Mortality and morbidity risks from alcohol consumption in Australia:

Analyses using an Australian adaptation of the Sheffield Alcohol Policy Model (v2.7) to inform the development of new alcohol guidelines

Final report

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Acronyms

AAF	Alcohol Attributable Fraction
AC	Adenocarcinoma
AR	Absolute Risk
AIHW	Australian Institute of Health and Welfare
IHD	Ischaemic Heart Disease
MR	Mendelian Randomisation
NDSH	National Drug Strategy Household (survey)
NHMRC	National Health and Medical Research Council
RAHRA	Reducing Alcohol-Related Harm (project)
RR	Relative Risk
QALY	Quality-Adjusted Life-Years
SA	Sensitivity Analysis
SAPM	Sheffield Alcohol Policy Model
SAPM-AU	The Australian adaptation of the Sheffield Alcohol Policy Model
SCC	Squamous Cell Carcinoma
WCRF	World Cancer Research Fund

Executive summary

Background to this report

The National Health and Medical Research Council (NHMRC) published the current Australian alcohol guidelines in 2009. These guidelines recommended that men and women drink no more two standard drinks per day (1 standard drink = 10g of pure ethanol). The NHMRC commissioned this report to inform the development of revised alcohol guidelines.

New evidence on alcohol-related health risks has emerged since 2009. In particular, there is increased evidence that low levels of alcohol consumption can cause some types of cancer and that many scientific studies have over-estimated the potential benefits of moderate alcohol consumption for protecting against cardiovascular disease (referred to hereafter as protective or cardioprotective effects). It is therefore important to base the revised guidelines on an updated analysis of the relevant evidence.

In line with recent practice in Australia and internationally, the committee developing the guidelines wishes to examine evidence on the risks to health associated with different levels and patterns of alcohol consumption. It also wishes to identify the alcohol consumption levels that correspond to a set of pre-specified risk thresholds. The 2009 guidelines are set at a level that corresponds approximately to the average drinker having a 1 in 100 chance of dying due to alcohol across their lifetime. The committee developing the 2009 guidelines judged this threshold to reflect an 'acceptable' level of risk from alcohol consumption. In making this judgement, they took account of wider societal standards for governing risks to population health and the risks individuals appear willing to engage in during their daily lives. Those developing guidelines for other countries have sometimes based their recommendations on alternative risk thresholds. For example, the European Reducing Alcohol-Related Harm (RAHRA) project recommended guidelines for seven countries based on a lower acceptable risk of a 1 in 1,000 chance of dying due to alcohol. Alternatively, the developers of the 2011 Canadian drinking guidelines based their recommendations on the consumption level at which the average drinkers' risk of dying due to alcohol exceeds that of the average person who does not drink.

Aims

This report aims to estimate for men and women who drink alcohol in Australia:

1. The lifetime risk of mortality and morbidity due to alcohol that is associated with different levels of alcohol consumption, and how those risks change depending on how drinkers spread their consumption across the week;
2. The consumption levels associated with a set of pre-specified risk thresholds, namely:
    a. A 1.0% lifetime alcohol-attributable mortality risk;
    b. Lifetime alcohol-attributable mortality risks of 0.1%, 0.2% and 2.0% (i.e. 1 in 1000, 1 in 500 and 1 in 50) to understand how sensitive the consumption level is to the exact definition of an acceptable risk;
    c. A 0.0% lifetime alcohol-attributable mortality risk, which is equivalent to the risk associated with not drinking.
3. How sensitive the results are to the use of alternative analytical methods and assumptions.

Overview of the methods

All analyses use a new adaptation of the Sheffield Alcohol Policy Model (SAPM) v2.7. SAPM is a mathematical simulation model previously used to appraise alcohol policy options in the UK and internationally. In particular, SAPM v2.7 informed development of the 2016 UK alcohol guidelines

The key data inputs into this Australian adaptation of SAPM (hereafter SAPM-AU) are current levels of alcohol consumption in Australia, current levels of alcohol-related mortality and morbidity (defined as person-specific hospital admissions) in Australia, and international or Australia-specific evidence relating different levels and patterns of alcohol consumption to risk of mortality or morbidity from 42 separate health conditions that are causally related to alcohol consumption.

SAPM divides the 42 health conditions into four categories:

1. *Partially-attributable, chronic*: These are conditions that can occur without alcohol consumption but for which the risk of occurrence changes with long-term exposure to alcohol (e.g. breast cancer). For a small number of primarily cardiovascular conditions within this category, lower levels of alcohol consumption may be associated with a reduced risk of occurrence relative to abstention from alcohol;
2. *Partially-attributable, acute*: These are conditions that can occur without alcohol consumption but for which the risk of occurrence changes with short-term exposure to alcohol (e.g. falls).
3. *Wholly-attributable, chronic*: These are conditions that cannot occur in the absence of alcohol consumption and for which the risk of occurrence changes with long-term exposure to alcohol (e.g. alcoholic liver disease);
4. *Wholly-attributable, acute*: These are conditions that cannot occur in the absence of alcohol consumption and for which the risk of occurrence changes with short-term exposure to alcohol (e.g. alcohol poisoning);

SAPM-AU defines drinkers' long-term exposure to alcohol as their mean weekly alcohol consumption in standard drinks and drinkers' short-term exposure to alcohol as the amount consumed on their heaviest drinking day during the last year (hereafter peak daily consumption). It divides the Australian population into 30 groups defined by their age and gender and then combines risk estimates for each condition to produce an overall estimate of each group's risk of dying due to alcohol for any given level of mean weekly and peak daily alcohol consumption. From these estimates, we can derive a set of risk curves for men and women describing how lifetime risk of alcohol-attributable mortality changes as mean weekly alcohol consumption increases. The curves vary depending on how drinkers spread their alcohol consumption across the week as this affects peak daily consumption and therefore the risk of acute conditions. For example, SAPM-AU assumes consuming 20 standard drinks in one day entails a larger risk of acute conditions than spreading those drinks evenly across seven days, even though the risk for chronic conditions stays the same (except for certain circumstances associated with chronic ischaemic heart disease – see main report).

Summary of main findings

Figure 1 shows the absolute lifetime risk of alcohol-attributable mortality at increasing levels of mean weekly alcohol consumption for men and women, assuming drinkers spread their consumption evenly across five days. This pattern is chosen for illustrative purposes only. Women are at greater risk of dying as a result of their drinking than men at all levels of alcohol consumption and this is the case irrespective of how many days drinkers spread their consumption across. Table 1 and Table 2 show the same information for men and women respectively in numerical form and for other drinking patterns where consumption is spread evenly across between one and seven days.

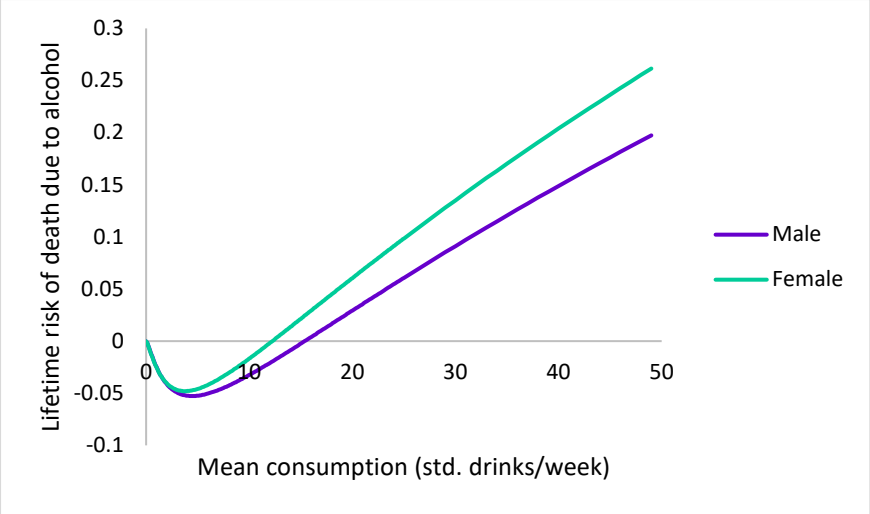

Figure 1: Absolute lifetime alcohol-attributable mortality risk for drinkers spreading their consumption evenly across five days per week

Table 1: Absolute lifetime risk of alcohol-attributable mortality for men by mean weekly consumption and days per week across which consumption is evenly spread

Mean consumption (std. drinks/week)	**Drinking days per week**						
	7	6	5	4	3	2	1
7	-4.9%	-4.9%	-4.7%	-4.2%	-3.2%	-0.9%	4.3%
14	-2.3%	-1.7%	-0.9%	0.3%	2.1%	5.0%	10.3%
21	1.4%	2.4%	3.6%	5.0%	6.9%	9.6%	14.8%
28	5.5%	6.7%	7.9%	9.4%	11.2%	13.5%	18.7%
35	9.7%	10.9%	12.1%	13.4%	15.1%	17.1%	22.3%
42	14.1%	15.0%	16.0%	17.2%	18.7%	20.8%	25.9%
49	18.5%	18.9%	19.7%	20.7%	22.1%	24.6%	29.5%

Table 2: Absolute lifetime risk of alcohol-attributable mortality for women by mean weekly consumption and days per week across which consumption is evenly spread

Mean consumption (std. drinks/week)	**Drinking days per week**						
	7	6	5	4	3	2	1
7	-3.9%	-3.9%	-3.7%	-3.2%	-2.3%	0.0%	4.0%
14	0.1%	0.6%	1.4%	2.5%	4.1%	6.9%	10.8%
21	5.1%	5.8%	6.8%	8.2%	9.8%	12.2%	16.0%
28	10.3%	11.0%	12.1%	13.4%	15.0%	16.7%	20.4%
35	15.3%	16.1%	17.0%	18.2%	19.6%	21.0%	24.5%
42	20.2%	20.9%	21.7%	22.7%	23.8%	25.2%	28.4%
49	24.8%	25.5%	26.1%	26.9%	27.8%	29.6%	32.5%

Key:

Overall protective effect
Overall lifetime risk of less than 1 in 1,000
Overall lifetime risk at least 1 in 1,000, but below 1 in 500
Overall lifetime risk at least 1 in 500, but below 1 in 100
Overall lifetime risk at least 1 in 100, but below 1 in 50
Overall lifetime risk at least 1 in 50, but below 1 in 10
Overall lifetime risk at least 1 in 10

Table 3 shows the consumption levels associated with the 1.0% absolute risk thresholds for mortality and the alternative mortality risk thresholds. Figures in the table correspond to the level of consumption (in standard drinks per week) associated with a lifetime risk of death caused by alcohol, according to the extent to which individuals spread their drinking across the week.

The consumption level associated with the 1.0% threshold varies between 4.1 and 20.2 standard drinks per week for men and 4.7 and 15.3 for women. These figures do not change substantially for the alternative risk thresholds. Irrespective of drinking pattern, the consumption level associated with these thresholds varies by no more than 3.5 standard drinks per week for men and 2.9 for women.

Table 3 also shows the results of the sensitivity analyses. It suggests that the consumption level associated with the 1.0% absolute risk threshold for mortality is subject to substantial uncertainty due to the scientific debate regarding the existence and extent of any protective effects arising from lower levels of alcohol consumption. Introducing threshold consumption levels into the calibrated risk relationships (i.e. those estimated within SAPM-AU) below which the risk of drinking is equal to the risk of abstaining did not substantially affect the results. Using an all-cause mortality approach with a single all-cause risk function, rather than synthesising risks for 42 separate conditions, led to a substantially higher consumption being associated with the 1.0% threshold. This approach could not take account of variation in drinking patterns as it relates both acute and chronic risks to mean weekly consumption and we describe additional important problems with this approach in the main report.

Table 3: Estimated consumption levels (std. drinks/week) corresponding to different absolute and relative mortality risk thresholds in the base case model and in sensitivity analyses

	Risk level								
	RR= Minimum	RR= 1.0	AR= 0.1%	AR= 0.2%	AR= 1.0%	AR= 2.0%	SA1: No protective effects	SA2: Threshold	SA3: All-cause
Men									
Daily	5.5	18.4	18.5	18.7	20.2	21.9	2.9	21	
6 times/week	5.1	16.9	17.1	17.2	18.6	20.2	2.8	19.6	
5 times/week	4	15.3	15.5	15.7	16.9	18.5	2.5	17.7	
4 times/week	3.5	13.4	13.6	13.7	14.9	16.4	2.6	15.7	29.0
3 times/week	2.6	11.2	11.3	11.4	12.5	13.8	2.5	13.2	
2 times/week	1.7	7.9	8	8.1	9	10.1	2.6	9.8	
Once/week	0.1	3.3	3.4	3.4	4.1	4.9	0	4.7	
Women									
Daily	4.5	13.8	14	14.1	15.3	16.7	2.3	15	
6 times/week	4.2	13.1	13.3	13.4	14.5	15.8	2.2	14	
5 times/week	3.9	12.2	12.3	12.5	13.5	14.8	2.2	12.9	
4 times/week	3.1	11	11.1	11.2	12.1	13.3	2.1	11.5	29.0
3 times/week	2.3	9.4	9.5	9.6	10.5	11.6	2.5	9.6	
2 times/week	1.9	6.9	7	7.1	7.8	8.8	2.2	7.1	
Once/week	0.8	4	4.1	4.1	4.7	5.4	0.1	3.8	

Shading indicates base case model. AR: Absolute risk; RR: Relative risk; SA: Sensitivity analysis. Risk thresholds for all sensitivity are AR=1.0%. SA1 excludes all protective effects from literature-based risk functions. SA2: inserts a threshold into all calibrated risk functions below which drinkers have the same risk as abstainers. SA3 uses a single all-cause mortality risk function rather than synthesising risk functions for 42 alcohol-related health conditions.

The sensitivity analyses addressing protective effects (SA1) and thresholds effects (SA2) relate to important points of scientific debate. As such, the findings of these sensitivity analyses should be considered alongside the base case results. To facilitate this, Figure 2 for men and Figure 3 for

women compare how absolute lifetime risk of alcohol-attributable mortality changes with increasing mean weekly alcohol consumption, assuming drinkers spread that consumption evenly across five days.

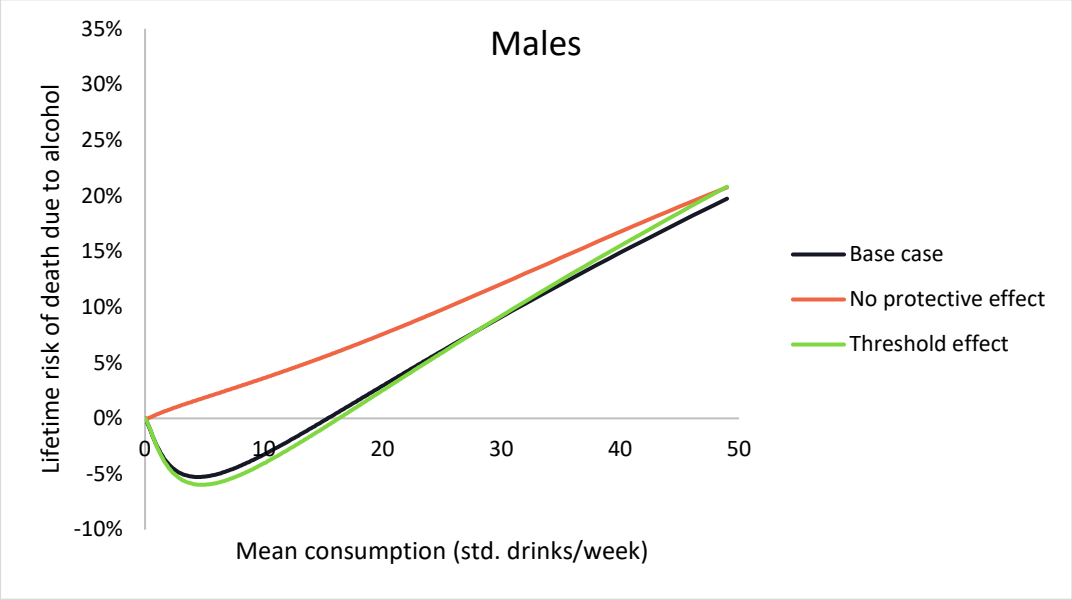

Figure 2: Mortality risks for men spreading their consumption evenly over five days under sensitivity analyses

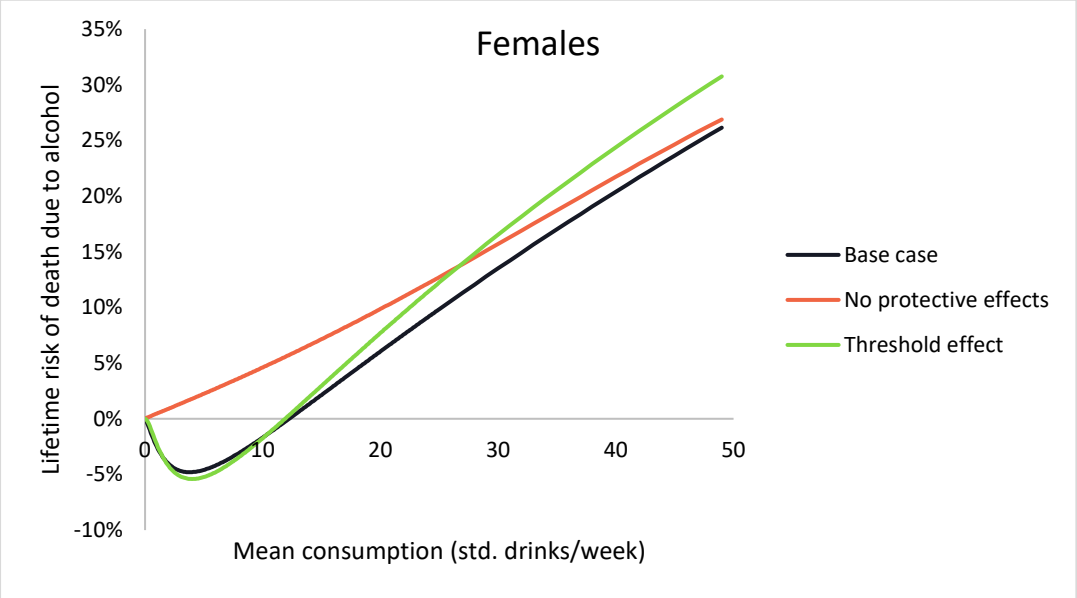

Figure 3: Mortality risks for women spreading their consumption evenly over five days under sensitivity analyses

The main report provides additional results for analyses of alcohol-attributable morbidity but these are not discussed in detail in this executive summary as guideline development committees in other countries have tended to foreground findings for mortality when presenting their decisions.

Implications of the results for setting a guideline alcohol consumption level

It is beyond the scope of this report to make specific recommendations on appropriate alcohol guidelines for Australia or to specify the processes by which NHMRC should develop such guidelines. The conclusions below seeks instead to highlight key points relating to our results for consideration

by NHMRC during the guideline development process and for readers seeking to understand how results from SAPM-AU can be used in that process.

The results above indicate that the general shape of the relationship between alcohol consumption and risk of alcohol-related mortality is curvilinear and may include reduced risks at moderate levels of alcohol consumption. The absolute level of mortality risk is much greater at higher consumption levels than lower consumption levels. The results also indicate that men are at a lower risk than women from alcohol consumption at all levels of consumption and that the risk of consuming a given amount of alcohol each week is lower when that consumption is spread evenly across a larger number of days.

The results also provide some indication of how evidence on alcohol-related health mortality risks has evolved since the previous 2009 Australian alcohol guidelines. Although the models are not directly comparable, it is clear that evidence of mortality risks at lower levels of alcohol consumption exerts a greater impact on the overall risk curve that was previously the case.

The sensitivity analyses indicate that the precise level of alcohol consumption associated with any particular mortality risk threshold is subject to substantial uncertainty. Similarly, the level of risk associated with any particularly alcohol consumption level is also uncertain. This is because of limitations in the underlying data and scientific evidence, and SAPM-AU itself. It is also due to major points of scientific debate, such as the existence and extent of any cardioprotective effects. The scientific debate over cardioprotective effects is extensive and the findings of multiple studies suggest there is substantial uncertainty regarding the existence of these effects. At a minimum, it is likely that standard epidemiological studies overestimate the size of any health benefits arising from moderate drinking and the consumption levels at which such benefits can be achieved.

All users of the results should bear in mind that the mortality and morbidity risk estimates presented in this report are the average risk for the population of men or women assuming that population all has the same consumption level and pattern. The results are not estimates of the risk faced by any given individual in the population as both the level of risk faced by an individual and the health conditions individuals are at risk from vary depending on a range of sociodemographic, psychological, biological and situational factors. For similar reasons, the risk curves do not describe how mortality or morbidity risks would change for an individual who changes their consumption, as this will depend on the individual's characteristics, drinking history and underlying health profile. Caution is therefore required to avoid providing misleading information when using individualised language to communicate the risk estimates to the public.

Finally, the analyses in this report examine only risks of mortality and morbidity for the drinker. They do not examine risks for other important outcomes that NHMRC may wish to consider. These outcomes include alcohol dependence, harms to people other than the drinker, non-health harms such as lost income or family problems, and increased or reduced well-being.

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1. Introduction

1.1. Background

The National Health and Medical Research Council (NHMRC) published the current Australian alcohol guidelines in 2009.[1] These guidelines recommended that men and women drink no more two standard drinks per day (one standard drink contains 10g of pure ethanol) as this reduces the risk of harm from alcohol-related disease or injury over a lifetime. They also recommend drinking no more than four standard drinks on a single occasion as this reduces the risk of alcohol-related injury arising from that occasion. The NHMRC is now developing revised alcohol guidelines and commissioned this report to inform the guideline development process.

New evidence on alcohol-related health risks has emerged since 2009. In particular, there is increased evidence that even low levels of alcohol consumption can increase drinkers' risk of experiencing some types of cancer.[2] An increased number of studies are also finding evidence that previous research may have overestimated any potential benefits to cardiovascular health that may arise from lower levels of alcohol consumption.[3-6] It is therefore important to base the revised guidelines on an updated analysis of the relevant evidence.

Increasingly, it is standard international practice to use an epidemiological modelling exercise to inform the development of alcohol consumption guidelines. This was the case for the 2009 Australian guidelines and also the 2011 Canadian guidelines, the 2016 UK guidelines and the 2017 French guidelines.[7-9] The European Union's Reducing Alcohol Related Harm (RARHA) project also used a similar model to recommend guidelines for seven European countries in 2015.[10] Such epidemiological models provide guideline developers with evidence, tailored to the population of interest (e.g. Australian drinkers), on the risks to health associated with different levels and patterns of alcohol consumption. They can also identify the alcohol consumption level that corresponds to one or more pre-specified risk thresholds. For example, NHMRC set the 2009 Australian guidelines at a level that corresponds approximately to the average drinker having a one per cent chance of dying due to alcohol across their life course. The committee that developed the guidelines judged this threshold to reflect an 'acceptable' level of risk from alcohol after taking account of wider societal standards for governing risks to population health and considering the risks individuals appear willing to take during their daily lives. Those developing guidelines for other countries have sometimes based their recommendations on alternative risk thresholds. The RAHRA project recommended guidelines for seven countries based on a lower acceptable risk of a 0.1% chance of dying due to alcohol,[10] drawing on a previous analysis of the public's willingness to accept voluntary and involuntary exposure to risks.[11,12] The developers of the 2011 Canadian guidelines based their recommendations on the consumption level at which the average drinkers' risk of dying due to alcohol exceeds that of the average abstainer, effectively adopting a zero additional risk from alcohol approach.[13] The NHMRC and its advisors continue to prioritise the 1% acceptable risk threshold, but are interested in assessing how the consumption level corresponding to this threshold varies when using other lower and higher risk thresholds.

1.2. Aims

The NHMRC commissioned this report to provide evidence relating to the points above. In particular, the report aims to estimate for men and women who drink alcohol in Australia:

1. The lifetime risk of mortality and morbidity due to alcohol that is associated with increasing levels of alcohol consumption, and how those risks change depending on how drinkers spread their consumption across the week;
2. The consumption levels associated with a set of pre-specified risk thresholds, namely:

a. A 1.0% (i.e. 1 in 100) lifetime alcohol-attributable mortality risk;
b. Lifetime alcohol-attributable mortality risks of 0.1%, 0.2% and 2.0% (i.e. 1 in 1,000, 1 in 500 and 1 in 50), to understand how sensitive the consumption level is to the exact definition of an acceptable risk;
c. A 0.0% lifetime alcohol-attributable mortality risk, which is equivalent to the risk associated with not drinking;
d. The minimum level of lifetime alcohol-attributable mortality risk, which is the nadir of the risk curve.

3. How sensitive the results are to the use of alternative analytical methods and assumptions.

Meeting these aims requires six steps. First, to identify and synthesise estimates of alcohol-related risks to health across a range of conditions for the Australian population. Second, to use this synthesised evidence to estimate the level of alcohol-attributable harm experienced in Australia arising from current drinking levels and patterns. Third, to model how these levels of harm would differ under alcohol consumption scenarios for the population. Fourth to derive risk curves from these scenarios describing drinkers in Australia's overall mortality and morbidity risk from different levels and patterns of alcohol consumption. Fifth, to identify the alcohol consumption levels corresponding to the pre-specified risk thresholds. Sixth, to re-run the analyses using alternative analytical methods of modelling assumptions and assess how the results differ to those in the original base case model.

2. Methods

2.1. Overview of the modelling approach

This report uses analyses completed with a new adaptation of the Sheffield Alcohol Policy Model (SAPM) v2.7. SAPM is a mathematical simulation model that we have previously used to appraise UK and international alcohol policy options.[14-19] It also provided evidence that informed the development of the 2016 UK alcohol gudielines.[8] The model comprises two modules. The first module estimates the impact of policy changes on alcohol consumption and the second module estimates the impact of alcohol consumption changes on rates of alcohol-related harm, including health conditions, crime and workplace absenteeism. The present analysis only uses the second of these modules and focuses on health outcomes. The new adaptation of SAPM used here, SAPM-AU, incorporates Australia-specific data on alcohol consumption and health outcomes as well as incorporating new epidemiological evidence from the literature reviews undertaken as part of the current guidelines revision process.[20]

We use SAPM-AU to estimate risk curves, similar to Figure 1, that describe the relationship between alcohol consumption and risk of mortality or morbidity from alcohol-related health conditions. SAPM-AU creates the risk curves by combining Australia-specific data on population demographics, alcohol consumption and health outcomes with literature and model-based estimates of alcohol-related health risks for 42 separate conditions. The resulting risk curves represent the average risk of alcohol-attributable mortality or morbidity across all 42 conditions, weighted to account for differences in average risk levels across the population. All 42 conditions are included in both mortality and morbidity analyses.

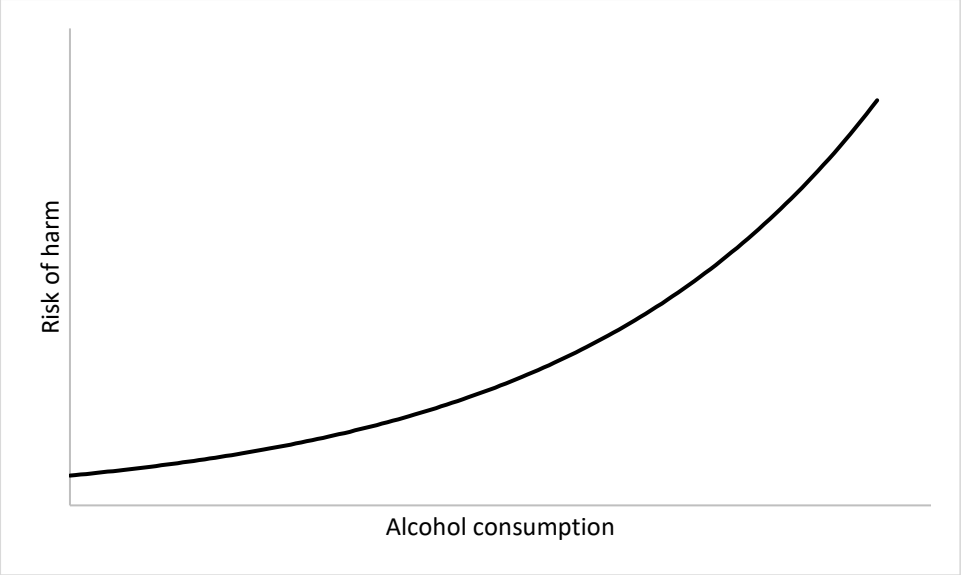


Figure 4: Example risk curve relating consumption levels to risk of alcohol-attributable harm

The estimation process has three stages. First, we estimate the absolute prevalence of mortality and morbidity in a single year across all conditions under a scenario where the entire Australian population abstains from drinking alcohol. Second, we compare these rates of harm with those estimated to occur when the Australian population all drink at the same level and pattern. We do this across a range of alcohol consumption levels to generate a series of risk estimates. For each consumption level, we also generate estimates for each of seven scenarios describing how many days drinkers spread their weekly alcohol consumption evenly across (e.g. drinking it all on one day each week or spreading it evenly across seven days). Third, we plot the risk estimates on a graph and fit a polynomial curve to them, which serves as the final risk curve.

We can use this approach to generate either absolute or relative risk curves but we focus on absolute risk in this report, as this is the metric used in the acceptable risk approached favoured by NHMRC. We derive separate risk curves for men and women and, where available data permit, for mortality and morbidity. These curves describe the relationship between:

- Mean weekly alcohol consumption and mortality/morbidity risk for chronic alcohol-related related conditions (see Table 1);
- Single occasion alcohol consumption and mortality/morbidity risk for acute alcohol-related conditions (see Table 1);
- Mean weekly alcohol consumption distributed evenly over one to seven days and overall alcohol-related mortality and morbidity risk.

Only the set of curves in the final bullet point are used to identify the alcohol consumption levels that correspond to particular risk thresholds.

2.2. Data

SAPM-AU requires recent datasets detailing individual-level alcohol consumption and prevalence of mortality and morbidity for alcohol-related health conditions and all other conditions to derive inputs to the model. It also requires data on population demographics to create accurate weighted averages of risk levels across the population.

2.2.1. Population demographics data

Data on the current age-sex breakdown of the Australian population come from figures published by the Australian Bureau of Statistics relating to the estimated population at 30th June 2017.[21] SAPM-AU requires population figure for each single year of age in the model (ages 18-89), however the published figures grouped ages 85-89 together. We estimated single year populations for these ages by partitioning the five-year figures for each gender assuming the same within-group age distribution to the 80-84 year-old age group.

2.2.2. Alcohol consumption data

Data on current levels and patterns of alcohol consumption come from the 2016 National Drug Strategy Household Survey (NDSH). The NDSH asks respondents questions about their typical alcohol weekly consumption using both graduated frequency and a simpler quantity-frequency approach.[22] Responses were converted to a single measure of mean weekly consumption, standard drinks per week (1 standard drink = 10 grams of ethanol) using a previously-described approach.[23] SAPM-AU also requires a measure of drinking patterns in order to estimate risks associated with acute harms (i.e. those harms associated with intoxication). This was taken from existing derived variables in the NDSH dataset describing respondents' drinking levels on their heaviest drinking day in the last year (referred to hereafter as peak daily consumption).

SAPM-AU separates modelled individuals taken from the NDSH into groups defined by gender and 15 age bands (18-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89). Although the NDSH includes data on each respondent's gender and age, it censors the age data for all respondents aged over 79. We randomly allocated these respondents to either the 80-84 or 85-89 year old age groups within SAPM-AU based on the proportion of the total adult population in each group within the population demographics data, stratified by gender.

The NDSH data also includes a range of survey weight variables. All analyses using SAPM-AU were undertaken using population weights that account for the survey design, with weights scaled up so that weighted totals match the total adult population of Australia.

2.2.3. Alcohol-related health condition data

The health data used within SAPM-AU come from the Australian Institute of Health and Welfare (AIHW). Mortality data certified by either a medical practitioner or a coroner were collected from death certificates. The number of deaths for each of the 42 health condition as well as for all other causes combined, was supplied for each of the 15 age groups included in the model, further stratified by gender. Data were provided pooled across the years 2012 to 2016. We converted these numbers into the average annual mortality rates for each condition, using population data for each year. Mortality data for one ICD-10 code was not available (X45 – accidental poisoning by and exposure to alcohol) and we obtained population-level data for this code from published Australian Bureau of Statistics data[24] and partitioned cases between age groups using the distribution of deaths from all accidental poisoning causes (X40-X49).[25] For one health condition, oesophageal cancer, an additional data processing step is required. Oesophageal cancer cases can be divided into two histological types – squamous cell carcinoma (SCC) and adenocarcinoma (AC). Only SCC is related to alcohol,[26] however these two types cannot readily be distinguished in mortality or hospital records using ICD-10 codes. We therefore use external evidence on the proportion of oesophageal cancer cases in Australia which fall into each histological type, by gender, in order to estimate the rates of SCC mortality and admissions.[27]

We derived the morbidity data used in the model from admissions counts reported in the National Hospital Morbidity Database from the period 01/01/2012 to 31/12/2016. The database provided

total counts of admissions for each age-gender group for each of the 42 health conditions included in the SAPM-AU. These are combined within the model with data on the average number of hospital admissions per year for somebody presenting with each of the 42 health conditions in order to estimate the underlying prevalence of each health condition within each modelled subgroup.

Table 4 shows a list of the 42 alcohol-related health conditions included within SAPM-AU. The NHMRC's review of alcohol-related health risks suggests alcohol plays a contributory role in each of these conditions.[20] The list is similar to that used in previous analyses using SAPM and other epidemiological modelling exercises.[8,28,29] Table 4 divides the conditions into four categories based on whether they are partly or wholly due to alcohol and whether they are due to chronic (i.e. mean weekly) or acute (i.e. peak daily) alcohol consumption.

- *Partially-attributable, chronic*: These are conditions that can occur without alcohol consumption but for which the risk of occurrence changes with long-term exposure to alcohol (e.g. breast cancer). For a small number of primarily cardiovascular conditions within this category, lower levels of alcohol consumption may be associated with a reduced risk of occurrence relative to abstention from alcohol;
- *Partially-attributable, acute*: These are conditions that can occur without alcohol consumption but for which the risk of occurrence changes with short-term exposure to alcohol (e.g. falls);
- *Wholly-attributable, chronic*: These are conditions that cannot occur in the absence of alcohol consumption and for which the risk of occurrence changes with long-term exposure to alcohol (e.g. alcoholic liver disease);
- *Wholly-attributable, acute*: These are conditions that cannot occur in the absence of alcohol consumption and for which the risk of occurrence changes with short-term exposure to alcohol (e.g. excessive alcohol blood levels).

2.2.4. Condition-specific risk functions

SAPM-AU uses an epidemiological approach to model the relationship between alcohol consumption and related harm. The fundamental components of the model are therefore relative risk functions relating mean weekly and peak daily consumption to level of absolute or relative risk for the 42 alcohol-related health conditions. The approach to identifying condition-specific risk functions differed for each of the four types of health condition.

2.2.4.1. Relative risk functions for partially alcohol-attributable chronic conditions

Figure 5 shows the risk functions linking mean weekly alcohol consumption to conditions partially attributable to alcohol. We take these risk functions from published systematic reviews and meta-analyses of the epidemiological research literature and Table 4 shows the source literature. Table 4 and Table 3 also indicate the conditions for which separate risk functions are available in the literature for men and women and for mortality and morbidity. Where separate risk functions are not available, we assume there is no difference in the risk relationship between these categories.

The selected risk functions imply a reduced risk of mortality or morbidity from the following conditions at some levels of mean weekly alcohol consumption: Non-Hodgkin's lymphoma, hypertension, chronic ischaemic heart disease, acute pancreatitis, and type II diabetes. The model also includes protective effects at lower levels of consumption for acute myocardial infarction, which is modelled as a function of peak day consumption.

Table 4: Alcohol-attributable health conditions included in SAPM-AU

Health condition	ICD-10 codes	Risk curve source
Partially alcohol-attributable chronic conditions		
Mouth, pharynx and larynx	C00–C14	WCRF review[30*]
Oesophageal cancer	C15	WCRF review[31]
Stomach cancer	C16	WCRF review[32]
Colorectal cancer	C18–C20	WCRF review[33]
Liver cancer	C22	WCRF review[34]
Pancreatic cancer	C25	WCRF review[35]
Breast cancer	C50	WCRF review[36†]
Prostate cancer	C61	Zhao et al.[37]
Non-Hodgkin's Lymphoma	C82–C85	Bagnardi et al.[26]
Hypertension	I10–I14	Briasoulis et al.[38]
Chronic ischaemic heart disease	I20–I25 excl. I21	Yang et al.[39]
Atrial fibrillation	I48	Larsson et al.[40]
Stroke	I60–I64	Patra et al.[41‡]
Other cerebrovascular diseases	I65–I67	Patra et al.[41]
Chronic hepatitis, fibrosis and cirrhosis of liver	K73-K74	Rehm et al.[42]
Fatty liver disease	K76.0	Rehm et al.[42]
Acute pancreatitis (other)	K85 excl. K85.2	Samokhvalov et al.[43]
Chronic pancreatitis (other)	K86 excl. K86.0	Samokhvalov et al.[43]
Tuberculosis	A15–A19	Lonnroth et al.[44]
Diabetes (Type II)	E11	Knott et al.[45]
Epilepsy and status epilepticus (seizures)	G40–G41	Samokhvalov et al.[46]
Pneumonia	J12–J18	Samokhvalov et al.[47]
Gout	M10	Wang et al.[48]
Partially alcohol-attributable acute conditions[§]		
Intentional self-harm	X60–X84	Calibrated
Unintentional falls (without hip fracture)	W00–W19, excl. S72.0-S72.2 as associated cause	Calibrated
Unintentional falls (with hip fracture)	W00–W19 with S72.0-S72.2 as associated cause	Calibrated
Accidental poisoning (other)	X40–X49 excl. T36-T50, T52-T65 as associated cause	Calibrated
Accidental poisoning (by drugs, medicaments, biological substances and other nonmedicinal substances)	X40–X49 with T36-T50, T52-T65 as associated cause	Calibrated
Motor vehicle injury	V01–V89	Calibrated
Other injury and poisoning with selected reported external cause range(s)	All other injury codes V01-Y34	Calibrated
Acute myocardial infarction	I21	Mostofsky et al.[49]
Wholly alcohol-attributable chronic conditions		
Alcoholic cardiomyopathy	I42.6	Calibrated
Alcoholic liver disease	K70	Calibrated
Acute pancreatitis (alcohol induced)	K85.2	Calibrated
Chronic pancreatitis (alcohol induced)	K86.0	Calibrated

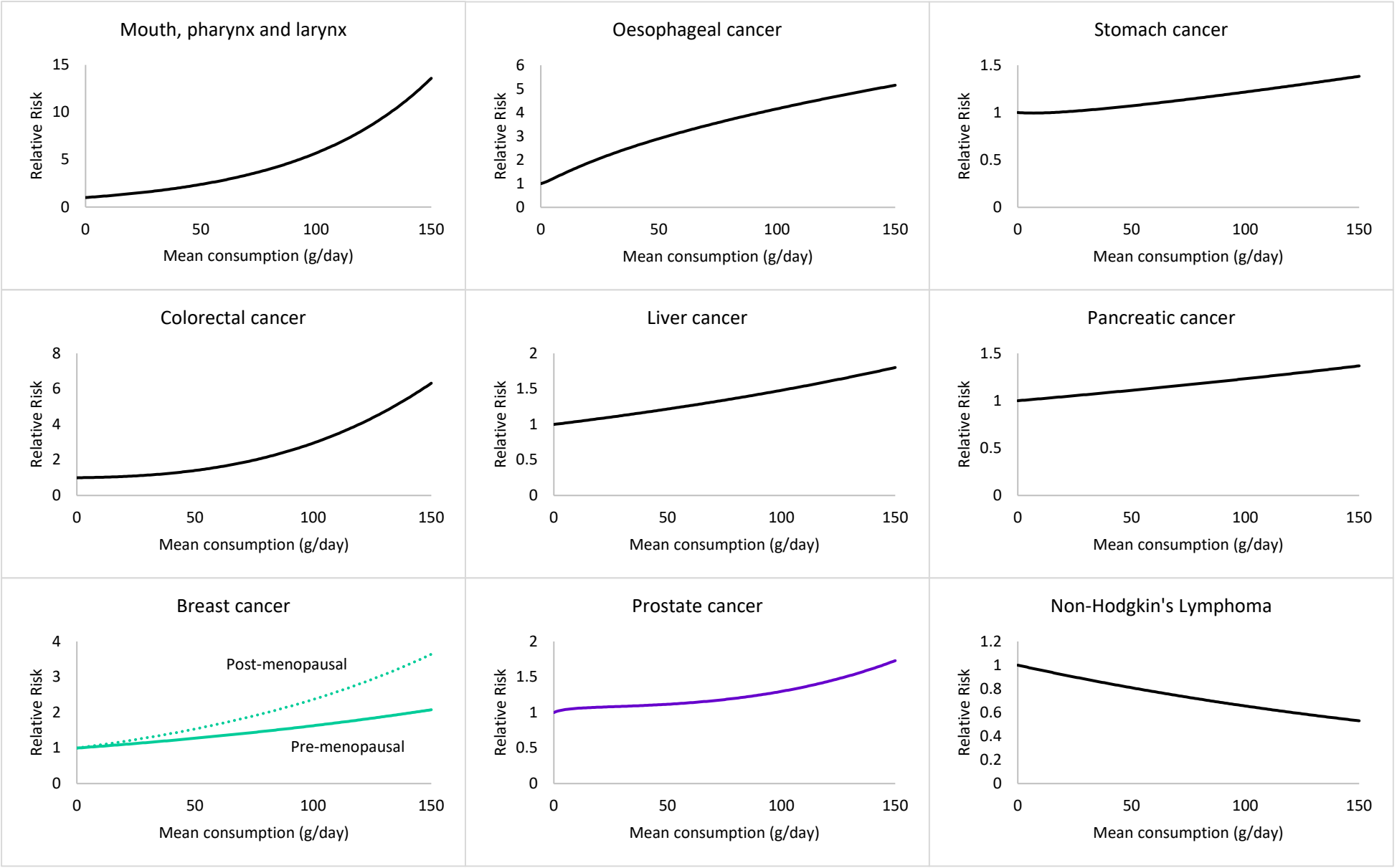
[*] WCRF: World Cancer Research Fund

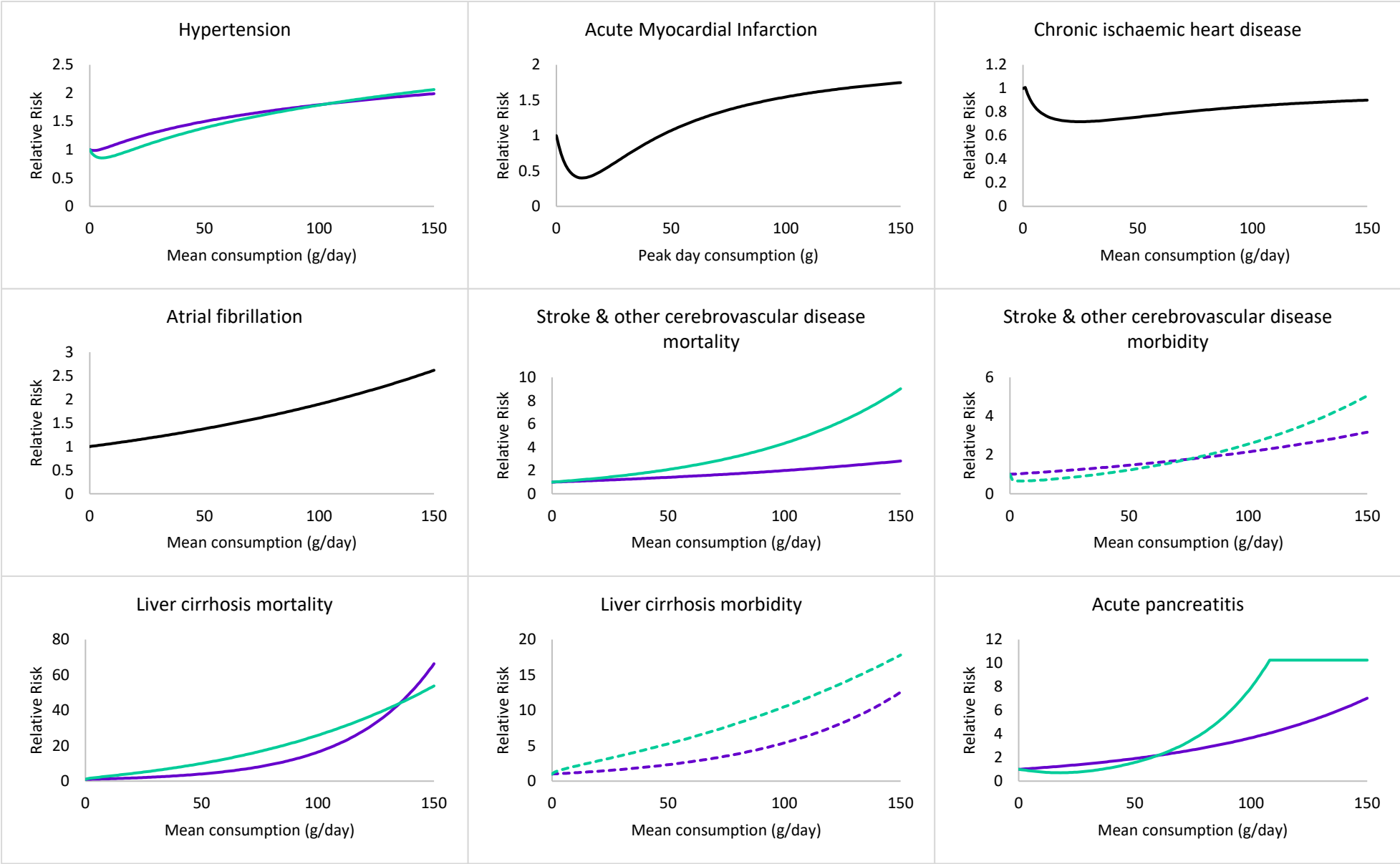
[†] This source provides separate risk curves for pre- and post-menopausal women. We apply the pre-menopausal curve to women aged under 50 and the post-menopausal curve to women aged 50+

[‡] This source differs from that identified in the NHMRC review as that did not include sufficient data on risks at higher levels of consumption

[§] Hospital data uses a slight variation on ICD-10 codes known as ICD-10-AM, this differs from the ICD-10 coding used in the mortality data only in the fact that at least one code S00-T75, T79 is required as the principal diagnosis code for the following conditions: Intentional self-harm, Unintentional falls (without hip fracture), Accidental poisoning (other), Motor vehicle injury and Other injuries.

Alcoholic gastritis	K29.2	Calibrated
Degeneration of nervous system due to alcohol	G31.2	Calibrated
Alcoholic polyneuropathy	G62.1	Calibrated
Alcoholic myopathy	G72.1	Calibrated
Alcohol-induced pseudo-Cushing's syndrome	E24.4	Calibrated
Mental and behavioural disorders due to alcohol	F10	Calibrated
Wholly alcohol-attributable acute conditions		
Excess alcohol blood levels	R78.0	Calibrated


Mouth, pharynx and larynx
Relative Risk
15
10
5
0
0
50
100
150
Mean consumption (g/day)
Oesophageal cancer
Relative Risk
6
5
4
3
2
1
0
0
50
100
150
Mean consumption (g/day)
Stomach cancer
Relative Risk
1.5
1
0.5
0
0
50
100
150
Mean consumption (g/day)
Colorectal cancer
Relative Risk
8
6
4
2
0
0
50
100
150
Mean consumption (g/day)
Liver cancer
Relative Risk
2
1.5
1
0.5
0
0
50
100
150
Mean consumption (g/day)
Pancreatic cancer
Relative Risk
1.5
1
0.5
0
0
50
100
150
Mean consumption (g/day)
Breast cancer
Relative Risk
4
3
2
1
0
Post-menopausal
Pre-menopausal
0
50
100
150
Mean consumption (g/day)
Prostate cancer
Relative Risk
2
1.5
1
0.5
0
0
50
100
150
Mean consumption (g/day)
Non-Hodgkin's Lymphoma
Relative Risk
1.2
1
0.8
0.6
0.4
0.2
0
0
50
100
150
Mean consumption (g/day)


Hypertension
Relative Risk
Mean consumption (g/day)
Acute Myocardial Infarction
Relative Risk
Peak day consumption (g)
Chronic ischaemic heart disease
Relative Risk
Mean consumption (g/day)
Atrial fibrillation
Relative Risk
Mean consumption (g/day)
Stroke & other cerebrovascular disease mortality
Relative Risk
Mean consumption (g/day)
Stroke & other cerebrovascular disease morbidity
Relative Risk
Mean consumption (g/day)
Liver cirrhosis mortality
Relative Risk
Mean consumption (g/day)
Liver cirrhosis morbidity
Relative Risk
Mean consumption (g/day)
Acute pancreatitis
Relative Risk
Mean consumption (g/day)

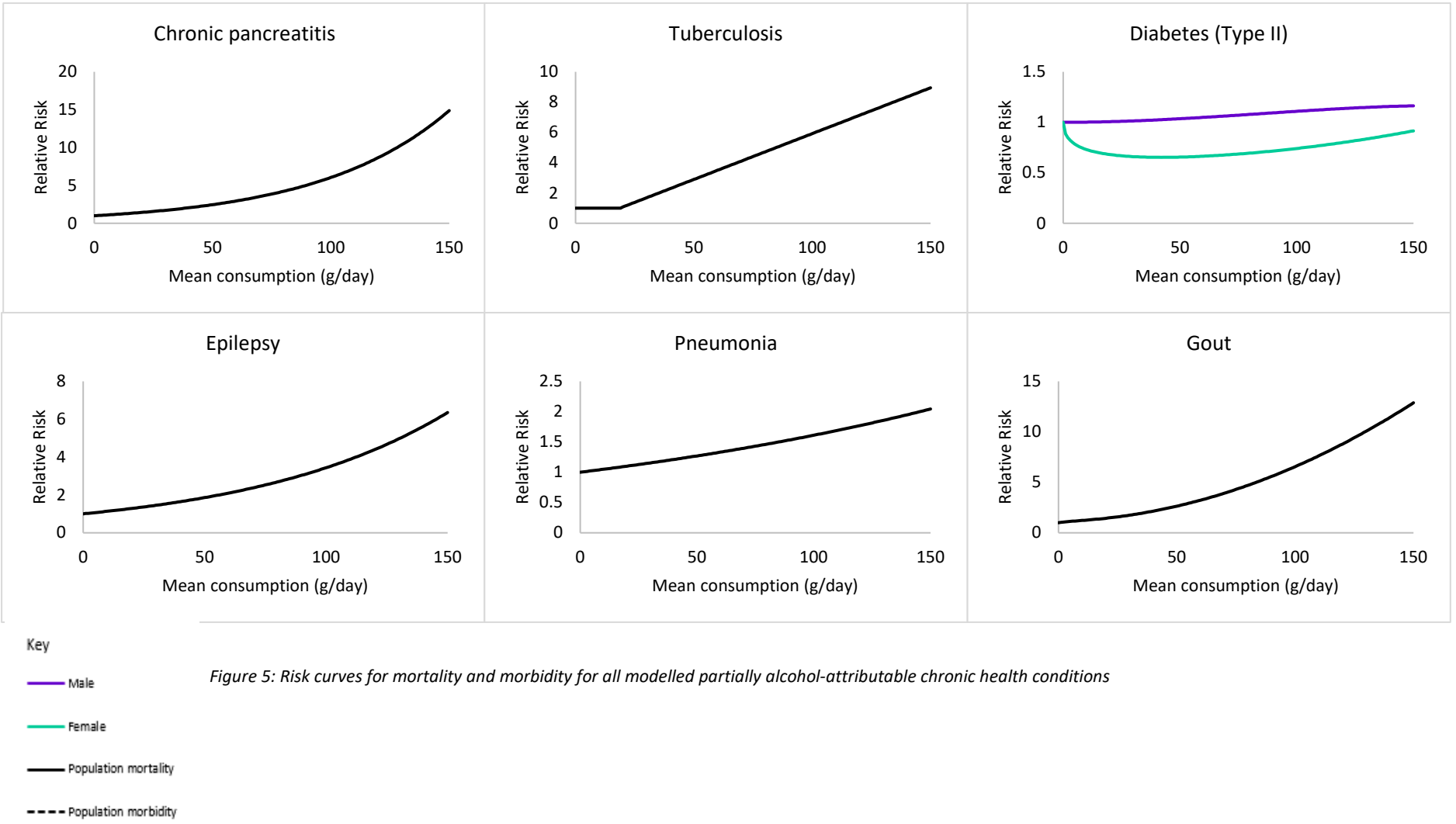


Figure 5: Risk curves for mortality and morbidity for all modelled partially alcohol-attributable chronic health conditions

2.2.4.2. Chronic ischaemic heart disease and binge drinking

Chronic ischaemic heart disease (IHD) is a special case in SAPM-AU as it is the only condition where we adjust a literature-based risk function to reflect additional evidence. The source for the main risk function suggests that all drinkers have a reduced risk of IHD relative to men or women who abstain from alcohol.[39] However, an earlier study from Roerecke and Rehm finds this reduced risk is substantially attenuated or eliminated for those who engage in heavy episodic drinking, defined as consuming six or more standard drinks on a single day, at least once a month.[50] SAPM-AU does not consider frequency of heavy episodic drinking directly so we incorporate this additional evidence using a method employed by Shield et al.[51] whereby the chronic IHD risk function is adjusted to assume that drinkers consuming more than six standard drinks per day on average (i.e. 42 standard drinks per week) have an IHD relative risk of 1.0 when the original risk function is less than RR=1.0 and follow the original risk function when RR≥1.0. This adjustment is limited and conservative as drinkers who consume less than 42 units per week will all still have a reduced risk of IHD despite many of them consuming more than six units on a single day at least once a month.

2.2.4.3. Relative risk functions for partially alcohol-attributable acute conditions

SAPM-AU takes account of evidence linking occasion-level drinking with risks of acute myocardial infarction which suggests that low levels of consumption have a temporary protective effect, while heavier drinking on an occasion leads to an increased risk of harm.[49]

Whilst some studies have calculated risk functions for other partially alcohol-attributable acute conditions, such as injuries, these are typically based on occasion-level risk, rather than annual risk. As such, incorporating such evidence into a harm model requires the detailed modelling of individual occasion-level drinking patterns.[52,53] In the absence of such detailed modelling for Australia we therefore use an alternative approach to derive risk functions linking peak daily consumption to risk of each of these conditions. This approach is based around the alcohol-attributable fraction (AAF).

The AAF describes the proportion of cases of an alcohol-attributable condition or group of conditions that would not occur if nobody drank alcohol. We derive the AAF using the following formula:

$$AF = \frac{\sum_{i=1}^{n} p_i \left(RR_i - 1\right)}{1 + \sum_{i=1}^{n} p_i \left(RR_i - 1\right)}$$

Equation 1

Where RR_i is the relative risk due to exposure to alcohol at consumption level *i*, p_i is the proportion of the population consuming alcohol at level *i* and *n* is the number of consumption levels. The numerator is therefore the excess expected number of cases of the condition due to alcohol consumption and the denominator is the total expected number of cases.

For these conditions the risk functions are calibrated using published AAFs and the distribution of peak day consumption in each of the 30 groups (as per Equation 1). The AAFs from the literature are used to calibrate a slope value to the risk function, for each of the 30 groups. This is done by using the solver functionality in MS Excel to minimise the error between the known AAFs from the literature and the AAFs implied in the Australian population by the calibrated risk function.

There are two necessary assumptions when computing a relative risk function from an AAF. First, we must assume a functional form (e.g. linear, quadratic, cubic). There is no clear consensus in the literature about the most appropriate functional form for dose-response curves such as this, with existing evidence supporting log-linear, linear and linear-log specifications. In the absence of either robust evidence or a clear rationale we therefore assume a linear form as the most parsimonious

option. Second, we must assume a consumption threshold below which the risk of consuming alcohol is equal to the risk of abstaining (see Figure 6 for examples of linear functions with different thresholds). In line with recent work to inform the 2016 UK drinking guidelines, we assume a threshold of 0 standard drinks and test this assumption in a sensitivity analysis.[8]

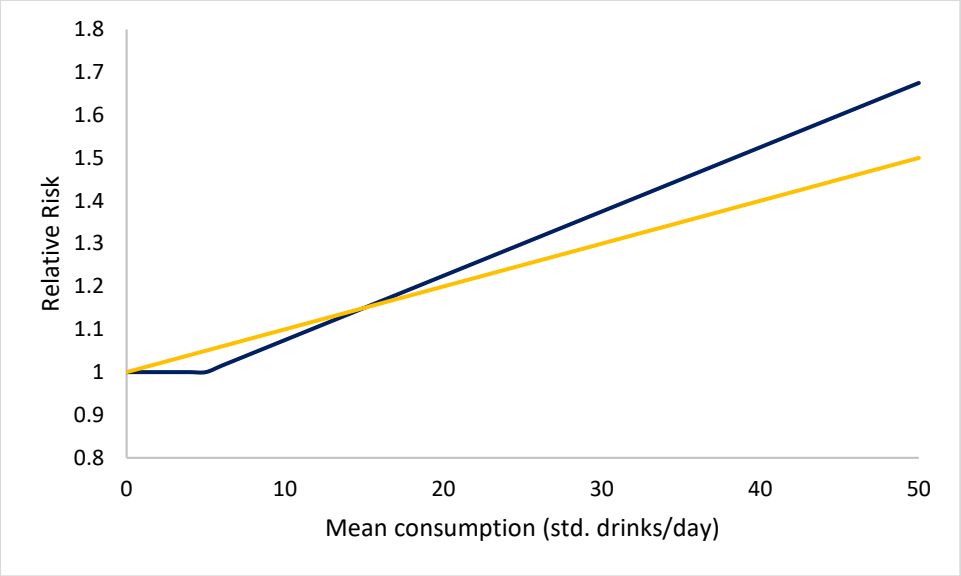


Figure 6: Illustrative risk functions with and without thresholds

2.2.4.4. Absolute risk functions for wholly alcohol-attributable chronic and acute conditions

It is not possible to use the AAF approach to derive a relative risk function for wholly alcohol-attributable conditions, as the AAF is 1.0 (or 100% of conditions are alcohol-attributable) by definition. This means there is no reference group to compare alcohol consumption levels to, as abstainers, also by definition, have no risk of experiencing wholly alcohol-attributable conditions.

We therefore adopt an alternative approach and calculate absolute risk functions for 30 age and gender groups (men and women, 15 age groups) based on the mortality rate or morbidity prevalence of the condition, the prevalence of different daily peak consumption levels and the population size of the age-gender group. As with the risk functions for partially alcohol-attributable acute conditions above, we need to assume a functional form and threshold for the risk function. We again assume a linear functional form and a threshold of zero in the base case, which we test in a sensitivity analysis.

2.3. Modelling procedure

The process of estimating the number of deaths and hospitalisations per annum that would occur at different levels of alcohol consumption and using these to estimate the risk curves and consumption levels corresponding to the risk thresholds has six steps. For brevity, we refer only to deaths below but the approach for hospitalisations is identical.

First, we derive the risk functions described above by inputting into SAPM-AU current levels of alcohol consumption and current mortality rates for each relevant condition for 30 age and gender groups (men and women in the 15 different age groups). The model then returns the current number of deaths per annum for each age-gender group, all men, all women and the whole population partitioned into five categories:

1. C1: Deaths for chronic alcohol-related conditions that are attributable to alcohol (e.g. deaths from oral cancers caused by alcohol);
2. C0: Deaths for chronic alcohol-related conditions that are not attributable to alcohol (e.g. deaths from oral cancers not caused by alcohol);
3. A1: Deaths from acute alcohol-related conditions that are attributable to alcohol (e.g. deaths from injuries caused by alcohol);
4. A0: Deaths from acute alcohol-related conditions that are not attributable to alcohol (e.g. deaths from injuries not caused by alcohol);
5. OD: Other deaths from causes unrelated to alcohol (e.g. deaths from lung cancer).

Second, we run an extreme what-if scenario in SAPM-AU to estimate the equivalent numbers of deaths if the modelled population drinks zero standard drinks per week. This gives a lower number of deaths than in the first step, as there are no deaths due to alcohol. This scenario allows us to quantify the number of deaths that are from alcohol-related conditions but are not attributable to alcohol or that are from conditions unrelated to alcohol (i.e. C0+A0+OD).

Third, we then run a series of 75 what-if scenarios in SAPM-AU that estimate the number of deaths that would occur if the entire modelled population has the same consumption behaviour. Specifically, we model mean weekly consumption levels ranging between 0 and 49 standard drinks per week (i.e. everyone drinks one standard drink per week, everyone drinks two standard drinks per week and so on). For each of these consumption levels, we also model seven drinking patterns representing how drinkers spread this consumption across the week. As there are an infinite number of ways that drinkers could spread their consumption across the week, we represent the breadth of these possibilities by assuming consumption is spread evenly across one, two, three, four, five, six or seven days. Crucially, these scenarios include the highest and lowest risk drinking patterns associated with a particular level of mean weekly consumption (i.e. where drinkers consume all of their alcohol on one day or spread it evenly across seven days). Therefore, we are modelling 75 scenarios comprising seven drinking patterns for each of 16 mean weekly consumption levels.

Fourth, we can then identify the number of deaths attributable to alcohol consumption in each of these scenarios (i.e. C1+A1) by comparing that scenario to the extreme no consumption scenario (i.e. C0+C1+A0+A1+OD – C0+A0+OD). Using the same information we can also calculate the proportion of all deaths that are attributable alcohol (i.e. [C1+A1] / [C0+C1+A0+A1+OD]). This is equivalent to the absolute lifetime risk of mortality under the simplifying assumption that the risk for alcohol- and non-alcohol-attributable mortality is constant over time. In practice, this means we are assuming that, for a given level and pattern of alcohol consumption, today's 16-24 year-olds will face the same alcohol-attributable mortality risk at age 65+ as is faced by today's people aged 65+. This assumption is necessary because SAPM-AU does not model underlying time trends and is cohort-based rather than individual-based (i.e. it does not directly model individuals across their life course and instead assumes they will take on the characteristics of previous cohorts when they enter a new age group). We can also use a similar approach to calculate the relative risk of death from an alcohol-related condition for any level and pattern of consumption (i.e. [C0+C1+A0+A1]/[C0+A0]).

Fifth, we convert the absolute risk estimates at each consumption level into risk curves by fitting fractional polynomial curves to the estimates[54] using the Stata 14 command *fracpoly*.

Sixth, we use the polynomial equations to identify the levels of consumption that correspond to the different risk thresholds and also to derive the absolute lifetime risk of alcohol-attributable mortality that corresponds to other consumption levels and patterns.

2.4. Sensitivity analyses

We conduct 3 sensitivity analyses (SA) to assess the impact of alternative assumptions, evidence and analytical methods on the results. These are summarised below and then explained in more detail:

SA1: Remove all protective effects included in the model;
SA2: Add lower thresholds to all calibrated risk functions below which drinkers do not face an elevated risk of harm compared to non-drinkers;
SA3: Substitute a single, all-cause mortality, risk curve in place of the 42 condition-specific curves.

2.4.1. SA1: Remove protective effects from all risk functions in which they are present

Risk functions for the following conditions in the base case model all include reduced mortality or morbidity risks relative to abstainers at some levels of alcohol consumption for men or women: acute myocardial infarction, chronic ischaemic heart disease, hypertension, stroke and diabetes. These apparent protective effects are subject to considerable scientific debate with regard to the size of the risk reduction, the associated levels and patterns of alcohol consumption and the possibility that the reduction is entirely an artefact of epidemiological methods.[3,6,50,55-57] Therefore, we conduct a sensitivity analysis where the risk curves set out in Figure 4 are adjusted to replace all sections below the RR=1 line with RR=1, i.e. all relative risks where RR<1 are set to RR=1. All other sections of the risk curves and all curves which do not include any protective effects are left unchanged. This has two effects on the model results: firstly, it changes the estimated number of deaths and hospital admissions from the affected conditions under the scenario where nobody drinks and secondly, it changes the estimated number of deaths and admissions from the affected conditions under the various alternative consumption level scenarios.

2.4.2. SA2: Adding threshold effects to risk functions for wholly alcohol-attributable conditions

There is uncertainty regarding the level of consumption above which mortality and morbidity risks for wholly alcohol-attributable conditions begin to rise. In the base case model, we assume this consumption threshold is zero for both chronic and acute conditions (i.e. that risk increases with any level of alcohol consumption) in line with the work undertaken as part of the 2016 UK drinking guidelines review. In this sensitivity analysis, we add thresholds to all calibrated risk curves for both acute and chronic conditions. In lines with the previous UK analysis these thresholds are set at 3.2 standard drinks per week for men and 2.4 standard drinks per week for women for chronic conditions and 3.2 and 2.4 standard drinks per day respectively for men and women for acute conditions. New risk functions are estimated for all calibrated health conditions using the same method described previously.

2.4.3. SA3: Substitute an all-cause mortality curve for a synthesis of 42 condition-specific curve

SAPM-AU undertakes a complicated synthesis of risk curves for 42 different alcohol-attributable conditions and for all other conditions combined. An alternative approach is to use a single risk curve describing the relationship between alcohol consumption and all-cause mortality. Epidemiological modellers have criticised all-cause mortality approaches as liable to produce biased findings[58,59] and, although such approaches do have merit with regard to simplicity, we instead take a condition-specific approach in the base case model for the following reasons:

- *Better understanding of drinking patterns*: A condition-specific approach can separate risks for chronic conditions associated with long-term alcohol consumption from risks for acute

conditions associated with consumption on a single occasion. This increases the ability of SAPM-AU to provide evidence on the risks associated with different patterns of alcohol consumption (i.e. how drinkers spread their consumption across the week);

- *Evidence tailored to the health profile of Australia*: A condition-specific approach allows SAPM-AU to reflect the distribution of deaths in Australia across different conditions. This matters because this distribution determines the shape of the overall mortality risk curve for alcohol consumption estimated by SAPM-AU. For example, if there are relatively few deaths from IHD in Australia, this condition will have less influence on the shape of the overall risk curve. In turn, this means any protective effects of moderate drinking would be smaller and associated with lower levels of consumption than if there were a relatively large number of IHD deaths.
- *All-cause mortality studies have suffer larger risks of uncontrolled confounding:* A condition-specific approach avoids associating alcohol consumption with deaths from conditions that are not alcohol-attributable. For example, smoking causes lung cancer while alcohol consumption does not; however, many smokers are also heavy drinkers. A condition-specific approach does not associate lung cancer deaths with alcohol but an all-cause mortality study will do so unless it controls properly for the co-occurrence of smoking and heavy drinking. Most all-cause studies do control for smoking but alcohol correlates with a wide range of health-promoting and health-harming factors and it is very difficult to satisfactorily control for all of these.

Instead, we conduct a sensitivity analysis where we use a single all-cause mortality risk curve in place of the 42 condition-specific risk curves. We take the all-cause curve from a meta-analysis by Stockwell et al.,[5] which is illustrated in Figure 7 below. This curve is similar to a widely cited one identified by Di Castelnuovo et al., but incorporates more recent primary studies.[60] For every individual in the NDSH we can then use this curve to assign them a relative risk of mortality compared to a non-drinker. By summing these risks, accounting for survey weights, and comparing the result to the raw sum of the weights (i.e. the summed risk in a world where everyone was a non-drinker and therefore had a relative risk of 1) thus produces the equivalent of an AAF for current all-cause mortality. From this we can estimate the total number of current all-cause deaths which are caused by alcohol (i.e. which could be averted if nobody drank). Finally, for any level of alcohol consumption we can calculate the number of deaths which would occur at that level by multiplying the estimated number of deaths in the zero-consumption scenario by the relative risk taken from the Stockwell risk curve. This gives us the proportion of deaths at that level of consumption which are attributable to alcohol, which is equivalent to the lifetime risk of death under the assumptions already outlined.

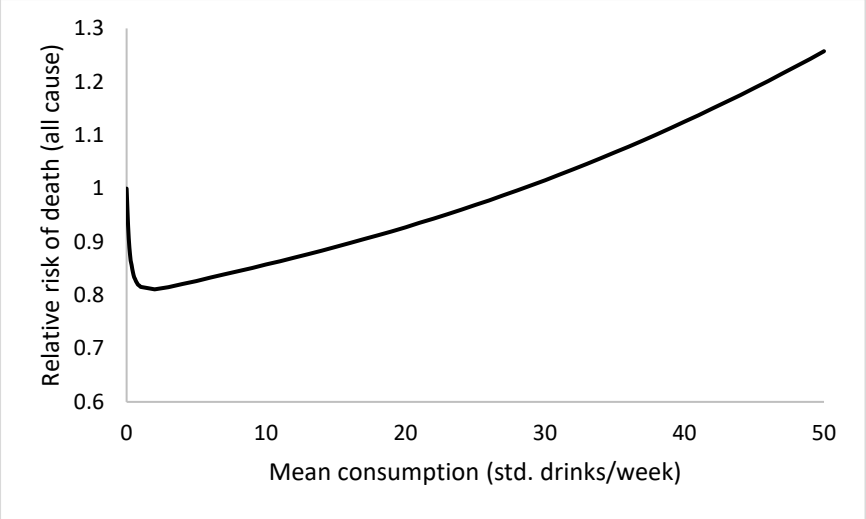


Figure 7: All-cause risk curve taken from Stockwell et al.

2.5. Key differences between SAPM-AU and SAPM v2.7

Readers may wish to compare analyses and results from SAPM-AU, which we use here, and SAPM v2.7, which we used for analyses that informed the 2016 UK alcohol guidelines. To facilitate this comparison, we list the key differences between these models below:

- The demographic composition, alcohol consumption, mortality and morbidity data used in the models are country-specific;
- SAPM-AU has a considerably more detailed age-structure, having 15 age bands in comparison to the 4, much broader, age bands included in SAPM v2.7.
- The set of alcohol-related health conditions used in the model and the literature-based risk relationships are not identical following the NHMRC's review of the most recent evidence. The most important differences are: (a) acute myocardial infarction is modelled separately here as an acute condition whereas it was combined with chronic ischaemic heart disease in SAPM v2.7; (b) the inclusion of several health conditions not present in SAPM v2.7, including stomach cancer, gout and non-Hodgkin's lymphoma; (c) the use of a different set of risk functions, including for conditions that are common to both models and (d) the recognition in SAPM-AU that only squamous cell carcinoma forms of oesophageal cancer are related to alcohol.

These differences mean that, while readers can make useful comparisons between the results of the UK and present analyses, readers should expect these results to differ. It is beyond the scope of this analysis to identify the differences between the models that contribute most to any variation in the results.

3. Results

3.1. Baseline mortality and morbidity

Table 5 shows that, based on current levels of alcohol consumption and alcohol-related harm in Australia, we estimate that there are a net total of 1,697 deaths per year caused by alcohol. These comprise 1,858 deaths from chronic causes and an estimated 161 deaths averted from acute causes, driven by the modelled protective effects of moderate drinking on acute myocardial infarction. Alcohol-attributable deaths account for 1.4% of all deaths in Australia.

Table 5 also shows that there are an estimated 128,907 hospital admissions per year attributable to alcohol, comprising 68,816 admissions from chronic causes and 60,091 admissions from acute causes. The number of deaths and admissions is substantially larger among men than women.

Table 5: Estimated annual burden of alcohol based on current levels of drinking

	Population	**Men**	**Women**
Alcohol-attributable deaths from chronic causes	1,858	1,316	541
Alcohol-attributable deaths from acute causes	-161	689	-849
Total deaths	1,697	2,005	-308
Proportion of all deaths	1.4%	3.0%	-0.5%
Alcohol-attributable admissions from chronic causes	68,816	47,011	21,805
Alcohol-attributable admissions from acute causes	60,091	44,184	15,907
Total morbidity	128,907	91,195	37,712

Figure 8 shows the number of deaths per year for different groups of conditions. Liver disease accounts for the most deaths, following by cancer and stroke. A large number of deaths are also due to injuries including motor vehicle injuries, falls and other injuries. Each year, alcohol consumption prevents an estimated 3,466 deaths from chronic ischaemic heart disease and acute myocardial infarction; however, this preventative effect is disputed,[55-57] and we discuss reasons for this in Section 4.3.1.2 of this report.

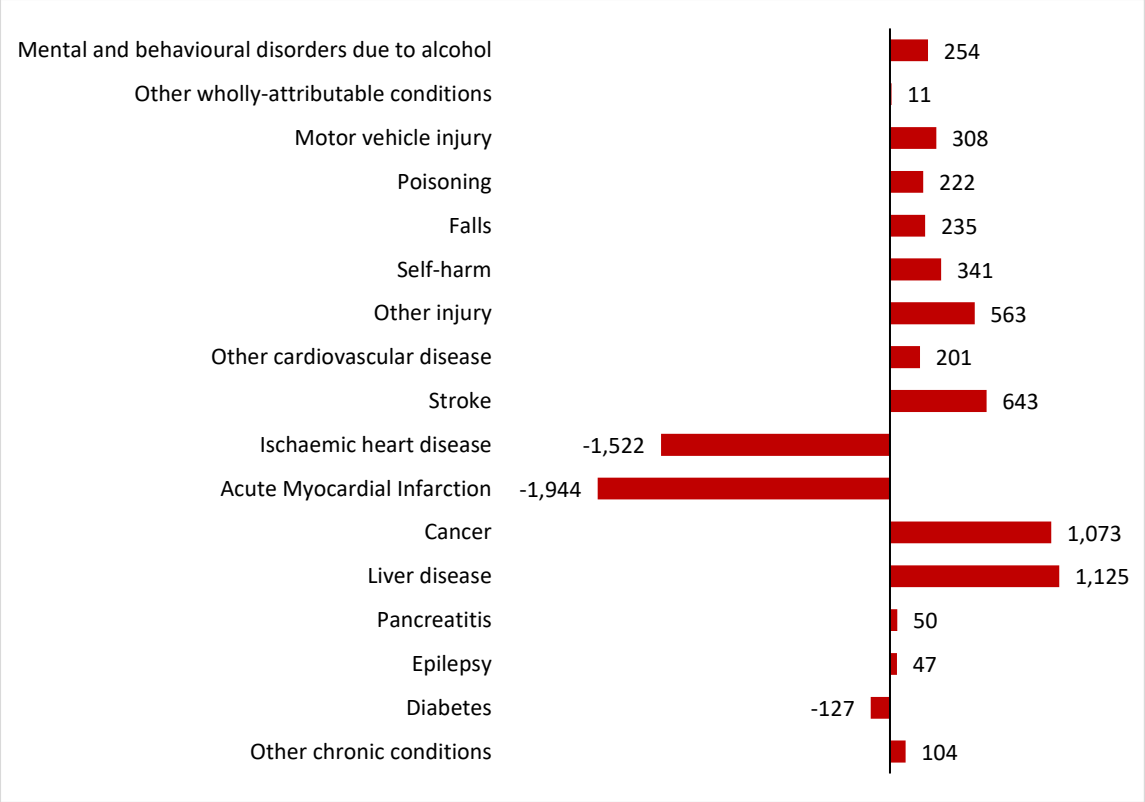


Figure 8: Estimated annual deaths caused by alcohol by condition type

Figure 9 shows the proportion of all deaths in each age-gender group in Australia that are attributable to alcohol. Among those aged 18-19, an estimated 17.5% of deaths among men and 12.9% of deaths among women are attributable to alcohol. This proportion decreases steadily with age and current alcohol consumption levels in Australia are estimated to lead to an overall reduction in annual mortality among men aged over 79 and women aged over 69.

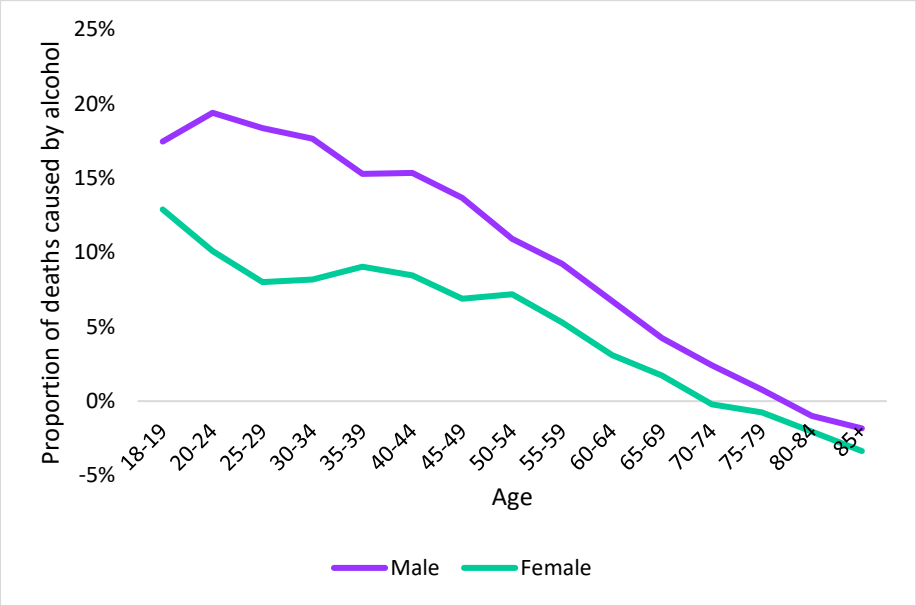


Figure 9: Proportion of all deaths which are caused by alcohol

Figure 10 shows the number of alcohol-attributable deaths in each age group. Alcohol-attributable deaths occur in all groups, although they are outweighed by deaths prevented in the oldest age groups. Deaths are particularly concentrated in middle-age, peaking at ages 55-59 for both men and women

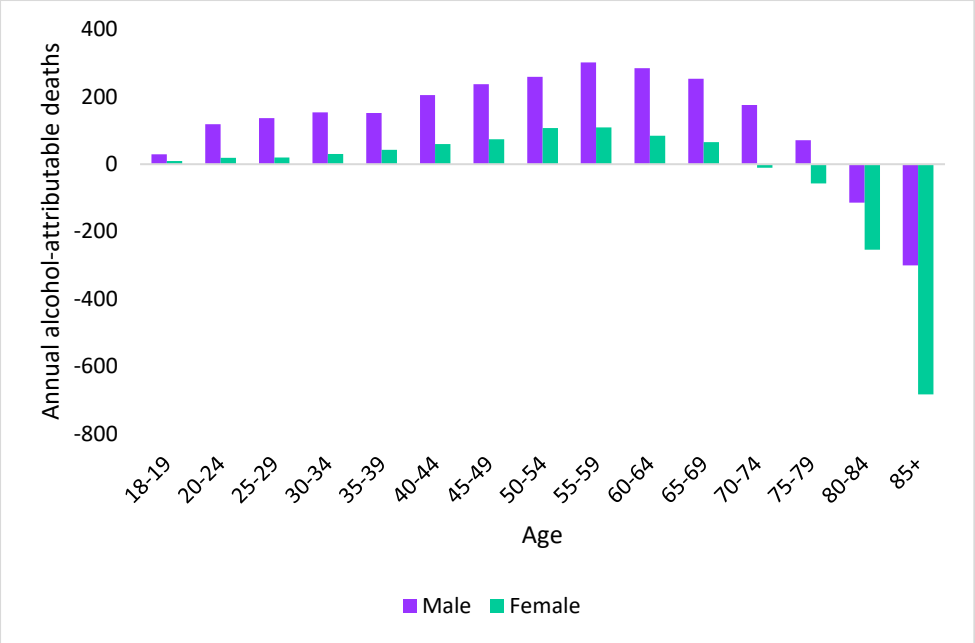


Figure 10: Annual alcohol-attributable deaths by age

3.2. Mortality risks at alternative consumption levels

Figure 11 presents absolute risk curves for men relating mean weekly consumption to total lifetime alcohol-attributable mortality risk depending on whether drinkers spread their consumption evenly across one to seven days. Figure 12 presents the same information for women

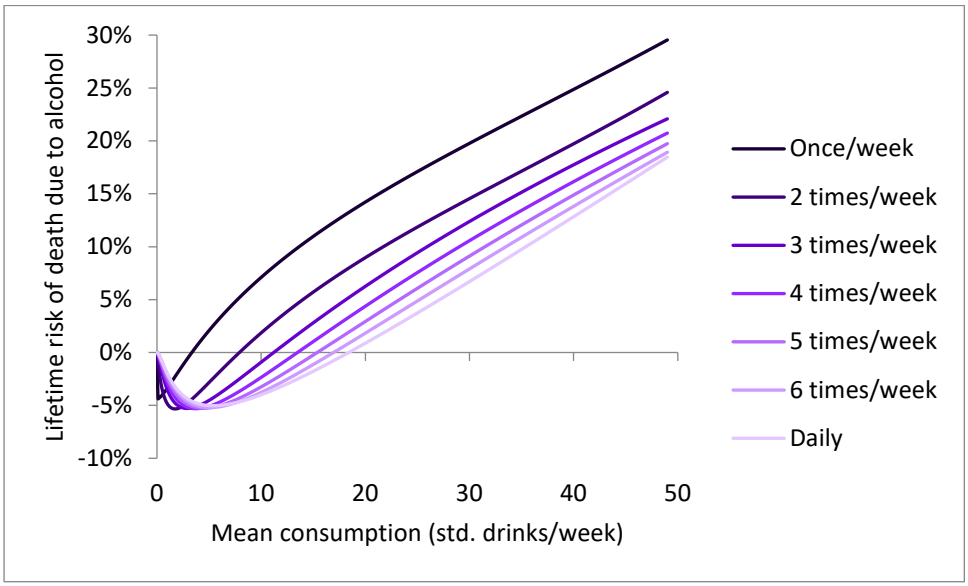


Figure 11: Absolute lifetime risks of death caused by alcohol for Australian men by drinking frequency

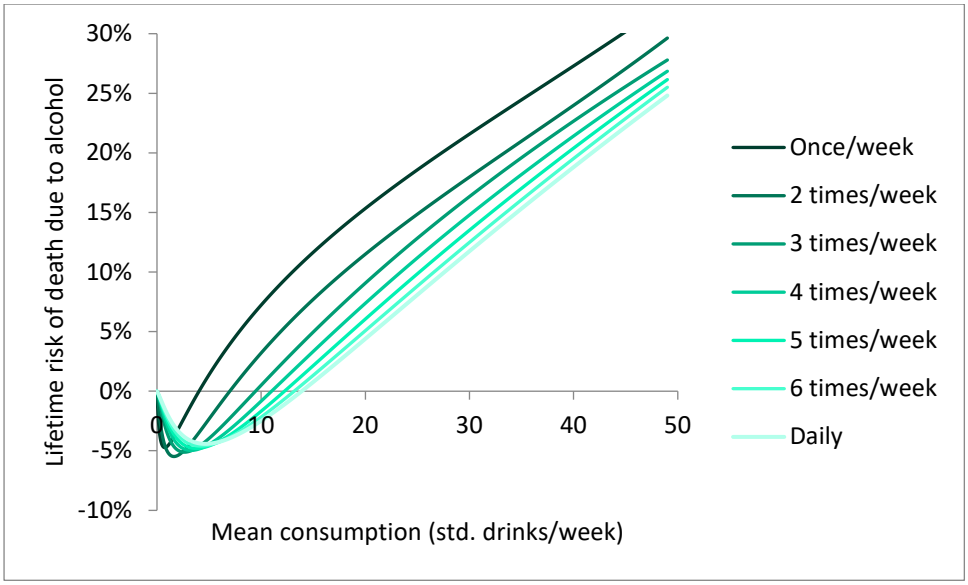


Figure 12: Absolute lifetime risks of death caused by alcohol for Australian women by drinking frequency

All of the risk curves show a reduced risk of mortality at low levels of alcohol consumption and then rise approximately linearly thereafter. The maximum reduction in absolute risk is around 5.0%, irrespective of how drinkers spread their consumption across the week. The reduction in risk extends to up to approximately 14 standard drinks per week for women and 18 for men among those who spread their consumption across seven days but only to approximately four standard drinks per week for those who consume all of their alcohol in a single day.

Figure 13 compares the risk curves for men and women who spread their consumption evenly across five days per week. This distribution of drinking is chosen purely for illustrative purposes. Women experience a higher risk of alcohol-attributable mortality than men at all levels of consumption, although the absolute difference is small at low consumption levels and larger at high consumption levels. For example, men experience an absolute lifetime alcohol-attributable mortality risk at 10 standard drink per week of -3.3% whereas the risk for women is -1.7%. At 28 standard drinks per week, the risk for men is 7.9% and for women it is 12.1%. This general trend applies irrespective of how many days drinkers spread their consumption across.

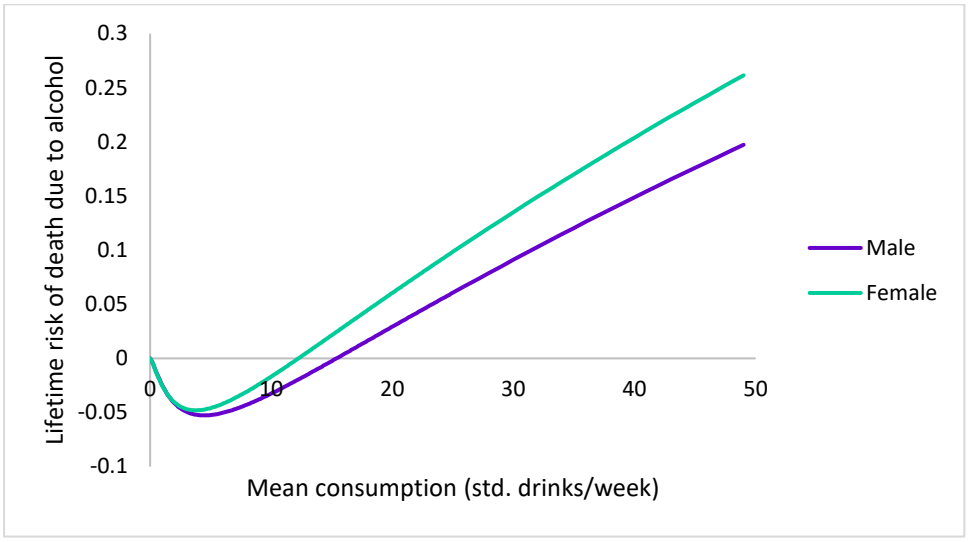


Figure 13: Absolute lifetime risk of death caused by alcohol for drinkers spreading consumption evenly over 5 days/week

Table 6 and Table 7 show the absolute lifetime risk of alcohol-attributable mortality associated with different levels and patterns of alcohol consumption.

Table 6: Absolute lifetime risk of alcohol-attributable mortality for men by mean weekly consumption and days per week across which consumption is evenly spread[**]

Mean consumption (std. drinks/week)	Drinking days per week						
	7	6	5	4	3	2	1
7	-4.9%	-4.9%	-4.7%	-4.2%	-3.2%	-0.9%	4.3%
14	-2.3%	-1.7%	-0.9%	0.3%	2.1%	5.0%	10.3%
21	1.4%	2.4%	3.6%	5.0%	6.9%	9.6%	14.8%
28	5.5%	6.7%	7.9%	9.4%	11.2%	13.5%	18.7%
35	9.7%	10.9%	12.1%	13.4%	15.1%	17.1%	22.3%
42	14.1%	15.0%	16.0%	17.2%	18.7%	20.8%	25.9%
49	18.5%	18.9%	19.7%	20.7%	22.1%	24.6%	29.5%

Table 7: Absolute lifetime risk of alcohol-attributable mortality for women by mean weekly consumption and days per week across which consumption is evenly spread.[††]

Mean consumption (std. drinks/week)	Drinking days per week						
	7	6	5	4	3	2	1
7	-3.9%	-3.9%	-3.7%	-3.2%	-2.3%	0.0%	4.0%
14	0.1%	0.6%	1.4%	2.5%	4.1%	6.9%	10.8%
21	5.1%	5.8%	6.8%	8.2%	9.8%	12.2%	16.0%
28	10.3%	11.0%	12.1%	13.4%	15.0%	16.7%	20.4%
35	15.3%	16.1%	17.0%	18.2%	19.6%	21.0%	24.5%
42	20.2%	20.9%	21.7%	22.7%	23.8%	25.2%	28.4%
49	24.8%	25.5%	26.1%	26.9%	27.8%	29.6%	32.5%

Key:

Overall protective effect
Overall lifetime risk of less than 1 in 1,000
Overall lifetime risk at least 1 in 1,000, but below 1 in 500
Overall lifetime risk at least 1 in 500, but below 1 in 100
Overall lifetime risk at least 1 in 100, but below 1 in 50
Overall lifetime risk at least 1 in 50, but below 1 in 10
Overall lifetime risk at least 1 in 10

3.3. Consumption levels corresponding to pre-specified risk thresholds

Table 8 summarises the consumption levels corresponding to a 1.0%, or 1 in 100, lifetime risk of death due to alcohol. The risk curve passes this threshold at between 4.1 and 20.2 standard drinks per week for men and between 4.7 and 15.3 standard drinks per week for women, depending on how many days drinkers spread their consumption across. If drinkers spread their consumption

[**] Note that Table 6 is also presented in the Executive Summary as Table 1.
[††] Note that Table 7 is also presented in the Executive Summary as Table 2.

evenly across five days per week, for example, the curve passes the 1.0% threshold at 16.9 standard drinks per week for men and 13.5 standard drinks per week for women.

Table 8: Number of standard drinks per week associated with a 1 in 100 lifetime risk of death due to alcohol, depending on number of times alcohol is consumed per week

	Men	Women	Population
Daily	20.2	15.3	17.4
6 times/week	18.6	14.5	16.4
5 times/week	16.9	13.5	15.1
4 times/week	14.9	12.1	13.4
3 times/week	12.5	10.5	11.4
2 times/week	9	7.8	8.7
Once/week	4.1	4.7	4.8

Table 9 presents equivalent consumption levels associated with a range of acceptable risk thresholds: 0.1% (1 in 1,000), 0.2% (1 in 500), 1.0% (1 in 100) and 2.0% (1 in 50). Alongside Figure 11 and Figure 12 this shows that that, irrespective of how drinkers spread their consumption across the week, the consumption levels corresponding to these risk thresholds varies by no more than 3.4 standard drinks for men and 2.7 standard drinks for women. If drinkers spread their consumption evenly across five days each week, for example, the consumption levels corresponding to the 0.1%, 0.2%, 1.0% and 2.0% thresholds are 15.5, 15.7, 16.9, 18.5 standard drinks per week for men and 12.3, 12.5, 13.5, 14.8 standard drinks per week for women.

Table 9: Number of standard drinks per week associated with alternative mortality risk thresholds, depending on number of times alcohol is consumed per week

	Risk level			
	0.1% (1 in 1,000)	0.2% (1 in 500)	1% (1 in 100)	2% (1 in 50)
Men				
Daily	18.5	18.7	20.2	21.9
6 times/week	17.1	17.2	18.6	20.2
5 times/week	15.5	15.7	16.9	18.5
4 times/week	13.6	13.7	14.9	16.4
3 times/week	11.3	11.4	12.5	13.8
2 times/week	8	8.1	9	10.1
Once/week	3.4	3.4	4.1	4.9
Women				
Daily	14	14.1	15.3	16.7
6 times/week	13.3	13.4	14.5	15.8
5 times/week	12.3	12.5	13.5	14.8
4 times/week	11.1	11.2	12.1	13.3
3 times/week	9.5	9.6	10.5	11.6
2 times/week	7	7.1	7.8	8.8
Once/week	4.1	4.1	4.7	5.4

3.4. Relative risks of drinking at different levels

Rather than looking at absolute risks, it is also possible to compare the risks of mortality from a condition related to alcohol associated with different levels and patterns of consumption to the risk associated with abstaining. Figure 14, for men, and Figure 15, for women, illustrate these relative risks compared to non-drinkers.

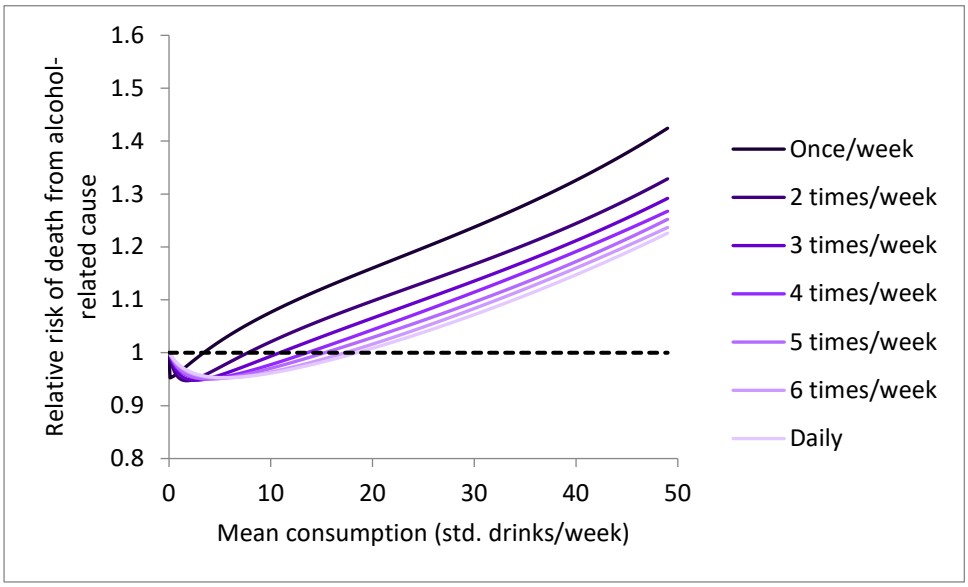


Figure 14: Relative risks for mortality associated with different levels of consumption compared to non-drinkers - males

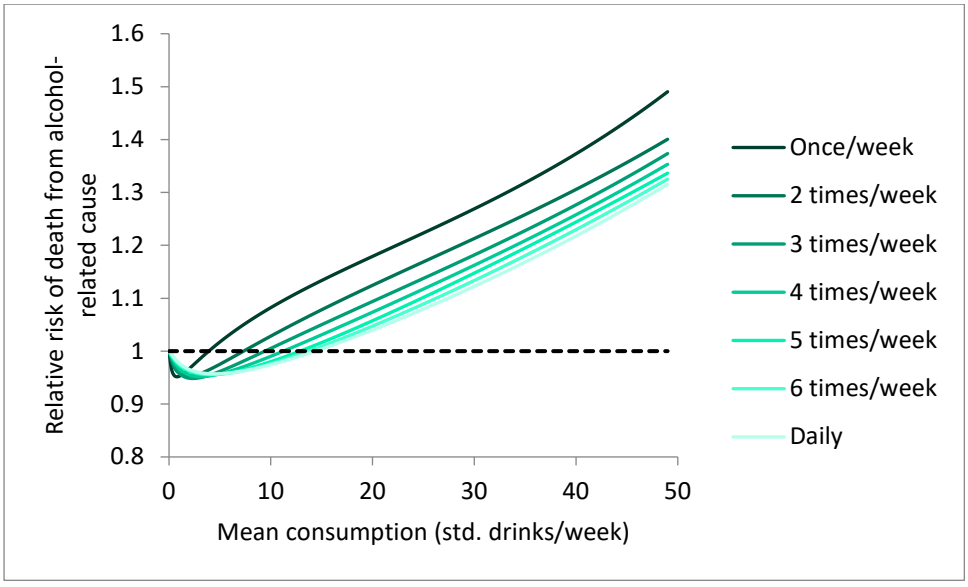


Figure 15: Relative risks for mortality associated with different levels of consumption compared to non-drinkers - females

Table 10 summarises the consumption levels associated with specific levels of relative risk. The level of consumption at which the risks of harm are equal to those of non-drinkers (where RR=1) varies between 3.3 and 18.4 standard drinks per week for men and 4.0 and 13.8 standard drinks per week for women, depending on how these are spread across the week. The level of consumption at which risk of harm is minimised is more similar between men and women, equating to 4.0 standard drinks for men and 3.9 for women for drinkers spreading their consumption over 5 days, for example. This level of drinking corresponds to an approximately 5.0% reduction in the risk of death from an alcohol-related condition.

Table 10: Number of standard drinks per week associated with selected relative risks of death from an alcohol-related condition, depending on number of times alcohol is consumed per week

	Male			Female		
	RR=1	RR= minimum	RR at minimum	RR=1	RR= minimum	RR at minimum
Daily	18.4	5.5	0.953	13.8	4.5	0.957
6 times/week	16.9	5.1	0.952	13.1	4.2	0.956
5 times/week	15.3	4.0	0.950	12.2	3.9	0.955
4 times/week	13.4	3.5	0.951	11	3.1	0.952
3 times/week	11.2	2.6	0.948	9.4	2.3	0.948
2 times/week	7.9	1.7	0.947	6.9	1.9	0.953
Once/week	3.3	0.1	0.953	4	0.8	0.952

3.5. Sensitivity analyses

Table 11 shows consumption level associated with the 1.0% risk threshold in the base case model and two sensitivity analyses; SA1 (no protective effects) and SA2 (threshold below which risk of harm is equivalent to that of an abstainer for all calibrated risk curves). The results differ only marginally between the base case model and SA2; however, removing protective effects from risk functions for all conditions has a large impact on the estimated consumption level, reducing it to less than three standard drinks a week for both men and women across all drinking pattern scenarios.

Table 11: Number of standard drinks per week associated with a 1% lifetime risk of death due to alcohol under alternative model assumptions, depending on number of times alcohol is consumed per week

	Male			Female		
	Base case	SA1: No protective effects	SA2: Threshold	Base case	SA1: No protective effects	SA2: Threshold
Daily	20.2	2.9	21	15.3	2.3	15
6 times/week	18.6	2.8	19.6	14.5	2.2	14
5 times/week	16.9	2.5	17.7	13.5	2.2	12.9
4 times/week	14.9	2.6	15.7	12.1	2.1	11.5
3 times/week	12.5	2.5	13.2	10.5	2.5	9.6
2 times/week	9	2.6	9.8	7.8	2.2	7.1
Once/week	4.1	0	4.7	4.7	0.1	3.8

The absolute lifetime risk of death due to alcohol at selected consumption levels for each drinking pattern are presented in Table 16 and Table 17 for SA1 and Table 18 and Table 19 for SA2. Using drinking over 5 days a week for illustrative purposes, Figure 16 and Figure 17 present the mortality risk curves for men and women respectively for the base case and the two sensitivity analyses. These demonstrate that the risk curve is approximately linear in SA1 when protective effects are removed, meaning the 1.0% risk threshold is reached at very low levels of consumption. It also shows that the risk curve for SA2 is similar to the base case model but steeper after the nadir for women, meaning women face markedly higher levels of risk at higher consumption levels than in the base case model.

Figure 16: Mortality risks for men spreading their consumption evenly over five days under sensitivity analyses[‡‡]

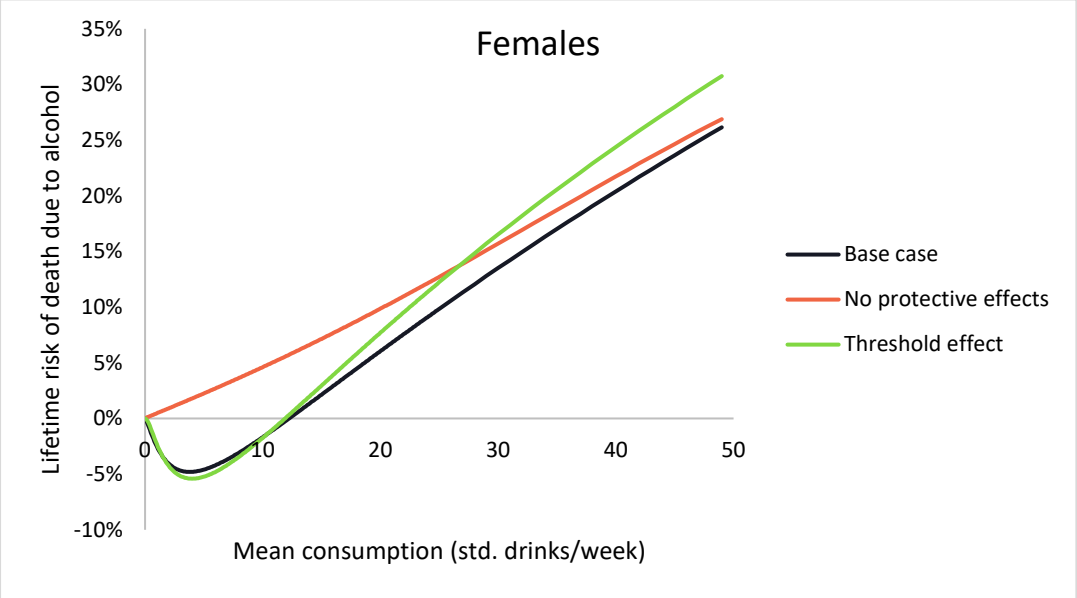


Figure 17: Mortality risks for women spreading their consumption evenly over five days under sensitivity analyses[§§]

3.5.1. All-cause mortality sensitivity analysis

The base case model accounts for age-and gender-specific patterns of alcohol consumption and health harms using condition-specific evidence on risks for 42 alcohol-related health conditions. Replacing this analytical approach with an approach using a single, all-cause mortality risk curve yields substantively different results. Whilst the broad pattern is similar, with protective effects at low levels of consumption and elevated risk at higher levels, the estimated extent of the protective effects is markedly larger and it extends to substantially higher levels of alcohol consumption. When using this modelling approach, SAPM-AU estimates 10,327 deaths would be prevented each year through current levels of alcohol consumption, when compared to a scenario where everyone

[‡‡] This figure is replicated in the Executive Summary as Figure 2
[§§] This figure is replicated in the Executive Summary as Figure 3.

abstained from alcohol. This contrasts with the estimated figure of 1,697 deaths *caused* by current levels of drinking from the more detailed base case analysis.

Converting this analysis into an absolute risk curve, we see a sharp fall in lifetime risk from very low levels of consumption, followed by a steady, almost linear increase. The estimated mortality risk for drinkers matches that of abstainers at 28 standard drinks per week and 29 standard drinks per week corresponds to a 1.0% lifetime risk of death due to alcohol.

Figure 18: Absolute lifetime alcohol-attributable mortality risk under using an all-cause mortality risk function

3.6. Morbidity risks

Morbidity results using a relative risk approach are presented here for the relationship between mean consumption and risk of morbidity from chronic conditions and for peak daily consumption and risk of morbidity from acute conditions. Due to the inherent challenges of modelling the full disease history of every individual in the Australian population across their life course, we do not attempt to model lifetime risks, or morbidity for other causes beyond the 42 health conditions included in the mortality analysis.

3.6.1. Morbidity risks for chronic alcohol-related conditions

Figure 19 shows the relative risk relationship between mean weekly alcohol consumption and morbidity for chronic alcohol-related conditions. Although there is a j-shaped curve, this applies only to women, while risk increases with any consumption for men.

Table 12 shows that the protective for women effect is also smaller, at approximately a 3.5% relative risk reduction and associated with lower consumption levels of below 3.9 standard drinks per week.

Above this level, risk increases curvilinearly, such that risk increases more steeply at higher consumption levels.

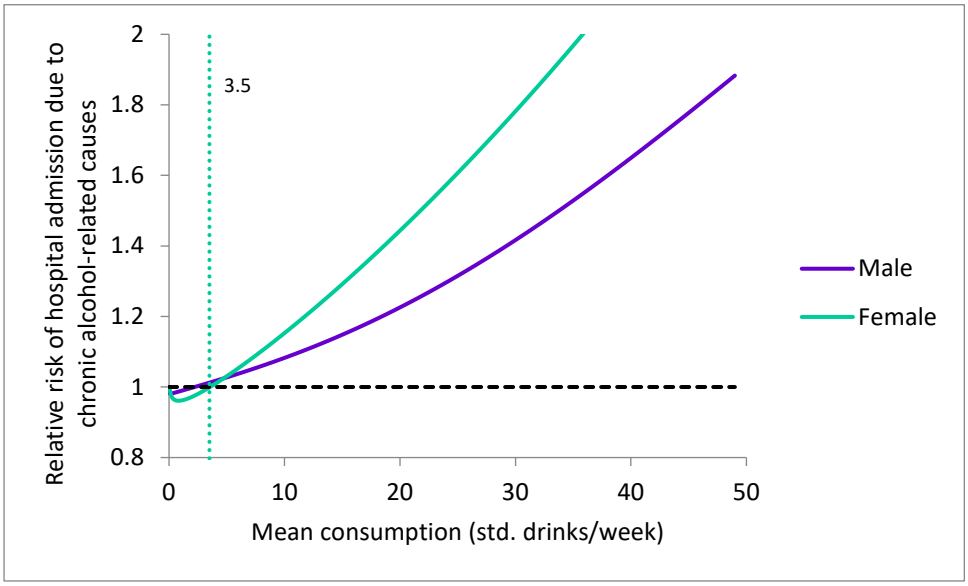


Figure 19: Relative risks of morbidity associated with chronic health conditions

Table 12: Number of standard drinks per week associated with selected relative risks of illness

	RR=1	RR= minimum	RR at minimum
Population	3.0	0.1	0.956
Male	0.0	0.1	0.980
Female	3.5	0.8	0.961

3.6.2. Morbidity risks for acute alcohol-related conditions

Figure 20 shows the relative risk relationship between peak daily consumption and morbidity for acute alcohol-related conditions. It suggests there is a small reduction in risk relative to abstainers associated with low levels of alcohol consumption. Table 13 shows this risk reduction peaks at 9% for men and 5% for women but only extends up to 2.1 and 1.7 standard drinks per week respectively. Above these levels risk increases curvilinearly but, unlike for chronic disease, risk increases less steeply for those drinking at high levels. Risks continue to increase substantively however across all modelled levels of consumption, which extend to 50 standard drinks on a single day.

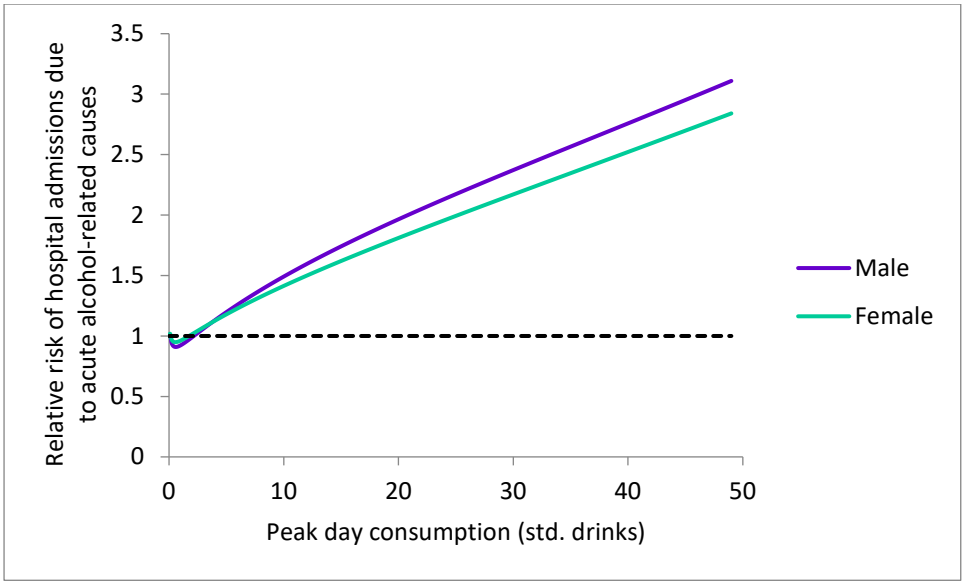


Figure 20: Relative risks of morbidity associated with acute health conditions

Table 13: Number of standard drinks per week associated with selected relative risks of illness

	RR=1	RR= minimum	RR at minimum
Population	1.9	0.6	0.929
Male	2.1	0.6	0.909
Female	1.7	0.7	0.951

4. Discussion

4.1. Summary of results

The above analysis of alcohol-attributable mortality risks for the Australian population show that risks are low in absolute terms for drinkers consuming within the current alcohol guidelines of two standard drinks per days for men and women. However, mortality risk increases as consumption rises above these guidelines and risks are large for both genders at higher levels of consumption. At all levels of consumption women experience higher risks from drinking than men and this is particularly true at higher levels of consumption.

Table 14 summarises the consumption level associated with different absolute lifetime alcohol-attributable mortality risk thresholds and in the different sensitivity analyses. Figure 21 shows the same results but only for the scenarios where drinkers spread their alcohol consumption evenly across five days. These results point to four key findings that we describe below.

Table 14: Estimated consumption levels (std. drinks/week) corresponding to different absolute and relative mortality risk thresholds in the base case model and in sensitivity analyses[***]

	Risk level								
	RR= Minimum	RR= 1.0	AR= 0.1%	AR= 0.2%	AR= 1.0%	AR= 2.0%	SA1: No protective effects	SA2: Threshold	SA3: All-cause
Men									
Daily	5.5	18.4	18.5	18.7	20.2	21.9	2.9	21	
6 times/week	5.1	16.9	17.1	17.2	18.6	20.2	2.8	19.6	
5 times/week	4	15.3	15.5	15.7	16.9	18.5	2.5	17.7	
4 times/week	3.5	13.4	13.6	13.7	14.9	16.4	2.6	15.7	29.0
3 times/week	2.6	11.2	11.3	11.4	12.5	13.8	2.5	13.2	
2 times/week	1.7	7.9	8	8.1	9	10.1	2.6	9.8	
Once/week	0.1	3.3	3.4	3.4	4.1	4.9	0	4.7	
Daily	4.5	13.8	14	14.1	15.3	16.7	2.3	15	
6 times/week	4.2	13.1	13.3	13.4	14.5	15.8	2.2	14	
5 times/week	3.9	12.2	12.3	12.5	13.5	14.8	2.2	12.9	
4 times/week	3.1	11	11.1	11.2	12.1	13.3	2.1	11.5	29.0
3 times/week	2.3	9.4	9.5	9.6	10.5	11.6	2.5	9.6	
2 times/week	1.9	6.9	7	7.1	7.8	8.8	2.2	7.1	
Once/week	0.8	4	4.1	4.1	4.7	5.4	0.1	3.8	

Shading indicates base case model. AR: Absolute risk; RR: Relative risk; SA: Sensitivity analysis. Risk thresholds for all sensitivity are AR=1.0%. SA1 excludes all protective effects from literature-based risk functions. SA2: inserts a threshold into all calibrated risk functions below which drinkers have the same risk as abstainers. SA3 uses a single all-cause mortality risk function rather than synthesising risk functions for 42 alcohol-related health conditions.

[***] Note that Table 14 is also presented in the Executive Summary as Table 3.

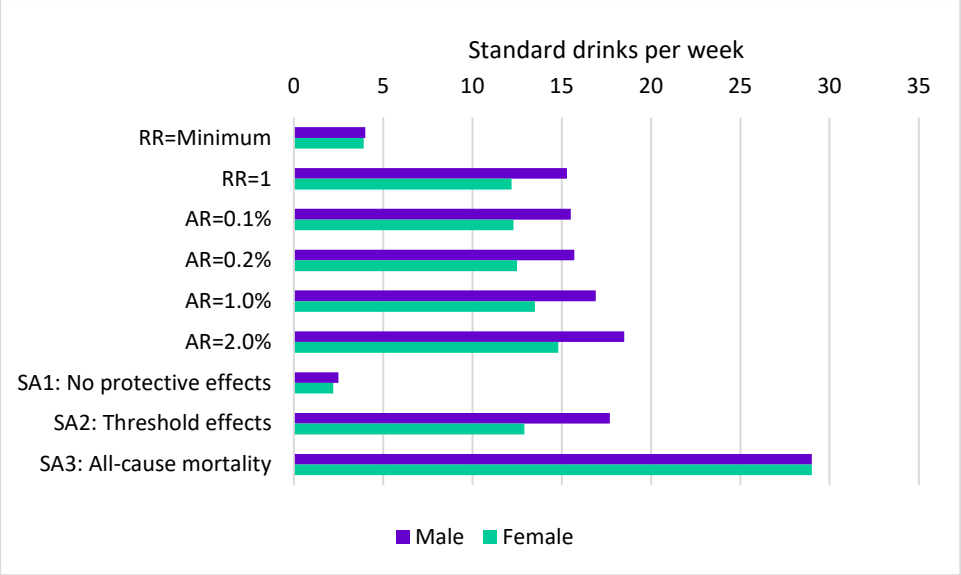


Figure 21: Number of standard drinks per week associated with selected risk thresholds and sensitivity analysis - based on consumption spread over 5 days

First, the base case model suggests the consumption level associated with the 1.0% threshold is between 4.1 and 20.2 standard drinks per week for men and between 4.7 and 15.3 standard drinks for women depending on how drinkers spread their consumption across the week. The consumption level associated with the risk threshold is necessarily lower when spreading consumption across fewer days, as the structure of SAPM assumes that drinking more per occasion increases drinkers' risk of experiencing acute harm without changing their risk of chronic harm (excepting the minor adjustment for chronic ischaemic heart disease described in Section 2.2.4.2).

Second, the consumption levels associated with alternative risk thresholds ranging between 0.0% (RR=1.0) and 2.0% differ to a small but substantive degree. For example, for drinkers spreading their consumption evenly across five days per week, they range between 15.3 and 18.5 standard drinks per week for men and between 12.2 and 14.8 standard drinks per week for women. This modest variation is due to the gradient of the risk curve, which is relatively steep such that risks do not increases sharply with rising consumption, and vice versa. The nadir of the risk curve, which provides the lowest risk consumption level, is much lower at below six standard drinks per week for men and women in all drinking pattern scenarios.

Third, the consumption levels associated with the 1.0% risk threshold vary substantially across the sensitivity analyses. If protective effects are removed from all risk functions, the associated consumption level is below three standard drinks per week for men and women in all drinking pattern scenarios. In contrast, adding thresholds to calibrated risk functions below which risk is identical to non-drinkers has only a marginal impact on estimated level of risk, at least at the levels of consumption that are being assessed in this analysis. Using an all-cause mortality approach, rather than a more detailed condition-specific approach, gives a markedly higher suggested level of consumption for any chosen level of risk, although we describe important problems with this approach in Section 2.4.3 of the methods of this report. Therefore, the no protective effects sensitivity analysis presents the greatest challenge as it relates to an unresolved scientific debate that appears to have substantial implications for the level of alcohol consumption that is associated with the 'acceptable risk' threshold.

Fourth, across all of the analyses, the consumption level associated with the various risk thresholds is lower for women for men. This reflects the higher risks faced by women at all modelled levels of consumption and for all drinking patterns. The difference in alcohol-related mortality risk between men and women is small at low levels of consumption and larger at higher levels of consumption. This reflects a number of features of the baseline data synthesised by SAPM, including the larger reduction in risk for cardiovascular disease and diabetes at lower levels of consumption for women, the higher risk of acute alcohol-related health problems faced by women compared to men drinking at the same level, the higher risk of chronic disease, particularly at higher consumption levels for women and differences between men and women in the conditions they are at greatest risk for (e.g. women are at greater risk for breast cancer).

4.1.1. Comparison with previous analyses and guidelines

In the base case model, the consumption level associated with a 1.0% lifetime alcohol-attributable mortality does not differ substantially from the current Australian alcohol guidelines of two standard drinks per day for men and women (i.e. 14 standard drinks per week). The epidemiological modelling that informed the previous alcohol guidelines differed from the present analysis, most notably by excluding all protective effects from the base case model, making it more similar to our first sensitivity analysis than our base case model. However, evidence on alcohol-related risks has developed substantially since 2009, when that modelling was completed. For example, the diseases modelled for the 2009 guidelines did not include colorectal cancer and we use risk functions from meta-analyses that were mostly not available in 2009. These updated meta-analyses tend to show larger risks from alcohol consumption, particularly at low consumption levels. The sociodemographic and health profile of the Australian population has also changed. In combination, these factors mean it should not be considered surprising that the results of our first sensitivity analysis and the results of the 2009 model are markedly different.

Researchers have conducted similar modelling exercises in the UK, France and for seven European nations in the Reducing Alcohol Related Harm (RARHA) study.[8,61,62] These exercises use meta-analyses of alcohol-related health risks that are more similar to those used in the present analysis than the modelling for the 2009 alcohol guidelines. They also all include protective effects in the base case model, although only the UK modelling (which the present authors conducted using SAPM) explored variation in risk by pattern of drinking. The estimated consumption levels associated with a 1.0% lifetime alcohol-attributable mortality risks are broadly in line with the present findings in all of these analyses, as shown in Table 15. The UK, 2016 estimate for men is somewhat lower than for the other models. This merits further investigation and may relate to differences in the sociodemographic or baseline health profile of the UK population.

Table 15: Comparison of number of standard drinks per week associated with 1.0% absolute lifetime risk of alcohol-attributable mortality in four modelling exercises (assuming drinkers spread consumption evenly across five days where drinking pattern-specific estimates are available).

	Men	Women
RARHA, 2015	18.5	10.5
UK, 2016	10.4	13.8
France, 2017	18.5	11.6
Australia, 2019	16.9	13.5

4.2. Strengths of the analysis

The analyses presented here draw on the best available evidence Australian and international evidence. This includes recent Australian Government data detailing levels of alcohol consumption,

mortality and morbidity as well as population demographics. These come from either national administrative datasets, nationally-representative population surveys or census data. It also includes the most recent, methodologically robust systematic reviews and meta-analyses of international evidence on alcohol-related health risks published in scientific journals, identified in consultation with the NHMRC's guideline development committee following their extensive review of this evidence.

This evidence is combined using a new Australian adaptation of the Sheffield Alcohol Policy Model (SAPM). SAPM is a well-established policy analysis tool and analyses using SAPM have informed national policy decisions in the UK and Ireland and legal decisions in the UK Supreme Court and the European Court of Justice, as well as being published in leading scientific journals.[16,63-65] A particular strength of SAPM is its synthesis of evidence for 42 different health conditions that arise from either long-term or single occasions of alcohol consumption. The modelling techniques used in SAPM follow best practice in assessing alcohol-related health risks and are comparable to those used in the Global Burden of Disease Study,[28] as well as previous analyses that have informed the development of alcohol guidelines.[1,10]

The primary results are supported by a series of secondary and sensitivity analyses that allow readers to assess how the consumption level associated with key risk thresholds varies when using alternative thresholds or when making different assumptions regarding key uncertainties in the evidence and analytical approach underpinning the model.

4.3. Limitations of the analysis

The findings described above are subject to important limitations. These relate to both the underlying epidemiological evidence base on alcohol-related health risks that provides the inputs to SAPM and to the SAPM methodology itself. We discuss these two sets of limitations below.

4.3.1. Limitations of the underlying epidemiological evidence

The key input data for SAPM are estimates of alcohol-related health risks taken primarily from meta-analysis of results from previous case control and cohort studies. SAPM uses the most up-to-date and high quality meta-analyses, as described in the Methods section of this report. However, these studies have well-understood limitations, which we describe in turn below.

4.3.1.1. Under-estimation of alcohol consumption

Most epidemiological surveys underestimate levels of alcohol consumption in the study population by between 40% and 70% when compared with more robust, aggregate-level data sources for the same population, such as government alcohol taxation data or sales data.[66,67] This implies that, all else being equal, epidemiological studies are likely to over-estimate the level of risk associated with a given level of consumption.

Underestimation of alcohol consumption occurs for a number of reasons including the omission or under-representation of heavier drinkers within the study population,[67] the validity of questions used to measure alcohol consumption,[68-72] under-reporting of alcohol consumption by survey respondents for intentional reasons, such as social desirability bias, or unintentional reasons, such as lacking awareness of the size of self-poured drinks,[73,74] and inaccurate processing of data by researchers.[75] These problems do not fundamentally undermine evidence on alcohol-related health risks. Epidemiological studies are still able to provide evidence of whether this is a dose-response relationships between alcohol consumption and risk of alcohol-related health outcomes and this evidence is only one of several types of evidence used when assessing whether alcohol is causally those outcomes.[76] Further, although the precise level of risk associated with a given level of

consumption may be overestimated, the general pattern of results indicating that low levels of consumption entail a small degree of risk and higher levels of consumption entail a large degree of risk, remains accurate. Analyses of alcohol consumption data have also shown that epidemiological surveys are still able to identify reliably heavier and lighter drinks and thus identify those who are at higher and lower risk from their drinking.[72,77]

Established methods exist to adjust for these problems within population-level analyses,[78] but individual-level adjustments are more speculative as there are no gold standard individual-level data to assess adjustments against and the research literature offers only limited understanding of the extent to which consumption is under- or over-estimated for different groups within the population. In the absence of robust adjustment techniques that can be used in the present analysis, the implications of this limitation should be borne in mind when using the results to inform selection of new Australian alcohol guidelines.

4.3.1.2. The existence and extent of alcohol-related cardioprotective effects

There is extensive debate within the scientific literature as to whether lower levels of alcohol consumption provide a benefit to cardiovascular health. A large number of epidemiological studies show that drinkers who consume alcohol at low levels have a lower risk of mortality and morbidity for several cardiovascular diseases when compared to abstainers.[79] This finding is often repeated in studies of all-cause mortality,[5,60] suggesting that any health benefits of moderate drinking outweigh the mortality risks for cancer and other conditions at these lower levels of consumption. However, an increasing number of studies challenge these findings and we summarise their arguments and evidence below. In doing so, we highlight a number of key points relating to recent high profile studies in this area.

The most common criticism of studies showing cardioprotective effects is that they have a number of limitations and biases that affect most epidemiological studies of alcohol-related health risks. These include using lifetime abstainers as a reference group within analyses, when this group is very different to the general population,[80,81] misclassifying ex-drinkers as abstainers, even though the latter have elevated health risks,[82,83] excluding people from cohort studies if they have health problems at baseline[55] and controlling inadequately for confounding factors in the relationship between alcohol and cardiovascular disease.[80,84-89] Stockwell et al. found that controlling for or excluding studies with such biases in a meta-analysis of alcohol's relationship with all-cause mortality attenuated the cardioprotective effect to non-significance, although this may be due to only a small number of studies remaining in the analysis after the exclusions (e.g. only 13 out of an initial 87 selected studies had no abstainer biases).[5] Wood et al. also found no evidence that alcohol consumption reduced all-cause mortality risks when pooling data from 83 prospective studies and comparing occasional drinkers to those with higher consumption levels.[6] They also found large differences in all-cause mortality risk between non-drinkers and occasional drinkers, supporting the view that non-drinkers differ from the general population in ways that are difficult to adjust for within analyses, although some argue the same is true of occasional drinkers.[83,90] Wood et al. also found that moderate alcohol consumption is associated with reduced risk for certain cardiovascular diseases, particularly myocardial infarction and coronary heart disease. As such, their results suggest that cardioprotective effects may exist but are outweighed by the elevated risks for other conditions, such as cancer, associated with moderate alcohol consumption. Future studies are likely to replicate this finding in populations where cardiovascular disease rates are declining and thus play a smaller role than previously in determining the shape of the overall risk function linking alcohol to all-cause mortality.

A second set of arguments and evidence challenging cardioprotective effects comes from Mendelian Randomisation (MR) studies. These studies seek to establish whether alcohol consumption causes cardioprotective effects or whether they are due to residual confounding. They do this by testing for an association between genes known to affect alcohol consumption and alcohol-related health outcomes.[91] The underlying logic is that if a particular genotype is associated with an increased or decreased risk for the health outcome, this can only be due to the effect of the genotype on alcohol consumption. The effect of alcohol on the health outcome must therefore be causal.

MR studies require identification of one or more genes that only affect alcohol-related health outcomes via alcohol consumption. One candidate is the so-called 'flushing gene', which slows metabolising of alcohol and makes it uncomfortable for those with the genotype to drink any more than small amounts of alcohol.[3] The flushing gene is highly prevalent in Asian populations but is also present in a small minority of individuals of European descent.[92] The MR studies that examine cardioprotective effects do not provide evidence to support the existence of cardioprotective effects, although some of these studies obtain inconclusive non-significant effects or use genotypes to represent alcohol consumption in general rather than moderate consumption.[3,4,93-96] We discuss two key Mendelian Randomisation studies below, which both claim to provide results that are more conclusive and examine cardiovascular risks at different consumption levels.

Holmes and Dale et al. pooled genotyped data from individuals of European ancestry recruited to 56 separate studies and used an MR approach to examine risk of cardiovascular outcomes.[4] Their results show that carriers of the flushing gene consumed less alcohol and were less likely to die of coronary heart disease during the follow-up period than non-carriers, even when both genetic groups reported either light drinking, moderate drinking or heavy drinking. Caution is required as Holmes and Dale et al.'s results are not all statistically significant and there was evidence that non-drinkers who carried the flushing gene were at greater stroke mortality risk than non-carriers, suggesting a violation of the assumption that differences in outcomes between carriers and non-carriers are only due to alcohol use. Nonetheless, the results of this study suggest that increased drinking does not protect against cardiovascular disease at any level of consumption.

Millwood et al. used data from a cohort study of individuals resident in ten regions of China to examine how risk of cardiovascular disease outcomes among men varied depending on their genotype for two variants of the flushing gene.[3] The main results suggest there is no causal relationship between alcohol consumption and cardioprotective effects for stroke, although secondary analyses show limited evidence in favour of causal cardioprotective effects for both myocardial infarction and coronary heart disease. This makes it difficult to reach a firm conclusion on the overall implications of the study for the existence of cardioprotective effects.

The final major area of concern regarding evidence for cardioprotective effects is the lack of clear biological mechanisms. It is beyond the scope of this report to discuss proposed or evidenced mechanisms by which moderate alcohol consumption may improve cardiovascular health and these are discussed elsewhere.[97,98] We limit our discussion to noting that while there is evidence of alcohol's effects on important biomarkers on the developmental pathway for cardiovascular disease, there is no scientific consensus on whether this evidence amounts to a robust biological explanation for cardioprotective effects.

Overall, the research discussed above suggests there is good reason to be concerned about the existence, scale and associated consumption level of any cardioprotective effect. It is beyond the scope of this report to provide a judgement on whether the avilable evidence is conclusive regarding these concerns. We simply note that there is robust evidence that, at a minimum, the

cardioprotective effect observed in standard epidemiological studies is over-estimated. SA1, which examines the effect of removing all protective effects from SAPM, indicates the impact such overestimation may have on our results. The need to align judgements on the existence of cardioprotective effects with the weight placed on the base case analysis versus SA1 should be borne in mind when communicating to the public the final guidelines and the role of the present report in developing that guideline.

4.3.1.3. Other limitations of epidemiological studies

Many of the biases and limitations raised in the debate over cardioprotective effects apply to alcohol epidemiology in general (e.g. misclassification of abstainers, residual confounding and inappropriate reference groups). There are however additional limitations of note. These include linking alcohol consumption at only one point in time to health outcome rather than examining the effect of a trajectory of consumption across the time period during which a health condition developed,[99] not accounting for differences in drinking patterns, such as heavy episodic drinking, between those with the same level of weekly consumption,[100] reducing the precision of consumption estimates within meta-analyses by synthesising different consumption measures or creating categorical measures (e.g. 1-3 standard drinkers per day) from continuous data,[83,100] and small samples of drinkers consuming at higher consumption levels, as these drinkers are less likely to take part in longitudinal studies.

An increasing body of research is examining the impact of these limitations on risk estimates within alcohol epidemiology,[100-103] but it is not yet possible to judge how they may affect the results of a complex epidemiological modelling exercise such as the present analysis. As such, and in line with the limitations regarding underestimation of alcohol consumption, readers should consider the findings of the base case analysis subject to a significant degree of unquantified uncertainty, in addition to the quantified uncertainty demonstrated by the sensitivity analyses.

4.3.2. Limitations of SAPM-AU

SAPM-AU is also subject to a number of limitations, which we discuss below.

First, the limited availability of suitable data and evidence hinders modelling of the relationship between single occasions of drinking and acute alcohol-attributable health conditions. Much of the relevant epidemiological literature examines this relationship at the occasion-level,[104,105] but the NDSHS data only provide a limited insight into drinking at the occasion-level, including measures of frequency of heavy drinking and number of days consuming at particular levels. In analyses of alcohol pricing policies using the English version of SAPM, we address this problem using a model of the relationship between drinkers' average weekly consumption and their number of drinking occasion per week, consumption per occasion and variability in consumption per occasion.[106,107] However, we cannot use this approach for the present analyses as it assumes variability in consumption across the population, whereas SAPM-AU (and the version of SAPM used to develop the UK guidelines) assume consumption is uniform across the population to derive risk estimates.

Second, we do not provide measures of statistical uncertainty (e.g. confidence intervals) around our results. This is because SAPM-AU draws on sources of evidence that often do not report statistical uncertainty. More importantly, the limitations in SAPM-AU and the wider epidemiological evidence-base, which we discuss above, contribute substantial methodological uncertainty. This means any confidence interval would potentially mislead readers regarding the precision of our results, as it would pertain only to one part of the uncertainty that is known to exist around any given result. Instead, we examine uncertainty via a set of scenario analyses investigating the sensitivity of the

results to particular alternative assumptions, evidence or modelling methodologies, as described in Section 2.4.

Third, the analysis relies on a synthesis of Australian data with international evidence on alcohol-related health risks. Although we prefer to use high quality Australia-specific evidence where this is available, we largely take the risk functions that underpin our analysis from meta-analyses of the relevant international research literature. These meta-analyses draw on a greater weight of evidence than individual studies typically provide and offer a more accurate estimate of alcohol-related health risks than any individual Australian study could provide. As such, meta-analyses are regarded as the gold-standard of epidemiological evidence, even though they combine findings from different times and places.

Fourth, SAPM-AU does not explicitly estimate risks for occasional drinkers or ex-drinkers as distinct from lifetime abstainers. This is largely because meta-analyses often do not provide evidence on which to base such estimates. Instead, meta-analytic studies often seek to adjust their analyses to account for the misclassification of abstainers in some primary studies.[42,79] In other cases, the meta-analytic studies finds no meaningful difference in risk between abstainers and occasional drinkers.[26]

Fifth, our operationalisation of Rehm et al.'s method for adjusting the chronic ischaemic heart disease risk function to account for the effects of heavy episodic drinking is conservative.[108] In line with Rehm et al., we assume anyone who definitely consumes more than 60g (six standard drinks) on a single day receives no cardioprotective benefit from drinking. We implement this by removing the small remaining protective effect for those consuming above 420g per week (i.e. 60g per week). This means drinkers who consume less than 420g per week and more than 60g on any one day still receive protective effects. In this regard, SAPM-AU is likely to overestimate the extent of cardioprotective effects.

Finally, SAPM-AU only provides risk estimates for mortality and morbidity separately rather than in a single metric, such as quality-adjusted life-years (QALYs). The potential years of life lost for different consumption levels and patterns is also not provided and this introduces uncertainty regarding the extent to which premature mortalities occur at younger or older ages.

4.4. Considerations when using the results to inform development of alcohol guidelines

It is beyond the scope of this report to make specific recommendations on appropriate alcohol guidelines for Australia or to specify the processes by which NHMRC should develop such guidelines. The conclusions below seeks instead to highlight key points relating to our results for consideration by NHMRC during the guideline development process and for readers seeking to understand how results from SAPM-AU can be used in that process.

The results above indicate that the general shape of the relationship between alcohol consumption and risk of alcohol-related mortality and morbidity is curvilinear and may include reduced risks at moderate levels of alcohol consumption. The absolute level of mortality or morbidity risks is much greater at higher consumption levels than lower consumption levels. The results also indicate that men are at a lower risk than women from alcohol consumption at all levels of consumption and that the risk of consuming a given amount of alcohol each week is lower when that consumption is spread evenly across a larger number of days.

The results also provide some indication of how evidence on alcohol-related health risks has evolved since the previous 2009 Australian alcohol guidelines. Although the models are not directly

comparable, it is clear that evidence of health risks at lower levels of alcohol consumption exerts a greater impact on the overall risk curve that was previously the case.

The sensitivity analyses indicate that the precise level of alcohol consumption associated with any particular risk threshold is subject to substantial uncertainty. Similarly, the level of risk associated with any particular alcohol consumption level is also uncertain. This is because of limitations in the underlying data and scientific evidence, and SAPM-AU itself. It is also due to major points of scientific debate, such as the existence and extent of cardioprotective effects.

All users of the results should bear in mind that the risk estimates are the average risk for the population of men or women assuming that population all has the same consumption level and pattern. The results are not estimates of the risk faced by any given individual in the population as both the level of risk faced by an individual and the health conditions individuals are at risk from vary depending on a range of sociodemographic, psychological, biological and situational factors. For similar reasons, the risk curves do not describe how mortality or morbidity risks would change for an individual who changes their consumption, as this will depend on the individual's characteristics, drinking history and underlying health profile. Caution is therefore required to avoid providing misleading information when using individualised language to communicate the risk estimates to the public.

Finally, the analyses above examine only risks of mortality and morbidity for the drinker. They do not examine risks for other important outcomes that NHMRC may wish to consider. These outcomes include alcohol dependence, harms to people other than the drinker (including to foetuses), non-health harms such as lost income or family problems, and increased or reduced well-being. The analyses also do not examine risks for conditions where causality is complex or still to be established that may have a large effect of the overall risk curve such as dementia and depression.

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Appendix – Supplementary tables

Sensitivity Analysis 1: Removal of protective effects

Table 16: Absolute lifetime risk of alcohol-attributable mortality for men by mean weekly consumption and days per week across which consumption is evenly spread under SA1

Mean consumption (std. drinks/week)	Drinking days per week						
	7	6	5	4	3	2	1
7	2.5%	2.5%	2.6%	2.6%	2.8%	3.4%	7.5%
14	4.9%	5.0%	5.1%	5.6%	6.2%	7.8%	13.4%
21	7.4%	7.6%	8.0%	8.7%	9.9%	12.1%	17.7%
28	10.1%	10.5%	11.1%	12.1%	13.6%	15.9%	21.0%
35	12.9%	13.5%	14.4%	15.5%	17.1%	19.1%	23.9%
42	16.0%	16.7%	17.7%	18.8%	20.2%	22.1%	27.1%
49	19.3%	20.1%	20.7%	21.7%	22.9%	25.0%	31.3%

Table 17: Absolute lifetime risk of alcohol-attributable mortality for women by mean weekly consumption and days per week across which consumption is evenly spread under SA1

Mean consumption (std. drinks/week)	Drinking days per week						
	7	6	5	4	3	2	1
7	3.1%	3.1%	3.2%	3.2%	3.2%	3.8%	7.7%
14	6.4%	6.5%	6.6%	6.9%	7.3%	8.8%	13.4%
21	9.9%	10.1%	10.4%	11.0%	11.7%	13.7%	18.3%
28	13.7%	14.0%	14.5%	15.3%	16.2%	18.3%	22.6%
35	17.6%	18.0%	18.7%	19.6%	20.6%	22.3%	26.5%
42	21.7%	22.2%	22.9%	23.7%	24.7%	26.0%	30.1%
49	25.9%	26.4%	26.9%	27.6%	28.1%	29.8%	33.5%

Key:

Overall protective effect
Overall lifetime risk of less than 1 in 1,000
Overall lifetime risk at least 1 in 1,000, but below 1 in 500
Overall lifetime risk at least 1 in 500, but below 1 in 100
Overall lifetime risk at least 1 in 100, but below 1 in 50
Overall lifetime risk at least 1 in 50, but below 1 in 10
Overall lifetime risk at least 1 in 10

Sensitivity Analysis 2: Addition of threshold effects

Table 18: Absolute lifetime risk of alcohol-attributable mortality for men by mean weekly consumption and days per week across which consumption is evenly spread under SA2

Mean consumption (std. drinks/week)	Drinking days per week						
	7	6	5	4	3	2	1
7	-5.5%	-5.6%	-5.5%	-5.1%	-4.2%	-1.9%	4.3%
14	-2.9%	-2.5%	-1.5%	-0.3%	1.6%	4.9%	12.0%
21	0.9%	1.9%	3.2%	4.8%	7.0%	10.6%	18.0%
28	5.2%	6.4%	7.9%	9.6%	11.9%	15.5%	23.1%
35	9.7%	11.0%	12.4%	14.1%	16.4%	19.8%	27.6%
42	14.3%	15.4%	16.7%	18.3%	20.5%	23.8%	31.7%
49	19.0%	19.8%	20.8%	22.3%	24.3%	27.5%	35.4%

Table 19: Absolute lifetime risk of alcohol-attributable mortality for women by mean weekly consumption and days per week across which consumption is evenly spread under SA2

Mean consumption (std. drinks/week)	Drinking days per week						
	7	6	5	4	3	2	1
7	-4.3%	-4.4%	-4.2%	-3.6%	-2.3%	0.8%	8.2%
14	0.2%	0.9%	2.0%	3.6%	6.3%	11.0%	20.1%
21	5.9%	7.1%	8.6%	10.7%	13.9%	18.9%	28.5%
28	11.7%	13.2%	14.8%	17.1%	20.3%	25.3%	35.2%
35	17.4%	18.9%	20.6%	22.8%	25.9%	30.7%	40.7%
42	23.0%	24.2%	25.9%	28.0%	30.8%	35.3%	45.3%
49	28.3%	29.3%	30.8%	32.6%	35.2%	39.4%	49.4%

Key:

Overall protective effect
Overall lifetime risk of less than 1 in 1,000
Overall lifetime risk at least 1 in 1,000, but below 1 in 500
Overall lifetime risk at least 1 in 500, but below 1 in 100
Overall lifetime risk at least 1 in 100, but below 1 in 50
Overall lifetime risk at least 1 in 50, but below 1 in 10
Overall lifetime risk at least 1 in 10