken as basis for derive AAFs. Another limitation of this analysis was that the CADUMS survey also reported a low response rate, only 36.5%. Overall, then, the CADUMS would suffer from underestimation of alcohol consumption stemming from two sources – the use of the telephone interview, and the oversampling of married and educated persons. However, it should be noted that the average alcohol consumption estimate was explicitly up-shifted to account for this undercoverage issue to better approximate true per-capita consumption. Thus, non-response, although high in the CADUMS, should not have resulted in a meaningful bias of alcohol

consumption data, although other sources of error in this survey may have underestimated the prevalence of average drinking and binge drinking.

Another limitation of this analysis is the fact that the same relative risk relationship was used for all non-motor vehicle collision deaths. While this was necessary given the available data in the literature in the original meta-analysis (243), there are almost certainly variations in risk for individual injury types. To further stabilize the risk functions and "parse out" individual risks for injury subtypes, more data points are needed to carry future meta-analyses, showing a need for more studies in this area.

An important point to discuss is why binge drinking had such a low impact on injury compared to average daily consumption, since most evidence points to heavy drinking leading to intoxication as the main mode of the incidence of alcohol-attributable injury (19, 34, 35).

The method to calculate the AAFs for binge drinking uses only a mean and, therefore, binge consumption is based on a point estimate. The method used to calculate the AAFs for average consumption uses a distribution and, therefore, average consumption calculates the relative risk for all levels of intake. We assume that the RR we calculated for binge drinking using a point estimate would be equal to the average RR we would obtain if we used a distribution approach; however, since the RR functions are not linear, these two estimates will never be equal. We are limited to using a point estimate method since the calculation of binge AAFs is based on knowledge we do not have of the distribution of binge consumption.

The Monte Carlo approach to derive confidence intervals was necessary, as there are no numeric derivations possible. It follows similar approaches in disease modeling and risk factor epidemiology (e.g., (253, 254).

5.6 Conclusions

Overall, the described method included the main parameters known from the literature. Future research is necessary to refine the risk function, as there may be cultural differences in risk based on different environments (consider, e.g., the impact of highway safety on the impact of alcohol on highway fatalities). Similarly, the modeling of binge drinking distributions and potential interactions between binge drinking and average volume of alcohol consumption (255) may be improved based on new research. However, overall, the presented data allows for estimating the

impact of alcohol consumption on traffic safety based on the best evidence to date, and should be used in new estimates of alcohol-attributable burden.

5.7 Competing Interests

The authors declare they have no competing interests.

5.8 Author's Contributions

BT participated in the design of the work, the conceptualization and development of its methods, statistical analysis with respect to binge risk and drafted the manuscript. KS performed some statistical analysis and wrote selected sections of the methods. JR conceived of the study, participated in its design and coordination, and was involved in drafting the manuscript.

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6 Manuscript 4: The relationship between alcohol consumption and fatal motor vehicle injury: high risk at low alcohol levels

Citation:

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6.1 Abstract

Background: Alcohol consumption causes motor vehicle collision (MVC) injury in a dose-response fashion. However, the relationship between how this risk is different with respect to fatal and non-fatal outcomes is not clear. A meta-analysis has already been completed for alcohol and consumption and non-fatal MVC injury, but none exists for fatal injury. Thus, an analysis of the acute dose-response relationship between alcohol and motor vehicle injury death is warranted to generate single occasion- and dose-specific relative risks for the first time.

Methods: A systematic literature review and inverse-variance weighted, random effects meta-analysis was conducted to fill this gap. Fractional polynomial regression was used to model the dose-response relationship. Usual tests of heterogeneity and publication bias were run.

Results: Five studies meeting the inclusion criteria of this analysis were selected. At all levels of BAC, the odds ratio (OR) of fatal motor vehicle injury was significant. Overall, the 5 combined studies yielded an OR of fatal injury of 1.74 (95% CI: 1.43 – 2.14) for every 0.02% increase in BAC. At 0.08, the legal limit in most countries, the OR was 13.0 (95% CI: 11.1 – 15.2).

Conclusions: The risk of fatal motor vehicle injury is very high, even at low and moderate doses of alcohol consumption. This study is able to definitively show and quantify the increased OR for fatal motor vehicle injury compared to non-fatal injury for the first time. This analysis showed some evidence of both study heterogeneity and publication bias, likely due to the increased variation we could expect from a small study number. The alcohol-caused fatal motor vehicle injury literature is sparse with respect to dose-response information. More studies investigating this relationship and other injury types are recommended in this area to be able to calculate stable estimates of risk overall and by injury type specifically.

Keywords: alcohol, motor vehicle injury, mortality, risk, meta-analysis

6.2 Introduction

There is little doubt that alcohol consumption causes injury (19). Alcohol has been shown to be causal for a wide range of injuries through a number of studies, including cross-sectional (24, 27, 110, 123, 124), case-crossover (125, 256), and case-control analyses (23, 39, 128). The most important relationship, however, from a burden of disease, risk relationship, and public health standpoint, is the risk of injury from alcohol-attributable motor vehicle collisions (MVC). The relationship between alcohol and motor vehicle crashes is well established. Since the original Grand Rapids study of 1964 (85) and the subsequent re-analyses from Hurst (86), which resolved the famous "dip" in risk at low alcohol blood alcohol concentration (BAC) levels, this relationship has been characterized by a linear, dose-response relationship. It has persisted throughout time (85, 129), in different countries and cultures (133, 134), for the young and old, and men and women alike (18, 243). Despite this, though, the field of alcohol consumption and motor vehicle injury is far from homogeneous. In particular, two particular problem areas exist: exposure measurement and outcome measurement. The first pertains to the use of usual consumption patterns to assess the risk of injury, which is in direct opposition to the model of acute alcohol consumption causing harm i.e. information on usual consumption patterns does not capture the influence of alcohol on a particular episode of injury. What's more, it may not even relate to the event when the injury occurred and, even when acute exposure is measured and we can be certain the alcohol consumption occurred prior to the injury, many studies only report a dichotomous (YES/NO) measure of alcohol consumption, which does not permit risk curve generation. The second gap in the literature reflects outcome measurement. Of this, there are two separate issues – the first is separating out injury by type (motor vehicle versus suicide, for example), and the second, which is directly applicable to this study, is separating out relative risks or odds ratios for fatal and non-fatal injury, respectively. There is some literature that points to alcohol-attributable injury death having a higher dose-response risk than for non-fatal injury, particularly with respect to head injuries (115-117) and this is certainly reflected in burden of disease estimates (3, 4, 242), but quantification of this mortality-specific dose-response risk curve is non-existent for MVC mortality specifically and fatal injury generally. Dose-specific curves for non-fatal motor vehicle injury have been previously developed and

published by our research group for non-fatal injury with some separation by injury type (243), so the current work will aim to build on and add to this knowledge.

This systematic review and meta-analysis will fill a much-needed gap in the alcohol-injury literature by providing data that will enable the development of stable dose-response risk curves for alcohol consumption and MVC fatal injury where none currently exist. Originally, it was hoped that this analysis would be able to add other injury outcomes to this analysis, but this was not possible due to inadequate numbers of studies for other types of fatal injury.

6.3 Materials and Methods

This study was completed in four main phases: (1) the systematic search, (2) the data extraction, (3) the meta-analysis, and (4) the dose-response curve-generating step. Before these, however, it was necessary to identify key concepts and definitions of fatal injury outcomes. For completion of steps 3 and 4, the authors used STATA software version 10.1 (Stata Corporation, College Station, TX).

6.3.1 Case Definition

The definition of fatal injury was purposefully broad in the sense that no strict adherence to ICD codes or rigid diagnostic criteria was followed, since, at least in earlier phases of article selection, some studies only used qualitative descriptions of motor vehicle injury (e.g. “crash”, “accident”) while others used more traditional ICD-9 or ICD-10-based definitions. Most studies were either MVC studies based on roadside collision data (e.g. (225)), medical record/coroner’s file review (e.g. (128), or combination of the two (e.g. (135)).

6.3.2 Systematic Review

A systematic review of the literature published between 1 January, 1980 and 31 December, 2010 was completed. Databases queried were Medline, EMBASE, CINAHL, PubMED, Google Scholar, CABS, WHOLIST, SIGLE, ETOH, Alcohol in Moderation, and ISI Web of Science using a pre-defined key word algorithm. Initially, the search was quite relaxed in order to cast the widest net from which articles could be selected. It combined the search terms “alcohol”

AND “case control” OR “case crossover” AND “risk” AND “injury” OR specific outcomes: “motor vehicle collisions”, “poisonings”, “falls”, “suicide”, “homicide”, “drowning”, and was restricted to full articles (excluded reviews, editorials, and letters) of human studies only. After removing duplicate titles, suitable abstracts were selected from the total pool of identified citations and were excluded from further investigation if at least one of the following criteria were met:

1. No indication of any information pertaining to an association between alcohol and injury mortality
2. The study was NOT a case-control or cohort
3. Inappropriate exposure data: No dose-response information presented (e.g., “yes” versus “no” alcohol consumption was unacceptable in this case). All studies included in this review used BAC as the main measure of acute alcohol consumption.
4. The article did not measure fatal injury specifically or did not specify only fatal injury
5. Acute consumption immediately preceding the injury was not presented e.g. only average or some measure of usual consumption was used

In the event no abstract was available or existed, the full journal article was obtained and the abstract was reviewed and assessed based on the same criteria as the abstract selection phase. For non-English articles, a native speaker of the language in which the article was written completed the translation. For those abstracts selected for further investigation, the full article was obtained and judged based on the same five criteria. Only those articles that did NOT meet any of the five exclusion criteria were selected for data extraction and were included in the analysis portion of this study. Lastly, full reference lists of selected articles and key reviews were hand-searched to identify any studies that may have been missed in the systematic search.

6.3.3 Data extraction

Information about the level of alcohol exposures in each study, the number of cases at each exposure level, the total population at risk at each exposure level, the adjusted estimates of relative risk (RR) or odds ratios (OR), and the corresponding upper and lower 95% confidence intervals of the adjusted RR were all recorded. When ranges of BAC were given, the midpoint between the upper and lower bound was taken. In cases where no upper bound for the highest

category existed, 75% of the length of the previous category range was added to the low bound and this measure was used.

6.3.4 Meta-analysis

Step 1: Once the data had been abstracted and inputted into Stata, log-linear dose- response models were generated for each single study using the glst command, which accounts for correlation among RRs within the same study due to the identical reference group (257). The summary estimates for each study were then used as input into the metan command within Stata, but the non-summarized data was used for the curve-generating step.

Step 2: Quantifying the heterogeneity of risk estimates across all studies was important given the diversity of study methods, effect sizes, and controlled variables (147). Heterogeneity was quantitatively assessed among studies by using both the Q statistic and the I^2 statistic (148). To assess publication bias, two independent tests were used - Begg's and Egger's regression asymmetry test for publication (215, 216). This was done to investigate whether the existing literature was reflective of all studies (i.e. to assess whether the published literature is biased), including negative or null associations, as well as those reporting positive associations and high-risk estimates. If the studies were found to be highly heterogeneous and a large amount of between-study variation existed, it would be important to account for this variation by using a random effects model. If the opposite were true, a fixed effects model may be justified (217, 218).

Step 3: The meta-analysis step was the curve-generating step, using linear and first-order fractional polynomial regression of the inverse-variance weighted data to estimate a best fitting curve to the data according to Royston (146). First order fractional polynomials take the general form shown in Equation 1 :

$$\text{Log}\,(RR \mid x) = ß_1 x^{P1} \qquad \text{(Equation 1)}$$

$$\text{Log}\,(RR \mid x) = ß_1 x^{P1} + ß_2 x^{P2} \qquad \text{(Equation 1)}$$

Where x is the alcohol exposure level (in BAC (g/dL%), P^1 and P^2 are the polynomial powers, and $ß_1$ and $ß_2$ are the corresponding coefficients. No intercept term exists since all models have a

start point of Log RR = 0 (OR/RR = 1 at zero consumption). For first-order models, P^1 takes values from -2 to +3 and for second order models, P^1 or P^2 can take on any of these values, for a total of 44 different possible models available to fit the dose-response data. For model fitting, models were tested systematically from least to most complicated (linear, first order, second order) using the GLST command in STATA (257).

Best-fit curves or lines were assessed using standard goodness-of-fit statistics, with an emphasis on decreased deviance (gain) compared to the referent model. Comparisons of curves to determine the best fit were made using a Chi-square distribution, as recommended by Royston and Altman (149), using the linear (P = 1) as the referent for all first-order polynomials and the quadratic ($P^1 = 1$, $P^2 = 2$) as the referent for all second-order polynomials.

6.4 Results

Figure 6-1 illustrates the search and article selection process, with numbers of articles retrieved in the main and hand searches and numbers discarded at the title/abstract and full article selection phases.

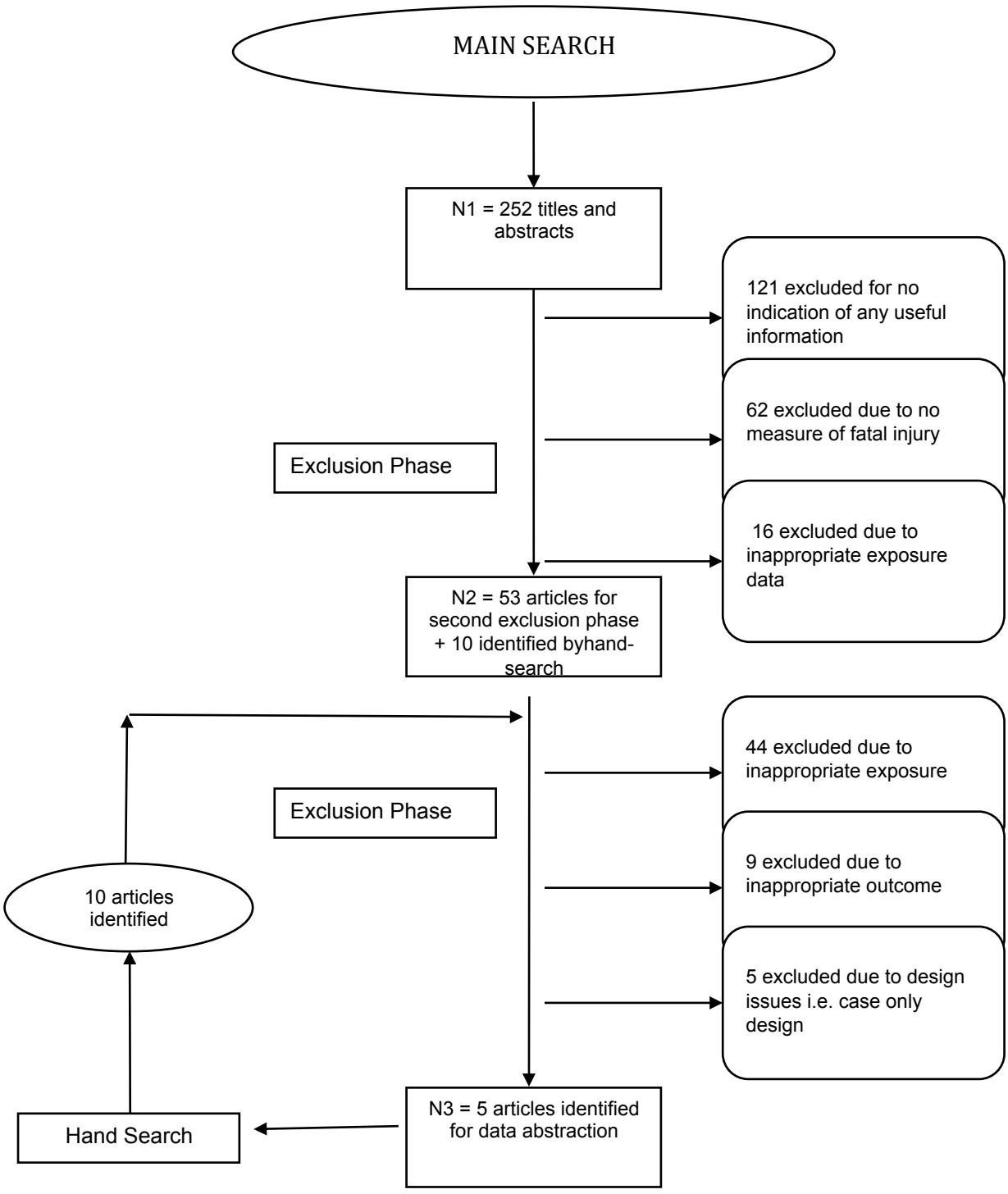

Figure 6-1 Flowchart illustrating the sequential process and results of the systematic review of the relationship between alcohol and motor vehicle injury.

6.4.1 Systematic Review

The systematic review identified 5 articles (128, 135, 225, 258, 259) assessing the relationship between acute alcohol and fatal motor vehicle injury. One of the articles presented six separate analyses (135) by age and gender. Thus, overall, 10 datasets from the 5 articles were included in this meta-analysis (see Table 6-1 for a description of each study). All of the studies reported data on BAC and motor vehicle crashes except for one (128) which was a study of alcohol and boating fatalities.

Table 6-1 Description of studies identified by the search that were included in the systematic review

Study	Year	Location	Design	Cases	Controls	Age	Sex	Covariates
Smith et al. (128)	2001	USA	Case-control	221	3943	43.5	Both	1, 2, 3, 4, 5, 6, 7
Haworth et al.(259)	2000	AUS	Case-control	114	847	27.5	Both	1, 2, 5, 6
Keall et al. (225)	2004	NZ	Case-control	85	85, 163	15+*	Both	CE**
Zador et al. (M:16-20) (135)	2000	USA	Case-control	432	609	16-20	Men	CE
Zador et al. (M:21-34) (135)	2000	USA	Case-control	1040	1652	21-34	Men	CE
Zador et al. (M:35+) (135)	2000	USA	Case-control	659	1508	35+	Men	CE
Zador et al. (F:16-20) (135)	2000	USA	Case-control	89	322	16-20	Women	CE
Zador et al. (F:21-34) (135)	2000	USA	Case-control	191	762	21-34	Women	CE
Zador et al. (F:35+) (135)	2000	USA	Case-control	134	702	35+	Women	CE
Evans & Frick (260)	1993	USA	Case-control	307	1149	N/A*	Both	CE

* not reported or estimable

** CE = crude estimate only, unadjusted

Figure 6-2 shows the forest plot of the relative contributions of each study to the pooled estimate, which estimated that the odds of fatal motor vehicle injury increased by 1.74 (95% CI: 1.43 – 2.14) for every 0.02 % increase in BAC. The assessment of heterogeneity for all studies

indicated significant heterogeneity between these studies (Q-statistic = 1504.5 df = 9 I^2 = 99.4% p < 0.0001), which was acceptable given the small number of studies and their widely varying collection methods. The meta-analysis was run as a random effects model in order to account for this variability. Publication bias was detected by the Begg's (p = 0.421) and Egger's (p = 0.032) tests, but both of these tests have been reported to have lower power when study numbers are low (215, 216), although the visual inspection of the funnel plot (Figure 6-3), showed scarcity of studies reporting lower or null effects.

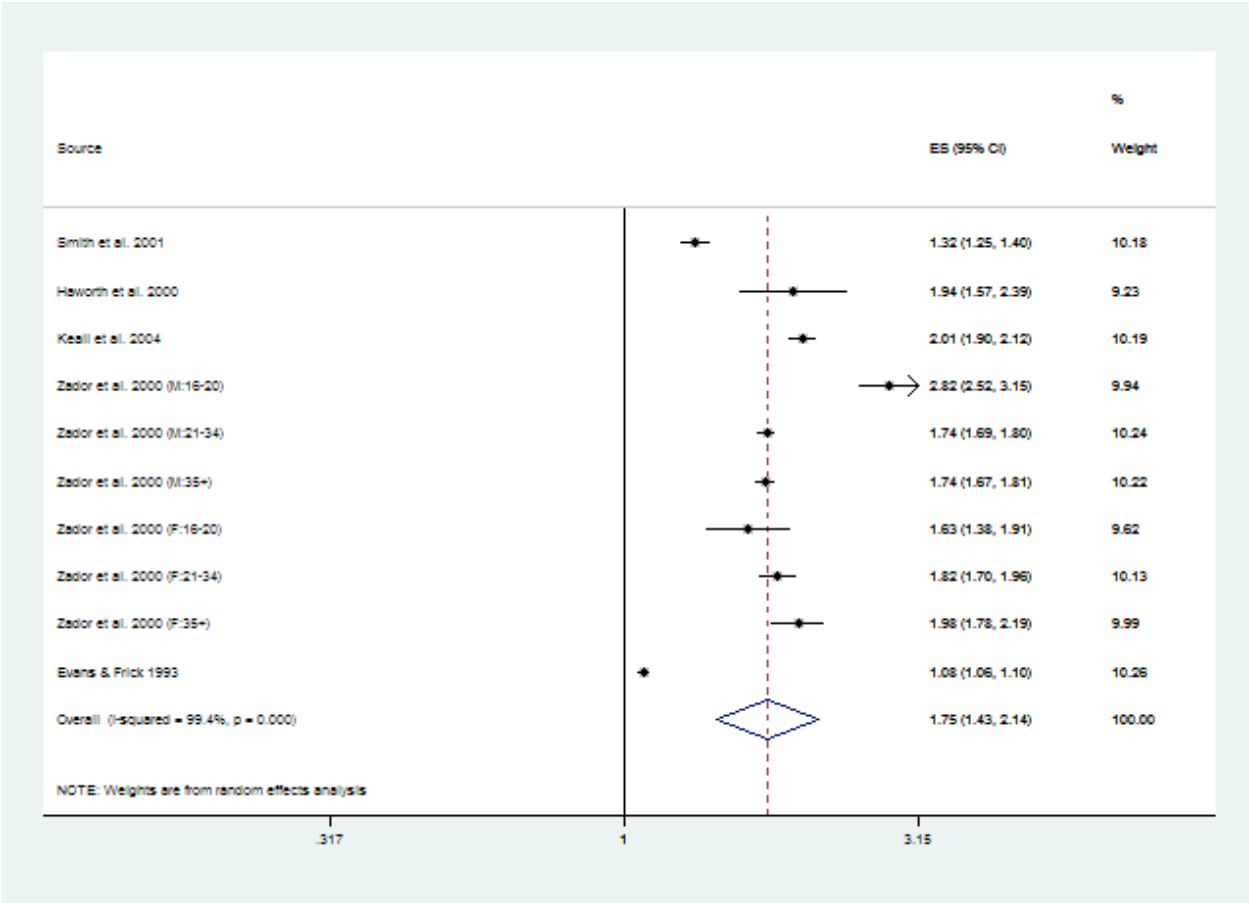

Figure 6-2 Forest plot for all studies of fatal motor vehicle injury and estimated relative risks associated with a 0.02% increase in BAC: Estimates were derived from a random effects linear model.

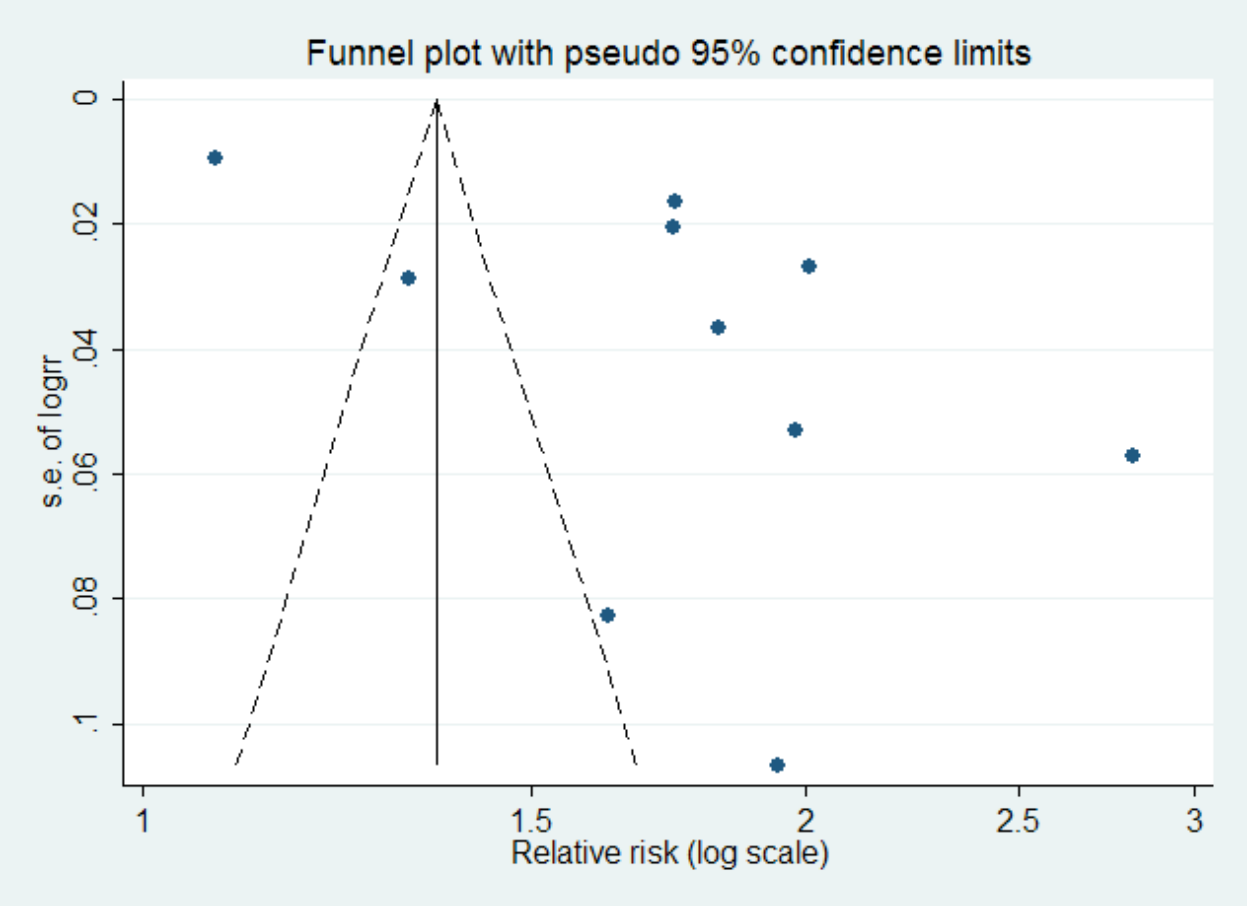

Figure 6-3 **Funnel plot for all studies of alcohol consumption and fatal motor vehicle injury.**

6.4.2 Fractional polynomial regression

The results of the fractional polynomial regression (Figure 4) showed a strong dose-response relationship between BAC and fatal motor vehicle injury. Initially, the linear model was fit to the pooled data, and then a first-order best-fit curve was attempted to try and improve the fit of the line to the data. The best-fit fractional polynomial was $P^1 = 0.5$ and $P^2 = 0.5$, which had a significantly lower deviance score than either the linear single-order, or the quadratic polynomial. Figure 6-4 shows the relationship between BAC and OR for fatal motor vehicle injury from BAC = 0 to 0.5% and Figure 5 shows only it up to 0.24 to highlight the risk at low BAC levels.

At a BAC of 0.5%, the maximum odds ratio of alcohol-attributable fatal injury was 595.05 (95% CI: 223.5 – 1584.0). At a BAC level of 0.02 (roughly the equivalent of one standard drink), this analysis estimated the OR to be 3.64 (95% CI: 3.37 – 3.94) (see Figure 5). At the legal limit of 0.08, the legal BAC limit in most countries, the OR was calculated to be 13.0 (95% CI: 11.1 – 15.2) (see Figure 6-5). At levels above 0.08, the curve started to get much steeper with exponentially larger increases in fatal motor vehicle injury risk at these levels.

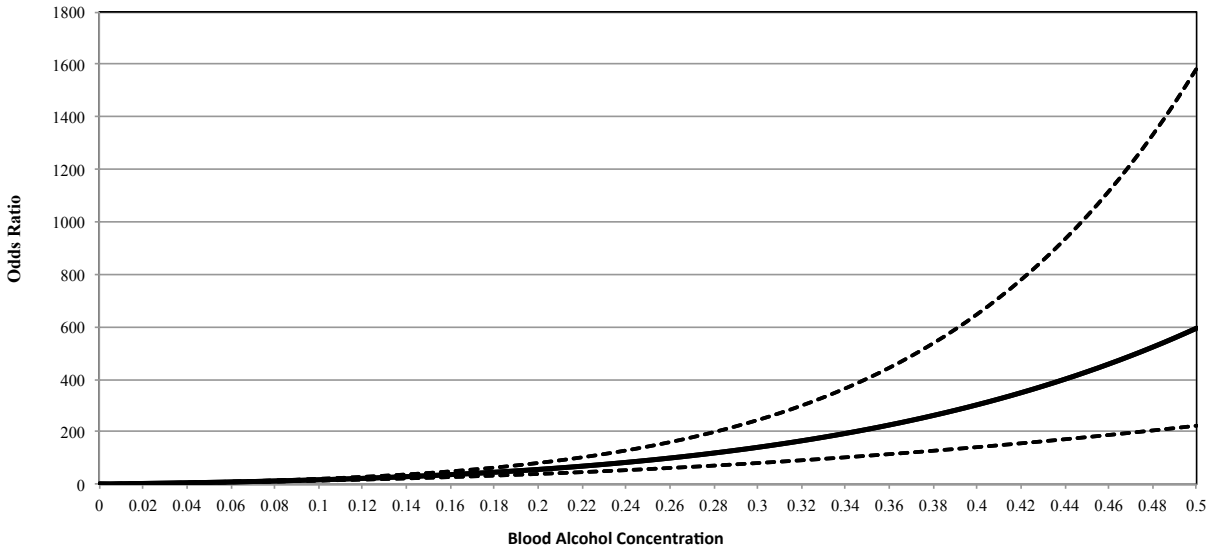

Figure 6-4 Dose-response curve for the BAC level and the odds of a fatal motor vehicle injury for all 5 studies combined for BAC levels from 0 to 0.5%.

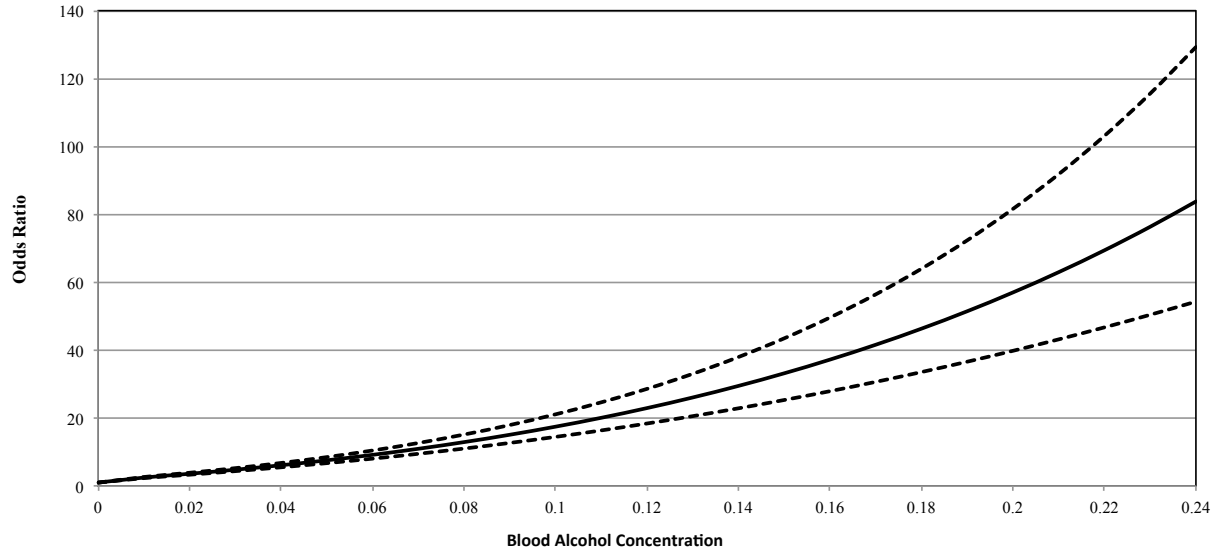

Figure 6-5 Dose-response curve for the BAC level and the odds of a fatal motor vehicle injury for all 5 studies combined at low levels of alcohol consumption at BAC levels from 0 to 0.24%.

6.4.3 Sensitivity Analysis

A post-hoc sensitivity analysis was performed due to the inclusion of 6 different Zador et al datasets in the meta-analysis, in order to test whether the inclusion of six separate datasets had any more influence over the pooled estimate than just one aggregated dataset from this study. For this analysis, the six Zador datasets were aggregated together to make one dataset only, resulting in 5 datasets being entered into the meta-analysis instead of 10. To aggregate the 6 Zador datasets, the relative risks were linearized by taking the natural logarithm of the RR across each BAC level and then a weighted average was computed by the number of cases in order to correctly combine each age- and sex-specific across each BAC level. Next, the same meta-analysis steps were applied to this new dataset, but instead of representing 6 studies, Zador et al, now only represented one study. Figure 6-6 shows the forest plot of the meta-analysis. For every 0.02% increase in BAC, the OR was found to increase by 1.60 (1.17 – 2.20), which was not statistically significantly different from the meta-analysis which included all six datasets from Figure 6-2, since the confidence interval was covered. The heterogeneity assessment remained significant ($p<0.0001$), $I^2 = 99.6\%$.

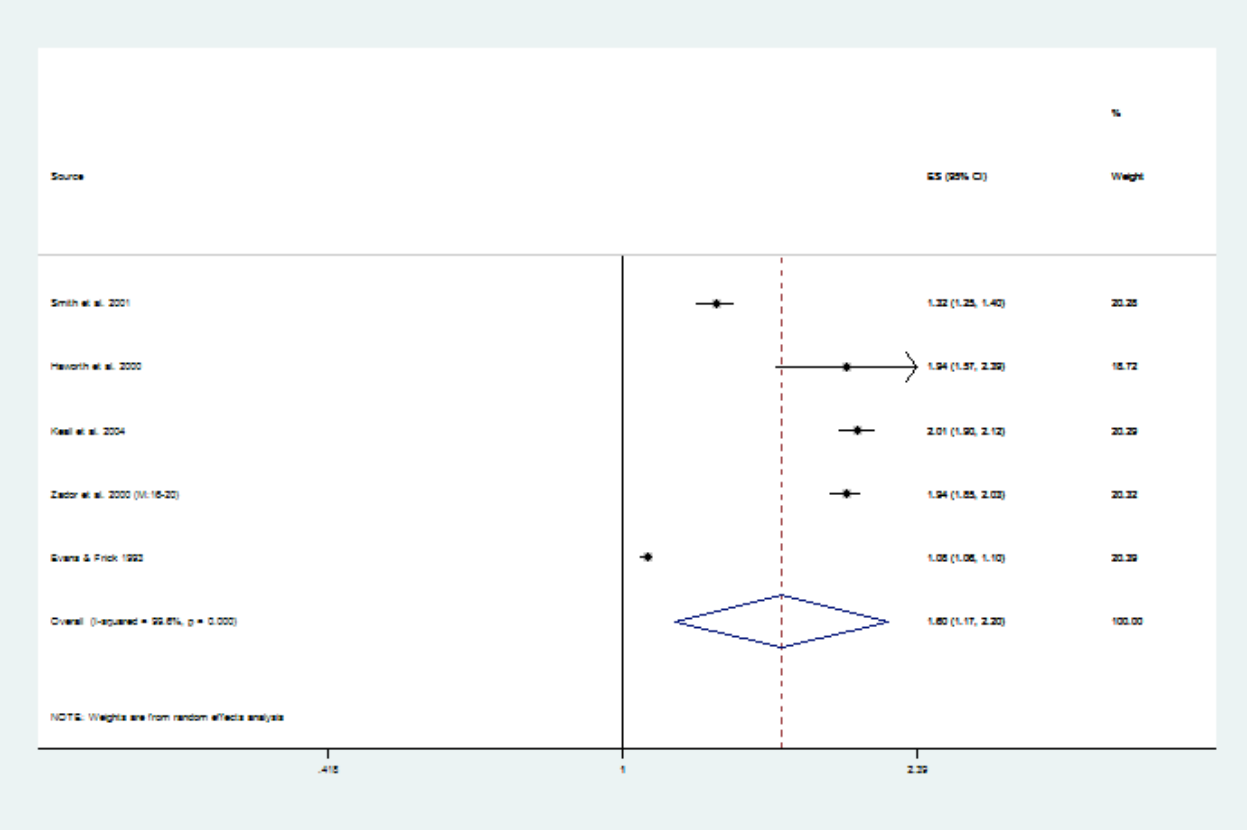

Figure 6-6 **Forest plot for the sensitivity analysis for which Zador et al. was aggregated across BAC categories. Estimates of OR for a corresponding 0.02 % increase in BAC were derived from a random effects linear model.**

6.5 Discussion

This is the first meta-analysis to quantify the overall relationship between acute alcohol consumption and the risk of fatal motor vehicle crash injury. One previous meta-analysis (by this author) on alcohol and the risk of non-fatal motor vehicle injury has been published and provides the closest comparison due to similar methodology (243). Although the alcohol consumption measure differed (grams of alcohol consumed 3 hours prior to the injury versus BAC), the odds of fatal injury due to motor vehicle collisions were significantly higher compared to non-fatal injury at similar alcohol consumption levels, definitively showing this comparison quantitatively for the first time. In this study, an OR of 1.75 (95% CI: 1.43 – 2.14) per 0.02 % rise in BAC was found, whereas for no-fatal motor vehicle injury the OR was 1.24 (95% CI: 1.18-1.31) for approximately a 1 drink increase (which generally results in a BAC of about 0.02) (261). What's more, the risk curve for fatal injury was consistently far steeper than for non-fatal injury at all levels of alcohol consumption.

Before discussing these results further, it is important to discuss some of the limitations of this analysis. First, it is important to recognize the contribution of the Zador et al. (135) paper, which contributed 6 data sets out of 10 used in the main analysis. Despite the Zador et al. study being a very high quality study, by its mere inclusion, over half of the datasets would be subject to the same biases inherent to this one study alone. To investigate the influence of the inclusion of all 6 Zador papers, the sensitivity analysis was complete, this time pooling the Zador data into 1 study only by aggregating the samples and RR across BAC categories. The sensitivity analysis showed that the aggregation made no appreciable difference to the meta-analytic results either quantitatively nor qualitatively compared to the six separate datasets. So, for this analysis, the main analysis included all 6 separate datasets simply for the reason that aggregating this data would result in valuable information being lost in an already small dataset, leading to the estimation of a less precise estimate.

Second, this systematic review only resulted in only 5 eligible papers, which highlights how understudied the relationship between acute alcohol consumption and fatal motor vehicle injury is compared to non-fatal motor vehicle injury, and highlights the major disparities between the study of fatal and non-fatal injuries generally. Exposure data for studies of fatal injury tends to rely more on data from coroner's reports, mortality statistics, and police files

compared to in-hospital and in-person questionnaires of case-control or case-crossover data that characterizes investigations of alcohol-attributable non-fatal injuries, which tend to be based on self-reported consumption in emergency room settings (130, 231, 262, 263), making access to cases more difficult and time-intensive. As well, measuring the relationship between acute alcohol consumption and fatal injury may be more difficult than for non-fatal injury and may tend to underestimate the true relationship between alcohol and fatal injury, particularly given that BAC calculations may result in underestimation of true consumption (238, 261). BAC is often measured long after the initial collision took place, which may underestimate the true exposure (e.g. (225)) and thus the dose-specific relative risk, making the results of the current analysis conservative. The time between and injury occurring and the forensic pathological investigation may be some time, and time – and temperature – dependent degradation ethanol metabolites in blood have been reported in the forensic pathology literature (264, 265). The overestimation of BAC may also be possible, although unlikely, due to a build-up of ethanol-producing bacteria that may occur after death, (266, 267). In recent years (since the mid-nineteen nineties), this problem has largely been resolved via the testing of other bodily fluids, such as vitreous humor, where ethanol levels have been shown to be very stable over time (268).

Third, control selection is also important in this relationship. For a number of studies included in this report, control groups were made up of severely injured individuals (260) or population controls (135, 225). Using the injured group as a reference would underestimate the OR since the likelihood of all non-fatal injury is also increased with alcohol consumption, thereby falsely deflating the resulting OR compared to a non-injured control group.

Fourth, prior research in this area has shown that the relationship between alcohol and injury may be confounded by usual drinking patterns, risk-taking behavior and substance use (228). Studies included in this meta-analysis did not control for these factors, or only controlled just one or two of them. This means the overall pooled estimate may be biased from the outset with respect to these confounders. On the other side of this argument, though, is that explicitly controlling for some of these types of confounders may lead to biased risk estimates due to the fact that alcohol and risk-taking behavior, for example, are on the causal path from alcohol consumption to injury. Decisions to engage in activities that are likely to lead to an injury are positively influenced to a large degree by the consumption of alcohol, so over-controlling by including these confounders would result in incorrect RR/OR as well (61, 62, 168).

This meta-analysis summarized the available, high quality literature to date on the relationship between acute alcohol consumption and death from motor vehicle collisions. At all levels of consumption, the odds of dying in a motor vehicle crash were significantly higher than for zero alcohol consumption, and were approximately 13 times higher at the current legal limit of BAC = 0.08. The policy implications of this are obvious – at this BAC, the risk is simply too high and efforts to lower the legal limit while operating a motor vehicle must be increased based on this available evidence. There is clear evidence that, upon a reduction in the legal limit from BAC = 0.10 to 0.08 reduced fatal collisions in the US (269, 270), but the implications from this report would call for even more drastic measures, to 0.05, or even lower, particularly in younger drivers, who appear to be at the most risk based on single studies (135).

Clearly, risk relationship studies of alcohol-attributable fatal motor vehicle injuries is an area of research that is in need of more, higher quality studies. In order to get more stable risk curves at all levels of alcohol consumption that will inform public health and burden of disease and monitoring-type analyses that are informed by risk modeling (242). In particular, studies that separate injury types and present sex-specific data are needed. However, there are significant barriers to completion of these studies, most notably in the areas of exposure assessment, selection of control groups, and access to and completeness of secondary data sources with relevant exposure information.

7 Discussion

This section will form a summary section to summarize the work of this thesis and to address any outstanding methodological or interpretation issues that exist within this work. This section can thus be seen as the final piece of this thesis, whose purpose is to discuss the entire work as a whole, and to set clear statements about its strengths, its limits, its uses, and its relevance to alcohol-injury epidemiology and public health generally.

7.1 Summary of contributions

To summarize this thesis, we should revisit the introduction, which outlined the 5 areas in which this work proposed to make improvements. Below, these 5 statements are reprinted with a response based on the work in the four articles that make up the bulk of the work of this thesis.

1. Move away from traditional per-occasion/average daily volume risks to lifetime risks so comparison with environmental exposures is possible and meaningful.

Response: The first paper (175) introduced the lifetime approach and published, for the first time, the quantification of an adult lifetime of drinking alcohol, albeit at defined, theoretical levels to show how increases or decreases of these levels resulted in corresponding increases or decreases in the risk of alcohol-attributable injury. It formed the basis of the lifetime approach, and was the paper from which all other improvements, calculations, and analyses were based.

2. Incorporate patterns of drinking and average daily consumption into the same model of lifetime risk.

Response: The first and third (271) papers incorporated both binge drinking and average daily amounts into the same model of lifetime risk, each contributing their own alcohol-specific risk, and then were added together to quantify their combined risk. Since drinking is made up of both types of consumption, this represented a significant

step forward in the complexity of modeling drinking behaviour and its effect on risk of injury.

3. Account for changes in average daily drinking and binge occasions over a lifetime to present an adaptive lifetime risk model that better approximates a "drinking lifetime". This will require measuring daily average drinking and binge occasions/amounts for each age and sex in Canada for the year 2005.

Response: This was a key component of the third manuscript and built significantly on the progress of Manuscript 1, where the binge drinking behaviour and average daily amounts were modeled based on the best available survey data, by age and sex for the Canadian population. This directly modeled the drinking behaviour of Canadians and was thus applicable to this population. Numerous improvements to better model the average consumption were employed to better approximate the true average consumption reflected in sales data.

4. Address the possibility of differential per-occasion risk profiles for both injury type and severity where possible through meta-analysis and incorporate these into the lifetime risk approach.

Response: Manuscript 2 (243) and 4 (272) were meta-analyses that resulted in brand new relative risk functions for morbidity (MVC and non-MVC injury) and for mortality (MVC injury only) where none previously existed. The results from (243) were incorporated directly into the third article (271), meaning the consumption-specific RR could be used to develop alcohol-attributable fractions that directly reflected the changing consumption patterns of Canadian adults. The results from the fourth article (mortality RR) are shown in Chapter 7 of this thesis and will be used in all future calculations, including those planned for the WHO Comparative Risk Assessment as part of the 2012 Global Burden of Disease. Incorporating these risk functions in new calculations of the MVC mortality AAF is in process and will constitute a fifth article comparing previous estimates of MVC mortality with the new, RR-based calculations, thus making an important scientific contribution in its own right and as a direct extension of the work of this thesis. It showed, empirically for the first time, that the risk for MVC injury mortality was significantly higher than for non-

fatal MVC injury at the same dose of alcohol. Future work aims to develop a similar risk function for fatal non-MVC injury, but presently the scarcity of useable data available for a meta-analytic model does not allow for such calculations. Future work will involve developing studies to model the relationship between fatal non-MVC injury and alcohol consumption.

5. Incorporate a variance estimate into the risk estimation strategy and providing confidence intervals for estimates of lifetime risk. This will require measuring and combining random error in alcohol measurement, liver metabolism data, and the error in relative risk estimation.

Response: This was a technically complex and computationally intensive process that resulted in the error estimation around the new AAF, presented for the first time in article 3 (272). This required creating a "distribution of distributions" using Monte Carlo simulations. For all inputs with variance estimates, a probability-based distribution of the AAF was created by calculating the AAF 10,000 times (based on the individual distributions of each input) until it converged on one estimate (the "mean" AAF). The variance around this estimate after 10,000 iterations was the variance of this mean, from which a 95% confidence interval could be easily created. This was computationally intensive, requiring the same 10,000 iterations for each AAF estimate (by age, sex, injury category, binge consumption and average consumption level, respectively, and separately for mortality and morbidity).

7.2 Limitations

There are a number of limitations in this work that could not be adequately addressed within the four main papers due to either word restrictions imposed by journals (3500 – 4000 on average), or simply that the overall focus of the manuscript precluded an in-depth look at one of the limitations. So these will be addressed below.

7.2.1 Use of the CADUMS dataset

The CADUMS data was the source of all of the alcohol consumption data, but the survey had a very low response rate. The survey reported a response rate of 36.5%, with 15, 801 individuals in the final dataset (138). It was these individuals that provided binge drinking estimates and average daily consumption data. Given, the low response rate, it is important to discuss the impact of sampling bias on the alcohol consumption data and thus the bias in the measure itself.

The traditional notion of low response rate is that it results in lower quality, biased data and thus less accurate results (273-276). However, this is only true if nonresponse is associated with a different response profile than those who did respond, which then would lead to non-response error, meaning that parameters such as means, proportions, and other population estimators will be biased (277). It has been previously demonstrated that higher response rates do not necessarily change the distribution of alcohol consumption when the response rate is between 30% - 60% and similar sampling methods are used (150, 245), and although telephone surveys may result in slightly lower estimates for alcohol and drug use compared to mail-in or in-person interviews, the explicit inclusion of alcohol questions has no effect on response rate (278). Similarly, Gmel did find that the use of telephone-based survey methods resulted in underestimation of the prevalence of alcohol consumption overall but that non-responders did not differ with from those who did choose to respond (278, 279). In a study investigating the effects of non-response on alcohol consumption variables in a Swedish telephone-based alcohol survey, Wennberg et al. found no differences between responders and non-responders on alcohol consumption measures (280).

Prior research in the area of telephone-based surveys, their limitations, and methods to improve their accuracy were evaluated recently by Shield and Rehm (281). For their analysis, the CADUMS 2008 dataset was used and thus their findings are directly applicable to the relative strengths and weaknesses of this survey as it was used in this thesis. There were three main findings: (1) ignoring people who are homeless, institutionalized and/or do not have a home phone may lead to an underestimation of the prevalence of alcohol consumption; (2) weighting of observations to population demographics may lead to an increase in the design effect, does not necessarily address the underlying selection bias, and may lead to overly influential observations; and (3) the accurate characterization of alcohol consumption patterns obtained by triangulating the data with the adult per capita consumption estimate is essential for comparative

analyses and intervention planning especially when the alcohol coverage rate is low like in the CADUMS 2008. With respect to the first two findings, many surveys, in particular those that are telephone-based, suffer from selection bias simply by virtue of their data collection method, thus simply weighting to standard populations does not necessarily solve this problem. Upshifting the low survey-based results to approximate per-capita consumption levels (about 80% of per-capita consumption), however, corrects for this underestimation on a population level. To account for the biased population distribution from the survey, the work of Kehoe and others (83, 244) was used to calculate the shape and scale parameters using a simple relationship between mean alcohol consumption and its standard deviation (see (282).

So what does all of this mean for the initial low response rate in the CADUMS? If the CADUMS showed that non-responders were not significantly different from the responders on alcohol consumption variables, the results of the CADUMS would not be considered invalid or biased as a result of the non-response on these particular variables. Work on the CADUMS itself shows promising results in this regard - prior work found that the weighted CADUMS represents the Canadian population well when compared with the census on age, sex, and province of residence (139). However, the CADUMS was found to oversample married people and those with university education slightly, which may lead to lower estimates of alcohol consumption within drinking populations. Overall, then, the CADUMS would suffer from underestimation of alcohol consumption stemming from two sources – the use of the telephone interview, and the oversampling of married and educated persons. However, since these were acknowledged, accounted, and adjusted for using empirical data, the non-response, although high in the CADUMS, should not have resulted in a meaningful bias of alcohol consumption data. What's more, the results of this survey can be considered generalizable to the general Canadian population. Overall then, the result is comparable to other countries due to upshifting, with the net consequence leading to a slightly lower, and thus more conservative, estimate of the AAF.

7.2.2 The "Original" AAF

In article 1 (175) and the later work that built on it and/or used the main method described in the articles that followed form this work (207, 242, 271, 283, 284), the total injury risk was broken down into two portions: the alcohol-attributable portion and the non-alcohol-attributable portion (this was called the "baseline risk" in the first article). This non-alcohol-attributable portion was the baseline risk, upon which the new, multi-dimensional risk of injury morbidity/mortality was

built on, as described in that article and the third article (271). In order to separate the alcohol-attributable portion of injury risk from the total risk, the total risk had to be multiplied by some factor that described the alcohol-attributable risk, or in other words, a pre-existing estimate of the alcohol-attributable fraction. For this first step, the most of the AAF for each injury outcome was obtained from the original Comparative Risk Assessment of the World Health Organization (see (4)). The only two that were not obtained this way were traffic collisions and fire injury. These were obtained from (164, 170) for MVC and from (166) for fire mortality. For the AAF from the CRA, these were specific to certain age groups, in some cases by gender, and for each injury outcome for the Americas A region (composed of Canada, United States of America, and Cuba). They were adjusted to Canada based on the relative difference between the CRA estimate for MVC and the MVC injury AAF that was actually used, resulting in an increase in the original AAF, meaning the baseline risk was lowered, making the new alcohol-attributable risk calculations a conservative estimate.

7.2.3 Error in the Widmark equation

A critical element of the meta-analyses and the dose-response RR of this thesis is the conversion of BAC estimates to grams of ethanol consumed prior to an injury event occurring. Obviously, with any calculation of this type there is an error estimate associated with it, since there are a number of variables that are assumed to be constant for the purposes of carrying out such a calculation, but which are not in practice. In the modern Widmark formula used in this thesis,

$$N = \frac{W\, r[C_t + \beta_t]}{dZ}$$

where N = number of drinks

W = body weight

r = volume of distribution (L/Kg)

C_t = blood alcohol concentration

β_t = alcohol elimination rate

d = density of alcohol

Z = concentration of alcoholic drink

In this thesis, as in all Widmark equations, r, β_t, and d were fixed, N was the number of 13.6 gram standard drinks, W was fixed for men and women separately, based on the average weights of Canadian men and women, and Z was fixed for each beverage type separately (beer, wine, and spirits). Recent work into estimating the error around the Widmark equation was used in this thesis (238), and was based on Table 1 in this article (see Table 7-1):

Table 7-1 Estimates of uncertainty in the Widmark equation used to convert blood alcohol concentration to number of Canadian standard drinks.

Variable	Value	Uncertainty (SD)	% CV
Gender	Male		
W	180 lbs	3.6 lbs	2%
r	0.73 L/kg	0.067 L/kg	9.2%
$\mathbf{C_t}$	0.0012 kg/L	0.000043 Kg/L	3.6%
$\boldsymbol{\beta_t}$	0.000148 kg/L/h	0.000032 kg/L/h	22%
t	3 h	0.06 h	2%
d	0.82 oz/fl. oz	0.0082 oz/fl. oz	1%
Z	0.48 fl. oz/drink	0.014 fl. oz/drink	3%

7.2.4 Residual confounding in the relative risk estimate

One of the most important drivers in the alcohol-attributable fraction calculations of this thesis was the injury- and dose-specific relative risk. The source of these relative risks was meta-analysis, which pooled a number of etiologic studies for each injury type and separately for morbidity and mortality. However, although each of these individual studies measured the relationship between alcohol and injury, they each measured different confounding variables and used different measurement techniques. Thus, the RR estimates from each individual study may be biased due to the imprecise measurement or omission of certain covariates that may confound the relationship between alcohol and injury, commonly termed residual confounding (285). Thus, as each RR may be biased due to residual confounding, the RR function produced from the meta-analysis may also be subject to the same limitations (286).

Previous work and discussion of the effect of residual confounding has shown that bias due to measurement error of covariates can be substantial (285, 287) and can lead to both over- and under-estimation of resulting risk estimates. However, the use of adjusted RR estimates in meta-analysis, as both of the meta-analyses in this thesis were, can guard against residual confounding, provided the models were not over- or under-adjusted, and can result in a more precise estimate of the effect (288). The use of meta-analysis thus cannot get rid of residual confounding if it is already present in the study-level RRs, but benefits greatly from the use of high-quality studies that use adequately adjusted modeling of the effect (289). To understand the

effects of residual confounding on the RR estimates used in this thesis, we must consider possible confounders in the relationship between alcohol and injury, and then consider the studies used in the meta-analyses published as part of this thesis. The existing literature points to a number of potential confounders in the relationship between alcohol and injury, such as age, sex, hour of day, fatigue level, location, risk-taking behaviour or propensity to take risks, weather conditions, and other comorbid health conditions, among others. To varying degrees, these were controlled for independently and in combination, but it should be noted that even in cases where no controlling of additional covariates was done (as in the case of (256), for example), the RR estimate was well within the range found by other studies that did control for these variables (see Figure 4-3 and Figure 4-4). It is thus highly unlikely that there is some antecedent or other variable that has been grossly mismeasured or omitted from inclusion in the modeling or missed altogether. What's more, in the case of alcohol and injury, consensus of a large body of literature that uses disparate sources of data all point to similar estimates of a relationship lead to the assertion that either all of the available evidence is flawed in the same way, or that the answer, based on best available current evidence, is estimated, but at least mostly correct and having properties whereby the error around the point estimate may be computed. For the 2 meta-analyses presented in this thesis, we make the assumption of the latter, in that the relationship is causal and mostly correct based on the available evidence, and formulated a way to measure its error. Certain non-systematic measurement error does exist, as in all observational study, but such error would bias effect sizes towards the null, making the RR overall a conservative estimate, which is much more acceptable in the context of risk evidence and policy development, than an overestimate.

7.2.5 How will population-level data guide consumer choices?

A central important tenet of this thesis was the provision of empirical data to guide the subsequent development of low-risk drinking guidelines. However, previous readers of this thesis and the thesis proposal correctly questioned the validity of using population-level data, such as lifetime-attributable morbidity and mortality, and the AAF, to guide low-risk drinking guidelines, which, while rooted in policy, are ultimately developed in order to guide individual-level choices, a case of ecologic fallacys This will not be a discussion of why low-risk drinking guidelines are needed, for which there are ample sources of information (see, for example, (33, 290-292)). Rather, this will be a discussion of how the evidence presented in this thesis, which

combines population-level data, can be used, translated, and made relevant to adult consumers of alcohol to help guide individual-level choices.

Low-risk drinking guidelines provide a resource for a wide range of groups and individuals, including health professionals, community groups, industry, professional organizations, schools and educational bodies. They will also inform policy makers, planners, decision makers, and those responsible for providing alcohol, who have a broader responsibility to the community and whose decisions and advice may influence the health of communities. As an illustration, consider the case of seatbelt laws, for which there existed causal evidence through observational study that the use of seatbelts in motor vehicles was preventive of injury and death in a motor vehicle collision (please see (293) for a thorough review of the evidence). Along with this evidence, estimates of the attributable fraction of deaths saved through the use of seatbelts were published, analogous to the AAF in alcohol epidemiology (293). Thus, law and policy to reflect this population-level risk was developed to influence individuals to start buckling up (see http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_90h08_e.htm for the law in Ontario, Canada). As new estimates of increased proportions of people wearing seatbelts became available, and new mortality data on deaths from motor vehicle collisions became available, it was possible to attribute some of these savings in mortality to seatbelt laws (293-295). Enforcement of the seatbelt law at the individual level was also introduced, thereby making population-level policy relevant to the individual, despite the lack of a decisive clinical trial, for example.

Another example to consider is policy about lifetime exposures to other harmful substances, whether asbestos, as occurred in this country mid-1990's, or other foodstuffs such as exposures to methyl mercury in wild fish (296). Information about limiting one's aggregate exposure to such materials is analogous to that of alcohol – we understand that the risk grows cumulatively, and continued exposure to each results in increases in the risk of certain negative health outcomes. Policy and guidelines around asbestos exists in this country (REF) and others, as does exposure to methyl mercury in seafood, even though the evidence around these outcomes is population-level data. In fact, where dangerous goods or materials are concerned, gold-standard, studies such as randomized-controlled trials are not feasible nor ethically possible.

So too in the acute effects of alcohol – guidelines and policy to reduce incidences of binge drinking or to shift populations to healthier drinking patterns filter down through the same avenues, from empirical evidence to family physicians, family or community-based education and advice, and enforcement. Guidelines are meant to express the best evidence to date and resulting policy is created with the purpose of informing and protecting the general public (290). So, while community-level policy cannot protect an individual from making certain choices about his or her exposure to alcohol, there is a responsibility of the scientific community to create knowledge about harmful exposures, and in turn, the responsibility of governments and public health agencies to translate this knowledge to consumers. This thesis, as a scientific document, aims to do the former while informing the latter. Early iterations of this work (mainly manuscript 1 of this thesis) provided much of the scientific evidence for development of Australian Low-Risk Drinking Guidelines in 2009 (297).

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Appendices

Appendix 1: Example of R-code used to generate Monte Carlo simulation for computing the variance of the AAF.

```
############# Definition of Relative Risk Functions as well as the
Variances and Covariances of the parameters  ###########


############# Note: the Relative Risk functions have sometimes been
changed at the extremities, therefore, in   ###########

############# order to be able to simulate our RR functions with
different beta parameters, the easiest is to   ###########

############# change the functions parameters compared to the previous
ones. Namely, instead of being only a    ###########

############# function of x, the relative risk functions will be
functions of x and the different betas.       ###########

############# To calculate the Confidence Intervals, we will therefore
first generate the beta coefficients     ###########

############# and then plug them into our Relative Risk function that
we can use to calculate the AAFs.     ###########




############# The values of the relative risks for former drinkers are
given as their logarithmic values and    ###########

############# the variance applies to these logarithmic parameters.
Therefore, for the simulations, we'll have  ###########

############# To simulate n logarithmic values and take the
exponential                              ###########
```

```
#######e.g. for 1 injury#######


####### MVCMA #######

####### MVCMA #######



#### male ####


RRmvcma =

mvcmabetas =

mvcmacovar =

lnRRmvcmaform=

lnRRmvcmaformvar=

mvcmale = list ("MVC - MEN", RRmvcma, mvcmabetas,
mvcmacovar,lnRRmvcmamaform,lnRRoralmaformvar)



#### female ####



RRmvcfe =

mvcfebetas =

mvcfecovar =

lnRRmvcfeform=
```

```
lnRRmvcfeformvar=

mvcfemale = list ("MVC - WOMEN", RRmvcfe, mvcfebetas,
mvcfecovar,lnRRmvcmafeform,lnRRoralfeformvar)





#################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞   INPUT FILE
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞#############################

#################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞   INPUT FILE
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞#############################

#################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞   INPUT FILE
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞#############################

#################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞   INPUT FILE
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞#############################


############ Reading in and Formatting the input file ############

############ Reading in and Formatting the input file ############


######## The inputs are as follows:

######## REGION - SEX - AGE CATEGORY - %LIFETIME ABSTAINERS - %FORMER
DRINKERS - %DRINKERS - POPULATION WEIGHT - RELATIVE COEFFICIENT - PCA
(by sex) - SE of PCA

##### The AGE_CATEGORY variables have to be numbers. This is required
in order for the program to recognize the different categories
automatically. This will enable

##### us to change the number of age categories at any time
```

```
##### ATTENTION: PCA HAS TO BE GIVEN IN LITRES/YEAR!!! IT IS ALSO A
REDUNDANT NUMBER INSIDE EACH REGION AS IT REPRESENTS THE TOTAL PCA OF
THE REGION IN QUESTON.

##### IT IS KEPT REDUNDANT ONLY FOR THE SIMPLICITY OF THE PROGRAM
DESIGN.

##### IN ADDITION TO THAT, THE PROGRAM WILL TAKE THE 80% OF THE INPUT
PCA



input=read.delim("AAFinputfile.txt", header=F,
colClasses=c("character","numeric","numeric","numeric","numeric","nume
ric","numeric","numeric","numeric","numeric"))

colnames(input)=c("REGION","SEX","AGE_CATEGORY","LIFETIME_ABSTAINERS",
"FORMER_DRINKERS","DRINKERS","POPULATION",
"RELATIVE_COEFFICIENT","PCA","VAR_PCA")

inputm = input[input$SEX==1,] ####### male dataset

inputmage=inputm[inputm$AGE_CATEGORY==1,]

prop_abs_male = inputmage$LIFETIME_ABSTAINERS

prop_form_male = inputmage$FORMER_DRINKERS



#### the list of regions will be used to compute the mean values ####

#### indeed, each region has 6 different entries (2x3 for sex    ####

#### and age group). We therefore need a non redundant list of   ####

#### the regions.                                                ####


agecategories_male=unique(inputmage$AGE_CATEGORY)

#### male ####
```

```
regions_male = unique(inputmage$REGION)



######## Determining the MEAN values #########

######## Determining the MEAN values #########

######## Determining the MEAN values #########


#### the generation of the mean values will need the use of a function
####

#### which we will be able to re-use for the CI by generating random
####

#### inputs and returning the output.                              ####


#### p1,p2 and p3 are the size of populations, a,b and c the relative
coefficients;                                        ####

#### the proportion of drinkers is directly related to the proportions
of abstainers and former drinkers. the rest is straightforward ####

#### THE OUTPUT IS A VECTOR OF THE X MEAN VALUES CORRESPONDING TO THE
X AGE GROUPS.                                              ####

compute_mu=function
(p1,p2,p3,a,b,c,prop_abs1,prop_abs2,prop_abs3,prop_form1,prop_form2,pr
op_form3, pca)

{

    #### calculating the mean consumption of the drinking population
####

    drk1=p1*(1-prop_abs1-prop_form1)

    drk2=p2*(1-prop_abs2-prop_form2)
```

```
    drk3=p3*(1-prop_abs3-prop_form3)

    pca_drinker = pca*(p1+p2+p3)/(drk1+drk2+drk3)

    mu1=pca_drinker*(drk1+drk2+drk3)/(drk1+b/a*drk2+c/a*drk3)

    mu2=b/a*mu1

    mu3=c/a*mu1

    mu=c(mu1,mu2,mu3)

    return(mu)

}



######## male population #######

n_agecategories_male = length(agecategories_male)


# The idea is to create a vector with NAs at the beginning and then
fill it. Then you don't have to use the combine-command so often which
slows things down.

mean_male=rep(NA, length = length(regions_male)*n_agecategories_male)


for (i in 1:length(regions_male))

{

    #### extracting the required information for each region ####

    info_male_region = inputm[inputm$REGION==regions_male[i],]


    #### calculating the mean values for each group

    population = info_male_region$POPULATION
```

```
    coeffs=info_male_region$RELATIVE_COEFFICIENT

    prop_abs=info_male_region$LIFETIME_ABSTAINERS

    prop_form = info_male_region$FORMER_DRINKERS

    pcalitresperyear=info_male_region$PCA[1]  #### the three values
for pca are redundant (one value only for the whole region), the
choice to take the first one is arbitrary of course

    pcagramsperday=pcalitresperyear*1000*0.789*0.8/365   #### This is
to calculate the 80% pca

    pca=pcagramsperday



    mean_region =
compute_mu(population[1],population[2],population[3],coeffs[1],coeffs[
2],coeffs[3],prop_abs[1],prop_abs[2],prop_abs[3],prop_form[1],prop_for
m[2],prop_form[3],pca)

    mean_male[i] = mean_region[1]

}



sd_male = 1.171*mean_male



k_male = mean_male^2/sd_male^2

theta_male = sd_male^2/mean_male



nmale = length (k_male)     ##### number of different distributions
corresponding to male populations







################### Calculation of AAF for male population
```

```
########################

################### Calculation of AAF for male population
########################

################### Calculation of AAF for male population
########################


#### male population ####

AAFinfolistmale = data.frame(matrix(NA,
nrow=nmale*length(relativeriskmale), ncol=5))

names(AAFinfolistmale) =
c("REGION","SEX","AGE_CATEGORY","DISEASE","AAF")

system.time(

for (i in 1:nmale) ### Group Loop

{



    ######## normalising gamma function ##############

    #### un-normalised gamma function

    prevalencegamma = function(x)
{dgamma(x,shape=k_male[i],scale=theta_male[i])}

    ncgamma1 = integrate(prevalencegamma, lower = 0, upper = 150)    #
str(ncgamma1) tells you it's a list of 5 and the value can be accessed
via ncgamma1$value



    #### normalised gamma function. This takes into account the
proportion of drinkers compared to the total number of individuals in
our population ####

    prevgamma=function(x) {(1-(prop_abs_male[i] +
prop_form_male[i]))*(1/ncgamma1$value)*dgamma(x,shape=k_male[i],scale=
theta_male[i])}
```

```
  #### filling the data frame with the group specific information

  n_diseasemale = length(relativeriskmale)

  AAFinfolistmale$REGION[(((i-1)*n_diseasemale)+1):(i*n_diseasemale)]
<- inputmage$REGION[i]

  AAFinfolistmale$SEX[(((i-1)*n_diseasemale)+1):(i*n_diseasemale)] <-
inputmage$SEX[i]

  AAFinfolistmale$AGE_CATEGORY[(((i-
1)*n_diseasemale)+1):(i*n_diseasemale)] <- inputmage$AGE_CATEGORY[i]



    #### Calculation of the AAFs for all injury categories ####



        for (p in 1:n_diseasemale)  ### injury Loop

        {

      integral = function (x)
{prevgamma(x)*(((relativeriskmale[[p]][[2]](x,relativeriskmale[[p]][[3
]][1],relativeriskmale[[p]][[3]][2],relativeriskmale[[p]][[3]][3],rela
tiveriskmale[[p]][[3]][4]))-1)) +1 )}

      integralgamma = integrate(integral, lower = 0, upper = 150)

            AAFgammamale=(prop_abs_male[i] +
prop_form_male[i]*exp(relativeriskmale[[p]][[5]]) +
integralgamma$value - 1)/(prop_abs_male[i] +
prop_form_male[i]*exp(relativeriskmale[[p]][[5]]) +
integralgamma$value)



      ##### creating a list of all information, the list contains:
####



        ##### filling the dataframe with the disease/injury specific
information
```

```
        AAFinfolistmale$DISEASE[((i-1)*n_diseasemale+p)] <-
relativeriskmale[[p]][[1]]

            AAFinfolistmale$AAF[((i-1)*n_diseasemale+p)] <-
AAFgammamale


        }### loop p, representing the injuries/diseases



}###loop i, representing the different groups

) ### HF: end of system.time


##### Printing output and writing to file #####

##### Printing output and writing to file #####


print(AAFinfolistmale)

write.table(AAFinfolistmale, file="AAFmale-AGEGROUP1.txt")



################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞ COMPUTING THE CONFIDENCE INTERVALS
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞#################

################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞ COMPUTING THE CONFIDENCE INTERVALS
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞#################

################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞ COMPUTING THE CONFIDENCE INTERVALS
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞#################

################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞ COMPUTING THE CONFIDENCE INTERVALS
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞#################
```

```
###### Further improvement step: instead of computing a certain number
of points we split

###### the code in m sets of nnn points


### m is the number of different sets of nnn points that will be
computed

m=150


filenames=read.delim("filenames.txt", header=F,
colClasses=c("character"))


for (t in 1:m)


{


################ The idea behind this section is the following: having
realised how       ################

################ difficult the expressions for the variances of our
functions quickly    ################

################ become, we will use the AAF function coded previously
and apply it to    ################

################ a set of randomly generated parameters. As we know
the distributions of  ################

################ our *first level* parameters, we can generate 10'000
points and apply    ################

################ the whole algorithm to this set of parameters the
evaluate the variance  ################

################ of the AAFs at the end of it.
             ################
```

```
################ This has to be done in 2 steps. We first need to
generate all the     ################

################ parameters needed for the second one as some of them
aren't straight  ################

################ forward and have to be simulated too.
            ################


#### defining number of simulations, usually 10'000

nnn=1000


####∞∞∞∞∞ GENERATING PARAMETERS FOR MALE POPULATION ∞∞∞∞∞####

####∞∞∞∞∞ GENERATING PARAMETERS FOR MALE POPULATION ∞∞∞∞∞####

####∞∞∞∞∞ GENERATING PARAMETERS FOR MALE POPULATION ∞∞∞∞∞####


#### generating proportions of abstainers, former drinkers and
drinkers. This is a binomial distribution considering a survey with
1'000 data points per sex-age group.

#### the output matrix is ordered in the following way: each line
represents the 10'000 generated parameters for one group.

#### in order to compute the mean values we need the prop_abstainers
for each region. To avoid 2 calculations these are combined together



prop_abs_listmale = NULL

prop_form_listmale = NULL

prop_drk_listmale = NULL

mean_male_list=NULL
```

```
mean_male_list_region=NULL


system.time(
for (i in 1:length(regions_male))
{
    #### extracting the required information for each region ####
    info_male_regionage =
inputmage[inputmage$REGION==regions_male[i],]
    info_male_region = inputm[inputm$REGION==regions_male[i],]


    #### calculating the mean values for each group
    population = info_male_region$POPULATION
    coeffs=info_male_region$RELATIVE_COEFFICIENT
    pcalitresperyear=info_male_region$PCA[1]
    var_pca=info_male_region$VAR_PCA[1]


    #### generating random values for pca
    pca_listlitresperyear=rnorm(nnn, pcalitresperyear, sqrt(var_pca))
    #### the following is to avoid having negative numbers as PCAs due
to the random distribution.


    for (h in 1:length(pca_listlitresperyear))
    {
        if (pca_listlitresperyear[h]<=0)
        {
```

```
            pca_listlitresperyear[h]=0.001

        }


    }

    pca_list=0.8*pca_listlitresperyear*1000*0.789/365




    mean_male_list_region=prop_abs_listmale_region=prop_form_listmale_
region=NULL ### obviously, this has to be reinitialised at each region
iteration

    for (k in 1:length(info_male_region$AGE_CATEGORY)) #### this
should usually be from 1 to 3

    {


    pabs=rnorm(nnn,info_male_region$LIFETIME_ABSTAINERS[k],sqrt(info_m
ale_region$LIFETIME_ABSTAINERS[k]*(1-
info_male_region$LIFETIME_ABSTAINERS[k])/1000))

        pform=rnorm(nnn,info_male_region$FORMER_DRINKERS[k],
sqrt(info_male_region$FORMER_DRINKERS[k]*(1-
info_male_region$FORMER_DRINKERS[k])/1000))



        #### It may happen that the generated proportions of
abstainers and former drinkers will be larger than 1. In this case, we
will set the propoprtion ####

        #### of drinkers to 0 and scale the other 2 down.
                                                                  ####



        for (h in 1:nnn)

        {
```

```
            if (pabs[h]+pform[h]>1)
            {
                sum=pabs[h]+pform[h]
                pabs[h]=pabs[h]/sum
                pform[h]=pform[h]/sum
            }
        }

        prop_abs_listmale_region=rbind(prop_abs_listmale_region, pabs)
### this is a 3xnnn matrix used for the computation of the mu values
below. These values are also stored in a greater matrix for further
use in prop_abs_listmale
        prop_form_listmale_region=rbind(prop_form_listmale_region,
pform)
    }

    prop_abs_listmale=rbind(prop_abs_listmale,
prop_abs_listmale_region[1,])
    prop_form_listmale=rbind(prop_form_listmale,
prop_form_listmale_region[1,])

        for (j in 1:nnn)
        {
            prop_abs=prop_abs_listmale_region[,j]
            prop_form = prop_form_listmale_region[,j]
            mean_region =
compute_mu(population[1],population[2],population[3],coeffs[1],coeffs[
```

```
2],coeffs[3],prop_abs[1],prop_abs[2],prop_abs[3],prop_form[1],prop_for
m[2],prop_form[3],pca_list[j])


    mean_male_list_region=cbind(mean_male_list_region,mean_region) ###
this generates a 3xnnn matrix containing the mu values for each
region, they will be placed in a bigger matrix mean_male_list

        }


    mean_male_list = rbind(mean_male_list, mean_male_list_region[1,])



}

) ### HF: system.time end


##### Generating the values for k and theta #####

ngroups = length (inputmage$AGE_CATEGORY)

k_list_male=NULL

for (i in 1:ngroups)

{

  k_list_male_group = rnorm (nnn, (1/1.171)^2,
sqrt(4*0.013^2/1.171^6))   # HF: 1 x nnn

  k_list_male=rbind(k_list_male,k_list_male_group)                  #
HF: ngroups x nnn

}


theta_list_male=NULL


for (i in 1:ngroups)
```

```
{

  theta_list_male_group = mean_male_list[i,]/k_list_male[i,]

  theta_list_male = rbind(theta_list_male, theta_list_male_group)

}


####### Generating the Betas for the Relative Risk Functions
##########


library("MASS")


#### male population ####

ndiseasesmale = length (relativeriskmale)

betacoefficients_male=list(rep(0,ndiseasesmale))

for (i in 1:ndiseasesmale)


{

betas = relativeriskmale[[i]][[3]]

covariance = relativeriskmale[[i]][[4]]

generatedbetas_disease = mvrnorm(nnn, betas, covariance)

betacoefficients_male[[i]]=t(generatedbetas_disease)  #### we
transpose only in order to have the values for each beta in a line and
not a column

}


RRform_male_list=NULL

for (i in 1:ndiseasesmale)
```

```
{

    lnRRform=rnorm(nnn,relativeriskmale[[i]][[5]],sqrt(relativeriskmal
e[[i]][[6]]))

    RRform_male_list_disease = exp(lnRRform)

    RRform_male_list=rbind(RRform_male_list,RRform_male_list_disease)
### this creates a vector ndiseasesmale X nnn -> each line corresponds
to an injury and contains nnn occurences



}






##################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞ DEFINING THE AAF FUNCTION THAT
WILL ITERATE THROUGH ALL THE POINTS
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞########################

##################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞ DEFINING THE AAF FUNCTION THAT
WILL ITERATE THROUGH ALL THE POINTS
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞########################

##################∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞ DEFINING THE AAF FUNCTION THAT
WILL ITERATE THROUGH ALL THE POINTS
∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞∞########################




#### for reasons of simplicity the code above to calculate the
expected values of the AAF will not be implemented as a function. ####

#### however, this could be a further improvement of the code if
there's more time                                  ####
```

```
#### male population ####


#variances is the final table with all the AAFs and their confidence
intervals

variances = data.frame(matrix(NA,
nrow=length(regions_male)*length(agecategories_male)*length(relativeri
skmale), ncol=6))

names(variances) =
c("REGION","SEX","AGE_CATEGORY","INJURY","AAF","VARIANCE")


system.time(


for (i in 1:nmale) ### Group Loop (sex/age/region)

{


##### improved code: for each iteration (of each region) we use a new
table which is deleted at the end of the operation thus limiting the
space used for the computation

AAFinfolistmalelist = data.frame(matrix(NA,
nrow=nnn*length(relativeriskmale), ncol=5))

names(AAFinfolistmalelist) =
c("REGION","SEX","AGE_CATEGORY","INJURY","AAF")

niterations_male=length(relativeriskmale)*nnn


  #### filling the data frame with the group specific information

  n_diseasemale = length(relativeriskmale)

  first_entry = 1
```

```
  last_entry =  n_diseasemale*nnn

  AAFinfolistmalelist$REGION[first_entry:last_entry] <-
inputmage$REGION[i]

  AAFinfolistmalelist$SEX[first_entry:last_entry] <- inputmage$SEX[i]

  AAFinfolistmalelist$AGE_CATEGORY[first_entry:last_entry] <-
inputmage$AGE_CATEGORY[i]



    for (z in 1:nnn)       ## iterations loop (calculates nnn AAFs for
each disease)

    {

        ######## normalising gamma function ##############

        #### un-normalised gamma function

        prevalencegamma = function(x)
{dgamma(x,shape=k_list_male[i,z],scale=theta_list_male[i,z])}

        ncgamma1 = integrate(prevalencegamma, lower = 0, upper =
150,stop.on.error=FALSE)

        if(ncgamma1$message=="OK")

        {



            #### normalised gamma function. This takes into account
the proportion of drinkers compared to the total number of individuals
in our population ####

            prevgamma=function(x) {(1-(prop_abs_listmale[i,z] +
prop_form_listmale[i,z]))*(1/ncgamma1$value)*dgamma(x,shape=k_list_mal
e[i,z],scale=theta_list_male[i,z])}



            #### Calculation of the AAFs for all disease/injury
categories ####
```

```
                for (p in 1:length(relativeriskmale))  ### Disease
Loop

                {



        integral = function (x)
{prevgamma(x)*(relativeriskmale[[p]][[2]](x,betacoefficients_male[[p]]
[1,z],betacoefficients_male[[p]][2,z],betacoefficients_male[[p]][3,z],
betacoefficients_male[[p]][4,z]))}

          integralgamma = integrate(integral, lower = 0, upper =
150,stop.on.error=FALSE)

                    if (integralgamma$message=="OK")

                    {


    AAFgammamale=(as.numeric(prop_abs_listmale[i,z]) +
as.numeric(prop_form_listmale[i,z])*as.numeric(RRform_male_list[p,z])
+ integralgamma$value - 1)/(as.numeric(prop_abs_listmale[i,z]) +
as.numeric(prop_form_listmale[i,z])*as.numeric(RRform_male_list[p,z])
+ integralgamma$value)

                    }

                    else

                    {

                        AAFgammamale=0

                    }




          ##### filling the dataframe with the disease specific
information

          AAFinfolistmalelist$DISEASE[((z-1)*n_diseasemale+p)] <-
relativeriskmale[[p]][[1]]

          AAFinfolistmalelist$AAF[((z-1)*n_diseasemale+p)] <-
```

```
AAFgammamale

          niterations_male=niterations_male-1

          print(c("#of iterations left for male population:
",niterations_male,"for region", i, "from set #",t))



                }### loop p, representing the injuries

        }

        else

        {

            ### in case the first integral didn't work (prevalence
assumed to be zero everywhere) we need to fill the corresponding AAF
line with zeros

            for (p in 1:length(relativeriskmale))  ### Disease Loop

            {



            AAFgammamale=0

            AAFinfolistmalelist$DISEASE[((z-1)*n_diseasemale+p)] <-
relativeriskmale[[p]][[1]]

            AAFinfolistmalelist$AAF[((z-1)*n_diseasemale+p)] <-
AAFgammamale

            niterations_male=niterations_male-1

        print(c("#of iterations left for male population:
",niterations_male,"for region",i,"from set #",t))







            }### loop p in the case where the first integral didn't
work
```

```
        }## end of is/else statement for the first integral


    } ###loop z, representing the different simulations of each group


    #### Now we evaluate the CI for the age/sex/region under test and
store the value in the final table

    write.table(AAFinfolistmalelist, file=toString(c("AAFoutputs for
", regions_male[i], "of set ", t)) ,sep=",")



    AAFlist_region=AAFinfolistmalelist[AAFinfolistmalelist$REGION==toS
tring(regions_male[i]),]


    for (j in 1:length(agecategories_male))

    {


    AAFlist_regionage=AAFlist_region[AAFlist_region$AGE_CATEGORY==agec
ategories_male[j],]


        for (k in 1:length(relativeriskmale))

        {


    AAFlist_regionagedisease=AAFlist_regionage[AAFlist_regionage$DISEA
SE==toString(relativeriskmale[[k]][1]),]


    varregagedisease=var(as.numeric(AAFlist_regionagedisease$AAF))
```

```
            ### finding the AAF corresponding to this CI in the
previously obtained matrix


    AAFreg=AAFinfolistmale[AAFinfolistmale[,1]==toString(regions_male[
i]),]


    AAFregage=AAFreg[AAFreg[,3]==as.numeric(agecategories_male[j]),]


    AAFregagedis=AAFregage[AAFregage[,4]==toString(relativeriskmale[[k
]][1]),]

            AAF=AAFregagedis$AAF



#### creating the entry for the final list

      entry <- ((i-
1)*length(agecategories_male)*length(relativeriskmale) + (j-
1)*length(relativeriskmale) + k)

      variances$REGION[entry] <-  regions_male[i]

      variances$SEX[entry] <-  AAFlist_regionagedisease$SEX[1]

      variances$AGE_CATEGORY[entry] <-  agecategories_male[j]

      variances$INJURY[entry] <-  toString(relativeriskmale[[k]][1])

      variances$AAF[entry] <-  AAF

      variances[entry,6] <- varregagedisease

        }


    }



}###loop i, representing the different groups
```

```
) ### HF: system.time end


print(variances)

write.table(variances, file=filenames[t,1],sep=",")

} ### t Loop for the different files
```

Copyright Acknowledgements