An Evaluation of the Alcohol Total Consumption Model and Development of the International Model of Alcohol Harms and Policies

by

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B.Sc. Applied Mathematics, University of Guelph, 2007
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A Dissertation Submitted in Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY

in Social Dimensions of Health Program

University of Victoria

Supervisory Committee

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Abstract

Alcohol is the most widely used psychoactive drug on earth and continues to be responsible for a substantial burden of death and disability. Mitigating these harms is an important focus of any healthful society. Population-level alcohol policy strategies may be employed to decrease these harms and improve population health. To assist towards these goals, this dissertation has two research objectives relating to the estimation and mitigation of alcohol harms: (1) to complete a series of studies regarding the Alcohol Total Consumption Model (TCM) and (2) to specify and test a novel alcohol health harms estimator and alcohol policy scenario modeler, the International Model of Alcohol Harms and Policies (InterMAHP).

The TCM is an important theory in alcohol studies and connects alcohol policies, *per capita* alcohol consumption and alcohol-attributable (AA) harms in a unified social theory. In brief, policies are expected to reflect on population-level consumption, which in turn is the most important predictor of alcohol harms. The TCM theorizes that change should flow directionally through the model – a policy expected to decrease consumption would be predicted to decrease alcohol harms. This theory has been critical towards informing alcohol control policies in the past five decades. In this dissertation, a series of studies were conducted to test the assumptions of the TCM, to test their continued viability. Study A is a comprehensive systematic review and series of meta-analyses that established the link between alcohol policies influencing day/hours of sale and outlet density and *per capita* consumption. Study B is a primary research study that examined the direct effect of a changed alcohol policy on alcohol-related ED visits, in the context of Saskatchewan. Studies C and D establish the link between alcohol consumption and AA mortality and morbidity through mathematical specification of InterMAHP. Next, the model was applied to the exemplar of AA mortality in Canada in 2016. Last, Study E extended InterMAHP functionalities to include modeling changes in AA harms expected from potential or realized *per capita* consumption changes resulting from policy change. An application was provided in the context of Québec.

The results of this dissertation research provide some support, in a modern context, to the relationships defined in the TCM. The findings suggest that the TCM continues to be a largely appropriate conceptual model in consideration of alcohol policy-making. InterMAHP provides global alcohol researchers with a novel model towards estimating the health harms of alcohol.

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List of Acronyms, Abbreviations and Mathematical Symbols

AA	Alcohol-Attributable
AAF	Alcohol-Attributable Fraction
AC	Adenocarcinoma
ARF	Absolute Risk Function
ARG	Alcohol Research Group
ARIMA	Auto-Regressive Integrated Moving Average
BC	British Columbia
CANSIM	Canadian Socio-Economic Information Management System
CanSUED	Canadian Substance Use Exposure Database
CIHR	Canadian Institutes of Health Research
CISUR	Canadian Institute for Substance Use Research
CMA	Census Metropolitan Area
CPI	Consumer Price Index
DALY	Disability-Adjusted Life Year
Dx	Diagnosis
ECAS	European Comparative Alcohol Study
ED	Emergency Department
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorder
FP	Fractional Polynomial
FP2	Two-Term Fractional Polynomial
g	Grams
g/day	Grams Ethanol per Day
GBD	Global Burden of Disease
GSRAH	Global Status Report on Alcohol and Health
GENACIS	Gender, Alcohol and Culture: An International Study
IARC	International Agency for Research on Cancer
ICD10	International Statistical Classification of Diseases and Related Health Problems, 10^{th} Revision

IHD	Ischaemic Heart Disease
IM# / IM	InterMAHP Condition Number
InterMAHP	International Model of Alcohol Harms and Policies
IS	Ischaemic Stroke
ITS	Intervention Time Series / Interrupted Time Series
IV	Inverse Variance
HIV	Human Immunodeficiency Virus
L	Litres of Ethanol (Pure Alcohol)
MUP	Minimum Unit Price / Minimum Price per Standard Drink
MVC	Motor Vehicle Collision
PCC	*Per Capita* Consumption (of Alcohol)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PDF	Probability Density Function
RR	Relative Risk
SAQ	Société des alcools du Québec (Quebec Alcohol Corporation)
SCC	Squamous Cell Carcinoma
SD	Standard Drink
SLGA	Saskatchewan Liquor and Gaming Authority
TCM	Total Consumption Model
USCDC	United States Centers for Disease Control and Prevention
WHO	World Health Organization
μ	Mean
σ	Standard Deviation

Acknowledgements

First, sincere thanks are in order to my supervisor, Dr. Tim Stockwell. I doubt that I would have made it to this stage without your mentorship and friendship. I remember walking into CISUR in 2014, still searching for an SDH advisor, and we hit it off right away. You've involved me in all sorts of academic projects and shenanigans I did not know existed across, so far, three continents and five countries. I've played more tennis games than I care to admit and in the strangest of places on earth. It's been a wild and rewarding ride!

Thank you to my committee members, Dr. Scott Macdonald and Dr. Russ Callaghan, for their insightful comments, encouragement and all-around good-naturedness. As well as their contributions, they are both sincere and easy-going professors. Scott and I famously traded a half-smashed greenhouse for 1/4th of a cord of firewood. I got the greenhouse. Russ will live on through time immemorial for his Stockwell Christmas Party appearance as the majestic, yet critically endangered, 'Callaghan Elk.'

Thanks are due to the Canadian Institutes for Health Research, the Canadian Institute for Substance Use Research, the University of Victoria, the Social Dimensions of Health Program and Island Health, all of which provided funding during my doctoral years to keep this dissertation on the rails towards completion.

My love and thanks to Mom and Dad, Gary Sherk and Ada Sherk, for a loving and supporting upbringing. A happy childhood is the best start anyone could ask for in life and mine was certainly that. And thanks to my brother, Thomas, for adeptly making up one half of the infamous 'Brothers Sherk,' a duo responsible for much trouble through the streets of Ridgeway.

Thanks also to my 'Western Family' who supported me through seemingly limitless free dinners and glasses of scotch, despite the topic of this dissertation. This includes my parents in-law, Randy and Tracy Young, and their kids and associated life partners: new sister Leta and new brothers Taylor and Joey.

Last and most, thanks to my favourite Young-child, my wife Kailyn. Thanks for your sweet and indefatigable support throughout the extra weekends and nights spent at UVic. And special thanks for your majority role in creating our greatest joys, our son Cameron and second son on the way! Thanks for your love every step of the way. I love you.

Dedication

I dedicate this dissertation to my Gramma, Helen Sherk, a.k.a ‘Gramdawg.’

I knew my Gramma for 28 years and never heard her say a bad word about anyone. She was a lovely influence on my life, and many others. She is missed.

Chapter 1: Introduction

1.1 The Burden of Alcohol Consumption and Alcohol Harms

1.1.1 Alcohol Consumption

Alcohol is by far the most widely used psychoactive drug on earth: more than 2,300,000,000 were identified as current drinkers in 2016 (World Health Organization, 2018). Globally, alcohol consumption *per capita* has been increasing, reaching 6.4 litres ethanol (pure alcohol) per person in 2016, a 16.4% increase since 2005 (World Health Organization, 2018). Among current drinkers, the average amount of ethanol consumed daily is significant: 32.8 g or the equivalent of almost 2.5 bottles of 5% beer. Countries with greater economic wealth have higher *per capita* consumption than do lower-income countries (World Health Organization, 2018). Into the future, *per capita* consumption is projected to further increase to 6.6 litres ethanol (L) / year in 2020 and 7.0 L / year in 2025; these would represent 3.1% and 9.4% increases, respectively.

Closer to home, alcohol use is commonplace in Canada – over 80% of adult Canadians report drinking in the past year. A recent comprehensive cost of substance use study reported *per capita* consumption of over 10.0 L for each of the years 2007 to 2014 (Canadian Substance Use Costs and Harms Scientific Working Group, 2018). The prevalence and quantity of alcohol use among Canadians is far higher than the global average. Over three times as many Canadians drink alcohol as use any other category of psychoactive substance, such as tobacco, cannabis or opioids (Canadian Substance Use Costs and Harms Scientific Working Group, 2018).

1.1.2 Alcohol Harms

Alcohol is the cause of a substantial global burden of mortality and disability. In 2016, alcohol was causally responsible for approximately 3 million global deaths, representing 5.3% of all deaths in that year, as well as 132.6 million disability-adjusted life years (DALYs), representing 5.1% of all DALYs in that year (World Health Organization, 2018). Alcohol was responsible for a higher proportion (7.2%) of premature deaths occurring in those under 70. The leading categories of alcohol-caused deaths were injuries (28.7%), digestive diseases (21.3%), cardiovascular diseases (19.0%) and cancer (12.6%).

In Canada in 2014, alcohol was estimated to be responsible for 14,800 deaths and 87,900 hospital stays and to cost society more than $14.6 billion in healthcare, economic and criminal justice outlays (Canadian Substance Use Costs and Harms Scientific Working Group, 2018). Comparing alcohol to other psychoactive substances, it is clear alcohol tops the list regarding societal costs.

Alcohol is causally related to more than 200 individual health diagnoses, according to the standard WHO classification entitled the International Statistical Classification of Disease and Related Health Problems, 10th revision (World Health Organization, 2016). When grouped by disease category, there are at least seven major harm condition groupings, including cancer, digestive conditions and injuries.

1.1.3 Motivation

Globally, alcohol use is the seventh leading behavioural risk factor for both deaths and DALYs, accounting for nearly 5.0% of total age-standardized deaths (GBD 2016 Alcohol Collaborators, 2018). However, among the population aged 15 to 49, alcohol consumption was the leading risk factor for death and disability in 2016. Further, 12.2% of all male deaths in this age group were estimated to be caused by alcohol (GBD 2016 Alcohol Collaborators, 2018).

It is therefore clear that the widespread consumption of alcohol and associated health conditions are major global issues worthy of substantial research attention. Leading scholars in alcohol research have forwarded suggestions for understanding and mitigating the harms caused by alcohol consumption (Chisholm et al., 2018; Rehm & Room, 2009; World Health Organization, 2000). Commonalities emerge among these suggestions, including collecting and

reporting data on alcohol sales and consumption, establishing comparable and reliable estimates of the harms caused by alcohol and evaluating potential policy strategies for decreasing harm. Given the clear health imperative for reducing alcohol harms, attention is now given to developing the theoretical basis and conceptual framework used throughout this dissertation, beginning with important historical contributions to the current knowledge base in alcohol research.

1.2 Theories and Models Regarding the Distribution of Alcohol Consumption

1.2.1 Single Distribution Theory

Largely, members of the public conceive of a dichotomy of alcohol users when considering alcohol use: ‘normal drinkers’ and ‘alcoholics.’ Even among academics, this dichotomous view of drinking was pervasive until the 1960s (Skog, 2006). However, it was during this same decade that French demographer Sully Ledermann initiated empirical research regarding the distribution of alcohol consumption along a continuous consumption scale in various countries and contexts. Based on his analyses, Ledermann made several novel hypotheses: first, that the distribution of alcohol consumption in a population of drinkers should follow a lognormal distribution and, second, that the shape of this distribution should be uniquely defined by average *per capita* consumption (Ledermann, 1956; Skog, 2006).

This hypothesis had several important conclusions, not least that similar societies with identical average *per capita* consumption would have a similar distribution of drinkers, by consumption level. This theory came to be known as ‘Single Distribution Theory,’ because societies sharing the same average consumption would, to a good approximation, share a single distribution (Ledermann, 1956). Ledermann proposed that this distribution would exhibit a lognormal shape due to the prevailing notion of the time that alcohol would follow a ‘social contagion’ effect and that human social phenomena followed multiplicative, and not additive, models (Skog, 2006). Single Distribution Theory was fiercely contested by academics due in large part to implicit conclusions suggested by its mathematical basis. In particular, if the theory were to hold, then the number of ‘heavy drinkers’, at the time termed ‘alcoholics’, is predicted uniquely by average societal consumption. Therefore, a direct conclusion of Single Distribution Theory is that alcoholism should be interpreted, at least in large part, as a societal issue and not

an individual weakness. The debate continued into the 1980s, when the following major theoretical article was published.

1.2.2 The Collectivity of Drinking Cultures

In 1985, Ole-Jørgen Skog released a landmark article regarding the Collectivity of Drinking Cultures, using Ledermann's theories as the foundation for a social-based theory regarding population consumption distributions (Skog, 1985). Skog posited that any theory regarding these distributions should be based on hypotheses about the factors influencing human drinking behaviours, rather than attempting to infer a data-driven mathematical distribution function.

Therefore, Skog developed what he called the theory of the Collectivity of Drinking Cultures. This idea was based on the observation that much of the drinking that occurs in a population occurs in groups and that the behaviour of an individual within the group is strongly influenced by group behaviour (Skog, 1985). Skog adopted tenets of Ledermann's original theory, stating that new factors introduced to act on populations would project onto individuals in a proportional way (e.g. a person who drinks 10 litres ethanol (L) per year would experience an increase of two L per year in the same way a person who consumes 5 L per year would perceive an increase of one L per year). Mathematically, this infers that factors acting upon individual behaviour follow a multiplicative rule; this multiplicity ensures a highly skewed distribution, such as the lognormal family of curves (Skog, 1985).

The Collectivity of Drinking Cultures drew largely on sociological theories of the day; in particular, the theory conceptualized that a drinking population consisted of an 'enormous social network', i.e. a system of actors tied together by different types of social relations which tend to produce coordination of their behaviour [(Skog, 1985), pg. 88]. Each individual in the network was connected indirectly, through one or more social ties, to nearly every other member of the society. These ties transmit social impulses between individuals and in this way, new impulses acting on individual members of society are broadcast through the network to reach multitudes of others (Skog, 1985).

Skog also took issue, as Ledermann had, with the 'drinker type' dichotomy, i.e. that some drinkers are inherently alcoholics and all others normal drinkers. His analysis of the skewedness of different population distributions led him to conclude that the skewedness of normal drinkers would have to overlap significantly with the distribution of alcoholics and hence there would be

no natural delineation between the two groups (Skog, 1985). Skog contended that these types of skewed distributions are common when studying the social sciences since human behaviour tends to follow the law of multiplicative effects. Skog's new theory presented the following corollaries, which continue to have high importance in alcohol research today (Skog, 1985):

(1) That the skewedness of the distribution of alcohol consumption is expected due to the multiplicative effects of human behaviour;
(2) That heavy drinkers (or "alcoholics") are responsible for little of this skewedness and that it is therefore more correct to conceive of alcoholism (or alcohol dependence) as an *effect* of this skewedness and not as its *cause*, and;
(3) That social influences between individual drinkers allow us to conceive of human populations as a collective when it comes to drinking behaviour and therefore that the entire society should move up and down the distribution of consumption in a relatively predictable way.

It is difficult to overstate the importance of these three conclusions to the development of the field of alcohol research; in fact, they continue to be central to many of the philosophies employed in alcohol public policy today.

This foundational work is summarized in the following statement [(Skog, 1985), pg. 91]:

> 'In conclusion, the data confirm that a collective drinking culture exists. Changes in *per capita* consumption would typically be expected to imply parallel changes in drinking habits among drinkers at all consumption levels. Therefore a drinking culture should not be conceived as an aggregate of independent individuals, but rather as a highly organized system of interdependent actors. The descriptive parameter 'mean consumption' therefore has a socio-cultural content which goes far beyond its technical content – an arithmetic sum of individual consumption levels.'

1.2.3 A Modern Single Distribution Theory: The Gamma Distribution

In a general sense, the main idea forwarded by Ledermann (1956) and Skog (1985) – this being that a population will move up and down the distribution of consumption in concert with average consumption - gained considerable acceptance and has been influential in alcohol policy debates to this day (Babor, Barbor, Caetano & Casswell, 2003; Babor et al., 2010; Gmel & Rehm, 2000).

The ways in which Skog's theory influenced alcohol policies will be discussed in the proceeding section. However, more specifically, academic challenges to the use of the lognormal distribution to approximate population consumption were continuous and ongoing (Gmel & Rehm, 2000), and even Skog himself considered other mathematical formulations for consumption curves, including the Gamma distribution (Skog, 1979; Skog, 1980).

It was widely discussed, in particular, that the skewed tail of the lognormal distribution was too fat, resulting in an unrealistically high estimation of the number of drinkers at high levels of consumption (Rehm et al., 2010). A series of articles were released in response in the early 2010s by Dr. Jürgen Rehm and colleagues; these articles collected consumption data from dozens of countries and contexts and aimed to evaluate a number of mathematical distributions with the goal of ascertaining the most appropriate generalized model for the distribution of alcohol consumption.

Rehm et al. (2010b) used data from the U.S.-based National Epidemiological Survey on Alcohol and Related Conditions (NESARC), a large, representative, alcohol-specific survey. The authors evaluated the fit of the lognormal, Weibull and Gamma distributions, as compared to the self-reported survey responses, by population subgroups based on gender and age group. The article concluded that fitting population consumption curves with the Gamma distribution was feasible; however, further research was suggested (Rehm et al., 2010b).

An article with key theoretical implications for this dissertation then took the above research to its conclusion. Kehoe et al. (2012) collected self-reported individual-level alcohol consumption data from 41 countries that had participated in the Gender, Alcohol and Culture: An International Study (GENACIS) and European Comparative Alcohol Study (ECAS) studies. Again, the lognormal, Weibull and Gamma distributions were tested, here against many more contexts and datasets. The authors concluded that, in a global context, the Gamma distribution was the recommended mathematical distribution, formally a probability density function (PDF), with which to model the continuous distribution of daily alcohol consumption, by population subgroups based on gender and age group (Kehoe et al., 2012).

The article contributed another foundational piece of information by studying the relationship between the mean (μ) and the standard deviation (σ) resulting from the Gamma distribution. By collecting 851 datasets from 66 countries, the authors report completing a robust analysis, which concluded that σ was highly dependent on μ, by gender. In fact, a one unit

increase in mean alcohol consumption was associated with a 1.258 unit increase in σ for women and a 1.171 unit increase in σ for men. As the Gamma distribution is uniquely defined by the above parameters μ and σ, and as σ can be collapsed to an expression based on μ, the normally two-parameter Gamma *can be expressed using only one parameter* (Kehoe et al., 2012; Sherk et al., 2017b). Notice this becomes a modern definition and functional application of Ledermann's original Single Distribution Theory, wherein the entire distribution of alcohol consumption can be defined using only mean consumption! This conclusion has provided broad implications for the estimation of alcohol harms and provides an important foundational finding for this dissertation.

1.2.4 The Distribution of Alcohol Consumption: Towards a Conceptual Framework

This 'modern Single Distribution Theory', employing the Gamma distribution for modeling consumption curves, has been used widely in alcohol harms estimation globally (Canadian Substance Use Costs and Harms Scientific Working Group, 2018; GBD 2016 Alcohol Collaborators, 2018; Lensvelt et al., 2018; World Health Organization, 2014, 2018). This section has discussed the historical development of this important technique, beginning with Ledermann's definition of the lognormal-based Single Distribution Theory (Ledermann, 1956), continuing with debates regarding Skog's Collectivity of Drinking Cultures (Skog, 1985) and concluding with the Gamma distribution technique itself.

It is noted that the data used to predict these consumption distributions were invariably self-reported drinking data. It is well-known that measures of self-reported consumption are significantly under-reported as compared to official sales or tax receipts measures (Stockwell, Zhao & Macdonald, 2014); however, note that these discerned distributions are concerned with the *shape* of the resulting predictive distributions and not the total alcohol consumed. Therefore, provided that under-reporting is proportional to average consumption, distribution shape measures would still be expected to be valid, e.g. De Lint (1976).

It is nearly certain that this Gamma distribution-based modeling technique will eventually be displaced by a more precise method for modeling population consumption curves: this is the nature of scientific progress and we should not shy away from improving existing techniques. However, in the present day, and founded on the theoretical bases presented above, this single-parameter Gamma distribution is the most advanced and widely-used methodology and so will

be used throughout this dissertation for modeling the continuous prevalence distribution of average daily alcohol consumption.

1.3 Alcohol Policy Responses to Consumption Theories

1.3.1 Influence of Single Distribution Theory: A Focus on Total Consumption

Before Single Distribution Theory, alcohol policies were largely directed at 'alcoholics', as the pervasive viewpoint was the dichotomy between heavy and more moderate alcohol users (Skog, 2006). It had been assumed that the most effective way to reduce societal alcohol harms was to provide individual treatment to heavy users. However, Single Distribution Theory suggested that an effective pathway towards reducing population-level alcohol harms would be instead to focus on the reduction of *per capita* consumption, thereby moving the entire population down the consumption spectrum in concert (Ledermann, 1956; Skog, 2006). This would have two simultaneous effects:

(1) The number of heavy users, and therefore the harm this group experiences, would be reduced, and;
(2) The remaining population of non-heavy drinkers would be exposed to less alcohol, thereby likely decreasing the harms in this group as well.

In response, leading academics in alcohol research began conceptualizing alcohol policy approaches that would target population-level, as opposed to individual-level, consumption. These broad, societal-level policies would take aim at the total consumption in society.

1.3.2 Alcohol Control Policies in Public Health Perspective

Building on Single Distribution Theory, a landmark book entitled *Alcohol Control Policies in Public Health Perspective*, known as the purple book due to its distinctive jacket colour, was published by Kettil Bruun and colleagues (Bruun et al., 1975). This book likely represents the most influential work in alcohol policy research. Bruun et al. (1975) began by drawing a decisive link between heavy drinking and various types of morbidity and mortality. Next, they concurred with Skog that 'the total consumption of alcohol seems to be distributed in a population in a

manner that is fairly stable from country to country [Bruun et al. (1975), p. 44];' lending further support for Single Distribution Theory.

These arguments are then used to formulate the 'total consumption approach' to alcohol control policies (Bruun et al., 1975). The authors report that in the decades before the purple book was published, public polices in regards to alcohol harms had focused on: (1) education with the goal of persuading the public not to engage in heavy drinking and (2) the identification, treatment and rehabilitation of heavy drinkers (Bruun et al., 1975). These policies had the effect of emphasizing a drinking dichotomy (alcoholics vs. normal drinkers) which the authors believed did not exist (as shown by single distribution theory). The authors implored public policymakers to employ a 'total consumption approach' to alcohol policy by restricting the availability of alcohol through alcohol control policies in order to reduce total societal consumption. They discussed different policies that could limit availability such as age limits, outlet density, hours of sale, alcohol content, beverage type, pricing and taxation. The total consumption approach was to target the overall consumption in a population, instead of targeting high volume drinkers.

This book was, and continues to be, hugely influential and refocused alcohol public policy efforts towards the total consumption approach to mitigating alcohol harms. A further important book then formalized and extended particular aspects of this approach.

1.3.3 Alcohol: No Ordinary Commodity

Scientific advances in the understanding, evaluation and sophistication of effective alcohol policy strategies in the three decades after the publication of *Alcohol Control Policies* were presented in *Alcohol: No Ordinary Commodity* (Babor et al., 2003) and revised in a 2nd edition (Babor et al., 2010).

Seven broad areas of alcohol policy were defined and evaluated: (1) taxes and price controls, (2) regulating physical availability, such as days and hours of sale and outlet density, (3) modifying the drinking context, (4) drunk driving prevention and countermeasures, (5) education strategies, (6) restrictions on advertising and marketing and (7) treatment and early intervention services (Babor et al., 2010). A comparison of this list to that presented in Bruun et al. (1975) shows that the modern list is far broader and includes a larger number of potentially effective alcohol policies. For example, four of the five specific policies listed in *Alcohol Control*

Policies: age limits, outlet density, hours of sale, alcohol content and beverage type would collapse into the physical availability policy area of this more recent list. The modern list therefore presents five additional areas of policy for consideration.

A further advance in *No Ordinary Commodity* was a comprehensive policy rating rubric, including dimensions regarding effectiveness, breadth of research support and amount of cross-national testing. Each of the seven broad areas above was divided into between three and eight specific policies, for a total of 42 policies. For example, pricing and taxation was divided into alcohol taxes, minimum price, bans on discounts and promotions, differential pricing by beverage type and special price on alcopops and other youth-oriented beverages. Each of these dimensions of pricing and taxation was then evaluated against the rubric (Babor et al., 2010). This book and the resulting policy efficacy ratings have been influential in the field.

1.3.4 Alcohol Policy Responses: Towards a Conceptual Framework

The theories regarding the population distribution of consumption discussed previously led influential thinkers in alcohol researchers to devote considerable thought to the definition of alcohol policies that would take advantage of this new scientific knowledge. Through these policy-focused developments of the 1970s (*Alcohol Control Policies*) through to the 1990s (Edwards, 1994, 1997) and early 2000s (*No Ordinary Commodity*), a holistic theory including both the policy to consumption and consumption to harm pieces of the puzzle, as well as knowledge regarding changes in that consumption, could now be specified, as will be described next.

1.4 Conceptual Framework of Dissertation

1.4.1 What is the Alcohol Total Consumption Model?

This holistic theory, including both the consumption to harm and policy to consumption components, is the alcohol 'total consumption model' (TCM), a unified theory that combined consumption theories and alcohol policy considerations. The basic structure of the TCM was defined in *Alcohol Control Policies* as:

> '…that changes in the overall consumption of alcoholic beverages have a bearing on the health of the people in any society. Alcohol control measures

> [policies] can be used to limit consumption: thus, control of alcohol availability becomes a public health issue' [(Bruun et al., 1975), p.90].

As this was one of the first, if not the first, definition of the TCM, it is a good beginning with several needed additions. First, it should have been made clear in the definition that decreased consumption should be expected to lead to decreased harms. However, it is reasonable to assume from the remaining content in Bruun et al. (1975) that the authors find this an implicit truth. Next, 'control of alcohol availability' defines too narrow a set of alcohol policies. Here the authors refer to economic and physical availability, but arguably should instead define any 'alcohol control policies' which would be expected to decrease *per capita* consumption, including for example broad-based education campaigns regarding the link between alcohol and cancer.

A more recent definition of the TCM was given by Sulkunen and Warsell (2012):

> 'It holds the view that the total consumption of alcohol determines the amount of alcohol-related problems in any population. Consequently, the [total] consumption level should be a key target of preventive alcohol policy and its measures – the … [total consumption] … should be a key indicator of policy success.' [p.217].

Again, we are led to assume the authors implicitly mean to state that higher consumption would lead to higher rates of harm and vice versa. Otherwise, Sulkunen and Warsell (2012) provide a clear and concise definition of the TCM with the added piece of total consumption being a key indicator of success in alcohol policymaking.

In order to make explicit the components of the TCM which are to be tested in the proceeding content chapters, the following subsection will define and depict the TCM as is to be used for the remainder of this dissertation.

1.4.2 Dissertation Framework: The Alcohol Total Consumption Model

It is necessary to explicitly define the TCM, as it will be the investigative lens used throughout this dissertation. The content chapters describing Studies A through E will set out either to test component relationships contained within the theory or to create a flexible model that can be subsequently used for this testing. Several conceptual underpinnings are discussed before the theory is defined. First, as is any theory in

alcohol research, the TCM is not a statement of fact, but a hypothesis of potential truth, which should be comprehensively tested. As alcohol research is not a discovery science and does not uncover universal truths, e.g. as physics discovers the speed of light, the TCM as defined here can never be 'proven,' but it can be considered, tested and potentially found to hold most or nearly all of the time in a variety of different contexts and populations. If it is found to largely hold in many contexts, then the scientific community may generally accept its hypotheses and implications, regardless of the inability to truly prove a social theory.

Next, the TCM is a population-level, as opposed to individual-level, theory: any individual may of course instantaneously decide to become a teetotaler, or to quadruple their drinking, regardless of the social, cultural or policy environments. The TCM concerns itself with population averages and therefore avoids the inexact science of predicting individual behaviour.

Last, a discussion of the terms 'total' versus 'average' consumption is provided. The TCM, as will be defined here, is more interested in average (*per capita*) consumption. That is, if a population of drinkers were twice as large as another, it would of course need to consume twice the ethanol to be expected to experience approximately the same consumption distribution. At the same time, this single population is evolving temporally by increasing or decreasing the number of drinkers included: if total ethanol consumed remained the same, but the population increased, average consumption would decrease accordingly. In both of these ways, a better nomenclature would have been provided by the name 'average consumption model' or 'average consumption approach.' However, due to the historical significance and importance of the TCM, the terminology 'total' will be maintained. A last potential pitfall of using 'total' above the more appropriate 'average' is this: the sole way of conceptualizing the TCM so that the terms total consumption and average consumption are identical is to freeze a moment in time and consider instantaneous changes occurring along the causal pathway. The fear is that this focus on instantaneous changes may bias policymaking towards fast-acting policies, such as pricing and hours of sale, above more sluggish policies such as broad-based education campaigns that may take years or even decades to influence behaviour in any

meaningful way. This is not to say that policies regarding pricing and hours of sale are not effective policies, only that they should be implemented as a component of an effective policy 'basket' that includes both fast- and slow-acting measures.

Figure I-1 defines the TCM used throughout this dissertation and the corresponding relationships along the policy to consumption to harm causal pathway. In its most distilled state and for a population of drinkers, alcohol policies will influence total alcohol consumption, which in turn will reflect onto the alcohol-caused harms experienced by the population. Directionality of change is a further component: if alcohol policies are enacted or modified in such a way as to decrease (increase) total consumption, it would be expected that alcohol harms would also decrease (increase).

The following two subsections expand on the policy to consumption and consumption to harm pathways.

1.4.2.1 Policies to Consumption

The first relationship in the TCM regards how population-level alcohol policies reflect onto population alcohol consumption. Based on the foundational theories provided by Single Distribution Theory and the Collectivity of Drinking Cultures, ideas such as Availability Theory emerged to forward policies that, when implemented, would be expected to influence total societal consumption. Next, milestone books, such as *Alcohol Control Policies* (Bruun et al., 1975), *Alcohol Policy and the Public Good* Edwards (1994) and *Alcohol: No Ordinary Commodity* (Babor et al., 2010), provided evidence regarding which policies are best employed to control this total consumption. Clearly, a *steady state* of the TCM must exist which represents the current state of alcohol policies and alcohol consumption. The current *per capita* consumption in a society comes about through the confluence of sociocultural norms, individual feelings and habits, economic factors such as household income, and the existing alcohol policies: it is what is occurring in the present day. Considering directional changes and from the standpoint of public health, the TCM may be conceptualized by enacting an additional or strengthened alcohol policy (or multiple policies) which would, all else being equal, have the expected effect of decreasing total (in fact, *per capita*) societal consumption. However, the reverse relationship should also hold and may be tested: if

an alcohol policy is weakened or removed, this would be expected to result in an increase in consumption.

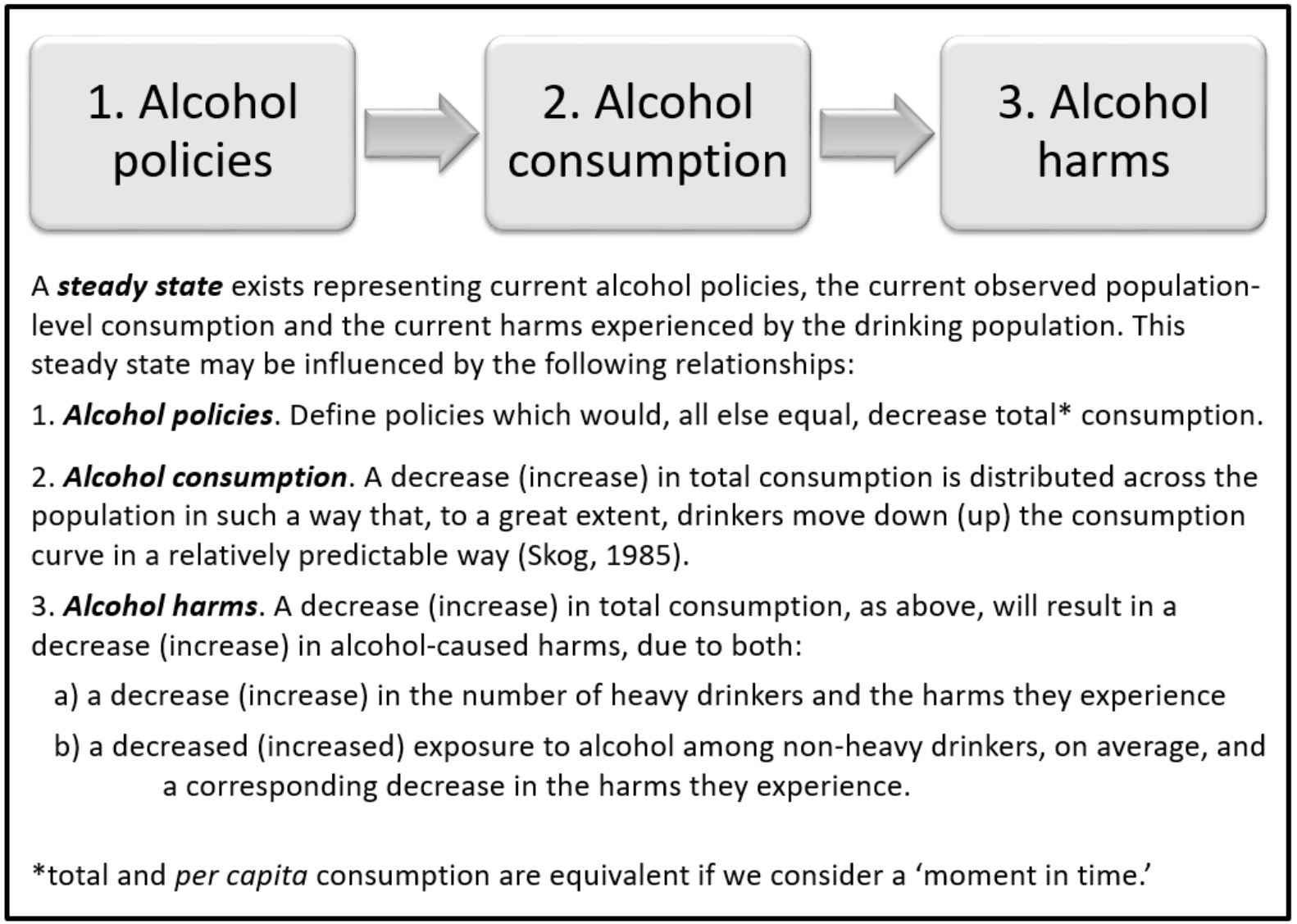
1.4.2.2 Consumption to Harms

It is clear that alcohol consumption causes health harms; in fact, drinking caused an estimated 3.4 million global deaths in 2016 (World Health Organization, 2018). Therefore, there must exist a steady state relationship between current societal alcohol consumption and population harm; this relationship defines the steady state relationship and is estimable. This dissertation will specify a model towards the estimation of this association.

Next, consider a directional relationship defined in the TCM, for example, a strengthened alcohol policy that is expected to, all else equal, decrease total consumption. An overwhelming literature, e.g. among many: Bagnardi et al. (2015), Knott, Bell and Britton (2015), Rehm et al. (2010c), Roerecke & Rehm (2010a, 2010b, 2012), Patra et al. (2010) and Zhao et al. (2017), reports a dose-response relationship between alcohol consumption and alcohol-attributable harm. The vast majority of these dose-response relationships are monotonically increasing in risk, i.e. the higher the alcohol consumption, the greater the risk of developing the health condition under study as compared to a lifetime abstainer. Therefore, under a policy expected to decrease total consumption, we largely expect a decrease in total harms, although for some important conditions, such as ischaemic heart disease (IHD) and ischaemic stroke (IS), debate exists as to the potential preventive effect of alcohol. This issue is discussed in detail in Chapters 4 and 5.

However, if a decrease in population-level consumption were to lead to an *increase* in alcohol-caused health harms, instead of the decrease expected by Figure I-1, this would represent a critical failure of the TCM. If this failure were repeated across many societies it would invalidate the TCM as a theory of interest in alcohol studies. Therefore, this dissertation considers this potentiality, as well as explicitly testing the change in consumption to change in harms relationship in Chapter 6, as described in more detail in the proceeding section.

Figure I-1: The conceptual framework and relationships defining the alcohol Total Consumption Model



1.5 Research Aims and Dissertation Overview

1.5.1 Research Aims

There are two aims of this dissertation. First, to conduct three studies testing the directional relationships of the alcohol total consumption model, to contribute to the literature regarding the TCM. Second, to develop the International Model of Alcohol Harms and Policies, a model that will establish the estimated link between current alcohol consumption and alcohol-caused health harms and further allow estimation of the potential health impact of changed alcohol policies. The goal of the content chapters was thus to:

(1) Complete a comprehensive systematic review of the literature regarding one pillar of availability theory, namely physical availability, to determine if weakened alcohol policies caused increased alcohol consumption in real-world policy situations (Study A);
(2) Conduct a primary research study examining the direct effect of a strengthened alcohol pricing policy on alcohol-related emergency departments in the Canadian province of Saskatchewan (Study B);
(3) Conceptualize and specify a novel, open access alcohol health harms estimator and alcohol policy scenario modeler, which mathematically formalizes the link between alcohol consumption and each type of alcohol-caused health harm; this is named the International Model of Alcohol Harms and Policies (InterMAHP) (Study C);
(4) Distill InterMAHP methodologies into a length which may be published as a journal article and further conduct a primary research study estimating alcohol-attributable mortality in Canada, 2016 as an exemplar of this model (Study D); and
(5) Conduct a research study estimating alcohol health harms and the potential health impact, in terms of changed alcohol-attributable mortality and hospitalizations, of the proposed implementation of a strengthened alcohol minimum unit price policy in Québec, Canada (Study E).

As the dissertation is *by publication*, these five content chapters (Chapters 2 to 6) regarding Studies A through E must be provided largely as they appear in press. Therefore, the following section motivates each study and provides context towards the overall flow of the

chapters, as this cannot be distributed into each chapter. As well, the purpose of the dissertation introduction and conclusion are discussed.

1.5.2 Dissertation Structure and Chapter Overview

Seven chapters comprise this dissertation, of which the five middle represent published or submitted manuscripts (studies A-E) in the field of alcohol research. Note that Studies A and B have been published as journal articles in the *Journal of Studies on Alcohol and Drugs* and *Drug and Alcohol Review*, respectively. Study C, due to its length, is published as an institutional publication by the Canadian Institute for Substance Use Research, Study D is currently under review in *Addiction* and Study E is complete and ready to be submitted pending presentation at an international conference. Each manuscript makes an original contribution to the literature: three of the content chapters test the relationships contained within the Total Consumption Model and two content chapters define a model for estimating the health harms of alcohol.

Chapter 1 (Introduction) motivates participation in alcohol research generally by providing a brief overview of the extent of harm caused by global and Canadian alcohol consumption. It then builds towards the Total Consumption Theory, a series of causal pathways from alcohol policies to consumption to harms, by detailing the historical development of key concepts in the field underpinning these relationships. It further describes the research aims and dissertation structure.

Chapter 2 (Study A) studied the first pathway in the TCM (alcohol policies to alcohol consumption) by conducting a systematic review studying the effect of policy changes regarding the physical availability of alcohol (days and hours of sale and outlet density) on *per capita* consumption. Quality criteria were employed to ensure estimate reliability. Novel meta-analyses estimated the effect of adding an additional day of alcohol sale on total alcohol, beer, wine and spirits consumption. The chapter's goal was to establish the link between policy and consumption and test the hypothesis that strengthened policies will decrease *per capita* consumption.

Chapter 3 (Study B) conducted a primary research study examining a significant alcohol policy strengthening natural experiment in Saskatchewan, Canada: the implementation of raised minimum alcohol prices for all beverage types on April 1st, 2010. This study set out to test the direct relationship between a certain alcohol policy and certain alcohol-caused harms. The effect

of this increased alcohol pricing on four categories of alcohol-related emergency department visits was tested using intervention time series analyses.

The first goal of Chapter 4 (Study C) was to establish the link between *per capita* alcohol consumption and alcohol-attributable (AA) mortality and morbidity (such as hospitalizations). This was accomplished by the development and mathematical specification of an open access alcohol health harms estimator, namely InterMAHP. First, this publication comprehensively specifies the Gamma distribution-based method of estimating the continuous prevalence distribution of average daily alcohol consumption, including novel specifications for binge-modified conditions such as IHD, IS and injuries. Next, the modern alcohol-attributable fraction (AAF) was derived from first principles. For each of 43 alcohol-related health conditions, e.g. colorectal cancer, liver cirrhosis and motor vehicle collisions, this guide then collates high-quality international meta-analyses informing the continuous relationship between average daily alcohol consumption and the risk of each condition, as compared to that of a lifetime abstainer. Finally, a methodology for integrating these components into estimates of alcohol-caused harm was detailed. The InterMAHP guide is open access at www.intermahp.cisur.ca. The website also provides a user interface and program software that automates the above calculations; however, the program software and interface should be considered an application of this dissertation and not a component of the dissertation itself.

A second aim of Chapter 4 (Study C) was to develop the capacity to predict the *changes* in AA death and morbidity that would be expected to occur due to *changes* in average alcohol consumption. This may be an important result for global researchers; if a research team can estimate the *per capita* consumption impact of a realized or projected alcohol policy, they can then predict the corresponding change in AA harms. Information of this type is highly sought after by policymakers towards the aim of justifying strengthened alcohol policies.

Chapter 5 (Study D) had two concurrent goals: first, to condense the specification of InterMAHP into a length suitable for journal article publication and, second, to employ InterMAHP to conduct a primary research study estimating AA mortality in Canada in 2016. Due to the first aim, there will necessarily be some repetition in this dissertation regarding the development of InterMAHP: this was unavoidable as both the comprehensive description of the model methodology (Study C) and the distilled, journal-suitable version (Study D) must be

included in the dissertation. The second aim was to estimate the extent of AA mortality, in the context of Canada.

Chapter 6 (Study E) conducted a primary research and modeling study which employed both main functionalities of the InterMAHP program: alcohol health harms estimation and alcohol policy scenario modeling. First, AA morbidity and mortality in the Canadian province of Québec were estimated using InterMAHP methodologies and software. Next, the article projected the health impact of the implementation of two proposed minimum unit pricing scenarios (CAD$1.50 and $1.75 per standard drink).

Chapter 7 (Conclusion) provides syntheses and key findings from each content chapter. Next, the overall contributions to the field are discussed in relation to the alcohol TCM and the development of InterMAHP. It then provides sections regarding implications and areas for future research in the field of alcohol research. Last, a concluding statement is provided.

Chapter 2: Alcohol Consumption and the Physical Availability of Take-Away Alcohol: Systematic Reviews and Meta-Analyses Regarding the Days and Hours of Sale and Outlet Density [Study A]

2.1 Abstract

Objective: Systematic reviews and meta-analyses were completed studying the effect of changes in the physical availability of take-away alcohol on *per capita* alcohol consumption. Previous reviews examining this topic have not focused on off-premise outlets nor completed meta-analyses.

Methods: Systematic reviews were conducted separately for policies affecting the temporal availability (days and hours of sale) and spatial availability (outlet density) of take-away alcohol. Studies were included up to December 2015. Quality criteria were used to select papers that studied the effect of changes in these policies on alcohol consumption with a focus on natural experiments. Random-effects meta-analyses were applied to produce the estimated effect of an additional day of sale on total and beverage-specific consumption.

Results*:* Separate systematic reviews identified seven studies regarding days and hours of sale and four studies regarding density. The majority of papers included in these systematic reviews, for days/hours of sale (7/7) and outlet density (3/4), concluded that restricting the physical availability of take-away alcohol reduced *per capita* alcohol consumption. Meta-analyses studying the effect of adding one additional day of sale found that this was associated with *per capita* consumption increases of 3.4% (95% CI: 2.7,4.1) for total alcohol, 5.3% (3.2,7.4) for beer, 2.6% (1.8,3.5) for wine and 2.6% (2.1,3.2) for spirits. The small number of included studies regarding hours of sale and density precluded meta-analysis.

Conclusion: This study suggests that decreasing the physical availability of take-away alcohol will decrease *per capita* consumption. As decreasing *per capita* consumption has been shown to reduce alcohol-related harm, restricting the physical availability of take-away alcohol would be expected to result in improvements to public health.

2.2 Introduction

Alcohol consumption and particular patterns of drinking are associated with myriad health and social harms including chronic disease, injury and crime (Babor et al., 2010). Despite substantial evidence of these harms, high levels of consumption persist and alcohol remains one of the leading causes of preventable death and injury worldwide (World Health Organization, 2014, 2018). An increase in *per capita* consumption will increase the level of drinking in all consumption groups, from light to heavy drinkers; this is referred to as 'Single Distribution Theory' (Ledermann, 1956; Skog, 1985). An important corollary of this theory should be a marked association between average drinking levels and alcohol-related harm rates. A large number of studies have indeed substantiated this relationship: for a review, see Norström and Ramstedt (2005). In turn, an important component of public health policy regarding alcohol is limiting *per capita* consumption (Bruun et al., 1975).

A key issue, from a public health perspective, is thus to identify policies which can be employed by governments to decrease *per capita* drinking levels. Research suggests that regulating prices, physical availability and alcohol advertising may be efficient strategies for targeting consumption (Babor et al., 2010). Comprehensive reviews, e.g. Wagenaar, Salois and Komro (2009) and Elder et al. (2010), have previously investigated the relationship between pricing and consumption. A recent Cochrane review found inconsistent evidence regarding the effect of advertising bans on consumption (Siegfried et al., 2014) and a recent systematic review found some evidence of increased alcohol consumption in youth who were exposed to advertising (Jernigan et al., 2016) . However, for reasons explained below, there remains a dearth of more precise knowledge studying the effect of changes in spatial and temporal availability on *per capita* consumption.

For policymakers to make evidence-informed decisions regarding the implementation of alcohol policies, data detailing the effects of these policies must be presented at an appropriate level of granularity. Previous reviews regarding physical availability, e.g. (Bryden, Roberts, McKee & Petticrew, 2012; Campbell et al., 2009; Hahn et al., 2010; Holmes, et al., 2014; Middleton et al., 2010; Popova, Giesbrecht, Bekmuradov & Patra, 2009), have presented highly aggregated measures of exposures and outcomes of interest. For example, within-study density measures often aggregate on-premise establishments (bars, restaurants) and off-premise outlets

(take-away stores) into a generic category containing all alcohol outlets. For public health officials to determine the best course of action, more granular information, by outlet type, is needed so that policies may be chosen to give the greatest health benefit. Further, where possible, it is useful to combine the available estimates of policy effects into a single result using meta-analysis to provide an average effect across time and space. The lack of meta-analyses may be seen as a limitation of previous availability reviews (Bryden et al., 2012; Campbell et al., 2009; Hahn et al., 2010; Holmes, et al., 2014; Middleton et al., 2010; Popova et al., 2009).

The aim of the present paper is thus to perform a series of systematic reviews and meta-analyses detailing the relationship between policies regulating the physical availability of take-away alcohol and *per capita* consumption. Take-away, or off-premise, alcohol is that sold which cannot be consumed on the premises as would be done in a bar or restaurant. Physical availability is divided into temporal availability (days and hours of sale) and spatial availability (outlet density): separate systematic reviews are completed for these two categories. The study attains greater specificity than previously published by limiting results to the relationship between the temporal and spatial availability of take-away alcohol on *per capita* consumption. This focus on the policy to consumption relationship will aid policy-makers in translating the results of the study into effective policy that can differentially target outlet types. In line with previous reviews, e.g. Hahn et al. (2010) & Middleton et al. (2010), quality criteria are applied to align constituent studies with the goal of studying policy interventions, with an eye to highlighting policy implications. Meta-analyses are calculated for the effect of allowing an additional day of sale per week on total and beverage-specific *per capita* alcohol consumption.

2.3 Methods

2.3.1 Systematic Reviews

Separate systematic review processes, following the methods described below, were completed for each of the temporal availability (days/hours of sale) and spatial availability (outlet density) of take-away alcohol.

2.3.1.1 Systematic Review Registration

This study has been registered with PROSPERO (Booth et al., 2012), the international prospective register of systematic reviews; the registration number is CRD42016040103.

2.3.1.2 Search Strategy and Selection Criteria

A novel review process was employed for this study and is therefore detailed below. A difference from other systematic reviews was the formation of a literature base from recent systematic reviews; this was then supplemented with a systematic review update. As there were a number of recent reviews covering broader research questions in this area (i.e. more than the effect of the physical availability of take-away alcohol on *per capita* consumption), it was decided to use the papers identified by these completed reviews as a literature base. The project team decided to identify the four most recent systematic reviews from which to draw the literature base, in order to balance breadth and pragmatism. Modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams are shown in Figure A-1 for days and hours of sale and in Figure A-2 for outlet density (Moher, Liberati, Tetzlaff & Altman, 2009). The strategy employed the steps below, completed in duplicate with differences resolved through discussion or, if necessary, mediation by a third team member. This process was completed separately for each research area (temporal and spatial availability of take-away alcohol). The steps were as follows:

(1) A systematic review was conducted, searching for systematic reviews subject to inclusion and exclusion criteria 1, 2 and 4 below. This systematic review for reviews was completed in February 2016 using Web of Science and the Cochrane Database of Systematic Reviews. A secondary search was conducted in Google Scholar and expert advice was solicited from the panel of team members. The search terms used are specified in Appendix A-1. The identified systematic reviews (shown in Appendix A-2, included reviews in bold) were read in full and their constituent papers extracted to create the literature base in each research area.

(2) A systematic literature review was subsequently conducted to update the literature base to papers published up to and including December 2015. A systematic review was conducted in March 2016 using Web of Science and a secondary search was conducted

using Google Scholar. The period searched was from the least recent systematic review study period end date identified in (1) until December 2015. This was chosen to maximize the number of constituent papers in our study, as inclusion/exclusion criteria may differ across systematic reviews.

(3) Studies identified in both (1) and (2) constituted the identified literature. The resulting articles were then screened against our inclusion and exclusion criteria by title and abstract by using a coding template developed to standardize project practices. Remaining papers were acquired in full text.

(4) Full text papers were evaluated against our quality criteria and papers were fully coded for information regarding authorship, study context, exposure, study description and relevant findings. The expert group reviewed the list of included studies and suggested additions to ensure a more comprehensive list of studies.

2.3.1.3 Inclusion and Exclusion Criteria

For inclusion, individual articles had to meet the following criteria:

(1) Explicitly study an exposure of interest (hours of sale, days of sale, outlet density of take-away alcohol);
(2) Explicitly study the outcome of interest (*per capita* alcohol consumption – total alcohol consumption or beverage-specific consumption);
(3) Be categorized in Tier 1 or 2 of the quality criteria below;
(4) Be written in English;
(5) Be primary research; and
(6) Be published in 1991 or later (to provide a study period of 25 years, as societies and their responses to interventions will change over time).

2.3.1.4 Quality Criteria

It is rarely feasible to design randomized controlled trials (RCTs) to study the effect of alcohol policies. In the absence of RCTs, alcohol policy researchers have turned to quasi-experimental research designs, in particular natural experiments. Natural experiments attempt to determine the impact of policy interventions by measuring the outcome of interest both pre- and post-

implementation of a policy (e.g. before and after Sunday sales were made legal) or policy proxy (e.g. changes in alcohol outlet density over time due to market forces). Natural experimental designs can be made more robust by the use of simultaneous control measurements, e.g. observations in a neighbouring jurisdiction where the studied policy was not changed (Babor et al., 2010); in fact, in interpreting causation, maximum statistical confidence is achieved by using time-series designs with contemporaneous controls (Cook & Campbell, 1979; Shadish, Cook & Campbell, 2002). Policy or proxy interventions can be either sudden or gradual; for example, allowing Sunday sales would result in a sudden change in opening hours while allowing private alcohol outlets would lead to a gradual change in density as stores are added over time As our intent was to draw conclusions on the effectiveness of policies regarding the physical availability of take-away alcohol by studying its effect on *per capita* consumption, three quality tiers were defined in consideration of the information above:

Tier 1 – Pre-/post- natural experiments with simultaneous control observations

Tier 2 – Pre-/post- natural experiments with no control observations

Tier 3 – All other studies (e.g. cross-sectional)

Articles in Tiers 1 and 2 were included in the review after the application of the quality criteria. Tier 3 studies were excluded from our analysis, but are included in Appendix A-3 for reference.

2.3.2 Standardizing Effect Sizes and Standard Errors for Meta-Analyses

Due to limitations in the number of identified articles for hours of sale (N=1) and outlet density (N=4) which met the quality criteria, meta-analyses were only conducted for days of sale (N=6). To complete these meta-analyses, it was necessary to standardize effect sizes into comparable measures across the identified studies. Further, meta-analyses require standard error values for inverse variance weighting (Woodward, 2013); these were not available for each study. To create comparable measures for days of sale, a research question was developed and applied to each study: when alcohol sales were allowed on one additional day per week, what was the estimated change in *per capita* total and beverage-specific alcohol consumption? The articles regarding days of sale were consistent in presenting results that could be interpreted to answer this question; however, associated standard errors were not always included. When standard errors were not presented in the article, they were calculated from information provided. Where t-

values were provided, e.g. Stehr (2007), standard errors were calculated as $SE_i = \hat{\theta}_i / t_i$ for study i, where $\hat{\theta}$ is the estimated effect size (Higgins & Green, 2008). Where only p-values were provided, e.g. (Yörük, 2014), z-values were calculated from the p-value and standard errors were calculated as $SE_i = \hat{\theta}_i / z_i$ (Altman & Bland, 2011; Higgins & Green, 2008).

2.3.3 Meta-Analyses

Meta-analyses were conducted to calculate the effect of one additional day of alcohol sale on *per capita* consumption. All calculations for these meta-analyses were completed using Comprehensive Meta-Analysis version 3.3 (Borenstein, 2013). Meta-analyses combined the standardized effect sizes identified above which quantified the effect on *per capita* consumption of allowing one additional day of sale. Meta-analyses were completed for total alcohol consumption and beverage-specific consumption (beer, wine and spirits).

Meta-analyses were completed in two steps. First, for each category (total alcohol, beer, wine and spirits), articles which studied similar contexts and situations were identified. For example, three articles studied an experiment in Sweden which, in two phases, allowed the sale of alcohol on Saturdays (Grönqvist & Niknami, 2014; Norström & Skog, 2003; Norström & Skog, 2005) and two articles studied allowing sales on Sunday in the United States (Stehr, 2007; Yörük, 2014). In order to avoid overweighting the results from a similar context in the overall estimate, the results of these studies were first combined into a context-specific measure using fixed-effects meta-analysis, described in more detail below. Second, these context-specific results were combined with the estimates from other studies to produce a final result using random-effects meta-analysis. In addition to this two-step process that combined context-specific measures, sensitivity analyses were completed which combined studies individually using random-effects. These sensitivity analyses for total and beverage-specific alcohol closely matched the two-step procedure and are therefore not presented.

Fixed effects meta-analysis assumes a true overall quantity that all studies are estimating while random effects assumes that the true quantities from individual studies are drawn from an underlying normal distribution (Woodward, 2013). Fixed effects meta-analysis was used for the context-specific combination of results as the constituent studies used similar sources of information from the same context. In the second step, effect sizes from differing contexts were

combined using random effects methods as they would not be expected to have the same true overall quantity.

In the fixed effects model, estimates are combined using inverse variance (IV) weighting, where weights are calculated as $w_i = 1/SE_i^2$ (Woodward, 2013). The combined effect size from the fixed effects model is calculated as $\bar{\theta}_{fx} = \Sigma\left(w_i\hat{\theta}_i\right)/\Sigma\, w_i$ and the standard error of the combined estimate is calculated as $SE_{fx}=1/\sqrt{\sum w_i}$. In random effects meta-analysis, studies are expected to be more heterogeneous with respect to the effect of the policy exposure on consumption (Woodward, 2013). To test this, the homogeneity test statistic is calculated as $Q = \Sigma\, w_i\left(\hat{\theta}_i - \hat{\theta}_{fx}\right)^2$. When compared with a chi-square statistic on k-1 degrees of freedom, where k is the number of studies, a statistically significant Q indicates a heterogeneous distribution (Woodward, 2013). As random effects assume an underlying probability distribution, the standard error for each effect size has both within-study and between-study components (Lipsey & Wilson, 2001). Calculating $D = (k-1)(k\,\overline{w}^2 - s_w^2)/k\overline{w}$ allows us to estimate the between-study component of the error as $\hat{\tau}^2 = (Q-k+1)/D$ when $Q > k-1$. If $Q \leq k-1$ then $\hat{\tau}^2$ is taken to be zero and the random effect model collapses to the fixed effects model. IV weights for the random effect model are then calculated as $1/\left((1/w_i) + \hat{\tau}^2\right)$. The random effects model is more conservative, producing wider confidence limits around the estimated effect size (Lipsey & Wilson, 2001).

2.4 Results

2.4.1 Systematic Reviews

2.4.1.1 Days and Hours of Sale

As described in the methods, four systematic reviews were identified and used to create the literature base for days and hours of sale; these produced 181 papers (see Figure A-1). The systematic review update, used to update the systematic review to December 2015, identified an additional 1,331 papers and two papers were added by content experts on the research team. This resulted in 1,514 papers, which then had duplicates removed and were screened by title and abstract against our inclusion and exclusion criteria. The high percentage of exclusions at the screening stage was due to the relatively strict inclusion and exclusion criteria, which required

studies to evaluate both an exposure and outcome of interest; for example, a significant number of papers studied an outcome on a particular harm such as violent crime and did not directly or indirectly consider consumption. Nine papers were forwarded from the screening stage to eligibility and were included in our full-text review. Of the nine papers reviewed in full, seven met our quality criteria; these are summarized in Table A-1. Six of these articles studied the effect of allowing alcohol sales on either Saturday or Sunday (Carpenter & Eisenberg, 2009; Grönqvist & Niknami, 2014; Norström & Skog, 2003; Norström & Skog, 2005; Stehr, 2007; Yörük, 2014) and one studied the effect on consumption of differing hours of sale in regions of Russia (Kolosnitsyna, Sitdikov & Khorkina, 2014).

The six articles which studied the effect of an additional day of sale on *per capita* consumption were from three countries: Sweden (three articles), the United States (two articles) and Canada (one article). The three Swedish articles studied different time periods of the same experiment with Saturday sales in which the country was divided into experimental, buffer and control areas in Phase I and Saturday sales were allowed in the entire country in Phase II (Grönqvist & Niknami, 2014; Norström & Skog, 2003; Norström & Skog, 2005). Norström & Skog studied both Phase I (Norström & Skog, 2003) and Phase II (Norström & Skog, 2005). When pooling the experimental areas in Phase I, the authors concluded that an additional day of sale led to *per capita* consumption increases of 3.3% for total alcohol, 7.0% for beer, 2.0% for wine consumption, and 3.0% for spirits. Their article studying Phase II reported similar effect sizes. Grönqvist and Niknami (2014) analyzed the effect of Phase I on total consumption as a component of an article studying changes in crime outcomes. The authors reported a 4.6% increase in *per capita* consumption of total alcohol.

Yörük (2014) and Stehr (2007) both employed natural experimental designs to assess the effect of Sunday sales bans in the U.S. Yörük (2014) compared five experimental states which repealed Sunday sales bans to 12 control states in which bans remained in place; the author reported a 2.8% increase in *per capita* consumption of total alcohol and a 4.0% increase in beer consumption. Stehr (2007) included all 50 U.S. states for the period 1990 to 2004 - 12 states repealed their Sunday sales bans during this time period. A 3.5% increase in *per capita* beer consumption and a 7.5% increase in *per capita* spirits consumption were reported.

Figure A-1: Modified PRISMA flow diagram for the effect of the days and hours of sale of take-away alcohol outlets on *per capita* consumption

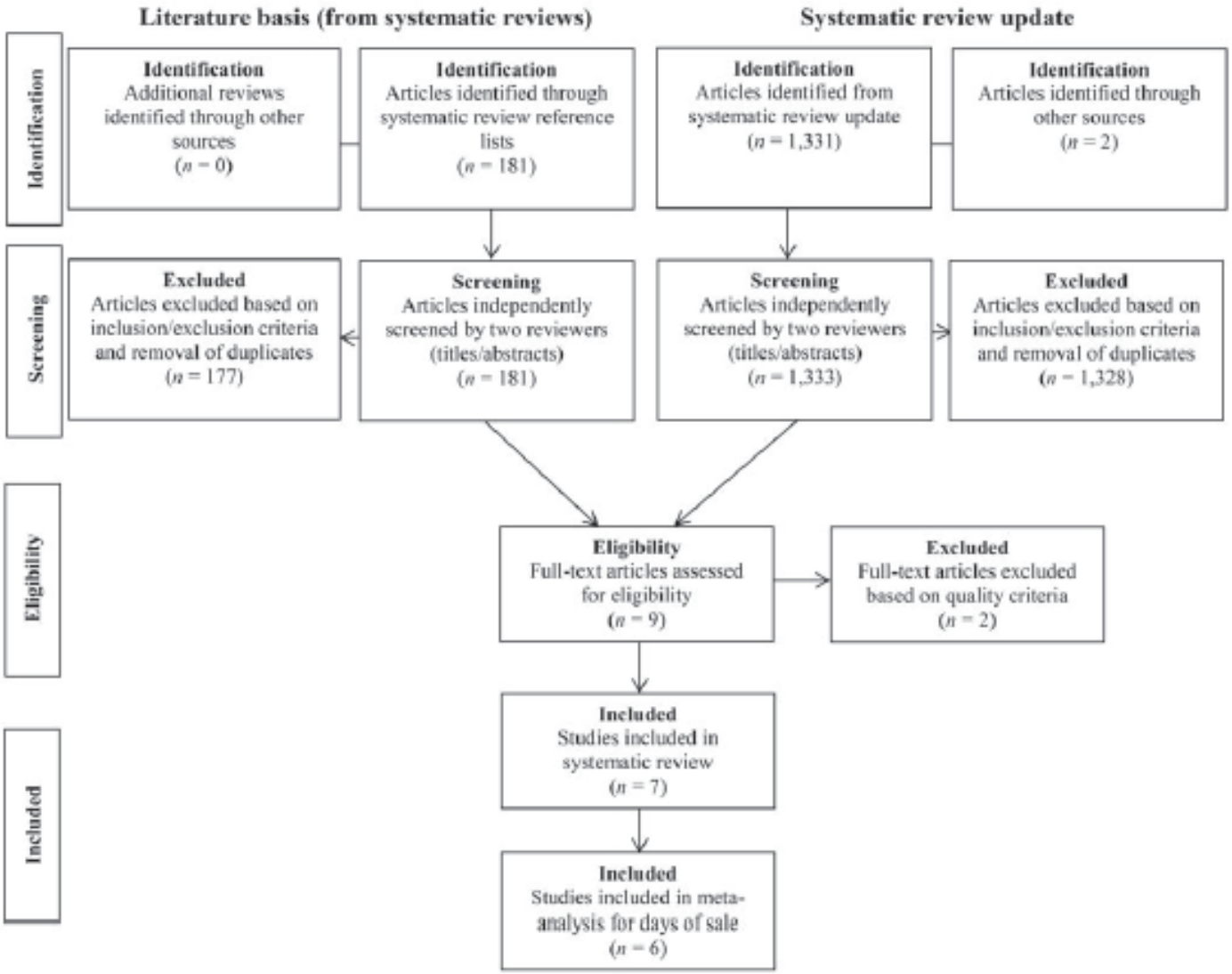


Figure A-2: Modified PRISMA flow diagram for the effect of the density of take-away alcohol outlets on *per capita* consumption

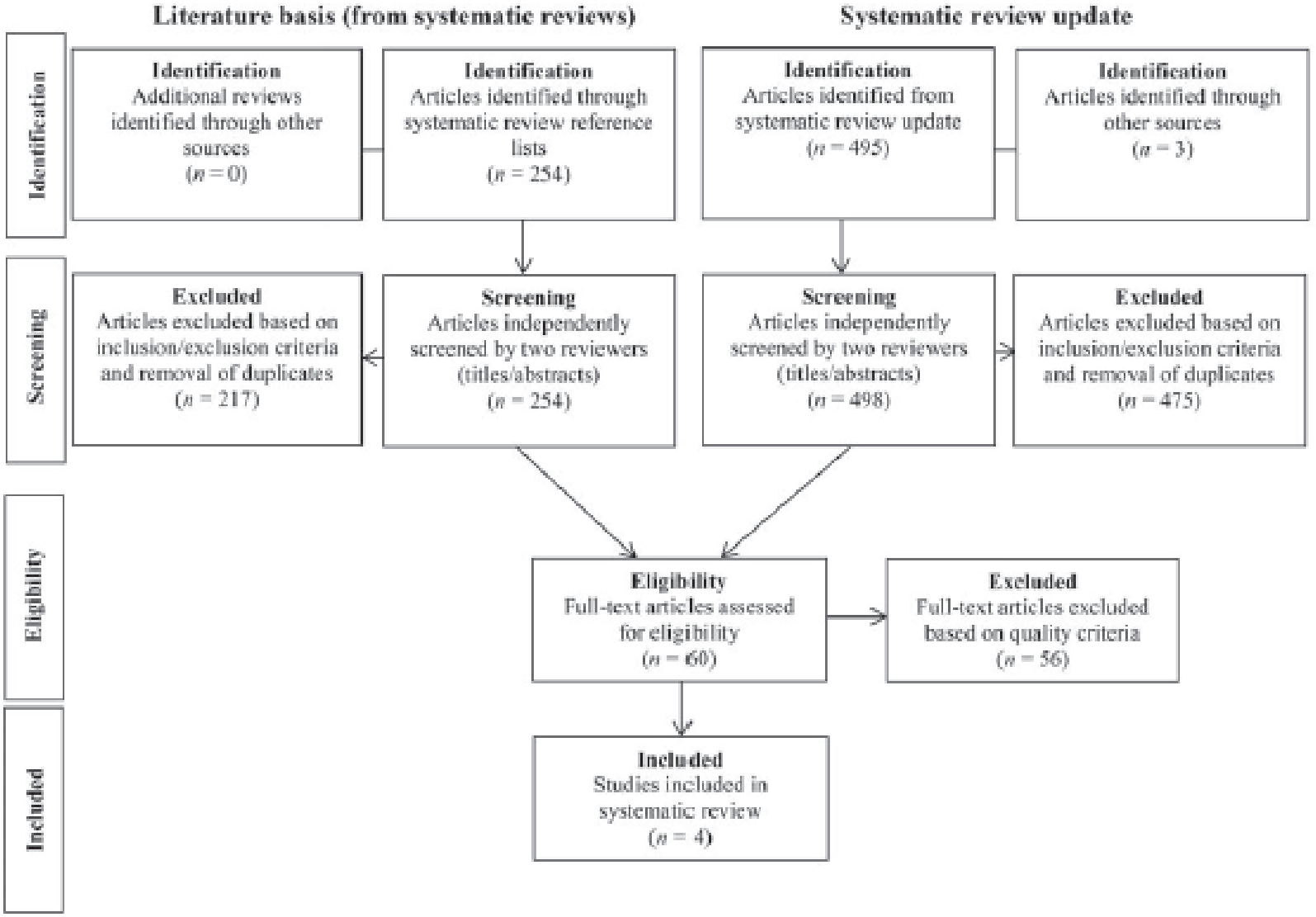


Table A-1: List of included studies for the effect of the days and hours of sale of take-away outlets on *per capita* alcohol consumption

Author(s), date	*Study context: Country & year*	*Intervention studied*	*Study description*	*Findings*
Days of sale (6)				
Gronqvist & Niknami (2014)	Sweden 1998-2001	Removal of Saturday sales restrictions	Studied Phase 1 of a natural experiment in Sweden which removed Saturday sales restrictions in 2000. Sales data acquired from Systembolaget, the Swedish government alcohol retail monopoly.	The author's preferred linear trend model calculated a significant parameter estimate of 0.045 (SE 0.016).
Yörük (2014)	United States 1990-2007	Removal of Sunday sales restrictions	Seventeen US states (5 treatment and 12 control) were studied from 1990-2007 using a time series design with acquired sales data.	Combining the five treatment states gives significant parameter estimates for total consumption (0.028) and beer consumption (0.039).
Carpenter & Eisenberg (2009)	Canada 1994-1999	Removal of Sunday sales restrictions	A natural experimental approach was constructed comparing provinces with Sunday restrictions to those without. National-level survey data was used (n=95,970).	The author's time series model found a non-significant increase of 0.028 (SE 0.60) self-reported drinks per week compared to a mean rate of 3.06/week.
Stehr (2007)	United States 1990-2004	Removal of Sunday sales restrictions	Quantified the effect of series of natural experiments wherein twelve states removed restrictions on Sunday sales. Sales data from all 50 states for 15 years was acquired.	Parameter estimates from the author's full model were: Beer consumption = 0.034 (t 1.46) Spirits consumption = 0.072 (t 3.30)
Norström & Skog (2005)	Sweden 1995-2002	Removal of Saturday sales restrictions	Studied Phase 2 of the Swedish Saturday sales experiment from July	ARIMA time-series modeling found the following parameter estimates:

			2001 to July 2002. Results from Phase I of the study were re-assessed.	Total 0.035 (SE 0.005); Beer 0.052 (SE 0.008); Wine 0.033 (SE 0.006); Spirits 0.022 (SE 0.004).
Norström & Skog (2003)	Sweden 1995-2001	Removal of Saturday sales restrictions	Studied Phase 1 of the Swedish Saturday sales experiment. The country was divided into experimental, control and buffer areas.	ARIMA time-series modeling found the following parameter estimates: Total 0.032 (SE 0.006); Beer 0.068 (SE 0.009); Wine 0.020 (SE 0.006); Spirits 0.030 (SE 0.004).
Hours of sale (1)				
Kolosnitsyna *et al.* (2014)	Russia 2009-2010	Greater hours of sale allowed - Total number of hours, morning opening hours and evening closing hours	Sales data and survey data were used to examine differences in Russian regions. A natural experiment occurred in 2009 wherein regions gained the ability to regulate opening hours; consumption data before and after this change were studied.	For effect on total consumption, parameter estimates were: Total no. of hours of sale = 0.008 (SE 0.003) Time when sales end in the evening = 0.076 (SE 0.015) Time when sales begin in the morning = -0.025 (SE 0.006).

Table A-2: List of included studies for the effect of the density of take-away outlets on *per capita* alcohol consumption

Author(s), date	*Study context: Country & year*	*Intervention studied*	*Study description*	*Findings*
Population-level studies (3)				
Stockwell, Zhao, Macdonald, Pakula, Gruenewald, & Holder (2009)	Canada 2003-2008	An increase in take-away alcohol outlet density due to the partial privatization of alcohol retail in British Columbia, Canada.	A multi-level regression analysis design was used to study a natural experiment where a retail monopoly was partially privatized. Alcohol sales data by beverage category and data providing the number of alcohol outlets were acquired from administrative sources.	The author's full model found that the density of take-away outlets significantly increased *per capita* consumption. The authors also provided elasticities (not included in article). They were: Total 0.149 (SE 0.022); Beer 0.126 (SE 0.022); Wine 0.254 (SE 0.026); Spirits 0.135 (SE 0.024)
Trolldal (2005)	Canada 1951-2000	Changes in take-away alcohol outlet density over time.	A time-series dataset with information on *per capita* sales and take-away outlet density was used to approximate a natural experiment for four Canadian provinces.	ARIMA time series models produce the following effect sizes of take-away alcohol outlet density on beverage-specific sales (for four provinces, pooled): Total 0.07 (SE 0.13); Beer 0.02 (SE 0.10); Wine 0.04 (SE 0.17); Spirits 0.41 (SE 0.21).
Xie, Mann, & Smart (2000)	Canada 1968-1986	Changes in take-away alcohol outlet density over time.	As part of a study on alcohol policy measures and liver cirrhosis, a time-series dataset with information on *per capita* sales and take-away outlet density was created which approximated a natural experiment.	The authors found greater take-away outlet density to be significantly positively associated (0.19, $p<0.05$) with increased *per capita* consumption.

Individual-level studies (1)

Brenner, Borrell, Barrientos-Gutierrez, & Diez Rouz (2015)	United States 2000-2010	Natural changes in take-away alcohol outlet density due to participants moving homes	This longitudinal study examined the effect of changes in outlet density on daily consumption. Participants aged 45-84 were surveyed once at baseline with four follow-up surveys conducted at 1.5-2 year intervals (n=6,163).	A one standard deviation increase in take-away outlet density was found to have a significant effect on weekly consumption in both men and women: Men 1.07 ($p<0.05$); Women 1.11 ($p<0.05$).

Carpenter and Eisenberg (2009) assessed the effect of lifting a Sunday alcohol sales ban in the province of Ontario in 1997. The authors found a non-significant 0.9% increase in consumption of total alcohol.

The study by Kolosnitsyna et al. (2014) examined the effect of hours of sale on *per capita* consumption. In 2009, Russian regions gained the autonomy to independently restrict the hours of alcohol sale. This created a natural experiment with various changes in opening hours by region, which the authors used to estimate the effect of hours of sale on total consumption. The study reported that later evening opening hours were significantly related to total consumption: each additional hour of sale led to a 7.9% increase in alcohol sales.

2.4.1.2 Outlet Density

Analyzing the four identified systematic reviews used to create the literature base identified 254 articles (see also Figure A-2). The systematic review update subsequently identified 498 papers and two papers were added due to expert consultation. The resulting 754 articles were screened by title and abstract in duplicate. Fifty-nine papers were deemed eligible to continue to the full text review stage and four papers met our quality criteria. Table A-2 summarizes the included articles.

Of the four included studies, three took place in Canada and were population-level studies (Stockwell et al., 2009; Trolldal, 2005; Xie, Mann & Smart, 2000) and one individual-level study took place in the United States (Brenner, Borrell, Barrientos-Gutierrez & Roux, 2015). Stockwell et al. (2009) examined the effect of increasing take-away alcohol outlet density due to a partial privatization of alcohol retail in British Columbia between 2003 and 2008. The authors found that a 1.0% increase in take-away outlet density was associated with a 0.15% increase in total alcohol consumption, as well as significant increases in beverage-specific consumption. Xie et al. (2000) found significant results supporting the hypothesis that greater take-away outlet density is associated with higher consumption; however, Trolldal (2005), found non-significant effects using a study period of 1951 to 2000. In these studies, outlet density was operationalized by calculating the number of stores per residents: in Stockwell et al. (2009) and Xie et al. (2000) it was density per 10,000 residents and in Trolldal (2005) it was density per 100,000 residents.

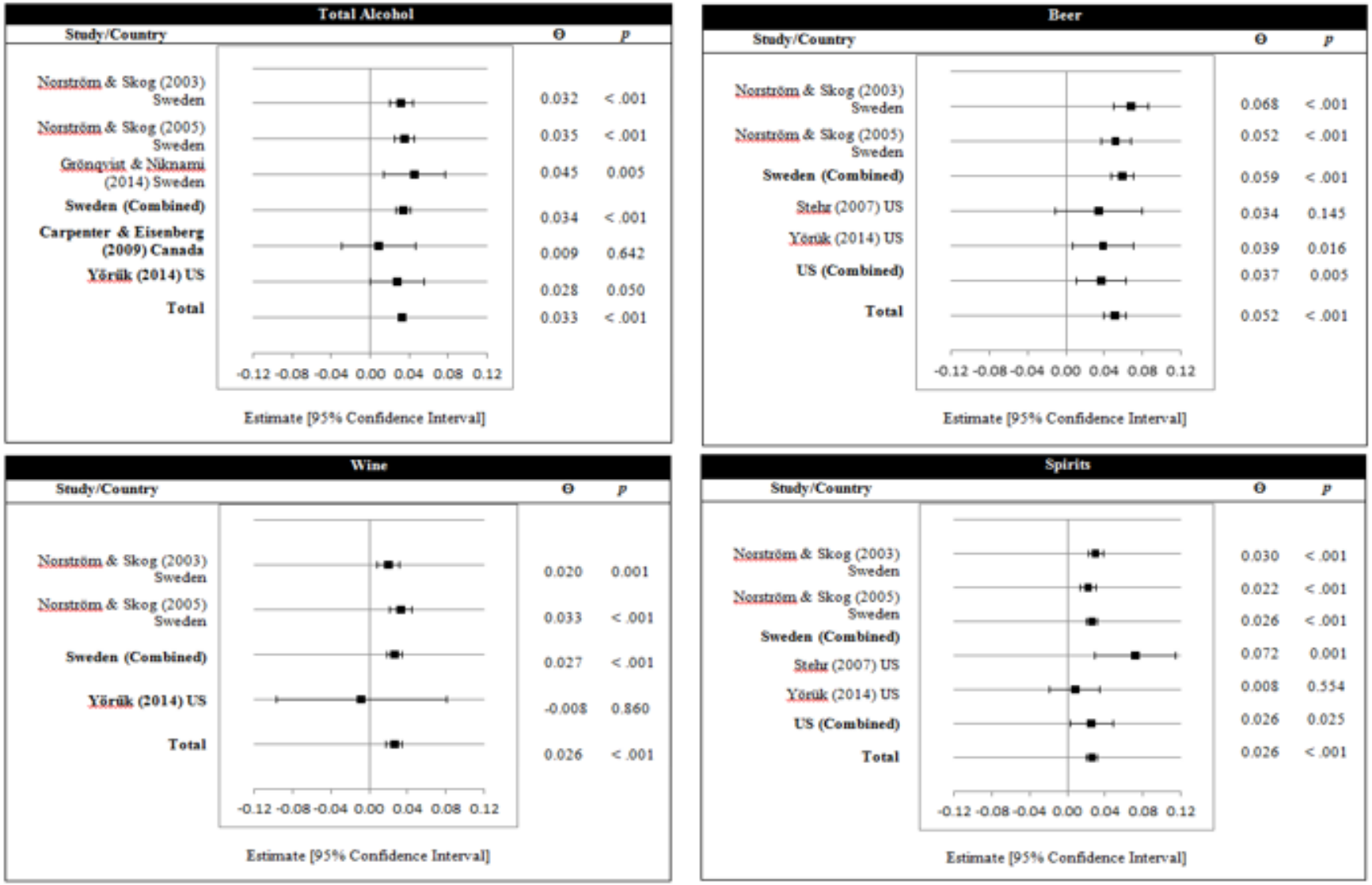
The U.S.-based, individual-level study by Brenner et al. (2015) took place between 2000 and 2010 and examined changes in alcohol consumption which occurred when participants relocated to areas with changed outlet density. The study reported that a one standard deviation increase in outlet density was associated with a significant 11% increase in alcohol consumption for women and a significant 7% increase in consumption for men.

2.4.2 Meta-Analyses Regarding Days of Sale

A priori, our intention was to complete meta-analyses regarding the effect of days of sale, hours of sale and outlet density on *per capita* consumption. However, once systematic reviews were completed, the paucity of studies and of comparable results on hours of sale and density excluded those dimensions of physical availability from the possibility of meta-analysis. As there were six high-quality studies regarding days of sale, many of which included beverage-specific results, it was possible to complete meta-analyses of the effect of days of sale on *per capita* consumption of total and beverage-specific alcohol.

Results are presented in Figure A-3. Five studies included total alcohol consumption as an outcome and all of these estimated that an additional day of sale increased *per capita* alcohol consumption (four were statistically significant). The significant combined effect size was estimated to be 0.033 (95% CI: 0.026, 0.040), suggesting one additional day of sale was associated with a 3.4% increase in total *per capita* consumption. Beverage-specific results were also positive and highly significant: for beer, a 5.3% (95%CI: 3.2%, 7.4%) increase in *per capita* consumption, for wine, a 2.6% (95%CI: 1.8%, 3.5%) increase and for spirits, a 2.6% (95%CI: 2.1%, 3.2%) increase. Of note is the consistency of effect sizes in each of the four panels of Figure A-3 - the meta-analyses paint a consistent picture of the effect on total consumption of an additional day of alcohol sale.

Figure A-3: Forest plots showing the effect of one additional day of sale on *per capita* total and beverage-specific consumption



2.5 Discussion

The results are generally consistent with previous systematic reviews relating physical availability and alcohol-related outcomes; however, we provide greater specificity by focusing on the physical availability of take-away alcohol and conducting novel meta-analyses regarding the effect of an additional day of sale on *per capita* drinking. The conducted meta-analyses of high quality days of sale studies provide compelling evidence that one additional day of sale will lead to increased aggregate and beverage-specific alcohol consumption. The small number of studies found suggests that increasing hours of sale and outlet density may lead to increased consumption.

Previous reviews which have gathered evidence on broader exposures and outcomes have concluded that a majority of studies support a link between increased physical availability and increased alcohol-related outcomes, such as alcohol consumption (Bryden et al., 2012; Campbell et al., 2009; Hahn et al., 2010; Middleton et al., 2010; Popova et al., 2009). Among these reviews, the strongest conclusion is given for the effect of an additional day of sale (Middleton et al., 2010). The findings of the present study support and strengthen this previous conclusion.

The results provide evidence to suggest that restricting the physical availability of take-away alcohol is an effective strategy for decreasing *per capita* alcohol consumption. Temporal availability may be restricted by regulating the days and hours of allowed alcohol sale and spatial availability may be influenced by stricter licensing laws for take-away outlets or government monopoly control of alcohol retail stores. The results from meta-analyses regarding days of sale provided particularly strong evidence. From the consistency of effect sizes presented in Figure A-3, it is clear that there is a high level of agreement between studies from across different societal contexts and beverage types. The vast majority of individual study effect sizes show a significant and positive association between allowing an additional day of sale and the total and beverage-specific *per capita* consumption of alcohol.

As with all systematic reviews, results are only as good as the assumptions and methods used to filter results and calculate meta-analyses. It is our opinion that our inclusion, exclusion and quality criteria led to the inclusion of studies which best captured the concept of interest, i.e. only natural experiments were included in order to best study policy interventions. This had the effect of disqualifying many cross-sectional studies that compared sites with different policies. It

was not our intention to declare these other studies invalid, but only to choose, in this circumstance, which studies we thought would best answer the question at hand. The generalizability of the results presents another limitation; all included studies were from developed nations and acquiring the data needed to study natural policy experiments is known to be more difficult in emerging economies (Babor et al., 2010). The dissimilarities between developed and emerging economies preclude the ability to extend these results. Lastly, a recent critical review discusses challenges in aggregating take-away outlets. Though this is better than aggregating all types of outlets, it fails to consider the wide variety of take-away shops in the marketplace (Holmes, et al., 2014). Each limitation presents an opportunity for future work. There is a need for more studies examining the effect of changes in the physical availability of take-away alcohol on *per capita* consumption. Further, in emerging economies, emphasis should be placed on building data collection capacity, e.g. the collection of comprehensive alcohol sales data (Rehm & Room, 2009).

2.6 Acknowledgements and Conflict of Interest Statement

This work was supported by a Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Canada Graduate Scholarship (CGS-D) and a joint Island Health - Canadian Institute for Substance Use Research (CISUR) Graduate Research Scholarship awarded to the first author.

The study was partly funded by Systembolaget, the Swedish government alcohol monopoly that reports to the Minister for Health and has a mandate to protect the health and safety of the population. Funds cover part-time salary for the first author, as well as travel expenses and minor fees for co-authors. Systembolaget has agreed for the investigative team to be fully independent and responsible for the content of all publications arising from the project.

Chapter 3: The Effect on Emergency Department Visits of Raised Alcohol Minimum Prices in Saskatchewan, Canada [Study B]

3.1 Abstract

Introduction: The province of Saskatchewan, Canada introduced minimum prices graded by alcohol strength in April 2010. Previous research found this intervention significantly decreased alcohol consumption and alcohol-attributable morbidity; we aim to test the association between the intervention and the rate of emergency department (ED) visits in four alcohol-related injury categories (motor vehicle collisions [MVCs], assaults, falls and total alcohol-related injuries).

Methods: Data on ED visits in the city of Regina were obtained from the Saskatchewan Ministry of Health. Auto-regressive integrated moving average time series models were used to test the immediate and lagged effects of the pricing intervention on rates of alcohol-related nighttime ED visits and controlled for daytime rates of ED visits, economic variables, linear and seasonal trends, and auto-regressive and moving average effects.

Results: The implementation of an alcohol minimum pricing strategy in Saskatchewan was associated with a decrease in MVC-related ED visits for women aged 26+ after a six month lag period (-39.4%, $p<0.001$). There was no significant abrupt effect of the intervention on ED visits of four injury types in any of four gender-age categories; however, rates of ED visits among young males for MVCs and assaults decreased substantially during the study period.

Discussion: The minimum pricing policy change led to a lagged decrease in motor vehicle-collision-related ED visits for women older than 25. Of note, there did not appear to be an instantaneous effect on the rate of alcohol-related injury ED visits immediately after the policy implementation nor lagged effects for other gender-age groups.

3.2 Introduction

Alcohol consumption takes a significant toll on public health, both globally and in Canada. Previous studies have estimated that alcohol-attributable deaths comprised 7.1% of all deaths and 9.3% of all disability-adjusted life years lost for Canadians under 70 (Shield et al., 2012). Alcohol consumption has been shown to contribute greatly to the burden of disease in Canada, leading to public health burdens such as cancer, motor vehicle collisions (MVCs) and cirrhosis of the liver (Shield et al., 2012). It has been estimated that for each one litre *per capita* increase in pure alcohol consumption in Canada there is an associated 2.9% increase in all-cause mortality (Norstrom, 2004), a 30% increase in alcoholic liver cirrhosis (Ramstedt, 2003) and a 4.0% increase in total suicide (Ramstedt, 2005). Further, international research has shown that alcohol use places a substantial burden on emergency departments (EDs). For example, an analysis of data from EDs spanning 18 countries, including Canada, reported that approximately 40.1% of assault-related injuries, 14.3% of fall injuries and 11.1% of MVCs were attributable to the drinking of alcohol (Cherpitel et al., 2015).

The World Health Organization states that the most effective policies for reducing the global burden of illness from alcohol are controlling price and physical availability (World Health Organization, 2011). In Canada, alcohol control policies such as pricing have proven to be a promising strategy for reducing the total public health burden associated with alcohol consumption (Stockwell, Auld, Zhao & Martin, 2012). Meta-analyses have shown that increased alcohol prices are associated with decreased alcohol consumption (Wagenaar et al., 2009) and alcohol-related morbidity and mortality, violence and impaired driving (Wagenaar, Tobler & Komro, 2010).

In the Canadian province of Saskatchewan, the Saskatchewan Liquor and Gaming Authority (SLGA) has a monopoly on alcohol distribution and is provided the authority to control alcohol minimum pricing. On April 1st, 2010, the SLGA implemented a comprehensive set of minimum prices across multiple beverage categories which were also made partially 'alcohol volumetric' (i.e. graded by alcohol strength). The evolution of alcohol minimum prices in Saskatchewan for different beverage types is depicted in a previous article by our group (Stockwell et al., 2012) and is reprinted with permission in Appendix B-1. It is important to note that since the SLGA has a monopoly on distribution these minimum prices apply both to sales in

liquor stores (off-premise outlets) and to prices paid by owners of bars and restaurants (on-premise outlets).

In Saskatchewan, the impact of these higher minimum prices on alcohol consumption and alcohol-related crime has been previously studied by our team (Stockwell et al., 2012; Stockwell et al., 2017c). In Stockwell et al. (2012), it was found that a 10.0% increase in alcohol minimum price was associated with a 10.1% reduction in the consumption of beer, a 4.6% reduction in the consumption of wine and a 5.9% reduction in the consumption of spirits, all of which were highly statistically significant. Importantly for the study design of the current article, a post-hoc analysis testing the lagged effect of the minimum price increase on consumption was conducted in Stockwell et al. (2017c), with significant lagged reductions found after 3 and 4 months. In another Canadian province, British Columbia, increased alcohol minimum prices have been found to be associated with decreased consumption, alcohol-attributable hospitalizations and mortalities and alcohol-related crime (Stockwell et al., 2009b; Stockwell et al., 2013; Zhao et al., 2013; Stockwell et al., 2015).

Returning to research studying alcohol consumption and ED visits, there is evidence that harms related to alcohol are most prevalent among males, with 75% of alcohol-related ED visits involving men (Shults et al., 2009), and younger age groups, as the rate of alcohol-related ED visits peak in one's twenties; this led us to stratify our analyses in the current study by gender and age group (13 to 25, 26 and older). Due to data limitations in the choice of age group, we could not include those 25 to 29 in the younger age group without significantly extending the upper age limit; this stratification was also chosen to best approximate the divide between youth and adult patterns of consumption. Lastly, there is strong evidence that nighttime injuries are more highly correlated with alcohol use than daytime injuries (Voas, Romano & Peck, 2009).

Given the compelling evidence that increased alcohol minimum prices lead to decreased alcohol consumption (Stockwell et al., 2012), together with the fact that alcohol consumption is highly related to certain types of ED visits (Cherpitel et al., 2015), this article tests the hypothesis that increased alcohol minimum prices were associated, in the time period following policy implementation, with decreased rates of nighttime ED visits in four alcohol-related injury categories: (1) total alcohol-related injuries, (2) motor vehicle collisions, (3) assaults and (4) falls in the four age-gender groups described above. Further, as evidence discussed previously

suggests younger males may be more affected than other populations, we give specific attention to this population subgroup most at risk.

3.3 Methods

3.3.1 Data sources

3.3.1.1 Emergency Department Data

Aggregate data were requested from the Saskatchewan Ministry of Health presenting the number of monthly ED visits in four alcohol-related diagnosis categories: (1) total alcohol-related injuries, (2) motor vehicle collisions, (3) assaults and (4) falls. Visits were grouped into these diagnosis categories based on the most responsible diagnosis field present on individual patient records. The total alcohol-related injuries category constitutes the other three categories, as well as poisonings, drownings, fires and other injury diagnoses that are causally related to alcohol. Diagnoses were coded using the International Classification of Diseases, 10th revision (Canadian Institute for Health Information, 2015). ED visit categories were taken from the U.S. Centers for Disease Control and Prevention's Alcohol-Related Disease Impact (ARDI) project and are listed in Appendix B-2 (Centers for Disease Control and Prevention, 2013). As the minimum pricing intervention occurred on April 1st, 2010, data were requested for April 1st, 2006 to March 31st, 2012 to align with Canadian healthcare fiscal years and to provide four years of data before and two years of data after the policy intervention. At the time data was requested, data ending in March 2012 was the most recent available.

The completeness of health data in Saskatchewan differs by hospital of care. For the study period in question, complete data were only available for the two largest cities in the province, Regina and Saskatoon. As well, due to funding deficits, data from Saskatoon did not receive diagnosis coding information in healthcare fiscal year 2010/11. These factors limited the data available for this study to that representing all ED visits from hospitals in the city of Regina, which represented approximately 17.3% of the provincial population in 2012 (Statistics Canada, 2013). Data were further categorized by gender, age group and time of day (daytime ED visits were records with an admission time of between 7:00am and 9:59pm and nighttime ED visits were records with an admission time between 10:00pm and 6:59am).

As previous studies have shown that certain types of ED visits, such as those related to assaults, falls and motor vehicle collisions, are more likely to be attributable to alcohol (Cherpitel et al., 2015; Shults et al., 2009), the analyses focused on the impact of increased alcohol minimum prices on the population-based time series rates representing ED visits in these categories, as well as the total rate of all alcohol-related injury visits.

3.3.1.2 Population Data and Population-Based Rates

Population estimates on July 1st for each year in the study period were attained for the Census Metropolitan Area (CMA) of Regina (Statistics Canada, 2013). Estimates were summarized to match the gender-age groups in our study. Monthly estimates for study population subgroups were interpolated using the cubic spline method in SAS PROC EXPAND (SAS Institute, 2011), wherein a segmented third-degree polynomial is fit to existing time series data points for the purpose of interpolation.

Monthly population-based rates of the four categories of ED visit were calculated by dividing the monthly ED visits by injury category, gender, age group and time of day by the corresponding monthly population in each gender and age. Rates were adjusted for the number of days in each month. This resulted in 32 time series (two genders by two age groups by two times of day by four visit categories) with 72 (six years by 12 months) observations each.

3.3.1.3 Consumer Price Index Data

Monthly consumer price index (CPI) figures were obtained from Statistics Canada's CANSIM database for the CMA of Regina. The CPI is an indicator of changes in prices paid by consumers, created by measurement of a standard basket of necessary goods. (Statistics Canada, 2015b).

3.3.1.4 Minimum Price Data in Saskatchewan

Minimum prices during the study period were received from the Saskatchewan Liquor and Gaming Authority. Average minimum alcohol prices were calculated for all beverage types combined and for three subcategories: beer, wine and spirits. A detailed description of these

calculations is provided in a previous study (Stockwell et al., 2012); see also Appendix B-1. Minimum prices were further adjusted by the CPI for Regina to control for the effects of economic changes and inflation.

3.3.1.5 Income Data

Median individual incomes by gender were attained for the CMA of Regina by calendar year (Statistics Canada, 2015a). Monthly estimates were interpolated using the cubic spline method discussed previously and were CPI-adjusted.

3.3.2 Statistical Analyses

Multivariate Autoregressive Integrated Moving Average (ARIMA) time series modeling (Box & Jenkins, 1976) was used to estimate the binary intervention effect of the increased minimum price on April 1st, 2010. Separate models were also fitted which treated the CPI-adjusted minimum price of each of four beverage categories (all alcohol, beer, wine and spirits) as continuous covariates in the time series model. Population-based rates, as well as covariates, were log-transformed before the modeling stage to make the variance stationary (Pankratz, 1983). Models for each time series are presented in the results in standard notation in Table B-2.

ARIMA modeling allows time series to be adjusted for trend (d-parameter), autoregressive (p-parameter) and moving average (q-parameter) effects when appropriate (Box & Jenkins, 1976). To determine if linear trend and seasonality were present, time series of population-based rates of nighttime ED visits were analyzed.

Intervention time series (ITS) with ARIMA modeling was used for this analysis. For each time series of ED visit rates, five intervention variables were tested: (1) a binary intervention taking the value of 0 before the intervention, which occurred on April 1st, 2010, and 1 after the intervention (McDowall, McCleary, Meidinger & Hay Jr., 1980), (2) CPI-adjusted average minimum price, (3) CPI-adjusted beer minimum price, (4) CPI-adjusted wine minimum price and (5) CPI-adjusted spirits minimum price. CPI-adjusted minimum alcohol prices were previously calculated and the methodology detailed (Stockwell et al., 2012).

Model covariates were chosen a priori. As income is positively correlated with alcohol consumption (Stockwell et al., 2012) and as decreased consumption is the hypothesized

mediating effect between increased minimum prices and decreased ED visits, it was necessary to include this variable as a covariate in all model testing. Further, rates of nighttime ED visits were used as the main time series of interest since there is strong evidence that alcohol-related injuries are more likely to occur at nighttime (Voas et al., 2009). The rates of daytime ED visits were used as a control variable in the fully-adjusted model as this control variable captures population-level changes in healthcare utilization and is expected to be unaffected by the change in minimum pricing.

For each model, both a partially-adjusted and fully-adjusted model were specified. The partially-adjusted models control for CPI-adjusted income, while fully-adjusted models also control for daytime ED visits of the same category. As dependent and covariate time series were log-transformed, the parameter estimate of the binary intervention variables can therefore be interpreted as the percent change in ED visits that are associated with the minimum price intervention being implemented abruptly and permanently. When the dependent variable is coded as a continuous average or beverage-specific minimum price, the parameter estimate can be interpreted as the percent change in ED visits due to a 1.0% increase in minimum price. In the binary intervention model, the effect is interpreted as the coefficient estimate multiplied by 100%. The lagged effects of the intervention were tested up to six months using the fully-adjusted, binary intervention model.

A previous study by our team that investigated the relationship between this minimum price intervention and crime found significant lagged effects of the intervention on *per capita* consumption, at monthly lags 3 to 5 (Stockwell et al., 2017c). Additionally, a lagged effect on violent crimes among men was found for monthly lags 4 to 6. These previous results were used as motivation to test the lagged effect of the intervention on alcohol-related injury ED visits in the current study between monthly lags 3 and 6. Given the large number of statistical tests conducted, it was decided to use a Bonferroni family-wise correction (Bland & Altman, 1995) when interpreting our results to reduce the chance of Type I error. Test families were divided by population subgroup and model type (intervention vs. continuous covariate).

All statistical analyses were completed using SAS version 9.4 statistical software (SAS Institute, 2011). ARIMA modeling was carried out using the SAS PROC ARIMA procedure, specifying p, d and q parameters as evidenced by the data (SAS Institute, 2011).

3.3.3 Statement of Ethics

As this study used de-identified and highly aggregated administrative health and other data, no ethics approval was required.

3.4 Results

Results of the statistical testing for linear and seasonal time series trends are shown in Table B-1. If a significant linear trend was identified, time series were differenced by d=1. If a seasonal effect was identified, time series were further differenced by d=12.

Appendix B-3 presents panel figures of unadjusted monthly rates of nighttime ED visits by four injury categories for each of four gender-age groups. A comparison between visual trends in Appendix B-3 and the results shown in Table B-1 reveals a trend of decreasing rates of total alcohol-related injuries, MVCs and assaults for males aged 13 to 25 throughout the study period. As well, rates of assault appear to peak in the summer each year for all gender-age groups except for females aged 13 to 25, which is substantiated by the statistical tests for seasonality.

Table B-2 presents partially-adjusted and fully-adjusted results for the binary intervention and continuous average minimum price models; the results from the beer, wine and spirits minimum price models are presented in Appendix B-4. For the binary intervention model, partially-adjusted results show that there was not a statistically significant abrupt permanent change in any of 16 (four injury categories by four age-gender groups) categories. The fully-adjusted results for the same model likewise find no statistical change in the rate of alcohol-related ED visits in any of 16 categories. For the continuous average minimum price model, results adjusted for CPI-adjusted income find the implementation of higher minimum prices was not associated with changes in any of 16 rate time series of alcohol-related ED visits. For this model, with additional control for corresponding daytime rates (fully-adjusted results), none of 16 rate series showed a statistically significant change.

Table B-1: Tests for linear trend and seasonality

Time series of logged nighttime ED visit rates		Test for trend			Test for seasonality	
Gender, age group	**Type of ED visit**	**Parameter Estimate**	**t-value**	**Pr > |t|**	**F-value**	**Pr > F**
Males, 13 to 25	Total alcohol-related	**-0.0049**	**-3.71**	**0.0004**	**6.29**	**<.0001**
	Motor vehicle collisions	**-0.0067**	**-2.30**	**0.0241**	1.55	0.1386
	Assaults	**-0.0070**	**-3.91**	**0.0002**	**4.97**	**<.0001**
	Falls	0.0004	0.25	0.8047	0.60	0.8183
Females, 13 to 25	Total alcohol-related	-0.0008	-0.63	0.5332	1.77	0.0789
	Motor vehicle collisions	-0.0015	-0.44	0.6592	0.72	0.7165
	Assaults	-0.0026	-1.41	0.1627	1.58	0.1287
	Falls	0.0028	1.32	0.1902	0.55	0.8577
Males, 26 and over	Total alcohol-related	0.0003	0.32	0.7522	**5.05**	**<.0001**
	Motor vehicle collisions	0.0032	0.95	0.3475	**2.40**	**0.0155**
	Assaults	-0.0022	-1.44	0.1553	**3.32**	**0.0013**
	Falls	**0.0042**	**2.62**	**0.0107**	**2.18**	**0.0274**
Females, 26 and over	Total alcohol-related	-0.0006	-0.66	0.5111	**3.80**	**0.0004**
	Motor vehicle collisions	-0.0007	-0.21	0.8368	1.44	0.1776
	Assaults	-0.0020	-0.89	0.3777	**2.33**	**0.0184**
	Falls	0.0012	1.07	0.2877	1.74	0.0865

Notes:

Significant results at the 5% level in **bold**. Seasonality is tested with a Type 3 Test of fixed effects with 11 numerator degrees of freedom and 60 denominator degrees of freedom.

ED: Emergency department.

Table B-2: Estimated changes in rates of ED visits by category, age and gender groups associated with an alcohol minimum price increase in Saskatchewan, Canada

			Intervention model				**Continuous average minimum price model**			
			Partially-adjusted		**Fully-adjusted**		**Partially-adjusted**		**Fully-adjusted**	
Gender-Age Group	**ED visit category**	**ARIMA model**	**Parameter estimate**	**p-value**	**Parameter estimate**	**p-value**	**Parameter estimate**	**p-value**	**Parameter estimate**	**p-value**
Males, 13 to 25	Total A-R	(0,1,1) x$(0,1,1)_{12}$	-0.0033	0.9737	0.0354	0.7174	-0.1231	0.8836	0.2889	0.7031
	MVC	(0,1,1)	0.1546	0.6771	-0.2310	0.3586	0.0727	0.9805	-0.0085	0.9974
	Assaults	(0,1,1) x$(0,1,1)_{12}$	-0.0537	0.6885	-0.0070	0.9581	-0.4912	0.6651	0.2371	0.8245
	Falls	none	0.1086	0.2626	0.1070	0.2834	2.1311	0.0497	2.1208	0.0542
Females, 13 to 25	Total A-R	none	0.0335	0.6299	0.0122	0.8557	0.4536	0.5686	0.3481	0.6479
	MVC	none	0.0150	0.9342	0.0253	0.8904	1.1647	0.5755	1.2745	0.5424
	Assaults	none	0.1190	0.2346	0.1144	0.2506	1.9677	0.0839	1.9949	0.0776
	Falls	(0,1,1)	0.0479	0.7282	0.0495	0.7239	0.4043	0.7967	0.5056	0.7516
Males, 26 and over	Total A-R	$(0,1,1)_{12}$	0.0355	0.4549	0.0323	0.4948	0.41300	0.4223	0.3922	0.4506
	MVC	$(0,1,1)_{12}$	-0.1015	0.6056	-0.1230	0.5354	-0.1585	0.9414	-0.6130	0.7817
	Assaults	(0,0,5) x$(0,1,1)_{12}$	-0.0572	0.3711	-0.0759	0.2397	-0.4698	0.5198	-0.7704	0.3007
	Falls	(0,1,1) x$(0,1,1)_{12}$	0.1644	0.4695	0.1769	0.2978	0.8739	0.6490	0.9699	0.5289
Females, 26 and over	Total A-R	$(0,1,1)_{12}$	0.0074	0.8791	0.0049	0.9229	0.2083	0.6964	0.1941	0.7210
	MVC	(1,0,1)	-0.2365	0.4035	-0.2409	0.1179	-2.6638	0.3667	-2.5658	0.1630
	Assaults	$(0,1,1)_{12}$	0.0164	0.8917	0.0191	0.8740	0.5017	0.6949	0.4399	0.7303
	Falls	(2,0,0)	0.0248	0.5990	0.0173	0.7210	0.2208	0.6838	0.1627	0.7686

Notes

1. ARIMA models are given in standard notation. For example, the ARIMA model chosen for assaults among males 13 to 25 has d=1, q=1 (corresponding to a linear trend and moving average term of 1) and has D=12, Q=12 (corresponding to a seasonal trend with a moving average term).
2. The estimate of the intervention effect is the percent change (estimate x 100) in the rate of ED visits. In the average minimum price model, the estimate is the percent change in the rate of ED visits associated with a 1.0% increase in minimum price.
3. Bonferroni family-wise correction applied to α=0.05 level, with eight tests per family. Significance levels <0.05/8=0.00625 in boldface (**none**).

ED: Emergency department.

ARIMA: Auto-regressive integrated moving average.

Total A-R: Total alcohol-related injury visits.

MVC: Motor vehicle collisions.

Table B-3: Monthly lagged effects from Month 3 to Month 6 for the effect of a minimum price intervention on rates of different types of ED visits by gender-age group

		Males, 13 to 25		Females, 13 to 25		Males, 26 and over		Females, 26 and over	
	Lag	**Estimate**	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**	**Estimate**	**p-value**
Total alcohol-related injuries	Month 3	0.01763	0.8188	0.0041449	0.9528	0.05423	0.2839	-0.003399	0.9467
	Month 4	-0.00587	0.9480	-0.01329	0.8497	0.06026	0.2479	0.000350	0.9946
	Month 5	0.04043	0.6178	-0.01745	0.8076	0.08382	0.1163	0.005077	0.9189
	Month 6	0.06653	0.3668	-0.01333	0.8565	0.07956	0.1447	0.01331	0.7925
Motor vehicle collisions	Month 3	-0.17950	0.5102	0.07060	0.7159	0.09427	0.6279	-0.23649	0.1582
	Month 4	0.17642	0.3019	0.02648	0.8920	0.14172	0.4775	-0.29056	0.0199
	Month 5	-0.14483	0.5379	-0.005783	0.9769	0.25200	0.2256	-0.30962	0.0344
	Month 6	0.05416	0.7764	0.01184	0.9537	0.27143	0.2029	**-0.39426**	**0.0007**
Assaults	Month 3	0.01244	0.9189	0.06833	0.5143	-0.07569	0.3064	0.01584	0.8971
	Month 4	-0.10592	0.4829	0.01769	0.8695	-0.06995	0.3659	-0.000085	0.9994
	Month 5	-0.05111	0.6977	-0.01663	0.8822	-0.09505	0.2073	-0.04768	0.7021
	Month 6	-0.11291	0.4216	-0.02050	0.8572	-0.10207	0.1786	-0.08216	0.5105
Falls	Month 3	0.08458	0.4502	0.15177	0.2648	0.31260	0.0248	0.03829	0.4686
	Month 4	0.03239	0.7777	-0.16762	0.1821	0.36313	0.0633	0.02228	0.6819
	Month 5	0.14586	0.1892	0.25318	0.0788	0.32081	0.1135	0.02349	0.6568
	Month 6	0.15131	0.1866	0.25592	0.0633	0.19656	0.2463	0.05740	0.2848

Notes:

1. The estimates of lagged effects of the intervention effect are the percent change (estimate x 100) in the rate of ED visits.

2. Bonferroni family-wise correction applied to α=0.05 level, with 16 tests per family. Significance levels <0.05/16=0.003125 in boldface.

ED: Emergency department.

Taken together, these results conclude that the implementation of higher alcohol minimum prices in Saskatchewan did not appear to be significantly associated with an abrupt effect on alcohol-related ED visits in any of the four injury categories by four age-gender groups. More comprehensive results, including estimates from the beer, wine and spirits minimum price models can be found in Appendix B-4.

Results of the tested lagged effects are presented in Table B-3. There was a significant lagged reduction in motor vehicle collision-related ED visits for women aged 26 and over in the intervention model. The minimum price intervention was associated with a lagged 39.4% reduction in MVA visits in month 6. These lagged associations correspond broadly to the lagged effect of the intervention found on consumption in previous work (Stockwell et al., 2017c).

3.5 Discussion

This study aimed to discern the effect of the implementation of a higher alcohol minimum price on nighttime ED visits in four alcohol-related injury categories. Our results support the existence of a significant lagged effect of an alcohol minimum price intervention on motor vehicle collision-related visits for women aged 26 and over. The implementation of new, higher minimum price levels in Saskatchewan was associated with an approximately 40% reduction in MVCs for this population six months after the policy intervention. It was appropriate to test for lagged effects as previous research had identified a lagged effect of the intervention on alcohol consumption occurring at on-premise locations such as bars and restaurants (Stockwell et al., 2017a); this may reflect a stockpiling of still-cheap alcohol by establishments in the months before the policy was applied. On-premise pricing would then increase to reflect price changes only after stockpiles were diminished, resulting in delays of several months before owners passed these increased prices on to consumers. We note that our previous analysis regarding the effect of this pricing policy on consumption (Stockwell et al., 2012) did not decompose consumption decreases by gender and age group. Due to this large decrease in MVC-related visits for women 26 and older, it may be that the consumption decrease would be found to be greatest for this population; this is an interesting direction for future work in this area.

Most notably, the modeling of the immediate effect of the intervention on four categories of alcohol-related injury ED visits showed no effect of the intervention on the rate of these visits.

Given that our team's previous work studying this price intervention in Saskatchewan found decreased consumption and crime (Stockwell et al., 2012; Stockwell et al., 2017a), and taken in combination with work in British Columbia showing a strong effect of pricing policies on consumption and morbidity (Stockwell et al., 2009b; Stockwell et al., 2013), it is surprising that there was no detected immediate association between the pricing intervention and the rate of alcohol-related injury ED visits. It is possible that the study limitations discussed below may have obscured any true effect of the minimum price intervention on rate time series. We note that the rate of ED visits among males 13 to 25 for total alcohol-related injuries, MVCs and assaults decreased substantially during the study period; however, the analyses did not find a statistical link between this decrease and the minimum price intervention. It may be that already decreasing rates within this gender-age group most impacted by alcohol-related injuries may have made it more difficult to detect significant changes associated with the intervention itself due to the statistical removal of the trend term in ARIMA modeling (SAS Institute, 2011). Further, a previous analysis on lagged consumption changes due to the intervention (Stockwell et al., 2017c) concluded that off-premise sales were abruptly affected while on-premise sales decreased only after a period of 3-4 months. We suggest there could therefore be a diffuse impact on the acute alcohol-related ED visits studied here because of the mixture of immediate impacts on off-premise sales and more delayed impacts on on-premise sales.

An important aim of this study was to test the hypothesis that the minimum price intervention was associated with decreased rates of alcohol-related ED visits. This main hypothesis was not substantiated by our study results. We note that the publication of largely null results shows a commitment to the scientific process and provides a counterbalance to the critique of publication bias – that significant results supporting author's hypotheses are more likely to be published than findings that do not support those hypotheses. Further, null results are important for the accuracy of meta-analyses that may be built from constituent studies such as this.

This study draws from significant strengths. The administrative data used were of excellent quality: ED data comprised a census of all ED visits in the study location and minimum pricing information was received directly from the government agency responsible for setting alcohol policy. As well, data used for adjustment, such as income and CPI information, was drawn from comprehensive government sources. Next, the acquired administrative data allowed

the construction of time series with 72 monthly values, well above the minimum needed for ARIMA time series analysis.

A number of limitations of this study must be acknowledged. Due to limitations with data reporting and collection, the ED data obtained from this study only includes information from hospitals in one major city, Regina, which contains approximately 20% of the provincial population. It is likely that higher population coverage would result in more stable ED rate time series and conceivable that this would lead to the finding of more significant intervention effects. As with any ecological study, the dependent variables may be influenced by variables beyond our control and measurement, which could potentially confound the relationships of interest. We adjusted for economic variables, such as CPI and personal income, as these are known to have a strong influence on alcohol purchasing and consumption. Our time series analysis included six years of data described monthly, resulting in 72 data points. Though this meets the minimum number of observations necessary for specification of ARIMA models, only two years of data were available after the implementation of the minimum price; this may weaken the interpretation of effect. Last, we note that alcohol sales in the two year period before the minimum price intervention coincided with the global financial crisis and associated decreased purchasing power which may have had the effect of moderating the abrupt effect of the intervention. In light of these limitations, and as with any study, the results should be interpreted with caution and considered in the context of a wider literature on alcohol policy and public health.

3.6 Conclusion

To conclude, this study provides evidence that increased alcohol minimum prices in Saskatchewan were associated with a lagged decrease in alcohol-related injury ED visits through the reduction of motor vehicle accident visits for adult women. Notably, the main study hypothesis, that this policy intervention would be associated with an abrupt decrease in alcohol-related injury ED visits, was not substantiated. However, taken together with other research regarding this intervention, which reported reduced consumption (Stockwell et al., 2012) and alcohol-related crime (Stockwell et al., 2017c), it appears that Saskatchewan’s application of

higher minimum prices to alcohol is likely to have been associated with generally positive health and safety benefits.

3.7 Acknowledgements

This study was supported by a Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award (CGS-D) and a University of Victoria President's Scholarship awarded to the first author.

The authors would like to thank the Saskatchewan Ministry of Health for providing the ED data and the Saskatchewan Liquor and Gaming Authority for providing the alcohol sales and pricing data.

The first author would like to thank CISUR Scientist Dr. Jinhui Zhao for his advice regarding the SAS ARIMA statistical analyses.

Chapter 4: Development and Specification of the International Model of Alcohol Harms and Policies: A Comprehensive Guide to the Estimation of Alcohol-Attributable Morbidity and Mortality [Study C]

4.1 Introduction

The International Model of Alcohol Harms and Policies (InterMAHP) is intended to provide comprehensive methods and support to international alcohol epidemiologists in order to allow the calculation of alcohol-attributable fractions (AAFs) for their region, be it a country, province, state or city. Given a set of typically available data on alcohol exposure and prevalence, as well as count data on the number of hospitalizations and deaths within their region, InterMAHP allows users to calculate, using internationally standardized and well-documented methodologies, AAFs for all alcohol-related conditions.

Figure C-1: InterMAHP Logo

It is the hope of the authors that this comprehensive guide will provide the international alcohol epidemiology community with a *standard set of methodologies* which, when adopted by a critical number of alcohol researchers, will result in more comparable estimates of alcohol-attributable (AA) harm across global jurisdictions. Although InterMAHP comes with a default set of assumptions (such as which risk curves to use and which factors to apply to *per capita* consumption), it was also designed to be easily adaptable should researchers prefer to change

these assumptions to meet their needs or assumption for their region. For example, all relative risk (RR) functions are easily exchangeable at the input stage.

It is important to note that InterMAHP is a methodological supplement to, but not a replacement for, programs of work calculating and interpreting AA harms. There is a significant volume of work which cannot be generalized to the international level; this includes understanding the design of a region's administrative health databases, local area knowledge on surveys designed to capture drinking prevalence and relative consumption and the sources and validity of alcohol sales data, all of which are necessary to any project towards estimating AA harms.

In some regards, InterMAHP comprises an updated version of the alcohol section of the well-recognized English and Holman publication (English et al., 1995). Similarities between the two reports are significant: the relative risk relationship for each alcohol-related condition is studied and reported, though English et al. (1995) completed many meta-analyses as part of the report, general considerations for estimating alcohol-attributable morbidity and mortality are treated and AAF methodologies are presented. However, an important extension of InterMAHP is the creation and distribution of a downloadable program tool which, given certain necessary input, automates the calculation of AAFs.

InterMAHP also provides several novel functionalities to alcohol epidemiologists in the ability to (1) study the contribution to overall AAFs of four user-specified drinking groups (former, light, moderate and heavy drinkers) and (2) dynamically change the upper limit of consumption among the drinking population in their region. These functionalities are described in detail in Section 4.6.

4.2 Statements Regarding Replicability, Modularity and GATHER

4.2.1 A Statement on Replicability

This guide is meant to make InterMAHP AAF calculations completely replicable, i.e one should be able to re-create the InterMAHP AAF program given the detailed methodologies outlined herein. Our aim is that every value, assumption, calculation, risk function and risk estimate is comprehensively sourced down to the article and table number. We also include the citation of any personal correspondence between the authorship team of this guide and article authors,

where acquiring unpublished information was necessary (such as the functional RR equation, which are often not included in the published version).

It is likely that the least transparent methodology in this guide is the one given for injuries. Although the main relationship between chronic alcohol consumption and injury is taken from the published literature (Corrao, Bagnardi, Zambon & Arico, 1999), a custom analysis was completed in order to calculate the risk of binge drinking as compared to the risk of non-binge drinking, controlling for average drinking volume. This analysis has not been published and therefore the methods are presented in Section 4.5.4.3. It is currently under review in *Addiction*; information on the method is available upon request and detailed methodologies presented in the article are beyond the scope of this dissertation. This is the only instance in this guide where a published source is not given for the assumptions and values involved in the methodologies.

4.2.2 Modularity of Relative Risk Functions and Estimates

InterMAHP was designed in order to make it a simple process to replace the RR functions representing the dose-response relationship for current drinkers and the categorical RR estimates for former drinkers. Although InterMAHP comes with a default set of RR functions and estimates (see Table C-2), this default set is easily adapted to region-specific RR information. In this way, InterMAHP can be easily updated when more recent meta-analyses for a certain condition become available or if your team would prefer to use a region-specific meta-analysis for certain relative risks.

4.2.3 A Statement on GATHER Compatibility

The Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (Stevens et al., 2016) define best reporting practices for estimating population health. GATHER forwards 18 items necessary for best reporting practice.

InterMAHP is GATHER compatible, except for item #16, uncertainty estimates. InterMAHP does not currently automate the calculation of quantitative uncertainty estimates; however, note that subsequent versions of InterMAHP will be expanded to include uncertainty estimates using Monte Carlo (MC) simulations.

4.3 General Methods for Calculating AA Morbidity and Mortality

This section provides an overview of the general methods for calculating AA morbidity and mortality. Significant efforts in the field have previously tackled this issue (English et al., 1995; World Health Organization, 2000) and so this section provides only a general overview; readers may turn to more comprehensive treatments, if necessary. Table C-1 presents a step-by-step procedure which will result in estimates of AA morbidity and mortality in your region; the remainder of this section will expand on each step.

4.3.1 Estimation of Exposure to Alcohol, Consumption and Prevalence

Region-specific data will be required in order to drive the estimation of InterMAHP AAFs based on the unique input from your region. If your team has been working in alcohol research for some time, it is likely that you collectively have strong knowledge of the information sources necessary to estimate the consumption and prevalence data needed to run the InterMAHP program. Specifically, you will need to acquire:

(1) an estimate of *per capita* alcohol consumption (in litres ethanol per year) for the population aged 15+;
(2) a likely survey-based measure of the relative alcohol consumption among the population subgroups defined by InterMAHP;
(3) by subgroup, the prevalence of current drinkers;
(4) by subgroup, the prevalence of binge drinkers;
(5) by subgroup, the prevalence of former drinkers, and;
(6) by subgroup, the prevalence of lifetime abstainers.

The calculation of these data requires specific knowledge of the sources of information used, for example the survey design and weighting schema for each prevalence source. It is currently beyond the scope of this dissertation to discuss general survey calculations such as item nonresponse treatment and imputation or weighting and therefore this expertise falls to each region to understand their data sources comprehensively. Additional considerations for calculating these estimates are now discussed.

Table C-1: Procedure list for the estimation of alcohol-attributable mortality and morbidity

Step	Description	Source
1 **Estimate population exposure to alcohol**	Using data available in your region, information must be collected on *per capita* consumption, relative consumption among gender-age population subgroups and drinking and bingeing prevalences.	Your region
2 **Identify alcohol-related conditions**	Comprehensively review the alcohol epidemiological literature to decide which conditions and diseases are causally related to alcohol consumption. InterMAHP provides a standard list that is detailed in Table C-2.	InterMAHP provides standard list
3 **Operationalize alcohol-related conditions**	Typically, medical diagnoses in health databases are represented by ICD10 codes. For each alcohol-related condition identified in Step 2, the ICD10 codes corresponding to the condition must be identified (e.g. liver cancer is identified by ICD10 code C22). The InterMAHP crosswalk is specified in Table C-2.	InterMAHP provides standard ICD10 crosswalk
4 **Enumerate alcohol-related morbidity and mortality for each condition**	In order to apply AAFs, the total number of morbidities and mortalities for each alcohol-related condition must be enumerated in your region, by population subgroup.	Your region

5 **Assign alcohol-related conditions as 100% or partially-attributable**	Wholly/100% attributable conditions have, by definition, AAFs = 1.0, while AAFs for partially-attributable conditions must be calculated by either the direct or indirect method.	InterMAHP provides standard list
6 **Decide between direct and indirect AAFs for partially-attributable conditions**	AAFs for partially-attributable conditions can be calculated using either the direct or indirect method. Considerations towards this decision are expanded upon in Section 4.3.6.	Your region / InterMAHP provides advice
7 **Calculate AAFs for partially attributable conditions**	All partially attributable conditions will need AAFs. These may be either direct or indirect AAFs. InterMAHP will automatically calculate indirect AAFs for all partially attributable alcohol-related conditions.	InterMAHP automates the calculation of indirect AAFs based on your input
8 **Multiply enumerated counts by AAFs to estimate AA harms**	Once enumerated totals and AAFs are calculated, these two results are multiplied together to produce the burden of AA morbidity and mortality in your region.	Your region

4.3.1.1 Estimation of Total Per Capita Consumption

An estimate of *per capita* consumption (PCC) for the entire population aged 15 and older in each region and year of interest is necessary as input. There are two sources typically used as basis for these estimates: (1) official sales or tax receipts and (2) survey-based estimates of self-reported consumption. Each source has potential positives and negatives, and a detailed review is beyond the scope of this document. However, briefly, official sales or tax receipts will not include spillage (i.e. wasted alcohol), tourist import/exports or alcohol made at home or in make-your-own stores. Conversely, it is well-known that there is significant underreporting of consumption in alcohol surveys, e.g. see Stockwell et al. (2016a) or Rehm & Room (2009) among many, and surveys may miss or under-sample certain drinking groups such as dependent drinkers and students. However, the InterMAHP methodology is indifferent to your choice and so functionally supports the choice of either source of information.

Once one of these methods has been decided upon as an estimate basis, you should consider modifying this value based on any additional, region-specific information available on additional factors, such as known imports/exports, spillage, alcohol made at home or in make-your-own stores. These decisions are left to your team as the local-area experts.

The final estimate of PCC, in litres of ethanol per year, will include any of these adjustments which you decide to make and will then be inputted into InterMAHP as a single figure (e.g. 9.0 litres / year) for the entire population 15+ (not broken down by gender-age population subgroup). The decision was made to import this figure for the population 15+ as this is typically how government sources make the data available at the country, province or state level.

4.3.1.2 Estimation of Prevalence and Relative Consumption

Survey-based information on the prevalence of current, binge, former and never drinkers, as well as a measure of relative consumption between population subgroups is necessary for InterMAHP. Five variables must be calculated for each population subgroup; these are listed previously in Section 4.3.1.

4.3.2 Causation and Identification of Alcohol-Related Conditions

A foundational step in calculating AA morbidity and mortality is identifying which conditions are causally related to the consumption of alcohol and therefore need to be considered when estimating harms. Identifying alcohol-related conditions has been undertaken over decades by the alcohol epidemiological and medical communities and continues to evolve. Generally, in order for alcohol to be accepted as causative for the development of a health condition, there must be an overwhelming consensus in the scientific literature on this association.

For InterMAHP, we have created our condition list from several articles and reports from members of the authorship group (Rehm et al., 2010a; Rehm et al., 2017a; Rehm, Sherk, Shield & Gmel, 2017). The InterMAHP alcohol-related condition list, with operationalizing ICD10 codes, InterMAHP number and condition category are shown in Table C-2. This table is complete with comprehensive causation sourcing as to the causative link between alcohol and each condition (Rehm et al., 2017a).

A limitation of InterMAHP is the exclusion of Fetal Alcohol Spectrum Disorder (FASD) / Fetal Alcohol Syndrome (FAS) from the list of alcohol-related conditions for which AAFs can be calculated. It has been shown that mortality data due to FASD/FAS is not well recorded (Rehm et al., 2017a; World Health Organization, 2014, 2018); due to this reason harm estimates may instead be made based on prevalence estimates on drinking during pregnancy (Popova et al., 2017). However, as this prevalence of drinking during pregnancy is much scarcer than the other prevalence information required for InterMAHP, it was decided to omit FASD/FAD in order to keep the data requirements more attainable.

Additionally, we note that FASD/FAD is a condition that is not experienced by the drinkers themselves and therefore falls into the category of harm-to-others. InterMAHP is currently focused on providing methodologies for calculating harm to drinkers only; however, we note that this is a source of underestimation in InterMAHP.

4.3.3 Operationalization of Alcohol-Related Conditions Using ICD10 Codes

Many countries have advanced administrative health data systems, i.e. when patients experience mortalities and morbidities it is commonplace to record the diagnoses associated with their event and other information such as gender and age; this information is then made broadly available to

researchers. To ensure international comparability, diagnoses are translated into International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) codes (World Health Organization, 2016). This classification is a comparable and comprehensive list of health diagnoses created and maintained by the World Health Organization (WHO). In InterMAHP, alcohol-related conditions (e.g. liver cirrhosis) are operationalized by their corresponding ICD10 codes (K70.* and K74.*). InterMAHP gives the example of ICD10 codes to operationalize alcohol-related conditions; however, it should be noted that it is possible to operationalize conditions using other categorizations such as ICD9, DSM-IV or DSM-5, but these definitions are not included in this methodological description of InterMAHP. Comprehensive ICD10 coding is provided in Table C-2.

4.3.4 Enumeration of Alcohol-Related Morbidity and Mortality for Each Condition

This step requires region-specific knowledge on the sources and format of mortality and morbidity databases, the structure and access to which vary greatly by international jurisdiction. For example, in the Canadian context, counts of hospitalization discharges by year, region, condition, gender and age group must be requested from the Canadian Institute for Health Information, the national organizer of all Canadian hospital discharge information. In order to collate similar national mortality data, it is necessary to acquire access to Statistics Canada's Vital Statistics Database, or submit a data request resulting in the same summary. However, in Sweden for mortality, there exists a publicly accessible website called the Swedish Health and Welfare Database that can be used to enumerate mortalities by ICD10 condition code, year, gender and age group. In short, the ease and availability of access to morbidity and mortality is highly dependent on your region and requires varying degrees of analytic sophistication to acquire and analyze. It therefore falls to your local knowledge of your region's health data systems to complete this step.

What is necessary, for each population subgroup of interest, is to tally the number of mortalities and morbidities that occurred for each alcohol-related condition in a given year. Many databases allow for entry of more than one diagnosis on each record or discharge. We must consider when to include the diagnosis codes present in Table C-2 in the enumeration of each condition. The default recommendation is, for all non-injury codes, to only count a record as an alcohol-related condition if the corresponding ICD10 code is the primary diagnosis of that

Table C-2: InterMAHP alcohol-related conditions with condition groupings, ICD10 code operationalization and causation references

Condition Group	Condition	IM #	ICD10 codes (Primary Dx)	ICD10 codes (External)	Partial or 100% attributable	Causation
(1) Communicable Diseases	Tuberculosis	(1).(1)	A15 – A19		Partial	Rehm et al. (2009)
	HIV	(1).(2)	B20 – B24, Z21		Partial	Williams et al. (2016) Rehm, Probst, Shield and Shuper (2017)
	Lower respiratory tract infections	(1).(3)	J09 – J22		Partial	A. Samokhvalov, H. Irving and J. Rehm (2010) Traphagen, Tian and Allen-Gipson (2015)
(2) Cancer	Oral cavity and pharynx cancer	(2).(1)	C00 – C05, C08 – C10, C12 – C14, D00.0		Partial	International Agency for Research on Cancer (2010) International Agency for Research on Cancer (2012) Bagnardi et al. (2015)
	Oesophageal cancer, squamous cell carcinoma	(2).(2)	C15, D00.1 (portional only)		Partial	
	Colorectal cancer	(2).(3)	C18 – C21, D01.0-D01.4		Partial	
	Liver cancer	(2).(4)	C22, D01.5		Partial	
	Pancreatic cancer	(2).(5)	C25, D01.7		Partial	
	Laryngeal cancer	(2).(6)	C32, D02.0		Partial	
	Breast cancer	(2).(7)	C50, D05		Partial	
(3)	Diabetes mellitus, Type 2	(3).(1)	E11, E13, E14		Partial	Howard, Arnsten and Gourevitch (2004)

Endocrine conditions	Alcohol-induced pseudo-Cushing's syndrome	(3).(2)	E24.4		100%	Alcohol-caused by definition
(4) Neuro-psychiatric conditions	Alcoholic psychoses	(4).(1)	F10.0, F10.3 – F10.9		100%	Alcohol-caused by definition
	Alcohol abuse	(4).(2)	F10.1		100%	Alcohol-caused by definition
	Alcohol dependence syndrome	(4).(3)	F10.2		100%	Alcohol-caused by definition
	Degeneration of nervous system due to alcohol	(4).(4)	G31.2		100%	Alcohol-caused by definition
	Epilepsy	(4).(5)	G40, G41		Partial	Bartolomei (2006) Barclay et al. (2008) Leach, Mohanraj and Borland (2012)
	Alcoholic polyneuropathy	(4).(6)	G62.1		100%	Alcohol-caused by definition
	Alcoholic myopathy	(4).(7)	G72.1		100%	Alcohol-caused by definition
(5) Cardiovascular conditions	Hypertension	(5).(1)	I10 – I15		Partial	Puddey and Beilin (2006) O'Keefe et al. (2014)
	Ischaemic heart disease	(5).(2)	I20 – I25		Partial	Mukamal and Rimm (2001) Collins et al. (2009) Roerecke and Rehm (2012) Zhao et al. (2017)
	Alcoholic cardiomyopathy	(5).(3)	I42.6		100%	Alcohol-caused by definition
	Atrial fibrillation and cardiac arrhythmia	(5).(4)	I47 – I49		Partial	Rosenqvist (1998) Mukamal, Ding and Djoussé (2006)

	Haemorrhagic stroke	(5).(5)	I60 – I62, I69.0 – I69.2		Partial	Puddey, Rakic, Dimmitt and Beilin (1999) Mazzaglia, Britton, Altmann and Chenet (2001)
	Ischaemic stroke	(5).(6)	I63 – I67, I69.3 – I69.4		Partial	Puddey et al. (1999) Mazzaglia et al. (2001) Collins et al. (2009)
	Oesophageal varices	(5).(7)	I85		Partial	Typically caused by liver cirrhosis
(6) Digestive conditions	Alcoholic gastritis	(6).(1)	K29.2		100%	Alcohol-caused by definition
	Liver cirrhosis	(6).(2)	K70,K74		Partial	Gao and Bataller (2011) Rehm et al. (2010)
	Acute pancreatitis	(6).(3)	K85.0 – K85.1, K85.8 – K85.9		Partial	Yadav and Lowenfels (2013) Lankisch, Apte and Banks (2015)
	Chronic pancreatitis	(6).(4)	K86.1 – K86.9		Partial	Lankisch et al. (2015) Braganza, Lee, McCloy and McMahon (2011) Majumder and Chari (2016)
	Alcohol-induced pancreatitis	(6).(5)	K85.2, K86.0		100%	Alcohol-caused by definition
(7) Motor vehicle collisions	Motor vehicle collisions	(7).(1)		V1*, Y85.0	Partial	Movig et al. (2004) Skog (2001)
(8) Unintentional injuries	Falls	(8).(1)		W00-W19, Y30	Partial	Smith, Branas and Miller (1999)
	Drowning	(8).(2)		W65 – W74	Partial	Smith et al. (1999)
	Fires	(8).(3)		X00 – X09, Y26	Partial	Smith et al. (1999)
	Accidental poisoning by	(8).(4)		X40-X44, X46-X49,	Partial	Smith et al. (1999)

	substances other than alcohol			Y10-Y14, Y16-Y19		
	Accidental poisoning by alcohol	(8).(5)	T51	X45, Y15	100%	Alcohol-caused by definition
	Other unintentional injuries	(8).(6)		V2*, W20 – W64, W75 – W84, X10 – X33, Y20, Y22-Y25, Y27-Y29, Y31-Y34, Y85.9, Y86, Y87.2, Y89.9	Partial	Included in WHO Global Burden of Disease and Global Status Report on Alcohol and Health studies
(9) Intentional injuries	Intentional self-poisoning by substances other than alcohol	(9).(1)		X60-X64, X66-X69	Partial	Smith et al. (1999)
	Intentional self-poisoning by alcohol	(9).(2)	T51	X65	100%	Alcohol-caused by definition
	Other intentional self-harm	(9).(3)		X70-X84, Y87.0	Partial	Included in WHO Global Burden of Disease and Global Status Report on Alcohol and Health studies
	Assault / homicide	(9).(4)		X85 – Y09 Y87.1	Partial	Smith et al. (1999)

	Other intentional injuries	(9).(5)		Y35, Y89.0	Partial	Included in WHO Global Burden of Disease and Global Status Report on Alcohol and Health studies

V1*: V02.1, V02.9, V03.1, V03.9, V04.1, V04.9, V09.2, V09.3, V12.3 – V12.9, V13.3 – V13.9, V14.3 – V14.9, V19.4, V19.5, V19.6, V19.9, V20.3 – V20.9, V21.3 – V21.9, V22.3 – V22.9, V23.3 – V23.9, V24.3 – V24.9, V25.3 – V25.9, V26.3 – V26.9, V27.3 – V27.9, V28.3 – V28.9, V29.4, V29.5, V29.6, V29.9, V30.4 – V30.9, V31.4 – V31.9, V32.4 – V32.9, V33.4 – V33.9, V34.4 –, V34.9, V35.4 – V35.9, V36.4 – V36.9, V37.4 – V37.9, V38.4 – V38.9, V39.4, V39.5, V39.6, V39.9, V40.4 – V40.9, V41.4 – V41.9, V42.4 – V42.9, V43.4 – V43.9, V44.4 – V44.9, V45.4 – V45.9, V46.4 – V46.9, V47.4 – V47.9, V48.4 – V48.9, V49.4, V49.5, V49.6, V49.9, V50.4 – V50.9, V51.4 – V51.9, V52.4 – V52.9, V53.4 – V53.9, V54.4 – V54.9, V55.4 – V55.9, V56.4 – V56.9, V57.4 – V57.9, V58.4 – V58.9, V59.4, V59.5, V59.6, V59.9, V60.4 – V60.9, V61.4 – V61.9, V62.4 – V62.9, V63.4 – V63.9, V64.4 – V64.9, V65.4 – V65.9, V66.4 – V66.9, V67.4 – V67.9, V68.4 – V68.9, V69.4, V69.5, V69.6, V69.9, V70.4 – V70.9, V71.4 – V71.9, V72.4 – V72.9, V73.4 – V73.9, V74.4 – V74.9, V75.4 – V75.9, V76.4 – V76.9, V77.4 – V77.9, V78.4 – V78.9, V79.4, V79.5, V79.6, V79.9, V80.3, V80.4, V80.5, V81.1, V82.1, V83.4, V84.4, V85.4, V86.0, V86.1, V86.3, V87.0 – V87.9, V89.2, V89.3, V89.9

V2*: All other ICD10 codes beginning with V.

record (sometime called most responsible diagnosis, depending on the region). In Table C-2, these conditions have ICD10 codes in the *ICD10 codes (Primary Dx)* column.

Injury categories, and in particular poisonings, must be treated with more care as there are often multiple alcohol-related diagnoses on the same record and they do not necessarily appear in the primary diagnosis position. Consider the following example of a driver involved in a motor vehicle collision with another car (ICD10 code V43.5) which resulted in a broken leg (specifically a fracture of the upper end of the tibia, represented by S82.1) of an involved patient. The primary diagnosis, the main reason why the patient is in hospital, is coded as S82.1; however, for our purposes, we require an external cause code that contains the information that the patient is in the hospital because of a motor vehicle collision. To our knowledge, this is virtually always coded elsewhere on the record; depending on the jurisdiction, this may be recorded as an external cause of injury code or a secondary diagnosis. Again, in short, knowledge of this coding structure, and how to interpret it in relation to alcohol-related injury codes, is a necessary component of any project detailing AA harms.

In our experience, it is best to follow these steps in order to categorize each record (discharge, death record) as an alcohol-related condition, if necessary:

(1) First categorize each record by primary diagnosis. This applies to all non-injury conditions, as well as injury poisonings with a primary diagnosis of T36-T65 or T95-T98.
(2) For records classified as injury poisoning in (1), next search for intent, i.e. whether the poisoning was intentional or accidental. This is done by searching the other diagnoses present on the record for the codes listed in Table C-2 for IM# (8).(4), (8).(5), (9).(1), (9).(2). Poisonings are often complex in terms of clinical causation and may have multiple ICD10 codes present from this list. We recommended using the first one present as diagnoses are typically listed, at least approximately, in order of importance.
(3) For remaining records, which will be injury non-poisoning conditions, search for the first alcohol-related external cause code present on the record. These are the codes listed in Table C-2, column *ICD10 codes (External)*.

We note it is important that each record only be counted in one alcohol-related condition category; otherwise it will lead to significant overestimation of alcohol harms, particularly in regards to injury poisonings.

We further note a conceptual difference between mortality and morbidity when enumerating these conditions. Mortality, by definition, can only occur once per individual. However, typically a 'morbidity' here is an event (such as an inpatient hospitalization or ED visit) that can be experienced more than once by an individual in a given region/year.

4.3.4.1 Special Considerations for Oesophageal Cancer

From Table C-2, we see a special consideration when operationalizing oesophageal cancer using ICD10 codes. Oesophageal cancer is comprised of two main sub-types: squamous cell carcinoma (SCC) and adenocarcinoma (AC); however, alcohol is only causally related to oesophageal SCC (Bagnardi et al., 2015). Further, oesophageal cancer cannot be differentiated into oesophageal SCC or AC by ICD10 coding. It is therefore necessary to acquire a region-specific estimate of the percentage of all oesophageal cancers that are oesophageal SCC and apply this proportional estimate to the enumerated quantity of oesophageal cancers. If this is not done, the number of alcohol-attributable oesophageal cancers will be overestimated.

4.3.5 Assignment of Alcohol-Related Conditions as 100% or Partially Attributable

This and the proceeding two sections will describe three steps necessary to arrive at a complete list of AAFs for each health condition, gender and age group. First, alcohol-related conditions are divided into those that are 100% attributable to alcohol and those that are partially attributable to alcohol. Conditions are categorized as either 100% or partially attributable in Table C-2. Conditions 100% (or wholly) attributable to alcohol are, by definition, caused by drinking. For example, for alcohol dependence syndrome, F10.2, consumption of alcohol is necessary for development of this condition (Rothman, Greenland & Lash, 2008). In the absence of alcohol, it would not be possible for anyone to develop alcohol dependence: therefore, by definition, the AAF of alcohol dependence syndrome is 1.0.

4.3.6 Direct vs. Indirect AAFs for Partially Attributable Conditions

From above, AAFs are set to 1.0 for 100% attributable conditions. For some of the remaining partially attributable conditions, AAFs may be calculated by either the direct or the indirect

method. It may be possible to calculate direct AAFs for conditions/events where it is conceivable to simply test whether involved individuals have consumed alcohol (either by BAC level testing or self-reports) and therefore whether it is likely or certain that alcohol was the cause of the event (Smith et al., 1999; World Health Organization, 2000). Direct AAFs may only be applied to acute conditions, i.e. injuries, and are typically country- or region-specific, as it would be difficult to apply direct AAFs in another context unless the settings are broadly similar (World Health Organization, 2000). Note further the consideration that direct AAFs implicitly assume that a certain level of alcohol use (e.g. BACs above 0.05%) implies direct causation (Canadian Substance Use Costs and Harms Scientific Working Group, 2018; World Health Organization, 2000), unless a correction is made regarding this issue. Despite these potential pitfalls, the local, context-specific nature of direct AAFs lead us to recommend that indirect AAFs calculated by InterMAHP be replaced with region-specific direct AAF, wherever possible.

An example where direct AAFs can be calculated is provided by Canadian motor vehicle collision mortalities. A series of annual reports published by the Canadian Council of Motor Transport Administrators tallies the total number of motor vehicle accident fatalities and the proportion of these for which the driver tested positive for alcohol (Brown, Vanlaar & Robertson, 2017). If this direct calculation, based on coroner's reports and immediate testing of blood alcohol content, is believed more reliable than the calculation of an indirect AAF for motor vehicle collisions, then this direct AAF may be substituted to estimate the number of motor vehicle collisions that are alcohol-attributable (Canadian Substance Use Costs and Harms Scientific Working Group, 2018).

4.3.7 Calculation of AAFs for Partially Attributable Conditions

For all remaining conditions, AAFs will be calculated using the indirect (or epidemiological) AF method. Indirect AAFs are calculated using the InterMAHP AAF formula, presented and fully treated in Section 4.5, similar to that employed by the WHO Global Status Reports on Alcohol and Health (World Health Organization, 2014, 2018). Briefly, information on alcohol consumption and prevalence in a region is composed with meta-analyzed relative risk curves representing the dose-response relationship between alcohol and each related condition, as well as the relative risk of former drinkers.

InterMAHP automates and standardizes the calculation of region-specific indirect AAFs based on regional information regarding alcohol consumption and prevalence. Resulting AAFs will be broadly comparable to other international estimates created using the same set of InterMAHP methodologies, allowing for increased international benchmarking and comparison.

4.3.8 Multiplication of Morbidity and Mortality Counts by AAFs

Lastly, by each year, region, condition, gender and age group, the enumerated count of morbidities and mortalities is multiplied by the AAF for the same row. The product is the number of AA morbidities and mortalities; these results can then be aggregated to provide summary tables and overall estimates of AA harm in your region.

4.4 InterMAHP Inputs

This section of the original publication is presented in Appendix C-1. This was done as it largely relates to the online component of InterMAHP, namely the user interface and backend software programming. Recall the online software component is an application of the methodologies defining InterMAHP, but it is outside the scope of this dissertation.

4.5 Methods for Calculating InterMAHP Alcohol-Attributable Fractions

This section provides a detailed description of the methods used by InterMAHP to calculate AAFs. As discussed in the introduction under replicability, the intent of this guide is to provide methods and sources to the extent that the functionality of the InterMAHP program could be entirely replicated based only on the contents presented here: the methods are fully comprehensive.

4.5.1 Modeling the Continuous Prevalence Distribution of Daily Alcohol Consumption

Methods for modeling the continuous prevalence distribution of average daily alcohol consumption in a population given only *per capita* consumption have been described using the Gamma distribution (Kehoe et al., 2012; Rehm et al., 2010b); a probability distribution in the

same family as the Lognormal distribution. As previously discussed in the Introduction, this is a modern functional application of Ledermann's single distribution theory (Skog, 2006), but applied to six population subgroups as opposed to the entire population. Kehoe et al. (2012) modeled the relationship between the mean (μ) and standard deviation (σ) of *per capita* consumption in 66 countries and reported that they formed a consistent ratio, by gender. Using this ratio (σ / μ = 1.258 for women; σ / μ = 1.171 for men) allows us to collapse the usually two-parameter Gamma distribution to a one-parameter distribution (Kehoe et al., 2012). The foundational analyses for this conclusion are presented in a series of articles on the choice of the Gamma distribution and the relationship between the mean and standard deviation (Kehoe et al., 2012; Rehm et al., 2010b). Note that the Gamma distribution is defined by a shape and scale parameter; however, these parameters can also be expressed using only the mean (μ) and standard deviation (σ). It is therefore possible, given the gender-specific ratios above, to reduce the shape and scale parameters to expressions containing only μ; effectively this collapses the Gamma distribution to a single parameter and allows us to model the prevalence distribution using only *per capita* consumption.

This advance allows us to define a Gamma distribution-based prevalence function, which represents the continuous prevalence distribution of average daily alcohol consumption of the current drinkers in a population subgroup, by the following specification:

$$P(x) = \frac{P_{CD}}{nc} f(x;\mu) \qquad \textbf{\textit{Formula C-1}}$$

where *x* is average daily ethanol consumption in grams/day, P_{CD} is the prevalence of current drinkers for each population subgroup in your region, $f(x;\mu)$is the probability density function of the Gamma distribution with a given mean μ, nc is a normalizing correction as formulated in Formula C-2 below (Gmel, Shield, Kehoe-Chan & Rehm, 2013) and *z* is the user-defined upper limit of consumption in your region. If desired, Rehm et al. (2010b) present the mathematical formulation of the Gamma distribution. For a more detailed treatment of the normalizing constant, nc, and an example in a group with high consumption, see Gmel et al. (2013):

$$nc = \int_{0.03}^{z} f(x;\mu)\,dx \qquad \textbf{\textit{Formula C-2}}$$

$P(x)$ represents the prevalence of drinking at each average daily drinking level *x*. The normalizing constant, *nc*, is applied because the usual range of the Gamma distribution is $(0, \infty)$; however, since we restrict the range to $(0.03, z)$ this small adjustment is made so the integration of $P(x)$ over the selected range will equal P_{CD}, the prevalence of current drinkers. This is a requirement of the formulation.

Given this formula and for each population subgroup, we can now mathematically specify the prevalence of drinking at each drinking level *x* in g/day given only P_{CD}, the prevalence of current drinkers and μ, the mean consumption among drinkers in that subgroup. The resulting drinking prevalence curve for each population subgroup is necessary for the calculation of the InterMAHP AAF.

4.5.2 Relative Risk Functions and Estimates Associated with Alcohol Consumption

There are two risk relationships needed in order to fully specify the InterMAHP AAF formula:

(1) for current drinkers - a continuous dose-response relationship between average daily alcohol consumption and the RR of condition morbidity or mortality; and
(2) for former drinkers – a categorical RR estimate.

For each of these relationships, the risk is relative to that of a lifetime abstainer.

4.5.2.1 Continuous Relative Risk Functions for Current Drinkers

For each partially attributable alcohol-related condition, a continuous dose-response relationship between average daily ethanol consumption and risk was estimated by using the most up-to-date, comprehensive meta-analysis existing in the alcohol epidemiological literature. We considered applying quality criteria at this stage, but there are so few meta-analyses for the vast majority of alcohol-related conditions - usually only one, sometimes two – that these criteria would have little effect. This work builds on the foundational work of members of the authorship group, e.g. Rehm et al., (2010a), Rehm et al. (2017a) and Rehm et al. (2017c). A comprehensive update of

continuous RR relationships, as well as the categorical risk experienced by former drinkers, was recently undertaken by members of the authorship group for the purposes of InterMAHP and the 2018 Global Status Report on Alcohol and Health (Rehm et al., 2017c; World Health Organization, 2018).

It was necessary to lean heavily on the methodologies used by the authors of each meta-analysis in regards to modeling the dose-response relationship. However, it is noted that the vast majority of meta-analyses in alcohol epidemiology use the two-term fractional polynomial (FP2) method of modeling dose-response relationships, described in detail in Royston and Sauerbrei (2008) and initially described in Royston, Ambler and Sauerbrei (1999). Briefly, the FP2 method tests 36 two-term and 8 one-term polynomials, with coefficients taken from the limited set [-2,-1,-0.5,0,0.5,1,2,3], where 0 represents $\ln(x)$ and for a two-term polynomial with powers $p_1 = p_2 = p$, x is represented by the vector $x^p = (x^p, x^p lnx)$. Two-term polynomials must show statistical preference as compared to the one-term linear model to be selected. The best fitting polynomial of the 44 tested is selected. More detailed explanations are provided in Royston and Sauerbrei (2008), as well as in many of the meta-analyses which use the FP2 method.

Table C-3 provides a summary table of all partially-attributable alcohol-related conditions in InterMAHP, along with the associated sources for continuous RR functions for current drinkers and categorical RR point estimates for former drinkers. Notice that for some conditions there are distinct RR functions by gender, by outcome (mortality or incidence), or by both. This is broadly based on the amount of epidemiological research that has been done between alcohol consumption and the condition in question. For example, among the seven cancers for which alcohol is definitively causative, only two (colorectal cancer and breast cancer) have differential dose-response relationships by gender. The meta-analysis used for cancer RR functions (Bagnardi et al., 2015), tested for differential effects by each cancer type; however, only colorectal and breast were differential.

Appendix C-2 presents a comprehensive treatment of all partially attributable alcohol-related conditions, including continuous dose-response relationships and categorical RR estimates for former drinkers. Appendix C-2 provides a detailed one-page report for each condition (possibly divided by gender and outcome differences), including comprehensive sourcing, graphs depicting continuous RR curves and notes on methods and abstainer biases.

Table C-3: Continuous and categorical relative risk sources for partially-attributable alcohol-related conditions, by condition group, condition, gender and outcome

Condition Group	Condition	Inter MAHP Number	Gender (Men vs. Women)	Outcome (Morbidity vs. Mortality)	Source for dose-response for current drinkers	Source for RR former drinkers
(1) Communicable diseases	Tuberculosis	(1).(1)	Combined	Combined	Imtiaz et al. (2017) Table 2	N/A as $RR_{FD} = 1.0$
	HIV	(1).(2)	Men	Combined	Rehm et al. (2017b)	N/A as $RR_{FD} = 1.0$
			Women	Combined	Rehm et al. (2017b)	N/A as $RR_{FD} = 1.0$
	Lower respiratory tract infections	(1).(3)	Combined	Combined	A. Samokhvalov et al. (2010) Figure 3	N/A as $RR_{FD} = 1.0$
(2) Cancer	Oral cavity and pharynx cancer	(2).(1)	Combined	Combined	Bagnardi et al. (2015) Figure 3	Marron et al. (2009) Table 2
	Oesophageal cancer	(2).(2)	Combined	Combined	Bagnardi et al. (2015) Figure 3	Marron et al. (2009) Table 2
	Colorectal cancer	(2).(3)	Men	Combined	Bagnardi et al. (2015) Table 3	Schütze et al. (2011) Table 2
			Women	Combined	Bagnardi et al. (2015) Table 3	Schütze et al. (2011) Table 2
	Liver cancer	(2).(4)	Combined	Combined	Corrao, Bagnardi, Zambon & La Vecchia (2004) Figure 3	Schütze et al. (2011) Table 2
	Pancreatic cancer	(2).(5)	Combined	Combined	Bagnardi et al. (2015) Figure 3	Schütze et al. (2011) Table 2
	Laryngeal cancer	(2).(6)	Combined	Combined	Bagnardi et al. (2015) Figure 3	Marron et al. (2009) Table 2
	Breast cancer	(2).(7)	Combined	Combined	Bagnardi et al. (2015)	Schütze et al. (2011)

					Figure 3	Table 2
(3) Endocrine conditions	Diabetes mellitus, Type 2	(3).(1)	Men	Combined	Knott et al. (2015) Figure 3	Reported in Rehm et al. (2010a) from Baliunas et al. (2009)
			Women	Combined	Knott et al. (2015) Figure 3	Reported in Rehm et al. (2010a) from Baliunas et al. (2009)
(4) Neuropsychiatric conditions	Epilepsy	(4).(5)	Combined	Combined	Samokhvalov, Irving, Mohapatra & Rehm (2010) Figure 3	N/A as $RR_{FD} = 1.0$
(5) Cardiovascular conditions	Hypertension	(5).(1)	Men	Combined	Roerecke et al. (in press)	Roerecke et al. (in press)
			Women	Combined	Roerecke et al. (in press)	Roerecke et al. (in press)
	Ischaemic heart disease	(5).(2)	Men	Mortality two options	Zhao et al. (2017) Table 3	Roerecke & Rehm (2010b) Table 3
			Men	Mortality two options	Roerecke & Rehm (2012) Figure 2	Roerecke & Rehm (2010b) Table 3
			Women	Mortality	Roerecke & Rehm (2012) Figure 2	Roerecke & Rehm (2010b) Table 3
			Men	Morbidity two options	Zhao et al. (2017) Table 3	Roerecke & Rehm (2010b) Table 3
			Men	Morbidity two options	Roerecke & Rehm (2012) Figure 2	Roerecke & Rehm (2010b) Table 3
			Women	Morbidity	Roerecke & Rehm (2012) Figure 2	Roerecke & Rehm (2010b) Table 3

	Atrial fibrillation and cardiac arrhythmia	(5).(4)	Combined	Combined	Samokhvalov, Irving & Rehm (2010) Figure 3	Larsson, Drca & Wolk (2014) Table 1
	Haemorrhagic stroke	(5).(5)	Men	Mortality	Patra et al. (2010) Figure 6	Larsson, Wallin, Wolk & Markus (2016) Table S2
			Women	Mortality	Patra et al. (2010) Figure 6	Larsson et al. (2016) Table S2
			Men	Morbidity	Patra et al. (2010) Figure 6	Larsson et al. (2016) Table S2
			Women	Morbidity	Patra et al. (2010) Figure 6	Larsson et al. (2016) Table S2
	Ischaemic stroke	(5).(6)	Men	Mortality	Patra et al. (2010) Figure 7	Larsson et al. (2016) Table S2
			Women	Mortality	Patra et al. (2010) Figure 7	Larsson et al. (2016) Table S2
			Men	Morbidity	Patra et al. (2010) Figure 7	Larsson et al. (2016) Table S2
			Women	Morbidity	Patra et al. (2010) Figure 7	Larsson et al. (2016) Table S2
(6) Digestive conditions	Liver cirrhosis	(6).(2)	Men	Mortality	Rehm et al. (2010c) Figure 2	Roerecke et al. (in press)
			Women	Mortality	Rehm et al. (2010c) Figure 2	Roerecke et al. (in press)
			Men	Morbidity	Rehm et al. (2010c) Figure 2	Roerecke et al. (in press)
			Women	Morbidity	Rehm et al. (2010c) Figure 2	Roerecke et al. (in press)
	Acute pancreatitis	(6).(3)	Men	Combined	Samokhvalov, Rehm & Roerecke (2015) Figure 3, Table 2	Samokhvalov et al., (2015) In discussion
			Women	Combined	Samokhvalov et al. (2015) Figure 4, Table 2	Samokhvalov et al., (2015) In discussion

	Chronic pancreatitis	(6).(4)	Combined	Combined	Samokhvalov et al. (2015) Figure 2, Table 2	Samokhvalov et al., (2015) In discussion
(7) Motor vehicle accidents	Motor vehicle accidents	(7).(1)	Combined	Mortality	Dose-response relationship: Corrao et al. (1999) Table 8 Binge-modified factor: custom analysis from NHIS	N/A as $RR_{FD} = 1.0$
			Combined	Morbidity		N/A as $RR_{FD} = 1.0$
(8) Unintentional injuries	Fires, poisonings, falls, drowning, other unintentional	(8).(1) (8).(2) (8).(4) (8).(5) (8).(6)	Combined	Mortality	Dose-response relationship: Corrao et al. (1999) Table 8 Binge-modified factor: custom analysis from NHIS	N/A as $RR_{FD} = 1.0$
			Combined	Morbidity		N/A as $RR_{FD} = 1.0$
(9) Intentional injuries	Self-inflicted injuries, assault/homicide other intentional	(9).(1) (9).(3) (9).(4)	Combined	Mortality	Dose-response relationship Corrao et al. (1999) Table 8 Binge-modified factor: custom analysis from NHIS	N/A as $RR_{FD} = 1.0$
			Combined	Morbidity		N/A as $RR_{FD} = 1.0$

Note that for oesophageal varices, which are typically caused by liver scar tissue resulting from liver disease, the same AAF as that used for liver cirrhosis is used, by subgroup (Canadian Substance Use Costs and Harms Scientific Working Group, 2018; World Health Organization, 2018). Therefore, oesophageal varices does not have a separate page summary in Section 6.

4.5.2.2 Special Case: Relative Risk Functions for Ischaemic Heart Disease in Men

As seen in Table C-3, virtually all conditions in InterMAHP have default sources for the dose-response and categorical former RR relationships. However, a significant and potentially controversial choice is the source of the dose-response relationship between alcohol consumption and ischaemic heart disease (IHD) morbidity and mortality in males. IHD is one of the leading causes of both mortality and morbidity, in general. In relation to alcohol, there is an ongoing debate in the literature over the potential cardioprotection of alcohol at low to moderate daily doses. Multiple skeptical perspectives on alcohol and cardioprotection (Chikritzhs, Fillmore & Stockwell, 2009; Holmes et al., 2014; Juonala et al., 2009; Naimi et al., 2005; Naimi et al., 2017; Pletcher et al., 2005; Zhao et al., 2017), as well as on alcohol and protection from all-cause mortality (Bergmann et al., 2013; Fillmore et al., 2006; Stockwell et al., 2016b) have been recently published. These are counterbalanced by meta-analyses (Brien et al., 2011; Roerecke & Rehm, 2010b, 2012; Ronksley et al., 2011) and most observational studies, which have indeed shown a cardioprotective effect.

To recognize this debate, we have provided two options for each of IHD morbidity in men and IHD mortality in men. Project teams can decide between these options based on their understanding of the literature of the cardioprotective effect of alcohol. The two options are Zhao et al. (2017) and Roerecke & Rehm (2012). Zhao et al. is a more recent meta-analysis studying the relationship between consumption and IHD mortality. Further, this article explicitly accounts for abstainer biases and there is an accounting for the mean age of the epidemiological cohorts that constitute the meta-analysis as a means of controlling for other forms of lifetime selection bias. However, continuous, gender-differential relative risk functions were not calculated as part of the article. Upon request, J. Zhao produced a continuous risk function based on the results presented in the top panel of Table 3 for IHD mortality in men. This shows no cardioprotection at any level of alcohol intake but, rather, a monotonically increasing risk of IHD with rising consumption. Due to the small number of studies regarding women, an analogous curve could

not be created for women. Nonetheless, the categorical RR estimates for women indicated some cardioprotection for low volume alcohol intake, consistent with Roerecke & Rehm (2012). Roerecke & Rehm (2012) does not explicitly account for abstainer biases at the study design stage; however, the authors account for abstainer bias by decomposing RR results from studies which pooled former and never drinkers. They do not take account of other potential lifetime selection biases, however, that may come into play with studies recruiting participants later in life.

It is the responsibility of your project team to decide among these possible sources based on your understanding of the literature. Note that it may be prudent to choose a primary method and a secondary method, which may then be used as a sensitivity analysis. These choices lead to the following options:

(1) Use Zhao et al. (2017) for IHD mortality in men and Roerecke & Rehm (2012) for IHD morbidity in men. This choice results in a consistent pattern of gender-based risk relationships to those reported by Knott et al. (2015) in relation to Type 2 Diabetes, another condition where protective effects of low volume alcohol use are sometimes observed for women but not men.
(2) Use Zhao et al. (2017) for both IHD mortality and morbidity in men. The IHD mortality curve calculated by J. Zhao would here be used for IHD morbidity. This may result in an overestimate of IHD morbidity in men as, for most alcohol-related conditions, mortality RRs tend to be higher than for morbidity at equivalent consumption levels. However, it assumes that controlling for lifetime selection bias has a more profound effect resulting in more accurate estimates overall.
(3) Use Roerecke & Rehm (2012) for both IHD mortality and morbidity in men. This choice has the advantage of providing a consistent source for continuous risk relationships for both mortality and morbidity, for both men and women.

Both options for IHD mortality and IHD morbidity are included in the RR one-pagers presented in Appendix C-2. Recall, also, that changing between RR functions for IHD mortality and morbidity is as simple as replacing one line in the RR input spreadsheet. All calculations will then follow through the InterMAHP AAF calculations. This choice has major implications for the final estimate of overall AA harm as IHD is one of the most common causes of mortality and morbidity and the two methods may give significantly different estimates depending on

consumption and prevalence in the region under study. It is critical that your team understands this literature and makes a final decision that best suits interpretation in your region.

4.5.2.3 Extrapolating Relative Risk Functions in InterMAHP

Previous WHO Global Burden of Disease (of alcohol) (World Health Organization, 2009) and Global Status Reports on Alcohol and Health (World Health Organization, 2014, 2018) have defined the upper limit of consumption at 150 g/day, which has the effect of truncating relative risk functions above 150g/day. However, research suggests that truncating the consumption distribution and relative risk functions at 150 g/day can lead to significant underestimation of AAFs (Gmel et al., 2013). For example, Gmel et al. (2013) conclude that restricting the upper limit of consumption to 150g/day may have led to the underestimation of alcohol-attributable mortality in the European Union by as much as 25.5% in men and 8.0% in women.

Taken with evidence from Canada showing that individuals taking part in Managed Alcohol Programs chronically consume an average of about 250 g/day ethanol (Stockwell et al., 2018a), this may suggest that providing the option to increase a region's upper limit of consumption beyond 150g/day may be prudent. We have therefore allowed the user to dynamically define the upper limit of consumption based on region-specific information; it is therefore necessary to outline the methodology used to define RR functions above 150 g/day.

Firstly, consider using the functional equation representing the RR functions at consumption levels above 150 g/day. As can be seen by a detailed study of the RR one-pagers in Appendix C-2, for many conditions this would result in an extremely steep, nearly vertical relative risk function above 150 g/day (e.g. (6).(2) *liver cirrhosis mortality, men*). Royston and Sauerbrei (2008) describe how the FP2 modeling technique should not be used to extrapolate RR functions too far outside the range of observed data; this is also a general statistical principle. Therefore the extrapolation of RR functions above 150g/day is instead completed using one of two methods, which each user may choose between:

(1) Capped – in this method, the RR function is capped at the value it reaches at 150 g/day. It then takes on this value of RR(150) for all consumption levels above 150 g/day. See the RR one-pagers for each condition/gender/outcome in Appendix C-2 for a graphical depiction of this method.

(2) Linear – based on linear extrapolation of the slope calculated between 100 and 150 g/day. Here, the average slope of the relative risk function between 100 and 150 g/day is calculated using *Formula C-3* below. For values above 150 g/day, the relative risk is then calculated using *Formula C-4*.

$$slope = \frac{RR(150) - RR(100)}{150 - 100} \qquad \textbf{\textit{Formula C-3}}$$

$$RR(x > 150) = RR(150) + slope(x - 150) \qquad \textbf{\textit{Formula C-4}}$$

The default choice in InterMAHP is the more conservative capped method. The linear extrapolation method is based loosely on the online appendix in Gmel et al. (2013); however, in InterMAHP, all functions are extrapolated beginning at 150 g/day for consistency.

4.5.2.4 Extrapolating Relative Risk Functions for Ischaemic Heart Disease

The methodology above applies to all conditions, except for IHD. Due to the volatile nature of several IHD RR functions beginning at approximately 125g/day, the methodology above is modified by capping IHD functions at RR(100) for the capped method and extrapolating the linear slope from x=50 to x=100 beyond RR(100) for the linear method.

4.5.2.5 Categorical Relative Risk Estimates for Former Drinkers

The second piece of the RR puzzle for each condition/gender/outcome is an RR point estimate for former drinkers. Table C-3 shows a summary table of all former drinker RR sources. Appendix C-2 presents RR one-pagers which comprehensively describe the source and, if necessary, calculations or justifications for the choice of former drinker RR estimates.

4.5.3 Considerations in Matching Per Capita Consumption to Epidemiological Studies

A final discussion before moving to the calculation of InterMAHP AAFs concerns the applicability of *per capita* consumption data, based on sales or surveys, to that used by epidemiological studies to calculate RR estimates and functions. The *per capita* consumption

estimate in the consumption and prevalence input spreadsheet used by InterMAHP should be the most comprehensive estimate available in your region. However, we note that self-reported consumption in epidemiological studies may be underreported as compared to a measure of recorded plus unrecorded consumption and this may affect the comparability of this estimate with consumption estimates used to produce epidemiological relative risks.

A recent article by our team studied this issue in detail (Stockwell et al., 2018c). The analyses compared the coverage of self-reporting drinking from epidemiological cohort studies as compared to standardized *per capita* figures derived from alcohol sales and tax receipt data. The article concluded that an adjustment factor of 0.80 should be applied to *per capita* figures based on sales to 'downshift' consumption curves to more closely match those from the epidemiological studies from that provide RR information (Stockwell et al., 2018c). This 0.80 factor has been used widely to provide a better consumption data match (GBD 2016 Alcohol Collaborators, 2018; World Health Organization, 2014, 2018) and was originally based on the recommendation of the technical advisory committee for the WHO. Note that this correction factor can be easily modified when using InterMAHP.

4.5.4 InterMAHP Alcohol-Attributable Fraction Methodology

4.5.4.1 General AAF Methodology

The continuous drinking prevalence distributions and dose-response RR functions, as well as the categorical prevalence of former drinkers and relative risks, described in the preceding sections, are now composed together to calculate InterMAHP AAFs.

The specification of the InterMAHP indirect AAF is the following formulation that uses a continuous distribution of current drinkers and a categorical definition of former drinkers. It is of the same family of modern AAFs as that used by the World Health Organization to produce the Global Status Reports on Alcohol and Health (World Health Organization, 2014, 2018) and previous Global Burden of Disease (of alcohol) studies (GBD 2016 Alcohol Collaborators, 2018). Previous research has suggested that continuous attributable fractions are more mathematically appropriate than categorical attributable fractions where the data exists to model continuous exposures and relative risks (Kehoe et al., 2012). Further, we note that a continuous

attributable fraction is the natural formulation; clearly, natural exposure to alcohol occurs in a continuous and not categorical manner.

The following specification is therefore used for all partially attributable alcohol-related conditions, except for conditions that are modified by bingeing behaviour: (1) IHD and (2) ischaemic stroke (IS) and (3) injuries - these are discussed in a proceeding section. The general AAF for all other conditions is specified by the following form (as always, for each region, year, alcohol-related condition, gender and age group):

$$AAF = \frac{P_{FD}[RR_{FD} - 1] + \int_{0.03}^{z} P(x)[RR(x) - 1]\,dx}{1 + P_{FD}[RR_{FD} - 1] + \int_{0.03}^{z} P(x)[RR(x) - 1]\,dx} \qquad \textbf{\textit{Formula C-5}}$$

where $P_{FD}$is the prevalence of former drinkers, RR_{FD} is the categorical RR of former drinkers, $P(x)$is the distribution of current drinking at level *x* in grams of ethanol per day as defined in *Formula C-1*, $RR(x)$ is the continuous RR function for each condition-gender-outcome, 0.03 is the lower limit of consumption (defined as one standard drink in the previous year = 12g/365) and *z* is the user-defined upper limit of average daily consumption.

Formula C-5 is an excess risk (also called classical or Levin) formulation of the AAF (Hanley, 2001), which uses the excess risk quantity ($RR - 1$), multiplied by population prevalences, to arrive at the attributable fraction result. We note that this formula, save for differing limits of integration, is mathematically identical to the second formula presented in (Kehoe et al., 2012); however, composition of the formula is significantly altered and so this may be difficult to discern. We suggest InterMAHP's *Formula C-5* is a more intuitive and flexible formulation of the modern AAF and we therefore use this formulation throughout this document. Specifically, preserving the denominator value as the total risk experienced by the population in regards to a particular condition (i.e. 1 + the excess risk of alcohol consumption), allows the unique decomposition of the numerator in order to study different drinking groups, such as light, moderate and heavy drinkers. This important additional functionality is given a more detailed treatment in Section 4.6.

Note further that in Kehoe et al. (2012), the $\frac{P_{CD}}{nc}$ term is implicitly defined as a component of $P(x)$, while in *Formula C-1* it is explicitly defined. However, it is important to state that this

adjustment must always be present in the calculation of any continuous AAF calculation using the Gamma distribution.

4.5.4.2 Special Cases of AAFs: Ischaemic Heart Disease and Ischaemic Stroke

The dose-response risk relationships between alcohol consumption and IHD and IS are modified by the removal of the protective effect for persons engaged in binge drinking (Rehm, Shield, Roerecke & Gmel, 2016; Roerecke & Rehm, 2010a, 2012). The removal of this protective effect for ischaemic conditions is paralleled in recent versions of the Global Burden of Disease studies (GBD 2016 Alcohol Collaborators, 2018) and Global Status Reports on Alcohol and Health (World Health Organization, 2014, 2018). *Formula C-5* is therefore modified for these two conditions by the following steps:

(1) For each gender-age subgroup, the prevalence of current drinkers who consume an average daily amount above the daily threshold which defines regional binge drinking is calculated. These drinkers are guaranteed to be bingers since their daily consumption is above the amount defined a binge occasion; they are denoted 'chronic bingers' with prevalence P_{CB}. The prevalence is calculated as:

$$P_{CB} = \int_{c}^{z} P(x)dx \qquad \textbf{\textit{Formula C-6}}$$

where c is the gender-specific, user-defined binge level and other quantities are as defined in *Formula C-5*.

We note that although rare, it is possible that the Gamma-calculated P_{CB} is greater than the survey-defined P_{BD} for a particular population subgroup. In testing using dozens of global regions, this occurred only for region-subgroups with a very low prevalence of current drinkers. Further, the effects on the AAFs were exceedingly small. However, for completeness and accuracy, the following automatic check and correction is completed by InterMAHP:

(a) InterMAHP checks to ensure that the Gamma-based P_{CB} is less than the survey- and input-defined P_{BD}. If this is not the case, InterMAHP sets P_{CB}=P_{BD}.

(b) Further, if $P_{CB} > P_{BD}$, this corresponds mathematically to the overestimation of the integral portion $\int_c^z P(x)[RR_{BD}(x) - 1]dx$ in *Formula C-7*. It is therefore deflated by a factor of $\frac{P_{BD}}{P_{CB}}$.

(2) The remaining bingers, denoted 'non-chronic bingers' (drinkers who binge, but do not consume above the binge threshold daily) is then calculated as $P_{NCB} = P_{BD} - P_{CB}$, where P_{BD} is the survey-defined prevalence of binge drinking in your region and is from the consumption and prevalence input spreadsheet.

(3) Now that the prevalence of bingeing has been divided between chronic and non-chronic bingers, the AAF formula may be modified in the following way for IHD and IS, where the numerator of the AAF becomes:

$$\begin{aligned} AAF(numerator) = {} & P_{FD}[RR_{FD} - 1] \\ & + \left[\frac{P_{CD} - P_{BD}}{P_{CD} - P_{CB}}\right] \int_{0.03}^{c} P(x)[RR(x) - 1]\, dx \\ & + \left[\frac{P_{BD} - P_{CB}}{P_{CD} - P_{CB}}\right] \int_{0.03}^{c} P(x)[RR_{BD}(x) - 1]\, dx \\ & + \int_c^z P(x)[RR_{BD}(x) - 1]dx \end{aligned} \qquad \textbf{\textit{Formula C-7}}$$

and the complete alcohol-attributable fraction is calculated by:

$$AAF = \frac{AAF(numerator)}{1 + AAF(numerator)} \qquad \textbf{\textit{Formula C-8}}$$

All quantities in *Formula C-7* have been previously defined in *Formula C-5*, except for:

$$RR_{BD}(x) = \max(RR(x), 1) \qquad \textbf{\textit{Formula C-9}}$$

Formula C-9 has the straightforward effect of removing the protective effect for binge drinkers when $RR(x) < 1$.

4.5.4.3 Special cases of AAFs: Injuries

The following method for injuries was formulated and tested at an Alcohol and Injury Working Group meeting including several authors of this publication, as well as members of Alcohol Research Group (ARG). It is a distributional method based on the relationship between average daily alcohol consumption and the meta-analyzed risk of injury (Corrao et al., 1999). It is similar in concept and builds upon methods recently used by the World Health Organization (Shield, Rylett & Rehm, 2016) and developed by members of the authorship team; however, the binge-specific component of the formula will now be based on region-specific and user-inputted data regarding the prevalence of binge drinking, instead of on a scaling constant as previously used (World Health Organization, 2014).

The modified structure of the attributable fraction formula is identical to that for IHD and IS discussed above wherein the prevalence of chronic bingers is first calculated from the gender-specific binge definition and the Gamma distribution. For injuries, however, there is no excess risk for former drinkers and so the binge-modified AAF is reduced to:

$$\begin{aligned} AAF(numerator) \\ &= \left[\frac{P_{CD} - P_{BD}}{P_{CD} - P_{CB}}\right] \int_{0.03}^{c} P(x)[RR(x) - 1]\, dx \\ &+ \left[\frac{P_{BD} - P_{CB}}{P_{CD} - P_{CB}}\right] \int_{0.03}^{c} P(x)\left[RR_{BD,i}(x) - 1\right] dx \\ &+ \int_{c}^{z} P(x)\left[RR_{BD,i}(x) - 1\right] dx \end{aligned} \qquad \textbf{\textit{Formula C-10}}$$

where $RR(x)$is the risk of injury at consumption level *x*, from Corrao et al. (1999). All other quantities have been previously defined in *Formula C-5*, except:

$$RR_{BD,i}(x) = BingeFactor_i * RR(x) \qquad \textbf{\textit{Formula C-11}}$$

where i represents each of three injury categories. Injuries are divided into three categories: MVCs, intentional injuries and unintentional injuries, see also Appendix C-2 for RR functions corresponding to each injury category. The complete AAF is calculated using *Formula C-8*.

InterMAHP binge factors ($BingeFactor_i$ above) represent the ratio of the relative risk of bingers divided by non-bingers at the same average consumption level, and so conceptually capture the risk of bingeing over and above that of non-binge consumption. Risk ratios were calculated for this project using linked data on drinking, bingeing and mortality from 134,237 individuals in the National Health Interview Survey, a representative survey conducted in the United States by the U.S. Census Bureau. The calculated binge factors were 1.49 for MVCs, 1.70 for intentional injury and 1.48 for unintentional injury. The derivation of these binge factors, for each injury category, is the topic of a separate publication, currently under review, completed in collaboration with members of the Centre for Addiction and Mental Health and ARG.

4.6 Methods Specifying Additional InterMAHP Functionality

This section treats several added components to functionality in InterMAHP that are more specific than the general methods described above. To our knowledge, these functional additions are novel to the alcohol research literature.

4.6.1 Calculating AAFs by Drinking Categories

A significant advance of InterMAHP is the built-in functionality to calculate the AA harm experienced by different categories of drinkers. This built-in ability allows users to dynamically specify drinking categories and receive as output alcohol-attributable fractions for four drinking categories: former drinkers, light drinkers, moderate drinkers and heavy drinkers. Users dynamically input the consumption level in grams per day that defines low, moderate and heavy drinkers for their analysis.

4.6.1.1 Drinking Category AAFs: General Case

Recall from *Formula C-5* that InterMAHP's AAF formula is defined as the excess risk formulation of the population attributable fraction formula. Defined in this way, it is possible to

decompose the numerator into constituent pieces and calculate different proportions of the total AAF. To mathematically formulate this, define light drinkers as those who drink between 0.03 and *a* g/day, moderate drinkers as those who drink between *a* and *b* g/day and heavy drinkers as those who drink between *b* and *z g/day*, where *z* is the user-defined upper limit of consumption. The integral in the numerator of the AAF formula can be decomposed as follows to study four drinking groups, as below. Note, the numerator and denominator are presented separately only for readability, as the formula is difficult to present as one equation.

$$AAF(numerator) = P_{FD}[RR_{FD} - 1] + \int_{0.03}^{a} P(x)[RR(x) - 1]\,dx + \int_{a}^{b} P(x)[RR(x) - 1]\,dx + \int_{b}^{z} P(x)[RR(x) - 1]\,dx \qquad \textbf{Formula C-12}$$

$$AAF(denominator) = 1 + P_{FD}[RR_{FD} - 1] + \int_{0.03}^{z} P(x)[RR(x) - 1]\,dx \qquad \textbf{Formula C-13}$$

$$AAF = \frac{AAF(numerator)}{AAF(demoninator)} \qquad \textbf{Formula C-14}$$

Studying *Formula C-12* allows us to explicitly define this decomposition for the four drinking groups:

$$AAF_{FD} = \frac{P_{FD}[RR_{FD} - 1]}{1 + P_{FD}[RR_{FD} - 1] + \int_{0.03}^{z} P(x)[RR(x) - 1]\,dx} \qquad \textbf{Formula C-15}$$

$$AAF_{LD} = \frac{\int_{0.03}^{a} P(x)[RR(x) - 1]\,dx}{1 + P_{FD}[RR_{FD} - 1] + \int_{0.03}^{z} P(x)[RR(x) - 1]\,dx} \qquad \textbf{Formula C-16}$$

$$AAF_{MD} = \frac{\int_{a}^{b} P(x)[RR(x) - 1]\,dx}{1 + P_{FD}[RR_{FD} - 1] + \int_{0.03}^{z} P(x)[RR(x) - 1]\,dx} \qquad \textbf{Formula C-17}$$

$$AAF_{HD} = \frac{\int_b^z P(x)[RR(x) - 1]\,dx}{1 + P_{FD}[RR_{FD} - 1] + \int_{0.03}^z P(x)[RR(x) - 1]\,dx} \qquad \textbf{\textit{Formula C-18}}$$

where, for each gender, AAF_{FD} is the attributable fraction for former drinkers, AAF_{LD} is the AAF for light drinkers (defined between 0.03 and a_w for women and between 0.03 and a_m for men, AAF_{MD} is the AAF for moderate drinkers (defined between a_w and b_w for women and a_m and b_m for men) and AAF_{HD} is the AAF for heavy drinkers (defined between b_w and z for women and b_m and z for men).

It is important to note that the four components above sum to the whole, meaning we can choose to study drinking groups, but if this is not our objective, the components may be ignored and the sum total used to study total alcohol-attributable harm, as usual.

$$AAF_{Total} = AAF_{FD} + AAF_{LD} + AAF_{MD} + AAF_{HD} \qquad \textbf{\textit{Formula C-19}}$$

4.6.1.2 Drinking Category AAFs: Special Cases

The specification of drinking category-based AAF components for the three binge-modified cases are the most mathematically complex scenario. Note that the special cases of IHD, IS and injuries are nearly identical except for a differing $RR_{BD}(x)$ function within them. Recalling the differing definition of $RR_{BD}(x)$ from *Formula C-9* and *Formula C-11* allows us to define the below decomposition for the three special cases together; the AAF numerator components for the four drinking categories become:

$$AAF_{FD}(numerator) = P_{FD}[RR_{FD} - 1] \qquad \textbf{\textit{Formula C-20}}$$

$$AAF_{LD}\,(numerator) = \left[\frac{P_{CD}-P_{BD}}{P_{CD}-P_{CB}}\right]\int_{0.03}^{a} P(x)[RR(x)-1]\,dx + \left[\frac{P_{BD}-P_{CB}}{P_{CD}-P_{CB}}\right]\int_{0.03}^{a} P(x)[RR_{BD}(x)-1]\,dx$$

Formula C-21

$$AAF_{MD}(numerator) = \left[\frac{P_{CD}-P_{BD}}{P_{CD}-P_{CB}}\right]\int_{a}^{b} P(x)[RR(x)-1]\,dx + \left[\frac{P_{BD}-P_{BAT}}{P_{CD}-P_{CB}}\right]\int_{a}^{b} P(x)[RR_{BD}(x)-1]\,dx$$

Formula C-22

$$AAF_{HD}(numerator) = \left[\frac{P_{CD}-P_{BD}}{P_{CD}-P_{CB}}\right]\int_{b}^{c} P(x)[RR(x)-1]\,dx + \left[\frac{P_{BD}-P_{CB}}{P_{CD}-P_{CB}}\right]\int_{b}^{c} P(x)[RR_{BD}(x)-1]\,dx + \int_{c}^{z} P(x)[RR_{BD}(x)-1]dx$$

Formula C-23

Lastly, the AAF for each of the four drinking groups is calculated using the following formula and by replacing the numerator with each of the four drinking groups - only the example of former drinkers(AAF_{FD}) is shown, but the other three are analogous.

Formula C-24

$$AAF_{FD} = \frac{AAF_{FD}(numerator)}{1 + AAF_{FD}(num) + AAF_{LD}\,(num) + AAF_{MD}(num) + AAF_{HD}(num)}$$

4.6.2 Dynamic Upper Limit of Consumption

To our knowledge, an AAF calculator with a dynamic upper limit of consumption has not previously been created. InterMAHP allows the user to define the upper limit of consumption that is most appropriate for their region, based on available evidence.

As discussed previously, global studies have typically set the upper limit of consumption at 150 g/day (GBD 2016 Alcohol Collaborators, 2018; World Health Organization, 2014, 2018). However, research suggests that capping the alcohol consumption distribution and relative risk functions can lead to significantly lower AAFs (Gmel et al., 2013). Combined with evidence from Canada showing that individuals taking part in Managed Alcohol Programs (MAPs) chronically consume *on average* about 250 g/day ethanol (Stockwell et al., 2018a), InterMAHP provides users with the ability to increase their region's upper limit of consumption beyond 150g/day. Therefore, users have the ability to define the upper limit of consumption, represented by *z* in *Formula C-5*.

Since all RR functions are monotonically increasing after approximately 60g/day ethanol, increasing the upper limit of consumption, *z*, will produce higher AAF values. However, the value *z* in your region should be chosen based on available region-specific evidence regarding the upper limit of chronic daily consumption.

4.6.3 Methodological Section Note

It is important to note that the preceding section present formulas containing the user-defined limits *a*, *b* and *c*. Recall that for each of these, there are functionally two values, differentiated by gender: $a_w, b_w, c_w, a_m, b_m, c_m$.

For ease of presentation and discussion, these are generalized by dropping the subscript terms and only using *a*, *b* and *c*; however, functionally in the InterMAHP program there are two formulas, one specific to women and one to men, for each formula presented here which includes one or more of these terms.

4.7 Relative Risk Summary Pages

For each partially-attributable alcohol-related condition, Appendix C-2 section provides a one page reference that includes all source information, relative risk functions and values, ICD10 codes, comments and considerations regarding how studies controlled for abstainer biases, as well as figures depicting the dose-response relative risk functions. These summaries were designed for InterMAHP, to be usable and printable on a single page for each condition, by gender and outcome where necessary.

Note that for the figures, the vertical and horizontal axes are not labeled due to space restrictions: the horizontal axis represents average alcohol consumption in grams per day and the vertical axis corresponds to the relative risk as compared to lifetime abstainers.

4.8 Acknowledgements

This work was supported by a Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award (CGS-D) from the Canadian Institutes of Health Research.

The authors are indebted to the following colleagues for their input on various stages of this project. We wish to thank Colin Angus (Sheffield Alcohol Policy Group, University of Sheffield, Sheffield, UK) for a detailed review of a draft version of this document and Dr. Tim Naimi (Boston Medical Center, Boston University School of Public Health, Boston, USA) for input on draft versions of this document.

We wish to thank Eveline Lensvelt and Dr. Tanya Chikritzhs (National Drug Research Institute, Curtin University, Perth, Australia) for testing successive versions of the InterMAHP interface with Australian data, as well as reviewing a version of this guide. Their help was invaluable during the software development process.

We extend our gratitude to Jakob Manthey (Centre for Addiction and Mental Health, Toronto, Canada) who completed the National Household Interview Survey analysis on binge drinking and injury that is used to drive estimates of injury AAFs.

Chapter 5: The International Model of Alcohol Harms and Policies: A New Model for Estimating Alcohol Harms with an Application to Alcohol-Attributable Mortality in Canada, 2016 [Study D]

5.1 Abstract

What is the International Model of Alcohol Harms and Policies? The International Model of Alcohol Harms and Policies (InterMAHP) is a novel, open access alcohol harms estimator. InterMAHP consists of methodologies and program software designed to assist alcohol research teams in estimating alcohol-attributable (AA) mortality and morbidity, by region, based on standard population data concerning *per capita* alcohol consumption and enumerated disease burden. It is freely available from www.intermahp.cisur.ca.

Background and aims: Data on health harms caused by alcohol are required by policymakers for setting health priorities; however, these estimations are resource intensive and estimates vary substantially by method. As a result, many countries, states and regions do not track these harms. InterMAHP addresses this limitation by automating the estimation of AA harms. Application is then illustrated through the provision of updated estimates of AA mortality in Canada.

Methods: Mortality counts and *per capita* alcohol sales were obtained from Statistics Canada. Drinking and bingeing prevalences were obtained from the Canadian Substance Use Exposure Database. InterMAHP automated the calculation of AA fractions using the modern AAF formulation and a Gamma distribution to specify the continuous distribution of consumption.

Findings: Alcohol is a leading driver of mortality in Canada. In 2016, there were more than 14,800 (95% CI: 12,435 - 17,127) AA deaths, representing 5.5% of all deaths. This burden is borne disproportionately by men (79%). Among condition categories, cancer is the leading cause of AA mortality in both men and women. By individual health conditions, ischaemic heart disease is the leading cause of AA death for both genders.

Conclusions*:* InterMAHP has the potential to assist public health researchers globally in estimating alcohol harms. This open access software was then used to estimate AA mortality in Canada, which was shown to be substantial. Policies proven to reduce alcohol consumption and related harms should be considered to reduce this substantial and preventable burden of disease.

5.2 Introduction

Reliable and comparable estimation of the population health harms caused by alcohol consumption, such as alcohol-attributable (AA) morbidity and mortality, are needed by policymakers to set health priorities and formulate protective alcohol policies. A comparison of the methods of region-specific applications, such as the United States Centers for Disease Control and Prevention's Alcohol-Related Disease Impact tool (United States Centers for Disease Control and Prevention, 2008), the Canadian Institute for Substance Use Research's Alcohol and Other Drug Monitoring System (Stockwell et al., 2009a) and Australia's National Alcohol Indicators Project (Chikritzhs, 2009), finds that divergent assumptions and methodologies may lead to results which differ significantly, though the goal of these tools is equivalent. For example, an evaluation of eight methods of estimating AA deaths in Finland and France produced results that differed by as much as a factor of five, depending on the methodology employed (Trias-Llimós, Martikainen, Mäkelä & Janssen, 2018). The alcohol research community could benefit in comparability of results from the development of a set of standardized methodologies for estimating AA morbidity and mortality. In response, we specify the International Model of Alcohol Harms and Policies (InterMAHP), an open access set of methods and software developed for estimating AA harms.

Previous publications have brought some measure of international comparability to the estimation of AA mortality and morbidity. Notably, English and Holman's *The Quantification of Drug-Caused Morbidity and Mortality in Australia, 1995* (English et al., 1995) provided guidance to alcohol epidemiologists. However, methodologies have advanced considerably in the past two decades, in particular through the publication of dozens of updated meta-analyses, which quantify the risk of alcohol consumption as a continuous function (see Table C-3). The WHO's Global Status Reports on Alcohol and Health (World Health Organization, 2014, 2018) and the Global Burden of Disease comparative risk assessment (GBD 2016 Alcohol Collaborators, 2018) have estimated the harms of alcohol globally. However, these estimates are constrained by the lack of an open access, dynamic model that countries or regions may use to independently estimate alcohol harms using similar methods, but with region-specific data, parameters, assumptions and values.

To address this constraint, we have developed a set of methodologies and a downloadable software program which comprise an internationally standardized model for estimating AA morbidity and mortality (Sherk et al., 2017a; Sherk et al., 2017b). This article will describe the methodologies employed by InterMAHP and illustrate its use by estimating AA mortality in Canada in 2016.

Alcohol consumption is a major contributor to the burden of disease in Canada, causing approximately 88,000 hospitalizations and costing Canadian society $14.6 billion in 2014 (Canadian Substance Use Costs and Harms Scientific Working Group, 2018). Previous estimates of AA mortality have ranged between 4,000 (Shield et al., 2012) and 8,000 (Stockwell et al., 2007) deaths per year. We update these estimates for 2016, the most recent year for which Canadian vital statistics were available.

5.3 Methods

5.3.1 Methods for the International Model of Alcohol Harms and Policies

InterMAHP uses a condition-based epidemiological attributable fraction approach for estimating AA harms. To utilize this technique, InterMAHP provides guidance on the following necessary steps towards estimating AA morbidity and mortality in a region:

(1) Identification, operationalization and categorization of health conditions which are causally related to alcohol (from now on termed alcohol-related conditions);
(2) Enumeration of morbidity and mortality for these alcohol-related conditions;
(3) Estimation of population exposure to alcohol for dimensions of consumption which are causally related to condition risk (at minimum, daily average ethanol consumption; for some conditions, also binge drinking prevalence);
(4) Modeling the continuous prevalence distribution of average daily alcohol consumption;
(5) Identification of relative risk (RR) functions and estimates for each alcohol-related condition;
(6) Calculation of alcohol-attributable fractions (AAFs) for each alcohol-related condition; and
(7) Combining counts and AAFs to arrive at final estimates of AA morbidity and mortality.

Due to length restrictions, a complete methodological treatment is not provided; though this comprehensive description was provided in Chapter 4. Recall, as the current chapter aims to distill the preceding chapter to a length suitable for publication, there is necessarily some duplication between Chapters 4 and 5.

(1) Identification, operationalization and categorization of alcohol-related conditions

A foundational step in quantifying AA harms is the identification of health conditions that are causally related to the consumption of alcohol, operationalizing these conditions through the use of ICD10 codes and categorizing them as wholly or partially attributable to alcohol. The suggested list is based on previous research informing global comparative risk assessments (Rehm et al., 2010; Rehm et al., 2017a; Rehm et al., 2017c; Rehm & Imtiaz, 2016a); the final list in a given region will also depend on data availability. For example, global datasets tend to have only a limited number of condition categories available, whereas vital statistics or administrative health data in high income countries may allow for more detailed categorization (Rehm & Imtiaz, 2016; Rehm & Mathers, 2009).

Table C-2 (presented previously in Chapter 4) presents the alcohol-related conditions identified in InterMAHP, along with attribution (100% or partial) and sourcing for continuous dose-response relationships and risk estimates for former drinkers. Where possible and based on the literature, differential risk estimates are provided by gender and outcome (morbidity vs. mortality). Table C-2 presents ICD10 code operationalization of each condition. Condition categories and conditions were logically ordered by corresponding ICD10 codes.

(2) Enumeration of morbidity and mortality for alcohol-related conditions

For each population subgroup of interest, the number of morbidities (e.g. hospitalizations) and mortalities must be enumerated for each alcohol-related condition. This step requires local knowledge of regional health data systems and varying degrees of analytical effort based on the reporting rules employed by those systems.

This is an example of health services research [HSR; (Bowling, 2014)] and is completed by the project team (or through summary information requested from the appropriate regional or national agencies). InterMAHP then assists with the attribution of a fraction of this enumerated morbidity and mortality to alcohol.

An important consideration presents itself during this step as multiple ICD10 codes may, and often do, appear on each record (e.g., up to 25 may be present in Canadian morbidity data). A foundational step in HSR requires the choice of a diagnosis-weighting algorithm to ensure that a subsequent summation across all records would sum to the total number of records. This is done by ensuring the weighting algorithm sums to 1.0 within each record. The algorithm typically used in alcohol epidemiology is called the 'primary diagnosis algorithm' and follows logical steps in this order: (1) for non-injuries, the primary diagnosis is given a weight a 1.0 and all other diagnoses on the record are given a weight of zero, and (2) for injuries, the first existing external cause code (ICD10 code begins with V,W,X,Y) is given a weight of 1.0 and all others zero (Canadian Substance Use Costs and Harms Scientific Working Group, 2018; World Health Organization, 2014). This standard weighting algorithm is often applied implicitly (i.e. without clear explanation). We recommend care is taken in weighting design as an error at this stage can lead to the introduction of significant estimation error.

(3) Estimation of population exposure to alcohol

Information must be collected concerning regional population exposure to alcohol in the form of estimates of *per capita* consumption and the prevalence of current, binge and former drinkers and lifetime abstainers. This information is needed by each population subgroup (for example, by gender and age group) at the InterMAHP input stage. *Per capita* consumption estimates should, wherever possible, include adjustments for unrecorded consumption, imported and exported alcohol, tourist consumption, wastage, and other measures which may affect the final estimations.

(4) Modelling the continuous prevalence distribution of daily average alcohol consumption

Methods exist for modeling the continuous prevalence distribution of average daily alcohol consumption using a Gamma distribution (Kehoe et al., 2012; Rehm et al., 2010b) and have been used to estimate alcohol's contribution to the Global Burden of Disease (GBD 2016 Alcohol Collaborators, 2018; World Health Organization, 2014, 2018). The InterMAHP software automates the calculation of a continuous prevalence distribution of average daily drinking for each population subgroup, given the required inputs and the formulations below.

A study of the relationship between the mean (μ) and standard deviation (σ) of Gamma distributions in 66 countries reported that they formed a consistent ratio, by gender (Kehoe et al., 2012). Using this information, the normally two-parameter Gamma distribution is collapsed to a single parameter, depending solely on mean consumption, μ. If we denote the probability density function of this one-parameter Gamma distribution as $f(x;\mu)$, InterMAHP calculates the continuous prevalence distribution in each population subgroup using:

$$P(x) = \frac{P_{CD}}{nc} f(x;\mu) \qquad \textbf{\textit{Formula D-1}}$$

where x is average ethanol consumption in grams/day, P_{CD} is the prevalence of current drinkers and *nc* is the necessary normalizing constant (Gmel et al., 2013). See Gmel et al. (2013) for the mathematical formulation of the Gamma distribution. Mean consumption in each population subgroup may be multiplied by 0.80, in order to account for the fact that underreporting in epidemiological cohort studies, from which relative risk estimates are derived, is less than in typical population surveys reporting alcohol consumption (Stockwell et al., 2018c); however, this parameter is dynamic at input.

(5) Identification of relative risk functions and estimates for each alcohol-related condition

InterMAHP provides users with a default set of continuous relative risk functions for current drinkers and categorical relative risk estimates for former drinkers for each alcohol-related condition, as these are the inputs needed for the modern AAF formula below. However, project teams may choose to replace the default functions and estimates.

The InterMAHP default list shown in Table C-3 presents meta-analyses estimating the risk relationship between chronic alcohol consumption and each partially-attributable alcohol-related condition. This work builds on the foundational work of Jürgen Rehm and colleagues (Rehm et al., 2010; Rehm et al., 2017a; Rehm et al., 2017c) and includes a recent update for the InterMAHP project and the 2018 Global Status Report on Alcohol and Health (Rehm et al., 2017c; Sherk et al., 2017b).

A special case is provided in Table C-3 for the relationship between ischaemic heart disease (IHD) and drinking in men. There is debate in the literature regarding the

cardioprotective effect of alcohol consumption, as some meta-analyses and observational studies, e.g. (Brien et al., 2011; Roerecke & Rehm, 2012; Ronksley et al., 2011), have shown a protective effect at low to moderate drinking levels. This finding is counterbalanced by a recent meta-analysis accounting for abstainer bias and mean cohort age (Zhao et al., 2017) and mounting skepticism regarding the phenomenon (Chikritzhs et al., 2009; Holmes et al., 2014; Naimi et al., 2017). InterMAHP includes the RR functions for both meta-analyses (Roerecke & Rehm, 2012; Zhao et al., 2017), in recognition of the continuing debate on this topic. It is the responsibility of the project team to apply these based on their interpretation of the literature in the context of the region under study.

(6) Calculation of alcohol-attributable fractions (AAFs) for each alcohol-related condition

The previous two steps have provided the necessary information for InterMAHP to automate the calculation of AAFs for each alcohol-related condition, by population subgroup. During this step, conditions are divided by InterMAHP into those conditions related to (a) one-dimensional chronic drinking and (b) two-dimensional (chronic and acute) drinking (Rehm et al., 2010a; Rehm et al., 2017a):

(a) The AAFs for one-dimensional conditions are calculated using the following excess risk formulation, modified from Kehoe et al. (2012):

$$AAF = \frac{P_{FD}[RR_{FD} - 1] + \int_{0.03}^{z} P(x)[RR(x) - 1]\,dx}{1 + P_{FD}[RR_{FD} - 1] + \int_{0.03}^{z} P(x)[RR(x) - 1]\,dx} \qquad \textbf{\textit{Formula D-2}}$$

where $P(x)$ is the continuous prevalence distribution of alcohol consumption, as denoted in *Formula D-1*, x is average daily alcohol consumption in g/day, P_{FD} is the prevalence of former drinkers, RR_{FD} is the categorical RR of former drinkers, $RR(x)$ is the continuous RR function for each condition-gender-outcome shown in Appendix C-2, 0.03 is the lower limit of daily consumption and *z* is the upper limit of daily consumption.

(b) The AAFs for two-dimensional conditions are calculated using a component-wise formula which divides the drinking population into chronic bingers, non-chronic bingers and non-bingers and augments the risk of bingers to remove any protective effect, as

previously stated (Rehm et al., 2016b; Roerecke & Rehm, 2010a, 2012). The prevalence of chronic bingers, namely those who consume an average daily amount above the binge drinking threshold (denoted by c), is first calculated:

$$P_{CB} = \int_{c}^{z} P(x)\, dx \qquad \textbf{\textit{Formula D-3}}$$

This prevalence is used to separate the AAF formula into proportional components, in order to arrive at the final form shown in Appendix D-1. Note this final form can be inferred from *Formulas C-7, C-8, C-9 and C-11* derived previously in Chapter 4.

(7) Combining counts and AAFs to arrive at final estimates of AA morbidity and mortality

The enumerated morbidity and mortality counts from Step 2, by population subgroup, are multiplied by the AAFs provided by InterMAHP in Step 6.

5.3.2 Methods for the Estimation of Alcohol-Attributable Mortality in Canada, 2016

5.3.2.1 Data Sources

Record-level mortality data for 2016 were summarized using Statistics Canada's Vital Statistics Deaths Database (Statistics Canada, 2016a). Each record was grouped into *up to one* alcohol-related condition using the weighting algorithm described in Step 2 above. Conditions were operationalized using ICD10 codes as presented in Table C-2.

Alcohol consumption and prevalence information for Canada in 2016 were obtained from the following sources:

(1) *per capita* alcohol sales for the population 15 and older were obtained from Statistics Canada's Canadian Socio-Economic Information Management System (CANSIM) database (Statistics Canada, 2016b) and were adjusted to account for estimated unrecorded consumption in Canada (Macdonald, 1999);

(2) the prevalences of current, binge and former drinkers and lifetime abstainers were obtained from the Canadian Institute for Substance Use Research's Canadian Substance

Use Exposure Database (CanSUED) (Canadian Substance Use Costs and Harms Scientific Working Group, 2018);

(3) the relative amount of alcohol consumed by each gender-age subgroup was taken from CanSUED (Canadian Substance Use Costs and Harms Scientific Working Group, 2018).

Population figures at July 1st, 2016 were taken from CANSIM (Statistics Canada, 2018).

5.3.2.2 Estimation of Alcohol-Attributable Mortality

Steps 1, 3, 4 and 5 in section 5.3.1 above were automated by InterMAHP. For this estimation, we used the InterMAHP list of alcohol-related conditions and the ICD10 code operationalization given in Table C-2. The collected data sources were formatted as required by InterMAHP and run on August 15th, 2018.

InterMAHP recommends including the following statement for the purposes of comparability. For the RR function relating IHD mortality and morbidity in males and alcohol consumption we used Zhao et al. (2017); we concluded that this article provided the most recent meta-analysis on the risk of IHD in men. We used the following dynamic parameters when running the InterMAHP program: a correction factor of 0.8 (Stockwell et al., 2018c), an upper limit of consumption of 250 g/day (Stockwell et al., 2017b) and the linear RR extrapolation method defined in Section 4.5.2.3. The Canadian binge drinking definition is 4+ standard drinks (SD; 53.8+ g) for women and 5+ SDs (67.3+ g) for men. A Canadian SD is 13.45 g ethanol; this is equivalent to the amount of ethanol contained in a 341mL bottle of 5.0% alcohol by volume beer.

InterMAHP automated the production of output files containing mortality AAFs which were then multiplied by the enumerated mortality counts from Step 2 to arrive at the final estimates of AA mortality.

5.3.2.3 Estimation of Confidence Intervals

Confidence intervals for AAFs were estimated following the methods presented in Gmel et al. (2011). Using a Monte Carlo approach, model parameters were randomly drawn across 10,000 draws and model calculations were followed forward for each condition, gender and age group.

The resulting distribution was used to create 95% confidence intervals by selecting values representing the 2.5th and 97.5th percentiles.

5.4 Results

Alcohol-attributable (AA) deaths in Canada are presented in Table D-1, by condition category, condition and gender. In 2016, alcohol was causally responsible for 14,801 (95% CI: 12,435–17,127) deaths, representing 5.5% of total Canadian mortality. The leading cause of AA deaths by condition category continued to be cancer, which caused 4,582 (3,985–5,130) AA deaths in 2016 and was the leading category of AA mortality across eight years of a previous national study (Canadian Substance Use Costs and Harms Scientific Working Group, 2018). Cancer was followed by cardiovascular conditions and digestive conditions, which caused 3,116 deaths (2,157–4,181) and 2,611 deaths (2,346–2,805), respectively. This overall top-three order was preserved in men; however, in women, cancer caused 1,162 deaths (966-1,365) and was followed by digestive conditions (830 deaths; 95% CI 772-882) and cardiovascular conditions (583 deaths; 95% CI 70-1,229). The total burden of AA mortality in this five-year period was disproportionately borne by men (78.9%).

By individual health condition, IHD was the leading cause of AA mortality for both men (1,664 deaths; 95% CI 1,446-1,849) and women (1,131 deaths; 95% CI 822-1,506). Among men, IHD was closely followed by liver cirrhosis (1,654 deaths; 95% CI 1,457-1,786) and colorectal cancer (1,330 deaths; 95% CI 1,195-1,453). Among women, liver cirrhosis (779 deaths; 95% CI 728-824) and breast cancer (469 deaths; 95% CI 368-579) followed IHD as the conditions with the highest burden.

A net protective effect of alcohol consumption was shown for diabetes in women (378 deaths prevented; 95% CI -428 to -329) and for ischaemic stroke (IS) in both women (1,104 deaths prevented; 95% CI -1,104 to -952) and men (56 deaths prevented; 95% CI -175 to 59).

AA deaths in Canada for 2016, by gender and age group (15 to 34, 35 to 64, 65+) are shown in Table D-2. A large burden of mortality was borne by seniors, with 54% of AA deaths accruing to those 65+; however, a significant burden continues to be experienced by those 15 to 34 years of age (8%) and especially 35 to 64 years of age (38%). This breakdown of AA mortality by age group is largely consistent across genders.

Table D-1: Alcohol-attributable deaths in Canada, by condition category, condition, and gender, 2016

			Women	**Men**	**Combined**
Condition Category	**IM#**	**Condition**	**Estimated AA Deaths** (95% CI)	**Estimated AA Deaths** (95% CI)	**Estimated AA Deaths** (95% CI)
(1) Communicable diseases	(1).(1)	Tuberculosis	**4.5** (3.4, 5.8)	**26.1** (20.8, 30.5)	**30.6** (24.2, 36.2)
	(1).(2)	HIV	**0.6** (0.3, 1.0)	**7.7** (5.1, 10.0)	**8.3** (5.4, 11.0)
	(1).(3)	Lower respiratory tract infections	**113.8** (87.7, 141.6)	**312.3** (247.1, 375.4)	**426.2** (334.8, 517.0)
Subtotal of condition category			**118.9** (91.4, 148.3)	**346.1** (273.1, 415.8)	**465.0** (364.4, 564.2)
(2) Cancer	(2).(1)	Oral cavity and pharynx cancer	**82.1** (65.6, 99.7)	**430.5** (362.2, 484.2)	**512.6** (427.7, 583.9)
	(2).(2)	Oesophageal cancer	**126.5** (106.2, 146.3)	**830.2** (731.2, 908.9)	**956.7** (837.4, 1055.2)
	(2).(3)	Colorectal cancer	**132.0** (111.5, 153.8)	**1,330.4** (1,195.4, 1,453.3)	**1,462.4** (1,306.9, 1,607.1)
	(2).(4)	Liver cancer	**257.8** (232.5, 280.4)	**401.2** (355.6, 442.2)	**658.9** (588.2, 722.5)
	(2).(5)	Pancreatic cancer	**82.9** (73.1, 92.7)	**321.1** (286.3, 353.6)	**404.0** (359.4, 446.3)
	(2).(6)	Laryngeal cancer	**10.9** (9.1, 12.9)	**106.7** (88.5, 122.9)	**117.6** (97.5, 135.8)
	(2).(7)	Breast cancer	**469.3** (367.6, 579.4)	**n/a**	**469.3** (367.6, 579.4)
Subtotal of condition category			**1,161.5** (965.6, 1,365.2)	**3,420.0** (3,019.2, 3,765.1)	**4,581.6** (3,984.7, 5,130.3)

(3) Endocrine conditions	(3).(1)	Diabetes	**-377.8** (-428.3, -328.7)	**160.3** (138.9, 180.8)	**-217.5** (-289.3, -147.9)
Subtotal of condition category			**-377.8** (-428.3, -328.7)	**160.3** (138.9, 180.8)	**-217.5** (-289.3, -147.9)
(4) Neuropsychiatric conditions	(4).(1)	Alcoholic psychoses	**40.0**	**150.0**	**190.0**
	(4).(2)	Alcohol abuse	**51.0**	**127.0**	**178.0**
	(4).(3)	Alcohol dependence	**123.0**	**408.0**	**531.0**
	(4).(4)	Degeneration of nervous system due to alcohol	**3.0**	**14.0**	**17.0**
	(4).(5)	Epilepsy	**15.5** (11.9, 19.4)	**44.7** (35.6, 52.7)	**60.2** (47.5, 72.1)
	(4).(6)	Alcoholic polyneuropathy	**0.0**	**1.0**	**1.0**
	(4).(7)	Alcoholic myopathy	**0.0**	**0.0**	**0.0**
Subtotal of condition category			**232.5** (228.9, 236.4)	**744.7** (735.6, 752.7)	**977.2** (964.5, 989.1)
(5) Cardiovascular conditions	(5).(1)	Hypertension	**91.8** (59.1, 131.4)	**308.2** (272.2, 338.8)	**400.0** (331.3, 470.1)
	(5).(2)	Ischaemic heart disease	**1,130.5** (821.7, 1506.1)	**1,664.1** (1,466.3, 1,848.8)	**2,794.6** (2,288.0, 3,354.9)
	(5).(3)	Alcoholic cardiomyopathy	**21.0**	**68.0**	**89.0**
	(5).(4)	Atrial fibrillation and cardiac arrhythmia	**101.0** (79.0, 124.6)	**212.5** (168.5, 254.8)	**313.5** (247.5, 379.4)
	(5).(5)	Haemorrhagic stroke	**341.2** (291.0, 396.6)	**329.8** (281.1, 375.9)	**671.0** (572.2, 772.6)

	(5).(6)	Ischaemic stroke	**-1,104.3** (-1,204.2, -952.3)	**-56.3** (-174.6, 58.5)	**-1,160.6** (-1,378.8, -893.9)
	(5).(7)	Oesophageal varices	**1.9** (1.8, 2.1)	**6.8** (6.0, 7.4)	**8.8** (7.8, 9.4)
Subtotal of condition category			**583.2** (69.5, 1,229.4)	**2,533.1** (2,087.6, 2,952.1)	**3,116.3** (2,157.0, 4,181.5)
(6) Digestive conditions	(6).(1)	Alcoholic gastritis	**0.0**	**7.0**	**7.0**
	(6).(2)	Liver cirrhosis	**778.5** (728.1, 824.2)	**1,654.2** (1,457.2, 1,786.0)	**2,432.8** (2,185.2, 2,610.2)
	(6).(3)	Acute pancreatitis	**32.2** (26.2, 38.5)	**61.5** (53.7, 68.6)	**93.7** (79.9, 107.1)
	(6).(4)	Chronic pancreatitis	**9.8** (8.8, 10.9)	**17.9** (15.3, 20.0)	**27.7** (24.1, 31.0)
	(6).(5)	Alcohol-induced pancreatitis	**9.0**	**41.0**	**50.0**
Subtotal of condition category			**829.5** (772.0, 882.6)	**1,781.6** (1,574.2, 1,922.6)	**2,611.1** (2,346.2, 2,805.2)
(7) Motor vehicle collisions	(7).(1)	Motor vehicle collisions	**66.7** (57.5, 75.4)	**299.4** (266.8, 329.7)	**366.1** (324.3, 405.1)
Subtotal of condition category			**66.7** (57.5, 75.4)	**299.4** (266.8, 329.7)	**366.1** (324.3, 405.1)
(8) Unintentional injuries	(8).(1)	Falls	**157.9** (126.1, 189.1)	**434.4** (375.9, 489.6)	**592.3** (502.0, 678.7)
	(8).(2)	Drowning	**7.0** (6.0, 8.0)	**45.6** (40.5, 50.3)	**52.6** (46.5, 58.2)
	(8).(3)	Fires	**6.2** (5.3, 7.1)	**28.5** (25.1, 31.6)	**34.7** (30.4, 38.8)

	(8).(4)	Accidental poisoning by substances other than alcohol	**116.6** (101.1, 131.2)	**553.8** (495.0, 608.4)	**670.4** (596.2, 739.6)
	(8).(5)	Accidental poisoning by alcohol	**53.0**	**137.0**	**190.0**
	(8).(6)	Other unintentional injuries	**26.9** (22.4, 31.3)	**195.2** (172.2, 216.7)	**222.1** (194.7, 248.0)
Subtotal of condition category			**367.7** (314.0, 419.6)	**1,394.4** (1245.7, 1533.6)	**1,762.1** (1559.7, 1953.2)
(9) Intentional injuries	(9).(1)	Intentional self-poisoning by substances other than alcohol	**53.4** (45.8, 60.5)	**130.7** (117.2, 143.2)	**184.1** (163.0, 203.7)
	(9).(2)	Intentional self-poisoning by alcohol	**9.0**	**11.0**	**20.0**
	(9).(3)	Other intentional self-harm	**108.6** (95.2, 121.0)	**715.0** (644.4, 780.2)	**823.6** (739.6, 901.2)
	(9).(4)	Assault / homicide	**13.9** (12.1, 15.6)	**94.0** (85.5, 101.8)	**107.9** (97.6, 117.4)
	(9).(5)	Other intentional injuries	**0.0**	**3.7** (3.3, 4.0)	**3.7** (3.3, 4.0)
Subtotal of condition category			**185.0** (162.2, 206.1)	**954.4** (861.3, 1,040.3)	**1,139.4** (1,023.5, 1,246.3)
GRAND TOTAL			**3,167.3** (2,232.7, 4,234.3)	**11,634.0** (10,202.4, 12,892.7)	**14,801.3** (12,435.1, 17,127.0)

Notes: AA: alcohol-attributable; IM#: InterMAHP condition number

Columns may not sum exactly due to rounding.

Conditions wholly (100%) attributable to alcohol do not have confidence intervals, as they are not applicable.

Table D-2: Alcohol-attributable deaths in Canada, by gender and age group, 2016

Age group	Women	Men	Combined
	Estimated AA Deaths (95% CI)	**Estimated AA Deaths (95% CI)**	**Estimated AA Deaths (95% CI)**
15-34	**226.0** (203.0, 248.2)	**868.3** (793.3, 935.3)	**1,094.3** (996.3, 1,183.5)
35-64	**1,201.4** (1,011.0, 1,406.4)	**4,121.2** (3,667.0, 4502.0)	**5,322.6** (4,678, 5,908.4)
65+	**1,739.9** (1,018.7, 2,579.8)	**6,644.4** (5,742.1, 7,455.4)	**8,384.3** (6,760.8, 10,035.2)
Total	**3,167.3** (2,232.7, 4,234.3)	**11,634.0** (10,202.4, 12,892.7)	**14,801.3** (12,435.1, 17,127.0)

Notes: AA: alcohol-attributable.

Columns may not sum exactly due to rounding.

5.5 Discussion

The International Model of Alcohol Harms and Policies is the first open access collection of methodologies and program software for estimating AA mortality and morbidity. The goal of InterMAHP is to provide a customizable set of methodological options within a standardized framework, as well as novel software, which may be used to support international research teams in estimating alcohol harms in their region. Given customary inputs, such as *per capita* consumption and drinking prevalence, InterMAHP fully automates the calculation of AAFs. InterMAHP's methods are further designed to be *fully replicable*. That is, given this article and the more comprehensive methods provided in Chapter 4, one should be able to recreate the InterMAHP AAF calculations, if desired.

Though some estimation options, such as the use of the modern AAF formula, are standardized in InterMAHP, the software provides increased flexibility to potential users at the input stage through a dynamic user interface. For example, users may replace RR functions, define their region's binge drinking level and upper limit of daily consumption and choose customized data sources for *per capita* consumption and drinking prevalences; these choices would then be carried through the automated calculations performed by InterMAHP. This article presents the first in a series of planned InterMAHP releases; subsequent versions will add additional functionalities, such as dynamically calculating the change in AA mortality and morbidity, which would be expected to occur given a change in *per capita* consumption.

InterMAHP has inherent limitations. As it employs the modern AAF formulation, it cannot complete sensitivity analyses using other methods of estimating AA morbidity and mortality, such as the alternative methodologies suggested in Trias-Llimós et al. (2018). However, we note that the method using the modern AAF formulation is used extensively. The use of the Gamma distribution to estimate the continuous prevalence distribution of average daily alcohol consumption may result in higher AAF estimates than choosing a distribution of best-fit for each population grouping, according to Parish et al. (2017). InterMAHP does not separately calculate harms-to-others, resulting in the likely underestimation of overall AA mortality and morbidity. Lastly, InterMAHP does not currently automate the calculation of uncertainty estimates. For the purposes of this article, a separate module was built to implement this functionality. Uncertainty estimation will be added to subsequent InterMAHP versions.

Furthermore, InterMAHP is a methodological supplement to, but not a replacement for, programs of work that estimate AA morbidity and mortality. Many areas of estimation are difficult to generalize internationally; therefore, regional expertise is necessary to properly employ InterMAHP's functionality.

It is important to note the significance of the RR function chosen for IHD mortality in men to any exercise estimating AA harms. For example, the 2016 Global Burden of Disease study, using the risk functions in Roerecke & Rehm (2012) and categorical former drinker risk estimates in Roerecke & Rehm (2010b), estimated that alcohol use prevented 2,181 IHD deaths among men in Canada (Institute for Health Metrics and Evaluation, 2017), compared to our estimate of 1,664 deaths caused. This difference of nearly 3,850 AA deaths (about 25% of total AA mortality) is caused largely by the IHD meta-analysis chosen, thereby highlighting the importance of this choice.

5.6 Conclusion

We recommend the International Model of Alcohol Harms and Policies as a set of methodologies and assumptions, which may provide a more standardized international framework for estimating AA morbidity and mortality. We suggest that the use of InterMAHP, with clearly stated parameter choices, may lead to more comparable results in the global context, while providing the flexibility for estimation to be tailored to region-specific needs and inputs. Greater transparency regarding methods will make it easier to determine how different assumptions (e.g. the choice of IHD relative risk relationship) influence estimates of AA harms.

In Canada, alcohol causes a significant burden of mortality as this study estimates that nearly 6% of all deaths are caused by drinking. AA cancers cause the highest proportion of this burden: over 4,500 AA deaths in 2016 of 14,800 total AA mortalities. Public awareness campaigns should focus on this strong link between alcohol consumption and increased risk of cancer. Further, federal and provincial governments may consider implementing policies which have been shown to reduce alcohol consumption and related harms, such as minimum pricing (Sherk, Stockwell & Callaghan, 2018; Stockwell et al., 2012; Stockwell et al., 2017c), limiting days of sale (Norström & Skog, 2005; Sherk et al., 2018) and reducing store hours (Kolosnitsyna, Sitdikov & Khorkina, 2014).

5.7 Acknowledgements

This work was supported by a CIHR Frederick Banting and Charles Best Canada Graduate Scholarship Doctoral Award (CGS-D) awarded to the first author.

The authors would like to thank the following colleagues for their input at various stages of the InterMAHP project: Colin Angus (Sheffield Alcohol Policy Group, University of Sheffield); Tim Naimi (Boston Medical Center, Boston University School of Public Health); Eveline Lensvelt and Tanya Chikritzhs (National Drug Research Institute, Curtin University); and Jakob Manthey (Centre for Addiction and Mental Health).

Chapter 6: The Potential Health Impact of an Alcohol Minimum Unit Price in Québec, Canada: An Application of the International Model of Alcohol Harms and Policies [Study E]

6.1 Abstract

What is the International Model of Alcohol Harms and Policies? The International Model of Alcohol Harms and Policies (InterMAHP; www.intermahp.cisur.ca) is an open access alcohol harms estimator and policy scenario modeler. InterMAHP consists of methods and a web-based user interface to assist alcohol researchers in estimating alcohol-attributable mortality and morbidity and the changes in these harms under different alcohol policy scenarios.

Objectives: We specify methodologies to model changes in harm under alcohol policy scenarios. An alcohol minimum unit price (MUP) is a strategy gathering international support; we therefore employ InterMAHP to estimate the potential health benefits of introducing a MUP in Québec.

Method: Aggregated mortality and hospitalization data were sourced from official sources. Alcohol sales and pricing data were obtained from the partial government retail monopoly and Nielsen. Exposure data were from the Canadian Substance Use Exposure Database. Average price changes under two MUP scenarios were estimated. InterMAHP automated the estimation of observed alcohol-attributable (AA) harm and that projected to occur under each scenario.

Results: Alcohol caused 2,850 deaths and 24,694 hospitalizations in Québec in 2014. Introducing a MUP of CAD$1.50 was estimated to reduce consumption by 4.4%, AA deaths by 5.9% (95%CI: 0.2%, 11.7%) and AA hospital stays by 8.4% (3.2%, 13.7%). A higher MUP of CAD$1.75 was estimated to reduce AA deaths by 11.5% (5.9%, 17.2%) and AA hospital stays by 16.3% (11.2%, 21.4%).

Conclusions: We specify novel methods and software to assist researchers in estimation of the health impact of alcohol policy changes. Application of these methods indicates that a MUP of between CAD$1.50 and $1.75 would substantially reduce the alcohol-caused burden of disease in Québec.

6.2 Introduction

Alcohol is responsible for a high burden of disease globally, causing approximately three million deaths and 133 million disability-adjusted life years lost annually (World Health Organization, 2018). To address this, the World Health Organization released the Global Strategy to Reduce the Harmful Use of Alcohol (World Health Organization, 2010), which forwarded policy options and interventions across ten key areas, including alcohol pricing policies, physical availability and marketing. Among these, pricing options have consistently earned the highest feasibility and impact rankings when measured by alcohol policy experts (Babor et al., 2010; Bruun et al., 1975; Nelson et al., 2013). A recent analysis of alcohol policy 'best buys' concluded that pricing strategies had the highest cost-effectiveness among global policy strategies (Chisholm et al., 2018). Comprehensive meta-analyses have reported that a 10% increase in the price of alcohol would lead to a 4.4% decrease in alcohol sales (Wagenaar, Salois & Komro, 2009) and that price increases were likewise associated with a host of health benefits, including decreased alcohol-related disease and injury, violence and motor vehicle collisions (Wagenaar, Tobler & Komro, 2010).

An alcohol minimum pricing strategy gathering international support is a minimum unit price (MUP); this strategy sets a floor retail price below which a standard drink, defined by pure alcohol content (in Canada, 13.45g ethanol), cannot be sold. MUP policies are applied to all alcoholic beverages, including beer, wine, spirits, cider, coolers and premixed drinks, and have the effect of reducing or preventing the sale of cheap, high strength drinks, i.e. the drinks with the highest 'bang for the buck.' A MUP includes sales tax, i.e. it is the final retail price of the alcohol sold. Studies have targeted this cheap alcohol as a cause of hazardous alcohol use and heavy drinkers are theorized to experience the greatest health benefit, in terms of decreased consumption, on the implementation of a MUP (Holmes et al., 2014). MUP policies are easy to understand and communicate to the public: they associate a beverage category-unified floor price with all alcoholic drinks, though typically there are separate MUP levels for off-premise and on-premise sales.

A MUP of 50p per 8g pure alcohol 'unit' was introduced in Scotland in May 2018 (Giles, Robinson & Beeston, 2018); this would correspond in Canada to ~CAD$1.45/SD (converted online 23-Dec-18). Though early in the MUP evaluation process, a six-month post-

implementation briefing note from NHS Health Scotland reported a smaller increase in pure alcohol volume sold in Scotland (4%) than in England and Wales (7%), i.e. a relative decrease in the experimental group as compared to the control group (Giles et al., 2018). If subsequent and final evaluations provide similar results, it may add further impetus to international calls for MUP policy strategies.

In Canada, alcohol causes pronounced harm: 14,800 deaths and $14.6 billion in healthcare, lost production and criminal justice costs in 2014 (Canadian Substance Use Costs and Harms Scientific Working Group, 2018). In response, several Canadian provinces have implemented minimum pricing strategies, which have been shown to lead to decreases in alcohol consumption (Stockwell et al., 2009b; Stockwell et al., 2012), alcohol-attributable (AA) deaths (Zhao et al., 2013), AA hospital visits (Stockwell, Zhao, Martin & Macdonald, 2013) and certain types of alcohol-related crime (Stockwell et al., 2017c; Stockwell et al., 2015).

The Canadian province of Québec has not implemented a MUP strategy, though there exists a minimum price per litre of beer beverage (not per SD). In 2009, the recommended MUP for Canadian off-premise alcohol sales was $1.50 (Thomas, Stockwell & Wettlaufer, 2017), which would have been just above $1.75 in 2018 (http://inflationcalculator.ca/quebec). Policymakers considering the introduction of one of these MUP levels are well served by projections of the changes in sales, consumption and AA harms that would occur if they were to take action. The aims of this study were therefore twofold:

(1) to estimate the effect on alcohol prices, sales and consumption of two MUP scenarios in Québec, representing a $1.50 (Scenario 1) and $1.75 (Scenario 2) MUP per Canadian SD; and

(2) based on the above estimated consumption changes, specify and employ methods which automate the estimation of the changes in alcohol-attributable (AA) mortality and hospitalizations under each scenario.

The recent development of an open access alcohol harms and policy modeler, the International Model of Alcohol Harms and Policies (InterMAHP), made possible the second study aim (see: www.intermahp.cisur.ca). The alcohol harms estimation functionality of InterMAHP was previously described in Chapters 4 and 5; however, the capability of estimating changes in AA harms has been added to facilitate alcohol policy scenario analyses.

It is critical for jurisdictions to develop the capacity to estimate the health benefits that may be experienced when potentially health-protective alcohol policies, such as MUP strategies, are employed. Such estimates may provide important guidance to policymakers before such laws are enacted. InterMAHP provides this functionality to public health professionals globally and is the first open access alcohol harms estimator and alcohol policy scenario modeler.

6.2 Methods

6.2.1 Data Sources

Per capita consumption and data on patterns of alcohol use in Québec for 2014 were taken from the Canadian Substance Use Exposure Database (CanSUED), a customized database maintained by the Canadian Institute for Substance Use Research (Canadian Substance Use Costs and Harms Scientific Working Group, 2018). Record-level inpatient hospitalization data were sourced from the Québec hospital patient information system of the Ministère de la Santé et des Services sociaux. Mortality data were obtained from Québec's Registre des événements démographiques, a vital statistics database.

Product-level alcohol sales data for wine, spirits and liqueurs were obtained from the partial government retail monopoly, Société des alcools du Québec (SAQ). As about 85% of beer products were sold in convenience and grocery stores, a sample of beer sales data were purchased from the market research company AC Nielsen that included brand names, prices and container sizes.

6.2.2 General Approach to the Estimation of AA Mortality and Morbidity

The following generalized approach for estimating AA mortality and morbidity was used. A more comprehensive description can be found in Chapter 4.

(1) Enumerating alcohol-related morbidity and mortality

Alcohol-related conditions were identified and operationalized as in Table C-2. Each record in the death and hospitalization data was tallied as up to one alcohol-related condition (i.e. a mortality record may be counted towards zero or one alcohol-related health condition, depending

on the diagnosis codes present) using the primary cause algorithm. This assigns a weight of 1.0 to the primary cause of death, while for hospitalization records, the primary diagnosis was assigned a weight of 1.0 unless the record was an injury or poisoning (ICD10 begins with S or T). In the case of injury or poisoning the record was searched for the first external cause code (ICD10 begins with V,W,X,Y), which was given a weight of 1.0. All other diagnoses were given a weight of zero; this primary cause algorithm is standard practice in alcohol epidemiology (World Health Organization, 2014, 2018). These counts were then collected into population subgroups defined by gender and age group. The age groups for this study were defined as 00-14, 15-34, 35-64 and 65+ as these were the default groups recommended by InterMAHP and match those used in the 2018 WHO Global Status Report on Alcohol and Health (World Health Organization, 2018).

(2) Estimation of alcohol-attributable fractions

Conditions wholly-attributable to alcohol were assigned an AAF=1.0, by definition. For partially-attributable conditions, the estimation of indirect AAFs was automated by InterMAHP. The program software employs the modern AAF formula as presented in Chapters 4 and 5, modified from Kehoe et al. (2012). The modern AAF required the following information:

(a) A continuous prevalence distribution of average daily alcohol consumption for each population subgroup

For each population subgroup, the continuous prevalence distribution was calculated using a single-parameter definition of the Gamma distribution (Kehoe et al., 2012; Rehm et al., 2010). This formulation of the Gamma distribution is uniquely defined in each population subgroup by mean consumption.

(b) Relative risk functions and estimates for each alcohol-related condition

RR functions for current drinkers and RR point estimates for former drinkers were collected from the international meta-analytic literature for InterMAHP and are similar to those used in the 2018 GSRAH (Rehm et al., 2017; World Health Organization, 2018).

(3) Estimation of alcohol-attributable mortality and morbidity

Steps 1 and 2 created counts and AAFs for each condition, gender and age group for Québec in 2014. As the final step, AA harm estimates were produced by multiplying the enumerated count by the AAF, for each alcohol-related condition, gender, age group and outcome (mortality or hospitalization).

6.2.3 Estimated Impact of MUP Scenarios on Alcohol Prices and Consumption

Changes in *per capita* consumption under each MUP scenario were estimated using the following strategy. First, product-level SAQ and Nielsen data were used to estimate the volume-weighted effective price paid per SD across beverage and outlet types. Next, under the two MUP scenarios of $1.50/SD and $1.75/SD, we calculated the percentages of products and ethanol by volume that were currently cheaper than the MUP. The scenarios were then 'implemented'- this had the hypothetical effect of raising all product-level prices to at least the floor MUP – and adjusted volume-weighted effective prices paid per SD were calculated. This resulted in an overall percentage change in average alcohol prices in each scenario.

These percentage changes in average prices were used to estimate the potential change in alcohol sales, used as a proxy for consumption, by applying a contextualized price elasticity of alcohol demand: -0.34 from a previous study in the Canadian province of British Columbia (BC) (Stockwell et al., 2012b). Québec and BC have been shown to have relatively similar levels and patterns of consumption (Paradis, Demers & Picard, 2010).

Next, as the Gamma distribution-defined continuous prevalence distribution of average daily alcohol consumption depends only on the mean consumption in each population subgroup, we were able to model the changes in each Gamma distribution by applying these percentage consumption changes. This process was fully automated by InterMAHP.

6.3.3 Estimated Impact of MUP Scenarios on AA Mortality and Morbidity

(1) Estimation of changes in the prevalence of binge, current and former drinkers

The AAFs for injuries (World Health Organization, 2018), IHD and IS (Rehm et al., 2017a) are modified by binge drinking prevalence. It was therefore necessary to estimate changes to the

prevalence of binge drinkers under each MUP scenario. In Canada, binge drinking is defined as 5+/4+ SDs per occasion for men/women (Canadian Substance Use Costs and Harms Scientific Working Group, 2018).

Estimation of this prevalence change for each scenario was automated by InterMAHP by calculating the prevalence of 'chronic bingers' using the Gamma distribution for the base case and each scenario in turn. 'Chronic bingers' were drinkers who, on average, consumed 5+ SDs daily for men or 4+ SDs daily for women and the prevalence was calculated by:

$$P_{CB} = \int_{c}^{z} P(x)dx \qquad \textbf{\textit{Formula E-1}}$$

where P_{CB} is the prevalence of chronic bingers, *z* is an estimate of the upper limit of daily consumption, *c* is the definition of bingeing in g ethanol per occasion and $P(x)$ is the continuous prevalence distribution of average daily alcohol consumption . Next, the resulting binge prevalence was calculated as:

$$P_{BD,Sx} = P_{BD,Base} * \frac{P_{CB,Sx}}{P_{CB,Base}} \qquad \textbf{\textit{Formula E-2}}$$

where $P_{BD,Sx}$ is the prevalence of binge drinking in scenario *x* and $P_{BD,Base}$ is the prevalence of binge drinking in the base case.

In each scenario, it was assumed that the changes in consumption did not change the prevalence of former drinkers or current drinkers. This potential policy change would be expected to affect former drinker status and estimating zero change in the prevalence of current drinkers followed previous alcohol policy analyses (Stockwell et al., 2017a; Stockwell et al., 2018b).

(2) Estimation of changes for partially-attributable conditions

AAFs for partially-attributable conditions were calculated by InterMAHP using the modern AAF formula and Gamma distribution. An adjusted Gamma distribution in each scenario was uniquely estimable based on the calculated percentage consumption change (since the employed Gamma distribution is dependent only on average daily consumption). This change follows through the AAF calculation to provide an adjusted AAF in each scenario for each alcohol-related condition, gender and age group.

Next, an adjustment was applied which allowed for modification of the total number of deaths or hospitalizations in each condition, gender and age group (i.e. the count to which the AAF was subsequently applied):

$$M_{Sx} = M_{Base} + (M_{Sx}AAF_{Sx} - M_{Base}AAF_{Base}) \qquad \textbf{\textit{Formula E-3}}$$

where total mortality in scenario *x* (M_{Sx}) equals mortality in the base case (M_{Base}) plus an adjustment representing the difference in AA mortality in scenario *x* ($M_{Sx}AAF_{Sx}$) and the base case ($M_{Base}AAF_{Base}$). Rearranging *Formula E-3* allows us to solve for the adjustment factor, which is now presented as a component of the final calculation:

$$AAM_{Sx} = M_{Sx} \times AAF_{Sx} = M_{Base} \times \frac{1 - AAF_{Base}}{1 - AAF_{Sx}} \times AAF_{Sx} \qquad \textbf{\textit{Formula E-4}}$$

where AAM_{Sx} is the number of alcohol-attributable deaths under scenario *x*, the fraction is the adjustment factor and AAF_{Base} and AAF_{Sx} are the InterMAHP-calculated AAFs under the base case and scenario *x* (Sherk et al., 2017b; Stockwell et al., 2017a; Stockwell et al., 2018b).

(3) Estimation of changes for wholly-attributable conditions

As wholly-attributable conditions have AAFs of 1.0, by definition, it was necessary to create methodology towards estimating the change in these conditions under differing consumption scenarios. This method has been specified in detail (Churchill et al., Under Review), is employed in the Sheffield Alcohol Policy Model (Brennan et al., 2015) and has been used in previous

policy modeling projects (Stockwell et al., 2017a; Stockwell et al., 2018b). Briefly, an absolute risk function (ARF) was estimated for each condition, gender and age group. The ARF was then functionally analogous to the RR functions for current drinkers used in the modern AAF formula for partially-attributable conditions. Integrating the adjusted Gamma distribution, in each scenario, against the ARF provides an estimated change in the number of wholly-attributable conditions.

(4) InterMAHP: Estimation of changes to alcohol-attributable mortality and morbidity

InterMAHP automates the necessary calculations in the three preceding subsections and estimates the impact on AA mortality and morbidity given the projected changes in alcohol consumption under the two MUP scenarios. These computations are completed at the most granular level – health condition by gender by age grouping.

6.3.4 Estimation of Confidence Intervals

Confidence intervals for AAFs were estimated following the methods presented in Gmel et al. (2011). Briefly, a Monte Carlo approach was employed, which consisted of randomly drawing all model parameters 10,000 times and following model calculations through for each condition, gender and age group. The resulting model outputs were treated as a distribution and 95% confidence intervals were created by selecting values representing the 2.5^{th} and 97.5^{th} percentiles.

6.3.5 Statistical Analyses

InterMAHP is programmed in R version 3.5 (R Core Team, 2018). The statistical package SAS 9.3 (SAS Institute, 2011) was employed to apply AAFs to mortality and hospitalization counts and for the aggregation of results.

6.4 Results

6.4.1 Alcohol Prices and Consumption, Observed and Estimated Impact of MUP Policies

The observed number of products and ethanol volume representing alcohol sales in Québec in 2014 are shown in Table E-1, by beverage category. There were 18,914 products sold which contained 59.9 million litres of ethanol. The remaining columns present the quantity and percentage of products and ethanol volume that would be affected by each MUP scenario. A MUP of $1.50 would affect only 2.5% of products; however, these products account for 24.1% of ethanol sales. A $1.75 MUP would affect only 5.4% of products, but more than half (56.3%) of sales by ethanol volume. Among beverage categories, spirits would be the most affected by this implementation, as 68.5% and 82.6% of ethanol volume, respectively, would be subject to a price increase under the MUP scenarios. Wine would be the least affected by MUP strategies, as only 1.0% of products and 11.9% of ethanol would be affected by the $1.50 MUP and only 2.6% of products and 32.8% of ethanol would be affected by the $1.75 MUP.

Table E-2 summarizes the impact of each MUP scenario on average alcohol prices in each beverage category and overall. The implementation of a $1.50 MUP would result in a 12.8% increase in average alcohol price, whereas the higher $1.75 MUP would result in a 25.3% increase.

The application of the price elasticity in the Canadian context (-0.34, see methods) results in estimated reductions *in per capita* consumption of 4.35% in the first scenario and 8.59% in the second scenario.

Table E-1: Observed alcohol sales, and volume and percentage of ethanol affected by MUP scenarios, by beverage category and total, Québec 2014

	Observed		***Number and percentage of products and volume affected by Scenario 1 - $1.50 MUP***				***Number and percentage of products and volume affected by Scenario 2 - $1.75 MUP***			
	Products	***Ethanol volume***	***Products***		***Ethanol volume***		***Products***		***Ethanol volume***	
Beverage category	***No.***	***Volume (1,000 L)***	***No.***	***%***	***Volume (1,000 L)***	***%***	***No.***	***%***	***Volume (1,000 L)***	***%***
Beer, cider, coolers	1 343	31 700	81	6.0 %	6 690	21.1 %	198	14.7 %	20 693	65.3 %
Wine	15 176	19 173	149	1.0 %	2 290	11.9 %	388	2.6 %	6 295	32.8 %
Fortified wine, liqueurs	826	2 469	22	2.7 %	934	37.9 %	60	7.3 %	1 307	52.9 %
Spirits	1 569	6 589	223	14.2%	4 516	68.5 %	314	20.0 %	5 444	82.6 %
Total	**18 914**	**59 932**	**475**	**2.5%**	**14 430**	**24.1 %**	**960**	**5.4 %**	**33 739**	**56.3 %**

MUP: Minimum unit price / minimum price per standard drink

Columns may not sum due to rounding.

Table E-2: Estimated impact of MUP scenarios on average alcohol price, by beverage category and total, Québec 2014

Beverage category	***Scenario 1 - $1.50 MUP***	***Scenario 2 - $1.75 MUP***
Beer, cider, coolers	12.1%	26.4 %
Wine	13.2 %	16.4 %
Fortified wine, liqueurs	10.6 %	14.9 %
Spirits	16.2 %	31.1%
Total*	**12.8 %**	**25.3 %**

MUP: Minimum unit price / minimum price per standard drink

Columns may not sum due to rounding.

*Weighted by sales volume from Table 1

6.4.2 AA Mortality, Observed and Estimated Impact of MUP Policies

Alcohol-attributable (AA) deaths in Québec in 2014, by health condition category, are shown in Table E-3 for the observed case, Scenario 1 ($1.50 MUP) and Scenario 2 ($1.75 MUP). Alcohol was found to be causally responsible for 2,850 deaths (95% CI: 2,685-3,012) in Québec. Among condition categories, cancer caused the highest burden of AA mortality at 1,013 deaths, followed by cardiovascular conditions (723 deaths), unintentional injuries (267 deaths) and intentional injuries (266 deaths).

Under two potential MUP policy implementations, the modeling methodologies employed found significant reductions in AA mortality under each scenario. Implementing a MUP of $1.50 would have the result of preventing 169 AA deaths (95% CI: -333, -7) in Québec in 2014; this corresponds to a decrease of -5.9%. Scenario 2, which modeled a higher MUP of $1.75, was estimated to result in 2,523 AA mortalities, a decrease of 327 deaths (11.5%) as compared to the observed result. By condition category, neuropsychiatric conditions were most responsive to potential policy change, with estimated 12.0% and 23.2% reductions in AA deaths in Scenario 1 and 2, respectively.

AA deaths, by gender and age group, are shown in Table E-4. Alcohol caused nearly four times more deaths among men (2,228 deaths, 95% CI 2,140-2,313) than women (622 deaths, 95% CI 544-699). We observed a gradient in the harm reduction response under these MUP scenarios: in each scenario, younger age groups experienced a greater proportional reduction in mortality than do older age groups. Women also experienced more protection in each of Scenario 1 and Scenario 2, relative to men.

More detailed information regarding AA mortality under each scenario and by 41 alcohol-related health conditions is shown in Appendix E-1. Under each MUP scenario, alcohol dependence would have the largest absolute decrease in mortality, as a $1.50 MUP was estimated to prevent 38 deaths and a $1.75 MUP was estimated to prevent 73 deaths from this condition. Other conditions with substantial absolute decreases were other intentional self-harm, such as suicide (18 fewer deaths in Scenario 1 and 35 fewer deaths in Scenario 2), IHD (16 and 30) and colorectal cancer (10 and 20).

Table E-3: Alcohol-attributable mortality, observed and under two MUP scenarios, by condition category, Québec 2014

Condition Category	***Quebec in 2014***	***Scenario 1 - $1.50 MUP***		***Scenario 2 - $1.75 MUP***	
	Observed *(95% CI)*	**Estimate** *(95% CI)*	**Percent Change** *(95% CI)*	**Estimate** *(95% CI)*	**Percent Change** *(95% CI)*
(1) Communicable diseases	**131** *(125, 136)*	**124** *(119, 129)*	**-5.3%** *(-9.2%, -1.5%)*	**118** *(113, 123)*	**-9.9%** *(-13.7%, -6.1%)*
(2) Cancer	**1 013** *(964, 1 062)*	**979** *(930, 1 027)*	**-3.4%** *(-8.2%, +1.4%)*	**946** *(897, 994)*	**-6.6%** *(-11.5%, -1.9%)*
(3) Diabetes	**-125** *(-145, -106)*	**-124** *(-143, -105)*	**n/a**	**-122** *(-142, -103)*	**n/a**
(4) Neuropsychiatric conditions	**375** *(375, 376)*	**330** *(328, 332)*	**-12.0%** *(-12.5%, -11.5%)*	**288** *(285, 292)*	**-23.2%** *(-24%, -22.1%)*
(5) Cardiovascular conditions	**723** *(665, 782)*	**694** *(636, 752)*	**-4.0%** *(-12%, +4%)*	**667** *(610, 725)*	**-7.7%** *(-15.6%, +0.3%)*
(6) Digestive conditions	**118** *(116, 121)*	**111** *(108, 113)*	**-5.9%** *(-8.5%, -4.2%)*	**104** *(101, 106)*	**-11.9%** *(-14.4%, -10.2%)*
(7) Motor vehicle collisions	**81** *(78, 84)*	**75** *(71, 78)*	**-7.4%** *(-12.3%, -3.7%)*	**68** *(65, 71)*	**-16.0%** *(-19.8%, -12.3%)*
(8) Unintentional injuries	**267** *(253, 281)*	**246** *(233, 259)*	**-7.9%** *(-12.7%, -3%)*	**227** *(215, 239)*	**-15.0%** *(-19.5%, -10.5%)*
(9) Intentional injuries	**266** *(254, 277)*	**246** *(235, 257)*	**-7.5%** *(-11.7%, -3.4%)*	**227** *(216, 237)*	**-14.7%** *(-18.8%, -10.9%)*
Grand Total	**2 850** (2 685, 3 012)	**2 681** (2 517, 2 843)	**-5.9%** (-11.7%, -0.2%)	**2 523** (2 360, 2 683)	**-11.5%** (-17.2%, -5.9%)

MUP: Minimum unit price / minimum price per standard drink. Columns may not sum due to rounding.

Table E-4: Alcohol-attributable mortality, observed and under two MUP scenarios, by gender and age group, Québec 2014

Gender & Age Group		***Quebec in 2014***	***Scenario 1 - $1.50 MUP***		***Scenario 2 - $1.75 MUP***	
		Observed *(95% CI)*	**Estimate** *(95% CI)*	**Percent Change** *(95% CI)*	**Estimate** *(95% CI)*	**Percent Change** *(95% CI)*
Women	**Total**	**622** *(544, 699)*	**574** *(498, 650)*	**-7.7%** *(-19.9%, +4.5%)*	**531** *(456, 605)*	**-14.6%** *(-26.7%, -2.7%)*
	15-34	**37** *(35, 38)*	**33** *(32, 34)*	**-10.8%** *(-13.5%, -8.1%)*	**30** *(28, 31)*	**-18.9%** *(-24.3%, -16.2%)*
	35-64	**176** *(165, 187)*	**161** *(150, 171)*	**-8.5%** *(-14.8%, -2.8%)*	**146** *(136, 157)*	**-17%** *(-22.7%, -10.8%)*
	65+	**409** *(344, 474)*	**380** *(316, 444)*	**-7.1%** *(-22.7%, +8.6%)*	**354** *(291, 417)*	**-13.4%** *(-28.9%, +2%)*
Men	**Total**	**2 228** *(2 140, 2 313)*	**2 107** *(2 020, 2 194)*	**-5.4%** *(-9.3%, -1.5%)*	**1 992** *(1 904, 2 079)*	**-10.6%** *(-14.5%, -6.7%)*
	15-34	**144** *(141, 148)*	**134** *(130, 137)*	**-6.9%** *(-9.7%, -4.9%)*	**123** *(120, 127)*	**-14.6%** *(-16.7%, -11.8%)*
	35-64	**721** *(699, 741)*	**672** *(650, 693)*	**-6.8%** *(-9.8%, -3.9%)*	**625** *(603, 647)*	**-13.3%** *(-16.4%, -10.3%)*
	65+	**1 362** *(1 300, 1 423)*	**1 301** *(1 239, 1 363)*	**-4.5%** *(-9%, +0.1%)*	**1 243** *(1 180, 1 304)*	**-8.7%** *(-13.4%, -4.3%)*
Grand Total		**2 850** (2 685, 3 012)	**2 681** (2 517, 2 843)	**-5.9%** (-11.7%, -0.2%)	**2 523** (2 360, 2 683)	**-11.5%** (-17.2%, -5.9%)

MUP: Minimum unit price / minimum price per standard drink. Columns may not sum due to rounding.

6.4.3 AA Hospitalizations, Observed and Estimated Impact of MUP Policies

Table E-5 presents AA hospitalizations, by condition category. Alcohol caused 24,694 (95% CI: 23,338-26,017) hospitalizations in Québec in 2014. About 49% of these AA hospitalizations were caused by unintentional injuries such as falls and accidental poisonings due to alcohol and other substances. After unintentional injuries, neuropsychiatric conditions (3,911 AA hospitalizations), cancer (3,250), digestive conditions (2,626) and communicable disease (1,594) were responsible for 1,000 or more AA hospital stays. Alcohol consumption was estimated to prevent hospital stays for diabetes and cardiovascular conditions; however, each MUP scenario resulted in benefits in these categories as well (i.e. more hospital stays were prevented).

Generally, our results support that AA hospitalizations were more responsive to MUP policy changes than AA mortalities. For example, under Scenario 2, it was found that AA hospitalizations would decrease by 16.3%, while AA deaths would decrease by 11.5%. Neuropsychiatric conditions, unintentional injuries and intentional injuries were the three condition categories most responsive to policy change. Significant and substantial decreases in AA hospitalizations were estimated in each of Scenario 1 (2,063 fewer hospital stays) and Scenario 2 (4,014 fewer hospital stays).

AA hospitalizations, by gender and age group, are presented in Table E-6. As with the mortality estimates, men (19,464; 95%CI 18,776-20,138) experienced nearly four times as many hospitalizations as women (5,229; 95%CI 4,562-5,879). Again, women were estimated to experience greater proportional benefit than men from these policy changes. Harm reduction gradients by age group were differential by gender: for women, older age groups would experience a greater proportional reduction in harms (save for the small sample size in the 00-14 age group); however, for men, the findings show that younger age groups would benefit more from these policy changes.

Appendix E-2 shows AA hospitalizations, observed and under each MUP scenario, by health condition. There are 1,000 or more AA hospitalizations for each of alcohol psychoses, alcohol dependence, atrial fibrillation and cardiac arrhythmia, falls and other unintentional injuries. Of these, alcohol psychoses and dependence were projected to experience the largest relative decreases in each policy scenario. In the base case and in each scenario, alcohol was estimated to prevent more than 1,350 hospitalizations due to IHD.

Table E-5: Alcohol-attributable hospitalizations, observed and under two MUP scenarios, by condition category, Québec 2014

Condition Category	***Quebec in 2014***	***Scenario 1 - $1.50 MUP***		***Scenario 2 - $1.75 MUP***	
	Observed *(95% CI)*	**Estimate** *(95% CI)*	**Percent Change** *(95% CI)*	**Estimate** *(95% CI)*	**Percent Change** *(95% CI)*
(1) Communicable diseases	**1 594** *(1 531, 1 658)*	**1 517** *(1 457, 1 579)*	**-4.8%** *(-8.6%, -0.9%)*	**1 443** *(1 385, 1 502)*	**-9.5%** *(-13.1%, -5.8%)*
(2) Cancer	**3 250** *(3 108, 3 390)*	**3 119** *(2 979, 3 258)*	**-4.0%** *(-8.3%, +0.2%)*	**2 993** *(2 855, 3 131)*	**-7.9%** *(-12.2%, -3.7%)*
(3) Diabetes	**-133** *(-154, -112)*	**-132** *(-153, -112)*	**n/a**	**-131** *(-152, -111)*	**n/a**
(4) Neuropsychiatric conditions	**3 911** *(3 899, 3 923)*	**3 443** *(3 415, 3 472)*	**-12.0%** *(-12.7%, -11.2%)*	**3 015** *(2 975, 3 056)*	**-22.9%** *(-23.9%, -21.9%)*
(5) Cardiovascular conditions	**-340** *(-658, -28)*	**-542** *(-850, -238)*	**n/a**	**-731** *(-1 030, -436)*	**n/a**
(6) Digestive conditions	**2 626** *(2 544, 2 705)*	**2 510** *(2 427, 2 590)*	**-4.4%** *(-7.6%, -1.4%)*	**2 399** *(2 315, 2 480)*	**-8.6%** *(-11.8%, -5.6%)*
(7) Motor vehicle collisions	**620** *(593, 647)*	**577** *(550, 602)*	**-6.9%** *(-11.3%, -2.9%)*	**534** *(509, 558)*	**-13.9%** *(-17.9%, -10.0%)*
(8) Unintentional injuries	**12 190** *(11 543, 12 816)*	**11 240** *(10 640, 11 824)*	**-7.8%** *(-12.7%, -3.0%)*	**10 334** *(9 780, 10 877)*	**-15.2%** *(-19.8%, -10.8%)*
(9) Intentional injuries	**976** *(932, 1 018)*	**899** *(857, 939)*	**-7.9%** *(-12.2%, -3.8%)*	**824** *(785, 863)*	**-15.6%** *(-19.6%, -11.6%)*
Grand Total	**24 694** (23 338, 26 017)	**22 631** (21 322, 23 914)	**-8.4%** (-13.7%, -3.2%)	**20 680** (19 421, 21 919)	**-16.3%** (-21.4%, -11.2%)

MUP: Minimum unit price / minimum price per standard drink.

Columns may not sum due to rounding.

Table E-6: Alcohol-attributable hospitalizations, observed and under two MUP scenarios, by gender and age group, Québec 2014

Gender		**Quebec in 2014**	***Scenario 1 - $1.50 MUP***		***Scenario 2 - $1.75 MUP***	
	Age Group	**Observed** *(95% CI)*	**Estimate** *(95% CI)*	**Percent Change** *(95% CI)*	**Estimate** *(95% CI)*	**Percent Change** *(95% CI)*
Women	**Total**	**5 229** *(4 562, 5 879)*	**4 473** *(3 848, 5 086)*	**-14.5%** *(-26.4%, -2.7%)*	**3 784** *(3 199, 4 359)*	**-27.6%** *(-38.8%, -16.6%)*
	00-14	**17** *(17, 17)*	**15** *(15, 15)*	**-11.8%** *(-11.8%, -11.8%)*	**13** *(12, 13)*	**-23.5%** *(-29.4%, -23.5%)*
	15-34	**1 222** *(1 165, 1 277)*	**1 100** *(1 045, 1 154)*	**-10%** *(-14.5%, -5.6%)*	**986** *(934, 1 037)*	**-19.3%** *(-23.6%, -15.1%)*
	35-64	**3 080** *(2 833, 3 323)*	**2 700** *(2 465, 2 932)*	**-12.3%** *(-20%, -4.8%)*	**2 351** *(2 130, 2 571)*	**-23.7%** *(-30.8%, -16.5%)*
	65+	**910** *(546, 1 261)*	**659** *(322, 986)*	**-27.6%** *(-64.6%, +8.4%)*	**434** *(123, 738)*	**-52.3%** *(-86.5%, -18.9%)*
Men	**Total**	**19 464** *(18 776, 20 138)*	**18 158** *(17 474, 18 829)*	**-6.7%** *(-10.2%, -3.3%)*	**16 896** *(16 222, 17 561)*	**-13.2%** *(-16.7%, -9.8%)*
	00-14	**22** *(22, 22)*	**20** *(20, 20)*	**-9.1%** *(-9.1%, -9.1%)*	**18** *(18, 18)*	**-18.2%** *(-18.2%, -18.2%)*
	15-34	**3 458** *(3 372, 3 543)*	**3 222** *(3 135, 3 308)*	**-6.8%** *(-9.3%, -4.3%)*	**2 992** *(2 905, 3 078)*	**-13.5%** *(-16%, -11%)*
	35-64	**9 298** *(9 027, 9 561)*	**8 650** *(8 376, 8 915)*	**-7.0%** *(-9.9%, -4.1%)*	**8 025** *(7 752, 8 290)*	**-13.7%** *(-16.6%, -10.8%)*
	65+	**6 686** *(6 356, 7 011)*	**6 265** *(5 944, 6 585)*	**-6.3%** *(-11.1%, -1.5%)*	**5 861** *(5 546, 6 174)*	**-12.3%** *(-17.1%, -7.7%)*
Grand Total		**24 694** (23 338, 26 017)	**22 631** (21 322, 23 914)	**-8.4%** (-13.7%, -3.2%)	**20 680** (19 421, 21 919)	**-16.3%** (-21.4%, -11.2%)

MUP: Minimum unit price / minimum price per standard drink. Columns may not sum due to rounding.

6.5 Discussion

We present a series of novel alcohol policy modeling results calculated through use of the International Model of Alcohol Harms and Policies, the first open access model for estimating AA harms and changes in harms resulting from alcohol policy changes. This is the second in a series of two articles specifying InterMAHP methodologies and employing the model in studying different dimensions of alcohol research: (1) estimating alcohol-attributable (AA) morbidity and mortality, presented in Chapters 4 and 5, and (2) estimating the potential impact of alcohol policies on these AA harms.

Global alcohol researchers, given a standard set of data regarding regional alcohol consumption and prevalence and enumerated mortality/morbidity counts, may use InterMAHP's base functionality to automate the calculation of AA fractions and harms. This article presents an extension of this base function, wherein *changes* in AA harms may be estimated given the same set of standard data above and an estimate of the *change* in *per capita* consumption realized or expected from a given alcohol policy.

The results presented in this modeling study suggest that implementing an alcohol minimum unit price in Québec would lead to significant reductions in both deaths and hospitalizations caused by alcohol. If Québec had previously implemented a MUP of $1.50, the drinking population would have experienced 169 fewer deaths and 2,063 fewer hospital stays in 2014. If government had instead enacted a MUP of $1.75, Québécois would have experienced 327 fewer deaths and 4,014 fewer hospital stays in 2014. Conceptually, the results assume the policy had been implemented previously to 2014, far enough in the past for AA chronic conditions, such as breast cancer, colorectal cancer and liver cirrhosis to develop.

The results provide evidence that MUP policies differentially benefit younger age groups regarding the prevention of alcohol-caused death. A harm reduction gradient was observed, for both men and women, wherein the 15-34 age group experienced the greatest proportional reduction in mortality under each MUP scenario, followed by the 35-64 and 65+ age groups. Policymakers may consider this result, as policies benefiting younger age groups will save more potential years of life and increase economic production by a greater amount than those benefiting older age groups.

6.6 Limitations

This study has limitations. It is a modeling exercise regarding proposed alcohol policy changes and not a study of implemented polices. InterMAHP's modeling strategy estimates AA harms through use of the extensively used modern AAF formulation; however, as many as seven alternate methods exist (Trias-Llimós et al., 2018). Parish et al. (2017) found that the single-parameter Gamma distribution employed by InterMAHP may result in higher AAF estimates as compared to completion of comprehensive distributional best-fit analyses in each population subgroup. Last, InterMAHP does not separately enumerate AA harms-to-others; this will lead to underestimation of total AA harms.

There are reasons to believe the estimated effects of the MUP policies may be underestimated by our study. First, when calculating *per capita* consumption changes resulting from MUP implementation, we used a price elasticity of -0.34 from British Columbia. Research from another Canadian province, Saskatchewan, reported a price elasticity of -0.84, more than twice the magnitude of the estimate used here. If this larger elasticity, or a weighted average of the two, had been used in this study, consumption change estimates, and therefore the estimated reductions in harm, would be far higher than presented. Next, our hypothetical MUP implementation increased all alcohol priced below each scenario's MUP up to that threshold. This led to product clustering at the MUP in each scenario. We did not employ 'knock-on' pricing effects, wherein the prices of some of these products are increased in order to differentiate from these new cheapest products. Employing 'knock-on' effects would further increase consumption change and harm change estimates.

6.7 Conclusion

We forward the International Model of Alcohol Harms and Policies as an open access set of methodologies and software, designed to assist global alcohol researchers towards estimation of the health impacts of realized or hypothetical alcohol policy changes in their region. Estimates of these health impacts are critical for policymakers engaged in evidence-based decision-making. InterMAHP makes possible timely and comparable estimates of changes in AA harms based on *per capita* consumption changes brought about by alcohol policy change.

Alcohol causes substantial harm in Québec, Canada. In 2014, drinking was causally responsible for 2,850 deaths and 24,694 hospital stays in the province. Of these deaths, 1,013 (36%) were caused by AA cancers. The government of Québec, as well as national and sub-national governments worldwide, may consider implementing alcohol MUP strategies, which have been shown to reduce alcohol consumption and related harms (Stockwell et al., 2012; Stockwell et al., 2017c). This modeling study suggests that implementing an alcohol MUP in the range of $1.50 to $1.75 in Québec would result in a significant and lasting reduction in the health harms caused by alcohol in society.

6.8 Acknowledgements

This work was supported by a CIHR Frederick Banting and Charles Best Canada Graduate Scholarship (CGS-D) awarded to the first author.

Chapter 7: Conclusion

This concluding chapter serves as a summary of the program of research described in this dissertation. As Chapters 2 through 6 were written as stand-alone manuscripts for publication, conclusions between articles regarding the overall scope of this dissertation are therefore discussed here.

This chapter begins with a brief synthesis of the five content chapters, linking back to the role of each in the overall conceptual framework of this dissertation. Next, contributions and key findings will be discussed and concluding implications for different areas of alcohol research will be considered. Finally, areas for future work and a brief concluding statement will close the dissertation.

7.1 Chapter Syntheses and Key Study Findings

The objectives of this dissertation followed two main avenues of study:

(1) to complete component-wise tests of the Alcohol Total Consumption Model; and

(2) to mathematically specify, develop and provide exemplar applications of a novel alcohol health harms estimator and alcohol policy scenario modeler, the International Model of Alcohol Harms and Policies.

These objectives were towards the goals of improving the alcohol research community's understanding of the TCM and making easier the regional estimation of both alcohol health harms and the projected impact of realized or hypothesized alcohol policy changes.

Study A presented a secondary study that investigated the alcohol policy to alcohol consumption component of the TCM. It completed a series of systematic reviews regarding the relationship between the physical availability of off-premise alcohol, including days and hours of sale and outlet density, and *per capita* (total) alcohol consumption. Study A found that the majority of included studies for days and hours of sale (7 out of 7) and outlet density (3 out of 4) concluded that restricting the physical availability of off-premise alcohol reduced *per capita* consumption. This study further conducted meta-analyses novel to the literature regarding the effect of one additional day of sale on *per capita* consumption. The addition of one day of sale was found to be associated with a 3.4% increase in total consumption.

Study B conducted a primary research study that examined the direct effect of a changed alcohol policy on alcohol harms, namely alcohol-related ED visits. The main finding was that the implementation of increased alcohol minimum prices in Saskatchewan was not significantly associated with an abrupt effect on ED visits in any of four alcohol-related injury categories. However, a significant six month-lagged decrease in MVC-related ED visits for women aged 26 and older was found.

Study C established a method of quantifying the link between alcohol consumption and alcohol-caused mortality and morbidity through the development and mathematical specification of an open access alcohol harms estimation model, InterMAHP. This study developed novel methods towards estimating alcohol harms and was the basis for the creation of an open access InterMAHP version for use by global alcohol research teams. A further aim of Study C was as a building block towards Studies D and E, which provided further insight into the health harms caused by alcohol (Study D) and allowed further testing of the directional relationships contained in the TCM (Study E).

Study D distilled the comprehensive methodologies developed in Study C into a length suitable for journal article publication. Next, it conducted a primary research study estimating the extent of alcohol-attributable mortality in Canada in 2016. Alcohol was found to be a leading driver of mortality, as it was causally responsible for more than 14,800 deaths in 2016, representing 5.5% of all Canadian mortality. Cancer was found to be the leading categorical

cause of AA deaths in both men and women, an important conclusion for public education campaigns regarding alcohol harms.

Lastly, Study E had two main goals: (1) to formalize the InterMAHP methodologies used to estimate the *changes* in harms expected to occur based on proposed or realized alcohol policy change and (2) to conduct a primary research study as an exemplar of the first goal, which estimated the potential health impact of implementing a strengthened alcohol MUP policy in Québec, Canada. Using InterMAHP methodologies, it was estimated that alcohol caused 2,850 deaths and 24,694 hospitalizations in Québec in 2014. It was further estimated that the implementation of a MUP in the range of CAD$1.50 – 1.75 would result in significant improvements in population health, experienced as reductions in alcohol-caused death and disability.

7.2 Contributions

The research studies completed in this dissertation make a novel and significant contribution to the literature in the field of alcohol research. First, overall contributions that address the two overarching objectives: (1) to complete a component-wise study of the TCM and (2) to develop and test InterMAHP are discussed. Then, contributions to alcohol research in Canada, through the InterMAHP applications in Studies D and E, are detailed.

7.2.1 A Study of the Alcohol Total Consumption Model

This dissertation presented a series of interrelated chapters that studied components of the alcohol TCM, an important theory in alcohol research. Largely, but by no means completely, the hypotheses defined by the TCM were substantiated by the research presented here.

Study A established a strong link between alcohol availability policies, namely days and hours of sale and outlet density, and *per capita* consumption, an important TCM hypothesis. Separate systematic reviews were completed for each of outlet density and days/hours of sale; these reviews found evidence that largely supported the concept that increased physical availability of take-away alcohol led to increased total consumption, as theorized by the TCM. Further, novel meta-analyses formalized this result for days of sale: when effect sizes from

different societies and policy changes were statistically composed, the result estimated a statistically significant increase in consumption when a day of sale was added.

However, and notably, Study B provided results largely contradictory to what is hypothesized by the TCM. This primary research article investigated the effect of increased alcohol minimum prices in Saskatchewan on alcohol-related ED visits in four categories and four population subgroups. The study found no significant abrupt effect on alcohol-related ED visits after the policy intervention; this was contrary to the hypotheses at the outset of the study. The study did report a significant six month-lagged effect on certain types of ED visits. However, as discussed in Chapter 3, this study had significant limitations regarding data access wherein ED data could only be acquired for about 17% of the provincial population. This limitation may have affected the generalizability of the results and the ability of the research methodology to detect a study effect. The publication of these largely null results may be seen to show a commitment to the scientific process. The null results from this study regarding an abrupt intervention effect should be interpreted together with other research regarding this price policy implementation in Saskatchewan that showed decreased alcohol consumption (Stockwell et al., 2012) and decreased alcohol-related crime (Stockwell et al., 2017c). Additionally, a larger scientific literature has largely concluded that alcohol policy strategies are effective at reducing alcohol-related harms (Wagenaar, Tobler & Komro, 2010).

Studies C and D first developed a methodology to estimate the AA death and disability caused by population-level consumption, i.e. these two studies mathematically established the relationship between alcohol consumption and alcohol health. This is not an evaluation of the TCM, *per se*, as the relationships meant to be tested within the model are defined most by the directional relationships involved, i.e. that policies designed to decrease consumption do so and that this decreased consumption leads to fewer alcohol-caused health harms. However, it is a quantification of the TCM steady state, as described in Figure I-1, which relates consumption in a certain society, and at the current time, with health harms experienced by that society. Next, the development of InterMAHP was a goal of the dissertation onto itself: to develop a generalized methodology that may be used by other research teams based on available local data.

Study D then additionally provided an exemplar of this quantification in the example of Canada in 2016. Alcohol was found to be cause a significant burden of ill-health in this context and was responsible for 5.5% of total mortality. It was important to evaluate an implicit

assumption of the TCM: namely, that alcohol consumption leads to increased health harms. This is not necessarily inherently obvious, especially considered in light of the debate regarding the potential of moderate alcohol consumption to have a protective effect on the development of IHD (Roerecke & Rehm, 2012), ischaemic stroke (Patra et al., 2010) and diabetes (Knott et al., 2015). However, the results of Study D provide strong evidence that alcohol consumption does lead to increased AA mortality, at least in the Canadian context. And indeed, increased deaths and disability due to alcohol use is nearly universally supported by other global (World Health Organization, 2011, 2014, 2018) and national studies (Canadian Substance Use Costs and Harms Scientific Working Group, 2018; Chikritzhs, 2009; United States Centers for Disease Control and Prevention, 2008).

Study E provided a further quantification of the extent of AA mortality and hospitalization based on observed drinking patterns in Québec. However, its main avenue of research studied the *changes* in AA harms that would be expected based on a posited *change* in consumption resulting from the proposed implementation of an alcohol MUP. The TCM hypothesizes that a decrease in total consumption would result in a decrease in AA harms: this modeling study supported that assumption, as significant decreases in both deaths and hospitalizations were estimated in each of two MUP scenarios. It is noted that the study results supporting this hypothesis only hold with the exact inputs and assumptions used by InterMAHP in this analysis. That is, different results would be obtained if different relative risk functions than those shown in Appendix C-2 were used or if different dynamic inputs were used during InterMAHP AAF estimation. Therefore, the result that decreased consumption was modeled to decrease harm is not generalizable beyond the assumption and inputs chosen for this run. However, in relation to the possible universe of inputs, it is likely that only a small fraction of the total, and possibly none at all, would lead to results that did not support the hypothesis that decreased consumption would lead to decreased health harms.

Taken as a whole, Studies A, B and E provide some evidence to support the TCM as defined for this dissertation; however, this evidence was not conclusive and, in Study B, was largely contradictory. As it is a series of systematic reviews and meta-analyses, Study A provides the strongest evidence to support the TCM, in particular the directional relationship between certain alcohol control polices and *per capita* alcohol consumption. Study E lent support, given a certain set of inputs and assumption, to the TCM hypothesis that decreased consumption would

results in decreased alcohol-caused mortality and morbidity in the context of one Canadian province. These results were counterbalanced by the largely null results of Study B, which concluded that a minimum price policy intervention in Saskatchewan did not have an abrupt and permanent effect on the rate of ED visits in any of four alcohol-related injury categories. On the other hand, Study B did find a significant six month-lagged decrease in MVCs for one gender-age group and the ability of the study to detect other results of significance may have been confined by substantial data limitations.

In relation to the TCM, Studies C and D do not directly test the model's directional relationships; instead these studies: (1) test an implicit assumption of the TCM, i.e. that alcohol consumption leads to alcohol-caused harm, instead of providing an overall health-protective effect and (2) build the capacity, through the development of InterMAHP, to further test the consumption to harm component of the TCM, which is then completed in Study E.

As laid out in Chapter 1, 'theories' in alcohol studies can never be proven as can those in discovery sciences. Instead, a weight of careful, detailed studies must accumulate across a wide of contexts and cultures before conclusions can be attempted. The findings from these five studies may be seen to modestly add to the literature studying the TCM. Based only on the studies in this dissertation, it is concluded that there is some evidence, which is not conclusive, that the TCM continues to be a useful theory in alcohol studies.

7.2.2 Development of the International Model of Alcohol Harms and Policies

Studies C, D and E focused on the development and application of a novel model for estimating alcohol harms and forecasting the health impact of proposed or realized alcohol policy changes. Together, the methodologies developed and specified in these three chapters laid the groundwork for the creation of an open access program, now available at www.intermahp.cisur.ca, which provides significant automation to global research teams interested in estimating alcohol harms or projecting the impact of alcohol policies.

A model exists that provides some of the same functionalities as InterMAHP, namely the Sheffield Alcohol Policy Model (SAPM). However, because SAPM must be contracted and is not freely available for use, InterMAHP provides the contribution to the field of being the first open access alcohol health harms estimator and policy scenario modeler. It was built for research teams to integrate easily into existing and upcoming projects, and uses data that is typically

standardized in the field. InterMAHP may therefore provide global researchers with a tool that can expand their potential project output, automate components of existing projects and encourage alcohol policy projects that would not previously have been attempted. It may further provide increased comparability across international alcohol harm estimates, due to methodological standardization.

7.2.3 Alcohol-Attributable Mortality in Canada

Study D provides the most up-to-date estimates of AA mortality in Canada. This application of InterMAHP provided more recent results, by two years, than Canada's flagship substance use costs and harms project, which presented results up to 2014 (Canadian Substance Use Costs and Harms Scientific Working Group, 2018). Study D made clear that alcohol caused a substantial burden of mortality in Canada, as alcohol was causally responsible for more than 14,800 mortalities in 2016.

Another contribution was brought about by the built-in ability of InterMAHP to focus on condition category sub-analyses, specifically those regarding AA cancers. Among the 14,800 AA deaths in Canada, cancer was the condition category responsible for the highest level of mortality, causing almost 4,600 (31%) of these deaths.

7.2.4 Projected Impact of an Alcohol Minimum Unit Price in Québec

Study E provides the first Canadian, and one of the first global, studies regarding the *projected* impact of an alcohol minimum unit price on AA morbidity and mortality. The development of InterMAHP made possible the research in Study E estimating the health impact of an increased MUP of CAD$1.50 or $1.75 in Québec. InterMAHP has also been used to estimate this same impact in the Canadian province of British Columbia as a component of a separate project. The results in Québec provide a substantial contribution to the field of alcohol policy research, as the findings of this modeling study strongly support the effectiveness of MUP in order to mitigate population-level alcohol harms. For example, a MUP of $1.75 would be expected to decrease total alcohol consumption by 8.6%, AA mortality by 11.5% and AA hospitalizations by 16.3%. These results provide evidence for policymakers considering alcohol control policies designed to be more protective of population health.

7.3 Implications

The contributions above provide the following implications for the estimation of AA mortality and morbidity and for alcohol policy research.

7.3.1 Estimation of Alcohol-Attributable Morbidity and Mortality

The development, specification and successful testing of InterMAHP provides the alcohol research community the option of using an automated, open access methodology for the estimation of AA morbidity and mortality in their region. InterMAHP may be used as a standardized supplement to existing programs of research studying alcohol harms and may ease the learning the curve for research teams considering taking on such programs.

InterMAHP may decrease the person-time and analytical sophistication needed by research teams choosing to integrate these methods and software into their work plans. It may also begin to provide a measure of international comparability as research teams employing InterMAHP will be choosing a foundational set of similar methodologies.

7.3.2 Alcohol Policy Research

The policy modeling component of InterMAHP is novel for an open access program. The automated nature of the InterMAHP methodologies, combined with the standardized data inputs necessary for its use, may allow many more international teams to conduct policy modeling experiments in their jurisdictions. As more and better research accumulates, this may provide added impetus towards policymakers to deploy health-protective alcohol policies.

7.3.3 Alcohol Policy Change in Canada

The research presented here, in particular the findings from Study E, could potentially contribute to meaningful alcohol policy change in Canada. Study E estimated that a MUP policy intervention in Québec would result in significant improvement to population health. It is possible that these findings will encourage legislators in Québec, and other Canadian jurisdictions, to seriously consider this particularly effective alcohol control policy.

7.4 Areas for Future Research

The research presented here opens several potential avenues for future work along both theoretical and empirical lines of inquiry. Along the theoretical lines, availability theory is widely discussed in alcohol studies and typically refers to both economic availability (i.e. alcohol pricing and taxation strategy) and physical availability (i.e. hours and days of sale and outlet density). However, a focus on these two pillars of availability may have disadvantaged other potentially effective policy levers. I believe availability theory should include all alcohol control policies that have the potential to decrease population-level *total* alcohol consumption, i.e. any policy that would fit into the framework of the TCM as defined in this dissertation. A future article is conceptualized which will define a further availability pillar, called 'sociocultural availability' – this will expand the availability umbrella to include potentially effective, yet slow-acting and hard to measure, policies such as broad-based education campaigns detailing the link between alcohol and cancer. 'Sociocultural availability' will include policies that change the sociocultural attitude towards alcohol and gradually shift societies towards lower consumption. The analog here is from tobacco control: cigarettes went from a ubiquitous part of North American society in the 1960s to a substance use practice that was close to taboo in only 50 years – can the same be accomplished with alcohol?

Following the empirical and mathematical line of inquiry, a further article will formalize and provide an application of another novel component of InterMAHP – the ability to study the harm experienced by different drinking groups, e.g. low, medium and high volume, defined by average daily consumption. Although methodologically detailed in Study C, it was beyond the scope of this dissertation to provide a further article with an application exemplar of this novel functionality. However, this work will be completed in partnership with members of the British Columbia (BC) Ministry of Health, will study the issue in BC and is expected to be completed shortly.

There are several potential improvements that may be made in future to InterMAHP. First, InterMAHP exclusively uses the Gamma distribution-based modern AAF, described in Studies C and D, to estimate attributable fractions. However, a recent article makes clear that other methods exist and, though not currently widely used, may provide AA harms estimates with increased precision (Parish et al., 2017). This study tested a dynamic, best fit approach to

the choice of distribution used to model the continuous prevalence of average daily consumption. It was found that the single parameter Gamma distribution did not always prove to be the distribution of best fit. These findings have potential implications for the Single Distribution Theory, as defined by Ledermann (1956) and, by extension, to the modern Gamma-distribution based AAF used by InterMAHP. However, this article only presents consumption distribution fitting for a single context (the United States), and so more research into this area is needed before the full implications are known (Parish et al., 2017).

Another potential addition to InterMAHP would be the automation of added AA harm estimation techniques, e.g. six additional methods were discussed in Trias-Llimós et al. (2018) above the method used by InterMAHP.

Next, the last major advance in methodology regarding the estimation of AA harms occurred around 10 years ago and involved upgrading this estimation from one to two dimensions. Functionally, this refers to the definition of the modern AAF, detailed in Studies C and D, which uses RR functions instead of point estimates. After the meta-analyzed creation of continuous RR functions, as opposed to categorical RR point estimates, for all alcohol-related conditions, it became possible to employ the modern AAF. The next major advance in AA harms methods may arise from the same source: an increase in dimensionality. Dr. Stockwell and I have discussed this at length, in short, it would involve creating relative risk *surfaces* (i.e. 3-D instead of 2-D). Likely, the additional axis provided by this increase in dimensionality would represented a measure of drinking *intensity* and so both average daily consumption and drinking patterns could be considered, instead of only chronic consumption as AAFs are currently formulated. RR surfaces could theoretically provide more accurate AA harms estimates than current methods.

Finally, and as discussed in the previous section, the provision of InterMAHP has implications for future research regarding alcohol harms estimation and alcohol policy scenario modeling. The international alcohol research community now has the option to employ a flexible, open access resource that could potentially decrease the person-power necessary to complete alcohol harms and policy projects. InterMAHP is adaptable to new epidemiological knowledge in the alcohol field, such as new condition-specific meta-analyses. It is conceivable that this may lead to increased productivity regarding future work in these areas.

7.5 Concluding Statement

It is clear from the findings presented in this dissertation, and from research from countries the world over, that alcohol is responsible for an enormous amount of death and disability in global societies. Alcohol is by far the most widely used, and most likely the most harmful, psychoactive substance on earth. However, there are hopeful avenues for reducing these immense harms, such as the measured implementation of proven alcohol control policies. The reliable estimation of alcohol-caused harms and the ability to project the health impact of proposed alcohol control policies are necessities when it comes to informing public and policy debates regarding alcohol consumption and potential policies. These issues are addressed by the research presented herein and novel, open access methodologies are created towards assisting with both of these goals. Hopefully, this dissertation may provide a small contribution to the large issue of reducing the societal harm caused by alcohol.

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Appendix A: Supplementary Material for Study A

Appendix A-1: Search Terms Used

Outlet density	(outlet* OR store* OR premise*) AND (density OR densities OR availability OR proximity OR access* OR neighbourhood* OR neighborhood* OR environment OR environmental OR community OR communities)
Days and hours of sale	(opening hours OR hours of opening OR trade hours OR hours of trade OR opening days OR days of opening OR trade days OR days of trade OR availability OR trading hours)
All	(alcohol* OR liquor* OR ethanol* OR beer OR wine OR spirit OR spirits OR beverage* OR bing* OR heavy episod* OR heavy consum*)
All	(consume OR consumed OR consumption OR drink* OR sale*)
All systematic review stage	(systematic* OR review OR meta-analys* OR meta analys* OR meta-regression* OR meta regression*)

Appendix A-2: Systematic Reviews Used to Create Literature Base

Days and hours of sale		
No.	Citation	Description
1	**Holmes, J., Guo, Y., Maheswaran, R., Nicholls, J., Meier, P. S., & Brennan, A. (2014). The impact of spatial and temporal availability of alcohol on its consumption and related harms: a critical review in the context of UK licensing policies. *Drug and alcohol review*, *33*(5), 515-525.**	A descriptive review of the literature on the relationship between spatial and temporal availability of alcohol and consumption and related harms; to summarize the methodologies, identify evidence gaps and limitations, and make recommendations for future research.
2	**Middleton, J. C., Hahn, R. A., Kuzara, J. L., Elder, R., Brewer, R., Chattopadhyay, S., ... & Task Force on Community Preventive Services. (2010). Effectiveness of policies maintaining or restricting days of alcohol sales on excessive alcohol consumption and related harms. *American journal of preventive medicine*, *39*(6), 575-589.**	The methods of the Guide to Community Preventive Services were used to synthesize scientific evidence on the effectiveness of laws and policies maintaining or reducing the days when alcoholic beverages may be sold for preventing excessive alcohol consumption and related harms. Included both on- and off- premise outlets.
3	**Hahn, R. A., Kuzara, J. L., Elder, R., Brewer, R., Chattopadhyay, S., Fielding, J., ... & Task Force on Community Preventive Services. (2010). Effectiveness of policies restricting hours of alcohol sales in preventing excessive alcohol consumption and related harms. *American journal of preventive medicine*, *39*(6), 590-604.**	Evaluated the effect of changing hours of sale of alcohol of on-premise outlets in high income countries (UK, Iceland, and Australia) on excessive alcohol consumption and related harms (e.g., ER admissions). Studies assessing the effects of changing hours of sale by less than 2 hours and by 2 or more hours were assessed separately.
4	**Popova, S., Giesbrecht, N., Bekmuradov, D., & Patra, J. (2009). Hours and days of sale and density of alcohol outlets: impacts on alcohol consumption and damage: a systematic review. *Alcohol and alcoholism*, *44*(5), 500-516.**	A systematic review of research on the availability of alcohol: hours and days of sale and density of alcohol outlets in relation to alcohol consumption, drinking patterns and damage from alcohol.

5	Stockwell, T., & Chikritzhs, T. (2009). Do relaxed trading hours for bars and clubs mean more relaxed drinking? A review of international research on the impacts of changes to permitted hours of drinking. *Crime Prevention & Community Safety*, *11*(3), 153-170.	Sought to evaluate the public health and safety impacts of changes to liquor trading hours for on premise consumption – namely 'pubs' and clubs in the United Kingdom, 'hotels' and 'taverns' in Australia and New Zealand and 'bars' in North America.

Outlet density

No.	Citation	Description
1	Gmel, G., Holmes, J., & Studer, J. (2015). Are alcohol outlet densities strongly associated with alcohol-related outcomes? A critical review of recent evidence. *Drug and Alcohol Review*, 35(1), 40-54.	A review of research assessing the association between alcohol outlet density and (1) assaultive or intimate partner violence at the aggregate level or (2) other alcohol related outcomes at the individual level (e.g., binge drinking, frequency of drinking)
2	**Holmes, J., Guo, Y., Maheswaran, R., Nicholls, J., Meier, P. S., & Brennan, A. (2014). The impact of spatial and temporal availability of alcohol on its consumption and related harms: a critical review in the context of UK licensing policies. *Drug and alcohol review*, *33*(5), 515-525.**	A descriptive review of the literature on the relationship between spatial and temporal availability of alcohol and consumption and related harms; to summarize the methodologies, identify evidence gaps and limitations, and make recommendations for future research.
3	**Bryden, A., Roberts, B., McKee, M., & Petticrew, M. (2012). A systematic review of the influence on alcohol use of community level availability and marketing of alcohol. *Health & place*, *18*(2), 349-357.**	The aim of this systematic review was to explore evidence on the influence of community level availability and marketing of alcohol on alcohol use.
4	**Popova, S., Giesbrecht, N., Bekmuradov, D., & Patra, J. (2009). Hours and days of sale and density of alcohol outlets: impacts on alcohol consumption and damage: a systematic review. *Alcohol and alcoholism*, *44*(5), 500-516.**	A systematic review of research on the availability of alcohol: hours and days of sale and density of alcohol outlets in relation to alcohol consumption, drinking patterns and damage from alcohol.
5	**Campbell, C. A., Hahn, R. A., Elder, R., Brewer, R., Chattopadhyay, S., Fielding, J., ... & Task Force on**	The authors investigated the effects of outlet density on alcohol consumption and related harms, including medical harms, injury,

	Community Preventive Services. (2009). The effectiveness of limiting alcohol outlet density as a means of reducing excessive alcohol consumption and alcohol-related harms. *American journal of preventive medicine, 37*(6), 556-569.	crime and violence. Primary evidence was used from interrupted time-series studies: the privatization of alcohol sales, alcohol bans, and changes in license arrangements – all of which affected outlet density. Correlational studies provided secondary evidence.
6	Livingston, M., Chikritzhs, T. & Room, R. (2007). Changing the density of alcohol outlets to reduce alcohol-related problems. *Drug and alcohol review*, *26*(5), 557-566.	The authors review the research literature on the effects of density of alcohol sales outlets on alcohol consumption and alcohol-related problems; suggest a new way of conceptualizing the relationships; and discuss the implications for reducing alcohol-related harm.

Systematic Reviews in **boldface** were used to construct the literature basis.

Note: It was decided to exclude the review by Gmel et al. (2015) from the creation of the literature base as it only included papers published between January 2009 and October 2014 and our intention was to create a broad literature base. Constituent studies from this review would be picked up by our systematic review update.

Appendix A-3: Tier 3 Studies for Days and Hours of Sale and Outlet Density

APA Reference	Study Description
Hours and days of sale (2)	
Cook, W. K., Bond, J., & Greenfield, T. K. (2014). Are alcohol policies associated with alcohol consumption in low-and middle-income countries? *Addiction*, *109*(7), 1081-1090.	Examined the relationships between four alcohol control policies (physical availability, minimum legal drinking age, motor vehicle operation and alcohol advertising) and alcohol consumption in low and middle-income countries.
Douglas, M. (1998). Restriction of the hours of sale of alcohol in a small community: a beneficial impact. *Australian and New Zealand Journal of Public Health*, *22*(6), 714-719.	Evaluated the effect of increased restrictions on alcohol availability, including reduced trading hours of take-away alcohol, on consumption, crime and hospitalizations.
Outlet density (56)	
Abbey, A., Scott, R. O., & Smith, M. J. (1993). Physical, subjective, and social availability: their relationship to alcohol consumption in rural and urban areas. Addiction (Abingdon, England), 88(4), 489-499.	This paper studies the physical, subjective and social availability of alcohol on alcohol consumption.
Ahern, J., Balzer, L., & Galea, S. (2015). The roles of outlet density and norms in alcohol use disorder. *Drug and alcohol dependence*, *151*, 144-150.	This study looks at whether alcohol outlet density shapes alcohol consumption and alcohol use disorders.
Astudillo, M., Kuendig, H., Centeno-Gil, A., Wicki, M., & Gmel, G. (2014). Regional abundance of on-premise outlets and drinking patterns among Swiss young men: District level analyses and geographic adjustments. *Drug and alcohol review*, *33*(5), 526-533.	This study examined the associations of alcohol outlet density with specific alcohol outcomes among young men in Switzerland.
Ayuka, F., Barnett, R., & Pearce, J. (2014). Neighbourhood availability of alcohol outlets and hazardous alcohol consumption in New Zealand. *Health & place*, *29*, 186-199.	This study examines whether the availability of alcohol is associated with alcohol consumption.

Bernstein, K.T., Galea, S., Ahern, J., Tracy, M., & Vlahov, D. (2007). The built environment and alcohol consumption in urban neighborhoods. Drug and alcohol dependence, 92, 244-252.	This study looks at the relationship between neighbourhood environments and recent alcohol use.
Cederbaum, J. A., Petering, R., Hutchinson, M. K., He, A. S., Wilson, J. P., Jemmott III, J. B., & Jemmott, L. S. (2015). Alcohol outlet density and related use in an urban Black population in Philadelphia public housing communities. *Health & place*, *31*, 31-38.	This study examined the influence of individual, family and environment on alcohol use.
Chaloupka, F.J., & Wechsler, H. (1996). Binge drinking in college: the impact of price, availability, and alcohol control policies. Contemporary economic policy, 14(4), 112-124.	This study looks at the effect of alcohol control policies, price, and availability on alcohol consumption and binge drinking among young adults and youth.
Chen, K. H., Chen, C. Y., Liu, C. Y., Lin, Y. C., Chen, W. J., & Lin, K. M. (2011). Multilevel influences of school and family on alcohol-purchasing behaviors in school-aged children. *Drug and alcohol dependence*, *114*(2), 127-133.	This study looked the effect of multiple factors including density of convenience stores selling alcohol on alcohol purchases.
Connor, J. L., Kypri, K., Bell, M. L., & Cousins, K. (2010). Alcohol outlet density, levels of drinking and alcohol-related harm in New Zealand: a national study. *Journal of epidemiology and community health*, jech-2009.	This study examined the effect of outlet density on alcohol consumption and harms in New Zealand.
Cook, W. K., Bond, J., & Greenfield, T. K. (2014). Are alcohol policies associated with alcohol consumption in low-and middle-income countries?.*Addiction*, *109*(7), 1081-1090.	This study examined the association between alcohol policies in four areas and alcohol consumption in low and middle-income countries.
Davis, B., & Grier, S. (2015). A tale of two urbanicities: Adolescent alcohol and cigarette consumption in high and low-poverty urban neighborhoods.*Journal of Business Research*, *68*(10), 2109-2116.	This study looked at adolescent cigarette and alcohol consumption and how consumption varies by neighbourhood characteristics.
Gruenewald, P. J., Johnson, F. W., & Treno, A. J. (2002). Outlets, drinking and driving: a multilevel analysis of availability. Journal of studies on alcohol, 63(4), 460-468.	This study examined the relationship between alcohol outlet density and self-reported drinking patterns, preferred drinking location, driving after drinking and driving while drunk.

Gruenewald, P. J., Ponicki, W. R., & Holder, H. D. (1993). The Relationship of Outlet Densities to Alcohol Consumption: A Time Series Cross-Sectional Analysis. *Alcoholism: Clinical and Experimental Research*, *17*(1), 38-47.	This study uses data from the United States to look at the relationship between beverage prices and alcohol availability on alcohol sales.
Gruenewald, P. J., Remer, L. G., & LaScala, E. A. (2014). Testing a social ecological model of alcohol use: the California 50-city study. *Addiction*, *109*(5), 736-745.	This study examined community alcohol availability and individual drinking patterns.
Huckle, T., Huakau, J., Sweetsur, P., Huisman, O., & Casswell, S. (2008). Density of alcohol outlets and teenage drinking: living in an alcogenic environment is associated with higher consumption in a metropolitan setting. *Addiction*, *103*(10), 1614-1621.	This study looks at the relationship between physical, socio-economic and social environments, and alcohol consumption.
Iritani, B. J., Waller, M. W., Halpern, C. T., Moracco, K. E., Christ, S. L., & Flewelling, R. L. (2013). Alcohol outlet density and young women's perpetration of violence toward male intimate partners. *Journal of family violence*, *28*(5), 459-470.	This study looks at the relationship between alcohol outlet density, alcohol use, and intimate partner violence.
Kavanagh, A. M., Kelly, M. T., Krnjacki, L., Thornton, L., Jolley, D., Subramanian, S. V., ... & Bentley, R. J. (2011). Access to alcohol outlets and harmful alcohol consumption: a multi-level study in Melbourne, Australia.*Addiction*, *106*(10), 1772-1779.	This study examines the association between access to alcohol outlets and alcohol consumption.
Kypri, K., Bell, M. L., Hay, G. C., & Baxter, J. (2008). Alcohol outlet density and university student drinking: a national study. *Addiction*, *103*(7), 1131-1138.	This study examines outlet density and its association with drinking levels and drinking-related problems.
Leslie, H. H., Ahern, J., Pettifor, A. E., Twine, R., Kahn, K., Gómez-Olivé, F. X., & Lippman, S. A. (2015). Collective efficacy, alcohol outlet density, and young men's alcohol use in rural South Africa. *Health & place*, *34*, 190-198.	This study looks at alcohol outlet density, community collective efficacy and young men's drinking in South Africa.
Livingston, M., Laslett, A. M., & Dietze, P. (2008). Individual and community correlates of	This study examines the association between community-level factors

young people's high-risk drinking in Victoria, Australia. *Drug and alcohol dependence*, *98*(3), 241-248.	including outlet density and high-risk drinking.
Lo, C. C., Weber, J., & Cheng, T. C. (2013). A Spatial Analysis of Student Binge Drinking, Alcohol-Outlet Density, and Social Disadvantages. *The American Journal on Addictions*, *22*(4), 391-401.	This study looked at the effect of community factors including outlet density on student binge drinking.
McKinney, C. M., Chartier, K. G., Caetano, R., & Harris, T. R. (2012). Alcohol availability and neighborhood poverty and their relationship to binge drinking and related problems among drinkers in committed relationships. *Journal of interpersonal violence*, *27*(13), 2703-2727.	This study examines the relationship of alcohol outlet density and poverty with binge drinking and alcohol-related problems among married or cohabitating people.
Moore, R. S., Ames, G. M., & Cunradi, C. B. (2007). Physical and social availability of alcohol for young enlisted naval personnel in and around home port. *Substance Abuse Treatment, Prevention, and Policy*, *2*(1), 1.	This study looks at the physical availability of alcohol and its effect on alcohol use among men enlisted in the U. S. Navy.
Murphy, A., Roberts, B., Ploubidis, G.B., Stickley, A., & McKee, M. (2014). Using multi-level data to estimate the effect of an 'alcogenic' environment on hazardous alcohol consumption in the former Soviet Union. *Health Place, 27, 205-211.*	This study assessed community level characteristics and their effect on alcohol consumption in the former Soviet Union.
Pasch, K. E., Hearst, M. O., Nelson, M. C., Forsyth, A., & Lytle, L. A. (2009). Alcohol outlets and youth alcohol use: Exposure in suburban areas. *Health & place*, *15*(2), 642-646.	This study examined how alcohol outlet densities around schools influenced alcohol use among high school students.
Paschall, M.J., Grube, J.W., Thomas, S., Cannon, C., & Treffers, R. (2012). Relationships Between Local Enforcement, Alcohol Availability, Drinking Norms, and Adolescent Alcohol Use in 50 California Cities. Journal of Studies on Alcohol and Drugs, 73(4) 657-665.	This study estimates impact of alcohol outlet density and other factors on youth alcohol consumption.
Pereira, G., Wood, L., Foster, S., & Haggar, F. (2013). Access to alcohol outlets, alcohol consumption and mental health. *PLoS One*, *8*(1), e53461.	This study investigated exposure to alcohol outlets and its relationship to alcohol use and mental health morbidity.

Pollack, C. E., Cubbin, C., Ahn, D., & Winkleby, M. (2005). Neighbourhood deprivation and alcohol consumption: does the availability of alcohol play a role?. *International journal of epidemiology*, *34*(4), 772-780.	This study examines the relationship between neighbourhood-level deprivation, alcohol availability, and alcohol consumption.
Reboussin, B. A., Song, E. Y., & Wolfson, M. (2011). The impact of alcohol outlet density on the geographic clustering of underage drinking behaviors within census tracts. *Alcoholism: Clinical and Experimental Research*, *35*(8), 1541-1549.	This study looks at how outlet density influences the clustering of alcohol use and harms among youth under the legal drinking age.
Rowland, B., Toumbourou, J.W., & Livingston, M. (2015). The Association of Alcohol Outlet Density With Illegal Underage Adolescent Purchasing of Alcohol, Journal of Adolescent Health, 56, 146-152.	This study examines whether outlet density is associated with increased alcohol purchases by people under the legal drinking age in Australia.
Rowland, B., Toumbourou, J. W., Satyen, L., Tooley, G., Hall, J., Livingston, M., & Williams, J. (2014). Associations between alcohol outlet densities and adolescent alcohol consumption: A study in Australian students. *Addictive behaviors*, *39*(1), 282-288.	This study examines the relationship between the density of alcohol sales outlets in specific geographic communities and adolescent alcohol consumption
Schonlau, M., Scribner, R., Farley, T. A., Theall, K. P., Bluthenthal, R. N., Scott, M., & Cohen, D. A. (2008). Alcohol outlet density and alcohol consumption in Los Angeles county and southern Louisiana. *Geospatial health*, *3*(1), 91.	This study looks at the density of alcohol outlets and its relationship with alcohol consumption in Los Angeles county and southern Louisiana.
Schootman, M., Deshpande, A. D., Lynskey, M. T., Pruitt, S. L., Lian, M., & Jeffe, D. B. (2013). Alcohol outlet availability and excessive alcohol consumption in breast cancer survivors. *Journal of primary care & community health*, *4*(1), 50-58.	This study examines how outlet density influences heavy alcohol consumption among breast cancer survivors.
Scribner, R. A., Cohen, D. A., & Fisher, W. (2000). Evidence of a structural effect for alcohol outlet density: a multilevel analysis. *Alcoholism: Clinical and Experimental Research*, *24*(2), 188-195.	This study looks at the effects of alcohol outlet density on alcohol use and drinking norms.

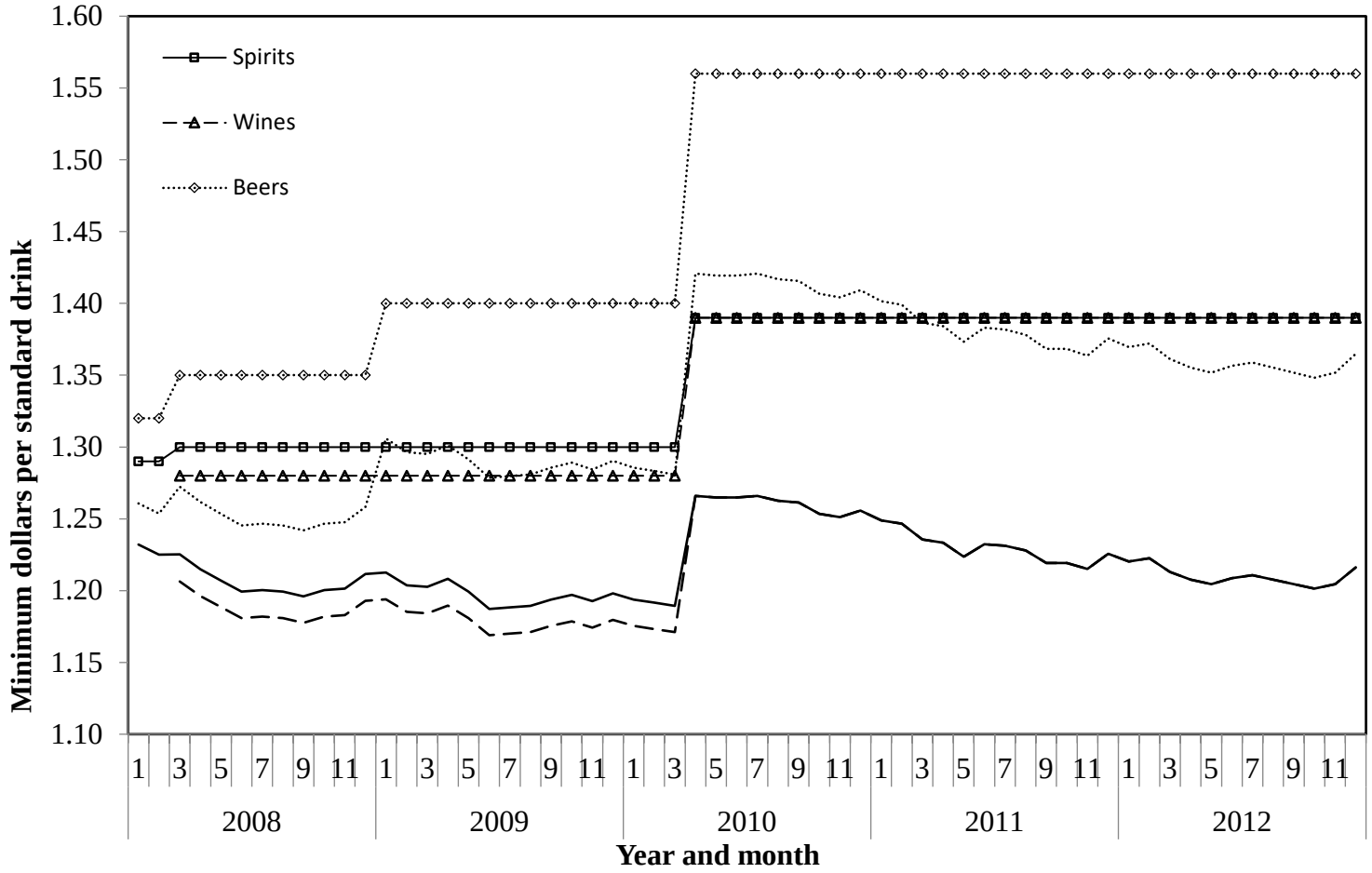
Shih, R. A., Mullins, L., Ewing, B. A., Miyashiro, L., Tucker, J. S., Pedersen, E. R., & ... D'Amico, E. J. (2015). Associations between neighborhood alcohol availability and young adolescent alcohol use. Psychology Of Addictive Behaviors, 29(4), 950-959.	This study looks at the association between outlet density and alcohol use among adolescents.
Shimotsu, S. T., Jones-Webb, R. J., MacLehose, R. F., Nelson, T. F., Forster, J. L., & Lytle, L. A. (2013). Neighborhood socioeconomic characteristics, the retail environment, and alcohol consumption: A multilevel analysis. *Drug and alcohol dependence*, *132*(3), 449-456.	This study looks at the effects of neighbourhood characteristics, including alcohol outlet density, on alcohol consumption.
Stanley, L. R., Henry, K. L., & Swaim, R. C. (2011). Physical, social, and perceived availabilities of alcohol and last month alcohol use in rural and small urban communities. *Journal of youth and adolescence*, *40*(9), 1203-1214.	This study looks at the effect of physical, social and perceived availability of alcohol on alcohol consumption in small and rural communities.
Stout, E. M., Sloan, F. A., Liang, L., & Davies, H. H. (2000). Reducing harmful alcohol-related behaviors: effective regulatory methods. *Journal of Studies on Alcohol*, *61*(3), 402-412.	This study looks at the effect of physical availability of alcohol and other factors on heavy episodic drinking and drinking while intoxicated.
Theall, K. P., Scribner, R., Cohen, D., Bluthenthal, R. N., Schonlau, M., Lynch, S., & Farley, T. A. (2009). The neighborhood alcohol environment and alcohol-related morbidity. *Alcohol and alcoholism*, *44*(5), 491-499.	This study examined the association between outlet density and self-reported alcohol-related health outcomes and to determine whether the relationship between morbidity and alcohol outlet density is mediated by individual alcohol consumption.
Toomey, T.L., Erickson, D.J., Carlin, B.P., Quick, H.S., Harwood, E.M., Lenk, K.M., & Ecklund, A.M. (2012). Is the Density of Alcohol Establishments Related to Nonviolent Crime?	This study looks at the density of alcohol outlets and it association to neighbourhood crime and alcohol consumption.
Treno, A. J., Ponicki, W. R., Remer, L. G. and Gruenewald, P. J. (2008), Alcohol Outlets, Youth Drinking, and Self-Reported Ease of Access to Alcohol: A Constraints and Opportunities Approach. Alcoholism: Clinical and Experimental Research, 32: 1372–1379.	This study looks at how youth drinking was affected by availability of alcohol.

Truong, K. D., & Sturm, R. (2007). Alcohol outlets and problem drinking among adults in California. *Journal of studies on alcohol and drugs*, *68*(6), 923-933.	This study looks at the relationship between the alcohol environment and excessive alcohol consumption and heavy episodic drinking.
Truong, K. D., & Sturm, R. (2009). Alcohol environments and disparities in exposure associated with adolescent drinking in California. *American Journal of Public Health*, *99*(2), 264-270.	This study looks at the socioeconomic disparities in alcohol environments and their relationship to alcohol use.
Van Oers, J. A., & Garretsen, H. F. (1993). The geographic relationship between alcohol use, bars, liquor shops and traffic injuries in Rotterdam.*Journal of studies on alcohol*, *54*(6), 739-744.	This study looks at the relationship of alcohol outlet density and other factors with alcohol use and traffic injuries.
Waller, M. W., Iritani, B. J., Christ, S. L., Clark, H. K., Moracco, K. E., Halpern, C. T., & Flewelling, R. L. (2011). Relationships among alcohol outlet density, alcohol use, and intimate partner violence victimization among young women in the United States. *Journal of interpersonal violence*, 0886260511431435.	This study looks at the relationship between outlet density, alcohol use and intimate partner violence.
Waller, M. W., Iritani, B. J., Christ, S. L., Halpern, C. T., Moracco, K. E., & Flewelling, R. L. (2013). Perpetration of intimate partner violence by young adult males: the association with alcohol outlet density and drinking behavior. *Health & place*, *21*, 10-19.	This study looks at the association between alcohol outlet density and male to female intimate partner violence.
Waller, M. W., Iritani, B. J., Flewelling, R. L., Christ, S. L., Halpern, C. T., & Moracco, K. E. (2012). Violence victimization of young men in heterosexual relationships: does alcohol outlet density influence outcomes?. *Violence and victims*, *27*(4), 527.	This study examined whether outlet density was associated with violence against heterosexual men by their female partners.
Wang, S.-H., Lin, I.-C., Chen, C.-Y., Chen, D.-R., Chan, T.-C. & Chen, W. J. (2013), Availability of convenience stores and adolescent alcohol use in Taiwan: a multi-level analysis of national surveys. Addiction, 108: 2081–2088.	This study looks at the availability of alcohol in convenience stores in Taiwan and youth alcohol consumption.

Weitzman, E. R., Folkman, A., Folkman, M. K. L., & Wechsler, H. (2003). The relationship of alcohol outlet density to heavy and frequent drinking and drinking-related problems among college students at eight universities. *Health & place*, *9*(1), 1-6.	This study looks at the effect of outlet density on heavy and frequent drinking and drinking related problems.

Appendix B: Supplementary Material for Study B

Appendix B-1: Minimum Prices for Beer, Wine and Spirits in Saskatchewan, 2008-2012

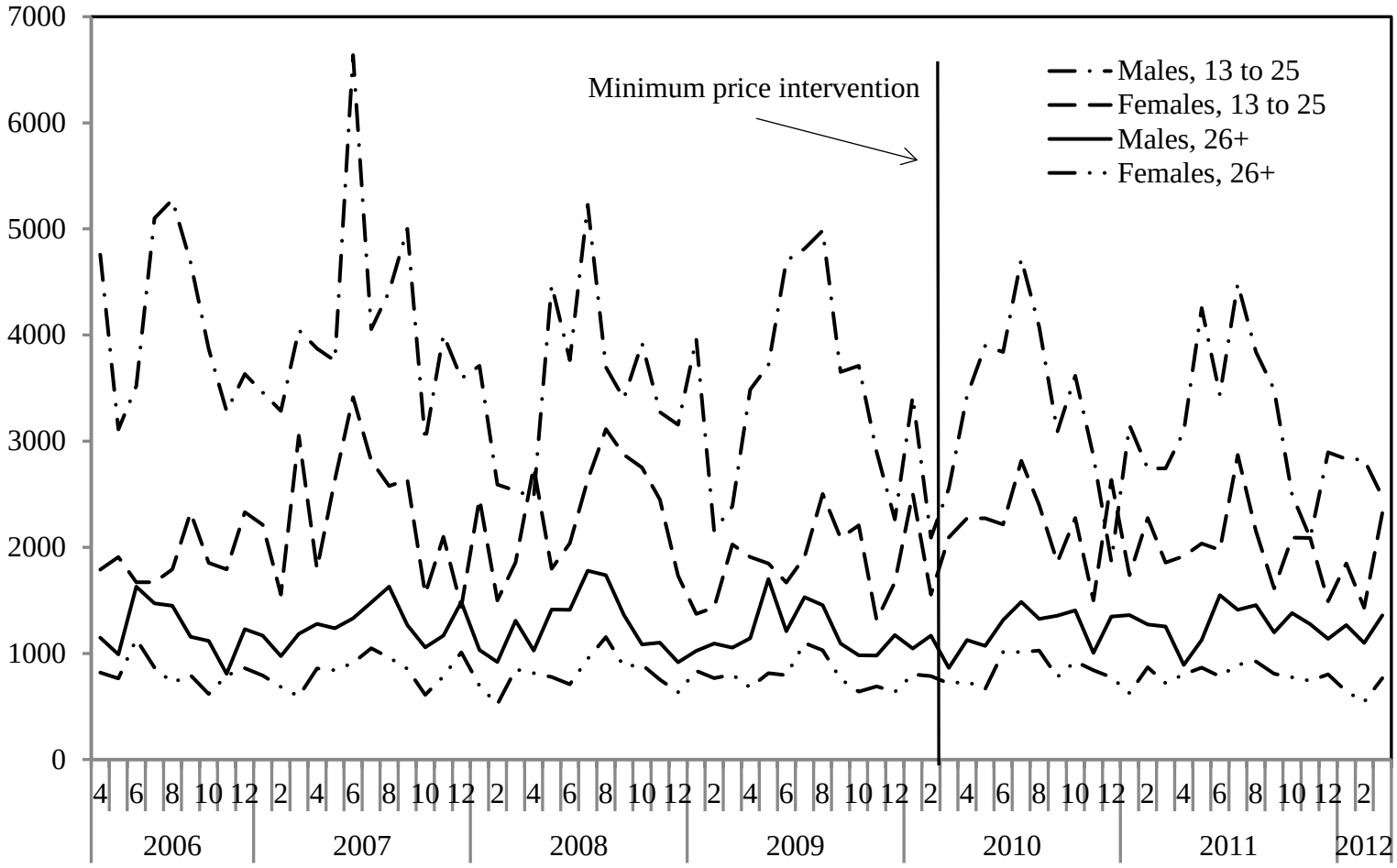


Appendix B-2: Emergency Department Visit Categorizations by ICD10 Codes

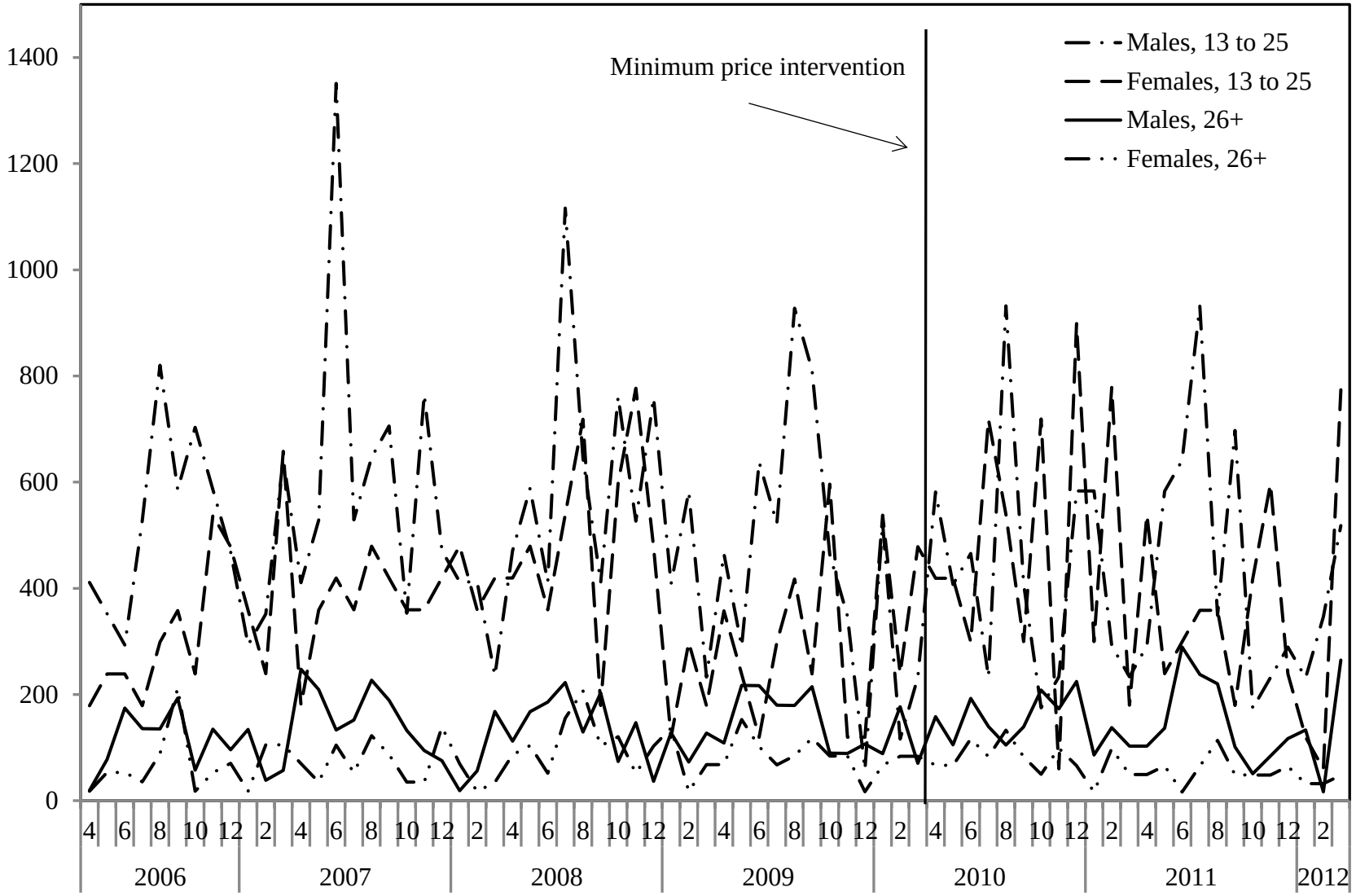
ED visit category	**Subcategory**	**ICD10 Codes**
Assaults	Assaults	X85-Y09, Y87.1
Falls	Fall injuries	W00-W19
Motor vehicle collisions	Motor vehicle collisions (traffic)	V02(.1, .9), V03(.1, .9), V04(.1, .9), V09.2, V12-V14(.3-.9), V19.4-V19.6, V20-V28(.3-.9), V29.4-V29.9, V30-V39(.4-.9), V40-V49(.4-.9), V50-V59(.4-.9), V60-V69(.4-.9), V70-V79(.4-.9), V80.3-V80.5, V81.1, V82.1, V83-V86(.0-.3), V87.0-V87.8, V89.2
Total alcohol-related injury visits	Assaults + Falls + Motor vehicle collisions + all codes below	
AlcoholSelfHarm	Intentional self-poisoning by and exposure to alcohol	X65
AlcoholUse	Alcohol-use disorders	F10
Air	Air-space travel	V95-V97
Aspiration	Aspiration	W78-W79
Drown	Drowning injuries	W65-W74
Fire	Exposure to smoke, fire and flames	X00-X09
Firearm	Discharge from firearm	W32-W34
Hypothermia	Exposure to excessive natural cold	X31
MVCnonTraffic	Motor vehicle collisions (traffic)	V02.0, V03.0, V04.0, V09.0, V12-V14(.0-.2), V19.0-V19.3, V20-V28(.0-.2), V29.0-V29.3, V30-V39(.0-.3),V40-V49(.0-.3), V50-V59(.0-.3), V60-V69(.0-.3), V70-V79(.0-.3), V81.0, V82.0, V83-V86(.4-.9), V88.0-V88.8, V89.0
Occupational	Occupational/machine injuries	W24-W31, W45

ED visit category	**Subcategory**	**ICD10 Codes**
OtherVehicle	Other road vehicle accidents	V01, V05-V06, V09.1, V09.3, V09.9, V10-V11, V15-V18, V19.3, V19.8-V19.9, V80.0- V80.2, V80.6-V80.9, V81.2- V81.9, V82.2-V82.9, V87.9, V88.9, V89.1, V89.3, V89.9
Water	Water transport accidents	V90-V94
OtherPoisoning	Poisoning (not alcohol)	X40-X49 (except X45)
OtherSelfHarm	Intentional self-harm	X60-X84, (except X65) Y87.0

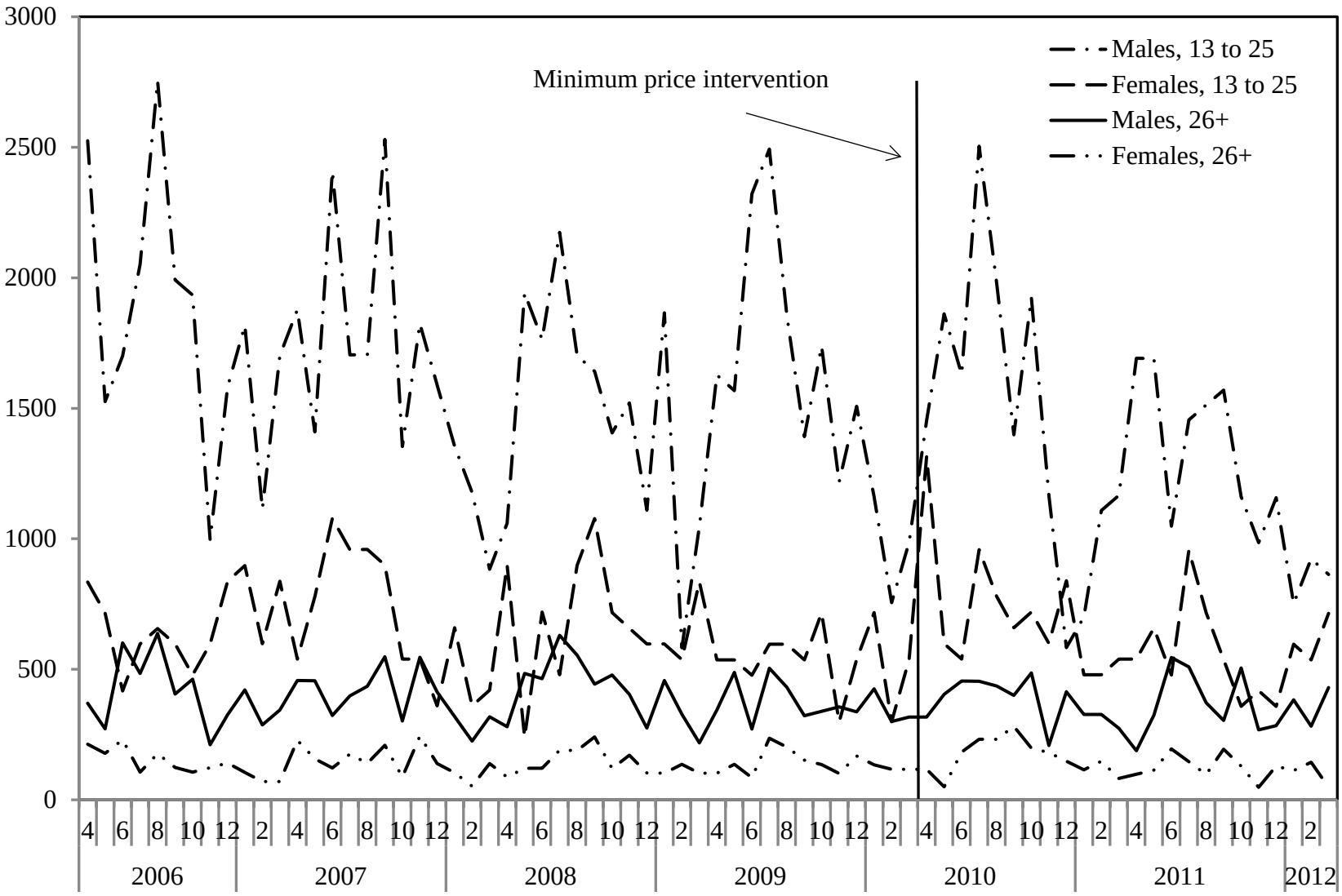
Appendix B-3: Monthly Rates of Nighttime ED Visits per 100,000 Population in Four Injury Categories and Four Gender-Age Groups, Saskatchewan, April 2006 to March 2012



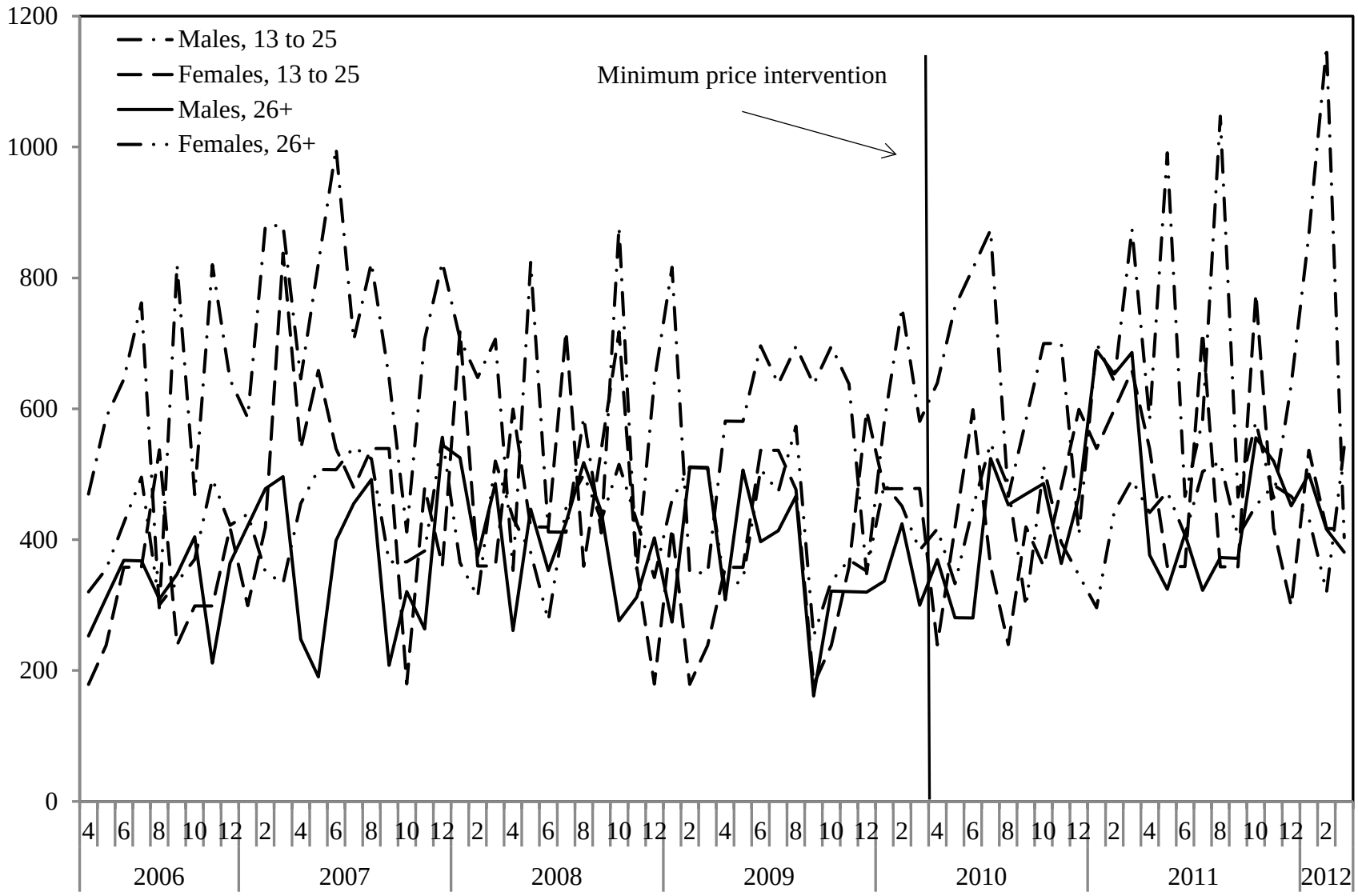
Total alcohol-related injuries



Motor vehicle collisions


3000
2500
2000
1500
1000
500
0
Minimum price intervention
Males, 13 to 25
Females, 13 to 25
Males, 26+
Females, 26+
4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2
2006
2007
2008
2009
2010
2011
2012

Assaults


Males, 13 to 25
Females, 13 to 25
Males, 26+
Females, 26+
Minimum price intervention
1200
1000
800
600
400
200
0
4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2 4 6 8 10 12 2
2006
2007
2008
2009
2010
2011
2012

Falls

Appendix B-4: Estimated Abrupt Changes in Rates of ED Visits by Gender and Age Groups Associated with an Alcohol Minimum Price Increase in Saskatchewan, Canada

		Partially-adjusted				Fully-adjusted			
	Model	**Estimate**	**StdError**	**t-value**	**p-value**	**Estimate**	**StdError**	**t-value**	**p-value**
Total alcohol-related, Males, 13 to 25									
Intervention*	$(0,1,1)$ $x(0,1,1)_{12}$	-0.003287	0.09935	-0.03	0.9737	0.03540	0.09729	0.36	0.7174
Average MP		-0.12317	0.83728	-0.15	0.8836	0.28890	0.75400	0.38	0.7031
Beer MP		-0.18400	0.94775	-0.19	0.8468	0.26510	0.92672	0.29	0.7759
Wine MP		-0.34239	0.47278	-0.72	0.4720	-0.42069	0.42019	-1.00	0.3212
Spirits MP		-0.35198	1.25191	-0.28	0.7796	0.36963	1.12443	0.33	0.7436
Motor vehicle collisions, Males, 13 to 25									
Intervention*	$(0,1,1)$	0.15460	0.36963	0.42	0.6771	-0.23102	0.24990	-0.92	0.3586
Average MP		0.07267	2.96859	0.02	0.9805	-0.008526	2.55992	-0.00	0.9974
Beer MP		-2.74564	2.41210	-1.14	0.2590	-2.63062	2.28561	-1.15	0.2538
Wine MP		-0.99238	1.03043	-0.96	0.3389	-1.11270	0.92062	-1.21	0.2310
Spirits MP		1.08749	3.77077	0.29	0.7739	1.84263	3.31444	0.56	0.5801
Assaults, Males, 13 to 25									
Intervention*	$(0,1,1)$ $x(0,1,1)_{12}$	-0.05371	0.13329	-0.40	0.6885	-0.00696	0.13180	-0.05	0.9581
Average MP		-0.49115	1.12851	-0.44	0.6651	0.23712	1.06439	0.22	0.8245
Beer MP		-0.46480	1.28314	-0.36	0.7186	0.13296	1.26907	0.10	0.9169
Wine MP		-0.01620	0.77975	-0.02	0.9835	-0.15755	0.72263	-0.22	0.8282
Spirits MP		-0.83698	1.65749	-0.50	0.6156	0.21626	1.64660	0.13	0.8960
Falls, Males, 13 to 25									
Intervention*	none	0.10863	0.09618	1.13	0.2626	0.10695	0.09892	1.08	0.2834
Average MP		2.13116	1.06705	2.00	0.0497	2.12081	1.08242	1.96	0.0542
Beer MP		1.48123	1.05673	1.40	0.1655	1.46580	1.07821	1.36	0.1785
Wine MP		-1.03463	0.59661	-1.73	0.0874	-1.03318	0.60060	-1.72	0.0899

Spirits MP		4.39605	1.80955	2.43	0.0177	4.44493	1.82306	2.44	0.0174
Total alcohol-related, Females, 13 to 25									
Intervention*	none	0.03354	0.06929	0.48	0.6299	0.01220	0.06681	0.18	0.8557
Average MP		0.45360	0.79186	0.57	0.5686	0.34806	0.75871	0.46	0.6479
Beer MP		0.19735	0.79622	0.25	0.8050	0.12691	0.76188	0.17	0.8682
Wine MP		0.44080	0.49080	0.90	0.3722	0.38279	0.47019	0.81	0.4184
Spirits MP		1.49657	1.40294	1.07	0.2898	1.50197	1.34004	1.12	0.2663
Motor vehicle collisions, Females, 13 to 25									
Intervention*	none	0.01503	0.18140	0.08	0.9342	0.02527	0.18263	0.14	0.8904
Average MP		1.16471	2.06993	0.56	0.5755	1.27456	2.08186	0.61	0.5424
Beer MP		-0.01224	2.08210	-0.01	0.9953	0.0057883	2.08996	0.00	0.9978
Wine MP		0.20368	1.29011	0.16	0.8750	0.13505	1.29881	0.10	0.9175
Spirits MP		5.79336	3.63077	1.60	0.1151	6.09147	3.65335	1.67	0.1000
Assaults, Females, 13 to 25									
Intervention*	none	0.11899	0.09922	1.20	0.2346	0.11436	0.09870	1.16	0.2506
Average MP		1.96770	1.12177	1.75	0.0839	1.99488	1.11330	1.79	0.0776
Beer MP		1.79660	1.13010	1.59	0.1165	1.82849	1.12171	1.63	0.1077
Wine MP		0.54898	0.71000	0.77	0.4420	0.50998	0.70636	0.72	0.4728
Spirits MP		4.18493	1.98003	2.11	0.0382	4.32729	1.96331	2.20	0.0309
Falls, Females, 13 to 25									
Intervention*	(0,1,1)	0.04786	0.13716	0.35	0.7282	0.04945	0.13943	0.35	0.7239
Average MP		0.40435	1.56338	0.26	0.7967	0.50567	1.59119	0.32	0.7516
Beer MP		-0.000769	1.57111	-0.00	0.9996	0.09839	1.59783	0.06	0.9511
Wine MP		-0.56379	0.95917	-0.59	0.5586	-0.54993	0.97286	-0.57	0.5738
Spirits MP		0.80951	2.75114	0.29	0.7695	1.09063	2.80234	0.39	0.6984
Total alcohol-related, Males, 26 and over									
Intervention*	$(0,1,1)_{12}$	0.03552	0.04721	0.75	0.4549	0.03295	0.04795	0.69	0.4948
Average MP		0.41300	0.51095	0.81	0.4223	0.39228	0.51635	0.76	0.4506
Beer MP		0.18354	0.52251	0.35	0.7267	0.16146	0.52729	0.31	0.7606
Wine MP		-0.03964	0.30740	-0.13	0.8978	-0.03542	0.30992	-0.11	0.9094
Spirits MP		0.94868	0.83877	1.13	0.2628	0.93266	0.84544	1.10	0.2747
Motor vehicle collisions, Males, 26 and over									
Intervention*	$(0,1,1)_{12}$	-0.10153	0.19555	-0.52	0.6056	-0.12295	0.19714	-0.62	0.5354

Average MP		-0.15853	2.14869	-0.07	0.9414	-0.61302	2.20195	-0.28	0.7817
Beer MP		-0.15926	2.17326	-0.07	0.9418	-0.39852	2.20431	-0.18	0.8572
Wine MP		0.61397	1.28990	0.48	0.6359	0.66307	1.31532	0.50	0.6162
Spirits MP		1.52337	3.55744	0.43	0.6701	0.47729	3.67690	0.13	0.8972
Assaults, Males, 26 and over									
Intervention*	$(0,0,5)$ $x(0,1,1)_{12}$	-0.05718	0.06343	-0.90	0.3711	-0.07591	0.06386	-1.19	0.2397
Average MP		-0.46984	0.72529	-0.65	0.5198	-0.77041	0.73738	-1.04	0.3007
Beer MP		-0.72552	0.70800	-1.02	0.3099	-0.97080	0.70677	-1.37	0.1752
Wine MP		0.02358	0.46310	0.05	0.9596	0.14169	0.47151	0.30	0.7649
Spirits MP		0.23660	1.30628	0.18	0.8569	-0.28674	1.35454	-0.21	0.8331
Falls, Males, 26 and over									
Intervention*	$(0,1,1)$ $x(0,1,1)_{12}$	0.16444	0.22578	0.73	0.4695	0.17689	0.16826	1.05	0.2978
Average MP		0.87391	1.90943	0.46	0.6490	0.96990	1.53022	0.63	0.5289
Beer MP		1.07871	2.01937	0.53	0.5954	1.25796	1.81740	0.69	0.4918
Wine MP		0.58875	0.57792	1.02	0.3128	0.40854	0.60986	0.67	0.5058
Spirits MP		1.05804	2.57541	0.41	0.6828	1.18087	2.10664	0.56	0.5774
Total alcohol-related, Females, 26 and over									
Intervention*	$(0,1,1)_{12}$	0.0074354	0.04865	0.15	0.8791	0.0049055	0.05044	0.10	0.9229
Average MP		0.20833	0.53130	0.39	0.6964	0.19409	0.54069	0.36	0.7210
Beer MP		0.29819	0.54826	0.54	0.5886	0.28416	0.55892	0.51	0.6132
Wine MP		0.40100	0.34248	1.17	0.2465	0.42619	0.37293	1.14	0.2580
Spirits MP		0.52313	0.91217	0.57	0.5686	0.51051	0.92153	0.55	0.5818
Motor vehicle collisions, Females , 26 and over									
Intervention*	$(1,0,1)$	-0.23648	0.28130	-0.84	0.4035	-0.24085	0.15200	-1.58	0.1179
Average MP		-2.66380	2.93117	-0.91	0.3667	-2.56581	1.81891	-1.41	0.1630
Beer MP		-1.76274	3.19090	-0.55	0.5825	-1.68922	1.67213	-1.01	0.3161
Wine MP		1.41837	1.50847	0.94	0.3505	1.49157	1.06307	1.40	0.1653
Spirits MP		-3.57847	4.17730	-0.86	0.3947	-3.18028	3.06758	-1.04	0.3036
Assaults, Females , 26 and over									
Intervention*	$(0,1,1)_{12}$	0.01640	0.11989	0.14	0.8917	0.01910	0.11990	0.16	0.8740
Average MP		0.50171	1.27282	0.39	0.6949	0.43994	1.26990	0.35	0.7303
Beer MP		1.11187	1.31377	0.85	0.4009	1.06837	1.31112	0.81	0.4186
Wine MP		1.30644	0.82067	1.59	0.1169	1.29550	0.81121	1.60	0.1159

Spirits MP		0.71671	2.17706	0.33	0.7432	0.44092	2.19099	0.20	0.8412
Falls, Females , 26 and over									
Intervention*	(2,0,0)	0.02479	0.04693	0.53	0.5990	0.01731	0.04827	0.36	0.7210
Average MP		0.22081	0.53990	0.41	0.6838	0.16267	0.55075	0.30	0.7686
Beer MP		0.04716	0.54694	0.09	0.9315	-0.005738	0.55680	-0.01	0.9918
Wine MP		-0.20249	0.34690	-0.58	0.5613	-0.28284	0.35704	-0.79	0.4311
Spirits MP		0.44333	0.97893	0.45	0.6521	0.37492	0.99405	0.38	0.7072

Notes

1. ARIMA models are given in standard notation. For example, the ARIMA model chosen for assaults has d=1, q=1 (corresponding to a linear trend and moving average term of 1) and has D=12, Q=12 (corresponding to a seasonal trend with a moving average term).
2. *The estimate of the intervention effect is the percent change (estimate x 100) in the rate of ED visits. In the four minimum price models (average, beer, wine, spirits), the estimate is the percent change in the rate of ED visits associated with a 1.0% increase in minimum price.
3. Bonferroni family-wise correction applied to α=0.05 level, with eight tests per family. Significance levels <0.05/8=0.00625 in boldface (**none**).

ED: Emergency department; MP: minimum price; total alcohol-related is total alcohol-related injury ED visits

Appendix C: Supplementary Material for Study C

Appendix C-1: InterMAHP Input Section From Comprehensive Guide

In order to run the InterMAHP program, you will have to understand the input needed. Input is loaded into InterMAHP using two spreadsheets (one regarding alcohol consumption and drinking prevalence and one regarding RR relationships). Each spreadsheet and the InterMAHP interface are described below.

Consumption and prevalence input

The consumption and prevalence input spreadsheet collects the necessary information from your region regarding *per capita* consumption, relative drinking between population subgroups and prevalences of current, binge and former drinkers and lifetime abstainers. These are the variables described in detail in Section 4.3.1. The following screenshot shows the format of the consumption and prevalence input spreadsheet. Next, each variable is then described.

Screenshot of InterMAHP consumption and prevalence input spreadsheet

Region	Year	Gender	Age_Group	Population	PCC_litres_year	Correction_factor	Relative_consumption	P_LA	P_FD	P_CD	P_BD
Your region	2013	Female	15 to 34	1193	9.00	0.8	5.6208	0.1004	0.0416	0.858	0.3432
Your region	2013	Female	35 to 64	1823	9.00	0.8	3.5191	0.0753	0.0307	0.894	0.2128
Your region	2013	Female	65+	1009	9.00	0.8	1.8913	0.1346	0.0504	0.815	0.1353
Your region	2013	Male	15 to 34	1254	9.00	0.8	10	0.0995	0.0215	0.879	0.4817
Your region	2013	Male	35 to 64	1863	9.00	0.8	7.1547	0.0321	0.0429	0.925	0.457
Your region	2013	Male	65+	844	9.00	0.8	3.8947	0.0803	0.0417	0.878	0.3415

(1) **Region** – region name. This is the name of the country, province, state, city or other subregion for which you would like to study AA morbidity and/or mortality. Multiple regions may be run concurrently.

(2) **Year** – year of study. Multiple years may be run concurrently.

(3) **Gender** – information is divided by gender.

(4) **Age_Group** – information is divided by age group (15 to 34, 35 to 64, 65+).

(5) **Population** – the population in each of the six gender-age group-defined population subgroups.

(6) **PCC_litres_year –** the best estimate of *per capita* consumption for the population 15+ in litres of ethanol per year. Notice, this figure is apportioned by population subgroup, it is for the entire population 15+. This was done as this number is typically available in aggregate, i.e. from government sources; it is then automatically divided amongst the population subgroups by the InterMAHP program.

(7) **Correction_factor** – a correction factor is applied to PCC to account for potential overestimation when using recorded plus unrecorded consumption values as compared to epidemiological studies from which RR functions and estimates are taken.

(8) **Relative_consumption** – taken from surveys, this is the relative per person alcohol consumption in each of the six gender-age population subgroups. This information is necessary to apportion PCC into the six subgroups. In the screenshot above, for example, females aged 15 to 34 are estimated to drink 5.6208/10.00 = 56.208% as much as males aged 15 to 34 on a per person basis. In practice, this variable typically comes from surveys which may collect information on the number of standard drinks (SD) per day, SD/week, SD/year, grams/day or any measure of drinking amount per unit time.

(9) **P_LA** – in each population subgroup, the prevalence of lifetime abstainers. Lifetime abstainers are defined as people who have never consumed one SD.

(10) **P_FD** – in each population subgroup, the prevalence of former drinkers. Former drinkers are defined as people who have consumed one SD or more in their lifetime, but have not consumed at least one SD in the past year.

(11) **P_CD** – in each population subgroup, the prevalence of current drinkers. Defined as people who have consumed one SD or more in the past year.

Note: as P_LA + P_FD + P_CD = 1.00, by definition, you must only find sources for two of these variables.

(12) **P_BD** – in each population subgroup, the prevalence of binge drinkers among the population (not among drinkers). Defined as people who have had one or more binge occasions in the past month.

Note that all prevalence values must be presented as prevalence proportions (i.e. 0.50) and not percentages (i.e. 50% or 50.0).

Relative risk input

The RR input spreadsheet collects all necessary RR information, both for continuous dose-response curves and former drinker RR point estimates, in one location for ease of use, adaptability and transparency. The following screenshot shows the format of the RR input spreadsheet and each variable is then described.

Two-part screenshot of InterMAHP relative risk input spreadsheet

A	B	C	D	E	F	G	H	I	J	K
IM	Condition	Gender	Outcome	RR_FD	BingeF	Function	B1	B2	B3	B4
(1).(1)	Tuberculosis	Male	Combined	1.000000	.	FP	0.0000000	0.0000000	0.0000000	0.0000000
(1).(1)	Tuberculosis	Female	Combined	1.000000	.	FP	0.0000000	0.0000000	0.0000000	0.0000000
(1).(2)	HIV	Male	Combined	1.000000	.	Step	.	.	.	.
(1).(2)	HIV	Female	Combined	1.000000	.	Step	.	.	.	.

B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15	B16
0.0000000	0.0179695	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
0.0000000	0.0179695	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
.	.	.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.	.	.

(1) **IM** – InterMAHP condition number. See Table C-2 for correspondence between all alcohol-related conditions and their InterMAHP numbers.

(2) **Condition** – name of alcohol-related condition.

(3) **Gender** - male or female. As many conditions have differential RR estimates for former drinkers, all conditions have one line in the spreadsheet for males and one for females. These can be identical, e.g. tuberculosis, but are often different, e.g. colorectal cancer (different RR function and RR former value) and liver cancer (same RR function, but different RR former value).

(4) **Outcome** – this may be morbidity, mortality or combined. Where supported by the meta-analyses used, relationships are divided by mortality and morbidity; however, for many conditions this division is not present and therefore the curves and values are identical for mortality and morbidity.

(5) **RR_FD** – for each condition, gender and outcome, the relative risk of former drinkers as compared to lifetime abstainers. See Table C-2 and Appendix C-2.

(6) **BingeF** – binge factor which only applies to the three injury categories. All other values are left blank. The binge factor represents the risk ratio of bingers to non-bingers at the same average consumption level; see Section 4.5.4.3 for a comprehensive description.

(7) **Function** – represents the functional form of the continuous dose-response relationship between alcohol and each condition/gender/outcome. FP stands for the two-term fractional polynomial technique (Royston et al., 1999; Royston & Sauerbrei, 2008) used by the vast majority of authors of alcohol dose-response meta-analyses (see Section 3.2.1 for expanded treatment). There are three exceptions to this: HIV is defined as a step function, while hypertension and acute pancreatitis (women) are defined by splines.

Note: As InterMAHP uses this input spreadsheet to read in RR functions in FP form, they are easily modifiable by changing the function you would like to use, while following the form in the formula below. However, the RR functions for HIV, hypertension and acute pancreatitis are necessarily hardcoded into the SAS backend program due to their complexity and are therefore more difficult to update.

(8) **B1** to **B16** – these 16 variables represent the following formula. FP2 fractional polynomials must fit the form represented by the formula below, where either one or two of the betas is non-zero. It is therefore easy to represent FP2 functional equations as a series of 16 betas. For example, tuberculosis has β_6 =0.0179695, while all other betas are zero. Therefore, using the formula below, for tuberculosis, $lnRR(x) = 0.0179695x$.

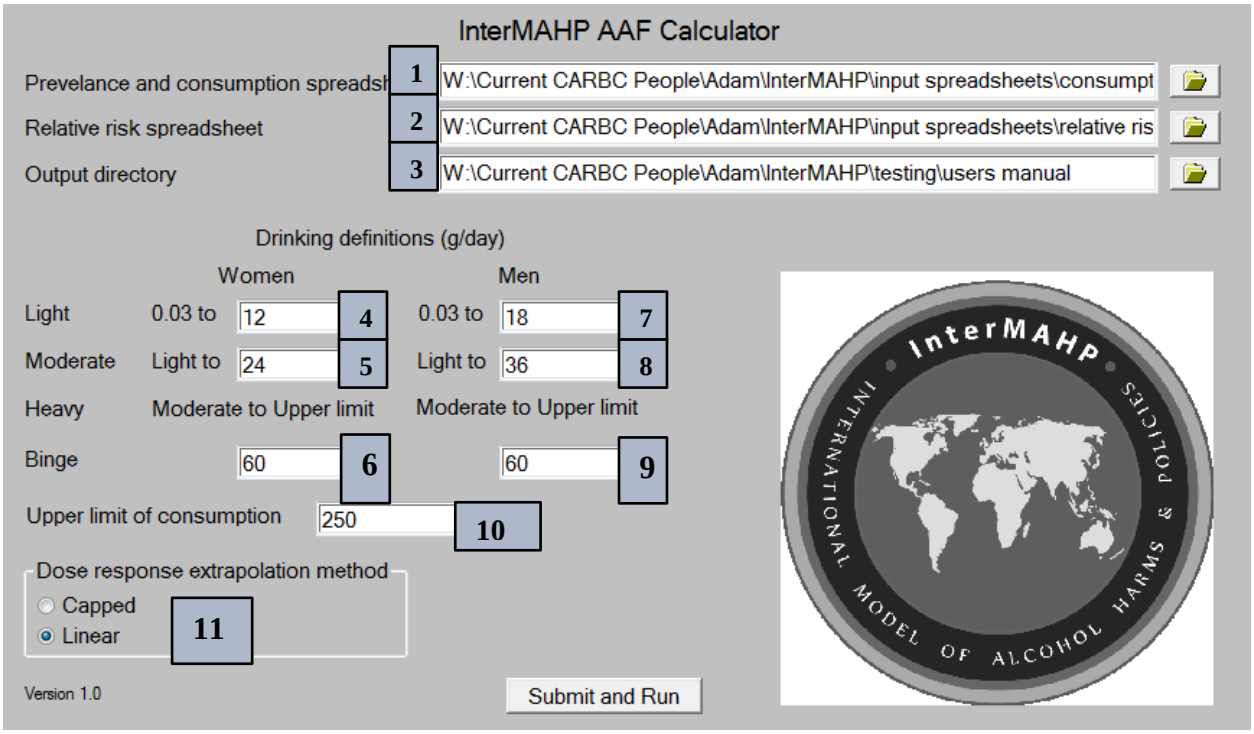
$$lnRR(x) = \beta_1 x^{-2} + \beta_2 x^{-1} + \beta_3 x^{-\frac{1}{2}} + \beta_4 \ln x + \beta_5 x^{\frac{1}{2}} + \beta_6 x +$$
$$\beta_7 x^2 + \beta_8 x^3 + \beta_9 x^{-2} \ln x + \beta_{10} x^{-1} \ln x + \beta_{11} x^{-\frac{1}{2}} \ln x +$$
$$\beta_{12} (\ln x)^2 + \beta_{13} x^{\frac{1}{2}} \ln x + \beta_{14} x \ln x + \beta_{15} x^2 \ln x + \beta_{16} x^3 \ln x$$

InterMAHP AAF calculator program: User interface

InterMAHP is written in SAS with a graphical user interface as the frontend and the functional code as the backend. The input spreadsheets and AAF program were designed in such a way that it is rarely or never necessary for users to modify the backend program. Therefore, no familiarity with the SAS programming language is necessary in order to run InterMAHP; however, SAS must be installed on the computer or server which will be used to run InterMAHP.

The following screenshot depicts the InterMAHP user interface and each component is then described, corresponding to the number one through 11 in the screenshot.

Screenshot of the InterMAHP AAF Calculator program user interface



(1) Input prevalence and consumption .csv spreadsheet you have prepared for your region(s). Hit the browse button on the right hand side and locate the .csv.

(2) Input relative risk .csv spreadsheet. Choose to use the InterMAHP- provided RR functions and estimates, or update the ones you have chosen to update. Locate using the browse button on the right hand side.

(3) Choose an output directory for the program output.

(4) Define the light drinking group for women as the lower limit of consumption (0.03 g/day) to this inputted value in g/day. Throughout the rest of this guide, the value you choose is denoted a_w. The lower limit of consumption (0.03 g/day) is defined as those who have had one standard drink or more in the past year (12g/365=0.03g/day).

(5) Define the moderate drinking group for women as a_w (as above) to this inputted value in g/day. Throughout the guide, this value is denoted b_w.

(6) Define the binge level definition for women in your region (or in the survey you are using). Throughout the guide, this value is denoted c_w.

(7) Identical to (4), except for men. Inputted value denoted a_m.

(8) Identical to (5), except for men. Inputted value denoted b_m.

(9) Identical to (6), except for men. Inputted value denoted c_m.

(10) Define the theoretical upper limit of average daily consumption in your region, based on the best available information. Throughout the guide, this value is denoted z.

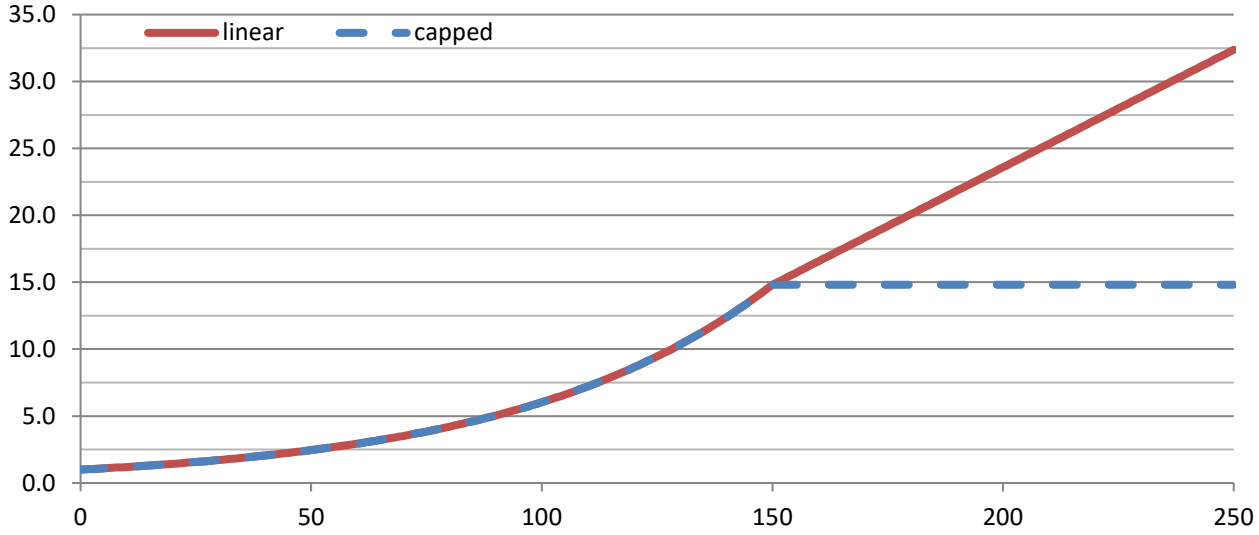
(11) Choose the method used to extrapolate relative risk functions above 150 g/day. See Section 4.5.2.3 for a comprehensive discussion of this choice.

Appendix C-2: Relative Risk Summary Pages

(1).(1) Tuberculosis

Condition category: (1) Communicable diseases
ICD10 codes: A15 to A19

	Current drinkers	Former drinkers
Source	Imtiaz et al. (2017) Table 2	There is no increased risk for former drinkers
Relative risk Equation or estimate	$\ln RR(x) = 0.0179695x$ $RR(x)$=exp(0.0179695x)	RR_{FD} = 1.00
Comments	Relative risk function received directly from members of authorship group who are members of this project. Note coefficient presented in Table 2 is exp(0.0179695) = round(1.0181).	
Control for abstainer bias Does the article control for?	Not applicable. There is no increased risk for former drinkers.	



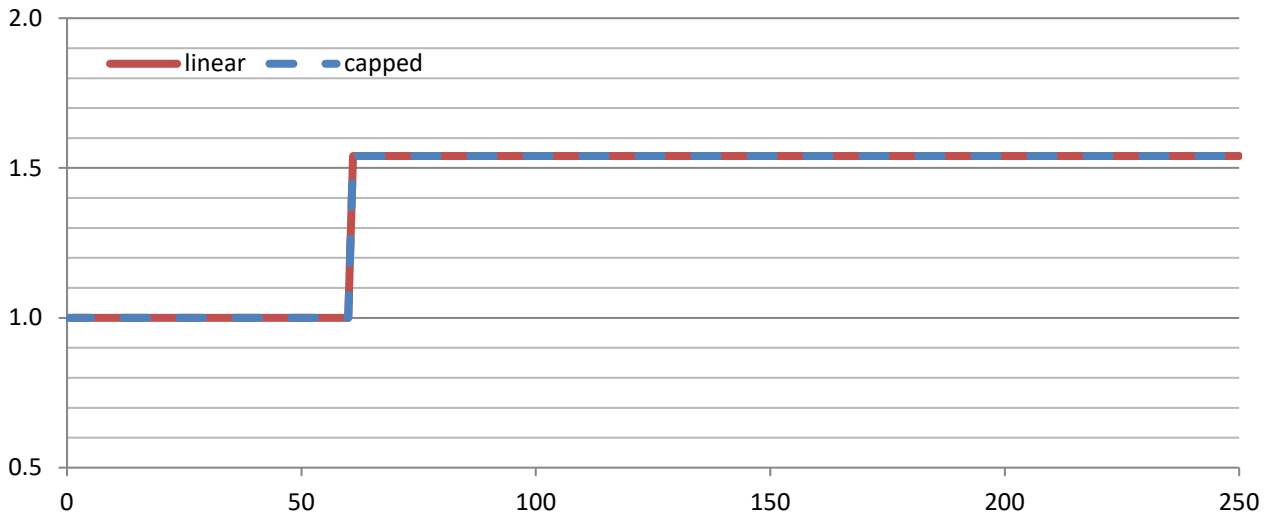
Source

Imtiaz, S., Shield, K. D., Roerecke, M., Samokhvalov, A. V., Lönnroth, K., & Rehm, J. (2017). Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. *European Respiratory Journal*, *50*(1), 1700216.

(1).(2) HIV, men

Condition category: (1) Communicable diseases
ICD10 codes: B20 to B24, Z21

	Current drinkers	Former drinkers
Source	Rehm et al. (2017) Presented in article section entitled *Quantification of the effect of alcohol use on HIV*	There is no increased risk for former drinkers
Relative risk Equation or estimate	Step function: $RR = \begin{cases} 1.00, 0 < x < 61 \\ 1.54, 61 \leq x \leq z \end{cases}$	RR_{FD} = 1.00
Comments	Relative risk function received directly from members of authorship group who are members of this project.	Note: HIV is the only condition for which step functions are present in InterMAHP. For step functions, the linear and capped methods are equivalent.
Control for abstainer bias Does the article control for abstainer bias?	Not applicable. There is no increased risk for former drinkers.	



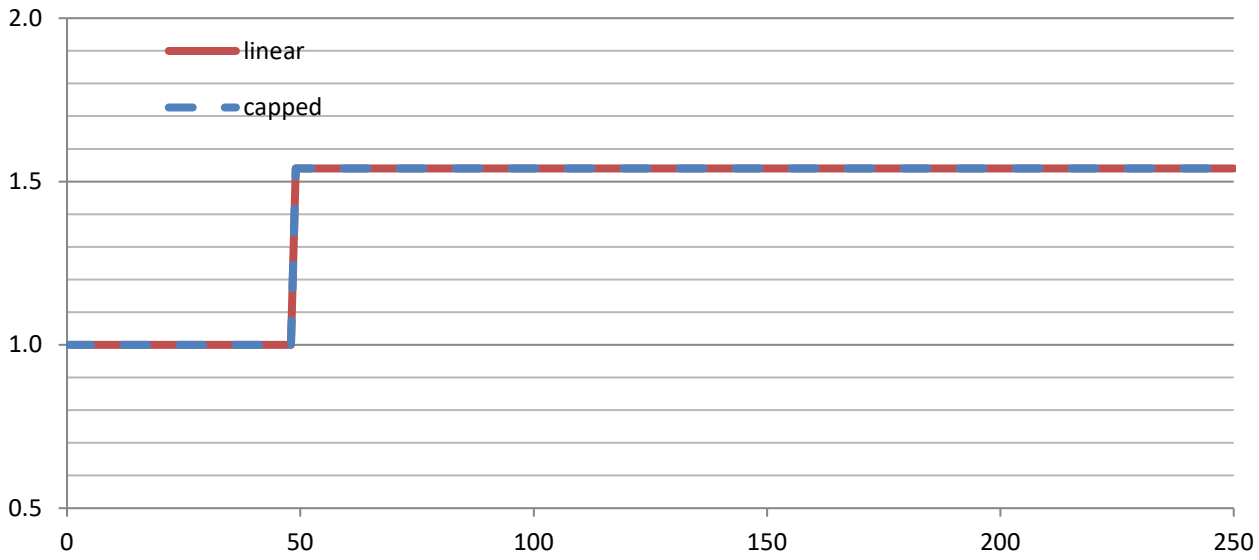
Source

Rehm, J., Probst, C., Shield, KD, Shuper, PA. (2017). Does alcohol use have a causal effect on HIV incidence and disease progression? A review of the literature and a modeling strategy for quantifying the effect. *Population Health Metrics , 15(4)*. doi10.1186/s12963-017-0121-9

(1).(2) HIV, women

Condition category: (1) Communicable diseases
ICD10 codes: B20 to B24, Z21

	Current drinkers	Former drinkers
Source	Rehm et al. (2017) Presented in article section entitled *Quantification of the effect of alcohol use on HIV*	There is no increased risk for former drinkers
Relative risk Equation or estimate	Step function: $RR = \begin{cases} 1.00, 0 < x < 49 \\ 1.54, 49 \leq x \leq z \end{cases}$	RR_{FD} = 1.00
Comments	Relative risk function received directly from members of authorship group who are members of this project.	Note: HIV is the only condition for which step functions are present in InterMAHP. For step functions, the linear and capped methods are equivalent.
Control for abstainer bias Does the article control for abstainer bias?	Not applicable. There is no increased risk for former drinkers.	



Source

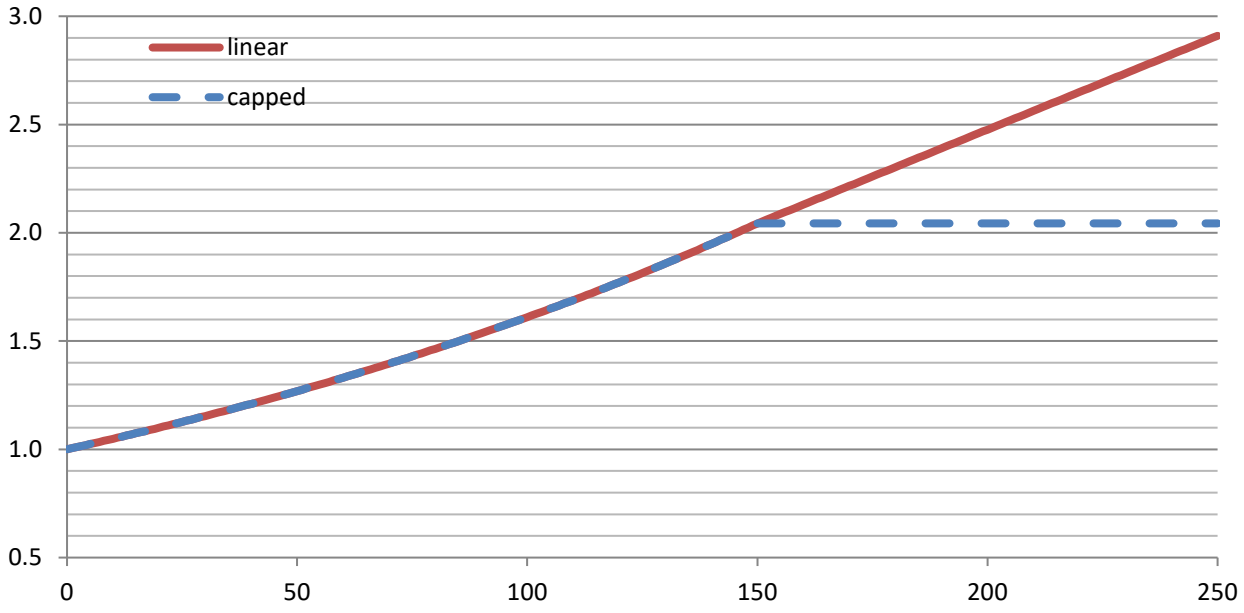
Rehm, J., Probst, C., Shield, KD, Shuper, PA. (2017). Does alcohol use have a causal effect on HIV incidence and disease progression? A review of the literature and a modeling strategy for quantifying the effect. *Population Health Metrics , 15(4)*. doi10.1186/s12963-017-0121-9

(1).(3) Lower respiratory tract infections

Condition category: (1) Communicable diseases

ICD10 code(s): J09 to J22

	Current drinkers	Former drinkers
Source	Samokhvalov et al. (2010) Figure 3	There is no increased risk for former drinkers
Relative risk Equation or estimate	$\ln RR(x) = 0.004764038x$ $RR(x)=\exp(0.004764038x)$	RR_{FD} = 1.00
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias?	Not applicable. There is no increased risk for former drinkers.	



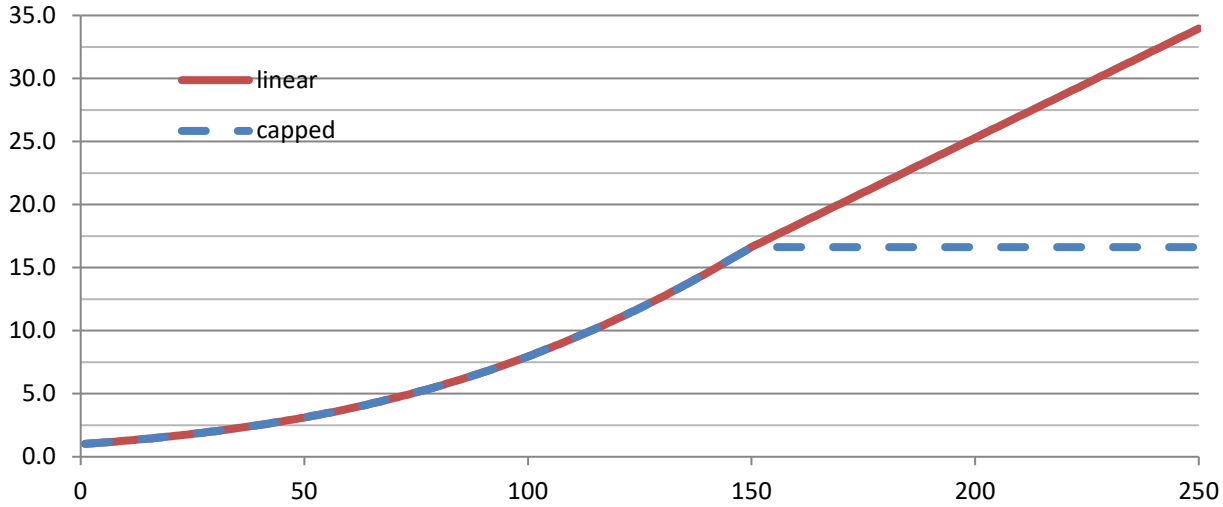
Source

Samokhvalov, A. V., Irving, H. M., & Rehm, J. (2010). Alcohol consumption as a risk factor for pneumonia: a systematic review and meta-analysis. *Epidemiology & Infection*, *138*(12), 1789-1795.

(2).(1) Oral cavity and pharynx cancer

Condition category: **(2) Cancer**
ICD10 codes: **C00 to C05; C08 to C10; C12 to C14, D00.0**

	Current drinkers	Former drinkers
Source	Bagnardi et al. (2015) Figure 3	Marron et al. (2009) Table 2, top panel of results
Relative risk Equation or estimate	$\ln RR(x) = 0.02474x - 0.00004x^2$ $RR(x)=\exp(0.02474x - 0.00004x^2)$	RR_{FD} = 1.16
Comments	Functional equation for continuous curve depicted in Figure 3 obtained through personal correspondence between AS and V. Bagnardi, dated 25-July-2017. Bagnardi et al. tested for differential dose-response relationship by gender and found none.	RR_{FD} rescaled as current drinkers were the referent in Table 2. RR_{FD}=0.85/0.73 = 1.16 Estimate from "head and neck" category used as oral cavity and oro/hypopharynx were separated. Pooled analysis from broad international sources.
Control for abstainer bias Does the article control for abstainer bias?	No. The meta-analysis does not explicitly control for abstainer bias in the meta-regression.	Yes. As this article was concerned with the cessation of drinking, lifetime abstainers and former drinkers were separated in the study design.



Sources

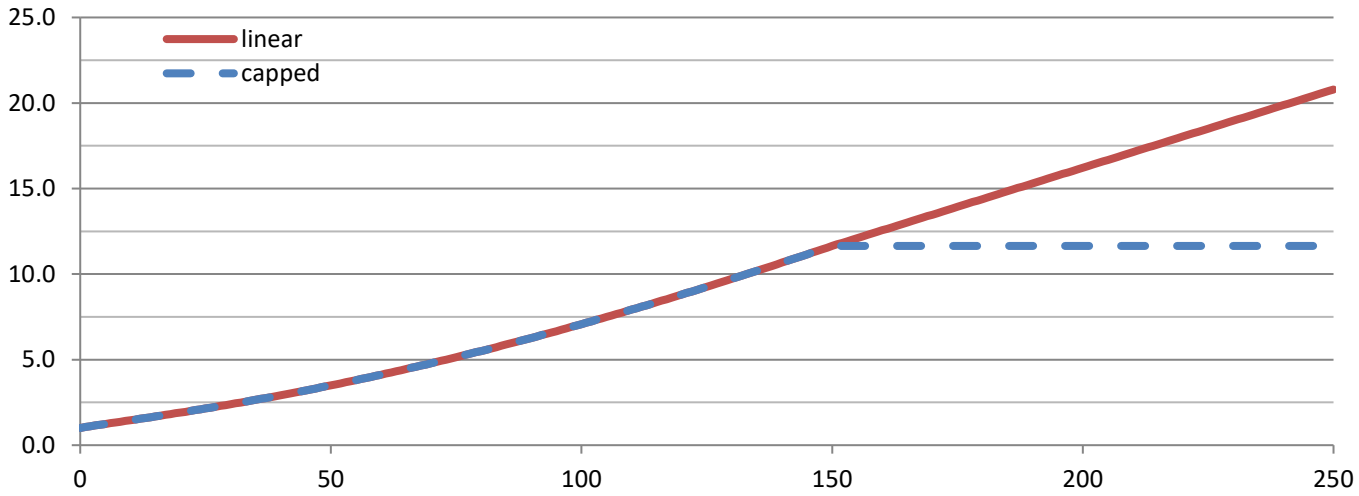
Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V.,Scotti, L.,Jenab, M., Turati, F.,Pasquali, E., Pelucchi, C., Galeone, C., Belloco, R., Negri, E., Corrao, G., Boffeta, P.& La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British journal of cancer*, 112(3), 580.

Marron, M., Boffetta, P., Zhang, Z. F., Zaridze, D., Wünsch-Filho, V., Winn, D. M., ... & Smith, E. (2009). Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *International journal of epidemiology*, *39*(1), 182-196.

(2).(2) Oesophageal cancer, squamous cell carcinoma (SCC)

Condition category: **(2) Cancer**
ICD10 codes: **C15, D00.1 (portional - only SCC and not adenocarcinoma)**

	Current drinkers	Former drinkers
Source	Bagnardi et al. (2015) Figure 3	Marron et al. (2009) Table 2, top panel of results
Relative risk Function or estimate	$\ln RR(x) = 0.0559x - 0.00789x \ln x$ $RR(x)$=exp$(0.0559x - 0.00789x \ln x)$	RR_{FD} = 1.16
Comments	Functional equation for continuous curve depicted in Figure 3 obtained through personal correspondence between AS and V. Bagnardi, dated 25-July-2017. Bagnardi et al. tested for differential dose-response relationship by gender and found none.	RR_{FD} rescaled as current drinkers were the referent in Table 2. RR_{FD}=0.85/0.73 = 1.16 Estimate from "head and neck" category used as oral cavity and oro/hypopharynx were separated. Pooled analysis from broad international sources.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. The meta-analysis does not explicitly control for abstainer bias in the meta-regression.	Yes. As this article was concerned with the cessation of drinking, lifetime abstainers and former drinkers were separated in the study design.



Sources

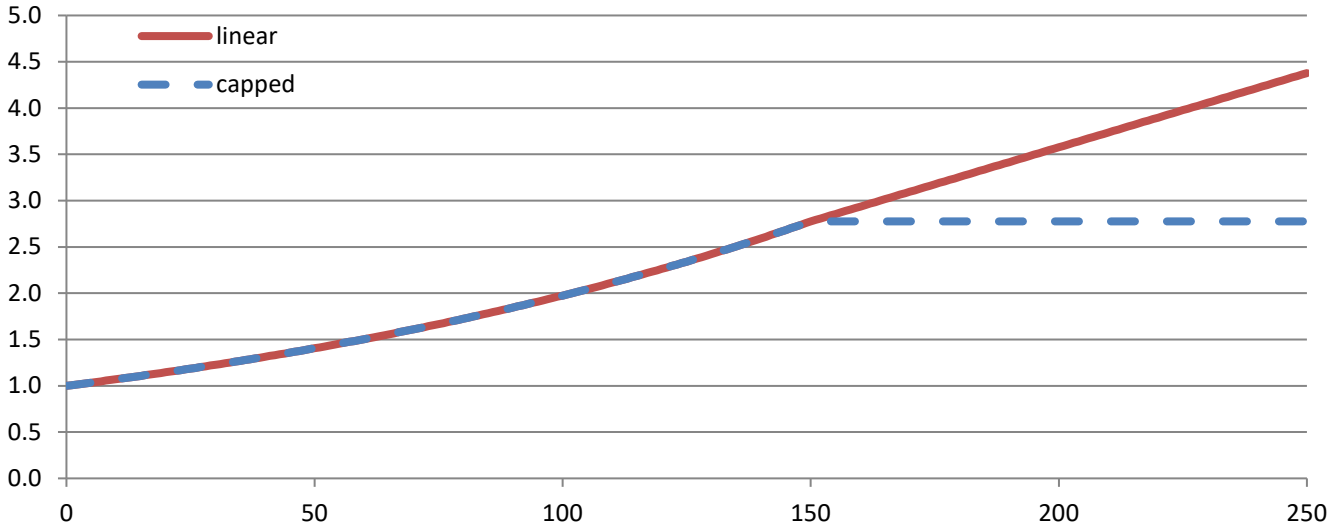
Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V.,Scotti, L.,Jenab, M., Turati, F.,Pasquali, E., Pelucchi, C., Galeone, C., Belloco, R., Negri, E., Corrao, G., Boffeta, P.& La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British journal of cancer*, 112(3), 580.

Marron, M., Boffetta, P., Zhang, Z. F., Zaridze, D., Wünsch-Filho, V., Winn, D. M., ... & Smith, E. (2009). Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *International journal of epidemiology*, *39*(1), 182-196.

(2).(3) Colorectal cancer, men

Condition category: **(2) Cancer**
ICD10 codes: **C18 to C21, D01.0 to D01.4**

	Current drinkers	Former drinkers
Source	Bagnardi et al. (2015) Table 3	Schütze et al. (2011) Table 2
Relative risk Function or estimate	$\ln RR(x) = 0.006806x$ $RR(x)=\exp(0.006806x)$	RR_{FD} = 2.19
Comments	Test for heterogeneity showed differential effect for men and women. Continuous relative risk function based on the categorical information presented in Table 3 obtained through personal correspondence between AS and V. Bagnardi, dated 25-July-2017.	Based on the prospective cohort EPIC study (European Prospective Investigation into Cancer and Nutrition). Data analyzed from eight western European countries; context therefore not as broad as a large meta-analysis.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. The meta-analysis does not explicitly control for abstainer bias in the meta-regression.	Yes. EPIC asks respondents their alcohol use at ages 20,30,40,50 and recruitment. Accurate measure of lifetime abstention.



Sources

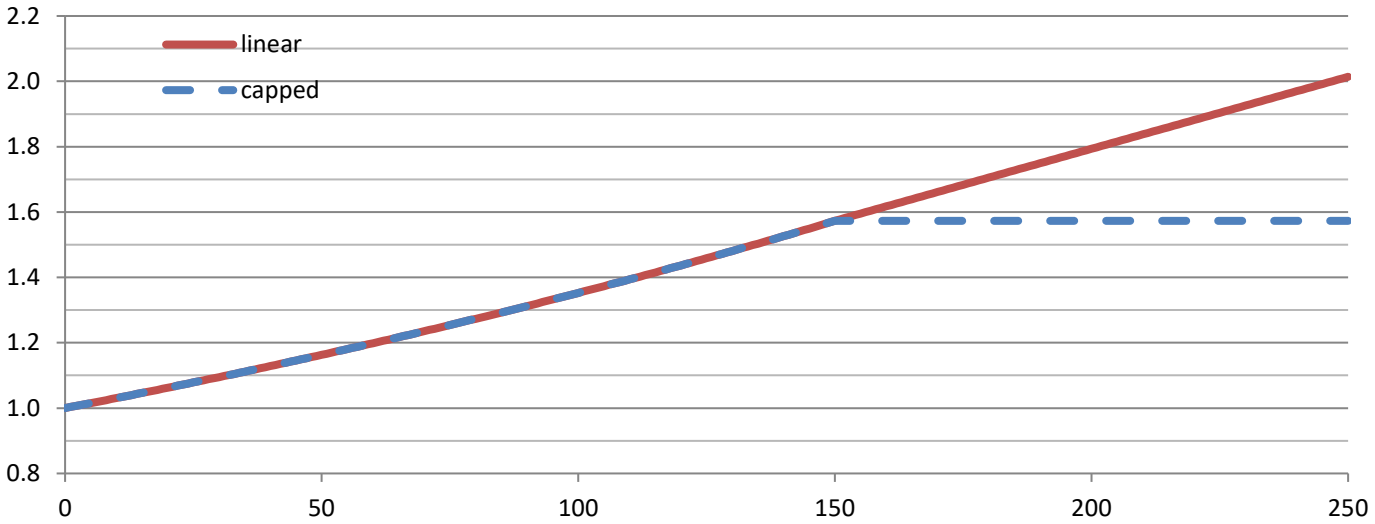
Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V.,Scotti, L.,Jenab, M., Turati, F.,Pasquali, E., Pelucchi, C., Galeone, C., Belloco, R., Negri, E., Corrao, G., Boffeta, P.& La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British journal of cancer*, 112(3), 580.

Schütze, M., Boeing, H., Pischon, T., Rehm, J., Kehoe, T., Gmel, G., ... & Clavel-Chapelon, F. (2011). Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. *Bmj*, *342*, d1584.

(2).(3) Colorectal cancer, women

Condition category: **(2) Cancer**
ICD10 codes: **C18 to C21, D01.0 to D01.4**

	Current drinkers	Former drinkers
Source	Bagnardi et al. (2015) Table 3	Schütze et al. (2011) Table 2
Relative risk Function or estimate	$\ln RR(x) = 0.003020x$ $RR(x)=\exp(0.003020x)$	RR_{FD} = 1.05
Comments	Test for heterogeneity showed differential effect for men and women. Continuous relative risk function based on the categorical information presented in Table 3 obtained through personal correspondence between AS and V. Bagnardi, dated 25-July-2017.	Based on the prospective cohort EPIC study (European Prospective Investigation into Cancer and Nutrition). Data analyzed from eight western European countries; context therefore not as broad as a large meta-analysis.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. The meta-analysis does not explicitly control for abstainer bias in the meta-regression.	Yes. EPIC asks respondents their alcohol use at ages 20,30,40,50 and recruitment. Accurate measure of lifetime abstention.



Sources

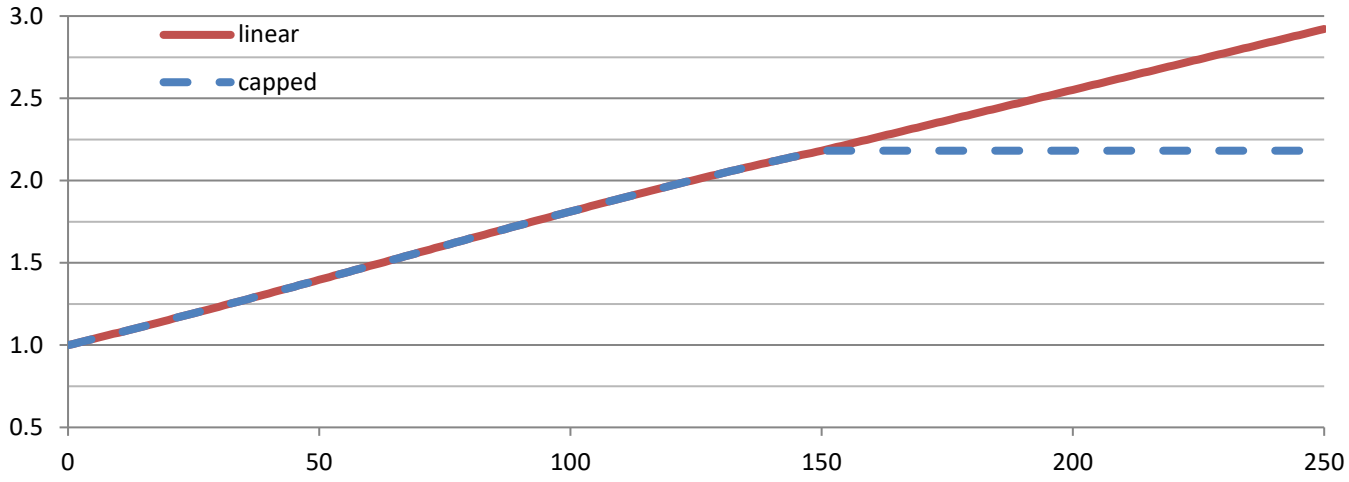
Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V.,Scotti, L.,Jenab, M., Turati, F.,Pasquali, E., Pelucchi, C., Galeone, C., Belloco, R., Negri, E., Corrao, G., Boffeta, P.& La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British journal of cancer*, 112(3), 580.

Schütze, M., Boeing, H., Pischon, T., Rehm, J., Kehoe, T., Gmel, G., ... & Clavel-Chapelon, F. (2011). Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. *Bmj*, *342*, d1584.

(2).(4) Liver cancer

Condition category: **(2) Cancer**
ICD10 codes: **C22, D01.5**

	Current drinkers	Former drinkers
Source	Corrao et al. (2004) Figure 1	Schütze et al. (2011) Table 2
Relative risk Function or estimate	$\ln RR(x) = 0.00742949x - 0.0000148593x^2$ $RR(x)=\exp(0.00742949x - 0.0000148593x^2)$	RR_{FD} (men) = 1.54 RR_{FD} (women) = 2.28
Comments	Functional equation for continuous curve depicted in Figure 1 obtained previously from Corrao et al. by JR. Corrao et al. (2004) is used instead of Bagnardi et al. (2015) due to the instability of the function for liver cancer. It has a cubic term and therefore increases dramatically above 100g/day. The decision to use Corrao is the same as was used in the WHO 2018 Global Status Report on Alcohol and Health.	Based on the prospective cohort EPIC study (European Prospective Investigation into Cancer and Nutrition). Data analyzed from eight western European countries; context therefore not as broad as a large meta-analysis. RR_{FD} (men) same as that for total cancer as there were not enough cases to uniquely estimate for liver cancer.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. The meta-analysis does not explicitly control for abstainer bias in the meta-regression.	Yes. EPIC asks respondents their alcohol use at ages 20,30,40,50 and recruitment. Accurate measure of lifetime abstention.



Sources

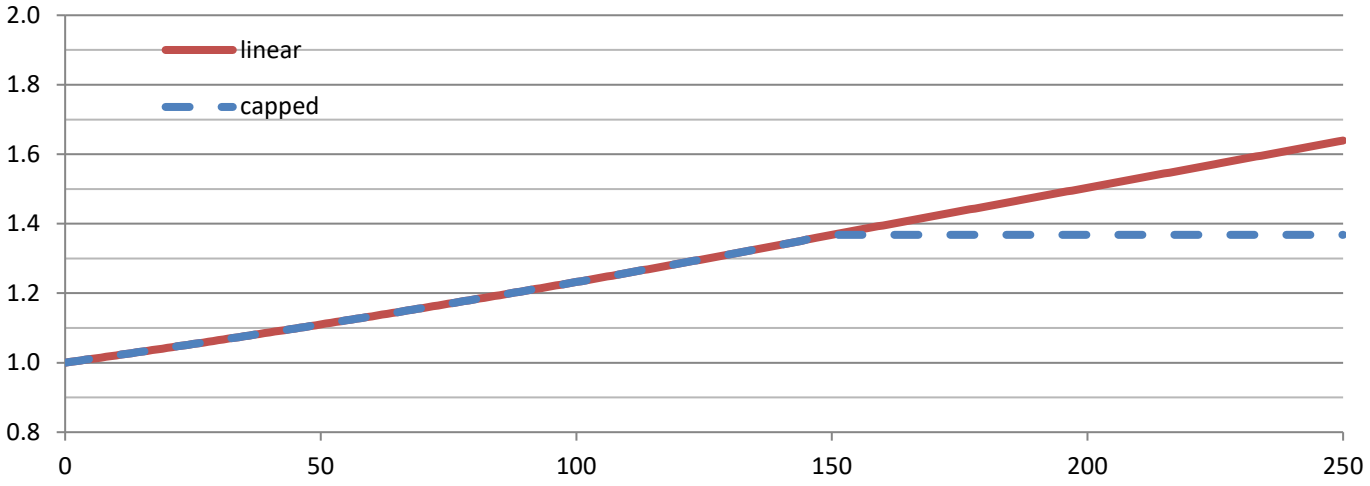
Corrao, G., Bagnardi, V., Zambon, A., & La Vecchia, C. (2004). A meta-analysis of alcohol consumption and the risk of 15 diseases. *Preventive medicine*, *38*(5), 613-619.

Schütze, M., Boeing, H., Pischon, T., Rehm, J., Kehoe, T., Gmel, G., ... & Clavel-Chapelon, F. (2011). Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. *Bmj*, *342*, d1584.

(2).(5) Pancreatic cancer

Condition category: **(2) Cancer**
ICD10 codes: **C25, D01.7**

	Current drinkers	Former drinkers
Source	Bagnardi et al. (2015) Figure 3	Schütze et al. (2011) Table 2
Relative risk Function or estimate	$\ln RR(x) = 0.002089x$ $RR(x)$=exp$(0.002089x)$	RR_{FD}(men) = 1.54 RR_{FD}(women) = 1.10
Comments	Functional equation for continuous curve depicted in Figure 3 obtained through personal correspondence between AS and V. Bagnardi, dated 25-July-2017. Bagnardi et al. tested for differential dose-response relationship by gender and found none.	Results for total cancer used as no condition-specific results available. Based on the prospective cohort EPIC study (European Prospective Investigation into Cancer and Nutrition). Data analyzed from eight western European countries; context therefore not as broad as a large meta-analysis.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. The meta-analysis does not explicitly control for abstainer bias in the meta-regression.	Yes. EPIC asks respondents their alcohol use at ages 20,30,40,50 and recruitment. Accurate measure of lifetime abstention.



Sources

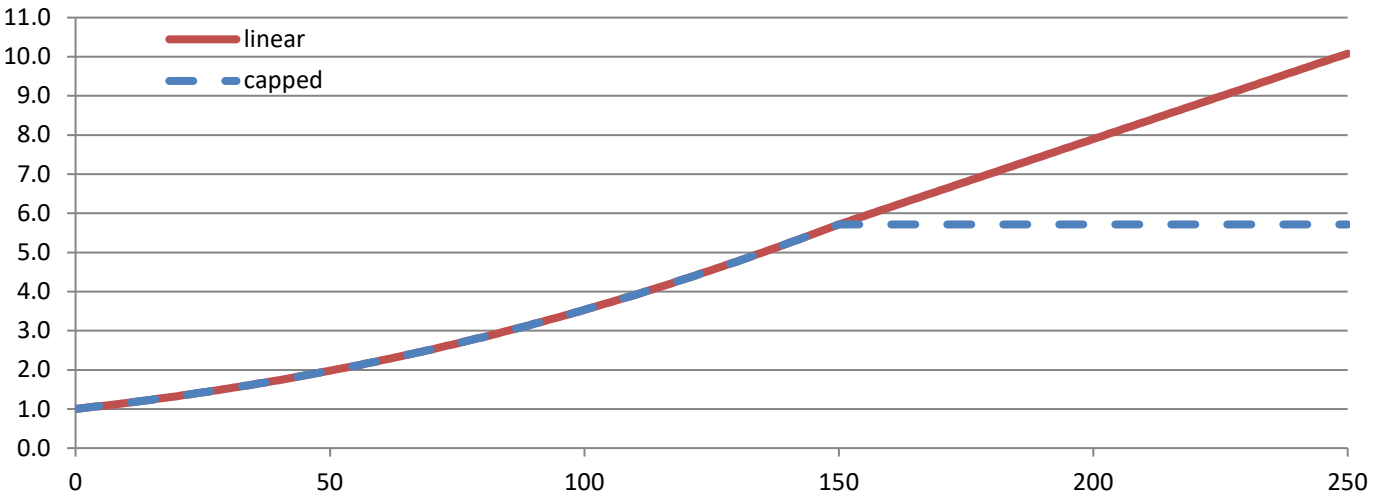
Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V.,Scotti, L.,Jenab, M., Turati, F.,Pasquali, E., Pelucchi, C., Galeone, C., Bellocco, R., Negri, E., Corrao, G., Boffeta, P.& La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British journal of cancer*, 112(3), 580.

Schütze, M., Boeing, H., Pischon, T., Rehm, J., Kehoe, T., Gmel, G., ... & Clavel-Chapelon, F. (2011). Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. *Bmj*, *342*, d1584

(2).(6) Laryngeal cancer

Condition category: **(2) Cancer**
ICD10 codes: **C32, D02.0**

	Current drinkers	Former drinkers
Source	Bagnardi et al. (2015) Figure 3	Marron et al. (2009) Table 2, top panel of results
Relative risk Function or estimate	$\ln RR(x) = 0.01462x - 0.00002x^2$ $RR(x)$=exp$(0.01462x - 0.00002x^2)$	RR_{FD} = 1.18
Comments	Functional equation for continuous curve depicted in Figure 3 obtained through personal correspondence between AS and V. Bagnardi, dated 25-July-2017. Bagnardi et al. tested for differential dose-response relationship by gender and found none.	RR_{FD} rescaled as current drinkers were the referent in Table 2. RR_{FD}=0.79/0.67 = 1.18 Estimate from "head and neck" category used as oral cavity and oro/hypopharynx were separated. Pooled analysis from broad international sources.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. The meta-analysis does not explicitly control for abstainer bias in the meta-regression.	Yes. As this article was concerned with the cessation of drinking, lifetime abstainers and former drinkers were separated in the study design.



Sources

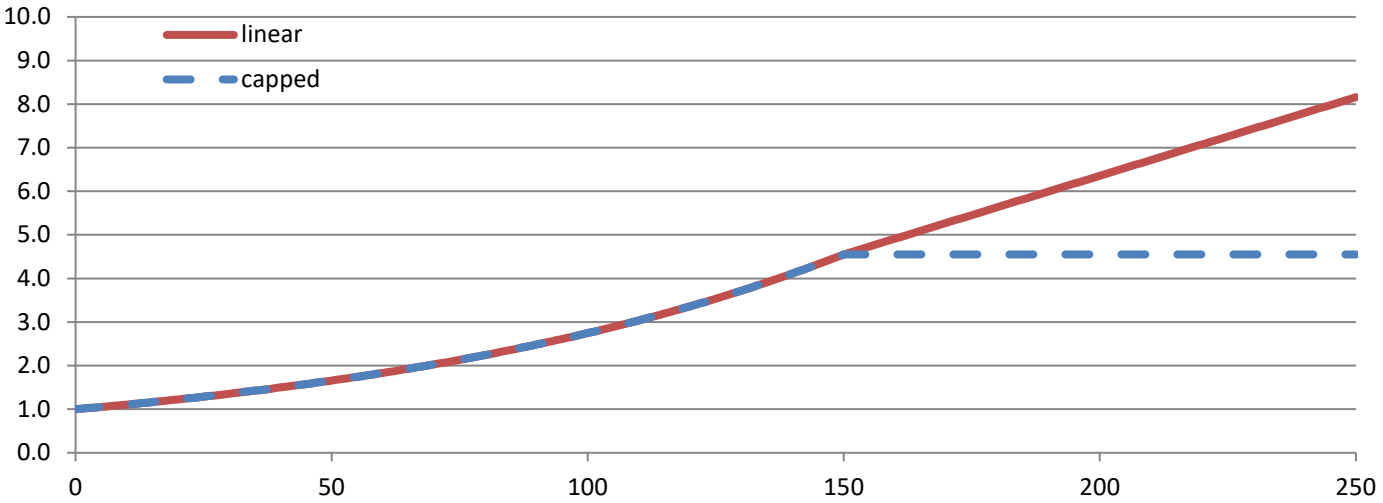
Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V.,Scotti, L.,Jenab, M., Turati, F.,Pasquali, E., Pelucchi, C., Galeone, C., Belloco, R., Negri, E., Corrao, G., Boffeta, P.& La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British journal of cancer*, 112(3), 580.

Marron, M., Boffetta, P., Zhang, Z. F., Zaridze, D., Wünsch-Filho, V., Winn, D. M., ... & Smith, E. (2009). Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *International journal of epidemiology*, *39*(1), 182-196.

(2).(7) Breast cancer, women

Condition category: **(2) Cancer**
ICD10 codes: **C50, D05**

	Current drinkers	Former drinkers
Source	Bagnardi et al. (2015) Table 3	Schütze et al. (2011) Table 2
Relative risk Function or estimate	$\ln RR(x) = 0.0101018x$ $RR(x)=\exp(0.0101018x)$	RR_{FD} = 1.03
Comments	Functional equation for continuous curve depicted in Figure 3 obtained through personal correspondence between AS and V. Bagnardi, dated 25-July-2017. Bagnardi et al. tested for differential dose-response relationship by gender and found none.	Based on the prospective cohort EPIC study (European Prospective Investigation into Cancer and Nutrition). Data analyzed from eight western European countries; context therefore not as broad as a large meta-analysis.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. The meta-analysis does not explicitly control for abstainer bias in the meta-regression.	Yes. EPIC asks respondents their alcohol use at ages 20,30,40,50 and recruitment. Accurate measure of lifetime abstention.



Sources

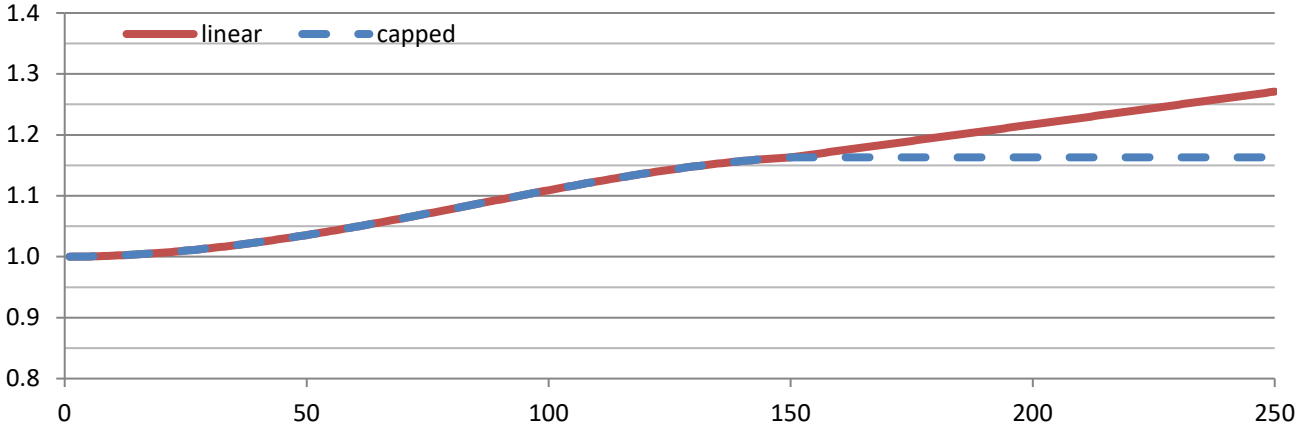
Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V.,Scotti, L.,Jenab, M., Turati, F.,Pasquali, E., Pelucchi, C., Galeone, C., Belloco, R., Negri, E., Corrao, G., Boffeta, P.& La Vecchia, C. (2015). Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *British journal of cancer*, 112(3), 580.

Schütze, M., Boeing, H., Pischon, T., Rehm, J., Kehoe, T., Gmel, G., ... & Clavel-Chapelon, F. (2011). Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study. *Bmj*, *342*, d1584.

(3).(1) Type 2 diabetes mellitus, men

Condition category: **(3) Endocrine conditions**
ICD10 codes: **E11,E13, E14**

	Current drinkers	Former drinkers
Source	Knott et al. (2015) Figure 3	Reported in Rehm et al. (2010), Table 4; calculated as part of Baliunas et al. (2009) but not presented
Relative risk Function or estimate	$\ln RR(x) = 0.00001763703x^2 - 0.0000000728256x^3$ $RR(x)=\exp(0.00001763703x^2 - 0.0000000728256x^3)$	RR_{FD} = 1.18
Comments	Functional equation for continuous curve depicted in Figure 3 obtained through personal correspondence between AS and C. Knott, dated 31-July-2017.	Relative risks for former drinkers were calculated as a component of Baliunas et al. (2009); however, they were not reported in that article. They were later reported in Rehm et al. (2010), an article produced by many of the same authors.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. An analysis restricted to strictly-defined lifetime abstainers was completed by Knott et al. and presented in Suppl.Fig.S1. It was decided not to use these results due to the small number of included studies.	Yes. Baliunas et al. reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.



Sources

Knott, C., Bell, S., & Britton, A. (2015). Alcohol consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies. *Diabetes care*, *38*(9), 1804-1812.

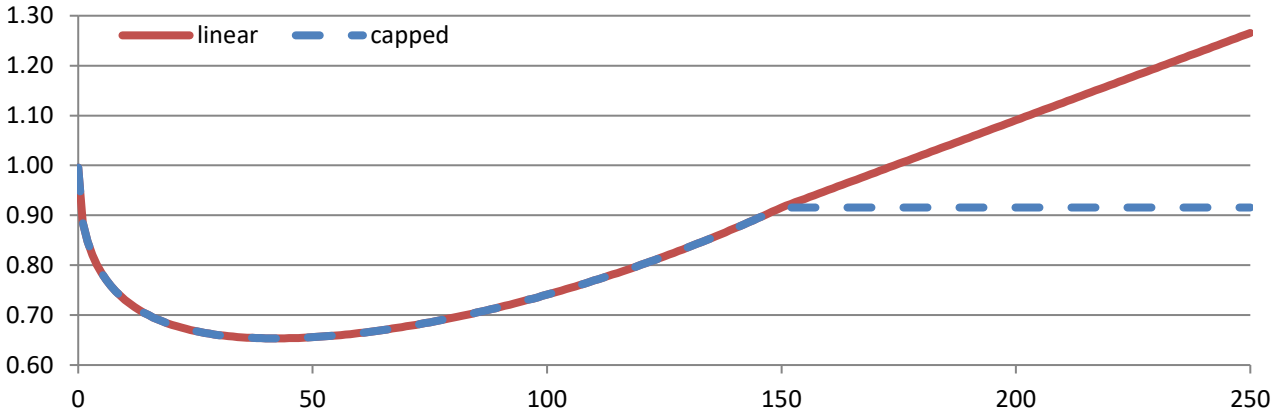
Rehm, J., Baliunas, D., Borges, G. L., Graham, K., Irving, H., Kehoe, T., ... & Roerecke, M. (2010). The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction*, *105*(5), 817-843.

Baliunas, D. O., Taylor, B. J., Irving, H., Roerecke, M., Patra, J., Mohapatra, S., & Rehm, J. (2009). Alcohol as a risk factor for type 2 diabetes. *Diabetes care*, *32*(11), 2123-2132.

(3).(1) Type 2 diabetes mellitus, women

Condition category: **(3) Endocrine conditions**
ICD10 codes: **E11,E13, E14**

	Current drinkers	Former drinkers
Source	Knott et al. (2015) Figure 3	Reported in Rehm et al. (2010), Table 4; calculated as part of Baliunas et al. (2009) but not presented.
Relative risk Function or estimate	$\ln RR(x) = -0.1313991\sqrt{x} + 0.01014239x$ $RR(x)=\exp(-0.1313991\sqrt{x} + 0.01014239x)$	RR_{FD} = 1.14
Comments	Functional equation for continuous curve depicted in Figure 3 obtained through personal correspondence between AS and C. Knott, dated 31-July-2017.	Relative risks for former drinkers were calculated as a component of Baliunas et al. (2009); however, they were not reported in that article. They were later reported in Rehm et al. (2010), an article produced by many of the same authors.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. An analysis restricted to strictly-defined lifetime abstainers was completed by Knott et al. and presented in Suppl.Fig.S1. It was decided not to use these results due to the small number of included studies.	Yes. Baliunas et al. reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.



Sources

Knott, C., Bell, S., & Britton, A. (2015). Alcohol consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies. *Diabetes care*, *38*(9), 1804-1812.

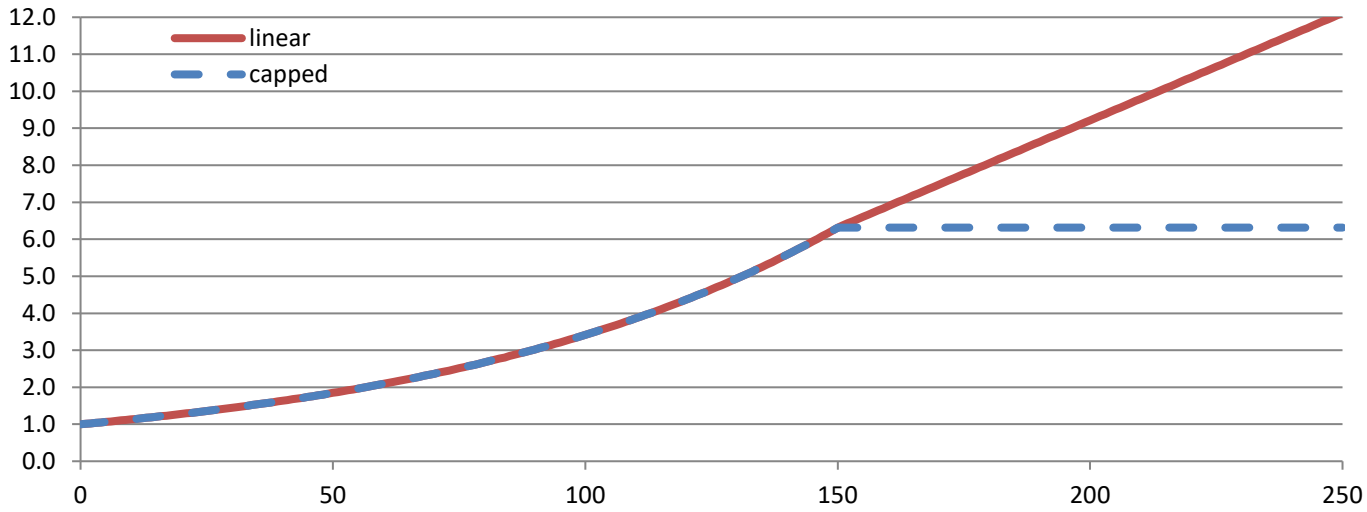
Rehm, J., Baliunas, D., Borges, G. L., Graham, K., Irving, H., Kehoe, T., ... & Roerecke, M. (2010). The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction*, *105*(5), 817-843.

Baliunas, D. O., Taylor, B. J., Irving, H., Roerecke, M., Patra, J., Mohapatra, S., & Rehm, J. (2009). Alcohol as a risk factor for type 2 diabetes. *Diabetes care*, *32*(11), 2123-2132.

(4).(5) Epilepsy

Condition category:	**(4) Neuropsychiatric conditions**
ICD10 code(s):	**G40,G41**

	Current drinkers	Former drinkers
Source	Samokhvalov et al. (2010) Figure 3	Leone et al. (1997) Rehm et al. (2017)
Relative risk Function or estimate	$\ln RR(x) = 0.0122861x$ $RR(x)=\exp(0.0122861x)$	RR_{FD}=1.00
Comments	Relative risk function received directly from members of authorship group who are members of this project.	There is no evidence that former drinking is correlated to the risk of an epileptic seizure: see interpretation in Rehm et al. (2017) of Leone et al. (1997)
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. It does not appear that the meta-analysis specifically quantified whether constituent studies were affected by abstainer biases.	



Sources

Samokhvalov, A. V., Irving, H., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption, unprovoked seizures, and epilepsy: A systematic review and meta-analysis. *Epilepsia*, *51*(7), 1177-1184.

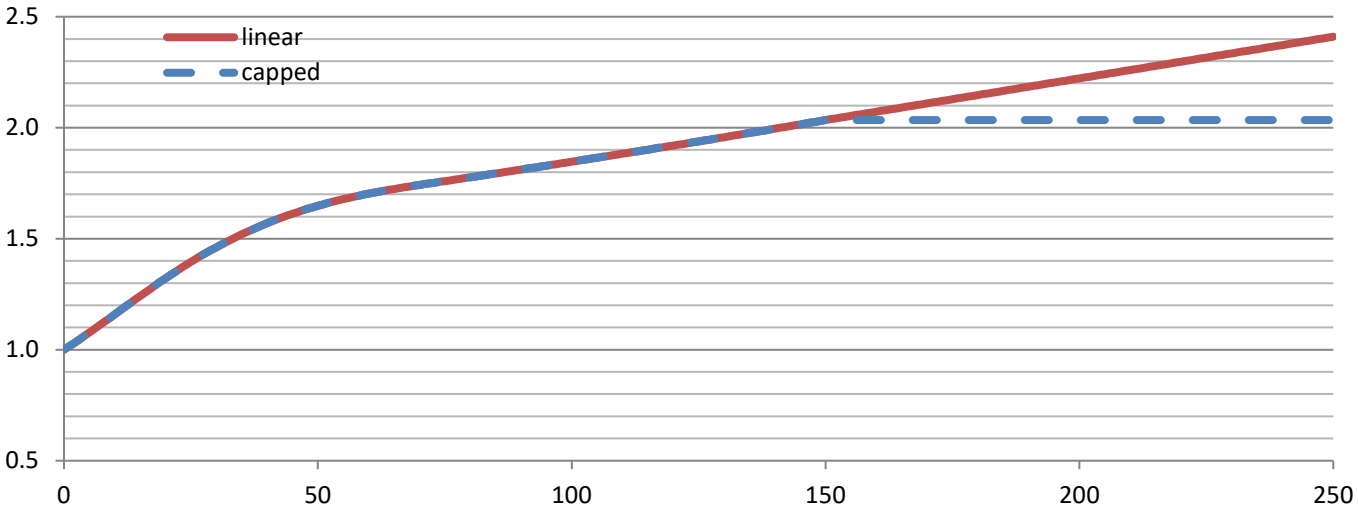
Rehm, J., Sherk, A., Shield, K.D., & Gmel, G. (2017). Risk relations between alcohol use and non-injury causes of death. Version 2: September 2017. Toronto, Canada: Centre for Addiction and Mental Health. ISBN: 978-1-77114-399-8.

Leone, M., Bottacchi, E., Beghi, E., Morgando, E., Mutani, R., Amedeo, G., ... & Ceroni, L. R. (1997). Alcohol use is a risk factor for a first generalized tonic-clonic seizure. *Neurology*, *48*(3), 614-620.

(5).(1) Hypertension, men

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I10 to I15**

	Current drinkers	Former drinkers
Source	Roerecke et al. (in press) Also reported in Rehm et al. (2017)	Roerecke et al. (in press) Rehm et al. (2017)
Relative risk Function or estimate	$\ln RR(x) = \begin{cases} 0.0150537x - \frac{0.0156155x^3}{75^2}, 0 < x < 21 \\ 0.0150537x - 0.0156155\frac{x^3 - \frac{75(x-21)^3}{(75-21)}}{75^2}, 21 \le x < 75 \\ 0.0150537x - 0.0156155\frac{x^3 - \frac{75(x-21)^3 - 21(x-75)^3}{(75-21)}}{75^2}, x \ge 75 \end{cases}$	RR_{FD} = 1.03
Comments	Relative risk function received directly from members of authorship group who are members of this project. Article in press at the time of InterMAHP publication.	Article in press at the time of InterMAHP publication.
Control for abstainer bias	Unknown. Article not yet published.	Unknown. Article not yet published.



Sources

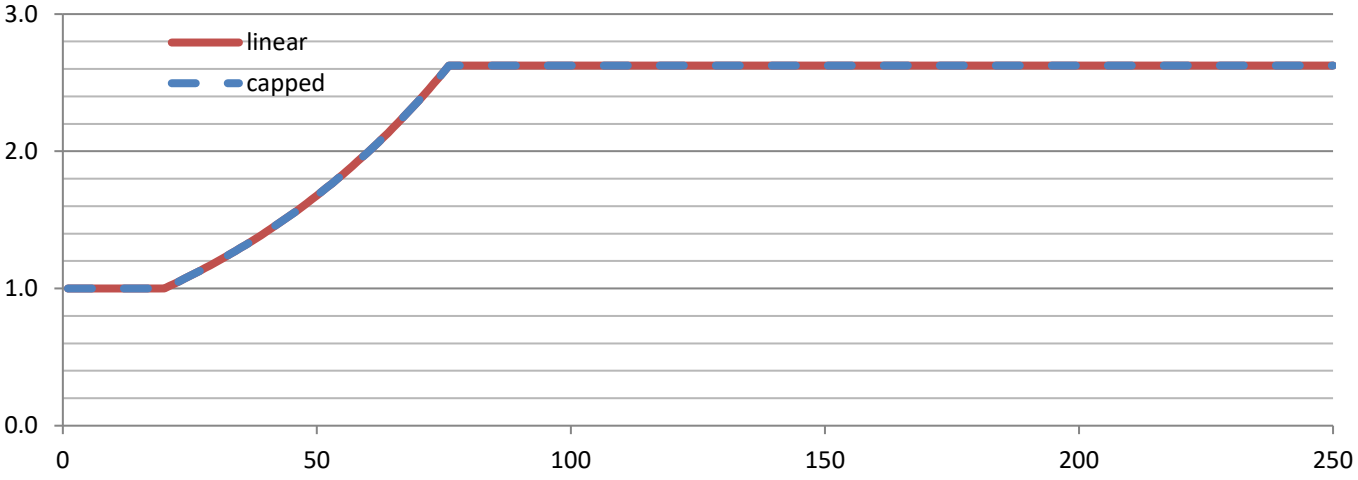
Roerecke, M., Tobe, S., Kaczorowski, J., Bacon, SL, Vafaei, A., Hasan, OSM, Krishnan, RJ, Raifu, AO, Rehm, J. (in press). The relationship between alcohol consumption and sex-specific incidence of hypertension: a systematic review and meta-analysis of cohort studies. Centre for Addiction and Mental Health. Toronto, Canada: CAMH.

Rehm, J., Sherk, A., Shield, K.D., & Gmel, G. (2017). Risk relations between alcohol use and non-injury causes of death. Version 2: September 2017. Toronto, Canada: Centre for Addiction and Mental Health. ISBN: 978-1-77114-399-8.

(5).(1) Hypertension, women

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I10 to I15**

	Current drinkers	Former drinkers
Source	Roerecke et al. (in press) Also reported in Rehm et al. (2017)	Roerecke et al. (in press)
Relative risk Function or estimate	$\ln RR(x) = \begin{cases} 0, 0 < x < 18.9517 \\ -0.0154196x + 0.0217586\,x^3 - \frac{20(x-10)^3 - 10(x-20)^3}{(20-10)}{20^2}, 18.9517 \le x < 75 \\ 0.9649937, x \ge 75 \end{cases}$	RR_{FD} = 1.05
Comments	Relative risk function received directly from members of authorship group who are members of this project. Article in press at the time of InterMAHP publication.	Article in press at the time of InterMAHP publication.
Control for abstainer bias	Unknown. Article not yet published.	Unknown. Article not yet published.



Sources

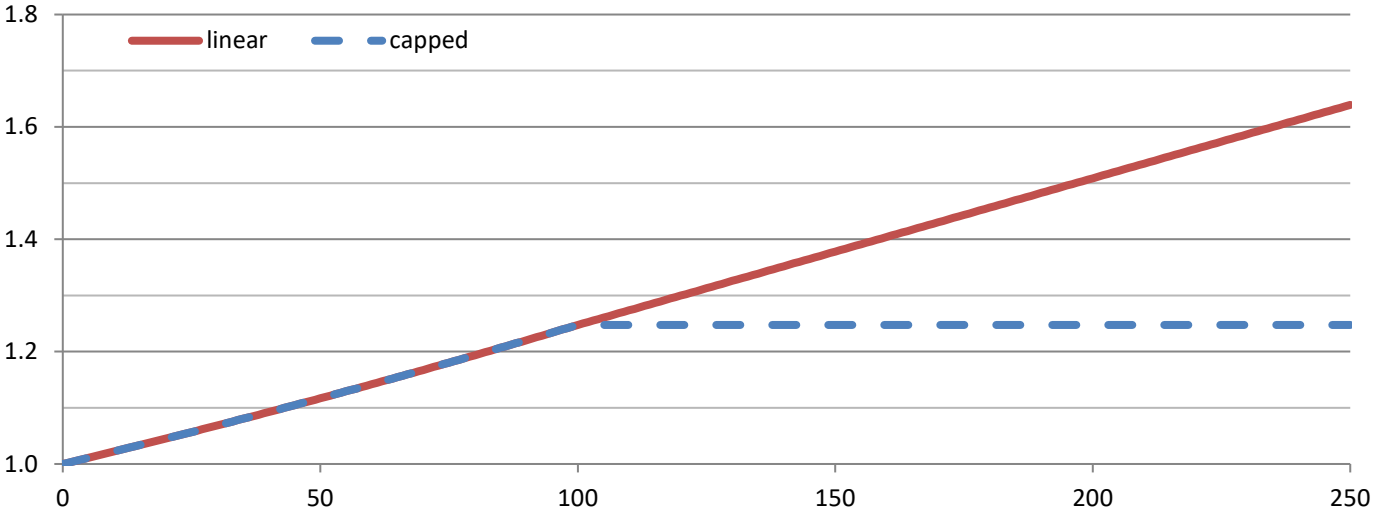
Roerecke, M., Tobe, S., Kaczorowski, J., Bacon, SL, Vafaei, A., Hasan, OSM, Krishnan, RJ, Raifu, AO, Rehm, J. (in press). The relationship between alcohol consumption and sex-specific incidence of hypertension: a systematic review and meta-analysis of cohort studies. Centre for Addiction and Mental Health. Toronto, Canada: CAMH.

Rehm, J., Sherk, A., Shield, K.D., & Gmel, G. (2017). Risk relations between alcohol use and non-injury causes of death. Version 2: September 2017. Toronto, Canada: Centre for Addiction and Mental Health. ISBN: 978-1-77114-399-8.

(5).(2) Ischaemic heart disease mortality, men (two options)

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I20 to I25**

	Current drinkers	Former drinkers
Source	Zhao et al. (2017) Table 3, top panel, fully-adjusted results, custom analysis (see comments)	Roerecke & Rehm (2010b) Table 3
Relative risk Function or estimate	$\ln RR(x) = 0.002211x$ $RR(x)=\exp(0.002211x)$	RR_{FD} = 1.25
Comments	Fully-adjusted model for the younger age cohort in Table 3 was re-analyzed by the first author upon request to include a gender breakdown and to provide a continuous relationship. Results received through personal correspondence between AS, TS and J. Zhao (dated 14-Oct-17).	Results stratified by gender and endpoint (outcome) used.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study explicitly controlled for abstainer biases selecting studies with no bias and selecting younger cohorts, among other methods. See article for full methodology.	Yes, considered. The reference group was operationalized as "long-term abstainers or very light drinkers."



Sources

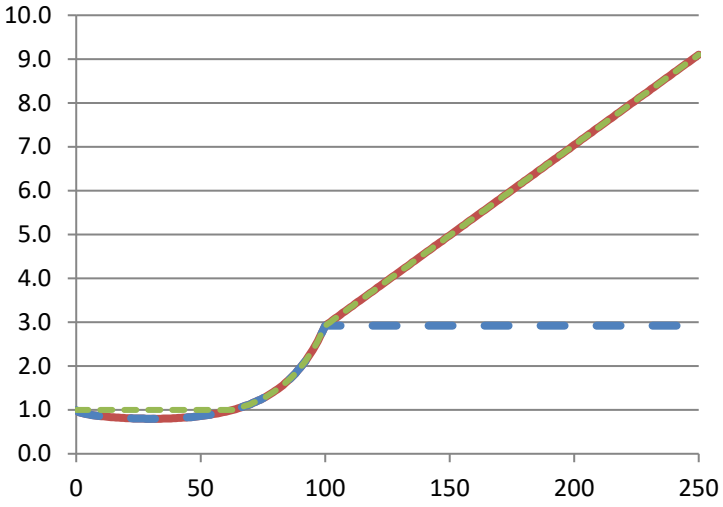
Zhao, J., Stockwell, T., Roemer, A., Naimi, T., Chikritzhs, T. (2017). Alcohol consumption and mortality from coronary heart disease: An updated meta-analysis of cohort studies. *Journal of Studies on Alcohol and Drugs, 78,* 375-386.

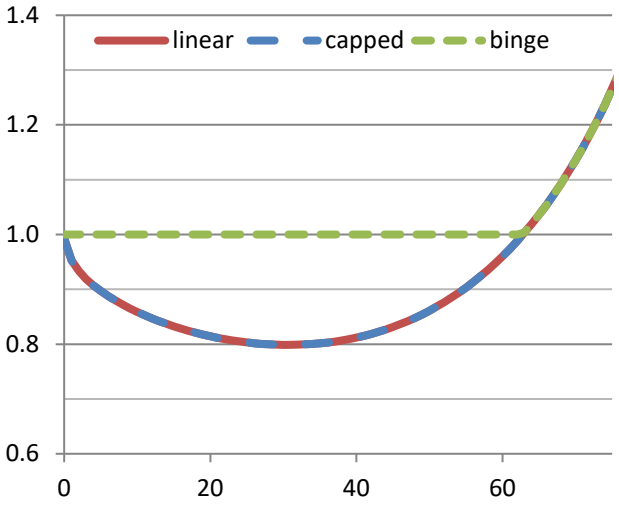
Roerecke, M., & Rehm, J. (2010b). Ischemic heart disease mortality and morbidity rates in former drinkers: a meta-analysis. *American journal of epidemiology, 173*(3), 245-258.

(5).(2) Ischaemic heart disease mortality, men (two options)

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I20 to I25**

	Current drinkers	Former drinkers
Source	Roerecke & Rehm (2012) Figure 2 Roerecke & Rehm (2010a) From text, e.g. in abstract	Roerecke & Rehm (2010b) Table 3
Relative risk Function or estimate	$\ln RR(x) = -0.04870068\sqrt{x} + 0.000001559x^3$ $RR(x)=\exp(-0.04870068\sqrt{x} + 0.000001559x^3)$	RR_{FD} = 1.25
Comments	Relative risk function received directly from members of authorship group who are members of this project. Roerecke & Rehm (2010a) modifies the RR curve for bingers by removing the protective effect (i.e. RR=1.0).	Results stratified by gender and endpoint(outcome) used. Note: In the figure below, the binge level is set at 60g/day; therefore RR=1.0 above this as this portion of the population is guaranteed to binge.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	Yes, considered. The reference group was operationalized as "long-term abstainers or very light drinkers."





Sources

Roerecke, M., & Rehm, J. (2012). The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. *Addiction*, *107*(7), 1246-1260.

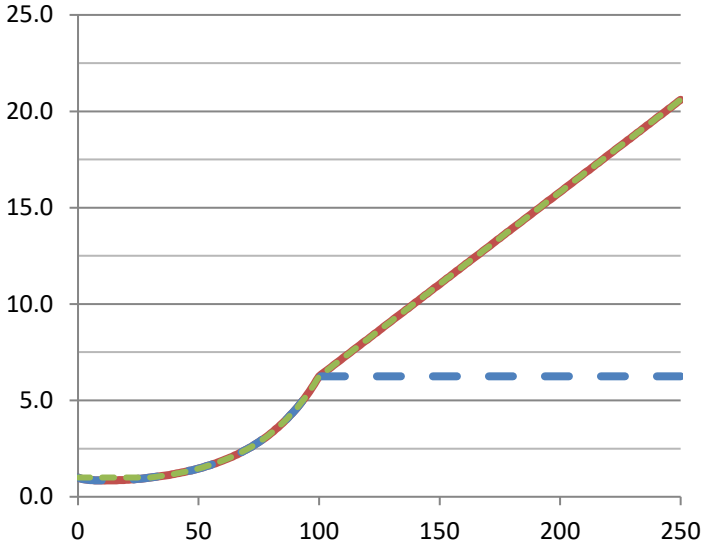
Roerecke, M., & Rehm, J. (2010a). Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. *American journal of epidemiology*, *171*(6), 633-644.

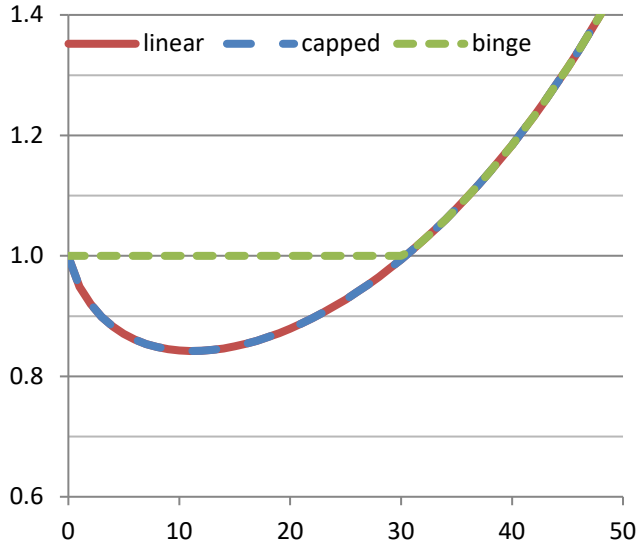
Roerecke, M., & Rehm, J. (2010b). Ischemic heart disease mortality and morbidity rates in former drinkers: a meta-analysis. *American journal of epidemiology*, *173*(3), 245-258.

(5).(2) Ischaemic heart disease mortality, women

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I20 to I25**

	Current drinkers	Former drinkers
Source	Roerecke & Rehm (2012) Figure 2 Roerecke & Rehm (2010a) From text, e.g. in abstract	Roerecke & Rehm (2010b) Table 3
Relative risk Function or estimate	$\ln RR(x) = -0.0525288x + 0.0153856x \ln x$ $RR(x)=\exp(-0.0525288x + 0.0153856x \ln x)$	$RR_{FD} = 1.54$
Comments	Relative risk function received directly from members of authorship group who are members of this project. Roerecke & Rehm (2010a) modifies the RR curve for bingers by removing the protective effect (i.e. RR=1.0).	Results stratified by gender and endpoint (outcome) used. **Current**: In the figure below, the binge level is set at 60g/day; therefore RR=1.0 above this as this portion of the population is guaranteed to binge.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	Yes, considered. The reference group was operationalized as "long-term abstainers or very light drinkers."





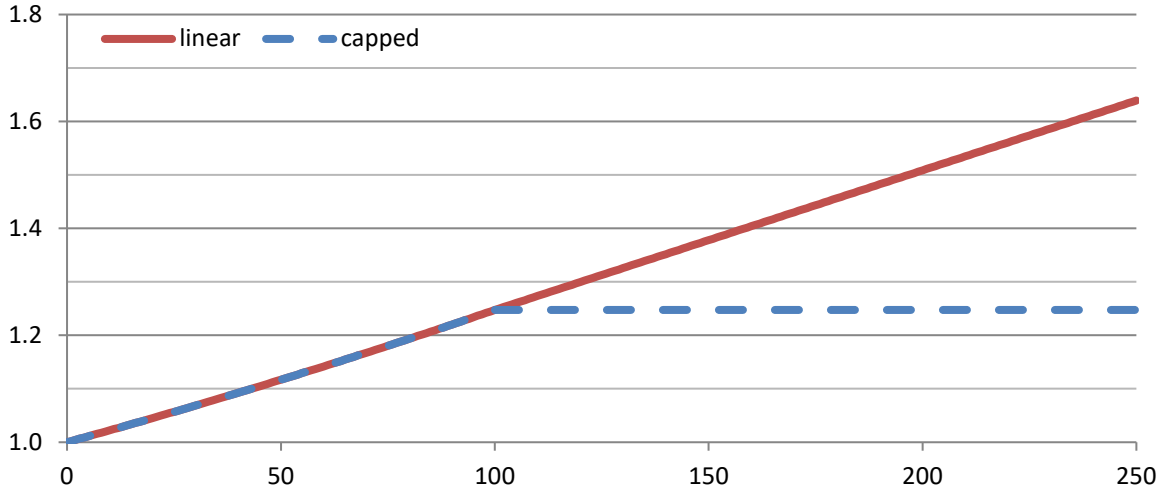
Sources

Roerecke, M., & Rehm, J. (2012). The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. *Addiction*, *107*(7), 1246-1260.
Roerecke, M., & Rehm, J. (2010a). Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. *American journal of epidemiology*, *171*(6), 633-644.
Roerecke, M., & Rehm, J. (2010b). Ischemic heart disease mortality and morbidity rates in former drinkers: a meta-analysis. *American journal of epidemiology*, *173*(3), 245-258.

(5).(2) Ischaemic heart disease morbidity, men (two options)

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I20 to I25**

	Current drinkers	Former drinkers
Source	Zhao et al. (2017) Table 3, top panel, fully-adjusted results, custom analysis (see comments)	Roerecke & Rehm (2010b) Table 3
Relative risk Function or estimate	$\ln RR(x) = 0.002211x$ $RR(x)=\exp(0.002211x)$	RR_{FD} = 1.25
Comments	Fully-adjusted model for the younger age cohort in Table 3 was re-analyzed by the first author upon request to include a gender breakdown and to provide a continuous relationship. Results received through personal correspondence between AS, TS and J. Zhao (dated 14-Oct-17).	Results stratified by gender and endpoint (outcome) used. Note: in this option, the RR function from IHD mortality in men, calculated by J. Zhao from the article below, is used as the RR function for IHD morbidity in men.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study explicitly controlled for abstainer biases selecting studies with no bias and selecting younger cohorts, among other methods. See article for full methodology.	Yes, considered. The reference group was operationalized as "long-term abstainers or very light drinkers."



Sources

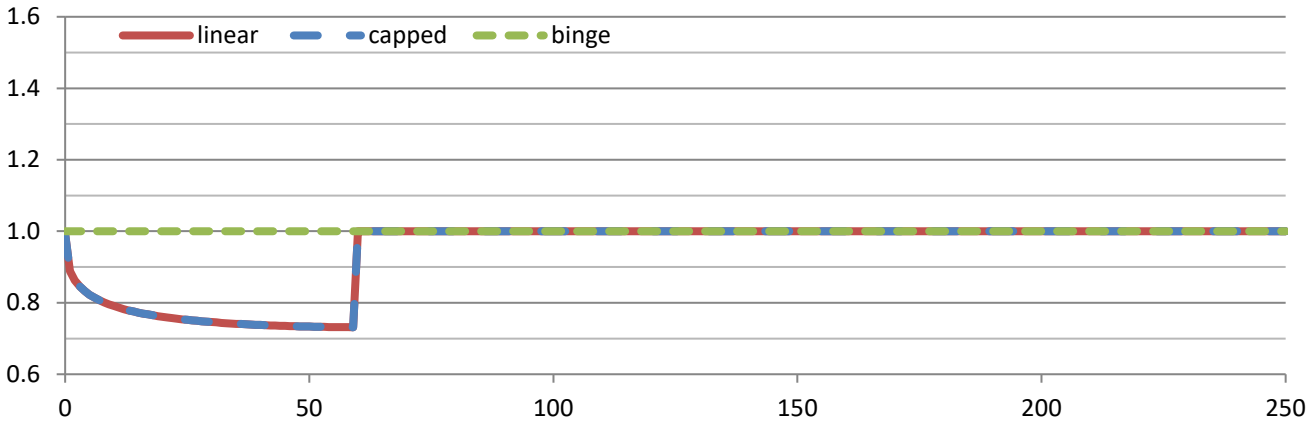
Zhao, J., Stockwell, T., Roemer, A., Naimi, T., Chikritzhs, T. (2017). Alcohol consumption and mortality from coronary heart disease: An updated meta-analysis of cohort studies. *Journal of Studies on Alcohol and Drugs, 78,* 375-386.

Roerecke, M., & Rehm, J. (2010b). Ischemic heart disease mortality and morbidity rates in former drinkers: a meta-analysis. *American journal of epidemiology, 173*(3), 245-258.

(5).(2) Ischaemic heart disease morbidity, men (two options)

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I20 to I25**

	Current drinkers	Former drinkers
Source	Roerecke & Rehm (2012) Figure 2 Roerecke & Rehm (2010a) From text, e.g. in abstract	Roerecke & Rehm (2010b) Table 3
Relative risk Function or estimate	$\ln RR(x) = -0.1178113\sqrt{x} + 0.0189\sqrt{x}\ln x$ $RR(x)=\exp(-0.1178113\sqrt{x} + 0.0189\sqrt{x}\ln x)$	$RR_{FD} = 0.85$
Comments	Relative risk function received directly from members of authorship group who are members of this project. Roerecke & Rehm (2010a) modifies the RR curve for bingers by removing the protective effect (i.e. RR=1.0). In the figure below, the binge level is set at 60g/day; therefore RR=1.0 above this as this portion of the population is guaranteed to binge.	Results stratified by gender and endpoint(outcome) used. Note: linear and capped curves are identical.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	Yes, considered. The reference group was operationalized as "long-term abstainers or very light drinkers."



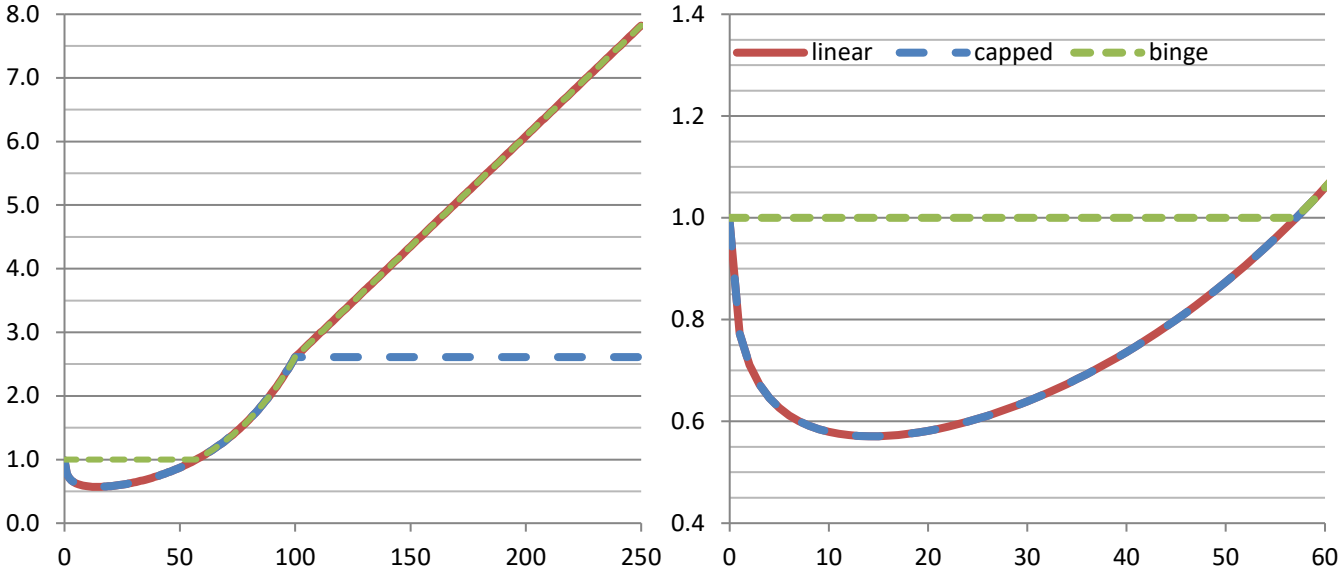
Sources

Roerecke, M., & Rehm, J. (2012). The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. *Addiction*, *107*(7), 1246-1260.
Roerecke, M., & Rehm, J. (2010a). Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. *American journal of epidemiology*, *171*(6), 633-644.
Roerecke, M., & Rehm, J. (2010b). Ischemic heart disease mortality and morbidity rates in former drinkers: a meta-analysis. *American journal of epidemiology*, *173*(3), 245-258.

(5).(2) Ischaemic heart disease morbidity, women

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I20 to I25**

	Current drinkers	Former drinkers
Source	Roerecke & Rehm (2012) Figure 2 Roerecke & Rehm (2010a) From text, e.g. in abstract	Roerecke & Rehm (2010b) Table 3
Relative risk Function or estimate	$\ln RR(x) = -0.296842\sqrt{x} + 0.0392805x$ $RR(x)=\exp(-0.296842\sqrt{x} + 0.0392805x)$	$RR_{FD} = 1.05$
Comments	Relative risk function received directly from members of authorship group who are members of this project. Roerecke & Rehm (2010a) modifies the RR curve for bingers by removing the protective effect (i.e. RR=1.0).	Results stratified by gender and endpoint used. **Current**: In the figure below, the binge level is set at 60g/day; therefore RR=1.0 above this as this portion of the population is guaranteed to binge.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	Yes, considered. The reference group was operationalized as "long-term abstainers or very light drinkers."



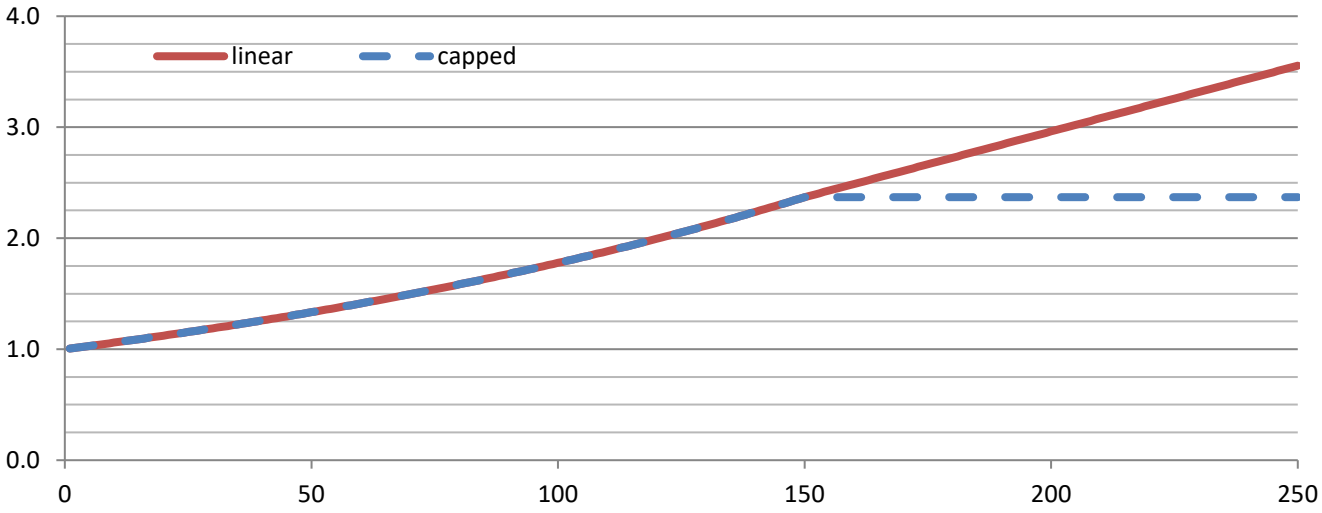
Sources

Roerecke, M., & Rehm, J. (2012). The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. *Addiction*, *107*(7), 1246-1260.
Roerecke, M., & Rehm, J. (2010a). Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. *American journal of epidemiology*, *171*(6), 633-644.
Roerecke, M., & Rehm, J. (2010b). Ischemic heart disease mortality and morbidity rates in former drinkers: a meta-analysis. *American journal of epidemiology*, *173*(3), 245-258.

(5).(4) Atrial fibrillation and cardiac arrhythmia

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I47 to I49**

	Current drinkers	Former drinkers
Source	Samokhvalov et al. (2010) Figure 3	Larsson et al. (2014) Table 1, right column of results Also reported in Rehm et al. (2017)
Relative risk Function or estimate	$\ln RR(x) = 0.00575183x$ $RR(x)=\exp(0.00575183x)$	RR_{FD}=1.01
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	No. The methods of this article do not describe a methodology for controlling for potential abstainer bias in the constituent studies.	No. The methods of this article do not describe a methodology for controlling for potential abstainer bias in the constituent studies.



Sources

Samokhvalov, A. V., Irving, H. M., & Rehm, J. (2010). Alcohol consumption as a risk factor for atrial fibrillation: a systematic review and meta-analysis. *European Journal of Cardiovascular Prevention & Rehabilitation*, *17*(6), 706-712.

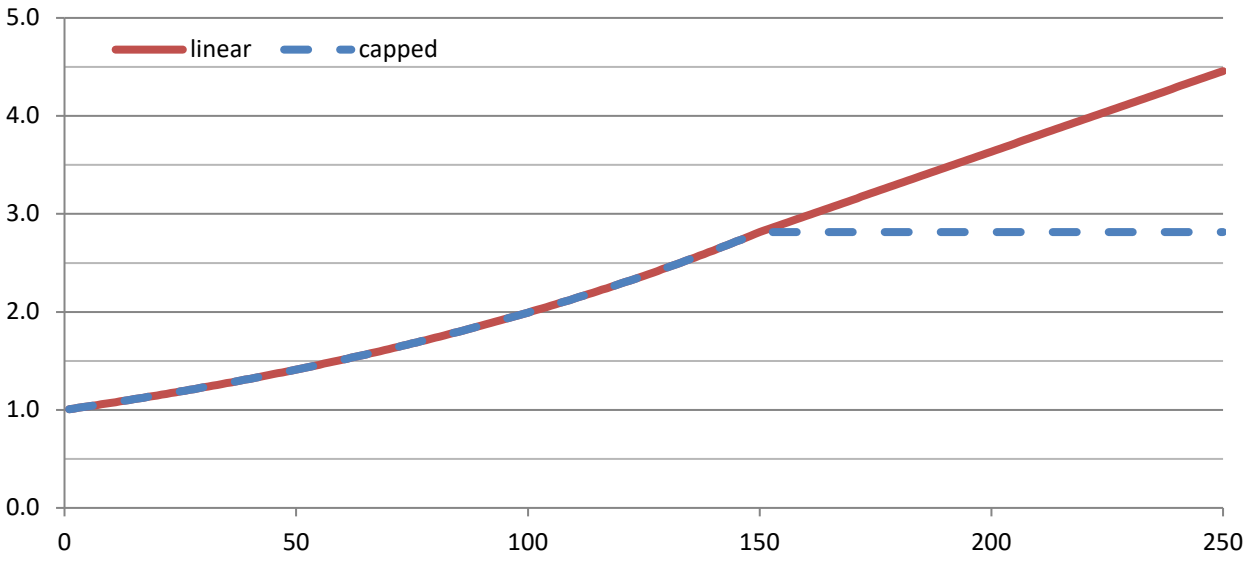
Larsson, S. C., Drca, N., & Wolk, A. (2014). Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *Journal of the American College of Cardiology*, *64*(3), 281-289.

Rehm, J., Sherk, A., Shield, K.D., & Gmel, G. (2017). Risk relations between alcohol use and non-injury causes of death. Version 2: September 2017. Toronto, Canada: Centre for Addiction and Mental Health. ISBN: 978-1-77114-399-8.

(5).(5) Haemorrhagic stroke mortality, men

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I60 to I62, I69.0 to I69.2**

	Current drinkers	Former drinkers
Source	Patra et al. (2010) Figure 6	Larsson et al. (2016) Supplementary Table S2, pooled analysis
Relative risk Function or estimate	$\ln RR(x) = 0.006898937x$ $RR(x)=\exp(0.006898937x)$	RR_{FD} = 1.36
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	No. This study does not explicitly account for abstainer bias.



Sources

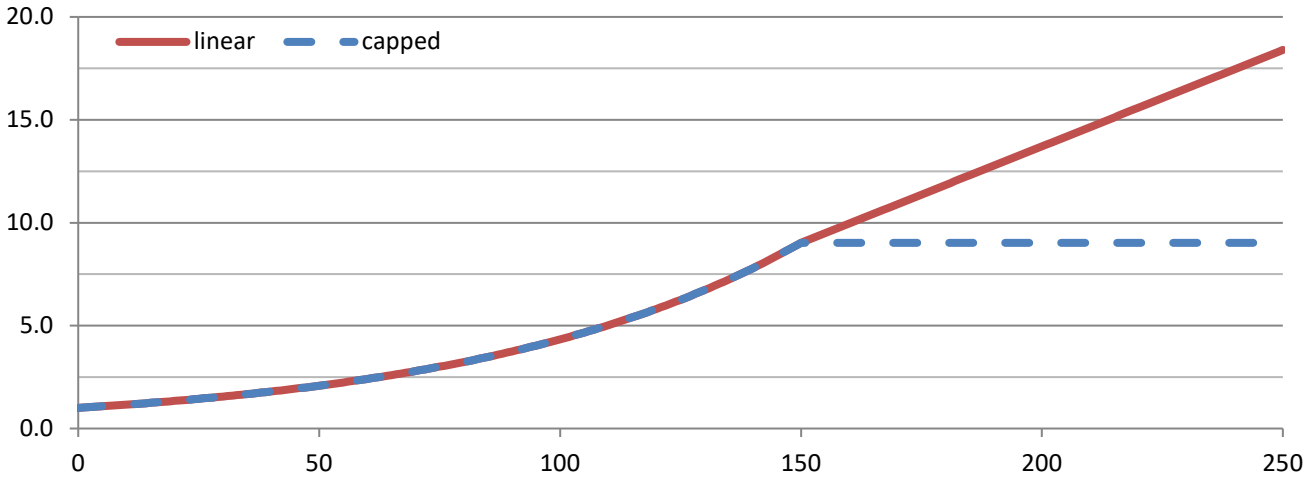
Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC public health*, *10*(1), 258.

Larsson, S. C., Wallin, A., Wolk, A., & Markus, H. S. (2016). Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC medicine*, *14*(1), 178.

(5).(5) Haemorrhagic stroke mortality, women

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I60 to I62, I69.0 to I69.2**

	Current drinkers	Former drinkers
Source	Patra et al. (2010) Figure 6	Larsson et al. (2016) Supplementary Table S2, pooled analysis
Relative risk Function or estimate	$\ln RR(x) = 0.01466406x$ $RR(x)=\exp(0.01466406x)$	RR_{FD} = 1.36
Comments	Relative risk function received directly from members of authorship group who are members of this project.	**Note**: the functional form of this curve is misreported in Patra et al. (2010) as $\beta_1 \ln x + \beta_2 x$. The correct functional form used here was received by KDS from first author on 29-Aug-17.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	No. This study does not explicitly account for abstainer bias.



Sources

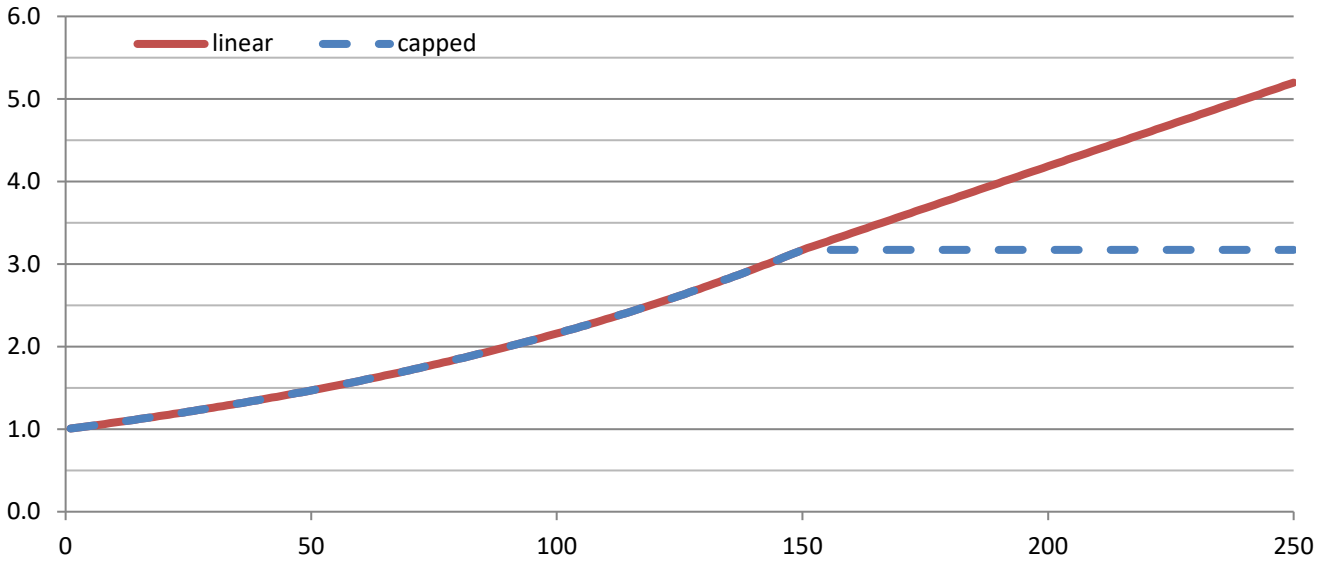
Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC public health*, *10*(1), 258.

Larsson, S. C., Wallin, A., Wolk, A., & Markus, H. S. (2016). Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC medicine*, *14*(1), 178.

(5).(5) Haemorrhagic stroke morbidity, men

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I60 to I62, I69.0 to I69.2**

	Current drinkers	Former drinkers
Source	Patra et al. (2010) Figure 6	Larsson et al. (2016) Supplementary Table S2, pooled analysis
Relative risk Function or estimate	$\ln RR(x) = 0.007695021x$ $RR(x)=\exp(0.007695021x)$	RR_{FD} = 1.36
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	No. This study does not explicitly account for abstainer bias.



Sources

Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC public health*, *10*(1), 258.

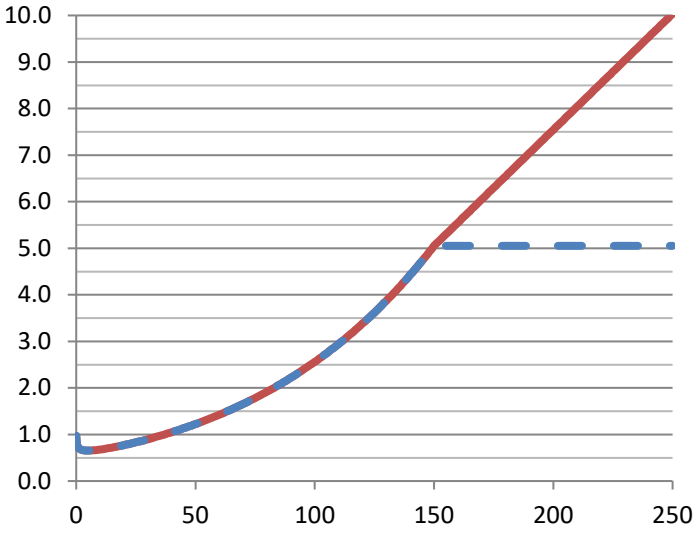
Larsson, S. C., Wallin, A., Wolk, A., & Markus, H. S. (2016). Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC medicine*, *14*(1), 178.

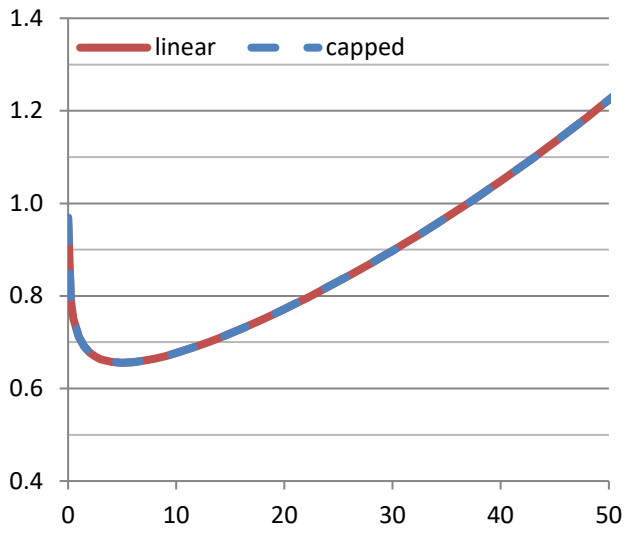
(5).(5) Haemorrhagic stroke morbidity, women

Condition category: **(5) Cardiovascular conditions**

ICD10 codes: **I60 to I62, I69.0 to I69.2**

	Current drinkers	Former drinkers
Source	Patra et al. (2010) Figure 6	Larsson et al. (2016) Supplementary Table S2, pooled analysis
Relative risk Function or estimate	$\ln RR(x) = -0.340861\sqrt{x} + 0.0944208\sqrt{x}\ln x$ $RR(x)=\exp(-0.340861\sqrt{x} + 0.0944208\sqrt{x}\ln x)$	RR_{FD} = 1.36
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	No. This study does not explicitly account for abstainer bias.





Sources

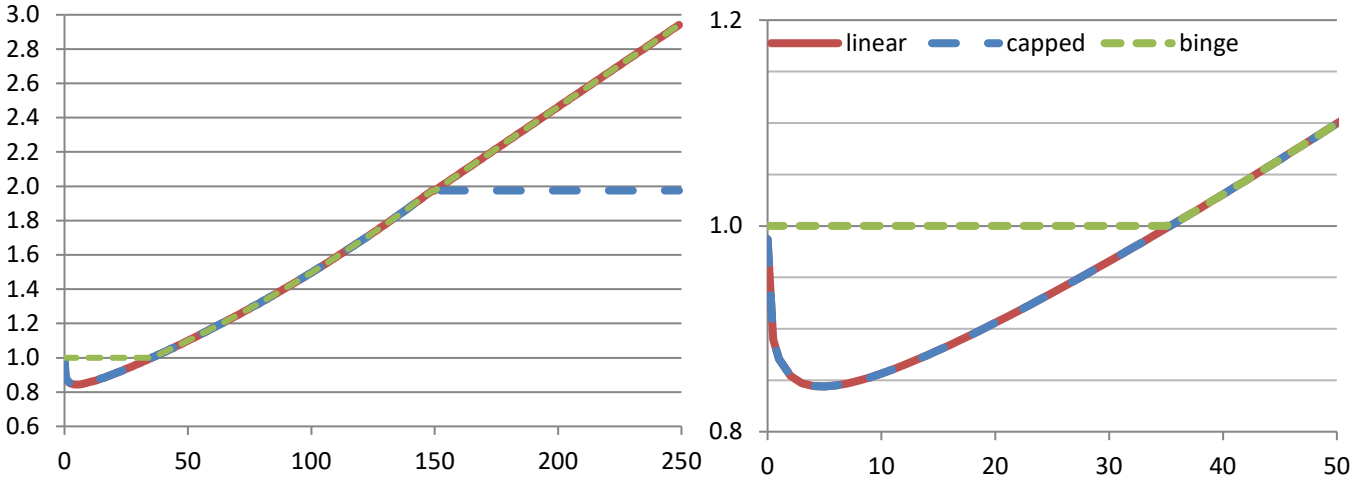
Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC public health*, *10*(1), 258.

Larsson, S. C., Wallin, A., Wolk, A., & Markus, H. S. (2016). Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC medicine*, *14*(1), 178.

(5).(6) Ischaemic stroke mortality, men

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I63 to I67, I69.3**

	Current drinkers	Former drinkers
Source	Patra et al. (2010) Figure 7 Rehm et al. (2016) From text, in methods	Larsson et al. (2016) Supplementary Table S2, pooled analysis
Relative risk Function or estimate	$\ln RR(x) = -0.1382664\sqrt{x} + 0.03877538\sqrt{x}\ln x$ $RR(x)=\exp(-0.1382664\sqrt{x} + 0.03877538\sqrt{x}\ln x)$	RR_{FD} = 0.97
Comments	Relative risk function received directly from members of authorship group who are members of this project. Rehm et al. (2016) modifies the RR curve for bingers by removing the protective effect (i.e. RR=1.0).	Note: In the figure below, the binge level is set at 60g/day; therefore RR=1.0 above this as this portion of the population is guaranteed to binge.
Control for abstainer bias Does the article control for abstainer bias?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	No. This study does not explicitly account for abstainer bias.

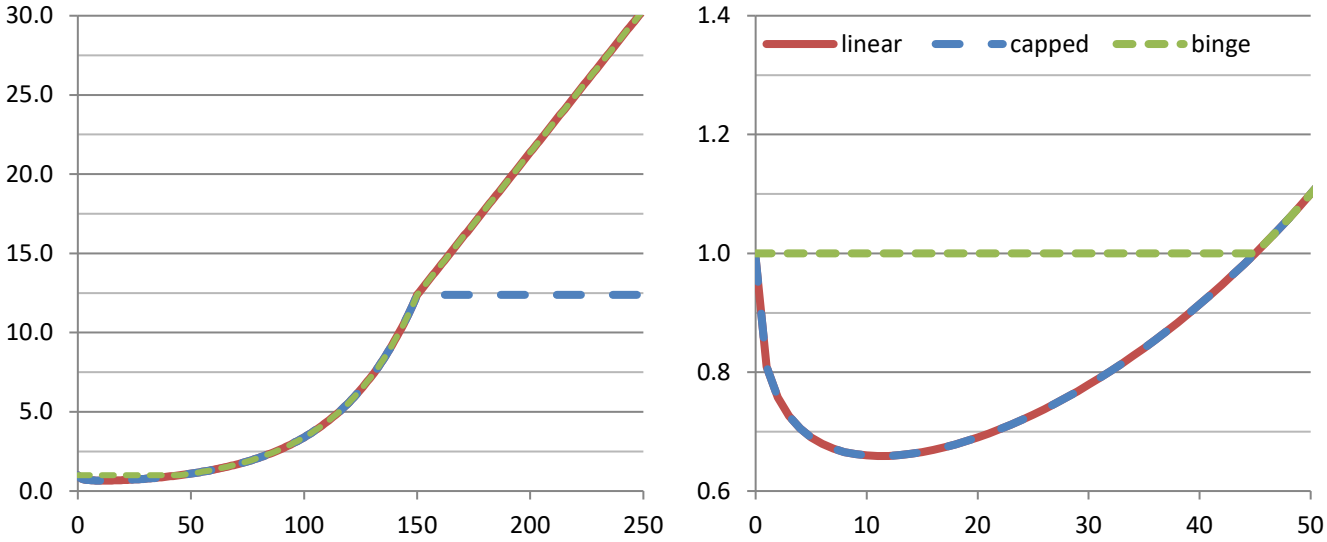


Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC public health*, *10*(1), 258.
Larsson, S. C., Wallin, A., Wolk, A., & Markus, H. S. (2016). Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC medicine*, *14*(1)
Rehm, J., Shield, K. D., Roerecke, M., & Gmel, G. (2016). Modelling the impact of alcohol consumption on cardiovascular disease mortality for comparative risk assessments: an overview. *BMC Public Health*, *16*(1), 363.

(5).(6) Ischaemic stroke mortality, women

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I63 to I67, I69.3**

	Current drinkers	Former drinkers
Source	Patra et al. (2010) Figure 7 Rehm et al. (2016) From text, in methods	Larsson et al. (2016) Supplementary Table S2, pooled analysis
Relative risk Function or estimate	$\ln RR(x) = -0.248768\sqrt{x} + 0.03708724x$ $RR(x)=\exp(-0.248768\sqrt{x} + 0.03708724x)$	$RR_{FD} = 0.97$
Comments	Relative risk function received directly from members of authorship group who are members of this project. Rehm et al. (2016) modifies the RR curve for bingers by removing the protective effect (i.e. RR=1.0).	Note: In the figure below, the binge level is set at 60g/day; therefore RR=1.0 above this as this portion of the population is guaranteed to binge.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	No. This study does not explicitly account for abstainer bias.

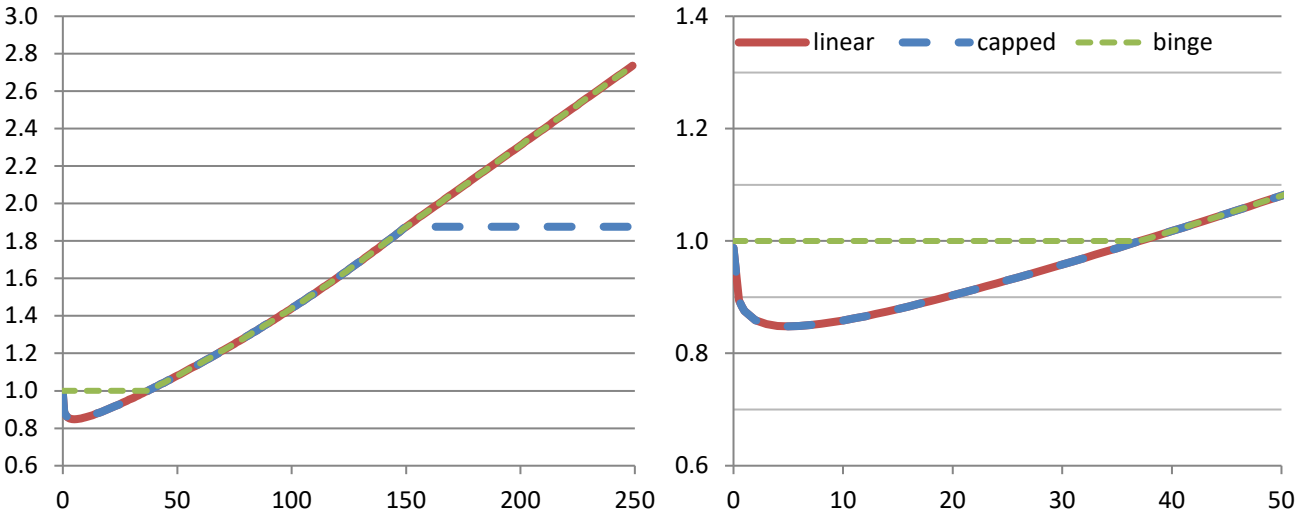


Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC public health*, *10*(1), 258.
Larsson, S. C., Wallin, A., Wolk, A., & Markus, H. S. (2016). Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC medicine*, *14*(1)
Rehm, J., Shield, K. D., Roerecke, M., & Gmel, G. (2016). Modelling the impact of alcohol consumption on cardiovascular disease mortality for comparative risk assessments: an overview. *BMC Public Health*, *16*(1), 363.

(5).(6) Ischaemic stroke morbidity, men

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I63 to I67, I69.2**

	Current drinkers	Former drinkers
Source	Patra et al. (2010) Figure 7 Rehm et al. (2016) From text, in methods	Larsson et al. (2016) Supplementary Table S2, pooled analysis
Relative risk Function or estimate	$\ln RR(x) = -0.132894\sqrt{x} + 0.03677422\sqrt{x}\ln x$ $RR(x)=\exp(-0.132894\sqrt{x} + 0.03677422\sqrt{x}\ln x)$	RR_{FD} = 0.97
Comments	RR function received directly from members of authorship group who are members of this project. Rehm et al. (2016) modifies the RR curve for bingers by removing the protective effect (i.e. RR=1.0).	Note: In the figure below, the binge level is set at 60g/day; therefore RR=1.0 above this as this portion of the population is guaranteed to binge.
Control for abstainer bias Does the article control for?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using standard methods.	No. This study does not explicitly account for abstainer bias.

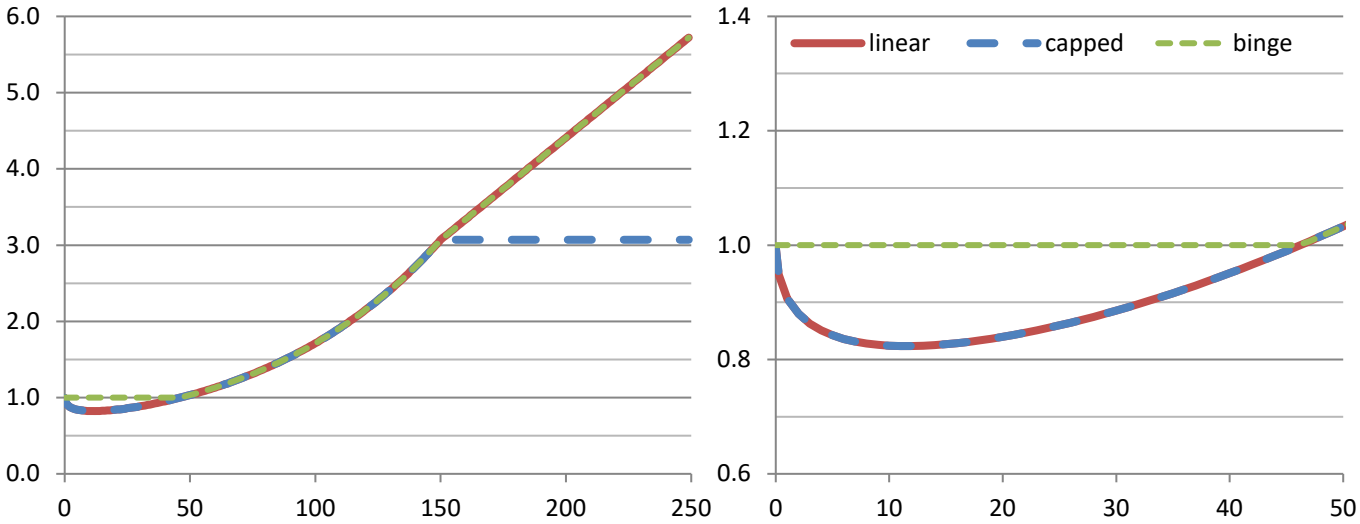


Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC public health*, *10*(1), 258.
Larsson, S. C., Wallin, A., Wolk, A., & Markus, H. S. (2016). Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC medicine*, *14*(1)
Rehm, J., Shield, K. D., Roerecke, M., & Gmel, G. (2016). Modelling the impact of alcohol consumption on cardiovascular disease mortality for comparative risk assessments: an overview. *BMC Public Health*, *16*(1), 363.

(5).(6) Ischaemic stroke morbidity, women

Condition category: **(5) Cardiovascular conditions**
ICD10 codes: **I63 to I67, I69.2**

	Current drinkers	Former drinkers
Source	Patra et al. (2010) Figure 7 Rehm et al. (2016) From text, in methods	Larsson et al. (2016) Supplementary Table S2, pooled analysis
Relative risk Function or estimate	$\ln RR(x) = -0.114287\sqrt{x} + 0.01680936x$ $RR(x)=\exp -0.114287\sqrt{x} + 0.01680936x$)	RR_{FD} = 0.97
Comments	Relative risk function received directly from members of authorship group who are members of this project. Rehm et al. (2016) modifies the RR curve for bingers by removing the protective effect (i.e. RR=1.0).	Note: In the figure below, the binge level is set at 60g/day; therefore RR=1.0 above this as this portion of the population is guaranteed to binge.
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. This study reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	No. This study does not explicitly account for abstainer bias.



Patra, J., Taylor, B., Irving, H., Roerecke, M., Baliunas, D., Mohapatra, S., & Rehm, J. (2010). Alcohol consumption and the risk of morbidity and mortality for different stroke types-a systematic review and meta-analysis. *BMC public health*, *10*(1), 258.

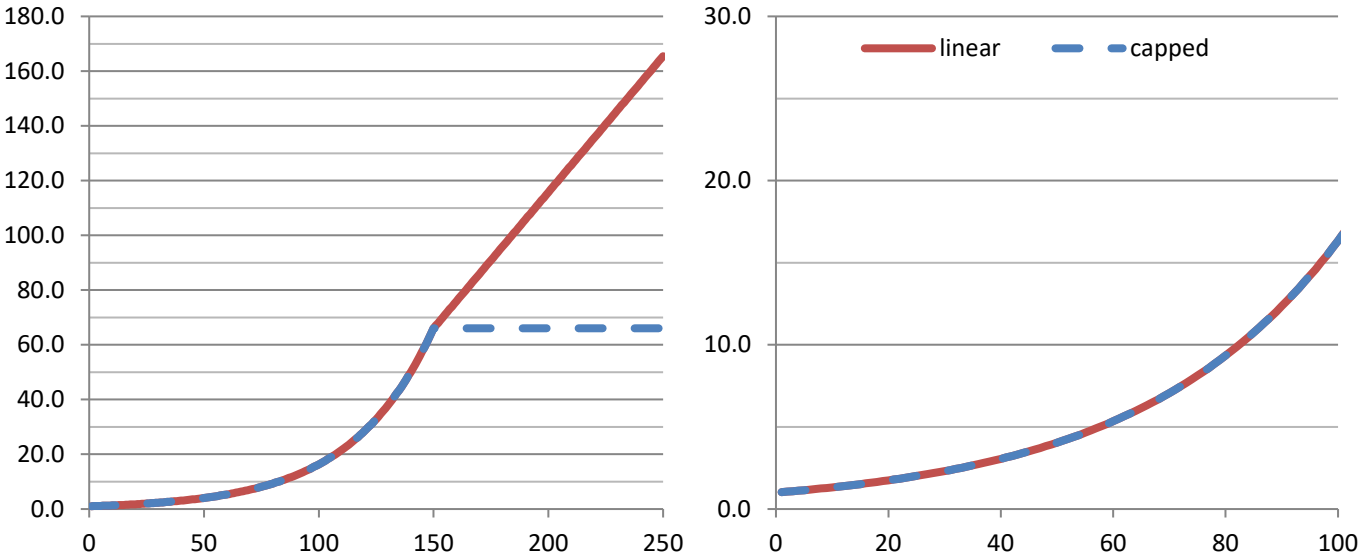
Larsson, S. C., Wallin, A., Wolk, A., & Markus, H. S. (2016). Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. *BMC medicine*, *14*(1), 178.

Rehm, J., Shield, K. D., Roerecke, M., & Gmel, G. (2016). Modelling the impact of alcohol consumption on cardiovascular disease mortality for comparative risk assessments: an overview. *BMC Public Health*, *16*(1), 363.

(6).(2) Liver cirrhosis mortality, men

Condition category: **(6) Digestive conditions**
ICD10 codes: **K70,K74**

	Current drinkers	Former drinkers
Source	Rehm et al. (2010) Figure 2	Roerecke et al. (2017) CAMH working report Also reported in Rehm et al. (2017)
Relative risk Function or estimate	$\ln RR(x) = 0.02793524x$ $RR(x)=\exp(0.02793524x)$	RR_{FD} = 3.26
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. Rehm et al. (2010a) reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	Not known – not yet finalized.



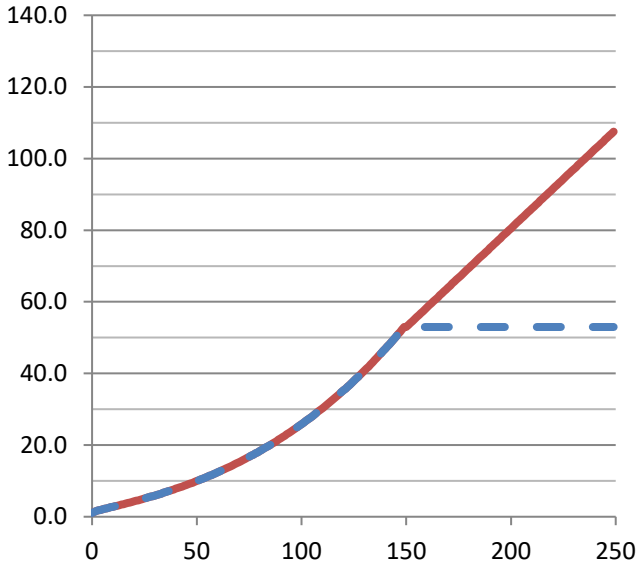
Sources

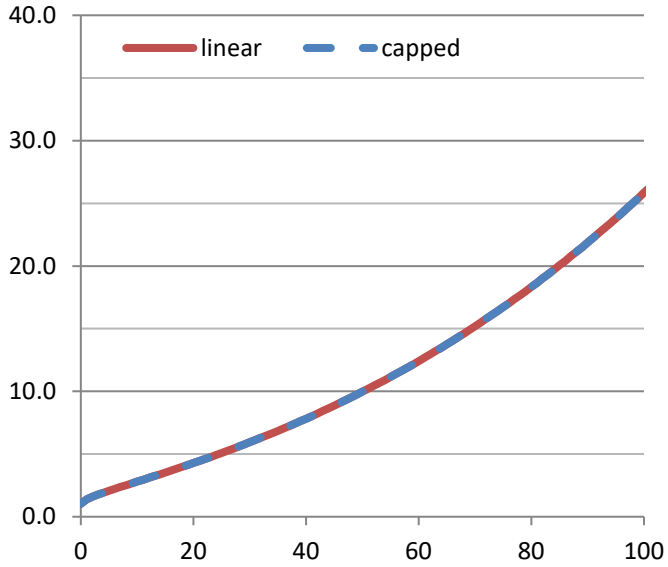
Rehm, J., Taylor, B., Mohapatra, S., Irving, H., Baliunas, D., Patra, J., & Roerecke, M. (2010). Alcohol as a risk factor for liver cirrhosis: A systematic review and meta-analysis. *Drug and alcohol review*, *29*(4), 437-445.
Roerecke et al. (2017) CAMH working paper.
Rehm, J., Sherk, A., Shield, K.D., & Gmel, G. (2017). Risk relations between alcohol use and non-injury causes of death. Version 2: September 2017. Toronto, Canada: Centre for Addiction and Mental Health. ISBN: 978-1-77114-399-8.

(6).(2) Liver cirrhosis mortality, women

Condition category: **(6) Digestive conditions**
ICD10 codes: **K70,K74**

	Current drinkers	Former drinkers
Source	Rehm et al. (2010) Figure 2	Roerecke et al. (2017) CAMH working report Also reported in Rehm et al. (2017)
Relative risk Function or estimate	$\ln RR(x) = 0.32520349\sqrt{x}$ $RR(x)=\exp(0.32520349\sqrt{x})$	RR_{FD} = 3.26
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. Rehm et al. (2010a) reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	Not known – not yet finalized.





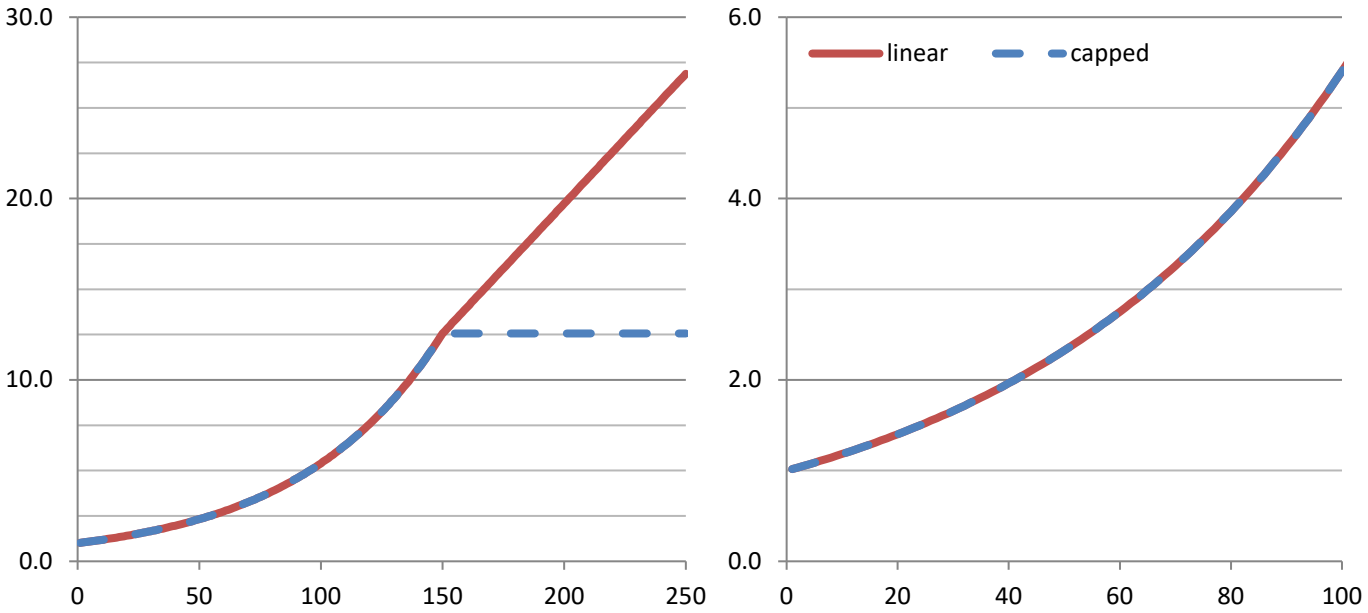
Sources

Rehm, J., Taylor, B., Mohapatra, S., Irving, H., Baliunas, D., Patra, J., & Roerecke, M. (2010). Alcohol as a risk factor for liver cirrhosis: A systematic review and meta-analysis. *Drug and alcohol review*, *29*(4), 437-445.
Roerecke et al. (2017) CAMH working paper.
Rehm, J., Sherk, A., Shield, K.D., & Gmel, G. (2017). Risk relations between alcohol use and non-injury causes of death. Version 2: September 2017. Toronto, Canada: Centre for Addiction and Mental Health. ISBN: 978-1-77114-399-8.

(6).(2) Liver cirrhosis morbidity, men

Condition category: **(6) Digestive conditions**
ICD10 codes: **K70,K74**

	Current drinkers	Former drinkers
Source	Rehm et al. (2010) Figure 2	Roerecke et al. (2017) CAMH working report Also reported in Rehm et al. (2017)
Relative risk Function or estimate	$\ln RR(x) = 0.01687111x$ $RR(x)=\exp(0.01687111x)$	RR_{FD} = 3.26
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. Rehm et al. (2010a) reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	Not known – not yet finalized.



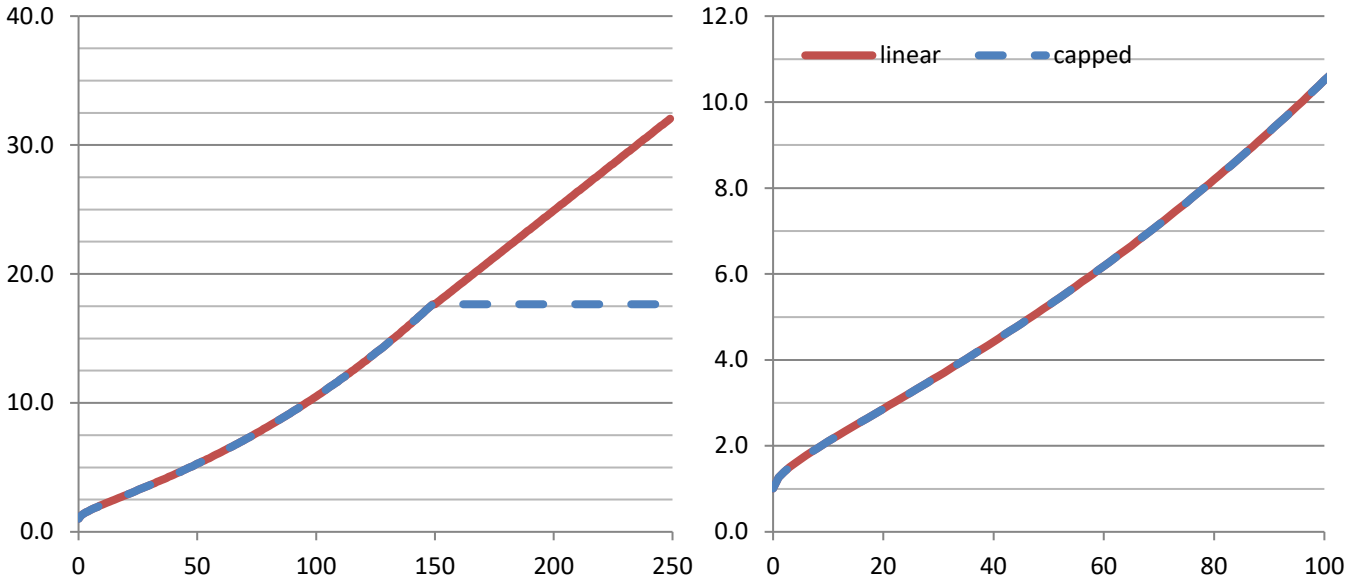
Sources

Rehm, J., Taylor, B., Mohapatra, S., Irving, H., Baliunas, D., Patra, J., & Roerecke, M. (2010). Alcohol as a risk factor for liver cirrhosis: A systematic review and meta-analysis. *Drug and alcohol review*, *29*(4), 437-445.
Roerecke et al. (2017) CAMH working paper.
Rehm, J., Sherk, A., Shield, K.D., & Gmel, G. (2017). Risk relations between alcohol use and non-injury causes of death. Version 2: September 2017. Toronto, Canada: Centre for Addiction and Mental Health. ISBN: 978-1-77114-399-8.

(6).(2) Liver cirrhosis morbidity, women

Condition category: **(6) Digestive conditions**
ICD10 codes: **K70,K74**

	Current drinkers	Former drinkers
Source	Rehm et al. (2010) Figure 2	Roerecke et al. (2017) CAMH working report Also reported in Rehm et al. (2017)
Relative risk Function or estimate	$\ln RR(x) = 0.2351821\sqrt{x}$ $RR(x)=\exp(0.2351821\sqrt{x})$	RR_{FD} = 3.26
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. Rehm et al. (2010a) reweighted relative risk results from studies which pooled former and never drinkers as abstainers using a standard methodology.	Not known – not yet finalized.



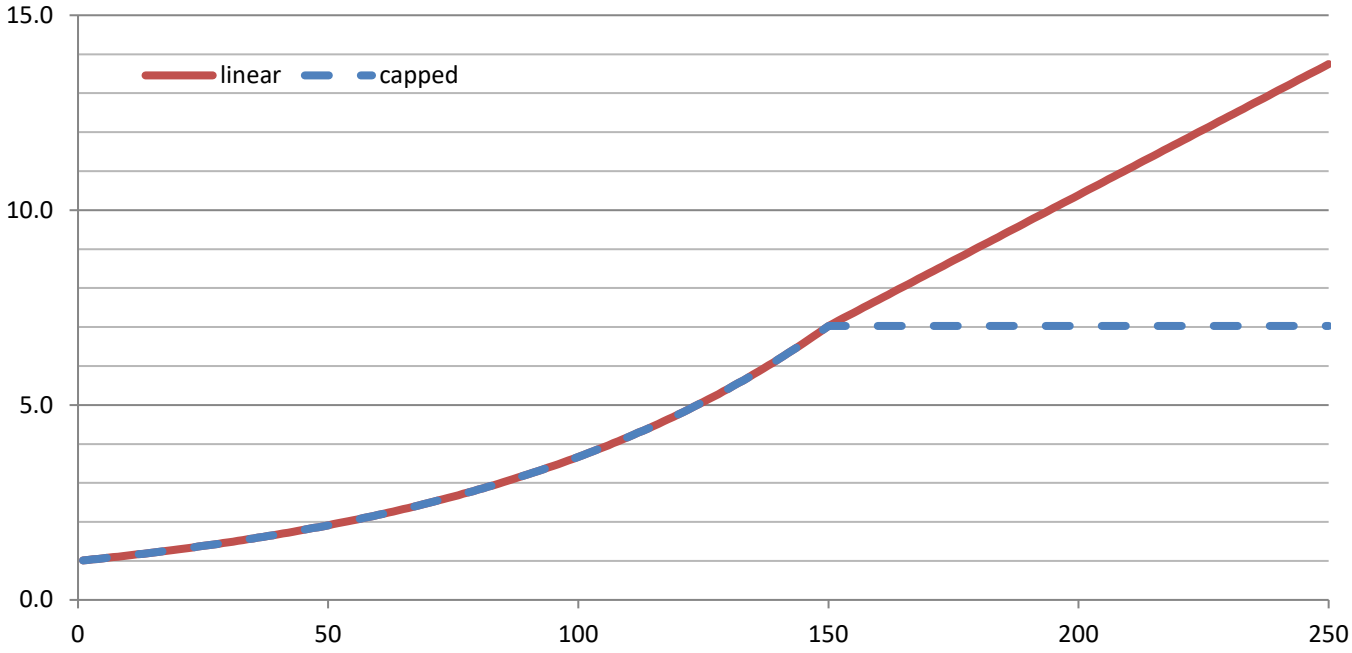
Sources

Rehm, J., Taylor, B., Mohapatra, S., Irving, H., Baliunas, D., Patra, J., & Roerecke, M. (2010). Alcohol as a risk factor for liver cirrhosis: A systematic review and meta-analysis. *Drug and alcohol review*, *29*(4), 437-445.
Roerecke et al. (2017) CAMH working paper.
Rehm, J., Sherk, A., Shield, K.D., & Gmel, G. (2017). Risk relations between alcohol use and non-injury causes of death. Version 2: September 2017. Toronto, Canada: Centre for Addiction and Mental Health. ISBN: 978-1-77114-399-8

(6).(3) Acute pancreatitis, men

Condition category: **(6) Digestive conditions**
ICD10 codes: **K85.0, K85.1, K85.8, K85.9**

	Current drinkers	Former drinkers
Source	Samokhvalov et al. (2015) Figure 3, Table 2	Samokhvalov et al. (2015) Reported in discussion
Relative risk Function or estimate	$\ln RR(x) = 0.013x$ $RR(x)=\exp(0.013x)$	$RR_{FD} = 2.20$
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. Samokhvalov et al. (2015) gave priority to studies where lifetime abstainers were the risk reference group.	Yes. Samokhvalov et al. (2015) gave priority to studies where lifetime abstainers were the risk reference group.



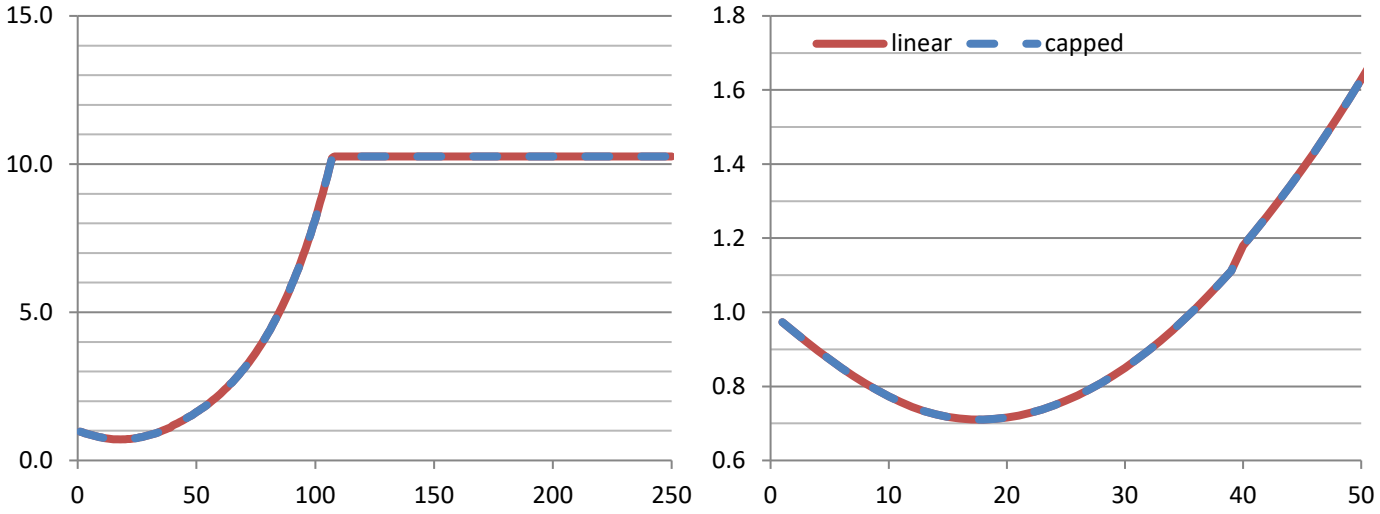
Sources

Samokhvalov, A. V., Rehm, J., & Roerecke, M. (2015). Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic review and a series of meta-analyses. *EBioMedicine*, *2*(12), 1996-2002.

(6).(3) Acute pancreatitis, women

Condition category: **(6) Digestive conditions**
ICD10 codes: **K85.0, K85.1, K85.8, K85.9**

	Current drinkers	Former drinkers
Source	Samokhvalov et al. (2015) Figure 4, Table 2	Samokhvalov et al. (2015) Reported in discussion
Relative risk Function or estimate	$\ln RR(x) = \begin{cases} -0.0272886x, 0 < x < 3 \\ -0.0272886x + 0.0611466\frac{(x-3)^3}{37^2}, 3 \le x < 15 \\ -0.0272886x + 0.0611466\frac{(x-3)^3 - \frac{37(x-15)^3}{25}}{37^2}, 15 \le x < 40 \\ -0.0272886x + 0.0611466\frac{(x-3)^3 - \frac{37(x-15)^3 - 12(x-40)^3}{25}}{37^2}, 40 \le x < 108 \\ 2.327965, x \ge 108 \end{cases}$	$RR_{FD} = 2.20$
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abs. bias	Yes, for both current and former drinkers. Samokhvalov et al. (2015) gave priority to studies where lifetime abstainers were the risk reference group.	.



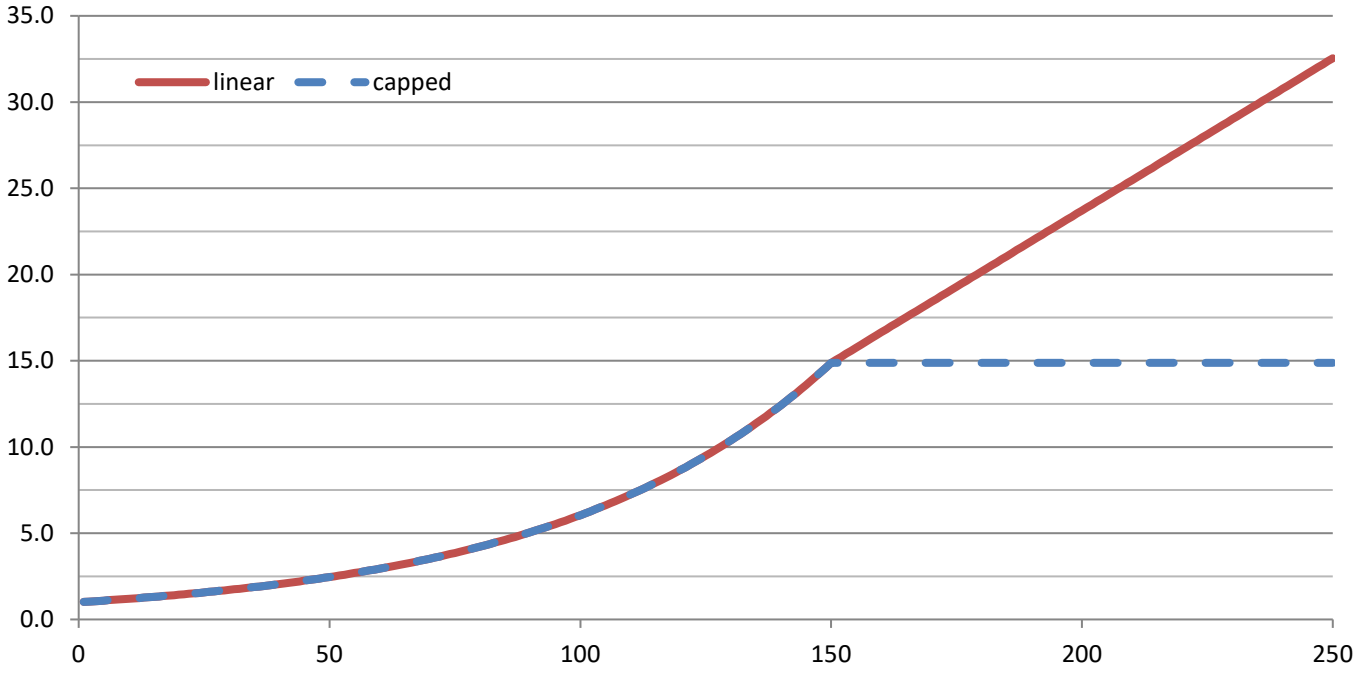
Sources

Samokhvalov, A. V., Rehm, J., & Roerecke, M. (2015). Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic review and a series of meta-analyses. *EBioMedicine*, *2*(12), 1996-2002.

(6).(4) Chronic pancreatitis

Condition category: **(6) Digestive conditions**
ICD10 codes: **K86.1 to K86.9**

	Current drinkers	Former drinkers
Source	Samokhvalov et al. (2015) Figure 2, Table 2	Samokhvalov et al. (2015) Reported in discussion
Relative risk Function or estimate	$\ln RR(x) = 0.018x$ $RR(x)=\exp(0.018x)$	$RR_{FD} = 2.20$
Comments	Relative risk function received directly from members of authorship group who are members of this project.	
Control for abstainer bias Does the article control for abstainer bias? If so, how?	Yes. Samokhvalov et al. (2015) gave priority to studies where lifetime abstainers were the risk reference group.	Yes. Samokhvalov et al. (2015) gave priority to studies where lifetime abstainers were the risk reference group.



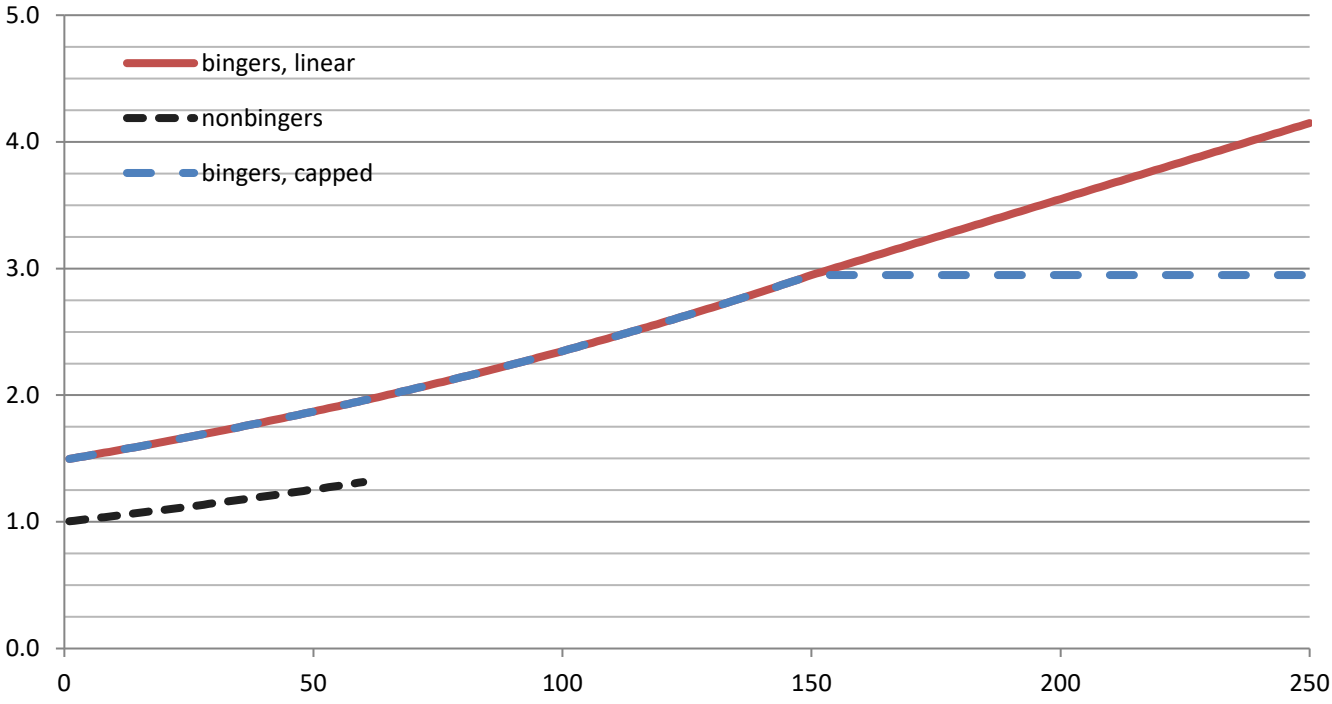
Sources

Samokhvalov, A. V., Rehm, J., & Roerecke, M. (2015). Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic review and a series of meta-analyses. *EBioMedicine*, *2*(12), 1996-2002.

(7).(1) Motor vehicle collisions

Condition category: **(7) Injuries – motor vehicle collisions**
ICD10 codes: **V1* (shown in XXX), Y85.0**

	Current drinkers, nonbinge	Current drinkers, binge
Source	Corrao et al. (1999) Table 2	Custom analysis from U.S. Census Bureau's National Health Interview Survey (see Chapter 5)
Relative risk Equation or estimate	$\ln RR(x) = 0.00455x$ $RR(x)$=exp(0.00455x)	$RR(x)$=1.49*exp(0.00455x)
Comments		In the graph below, the binge level is defined as 60 grams. Therefore, all drinkers above 60g/day are guaranteed to be bingers.
Control for abstainer bias Does the article control for abstainer bias?	Not applicable. There is no increased risk for former drinkers.	**Former drinkers**. There is no increased risk for former drinkers, RR_{FD} = 1.00



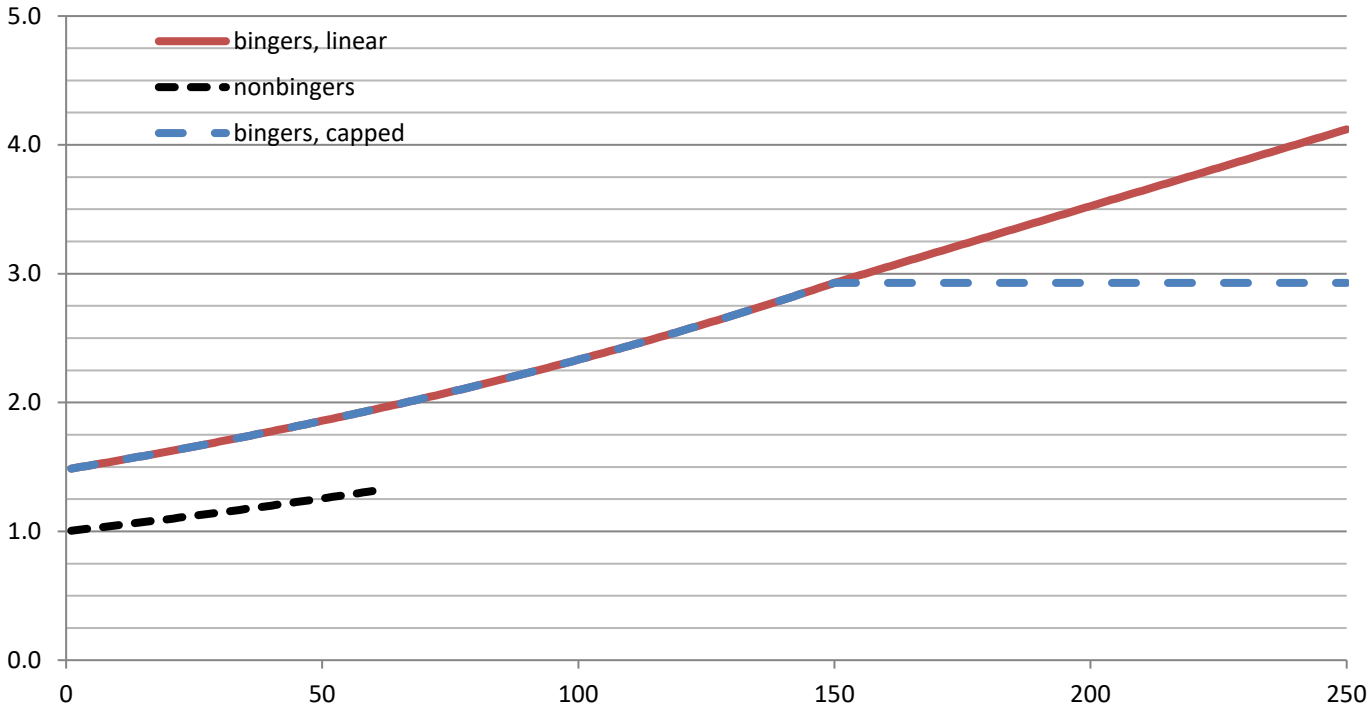
Source

Corrao, G., Bagnardi, V., Zambon, A., & Arico, S. (1999). Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. *Addiction, 94*(10), 1551-1573.

(8).(1),(2),(3),(4),(6) Unintentional injuries

Condition category: **(8) Injuries – unintentional injuries**
ICD10 codes: **Many, see Table 2**

	Current drinkers, nonbinge	Current drinkers, binge
Source	Corrao et al. (1999) Table 2	Custom analysis from U.S. Census Bureau's National Health Interview Survey (see Chapter 5)
Relative risk Equation or estimate	$\ln RR(x) = 0.00455x$ $RR(x)$=exp$(0.00455x)$	$RR(x)$=1.48*exp$(0.00455x)$
Comments		In the graph below, the binge level is defined as 60 grams. Therefore, all drinkers above 60g/day are guaranteed to be bingers.
Control for abstainer bias Does the article control for abstainer bias?	Not applicable. There is no increased risk for former drinkers.	**Former drinkers**. There is no increased risk for former drinkers, RR_{FD} = 1.00



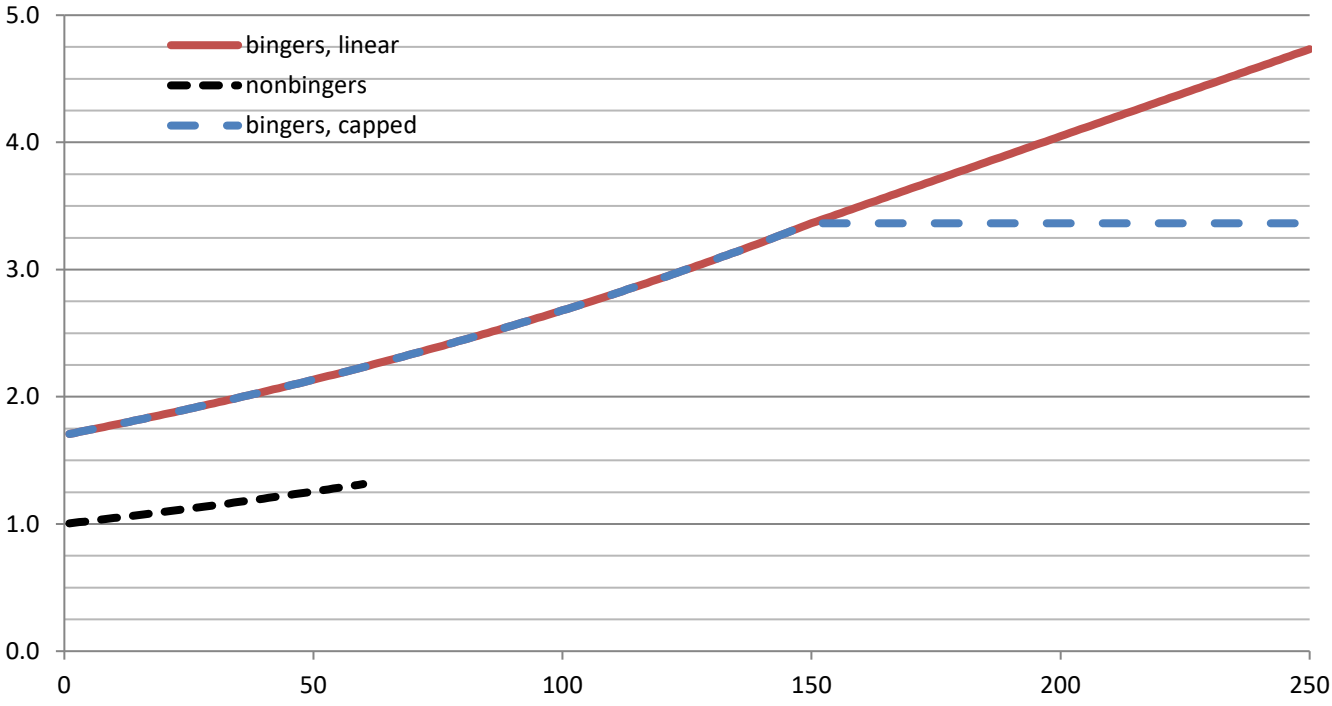
Source

Corrao, G., Bagnardi, V., Zambon, A., & Arico, S. (1999). Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. *Addiction, 94*(10), 1551-1573.

(9).(1),(3),(4),(5) Intentional injuries

Condition category: **(9) Injuries – intentional injuries**
ICD10 codes: **Many, see Table 2**

	Current drinkers, nonbinge	Current drinkers, binge
Source	Corrao et al. (1999) Table 2	Custom analysis from U.S. Census Bureau's National Health Interview Survey (see Chapter 5)
Relative risk Equation or estimate	$\ln RR(x) = 0.00455x$ $RR(x)$=exp$(0.00455x)$	$RR(x)$=1.70*exp$(0.00455x)$
Comments		In the graph below, the binge level is defined as 60 grams. Therefore, all drinkers above 60g/day are guaranteed to be bingers.
Control for abstainer bias Does the article control for abstainer bias?	Not applicable. There is no increased risk for former drinkers.	**Former drinkers**. There is no increased risk for former drinkers, RR_{FD} = 1.00



Source

Corrao, G., Bagnardi, V., Zambon, A., & Arico, S. (1999). Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. *Addiction, 94*(10), 1551-1573.

Appendix D: Supplementary Material for Study D

Appendix D-1: Complete Alcohol-Attributable Fraction Formulation for Special Cases

$$\frac{P_{FD}[RR_{FD}-1]+\left[\frac{P_{CD}-P_{BD}}{P_{CD}-P_{CB}}\right]\int_{0.03}^{c}P(x)[RR(x)-1]\,dx+\left[\frac{P_{BD}-P_{CB}}{P_{CD}-P_{CB}}\right]\int_{0.03}^{c}P(x)[RR_{BD}(x)-1]\,dx+\int_{c}^{z}P(x)[RR_{BD}(x)-1]dx}{1+\ P_{FD}[RR_{FD}-1]+\left[\frac{P_{CD}-P_{BD}}{P_{CD}-P_{CB}}\right]\int_{0.03}^{c}P(x)[RR(x)-1]\,dx+\left[\frac{P_{BD}-P_{CB}}{P_{CD}-P_{CB}}\right]\int_{0.03}^{c}P(x)[RR_{BD}(x)-1]\,dx+\int_{c}^{z}P(x)[RR_{BD}(x)-1]dx}$$

Appendix E: Supplementary Material for Study E

Appendix E-1: Alcohol-Attributable Mortality, Observed and Under Two MUP Scenarios, by Condition, Québec 2014

			Quebec in 2014	Scenario 1 - $1.50	Scenario 2 - $1.75
Condition Category	**IM#**	**Condition**	**Observed** (95% CI)	**Estimate [Δ%]** (95% CI)	**Estimate [Δ%]** (95% CI)
(1) Communicable diseases	(1).(1)	Tuberculosis	**11.8** *(11.4, 12.2)*	**10.9 [-7.6%]** *(10.6, 11.3)*	**10.2 [-13.6%]** *(9.8, 10.5)*
	(1).(2)	HIV	**suppressed**	**suppressed**	**suppressed**
	(1).(3)	Lower respiratory tract infections	**115.8** *(111.0, 120.7)*	**110.3 [-4.7%]** *(105.7, 115.0)*	**105.0 [-9.3%]** *(100.6, 109.5)*
		Subtotal of condition category	**130.6** *(125.2, 136.0)*	**124.0 [-5.1%]** *(118.9, 129.3)*	**117.7 [-9.9%]** *(112.8, 122.8)*
(2) Cancer	(2).(1)	Oral cavity and pharynx cancer	**129.1** *(125.8, 132.4)*	**121.1 [-6.2%]** *(117.8, 124.4)*	**113.4 [-12.2%]** *(110.1, 116.7)*
	(2).(2)	Oesophageal cancer	**74.1** *(72.5, 75.8)*	**70.7 [-4.6%]** *(69.0, 72.3)*	**67.3 [-9.2%]** *(65.6, 69.0)*
	(2).(3)	Colorectal cancer	**406.4** *(384.4, 427.8)*	**396.2 [-2.5%]** *(374.1, 417.7)*	**386.3 [-4.9%]** *(364.1, 407.9)*
	(2).(4)	Liver cancer	**138.3** *(130.3, 146.0)*	**135.5 [-2.0%]** *(127.5, 143.3)*	**132.9 [-3.9%]** *(124.8, 140.6)*
	(2).(5)	Pancreatic cancer	**91.6** *(84.4, 98.7)*	**90.1 [-1.6%]** *(82.9, 97.2)*	**88.6 [-3.3%]** *(81.4, 95.7)*
	(2).(6)	Laryngeal cancer	**39.8** *(38.6, 41.0)*	**37.8 [-5.0%]** *(36.6, 39.0)*	**35.9 [-9.8%]** *(34.7, 37.0)*

	(2).(7)	Breast cancer	**133.9** *(128.1, 139.9)*	**127.6 [-4.7%]** *(122.0, 133.4)*	**121.6 [-9.2%]** *(116.3, 127.2)*
		Subtotal of condition category	**1 013.3** *(964.0, 1 061.7)*	**979.0 [-3.4%]** *(929.9, 1 027.3)*	**945.9 [-6.7%]** *(897.1, 994.0)*
(3) Endocrine conditions	(3).(1)	Diabetes	**-125.0** *(-144.7, -105.8)*	**-123.6 [n/a]** *(-143.2, -104.6)*	**-122.1 [n/a]** *(-141.5, -103.3)*
		Subtotal of condition category	**-125.0** *(-144.7, -105.8)*	**-123.6** *(-143.2, -104.6)*	**-122.1** *(-141.5, -103.3)*
(4) Neuropsychiatric conditions	(4).(1)	Alcoholic psychoses	**44.0** *(44.0, 44.0)*	**38.4 [-12.7%]** *(38.1, 38.6)*	**33.2 [-24.5%]** *(32.8, 33.6)*
	(4).(2)	Alcohol abuse	**suppressed**	**suppressed**	**suppressed**
	(4).(3)	Alcohol dependence	**304.0** *(304.0, 304.0)*	**265.9 [-12.5%]** *(264.4, 267.2)*	**230.9 [-24%]** *(228.4, 233.4)*
	(4).(4)	Degeneration of nervous system due to alcohol	**suppressed**	**suppressed**	**suppressed**
	(4).(5)	Epilepsy	**20.2** *(19.5, 20.9)*	**19.1 [-5.4%]** *(18.4, 19.7)*	**17.9 [-11.4%]** *(17.3, 18.6)*
	(4).(6)	Alcoholic polyneuropathy	**suppressed**	**suppressed**	**suppressed**
	(4).(7)	Alcoholic myopathy	**suppressed**	**suppressed**	**suppressed**
		Subtotal of condition category	**375.2** *(374.5, 375.9)*	**329.9 [-12.1%]** *(327.6, 332.2)*	**288.4 [-23.1%]** *(284.8, 291.8)*
(5) Cardiovascular conditions	(5).(1)	Hypertension	**94.4** *(90.7, 98.3)*	**90.7 [-3.9%]** *(87.1, 94.3)*	**87.0 [-7.8%]** *(83.5, 90.5)*
	(5).(2)	Ischaemic heart disease	**429.8** *(383.8, 475.5)*	**414.0 [-3.7%]** *(368.1, 459.6)*	**399.6 [-7.0%]** *(353.8, 445.2)*
	(5).(3)	Alcoholic cardiomyopathy	**suppressed**	**suppressed**	**suppressed**
	(5).(4)	Atrial fibrillation and cardiac arrhythmia	**83.8** *(80.5, 87.2)*	**79.8 [-4.8%]** *(76.6, 83.1)*	**76.0 [-9.3%]** *(72.9, 79.1)*

	(5).(5)	Haemorrhagic stroke	**106.6** *(102.0, 111.2)*	**102.7 [-3.7%]** *(98.2, 107.3)*	**99.1 [-7.0%]** *(94.5, 103.6)*
	(5).(6)	Ischaemic stroke	**-8.6** *(-9.4, -7.9)*	**-9.1 [n/a]** *(-9.8, -8.4)*	**-9.5 [n/a]** *(-10.2, -8.8)*
	(5).(7)	Oesophageal varices	**12.4** *(12.2, 12.6)*	**11.5 [-7.3%]** *(11.3, 11.7)*	**10.7 [-13.7%]** *(10.5, 10.9)*
		Subtotal of condition category	**723.3** *(664.7, 781.8)*	**694.4 [-4.0%]** *(636.2, 752.5)*	**667.3 [-7.7%]** *(609.6, 725.0)*
(6) Digestive conditions	(6).(1)	Alcoholic gastritis	**suppressed**	**suppressed**	**suppressed**
	(6).(2)	Liver cirrhosis	**112.9** *(111.0, 114.8)*	**105.5 [-6.6%]** *(103.4, 107.5)*	**98.6 [-12.7%]** *(96.4, 100.7)*
	(6).(3)	Acute pancreatitis	**suppressed**	**suppressed**	**suppressed**
	(6).(4)	Chronic pancreatitis	**suppressed**	**suppressed**	**suppressed**
	(6).(5)	Alcohol-induced pancreatitis	**suppressed**	**suppressed**	**suppressed**
		Subtotal of condition category	**118.4** *(116.0, 120.6)*	**110.8 [-6.4%]** *(108.3, 113.1)*	**103.6 [-12.5%]** *(101.1, 106.1)*
(7) Motor vehicle collisions	(7).(1)	Motor vehicle collisions	**81.0** *(77.7, 84.2)*	**74.5 [-8.0%]** *(71.4, 77.6)*	**68.4 [-15.6%]** *(65.4, 71.2)*
		Subtotal of condition category	**81.0** *(77.7, 84.2)*	**74.5 [-8.0%]** *(71.4, 77.6)*	**68.4 [-15.6%]** *(65.4, 71.2)*
(8) Unintentional injuries	(8).(1)	Falls	**86.8** *(81.2, 92.2)*	**79.8 [-8.1%]** *(74.7, 84.8)*	**73.3 [-15.6%]** *(68.6, 77.8)*
	(8).(2)	Drowning	**12.7** *(12.2, 13.2)*	**11.8 [-7.1%]** *(11.3, 12.3)*	**10.9 [-14.2%]** *(10.5, 11.4)*
	(8).(3)	Fires	**11.3** *(10.7, 11.9)*	**10.4 [-8.0%]** *(9.8, 11.0)*	**9.6 [-15.0%]** *(9.0, 10.1)*
	(8).(4)	Accidental poisoning by substances other than alcohol	**11.3** *(10.8, 11.8)*	**10.4 [-8.0%]** *(9.9, 10.9)*	**9.6 [-15.0%]** *(9.2, 10.1)*

	(8).(5)	Accidental poisoning by alcohol	**32.0** *(32.0, 32.0)*	**29.8 [-6.9%]** *(29.7, 29.9)*	**27.7 [-13.4%]** *(27.5, 27.9)*
	(8).(6)	Other unintentional injuries	**113.0** *(106.1, 119.7)*	**104.1 [-7.9%]** *(97.7, 110.3)*	**95.6 [-15.4%]** *(89.8, 101.3)*
		Subtotal of condition category	**267.1** *(252.8, 280.9)*	**246.4 [-7.7%]** *(233.3, 259.3)*	**226.7 [-15.1%]** *(214.6, 238.6)*
(9) Intentional injuries	(9).(1)	Intentional self-poisoning by substances other than alcohol	**suppressed**	**suppressed**	**suppressed**
	(9).(2)	Intentional self-poisoning by alcohol	**suppressed**	**suppressed**	**suppressed**
	(9).(3)	Other intentional self-harm	**242.0** *(231.6, 252.1)*	**224.0 [-7.4%]** *(213.9, 233.7)*	**206.5 [-14.7%]** *(196.8, 215.9)*
	(9).(4)	Assault / homicide	**18.0** *(17.2, 18.8)*	**16.6 [-7.8%]** *(15.9, 17.4)*	**15.3 [-15.0%]** *(14.6, 16.0)*
	(9).(5)	Other intentional injuries	**suppressed**	**suppressed**	**suppressed**
		Subtotal of condition category	**265.8** *(254.3, 276.9)*	**245.9 [-7.5%]** *(234.9, 256.7)*	**226.7 [-14.7%]** *(216.1, 237.0)*
		GRAND TOTAL	**2 849.7** *(2 684.6, 3 012.2)*	**2 681.4 [-5.9%]** *(2 517.2, 2 843.2)*	**2 522.6 [-11.5%]** *(2 360.0, 2 683.3)*

Notes:

Δ%: percent change (in each scenario); IM#: InterMAHP condition number; MUP: Minimum unit price

Columns may not sum due to rounding

Appendix E-2: Alcohol-Attributable Hospitalizations, Observed and Under Two MUP scenarios, by Condition, Québec 2014

			Quebec in 2014	Scenario 1 - $1.50	Scenario 2 - $1.75
Condition Category	**IM#**	**Condition**	**Observed** (95% CI)	**Estimate [Δ%]** (95% CI)	**Estimate [Δ%]** (95% CI)
(1) Communicable diseases	(1).(1)	Tuberculosis	**56.2** *(54.5, 57.8)*	**52.3 [-6.9%]** *(50.7, 53.9)*	**48.6 [-13.5%]** *(47.1, 50.2)*
	(1).(2)	HIV	**suppressed**	**suppressed**	**suppressed**
	(1).(3)	Lower respiratory tract infections	**1 533.3** *(1 472.3, 1 595.4)*	**1 460.7 [-4.7%]** *(1 402.1, 1 520.4)*	**1 390.1 [-9.3%]** *(1 333.8, 1 447.4)*
		Subtotal of condition category	**1 594.0** *(1 531.1, 1 657.9)*	**1 517.2 [-4.8%]** *(1 456.8, 1 578.7)*	**1 442.6 [-9.5%]** *(1 384.5, 1 501.7)*
(2) Cancer	(2).(1)	Oral cavity and pharynx cancer	**522.1** *(509.4, 534.8)*	**489.5 [-6.2%]** *(476.8, 502.1)*	**458.3 [-12.2%]** *(445.7, 470.9)*
	(2).(2)	Oesophageal cancer	**99.5** *(97.4, 101.7)*	**94.8 [-4.7%]** *(92.7, 97.0)*	**90.3 [-9.2%]** *(88.2, 92.4)*
	(2).(3)	Colorectal cancer	**1 172.8** *(1 110.1, 1 233.4)*	**1 141.6 [-2.7%]** *(1 078.6, 1 202.6)*	**1 111.3 [-5.2%]** *(1 048.1, 1 172.7)*
	(2).(4)	Liver cancer	**187.3** *(176.8, 197.4)*	**183.2 [-2.2%]** *(172.7, 193.3)*	**179.2 [-4.3%]** *(168.7, 189.3)*
	(2).(5)	Pancreatic cancer	**114.3** *(105.4, 123.2)*	**112.4 [-1.7%]** *(103.4, 121.2)*	**110.4 [-3.4%]** *(101.4, 119.3)*
	(2).(6)	Laryngeal cancer	**211.6** *(205.5, 217.7)*	**201.0 [-5%]** *(195.0, 207.0)*	**190.7 [-9.9%]** *(184.9, 196.6)*
	(2).(7)	Breast cancer	**942.2** *(903.6, 982.1)*	**896.8 [-4.8%]** *(859.8, 935.0)*	**853.2 [-9.4%]** *(818.0, 889.7)*

		Subtotal of condition category	**3 250.0** *(3 108.2, 3 390.2)*	**3 119.3 [-4%]** *(2 979.1, 3 258.2)*	**2 993.4 [-7.9%]** *(2 855.0, 3 130.9)*
(3) Endocrine conditions	(3).(1)	Diabetes	**-132.9** *(-154.2, -112.0)*	**-132.2** *(-153.4, -111.5)*	**-131.4** *(-152.4, -110.9)*
		Subtotal of condition category	**-132.9** *(-154.2, -112.0)*	**-132.2** *(-153.4, -111.5)*	**-131.4** *(-152.4, -110.9)*
(4) Neuropsychiatric conditions	(4).(1)	Alcoholic psychoses	**2 203.0** *(2 203.0, 2 203.0)*	**1 924.0 [-12.7%]** *(1 913.5, 1 934.2)*	**1 669.1 [-24.2%]** *(1 650.5, 1 687.0)*
	(4).(2)	Alcohol abuse	**264.0** *(264.0, 264.0)*	**230.3 [-12.8%]** *(229.0, 231.5)*	**199.5 [-24.4%]** *(197.3, 201.7)*
	(4).(3)	Alcohol dependence	**1 023.0** *(1 023.0, 1 023.0)*	**891.8 [-12.8%]** *(886.8, 896.6)*	**772.2 [-24.5%]** *(763.5, 780.7)*
	(4).(4)	Degeneration of nervous system due to alcohol	**34.0** *(34.0, 34.0)*	**32.5 [-4.4%]** *(32.5, 32.6)*	**31.1 [-8.5%]** *(31.1, 31.1)*
	(4).(5)	Epilepsy	**370.0** *(357.9, 382.2)*	**348.6 [-5.8%]** *(336.8, 360.5)*	**328.0 [-11.4%]** *(316.6, 339.6)*
	(4).(6)	Alcoholic polyneuropathy	**17.0** *(17.0, 17.0)*	**16.3 [-4.1%]** *(16.3, 16.3)*	**15.5 [-8.8%]** *(15.5, 15.6)*
	(4).(7)	Alcoholic myopathy	**suppressed**	**suppressed**	**suppressed**
		Subtotal of condition category	**3 911.0** *(3 898.9, 3 923.2)*	**3 443.5 [-12%]** *(3 414.9, 3 471.6)*	**3 015.4 [-22.9%]** *(2 974.5, 3 055.7)*
(5) Cardiovascular conditions	(5).(1)	Hypertension	**127.0** *(122.6, 131.5)*	**122.0 [-3.9%]** *(117.8, 126.4)*	**117.1 [-7.8%]** *(113.0, 121.4)*
	(5).(2)	Ischaemic heart disease	**-1 358.9** *(-1 570.2, -1 153.1)*	**-1 451.0** *(-1 655.5, -1 250.7)*	**-1 535.2** *(-1 733.2, -1 341.1)*
	(5).(3)	Alcoholic cardiomyopathy	**41.0** *(41.0, 41.0)*	**39.3 [-4.1%]** *(39.2, 39.3)*	**37.5 [-8.5%]** *(37.5, 37.6)*
	(5).(4)	Atrial fibrillation and cardiac arrhythmia	**1 081.3** *(1 041.6, 1 121.7)*	**1 029.7 [-4.8%]** *(991.5, 1 068.6)*	**979.5 [-9.4%]** *(942.8, 1 017.0)*

	(5).(5)	Haemorrhagic stroke	**82.5** *(59.6, 104.9)*	**69.7 [-15.5%]** *(47.0, 92.1)*	**57.6 [-30.2%]** *(35.0, 79.9)*
	(5).(6)	Ischaemic stroke	**-356.9** *(-395.2, -319.2)*	**-393.3** *(-430.6, -356.4)*	**-427.7** *(-464.2, -391.8)*
	(5).(7)	Oesophageal varices	**43.6** *(42.5, 44.6)*	**41.7 [-4.4%]** *(40.6, 42.8)*	**39.9 [-8.5%]** *(38.8, 41.1)*
		Subtotal of condition category	**-340.5** *(-658.1, -28.4)*	**-541.9** *(-850.0, -237.9)*	**-731.2** *(-1 030.3, -435.9)*
(6) Digestive conditions	(6).(1)	Alcoholic gastritis	**94.0** *(94.0, 94.0)*	**90.0 [-4.3%]** *(90.0, 90.1)*	**86.1 [-8.4%]** *(86.1, 86.2)*
	(6).(2)	Liver cirrhosis	**962.5** *(938.2, 985.5)*	**923.0 [-4.1%]** *(898.0, 946.7)*	**885.1 [-8%]** *(859.5, 909.7)*
	(6).(3)	Acute pancreatitis	**803.9** *(750.6, 855.6)*	**764.5 [-4.9%]** *(711.1, 816.3)*	**727.5 [-9.5%]** *(674.0, 779.4)*
	(6).(4)	Chronic pancreatitis	**121.6** *(117.6, 125.6)*	**115.4 [-5.1%]** *(111.2, 119.4)*	**109.4 [-10%]** *(105.3, 113.5)*
	(6).(5)	Alcohol-induced pancreatitis	**644.0** *(644.0, 644.0)*	**617.1 [-4.2%]** *(616.9, 617.3)*	**590.7 [-8.3%]** *(590.3, 591.1)*
		Subtotal of condition category	**2 626.1** *(2 544.3, 2 704.7)*	**2 509.9 [-4.4%]** *(2 427.3, 2 589.8)*	**2 398.9 [-8.7%]** *(2 315.2, 2 479.8)*
(7) Motor vehicle collisions	(7).(1)	Motor vehicle collisions	**620.4** *(592.8, 647.2)*	**576.5 [-7.1%]** *(550.3, 602.1)*	**534.0 [-13.9%]** *(509.3, 558.3)*
		Subtotal of condition category	**620.4** *(592.8, 647.2)*	**576.5 [-7.1%]** *(550.3, 602.1)*	**534.0 [-13.9%]** *(509.3, 558.3)*
(8) Unintentional injuries	(8).(1)	Falls	**4 589.0** *(4 301.9, 4 866.7)*	**4 211.5 [-8.2%]** *(3 950.4, 4 466.2)*	**3 855.3 [-16%]** *(3 618.1, 4 087.7)*
	(8).(2)	Drowning	**suppressed**	**suppressed**	**suppressed**
	(8).(3)	Fires	**33.4** *(32.0, 34.8)*	**31.0 [-7.2%]** *(29.6, 32.3)*	**28.7 [-14.1%]** *(27.4, 29.9)*

	(8).(4)	Accidental poisoning by substances other than alcohol	**166.5** *(157.4, 175.4)*	**153.1 [-8%]** *(144.6, 161.4)*	**140.4 [-15.7%]** *(132.6, 148.0)*
	(8).(5)	Accidental poisoning by alcohol	**62.0** *(62.0, 62.0)*	**57.9 [-6.6%]** *(57.8, 58.1)*	**54.0 [-12.9%]** *(53.6, 54.3)*
	(8).(6)	Other unintentional injuries	**7 334.7** *(6 986.0, 7 673.0)*	**6 782.4 [-7.5%]** *(6 454.4, 7 102.3)*	**6 252.3 [-14.8%]** *(5 945.1, 6 553.1)*
		Subtotal of condition category	**12 189.6** *(11 543.0, 12 816.0)*	**11 239.6 [-7.8%]** *(10 640.3, 11 824.1)*	**10 334.1 [-15.2%]** *(9 780.1, 10 876.6)*
(9) Intentional injuries	(9).(1)	Intentional self-poisoning by substances other than alcohol	**391.6** *(371.0, 411.4)*	**358.0 [-8.6%]** *(338.6, 376.8)*	**326.0 [-16.8%]** *(307.8, 343.6)*
	(9).(2)	Intentional self-poisoning by alcohol	**suppressed**	**suppressed**	**suppressed**
	(9).(3)	Other intentional self-harm	**208.3** *(199.2, 217.1)*	**192.1 [-7.8%]** *(183.4, 200.6)*	**176.6 [-15.2%]** *(168.2, 184.7)*
	(9).(4)	Assault / homicide	**372.0** *(358.0, 385.5)*	**344.9 [-7.3%]** *(331.3, 358.1)*	**318.6 [-14.4%]** *(305.4, 331.4)*
	(9).(5)	Other intentional injuries	**suppressed**	**suppressed**	**suppressed**
		Subtotal of condition category	**976.0** *(932.1, 1 018.2)*	**898.7 [-7.9%]** *(856.9, 939.3)*	**824.5 [-15.5%]** *(784.7, 863.2)*
		GRAND TOTAL	**24 693.6** *(23 338.2, 26 017.0)*	**22 630.6 [-8.4%]** *(21 322.2, 23 914.4)*	**20 680.3 [-16.3%]** *(19 420.6, 21 919.4)*

Notes:

Δ%: percent change (in each scenario); IM#: InterMAHP condition number

MUP: Minimum unit price / minimum price per standard drink

Columns may not sum due to rounding