Alcohol Consumption and Cancer Incidence and Mortality in Australia: A Prospective Cohort Analysis of the New South Wales 45 and Up Study.

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Statement of Originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Peter Sarich

"*To alcohol! The cause of, and solution to, all of life's problems.*"

- Homer Simpson

Abstract

In 2011, it was estimated that over 5% of the burden of disease and injury in Australia was attributable to alcohol consumption. In 2013, 81% of Australian adults consumed alcohol at least occasionally, while 19% exceeded the Australian drinking guideline of no more than two standard drinks per day. There is a clear relationship between alcohol consumption and diseases such as cancer and liver disease, but whether there are beneficial effects afforded by moderate alcohol consumption on other health outcomes, such as all-cause and cardiovascular mortality, remains controversial. A systematic review of systematic reviews of the impact of alcohol on all-cause mortality was performed, which identified a number of methodological biases, such as the 'sick-quitter effect', which may explain part or all of these associations. Whether patterns of drinking such as heavy episodic drinking alter risk of cancer beyond total alcohol consumption is also under-researched.

Data from the New South Wales 45 and Up Study (2006-2014) linked to cancer registry and death records were used to examine 1) the clustering of behavioural risk factors, including alcohol consumption, among participants by country of birth; 2) examination of the 'sick quitter' effect by quantifying the association of newly acquired health conditions with alcohol consumption cessation; 3) the impact of alcohol consumption and drinking pattern on cancer incidence; 4) the impact of alcohol consumption and drinking pattern on all-cause mortality and cause-specific mortality.

Alcohol consumption was associated with risk of a range of cancer and mortality outcomes, and drinking patterns were associated with risk independent of total alcohol consumption. It was shown that failure to account for the 'sick-quitter effect' may result in biased risk estimates, particularly underestimates of risk for cardiovascular disease and all-cause mortality. The finding that heavy episodic drinking independently increases cancer and mortality risk, and that mortality risk may be

underestimated due to ‘sick-quitter effect’, have implications for Australian drinking guidelines and strategies to reduce alcohol-related harm.

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Publications Arising from This Thesis

This thesis contains a published article:

- Sarich, P.E.A., Ding, D., Sitas, F., and Weber, M.F., *Co-occurrence of chronic disease lifestyle risk factors in middle-aged and older immigrants: A cross-sectional analysis of 264,102 Australians.* Prev Med, 2015. **81**: p. 209-215.

This thesis also contains three articles which are prepared for publication:

- Sarich, P., Canfell, K., Banks, E., Paige, E., Egger, S., Joshy, G., Korda, .R, and Weber, M., *A prospective study of health conditions related to alcohol consumption cessation among 97,852 drinkers aged 45 and over in Australia*.
- Sarich, P., Canfell, K., Egger, S., Banks, E., Joshy, G., and Weber, M., *Alcohol consumption, drinking patterns and cancer incidence in the 45 and Up Study*.
- Sarich, P., Canfell, K., Egger, S., Banks, E., Joshy, G., and Weber, M., *Alcohol consumption, drinking patterns and cause-specific mortality in the 45 and Up Study*.

Statement of Author's Contribution

Chapter 1 of this thesis is an introduction to alcohol and the Australian context. I reviewed the literature and wrote this chapter. Marianne Weber reviewed this chapter and provided feedback.

Chapter 2 of this thesis is a narrative review of alcohol consumption and risk of disease and injury. I reviewed the literature and wrote this chapter. Marianne Weber reviewed this chapter and provided feedback.

Chapter 3 of this thesis is a systematic review of alcohol consumption and all-cause mortality. I reviewed the literature and wrote this chapter. Marianne Weber reviewed this chapter and provided feedback.

Chapter 4 of this thesis outlines the methods and introduces the 45 and Up Study. I wrote this chapter. Marianne Weber, Karen Canfell and Sam Egger contributed to the methods for this chapter. Marianne Weber reviewed this chapter and provided feedback.

Chapter 5 of this thesis compares the 45 and Up Study to other representative health surveys. I reviewed the literature and wrote this chapter. Marianne Weber reviewed this chapter and provided feedback.

Chapter 6 of this thesis investigates the co-occurrence of chronic disease lifestyle risk factors in middle-aged and older immigrants in the 45 and Up Study. Marianne Weber and I planned the analyses. I performed the analyses and wrote this chapter. Marianne Weber reviewed this chapter and provided feedback.

Chapter 6 of this thesis also contains a publication: Sarich, P.E.A., Ding, D., Sitas, F., and Weber, M.F., *Co-occurrence of chronic disease lifestyle risk factors in middle-aged and older immigrants: A cross-sectional analysis of 264,102 Australians.* Prev Med, 2015. **81**: p. 209-215. I co-designed the study along with the co-authors. Sam Egger provided statistical advice. I performed the analyses and

drafted the manuscript. Ding Ding, Freddy Sitas and Marianne Weber reviewed the manuscript and provided feedback.

Chapter 7 of this thesis investigates the association between illness and change in alcohol consumption in the 45 and Up Study. Marianne Weber and I planned the analyses. I performed the analyses and wrote this chapter. Marianne Weber reviewed this chapter and provided feedback.

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Chapter 8 of this thesis investigates the association between alcohol consumption and cancer risk in the 45 and Up Study. Marianne Weber and I planned the analyses. I performed the analyses and wrote this chapter. Marianne Weber reviewed this chapter and provided feedback.

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Chapter 9 of this thesis investigates the association between alcohol consumption and all-cause and cause-specific mortality risk in the 45 and Up Study. Marianne Weber and I planned the analyses. I performed the analyses and wrote this chapter. Marianne Weber reviewed this chapter and provided feedback.

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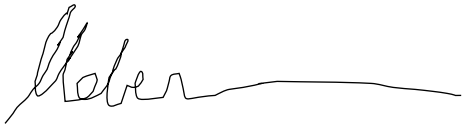
Chapter 10 of this thesis discusses the implications of the findings of the preceding chapters. I wrote this chapter. Marianne Webber and Karen Canfell reviewed this chapter and provided feedback.

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Peter Sarich

28 June 2018

As the supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.



Dr Marianne Weber

28 June 2018

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Abbreviations

ABS	Australian Bureau of Statistics
AC	Adenocarcinoma
AIC	Akaike Information Criterion
ALDH	Aldehyde Dehydrogenase
AMD	Adjusted Mean Difference
ARIA+	Accessibility/Remoteness Index of Australia
ASD	Australian Standard Drinks
BAC	Blood Alcohol Concentration
BMI	Body Mass Index
CDRI	Chronic Disease Risk Index
CHeReL	Centre for Health Record Linkage
CI	Confidence Interval
COD-URF	Cause of Death Unit Record File
CVD	Cardiovascular Disease
DNA	Deoxyribonucleic Acid
DVA	Department of Veterans' Affairs
ESC	English-Speaking Countries
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases, version 10
IHD	Ischaemic Heart Disease
IQR	Interquartile Range
LDL	Low Density Lipoprotein
MOS-PF	Medical Outcomes Study Physical Functioning
NDSHS	National Drug Strategy Household Survey
NHL	Non-Hodgkin Lymphoma

NHMRC	National Health and Medical Research Council
NHS	National Health Survey
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NSW	New South Wales
NZ	New Zealand
OR	Odds Ratio
PA	Physical Activity
PAF	Population Attributable Fraction
PHS	Population Health Survey
PSA	Prostate Specific Antigen
RBDM	Registry of Births, Deaths and Marriages
ROBIS	Risk Of Bias In Systematic Reviews
RR	Relative Risk
RRR	Relative Risk Ratio
RTD	Ready-To-Drink
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
UK	United Kingdom
USA	United States of America
v/v	volume/volume
WCRF	World Cancer Research Fund
WHO	World Health Organisation

Chapter 1 – Alcohol and the Australian Context

Chapter summary

This chapter outlines the definition of alcohol, alcohol metabolism and the acute effects of alcohol on the body. It then presents an overview of alcohol in the Australian context: the history of alcohol in Australia and its current role in Australian society; efforts by government and public health organisations to reduce the harm caused by alcohol; Australian health guidelines; and the prevalence of alcohol consumption. Finally, methodological issues in observational studies of alcohol consumption are discussed. Together, these sections explore the complex relationship of alcohol with Australian society, and provide a local context to the subsequent chapters exploring the harms of alcohol consumption. Finally, the aims of this thesis are stated.

1.1 – Overview of Alcohol

Alcohol

'Alcohol' is the colloquial name for ethanol, one of many alcoholic compounds[1]. Ethanol is a colourless and volatile liquid at room temperature, with a pleasant odour but a burning taste. It has the chemical formula $CH_3CH_2O_2$ and a molecular mass of 46 g/mol. Ethanol is produced from the fermentation of carbohydrates and its primary culinary use is in alcoholic beverages. Small amounts of ethanol can also be found in some food products, including sauces, cakes and chocolates[2]. As well as being the active ingredient of alcoholic beverages, ethanol is also used industrially as a solvent, preservative, disinfectant and fuel[1].

When ingested, alcohol acts as a central nervous system depressant and promotes feelings of relaxation, sociability and disinhibition[3]. It also inhibits the action of the pituitary gland resulting in reduced secretion of anti-diuretic hormone, causing reduced reabsorption of water in the kidneys and then dehydration. With increasing consumption, alcohol causes a range of negative acute effects including incoordination, drowsiness, interrupted sleep patterns, nausea and vomiting, and at very high levels unconsciousness and loss of breathing[3]. Alcohol consumption is associated with risk of injury and a number of diseases, including cancer, cardiovascular disease, liver disease, malnutrition and foetal alcohol spectrum disorder[3]. Alcohol consumption was responsible for 5.1% of the burden of disease and injury in Australia in 2011[4].

Metabolism of alcohol

Alcohol is primarily metabolised in the liver, with the stomach playing a minor role. In the liver, ethanol is converted to acetaldehyde by the enzyme alcohol dehydrogenase, and this is then oxidised to acetate by the enzyme aldehyde dehydrogenase (ALDH2)[5]. The majority of ethanol is converted to acetaldehyde by alcohol dehydrogenase, however the enzymes catalase and cytochrome P450 2E1 also contribute to this process[6]. A small amount (< 10%) of ethanol is also excreted in sweat, urine and breath[5]. Acetate leaves the liver and travels to peripheral tissue where it is converted to acetyl CoA, which is then converted to carbon dioxide, water, fatty acids, ketone bodies and cholesterol.

There is much variation in the rate at which alcohol is metabolised from person to person, with typical values of between 7 and 10 grams of ethanol per hour[5]. The rate of metabolism increases with higher blood concentrations of ethanol, and also varies based on factors including sex, age, race, food intake before drinking, time of day, physical activity, liver disease status and the use of some medications which inhibit alcohol dehydrogenase, inhibit the mitochondrial respiration chain or inhibit the elimination of acetaldehyde[5]. It is estimated that 15-40% of people of East Asian

ancestry have a less active form of aldehyde dehydrogenase, that causes increased acetaldehyde in the bloodstream. This causes vasodilation and nausea, and persons with this condition consume little alcohol[5].

1.2 – Alcohol in Australia

History of alcohol in Australian society

Alcohol in Australia predates European colonisation, with evidence that Aboriginal Australians produced mild alcoholic beverages from the fermentation of native plants[7]. In addition, it is known that Indonesian fishermen traded in alcohol with Aboriginal communities in Northern Australia[7]. From European colonisation, mass production of alcohol began in breweries and distilleries, and throughout the 19th century consumption increased during periods of wealth such as the gold rush and declined during economic recessions[7]. The most common beverage during this time was spirits such as rum, until this was overtaken by beer in the 1890s[7, 8]. There was a decline in consumption during each World War and the Great Depression, followed by increased consumption in the post-war era, reaching a peak in the 1970s[8]. There were significant changes in drinking culture during the 1960s and 1970s. Specifically, it became acceptable for women to consume alcohol with men at pubs, it was made legal for Aboriginal Australians to consume alcohol, and wine became popular as an alternative to beer[7, 8]. In the modern era alcohol is advertised across a broad spectrum of media, and is strongly associated with cultural and sporting events[7, 8]. The most common locations Australians consume alcohol are at home, a friend's house, at private parties, at restaurants and cafes and at licensed premises[9].

Classification of alcoholic beverages in Australia

The Australian Bureau of Statistics classifies alcoholic beverages into five categories – beer, wine, spirits, 'Ready-To-Drink' (RTD) pre-mixed beverages and cider[10]. The Australian Food Standards Code states that beer is produced through the yeast fermentation of cereal grains in the presence of hops[11], and depending on strength has a typical ethanol concentration of 2.7-4.9%

volume/volume (v/v)[3]. Wine is produced through the fermentation of grapes and has a typical ethanol concentration of 9.5-13% v/v[3, 11]. Spirits are produced through the distillation of fermented beverages to increase ethanol concentration to at least 37% v/v, and have a typical ethanol concentration of 37-40% v/v[3, 11]. RTDs, also known colloquially as 'alcopops', are a mixture of spirits and a non-alcoholic beverage such as soft drink, and have a typical ethanol concentration of 5-7% v/v[3]. Cider is produced through the fermentation of apples or a mixture of apples and pears, and has a typical ethanol concentration of 4-8% v/v[11, 12].

The alcohol industry in Australia

The production of alcohol in Australia generates $10.5 billion in annual revenue as of 2015[13]. Production is dominated by the beer and wine industries, accounting for 41% and 50% respectively of annual revenue in Australia. Spirit and cider production occurs on a much smaller scale, at 6% and 3% respectively. Two international companies together have an 84% market share of beer production in Australia: Lion Pty Ltd and SABMiller Beverages Investments Pty Ltd. These companies own some of Australia's oldest breweries, such as those producing Carlton Draught, James Boag and Victoria Bitter[14]. The wine industry is much more fragmented with the two largest companies, Treasury Wine Estates Ltd and Pernod Richard Pacific Holding Pty Ltd, together holding a 22% market share[13]. The two largest companies which produce spirits in Australia are Diageo Australia Ltd and Asahi Holdings (Australia) Pty Ltd with a combined market share of 39%, while Lion Pty Ltd and SABMiller Beverages Investments Pty Ltd have a combined market share of 66% of cider production.

The sale of alcohol in Australia generates $31.8 billion in annual revenue as of 2015[13]. The retail and wholesale sectors (consumption off-premises) and on-licence sector (consumption on-premises, which includes clubs, pubs, restaurants, nightclubs and casinos) each account for about half of the annual revenue in Australia from the sale of alcohol. Two Australian-owned companies, Woolworths

and Wesfarmers Ltd, together have a 64% market share of the retail sector. These companies own stores such as Dan Murphy's, BWS, Liquorland and Vintage Cellars[15]. Approximately 4.8 million Australian adults purchased alcohol from a retailer each week in 2014-2015[16]. The on-license sector is very fragmented, with Woolworths holding the largest market share at only 9%[13]. A small proportion of alcohol produced and consumed in Australia is unrecorded, comprising alcohol purchased internationally and brought to Australia by individuals legally, homemade alcohol, alcohol meant for industrial or medical purposes, and illegal or smuggled alcohol[17].

The alcohol industry spent $12.3 billion on advertising in Australia in 2011[13]. This includes traditional print, billboard, radio, television and online advertising and marketing, and via other methods such as branded merchandise, promotion at events and sports sponsorship[18]. Alcohol product placement in movies doubled in frequency between 1996 and 2015, while since 2010 alcohol has also increasingly been promoted on social media websites[19, 20]. There is a particularly strong association between alcohol advertising and sport in Australia, with some football codes receiving 25% of their income from alcohol sponsorship, and 95% of sponsored sportspeople receiving at least some sponsorship from the alcohol advertising[18]. These methods frequently reach persons under 18 years of age, with a 2017 survey finding that 77% of Australian parents report their children have been subjected to alcohol advertising. Advertising is self-regulated by the alcohol industry under the voluntary Australian Beverages Advertising Code, which has been criticised for its ineffectiveness[21]. For example, marketing is often misleading regarding the risks of alcohol such as increased cancer risk[22]. There is also an independent Alcohol Advertising Review Board which manages community complaints relating to alcohol advertising but it does not have legal power to enforce breaches of its code[23].

The alcohol industry is politically active and is organised into numerous associations and lobby groups, such as the Australian Hotels Association, the Australian Liquor Stores Association, the Brewers Association of Australia & New Zealand and Clubs Australia[24]. These groups often oppose

interventions aiming to reduce the burden of alcohol-related harm (that may reduce sales), such as mandatory health warning labels on alcoholic beverages, increasing alcohol taxation, restricting alcohol advertising and altering industry advertising self-regulation[24]. The alcohol industry is dependent on heavy drinkers for revenue, as the top decile of Australian drinkers, who consume six standard drinks per day on average, account for 53% of all alcohol consumed in Australia[13]. Since 2005, the alcohol industry has funded DrinkWise, a non-profit organisation "*focused on promoting change towards a healthier and safer drinking culture in Australia*"[14, 15, 25]. DrinkWise has been criticised as being in reality a public relations organisation with vested interests, and a recent DrinkWise campaign was found to be ineffective in promoting behaviour change whilst simultaneously reinforcing positive aspects of alcohol consumption[25, 26].

Public health efforts to reduce alcohol-related harm in Australia

Public health initiatives relating to alcohol consumption before the 1950s were focused on the impacts of public drunkenness[7]. There were numerous efforts to curtail the social harms caused by alcohol, such as attempted prohibition during the gold rush, middle-class Christian groups advocating for the moderation of supply to lower-class groups during the 19th and early 20th centuries, a poorly-enforced prohibition attempt in the Australian Capital Territory from 1911 to 1928, and the legal requirement for all alcohol establishments to close at 6pm during the middle of the 20th century[7, 8, 27]. In recent years there has been an increasing policy response to alcohol-related harm from federal, state and local governments to address the growing evidence of harm related to alcohol consumption. World Health Organisation (WHO) member states (including Australia) endorsed a global strategy to reduce the harmful use of alcohol in 2010, in which harmful use was defined as causing "*detrimental health and social consequences for the drinker, the people around the drinker and society at large, as well as the patterns of drinking that are associated with increased risk of adverse health outcomes*"[17]. In 2013 these member states endorsed a global

action plan for the prevention and control of non-communicable diseases which included a voluntary target of a 10% reduction in the harmful use of alcohol at the national level[17].

Initiatives in Australia are guided by the National Alcohol Strategy within the National Drug Strategy framework, which is a collaboration between federal and state governments and non-government organisations[28]. There are over 90 public health organisations working to reduce alcohol-related harm in Australia such as the Foundation for Alcohol Research & Education, the National Alliance for Action on Alcohol and the Public Health Association of Australia[29]. According to a review of alcohol policy in Australia from 2014, there are seven distinctive policy areas which can be used to reduce the burden of alcohol consumption: pricing and taxation, regulating physical availability, modifying the drinking environment, drink-driving countermeasures, education and persuasion, restrictions on marketing and treatment and early intervention[30]. Economic cost-effectiveness analyses have found that the optimum set of alcohol policies to reduce alcohol-related harm include, in order from most to least cost-effective: alcohol taxation, banning alcohol advertising, raising the legal drinking age from 18 to 21 years, primary care interventions, alcohol licensing controls, anti-drink-driving campaigns and roadside random breath testing[31]. Only some of these policies have been implemented in Australia, including taxation, policies relating to regulating the physical environment, and education.

There are three national taxes related to alcoholic beverages – the alcohol excise tax, the wine equalisation tax and the goods and services tax[30]. There is an additional 'alcopop tax' on RTDs, and most states have passed legislation enabling the restriction of price discounting, although implementation varies from state to state[30].

There are many policies in Australia relating to regulating physical availability, such as a national legal alcohol purchase age of 18 years, the banning of alcohol sales in high-risk communities such as in individual towns in the Northern Territory, time of day sale restrictions in all states and territories,

outlet density restrictions in all states and territories and the prohibition of drinking in public places often enacted by local governments[30].

Policies relating to modifying the drinking environment implemented in Australia include the training of staff in the responsible service of alcohol in all states and territories, server liability for serving intoxicated persons in all states and territories, voluntary codes of bar practice in some local areas, late-night lockouts of pubs and clubs in New South Wales, Queensland and South Australia, and police enforcement of laws on-premises and special powers such as banned drinker registers and the emergency closure of premises, the extent of which varies by state and territory[30].

Drink-driving countermeasures used in Australia include advertising campaigns, a national blood alcohol concentration of 0.05% for most drivers and 0.00% for novice drivers, roadside random breath testing and penalties including fines, license suspension and imprisonment depending on severity of offence[30]. For repeat offenders, all states mandate the installation of breath testing systems that can prevent their car from being started.

Policies relating to education and persuasion in Australia include alcohol education as part of schooling in all states and territories, voluntary drink warning labels and government mass media campaigns[30]. Voluntary drink warning labels were introduced by the alcohol industry in Australia in 2011, however as of 2013 these warnings were only present on about one third of products[32]. Mass media campaigns are commonly funded by state and federal governments, and past themes have included the harms related to drink-driving, violence, heavy episodic drinking and underage drinking[30].

There are few restrictions on alcohol marketing in Australia, and the impact of alcohol marketing far outweighs that of government mass media campaigns[30]. Television advertising is only allowed by the Commercial Television Industry Code of Practice 2015 after 8:30pm during programs rated M15+ or greater, however there is an exception for sporting events which do not have a time of day restriction[33]. The South and Western Australian governments have recently announced an ending

of alcohol advertising on public transport[34]. New South Wales has liquor promotion guidelines however these do not apply to packaged alcohol outlets and are not effectively enforced[30].

Efforts relating to treatment and early intervention for persons with alcohol use disorders include workplace programs targeting at-risk drinkers with brief interventions, self-help programs such as Alcoholics Anonymous and 'sobering-up centres'[30].

Alcohol consumption health guidelines

The 'Australian Guidelines to Reduce Health Risks from Drinking Alcohol' were published by the National Health and Medical Research Council (NHMRC) in 2009 and are currently under review[3]. There are four guidelines. The first two guidelines recommend that healthy men and women should consume a maximum of 2 standard drinks on any day to reduce "*the lifetime risk of harm from alcohol-related disease or injury*", and a maximum of 4 standard drinks on any day to reduce "*the risk of alcohol-related injury arising from that occasion*". The third guideline states that children under 18 years old should not drink alcohol, especially children under 15 years old, and that the age of initiation to alcohol should be as late as possible for those aged 15 to 17 years old. The final guideline states that women who are planning a pregnancy, pregnant or breastfeeding should not drink alcohol. Appendix A1 of the guidelines discusses specific situations where drinking increases risk of harm, such as when taking medications, driving a motor vehicle, operating machinery, engaging in high-risk recreational activities and supervising children.

Despite the first guideline recommending a maximum of two standard drinks on any day, in the supporting documentation for the guidelines, it is reported that any amount of alcohol consumption carries a lifetime risk of harm from disease or injury[3]. The cut point was chosen arbitrarily so that the lifetime risk would remain below 1 in 100. This fact is poorly understood by the Australian public according to the *National Drug Strategy Household Survey*. In Australia in 2013, 9% of men correctly

answered that there was no level of alcohol consumption that did not increase one's risk of lifetime harm, 56% thought there was a level of consumption above zero that did not increase risk, and 36% stated that they did not know[9]. For women, 13% answered correctly, 42% answered incorrectly and 45% did not know.

There was formerly a guideline to have one or two alcohol-free days per week in 2001[35]. The rationale for this was that although the evidence for effect on health was limited, it may help people control their drinking habits and avoid alcohol dependency. This recommendation did not appear in the 2009 guidelines, although it is mentioned in the explanatory document that alcohol-free days can further reduce the lifetime risk of disease and injury[3].

Alcohol consumption also appears in the 2013 Australian Dietary Guidelines, which state that one should "*limit intake*", and that "*not drinking alcohol is the safest option*" for pregnant or breastfeeding women and for women planning a pregnancy[36]. A companion poster, the Australian Guide to Healthy Eating, states that for the general population alcohol should be consumed "*only sometimes and in small amounts*".

Alcohol health guidelines vary from country to country. Table 1.1 shows a comparison in Australian standard drinks of the alcohol health guidelines of Australia[3], Canada[37], New Zealand[38], the United Kingdom[39, 40] and the United States[41]. The guidelines in all five countries are consistent regarding alcohol consumption during pregnancy, under the legal drinking age, and in situations such as when using certain medication and undertaking high-risk activities. In addition, all guidelines state that individuals who do not currently drink alcohol should not start. The differences are predominantly found in recommendations for reducing long-term risk to health, short-term risk of injury and for drinking when breastfeeding. In terms of maximum weekly alcohol consumption, the guidelines with the lowest cut-point to minimise long-term risk for men are the United Kingdom guidelines (11.2 Australian standard drinks/week) and for women the United States guidelines (9.8 Australian standard drinks/week). The guidelines with the highest cut-point for men are the

Canadian guidelines (20.2 Australian standard drinks/week) and for women the Australian guidelines (14 standard drinks/week). The differences in guidelines by country may reflect different sources taken into consideration, different methods used to calculate risk, and also the arbitrary level of risk that is considered reasonable. In both the Australian and United Kingdom guidelines the accepted lifetime level of risk of mortality was up to 1%, while the Canadian guidelines instead selected the cut-point where the number of deaths caused and prevented by alcohol consumption were balanced (assuming that moderate drinking is causally associated with decreased risk of all-cause mortality). The New Zealand guidelines do not state a level of accepted risk but do state that the Australian and Canadian guidelines were used as the "*primary resource material*"[38]. Lastly, in the United States guidelines, neither the level of accepted risk nor the specific method used to calculate risk were stated.

Table 1.1. Alcohol consumption health guidelines in Australia and four other countries.

Country	Long-term risk	Short-term risk	Pregnancy and breastfeeding	Under legal drinking age[a]	High-risk situations[b]
Australia	≤ 2.0 ASD on any day	≤ 4.0 ASD on any day	None during pregnancy, none during breastfeeding	None; Delay initiation as long as possible	None
Canada	≤ 3 SD (4.0 ASD)/day and ≤ 15 SD (20.2 ASD)/week for men; ≤ 2 SD (2.8 ASD)/day and ≤ 10 SD (13.5 ASD)/week for women; "Some" non-drinking days per week	≤ 4 SD (5.4 ASD)/day for men and ≤ 3 SD (4.0 ASD)/day for women aged ≥ 25 years; ≤ 3 SD (4.0 ASD)/day for men and ≤ 2 SD (2.8 ASD)/day for women aged < 25 years	None during pregnancy, none before breastfeeding	None; Delay initiation as long as possible	None
New Zealand	≤ 3 SD (3 ASD)/day and ≤ 15 SD (15 ASD)/week for men; ≤ 2 SD (2 ASD)/day and ≤ 10 SD (10 ASD)/week for women; ≥ 2 non-drinking days per week	≤ 5 SD (5 ASD)/day for men and ≤ 4 SD (4 ASD)/day for women	None during pregnancy, breastfeeding not mentioned	None; Delay initiation as long as possible	None
United Kingdom	≤ 14 SD (11.2 ASD)/week, over at least 3 days	Limit total intake on any one occasion	None during pregnancy, breastfeeding not mentioned	None; If 15 to 17 year-olds do drink alcohol then never more than one day per week	None
United States	≤ 2 SD (2.8 ASD)/day for men; ≤ 1 SD (1.4 ASD)/day for women	< 5 SD (7.0 ASD) on any day and < 15 SD (21.0 ASD)/week for men; < 4 SD (5.6 ASD) on any day and < 8 SD (11.2 ASD)/week for women; do not mix alcohol with caffeine	None during pregnancy, breastfeeding not mentioned	None	None

[a]18 years in Australia, New Zealand, the United Kingdom and some provinces of Canada (Alberta, Manitoba and Quebec), 19 years in all other provinces of Canada, 21 years in the United States.
[b]Such as using certain medications, operating motor vehicles and machinery, high-risk recreational activities and supervising children. ASD, Australian Standard Drink (10 g of ethanol). SD, Standard Drink (13.45 g in Canada, 10 g in New Zealand, 8 g in the United Kingdom and 14 g in the United States).

Alcohol consumption prevalence

Australians aged ≥ 15 years consumed 12.2 L per capita in 2010 (17.3 L for men and 7.2 L for women), and this is projected to increase to 13.5 L in 2025[17]. The 2010 value is higher than in Canada, New Zealand, the United Kingdom and the United States (all between 9.2 and 11.6 L) and the global average (6.2 L). Of all alcohol consumed in Australia, 39.9% is consumed as beer, 37.5% as wine, 12.8% as spirits, 6.0% as RTDs and 3.8% as cider[10]. These proportions have changed over time. Compared to 2010-11, as a proportion of all alcoholic beverages consumed, beer and RTDs decreased, spirits did not change, and wine and cider increased[10]. Beer is the most common alcoholic beverage choice of men and wine the most common choice of women[9]. Spirits, RTDs and cider are consumed more frequently by younger people while wine is consumed more frequently by older people[42]. There is also evidence of seasonality in alcohol consumption, with beer consumed more frequently in summer months and wine in winter months[43].

The most recent drinking habits study in Australia is the *National Drug Strategy Household Survey* in 2013[9]. 81% of adults in 2013 were current drinkers, 8% were former drinkers and 11% were lifetime abstainers, while of current drinkers, 9% consumed alcohol daily, 49% at least weekly, and 43% less than weekly. There has been a slight decline in the proportion of persons aged ≥ 14 years who are current drinkers, falling from 82% in 2001 to 78% in 2013. In 2013, a higher proportion of male adults were current drinkers than females, at 84% and 78% respectively. For age groups between 18 and 59 years, the proportion of current drinkers was between 82 and 84%, declining to 79% in those aged 60-69 and 68% in those aged ≥ 70 years. The ≥ 70 years age group had the highest proportion of both former drinkers and lifetime abstainers at 15% and 17% respectively. The average age of initiation to alcohol in Australia in 2013 was 15.7 years, increasing from 14.8 years in 1995[9]. Of persons aged 12-17 years in 2013, 29% were current drinkers. Of women who were pregnant or breastfeeding in 2013, 47% and 63% respectively consumed at least some alcohol.

In 2013, 19% of adults (28% of men and 10% of women) were at risk of long-term harm according to the 2009 NHMRC guidelines by consuming greater than two standard drinks per day on average[9]. For all age groups between 18 and 69 years, the proportion was between 19% and 23%, declining to 10% in those aged ≥ 70 years at risk of long-term harm. In addition, 27% of adults (36% of men and 17% of women) were at risk of short-term harm by consuming greater than four standard drinks on a single occasion at least monthly[9]. This figure was highest in persons aged 18-24 years at 47% and lowest in persons aged ≥ 70 years at 6%. Finally, 7% of Australians aged ≥ 12 years consume alcohol at 'very high risk' levels by consuming greater than 10 standard drinks on a single occasion at least monthly[9]. This figure was highest in persons aged 18-24 years at 18% and lowest in persons aged ≥ 70 years at 1%. It was estimated that 3.5% of Australians aged ≥ 15 years had an alcohol use disorder in 2010[17]. Using a definition of ≥ 6 standard drinks per occasion at least monthly, 11% of Australians aged ≥ 15 years engaged in heavy episodic drinking in 2010, including 17% of males and 5% of females[17]. In Australia there is evidence of an association between heavy episodic drinking and the consumption of regular strength beer and RTDs, and less of an association for wine and low alcohol beer consumption[44].

Higher than recommended levels of alcohol consumption are more common in certain socio-demographic groups. Aboriginal and Torres Strait Islander Australians, persons living in regional and remote areas, persons with higher socio-economic status, persons currently employed rather than unemployed or unable to work and homosexual or bisexual persons have a higher prevalence of consuming alcohol at levels that put them at risk of long-term harm[9, 45]. There is only a slight association between having a mental health condition and risky alcohol consumption, however a stronger association for general psychological distress. There is also variation in alcohol consumption by country of origin for different immigrant groups in Australia[46, 47]. Persons born in non-English speaking countries have a lower prevalence of exceeding the long-term risk guideline than persons born in English-speaking countries and in Australia[45]. In 2013, the Northern Territory had the

highest proportion of persons exceeding the lifetime risk and single occasion risk guidelines, while New South Wales and Victoria had the lowest proportions[9].

Importantly, alcohol consumption is associated with other risk factors for chronic disease. For example, in the Australian population it has been reported that high risk drinkers have a higher prevalence of smoking, obesity (men only; inversely associated in women), large waist circumference, physical inactivity (men only; inversely associated in women), insufficient fruit intake and insufficient vegetable intake (men only; no difference in women)[48]. In a New South Wales study the consumption of alcohol was shown to co-occur with smoking but was also inversely associated with physical inactivity[49]. Thus, it was of interest to understand how alcohol consumption might co-occur with other lifestyle risk factors in the context of chronic disease risk. In some cases, the co-occurrence of two risk factors can cause a multiplicative increase in risk for an outcome, for example, drinking and smoking on cancer risk[50]. The quantification of the co-occurrence of drinking with other lifestyle risk factors is also relevant for understanding the potential extent to which these factors may confound associations between alcohol consumption and health outcomes.

It is important to note that there are methodological issues impacting the measurement of alcohol consumption that have implications for estimating the prevalence of drinking behaviours and the risk of harm associated with drinking. These include problems related to the measurement of alcohol itself such as measurement error and inconsistencies between countries in defining standard drink sizes and cut-points for harm, as well as other problems such as selection bias and choice of reference group. These issues are discussed in the next section.

1.3 – Methodological Issues in Observational Studies of Alcohol Consumption

Measurement of Alcohol Consumption

Measurement error in self-reported alcohol consumption

When measuring alcoholic beverage consumption the goal is to quantify ethanol intake. Studies that simply require participants to state how many drinks they consume may introduce measurement error in the ascertainment of ethanol consumed. The majority of epidemiological studies ask participants in an interview or survey about their usual quantity or frequency of alcoholic beverages per day or week, and sometimes with a guide as to what constitutes a standard drink of beer, wine and spirits[51]. Another common method is to ask participants to report their actual daily consumption during a period of time either retrospectively or prospectively. These quantities are often converted to grams of ethanol per day or week. Thus, measurement error can occur in a number of ways.

Study participants may have difficulty converting their intake into the units of alcohol required by the questionnaire, often resulting in an underestimation of alcohol consumption[51, 52]. As well as varying in ethanol concentration, alcoholic drinks can vary greatly in serving size. For instance, beer in Australia is commonly consumed as a 285 mL 'middy', a 330 mL bottle, a 375 mL can and a 425 mL 'schooner'[2], and a recent survey of Australians found participants had a mean of 1.58 standard drinks in their usual serving of wine purchased from off-license premises[53]. In the United States, beverages served at home were reported to contain an average of 1.28 Australian standard drinks for beer, 1.56 for wine, and 1.96 for spirits[54]. A review of studies conducted in Australia, the Netherlands, United States and United Kingdom also found that participants generally serve greater quantities than the standard drink in each country, and also underestimate the alcohol content of the drinks they serve[52]. The discrepancy was greatest for spirits and mixed-drinks, then wine, and

then beer, while knowledge of standard drink sizes was associated with more accurate beverage pouring. Therefore, even in studies providing guides as to what constitutes a serving size, asking participants to record alcoholic drinks will likely result in an underestimation of alcohol consumption, and may vary depending on the type of beverage.

Participants may also under-report their alcohol consumption due to concern that their drinking does not match societal norms, especially in the presence of an interviewer or family member[51, 55]. A related factor is whether the participant perceives that their responses will be confidential[56]. These issues can manifest through the mode of survey, as survey results have been found to vary depending on whether the study is conducted using a telephone or in-person interview, a paper questionnaire or a computer-assisted questionnaire[57-59]. Estimates of total alcohol consumption and the prevalence of heavy episodic drinking have been reported as higher when using mailed surveys in comparison to telephone surveys and computer-assisted interviews[57, 58], while web-based surveys result in a greater prevalence of heavy episodic drinking compared to both mailed and telephone surveys[59]. One advantage of the presence of an interviewer however is that data quality can be improved by easing participant burden when the survey design is complex[58]. In addition, it is important to consider cultural context when measuring alcohol consumption in specific populations[60]. For example, there has recently been a trial on the use of electronic aids such as digital 'apps' to assess alcohol consumption more accurately and in a culturally appropriate way for Aboriginal and Torres Strait Islanders[61]. This is important as it has been estimated that surveys of drinking in Aboriginal and Torres Strait Islanders can underestimate alcohol consumption by up to a factor of seven[61].

Responses also appear to be particularly sensitive to the style of questions asked. Harmful drinking was shown to be three times more prevalent with the use of 'graduated frequency' style questions (assessing how frequently in the past year participants consumed 1-2 drinks, 3-4 drinks, 5-7 drinks in a single day, etc.) compared to the more common method of 'quantity frequency' style questions

(assessing average quantity and frequency of alcohol consumption over a period of time – in this case, the past year)[62]. Harmful drinking was also five times more prevalent when using 'graduated frequency' style questions compared to the assessment of total consumption in the past week[62]. Further, participants using a prospective weekly drinking diary reported greater alcohol consumption and a higher prevalence of 6 or more drinks consumed on one occasion than participants using graduated frequency and quantity/frequency style questions[63]. A disadvantage of the usual quantity/frequency approach is that it can be difficult for participants to summarise their alcohol consumption into a single measure such as average drinks per week, given that patterns of drinking may not be consistent over time and can occur in a wide variety of settings[51].

Other question factors that may influence participant responses include the length of the period that participants are asked to report their usual alcohol consumption (from as little as in the previous day to as much as the previous 12 months), the use of open-ended or multiple choice responses, the ordering of multiple choice responses from low to high or high to low consumption, and the succinctness of questions to minimise participant burden[56]. It has also been reported that recording daily alcohol consumption prospectively in a diary can be burdensome and may cause the participant to alter their intake over the study period[51].

Finally, to adequately capture lifetime alcohol consumption (for either the purpose of measuring mean lifetime alcohol consumption or for ascertaining changes in drinking status over time) it is necessary to query both present alcohol consumption as well as consumption at one or multiple time points either retrospectively or prospectively[64]. This also helps to prevent bias from regression dilution, where current drinking may not be representative of past and future drinking (e.g. the classification of prior long-term heavy drinkers as current moderate drinkers and vice versa), which causes effect estimates to be biased towards the null[65, 66]. The majority of studies investigate current alcohol consumption at baseline rather than lifetime alcohol consumption, and there is variation in the methods used to capture lifetime alcohol consumption[64].

Variation in the definition of a standard drink

Because different alcoholic beverage types contain different quantities of ethanol, beverage labels and alcohol health guidelines require a reference alcohol measure so that consumers are informed of the amount of alcohol in each drink. The usual terms for this reference quantity are the 'standard drink' or a 'unit' of alcohol, however there is no international agreement on what constitutes a standard drink and there is wide variation from country to country.

The Australian standard drink is defined as an alcoholic beverage containing 10 g of ethanol, which is equal to 12.5 mL of ethanol[3]. A standard drink is 8 g of ethanol in the United Kingdom[39], 10 g in New Zealand[67], 13.45 g in Canada[37], 14 g in the United States[41] and 19.75 g in Japan[68]. Furthermore, the standard drink is frequently smaller than the typical beverage as served in a bar, restaurant or at home. According to Australian alcohol guidelines, a 425 mL glass of full strength beer contains 1.6 standard drinks, a 150 mL serving of wine contains 1.4-1.6 standard drinks, and a 30 mL nip of spirits contains 1 standard drink[3].

Variation in the description of drinking patterns

There are no consistent definitions for terms such as 'occasional', 'light', 'moderate' and 'heavy' drinking. A recent systematic review of alcohol consumption and cancer risk defined 'very light' drinking as ≤ 0.5 drinks per day, 'light' drinking as ≤ 1 drink per day and 'moderate' drinking as 1-2 drinks per day[69]. Other definitions of 'moderate' drinking have included < 1 drink per day[70], < 3 drinks per day[71], 2-3 drinks per day[72] and > 1 and < 4 drinks per day[73]. Sometimes definitions differ by sex, with a common definition of 'low' or 'moderate' drinking as ≤ 2 drinks per day for men and ≤ 1 drink per day for women[74-76]. The term 'occasional' drinking has been referred to as 1-11 drinks per year[77], ≤ 1 drink per week[78], 0.033-0.363 grams per day[77] or < 1.3 grams per day[78], while former drinking has been defined in the Australian *National Drug Strategy Household Survey* as "*consumed at least a full serve of alcohol, but not in the previous 12 months*"[9].

For heavy episodic drinking or 'binge' drinking there is also no consistent definition between studies[79]. The Australian alcohol guidelines do not have a classification for heavy episodic drinking, but do state that consuming ≤ 4 drinks per occasion lessens the short-term risk of injury on drinking occasions[3]. One of the more common definitions in studies of binge drinking, and the definition adopted by the USA's National Institute on Alcohol Abuse and Alcoholism (NIAAA), is ≥ 5 drinks (i.e. 7 Australian standard drinks) per occasion for men and ≥ 4 drinks (5.6 Australian standard drinks) for women on at least one day per month[75, 79]. These cut-points were chosen as they should induce a blood alcohol concentration (BAC) of 0.08 g/dL if consumed within two hours[75]. Other definitions have included ≥ 6 drinks per occasion for men and ≥ 4 drinks for women, ≥ 7 drinks per occasion for men and ≥ 6 for women for 'heavy binge drinking', ≥ 5 drinks per occasion for both sexes, ≥ 10 drinks and < 2 days per week, ≥ 100 drinks in < 21 days in a month for men and ≥ 80 for women, "*being drunk or very high from alcohol in past 90 days*", a 'binge drinking score' (i.e. calculated from drinks per hour, number of times 'drunk' in past 6 months and percentage of time 'intoxicated' when drinking), and a breath-measured blood alcohol concentration of ≥ 0.08[79]. Furthermore, the prevalence of heavy episodic drinking can vary depending on the length of time inquired. For example, a study querying about the past week will not capture participants who engage in heavy episodic drinking once per month or less frequently. Previous studies have defined a time period of past week, past 30 days, past six months and past year[79]. A review examining definitions of heavy episodic drinking recommended the following operational definition be used, adapted from the NIAAA definition: "*A pattern of drinking alcohol that brings BAC to 0.08 gram percent or above (≥5/4 for men/women in 2 hr) on more than one occasion within the past 6 months*"[79]. The period of six months was selected to ensure a window large enough to capture individual variation in frequency of heavy episodic drinking.

Selection bias in observational studies

Non-response bias is an important issue to consider in observational studies of alcohol consumption as it is possible that participants who consent may have different patterns of drinking to the general population. For example, a South Australian cohort study found that participants consumed alcohol at intermediate to high risk levels more frequently than participants in a representative continuous health surveillance study[80]. Non-representative sampling may occur if a study is conducted only on people living in regular housing, which may result in an underestimate of population alcohol consumption due to the exclusion of groups in society that may consume alcohol in higher than average amounts, such as the homeless, institutionalised people, the military and students living in dormitories[56].

Choice of reference group for estimates of relative risk

The magnitude and direction of relative risk estimates are dependent on the choice of reference group. In studies of alcohol exposure, the choice of reference group is often 'non-drinkers' however it is important to differentiate between lifetime abstainers and former drinkers. This is because former drinkers may have health conditions which caused them to quit drinking, and may predispose them to increased morbidity and mortality compared to lifetime abstainers[56, 77, 81]. A reference group of non-drinkers that combines former drinkers with lifetime abstainers will therefore result in an underestimate of the health risks for current drinkers. For example, an inverse association was reported between "light or moderate" drinking and risk of heart disease, stroke, colorectal cancer, liver cirrhosis, type 2 diabetes and Alzheimer's[82], while the risk curve for drinking and all-cause mortality is commonly found to be J-shaped (where moderate drinkers have a lower risk and heavy drinkers a higher risk than non-drinkers)[77]. This has been described as former drinker misclassification or the 'sick-quitter effect'. The sick-quitter effect is thought to be responsible for spurious protective associations where no plausible biological mechanisms exist. For example,

studies have reported associations between “moderate” alcohol consumption and reduced risk of hearing loss and hip fractures[82].

Aside from using lifetime abstainers as the reference group, one proposed solution to the sick-quitter effect is to assign former drinkers to the level of drinking intensity they reported before they quit[83]. This also reduces confounding by health status between drinkers and lifetime abstainers, whereby drinkers appear healthier because ‘sick-quitters’ are excluded from this group[83]. This is analogous to the ‘intention to treat’ principle in randomised controlled trials, whereby participants choosing to cease a treatment are still grouped with their initial exposure category to prevent selection bias[83, 84]. An alternative method which attempts to reduce confounding due to illness at baseline is to exclude participants with a history of disease (such as cancer and cardiovascular disease) from analysis, however this has the potential to introduce selection bias and induce false J-shaped associations[78, 85].

Few studies have examined the specific health reasons that drive people to quit drinking, especially in prospective studies[81]. This is an important gap in the research base, as in the 2013 *National Drug Strategy Household Survey* it was reported that 50% of Australians who reduced their alcohol consumption in the previous 12 months did so due to health reasons[9]. Two recent prospective studies examined health conditions associated with quitting or decreasing alcohol consumption[81, 86]. One study found associations with self-rated health, liver disease, hypertension, gastric disease, incident cardiovascular disease and cluster A personality disorders, but not prevalent cardiovascular disease, mood disorders, anxiety disorders or cluster B and C personality disorders[81]. The other study found associations with self-rated health and depressive symptoms[86]. There is a need to determine which diseases are associated with drinking cessation and reduction, including their relative importance. Understanding the nature of the sick-quitter effect will help inform methods to address it, and in turn enable robust alcohol-disease risk estimates.

Biased risk estimates of alcohol consumption may also be due to 'occasional drinker misclassification', whereby occasional drinkers are combined in the reference group with lifetime abstainers[77]. Measuring drinks per day rather than drinks per week and the use of categories such as 'almost never drink', 'rarely/never drink' and 'never or less than once a month' can lead to misclassification for occasional and former drinkers[87]. Like former drinkers, occasional drinkers (at least one standard drink per year but less than one per week) may have decreased their alcohol consumption due to ill-health. However two systematic reviews reported that occasional drinkers have a lower risk or no difference in risk of all-cause mortality compared to lifetime abstainers, and their inclusion in the reference group would therefore bias estimates of effect for drinkers upwards or not at all[77, 78].

Indeed, occasional drinkers may be a more appropriate reference group than lifetime abstainers. Similar to former drinkers, lifetime abstainers may not have begun drinking alcohol due to health reasons[78]. For example, it has been reported that having a long-standing illness throughout young adulthood is associated with lifetime abstention[88]. Thus, due to their comparatively poorer health status, using lifetime abstainers as the reference group may result in conservative estimates of the effects of drinking on health, and has been termed the 'sick non-starter effect'[88, 89]. Furthermore, inaccuracies in self-report have been documented for lifetime abstention. Two prospective studies that assessed alcohol consumption at multiple points in time found that 53% and 67% of persons claiming to be lifetime abstainers in the latest follow-up survey were in fact ex-drinkers, as they had reported being drinkers in previous surveys[90, 91]. The majority of these participants were previously light or moderate drinkers, however modelling showed that this misclassification could result in alcohol-attributable mortality being underestimated by 2-15% in men and 2-22% in women[90]. That study also found that 38% of participants reporting lifetime abstention at baseline then went on to report drinking in later surveys[90]. Given the unreliability of self-reported lifetime abstention, it has been proposed that lifetime abstainers and 'irregular lifetime light drinkers' combined could be used as an alternative reference group[90].

Gold standard methods for measuring alcohol consumption

A 2016 systematic review found there to be four international guidelines for the measurement of alcohol consumption[92]. These guidelines were published by the WHO in 2000, the Kettil Bruun Society in 2000, the American National Institute on Alcohol Abuse and Alcoholism in 2003, and the European Commission in 2010. All contained at least six questions. Typically, the questions asked about frequency of alcoholic beverage consumption in the previous 12 months, usual number of drinks on days that drinking occurred, frequencies and quantities for specific types of beverage (both usual and maximum), graduated frequency questions about heavy episodic drinking, and lastly questions about settings in which alcohol is consumed such as with meals, weekdays and weekends, alone or with others, at home, restaurants and bars. It should be noted that even if all of these prompts are used in order to capture alcohol consumption as completely as possible, the problems of non-response bias, non-representative sampling and the inaccurate measurement of irregular alcohol consumption remain[56, 92].

1.4 – Thesis Aims

Alcohol consumption is commonplace in Australia and is associated with substantial social and economic harm, including 5.1% of the national burden of disease and injury, second only to tobacco and overweight and obesity[4]. These harms are not evenly distributed however, with variation in alcohol consumption by certain population subgroups such as different immigrant groups, and a need for further evidence regarding differences in the co-occurrence of alcohol consumption with other risk factors by population subgroup, and implications for potential chronic disease risk. One of the most significant diseases caused by alcohol consumption is cancer, which contributes more to the national burden of disease and injury than any other health condition. Despite this, there have been few large-scale studies investigating the relationship between alcohol consumption and cancer in Australia. Investigations of cancer and other outcomes attributable to alcohol consumption in Australia have instead relied on internationally derived relative risks for their calculations[93-95].

The effects of alcohol on health are not straightforward, possibly because of the methodological complexities involved in observational studies of alcohol exposure. Specifically, 'moderate' alcohol consumption has been associated with a lower risk of disease and all-cause mortality compared to non-drinking, however there is a lack of consistency across studies around definitions of 'moderate' consumption, definitions of a 'standard drink', and definitions of harm. Furthermore, inverse associations may be partially or totally accounted for by methodological biases such as the 'sick-quitter effect'. The exact nature of the sick-quitter effect remains to be determined, with few prospective data on the specific illnesses that cause people to cease drinking[81]. A better understanding of these mechanisms will inform methods of investigating the impact of bias from the 'sick-quitter effect'.

Therefore, the overall aim of this thesis was to quantify the association between alcohol consumption and risk of cancer and mortality in Australia, and to examine whether risk estimates

are robust when taking into account methodological biases such as the ‘sick-quitter effect'. This was achieved by addressing a number of objectives, using a large, Australian prospective study, the 45 and Up Study[96]. These objectives were to:

1. Review of the association between alcohol consumption and disease and injury, with a particular focus on cancer (Chapter 2).

2. Systematically review previous systematic reviews and meta-analyses of the association between alcohol consumption and all-cause mortality (Chapter 3), and examine whether there is variation in review findings by:
    - Methodological quality and risk of bias.
    - Population sub-groups such as sex, age and smoking status.
    - Alcohol exposure measurement such as pattern of drinking and beverage type.
    - Primary study attributes such as level of adjustment and length of follow-up.

3. Investigate the clustering of alcohol consumption with other behavioural risk factors and assess potential variation by country of birth (Chapter 6).

4. Investigate the relationship between a variety of incident health conditions and drinking cessation (Chapter 7).

5. Investigate the association between alcohol consumption and cancer risk, exploring differences by sex, smoking status and region of birth, and estimate the absolute risk and population attributable risk of alcohol exposure for a range of cancer types (Chapter 8).

6. Investigate the association between alcohol consumption and risk of all-cause and cause-specific mortality, exploring differences by sex, smoking status and region of birth, and estimate the

absolute risk and population attributable risk of alcohol exposure for all-cause mortality (Chapter 9).

The methods used to address these objectives are summarised in Chapters 4 and 5. These objectives allowed for a thorough investigation of alcohol consumption and its relation to disease and mortality, and whether important risk estimates for Australia such as population attributable fractions for cancer and all-cause mortality are likely to be biased by the 'sick-quitter effect'. The findings of each chapter are considered together in the discussion and conclusions in Chapter 10.

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Chapter 2 – Narrative Review of Alcohol Consumption and Risk of Disease and Injury

Chapter summary

This chapter contains a narrative review of the relationship between alcohol consumption and risk of disease and injury, with a focus on cancer. The burden of disease and injury in Australia, estimates of the direction and magnitude of the association between drinking and disease, and hypothesised causal mechanisms were examined. Health conditions other than cancer, including infectious diseases, diabetes, nutritional deficiencies, overweight and obesity, dementia, neuropsychiatric conditions, cardiovascular disease, liver disease, pancreatitis, other digestive system diseases and external causes of morbidity and mortality are reviewed in detail in the Appendix A. The evidence is summarised and areas requiring further research are discussed.

2.1 – Background

Alcohol consumption impacts human health in a multitude of ways and is a major contributor to preventable morbidity and mortality. Globally, 5.9% of deaths and 5.1% of the burden of disease and injury in 2012 was attributable to alcohol[1]. Alcohol-related morbidity and mortality are higher in men and those living in higher income countries, and alcohol is the leading risk factor for morbidity and mortality in those aged between 15 and 49 years.

The burden of disease and injury attributable to alcohol consumption in Australia in 2011 was 5.1%, including 12.2% of the burden for mental health, 8.2% for gastrointestinal diseases, 4.8% for cardiovascular disease, 3.3% for cancer, 2.7% for infectious diseases, 2.0% for endocrine diseases, and 1.9% for neurological diseases[2]. Of all risk factors, alcohol contributed third-most to the

burden of disease and injury in Australia in 2011, behind smoking (9.0%) and overweight and obesity (5.5%)[2]. It was estimated that 4.7% of deaths in men and 3.0% of deaths in women in Australia in 2010 were attributable to alcohol consumption[3], and 3.2% of deaths for both sexes in 2012[1]. In New South Wales there were 13,517 presentations to emergency departments for alcohol-related problems in 2014, 53,933 alcohol-attributable hospitalisations in 2014-2015 and 1289 alcohol-attributable deaths in 2013[4]. Persons with lower socio-economic status experience greater harm from alcohol consumption than other persons for the same level of drinking[5], while Indigenous Australians have a burden of disease due to alcohol consumption approximately twice that of the general population[6].

Also significant is the economic cost of alcohol consumption to Australian society, which in 2004-2005 was estimated to be approximately $15 billion[7]. This figure takes into account government healthcare expenditure, premature death, welfare, work absenteeism and loss of productivity, premature retirement, crime and violence. Other effects on the community include offensive behaviour, noise, littering and vandalism[7]. The direct costs of alcohol consumption in Australia are comparable to those of other developed countries[8].

While there have been previous reviews examining the relationship between alcohol consumption and disease and injury, many gaps in the evidence base have been identified. For example, the relationship between drinking and risk of certain cancer types such as kidney and prostate cancer, whether low-volume alcohol consumption causally lowers cardiovascular disease risk, and whether patterns of drinking such as heavy episodic drinking modify risk of diseases such as type 2 diabetes and pancreatitis[9]. Causal mechanisms for the alcohol-disease relationship are uncertain or only hypothesised for many outcomes[9]. Therefore, there is need for a literature review to provide an up-to-date summary of the evidence regarding the relationship between alcohol consumption and risk of disease and injury including an overview of hypothesised causal mechanisms, along with recent estimates of alcohol-attributable burden in Australia to provide local context.

2.2 – Scope and Methods

The aim of this chapter was to provide a narrative review of the current evidence of the relationship between alcohol consumption and disease and injury, with a focus on cancer. Cancer contributed 19% to the national burden of disease and injury in 2011, the highest of any health condition[2]. Further, of all deaths attributable to alcohol in Australia in 2015, 36% were due to cancer, more than any other disease or injury[10]. For the sake of brevity, all other alcohol-related diseases are reviewed in Appendix A.

For each alcohol-disease relationship, estimates for the burden of disease in Australia (alcohol-attributable, where available), estimates of the direction and magnitude of association between alcohol consumption and risk of disease (using systematic reviews and meta-analyses, where available) and hypothesised causal mechanisms were reviewed. Gaps in the evidence base were also identified. The disease classification codes used in this chapter and Appendix A are from the International Classification of Diseases version 10 (ICD-10)[11].

2.3 – Results

Cancer (ICD-10: C00-97; D45-47)

Burden in Australia

Cancer was responsible for 19% of the total burden of disease in Australia in 2011[2]. The most recent year for which both cancer incidence and cancer death (underlying cause) data were available was 2013, shown in Table 2.1[12]. Alcohol consumption was estimated to be responsible for 2.8% of Australian cancer cases [13, 14]; including 31% of mouth and pharynx, 20% of larynx, 9% of oesophagus, 8% of colon, 12% of rectum, 13% of liver, and 6% of female breast cancer cases (Figure 2.1). The incidence of two alcohol-related cancers, breast and liver, has been increasing over time in Australia[15], although how much of this increase is attributable to alcohol consumption is unclear. The proportion of cancer deaths caused by alcohol consumption has been estimated at 3.5% in 2010[3, 16] and 2.4% in 2013[14].

Table 2.1. Cancer incidence and cancer deaths (underlying cause) in Australia in 2013[12, 17].

Cancer type (ICD-10 code)	n cases (%)	n deaths (%)
Prostate (C61)	19,233 (15.5)	3,112 (7.1)
Breast (C50)	16,045 (12.9)	2,892 (6.6)
Colorectum (C18-20)	14,962 (12.0)	4,162 (9.4)
Melanoma (C43)	12,744 (10.2)	1,617 (3.7)
Lung (C33-34)	11,174 (9.0)	8,217 (18.6)
Non-Hodgkin lymphoma (C82-85)	4,880 (3.9)	1,471 (3.3)
Mouth and pharynx (C00-14)	3,645 (2.9)	817 (1.9)
Leukaemia (C91-95)	3,359 (2.7)	1,645 (3.7)
Kidney (C64)	3,059 (2.5)	962 (2.2)
Pancreas (C25)	2,865 (2.3)	2,558 (5.8)
Other (Other C00-97;D45-47[a])	32,499 (26.1)	16,683 (37.8)
All types (C00-97;D45-47[a])	124,465 (100.0)	44,136 (100.0)

[a]Non-melanoma skin cancer excluded for incident cases and included for deaths. ICD-10, International Classification of Diseases, version 10.

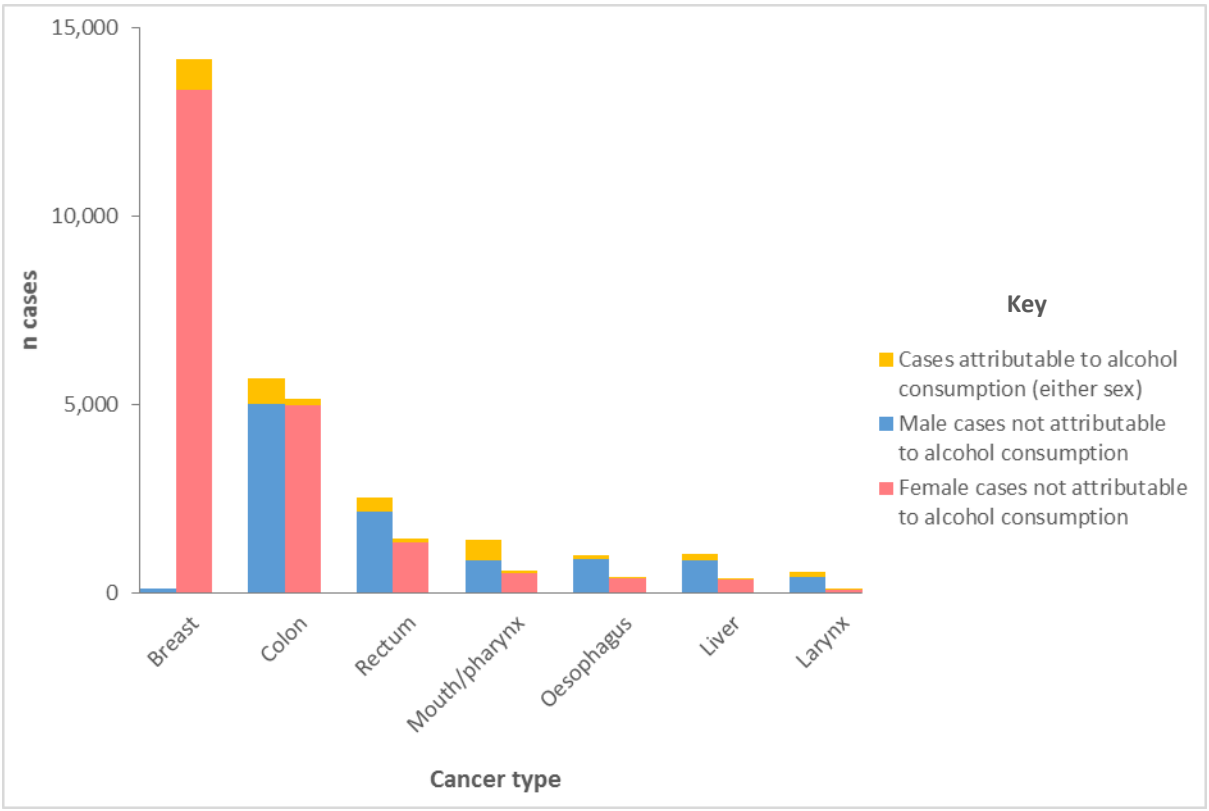

Figure 2.1. Cancer cases attributable to alcohol consumption in Australia in 2010 by sex[12, 13].

Epidemiology

The International Agency for Research on Cancer (IARC) classifies ethanol and alcoholic beverages as a group 1 carcinogens, meaning there is "*sufficient evidence*" for their carcinogenicity in humans[18]. The IARC reports that alcohol consumption is causally related to seven types of cancer – mouth, pharynx, larynx, oesophagus (stronger for evidence for squamous cell carcinoma (SCC) than adenocarcinoma), liver, colorectum and female breast[18, 19]. The World Cancer Research Fund (WCRF), reached a similar conclusion, stating there is a convincing level of evidence that alcohol consumption is causally related to cancers of the mouth, pharynx, larynx, oesophageal SCC, liver, colorectum and female breast[20, 21].

In addition, these organisations make conclusions for several other cancer types where the evidence for causality is not as strong. The IARC states there is evidence for an association between alcohol consumption and pancreatic cancer when consumption is > 30 grams ethanol per day, however it is

not clear whether the relationship is causal or due to residual confounding by smoking[19]. The IARC also concluded that there is no association with kidney or bladder cancer. The WCRF states there is a probable increased risk of stomach cancer, a probable decreased risk for kidney cancer, and limited evidence suggestive of an increased risk for pancreatic cancer above approximately 3 drinks per day.

For the remaining 16 cancer types assessed by the IARC the evidence was found to be inconsistent or lacking, with some studies reporting an increased risk with alcohol consumption and others a decreased risk. For cancer types with inconsistent evidence, it was stated that many studies lacked adjustment for important potential confounders, such as *Helicobacter pylori* infection status for stomach cancer. For all other cancer types analysed by the WCRF the evidence was limited and so no conclusion could be made. A summary of the IARC monographs and WCRF reports is shown in Table 2.2. For some additional cancer types, meta-analyses have found evidence of increased risk of cancers of the gallbladder[22], lung[22] (but not in never-smokers[23]), melanoma[22] and prostate[22, 24] with increasing alcohol consumption, and inverse associations for thyroid cancer[22, 25], Hodgkin lymphoma[22, 26] and non-Hodgkin lymphoma (NHL)[22, 27].

The relationship between alcohol consumption and cancer risk appears to be linear on an exponentiated scale[9]. There is no evidence for a safe threshold of drinking for which risk of cancer is not elevated, nor for any differences in risk by type of alcoholic beverage[20, 21]. Light alcohol consumption (up to 1 drink per day) has been found in a meta-analysis to increase risk of oesophageal SCC, mouth, pharynx and breast cancer[28-30], but not of larynx, colorectal or liver cancer[29].

Risk estimates for the majority of cancer types appear to be fairly robust. A systematic review and meta-analysis of alcohol consumption and risk of 23 cancer types reported that when the results were restricted to studies that adjusted for confounders, risk estimations were not materially changed (except for prostate cancer, where effect estimates became higher)[22]. Risks were also largely unaffected when examining alternative choices of reference group. For most cancer types

there was no evidence that risk estimates varied by study type, except for higher relative risks in case-control studies compared to cohort studies for mouth and pharynx cancer and in cohort studies compared to case-control studies for ovarian cancer. Risk estimates only differ by sex for colorectal cancer, with higher risk in men than women. There was also no variation in risk by the region the study was conducted in, with the exception of an increased risk of lung cancer in North American studies but not in European or Asian studies, and an association with decreased risk of NHL in European and Asian studies but not in North American studies.

Table 2.2. Relationship between alcohol consumption and cancer according to the IARC[18, 19] and the WCRF[20, 21].

Cancer type (ICD-10 code)	IARC	WCRF
Mouth and pharynx (C00-14)	Increased risk (RR 3 at 50 g/day); interaction with smoking	Convincing increased risk
Oesophagus (C15)	Increased risk (RR 2 at 50 g/day); interaction with smoking[a]	Convincing increased risk[a]
Stomach (C16)	Inconsistent evidence (increased risk in some studies)	Probable increased risk[b]
Colorectum (C18-20)	Increased risk (only at > 30 g/day; RR 1.4 at 50 g/day)	Convincing increased risk[c]
Liver (C22)	Increased risk, interaction with smoking	Convincing increased risk[b]
Gallbladder (C23-24)	-	Limited - no conclusion
Pancreas (C25)	Association with small increased risk (only at ≥ 30 g/day)	Suggestive increased risk[d]
Larynx (C32)	Increased risk (RR 2 at 50 g/day); interaction with smoking	Convincing increased risk
Lung (C33-34)	Inconsistent evidence (increased risk in some studies)	Limited - no conclusion
Melanoma (C43)	Inconsistent evidence	Limited - no conclusion[e]
Female breast (C50)	Increased risk (RR 1.5 at 50 g/day)	Convincing increased risk
Male breast (C50)	Inconsistent evidence	-
Vulva and vagina (C51-52)	Inconsistent evidence (increased risk in some studies)	-
Cervix (C53)	Inconsistent evidence (increased risk in some studies)	Limited - no conclusion[f]
Endometrium (C54.1)	Inconsistent evidence	Limited - no conclusion
Ovary (C56)	Little evidence for association	Limited - no conclusion
Prostate (C61)	Little evidence for association (increased risk in some studies)	Limited - no conclusion
Testis (C62)	Inconsistent evidence	-
Kidney (C64)	No association (decreased risk in some studies)	Probable decreased risk[g]
Bladder (C67)	No association	Limited - no conclusion
Brain (C71)	Inconsistent evidence	-
Thyroid (C73)	Inconsistent evidence (decreased risk in some studies)	-
Hodgkin lymphoma (C81)	Inconsistent evidence (decreased risk in some studies)	-
Non-Hodgkin lymphoma (C82-85)	Inconsistent evidence (decreased risk in some studies)	-
Multiple myeloma (C90.0)	Inconsistent evidence	-
Leukaemia (C91-95)	Inconsistent evidence	-

[a]Squamous cell carcinoma only; not enough evidence/no association for adenocarcinoma. [b]For alcohol consumption > 45 g/day. [c]For alcohol consumption > 30 g/day. [d]Limited-suggestive increased risk, for alcohol consumption > 3 drinks/day. [e]For all skin cancer. [f]For alcoholism. [g]For alcohol consumption ≤ 30 g/day. Relative risks are compared to non-drinkers. IARC, International Agency for Cancer Research. WCRF, World Cancer Research Fund. ICD-10, International Classification of Diseases version 10. RR, Relative Risk.

Several aspects of the relationship between alcohol consumption and cancer have been studied. One of these is the lag time between exposure to alcohol and cancer incidence, which remains unclear. Estimates of lag time have been reported for cancer mortality ranging from 10 to 25 years[31], while a recent multi-country ecological study estimated a lag time of approximately eight years for mortality from cancers of the mouth, pharynx, larynx and oesophagus[31]. Further, an Australian study examined mortality rates from all cancers combined and found the lag time with the strongest correlation with per capita alcohol consumption was ten years[32].

Another important aspect of the relationship between alcohol and cancer is the potential impact of change in alcohol consumption over time. For example, it has been reported that temporal variation in population-level alcohol consumption in Australia predicts changes in pharynx and oesophagus cancer mortality rates[33]. Whether or not, and by how much drinking cessation reduces the risk of cancer is also of interest. Regarding mouth, pharynx, larynx and oesophageal cancer, drinking cessation has been associated with decreased risk[18]. Further, a number of studies have investigated changes in alcohol consumption over the life course for breast cancer, and found that risk may be cumulative. For example, breast cancer risk due to alcohol consumption begins in young adulthood[34], and in the Nurses' Health Study it was found that alcohol consumption in earlier and later life each independently increased risk[35]. A recent cohort study examined change in alcohol consumption over time and found that postmenopausal women who increased their alcohol consumption over a five year period increased their risk of breast cancer after adjusting for total alcohol consumption at baseline, while no benefit was observed among those who decreased their alcohol consumption[36].

Potential interactions between alcohol consumption and other risk factors may also impact cancer risk. For example, alcohol and tobacco smoking have a multiplicative effect on the risk of cancers of the mouth, pharynx, larynx, oesophagus and liver[18, 19]. Interactions between alcohol and other known risk factors for cancer are an area for further research, including smoking for stomach and

lung cancer, weight status for colorectal and pancreatic cancer, folate status for colorectal cancer, hormone replacement therapy use for breast cancer, and hepatitis B and C viral infection for liver cancer[18, 19].

Evidence for an effect of pattern of drinking on cancer risk, such as heavy episodic drinking or drinking frequency, is scarce[9, 37]. Drinking patterns have been investigated in a number of different ways in relation to cancer risk. Specifically, risk has been quantified by drinking frequency (days per week of alcohol consumption), the highest number of drinks consumed in one day in a typical month, drinks per day of alcohol consumption (including "heavy episodic drinking"), daily moderate drinking, as well as daily heavy drinking. Further, there is great diversity in the methods that have been used to assess drinking patterns[38], which makes studies difficult to compare directly. An analysis of the Health Professionals Follow-up Study and Nurses' Health Study found that after adjusting for total alcohol consumption, neither the frequency of drinking in days per week or the highest number of drinks consumed in one day in a typical month were associated with risk of all cancers combined[37]. When combining the seven alcohol-related cancers identified by IARC, frequency of drinking (days per week of alcohol consumption) was positively associated with increased risk for men but not women, while highest number of drinks consumed in one day was associated with increased risk for women but not men. In contrast, a twelve country cohort study found no association of heavy episodic drinking with alcohol-related cancers combined, although the authors stated that the study was underpowered[39].

Other studies have reported that greater drinking frequency (i.e. increased drinking occasions) increased risk of mouth cancer[40], mouth and pharynx cancer[41], oesophageal cancer (men only)[42], stomach cancer (those with negative *H. pylori* status only)[43], prostate cancer[44] and total cancer (men only)[42], and no effect on risk of breast cancer[45, 46] or 15 cancer types[42]. Increased risk with drinks per day of alcohol consumption or heavy episodic drinking has been reported for stomach cancer (those with negative *H. pylori* status only)[43], pancreatic cancer[47],

lung cancer (smokers only)[48], breast cancer[46, 49] and prostate cancer[50], and also for total cancer mortality[51]. One study also found no effect on breast cancer risk for “sporadic” drinking or daily moderate drinking but an increased risk with daily heavier drinking[52]. The majority of these studies however did not, or only partially, adjusted for total alcohol consumption[40-44, 48-52], meaning it was not possible to determine whether drinking pattern affected risk independent of the overall amount of alcohol consumed. Overall, very few large prospective studies have examined drinking pattern and cancer risk, and no studies have examined multiple cancer types using a consistent methodology that included an adjustment for total alcohol consumption.

A final consideration in the alcohol-cancer relationship is that the impact on cancer incidence may differ to that for cancer mortality. This is because alcohol consumption may impact disease progression and survival among those already diagnosed with cancer, particularly for colorectal and breast cancer. Specifically, pre-diagnostic heavy alcohol consumption was reported to result in poorer survival for those diagnosed with colorectal cancer[53]. For breast cancer, the effects on recurrence and survival are somewhat inconsistent. For breast cancer recurrence, it has been reported that there is no association with pre-diagnosis drinking[54], no association with post-diagnosis drinking[54], a positive association with post-diagnosis drinking only in post-menopausal women[55], a positive association with pre- or post-diagnosis drinking as low as 6 grams per day[56], and a positive association with pre- or post-diagnosis drinking only in pre-menopausal women[54]. For breast cancer survival, it has been reported that there is no association with pre-diagnosis drinking[54, 57], no association with post-diagnosis drinking[54, 55], “weak evidence” of a positive association with post-diagnosis drinking in estrogen receptor negative cases (the authors state that the effect may be attributable to reverse causation)[57], and a positive association with pre- or post-diagnosis drinking > 20 grams per day[54]. The impact of pre- and post-diagnosis drinking on recurrence and survival for other cancer types has been less studied, and is an area for further investigation.

In conclusion, there are significant gaps in the research base for alcohol and cancer risk in several areas. These include the large number of cancer types for which a causal relationship with alcohol remains uncertain, the lag-time between alcohol exposure and occurrence of cancer, the possibility of interactions between alcohol and other risk factors, whether drinking patterns (particularly drinking frequency and heavy episodic drinking) modify cancer risk, and whether drinking influences cancer recurrence and survival.

Causal mechanisms

The causal mechanism of alcohol on cancers of the mouth, pharynx, larynx and oesophagus is thought to be the ethanol metabolite acetaldehyde, which has mutagenic effects on deoxyribonucleic acid (DNA) through the formation of DNA adducts[58]. This is most apparent in persons with a gene polymorphism associated with the inactive form of the enzyme aldehyde dehydrogenase (ALDH2), as this condition causes acetaldehyde to accumulate when alcohol is consumed[18, 58]. This genetic variant is common in East Asian populations[59]. Two other gene polymorphisms associated with alcohol dehydrogenase are ADH1B and ADH1C, which control the rate of acetaldehyde formation from ethanol. ADH1B has been shown to influence risk of these cancers[19, 58], however studies examining the effect of ADH1C polymorphism on cancer risk have been inconsistent. Oesophageal cancer can also be caused by alcohol relaxing oesophageal motility and increasing the propensity for reflux among heavy drinkers with gastro-oesophageal reflux disease[58].

The multiplicative effect of alcohol and smoking on risk of upper aerodigestive tract cancers (mouth, pharynx, larynx and oesophagus) has been hypothesised to be caused by ethanol-induced increases in the activity of cytochrome P450 2E1, which produces reactive oxygen species (highly reactive molecules that in turn form DNA adducts) and may also ‘activate’ the carcinogens present in tobacco smoke. Ethanol may act as a solvent for other carcinogens including tobacco smoke[18, 58]. Polymorphisms in cytochrome P450 2E1 may also result in increased production of reactive oxygen

species (and therefore DNA adducts) in the presence of alcohol consumption[58], but evidence supporting this hypothesis is weak[18].

For liver cancer, drinking causes liver inflammation, fibrosis and cirrhosis which in turn can develop into hepatocellular carcinoma. Drinking also contributes to liver cancer directly through acetaldehyde-induced DNA adduct formation, increased oxidative stress (higher than normal levels of reactive oxygen species) via glutathione depletion and iron accumulation, altered DNA methylation (which controls DNA transcription) via s-adenosylmethionine depletion, decreased tissue levels of retinoic acid which helps to regulate cell growth, increased permeability of the gut to endotoxins from microflora which cause liver injury, and through decreasing the number and activity of natural killer cells which have anti-tumour effects in the liver[18, 58, 60]. Alcohol consumption has a greater effect on risk in those with hepatitis B or C virus infection, haemochromatosis, non-alcoholic steatohepatitis and diabetes[18, 58, 61]. There may also be an interaction effect with smoking[18, 60]. Further detail of the mechanisms by which alcohol causes liver fibrosis and cirrhosis is provided in the liver disease section in Appendix A.

For colorectal cancer, it is hypothesised that acetaldehyde produced by the metabolism of ethanol by bacteria in the gut may have a genotoxic effect, and also that alcohol may disrupt the role of folate metabolism in DNA synthesis and methylation[9, 58]. Vitamin B_6 and B_{12} are also related to folate metabolism, and deficiencies in these factors associated with alcohol consumption may therefore increase the risk of colorectal cancer[58].

Drinking may cause breast cancer by increasing levels of oestradiol, androgens and insulin-like growth factor[9, 19, 58]. The elevation of oestradiol and androgen levels has been suggested to occur by alcohol consumption inhibiting sex steroid catabolism in the liver[19]. Methylenetetrahydrofolate reductase gene polymorphism (C677T) in combination with low folate status or heavy alcohol consumption is associated with an increased risk of breast cancer, suggesting that the disruptive effect of alcohol consumption on folate metabolism may play a role[18].

The possible mechanisms for carcinogenesis are less clear for other sites. For many cancer types the causative mechanism with alcohol consumption is not understood completely, and the relative importance of ethanol-induced redox effects, reactive oxygen species, metabolic changes and impact on other carcinogens remains unknown[19, 62]. The eight additional cancer types which have been associated with alcohol consumption are cancers of the pancreas, stomach, gallbladder, lung, skin (both melanoma and non-melanoma), prostate and myelodysplastic syndromes[22, 63, 64].

If causal, alcohol is hypothesised to cause pancreatic cancer via the inducement of chronic pancreatitis, which is a risk factor for pancreatic cancer[18]. The details of this process are explained in the pancreatitis section in Appendix A. Similarly, it has been hypothesised that heavy alcohol consumption causes gastritis which in turn may be a risk factor for stomach cancer[65], or instead that the relationship is explained by residual confounding from smoking or poor diet[22]. For these two cancer types, folate metabolism may also be important, as the aforementioned C677T polymorphism in combination with low folate status or heavy alcohol consumption is also associated increased risk of stomach and pancreatic cancer[18].

For gallbladder cancer, the stimulation of bile acid secretion by alcohol consumption is a hypothesised mechanism[66].

As the association between drinking and lung cancer may be limited to ever-smokers, the mechanism for this site may be through alcohol increasing the activity of cytochrome P450 activity and acting to ‘enhance’ the carcinogens present in tobacco smoke[23], or alternatively the relationship could be explained by residual confounding from smoking[22].

For melanoma, drinking may amplify skin damage during sun exposure, or could promote the development of melanoma directly via immunosuppression[22].

Possible mechanisms explaining the relationship between alcohol consumption and prostate cancer include the action of acetaldehyde and cytochrome P450 2E1, raised levels of estrogen and alterations to folate metabolism[24].

Finally, for myelodysplastic syndromes, alcohol may increase risk by decreasing immune system activity, by inducing bone marrow failure or through chromosomal changes in haematopoietic cells[63].

Although the evidence remains inconsistent, some studies find associations with drinking and decreased risk for kidney, thyroid, Hodgkin lymphoma and NHL cancers, as did a systematic review and meta-analysis for all four of these sites[22]. If the protective effect of alcohol consumption on kidney cancer exists, hypotheses to explain this relationship have included increased insulin sensitivity and protection against diabetes (a possible risk factor for kidney cancer), decreased risk of chronic renal failure (also a risk factor for kidney cancer), the diuretic effect of alcohol resulting in carcinogens coming into contact with renal cells for a shorter period and reducing hypertension (another kidney cancer risk factor), and finally the antioxidant effect of phenolic compounds in alcoholic drinks[67].

A proposed mechanism for the inverse relationship between thyroid cancer and alcohol is by the prevention of thyroid stimulating hormone from causing follicular thyroid cell proliferation[68].

For both Hodgkin lymphoma and NHL, the hypothesised mechanisms of the inverse relationship are that moderate alcohol consumption enhances the cellular and humoral immune response and increases insulin sensitivity, and has also been attributed to the antioxidant compounds in beer and wine[26, 27]. Alternatively, it has been suggested that the protective association for lymphoma is spurious and could be due to confounding by unknown factors or a form of the ‘sick-quitter effect’, whereby participants may have quit or reduced drinking in response to early symptoms, prior to diagnosis[22, 27].

Gene polymorphism is thought to play a role in risk for many cancer types[62]. Other than the aforementioned effects of polymorphisms in aldehyde dehydrogenase, alcohol dehydrogenase, cytochrome P450 2E1 and methylenetetrahydrofolate reductase, there are a number of gene polymorphisms which decrease the effectiveness of repair of oxidative DNA damage and may therefore increase susceptibility to the genotoxic effects of alcohol at many sites. These include polymorphisms of O_6-methylguanine-DNA methyltransferase, x-ray repair cross complementing 1, oxoguanine glycosylase 1 and nucleotide excision-repair genes[18]. For aldehyde dehydrogenase, there is currently not enough evidence to determine whether the inactive ALDH2 variant can cause cancer types other than those of the upper aerodigestive tract[18]. The effects of ethanol on cytochrome P450 2E1 activity may also cause DNA damage at other sites, including liver, breast and pancreas, however evidence for this in humans is limited[18, 19]. As well as gene polymorphism, gene expression may play an important role in risk, as alcohol-induced alterations to DNA methylation (which is involved in the control of DNA transcription) are a possible causal mechanism for many types of cancer[69].

Another factor which may have a role in the carcinogenesis of a range of cancer types is the inhibitory effect of alcohol consumption on the immune system[70]. There is evidence that drinking supresses both the innate and adaptive immune systems, including the aforementioned suppressive effect on natural killer cells as well as other mechanisms such as the inhibition of dendritic cell function and anti-tumour cytokine production[70]. Chronic alcohol consumption also stimulates the production of pro-inflammatory cytokines, which in turn may cause chronic inflammation and increased risk of cancer at a number of sites including the oesophagus, stomach, intestines and pancreas[70].

Apart from ethanol and its metabolites, there are other substances in alcoholic beverages that may cause cancer. Ethyl carbamate is a chemical found in alcoholic drinks that is classified as “probably carcinogenic to humans” by the IARC[18]. Ethyl carbamate is found in beer, wine, spirits and in some

foods such as bread, cheese and soy sauce. The highest concentrations are found in spirits. The IARC's conclusion is based exclusively on rodent studies, which found oral administration caused lymphoma, leukaemia, lung, mammary gland, stomach, heart and liver cancers[18]. Ethyl carbamate is metabolised by cytochrome P450 in the liver to form vinyl carbamate and then vinyl carbamate epoxide, which induce DNA damage. This has never been demonstrated in human studies, however the authors of the IARC monograph note that humans and rodents have very similar metabolic pathways for ethyl carbamate. Other than ethanol and ethyl carbamate, 16 further carcinogens and possible carcinogens can be found in alcoholic beverages, including acrylamide, arsenic, benzene, cadmium, formaldehyde and lead[71, 72]. Most of these substances are estimated to have a very low impact on cancer risk compared to ethanol however, with lead and arsenic being the two most important contributors[72].

Other alcohol-related disease and injury

Appendix A provides details on the wide variety of diseases and injury that contribute to alcohol-related mortality in Australia. These include certain infections, nutritional deficiencies, overweight and obesity, vascular dementia, alcohol-related dementia, Wernicke-Korsakoff syndrome, alcohol use disorder, epilepsy, neurodegeneration, liver disease, acute pancreatitis in men and chronic pancreatitis in both sexes, some other digestive system diseases such as alcoholic gastritis and intestinal malabsorption, and many types of external causes of morbidity and mortality such as injury, poisoning, drowning, self-harm and interpersonal violence including domestic violence.

For several other diseases – type 2 diabetes, acute pancreatitis in women, and many types of cardiovascular disease including ischaemic heart disease and ischaemic stroke – studies have sometimes reported a J- or U-shaped risk curve, where low-volume drinking is associated with reduced risk and heavy drinking with increased or similar risk compared to non-drinking.

For overweight and obesity, alcohol-related dementia, Wernicke-Korsakoff syndrome, neurodegeneration and liver disease, increased risk is observed with heavy drinking however the level of risk associated with low-volume drinking and whether a risk threshold exists (and at what level) are inconsistent or unknown. For Alzheimer's disease and depression, the evidence for a causal relationship with alcohol consumption is inconsistent. It is clear that for many health conditions a precise dose-response relationship with alcohol consumption has not yet been established from prospective studies, and there is a particular need to examine how biases, including selection bias due to the exclusion of participants with health conditions at baseline, residual confounding, the 'sick-quitter effect' and the misclassification of alcohol consumption affect those dose-response relationships.

Pattern of drinking also appears to be an important, independent determinant of risk for some outcomes. Heavy episodic drinking has been reported to be associated with an increased risk of HIV infection, diabetes, weight gain, cardiovascular disease including ischaemic heart disease, myocardial infarction, ischaemic stroke and haemorrhagic stroke, and liver disease. Drinking frequency has been associated with decreased risk of cardiovascular disease (low-volume, regular intake) and increased risk of liver cirrhosis (heavy, regular intake). Overall, the impact of alcohol consumption on human health has been widely investigated, however many questions regarding the strength and direction of specific alcohol-disease relationships remain.

Combined, the deaths caused by these diseases, including cancer, contribute substantially to the burden of disease and injury in Australia. As alcohol consumption is causally associated with such a diversity of health outcomes, it is also necessary to consider how the competing risks from these individual diseases come together to influence risk of all-cause mortality. Chapter 3 investigates the association between alcohol consumption and all-cause mortality in more detail, by performing a systematic review of previous systematic reviews and meta-analyses.

2.4 – Discussion and Conclusions

There is evidence that alcohol consumption is causally related with increased risk of at least seven types of cancer (mouth, pharynx, oesophagus, colorectum, liver, larynx and female breast) as well as a wide variety of diseases and injury that contribute to mortality in Australia. These include certain infections, nutritional deficiencies, overweight and obesity, vascular dementia, alcohol-related dementia, Wernicke-Korsakoff syndrome, alcohol use disorder, epilepsy, neurodegeneration, liver disease, acute pancreatitis in men and chronic pancreatitis in both sexes, some other digestive system diseases such as alcoholic gastritis and intestinal malabsorption, and many types of external causes of morbidity and mortality such as injury, poisoning, drowning, self-harm and interpersonal violence including domestic violence.

For 23 other types of cancer, evidence for a causal relationship with alcohol consumption remains inconsistent or unclear. For cancers of the stomach, gallbladder, pancreas, lung (in ever-smokers), skin (both melanoma and non-melanoma skin cancer), prostate and myelodysplastic syndromes, there is evidence of an association with alcohol consumption, however the evidence is not yet sufficient for IARC to conclude that these associations are causal. For Hodgkin lymphoma, NHL, and cancers of the kidney and thyroid, there is limited evidence of an inverse association with drinking, however it is uncertain whether these relationships are causal. Thus, further research on the size and direction of alcohol-related cancer outcomes is needed, particularly in Australia since almost all evidence to date has originated in other populations, where the level of exposure and risk profiles may differ. Although cancer risk estimates in relation to alcohol consumption have been demonstrated to be reasonably robust, for some cancers, in particular, those for which there is evidence of an inverse relationship, there is a need to systematically investigate the potential impact of residual confounding and other methodological factors such as the ‘sick-quitter effect’ on risk estimates.

Methodological biases such as the 'sick-quitter effect' and residual confounding are also alternative explanations for other diseases which have been associated with alcohol consumption in a J- or U-shaped risk curve, where low-volume drinking is associated with reduced risk and heavy drinking with increased or similar risk compared to non-drinking. Specifically, the 'sick-quitter effect' may bias associations due to individuals quitting drinking in response to ill-health. If non-drinkers are used as the reference group, the former drinkers within this group may have an elevated risk of the outcome, potentially causing the risk for drinkers to be underestimated or for inverse associations to be found. Therefore, there is also a need to investigate potential bias from residual confounding and the 'sick-quitter effect' on risk estimates for diseases other than cancer.

Pattern of drinking appears to be an important, independent determinant of risk for some outcomes, although for many health conditions, including cancer, Alzheimer's disease and pancreatitis, the influence of pattern of drinking on risk remains uncertain. In addition, many studies fail to adjust for total alcohol consumption, meaning that any independent effect of drinking pattern cannot be determined. Common drinking patterns investigated were heavy episodic drinking and drinking frequency, but for many health conditions, evidence is lacking. An issue unique to morbidity and mortality from external causes is that acute alcohol consumption is more important for risk of injury than usual alcohol consumption. This may have the implication that measures of drinking pattern (especially heavy episodic drinking) capture risk more accurately than total alcohol consumption. There is need for evidence on the impact of both drinking frequency and heavy episodic drinking on disease risk that incorporates proper adjustment for total alcohol consumption.

While there is an interaction between drinking and smoking on risk of cancers of the mouth, pharynx, larynx, oesophagus and liver, more evidence is needed regarding potential interactions between alcohol and other factors on disease. These include possible interactions with smoking for stomach and lung cancer, with folate status for colorectal cancer, with weight status for colorectal and pancreatic cancer, with hormone replacement therapy use for breast cancer, with hepatitis B

and C virus infection for liver cancer. Further research is also required to examine possible interaction effects with smoking for liver disease and with choledocholithiasis for pancreatitis.

In conclusion, the evidence is clear that alcohol consumption at even light to moderate doses is detrimental to health, however for many, indeed the majority, of examined health conditions, there is a need for prospective studies to establish precise dose-response relationships, and the influence of pattern of drinking (in particular, drinking frequency and heavy episodic drinking) and interactions with other risk factors on disease risk. The potential for methodological biases in prospective studies has made interpretation of the evidence difficult, and so there is a clear need for observational research that explores the impact of these biases on risk estimates, namely, residual confounding, the 'sick-quitter effect', misclassification of alcohol consumption, and selection bias. This thesis aimed to quantify the relationship of alcohol consumption and patterns of drinking on cancer incidence, and all-cause and cause-specific mortality using a large, population based cohort study, the 45 and Up Study. The impact of bias on risk estimates was systematically and comprehensively addressed for each disease outcome.

The focus of the next chapter is risk of all-cause mortality in relation to alcohol consumption. Diseases do not occur in isolation, and some diseases are more important determinants of mortality than others. It is therefore necessary to consider that the competing risks from these individual diseases come together to influence risk of all-cause mortality. The next chapter presents a systematic review of systematic reviews of the all-cause mortality risk of alcohol consumption.

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Chapter 3 – Systematic Review of Alcohol Consumption and All-Cause Mortality

Chapter summary

This chapter presents a systematic review of the literature for previous systematic reviews and meta-analyses of studies quantifying alcohol consumption in relation to all-cause mortality, with a particular focus on methodological quality and risk of bias. The influence of the following factors on the shape of the alcohol-mortality risk curve was examined: population sub-groups (sex, age, region or ethnicity, smoking status and cardiovascular disease status), the distribution of alcohol consumption in the cohort or population (average, standard deviation, proportion of non-drinkers and per capita alcohol consumption), alcohol exposure measurement (i.e., pattern of drinking including heavy episodic drinking and frequency of drinking, change in alcohol consumption over time, measurement of alcohol consumption at single or multiple time points, whether risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk, and beverage type) and primary study attributes (length of follow-up, sample size, year of publication, level of adjustment, modelling method, methodological quality, choice of reference group, and evidence of industry funding). The results are summarised and discussed in light of research gaps.

3.1 – Background

As a risk of preventable disease and injury, alcohol consumption is a major contributor to mortality in Australia and the rest of the world. It is estimated that 4.7% and 3.0% of deaths in men and women in Australia respectively in 2010[1], and 3.2% and 5.9% of deaths in Australia and the world in 2012 were attributable to alcohol consumption[2]. However, concerns regarding the methodological rigor of prospective studies of alcohol and mortality have been noted in the

literature[3], which may impact relative risk estimates. Because systematic reviews and meta-analyses of prospective studies underpin most burden of disease estimates, it is important for the results to be as accurate as possible[1, 2]. In particular, the use of a reference group that includes former drinkers may result in spurious inverse associations with moderate drinking, and an underestimate of the harms associated with heavy drinking[3, 4]. This is due to the 'sick quitter effect'. Other concerns relate to the adequacy of the measure of alcohol consumption used, the length of follow-up time, the age of the cohort, the inclusion or exclusion of participants with prior illness and the level of adjustment for confounding[4]. The shape of the risk curve with increasing amounts of alcohol consumption has been reported to vary by population sub-groups, such as by sex, age and region[5, 6]. Risk has also reported to vary according to drinking pattern, such as heavy episodic drinking and drinking frequency[7, 8]. Systematic reviews and meta-analyses have reached different conclusions regarding the shape of the all-cause mortality risk curve in relation to increasing levels of alcohol, with reviews finding a J-shaped relationship[5], no significant association[3], and a more recent review finding increased risk[4].

The aims of this chapter were to systematically review the literature for previous reviews and meta-analyses of alcohol consumption and all-cause mortality, to summarise review findings including the current state of the evidence regarding differences in risk relationship by population sub-groups, measures of alcohol exposure, primary study attributes, and to determine if differences in review findings can be accounted for by the choice of reference group used in meta-analyses and/or the quality of the systematic review methodology.

3.2 – Scope and Methods

Scope and inclusion criteria

Peer-reviewed journal articles were selected for inclusion if they were a systematic review (with or without a meta-analysis) of population cohort studies and/or case-control studies in persons aged 18 years or older, where the exposure was alcohol consumption and at least one of the outcomes was all-cause mortality. Articles were excluded if they were a narrative review or pooled analysis rather than a systematic review, if the participants were patients with a specific health condition rather than from the general population, if the exposure was not a quantity (such as 'alcohol use disorder', 'alcohol dependence' or 'alcoholism'), or if the article was not written in English. If an article did not explicitly state that it was a systematic review, yet still reported a search of the literature using at least one electronic database and otherwise appeared to be a systematic review, it was included.

Search strategy

Articles were extracted by one reviewer (Peter Sarich) from four databases (PubMed, MedLine, Embase and the Cochrane Library) to 4/12/2017. The search terms and restrictions used in each database query are shown in Table 3.1. References lists of included articles were also searched for relevant articles.

Table 3.1. Search terms and restrictions in database queries.

Database	Search terms	Additional restrictions
PubMed	(alcohol[TIAB] OR ethanol[TIAB]) AND (mortality[TIAB] OR death[TIAB]) AND (systematic review[TIAB] OR systematic literature review[TIAB] OR structured review[TIAB] OR structured literature review[TIAB] OR meta analys*[TIAB] OR pooled analys*[TIAB])	Language: English
MedLine	(alcohol OR ethanol) AND (mortality OR death) AND (systematic review OR systematic literature review OR structured review OR structured literature review OR meta analys* OR pooled analys*)	Language: English
Embase	(alcohol OR ethanol) AND (mortality OR death) AND (systematic review OR systematic literature review OR structured review OR structured literature review OR meta analys* OR pooled analys*)	Language: English Database: Not MedLine
Cochrane Library	(alcohol OR ethanol) AND (mortality OR death)	None

Risk of bias assessment

Risk of bias was assessed in a number of ways. Firstly, the risk of bias in systematic reviews (ROBIS) tool, a recent instrument developed to assess risk of bias in systematic reviews (with or without quantitative meta-analyses) was used[9]. The ROBIS tool contains four domains: Study eligibility criteria (e.g. clear and appropriate inclusion criteria), identification and selection of studies (e.g. database search terms, searching multiple databases and non-database sources, using at least two reviewers), data collection and study appraisal (e.g. including a primary study summary table and assessing methodological quality) and synthesis and findings (e.g. assessing publication bias – except in reviews without a meta-analysis, appropriate synthesis of information). For each domain, five or six 'signalling questions' were answered, and if a 'no' was recorded for any of these questions then there was a 'high' level of concern for the domain. Otherwise there was a 'low' level of concern for the domain. An exception was when the review did not contain a meta-analysis, for which the absence of a test for publication bias did not automatically cause the 'synthesis and findings' domain to be considered high concern. If there was a 'high' level of concern for at least one domain and the review did not address in the discussion all of the concerns raised by the signalling questions, then

the review was considered at 'high' risk of bias. Otherwise the review was considered at 'low' risk of bias.

Another method used to assess risk of bias, specific to studies of alcohol consumption, was whether the review/meta-analysis used in the main analysis was a reference group of lifetime abstainers, or if former and/or occasional drinkers were also included. If the reference group contained either of the latter two groups, it was noted if a sensitivity analysis was performed using a reference group of lifetime abstainers. If a review included former drinkers in the reference group, this would be expected to bias risk estimates for drinking downward, while if occasional or light drinkers were included, this would be expected to bias risk estimates for drinking upward[3] (the latter scenario could also theoretically bias risk estimates for drinking downward if a substantial portion of occasional or light drinkers were former heavy drinkers). If a review did not state which reference group was used, but included a mixture of primary studies with reference groups of non-drinkers and lifetime abstainers, the reference group of the review was considered to be non-drinkers. It should be noted that although the use of lifetime abstainers as a reference group has been recommended[3, 4], the results may still be biased because lifetime abstainers have been reported to have unfavourable socio-demographic, health status and behavioural risk factors compared to moderate drinkers[10]. Other suggestions for mitigating bias have included the use of light drinkers as the reference group[11], or lifetime abstainers and light drinkers combined[12]. It was noted if a review used an alternative reference group such as these.

Finally, the author affiliations, sources of funding and conflict of interest statements of reviews were examined for any evidence of alcohol industry funding or any other potential conflicts of interest.

Review synthesis

The results of all reviews that reported risk estimates for the general population (without any restrictions by sub-population, such as sex or region) were summarised and compared. To examine possible heterogeneity in results by sub-population (e.g. sex, age), measure of alcohol exposure (e.g. pattern of drinking, change in alcohol consumption over time, beverage type) or primary study methodology (e.g. length of follow-up, level of adjustment), reviews which reported sub-analyses (including any sensitivity analyses, result stratifications or restrictions) by these topics or any other topic were summarised and compared. For each topic, the proportion of reviews with a reference group containing only lifetime abstainers and at low risk of bias were examined.

When assessing the level of evidence for the alcohol-mortality risk relationship overall and for each sub-analysis, the following categories were used:

- Lack of evidence: The reviews did not address this outcome.
- Inconsistent evidence: The reviews reported different findings for this outcome.
- Limited evidence: The reviews reported consistent findings for this outcome, but all reviews were considered at high risk of bias and/or used a reference group containing former drinkers.
- Good evidence: The reviews reported consistent findings for this outcome, and at least one review was considered at low risk of bias and used a reference group without former drinkers.

3.3 – Results

Literature search

The database queries returned a total of 1048 results, including 414 from PubMed, 391 from MedLine, 161 from Embase and 82 from the Cochrane Library. In addition, 12 potentially relevant articles were identified from the reference lists of included articles. In total, 1060 journal articles were considered for inclusion. 21 articles, representing 18 individual systematic reviews (3 reviews had two articles), were included in the analysis. A flow diagram of the article retrieval process is shown in Figure 3.1.

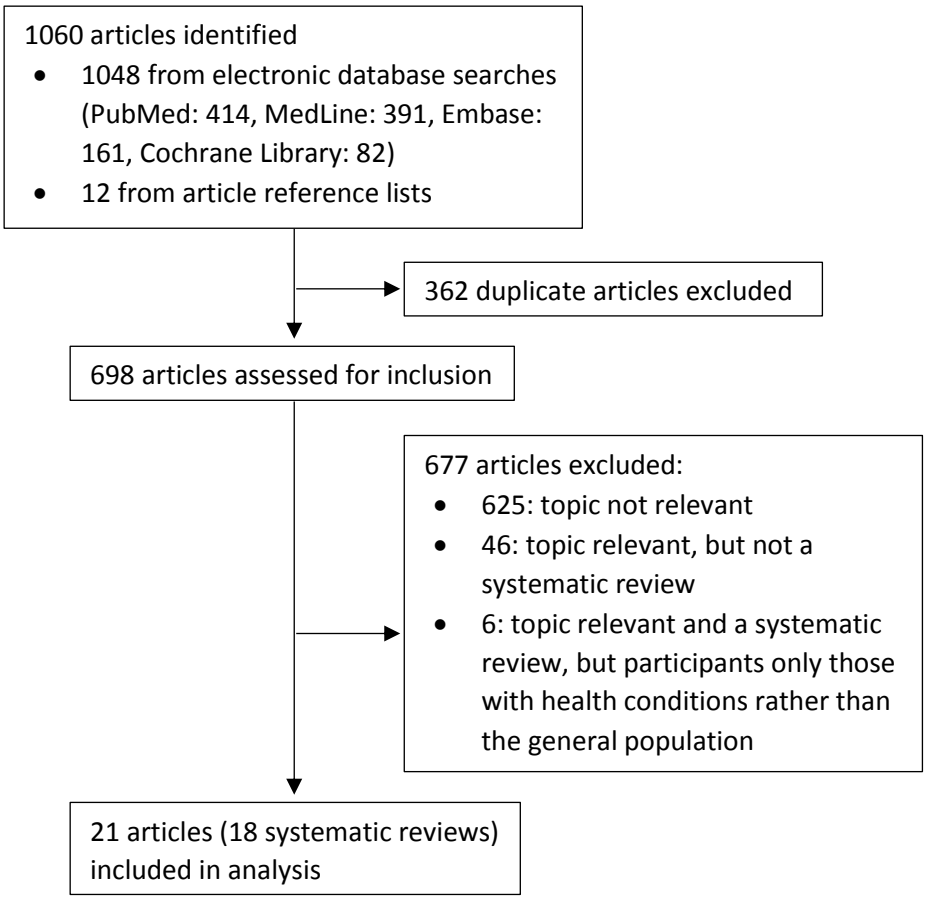

Figure 3.1. Flow diagram of the article retrieval and assessment process.

Review characteristics and risk of bias assessment

The characteristics of included reviews are shown in Table 3.2. The largest review in terms of number of included primary studies (87), number of participants (3,998,626) and number of deaths (367,103) was Stockwell et al., (2016)[4]. Some reviews did not report number of participants and/or deaths. Few reviews included case-control studies. 14 of 18 reviews performed a quantitative meta-analysis. There were sub-analyses, sensitivity analyses or result stratifications or restrictions by sex[4, 5, 13-21], age[3, 4, 15, 16, 18, 22], population (region or ethnicity)[4, 5, 14, 15, 18, 20, 21, 23], smoking status[3], exclusion of participants with pre-existing cardiovascular disease[15, 24], distribution of alcohol consumption in the cohort or population[16, 20], measurement of alcohol consumption at multiple time points[19], beverage type[25], follow-up duration[5, 16, 20, 21], primary study sample size[5, 20, 21], primary study year of publication[5, 20], level of adjustment[4, 5, 15, 20, 21], model[17, 19], primary study methodological quality[4, 21], choice of reference group[3-5, 15, 16, 20] and evidence of industry funding[26]. No review examined the effect of pattern of drinking (e.g. heavy episodic drinking, frequency of drinking), change in alcohol consumption over time or whether risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk. 11 of 18 reviews aimed to answer specific questions, and were restricted to studies which reported risk estimates by sex[5, 15, 20, 21], studies of participants in older age[22], 'primarily European-origin populations'[14], no 'participants of African or Asian origin'[18], Korean subjects[23], participants without pre-existing cardiovascular disease[24], studies which measured alcohol consumption at multiple time points[19], studies of specific beverage types[25], and studies that also assessed cardiovascular outcomes[24].

The reference group used in the main analysis of each review/meta-analysis is shown in Table 3.3. Three of 18 reviews/meta-analyses used a reference group of lifetime abstainers in the main analysis, without former or occasional drinkers. In one case it appears that only primary studies with a lifetime abstainer category were included (with any former or occasional drinker categories

excluded from the analysis entirely)[17], and in two cases primary studies using a reference group including former and/or occasional drinkers were included in some analyses, but the restriction to primary studies with a reference group of lifetime abstainers was a key aim of the review[3, 4]. A further 4 reviews/meta-analyses examined the restriction to primary studies with a reference group of lifetime abstainers in at least one sensitivity or sub-analysis[5, 15, 16, 20]. The remaining 11 reviews examined primary studies with a reference group containing former drinkers (± occasional drinkers). No review used a reference group containing occasional drinkers without former drinkers in the main anlaysis. In addition, no review used the alternative reference groups of light drinkers or light drinkers and lifetime abstainers combined in the main analysis, although one review used a reference group of occasional drinkers (≤ 1 drink/week or < 1.3 g/day) alone in one analysis[4].

The risk of bias assessment for each review is also shown in Table 3.3. Four of 18 reviews were considered to be at low risk of bias[4, 21, 23, 24]. The remaining 12 reviews were considered at high risk of bias. Reasons for the high risk of bias included the failure to specify eligibility criteria[27, 28], to search more than one electronic database[5, 13-15, 18, 22, 27, 28], to specify search terms[3, 13, 14, 17, 27, 28], to specify more than one reviewer for study selection and/or quality assessment[3, 5, 13, 15-19, 25, 27, 28], to provide a table summarising study characteristics[13, 18, 22, 28], to perform an assessment of primary study quality[3, 5, 13, 15-17, 19, 20, 27, 28] and to test for publication bias[3, 5, 13-18, 22, 27]. Two reviews were considered to have a high level of concern for only one of the four ROBIS domains. That is, Costanzo et al., (2011) would have been considered at low risk of bias if the article had specified that two reviewers were used for primary study quality assessment, while Wang et al., (2014) did not specify that the primary studies had been assessed for quality (and with at least two reviewers). Only one review was considered at high risk of bias in all four ROBIS domains[28]. Stockwell et al., (2016) was the only review to both use a reference group of lifetime abstainers and be considered at low risk of bias[4].

There was no evidence of potential conflicts of interest in any of the reviews. Two of 18 reviews appeared to have at least partial industry funding. Costanzo et al., (2011) was partially funded by *Cervisia Consulenze*[25], which appeared to be a consultant to the alcohol industry[29] (although it is stated that the funders had "*no role in the selection of articles or conduct of the analyses or drafting of the manuscript*"[25]). Park et al., (2015) was funded by the *Korea Institute of Oriental Medicine*[23], which appeared to be an organisation that researches traditional/herbal medicine[30] (although it is stated that there were no competing interests[23]).

Table 3.2. Characteristics of included systematic reviews.

Review	Primary study number and type[a]	n participants	n deaths	Sub-analysis, sensitivity analysis, stratification or restriction	Notes
Anderson et al., (1993)[13]	12 prospective	Not stated	Not stated	Sex	No meta-analysis
Bagnardi et al., (2004)[17]	29 cohort	1,731,466	171,869	Sex, model, ex-/occasional drinkers excluded	Focus on modelling fractional polynomials vs. cubic splines
Burger et al., (2004)[18]	27 prospective	Not stated	Not stated	Sex, age, ethnicity (no 'participants of African or Asian origin')	No meta-analysis. Focus on deriving alcohol guidelines for Germany
Cleophas (1999)[28]	8 cohort	307,591	Not stated	-	Main focus on CVD and beverage type
Costanzo et al., (2011)[25]	5 prospective	56,696	11,905	Beverage type	Wine consumption only. Main focus on CVD and beverage type
Di Castelnuovo et al., (2006)[5]	34 cohort	1,015,835	94,533	Sex, region, studies without ex-/occasional drinkers in reference group, follow-up duration, sample size, year of publication, level of adjustment	Only studies that reported risk estimates by sex
Fillmore et al., (2006)[3]	54 prospective	2,137,785	Not stated	Age, smoking status, studies without ex-/occasional drinkers in reference group	Focus on choice of reference group
Gmel et al., (2003)[16, 31]	50 cohort	Not stated	Not stated	Sex, age, follow-up duration, distribution of alcohol consumption in the cohort or population, separating ex-drinkers from non-drinkers	Focus on study characteristics
Holman et al., (1996)[14, 32]	16 cohort	1,084,733	122,381	Sex, region ('primarily European-origin populations' only)	Focus on Australian alcohol guidelines
Jayasekara et al., (2014)[19]	9 cohort	62,950	10,490	Sex, model	Studies measuring drinking at multiple time points only
Park et al., (2015)[23]	8 cohort, 1 nested case-control	1,432,387	46,053	Ethnicity ('Korean subjects' only)	Focus on Korean subjects and 'mild'[b] alcohol consumption
Poikolainen (1995)[27]	29 prospective	Not stated	136,665	-	No meta-analysis
Reid et al., (2002)[22]	20 cohort/case-control	Not stated	Not stated	Age ('older persons' only)	No meta-analysis. Focus on older persons
Ronksley et al., (2011)[24, 26]	31 cohort	844,414	Not stated	CVD status (no pre-existing CVD only), evidence of industry funding	Only studies that reported CVD outcomes. Main focus on CVD/industry funding
Stockwell et al., (2016)[4]	87 cohort	3,998,626	367,103	Sex, age, region, studies without ex-/occasional drinkers in reference group, occasional drinkers as reference group, level of adjustment, study quality	Focus on choice of reference group and study characteristics/quality

[a]Number of primary studies included in analyses where all-cause mortality was the outcome. [b]Lowest category of drinking in each primary study. CVD, Cardiovascular disease. RRR, Relative Risk Ratio.

Table 3.2. (Continued)

Review	Primary study number and type[a]	n participants	n deaths	Sub-analysis, sensitivity analysis, stratification or restriction	Notes
Wang et al., (2014)[20]	24 cohort	2,424,964	123,878	Sex, region, studies with lifetime abstainers as reference group, follow-up duration, sample size, year of publication, distribution of alcohol consumption in the cohort or population, level of adjustment	Only studies that reported risk estimates by sex. Focus on female-to-male RRR
White (1999)[15]	20 cohort	1,210,545	135,048	Sex, age, region, studies without ex-drinkers in reference group and/or without participants with pre-existing coronary heart disease, level of adjustment	Only studies that reported risk estimates by sex. Focus on level of alcohol consumption at which risk of mortality is lowest
Zheng et al., (2015)[21]	9 cohort, 1 case-cohort	191,099	Not stated	Sex, region, follow-up duration, sample size, level of adjustment, study quality	Only studies that reported risk estimates by sex. Focus on female-to-male RRR and CVD

Table 3.3. Reference group and risk of bias assessment in included systematic reviews.

Review	Reference group (in main analysis)	Former/occasional drinkers included in reference group	Risk of bias assessment (risk of bias in each ROBIS domain[a])	Notes
Anderson et al., (1993)[13]	Non-drinkers	Yes/Unclear	High (Low; High; High; Low)	-
Bagnardi et al., (2004)[17]	Lifetime abstainers	No/No	High (Low; High; High; High)	-
Burger et al., (2004)[18]	Non-drinkers	Yes/Yes	High (Low; High; High; Low;)	An unspecified number of included primary studies separated ex-drinkers and/or occasional drinkers from lifetime abstainers
Cleophas (1999)[28]	Non-drinkers	Yes/Unclear	High (High; High; High; Low)	-
Costanzo et al., (2011)[25]	Non-drinkers	Yes/Yes	High (Low; Low; High; Low)	3 of 5 primary studies had ex-drinkers in reference group, 1 of 5 studies had light drinkers in reference group. 3 of 5 studies did not adjust for total alcohol consumption
Di Castelnuovo et al., (2006)[5]	Non-drinkers[b]	Yes/Yes	High (Low; High; High; High)	27 of 56 risk curves did not have ex- or light drinkers in reference group. Stratification by whether study included ex- or light drinkers in reference group
Fillmore et al., (2006)[3]	Lifetime abstainers[c]	No/No	High (Low; High; High; High)	-
Gmel et al., (2003)[16, 31]	Non-drinkers[b]	Yes/No	High (Low; High; High; High)	In continuous analysis, a majority of primary studies used a reference group of non-drinkers. Categorical analysis separated ex-drinkers from lifetime abstainers
Holman et al., (1996)[14, 32]	Non-drinkers or ≤ 0.25 drinks/day	Yes/Yes	High (Low; High; Low; High)	-
Jayasekara et al., (2014)[19]	Non-drinkers	Yes/No	High (Low; High; High; Low)	"*Most*" primary studies separated ex-drinkers from lifetime abstainers
Park et al., (2015)[23]	Non-drinkers	Yes/Yes	Low (Low; Low; Low; Low)	3 of 9 primary studies separated ex-drinkers from lifetime abstainers
Poikolainen (1995)[27]	Non-drinkers	Yes/Unclear	High (High; High; High; Low)	Reference group was lifetime abstainers in 1 of 29 primary studies and < 3 drinks/day in 1 of 29 studies
Reid et al., (2002)[22]	Non-drinkers	Yes/Unclear	High (Low; High; High; Low)	An unspecified number of included primary studies separated ex-drinkers from lifetime abstainers
Ronksley et al., (2011)[24, 26]	Non-drinkers	Yes/No	Low (Low; Low; Low; Low)	Used lifetime abstainers as reference group in sub-analyses for cardiovascular disease but not for all-cause mortality
Stockwell et al., (2016)[4]	Lifetime abstainers[c,d]	No/No	Low (Low; Low; Low; Low)	-

[a]The four ROBIS domains are, respectively: Study eligibility criteria; Identification and selection of studies; Data collection and study appraisal; Synthesis and findings. [b]Lifetime abstainers as reference group in at least one sensitivity or sub-analysis. [c]Results also reported using a reference group containing former and/or occasional drinkers. [d]Results also reported using a reference group of occasional drinkers (< 1.3 g/day). ROBIS, Risk of bias in systematic reviews[9].

Table 3.3. (Continued)

Review	Reference group (in main analysis)	Former/occasional drinkers included in reference group	Risk of bias assessment (risk of bias in each ROBIS domain[a])	Notes
Wang et al., (2014)[20]	Non-drinkers[b]	Yes/Yes	High (Low; Low; High; Low)	The dose-response meta-analysis excluded ex- and occasional drinkers, and a sensitivity analysis for the categorical model excluded ex-drinkers
White (1999)[15]	Non-drinkers[b]	Yes/Unclear	High (Low; High; High; High)	Sensitivity analysis excluded primary studies with ex-drinkers in the reference group
Zheng et al., (2015)[21]	Non-drinkers or lowest drinking category	Yes/Yes	Low (Low; Low; Low; Low)	-

The J-shaped risk curve

Many reviews reported a J-shaped risk curve between alcohol consumption and all-cause mortality. There were a variety of features of the J-shaped risk curve discussed in the reviews, particularly when comparing subgroups and performing sensitivity analyses. An illustration of the reported features of the J-shaped risk curve is shown in Figure 3.2.

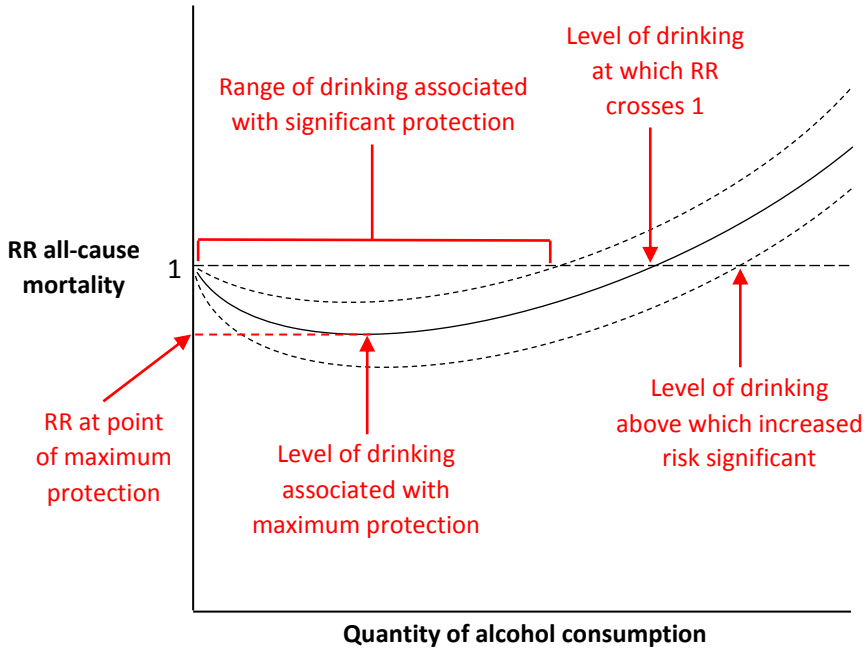

Figure 3.2. Illustration of the features of a J-shaped risk curve between alcohol consumption and all-cause mortality. RR, Relative Risk.

Review findings for the shape of the risk curve by methodological quality

The overall findings for each review on the shape of the alcohol consumption and all-cause mortality risk curve by ROBIS assessment and choice of reference group are summarised in Table 3.4. If a review reported results using multiple reference groups then the review was counted twice where applicable. Of the thirteen reviews considered at high risk of bias and used a reference group of non-drinkers, almost all found a U- or J-shaped risk curve. Three of these reviews included a sensitivity- or sub-analysis using a reference group of lifetime abstainers, so were reported in the table twice. Specifically, White (1999), Gmel et al., (2003) and Di Castelnuovo et al., (2006) still found a U- or J-shaped risk curve (although the inverse association was attenuated in two). Nine reviews were considered at low risk of bias or used a reference group of lifetime abstainers (but not both), with the majority finding a U- or J-shaped risk curve and the remainder no significant association (Zheng et al., (2015) found a U-shaped risk curve in men and no significant association in women, and did not report results for both sexes combined. Fillmore et al., (2006) found a J-shaped risk curve when including former and occasional drinkers in the reference group, and no significant association when using a reference group of lifetime abstainers. The one review which used a reference group of lifetime abstainers and was considered at low risk of bias, Stockwell et al., (2016), reported a positive association with risk. This review also performed an analysis that included former and occasional drinkers in the reference group, finding a J-shaped risk curve, and used a reference group of occasional drinkers alone, finding a positive association with risk.

Table 3.4. Summary of review findings in relation to the shape of risk curve of alcohol consumption and all-cause mortality by ROBIS assessment and choice of reference group.

		Shape of risk curve		
Review attributes	**n review findings[a]**	**U- or J-shaped**	**No association**	**Positive association**
High risk of bias and reference group of non-drinkers	13	[3, 5, 13-16, 18-20, 25, 27, 28]	[22]	-
High risk of bias and reference group of lifetime abstainers	5	[5, 15-17]	[3]	-
Low risk of bias and reference group of non-drinkers	4	[4, 21, 24]	[21, 23]	-
Low risk of bias and reference group of lifetime abstainers	1	-	-	[4]
Low risk of bias and reference group of occasional drinkers[b]	1	-	-	[4]

[a]Some reviews[3-5, 15, 16, 21] are reported twice or three times because separate results were reported in sub-group analyses. [b]≤ 1 drink/week or < 1.3 g/day. ROBIS, Risk of bias in systematic reviews[9].

Review findings – general population

Six of 18 reviews reported effect estimates for the general population, without stratification by a particular factor (e.g. sex, beverage type) or selection for a particular population (e.g. older persons) (Table 3.5)[3-5, 17, 27, 28]. It should be noted that two reviews were assumed to report effect estimates for the general population as they did not state any eligibility criteria[27, 28]. Four reviews reported a U- or J-shaped association between alcohol consumption and all-cause mortality[5, 17, 27, 28], with a level of drinking associated with maximum protection of 5 or 6 grams per day[17], 6 grams per day[5] or approximately 1 drink per day[27], and with significant protection until 37 grams per day[5]. The remaining two reviews used lifetime abstainers as the reference group[3, 4]. One reported no significant association between alcohol consumption and all-cause mortality (although the effect estimate confidence intervals appeared to be consistent with a J-shape)[3] while the other reported an increased risk[4]. Both reviews also reported a J-shaped relationship when including former and occasional drinkers in the reference group, and in one of the reviews, increased risk was reported only when using a reference group of occasional drinkers (≤ 1 drink/week or < 1.3 g/day) alone[4].

Reviews reported a significant increased risk at levels of intake ≥ 5 "drinks daily"[28], > 44 or > 46 grams per day[17], ≥ 45 grams per day[3] or > 4 drinks or ≥ 45 grams per day[4] when using a reference group of non-drinkers, and approximately > 38 grams per day[5] or > 6 drinks or ≥ 65 grams per day[4] when using a reference group of lifetime abstainers. Finally, in two reviews, former drinkers had similar effect estimates to heavy drinkers[3, 4]. The effect estimates for occasional drinkers were also similar to low-volume drinkers in these reviews.

Overall, the evidence for the association between moderate alcohol consumption and all-cause mortality is inconsistent. While all five of the reviews examining the relationship between alcohol consumption and all-cause mortality including former drinkers in the reference reported a U- or J-shaped association[3-5, 27, 28], the four reviews examining the relationship using lifetime abstainers

as the reference group reported different findings: a J-shaped relationship (maximum protection at 5 to 6 grams per day, relative risk at point of maximum protection 0.84 (99% confidence interval: 0.82-0.86))[5, 17], no significant association[3] and increased risk[4]. It is possible that some reviews using lifetime abstainers as the reference group may have been underpowered, due to a smaller number of primary studies included for analysis and/or a smaller-sized reference group compared to reviews using non-drinkers as the reference group.

There is good evidence that heavy drinking increases risk, with the level of risky drinking ranging from > 4 to > 6 drinks per day or approximately > 38 to ≥ 65 grams per day (one review reported no significant association, but was consistent with an elevated risk). There is good evidence for a positive association with risk when occasional drinkers are used as the reference group. There is also good evidence that former and heavy drinkers have a similar level of increased risk. The review which reported only an association with increased risk was the only one not considered at high risk of bias [4]. Therefore, the evidence is strongest for a positive association between alcohol consumption and all-cause mortality, rather than a J-shaped association.

Table 3.5. Review findings for the general population.

Review	Reference group	Risk of bias	Results (95% CI[a])
Bagnardi et al., (2004)[17]	Lifetime abstainers	High	Maximum protection at 5 g ethanol/day (fractional polynomial model) or 6 g/day (restricted cubic spline model). Significant increased risk above 44 g/day (fractional polynomial model) or 46 g/day (restricted cubic spline model)
Cleophas (1999)[28]	Non-drinkers	High	Significantly lower RR for 1-4 drinks daily ($p < 0.02$) Significantly higher RR for ≥ 5 drinks daily ($p < 0.01$)
Di Castelnuovo et al., (2006)[5]	Non-drinkers	High	Among 48 adjusted risk curves: Maximum protection at 6 g ethanol/day (RR 0.83 (0.82-0.85)). Protection significant until 37 g/day Among 27 risk curves using a reference group only of lifetime abstainers: Maximum protection at 5 g ethanol/day (RR 0.84 (0.82-0.86)). Protection significant until 30 g/day. Significant increased risk above ≈ 38 g/day
Fillmore et al., (2006)[3]	Lifetime abstainers	High	OR 0.94 (0.77-1.00) for occasional drinking[c] OR 0.95 (0.84-1.08) for light drinking[c] OR 0.99 (0.83-1.19) for moderate drinking[c] OR 1.24 (1.00-1.53) for heavy drinking[c] OR 1.18 (1.03-1.36) for former drinking No significant association in continuous analysis
Poikolainen (1995)[27]	Non-drinkers	High	Most studies found a U- or J-shaped risk curve. Most studies found the level of alcohol consumption associated with maximum protection to be one drink per day
Stockwell et al., (2016)[4]	Lifetime abstainers	Low	RR 0.94 (0.71-1.25) for occasional drinking[d] RR 0.90 (0.76-1.06) for low-volume drinking[d] RR 0.95 (0.80-1.13) for medium-volume drinking[d] RR 1.11 (0.93-1.32) for high-volume drinking[d] RR 1.42 (1.15-1.75) for higher-volume drinking[d] RR 1.31 (1.09-1.57) for former drinking

[a]99% CI for Di Castelnuovo et al., (2006). [b]In the meta-analysis of 48 adjusted curves. [c]Occasional drinking: ≥ 1 and < 12 drinks/year or ≥ 0.033 and ≤ 0.363 g ethanol/day; Light drinking: ≥ 1 drink/month and ≤ 2 drinks/day or ≥ 0.39 and < 25 g/day; Moderate drinking: > 2 and ≤ 4 drinks/day or ≥ 25 and < 45 g/day; Heavy drinking: > 4 drinks/day or ≥ 45 g/day. [d]Occasional drinking: Current drinker and ≤ 1 drink/week or < 1.3 g ethanol/day; Low-volume drinking: > 1 drink/week and ≤ 2 drinks/day or ≥ 1.3 and < 25 g/day; Medium-volume drinking: > 2 and ≤ 4 drinks/day or ≥ 25 and < 45 g/day; High-volume drinking: > 4 and ≤ 6 drinks/day or ≥ 45 and < 65 g/day; Higher-volume drinking: > 6 drinks per day or ≥ 65 g/day. CI, Confidence Interval. OR, Odds Ratio. RR, Relative Risk.

Review findings – by sex

11 of 18 reviews examined differences in the relationship between alcohol consumption and all-cause mortality by sex (Table 3.6)[4, 5, 13-21]. When restricted to men, 10 of 10 reviews reported a J- or U-shaped relationship[5, 13-21], while when restricted to women, 8 of 9 reviews reported a J- or U-shaped relationship[5, 13-18, 20] and 1 reported no significant association[21]. When men and women were compared directly, the results were mostly consistent for some outcomes and mostly inconsistent for others. One review tested for an interaction with sex and found no significant effect[4]. This was the only review that was both considered at low risk of bias and which used lifetime abstainers as the reference group. In other reviews, the level of drinking associated with maximum protection was consistently greater in men compared to women, with estimates for men varying between 6 and 19 grams per day or 7.7 to 12.9 units per week, and for women between 5 and 10 grams per day or 2.9 units per week[5, 15, 17, 18]. The range of drinking associated with significant protection was also larger in men compared to women[5, 14, 16, 21], except in one review where it was similar for both sexes[20]. The evidence for whether one sex had a lower minimum relative risk was inconsistent between reviews, with some reviews reporting a lower value in men[14, 16, 21], others in women[5, 17], and another review finding no difference[20]. Finally, in most reviews it was reported that the relative risk associated with heavy drinking was higher (or the risk was higher at lower levels of drinking) in women compared to men[5, 14, 16, 17, 20, 21]. Significant increased risk in men was reported at intakes ≥ 4 drinks per day[14], > 40 grams per day[16], approximately > 45 grams per day[5], > 60 grams per day[17] or ≥ 90 grams per day[20], and in women at intakes ≥ 2 drinks per day[14], > 30 grams per day[16], approximately > 35 grams per day[5], > 47 or > 51 grams per day[17] or ≥ 75 grams per day[20]. Finally, one review reported that former drinking compared to lifetime abstention was associated with greater risk in women compared to men[16].

It should be noted that two reviews had the explicit aim of comparing risk estimates in men and women, using what was termed the 'female-to-male relative risk ratio (RRR)' (the ratio of the relative risk in women compared to men, for a given level of alcohol consumption)[20, 21]. For example, if the relative risk for a given level of drinking was 1.5 in women and 1.2 in men, then the female-to-male RRR was 1.25. One review reported a significantly elevated female-to-male RRR at levels of intake greater than approximately 70 grams per day[20]. In sensitivity analyses, the female-to-male RRR for all drinkers combined compared to non-drinkers was unaffected by primary study region (Asia vs. not), cardiovascular disease status adjustment, cohort average alcohol consumption, duration of follow-up, primary study sample size and primary study year of publication, nor when using a reference group of lifetime abstainers. The other review reported a significantly elevated female-to-male RRR for moderate drinking but not low or heavy drinking (although the confidence intervals for both of the latter were consistent with a similar effect size to moderate drinking)[21]. In sensitivity analyses, the female-to-male RRR for heavy drinkers was affected by primary study country (significantly elevated for studies performed in the United States only), physical activity adjustment (significantly elevated when unadjusted only) and Newcastle-Ottawa Scale[33] (significantly elevated in lower quality studies only), and unaffected by primary study duration of follow-up, sample size, serum cholesterol adjustment and hypertension adjustment. In both of these reviews, the sensitivity analyses were not performed on the simple relative risks, and so these sensitivity tests are not considered in subsequent sections.

Overall, there is inconsistent evidence that the risk relationship between alcohol consumption and all-cause mortality differs by sex, with most reviews, but not all, finding that a greater range of moderate drinking is associated with protection for men than in women, that a significant increase in risk begins at a lower level of drinking in women than in men, and that heavy drinking is associated with a higher level of risk in women than in men. This may mean that men and women experience a different biological response to alcohol consumption. The majority of studies used non-drinkers as the reference group, which is of particular concern as one review found that the

association between former drinking and all-cause mortality differed by sex, meaning that the use of non-drinkers as the reference group could induce bias when investigating sex differences in the risk curve. Furthermore, the majority of reviews were considered at high risk of bias, with the one review both considered at low risk of bias and which used lifetime abstainers as the reference group finding no differences in the risk relationship by sex.

Table 3.6. Review findings by sex.

Review	Reference group (in analysis stratified by sex)	Risk of bias	Strata	Results (95% CI[a])
Anderson et al., (1993)[13]	Non-drinkers	High	Men	Eight of 12 studies found a J-shaped risk curve, one study only a significant increased risk in heavy drinkers, and three studies found no association
			Women	Results were "*similar*" in four studies
Bagnardi et al., (2004)[17]	Lifetime abstainers	High	Men	Maximum protection at 6 g ethanol/day (RR 0.82 (0.74-0.90), fractional polynomial model) or 7 g/day (RR 0.83 (0.74-0.93), restricted cubic spline model). Protection was significant until 28 g/day (both models). Significant increase in risk above 60 g/day (both models)
			Women	Maximum protection at 5 g/day (RR 0.76 (0.68-0.85), fractional polynomial model) or 6 g/day (RR 0.77 (0.68-0.88), restricted cubic spline model). Protection was significant until 24 g/day (both models). Significant increase in risk above 47 g/day (fractional polynomial model) or 51 g/day (restricted cubic spline model)
Burger et al., (2004)[18]	Non-drinkers	High	Men	Maximum protection at ≈ 19 g ethanol/day
			Women	Maximum protection at ≈ 10 g/day
Di Castelnuovo et al., (2006)[5]	Non-drinkers	High	Men	Maximum protection at 6 g ethanol/day (RR 0.83 (0.81-0.85)). Protection significant until 38 g/day. Significant increase in risk above ≈ 45 g/day
			Women	Maximum protection at 5 g/day (RR 0.82 (0.78-0.87)). Protection significant until 18 g/day. Significant increase in risk above ≈ 35 g/day
				Significant difference in risk curve between strata ($p < 0.001$)
Gmel et al., (2003)[16, 31]	Lifetime abstainers[b]	High	Men	RR 0.85 (0.83-0.87) for > 0-10 g ethanol/day RR 0.80 (0.78-0.82) for > 10-20 g/day RR 0.91 (0.89-0.94) for > 20-30 g/day RR 0.96 (0.93-1.00) for > 30-40 g/day RR 1.04 (1.01-1.07) for > 40-70 g/day RR 1.27 (1.23-1.31) for > 70-110 g/day RR 1.46 (1.33-1.60) for > 110 g/day RR 1.21 (1.10-1.32) for ex-drinkers
			Women	RR 0.87 (0.84-0.89) for > 0-10 g/day RR 1.01 (0.99-1.04) for > 10-30 g/day RR 1.40 (1.34-1.47) for > 30-50 g/day RR 1.43 (1.34-1.53) for > 50 g/day RR 1.44 (1.28-1.61) for ex-drinkers

[a]99% CI for Di Castelnuovo et al., (2006). [b]In categorical analysis. In main analysis (continuous model) a majority of included studies had a reference group of non-drinkers. [c]1 unit = 9 g ethanol. CI, Confidence Interval. RR, Relative Risk. RRR, Relative Risk Ratio for women vs. men.

Table 3.6. (Continued)

Review	Reference group (in analysis stratified by sex)	Risk of bias	Strata	Results (95% CI[a])
Holman et al., (1996)[14, 32]	Non-drinkers or ≤ 0.25 drinks/day	High	Men	RR 0.88 (0.86-0.90) for 0-0.9 drinks/day RR 0.84 (0.82-0.86) for 1-1.9 drinks/day RR 0.93 (0.91-0.95) for 2-2.9 drinks/day RR 1.01 (0.98-1.04) for 3-3.9 drinks/day RR 1.06 (1.03-1.10) for 4-4.9 drinks/day RR 1.20 (1.15-1.26) for 5-5.9 drinks/day RR 1.37 (1.33-1.40) for ≥ 6.0 drinks/day
			Women	RR 0.88 (0.86-0.90) for 0-0.9 drinks/day RR 0.94 (0.93-0.96) for 1-1.9 drinks/day RR 1.13 (1.10-1.16) for 2-2.9 drinks/day RR 1.33 (1.27-1.39) for 3-3.9 drinks/day RR 1.47 (1.39-1.56) for 4-4.9 drinks/day RR 1.47 (1.33-1.62) for 5-5.9 drinks/day RR 1.58 (1.49-1.69) for ≥ 6.0 drinks/day
Jayasekara et al., (2014)[19]	Non-drinkers	High	Men	RR 0.90 (0.81-0.99) for 1-29 g ethanol/day RR 1.19 (0.89-1.58) for 30-59 g/day RR 1.52 (0.78-2.98) for ≥ 60 g/day In cubic spline analysis, greater alcohol consumption not significantly associated with all-cause mortality at intakes ≤ 40 g ethanol/day, followed by an increase in risk at intakes > 40 g/day
			Women	Meta-analysis not possible
Stockwell et al., (2016)[4]	Lifetime abstainers	Low	-	Sex was tested as an effect modifier and was not significant
Wang et al., (2014)[20]	Non-drinkers	High	Men	RR 0.95 (0.92-0.98) for 10 g ethanol/day RR 0.92 (0.85-0.99) for 25 g/day RR 0.96 (0.83-1.10) for 50 g/day RR 1.15 (0.92-1.43) for 75 g/day RR 1.36 (1.02-1.80) for 90 g/day RR 1.56 (1.12-2.19) for 100 g/day
			Women	RR 0.93 (0.90-0.96) for 10 g/day (RRR 0.98 (0.94-1.02)) RR 0.91 (0.85-0.96) for 25 g/day (RRR 0.99 (0.90-1.09)) RR 1.09 (0.93-1.27) for 50 g/day (RRR 1.14 (0.92-1.40)) RR 1.74 (1.23-2.47) for 75 g/day (RRR 1.52 (1.01-2.29)) RR 2.65 (1.59-4.42) for 90 g/day (RRR 1.95 (1.08-3.49)) RR 3.70 (1.95-7.04) for 100 g/day (RRR 2.36 (1.15-4.88))
White (1999)[15]	Non-drinkers	High		United States:
			Men	Maximum protection at 7.7 (6.4-9.1) units/week[c]
			Women	Maximum protection at 2.9 (2.0-2.4) units/week
				United Kingdom:
			Men	Maximum protection at 12.9 (10.8-15.1) units/week
			Women	Meta-analysis not possible
Zheng et al., (2015)[21]	Non-drinkers or lowest drinking category	Low		Low alcohol intake (< 15 g ethanol/day):
			Men	RR 0.74 (0.60-0.92)
			Women	RR 0.87 (0.71-1.07) RRR 1.07 (0.98-1.17)
				Moderate alcohol intake (15-30 g/day):
			Men	RR 0.80 (0.68-0.95)
			Women	RR 0.95 (0.83-1.08) RRR 1.10 (1.00-1.21)
				Heavy alcohol intake (> 30 g/day):
			Men	RR 1.00 (0.81-1.22)
			Women	RR 1.20 (0.99-1.46) RRR 1.09 (0.99-1.21)

Review findings – by age

Six of 18 reviews reported effect estimates by age (Table 3.7)[3, 4, 15, 16, 18, 22]. Three reviews restricted to younger participants (< 40 years[18], < 45 years[16] and "young men"[15]). In two reviews a linear increased risk was found with increasing alcohol consumption[16, 18]. In the third review, which investigated the level of drinking associated with maximum protection, the value was determined to be zero (i.e. no level of drinking was associated with protection)[15].

Two reviews restricted to older participants (≥ 35 years[3] and aged ≥ 60 years at baseline or mean age of cohort ≥ 65 years at baseline[22]), with one review finding no difference in results for older participants compared to all participants (i.e. a J-shaped relationship when using a reference group including former drinkers and occasional drinkers and no significant association when using a reference group of lifetime abstainers)[3], and the other finding no significant association in the majority of primary studies examined[22]. One review, which found a J-shaped relationship overall, reported that older age did not significantly alter the level of drinking associated with maximum protection, the RR at the point of maximum protection, or the range of drinking associated with significant protection[16]. Finally, one review which found an association with increased risk overall, tested for an interaction with median age at baseline, finding no significant effect[4].

Overall, there is inconsistent evidence for differences in mortality risk by age. Alcohol consumption at younger ages may be associated with a linear increased risk of all-cause mortality, and at older ages with either a J-shaped relationship, or with increased risk, or no significant association. Two reviews reported no significant effect of age on risk estimates[4, 16], including the only review which was considered at low risk of bias[4]. The majority of reviews also used non-drinkers as the reference group, and differences in findings by age may therefore be related to less time having elapsed for heavy drinkers to experience negative health events and become former drinkers. Therefore, non-drinkers may be a less biased reference group in younger participants compared to older participants, resulting in J-shaped associations with mortality only in older participants.

Table 3.7. Review findings by age.

Review	Reference group	Risk of bias	Strata	Results
Burger et al., (2004)[18]	Non-drinkers	High	< 40 years	Linear relationship between increasing alcohol consumption and all-cause mortality
Fillmore et al., (2006)[3]	Lifetime abstainers	High	≥ 35 years	"*Similar results to the entire sample*"
Gmel et al., (2003)[16, 31]	Non-drinkers	High	< 45 years Older age	Men: Linear increase in risk with increasing alcohol consumption Men and women: No significant effect on level of alcohol consumption associated with maximum protection, the RR at the point of maximum protection, or the range of drinking associated with significant protection
Reid et al., (2002)[22]	Non-drinkers	High	Older persons[a]	4 of 20 primary studies reported an association with increased risk with increasing drinking, 4 studies reported an association with decreased risk, and 13 studies reported no association[b]
Stockwell et al., (2016)[4]	Lifetime abstainers	Low	-	Median age at baseline was tested as an effect modifier and was not significant
White (1999)[15]	Non-drinkers	High	Young men	Maximum protection at 0 units/week[c] (i.e. no level of drinking was associated with protection)

[a]Participants aged ≥ 60 years at baseline or mean age of cohort ≥ 65 years at baseline. [b]Studies do not add up to twenty because one study was an analysis of three cohorts which differed in findings. [c]1 unit = 9 g ethanol.

Review findings – by population (region or ethnicity)

Six of 18 reviews reported effect estimates by population (region or ethnicity) (Table 3.8)[4, 5, 14, 15, 18, 23]. In 4 reviews[4, 5, 14, 15], this was by the country or region the primary study was conducted in (e.g. United States, populations primarily of European origin), and in 2 reviews[18, 23] this was by ethnicity (e.g. studies with Korean subjects). Regarding region, two reviews compared primary studies performed in the United States and Europe[5, 15]. One review found a higher level of drinking associated with maximum protection in studies performed in the United Kingdom compared to studies performed in the United States in men, while a comparison for women was not possible due to lack of data for the United Kingdom[15]. The other review found a higher level of drinking associated with maximum protection in studies performed in Europe compared to studies performed in the United States for men (along with a lower relative risk at the point of maximum protection, and a larger range of drinking associated with protection), but no significant difference in women[5]. The same review also reported results for studies performed in Australia, China and Japan combined, finding all three factors to be higher than the results for the United States but lower than Europe for men, and no significant difference in women. A further review, which reported only an association with increased risk overall, tested for an interaction with country ("*Mainly Caucasian*" population (North America, Europe, Australia) vs. not (Japan, China, India)), finding no significant effect[4]. Finally, a review with the inclusion criteria of "*study populations primarily of European origin*" reported a J-shaped relationship between alcohol consumption and all-cause mortality[14]. Regarding ethnicity, one review which excluded "*studies on participants of African or Asian origin*" reported "*generally a U- or J-shaped dose-response relationship*"[18], while another review with the inclusion criteria of "*studies with Korean subjects*" examined only the association of 'mild' drinking compared to non-drinking, finding no significant effect (although the confidence intervals were consistent with a relative risk as low as 0.72)[23].

Overall, there is limited evidence for differences in mortality risk by population, with each review assessing different regions or ethnicities. There is limited evidence that moderate drinking is associated with lesser protection in the United States compared to the United Kingdom and Europe in men, and with a level of protection that is intermediate for Australia, China and Japan combined. However this evidence was provided by reviews considered at high risk of bias and using a reference group of non-drinkers. There is also limited evidence that 'mild' drinking is not associated with protection in persons with Korean ethnicity, although the review used non-drinkers as the reference group, did not calculate a result for a specific quantity of alcohol consumption, and may have been underpowered. Further reviews with inclusion criteria aiming to maximise Caucasian participants reported U- or J-shaped associations, but were considered at high risk of bias and used a reference group of non-drinkers. No identified reviews examined the populations of Africa, the Middle East, Latin America, the Pacific or other populations. This may be due to a lack of primary data, as in the review with the most primary studies, Stockwell et al., (2016), it was found that only 10 of 87 primary studies were based on populations that were not 'mainly Caucasian'[4]. Finally, there is good evidence for no difference in the risk relationship when comparing two specific sets of countries (North America, Europe and Australia combined and vs. Japan, China and India combined).

Table 3.8. Review findings by population (region or ethnicity).

Review	Reference group	Risk of bias	Population	Results (95% CI[a])
Burger et al., (2004)[18]	Non-drinkers	High	"Studies on participants of African or Asian origin" excluded	U- or J-shaped risk curve. Maximum protection at ≈ 19 g ethanol/day in men and ≈ 10 g/day in women. Significant increased risk beyond 24 g/day in some studies
Di Castelnuovo et al., (2006)[5]	Non-drinkers	High	United States; Europe; Australia/ Japan/China;	United States men: Maximum protection at 4 g ethanol/day (RR 0.84 (0.81-0.86)). Protection significant until 27 g/day European men: Maximum protection at 9 g ethanol/day (RR 0.76 (0.72-0.80)). Protection significant until 58 g/day Australian/Chinese/Japanese men: Maximum protection at 6 g ethanol/day (RR 0.82 (0.77-0.87)). Protection significant until 33 g/day Significant difference in risk curve between strata (p = 0.003) United States women: Maximum protection at 5 g ethanol/day (RR 0.81 (0.76-0.87)). Protection significant until 22 g/day European women: Maximum protection at 4 g ethanol/day (RR 0.80 (0.66-0.97)). Protection significant until 8 g/day Australian/Chinese/Japanese women: Maximum protection at 5 g ethanol/day (RR 0.88 (0.77-1.00)). Protection significant until 27 g/day No significant difference in risk curve between strata (p > 0.54)
Holman et al., (1996)[14, 32]	Non-drinkers or ≤ 0.25 drinks/day	High	"Study populations primarily of European origin"	Men: RR 0.88 (0.86-0.90) for 0-0.9 drinks/day RR 0.84 (0.82-0.86) for 1-1.9 drinks/day RR 0.93 (0.91-0.95) for 2-2.9 drinks/day RR 1.01 (0.98-1.04) for 3-3.9 drinks/day RR 1.06 (1.03-1.10) for 4-4.9 drinks/day RR 1.20 (1.15-1.26) for 5-5.9 drinks/day RR 1.37 (1.33-1.40) for ≥ 6.0 drinks/day Women: RR 0.88 (0.86-0.90) for 0-0.9 drinks/day RR 0.94 (0.93-0.96) for 1-1.9 drinks/day RR 1.13 (1.10-1.16) for 2-2.9 drinks/day RR 1.33 (1.27-1.39) for 3-3.9 drinks/day RR 1.47 (1.39-1.56) for 4-4.9 drinks/day RR 1.47 (1.33-1.62) for 5-5.9 drinks/day RR 1.58 (1.49-1.69) for ≥ 6.0 drinks/day
Park et al., (2015)[23]	Non-drinkers	Low	"Studies with Korean subjects"	OR 0.85 (0.72-1.01) for 'mild' drinking[b]
Stockwell et al., (2016)[4]	Lifetime abstainers	Low	"Mainly Caucasian" population	Mainly Caucasian population (North America, Europe, Australia) vs. not (Japan, China, India) was tested as an effect modifier and was not significant
White (1999)[15]	Non-drinkers	High	United Kingdom; United States	United Kingdom men: Maximum protection at 12.9 (10.8-15.1) units/week[c] United States men: Maximum protection at 7.7 (6.4-9.1) units/week United States women: Maximum protection at 2.9 (2.0-2.4) units/week

[a]99% CI for Di Castelnuovo et al., (2006). [b]Lowest category of alcohol consumption in each primary study. [c]1 unit = 9 g ethanol. CI, Confidence Interval. RR, Relative Risk. OR, Odds Ratio.

Review findings – by smoking status

One of 18 reviews reported effect estimates by smoking status[3]. Fillmore et al., (2006) reported that when using a reference group including former and occasional drinkers, alcohol consumption was associated with all-cause mortality in a J-shaped relationship while there was no significant association when using lifetime abstainers as the reference group. Regarding smoking status, risk estimates were only altered for 'heavier' drinking (> 4 drinks/day or ≥ 45 g/day), with a stronger association with all-cause mortality in current smokers compared to non-smokers. It was stated that heavier drinking and current smoking was associated with twice the risk of all-cause mortality than heavier drinking and non-smoking, but quantitative information on the alcohol-mortality relationship itself by smoking status was not reported. Ex-smoking was not examined, and there were no further details reported.

Overall, there is limited evidence the association of 'heavier' drinking with all-cause mortality is higher in current smokers than non-smokers, and that smoking status does not alter risk estimates for levels of drinking lower than 'heavier'. The review was considered at high risk of bias, did not separate ex-smokers from never-smokers, and also did not report any quantitative information about the alcohol-mortality relationship in each strata.

Review findings – by exclusion of participants with pre-existing cardiovascular disease

Two of 18 reviews reported effect estimates by the exclusion of studies containing participants with pre-existing coronary heart disease[15] or cardiovascular disease[24] (Table 3.9). In one review this was performed as a sensitivity test, with the rationale that subjects with coronary heart disease could potentially "*exaggerate the protective effect of moderate drinking*"[15]. The other review simply had the absence of pre-existing cardiovascular disease as an article inclusion criterion and did not state a rationale[24], but as the main outcomes were cardiovascular disease incidence and mortality, the exclusion of participants with pre-existing cardiovascular disease was presumably to prevent reverse causation. Both reviews reported that moderate drinking was associated with a decreased risk of all-cause mortality when participants with pre-existing cardiovascular disease were excluded. White (1999) examined the level of drinking associated with maximum protection for three strata separately (American men, American women and British men), finding that the exclusion of studies containing participants with pre-existing cardiovascular disease did not alter estimates for men, but in American women the estimate increased from 2.2 to 3.7 units per week[15]. A caveat was that this sensitivity test also excluded studies containing former drinkers, so it was not possible to tell which of these two factors (the exclusion of former drinkers or subjects with cardiovascular disease), or both, were responsible for the result. Ronksley et al., (2011) reported that among participants without pre-existing cardiovascular disease, drinkers had a lower relative risk of all-cause mortality compared to non-drinkers, while a J-shaped association was found when using multiple categories of drinking with significant increased risk (relative risk 1.30, 95% confidence interval: 1.22-1.38) at levels of intake > 60 grams per day[24]. These findings for increased risk are consistent with the results of the reviews examining the general population. The category of drinking with the lowest relative risk (0.83, 0.80-0.86) was 2.5 to 14.9 grams per day.

Overall, there is limited evidence of an association of moderate drinking with lower risk of all-cause mortality when participants with pre-existing cardiovascular disease are excluded. It cannot be

determined whether the level of drinking associated with maximum protection is altered by cardiovascular disease status, due to one review using inconsistent reference groups between the main and sensitivity analyses. No review was both considered at low risk of bias and used a reference group free of former drinkers.

Table 3.9. Review findings by exclusion of participants with pre-existing cardiovascular disease.

Review	Reference group (in no pre-existing CVD analysis)	Risk of bias	CVD Strata	Results (95% CI)
Ronksley et al., (2011)[24, 26]	Non-drinkers	Low	Subjects without CVD	RR 0.87 (0.83-0.92) for drinkers RR 0.83 (0.80-0.86) for 2.5-14.9 g ethanol/day[a] RR 1.30 (1.22-1.38) for > 60 g/day
White (1999)[15]	Inconsistent[b]	High	Subjects with CHD included; Subjects with CHD excluded	British men CHD included: Maximum protection at 13.0 units/week[c] CHD excluded: Maximum protection at 9.3 units/week No significant difference between strata (p = 0.43) American men CHD included: Maximum protection at 7.5 units/week CHD excluded: Maximum protection at 8.3 units/week No significant difference between strata (p = 0.59) American women CHD included: Maximum protection at 2.2 units/week CHD excluded: Maximum protection at 3.7 units/week Significant difference between strata (p = 0.005)

[a]The minimum relative risk. [b]Non-drinkers for the strata that included subjects with coronary heart disease and lifetime abstainers for the strata that excluded subjects with coronary heart disease. [c]1 unit = 9 g ethanol. CVD, Cardiovascular disease. CI, Confidence Interval. CHD, Coronary heart disease. RR, Relative Risk.

Review findings – by distribution of alcohol consumption in the cohort or population

One of 18 reviews reported effect estimates by the distribution of alcohol consumption in the cohort or population (Table 3.10)[16]. Gmel et al., (2003) examined four factors: the cohort average alcohol consumption among drinkers, the cohort standard deviation of alcohol consumption among drinkers, the cohort proportion of abstainers, and the per capita alcohol consumption in the population[16]. The three outcomes examined were the level of alcohol consumption associated with maximum protection, the relative risk at the point of maximum protection and the range of drinking associated with significant protection. In men, it was found that the cohort average alcohol consumption, the cohort standard deviation of alcohol consumption and the per capita alcohol consumption in the population were all positively associated with a higher level of drinking for the point of maximum protection and a larger range of drinking associated with significant protection. The cohort proportion of abstainers was inversely associated with these factors. None of the factors were associated with a change in the relative risk at the point of maximum protection. In women, the only significant factor was cohort standard deviation of alcohol consumption, which was positively associated with a higher level of drinking for the point of maximum protection and a larger range of drinking associated with significant protection.

Overall, there is limited evidence that the shape of the risk curve between alcohol consumption and all-cause mortality is influenced by the distribution of alcohol consumption in the cohort or population. The level of drinking for the point of maximum protection and the range of drinking associated with significant protection were positively associated with greater cohort average alcohol consumption (men only), greater cohort standard deviation of alcohol consumption (men and women), smaller cohort proportion of abstainers (men only) and with greater population per capita alcohol consumption (men only). There is also limited evidence that the relative risk at the point of maximum protection is not affected by these factors. The review was considered at high risk of bias and used non-drinkers as the reference group.

Table 3.10. Review findings by the distribution of alcohol consumption in the cohort or population.

Review	Reference group	Risk of bias	Strata of alcohol consumption	Results (95% CI)
Gmel et al., (2003)[16, 31]	Non-drinkers	High	Cohort average alcohol consumption;	Men: Greater average alcohol consumption associated with higher level of alcohol consumption for point of maximum protection, and no change in the RR at this point. Larger range of drinking associated with significant protection Women: No significant effect
			Cohort standard deviation of alcohol consumption;	Men and women: Greater standard deviation of alcohol consumption associated with higher level of alcohol consumption for point of maximum protection, and no change in the RR at this point. Larger range of drinking associated with significant protection
			Cohort proportion of abstainers	Men: Greater proportion of abstainers associated with lower level of alcohol consumption for point of maximum protection, and no change in the RR at this point. Smaller range of drinking associated with significant protection Women: No significant effect
			Per capita alcohol consumption[a];	Men: Greater per capita alcohol consumption associated with higher level of alcohol consumption for point of maximum protection, and no change in the RR at this point. Larger range of drinking associated with significant protection Women: No significant effect

[a]For the country the study was conducted in rather than for the cohort itself. CI, Confidence Interval. RR, Relative Risk.

Review findings – by measurement of alcohol consumption at single or multiple time points

One of 18 reviews reported effect estimates only for primary studies which measured alcohol consumption at multiple time points (average consumption measured either retrospectively or prospectively from baseline)[19]. It was remarked that few primary studies have captured alcohol consumption at multiple time points. Due to lack of data, a meta-analysis was only possible for men. Decreased risk was found for moderate drinking and increased risk for heavy drinking. Specifically, a relative risk of 0.90 (95% confidence interval: 0.81-0.99) was reported for an average consumption of 1-29 grams/day, while an average consumption greater than 40 grams/day was associated with significant increased risk. Altogether, the results were consistent with a J-shaped association. The review did not examine if results differed when using only baseline alcohol consumption as the exposure.

Overall, there is a lack of evidence for whether the association between alcohol consumption and all-cause mortality differs when measuring alcohol consumption at multiple time points compared to using only baseline alcohol consumption. The review was considered at high risk of bias and used a reference group of non-drinkers.

Review findings – by beverage type

One of 18 reviews reported effect estimates by beverage type[25]. For wine consumption a J-shaped risk curve was found, with maximum protection at 10 grams of ethanol per day and a relative risk of 0.75 (0.66-0.86) at this point. Protection was significant until 41 grams per day, and a significant increased risk was apparent at intakes greater than approximately 105 grams per day (with a relative risk of approximately 1.3 at this point). The review only retrieved two studies of beer and spirit consumption and therefore a meta-analysis was not performed for these beverage types. Three of the five primary studies did not adjust for total alcohol consumption, meaning that the results for wine consumption could be confounded by the consumption of beer and spirits.

Overall, there is limited evidence that wine consumption has a J-shaped association with all-cause mortality, but confounding by the consumption of other alcoholic beverages cannot be ruled out. There is a lack of evidence for beer and spirit consumption. The review was considered at high risk of bias and used a reference group of non-drinkers. There is therefore not enough evidence to determine whether risk of all-cause mortality differs by beverage type.

Review findings – by follow-up duration

Two of 18 reviews reported effect estimates by follow-up duration (Table 3.11)[5, 16]. Both reviews reported that a longer period of follow-up was associated with a higher relative risk at the point of maximum protection and a smaller range of drinking associated with significant protection. Gmel et al., (2003) reported that a longer period of follow-up was associated with a lower level of drinking for the point of maximum protection[16], while Di Castelnuovo et al., (2006) reported no difference[5]. Finally, Di Castelnuovo et al., (2006) reported that a longer period of follow-up was associated with a lower level of drinking associated with significant increased risk. It was not reported whether risk estimates for heavy drinking differed significantly by period of follow-up, and this was not clear from the graph provided in the article.

Overall, there is limited evidence that a longer period of follow-up attenuates the association of moderate drinking with protection from all-cause mortality in two ways. Namely, through an increased relative risk at the point of maximum protection and a smaller range of drinking associated with significant protection. The evidence was inconsistent whether the duration of follow-up alters level of drinking associated with maximum protection. There is also limited evidence that a longer period of follow-up results in a lower level of drinking associated with significant increased risk. Both reviews were considered at high risk of bias and used a reference group of non-drinkers.

Table 3.11. Review findings by follow-up duration.

Review	Reference group	Risk of bias	Follow-up duration	Results (95% CI[a])
Di Castelnuovo et al., (2006)[5]	Non-drinkers	High	≤ 10 years; > 10 years	≤ 10 years: Maximum protection at 6 g ethanol/day (RR 0.79 (0.75-0.82)). Protection significant until 37 g/day. Significant increased risk above ≈ 52 g/day > 10 years: Maximum protection at 6 g ethanol/day (RR 0.85 (0.73-0.87)). Protection significant until 34 g/day. Significant increased risk above ≈ 43 g/day Significant difference in risk curve between strata ($p < 0.001$)
Gmel et al., (2003)[16, 31]	Non-drinkers	High	Greater follow-up time	Men: Associated with lower level of alcohol consumption for maximum protection, a higher RR at this point, and a smaller range of drinking associated with significant protection Women: No significant effect

[a]99% CI for Di Castelnuovo et al., (2006). CI, Confidence Interval. RR, Relative Risk.

Review findings – by primary study sample size

One of 18 reviews reported effect estimates by primary study sample size (Table 3.12)[5]. Di Castelnuovo et al., (2006) found no significant difference in the shape of the risk curve by study sample size[5]. The review was considered at high risk of bias and used non-drinkers as the reference group. The evidence for no difference by primary study sample size is therefore limited.

Table 3.12. Review findings by primary study sample size.

Review	Reference group	Risk of bias	Sample size	Results (99% CI)
Di Castelnuovo et al., (2006)[5]	Non-drinkers	High	n ≤ 6000; n > 6000	n ≤ 6000: Maximum protection at 5 g ethanol/day (RR 0.83 (0.78-0.85)). Protection significant until 26 g/day. Significant increased risk above ≈ 55 g/day n > 6000: Maximum protection at 5 g ethanol/day (RR 0.85 (0.80-0.90)). Protection significant until 36 g/day. Significant increased risk above ≈ 45 g/day No significant difference in risk curve between strata (p = 0.61)

CI, Confidence Interval. RR, Relative Risk.

Review findings – by primary study year of publication

One of 18 reviews reported effect estimates by primary study year of publication (Table 3.13)[5]. Di Castelnuovo et al., (2006) found that earlier studies (1981-1998) reported a significantly lower risk associated with moderate drinking, maximum protection at a lower level of drinking, a smaller range of drinking associated with protection and a lower level of drinking associated with significant increased risk than studies published later (1999-2005)[5]. The relative risk associated with heavy drinking was also higher in earlier studies than in later studies. The review was considered at high risk of bias and used non-drinkers as the reference group. There is therefore not enough evidence to determine whether the risk relationship differs by primary study year of publication.

Table 3.13. Review findings by primary study year of publication.

Review	Reference group	Risk of bias	Study period	Results (99% CI)
Di Castelnuovo et al., (2006)[5]	Non-drinkers	High	1981-1998	Maximum protection at 5 g ethanol/day (RR 0.85 (0.82-0.87)). Protection significant until 29 g/day. Significant increased risk above ≈ 36 g/day
			1999-2005	Maximum protection at 8 g ethanol/day (RR 0.79 (0.76-0.82)). Protection significant until 48 g/day. Significant increased risk above ≈ 62 g/day
				Significant difference in risk curve between strata ($p < 0.001$)

CI, Confidence Interval. RR, Relative Risk.

Review findings – by level of adjustment

Three of 18 reviews reported effect estimates by level of adjustment (Table 3.14)[4, 5, 15]. In two reviews this was by level of adjustment in the primary studies[5, 15] and in one review this was by adjustment for study characteristics at the meta-analysis stage[4]. White (1999) examined whether primary study adjustment for 'smoking' or blood pressure altered the level of drinking associated with maximum protection, finding no material difference[15]. Di Castelnuovo et al., (2006) investigated incrementally how primary study adjustment for age, 'social status' and 'dietary factors' affected the alcohol-mortality relationship[5]. It was found that incremental adjustment for each of these factors were each associated with a significant changes to the shape of the risk curve. Adjustment for age had the largest effect, approximately halving the level of drinking associated with maximum protection, the magnitude of the relative risk at the point of maximum protection, and the range of drinking associated with significant protection[5]. The inclusion of social status and dietary factors reduced the range of drinking associated with significant protection but did not alter the other two factors. Adjustment also increased the effect estimate for heavy drinking. Stockwell et al., (2016) found that when adjusting for an increasing number of ten study characteristics at the meta-analysis stage (such as adjustment for smoking, adequacy of drinking measure and follow-up time), the association with protection for occasional, low- and medium-volume drinking compared to non-drinking was eliminated, while risk estimates for high- and higher-volume drinking were increased[4]. The level of drinking associated with significant increased risk, > 4 drinks per day or ≥ 45 grams per day, did not change. The selection of the ten study characteristics to include as covariates in the model was derived empirically.

Overall, there is limited evidence that adjustment at the primary study level for age, social status and dietary factors increases effect estimates for heavy drinking and substantially attenuates the observed relationship between alcohol consumption and protection against all-cause mortality (but does not eliminate it entirely), and limited evidence that adjustment for smoking and blood pressure

does not materially alter one aspect of the relationship – the level of drinking associated with maximum protection. Both reviews however were considered at high risk of bias and used non-drinkers as the reference group. As Stockwell et al., (2016) was considered at low risk of bias, there is also good evidence that the association of occasional, low- and medium-volume drinking with lowered risk of all-cause mortality can be accounted for by inter-study characteristics. Further, that when accounting for inter-study characteristics, effect estimates for heavy drinking are increased, and the level of drinking associated with significant increased risk does not change. While non-drinkers were used as the reference group for the level of adjustment analysis, this was accounted for through adjustment for primary study inclusion of former and/or occasional drinkers in the reference group.

Table 3.14. Review findings by level of adjustment.

Review	Reference group	Risk of bias	Strata	Results (95% CI[a])
Di Castelnuovo et al., (2006)[5]	Non-drinkers	High	Unadjusted	Maximum protection at 10 g ethanol/day (RR 0.64 (0.60-0.81)). Protection significant until 68 g/day
			Adjusted at least for age	Maximum protection at 6 g ethanol/day (RR 0.83 (0.82-0.85)). Protection significant until 37 g/day
			Further adjusted for social status	Maximum protection at 9 g ethanol/day (RR 0.82 (0.79-0.85)). Protection significant until 46 g/day
			Further adjusted for dietary factors	Maximum protection at 6 g ethanol/day (RR 0.82 (0.76-0.88)). Protection significant until 30 g/day
				Significant difference in risk curve between strata ($p < 0.04$ in all tests)
Stockwell et al., (2016)[4]	Non-drinkers	Low	Adjustment for study characteristics:	RR occasional drinking[b]:
			None	0.84 (0.79-0.89)
			6 characteristics[c]	0.86 (0.80-0.92)
			10 characteristics[c,d]	0.95 (0.85-1.05)
				RR low-volume drinking[b]:
			None	0.86 (0.83-0.90)
			6 characteristics[c]	0.89 (0.84-0.94)
			10 characteristics[c,d]	0.97 (0.88-1.07)
				RR medium-volume drinking[b]:
			None	0.95 (0.91-1.00)
			6 characteristics[c]	0.98 (0.92-1.04)
			10 characteristics[c,d]	1.07 (0.97-1.18)
				RR high-volume drinking[b]:
			None	1.12 (1.07-1.17)
			6 characteristics[c]	1.13 (1.06-1.20)
			10 characteristics[c,d]	1.24 (1.12-1.37)
				RR higher-volume drinking[b]:
			None	1.29 (1.22-1.36)
			6 characteristics[c]	1.32 (1.23-1.41)
			10 characteristics[c,d]	1.44 (1.30-1.60)
White (1999)[15]	Non-drinkers	High	Adjustment for smoking or blood pressure	The level of alcohol consumption associated with maximum protection did not change by more than 3 units per week[e]

[a]99% CI for Di Castelnuovo et al., (2006). [b]Occasional drinking: Current drinker and ≤ 1 drink/week or < 1.3 g ethanol/day; Low-volume drinking: > 1 drink/week and ≤ 2 drinks/day or ≥ 1.3 and < 25 g/day; Medium-volume drinking: > 2 and ≤ 4 drinks/day or ≥ 25 and < 45 g/day; High-volume drinking: > 4 and ≤ 6 drinks/day or ≥ 45 and < 65 g/day; Higher-volume drinking: > 6 drinks per day or ≥ 65 g/day. [c]Adjustment for sex, age, Caucasian or not, adequacy of drinking measure, former drinker bias and occasional drinker bias. [d]Follow-up years, inclusion or exclusion of participants with ill-health and adjustment for race and smoking. [e]1 unit = 9 g ethanol. CI, Confidence Interval. RR, Relative Risk.

Review findings – by model

Two of 18 reviews reported continuous effect estimates using different models (Table 3.15)[17, 19]. As alcohol consumption may not be associated with all-cause mortality in a linear relationship, it is important to determine the non-linear model that provides the best fit. Bagnardi et al., (2004) compared both the shape and fit the fit of the risk curves derived from linear, quadratic, fractional polynomial (second order) and restricted cubic spline (1 knot at the 25th percentile of alcohol consumption) models[17]. The fractional polynomial and restricted cubic spline models produced similar J-shaped risk curves and had a better fit than the quadratic model, which in turn had a better fit than the linear model. The quadratic model estimated a higher level of drinking associated with maximum protection (20 grams per day) compared to the fractional polynomial (5 grams) or restricted cubic spline (6 grams) models, but also a higher relative risk at the point of maximum protection. The level of drinking associated with significant increased risk was slightly lower when using the latter two models. It was concluded that both fractional polynomials and restricted cubic splines were useful and complementary, and should be used in preference to other models. Jayasekara et al., (2014) compared risk curves using linear and restricted cubic spline (3 knots at the 10th, 50th and 90th percentiles of alcohol consumption) models[19]. Using the linear model, a positive association between alcohol consumption and all-cause mortality was reported. In contrast to Bagnardi et al., (2004), the restricted cubic spline model did not produce a significant protective effect associated with moderate drinking, while still producing a significant increase in risk at intakes greater than 40 grams of ethanol per day. Significant non-linearity was detected (p = 0.02).

Overall, there is limited evidence that fractional polynomial or restricted cubic spline models should be selected over quadratic and linear models when modelling the relationship between alcohol consumption and all-cause mortality. Both reviews were considered at high risk of bias.

Table 3.15. Review findings by model.

Review	Reference group	Risk of bias	Strata	Results
Bagnardi et al., (2004)[17]	Lifetime abstainers	High	Linear	The worst fit of all models
			Quadratic	Better fit than linear model. Maximum protection at 20 g ethanol/day, significant increased risk above 52 g/day
			Fractional polynomial	Better fit than linear/quadratic models. Maximum protection at 5 g ethanol/day, significant increased risk above 44 g/day
			Restricted cubic spline	Better fit than linear/quadratic models. Maximum protection at 6 g ethanol/day, significant increased risk above 46 g/day
Jayasekara et al., (2014)[19]	Non-drinkers	High	Linear	In men, greater alcohol consumption associated with increased risk
			Restricted cubic spline	In men, greater alcohol consumption not significantly associated with all-cause mortality at intakes ≤ 40 g ethanol/day, followed by an increase in risk at intakes > 40 g/day (p non-linearity = 0.02)

Review findings – by primary study methodological quality

One of 18 reviews reported effect estimates by primary study methodological quality (Table 3.16)[4]. Among 13 primary studies with lifetime abstainers as the reference group, Stockwell et al., (2016) assessed the change in alcohol-mortality outcomes when analysing all 13 studies compared to restricting to 6 studies rated as higher quality. The criteria were: 'adequate' measure of mean alcohol consumption, adjustment for smoking status, median age < 60 years at baseline and ≥ 55 years at follow-up. One of the 13 primary studies was also excluded as it was determined to be an outlier (6 of 8 effect estimates in the study were 'extreme outliers')[4]. When restricted to the 6 high quality studies, the RR of all-cause mortality increased for medium- and higher-volume drinking, while there was no association for low- and high-volume drinking in either analysis.

There is limited evidence that primary study methodological quality impacted risk estimates, with lower quality studies potentially causing the risk associated alcohol consumption to be underestimated. While the Stockwell et al., (2016) review examined primary study quality, it did not use a validated scale such as the Newcastle-Ottawa Scale[33]. Although an advantage of the scale used by Stockwell et al., (2016) may be that it was more specific to alcohol consumption than a generic quality scale, it was not clear how the various factors were selected, how the cut-points of 55 and 60 years were selected, or whether other important factors may have been missed. Therefore, this analysis could be replicated using a validated quality assessment scale. Alternatively, the quality assessment scale that is specific to the biases accompanying studies of alcohol consumption used by Stockwell et al., (2016) could be externally validated.

Table 3.16. Review findings by primary study methodological quality.

Review	Reference group	Risk of bias	Strata	Results (95% CI)
Stockwell et al., (2016)[4]	Lifetime abstainers	Low		RR low-volume drinking[a]:
			13 studies	0.90 (0.76-1.06)
			6 higher quality studies	1.04 (0.95-1.15)
				RR medium-volume drinking[a]:
			13 studies	0.95 (0.80-1.13)
			6 higher quality studies	1.29 (1.06-1.56)
				RR high-volume drinking[a]:
			13 studies	1.11 (0.93-1.32)
			6 higher quality studies	1.07 (0.83-1.36)
				RR higher-volume drinking[a]:
			13 studies	1.42 (1.15-1.75)
			6 higher quality studies	1.85 (1.51-2.27)

[a]Low-volume drinking: > 1 drink/week and ≤ 2 drinks/day or ≥ 1.3 and < 25 g/day; Medium-volume drinking: > 2 and ≤ 4 drinks/day or ≥ 25 and < 45 g/day; High-volume drinking: > 4 and ≤ 6 drinks/day or ≥ 45 and < 65 g/day; Higher-volume drinking: > 6 drinks per day or ≥ 65 g/day. CI, Confidence Interval. RR, Relative Risk.

Review findings – by choice of reference group

Five of 18 reviews examined the effect of reference group choice on effect estimates (Table 3.17)[3-5, 15, 16]. All five reviews reported a J-shaped relationship when former drinkers (± occasional drinkers) were included in the reference group. The level of alcohol consumption associated with maximum protection was estimated to be 5 [3] or 8[5] grams per day for all participants, or in a review presenting results stratified by sex and region 2.2 units per week in American women, 7.5 units per week in American men and 13.0 units per week in British men[15]. The relative risk at the point of maximum protection was estimated to be 0.77[5] or 0.81[3] and with significant protection until 40.5[3] or 52[5] grams per day. When using a reference group of lifetime abstainers, three reviews still reported a J-shaped association[5, 15, 16], one reported no significant association[3] and one reported an association only with increased risk[4]. The reviews consistently reported at least an attenuation of the relative risk at the point of maximum protection[3-5]. Of the three reviews to report a J-shaped association, one found no significant difference in the level of drinking associated with maximum protection in men but a higher level of drinking for this point in women[15], another reported an attenuation in the level of drinking associated with maximum protection, the relative risk at this point and the range of drinking associated with protection[5], while the findings of the third review were not directly comparable as the results using the reference group of lifetime abstainers were reported categorically and the results using non-drinkers as the reference group were reported continuously[16]. The review which found no significant association when using a reference group of lifetime abstainers reported that, among primary studies using a reference group of lifetime abstainers, a J-shaped relationship was produced when former and occasional drinkers were combined with lifetime abstainers[3]. Finally, one review also reported an association only with increased risk when using a reference group of occasional drinkers[4].

Reviews reported a significant increased risk at levels of intake > 40 grams per day in men[16], > 20 grams per day in women[16], ≥ 45 grams per day (both sexes)[3], approximately > 70 grams per day (both sexes)[5] or > 4 drinks or ≥ 45 grams per day (both sexes)[4] when using a reference group of

non-drinkers, no increased risk with any level of drinking[3], approximately > 38 grams per day (both sexes)[5] or > 6 drinks or ≥ 65 grams per day (both sexes)[4] when using a reference group of lifetime abstainers and > 2 drinks or ≥ 25 grams per day when using a reference group of occasional drinkers (both sexes)[4]. Among the three reviews reporting the level of drinking associated with increased risk when using a reference group of both lifetime abstainers and of non-drinkers, the differences by choice of reference group were inconsistent. When using a reference group of lifetime abstainers, one reported a lower value[5], one a higher value[4] and one no increased risk with any level of drinking[3]. In these same three reviews, risk estimates for heavy drinking were higher when using a reference group of lifetime abstainers compared to non-drinkers in two reviews[4, 5], and unchanged in one review (although the confidence interval was still consistent with the magnitude of difference in the other two reviews)[3]. In the one review using all three reference groups, risk estimates for heavy drinking were highest when using a reference group of occasional drinkers[4].

Overall, using a reference group of non-drinkers consistently results in a J-shaped relationship between alcohol consumption and all-cause mortality, however the evidence for the shape of the risk relationship is inconsistent when using lifetime abstainers as the reference group. Each review reported a different result, including an unchanged level of drinking associated with maximum protection in men and a higher level in women, an attenuated J-shaped relationship, no significant association and an association only with increased risk. The latter result came from the only review which was considered at low risk of bias. There is however good evidence that using a reference group of lifetime abstainers at least attenuates the relative risk at the point of maximum protection and results in higher risk estimates associated with heavy drinking, but the evidence is inconsistent for whether the level of drinking associated with significant increased risk is altered. There is also good evidence that using a reference group of occasional drinkers results in an association only with increased risk, with the level of drinking associated with significant increased risk lower and risk estimates for heavy drinking higher than when using a reference group of lifetime abstainers or non-drinkers.

Table 3.17. Review findings by choice of reference group.

Review	Risk of bias	Reference group strata	Results (95% CI[a])
Di Castelnuovo et al., (2006)[5]	High	Former and/or light drinkers included	Maximum protection at 8 g ethanol/day (RR 0.77 (0.74-0.80)). Protection significant until 52 g/day. Significant increased risk above ≈ 70 g/day
		Former and/or light drinkers excluded	Maximum protection at 5 g ethanol/day (RR 0.84 (0.82-0.86)). Protection significant until 30 g/day. Significant increased risk above ≈ 38 g/day Significant difference in risk curve between strata ($p < 0.001$)
Fillmore et al., (2006)[3]	High		Continuous analysis:
		All studies	Relationship is significant. Maximum protection (OR 0.81) at 5 g ethanol/day, risk curve crosses OR 1.00 at 40.5 g/day
		No former or occasional drinkers in reference group	Relationship is not significant. (Maximum protection (OR 0.85) at 2 g ethanol/day, risk curve crosses OR 1.00 at 25.6 g/day)
			Categorical analysis:
		No former or occasional drinkers in reference group	OR 0.95 (0.84-1.08) for light drinking[b] OR 0.99 (0.83-1.19) for moderate drinking[b] OR 1.24 (1.00-1.53) for heavy drinking[b] OR 1.18 (1.03-1.36) for former drinking
		Combining former and occasional drinkers with lifetime abstainers	OR 0.91 (0.84-0.99) for light drinking OR 0.95 (0.81-1.11) for moderate drinking OR 1.24 (1.02-1.51) for heavy drinking
Gmel et al., (2003)[16, 31]	High	Continuous analysis with majority of studies including ex-drinkers	J-shaped risk curve for men and women
		Categorical analysis separating ex-drinkers from lifetime abstainers	J-shaped risk curve for men and women Men: RR 0.85 (0.83-0.87) for > 0-10 g ethanol/day RR 0.80 (0.78-0.82) for > 10-20 g/day RR 0.91 (0.89-0.94) for > 20-30 g/day RR 0.96 (0.93-1.00) for > 30-40 g/day RR 1.04 (1.01-1.07) for > 40-70 g/day RR 1.27 (1.23-1.31) for > 70-110 g/day RR 1.46 (1.33-1.60) for > 110 g/day RR 1.21 (1.10-1.32) for ex-drinkers Women: RR 0.87 (0.84-0.89) for > 0-10 g/day RR 1.01 (0.99-1.04) for > 10-30 g/day RR 1.40 (1.34-1.47) for > 30-50 g/day RR 1.43 (1.34-1.53) for > 50 g/day RR 1.44 (1.28-1.61) for ex-drinkers

[a]99% CI for Di Castelnuovo et al., (2006). [b]Light drinking: ≥ 1 drink/month and ≤ 2 drinks/day or ≥ 0.39 and < 25 g/day; Moderate drinking: > 2 and ≤ 4 drinks/day or ≥ 25 and < 45 g/day; Heavy drinking: > 4 drinks/day or ≥ 45 g/day. [c]Low-volume drinking: > 1 drink/week and ≤ 2 drinks/day or ≥ 1.3 and < 25 g/day; Medium-volume drinking: > 2 and ≤ 4 drinks/day or ≥ 25 and < 45 g/day; High-volume drinking: > 4 and ≤ 6 drinks/day or ≥ 45 and < 65 g/day; Higher-volume drinking: > 6 drinks per day or ≥ 65 g/day. [d]1 unit = 9 g ethanol. CI, Confidence Interval. RR, Relative Risk. OR, Odds Ratio.

Table 3.17. (Continued)

Review	Risk of bias	Reference group strata	Results (95% CI[a])
Stockwell et al., (2016)[4]	Low	Non-drinkers (former ± occasional drinkers in reference group)	RR 0.91 (0.83-1.00) for low-volume drinking[c] RR 1.00 (0.91-1.10) for medium-volume drinking[c] RR 1.17 (1.06-1.29) for high-volume drinking[c] RR 1.30 (1.17-1.45) for higher-volume drinking[c]
		Lifetime abstainers (no former or occasional drinkers in reference group)	RR 0.90 (0.76-1.06) for low-volume drinking RR 0.95 (0.80-1.13) for medium-volume drinking RR 1.11 (0.93-1.32) for high-volume drinking RR 1.42 (1.15-1.75) for higher-volume drinking RR 1.31 (1.09-1.57) for former drinking
		Occasional drinkers (≤ 1 drinks/week or < 1.3 g/day)	RR 1.19 (1.12-1.27) for lifetime abstention RR 1.02 (0.95-1.10) for low-volume drinking RR 1.13 (1.05-1.22) for medium-volume drinking RR 1.33 (1.24-1.44) for high-volume drinking RR 1.52 (1.40-1.66) for higher-volume drinking RR 1.45 (1.33-1.59) for former drinking
White (1999)[15]	High		British men:
		Ex-drinkers included	Maximum protection at 13.0 units/week[d]
		Ex-drinkers excluded	Maximum protection at 9.3 units/week
			No significant difference between strata (p = 0.43)
			American men:
		Ex-drinkers included	Maximum protection at 7.5 units/week
		Ex-drinkers excluded	Maximum protection at 8.3 units/week
			No significant difference between strata (p = 0.59)
			American women:
		Ex-drinkers included	Maximum protection at 2.2 units/week
		Ex-drinkers excluded	Maximum protection at 3.7 units/week
			Significant difference between strata (p = 0.005)

Review findings – by evidence of industry funding

One of 18 reviews reported effect estimates by evidence of industry funding[26]. No significant difference was found in effect estimate for drinkers vs. non-drinkers and all-cause mortality by level of concern about industry funding, with a risk ratio of 0.84 (0.78-0.91) in studies with some level of concern and 0.89 (0.83-0.96) in studies with no concern[26]. The limitations of the review include that it was considered at high risk of bias, used a reference group of non-drinkers and did not consider a dose-response relationship. It should also be noted the review excluded primary studies containing participants with pre-existing cardiovascular disease. The evidence for no difference by evidence of industry funding is therefore limited.

Review findings – by other factors

None of the 18 reviews examined the influence of drinking pattern (e.g. drinking frequency, heavy episodic drinking) on risk estimates, nor did any review examine the effect of change in alcohol consumption over time, or whether risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk.

There is a lack of evidence for the effect of these factors on the relationship between alcohol consumption and all-cause mortality.

3.4 – Discussion and Conclusions

In summary, the majority of reviews (13 of 18) reported a U- or J-shaped relationship between alcohol consumption and all-cause mortality in the main analysis, with three reviews finding no significant association with alcohol consumption[3, 22, 23], one review finding a U-shaped relationship in men and no significant association in women[21], and another review finding only an association with increased risk[4] (Table 3.4).

Findings for alcohol consumption and increased risk of all-cause mortality

In the majority of reviews, heavy drinking was associated with increased risk of all-cause mortality. Among meta-analyses of the general population, there is good evidence that the level of drinking associated with significant increased risk ranges from intakes > 4 to > 6 drinks per day or approximately > 38 to ≥ 65 grams per day[3-5, 17, 28]. A relative risk of 1.42 (95% confidence interval: 1.15-1.75) was associated with higher-volume drinking (> 6 drinks per day or ≥ 65 g/day), the highest level of drinking examined in a review considered at low risk of bias and using a reference group of lifetime abstainers[4]. One review reporting no significant association when using a reference group of lifetime abstainers, however the confidence intervals for the heavy drinking effect estimate were consistent with an elevated risk[3]. There is also good evidence that former drinkers have a similar risk of all-cause mortality to heavy drinkers, and that the level of drinking associated with increased risk is lower and the level of risk associated with heavy drinking is higher when using a reference group of occasional drinkers.

It should be noted that these results are similar to findings based on alternative methods of calculating all-cause burden of disease. For example, rather than measuring the association between alcohol consumption and all-cause mortality directly, the Global Burden of Disease Study summed

cause-specific incidence risk curves weighted by disability-adjusted life years to obtain an estimate of all-cause burden of disease[34]. The association was found to be monotonically increasing, with a relative risk of 1.5 at approximately 6 standard drinks (60 grams) per day. This is comparable to the findings of Stockwell et al., (2016) that consumption of > 6 drinks per day (≥ 65 g/day) was associated with an all-cause mortality relative risk of 1.42 (1.15-1.75)[4].

A summary of findings regarding the association between alcohol consumption and increased risk of all-cause mortality is shown in Table 3.18. Overall, there is good evidence that the relationship with increased risk differs by adjustment for primary study characteristics at the review level and by choice of reference group. There is limited evidence that the relationship with increased risk (for at least one of the two outcomes in the table) may differ by population (region or ethnicity), smoking status, follow-up duration, primary study publication date, adjustment at the primary study level, modelling method and primary study methodological quality, and limited evidence that it does not differ when excluding participants with pre-existing cardiovascular disease and by primary study sample size. The evidence is inconsistent regarding sex and age. There is a lack of evidence for differences by the distribution of alcohol consumption in the cohort or population, drinking pattern, change in alcohol consumption over time, measurement of alcohol consumption at single or multiple time points, beverage type and evidence of industry funding. The majority of reviews were considered at high risk of bias and used non-drinkers as the reference group, and the reviews examining subgroups were often inconsistent. There is also a lack of evidence for whether increased risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk. The lack of higher quality reviews may have biased the findings of this review, and therefore the comparisons (i.e. other than those from Stockwell et al., (2016)) should be heeded with caution. For almost all sub-analyses further evidence from high quality reviews and meta-analyses is required to clarify the level of drinking associated with significant increased risk, and the corresponding effect estimates.

Table 3.18. Synthesis of 18 systematic reviews and meta-analyses of the association between alcohol consumption and all-cause mortality: evidence for associations with increased risk in the general population and by sub-analysis.

Sub-analysis	n reviews	Minimum level of drinking associated with significant increased risk	Effect estimate (95% CI) in heavy drinkers
General population	6[3-5, 17, 27, 28]	Ranged from > 4 to > 6 drinks/day or approximately > 38 to ≥ 65 g/day (good evidence)	RR 1.42 (1.15-1.75) for higher-volume drinking[a] (good evidence)
Population subgroups			
Sex	11[4, 5, 13-21]	Evidence inconsistent	Evidence inconsistent
Age	6[3, 4, 15, 16, 18, 22]	Evidence inconsistent	Lack of evidence
Population (region or ethnicity)	6[4, 5, 14, 15, 18, 23]	No difference for North America/Europe/Australia vs. Japan/China/India (good evidence). Lack of evidence for other population comparisons	No difference for North America/Europe/Australia vs. Japan/China/India (good evidence). Lack of evidence for other population comparisons
Smoking status	1[3]	Lack of evidence	Higher in current smokers than non-current smokers (limited evidence)
No pre-existing cardiovascular disease	2[15, 24]	Similar to overall (limited evidence)	Similar to overall (limited evidence)
Distribution of alcohol consumption in cohort or population			
Cohort average alcohol consumption	1[16]	Lack of evidence	Lack of evidence
Cohort SD of alcohol consumption	1[16]	Lack of evidence	Lack of evidence
Cohort proportion of abstainers	1[16]	Lack of evidence	Lack of evidence
Per capita alcohol consumption	1[16]	Lack of evidence	Lack of evidence
Alcohol exposure measurement			
Pattern of drinking	0	Lack of evidence	Lack of evidence
Change in drinking over time	0	Lack of evidence	Lack of evidence
Measurement of alcohol consumption at single or multiple time points	1[19]	Lack of evidence	Lack of evidence
Whether risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk	0	Lack of evidence	Lack of evidence

[a]> 6 drinks per day or ≥ 65 g/day. Each review did not necessarily examine both outcomes. RR, Relative Risk. CI, Confidence Interval. SD, Standard Deviation.

Table 3.18. (Continued)

Sub-analysis	n reviews	Minimum level of drinking associated with significant increased risk	Effect estimate (95% CI) in heavy drinkers
Beverage type	1[25]	Approximately > 105 g/day for wine consumption (limited evidence), lack of evidence for beer and spirit consumption and for differences by beverage type	RR approximately 1.3 at 105 g/day, lack of evidence for beer and spirit consumption and for differences by beverage type
Primary study attributes			
Follow-up duration	2[5, 16]	Lower with longer follow-up duration (limited evidence)	Lack of evidence
Sample size	1[5]	No difference (limited evidence)	No difference (limited evidence)
Year of publication	1[5]	Higher with later publication date (limited evidence)	Higher with earlier publication date (limited evidence)
Level of adjustment (at primary study level)	2[5, 15]	Lack of evidence	Higher with adjustment for age, social status and dietary factors compared to no adjustment (limited evidence)
Level of adjustment (at review level)	1[4]	No difference with adjustment for primary study characteristics (good evidence)	Higher with adjustment for primary study characteristics (good evidence)
Modelling method	2[17, 19]	Lower when using fractional polynomial or restricted cubic spline models compared to quadratic model (limited evidence)	Lower when using fractional polynomial or restricted cubic spline models compared to quadratic model (limited evidence)
Primary study methodological quality	1[4]	Lower in higher quality studies (limited evidence)	Higher in higher quality studies (limited evidence)
Choice of reference group	5[3-5, 15, 16]	Lower when using reference group of occasional drinkers (good evidence). Evidence inconsistent for reference group of lifetime abstainers vs. non-drinkers	Higher when using a reference group of lifetime abstainers vs. non-drinkers, and higher still when using a reference group of occasional drinkers (good evidence)
Evidence of industry funding	1[26]	Lack of evidence	Lack of evidence

Findings for alcohol consumption and decreased risk of all-cause mortality

In reviews and meta-analyses of the general population, the evidence regarding a possible association of moderate drinking with reduced risk of all-cause mortality was inconsistent. Among the four reviews using a reference group of lifetime abstainers, two reported a J-shaped association[5, 17], one no significant association[3] and one only an association with increased risk[4]. The latter review was the only review considered at low risk of bias. Among these four reviews, the reported estimates for the range of drinking associated with decreased risk were either none[3, 4] or < 30 grams per day[5], for the level of drinking associated with maximum protection either none[3, 4] or 5 to 6 grams per day[5, 17], and for the relative risk at the point of maximum protection either 1.00 for lifetime abstention[3, 4] or 0.84 (99% confidence interval: 0.82-0.86) for 5 grams per day[5].

A summary of findings regarding the association between alcohol consumption and decreased risk of all-cause mortality is shown in Table 3.19. There is good evidence that that the relationship with decreased risk is accounted for by adjustment for primary study characteristics at the review level and that the relative risk is at least attenuated when using a reference group of lifetime abstainers instead of non-drinkers and is eliminated when using a reference group of occasional drinkers. There is limited evidence that the relationship with decreased risk may differ (for at least one of the three outcomes in the table) by population (region or ethnicity), the distribution of alcohol consumption in the cohort or population, follow-up duration, primary study publication date, adjustment at the primary study level (age, social status and dietary factors), modelling method and primary study methodological quality, and limited evidence that it does not differ by primary study sample size and adjustment at the primary study level for some other factors (smoking and blood pressure). The evidence is inconsistent regarding sex, age and choice of reference group. There is a lack of evidence for differences by smoking status, the exclusion of participants with pre-existing cardiovascular disease, drinking pattern, change in alcohol consumption over time, measurement of alcohol

consumption at single or multiple time points, beverage type and evidence of industry funding. There is also a lack of evidence for whether decreased risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk. The majority of reviews were considered at high risk of bias and used non-drinkers as the reference group, and the reviews examining subgroups were often inconsistent. For the general population and almost all sub-analyses further evidence from high quality reviews and meta-analyses is required to clarify the level of drinking associated with significant decreased risk, and the corresponding effect estimates.

Table 3.19. Synthesis of 18 systematic reviews and meta-analyses of the association between alcohol consumption and all-cause mortality: evidence for associations with decreased risk in the general population and by sub-analysis.

Sub-analysis	n reviews	Range of drinking associated with significant decreased risk	Level of drinking associated with maximum protection	Effect estimate (95% CI) at point of maximum protection
General population	6[3-5, 17, 27, 28]	No level of drinking protective or < 30 g/day (evidence inconsistent)	0 or 5 to 6 g/day (evidence inconsistent)	1.00 for lifetime abstention or 0.84 (0.82-0.86[a]) for 5 g/day (evidence inconsistent)
Population subgroups				
Sex	11[4, 5, 13-21]	Evidence inconsistent	Evidence inconsistent	Evidence inconsistent
Age	6[3, 4, 15, 16, 18, 22]	Evidence inconsistent	Evidence inconsistent	Evidence inconsistent
Population (region or ethnicity)	6[4, 5, 14, 15, 18, 23]	No difference for North America/Europe/Australia vs. Japan/China/India (good evidence). Smaller in United States vs. Europe for men, with Australia/Japan/China in between; no difference for women (limited evidence). Limited evidence 'mild' drinking not associated with protection in Korean persons. Lack of evidence for other population comparisons	No difference for North America/Europe/Australia vs. Japan/China/India (good evidence). Lower in United States vs. United Kingdom and Europe for men, with Australia/Japan/China in between; no difference for women (limited evidence). Lack of evidence for other population comparisons	No difference for North America/Europe/Australia vs. Japan/China/India (good evidence). Higher in United States vs. Europe for men, with Australia/Japan/China in between; no difference for women (limited evidence). Lack of evidence for other population comparisons

[a]99% confidence interval. Each review did not necessarily examine all three outcomes. RR, Relative Risk. CI, Confidence Interval. SD, Standard Deviation.

Table 3.19. (Continued)

Sub-analysis	n reviews	Range of drinking associated with significant decreased risk	Level of drinking associated with maximum protection	Effect estimate (95% CI) at point of maximum protection
Smoking status	1[3]	Lack of evidence	Lack of evidence	Lack of evidence
No pre-existing cardiovascular disease	2[15, 24]	Lack of evidence	Lack of evidence	Lack of evidence
Distribution of alcohol consumption in cohort or population				
Cohort average alcohol consumption	1[16]	Larger with greater average alcohol consumption in men, no difference in women (limited evidence)	Higher with greater average alcohol consumption in men, no difference in women (limited evidence)	No difference (limited evidence)
Cohort SD of alcohol consumption	1[16]	Larger with greater SD of alcohol consumption (limited evidence)	Higher with greater SD of alcohol consumption (limited evidence)	No difference (limited evidence)
Cohort proportion of abstainers	1[16]	Smaller with greater proportion of abstainers in men, no difference in women (limited evidence)	Lower with greater proportion of abstainers in men, no difference in women (limited evidence)	No difference (limited evidence)
Per capita alcohol consumption	1[16]	Larger with greater per capita alcohol consumption in men, no difference in women (limited evidence)	Higher with greater per capita alcohol consumption in men, no difference in women (limited evidence)	No difference (limited evidence)
Alcohol exposure measurement				
Pattern of drinking	0	Lack of evidence	Lack of evidence	Lack of evidence
Change in drinking over time	0	Lack of evidence	Lack of evidence	Lack of evidence
Measurement of alcohol consumption at single or multiple time points	1[19]	Lack of evidence	Lack of evidence	Lack of evidence
Whether risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk	0	Lack of evidence	Lack of evidence	Lack of evidence
Beverage type	1[25]	< 41 g/day for wine consumption (limited evidence), lack of evidence for beer and spirit consumption and for differences by beverage type	10 g/day for wine consumption (limited evidence), lack of evidence for beer and spirit consumption and for differences by beverage type	RR 0.75 (0.66-0.86) for wine consumption (limited evidence), lack of evidence for beer and spirit consumption and for differences by beverage type
Primary study attributes				
Follow-up duration	2[5, 16]	Smaller with longer follow-up duration (limited evidence)	Evidence inconsistent	Higher with longer follow-up duration (limited evidence)
Sample size	1[5]	No difference (limited evidence)	No difference (limited evidence)	No difference (limited evidence)

Table 3.19. (Continued)

Sub-analysis	n reviews	Range of drinking associated with significant decreased risk	Level of drinking associated with maximum protection	Effect estimate (95% CI) at point of maximum protection
Year of publication	1[5]	Larger with later publication date (limited evidence)	Higher with later publication date (limited evidence)	Lower with later publication date (limited evidence)
Level of adjustment (at primary study level)	2[5, 15]	Larger with adjustment for age, social status and dietary factors compared to no adjustment (limited evidence)	Lower with adjustment for age, social status and dietary factors compared to no adjustment; no difference with adjustment for smoking or blood pressure (limited evidence)	Higher with adjustment for age, social status and dietary factors compared to no adjustment (limited evidence)
Level of adjustment (at review level)	1[4]	No level of drinking protective with adjustment for primary study characteristics (good evidence)	0 g/day with adjustment for primary study characteristics (good evidence)	1.00 for non-drinking with adjustment for primary study characteristics (good evidence)
Modelling method	2[17, 19]	Lack of evidence	Lower when using fractional polynomial or restricted cubic spline models compared to quadratic model (limited evidence)	Lower when using fractional polynomial or restricted cubic spline models compared to quadratic model (limited evidence)
Primary study methodological quality	1[4]	No level of drinking protective among higher quality studies (limited evidence)	0 g/day among higher quality studies (limited evidence)	1.00 for lifetime abstention among higher quality studies (limited evidence)
Choice of reference group	5[3-5, 15, 16]	Evidence inconsistent for reference group of lifetime abstainers vs. non-drinkers. No level of drinking protective when using reference group of occasional drinkers	Evidence inconsistent for reference group of lifetime abstainers vs. non-drinkers. Drinker and ≤ 1 drink/week or > 0 and < 1.3 g/day when using reference group of occasional drinkers	Attenuation of association with protection for reference group of lifetime abstainers vs. non-drinkers (good evidence), evidence inconsistent for whether protection is eliminated. 1.00 for occasional drinking when using reference group of occasional drinkers
Evidence of industry funding	1[26]	Lack of evidence	Lack of evidence	Lack of evidence

Limitations of the systematic reviews and meta-analyses

Review findings overall and by subgroup were often not directly comparable due to differing aims, scope, inclusion criteria, methodological quality, meta-analysis methods and presentation of results. The heterogeneity in aims, scope and inclusion criteria is important, as it has previously been shown that differences in review search strategy and inclusion criteria can lead to differing conclusions[35]. For example, some reviews only included primary studies which also assessed the relationship between alcohol consumption and cardiovascular disease, or which reported risk estimates for both men and women, which may have caused biased and account for some of the differences in review findings. Many reviews also had methodological problems causing them to be considered at high risk of bias, including searching only one electronic database, not specifying search terms, not using at least two reviewers for study selection and/or quality assessment, not performing an assessment of primary study quality and not performing a test of publication bias. Only one of 18 reviews was both considered at low risk of bias and used a reference group of lifetime abstainers, and the results of that review materially differed from other reviews, reporting only a positive association of increased risk with increasing alcohol consumption[4]. The results of the other reviews should therefore be interpreted with caution. Finally, the use of different meta-analysis methods (such as continuous vs. categorical analysis), the use of different cut-points for categorical analyses and the presentation of different result outcomes (e.g. the level of drinking associated with maximum protection vs. the range of drinking associated with significant protection) meant the results of reviews were not directly comparable. This often necessitated the use of more simple comparisons in sub-analyses such as whether the level of risk is higher in one subgroup over another, although an attempt was made to compare more specific outcomes wherever possible.

Aside from the methodological differences and problems of the reviews themselves, each meta-analysis would be expected contain a mixture of studies of high and low quality, with different exclusion criteria and differing methods of measuring alcohol consumption and adjustment for

confounding. For example, in the review with the largest number of primary studies and participants, Stockwell et al., (2016), it was found that of 87 primary studies, 34 made exclusions for baseline disease or poor health while 53 did not, and 65 used a reference group containing former drinkers while 22 did not[4]. Most reviews did not examine primary study methodological quality or these other factors, and this may be another source of bias. Of all reviews, Stockwell et al., (2016) undertook the most comprehensive approach to examining the impact of primary study methodological quality and ten differences in inter-study characteristics (such as adjustment for confounding and inclusion criteria based on disease status), finding that these materially changed risk estimates. When taking these factors into account, the protective association of moderate drinking was eliminated and risk estimates for higher levels of drinking were increased. Primary study methodological heterogeneity therefore biases risk estimates for the general population, and so sub-analysis findings could potentially be biased as well. There is a need however for the quality assessment scale used by Stockwell et al., (2016) to be externally validated, or alternatively, the analysis could be replicated using a validated quality assessment scale.

Strengths and limitations

This systematic review has several strengths, including the use of multiple databases for article extraction to decrease the likelihood that relevant articles would be missed, the use of broad inclusion criteria enabling the examination of as many sub-analysis outcomes as possible and the use of the ROBIS tool and the consideration of reference group to examine results in light of risk of bias. This review also has a number of limitations. Firstly, only one reviewer performed the article extraction, data extraction and review quality appraisal. A second reviewer is required to ensure inter-rater reliability, which would lower the risk of error and potential bias that could result from one reviewer. Secondly, non-English journal articles were excluded, potentially limiting generalizability if there is heterogeneity in the alcohol-risk relationship across population groups.

Finally, as these reviews and meta-analyses are mostly based on cohort studies, the results are vulnerable to selection bias and the possibility of residual confounding by known and unknown factors. To be absolutely certain of the relationship between alcohol consumption and all-cause mortality (or for that matter, any disease) it may be necessary to perform a long-term randomised controlled trial, which has recently been proposed[36, 37]. However ethical and practical concerns have so far precluded the conduct of such a trial[38].

Conclusions

This review has identified 18 systematic reviews and meta-analyses of alcohol consumption and all-cause mortality, most of which were considered at high risk of bias. Almost all reviews considered at high risk of bias and using a reference group including former drinkers reported a J- or U-shaped risk curve, but reviews considered at low risk of bias or using a reference group of lifetime abstainers or occasional drinkers more frequently found no significant relationship or only an association with increased risk. There was no evidence of potential conflicts of interest in any of the reviews. Factors which may influence the alcohol-mortality association include sex, age, population (region or ethnicity), current smoking, the exclusion of participants with pre-existing cardiovascular disease, average cohort alcohol consumption, variability in cohort alcohol consumption, the proportion of non-drinkers in the cohort, per capita alcohol consumption in the population, length of follow-up, primary study year of publication, level of adjustment for confounders, modelling method, primary study methodological quality and choice of reference group. No evidence was found that the risk relationship is influenced by primary study sample size or by evidence of industry funding, however the evidence base for these factors was limited. Evidence was lacking for whether certain populations (e.g. Africa, the Middle East, Latin America), ex-smoking, pattern of drinking (including drinking frequency and heavy episodic drinking, independent of total alcohol consumption), change in alcohol consumption over time, measurement of alcohol consumption at single or multiple time

points, and beverage type influenced the risk relationship. Evidence was also lacking regarding whether risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk. For many of the other sub-analyses examined, the evidence was lacking for specific outcomes of the alcohol-mortality relationship. Unfortunately, for few sub-analyses and outcomes was the level of evidence considered to be 'good', owing to inconsistencies between reviews and the large proportion of reviews considered at high risk of bias or using a reference group including former drinkers.

In conclusion, the evidence base is largely limited, inconsistent or lacking. There is evidence however that the apparent protective effect of moderate drinking is questionable, and may be partly or wholly attributable to biases in primary study design including choice of reference group, inadequate measures of alcohol consumption and differences in adjustment for confounding and inclusion criteria. These same factors may also be responsible for underestimating the harms of higher levels of drinking. There is a need for further well-designed reviews and meta-analyses to confirm the influence of population subgroups, the distribution of alcohol consumption in the cohort or population, measures of alcohol exposure and primary study methodology on the shape of the alcohol-mortality risk curve, with a particular focus on associations between moderate drinking and decreased risk and heavier drinking and increased risk. In the absence of randomised controlled trials, cohort study analyses and meta-analyses must take the identified factors into account when interpreting the effects of alcohol consumption on all-cause mortality. Further, given that the risk relationship may vary by population around the world, there is a need for local Australian data.

The next chapter will outline the 45 and Up Study, a large, Australian prospective study, which was used to investigate the relationship between alcohol consumption and drinking pattern for a number of outcomes including cancer incidence and all-cause and cause-specific mortality. The important methodological factors identified in this and previous chapters were taken into consideration when

planning the analyses, particularly choice of reference group and other cohort study characteristics responsible for inter-study heterogeneity in results.

3.5 – References

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Chapter 4 – Methods: The 45 and Up Study

Chapter summary

This chapter outlines the methods for the remaining chapters and introduces the 45 and Up Study. The questionnaire items available and coding for important variables in the analyses are explained and the distribution of alcohol consumption by each variable is examined.

4.1 – The 45 and Up Study

Study population

The 45 and Up Study is a prospective cohort study of 266,794 people randomly sampled from the general population of New South Wales (NSW) between 2006 and 2009[1]. The majority of participants were sampled in 2008 and the median baseline questionnaire date is February 2008. Participants were randomly sampled from the Medicare Australia database and received a mailed invitation, consent form and self-administered questionnaire. The database contains records for all Australian citizens and permanent residents, along with some temporary residents and refugees. An additional 1.3% of participants joined the cohort without receiving an invitation by voluntarily contacting the study. Persons aged 80 years and over and those living in rural and remote areas were oversampled by a factor of two. The response rate to mailed invitations was estimated to be 18%, representing around 10% of the NSW population in this age group[1]. These proportions imply that over half of the NSW population aged at least 45 years was invited to participate in the study. All participants were aged at least 45 years at completion of the baseline questionnaire. Due to the relatively low response rate and the oversampling of key demographic groups, the study is not

necessarily representative of the population, however a comparison of the 45 and Up Study with the NSW *Population Health Survey* found consistent exposure-outcome relationships between the two studies[2].

Baseline questionnaire

The baseline questionnaire focused on socio-demographic information, health behaviours, health status, medical history and usage of medical services. Copies of the male and female baseline and follow-up questionnaires are available on the study's website[3]. There were three versions of the questionnaire, with changes to some variables[3]. Questionnaire version 1 was answered by 13.9% of participants, version 2 by 1.0% of participants and version 3 by 85.1% of participants. Questions with significant changes that were relevant to this project were those ascertaining daily consumption of red meat and processed meat, bowel screening history, breast screening history, depression, anxiety, asthma and hayfever (version 2 onwards) and physical activity (version 3). How these changes affected coding is explained for each variable in Section 4.2.

Follow-up questionnaire

Participants completed a 5-year follow-up questionnaire that was similar to the baseline questionnaire and was mailed from 2012 to 2016[4]. The first follow-up questionnaire data were available for 142,492 participants (53%). These data were used in Chapter 7, where factors related to quitting alcohol consumption between baseline and follow-up were characterised.

Data linkage and external data sources

The cancer and mortality outcomes quantified in chapters 8 and 9 were captured through record linkage of the 45 and Up Study to population-wide health datasets by the NSW Ministry of Health's Centre for Health Record Linkage (CHeReL). The CHeReL used a best practice approach in privacy preserving record linkage[5] and the open source probabilistic record linkage software Choice Maker[6]. The probabilistic matching process is known to be highly accurate (false-positive and false-

negative rates < 0.4%) and a more detailed description of the linkage process has been described elsewhere[7].

Linkage to the NSW Central Cancer Registry was used for cancer incidence outcome data in Chapter 8. The registry is administered by the NSW Cancer Institute (an agency of the NSW Government) and captures all primary cancers diagnosed in residents of NSW with the exception of non-melanoma skin cancer. Cancer incidence data was available from January 1994 to December 2010. Cancer diagnoses were coded according to the World Health Organisation International Classification of Diseases, version 10[8].

Mortality outcomes used in Chapter 9 were obtained via linkage to the NSW Registry of Births, Deaths and Marriages (RBDM) and the Australian Bureau of Statistics (ABS). Fact of death was captured to December 2014 from the RBDM and cause of death was captured to December 2012 from the ABS. Cause-specific mortality was coded according to the World Health Organisation International Classification of Diseases, version 10.

Ethics and study management

The 45 and Up Study was approved by the University of NSW Human Research Ethics Committee, while ethics approval for this specific project was granted by NSW Population Health Services Research Ethics Committee. The Sax Institute manages the study in partnership with Cancer Council NSW (the major partner), the National Heart Foundation of Australia (NSW Division), NSW Ministry of Health, beyondblue, NSW Government Family & Community Services – Carers, Ageing and Disability Inclusion and the Australian Red Cross Blood Service.

4.2 – Ascertainment of Baseline Covariates

This section outlines the baseline questionnaire items used for analysis. The variables listed are those which are common to several chapters, such as alcohol consumption and factors used for adjustment. All analyses were adjusted for socio-demographic characteristics (sex, age, remoteness, household income, highest level of education, health insurance status, partner status and country of birth). Additional behavioural and health-related factors were used to adjust for disease-specific models where specified. All variables included a missing indicator value for participants with missing data.

Socio-demographic characteristics

Alcohol consumption, cancer incidence, and mortality are known to vary by socio-demographic characteristics. For alcohol consumption in Australia, there is a higher prevalence of drinking at levels associated with risk of long-term harm among men, younger persons, persons living in regional and remote areas, persons with higher socio-economic status, persons who have never married, persons born in Australia and English-speaking countries[9, 10]. For cancer in Australia, there is a higher incidence among men, older persons, persons living in regional and remote areas (but not very remote areas) and persons with lower socio-economic status[11]. Cancer incidence varies by country of birth, with the many immigrant groups having a lower incidence of melanoma, colorectal, lung, breast and prostate cancer and a greater incidence of stomach and liver cancer compared to the Australian-born population[12]. Finally, mortality rates in NSW are higher in men, older persons, persons in living in regional and remote areas, persons with lower socio-economic status, persons born outside of Australia (especially in East, Southeast and South Asia) and Indigenous Australians[13]. Household income, highest level of education and health insurance

status were used as indicators of socio-economic status. It was not possible to access Indigenous status data in the 45 and Up Study.

Sex

The sex variable was provided by the study, and was obtained from Medicare. Sex was coded as a categorical variable with two values: Male; Female. There were no participants with missing data for sex.

Age

Age in years was calculated from two questions: "*What is your date of birth?*" and "*What is today's date?*". Ages ranged from 45.0 to 106.2 years, and the median age was 61.1 years. Age was used either as a continuous variable measured in years, or a categorical variable with five values: ≥ 45 and < 55 years; ≥ 55 and < 65 years; ≥ 65 and < 75 years; ≥ 75 and < 85 years; ≥ 85 years. There were no participants with missing data for age.

Remoteness

Remoteness was calculated from exact residential address and classified using the 2006 Accessibility/Remoteness Index of Australia (ARIA+), which is based on road distances to the nearest service centre[14]. Five categories are derived: Major city; Inner regional; Outer regional; Remote; Very Remote. For the purposes of analysis, participants in 'Remote' and 'Very Remote' areas were pooled to reduce variability. The areas of NSW classified by ARIA+ as major city are Sydney, Newcastle, Wollongong, the Central Coast, Tweed Heads and areas bordering the Australian Capital Territory[15].

Household income

Annual household income was obtained from the question: "*What is your usual yearly HOUSEHOLD income before tax, from all sources? (please include benefits, pensions, superannuation, etc)*". The

nine possible responses were "*less than $5,000 per year*", "*$5,000-$9,999 per year*", "*$10,000-$19,999 per year*", "*$20,000-$29,999 per year*", "*$30,000-$39,999 per year*", "*$40,000-$49,999 per year*", "*$50,000-$69,999 per year*", "*$70,000 or more per year*" and "*I would rather not answer this question*". These responses were collapsed into: < $30,000 per year; ≥ $30,000 and < $ 70,000 per year; ≥ $70,000 per year; "*I would rather not answer this question*" (which also included those with missing/invalid responses). "*I would rather not answer this question*" has been used as a category in previous analyses of the 45 and Up Study[16].

Highest level of education

The question used ascertain educational attainment was: "*What is the highest qualification you have completed?*". The six possible responses were "*No school certificate or other qualifications*", "*School or intermediate certificate (or equivalent)*", "*Higher school or leaving certificate (or equivalent)*", "*Trade/apprenticeship (e.g. hairdresser, chef)*", "*Certificate/diploma (e.g. childcare, technician)*" and "*University degree or higher*".

Health insurance status

Health insurance status was ascertained by: "*Which of the following do you have? (excluding Medicare)*". The five possible responses were "*Private health insurance – with extras*", "*Private health insurance – without extras*", "*Department of Veterans' Affairs white or gold card*", "*Health care concession card*" and "*None of these*".

Partner status

Partner status was defined by two values. That is, participants who responded, "*Single*", "*Widowed*", "*Divorced*" or "*Separated*" to the question, "What best describes your current situation?" were classified as, 1) Not married or living with a partner. Those who responded, "*Married*" or "*De facto/living with a partner* were classified as, 2) Married or living with a partner. Participants were

able to select multiple responses to this question. Therefore, this grouping was chosen due to the potential for living with a partner to influence health behaviours including alcohol consumption.

Country of birth

The questionnaire item, "*In which country were you born?*" had tick boxes for Australia, UK, Ireland, Italy, China, Greece, New Zealand, Germany, Lebanon, Philippines, Netherlands, Vietnam, Malta, Poland and "*other (please specify)*" with a free text space. This variable was coded and cleaned by the study coordinating centre. In analyses where country of birth was used for adjustment, it was collapsed into three values: Australia; Majority English-speaking countries (Canada, Ireland, New Zealand, the United Kingdom (UK) and the United States of America); Majority other language countries (all other countries). This grouping was chosen to divide participants born outside of Australia into two equal groups.

In Chapter 6, where country of birth was a key exposure of interest, country of birth was grouped into 13 regions: Australia; New Zealand; Oceania; East Asia; Southeast Asia; Central and South Asia; UK and Ireland; Western Europe; Eastern and Central Europe; Middle East and North Africa; Sub-Saharan Africa; North America; Central and South America. These regions were based on groupings used in the Global Burden of Disease Study and have been used previously in analyses of 45 and Up Study data[17, 18]. The countries included in each region are listed in Table 4.1. There were no participants born in countries that do not appear on this list. Further detail of participant numbers by country of birth is shown in Table B.1 in Appendix B.

Table 4.1. Region of birth classification.

Region of birth	Country of birth
Australia	Australia, Norfolk Island
New Zealand	New Zealand
Oceania	Cook Islands, Fiji, French Polynesia, Kiribati, Nauru, New Caledonia, Niue, Papua New Guinea, Samoa, Solomon Islands, Tonga, Vanuatu, Wallis and Fortuna
East Asia	China, Hong Kong, Japan, Macau, South Korea, Taiwan
Southeast Asia	Brunei Darussalam, Burma (Myanmar), Cambodia, East Timor, Indonesia, Laos, Malaysia, Philippines, Singapore, Sri Lanka, Thailand, Viet Nam
Central & South Asia	Afghanistan, Armenia, Bangladesh, Georgia, India, Kyrgyz Republic, Mongolia, Nepal, Pakistan
UK & Ireland	Channel Islands, Ireland, Isle of Man, Northern Ireland, Scotland, UK, Wales
Western Europe	Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Gibraltar, Greece, Iceland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland
Eastern & Central Europe	Albania, Belarus, Bosnia Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Moldova, Montenegro, Poland, Republic of Macedonia, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Ukraine, Union of Soviet Socialist Republics, Yugoslavia
Middle East & North Africa	Algeria, Bahrain, Egypt, Gaza Strip & West Bank, Iran, Iraq, Jordan, Lebanon, Libya, Morocco, Syria, Tunisia, Turkey, Yemen
Sub-Saharan Africa	Africa Unspecified, Botswana, Congo, East Africa, Ethiopia, Ghana, Kenya, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Nigeria, Senegal, Seychelles, South Africa, St Helena, Sudan, Tanzania, Uganda, Zambia
North America	Bermuda, Canada, United States
Central & South America	Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Dutch West Indies, Ecuador, El Salvador, Falkland Islands, Guatemala, Guyana, Jamaica, Mexico, Netherlands Antilles, Nicaragua, Panama, Paraguay, Peru, South America Unspecified, St Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela

UK, United Kingdom.

Length of time lived in Australia

The question used to derive length of time lived in Australia was "*What year did you first come to live in Australia for one year or more? (e.g. 1970)*". The questionnaire year was then used to calculate the number of years lived in Australia. Among participants not born in Australia, the median length of time lived in Australia was 39 years. Length of time lived in Australia was coded as a categorical variable with seven values: < 10 years; ≥ 10 and < 20 years; ≥ 20 and < 30 years; ≥ 30 and < 40 years; ≥ 40 years; Born in Australia.

Language spoken at home

The question used for language spoken at home was "*Do you speak a language other than English at home?*" with responses categorised as "*Yes*" or "*No*".

Key behavioural and physical characteristics

Alcohol consumption, cancer incidence, and mortality are known to vary by other lifestyle and health related factors. These factors, and how they are ascertained in the 45 and Up Study baseline questionnaire are detailed here.

Smoking, body mass and physical inactivity are risk factors for cancer[19] and mortality[20], while height has been adjusted for in previous cohort studies examining alcohol consumption and mortality[21-24]. Above-guideline drinking has been associated with a higher prevalence of smoking, obesity and physical inactivity compared to within-guideline drinking[25]. Drinking has been associated with greater height compared to non-drinking[21].

Smoking status and smoking intensity

Smoking status and intensity was included as a covariate in all cancer and mortality analyses, and was ascertained from the questions, "*Have you ever been a regular smoker?*" (*Yes*/*No*), "*How old were you when you started smoking regularly?*", "*Are you a regular smoker now?*" (*Yes*/*No*), "*If No – how old were you when you stopped smoking regularly?*" and "*About how much do you/did you smoke on average each day? (If you are an ex-smoker, how much did you smoke on average when you smoked?)*" with separate responses for 'cigarettes per day' and 'pipes and cigars per day'. Pipes or cigars were counted as one cigarette. The variable provided by the study classified > 200 cigarettes per day and > 100 pipes or cigars per day as invalid. Smoking status and intensity were combined into a single variable with seven values: Never smoker; Ex-smoker (≤ 15 cigarettes/day); Ex-smoker (> 15 cigarettes/day); Ex-smoker (missing cigarettes/day); Current smoker (≤ 15 cigarettes/day); Current smoker (> 15 cigarettes/day); Current smoker (missing cigarettes/day). The cut-point of 15 cigarettes was chosen as this was the median number of cigarettes/day among all ever-smokers. Some analyses used smoking status alone with three values (Never; Ex-smoker; Current) and some used two values (Never; Ever-smoker). Smoking duration was not considered as

this has been shown in the 45 and Up Study to be highly correlated with age, due to little variation in age commenced smoking[26]. When performing interaction tests and stratifications by smoking status, never-smoking vs. ever-smoking was used due to the small proportion of current smokers.

Height

Height was included as a covariate in the mortality analyses and was ascertained by the question, "*How tall are you without shoes (please give to the nearest cm or inch)*" with possible responses in cm or feet and inches. A variable provided by the study already had all heights converted to cm. Height was coded as a categorical variable with six values: Male, < 175 cm; Male, ≥ 175, < 180 cm; Male, ≥ 180 cm; Female, < 160 cm; Female, ≥ 160, < 165 cm; Female, ≥ 165 cm. These cut-points were chosen to divide each sex into approximate tertiles of height.

Body mass index

Body mass index (BMI) was included as a covariate in all cancer and mortality analyses. BMI was provided by the study, and the two questions used for its calculation were, "*How tall are you without shoes? (please give to the nearest cm or inch)*" with possible responses in cm or feet and inches and, "*About how much do you weigh?*" with possible responses in kg or stone and pounds. BMI ranged from 9.1 to 50.0 kg/m^2, and the median BMI was 26.3 kg/m^2. The variable provided by the study classified a height < 55 cm or > 240 cm as invalid, a weight < 35 kg or > 270 kg as invalid, and a BMI < 9 or > 50 kg/m^2 as invalid. BMI was coded according to the classifications used by the World Health Organisation: Underweight (BMI < 18.5 kg/m^2); Normal range (BMI ≥ 18.5 and < 25 kg/m^2); Overweight (BMI ≥ 25 and < 30 kg/m^2); Obese (BMI ≥ 30 kg/m^2). These cut-points were chosen to correspond with the World Health Organisation international BMI classification[27]. When performing interaction tests and stratifications by BMI, normal range vs. overweight or obese was used.

Physical activity

Physical activity was included as a covariate in all cancer and mortality analyses. The two questions used to ascertain physical activity were, "*How many TIMES did you do each of these activities LAST WEEK? (put "0" if you did not do this activity) …Walking continuously, for at least 10 minutes (for recreation or exercise or to get to or from places) …Vigorous physical activity (that made you breathe harder or puff and pant, like jogging, cycling, aerobics, competitive tennis, but not household chores or gardening) …Moderate physical activity (like gentle swimming, social tennis, vigorous gardening or work around the house)*" and "*If you add up all the time you spent doing each activity LAST WEEK, how much time did you spend ALTOGETHER doing each type of activity?*" for the same three sets of activities as the first question. Time spent in vigorous physical activity was given twice the weighting of lower intensity physical activity, as per the Active Australia survey[28]. Earlier versions of the questionnaire (versions 1 and 2) used different descriptions for each type of physical activity. For walking, "*Walking continuously, for at least 10 minutes*" was instead "*Walking briskly*". For moderate physical activity, the examples were instead "*like social tennis, golf, gentle swimming, vigorous gardening or work around the house*". For vigorous physical activity, the description was instead "*Vigorous leisure activities (that made you breathe harder or puff and pant, like aerobics, vigorous sport, cycling, swimming, running)*". Met-adjusted physical activity time ranged from 0 to 21,600 minutes per week, and the median was 420 minutes per week. Met-adjusted physical activity time > 21,600 minutes per week was classified as invalid. Physical activity time was categorised in line with the Australian physical activity guidelines[29]: Inactive (0 minutes/week); Insufficient (< 150 minutes/week); Sufficient (≥ 150 and < 300 minutes/week); High (≥ 300 minutes/week).

Weekly number of sessions of physical activity ranged from 0 to 1300, and the median was 8 sessions. Weekly number of sessions > 700 for any of the three types of physical activity was classified as invalid. Number of sessions of physical activity was used to calculate the Chronic Disease Risk Index examined in Chapter 6.

Sun exposure

Sun exposure is a risk factor for melanoma, while darker skin tone is associated with lower risk[30]. Alcohol consumption has been associated with outdoor leisure activities in Western countries[31]. Time spent outdoors was used as an indicator of sun exposure and skin tone as an indicator of susceptibility to harm from sun exposure. Time spent outdoors and skin tone were included as covariates in models where melanoma, non-alcohol-related cancer and total cancer were the outcomes.

Time spent outdoors

The questionnaire item was, "*About how many hours a DAY would you usually spend outdoors on a weekday and on the weekend?*" with separate responses for 'weekday' and 'weekend'. A weighted average (a weighting of 5 for weekday and 2 for weekend) was calculated to determine the average hours spent outdoors per day. Time spent outdoors ranged from 0 to 24 hours per day with a median of 2.86 hours per day. Time spent outdoors > 24 hours per day was classified as invalid. Time spent outdoors was coded as a categorical variable with four values: < 2 hours per day; ≥ 2 and < 4 hours per day; ≥ 4 and < 6 hours per day; ≥ 6 hours per day. The cut-points were chosen to dive the cohort into approximate quartiles.

Skin tone

The question used for skin tone was, "*What best describes the colour of the skin on the inside of your upper arm, that is your skin colour without any tanning?*" with the possible responses of "*Very fair*", "*Fair*", "*Light olive*", "*Dark olive*", "*Brown*", "*Black*". Skin tone was coded as a categorical variable with three values: Fair; Olive; Brown or black.

Dietary intake

Low fruit, vegetable, fibre consumption and greater red and processed meat consumption are risk factors for cancer[19, 32], and these variables have been adjusted for in a previous cohort study examining alcohol consumption and mortality[22]. Compared to never-drinking, drinking has been associated with lower fruit and vegetable consumption and with greater fibre, red meat and processed meat consumption[22]. In men, heavy drinking has also been associated with greater fruit, vegetable, red meat and processed meat consumption compared to light to moderate drinking, while in women an inverse association has been reported[22]. All dietary variables were adjusted for in the mortality analyses. The selection of dietary factors for adjustment for each cancer type in the cancer analysis was based on the World Cancer Research Fund Continuous Update Project[32].

Fruit consumption

The question used to ascertain fruit consumption was, "*About how many serves of fruit or glasses of fruit juice do you usually have each day? A serve is 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces (put "0" if you eat less than one serve a day)*" with responses for 'fruit' and 'fruit juice'. There was also a checkbox for "*I don't eat fruit*". In most analyses, fruit juice was excluded from the number of serves of fruit per day (fruit juice was only included in Chapter 6 for consistency with the Chronic Disease Risk Index). This is because the Australian dietary guidelines recommend against consuming fruit juice[33]. Serves of fruit per day ranged from 0 to 16, with a median of 2. Serves of fruit > 16 per day were classified as invalid. Fruit consumption was coded as a categorical variable with three values: < 1 serve per day; ≥ 1 and < 2 serves per day; ≥ 2 serves per day. The cut-point of 2 serves per day was chosen to correspond with the Australian dietary guideline for fruit consumption[33].

Vegetable consumption

Daily vegetable consumption was ascertained by the question, "*About how many serves of vegetables do you usually eat each day? A serve is half a cup of cooked vegetables or one cup of salad (please include potatoes and put "0" if less than one a day)*" with responses for 'cooked' and 'raw'/'salad' vegetables. There was also a checkbox for "*I don't eat vegetables*". Serves of vegetables per day ranged from 0 to 32, with a median of 3. Serves of raw or cooked vegetables > 16 per day were classified as invalid. Vegetable consumption was coded as a categorical variable with three values: < 3 serves per day; ≥ 3 and < 5 serves per day; ≥ 5 serves per day. The cut-point of 5 serves per day was chosen to correspond with the Australian dietary guideline for vegetable consumption[33]. The cut-point of 3 serves per day was chosen to divide the remaining vegetable consumers into two equal groups.

Fibre intake

The question used for fibre intake was, "*About how many of the following do you usually eat: slices or pieces of brown/wholemeal bread each week (also include multigrain, rye bread, etc.) … bowls of breakfast cereal each week*" with separate responses for 'bread' and 'breakfast cereal'. These two responses were summed to create a proxy for fibre intake. Serves of fibre per week ranged from 0 to 152, with a median of 14. Serves of breakfast cereal and bread > 45 and > 140 per week respectively were classified as invalid. Fibre intake was coded as a categorical variable with four values: < 7 serves per week; ≥ 7 and < 14 serves per week; ≥ 14 and < 21 serves per week; ≥ 21 serves per week. The cut-points were chosen to correspond with serves per day.

Red meat consumption

The question used for red meat consumption was "*About how many times each week do you eat: (please count all meals and snacks, put '0' if never eaten or eaten less than once a week) … beef, lamb or pork*". An earlier version of the questionnaire (version 1) asked "*… red meat*" rather than "*…*

beef, lamb or pork". There was also the question "*Please put a cross in the box if you NEVER eat: red meat … pork ham … any meat*". Number of times eating red meat per week ranged from 0 to 50, with a median of 3. Times eating red meat > 50 per week was classified as invalid. Red meat consumption was coded as a categorical variable with four values: 0 times per week; > 0 and ≤ 2 times per week; > 2 and ≤ 5 times per week; > 5 times per week. Although the Australian dietary guidelines recommend a maximum of 7 serves of red meat per week[34], only a small number of participants (3%) exceeded this. Therefore a cut-point of 5 serves per week was used so that the highest level of consumption group had a larger number of participants (11%). The cut-point of 2 was chosen to divide the remaining red meat consumers as close as possible into two equal-sized groups. It should be noted that the question referred to times consumed rather than number of serves, and no guide to serving size was provided.

Processed meat consumption

Weekly consumption of processed meat was ascertained by the question, "*About how many times each week do you eat: (please count all meals and snacks. put '0' if never eaten or eaten less than once a week) … processed meat (include bacon, sausages, salami, devon, burgers, etc)*". An earlier version of the questionnaire (version 1) did not include "*bacon*" as an example. There was also the question "*Please put a cross in the box if you NEVER eat: any meat*". Number of times eating processed meat per week ranged from 0 to 50, with a median of 1. Times eating processed meat > 50 per week was classified as invalid. Processed meat consumption was coded as a categorical variable with four values: 0 times per week; > 0 and ≤ 1 times per week; > 1 and ≤ 2 times per week; > 2 times per week. The cut-points were chosen to divide the cohort into approximate quartiles. It should be noted that the question referred to times consumed rather than number of serves, and no guide to serving size was provided.

Female reproductive characteristics

For women, low parity, first pregnancy at a later age, not breastfeeding, menopausal status, hormone replacement therapy (HRT) use and hormonal contraceptive use are risk factors for cancer[19, 32, 35]. Parity, menopausal status and HRT use have been adjusted for in previous cohort studies examining alcohol consumption and mortality[21, 22]. Drinking has been associated with a lower prevalence of ever breastfeeding and a greater prevalence of nulliparity, HRT use and hormonal contraceptive use[21, 22, 36, 37]. In different analyses of the European Prospective Investigation into Cancer and Nutrition study, drinking has been associated with a greater prevalence of pre-menopausal status[22] and a lower prevalence of post-menopausal status[21], but in one analysis had a U-shaped associated with post-menopausal status[37]. All female reproductive characteristics were adjusted for in the cancer analyses where cancers of the breast, endometrium and ovary, alcohol-related cancer, non-alcohol-related cancer and total cancer were the outcomes. In addition, hormonal contraceptive use and HRT use were included in the model for cancers of the liver and colorectum respectively. Parity, menopausal status and HRT use were adjusted for in the mortality analyses.

Parity and age at first birth

The two questions used to ascertain parity and age at first birth were, "*How many children have you given birth to? (please include stillbirths but do not include miscarriages, please write "0" if you have not had any children)*" and "*How old were you when you gave birth to your FIRST child?*". Number of children ranged from 0 to 20, with a median of 2. Number of children > 20 was classified as invalid. Parity and age at first birth was combined into a categorical variable with eight values: No children; 1 child, < 25 years; 1 child, ≥ 25 years; 2 children, < 25 years; 2 children, ≥ 25 years; ≥ 3 children, < 25 years; ≥ 3 children, ≥ 25 years; Male indicator. The cut-point of 25 years was chosen as this was the median age at first birth. In some analyses only parity was used. Parity was categorised with five levels: No children; 1 child; 2 children; ≥ 3 children; Male indicator.

Breastfeeding time

Breastfeeding was ascertained by the question, "*For how many months, in total, have you breastfed? (please add together all the time you spent breastfeeding all of your children; put "0" if you never breastfed)*". Months breastfed ranged from 0 to 400, with a median of 8. Months breastfed > 400 was classified as invalid. Breastfeeding time was coded as a categorical variable with five values: Never breastfed; > 0 and ≤ 12 months; > 12 and ≤ 24 months; > 24 months; Male indicator. The cut-points were chosen to divide the cohort into approximate quartiles.

Menopausal status

The question used for menopausal status was, "*Have you been through menopause?*" with the possible responses of "*No*", "*Not sure (because hysterectomy, taking HRT, etc.)*", "*My periods have become irregular*" and "*Yes*". Menopausal status was coded as a categorical variable with four values: Pre-menopausal; Irregular periods; Post-menopausal; Male indicator.

Hormonal contraceptive use

The question used for hormonal contraceptive use was, "*Have you ever used the pill or other hormonal contraceptives? (e.g. the combined pill, mini pill, contraceptive implant or injections*)" (*Yes*/*No*). Hormonal contraceptive use was coded as a categorical variable with three values: Never used; Ever used; Male indicator.

Hormone replacement therapy use

The two questions used for hormone replacement therapy use were, "*Have you ever used hormone replacement therapy (HRT)?*" and "*Are you currently taking HRT?*", (*Yes*/*No*). Hormone replacement therapy use was coded as a categorical variable with four values: Never used; Formerly used; Current user; Male indicator. When performing interaction tests by HRT use, never-used HRT vs. ever-used HRT was used.

Medical and health-related factors

Cancer screening history was adjusted for in the cancer analysis as it has the potential to bias estimates of effect for alcohol consumption and cancer risk[38]. Moderate drinking has been associated with increased cancer screening compared to non-drinking[38]. Aspirin use is associated with lower risk of oesophageal and colorectal cancer[39]. Drinking has a U-shaped relationship with aspirin use[40].

Self-rated overall health and physical functioning score were not adjusted for in the analyses, but were important exposure variables in the drinking cessation analysis and their restriction was considered as a sensitivity test to examine possible bias from the 'sick-quitter effect'.

Bowel screening history

Bowel screening history was included as a covariate in models where colorectum cancer, alcohol-related cancer and total cancer were the outcomes. The two questions used for bowel screening history were, "*Have you ever been screened for colorectal (bowel) cancer?*" (*Yes*/*No*) and, "*What year did you have the most recent one of these tests? (e.g. 2005)*". The questionnaire year was then used to calculate the number of years since last bowel screen. An earlier version of the questionnaire (version 1) asked "*about how many years ago was the most recent of these tests?*" rather than the year of most recent test. Bowel screening history categorised into three values: Not in the last 10 years; Yes, ≥ 2 and ≤ 10 years ago; Yes, < 2 years ago. The cut-point of 2 years was chosen to divide screened participants into two equal groups.

Breast screening history

Breast screening history was included as a covariate in models where breast cancer, alcohol-related cancer and total cancer were the outcomes. The two questions used for breast screening history were, "*Have you ever been for a breast screening mammogram?*" (*Yes*/*No*) and, "*If Yes, what year did you have your last mammogram? (e.g. 2005)*". The questionnaire year was then used to calculate

the number of years since last breast screen. An earlier version of the questionnaire (version 1) asked "*about how many years ago was your last mammogram?*" rather than the year of last mammogram. Breast screening history was categorised into four values: Not in the last 10 years; Yes, ≥ 2 and ≤ 10 years ago; Yes, < 2 years ago; Male indicator. The cut-point of 2 years was chosen to divide screened participants into two equal groups.

Prostate specific antigen (PSA) test use

PSA test use was included as a covariate in models where prostate cancer, non-alcohol-related cancer and total cancer were the outcomes. PSA test use was captured by the questions, "*Have you ever had a blood test ordered by your doctor to check for prostate disease? (PSA test)*" (*Yes*/*No*) and, "*How many times have you had a PSA test altogether?*". PSA test use was categorised into five values: Never; Yes, 1-3 times; Yes, > 3 times; Yes, times missing; Female indicator. The cut-point of 3 times was chosen to divide the tested participants into two equal groups.

Aspirin use

Aspirin use was included as a covariate in models where cancers of the oesophagus and colorectum, alcohol-related cancer and total cancer were the outcomes. Aspirin use was ascertained by the question, "*Have you taken any medications, vitamins or supplements for most of the last 4 weeks, including HRT and the pill?*" with checkboxes for "*aspirin for the heart*" and "*aspirin for other reasons*". If a participant checked either box they were classified as an aspirin user (No; Yes).

Self-rated overall health

Self-rated overall health was used as an exposure in the drinking cessation analysis and was ascertained by the question, "*In general, how would you rate your overall health?*" with the possible responses of "*Excellent*", "*Very good*", "*Good*", "*Fair*", "*Poor*". It has been reported that self-rated overall health is a valid and reliable measure of health status and is independently associated with mortality[41]. Self-rated overall health was coded as a categorical variable with two values:

Excellent, very good, good or fair; Poor. A restriction to fair or better health was considered as a sensitivity to test examine possible bias from the 'sick-quitter effect'.

Physical functioning score

Physical functioning score was used as an exposure in the drinking cessation analysis, and restriction to a score of ≥ 50% as a sensitivity test in the cancer and mortality analyses, and was ascertained by the Medical Outcomes Study Physical Functioning scale (MOS-PF) was used[42, 43]. Studies of the validity and reliability of the MOS-PF have found mixed results[44]. The question used was "*Does your health now LIMIT YOU in any of the following activities?"* with the possible responses of "*Yes, limited a lot*", "*Yes, limited a little*" and "*No, not limited at all*". The ten activities were:

- "*VIGOROUS activities (e.g. running, strenuous sports)*
- *MODERATE activities (e.g. pushing a vacuum cleaner, playing golf)*
- *Lifting or carrying shopping*
- *Climbing several flights of stairs*
- *Climbing one flight of stairs*
- *Walking one kilometre*
- *Walking half a kilometre*
- *Walking 100 metres*
- *Bending, kneeling or stooping*
- *Bathing or dressing yourself*'

Participants were assigned a physical functioning score between 0 and 100%, with 10 percentage points given for each response of "*No, not limited at all*", 5 points for each response of "*Yes, limited a little*" and 0 points for each response of "*Yes, limited a lot*". Physical functioning score was coded as a categorical variable with two values: ≥ 50%; < 50%. 17,714 participants (6.6%) were missing a response for one or more activities, but could still be allocated to one of the two groups with

certainty. The cut-point of < 50% was chosen to represent low physical functioning score, as this corresponded to an average response of greater than "*a little*" limitation.

4.3 – Ascertainment of Alcohol Consumption and Distribution by Covariates at Baseline in the 45 and Up Study

Ascertainment of alcohol consumption

Total alcohol consumption

The question used for total alcohol consumption was "*About how many alcoholic drinks do you have each week? One drink = a glass of wine, middy of beer or nip of spirits (put "0" if you do not drink, or have less than one drink each week)*". Total alcohol consumption ranged from 0 to 140 drinks/week, and the median was 4 drinks/week. The variable provided by the study classified > 140 drinks/week as invalid. In analyses were alcohol consumption was the key exposure, participants with missing alcohol consumption data were excluded.

It should be noted that the 45 and Up Study did not include a category for former drinking, as the question grouped all participants consuming less than one drink per week together without distinction. This was unfortunate as only very light drinkers could be used as a reference group rather than lifetime abstainers, and the effects of lifetime abstention, former drinking and occasional drinking (less than one drink per week) could not be estimated. The questions available in the 45 and Up Study were also much less comprehensive than the questions used in the 'gold standard' methods for measuring alcohol consumption described in Chapter 1. Therefore alcohol consumption in the 45 and Up Study was likely to have been underreported due to a lack of prompts regarding frequency of various quantities of intake, beverage types and the settings in which alcohol is consumed.

Drinks per week was analysed as both a categorical variable and a continuous variable. For analyses where alcohol consumption was reported as a categorical variable, there were six levels:

1. Non-drinker (< 1 drink/week)
2. ≥ 1 and ≤ 3.5 drinks/week (The cut-point of 3.5 drinks/week was chosen as it corresponds to 0.5 drinks/day which has been described as the upper limit of 'very light drinking'[45])
3. > 3.5 and ≤ 7 drinks/week
4. > 7 and ≤ 14 drinks/week
5. > 14 and ≤ 28 drinks/week (The cut-points of 14 and 28 drinks/week were chosen because they correspond with the Australian alcohol guidelines to minimise risk of long-term harm (≤ 2 drinks/day) and short-term harm (≤ 4 drinks/day) from drinking respectively[46])
6. > 28 drinks/week

Very light drinkers (≥ 1 and ≤ 3.5 drinks/week) were used as the reference group. The median quantity of alcohol consumption in this group was 2 drinks/week. A test for trend (p_{trend}) was also calculated for these categories excluding non-drinkers, using the median alcohol consumption in each group.

The non-drinking group used in analyses is a mix of three distinct drinking status groups: lifetime abstainers, former drinkers, and occasional drinkers (who consume less than one alcoholic drink per week). The questionnaire item did not allow these three groups to be distinguished, so the group is referred to as 'non-drinkers (< 1 drink/week)' in the analyses. The proportion of each, however, may be similar to the background population. That is, a 2007 representative survey of alcohol consumption estimated that of Australians aged 50-59 years consuming alcohol 'less than weekly', 68% were occasional drinkers, 16% former drinkers and 16% lifetime abstainers for persons, while for those aged ≥ 60 years, 50% were occasional drinkers, 25% former drinkers and 25% lifetime abstainers for persons [47]. These proportions for occasional and former drinkers were slightly higher in men than in women, while the lifetime abstainer proportion was lower in men. It should be noted that the relative proportions of each of these groups comprising 'non-drinkers' in the 45 and Up Study may differ from the background population due to the 18% response rate.

Total alcohol consumption in the cohort by sex is shown in Figure 4.1. Overall, 81,187 (32.7%) were non-drinkers at baseline, and 10,215 (3.8%) reported consuming more than 28 drinks per week. A higher proportion of women than men were non-drinkers, while a higher proportion of men were heavier drinkers.

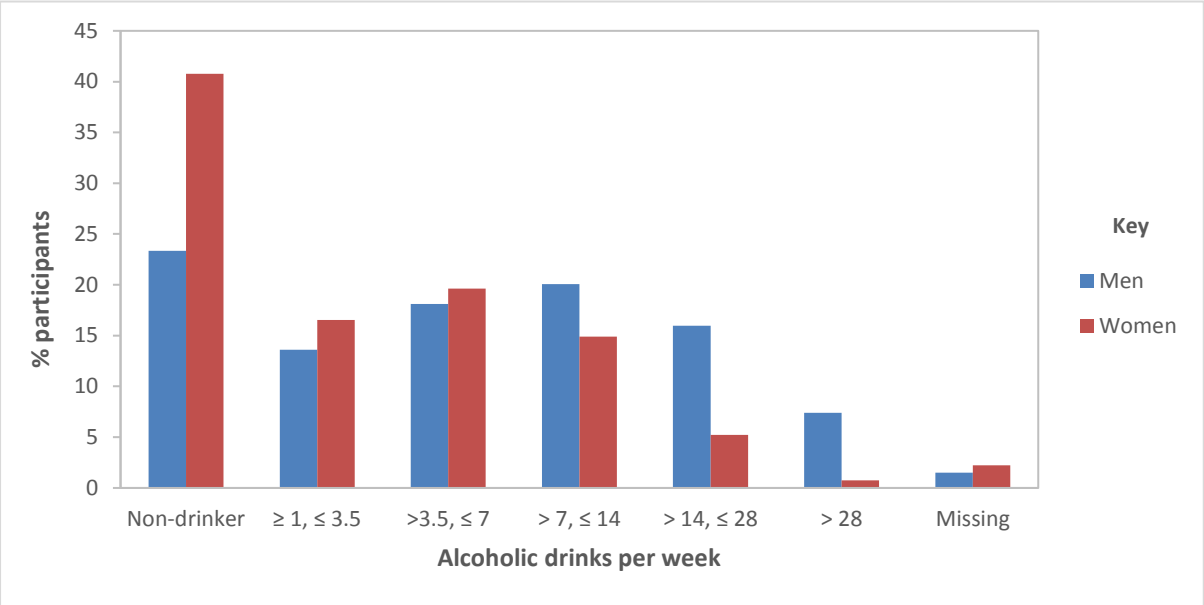

Figure 4.1. Total alcohol consumption at baseline by sex in the 45 and Up Study (2006-2009), New South Wales, Australia. Non-drinker: < 1 alcoholic drink per week.

Frequency of alcohol consumption

The drinking pattern variables were based on the methods used in recent analyses of the Nurses' Health Study and the Health Professionals Follow-up Study[48, 49]. These analyses both examined, separately, the influence of frequency of alcohol consumption and highest number of drinks consumed in a typical month on cancer risk, before and after adjusting for total alcohol consumption as a categorical variable.

The question used for frequency of alcohol consumption (drinking-days per week) was, "*On how many days each week do you usually drink alcohol?*". Among drinkers, the median was five drinking-days per week. Drinking frequency was coded as a categorical variable with four values: 1-2

days/week; 3-5 days/week; 6-7 days/week; Non-drinker. Analyses of drinking frequency used '1-2 days/week' as the reference group and non-drinkers were excluded. The median total alcohol consumption in the reference group was 2 drinks/week. A p_{trend} for these categorical variables was also calculated, excluding non-drinkers. The effects of drinking frequency on risk were reported both with and without an adjustment for total alcohol consumption as a log-linear continuous variable. Adjusting for total alcohol consumption provided an estimate of the independent effect of drinking frequency on risk. Specifically, whether daily or near-daily drinking is associated with a lower risk of harm than consuming the same total quantity of alcohol but over fewer occasions.

Frequency of alcohol consumption by sex is shown in Figure 4.2. A higher proportion of men than women consumed alcohol 6 or 7 days per week.

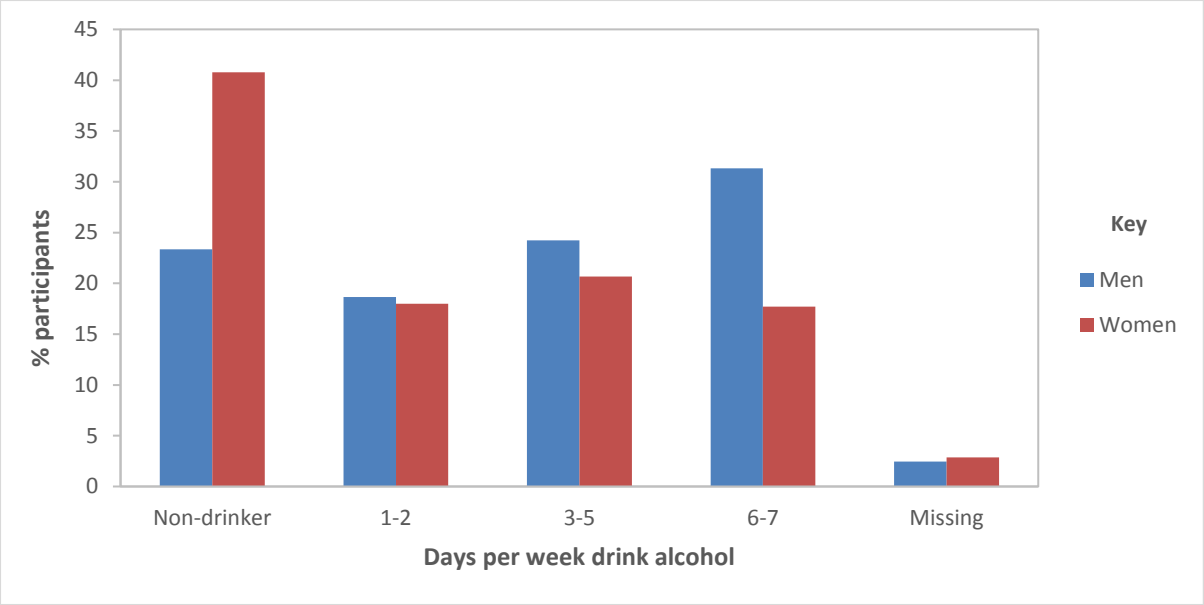

Figure 4.2. Frequency of alcohol consumption at baseline by sex in the 45 and Up Study (2006-2009), New South Wales, Australia. Non-drinker: < 1 alcoholic drink per week.

Drinks per drinking-day

The drinks per drinking-day variable was used rather than highest number of drinks consumed in a typical month due to the questions available in the 45 and Up Study questionnaire. This was

calculated as the average number of drinks consumed per day by dividing the number of drinks consumed per week by the number of drinking-days per week. This variable was used to examine whether there is an independent effect of drinks per drinking-day on harm beyond the effect of total alcohol consumption. The median was 2 drinks per day (Q1-Q3; 1-3). Drinks per drinking-day was coded as a categorical variable with four levels: ≤ 2 drinks per day; > 2 and ≤ 4 drinks per day; > 4 drinks per day; Non-drinker. The cut-points of 2 and 4 drinks per day were chosen because they correspond with the Australian alcohol guidelines to minimise risk of long-term harm and short-term harm from drinking respectively[46]. The cut-point of 4 is similar to the United States definition of heavy episodic drinking of, ≥ 5 drinks per occasion in men and ≥ 4 drinks in women (at least one day per month)[50]. For the purpose of analysis, '≤ 2 drinks per drinking-day' was assigned as the reference group and non-drinkers were excluded. The median total alcohol consumption in the reference group was 5 drinks/week. A p_{trend} was also calculated excluding non-drinkers. The analysis was performed both unadjusted and adjusted for total alcohol consumption as a log-linear continuous variable.

It should be noted that it was not possible to replicate the exact definition of the alcohol guidelines (≤ 2 and ≤ 4 drinks on *any* day of drinking) as only mean drinks per drinking-day could be calculated. In addition, due to the use of mean drinks per drinking-day, some participants who were in fact heavy episodic drinkers will have been grouped with less intense drinkers, potentially biasing results towards the null. For example, a participant consuming alcohol 2 days per week, with 5 drinks on one day and 1 on the other, would have been grouped with a participant consuming alcohol 2 days per week, with 3 drinks on both days. It is possible that the risk profile of these two participants differs but it was not possible to differentiate between them. If heavy episodic drinking was independently associated with increased risk of an outcome, averaging the total number of drinks across days of drinking may therefore result in risk estimates for the drinks per drinking-day variable to be underestimated. Finally, this variable only accounts for participants who usually consume at least one alcoholic drink per week, meaning that participants who engage in heavy episodic drinking

less frequently than once per week may have been excluded (e.g. once per month, as has been captured previously[49]). However, a possible advantage of the use of mean drinks per drinking-day may be that it is more representative of a participant's usual exposure to alcohol than highest number of drinks consumed in one day over a period of time.

Drinks per drinking-day by sex is shown in Figure 4.3. Men consumed more alcohol per drinking-day than women.

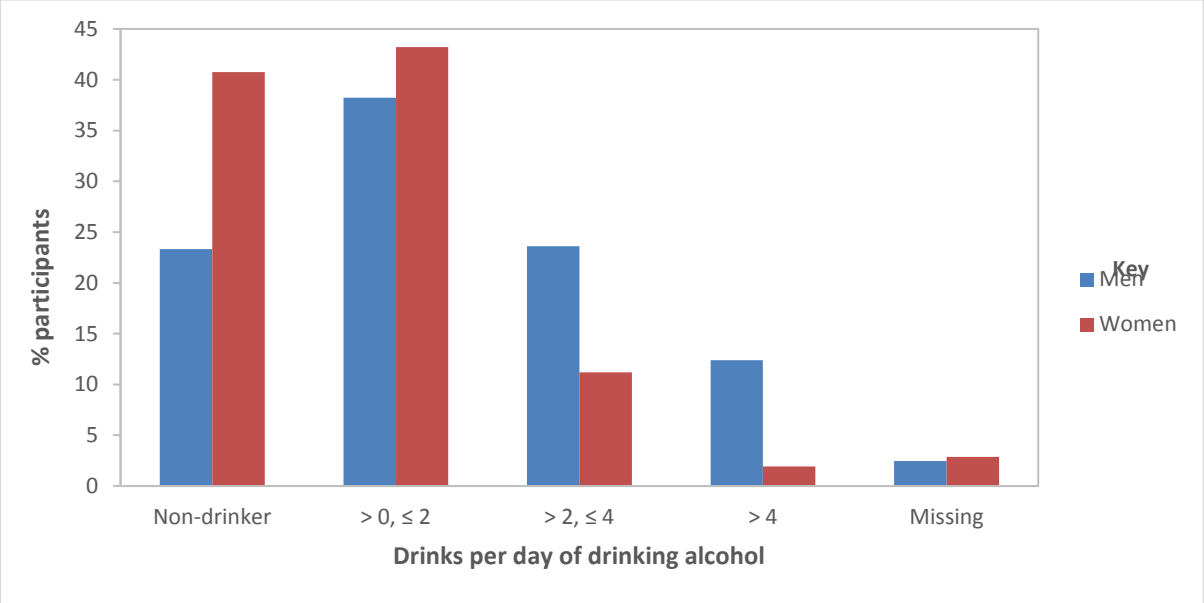

Figure 4.3. Drinks per drinking-day at baseline by sex in the 45 and Up Study (2006-2009), New South Wales, Australia. Non-drinker: < 1 alcoholic drink per week.

Drinking pattern

The three categories of frequency of alcohol consumption and three categories of drinks per drinking-day were combined to create a novel nine-category drinking pattern variable (see Table 4.2). The purpose of this variable was to examine the risks associated with more specific drinking patterns than those estimated by drinking frequency and drinks per drinking-day alone. This is necessary as there may be an interaction between drinking frequency and drinks per drinking-day.

Further, greater drinking frequency has been reported to be inversely related to both drinks per drinking-day and the proportion of days with heavy episodic drinking [51], and therefore drinking frequency and drinks per drinking-day could potentially confound the effect of each other. It should also be noted that the drinks per drinking-day variable includes regular heavy drinkers as well as heavy episodic drinkers – combining the drinking frequency and heavy episodic drinking variables enables these groups to be examined separately. The three by three table generated four categories of particular interest, specifically: "low-volume episodic drinkers", "low-volume frequent drinkers", "heavy episodic drinkers", "heavy frequent drinkers". The model was fitted with "low-volume episodic drinkers" (1-2 drinking-days per week, ≤ 2 drinks per drinking-day) as the reference group and non-drinkers were excluded. The median total alcohol consumption in the reference group was 2 drinks/week. Of particular interest are the comparisons between 'low-volume frequent drinkers' and 'low-volume episodic drinkers', and between 'heavy episodic drinkers' to 'low-volume episodic drinkers', to examine the effects of drinking frequency and heavy episodic drinking respectively.

Drinking pattern by sex among drinkers is shown in Table 4.3. Men consumed alcohol more frequently and consumed more alcohol per drinking-day than women.

Table 4.2. Drinking pattern variable.

	Drinks per drinking-day		
Drinking-days per week	**≤ 2**	**> 2 and ≤ 4**	**> 4**
1-2	Low-volume episodic drinker[a]	…	Heavy episodic drinker
3-5	…	…	…
6-7	Low-volume frequent drinker	…	Heavy frequent drinker

[a]Reference group. Non-drinkers excluded.

Table 4.3. Drinking pattern at baseline by sex among drinkers in the 45 and Up Study (2006-2009), New South Wales, Australia.

	Drinks per drinking-day (n participants)		
Drinking-days per week	**≤ 2**	**> 2 and ≤ 4**	**> 4**
Men			
1-2	14,925	5,151	3,012
3-5	15,656	10,311	4,041
6-7	16,723	13,754	8,281
Women			
1-2	21,050	3,595	1,078
3-5	22,552	6,295	697
6-7	18,214	6,124	995

Non-drinkers excluded (28,879 men and 58,308 women).

Distribution of total alcohol consumption by each drinking variable

The distribution of total alcohol consumption by each drinking variable is shown in Table 4.4. As expected, mean number of drinks per week was higher among participants who consumed alcohol on more days of the week and who consume greater drinks per drinking-day.

Table 4.4. Distribution of total alcohol consumption by drinking variables in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Alcoholic drinks per week	
Variable	**n**	**Mean (SD)**	**Median (Q1-Q3)**
Total alcohol consumption			
Non-drinker[a]	87,187	0.0 (0.0)	0 (0-0)
≥ 1, ≤ 3.5 drinks/week	40,491	2.0 (0.8)	2 (1-3)
> 3.5, ≤ 7 drinks/week	50,494	5.6 (1.1)	6 (5-7)
> 7, ≤ 14 drinks/week	46,117	11.0 (2.1)	10 (10-13)
> 14, ≤ 28 drinks/week	27,249	20.1 (3.7)	20 (17-21)
> 28 drinks/week	10,215	40.0 (13.6)	35 (30-42)
Missing	5,041	-[b]	-[b]
Drinking-days per week			
1-2 days/week	48,811	3.3 (3.1)	2 (1-4)
3-5 days/week	59,552	9.1 (6.5)	7 (5-10)
6-7 days/week	64,091	17.2 (12.1)	14 (9-21)
Missing	7,153	9.5 (11.5)	6 (3-12)
Drinks per drinking-day			
≤ 2 drinks/drinking-day	109,120	5.8 (3.8)	5 (2-8)
> 2, ≤ 4 drinks/drinking-day	45,230	14.3 (6.7)	15 (9-20)
> 4 drinks/drinking-day	18,104	29.2 (16.4)	30 (18-36)
Missing	7,153	9.5 (11.5)	6 (3-12)
Drinking pattern (drinking-days per week; drinks/drinking-day)			
1-2 days; ≤ 2 drinks/day	35,975	2.0 (1.0)	2 (1-2)
1-2 days; > 2, ≤ 4 drinks/day	8,746	5.0 (1.5)	5 (4-6)
1-2 days; > 4 drinks/day	4,090	10.3 (5.3)	10 (7-12)
3-5 days; ≤ 2 drinks/day	38,208	5.8 (2.3)	5 (4-7)
3-5 days; > 2, ≤ 4 drinks/day	16,606	12.3 (3.6)	12 (10-15)
3-5 days; > 4 drinks/day	4,738	24.6 (9.2)	22 (20-30)
6-7 days; ≤ 2 drinks/day	34,937	9.6 (3.2)	10 (7-12)
6-7 days; > 2, ≤ 4 drinks/day	19,878	20.0 (3.9)	20 (16-21)
6-7 days; > 4 drinks/day	9,276	39.8 (13.9)	35 (30-42)
Missing	7,153	9.5 (11.5)	6 (3-12)
Total	266,794	7.0 (9.7)	4 (0-10)

[a]< 1 alcoholic drink per week. [b]Not possible to calculate. SD, Standard Deviation. Q1, 25th percentile. Q3, 75th percentile.

Distribution of alcohol consumption by covariates

Socio-demographic characteristics

The association between alcohol consumption and socio-demographic characteristics in the 45 and Up Study has been examined previously[16]. It was reported that consuming any alcohol without current smoking was associated with being male, aged < 85 years, greater highest level of education and greater household income, while risky alcohol consumption (> 2 drinks per day) with current smoking was associated with being male, aged 45-64 years, lesser highest level of education and lower household income.

There was variation in alcohol consumption by every socio-demographic characteristic examined. Specifically, mean weekly alcoholic drinks was higher among men, participants aged less than 75 years, those living in regional and remote areas, those with higher annual household income, those with a trade or apprenticeship as their highest level of education, those without a healthcare concession card, those who were married or living with a partner, those born in Australia or other English-speaking countries, those who have lived in Australia longer, and those with English as the only language spoken at home (Table B.1, Appendix B). A high proportion of non-drinkers (> 40%) was found among women, those aged greater than 85 years, those with an annual household income less than $30,000, those with no school certificate, those holding a health care concession card, those not married or living with a partner, immigrants not born in majority English-speaking countries, immigrants living in Australia less than 20 years and those speaking a language other than English at home. A high proportion of participants consuming greater than 14 drinks per week (> 20%) was found in men and those with a trade or apprenticeship as their highest level of education.

Distribution of alcohol consumption by key behavioural and physical covariates

The association between alcohol consumption and key behavioural covariates in the 45 and Up Study has been examined previously[52]. A higher mean alcohol consumption was reported in participants who were ever-smokers compared to never-smokers, and those who were physically active rather than sedentary.

The distribution of alcohol consumption by key behavioural and physical covariates is shown in Table B.2 in Appendix B. Mean alcohol consumption was higher for participants who were ex- or current smokers, taller, overweight and had a high level of physical activity than in participants without these factors. Current smokers consuming greater than 15 cigarettes per day had the highest level of mean alcohol consumption and the highest proportion of participants consuming greater than 14 drinks per week out of all variables. Half of all participants who were physically inactive were non-drinkers. Men with a height greater than or equal to 180 cm had the lowest proportion of non-drinkers out of all variables.

Distribution of alcohol consumption by sun exposure covariates

The distribution of alcohol consumption by sun exposure covariates is shown in Table B.3 in Appendix B. Mean alcohol consumption was higher for participants who spent greater periods of time outdoors and who had a fair or olive skin tone than in participants without these factors.

Distribution of alcohol consumption by dietary factors

The distribution of alcohol consumption by dietary factors is shown in Table B.4 in Appendix B. Mean number of drinks per week was high among participants consuming low amounts of fruit, vegetables, fibre, and those consuming high amounts of red and processed meat. Over half of those who consumed no red meat were non-drinkers, and over 20% of those who consumed red meat more than 5 times per week were heavy drinkers.

Distribution of alcohol consumption by female reproductive characteristics

Alcohol consumption distributed by female reproductive characteristics is shown in Table B.5 in Appendix B. Mean weekly alcohol consumption was higher for participants with fewer children, with less breastfeeding time, who were pre-menopausal or had irregular periods, had ever used hormonal contraceptives and who were current users of hormone replacement therapy. Never users of hormonal contraceptives had the lowest mean weekly alcohol consumption, the highest proportion of non-drinkers, and the lowest proportion of participants consuming greater than 14 drinks per week.

Distribution of alcohol consumption by medical and health-related factors

The distribution of alcohol consumption by medical and health-related factors is shown in Table B.6 in Appendix B. Participants who recently had bowel and breast screening, in better self-rated overall health and with a greater physical functioning score had a higher level of mean alcohol consumption than participants without these characteristics. There were no clear differences in alcohol consumption by number of times prostate screened or by aspirin use. Participants with a physical functioning score < 25% and with missing aspirin use status had the highest proportion of non-drinkers out of all variables.

Conclusion

It has been shown that the distribution of alcohol consumption appears to vary by numerous key covariates that impact health. Therefore, these were accounted for by adjustment (and by stratification for sex and smoking status) in the cancer and mortality analyses. It is not appropriate to control for self-rated overall health, physical functioning score or other health-related factors such as disease status, as these are likely to be on the causal pathway between alcohol consumption and cancer and mortality. Adjusting for (or stratifying by, restricting by) a variable on the causal pathway between an exposure and outcome can cause overadjustment bias, likely biasing estimates of effect towards the null[53]. Confounding by illness at baseline was considered further in Chapter 7, and as a solution it was decided to perform a sensitivity test excluding participants with a low physical functioning score in the cancer and mortality analyses.

4.4 – Summary and Conclusions

Alcohol consumption is known to vary by key socio-demographic, lifestyle, and other health-related factors[9, 10, 25, 51]. This chapter described the covariates required for analysis including socio-demographic characteristics (sex, age, remoteness, household income, highest level of education, health insurance status, partner status, country of birth, length of time lived in Australia, language spoken at home), behavioural and physical factors (smoking status and intensity, height, BMI, physical activity, time spent outdoors, skin tone, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption), female reproductive characteristics (parity and age at first birth, breastfeeding time, menopausal status, HRT use, hormonal contraceptive use) and medical and health-related factors (bowel, breast and prostate cancer screening history, aspirin use, self-rated overall health and physical functioning score). Alcohol consumption was shown to vary by almost every one of these covariates. Accounting for these factors in analyses of alcohol consumption and health outcomes will minimise the potential for confounding. The next chapter compares the 45 and Up Study to other contemporaneous population based surveys.

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Chapter 5 – Comparison of the 45 and Up Study to Representative Health Surveys

Chapter summary

In this chapter, the distribution of variables in the 45 and Up Study are compared to population-based estimates using the 2008 New South Wales *Population Health Survey*, the Australian Bureau of Statistics New South Wales population estimates for June 2008, the 2007 *National Drug Strategy Household Survey* and the 2007-2008 *National Health Survey*.

5.1 – Comparison to Representative Health Surveys

This section compares how closely responses to the baseline survey of the 45 and Up Study match those of contemporaneous surveys of the NSW and Australian populations. Because the response rate of the 45 and Up Study is only around 18%, it is not likely to be representative of the general population. By comparing the prevalence of responses and outcomes of the 45 and Up Study cohort to other population based surveys of the same time period, the representativeness of socio-demographic, behavioural and health-related factors in the 45 and Up Study can be investigated. Surveys conducted as close as possible to the 45 and Up Study median baseline questionnaire date of February 2008 were examined.

New South Wales Population Health Survey (2008)

The 2008 NSW *Population Health Survey* (PHS) is one of the annual health surveys conducted by the NSW Department of Health[1]. Computer assisted telephone interviews of 12,485 residents of NSW

were conducted, of which 7,416 were aged ≥ 45 years. Participants were sampled via random digit dialling and the overall response rate was 63%. Participants of all ages including children were sampled, and the results were weighted to the Australian Bureau of Statistics (ABS) NSW population estimates for June 2008. Results for persons aged over 45 years were compared to the 45 and Up Study baseline responses. Although alcohol consumption was not reported in a way that could be compared to the 45 and Up Study (risky alcohol consumption based on the 2001 Australian alcohol guidelines, defined partially by highest number of drinks consumed in one day in the previous four weeks), comparable data were available online at NSW HealthStats[2].

The age and sex structure of the two surveys are compared in Table 5.1. Additional columns are included showing the sex and age distribution of the whole NSW population aged ≥ 45 years according to the ABS NSW population estimates for June 2008, and sex, age, partner status and country of birth data for the NSW population aged ≥ 45 years according to the 2006 census[3]. The 45 and Up Study had a higher proportion of men than the NSW PHS but a lower proportion of men compared to the NSW population estimates and the census. There was a higher proportion of participants aged < 65 years in the 45 and Up Study compared to the NSW PHS, a higher proportion of participants aged ≥ 55 years compared to the NSW population estimates, and a higher proportion of participants aged ≥ 55 and < 75 years compared to the census. There was also a higher proportion of participants married or living with a partner and born in Australia compared to the census.

Table 5.1. Distribution of socio-demographic characteristics in the baseline survey of the 45 and Up Study (2006-2009), New South Wales (NSW), the NSW Population Health Survey (2008), the Australian Bureau of Statistics NSW population estimates for June 2008 and the 2006 Census in NSW.

Characteristic	45 and Up Study (%) (95% CI)	NSW PHS 2008 (%)	ABS NSW population estimates for June 2008[a] (%)	2006 Census in NSW (%)
n participants	266,794	7,416	2,532,017	2,529,657
Sex				
Male	46.4 (46.2-46.6)	40.0	48.3	47.8
Female	53.6 (53.4-53.8)	60.0	51.7	52.2
Age (years)				
45-54	29.2 (29.0-29.4)	24.2	36.7	35.7
55-64	32.2 (32.0-32.4)	31.0	29.0	28.4
65-74	21.7 (21.6-21.9)	24.6	18.5	18.4
≥ 75	16.9 (16.8-17.1)	20.3	15.8	17.4
Married or living with partner				
No	25.1 (24.9-25.3)	-	-	31.0
Yes	74.9 (74.7-75.1)	-	-	69.0
Country of birth				
Australia	75.6 (75.4-75.7)	-	-	65.9
Other	24.4 (24.3-24.6)	-	-	34.1

Proportions exclude missing data. [a]Excludes residents of institutions. NSW, New South Wales. CI, Confidence Interval. PHS, Population Health Survey. ABS, Australian Bureau of Statistics.

The distribution of socio-demographic characteristics and lifestyle risk factors at baseline in the 45 and Up Study are compared to the NSW PHS in Table 5.2. Across all sex and age groups, a higher proportion of participants in the 45 and Up Study had private health insurance, had adequate physical activity, consumed ≥ 5 serves of vegetables per day, rated their health as good, very good or excellent and had breast screening within the past 2 years, while a lower proportion were current smokers. On the other hand, across all sex and age groups a higher proportion of participants in the 45 and Up Study consumed alcohol at least weekly and were overweight or obese (except men aged ≥ 75 years), while a lower proportion consumed ≥ 2 serves of fruit per day and consumed red meat < 3 times per week. Consumption of processed meat per week was similar between the two surveys for women, but a lower proportion of men in the 45 and Up Study consumed processed meat < 3 times per week in all age groups except 45-54 years.

Table 5.2. Distribution of socio-demographic characteristics and lifestyle risk factors in the baseline survey of the 45 and Up Study (2006-2009), New South Wales (NSW) and the NSW Population Health Survey (2008).

	Men (95% CI)				Women (95% CI)			
Study and characteristic	**45-54 years**	**55-64 years**	**65-74 years**	**≥ 75 years**	**45-54 years**	**55-64 years**	**65-74 years**	**≥ 75 years**
45 and Up Study								
n participants	31,435	39,073	29,507	23,754	46,417	46,749	28,511	21,348
Private health insurance (%)	68.2 (67.6-68.7)	70.0 (69.5-70.5)	63.0 (62.5-63.6)	53.1 (52.5-53.7)	67.8 (67.3-68.2)	69.4 (69.0-69.8)	60.2 (59.6-60.8)	52.2 (51.6-52.9)
Drink alcohol at least weekly (%)	78.7 (78.3-79.2)	79.5 (79.1-79.9)	75.6 (75.1-76.1)	68.7 (68.1-69.3)	64.4 (63.9-64.8)	61.4 (60.9-61.8)	53.8 (53.2-54.4)	43.9 (43.2-44.6)
Current smoker (%)	12.1 (11.7-12.4)	8.7 (8.5-9.0)	5.6 (5.3-5.8)	2.6 (2.4-2.8)	10.6 (10.3-10.9)	7.1 (6.9-7.4)	4.2 (4.0-4.4)	2.1 (1.9-2.3)
Overweight or obese[b] (%)	71.1 (70.6-71.7)	72.8 (72.4-73.3)	70.5 (69.9-71.0)	54.9 (54.3-55.6)	52.8 (52.3-53.2)	59.4 (58.9-59.8)	60.4 (59.8-61.0)	48.8 (48.1-49.5)
Adequate physical activity[c] (%)	68.8 (68.3-69.4)	70.7 (70.2-71.2)	72.5 (72.0-73.0)	61.2 (60.5-61.8)	71.6 (71.2-72.0)	74.0 (73.6-74.4)	71.1 (70.6-71.7)	53.3 (52.6-54.0)
≥ 2 serves of fruit per day (%)	46.2 (45.7-46.8)	48.9 (48.4-49.4)	51.3 (50.8-51.9)	53.9 (53.3-54.6)	58.0 (57.5-58.4)	65.7 (65.3-66.2)	69.1 (68.6-69.7)	67.3 (66.7-68.0)
≥ 5 serves of vegetables per day (%)	19.0 (18.6-19.5)	23.4 (23.0-23.8)	27.9 (27.4-28.4)	26.9 (26.3-27.5)	34.2 (33.8-34.6)	41.2 (40.7-41.6)	45.1 (44.5-45.7)	39.1 (38.4-39.7)
Consume red meat < 3 times per week (%)	35.3 (34.8-35.9)	32.3 (31.9-32.8)	31.2 (30.7-31.7)	33.5 (32.9-34.1)	42.3 (41.9-42.8)	38.4 (37.9-38.8)	35.9 (35.3-36.5)	37.7 (37.1-38.4)
Consume processed meat < 3 times per week (%)	76.0 (75.6-76.5)	78.3 (77.8-78.7)	80.1 (79.6-80.5)	80.4 (79.9-80.9)	88.5 (88.2-88.8)	89.4 (89.1-89.7)	89.5 (89.1-89.8)	88.7 (88.3-89.2)
Good/very good/excellent self-rated health (%)	88.0 (87.7-88.4)	86.4 (86.1-86.7)	85.1 (84.7-85.5)	76.8 (76.3-77.4)	90.0 (89.7-90.3)	89.0 (88.7-89.3)	86.5 (86.1-86.9)	74.4 (73.8-75.0)
Breast screening within past 2 years (%)	-	-	-	-	-	84.1 (83.8-84.5)[d]	-	-
NSW Population Health Survey 2008[a]								
n participants	729	914	709	588	1,065	1,382	1,115	914
Private health insurance (%)	67.1	65.6	57.6	48.4	66.0	66.5	56.1	49.1
Drink alcohol at least weekly (%)	61.5	65.7	60.3	54.8	45.0	43.7	36.4	30.5
Current smoker (%)	17.6	15.6	8.1	4.5	17.6	13.0	7.8	3.7
Overweight or obese[b] (%)	67.1	70.3	69.0	56.0	52.1	57.8	59.3	45.2
Adequate physical activity[c] (%)	59.9	57.1	52.4	43.5	50.1	50.9	39.9	26.4
≥ 2 serves of fruit per day (%)	51.7	51.5	56.8	59.9	61.7	67.5	72.8	72.8
≥ 5 serves of vegetables per day (%)	6.3	7.4	10.7	9.6	15.7	18.3	18.9	14.3
Consume red meat < 3 times per week (%)	38.9	42.3	44.8	43.7	43.7	44.9	47.3	49.1
Consume processed meat < 3 times per week (%)	74.7	80.4	82.9	85.5	88.3	91.7	89.5	88.6
Good/very good/excellent self-rated health (%)	82.4	76.2	77.3	71.5	79.1	76.5	71.4	68.1
Breast screening within past 2 years (%)	-	-	-	-	-	76.2[d]	-	-

Proportions exclude missing data. [a]Results weighted by age, sex, health area and probability of selection in household to match Australian Bureau of Statistics estimates for June 2008, excluding residents of institutions. [b]Body mass index ≥ 25 kgm^{-2}. [c]150 minutes of physical activity per week on at least 5 separate occasions, with time spent in vigorous physical activity was given twice the weighting of lower intensity physical activity. [d]Participants aged 50-69 years. NSW, New South Wales. CI, Confidence Interval.

National Drug Strategy Household Survey (2007)

The 2007 *National Drug Strategy Household Survey* (NDSHS), conducted by the Australian Institute of Health and Welfare, had a focus on alcohol, tobacco and illicit drug use[4]. Drop and collect surveys and computer assisted telephone interviews were conducted for 23,356 randomly sampled residents of Australia aged ≥ 12 years, with a response rate of 49%. The results were weighted to population estimates for 2007. Information on weekly alcohol consumption was available for NSW by 10 year age strata (thus it was only possible to make comparisons for participants aged ≥ 50 years).

The age and sex distribution of alcohol consumption and smoking status in the NDSHS and the 45 and Up Study are shown in Table 5.3. Compared to the 2007 NDSHS, a higher proportion of participants in the 45 and Up Study consumed alcohol at least weekly and were never smokers. The 45 and Up Study had fewer current smokers however the proportion of ex-smokers was similar across the two surveys.

National Health Survey (2007-2008)

The *National Health Survey* (NHS), was a random sample of 20,788 Australian residents aged ≥ 15 years, with a response rate of 91%[5]. Participants were interviewed in their homes by the Australian Bureau of Statistics and the results were weighted to population estimates for December 2007. The NHS had information on the consumption of alcohol 'at least weekly'. It should be noted that unlike the previous two surveys, the NHS captured alcohol consumption in the last week rather than usual alcohol consumption.

The distribution of alcohol consumption and other lifestyle risk factors at baseline the 45 and Up Study and in the 2007-2008 NHS are shown in Table 5.4. Compared to the NHS, a higher proportion of participants in the 45 and Up Study consumed alcohol at least weekly (except women aged ≥ 75 years) and consumed ≥ 5 serves of vegetables per day. Overall, a lower proportion of participants in

the 45 and Up Study were current smokers, overweight or obese and physically inactive. The proportion of participants consuming ≥ 2 serves of fruit per day varied by age group. Specifically, men aged < 55 years and women aged ≥ 55 and < 75 years in the 45 and Up Study consumed more fruit than those in the NHS, men aged ≥ 55 years and women aged < 55 years consumed less, and women aged ≥ 75 years consumed a similar amount. The proportion of participants with private health insurance was reported in the NHS by age but not by sex. For participants aged 45-54, 55-64, 65-74 and ≥ 75 years in the NHS, 59.0%, 62.0%, 55.4% and 44.5% had private health insurance, respectively. The corresponding proportions for the 45 and Up Study were all higher, at 67.9%, 69.7%, 61.7% and 52.7% respectively.

It should be noted that the surveys of the Australian population will not be as comparable to the 45 and Up Study as surveys of the NSW population. Other limitations of these comparisons include the 45 and Up Study oversampling participants aged ≥ 80 years and living in remote areas, different timings of sampling, different wording of questions, different methods of data collection such as via telephone interview rather than paper questionnaire, different response rates, the exclusion of persons in institutions such as nursing homes (nursing home residents were included in the 45 and Up Study) and the use of population weightings. Furthermore, the 2008 NSW PHS and the 2007-2008 NHS reported conducted surveys in languages other than English when required, while the 2007 NDSHS and the 45 and Up Study did not, potentially causing bias by English language ability.

Table 5.3. Comparison of alcohol consumption and smoking status by sex and age between the baseline survey of the 45 and Up Study (2006-2009), New South Wales and the Australian National Drug Strategy Household Survey (2007).

	45 and Up Study (%) (95% CI)				NDSHS 2007[a] (%)			
Characteristic	**Men, 50-59 years**	**Men, ≥ 60 years**	**Women, 50-59 years**	**Women, ≥ 60 years**	**Men, 50-59 years**	**Men, ≥ 60 years**	**Women, 50-59 years**	**Women, ≥ 60 years**
n participants	37,872	72,236	50,578	71,228	≈ 1,800[b]	≈ 3,100[b]	≈ 2,200[b]	≈ 3,700[b]
Alcohol consumption								
Non-drinker or drink less than weekly	20.8 (20.4-21.2)	25.7 (25.4-26.0)	36.9 (36.5-37.4)	47.1 (46.8-47.5)	34.5	39.4	54.2	58.9
Drink alcohol at least weekly	79.2 (78.8-79.6)	74.3 (74.0-74.6)	63.1 (62.6-63.5)	52.9 (52.5-53.2)	65.5	60.6	45.8	41.1
Smoking status								
Never smoker	52.2 (51.7-52.7)	45.2 (44.8-45.5)	62.2 (61.8-62.6)	68.7 (68.4-69.0)	40.0	39.8	56.6	63.1
Ex-smoker	37.3 (36.8-37.8)	49.7 (49.3-50.0)	29.1 (28.7-29.5)	27.1 (26.8-27.4)	38.3	48.3	27.4	27.4
Current smoker	10.5 (10.2-10.8)	5.2 (5.0-5.3)	8.7 (8.4-8.9)	4.2 (4.1-4.4)	21.8	11.9	16.1	10.6

Proportions exclude missing data. [a]Results weighted by age, sex and state to match Australian Bureau of Statistics estimates for June 2007. [b]Exact numbers by sex and age not reported; 23,356 participants (10,231 men and 13,125 women) in total aged ≥ 12 years. CI, Confidence Interval. NDSHS, National Drug Strategy Household Survey.

Table 5.4. Comparison of behavioural risk factors between the baseline survey of the 45 and Up Study (2006-2009), New South Wales and the Australian National Health Survey (2007-2008).

	Men (95% CI)				Women (95% CI)			
Study and characteristic	**45-54 years**	**55-64 years**	**65-74 years**	**≥ 75 years**	**45-54 years**	**55-64 years**	**65-74 years**	**≥ 75 years**
45 and Up Study								
n participants	31,435	39,073	29,507	23,754	46,417	46,749	28,511	21,348
Drink alcohol at least weekly (%)	78.7 (78.3-79.2)	79.5 (79.1-79.9)	75.6 (75.1-76.1)	68.7 (68.1-69.3)	64.4 (63.9-64.8)	61.4 (60.9-61.8)	53.8 (53.2-54.4)	43.9 (43.2-44.6)
Current smoker (%)	12.1 (11.7-12.4)	8.7 (8.5-9.0)	5.6 (5.3-5.8)	2.6 (2.4-2.8)	10.6 (10.3-10.9)	7.1 (6.9-7.4)	4.2 (4.0-4.4)	2.1 (1.9-2.3)
Overweight or obese[c] (%)	71.1 (70.6-71.7)	72.8 (72.4-73.3)	70.5 (69.9-71.0)	54.9 (54.3-55.6)	52.8 (52.3-53.2)	59.4 (58.9-59.8)	60.4 (59.8-61.0)	48.8 (48.1-49.5)
Inactive[d] (%)	4.6 (4.4-4.8)	4.9 (4.7-5.2)	4.9 (4.7-5.2)	9.0 (8.7-9.4)	4.5 (4.3-4.7)	4.4 (4.2-4.6)	5.5 (5.2-5.7)	14.4 (13.9-14.8)
≥ 2 serves of fruit per day (%)	46.2 (45.7-46.8)	48.9 (48.4-49.4)	51.3 (50.8-51.9)	53.9 (53.3-54.6)	58.0 (57.5-58.4)	65.7 (65.3-66.2)	69.1 (68.6-69.7)	67.3 (66.7-68.0)
≥ 5 serves of vegetables per day (%)	19.0 (18.6-19.5)	23.4 (23.0-23.8)	27.9 (27.4-28.4)	26.9 (26.3-27.5)	34.2 (33.8-34.6)	41.2 (40.7-41.6)	45.1 (44.5-45.7)	39.1 (38.4-39.7)
Australian NHS 2007-2008[a]								
Drink alcohol at least weekly (%)	76.0	72.5	68.2	60.2	61.9	60.6	52.8	45.4
Current smoker (%)	24.3	16.2	10.5	5.3	21.7	17.3	9.1	4.7
Overweight or obese[c] (%)	76.7	74.9	78.9	74.3	58.8	67.9	71.4	56.9
Inactive[d] (%)	38.4	35.0	37.1	51.5	33.3	37.3	41.2	58.9
≥ 2 serves of fruit per day (%)	43.3	53.5	62.5	63.6	58.8	64.8	67.5	66.8
≥ 5 serves of vegetables per day (%)	5.8	6.7-10.1[e]	14.0	10.0-12.6[e]	12.7	9.7-14.9[e]	13.3	9.0-13.7[e]

Proportions exclude missing data. [a]Results weighted by age, sex, area of usual residence and probability of selection in household to match Australian Bureau of Statistics estimates for December 2007, excluding persons living in very remote areas and residents of hotels, motels, caravan parks and institutions; n participants by sex and age not available; n participants for all ages ≥ 15 years = 20,788. [c]Body mass index ≥ 25 kgm^{-2}. [d]0 minutes of physical activity per week. [e]Exact proportion cannot be calculated due to supressed cells with small numbers. CI, Confidence Interval. NHS, National Health Survey.

Conclusion

In summary, it appears that participants in the 45 and Up Study have healthier lifestyle behaviours, better self-rated overall health and a higher prevalence of private health insurance than participants in contemporaneous, representative population-based health surveys. Although there were some exceptions such as a higher prevalence of drinking alcohol at least weekly and lower fruit consumption. Thus, the 45 and Up Study is possibly healthier than the overall NSW population. It should be noted that other factors may contribute to the differences in findings, such as differences in sampling method (e.g. the Medicare Australia database vs. random digit dialling) and data collection (e.g. the use of paper questionnaires vs. home interviews).

As the majority of participants in the 45 and Up Study were moderate drinkers (≤ 14 drinks/week), and as moderate drinking has previously been associated with good general health status and a range of healthy lifestyle behaviours such as physical activity and lower BMI compared to non-drinking[6], perhaps the higher prevalence of persons consuming alcohol at least weekly is to be expected in a healthier cohort. Unfortunately, the 45 and Up Study's measure of alcohol consumption was not comparable to the measures used in other surveys, meaning that the prevalence of within- and above-guideline drinking could not be compared. Specifically, it was not possible to determine if participants in the 45 and Up Study consumed > 2 or > 4 standard drinks on *any* day of alcohol consumption. Different measures of risky alcohol consumption were also reported in the three comparison surveys. The 2008 NSW PHS used a definition of "*1 or more of the following: consuming alcohol every day, consuming on average more than [4 if male/2 if female] standard drinks, consuming more than [6 if male/4 if female] on any 1 occasion or day.*"[1], the 2007 NDSHS used a similar definition but without the item of consuming alcohol every day[4], while the 2007-2008 NHS used a definition of "*average daily consumption of alcohol by persons aged 15 years and over for 3 days of the week prior to interview*" > 50 mL in men and > 25 mL in women[5]. Further, the use of differently worded questions to capture alcohol consumption between the surveys reduces

comparability, even when using a similar measure of alcohol consumption such as whether a participant consumed alcohol at least weekly. As was reported in Chapter 1, prevalence estimates for alcohol consumption are particularly sensitive to the style of question asked[7]. Another limitation was that the 2008 NHS captured alcohol consumption in the past week rather than usual alcohol consumption, which could potentially alter prevalence estimates as well. Overall, it appears possible but not certain that a higher proportion of participants in the 45 and Up Study consume alcohol at least weekly compared to the general population.

The selection of healthy participants into cohort studies and randomised controlled trials is known as the 'healthy volunteer effect', and when compared to the general population may lead to a lower observed incidence of cancer, cardiovascular disease and mortality[8, 9]. The possibility of a healthier cohort means that interpretations of prevalence estimates should be made with caution, as they may not be representative of the overall NSW population.

A detailed comparison of the 45 and Up Study with the NSW PHS found consistent exposure-outcome relationships between the two studies, meaning that the study will most likely provide generalisable results when analyses are based on internal comparisons within the cohort[10]. For example, consistent exposure-outcome relationships were found for BMI and odds of having diabetes, BMI and odds of having hypertension, remoteness and odds of having ≥ 2 serves of fruit per day, educational attainment and odds of obesity, and smoking status and odds of bowel screening in the past five years. However, this means that null results should be interpreted with caution.

5.2 – Summary and Conclusions

Comparing the 45 and Up Study to other population based surveys with a higher response rate was important to determine the representativeness of the cohort. The distribution of exposures in the 45 and Up Study were compared with similar measures of exposure in the NSW *Population Health Survey* (2008), the NSW data from the *National Drug Strategy Household Survey* (2007) and *National Health Survey* (2007-2008). Overall, 45 and Up Study participants were potentially healthier than the general population, similar to the 'healthy volunteer effect' described in other cohort studies[8, 9]. Specifically, a higher proportion of participants in the 45 and Up Study had private health insurance, had adequate physical activity or were physically active, consumed ≥ 5 serves of vegetables per day, and rated their health as good, very good or excellent, while a lower proportion were current smokers compared to the general population. On the other hand, a higher proportion of participants consumed alcohol at least weekly (except compared to women aged ≥ 75 years in the NHS) and a lower proportion consumed red meat < 3 times per week. The proportion overweight or obese was higher than the NSW PHS and lower than the NHS, while the proportion consuming ≥ 2 serves of fruit per day was lower than the NSW PHS and varied compared to the NHS depending on sex and age group. Finally, regarding alcohol consumption, the 45 and Up Study used measures mostly not comparable to the measures used in other surveys, and so the prevalence of within- and above-guideline drinking could not be compared.

The possibility of a healthier cohort means that lower rates of cancer and mortality may be observed than in the New South Wales general population. It also means that null associations should be interpreted with caution, although a previous analysis showed that majority of observed associations were consistent with observations from the more representative NSW PHS[10]. Overall, the large number of participants in the 45 and Up Study, the use of multiple measures of total alcohol consumption and drinking pattern and the consideration of a large number of important

covariates are strengths, and should enable the influence of alcohol consumption on risk of cancer and mortality to be examined thoroughly while ensuring that bias from confounding is minimised.

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Chapter 6 – Co-occurrence of Chronic Disease Lifestyle Risk Factors in Middle-aged and Older Immigrants

Chapter summary

This chapter contains a published article, which investigated the co-occurrence of five chronic disease lifestyle risk factors among immigrant groups in New South Wales (NSW) compared to the Australian-born population. This was achieved using the Chronic Disease Risk Index (CDRI) – a tool developed using the NSW population with risk factors weighted according to their contribution to burden of disease in Australia. The rationale for this work was that lifestyle risk factors for cancer and chronic disease do not often occur in isolation. Alcohol consumption was examined along with smoking, body mass index, physical inactivity, and insufficient fruit and vegetable consumption. Differences in CDRI score by both region of birth and number of years lived in Australia were examined. Immigrant groups at lower and higher potential risk of chronic disease than the Australian-born population were identified. The findings of the article were presented at the Population Health Congress 2015 (Hobart).

An additional set of analyses were performed that examined the distribution of drinking patterns by country of birth and years since migration. The CDRI incorporated a now outdated definition of harmful alcohol consumption and therefore the measure of alcohol consumption used in the published article for the CDRI was not comparable to the rest of this thesis. Differences in total alcohol consumption and drinking pattern and implications for the remaining chapters are discussed.

6.1 – Publication

The following article was published in the December 2015 issue of *Preventive Medicine*[1]. See Appendix C for a breakdown of participants by country and region of birth (Table C.1), and of decade first migrated to Australia for at least one year by region of birth (Table C.2).

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Co-occurrence of chronic disease lifestyle risk factors in middle-aged and older immigrants: A cross-sectional analysis of 264,102 Australians

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ABSTRACT

Background. The way in which lifestyle risk factors for chronic disease co-occur among people with different cultural backgrounds is largely unknown.

Methods. This study investigated chronic disease risk among immigrants aged ≥45 years in Australia by combining common lifestyle risk factors into a weighted chronic disease risk index (CDRI). Among 64,194 immigrants and 199,908 Australian-born participants in the 45 and Up Study (2006–2009), Poisson regression was used to derive relative risks (RR) and 95% confidence intervals (CI) for five risk factors (smoking, alcohol use, overweight/obesity, physical activity, diet) by place of birth adjusting for socio-demographic characteristics. Multiple linear regression was used to determine adjusted mean differences (AMDs) in CDRI score by place of birth and years lived in Australia.

Results. Immigrants had higher RRs of smoking than Australian-born participants, lower RRs of excessive alcohol consumption and overweight/obesity, and no difference in RR for physical inactivity and insufficient fruit/vegetable intake. Participants born in the Middle East/North Africa (AMD 3.5, 95% CI 2.7, 4.3), Eastern/Central Europe (1.3, 0.8, 1.9), and Western Europe (0.5, 0.1, 0.8) had higher mean CDRI scores than Australian-born participants, while participants born in East Asia (−7.2, −7.8, −6.6), Southeast Asia (−6.6, −7.2, −6.1), Central/South Asia (−3.1, −4.0, −2.1), Sub-Saharan Africa (−1.9, −2.6, −1.2) and the United Kingdom/Ireland (−0.2, −0.5, 0.0) had lower scores. CDRI score among immigrants generally approximated that of Australian-born participants with greater years lived in Australia.

Conclusions. This study reveals differences in potential risk of chronic disease among different immigrant groups in Australia.

Introduction

Non-communicable diseases have a major impact on premature morbidity and mortality, comprising around 55% of the burden of disease globally, and 85% in Australia (2010) (Murray et al., 2012a). A large proportion of the burden comes from chronic diseases that share many lifestyle risk factors including smoking, alcohol intake, physical inactivity and poor diet (Australian Institute of Health and Welfare, 2014).

While the population prevalence of individual lifestyle risk factors is routinely ascertained through national health surveys, it is important to consider that these risk factors do not often occur in isolation. Indeed, risk factors often cluster and can interact, where the risk of chronic disease may be elevated above that of the sum of each risk factor considered individually (Australian Institute of Health and Welfare, 2005, 2012). Lifestyle risk factor co-occurrence has also been shown to influence mortality, whereby mortality risk is proportionate to the number of healthy lifestyle behaviours adhered to (Loef and Walach, 2012). To better estimate chronic disease risk it is therefore necessary to study lifestyle risk factors in combination.

Risk factor prevalence and the burden of chronic disease vary greatly across different regions of the world (Murray et al., 2012a; World Health Organisation, 2014). For example, in 2007–2010, 36% of the Chinese population aged ≥50 years were found to have three or more chronic disease risk factors, compared to 45% for India, 56% for Russia and 69% for South Africa (Wu et al., 2015). In Australia (2007–2008), it was found that 64% of adults had at least three chronic disease risk factors, with males, those aged ≥75 years, those with disadvantaged socioeconomic status, and those living in rural areas having the greatest proportion (Australian Institute of Health and Welfare, 2012). However, the way in which chronic disease risk factors co-occur among people

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with different cultural backgrounds in Australia is largely unknown. Of twelve studies included in a systematic review of cardiovascular disease risk factors among immigrant groups in Australia, only one considered multiple risk factors together (Dassanayake et al., 2009). The Australian population has a relatively high proportion of immigrants (27% in 2011) and ethnic diversity (60% of immigrants originate from non-European countries and 53% speak a language other than English at home) (Australian Bureau of Statistics, 2012). Further, chronic disease incidence (Dassanayake et al., 2009; Hodge et al., 2004; Supramaniam et al., 2006) and mortality (Anikeeva et al., 2011, 2015), as well as individual risk factors (Centre for Epidemiology and Research, 2010; Singh and de Looper, 2002; Bennett, 1993) have been found to vary substantially in Australia by place of birth. For example, from 1981–2007, death from lung, stomach, and bladder cancer was more common among immigrants than the Australian-born population, whereas immigrants were less likely to die from colorectal cancer (Anikeeva et al., 2011). Death from cardiovascular disease was higher among immigrants from Eastern Europe (1997–2007), but lower for other parts of Europe, and lowest among Chinese Asians (Anikeeva et al., 2015). In the same period, the immigrant groups with the highest number of deaths from diabetes mellitus were those from Southern Europe, Eastern Europe, and Southern Asia (Anikeeva et al., 2015). Understanding how modifiable health behaviours may contribute to variations in health outcomes can potentially be achieved by exploring multiple risk factors.

There are various methods for quantifying multiple risk factors (McAloney et al., 2013), but it is important to account for the fact that some risk factors have stronger associations with chronic diseases than others. The Chronic Disease Risk Index (CDRI) developed by Miller and Bauman (2005) accounts for the proportional impact of each risk factor on disease using a population health survey in New South Wales (NSW), Australia (Miller and Bauman, 2005). This index takes into account the impact of each factor on loss of disability-adjusted life years in Australia (Miller and Bauman, 2005; Miller, 2003).

We applied this CDRI to self-reported health and lifestyle data from the baseline questionnaire of a large cohort study in NSW, the 45 and Up Study. We aimed to identify immigrant groups with higher or lower CDRI than Australian-born participants, and determine how this relationship varies by number of years lived in Australia.

Methods

Study sample

Baseline data from the Sax Institute's 45 and Up Study (2006–2009), a cohort study of 266,848 participants was used. The study is described elsewhere (Banks et al., 2008), but briefly, residents of NSW aged at least 45 years were randomly sampled from the general population using the Medicare Australia database. This database includes records for all citizens and permanent residents of Australia, and also some temporary residents and refugees. Persons aged 80 and over and those living in rural and remote areas were oversampled by a factor of two. The response rate to mailed invitations was estimated to be 18% (Banks et al., 2008). Ethics approval for the study was provided by the University of NSW Human Research Ethics Committee and the Cancer Council NSW Ethics Committee.

Place of birth and years lived in Australia

Immigrants were defined as persons who reported a country of birth other than Australia. To ensure adequate sample sizes for comparison, countries of birth were grouped into thirteen regions (see Table A.1 supplementary content). These are modified groups from the Global Burden of Disease Study and have been used previously to analyse 45 and Up Study data (Murray et al., 2012b; Weber et al., 2011). The regions were generated to maximise inter-region variation and minimise intra-region variation in infant mortality and adult morbidity and mortality (Murray et al., 2012b). Participants with missing or invalid places of birth were excluded from the analyses. Number of years lived in Australia was calculated using the survey date and year first lived in Australia for one year or more.

Chronic disease risk index (CDRI) and lifestyle risk factors

A CDRI score was calculated for each participant using the methods of Miller and Bauman (Miller and Bauman, 2005; Miller, 2003). Specifically, five self-reported risk factors (smoking, alcohol, BMI, physical activity and fruit and vegetable intake) were assigned values between 0 and 1 to capture the magnitude of associations with disability adjusted life years in Australia. These were then summed to create a CDRI score for each participant, with higher scores indicating greater chronic disease risk. Scores ranged from 0 to 3.8, and were re-scaled into a 100-point scale.

BMI (calculated from self-reported height and weight (Ng et al., 2011)) and physical activity (weekly number of sessions and time in minutes, with time spent in vigorous activity doubled as it was assumed to have twice the metabolic equivalent value of low and moderate activity (Australian Institute of Health and Welfare, 2003; Australian Government Department of Health, 2014)) were assigned risk values as per the original methodology (Miller and Bauman, 2005; Miller, 2003). Smoking status, alcohol and fruit and vegetable intake were modified as described below.

Current smoking was assigned a risk value of 1, former smoking 0.5 and never-smoking 0. We were not able to include a category for occasional smoking (assigned a value of 0.8).

Alcohol consumption was divided into 'low risk' (assigned a value of 0), 'hazardous' (assigned 0.3), and 'harmful' (assigned 0.4) levels. For men this equated to ≤4, >4 and ≤6, and >6 standard drinks per occasion respectively, and for women, ≤2, >2 and ≤4, and >4. We used days of drinking as a substitute for occasions of drinking.

Participants in the low tertile of fruit and vegetable intake (<3 serves of total fruit/vegetables per day) were assigned a value of 0.4, those in the moderate tertile (≥3 and <5 serves/day) a value of 0.2, and those in the high tertile (≥5 serves/day) a value of 0. Tertile cut-off values were based on the 2010 NSW Population Health Survey (Centre for Epidemiology and Research, 2011).

Participants with incomplete data for any of the five lifestyle risk factors were excluded from CDRI analyses.

Socio-demographic covariates

All socio-demographic covariates analysed are listed in Table 1. Remoteness was derived from postcode using the Accessibility/Remoteness Index for Australia (ARIA + 2006) (Glover and Tennant, 2003). A missing indicator variable was included for each factor.

Statistical analyses

We examined the distribution of socio-demographic characteristics by place of birth. All subsequent analyses were adjusted for sex, age, remoteness, education level, marital status, household income and health insurance status.

It has been shown that for binary outcomes, exponentiated linear coefficients estimated from Poisson regression provide valid estimates of adjusted relative risk, and robust standard errors produce confidence intervals that achieve nominal coverage (Zou, 2004; Greenland, 2004; Spiegelman and Hertzmark, 2005). This method has been referred to as modified Poisson regression, and was used to calculate the adjusted relative risk (RR) and 95% confidence interval (CI) of being in the highest risk category for each individual risk factor by place of birth. That is, being a current smoker, drinking a harmful level of alcohol, being obese, being physically inactive and being in the lowest tertile of fruit and vegetable intake.

Multiple linear regression was used to determine adjusted mean differences (AMDs) in CDRI score by place of birth and years lived in Australia. In each regression model, place of birth and socio-demographic covariates were the independent variables and CDRI score was the dependent variable. A test for trend between years lived in Australia and CDRI score (using the median value for each category of years lived in Australia: <10; 10–19; 20–29; 30–39; ≥40 years) was used for each region of birth.

Analyses were performed using SAS 9.3.

Results

266,848 participants completed the baseline questionnaire. 22 (0.008%) of these were excluded for being <45 years old. A further

Table 1
Socio-demographic characteristics by place of birth in the 45 and Up Study (2006–2009), New South Wales, Australia.

Place of birth	n [%]	Male (%)	Age (mean [SD]) (years)	Major city resident (%)	University degree (%)	Married or living with partner (%)	Household income[a] ≥$70 000 (%)	Private health insurance[b] (%)	Speak non-English at home (%)	Year arrived in Australia[c] (median [IQR])	Years lived in Australia (median [IQR])
Australia	199,908 [75.7]	45.4	62.5 [11.1]	39.9	21.6	74.6	24.0	67.4	2.3	–	–
New Zealand	5069 [1.9]	45.5	60.5 [10.4]	51.6	26.7	72.9	32.9	59.6	3.5	1977 [1968–1985]	31.1 [22.6–39.7]
Oceania	887 [0.3]	47.0	59.3 [10.2]	72.2	22.0	74.9	22.4	55.4	55.2	1979 [1964–1988]	29.1 [19.3–44.1]
East Asia	3231 [1.2]	45.2	59.7 [11.2]	91.3	42.1	80.4	17.8	64.8	85.4	1988 [1979–1994]	19.5 [14.1–28.7]
Southeast Asia	4487 [1.7]	42.3	59.3 [10.5]	83.4	40.9	76.6	20.8	55.9	74.9	1984 [1977–1990]	24.1 [18.1–31.1]
Central & South Asia	1357 [0.5]	60.2	61.3 [11.4]	79.7	58.0	81.1	30.1	62.6	53.4	1982 [1969–1992]	25.1 [15.4–38.3]
UK & Ireland	26,282 [10.0]	49.5	64.7 [11.3]	49.4	24.7	74.6	24.4	61.0	2.2	1966 [1958–1974]	41.3 [33.7–49.3]
Western Europe	11,534 [4.4]	52.9	66.1 [11.1]	58.2	16.7	73.0	15.4	55.2	53.9	1959 [1953–1969]	48.3 [38.6–54.3]
Eastern & Central Europe	3940 [1.5]	53.1	67.4 [11.8]	73.8	21.1	67.7	12.7	49.7	66.9	1961 [1951–1971]	46.4 [36.1–56.2]
Middle East & North Africa	2125 [0.8]	58.8	61.7 [11.0]	90.3	28.1	76.1	13.2	45.6	81.1	1973 [1966–1986]	35.1 [21.6–42.2]
Sub-Saharan Africa	2247 [0.9]	49.0	60.1 [10.6]	68.1	44.5	80.4	39.3	72.0	23.8	1982 [1971–1994]	25.2 [13.2–36.4]
North America	1768 [0.7]	44.4	60.2 [10.2]	51.6	64.0	74.3	40.4	74.4	4.5	1975 [1969–1986]	33.1 [21.3–39.1]
Central & South America	1267 [0.5]	43.6	60.2 [9.5]	84.0	25.3	71.6	15.2	47.1	83.4	1975 [1971–1986]	32.1 [21.4–36.3]
Total immigrants	64,194 [24.3]	49.5	63.5 [11.4]	60.9	27.8	74.5	22.7	58.9	31.7	1969 [1959–1982]	38.6 [25.8–48.7]
Total	264,102 [100.0]	46.4	62.7 [11.2]	45.0	23.1	74.5	23.6	65.3	9.4	–	–

Percentages include participants with missing or invalid responses. SD, standard deviation. IQR, interquartile range.
[a] Pre-tax annual household income from all sources in Australian dollars.
[b] Including Department of Veterans' Affairs white or gold card.
[c] Year first migrated to Australia for at least one year.

2724 participants (1.0%) were excluded for having missing or invalid responses for country of birth, leaving 264,102 participants.

The socio-demographic characteristics of participants by place of birth are shown in Table 1. Compared to Australian-born participants, a higher proportion of immigrants were male, lived in major cities, had university degrees and spoke a non-English language at home, while a lower proportion of immigrants were married or living with a partner, had an annual household income of at least $70,000 (Australian dollars), and had private health insurance. On average, immigrants were older than Australian-born participants. Of all regions of birth, participants born in Western Europe immigrated the earliest, with a median year of arrival of 1959, while participants born in East Asia immigrated most recently, with a median year of 1988.

The proportion of participants with each individual lifestyle risk factor is shown in Table 2. After adjusting for covariates, immigrants overall had a significantly higher RR of current smoking and a lower RR of harmful alcohol consumption and obesity than Australian-born participants.

Analyses from this point excluded 43,731 participants (16.4%) with missing or invalid responses for at least one of the five risk factors, leaving 220,371 participants. 17,273 (10.3%) Australian-born and 5659 (10.6%) immigrant participants had the lowest possible CDRI score of 0, while 32 (0.019%) Australian-born and 6 (0.011%) immigrant participants had scores ≥90.

For each region of birth, the mean CDRI score and adjusted mean difference (AMD) in CDRI score from Australian-born participants are shown in Table 3. The contribution of each risk factor to the adjusted mean CDRI score is shown in the supplementary content (**Figure A.1**). Mean CDRI scores ranged from 14.9 for participants from East Asia to 27.7 for participants from the Middle East and North Africa. There was significant variation in CDRI by place of birth ($p < 0.0001$). Participants born in all Asian regions, the United Kingdom (UK) and Ireland and Sub-Saharan Africa had lower CDRI scores than Australian-born participants. Significantly higher CDRI scores were observed for Western Europe, Eastern and Central Europe and the Middle East and North Africa.

The AMD in CDRI score by 10-year strata of years lived in Australia for each region of birth is shown in Fig. 1. 1949 (0.7%) participants with missing or invalid responses for age of migration were excluded, leaving 218,422 participants for these analyses. For immigrants overall, there was a significant increasing trend in AMD in CDRI score with increasing years lived in Australia ($p < 0.001$), with those living in Australia <10 years having an AMD of −3.4 and those living in Australia ≥40 years having an AMD of 0.6.

A significant increasing trend in AMD was found for participants born in Oceania, all Asian regions, the UK and Ireland and Western Europe, with those living in Australia <10 years having an AMD ranging between −9.5 and −1.9, and those living in Australia ≥40 years having an AMD ranging between −1.3 and 1.1. No significant trends in AMD were found for the remaining regions of birth.

Discussion

We found diversity in the co-occurrence of chronic disease lifestyle risk factors across different immigrant groups in the 45 and Up Study in NSW, Australia. Using the CDRI developed by Miller and Bauman, we found that only about 10% of both Australian-born and immigrant participants overall had the lowest possible risk of chronic disease. Participants born in Western Europe, Eastern and Central Europe, and the Middle East and North Africa had a mean CDRI score that potentially

Table 2
Lifestyle risk factors by place of birth using the maximum risk category for each risk factor in the chronic disease risk index in the 45 and Up Study (2006–2009), New South Wales, Australia.

Place of birth	Current smoker (%)	RR[a] (95% CI)	Harmful alcohol consumption[b] (%)	RR[a] (95% CI)	Obese[c] (%)	RR[a] (95% CI)	Physically inactive[d] (%)	RR[a] (95% CI)	Low fruit and vegetable intake[e] (%)	RR[a] (95% CI)
Australia	7.2	1.00	3.1	1.00	21.8	1.00	5.2	1.00	6.5	1.00
New Zealand	8.6	1.07 (0.97–1.17)	3.1	0.91 (0.78–1.08)	19.4	0.90 (0.85–0.96)	3.6	0.75 (0.64–0.87)	6.0	0.89 (0.80–1.00)
Oceania	6.4	0.64 (0.50–0.84)	2.9	0.80 (0.54–1.18)	22.3	0.99 (0.87–1.13)	4.7	1.03 (0.76–1.40)	6.7	0.93 (0.72–1.21)
East Asia	4.7	0.66 (0.57–0.78)	0.5	0.18 (0.11–0.29)	3.9	0.18 (0.15–0.22)	6.5	1.52 (1.32–1.74)	10.3	1.62 (1.46–1.81)
Southeast Asia	5.3	0.65 (0.57–0.73)	0.6	0.16 (0.11–0.24)	7.0	0.31 (0.28–0.35)	5.2	1.11 (0.97–1.27)	8.9	1.34 (1.22–1.49)
Central & South Asia	4.5	0.72 (0.56–0.91)	1.0	0.28 (0.16–0.50)	13.1	0.67 (0.58–0.77)	4.8	1.27 (0.99–1.62)	8.1	1.23 (1.02–1.48)
UK & Ireland	7.1	1.10 (1.04–1.15)	2.9	1.02 (0.95–1.11)	17.6	0.84 (0.81–0.86)	4.5	0.83 (0.78–0.88)	6.9	1.07 (1.02–1.13)
Western Europe	8.3	1.24 (1.16–1.32)	1.7	0.55 (0.48–0.64)	20.5	0.96 (0.92–0.99)	5.7	0.97 (0.90–1.06)	5.7	0.81 (0.75–0.88)
Eastern & Central Europe	8.8	1.21 (1.09–1.34)	1.7	0.51 (0.39–0.66)	21.6	1.05 (0.98–1.12)	7.2	1.20 (1.06–1.36)	6.2	0.84 (0.74–0.96)
Middle East & North Africa	14.1	1.49 (1.33–1.66)	0.7	0.18 (0.10–0.30)	27.4	1.23 (1.15–1.33)	9.0	1.70 (1.48–1.97)	6.3	0.74 (0.62–0.88)
Sub-Saharan Africa	4.9	0.80 (0.66–0.96)	1.3	0.37 (0.25–0.55)	13.9	0.69 (0.62–0.77)	3.7	0.96 (0.76–1.20)	6.3	1.06 (0.90–1.26)
North America	5.9	1.04 (0.85–1.26)	2.0	0.79 (0.56–1.12)	15.3	0.81 (0.72–0.91)	2.6	0.75 (0.55–1.02)	5.3	1.01 (0.82–1.24)
Central & South America	8.2	0.93 (0.77–1.13)	1.2	0.31 (0.19–0.53)	20.0	0.91 (0.81–1.02)	7.3	1.63 (1.33–1.99)	5.1	0.75 (0.59–0.96)
Total immigrants	7.4	1.05 (1.01–1.08)	2.1	0.68 (0.64–0.72)	17.2	0.81 (0.79–0.83)	5.1	1.00 (0.95–1.04)	6.8	1.02 (0.99–1.06)
Total	7.2	–	2.9	–	20.6	–	5.2	–	6.6	–

Percentages include participants with missing or invalid responses. RR, Relative Risk. CI, Confidence Interval.
[a] Adjusted for sex, age, remoteness, education level, marital status, household income and health insurance status.
[b] > 6 standard drinks per occasion if male; >4 if female.
[c] Body mass index ≥ 30 kgm^{-2}.
[d] Weekly physical activity time = 0 min.
[e] <3 serves of total fruit and vegetables per day.

puts them at greater risk of chronic disease than Australian-born participants. We also found that participants born in all Asian regions, the UK and Ireland, and Sub-Saharan Africa have a potentially lower risk of chronic disease than Australian-born participants. Further, participants born in Oceania and all Asian regions had mean CDRI scores that converged on that of Australian-born participants with increasing years lived in Australia. The same was true for immigrants from the UK and Ireland and Western Europe except for those living in Australia ≥40 years who had an estimated level of risk that slightly surpassed that of Australian-born participants.

The distribution of individual risk factors among immigrants in our study was similar to that reported in the NSW Population Health Survey (2006–2009) (Centre for Epidemiology and Research, 2010). For example, people born in China had lower rates of harmful alcohol consumption, smoking and obesity than the population average, but higher rates of physical inactivity and inadequate vegetable intake. The same pattern was observed for participants from East Asia in our study, more than half of whom were born in China. To our knowledge, only one other study has examined combinations of risk factors between immigrant groups in Australia. Feng et al. (2014) derived a risk index using unweighted, dichotomous variables in the 45 and Up Study (Feng et al., 2014). Their index, although primarily focused on dietary factors, identified differences between countries within a region. For example, of the three Eastern and Central European countries analysed, Russia had a significantly higher unhealthy lifestyle index than Australian-born participants, while Croatia and Poland were not significantly different (Feng et al., 2014). Together with our report, these studies highlight groups of immigrants with risky lifestyle behaviours.

It is unclear how the health profile of participants in this study may compare to that of their country of origin. Studies comparing multiple risk factors across countries are few. One study that directly compared data from six countries found that multiple risk factors occurred much more frequently in upper-middle income countries than in low-middle income countries (Wu et al., 2015). The authors suggested that lower-middle income countries are less likely to be exposed to risk factors associated with urban living (such as sedentary lifestyles and processed foods). However, immigrants are often a specific sub-group of their country of origin and are not necessarily representative of the population they left behind. Migration policies to Australia are complex, change over time and vary from a selection of skilled migrants using a points system to small groups of refugees accepted on humanitarian grounds (Statistics Section Department of Immigration and Multicultural Affairs, 2001). As such, socioeconomic factors among immigrant groups, such as educational attainment, can be higher than that of their home country (and Australian-born for that matter) (Australian Bureau of Statistics, 2007). Nevertheless, the immigrant groups with the lowest health risks in our study were also from low-middle income countries (e.g., those included in East and Southeast Asia), which suggests that some of the lifestyle patterns prior to migration may have been maintained.

A pattern of increasing CDRI score with increasing strata of years lived in Australia suggests that lifestyle behaviours may 'acculturate' for some immigrant groups, whereby immigrants tend to adopt the health behaviours of the host population over time (Bennett, 1993; Delavari et al., 2013). However, this was not observed for all regions of birth, and specifically, those with mean CDRI scores that were higher than Australian-born participants (i.e. immigrants from Eastern/Central Europe and the Middle East/North Africa). These immigrant groups tended to have higher CDRI scores regardless of the number of years lived in Australia. This may indicate that acculturation of health behaviours primarily occurs when immigrants adopt poorer health behaviours over time, but not the opposite. A review of acculturation and obesity appears to support this hypothesis, finding that seven of nine studies reported a positive association between higher acculturation and body weight variables, while three studies reported a negative

Table 3
Chronic disease risk index (CDRI) by place of birth in the 45 and Up Study (2006–2009), New South Wales, Australia.

Place of birth	Mean CDRI score (SD)	Adjusted[a] mean difference in CDRI score from Australian-born participants	Lower 95% CI	Upper 95% CI	*p*
Australia	23.0 (16.7)	–	–	–	–
New Zealand	22.6 (16.4)	−0.5	−0.9	0.0	0.06
Oceania	22.5 (16.9)	−0.9	−2.1	0.3	0.1
East Asia	14.9 (12.9)	−7.2	−7.8	−6.6	<0.0001
Southeast Asia	16.0 (13.8)	−6.6	−7.2	−6.1	<0.0001
Central & South Asia	18.6 (14.8)	−3.1	−4.0	−2.1	<0.0001
UK & Ireland	22.5 (16.0)	−0.2	−0.5	0.0	0.03
Western Europe	23.9 (16.1)	0.5	0.1	0.8	0.007
Eastern & Central Europe	24.6 (16.0)	1.3	0.8	1.9	<0.0001
Middle East & North Africa	27.7 (17.3)	3.5	2.7	4.3	<0.0001
Sub-Saharan Africa	19.6 (14.9)	−1.9	−2.6	−1.2	<0.0001
North America	20.1 (15.2)	−0.7	−1.5	0.1	0.08
Central & South America	23.0 (16.2)	−0.3	−1.3	0.6	0.5
Total immigrants	22.0 (16.0)	−0.8	−1.0	−0.6	<0.0001
Total	22.7 (16.5)	–	–	–	–

SD, Standard Deviation. CI, Confidence Interval.
[a] Adjusted for sex, age, remoteness, education level, marital status, household income and health insurance status.

association in females only (Delavari et al., 2013). As well as obesity, acculturation has been observed with physical activity and diet (Huang et al., 1996; Shah et al., 2015). For example, in a study of Japanese–American men in Hawaii it was found that those who retained a traditional Japanese diet and had spent more time living in Japan had a lower BMI, higher physical activity levels and a healthier diet, and a reduced prevalence of type 2 diabetes than those who adopted a 'Westernised' lifestyle (Huang et al., 1996).

Possible explanations for the differences in risk factor co-occurrence between immigrant groups are the diversity in levels of urbanisation and socioeconomic development in low-, middle- and high-income countries, and the rate of 'risk transition' from infectious disease burden to non-communicable diseases burden over time (Wu et al., 2015; World Health Organisation, 2009). Overweight and obesity, physical inactivity and dietary risk factors are all associated with increased urbanisation (Wu et al., 2015), and as low-income countries become wealthier there tends to be an increased burden of disease attributable to these three risk factors along with alcohol and tobacco use (World Health Organisation, 2009). In our study, this may partially explain why participants born in Sub-Saharan Africa and Asian regions had lower mean CDRI scores than Australian-born participants while participants born in American and European regions and the Middle East and North Africa had equal or higher CDRI scores, and the trend of increasing CDRI score with increasing years lived in Australia.

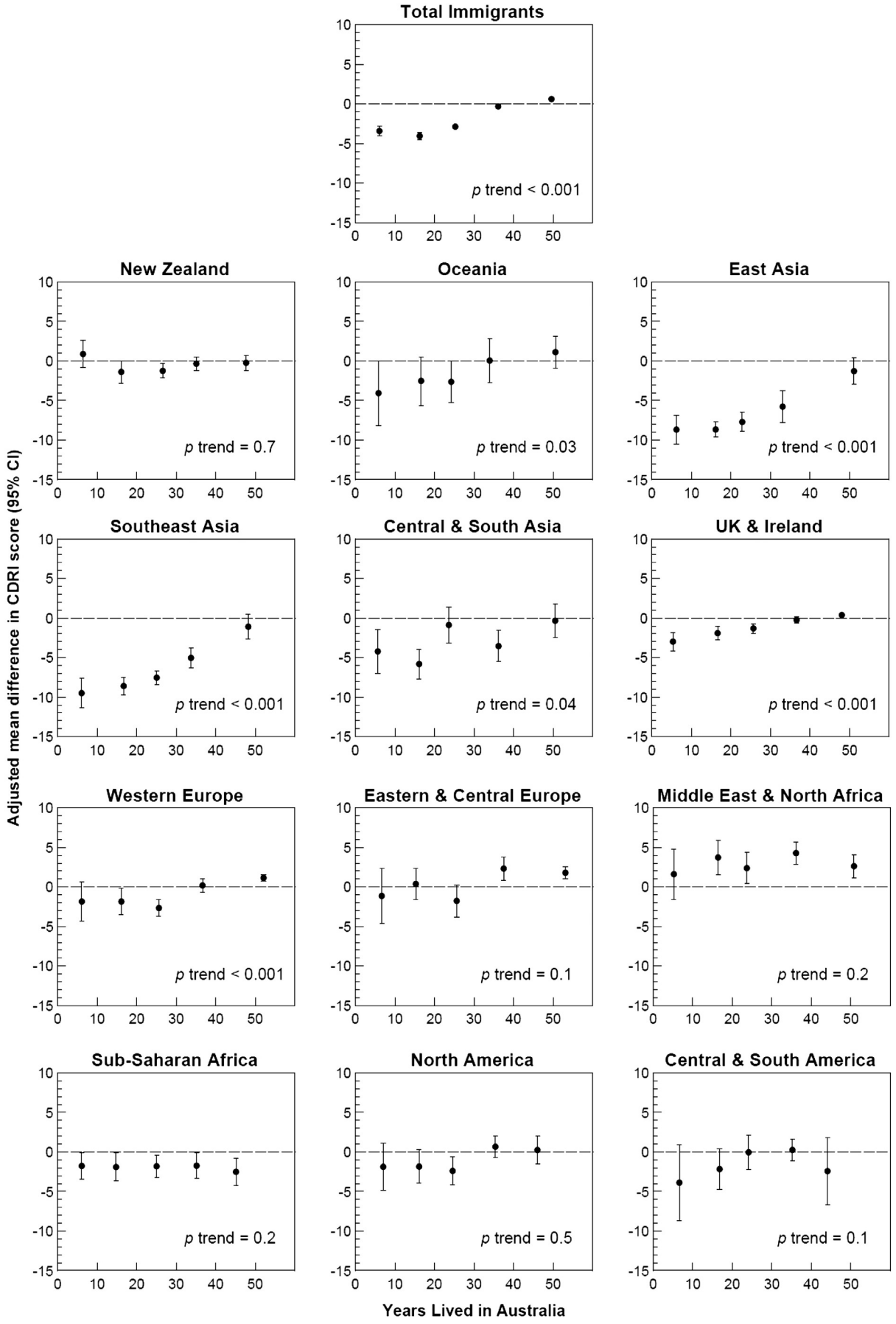
While individual risk factor analysis is informative, it cannot be used to estimate the overall level of chronic disease risk. For example, participants born in the three Asian regions had relatively high RRs of physical inactivity and inadequate fruit and vegetable intake, however they had the lowest mean CDRI scores. Conversely, participants born in Western Europe, Eastern and Central Europe and the Middle East and North Africa had relatively low RRs of harmful alcohol consumption and inadequate fruit and vegetable intake, yet had the highest mean CDRI scores. A cohort study in Hawaii found a dose response relationship between a similar version of a CDRI and a number of chronic disease outcomes (Meng et al., 1999). Although smoking accounted for over 50% of the CDRI's impact on mortality, and BMI 25%, the effects of negative health practises were cumulative. Therefore both individual and multiple risk factor analyses are necessary to obtain a complete picture of chronic disease risk.

This study has several limitations. Firstly, being a cross-sectional study, participants were not tracked over time, so it is possible that changing health behaviours in migrants' country of origin over time could partially explain the apparent trends, rather than acculturation. A limitation of the 45 and Up Study is the potential for selection bias due to the relatively low response rate (18%), where participants in certain population sub-groups, such as the highly economically disadvantaged, may be under-represented. Therefore caution is needed when generalising prevalence data to the NSW population. However, a direct comparison of the 45 and Up Study with the NSW Population Health Survey found consistent exposure-outcome relationships between the two studies, including variables related to lifestyle behaviours (Mealing et al., 2010). Another limitation is that some immigrant groups may be under-represented because the questionnaire was only available in English. The proportion of immigrants who spoke a non-English language at home in this study was 32%, lower than the 53% reported for first generation immigrants in the 2011 census (Australian Bureau of Statistics, 2012). This may suggest that immigrant participants selected in this study have a higher degree of acculturation than those in the general population of NSW, and so the AMDs in CDRI score may be biased towards the null. Caution must therefore be exercised when interpreting null results.

The CDRI is likely to have greater validity than most other approaches to co-occurrence analysis due to the use of multiple risk levels and assigning weights based on impact on loss of disability-adjusted life years, however it is not without limitations. Firstly, an assumption underlying the CDRI is that multiple risk factors have an additive effect on chronic disease, and therefore any potential multiplicative effects are not captured. Secondly, the multiple risk levels defined for alcohol consumption and inadequate physical activity are based on now outdated versions of national health guidelines (Australian Government Department of Health, 2014). Furthermore, the fruit and vegetable intake risk levels are based on tertiles of intake in NSW rather than health guidelines as for the other four risk factors. Updating the CDRI to account for current alcohol, physical activity and fruit and vegetable intake guidelines would confirm that the risk levels used reflect current evidence. Finally, a disadvantage common to all methods of co-occurrence analysis/combining risk factors, including the CDRI, is that they do not provide information about statistical associations between each of the individual risk factors (McAloney et al., 2013). An alternative method would be cluster analysis, where ascertaining the strength of relationships between risk factors means that risk factors that commonly occur together can be grouped and used to identify sub-populations with qualitatively different risk profiles (e.g. (Griffin et al., 2014)).

Conclusion

This study reveals differences in potential risk of chronic disease across immigrant groups in Australia. These results will assist policy makers in targeting culturally appropriate chronic disease prevention programmes to the groups with the highest need, and the specific behavioural risk factors to target for maximum impact on burden of disease in different immigrant groups. Future work in this area will focus


Total Immigrants
p trend < 0.001
New Zealand
p trend = 0.7
Oceania
p trend = 0.03
East Asia
p trend < 0.001
Southeast Asia
p trend < 0.001
Central & South Asia
p trend = 0.04
UK & Ireland
p trend < 0.001
Western Europe
p trend < 0.001
Eastern & Central Europe
p trend = 0.1
Middle East & North Africa
p trend = 0.2
Sub-Saharan Africa
p trend = 0.2
North America
p trend = 0.5
Central & South America
p trend = 0.1
Adjusted mean difference in CDRI score (95% CI)
Years Lived in Australia

on quantifying health outcomes in relation to the CRDI over time. It will be of interest whether the regions of birth identified in our study will have higher than average rates of chronic disease in the future.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2015.09.004.

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Fig. 1. Adjusted mean difference and 95% confidence intervals (CI) in chronic disease risk index (CDRI) score for each region of birth compared to Australian-born participants by years lived in Australia in the 45 and Up Study (2006–2009), New South Wales, Australia. Adjusted for sex, age, remoteness, education level, marital status, household income and health insurance status. Plotted at median value of each ten year stratum of years lived in Australia. p trend = 1 degree of freedom.

Supplementary Material

Table A.1: Countries of birth in each region used in the analyses.

Place of birth	Countries
Australia	Australia
New Zealand	New Zealand
Oceania	Cook Islands, Fiji, French Polynesia, Kiribati, Nauru, New Caledonia, Niue, Papua New Guinea, Samoa, Solomon Islands, Tonga, Vanuatu, Wallis and Futuna
East Asia	China, Hong Kong, Japan, Macau, South Korea, Taiwan
Southeast Asia	Brunei Darussalam, Burma (Myanmar), Cambodia, East Timor, Indonesia, Laos, Malaysia, Philippines, Singapore, Sri Lanka, Thailand, Vietnam
Central & South Asia	Afghanistan, Armenia, Bangladesh, Georgia, India, Kyrgyz Republic, Mongolia, Nepal, Pakistan
UK & Ireland	Ireland, United Kingdom
Western Europe	Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Gibraltar, Greece, Iceland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland
Eastern & Central Europe	Albania, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Moldova, Montenegro, Poland, Republic of Macedonia, Romania, Russia, Serbia, Slovakia, Slovenia, Ukraine
Middle East & North Africa	Algeria, Bahrain, Egypt, Gaza Strip and West Bank, Iran, Iraq, Jordan, Lebanon, Libya, Morocco, Syria, Tunisia, Turkey, Yemen
Sub-Saharan Africa	Botswana, Congo, Ethiopia, Ghana, Kenya, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Nigeria, Senegal, Seychelles, South Africa, St Helena, Sudan, Tanzania, Uganda, Zambia, Zimbabwe
North America	Bermuda, Canada, United States of America
Central & South America	Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Dutch West Indies, Ecuador, El Salvador, Falkland Islands, Guatemala, Guyana, Jamaica, Mexico, Netherlands Antilles, Nicaragua, Panama, Paraguay, Peru, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela

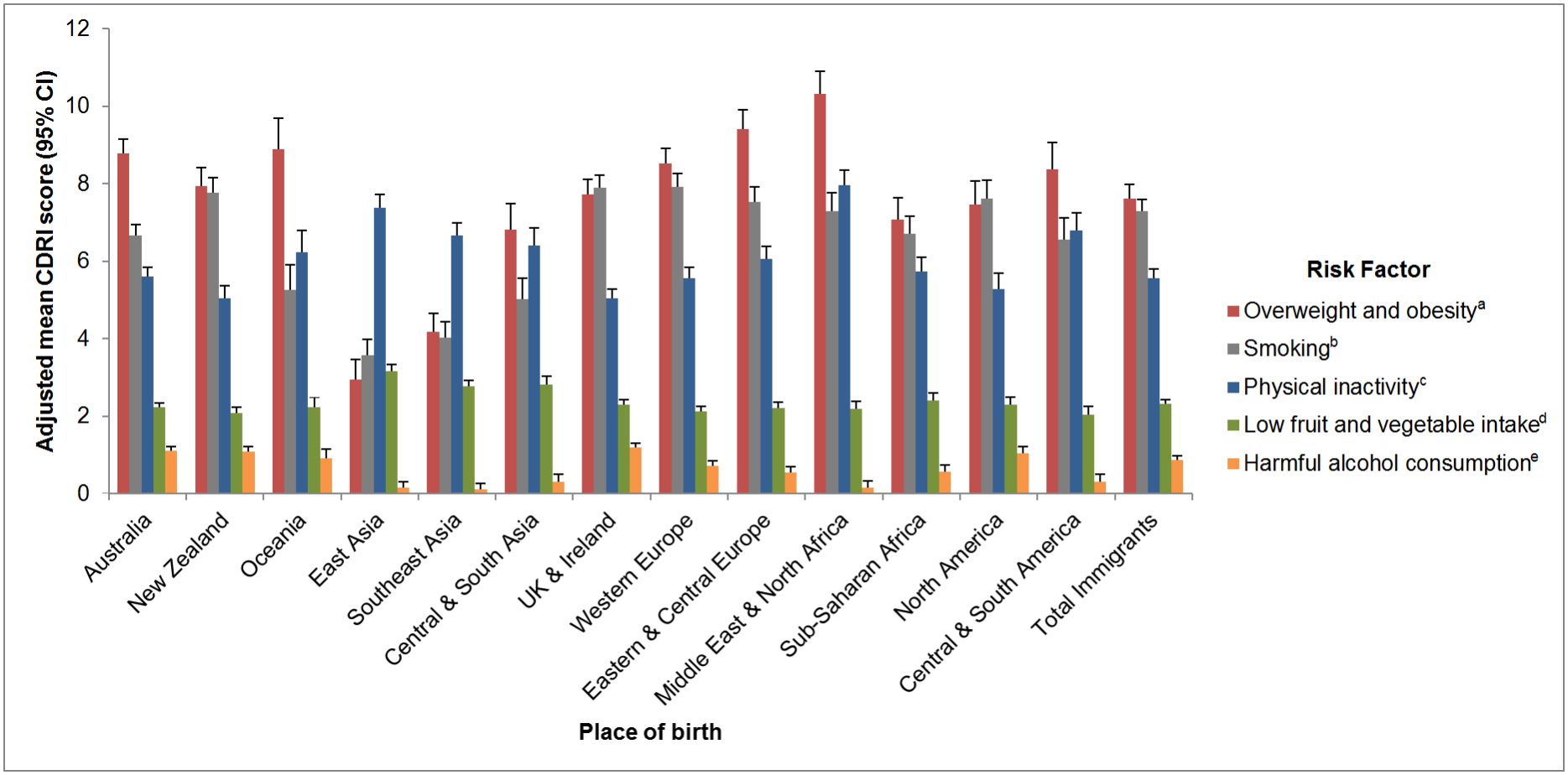

Figure A.1: Contribution of each risk factor to adjusted mean chronic disease risk index (CDRI) score and 95% confidence intervals (CI) by place of birth in the 45 and Up Study (2006-2009), New South Wales, Australia. Adjusted for sex, age, remoteness, education level, marital status, household income and health insurance status. [a]Body mass index ≥ 25 kgm^{-2}. [b]Current and former smoking. [c]Weekly physical activity time < 150 minutes or < 5 activity sessions per week. [d]< 3 serves of total fruit and vegetables per day. [e]> 4 standard drinks per occasion if male; > 2 if female.

6.2 – Additional Analyses

Additional analyses were conducted to investigate two further questions with regards to alcohol consumption and region of birth:

1. *How does the prevalence of alcohol consumption vary by region of birth?*
2. *Do differences in alcohol consumption behaviours by region of birth acculturate with greater time since migration?*

Rationale and Methods. The main analysis showed that the prevalence of harmful drinking, and the contribution of harmful drinking to the CDRI, varied by region of birth. Additional analyses were conducted to investigate whether the odds of consuming > 14 alcoholic drinks per week, daily or near-daily drinking (consuming alcohol 6-7 days per week) and mean > 4 drinks per drinking-day differed by region of birth, compared to Australian-born participants. These were calculated using logistic regression models adjusted for all the covariates used in the main analysis, both for all participants and after restriction to participants classified as current drinkers (≥ 1 drink per week).

The main analysis also suggested that health behaviours acculturate to those of the host country with greater time since migration. Thus, additional analyses investigated whether the odds of consuming > 14 alcoholic drinks per week by region of birth approximated that of Australian born participants with longer time since migration. These were calculated using logistic regression, including a test for linear trend using the median number of years lived in Australia in each category.

Results. Immigrants from most regions of birth had lower odds of consuming > 14 drinks per week, having 6-7 drinking-days per week and consuming > 4 drinks per drinking-day compared to Australian-born participants (Table 6.1). Participants born in English-speaking countries generally had higher odds for all three outcomes compared to participants born in non-English speaking countries. Participants born in the three Asian regions, the Middle East and North Africa and Central

and South America generally had lower odds ratios across the three outcomes compared to other regions of birth. The only region of birth with higher odds for any outcome compared to Australian-born participants was the United Kingdom and Ireland, with higher odds of both consuming > 14 drinks per week and having 6-7 drinking-days per week (among all participants).

When examining the odds of consuming > 14 drinks per week by time lived in Australia, there was a trend of increasing odds with greater number of years lived in Australia for most region of birth groups (Table 6.2). For participants born in the United Kingdom and Ireland there was a trend of decreasing odds. Only for Western Europe and English-speaking countries combined were there no significant trends.

Conclusions. Immigrants in the 45 and Up Study cohort appear to have lower levels of drinking that Australian born participants. Additionally, drinking pattern differed by region of birth, with higher odds of having 6-7 drinking-days per week and consuming > 4 drinks per drinking-day for participants born in English-speaking countries and Australia compared to participants born in non-English speaking countries. Further, although this is a cross-sectional study, the results suggest that alcohol consumption patterns among migrants may acculturate to that of Australian born participants.

Table 6.1. Odds of consuming greater than 14 drinks per week, consuming alcohol 6-7 days per week and consuming mean > 4 drinks per day of drinking by region of birth in the 45 and Up Study (2006-2009), New South Wales, Australia.

		OR (95% CI)		
Region of birth	**n**	**> 14 drinks/week**	**Consumed alcohol 6-7 days/week**	**Mean > 4 drinks/drinking-day**
Among all participants				
Australia	196,874	1.00	1.00	1.00
New Zealand	5,002	0.99 (0.91-1.07)	1.12 (1.05-1.20)	0.88 (0.78-0.98)
Oceania	868	0.70 (0.56-0.87)	0.64 (0.54-0.77)	0.95 (0.74-1.23)
East Asia	3,129	0.15 (0.12-0.19)	0.25 (0.22-0.29)	0.16 (0.12-0.23)
Southeast Asia	4,234	0.18 (0.15-0.22)	0.26 (0.23-0.29)	0.24 (0.19-0.30)
Central & South Asia	1,311	0.31 (0.25-0.39)	0.40 (0.34-0.48)	0.26 (0.18-0.37)
UK & Ireland	25,914	1.07 (1.03-1.11)	1.16 (1.13-1.20)	1.00 (0.95-1.05)
Western Europe	11,439	0.60 (0.56-0.64)	0.96 (0.92-1.01)	0.55 (0.50-0.60)
Eastern & Central Europe	3,537	0.45 (0.40-0.52)	0.62 (0.56-0.67)	0.45 (0.37-0.55)
Middle East & North Africa	2,041	0.16 (0.12-0.20)	0.29 (0.25-0.34)	0.16 (0.11-0.23)
Sub-Saharan Africa	2,237	0.49 (0.42-0.57)	0.79 (0.71-0.87)	0.48 (0.39-0.61)
North America	1,783	0.97 (0.85-1.11)	1.02 (0.92-1.14)	0.79 (0.64-0.98)
Central & South America	1,221	0.26 (0.20-0.35)	0.64 (0.55-0.75)	0.34 (0.24-0.47)
Majority ESC[a]	32,699	1.06 (1.02-1.09)	1.15 (1.12-1.18)	0.97 (0.92-1.02)
Majority Non-ESC[b]	30,054	0.41 (0.39-0.43)	0.63 (0.61-0.65)	0.42 (0.39-0.44)
Total Immigrants	62,753	0.74 (0.72-0.76)	0.90 (0.88-0.92)	0.70 (0.67-0.73)
Among drinkers only				
Australia	133,169	1.00	1.00	1.00
New Zealand	3,677	0.94 (0.86-1.02)	1.03 (0.96-1.11)	0.84 (0.75-0.94)
Oceania	462	0.94 (0.74-1.18)	0.83 (0.68-1.02)	1.32 (1.01-1.74)
East Asia	957	0.29 (0.23-0.37)	0.56 (0.48-0.65)	0.31 (0.22-0.43)
Southeast Asia	1,341	0.33 (0.27-0.39)	0.53 (0.46-0.60)	0.43 (0.34-0.55)
Central & South Asia	628	0.45 (0.36-0.57)	0.60 (0.50-0.71)	0.37 (0.26-0.55)
UK & Ireland	19,016	0.99 (0.95-1.02)	1.03 (0.99-1.06)	0.93 (0.88-0.98)
Western Europe	7,578	0.57 (0.53-0.60)	0.92 (0.88-0.97)	0.53 (0.48-0.58)
Eastern & Central Europe	2,045	0.46 (0.40-0.52)	0.64 (0.58-0.71)	0.46 (0.38-0.56)
Middle East & North Africa	871	0.21 (0.17-0.28)	0.41 (0.35-0.49)	0.23 (0.16-0.33)
Sub-Saharan Africa	1,485	0.52 (0.45-0.61)	0.87 (0.78-0.98)	0.52 (0.42-0.66)
North America	1,309	0.99 (0.86-1.14)	1.02 (0.91-1.15)	0.81 (0.65-1.01)
Central & South America	701	0.28 (0.21-0.37)	0.72 (0.61-0.86)	0.36 (0.25-0.52)
Majority ESC[a]	24,002	0.98 (0.95-1.01)	1.03 (1.00-1.06)	0.91 (0.86-0.95)
Majority Non-ESC[b]	16,086	0.48 (0.46-0.50)	0.77 (0.74-0.79)	0.49 (0.45-0.52)
Total Immigrants	40,088	0.76 (0.74-0.78)	0.92 (0.90-0.94)	0.73 (0.70-0.76)

[a]Canada, Ireland, New Zealand, the United Kingdom and the United States of America. [b]All other countries. Adjusted for sex, age, remoteness, education, household income, health insurance status and partner status. OR, Odds Ratio. CI, Confidence Interval. UK, United Kingdom. ESC, English-Speaking Countries.

Table 6.2. Odds of consuming greater than 14 drinks per week by region of birth and time lived in Australia in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Years lived in Australia: OR consume > 14 drinks/week[a] (95% CI)					
Region of birth	**n**	**< 10 years**	**10-19 years**	**20-29 years**	**30-39 years**	**≥ 40 years**	p_{trend}
New Zealand	4,798	0.49 (0.34-0.71)	0.64 (0.49-0.84)	0.93 (0.79-1.09)	1.20 (1.04-1.39)	1.12 (0.96-1.32)	< 0.001
Oceania	837	0.33 (0.13-0.84)	0.34 (0.18-0.66)	0.70 (0.44-1.09)	0.64 (0.37-1.09)	1.07 (0.76-1.50)	0.04
East Asia	3,045	0.13 (0.06-0.27)	0.06 (0.03-0.10)	0.09 (0.05-0.16)	0.13 (0.06-0.28)	0.55 (0.39-0.78)	< 0.001
Southeast Asia	4,089	0.02 (0.00-0.14)	0.08 (0.05-0.14)	0.12 (0.08-0.16)	0.27 (0.19-0.38)	0.54 (0.40-0.74)	< 0.001
Central & South Asia	1,273	0.08 (0.03-0.26)	0.09 (0.04-0.19)	0.32 (0.19-0.54)	0.42 (0.27-0.64)	0.73 (0.50-1.06)	< 0.001
UK & Ireland	24,844	1.18 (0.98-1.43)	1.27 (1.10-1.47)	1.17 (1.06-1.29)	1.16 (1.08-1.25)	0.99 (0.94-1.04)	< 0.001
Western Europe	10,742	1.07 (0.70-1.63)	0.57 (0.39-0.82)	0.65 (0.52-0.80)	0.58 (0.49-0.69)	0.60 (0.55-0.65)	0.68
Eastern & Central Europe	3,277	0.27 (0.10-0.75)	0.17 (0.09-0.33)	0.22 (0.14-0.37)	0.38 (0.27-0.53)	0.57 (0.48-0.67)	< 0.001
Middle East & North Africa	1,904	0.04 (0.01-0.27)	0.10 (0.04-0.23)	0.03 (0.01-0.13)	0.12 (0.08-0.20)	0.30 (0.21-0.43)	< 0.001
Sub-Saharan Africa	2,174	0.32 (0.21-0.48)	0.22 (0.13-0.37)	0.50 (0.38-0.67)	0.58 (0.42-0.80)	0.79 (0.58-1.07)	< 0.001
North America	1,738	0.65 (0.37-1.15)	0.93 (0.65-1.33)	0.79 (0.57-1.08)	1.03 (0.82-1.30)	1.32 (1.01-1.73)	0.04
Central & South America	1,143	0.13 (0.02-0.96)	0.13 (0.05-0.35)	0.26 (0.14-0.47)	0.24 (0.16-0.36)	0.95 (0.47-1.92)	0.001
Majority ESC[b]	31,380	0.91 (0.78-1.07)	1.05 (0.93-1.19)	1.07 (0.98-1.16)	1.16 (1.09-1.23)	1.01 (0.96-1.06)	0.56
Majority Non-ESC[c]	28,520	0.24 (0.19-0.31)	0.15 (0.12-0.18)	0.28 (0.25-0.32)	0.39 (0.35-0.43)	0.60 (0.56-0.64)	< 0.001
Total Immigrants	59,900	0.53 (0.46-0.60)	0.45 (0.41-0.49)	0.63 (0.59-0.68)	0.83 (0.79-0.88)	0.82 (0.79-0.86)	< 0.001

[a]Compared to Australian-born participants. [b]Canada, Ireland, New Zealand, the United Kingdom and the United States of America. [c]All other countries. Adjusted for sex, age, remoteness, education, household income, health insurance status and partner status. OR, Odds Ratio. CI, Confidence Interval. UK, United Kingdom. ESC, English-Speaking Countries.

6.3 – Discussion and Conclusions

Overall, immigrants in the 45 and Up Study had a higher odds of smoking, a lower odds of harmful alcohol consumption and overweight and obesity, and no difference in odds of physical inactivity and insufficient fruit and vegetable consumption compared to Australian-born participants. Using the CDRI, the regions of birth with the highest potential risk of chronic disease due the combination of these risk factors were the Middle East and North Africa, and Eastern and Central Europe, while the regions of birth with the lowest risk were East Asia, Southeast Asia and Central and South Asia. Further, differences in CDRI score between Australian-born participants and immigrants were largely attenuated with greater number of years since migration. Specifically, the risk profile of immigrants approximated that of the Australian-born participants the longer they had lived in Australia.

The risk factor contributing the most to CDRI score varied by region of birth, with the largest contributor being either smoking, overweight and obesity or physical inactivity depending on the region of birth group. Interestingly, across all regions of birth, harmful alcohol consumption contributed the least to CDRI scores. Alcohol contributed the most to CDRI scores among Australian-born participants and participants born in English-speaking countries.

Several additional analyses were performed. These showed that participants born in Australia and English-speaking countries had higher odds of the three different measures of alcohol consumption. That is, consuming > 14 drinks per week, having 6-7 drinking-days per week and consuming > 4 drinks per drinking-day compared to participants born elsewhere, even when restricted to drinkers. For almost all regions of birth the odds of consuming > 14 drinks per week increased with greater years lived in Australia.

The identified differences in chronic disease risk factors for key immigrant groups observed here can be used by policy makers and health workers to monitor chronic disease outcomes for these groups

and potentially plan targeted chronic disease prevention and/or education programmes to achieve maximal public health gain. The results also suggest that lifestyle behaviours 'acculturate' to the host population for certain groups over time, but possibly in the direction of worsening health behaviours only. Thus, interventions could target both the groups with the highest CDRI scores overall, as well as the groups with low CDRI scores that may be at risk of worsening over time. For alcohol consumption in particular, the increasing odds of consuming > 14 drinks per week with greater years lived in Australia was apparent for almost every region of birth group, particularly for participants born in non-English speaking countries. Future studies will determine whether the observed differences in CDRI scores and alcohol consumption by region of birth will result in overall differences in mortality and other health outcomes.

The next chapter investigated the relationship between incident health conditions and drinking cessation, to examine the nature of the 'sick-quitter effect' and potential strategies of addressing it.

6.4 – References

1. Sarich, P.E.A., et al., *Co-occurrence of chronic disease lifestyle risk factors in middle-aged and older immigrants: A cross-sectional analysis of 264,102 Australians.* Prev Med, 2015. **81**: p. 209-215.

Chapter 7 – The Association between Illness and Change in Alcohol Consumption

Chapter summary

This chapter contains an article prepared for publication, which investigated the association between incident disease and drinking cessation, with the aim of understanding the relative contributions of a variety of health conditions to the 'sick-quitter effect'. This was examined by comparing the odds of quitting drinking between baseline and the 5-year follow-up questionnaire, in relation to the occurrence of 28 health conditions and four general indicators of health. Sensitivity tests were performed to determine whether associations varied by sex, age and smoking status, whether associations remained unchanged with mutual adjustment for other health conditions, and whether associations between general indicators of health and drinking cessation were accounted for by the occurrence of specific health conditions and vice versa. The health conditions and general indicators of health with the greatest impact on drinking cessation were identified, and implications for further research and methods of addressing the 'sick-quitter effect' in prospective studies were discussed. The findings of the article were presented at the Australasian Epidemiological Association Annual Scientific Meeting 2017 (Sydney) and the 45 and Up Study Annual Forum 2017 (Sydney).

Additional analyses examined the association between incident health conditions and changes in drinking behaviour other than quitting (e.g. becoming a very light drinker), and a comparison of the effectiveness of different methods of addressing the 'sick-quitter effect' in reducing confounding by baseline health status. Implications of these results for the remaining chapters were discussed.

7.1 – Journal Article (Prepared for Publication)

The following article is prepared for publication. The results of the main analysis are additionally graphed in Figure D.1 in Appendix D (this graph did not appear in the article).

Title

A prospective study of health conditions related to alcohol consumption cessation among 97,852 drinkers aged 45 and over in Australia.

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Keywords

Alcohol, drinking, cessation, health behaviour, health condition, illness, disease, sick-quitter

4579 words.

Abstract

Background: Prior studies have suggested that people who develop serious health conditions are more likely to cease drinking alcohol (the 'sick-quitter effect'); the magnitude of this effect across a large range of diseases is uncertain. We quantified the 'sick-quitter effect' after diagnosis of a variety of health conditions.

Methods: We investigated the relationship of 28 health conditions and four general indicators of health to ceasing alcohol consumption among 97,852 drinkers aged ≥45 years between baseline (2006-2009) and median 5.3 years follow-up in the New South Wales (NSW) 45 and Up Study. Incident health conditions at follow-up were self-reported. Logistic regression quantified odds ratios (OR) and 95% confidence intervals (CI) of ceasing alcohol consumption at follow-up (vs continuing), in relation to illness, adjusted for socio-demographic characteristics.

Results: At follow-up, 9.6% (n=9438) of drinkers had ceased drinking. Drinking cessation was significantly associated with 24 of 32 health variables examined: 15.4% of participants with incident diabetes quit drinking (OR for quitting vs continuing 1.77, 95% CI 1.60-1.96), 16.4% with Parkinson's disease (1.71, 1.35-2.17), 17.8% with poor memory (1.68, 1.43-1.97), 19.2% with hip fracture (1.64, 1.30-2.06), 14.7% with stroke (1.45, 1.27-1.66), 12.5% with depression (1.40, 1.26-1.55), 15.0% with breast cancer (1.38, 1.18-1.61), 12.3% with heart disease (1.34, 1.25-1.44), and 13.3% with osteoarthritis (1.22, 1.12-1.33). Strong associations with quitting were observed in those with a decline in self-rated overall health (2.93, 2.53-3.40) and quality of life (2.68, 2.24-3.21). Findings were generally consistent for men and women, by age-group and by smoking status.

Conclusions: Diagnosis with a variety of health conditions appears to prompt drinking cessation in older adults. Reduced general health doubles or triples the odds of quitting, and odds of cessation are increased by 22-77% in those who reported diabetes, Parkinson's disease, poor memory, hip fracture, stroke, depression, breast cancer, heart disease and osteoarthritis.

Word count: 300

Introduction

Alcohol consumption is causally related to many health conditions, including various cancers, cardiovascular disease, liver disease and injury[1]. However the relationship of all-cause mortality and other health outcomes with alcohol is routinely reported to have a J-shaped risk curve, where light or moderate drinking is associated with lower risk than non-drinking and heavy drinking[2]. The J-shaped risk curve is often explained by the 'sick-quitter effect', whereby the "non-drinking" group appear to have a higher risk of negative health outcomes than light or moderate drinkers because it includes a large number of ex-drinkers, who have health conditions which both caused them to quit drinking and increase their risk of morbidity and mortality[2-5]. Using non-drinkers as a reference group in regression analyses will therefore lower the relative risk observed in drinkers. Furthermore, if the 'sick-quitter effect' is strong enough, it can produce spurious protective effect estimates among light and moderate drinkers, even for implausible outcomes such as hearing loss and hip fracture[5].

One method to overcome the 'sick-quitter effect' involves making a distinction between lifetime abstainers and ex-drinkers and using lifetime abstainers as the reference group; however lifetime abstainers also have a higher prevalence of ill-health than light and moderate drinkers which may also bias estimates of association[5]. Another practice in cohort studies is to exclude from the analysis persons who at baseline have one or more serious diseases, which may have caused them to quit or limit their alcohol intake. A recent meta-analysis of alcohol consumption and all-cause mortality found that 34 of 87 studies made exclusions for known prior disease[2]. Commonly, people with cancer, ischemic heart disease and stroke are excluded, although the selection of health conditions is inconsistent between studies, with other diseases such as thrombosis, type 2 diabetes, chronic obstructive pulmonary disease and liver disease also excluded[6-10]. Further, individuals often change their behaviour in response to feeling unwell, prior to the overt diagnosis of disease, so the practice of exclusion is unlikely to fully account for this issue[11, 12].

There are few large prospective studies that have quantified the relative relation of health conditions to drinking cessation. Health conditions previously reported to be associated with drinking cessation (or reduction) in prospective studies included poor/declining self-rated overall health[13-16], cancer[15], ischaemic heart disease[17], cardiovascular disease[16], liver disease[16], incident hospitalisation[18], depression[13], poor psychological health[16, 19], "longstanding illness"[19] and beginning prescription medications including anti-neoplastic agents, anti-thrombolytic agents and antidepressants[14]. Conversely, some studies did not find an association between negative health events[20], cancer[21], hypertension[16], cardiovascular disease[15], gastric disease[16], hospitalisation[21] and psychiatric diagnosis[21] with drinking cessation or reduction. One study reported differential effects by age, where younger drinkers were more likely to quit in relation to liver disease and older drinkers were more likely to quit in relation to cardiovascular disease[16]. Studies have also examined differential effects by sex[18] and smoking status[20]. Overall, these studies have differed in methodology and in number of participants (ranging from 1291 to 14,885; some were possible underpowered), and have mostly examined a small number of illnesses.

The aim of this study was to use data from a large cohort study to examine how newly-acquired health conditions are associated with alcohol drinking cessation, while testing for interactions with sex, age and smoking status.

Methods

Study sample

The Sax Institute's 45 and Up Study, a cohort study of New South Wales (NSW) residents, was used for the analysis. Detailed study methods have previously been described[22]. In summary, from 2006 to 2009 persons aged at least 45 years were randomly sampled from the Department of Human Services enrolment database and completed a baseline health and lifestyle questionnaire. The

database includes all citizens and permanent residents of Australia as well as some temporary residents and refugees. Persons residing in rural and remote areas and those aged 80 years and over were oversampled by a factor of two. Participants completed a follow-up questionnaire between 2012 and 2016, with a response rate of 53%. The study questionnaires are available at https://www.saxinstitute.org.au/our-work/45-up-study/questionnaires.

Ethics approval for the 45 and Up Study was granted by the University of NSW Human Research Ethics Committee and for this specific analysis by the NSW Population Health Services Research Ethics Committee.

Ascertainment of alcohol consumption patterns

Alcohol consumption was self-reported at baseline and follow-up with the question, "*About how many alcoholic drinks do you have each week?*". Those who reported 0 drinks at baseline were excluded from the main analysis. Those who reported ≥ 1 drink per week at baseline and 0 (indicating either no alcohol consumption or < 1 drink per week) at follow-up were considered quitters. Those who reported ≥ 1 drink per week at follow-up were considered continuing drinkers.

Ascertainment of health conditions

Health conditions were self-reported and included 28 health conditions and four indicators of general health. Participants who did not report the health condition at baseline and reported having the health condition at follow-up were considered a new case.

The 28 health conditions were captured by the following questionnaire items:

1) "*Has a doctor EVER told you that you have…*" female breast cancer, prostate cancer, melanoma, non-melanoma skin cancer, "other" cancer, heart disease, stroke, blood clot, high blood pressure

(except if only during pregnancy), diabetes (any type), Parkinson's disease, enlarged prostate, asthma, hayfever, depression and anxiety. At follow-up the checkbox for heart disease in the baseline questionnaire was replaced with three checkboxes: "*heart failure (cardiac failure, weak heart, enlarged heart)*", "*atrial fibrillation*" and "*other heart disease*". Ticking any of these three checkboxes at follow-up and not baseline was counted as a new case of heart disease. 12.6% of participants received an early version of the questionnaire which did not include an item for depression or anxiety, and only one item which combined "*asthma or hayfever*". These participants were set to missing for analyses of depression and anxiety. 2.3% of participants answered "yes" to "*asthma or hayfever*" and were set to missing for the separate analyses of asthma and hayfever.

2) "*In the last month have you been treated for…*" thyroid "*problems*", osteoarthritis and osteoporosis or low bone density.

3) "*In general, how would you rate your…*" eyesight, memory, and teeth and gums (excellent/very good/good/fair/poor. 'Poor' was defined as the condition being present and all other options taken as the condition being absent).

4) "*Have you had a broken/fractured bone in the last 5 years?*" (yes/no) for hip, and all other bones.

5) "*Do you feel you have a hearing loss?*" (yes/no).

6) "*How many of your own teeth do you have left?*" (0/1-9/10-19/≥ 20, with '0' defined as having the condition of having no teeth left).

7) "*About how many times a week are you usually troubled by leaking urine?*" (never/once a week or less/2-3 times/4-6 times/every day, with '2-3 times' or more defined as the condition being present and once a week or less as the condition being absent).

8) "*How often are you able to get and keep an erection that is firm enough for satisfactory sexual activity?*" (always/usually/sometimes/never/I would rather not answer the question, where 'never'

was defined as the condition being present and 'always', 'usually' or 'sometimes' taken as the condition being absent).

The four general health indicators were poor overall health, poor quality of life, needing help with daily tasks, and low physical functioning, captured respectively by the following questions: 1) "*In general, how would you rate your overall health?*" (excellent/very good/good/fair/poor), with 'poor' defined as the condition being present; 1) "*In general, how would you rate your quality of life?*" (excellent/very good/good/fair/poor), with 'poor' defined as the condition being present; 3) "*Do you regularly need help with daily tasks because of long-term illness or disability?*" (yes/no); 4) the Medical Outcomes Study scale for Physical Functioning (MOS-PF) was used[23, 24] where a score of 100 reflects good physical functioning and 0 as completely limited. A score of 50 was considered the critical cut-point. Participants whose score changed from ≥ 50 at baseline to below 50 at follow-up were defined as a new case of physical limitation.

Statistical analyses

Participants were included in the study if they were alcohol drinkers at baseline, completed both the baseline and follow-up questionnaire and did not have missing alcohol consumption data at baseline or follow-up. We first examined the distribution of socio-demographic and behavioural factors between those included and not included in the study.

Descriptive statistics were then used to report the proportion of those who quit drinking in relation to each newly acquired health condition. For each health variable, a logistic regression model was used to estimate adjusted odd ratios (OR) and 95% confidence intervals (CI) of quitting drinking at follow-up vs. continued drinking (dependent variable) for those who developed the condition compared to those who did not (independent variable). Participants who already had the condition at baseline, or who had missing data for the condition at baseline or follow-up, were excluded from the analysis of that health variable.

All analyses were adjusted for socio-demographic characteristics; missing indicators were included for incomplete data. Baseline socio-demographic covariates included for analysis were sex, age (45-54, 55-64, 65-74, 75-84, ≥ 85 years), highest level of education attained (no school certificate or other qualifications/school or intermediate certificate/higher school or leaving certificate/trade or apprenticeship/certificate or diploma/university degree or higher), annual pre-tax household income from all sources (< $30,000/$30,000 to $69,999/≥ $70,000 Australian dollars), health insurance status (none/health care concession card/Department of Veterans' Affairs white or gold card/private health insurance without extras/private health insurance with extras), partner status (married or living with partner/not), country of birth (Australia/Canada, Ireland, New Zealand, United Kingdom or United States/other) and remoteness of residence. Remoteness was derived from postcode using the Accessibility/Remoteness Index for Australia (ARIA+ 2006)[25].

To investigate whether the associations between each of the general health indicators (i.e., poor overall health, poor quality of life, needing help with daily tasks and low physical functioning score) with drinking cessation could be wholly accounted for by the selected 28 health conditions, we assessed how much the odds ratios were attenuated (towards the null) by incremental, additional adjustment for each of the 28 conditions (condition present at baseline/no condition at baseline or follow-up/condition at follow-up but not baseline/missing indicator). We also examined whether associations between quitting and each of the health conditions persisted when analyses were restricted to participants with good self-rated overall health and good general health indicators at follow-up. In sensitivity analyses, we investigated the effect of restricting the analysis to participants who had good, very good or excellent self-rated health at baseline and the extent to which relationships between quitting and health could be accounted for by poor self-rated health, by adjusting for poor overall health (poor health present at baseline/no poor health at baseline or follow-up/poor health at follow-up but not baseline/missing indicator).

Further sensitivity analyses addressed a number of possible interpretations of the data. 1) To assess the extent to which associations between illness and quitting drinking were explained by the presence/occurrence of other health conditions, we adjusted for all other health conditions concurrently. This analysis included participants who had health conditions at baseline, resulting in four categories for each health condition covariate (i.e., health condition present at baseline/no condition at baseline or follow-up/condition at follow-up but not baseline/missing indicator). The four general health indicators, as well as depression and anxiety were not included in this analysis. 2) To assess whether relationships between quitting and illness were affected by drinking intensity, we included number of drinks per week reported at baseline as a covariate. 3) To assess the extent to which associations could be explained by other lifestyle risk factors, we adjusted for a number of key risk factors at baseline. These were smoking status (never-smoker/ex-smoker/current smoker), body mass index (BMI; underweight, < 18.5 kgm^{-2}/normal range, ≥ 18.5 and < 25 kgm^{-2}/overweight, ≥ 25 and < 30 kgm^{-2}/obese, ≥ 30 kgm^{-2}), fruit consumption (< 1 serve/≥ 1 and < 2 serves/≥ 2 serves per day), vegetable consumption(< 3 serves/≥ 3 and < 5 serves/≥ 5 serves per day), and physical activity (0 min/> 0 and < 150 min/≥ 150 and < 300 min/≥ 300 min per week). Physical activity time was weighted according to the Active Australia Survey, with each minute of walking or moderate intensity physical activity counted as one minute and each minute of vigorous intensity physical activity counted as two minutes[26].

We tested for 2-way statistical interactions ($p < 0.05$) between each health variable and sex, age (45-64 or ≥ 65 years) and smoking status (ever/never smoked), and then examined potential differences in stratified analyses where appropriate.

A significance level of 5% was used in all analyses. Analyses were performed using SAS 9.4.

Results

266,878 participants completed the baseline questionnaire (Table 1), of whom 142,492 (53%) completed the follow-up questionnaire. Of participants with complete follow-up, those with missing information on alcohol consumption were excluded (4535, 3.2%) and a further 40,105 (28.1%) were non-drinkers at baseline and therefore excluded, leaving 97,852 (49,699 men and 48,153 women, median baseline age 59 years) participants in the study. Of the included participants, the median follow-up time was 5.3 years (Q1-Q3, 5.1-7.9 years; range: 1.6 to 10.7 years).

Overall, 9.6% of drinkers had ceased alcohol consumption at follow-up. Compared to participants who continued drinking, participants who quit drinking were slightly older on average and a higher proportion were women. At baseline, a lower proportion of quitters held a university degree, had an annual household income ≥ $70,000, held private health insurance and consumed > 14 alcoholic drinks per week compared to those who continued drinking. All health variables had < 5% missing data at baseline and/or follow-up, except for poor quality of life (5.3%), physical functioning score (11.1%), depression (12.6%), anxiety (12.6%), and erectile dysfunction (16.6%).

The proportion of new cases of the 28 health conditions who quit drinking varied from 8.4% of men with newly acquired erectile dysfunction to 19.2% of men and women who broke or fractured their hip (Table 2). Three of the four general health indicators had the highest proportions of new cases quitting drinking, with 27.3% of those reporting a decline in their overall health to poor ceasing alcohol consumption, as well as 26.6% of those reporting a decline in their quality of life to poor, and 20.3% of those reporting a change to needing regular help with daily tasks. Of those who quit drinking, 73% reported at least one new health condition, compared to 67% of those who continued drinking.

Of the 32 health variables examined, 24 were significantly associated with cessation (Table 3). Strong associations with quitting were found for all four of the general health indicators and for specific health conditions including diabetes, Parkinson's disease, poor memory and a broken/fractured hip.

Some common conditions that were also positively associated with quitting included breast cancer, other cancer, heart disease, stroke, osteoarthritis and depression, while for others such as prostate cancer, melanoma, non-melanoma skin cancer, asthma and hearing loss there was no significant association. No conditions were inversely associated with cessation. For all four general health indicators, the odds ratios of quitting were attenuated by the inclusion of all other health conditions in the models but remained significant (Table 4). Restriction to participants with good overall health at follow-up tended to attenuate all point estimates (Table 3). Restriction of analyses to participants with good general health indicators at follow-up further attenuated most associations.

The relationship of drinking cessation according to each of the health variables was broadly similar for men and women, across different age groups and among ever- and never-smokers (see Supplementary material), with a small number of exceptions. Of 92 tests for statistical interaction, 10 yielded statistically significant results. Bearing the number of statistical tests conducted in mind, significant statistical interactions were found for three health conditions by sex, where the relationship between diagnosis and quitting differed significantly between men and women: high blood pressure, urine leakage, and osteoporosis/osteopenia (Supplementary Table 1). For two conditions, the odds of quitting in relation to health variables were significantly higher among older versus younger participants: heart disease and erectile dysfunction (Supplementary Table 2). For four conditions, odds ratios were significantly attenuated in older versus younger participants: asthma, poor teeth and gums, needing help with daily tasks, and low physical functioning score. Differences by smoking status were only observed for broken/fractured other bone (Supplementary Table 3).

Adjusting for baseline drinking intensity and other lifestyle risk factors, and restricting analyses to persons with excellent/very good/good self-rated health at baseline did not materially alter OR estimates. Additionally, adjusting for the occurrence of the other specific health conditions ascertained in our study tended to attenuate OR point estimates slightly, however all remained

significant independent predictors of quitting except osteoporosis/osteopenia and poor teeth and gums. Adjusting for poor overall health tended to attenuate OR point estimates but all effects remained statistically significant (Supplementary Table 4).

Discussion

In this study, individuals diagnosed with a wide range of illnesses and/or having indicators of declining health were consistently more likely to quit drinking alcohol than those remaining in good health. Most of the 32 health variables were associated with quitting, and a decline in self-rated health to 'poor' was associated with almost triple the odds of drinking cessation. The health conditions associated with cessation were diverse and included diabetes, Parkinson's disease, poor memory, hip fracture, stroke, depression, breast cancer, heart disease and osteoarthritis.

The relationship of drinking cessation with the occurrence of new health conditions was broadly similar for men and women, and by smoking status at baseline, however a few differences by age were detected. Relationships between the 28 health conditions and quitting persisted even when analyses were restricted to participants with good overall health and/or good general health indicators at follow-up. Similarly, adjusting for all 28 health conditions attenuated but did not eliminate the association of each general health indicator to drinking cessation completely.

While previous research has demonstrated that socio-demographic factors, such as older age, low levels of education, lower income and retirement are associated with drinking cessation[16], the relative impact of specific health conditions is far less clear. Our results are consistent with prospective studies showing that drinking cessation (or reduction) is associated with cardiovascular disease[16] and ischaemic heart disease[17], and also with one study that reported increased odds of drinking cessation in relation to commencing certain medications to treat disease[14]. There are however inconsistencies between some of our results and prior research, as not all studies have reported significant decreased drinking for the health conditions we examined, including for

cardiovascular disease[15]. Our effect estimates for cancer (the highest of which was an odds ratio of 1.51) were also lower than one study examining all cancers combined, which found an odds ratio of almost four[15]. Differences in findings between studies could be explained by the diversity in study populations (including by health behaviours and health status), sample sizes, length of follow-up, use of prevalent vs. incident disease as the exposure, use of drinking reduction vs. cessation as the outcome, use of abstention as the base outcome group rather than continued drinking (e.g.[21]), and the covariates included for adjustment (e.g., adjusting for self-rated overall health[16]).

Indicators of general health such as self-rated overall health are often included in epidemiological questionnaires, and are useful because they are simple measures of health status that can be applied across different populations. We chose to examine a decline in overall health to poor, finding a strong association with drinking cessation. A number of previous studies have also reported associations with drinking cessation or reduction for various measures of overall health, including for less than very good health at baseline[16], fair or poor health at baseline[14], continuing fair or poor health[13] and a decline in health to fair or poor[13]. Not all studies reported a positive association however. One study examining worsened perceived health reported an inverse association with drinking cessation (0.77, 0.63-0.93)[15], while another examining and an index of 27 negative health events at baseline reported no significant association (however with only 1291 participants this was the smallest study, and may have been underpowered)[20]. Differences in findings between studies could reflect the use of differing general health indicator measures as the exposure, as well as the same factors responsible for differences in results for specific health conditions.

We have shown that a large number of health conditions may lead to the 'sick-quitter effect' for alcohol consumption, however there may be others which also contribute. We were not able to examine all possible health conditions, and the persistence of associations between the general health indicator variables and drinking cessation after adjustment for all other health conditions confirms that there are other health conditions not diagnosed or not examined here that also lead to

quitting. Some notable omissions from our study were chronic obstructive pulmonary disease, liver disease and kidney disease, which have been considered possible sources of bias in studies of alcohol consumption and mortality[6, 9]. Therefore there are likely several other health conditions not examined here that should be taken into account when addressing the 'sick-quitter effect'.

The exclusion of participants with health conditions or poor indicators of general health at baseline in studies of alcohol and health has both advantages and disadvantages. The quantity and breadth of health conditions related to drinking cessation found here and elsewhere suggests that the exclusion of participants with specific diseases at baseline in observational studies where alcohol is the exposure of interest is not practical and may only be partially effective in mitigating the 'sick-quitter effect'. For example, restricting an analysis to participants without any of the 24 significant health conditions reported here at baseline in the 45 and Up Study would mean excluding 76% of participants. The use of general health indicator variables such as self-rated overall health status is likely to be a better strategy to capture a person's total disease experience rather than focusing on specific health conditions; in our study this was also a better predictor of drinking cessation. For example, 14.2% of participants reported fair or poor self-rated health at baseline in the 45 and Up Study. It should be noted however, that when we restricted our analyses to participants with good overall health or good general health indicators at follow-up, although the associations between quitting and health conditions were attenuated, many of the health conditions remained significant predictors of quitting. Thus, accounting for general health indicators may not be a completely adequate method of addressing the 'sick-quitter effect'.

Another disadvantage of excluding participants with a health condition or poor health status at baseline is the potential for selection bias and the inducement of false J-shaped associations[27]. This is because the exclusion could create confounding between alcohol consumption and other risk factors for the outcome (e.g. cardiovascular disease risk factors if the outcome is cardiovascular disease). Alternative methods of addressing the 'sick-quitter effect' have been considered, including

using lifetime abstainers or light drinkers (or both) as the reference group[3, 28], calculating a log-linear trend in risk for drinkers only[29], assigning ex-drinkers to their former levels of drinking at analysis[30], ascertaining alcohol consumption at multiple time points (either retrospectively or prospectively from baseline)[10, 31] and excluding outcomes that occur early in the period of follow-up[9]. As the prevalence of fair or poor health increases with age[30], another option may be to restrict the study to younger participants who have had fewer health events causing them to reduce or quit drinking. For instance, 63% of participants aged 45-54 years in the 45 and Up Study reported any one of the 24 health conditions related to quitting at baseline compared to 95% of participants aged ≥ 75 years. These alternative methods of addressing the 'sick-quitter effect' could be used to avoid the potential for selection bias arising from exclusion.

Strengths of this study include the prospective design, large sample size, the consideration of a large number of health conditions and the use of incident rather than prevalent illness, allowing for appraisal of the relative relation of many health conditions and general health indicators to drinking cessation. A limitation is that 53% of participants had completed follow-up, which has potential to bias the results. Specifically, participants who developed more severe disease may have been less likely to complete the follow-up questionnaire, and more likely to quit drinking, which may mean our estimates are conservative. Further, persons who participate in cohort studies may be more health conscious than the general population, and so might reduce their drinking to a greater degree in response to incident health conditions. This may also mean that heavy drinkers are underrepresented in our analysis, however we found that adjusting for baseline levels of alcohol consumption did not materially alter our results. It has also been shown that participants tend to underreport alcohol consumption[32], meaning that the proportion of participants who quit drinking may be overestimated for both participants with and without incident health conditions, possibly biasing the odds ratios towards the null hypothesis if the error was non-differential. On the other hand, as participants were instructed to write '0' for alcohol consumption if they consumed less than one alcoholic drink per week, the proportion of participants who ceased drinking is likely to be

overestimated as some participants who became occasional drinkers will be misclassified as quitters. Again, if this misclassification was non-differential then it would be expected to bias the results towards the null hypothesis. Our results are also based on self-reported health outcomes, and therefore there may have been misclassification for some health conditions. This is especially true for conditions such as melanoma and non-melanoma skin cancer which are known to be reported inaccurately[33, 34].

The median follow-up period of participants included in our analysis was 5.3 years, however both the onset of illness and the decision to quit drinking could have occurred at any time between baseline and follow-up, and in any order. Our results suggest that the onset of disease could motivate an individual to improve their lifestyle behaviours[35], however we could not determine whether the decision to cease drinking was due to the onset of symptoms or the fact of diagnosis, or both. Finally, we were not able to capture those who may have quit in relation to a diagnosis early on in the study period but then restarted drinking by the point of follow-up. It would be of interest for future studies to examine follow-up at multiple time periods to investigate changes in consumption patterns in relation to the time of diagnosis, and the extent to which participants maintain their drinking cessation over longer time periods.

In conclusion, we provide evidence that the onset of a range of health conditions is associated with drinking cessation and therefore provide evidence for a widespread 'sick-quitter effect'. Alcohol consumption patterns are closely related to illness in a way that is likely to affect risk estimates for associations between alcohol and disease. Importantly, many health conditions were moderately or strongly associated with cessation, and not just health conditions commonly accounted for in studies of alcohol consumption such as cancer, ischaemic heart disease and stroke. Adjusting for the occurrence of specific health conditions did not completely remove associations between indicators of general health and drinking cessation, nor did adjusting for poor overall health. The breadth of health conditions related to drinking cessation is large enough that observational studies with

alcohol consumption as the exposure should use means other than the exclusion of specific health conditions to mitigate the 'sick-quitter effect'. There is a need for further large prospective cohort studies of incident health conditions and changes in drinking to replicate these findings in different populations, and to examine drinking trajectory across multiple time points, and during the course of a lifetime.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Tables

Table 1. Distribution of socio-demographic and behavioural characteristics in the 45 and Up Study (2006-2016), New South Wales, Australia for those who did and did not complete the follow-up questionnaire and those who did and did not quit alcohol consumption at follow-up.

Characteristic at baseline	Completed baseline questionnaire (n=266,878)	Completed follow-up questionnaire (n=142,492)	Included in analysis[a] (n=97,852)	Continued drinking (n=88,414)	Quit drinking (n=9438)
Male (%)	46.4	44.8	50.8	51.9	40.8
Mean age (SD)	62.7 (11.2)	60.8 (9.7)	60.2 (9.4)	60.0 (9.2)	62.0 (10.2)
Major city resident (%)	52.2	50.3	50.5	50.8	47.8
University degree (%)	23.1	28.5	31.9	32.6	24.5
Household income ≥ $70,000[b] (%)	23.5	29.5	34.7	36.1	21.5
Private health insurance[c] (%)	65.2	71.0	75.3	76.4	65.1
Married or living with partner (%)	74.4	78.3	81.0	81.8	74.1
Born in Australia (%)	74.9	77.9	78.2	78.2	77.8
Ever-smoker (%)	43.0	40.6	45.0	45.3	42.5
Overweight or obese[d] (%)	57.1	57.6	57.4	57.2	59.9
Inadequate physical activity[e] (%)	21.6	17.3	15.4	14.9	19.2
< 2 fruit serves per day[f] (%)	41.5	39.9	41.8	42.3	37.6
< 5 vegetable serves per day (%)	66.0	65.9	67.1	67.5	63.9
> 14 alcoholic drinks per week (%)	14.0	14.9	21.5	23.1	6.0

Percentages include participants with missing or invalid responses. [a]Completed follow-up questionnaire, alcohol consumption data not missing and consumed ≥ 1 alcoholic drink per week at baseline. [b]Pre-tax annual household income from all sources in Australian dollars. [c]Including Department of Veterans' Affairs white or gold card. [d]Body mass index ≥ 25 kgm^{-2}. [e]Weekly physical activity time < 150 weighted minutes, with each minute of walking or moderate intensity physical activity counted as one minute and each minute of vigorous intensity physical activity counted as two minutes. [f]Excludes fruit juice. SD, Standard Deviation.

Table 2. Proportion of participants in the 45 and Up Study (2006-2016), New South Wales, Australia who reported quitting alcohol consumption at follow-up by selected health variables.

	Condition not present at baseline or follow-up		Condition not present at baseline but present at follow-up	
	n	n quit (%)	n	n quit (%)
Health conditions				
Cancer				
Breast cancer (women)	44,524	5100 (11.5)	1307	196 (15.0)
Prostate cancer (men)	44,606	3368 (7.6)	2667	229 (8.6)
Melanoma	89,064	8569 (9.6)	3511	334 (9.5)
Non-melanoma skin cancer	60,673	5978 (9.9)	10,343	969 (9.4)
Other cancer	88,542	8217 (9.3)	4327	630 (14.6)
Cardiovascular disease				
Heart disease	79,323	7178 (9.0)	9383	1153 (12.3)
Stroke	94,362	8909 (9.4)	1840	271 (14.7)
Blood clot	92,507	8723 (9.4)	1893	255 (13.5)
High blood pressure	56,459	5071 (9.0)	9861	908 (9.2)
Endocrine conditions				
Diabetes	89,177	8097 (9.1)	3269	502 (15.4)
Thyroid problems	90,932	8501 (9.3)	2416	333 (13.8)
Genitourinary conditions				
Leaking urine > 1 time per week	73,946	6526 (8.8)	7577	913 (12.0)
Enlarged prostate (men)	37,619	2678 (7.1)	4598	415 (9.0)
Erectile dysfunction (men)	28,895	1747 (6.0)	6600	556 (8.4)
Conditions affecting mobility				
Parkinson's disease	97,059	9302 (9.6)	517	85 (16.4)
Osteoarthritis	86,553	7962 (9.2)	5240	699 (13.3)
Osteoporosis/osteopenia	90,489	8450 (9.3)	3319	439 (13.2)
Broken/fractured hip	97,156	9319 (9.6)	495	95 (19.2)
Broken/fractured other bone	81,061	7743 (9.6)	7546	738 (9.8)
Mental health conditions				
Depression	69,921	6163 (8.8)	3775	472 (12.5)
Anxiety	73,693	6630 (9.0)	4296	549 (12.8)
Poor memory	92,165	8681 (9.4)	1126	200 (17.8)
Other conditions				
Asthma	83,055	7833 (9.4)	2782	301 (10.8)
Hayfever	76,499	7321 (9.6)	5219	508 (9.7)
Hearing loss	44,416	4166 (9.4)	10,216	997 (9.8)
Poor eyesight	92,380	8711 (9.4)	869	148 (17.0)
Poor teeth and gums	88,238	8092 (9.2)	1548	228 (14.7)
No teeth left	89,342	8295 (9.3)	852	144 (16.9)
General health indicators				
Poor overall health	92,368	8594 (9.3)	971	265 (27.3)
Poor quality of life	91,433	8588 (9.4)	655	174 (26.6)
Need regular help with daily tasks	87,366	7740 (8.9)	4146	841 (20.3)
Physical functioning score < 50%	78,984	6542 (8.3)	4332	816 (18.8)

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) of quitting drinking by newly acquired health conditions among participants with good general health indicators at follow-up in the 45 and Up Study (2006-2016), New South Wales, Australia.

	OR quit drinking (95% CI)		
Health conditions	**Main analysis**	**Restricted to good overall health at follow-up[a]**	**Restricted to good general health indicators at follow-up[b]**
Cancer			
Breast cancer (women)	1.38 (1.18-1.61)	1.35 (1.13-1.62)	1.38 (1.13-1.68)
Prostate cancer (men)	1.05 (0.91-1.21)	0.96 (0.81-1.14)	0.91 (0.75-1.11)
Melanoma	1.00 (0.89-1.12)	0.95 (0.83-1.09)	0.84 (0.71-0.99)
Non-melanoma skin cancer	0.94 (0.88-1.01)	0.93 (0.86-1.01)	0.93 (0.85-1.02)
Other cancer	1.51 (1.38-1.65)	1.39 (1.24-1.55)	1.32 (1.16-1.49)
Cardiovascular disease			
Heart disease	1.34 (1.25-1.44)	1.23 (1.13-1.34)	1.16 (1.06-1.28)
Stroke	1.45 (1.27-1.66)	1.34 (1.13-1.60)	1.10 (0.88-1.38)
Blood clot	1.39 (1.22-1.60)	1.26 (1.06-1.49)	1.16 (0.95-1.42)
High blood pressure	0.98 (0.91-1.05)	0.97 (0.89-1.06)	0.99 (0.90-1.08)
Endocrine conditions			
Diabetes	1.77 (1.60-1.96)	1.61 (1.42-1.82)	1.52 (1.32-1.76)
Thyroid problems	1.32 (1.17-1.49)	1.29 (1.12-1.48)	1.29 (1.11-1.51)
Genitourinary conditions			
Leaking urine > 1 time per week	1.20 (1.11-1.29)	1.13 (1.03-1.23)	1.07 (0.97-1.19)
Enlarged prostate (men)	1.22 (1.09-1.37)	1.16 (1.02-1.32)	1.17 (1.01-1.36)
Erectile dysfunction (men)	1.29 (1.16-1.43)	1.20 (1.06-1.35)	1.18 (1.03-1.34)
Conditions affecting mobility			
Parkinson's disease	1.71 (1.35-2.17)	1.45 (1.05-2.00)	1.26 (0.84-1.91)
Osteoarthritis	1.22 (1.12-1.33)	1.17 (1.05-1.29)	1.10 (0.97-1.25)
Osteoporosis/osteopenia	1.16 (1.05-1.29)	1.08 (0.95-1.22)	1.00 (0.86-1.16)
Broken/fractured hip	1.64 (1.30-2.06)	1.51 (1.11-2.04)	1.29 (0.82-2.02)
Broken/fractured other bone	0.95 (0.88-1.03)	0.89 (0.81-0.98)	0.85 (0.76-0.94)
Mental health conditions			
Depression	1.40 (1.26-1.55)	1.32 (1.17-1.49)	1.28 (1.11-1.48)
Anxiety	1.38 (1.26-1.52)	1.40 (1.25-1.56)	1.32 (1.16-1.50)
Poor memory	1.68 (1.43-1.97)	1.53 (1.21-1.92)	1.73 (1.30-2.32)
Other conditions			
Asthma	1.07 (0.94-1.21)	1.10 (0.95-1.27)	1.14 (0.97-1.34)
Hayfever	0.99 (0.90-1.09)	0.99 (0.89-1.11)	0.99 (0.88-1.12)
Hearing loss	1.05 (0.97-1.13)	1.05 (0.97-1.14)	1.02 (0.93-1.12)
Poor eyesight	1.50 (1.25-1.79)	1.33 (1.03-1.73)	1.35 (0.98-1.87)
Poor teeth and gums	1.35 (1.17-1.57)	1.21 (0.99-1.47)	1.41 (1.13-1.76)
No teeth left	1.51 (1.26-1.82)	1.57 (1.26-1.97)	1.55 (1.18-2.02)

[a]Excellent, very good or good overall health at follow-up. [b]Excellent, very good or good overall health and quality of life, do not need regular help with daily tasks and physical functioning score ≥ 50% at follow-up. Adjusted for sex, age, remoteness, education, household income, health insurance status, partner status and country of birth.

Table 4. Odds ratios (OR) and 95% confidence intervals (CI) of quitting drinking among participants whose general health indicators declined to poor at follow-up, with adjustment for selected health conditions in the 45 and Up Study (2006-2016), New South Wales, Australia.

	OR quit drinking (95% CI)			
Adjustment factors	**Poor overall health**	**Poor quality of life**	**Need regular help with daily tasks**	**Physical functioning score < 50%**
Sociodemographic variables only (main analysis)	2.93 (2.53-3.40)	2.68 (2.24-3.21)	1.96 (1.81-2.13)	2.00 (1.84-2.18)
Cancer[a], heart disease and stroke	2.64 (2.27-3.06)	2.50 (2.08-2.99)	1.84 (1.70-2.01)	1.91 (1.75-2.08)
All significant health conditions except depression and anxiety[b]	2.13 (1.83-2.49)	2.03 (1.69-2.44)	1.63 (1.49-1.78)	1.71 (1.57-1.87)
All health conditions except depression and anxiety	2.12 (1.82-2.47)	2.04 (1.69-2.45)	1.63 (1.49-1.78)	1.71 (1.56-1.87)
All health conditions including depression and anxiety	2.09 (1.79-2.44)	1.96 (1.63-2.36)	1.60 (1.47-1.75)	1.68 (1.54-1.84)

[a]Breast cancer, prostate cancer, melanoma and other cancer, except not non-melanoma skin cancer. [b]Breast cancer, other cancer (except prostate cancer, melanoma and non-melanoma skin cancer), heart disease, stroke, blood clot, diabetes, thyroid problems, leaking urine > 1 time per week, enlarged prostate, erectile dysfunction, Parkinson's disease, osteoarthritis, osteoporosis/osteopenia, broken/fractured hip, poor memory, poor eyesight, poor teeth and gums and having no teeth left. All models adjusted for sex, age, remoteness, education, household income, health insurance status, partner status and country of birth.

Supplementary data

Supplementary Table 1. Odds ratios (OR) and 95% confidence intervals (CI) of quitting drinking at follow-up by health conditions newly acquired between baseline and follow-up by sex in the 45 and Up Study (2006-2016), New South Wales, Australia.

	OR quit drinking (95% CI)			
	Main analysis	**Men**	**Women**	$p_{interaction}$
Health conditions				
Cancer				
Melanoma	1.00 (0.89-1.12)	1.02 (0.87-1.19)	0.97 (0.82-1.16)	0.62
Non-melanoma skin cancer	0.94 (0.88-1.01)	0.87 (0.78-0.98)	1.00 (0.90-1.10)	0.17
Other cancer	1.51 (1.38-1.65)	1.59 (1.40-1.82)	1.44 (1.27-1.62)	0.18
Cardiovascular disease				
Heart disease	1.34 (1.25-1.44)	1.40 (1.27-1.55)	1.28 (1.16-1.42)	0.07
Stroke	1.45 (1.27-1.66)	1.40 (1.17-1.66)	1.50 (1.22-1.85)	0.91
Blood clot	1.39 (1.22-1.60)	1.58 (1.30-1.91)	1.24 (1.02-1.50)	0.06
High blood pressure	0.98 (0.91-1.05)	0.84 (0.75-0.95)	1.08 (0.98-1.20)	0.002
Endocrine conditions				
Diabetes	1.77 (1.60-1.96)	1.67 (1.45-1.91)	1.90 (1.64-2.20)	0.20
Thyroid problems	1.32 (1.17-1.49)	1.33 (1.01-1.75)	1.32 (1.15-1.51)	0.90
Genitourinary conditions				
Leaking urine > 1 time per week	1.20 (1.11-1.29)	1.42 (1.27-1.59)	1.06 (0.96-1.18)	< 0.001
Conditions affecting mobility				
Parkinson's disease	1.71 (1.35-2.17)	1.84 (1.35-2.50)	1.55 (1.06-2.25)	0.42
Osteoarthritis	1.22 (1.12-1.33)	1.22 (1.06-1.42)	1.23 (1.11-1.37)	0.72
Osteoporosis/osteopenia	1.16 (1.05-1.29)	1.48 (1.20-1.83)	1.09 (0.96-1.23)	0.005
Broken/fractured hip	1.64 (1.30-2.06)	1.57 (1.07-2.31)	1.71 (1.28-2.29)	0.97
Broken/fractured other bone	0.95 (0.88-1.03)	1.03 (0.89-1.18)	0.92 (0.83-1.01)	0.16
Mental health conditions				
Depression	1.40 (1.26-1.55)	1.55 (1.33-1.82)	1.30 (1.14-1.49)	0.09
Anxiety	1.38 (1.26-1.52)	1.49 (1.27-1.76)	1.33 (1.18-1.49)	0.27
Poor memory	1.68 (1.43-1.97)	1.69 (1.38-2.08)	1.64 (1.28-2.11)	0.63
Other conditions				
Asthma	1.07 (0.94-1.21)	1.09 (0.89-1.33)	1.05 (0.90-1.23)	0.77
Hayfever	0.99 (0.90-1.09)	0.99 (0.84-1.17)	0.99 (0.88-1.12)	0.99
Hearing loss	1.05 (0.97-1.13)	1.02 (0.90-1.15)	1.07 (0.97-1.18)	0.56
Poor eyesight	1.50 (1.25-1.79)	1.74 (1.35-2.26)	1.32 (1.02-1.71)	0.07
Poor teeth and gums	1.35 (1.17-1.57)	1.33 (1.09-1.62)	1.37 (1.11-1.70)	0.99
No teeth left	1.51 (1.26-1.82)	1.59 (1.24-2.02)	1.41 (1.06-1.87)	0.40
General health indicators				
Poor overall health	2.93 (2.53-3.40)	2.85 (2.34-3.47)	2.98 (2.39-3.72)	0.98
Poor quality of life	2.68 (2.24-3.21)	2.67 (2.11-3.38)	2.68 (2.03-3.54)	0.82
Need regular help with daily tasks	1.96 (1.81-2.13)	2.05 (1.81-2.33)	1.92 (1.72-2.15)	0.08
Physical functioning score < 50%	2.00 (1.84-2.18)	2.00 (1.67-2.28)	2.00 (1.79-2.24)	0.36

Adjusted for age, remoteness, education, household income, health insurance status, partner status and country of birth.

Supplementary Table 2. Odds ratios (OR) and 95% confidence intervals (CI) of quitting drinking at follow-up by health conditions newly acquired between baseline and follow-up by age in the 45 and Up Study (2006-2016), New South Wales, Australia.

	OR quit drinking (95% CI)			
	Main analysis	Age 45-64 years at baseline	Age ≥ 65 years at baseline	$p_{interaction}$
Health conditions				
Cancer				
Breast cancer (women)	1.38 (1.18-1.61)	1.41 (1.17-1.70)	1.01 (0.86-1.20)	0.65
Prostate cancer (men)	1.05 (0.91-1.21)	0.91 (0.72-1.15)	0.96 (0.86-1.08)	0.12
Melanoma	1.00 (0.89-1.12)	0.98 (0.83-1.15)	1.48 (1.30-1.67)	0.60
Non-melanoma skin cancer	0.94 (0.88-1.01)	0.92 (0.84-1.01)	1.46 (1.33-1.61)	0.27
Other cancer	1.51 (1.38-1.65)	1.54 (1.35-1.74)	1.37 (1.15-1.62)	0.66
Cardiovascular disease				
Heart disease	1.34 (1.25-1.44)	1.22 (1.10-1.35)	1.46 (1.33-1.61)	0.006
Stroke	1.45 (1.27-1.66)	1.57 (1.26-1.95)	1.37 (1.15-1.62)	0.34
Blood clot	1.39 (1.22-1.60)	1.45 (1.21-1.75)	1.33 (1.09-1.62)	0.53
High blood pressure	0.98 (0.91-1.05)	1.02 (0.93-1.12)	0.90 (0.79-1.03)	0.09
Endocrine conditions				
Diabetes	1.77 (1.60-1.96)	1.89 (1.66-2.15)	1.61 (1.37-1.88)	0.11
Thyroid problems	1.32 (1.17-1.49)	1.28 (1.10-1.48)	1.41 (1.15-1.73)	0.63
Genitourinary conditions				
Leaking urine > 1 time per week	1.20 (1.11-1.29)	1.18 (1.07-1.31)	1.22 (1.09-1.36)	0.80
Enlarged prostate (men)	1.22 (1.09-1.37)	1.35 (1.16-1.57)	1.09 (0.93-1.28)	0.07
Erectile dysfunction (men)	1.29 (1.16-1.43)	1.15 (1.00-1.32)	1.51 (1.29-1.77)	0.008
Conditions affecting mobility				
Parkinson's disease	1.71 (1.35-2.17)	1.82 (1.26-2.62)	1.61 (1.18-2.21)	0.65
Osteoarthritis	1.22 (1.12-1.33)	1.20 (1.07-1.35)	1.26 (1.12-1.42)	0.94
Osteoporosis/osteopenia	1.16 (1.05-1.29)	1.12 (0.97-1.31)	1.21 (1.04-1.40)	0.77
Broken/fractured hip	1.64 (1.30-2.06)	1.30 (0.81-2.09)	1.79 (1.37-2.33)	0.28
Broken/fractured other bone	0.95 (0.88-1.03)	0.92 (0.83-1.02)	1.00 (0.88-1.15)	0.47
Mental health conditions				
Depression	1.40 (1.26-1.55)	1.35 (1.19-1.52)	1.50 (1.26-1.79)	0.43
Anxiety	1.38 (1.26-1.52)	1.36 (1.21-1.52)	1.42 (1.20-1.69)	0.97
Poor memory	1.68 (1.43-1.97)	1.95 (1.54-2.48)	1.48 (1.20-1.82)	0.07
Other conditions				
Asthma	1.07 (0.94-1.21)	1.19 (1.03-1.38)	0.85 (0.68-1.06)	0.01
Hayfever	0.99 (0.90-1.09)	0.95 (0.85-1.07)	1.07 (0.91-1.26)	0.27
Hearing loss	1.05 (0.97-1.13)	1.02 (0.93-1.12)	1.10 (0.97-1.25)	0.31
Poor eyesight	1.50 (1.25-1.79)	1.43 (1.09-1.89)	1.53 (1.20-1.96)	0.88
Poor teeth and gums	1.35 (1.17-1.57)	1.54 (1.27-1.85)	1.13 (0.80-1.42)	0.02
No teeth left	1.51 (1.26-1.82)	1.54 (1.17-2.02)	1.51 (1.18-1.95)	0.68
General health indicators				
Poor overall health	2.93 (2.53-3.40)	3.02 (2.46-3.72)	2.81 (2.28-3.45)	0.52
Poor quality of life	2.68 (2.24-3.21)	2.72 (2.12-3.50)	2.62 (2.03-3.39)	0.65
Need regular help with daily tasks	1.96 (1.81-2.13)	2.19 (1.92-2.49)	1.83 (1.64-2.04)	0.02
Physical functioning score < 50%	2.00 (1.84-2.18)	2.28 (2.02-2.57)	1.79 (1.59-2.01)	0.001

Adjusted for sex, age, remoteness, education, household income, health insurance status, partner status and country of birth.

Supplementary Table 3. Odds ratios (OR) and 95% confidence intervals (CI) of quitting drinking at follow-up by health conditions newly acquired between baseline and follow-up by smoking status in the 45 and Up Study (2006-2016), New South Wales, Australia.

	OR quit drinking (95% CI)			
	Main analysis	**Never-smokers**	**Ever-smokers**	$p_{interaction}$
Health conditions				
Cancer				
Breast cancer (women)	1.38 (1.18-1.61)	1.54 (1.27-1.87)	1.13 (0.86-1.49)	0.08
Prostate cancer (men)	1.05 (0.91-1.21)	1.13 (0.92-1.37)	0.97 (0.79-1.19)	0.19
Melanoma	1.00 (0.89-1.12)	0.98 (0.84-1.15)	1.02 (0.85-1.21)	0.80
Non-melanoma skin cancer	0.94 (0.88-1.01)	0.97 (0.88-1.07)	0.90 (0.81-1.01)	0.26
Other cancer	1.51 (1.38-1.65)	1.53 (1.35-1.73)	1.53 (1.34-1.74)	0.81
Cardiovascular disease				
Heart disease	1.34 (1.25-1.44)	1.31 (1.19-1.44)	1.41 (1.27-1.56)	0.64
Stroke	1.45 (1.27-1.66)	1.58 (1.31-1.90)	1.35 (1.11-1.64)	0.17
Blood clot	1.39 (1.22-1.60)	1.38 (1.15-1.66)	1.41 (1.15-1.73)	0.94
High blood pressure	0.98 (0.91-1.05)	0.98 (0.89-1.09)	0.98 (0.88-1.10)	0.99
Endocrine conditions				
Diabetes	1.77 (1.60-1.96)	1.76 (1.52-2.03)	1.81 (1.57-2.08)	0.72
Thyroid problems	1.32 (1.17-1.49)	1.26 (1.07-1.48)	1.42 (1.19-1.70)	0.38
Genitourinary conditions				
Leaking urine > 1 time per week	1.20 (1.11-1.29)	1.20 (1.09-1.33)	1.20 (1.07-1.34)	0.66
Enlarged prostate (men)	1.22 (1.09-1.37)	1.18 (1.01-1.39)	1.26 (1.08-1.47)	0.87
Erectile dysfunction (men)	1.29 (1.16-1.43)	1.22 (1.05-1.42)	1.36 (1.18-1.57)	0.63
Conditions affecting mobility				
Parkinson's disease	1.71 (1.35-2.17)	1.94 (1.44-2.63)	1.41 (0.95-2.08)	0.18
Osteoarthritis	1.22 (1.12-1.33)	1.14 (1.02-1.29)	1.34 (1.19-1.52)	0.14
Osteoporosis/osteopenia	1.16 (1.05-1.29)	1.14 (1.00-1.31)	1.18 (1.00-1.40)	0.92
Broken/fractured hip	1.64 (1.30-2.06)	1.77 (1.30-2.43)	1.54 (1.09-2.17)	0.42
Broken/fractured other bone	0.95 (0.88-1.03)	0.88 (0.79-0.99)	1.04 (0.92-1.17)	0.04
Mental health conditions				
Depression	1.40 (1.26-1.55)	1.32 (1.14-1.52)	1.52 (1.31-1.75)	0.09
Anxiety	1.38 (1.26-1.52)	1.40 (1.23-1.60)	1.37 (1.19-1.58)	0.98
Poor memory	1.68 (1.43-1.97)	1.74 (1.38-2.19)	1.65 (1.33-2.06)	0.73
Other conditions				
Asthma	1.07 (0.94-1.21)	1.17 (0.99-1.38)	0.98 (0.82-1.18)	0.21
Hayfever	0.99 (0.90-1.09)	0.95 (0.84-1.08)	1.06 (0.91-1.22)	0.26
Hearing loss	1.05 (0.97-1.13)	1.01 (0.92-1.12)	1.11 (0.99-1.25)	0.24
Poor eyesight	1.50 (1.25-1.79)	1.68 (1.30-2.16)	1.35 (1.03-1.76)	0.25
Poor teeth and gums	1.35 (1.17-1.57)	1.15 (0.90-1.48)	1.54 (1.29-1.85)	0.0503
No teeth left	1.51 (1.26-1.82)	1.52 (1.13-2.06)	1.57 (1.24-1.99)	0.90
General health indicators				
Poor overall health	2.93 (2.53-3.40)	3.21 (2.57-4.00)	2.76 (2.26-3.37)	0.42
Poor quality of life	2.68 (2.24-3.21)	3.04 (2.32-3.99)	2.47 (1.94-3.14)	0.36
Need regular help with daily tasks	1.96 (1.81-2.13)	1.92 (1.71-2.16)	2.05 (1.82-2.31)	0.79
Physical functioning score < 50%	2.00 (1.84-2.18)	1.92 (1.70-2.16)	2.16 (1.91-2.43)	0.41

Adjusted for sex, age, remoteness, education, household income, health insurance status, partner status and country of birth.

Supplementary Table 4. Sensitivity analyses for odds ratios (OR) and 95% confidence intervals (CI) of quitting drinking at follow-up by health conditions newly acquired between baseline and follow-up in the 45 and Up Study (2006-2016), New South Wales, Australia.

	OR quit drinking (95% CI)					
	Main analysis[a]	Adjusted for other health conditions[a,b]	Adjusted for baseline drinking intensity[a,c]	Adjusted for lifestyle risk factors[a,d]	Participants with good health at baseline only[a,e]	Adjusted for poor overall health at baseline and/or follow-up[a,f]
Health conditions						
Cancer						
Breast cancer (women)	1.38 (1.18-1.61)	1.29 (1.10-1.51)	1.43 (1.21-1.69)	1.37 (1.17-1.60)	1.48 (1.25-1.74)	1.36 (1.16-1.59)
Prostate cancer (men)	1.05 (0.91-1.21)	0.91 (0.78-1.05)	1.08 (0.93-1.25)	1.05 (0.91-1.22)	1.06 (0.90-1.23)	1.05 (0.91-1.21)
Melanoma	1.00 (0.89-1.12)	0.96 (0.85-1.08)	1.04 (0.92-1.17)	1.01 (0.90-1.14)	0.97 (0.86-1.11)	1.00 (0.89-1.12)
Non-melanoma skin cancer	0.94 (0.88-1.01)	0.92 (0.85-0.99)	0.97 (0.90-1.04)	0.95 (0.89-1.03)	0.93 (0.86-1.01)	0.94 (0.87-1.01)
Other cancer	1.51 (1.38-1.65)	1.42 (1.30-1.56)	1.59 (1.44-1.75)	1.50 (1.37-1.64)	1.54 (1.39-1.69)	1.46 (1.33-1.60)
Cardiovascular disease						
Heart disease	1.34 (1.25-1.44)	1.24 (1.15-1.33)	1.37 (1.27-1.47)	1.32 (1.23-1.41)	1.33 (1.23-1.43)	1.31 (1.22-1.40)
Stroke	1.45 (1.27-1.66)	1.19 (1.04-1.37)	1.49 (1.29-1.72)	1.44 (1.26-1.65)	1.38 (1.18-1.61)	1.40 (1.23-1.61)
Blood clot	1.39 (1.22-1.60)	1.20 (1.04-1.38)	1.34 (1.16-1.54)	1.35 (1.18-1.54)	1.38 (1.19-1.61)	1.35 (1.18-1.55)
High blood pressure	0.98 (0.91-1.05)	0.93 (0.86-1.00)	1.03 (0.95-1.11)	0.95 (0.88-1.02)	0.98 (0.90-1.06)	0.97 (0.90-1.05)
Endocrine conditions						
Diabetes	1.77 (1.60-1.96)	1.62 (1.46-1.80)	1.68 (1.51-1.87)	1.59 (1.44-1.77)	1.69 (1.50-1.89)	1.72 (1.55-1.90)
Thyroid problems	1.32 (1.17-1.49)	1.21 (1.07-1.37)	1.24 (1.09-1.41)	1.29 (1.14-1.46)	1.33 (1.17-1.52)	1.29 (1.14-1.45)
Genitourinary conditions						
Leaking urine > 1 time per week	1.20 (1.11-1.29)	1.11 (1.03-1.20)	1.18 (1.09-1.28)	1.15 (1.07-1.25)	1.15 (1.06-1.25)	1.17 (1.08-1.26)
Enlarged prostate (men)	1.22 (1.09-1.37)	1.18 (1.05-1.32)	1.18 (1.05-1.32)	1.23 (1.10-1.37)	1.17 (1.03-1.32)	1.21 (1.09-1.35)
Erectile dysfunction (men)	1.29 (1.16-1.43)	1.24 (1.11-1.37)	1.29 (1.16-1.44)	1.28 (1.16-1.42)	1.28 (1.14-1.43)	1.27 (1.14-1.40)
Conditions affecting mobility						
Parkinson's disease	1.71 (1.35-2.17)	1.36 (1.06-1.75)	1.78 (1.38-2.30)	1.71 (1.35-2.17)	1.73 (1.33-2.25)	1.61 (1.27-2.05)
Osteoarthritis	1.22 (1.12-1.33)	1.13 (1.04-1.24)	1.28 (1.17-1.40)	1.18 (1.08-1.28)	1.20 (1.09-1.32)	1.19 (1.09-1.29)
Osteoporosis/osteopenia	1.16 (1.05-1.29)	1.09 (0.98-1.22)	1.19 (1.06-1.33)	1.19 (1.07-1.33)	1.16 (1.04-1.31)	1.14 (1.03-1.27)
Broken/fractured hip	1.64 (1.30-2.06)	1.56 (1.24-1.97)	1.82 (1.42-2.34)	1.64 (1.30-2.06)	1.81 (1.40-2.32)	1.57 (1.25-1.98)
Broken/fractured other bone	0.95 (0.88-1.03)	0.90 (0.83-0.98)	0.98 (0.90-1.07)	0.95 (0.88-1.04)	0.93 (0.86-1.02)	0.93 (0.86-1.01)
Mental health conditions						
Depression	1.40 (1.26-1.55)	1.25 (1.12-1.38)	1.42 (1.27-1.58)	1.38 (1.25-1.53)	1.34 (1.20-1.51)	1.35 (1.22-1.49)
Anxiety	1.38 (1.26-1.52)	1.26 (1.15-1.39)	1.37 (1.24-1.52)	1.37 (1.25-1.51)	1.41 (1.27-1.57)	1.35 (1.22-1.48)
Poor memory	1.68 (1.43-1.97)	1.46 (1.24-1.71)	1.75 (1.48-2.08)	1.68 (1.43-1.97)	1.69 (1.40-2.03)	1.50 (1.27-1.76)
Other conditions						
Asthma	1.07 (0.94-1.21)	0.96 (0.84-1.09)	1.05 (0.92-1.20)	1.04 (0.92-1.18)	1.11 (0.97-1.27)	1.04 (0.92-1.18)
Hayfever	0.99 (0.90-1.09)	0.95 (0.86-1.05)	0.98 (0.88-1.08)	0.99 (0.90-1.09)	1.01 (0.91-1.12)	0.98 (0.89-1.08)
Hearing loss	1.05 (0.97-1.13)	1.02 (0.94-1.10)	1.03 (0.95-1.11)	1.04 (0.97-1.12)	1.04 (0.97-1.13)	1.04 (0.97-1.12)
Poor eyesight	1.50 (1.25-1.79)	1.26 (1.05-1.52)	1.56 (1.29-1.90)	1.46 (1.22-1.76)	1.43 (1.15-1.78)	1.34 (1.11-1.61)
Poor teeth and gums	1.35 (1.17-1.57)	1.16 (1.00-1.34)	1.42 (1.21-1.66)	1.33 (1.15-1.54)	1.45 (1.23-1.71)	1.26 (1.09-1.46)
No teeth left	1.51 (1.26-1.82)	1.33 (1.10-1.61)	1.46 (1.20-1.78)	1.51 (1.26-1.82)	1.56 (1.27-1.93)	1.45 (1.20-1.75)
General health indicators						
Poor overall health	2.93 (2.53-3.40)	2.12 (1.82-2.47)	3.24 (2.76-3.81)	2.68 (2.31-3.11)	3.76 (3.06-4.62)	-
Poor quality of life	2.68 (2.24-3.21)	2.04 (1.69-2.45)	3.00 (2.46-3.65)	2.48 (2.07-2.97)	3.32 (2.64-4.18)	1.82 (1.49-2.21)
Need regular help with daily tasks	1.96 (1.81-2.13)	1.63 (1.49-1.78)	2.05 (1.88-2.25)	1.86 (1.71-2.02)	1.97 (1.78-2.16)	1.76 (1.61-1.92)
Physical functioning score < 50%	2.00 (1.84-2.18)	1.71 (1.56-1.87)	2.14 (1.96-2.35)	1.87 (1.72-2.04)	2.07 (1.89-2.27)	1.83 (1.68-2.00)

[a]Adjusted for sex, age, remoteness, education, household income, health insurance status, partner status and country of birth. [b]Also adjusted for the all other health conditions listed except depression, anxiety and general health indicators (categories: have had health condition at baseline; have not had at baseline or follow-up; have not had at baseline and have had at follow-up; missing indicator). [c]Also adjusted for baseline alcohol consumption. [d]Also adjusted for baseline smoking status, body mass index, physical activity time, fruit consumption and vegetable consumption. [e]Good/very good/excellent self-rated health at baseline. [f]Also adjusted for poor overall health (categories: poor health at baseline; no poor health at baseline or follow-up; poor health at follow-up but not at baseline; missing indicator).

7.2 – Additional Analyses

A number of additional analyses addressed important questions in relation to the 'sick-quitter effect'.

1. *Which health conditions are likely to contribute most to the 'sick-quitter effect'?*

Rationale and Method. As well as the odds of drinking cessation in relation to incident disease, the prevalence of disease is also important in terms of assessing which diseases are likely to contribute greatest to the 'sick-quitter effect'. For example, if a disease is strongly associated with drinking cessation but has a very low prevalence, it may contribute less to the 'sick-quitter effect' than a disease which is more modestly associated with drinking cessation but has a high prevalence. Therefore, the odds of each disease and general health indicator that was significantly associated with quitting drinking were plotted against its prevalence in the cohort to assess the relative importance of each (Figure 7.1).

Results. Poor health and quality of life at baseline had the highest odds ratios for quitting, but were among the least prevalent. Genitourinary conditions were the most prevalent at baseline, but were among the conditions with the lowest odds ratios. Low physical functioning score and diabetes appeared to be health variables with both a relatively high prevalence and high odds ratio.

Conclusions. For any health condition potentially related to the 'sick-quitter effect', when determining exclusion criteria to reduce bias, it is important to consider both its association with drinking cessation and its prevalence in the cohort.

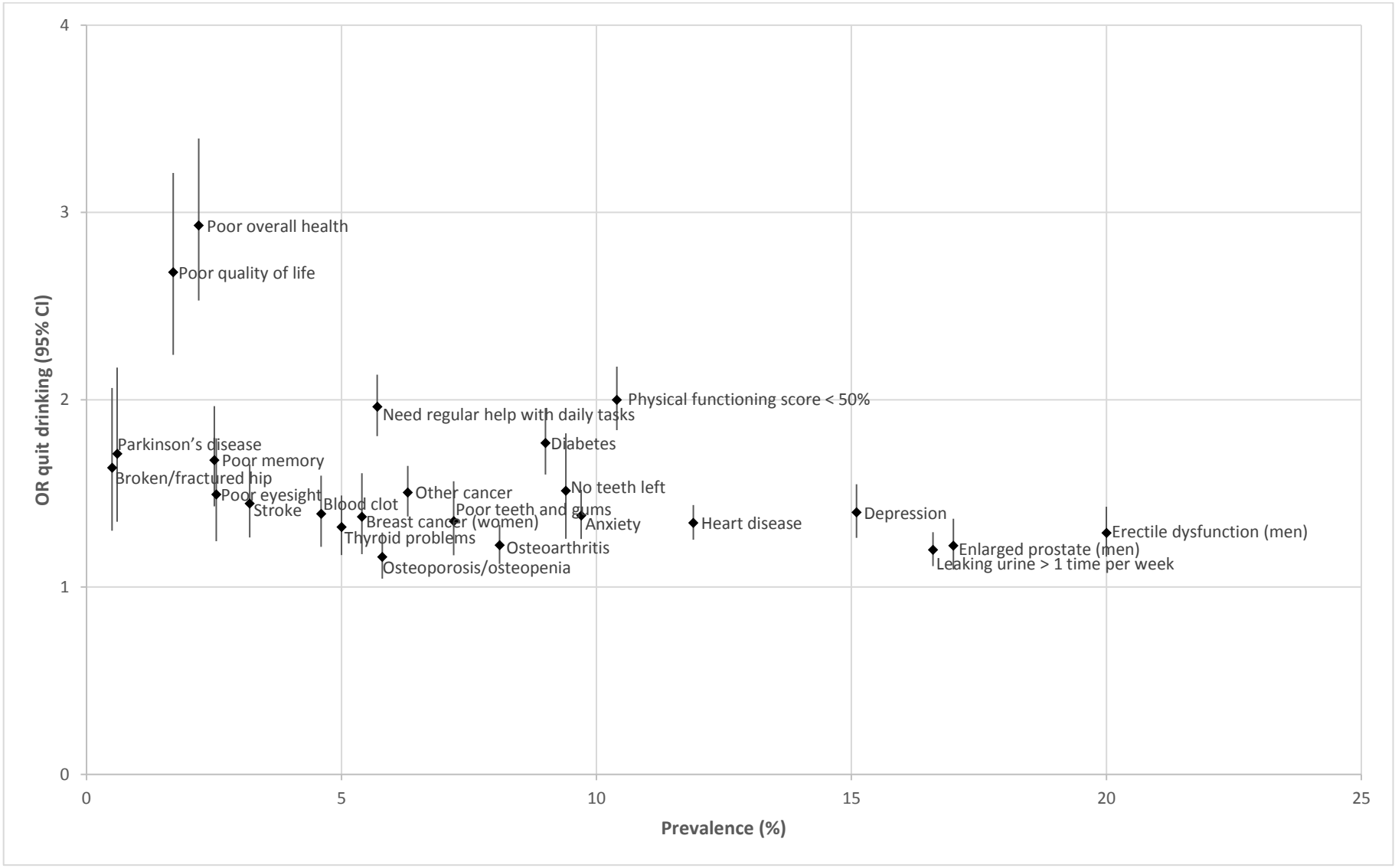

Figure 7.1. Prevalence of illnesses at baseline and odds of quitting drinking at five-year follow-up by illnesses newly acquired between baseline and follow-up in the 45 and Up Study (2006-2016), New South Wales, Australia. Only significant illnesses shown. OR, Odds Ratio. CI, Confidence Interval.

2. *Whether newly acquired health conditions are associated with reduction in overall intake (rather than complete cessation), a reduction in drinking frequency (i.e. number of drinking-days in the week), or an increase in drinks per drinking-day.*

Rationale and Method. Illness may be associated with a decrease in alcohol consumption rather than complete cessation[1]. Further, it has been reported that infrequent and heavy episodic drinkers have a higher prevalence of poor health compared to frequent and non-heavy episodic drinkers respectively[2]. Thus, persons may change their pattern of drinking in response to the occurrence of illness, as well as the total amount consumed. If for example, it is found that the occurrence of disease is associated with decreased drinking frequency, this would imply that apparent association of frequent drinking with better health outcomes may be overestimated and at least partially attributable to bias. In the same way, it may also be possible that the harms of heavy episodic drinking could be overestimated, if (although unlikely) the occurrence of disease is associated with an increase in mean drinks per drinking-day for the days on which participants remain drinking.

Logistic regression models were used to estimate the odds of 1) decreasing to low-volume drinking (≥ 1 and ≤ 3.5 drinks per week); 2) decreasing drinking frequency to 1-2 drinking-days per week; 3) increasing mean drinks per drinking-day to > 4. The models were adjusted for sex, age (categorical), remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and intensity, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height.

Results. At follow-up, 7748 participants had decreased to very light drinking, 7825 had decreased to infrequent drinking, and 3386 had increased to > 4 drinks per drinking-day. Eleven of 28 incident health conditions were associated with increased odds of reducing intake to very light levels and one (high blood pressure) with decreased odds (Table 7.1). The highest odds ratios were observed for

diabetes, breast cancer and stroke. However, the odds of quitting completely were higher than the odds of reducing intake across all diseases. All four indicators of general health were associated with increased odds of reducing intake, with the highest odds ratio observed for poor health.

Nine of 28 health conditions were associated with increased odds of becoming an infrequent drinker, with the highest odds found for diabetes, breast cancer and poor memory. All four indicators of general health were associated with increased odds, with the highest odds ratio observed for poor quality of life.

Seven of 28 health conditions were associated with increased odds of an increase in drinks consumed per drinking-day to > 4 and one (thyroid problems) with decreased odds. The highest odds were found for poor memory, poor teeth and gums and osteoarthritis. Only one of the four indicators of general health, low physical functioning score, was associated with increased odds.

Conclusions. The occurrence of disease and a decline in indicators of general health were associated with a reduction in alcohol consumption to the level of very light drinking (1-3.5 drinks/week), a decrease in drinking frequency to 1-2 drinking-days per week, and an increase in number of drinks consumed per drinking-day to > 4. An implication of these results is that just as the non-drinking group in a cohort study is likely to contain former drinkers who ceased drinking in association with the occurrence of ill-health, the very light drinking group is also likely to contain participants who have decreased their drinking in association with ill-health. Fewer health conditions were significantly associated with a decline to very light drinking compared to those associated with drinking cessation, and the odds ratios were generally smaller. This means that while the use of very light drinkers as a reference group may be vulnerable to bias from decreased drinking in response to ill-health (whereby risk estimates for moderate and heavy drinking may be underestimated), the effect is likely to be smaller than the 'sick-quitter effect'.

Similarly, the findings for illness and drinking pattern suggest that inverse associations between drinking frequency and negative health outcomes and positive associations between greater drinks

per drinking-day (or heavy episodic drinking) and negative health outcomes may be at least partially attributable to bias from changes in drinking patterns in response to ill-health. Compared to drinking cessation and decreased drinking, fewer diseases were significantly associated with changes in drinking pattern and the odds ratios were generally smaller. This indicates that bias from changes in drinking pattern in response to ill-health may have a smaller impact on risk estimates compared to the 'sick-quitter effect' and decreased drinking in response to ill-health.

The only indicator of general health significantly associated with all four changes in drinking pattern was low physical functioning score, indicating that the exclusion of participants with a low physical functioning score may allow for the most reliable risk estimates for the impact of alcohol-related harms.

Table 7.1. Odds of quitting drinking, decreasing to very light drinking, decreasing to infrequent drinking and increasing number of drinks per drinking-day at five-year follow-up by illnesses newly acquired between baseline and follow-up in the 45 and Up Study (2006-2016), New South Wales, Australia.

New illness	OR quit drinking[a] (95% CI)	OR decrease to very light drinking[b] (95% CI)	OR decrease to infrequent drinking[c] (95% CI)	OR increase to > 4 drinks per drinking-day[d] (95% CI)
Health conditions				
Cancer				
Breast cancer (women)	1.38 (1.18-1.61)	1.33 (1.11-1.59)	1.38 (1.15-1.66)	1.19 (0.80-1.77)
Prostate cancer (men)	1.05 (0.91-1.21)	1.18 (1.02-1.36)	1.22 (1.05-1.40)	1.02 (0.84-1.23)
Melanoma	1.00 (0.89-1.12)	0.95 (0.84-1.09)	0.99 (0.87-1.13)	1.12 (0.94-1.34)
Non-melanoma skin cancer	0.94 (0.88-1.01)	0.99 (0.92-1.08)	0.96 (0.89-1.04)	0.98 (0.87-1.10)
Other cancer	1.51 (1.38-1.65)	1.29 (1.16-1.44)	1.22 (1.09-1.36)	0.96 (0.80-1.16)
Cardiovascular disease				
Heart disease	1.34 (1.25-1.44)	1.12 (1.03-1.21)	1.06 (0.97-1.15)	1.04 (0.92-1.18)
Stroke	1.45 (1.27-1.66)	1.32 (1.12-1.55)	1.26 (1.06-1.49)	1.00 (0.77-1.30)
Blood clot	1.39 (1.22-1.60)	1.06 (0.90-1.26)	1.20 (1.02-1.42)	1.10 (0.85-1.41)
High blood pressure	0.98 (0.91-1.05)	0.92 (0.84-1.00)	0.96 (0.88-1.04)	1.20 (1.07-1.35)
Endocrine conditions				
Diabetes	1.77 (1.60-1.96)	1.39 (1.23-1.58)	1.51 (1.33-1.72)	0.83 (0.67-1.03)
Thyroid problems	1.32 (1.17-1.49)	1.31 (1.14-1.51)	1.14 (0.98-1.33)	0.71 (0.53-0.97)
Genitourinary conditions				
Leaking urine > 1 time per week	1.20 (1.11-1.29)	1.10 (1.01-1.21)	1.11 (1.01-1.21)	1.20 (1.05-1.37)
Enlarged prostate (men)	1.22 (1.09-1.37)	1.17 (1.04-1.32)	1.11 (0.98-1.25)	0.89 (0.76-1.03)
Erectile dysfunction (men)	1.29 (1.16-1.43)	1.07 (0.96-1.19)	1.13 (1.02-1.25)	1.02 (0.90-1.16)
Conditions affecting mobility				
Parkinson's disease	1.71 (1.35-2.17)	1.31 (0.97-1.78)	1.18 (0.86-1.64)	0.92 (0.55-1.53)
Osteoarthritis	1.22 (1.12-1.33)	1.13 (1.02-1.25)	1.07 (0.96-1.19)	1.22 (1.04-1.44)
Osteoporosis/osteopenia	1.16 (1.05-1.29)	1.13 (1.00-1.27)	1.07 (0.95-1.22)	0.91 (0.71-1.16)
Broken/fractured hip	1.64 (1.30-2.06)	1.15 (0.84-1.57)	0.92 (0.65-1.31)	1.10 (0.63-1.94)
Broken/fractured other bone	0.95 (0.88-1.03)	0.97 (0.89-1.06)	0.97 (0.89-1.06)	1.21 (1.07-1.38)
Mental health conditions				
Depression	1.40 (1.26-1.55)	1.11 (0.98-1.25)	1.11 (0.98-1.25)	1.16 (0.97-1.38)
Anxiety	1.38 (1.26-1.52)	1.14 (1.02-1.28)	1.04 (0.92-1.17)	0.98 (0.81-1.17)
Poor memory	1.68 (1.43-1.97)	1.15 (0.92-1.42)	1.27 (1.02-1.57)	1.51 (1.13-2.03)
Other conditions				
Asthma	1.07 (0.94-1.21)	1.01 (0.88-1.17)	0.98 (0.85-1.13)	0.90 (0.72-1.12)
Hayfever	0.99 (0.90-1.09)	0.95 (0.85-1.06)	0.94 (0.84-1.05)	0.97 (0.83-1.13)
Hearing loss	1.05 (0.97-1.13)	1.02 (0.94-1.11)	0.99 (0.91-1.08)	1.01 (0.89-1.14)
Poor eyesight	1.50 (1.25-1.79)	1.10 (0.87-1.41)	1.12 (0.88-1.44)	1.33 (0.93-1.91)
Poor teeth and gums	1.35 (1.17-1.57)	0.90 (0.74-1.10)	1.18 (0.98-1.42)	1.42 (1.10-1.82)
No teeth left	1.51 (1.26-1.82)	1.24 (0.97-1.58)	1.16 (0.89-1.49)	1.06 (0.72-1.55)
General health indicators				
Poor overall health	2.93 (2.53-3.40)	1.54 (1.23-1.92)	1.47 (1.17-1.85)	1.22 (0.85-1.74)
Poor quality of life	2.68 (2.24-3.21)	1.51 (1.15-1.98)	1.56 (1.19-2.05)	1.46 (0.98-2.17)
Need regular help with daily tasks	1.96 (1.81-2.13)	1.45 (1.30-1.62)	1.31 (1.17-1.48)	1.20 (0.99-1.45)
Physical functioning score < 50%	2.00 (1.84-2.18)	1.48 (1.33-1.65)	1.32 (1.18-1.48)	1.29 (1.07-1.55)

Models adjusted for sex, age, remoteness, education, household income, health insurance status, partner status and country of birth. [a]Among drinkers at baseline. [b]≥ 1 and ≤ 3.5 drinks per week, among drinkers consuming > 3.5 drinks per week at baseline. [c]Consume alcohol 1-2 days per week, among drinkers consuming alcohol 3-7 days per week at baseline. [d]Consume mean > 4 drinks per drinking-day, among drinkers consuming mean ≤ 4 drinks per drinking-day at baseline.

3. *Whether the prevalence of ill-health at baseline differs by total alcohol intake, drinking frequency and drinks per drinking-day.*

Rationale and Method. For risk estimates in the 45 and Up Study to be biased by the 'sick-quitter effect' and other changes in drinking behaviour in response to illness, the prevalence of poor health status must differ by levels of alcohol consumption and/or by drinking patterns.

Logistic regression was used to calculate odds ratios and 95% confidence intervals of having "poor" general health indicators at baseline across categories of total intake, drinking frequency and drinks per drinking-day. All models were adjusted for all covariates listed above. For drinking frequency and drinks per drinking-day, total alcohol consumption was included for adjustment and non-drinkers were excluded. For total alcohol consumption, significance was additionally calculated for drinkers alone.

Results. The odds of having poor indicators of general health at baseline by level of alcohol consumption is shown in Table 7.2. Compared to participants consuming ≥ 1 and ≤ 3.5 drinks per week, for all four indicators higher odds were found in non-drinkers, and lower odds in participants consuming > 3.5 and ≤ 28 drinks per week.

The odds of having poor indicators of general health at baseline by drinking pattern is shown in Table 7.3. Compared to participants consuming alcohol 1-2 days per week, for all four indicators lower odds were found in participants consuming alcohol more frequently. There were no significant differences in odds of poor quality of life by mean drinks per drinking-day. For the other three indicators, compared to participants consuming ≤ 2 drinks per drinking-day, lower odds were found in participants consuming > 2 and ≤ 4 drinks per drinking-day. For participants consuming > 4 drinks per drinking-day, higher odds of a physical functioning score < 50% were found, and no significant difference for the other general health indicators.

Conclusions. There were differences in the prevalence of general health indicators by total alcohol consumption, drinking frequency and drinks per drinking-day, even when adjusting for a variety of socio-demographic and health-related covariates. There was a U-shaped association for the prevalence of poor health status by total alcohol consumption, and an inverse association with drinking frequency. Therefore, risk estimates for the association between health outcomes and alcohol consumption and drinking patterns may be biased due to differences in health status between categories of drinking groups. For total alcohol consumption, even when using a reference group of very light drinkers, bias may not be completely removed.

Table 7.2. Odds of having poor general health indicators by alcohol consumption at baseline in the 45 and Up Study (2006-2009), New South Wales, Australia.

	OR of having illness by drinks/week (95% CI)							
Illness	**Non-drinker[a]**	**≥ 1, ≤ 3.5**	**> 3.5, ≤ 7**	**> 7, ≤ 14**	**> 14, ≤ 28**	**> 28**	p_{all}	$p_{drinkers}$
Poor overall health	1.45 (1.32-1.58)	1.00	0.77 (0.69-0.87)	0.69 (0.61-0.78)	0.69 (0.60-0.80)	0.88 (0.75-1.03)	< 0.001	< 0.001
Poor quality of life	1.29 (1.17-1.42)	1.00	0.75 (0.66-0.85)	0.73 (0.63-0.83)	0.72 (0.62-0.84)	0.96 (0.81-1.14)	< 0.001	< 0.001
Need regular help with daily tasks	1.27 (1.20-1.34)	1.00	0.81 (0.75-0.86)	0.74 (0.69-0.80)	0.72 (0.66-0.78)	0.79 (0.70-0.89)	< 0.001	< 0.001
Physical functioning score < 50%	1.37 (1.30-1.43)	1.00	0.85 (0.80-0.90)	0.78 (0.73-0.83)	0.83 (0.78-0.89)	0.96 (0.87-1.05)	< 0.001	< 0.001

Models adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]< 1 drink per week. OR, Odds Ratio. CI, Confidence Interval.

Table 7.3. Odds of having poor general health indicators by drinking pattern among drinkers at baseline in the 45 and Up Study (2006-2009), New South Wales, Australia.

	OR of having illness by drinking-days per week - adjusted for total alcohol consumption (95% CI)				OR of having illness by drinks per drinking-day - adjusted for total alcohol consumption (95% CI)			
Illness	**1-2**	**3-5**	**6-7**	***p***	**≤ 2**	**> 2, ≤ 4**	**> 4**	***p***
Poor overall health	1.00	0.80 (0.71-0.90)	0.75 (0.66-0.85)	< 0.001	1.00	0.84 (0.75-0.95)	1.04 (0.87-1.24)	0.002
Poor quality of life	1.00	0.70 (0.61-0.79)	0.73 (0.64-0.84)	< 0.001	1.00	0.88 (0.78-1.00)	0.97 (0.81-1.18)	0.13
Need regular help with daily tasks	1.00	0.83 (0.77-0.90)	0.81 (0.75-0.88)	< 0.001	1.00	0.87 (0.80-0.93)	1.12 (0.99-1.26)	< 0.001
Physical functioning score < 50%	1.00	0.83 (0.78-0.88)	0.85 (0.79-0.90)	< 0.001	1.00	0.90 (0.85-0.96)	1.13 (1.02-1.24)	< 0.001

Models adjusted for total alcohol consumption, sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. OR, Odds Ratio. CI, Confidence Interval.

4. *Whether the exclusion of participants with different types of health characteristics at baseline reduces the prevalence of disease in the cohort and decreases differences in health status between drinking group categories.*

Rationale and background. One method of mitigating potential bias from the 'sick-quitter effect' and other changes in drinking behaviour in response to illness is to exclude participants with certain indicators of pre-existing ill-health at baseline. Seven potential indicators of ill-health were examined here, and the impact of their exclusion on the prevalence of disease at baseline in the cohort and the odds of six selected health conditions across categories of total alcohol consumption and drinking pattern.

The seven indicators used for exclusion were participants with 1) poor overall health, 2) poor quality of life, 3) needing regular help with daily tasks, 4) a physical functioning score < 50%, 5) a pre-existing cancer diagnosis (excluding non-melanoma skin cancer) and/or cardiovascular disease diagnosis (heart disease or stroke), 6) those who died within the first three years of follow-up, and 7) those aged 65 years or older. The six conditions examined were cancer and cardiovascular disease combined (due to prior cohort studies of alcohol consumption and mortality commonly accounting for these diseases when considering the 'sick-quitter effect'), and diabetes, Parkinson's disease, hip fracture and poor memory (due to these diseases having the strongest association with drinking cessation in the main analyses).

The effect of the seven exclusion scenarios on the six health conditions was examined for 1) the unadjusted prevalence of disease at baseline in the cohort, and 2) the odds of the six diseases across categories of alcohol consumption. Logistic regression was used to calculate the odds and 95% confidence intervals of having each of the six diseases at baseline across categories of total alcohol consumption, drinking frequency and drinks per drinking-day, after adjustment for all covariates. Each disease was modelled separately for all seven exclusion scenarios and compared to the model with no exclusions.

Results. The number of participants and proportion with each of the six baseline health conditions by exclusion scenario are shown in Table 7.4. The exclusion of participants with poor physical functioning and participants aged 65 years or older reduced the prevalence of all six diseases to a greater degree than other exclusion scenarios, with the latter exclusion scenario appearing to be most effective. The exclusion of participants with poor quality of life appeared to reduce the prevalence of disease the least of any exclusion scenario.

The odds of having six specific diseases at baseline by level of alcohol consumption and method of exclusion is shown in Table 7.5. In the models with no exclusions, non-drinkers had higher odds of cardiovascular disease, diabetes, Parkinson's disease and poor memory compared to participants consuming ≥ 1 and ≤ 3.5 drinks per week, and for all six diseases, the odds ratio was significantly lower in at least one category of drinking with levels above 3.5 drinks/week. The exclusion of participants with poor physical functioning appeared to attenuate the odds ratios of non-drinkers to a greater degree than the other exclusion scenarios. For most scenarios, the variation in cardiovascular disease, diabetes, Parkinson's disease and poor memory remained significant across levels of alcohol consumption. Exceptions were the scenarios excluding participants aged ≥ 65 years and those needing help with daily tasks (when restricting to drinkers only), where Parkinson's disease was not significant.

The odds of having six specific diseases at baseline by drinking pattern and exclusion scenario is shown in Table 7.6. In the models with no exclusions, only diabetes and poor memory varied significantly by drinking frequency, with lower odds found in participants consuming alcohol > 2 days per week compared to 1-2 days per week. No exclusion scenario appeared to make a material difference to the odds for diabetes. The exclusion of participants with pre-existing cancer or cardiovascular disease eliminated the variation in poor memory across levels of drinking frequency. The exclusion of participants with poor overall health or those aged 65 years or older resulted in significant increased odds of Parkinson's disease for more frequent drinkers.

In the models with no exclusions, all diseases except cancer differed in the number of drinks per drinking-day, with lower odds of cardiovascular disease, Parkinson's disease and poor memory for participants consuming > 2 and ≤ 4 drinks per drinking-day, and with higher odds of diabetes and hip fracture and lower odds of cardiovascular disease for participants consuming > 4 drinks per drinking-day. The exclusion of participants with poor physical functioning appeared to attenuate the variation across drinking categories for most diseases to a greater degree than the other exclusion scenarios, with an overall effect only for diabetes and poor memory remaining significant. However, the exclusion of participants aged < 65 years attenuated the differences in diabetes to a greater degree than the exclusion of participants with poor physical functioning.

Conclusions. Overall, the exclusion of participants with a low physical functioning score appeared to be the most effective method examined here to test for bias from the 'sick-quitter effect' and other changes in drinking behaviours in response to ill-health. It appeared to be useful when examining total alcohol consumption and drinks per drinking-day, while no method appeared to be effective when examining drinking frequency. The exclusion of participants aged ≥ 65 years appeared to be most effective in reducing the prevalence of disease in the cohort.

Table 7.4. Prevalence of illnesses at baseline by exclusion scenario in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Prevalence at baseline (%)					
Exclusion scenario	**n participants (%)**	**Ever had cancer**	**Ever had CVD**	**Ever had diabetes**	**Ever had Parkinson's disease**	**Hip fracture in past 5 years**	**Poor memory**
No exclusion	261,740 (100.0)	16.9	13.9	8.9	0.6	0.5	2.5
Poor overall health	247,580 (94.6)	16.7	13.4	8.5	0.6	0.5	2.1
Poor quality of life	244,474 (93.4)	16.8	13.7	8.6	0.6	0.5	2.1
Need help with daily tasks	235,527 (90.0)	16.3	12.7	8.1	0.4	0.3	1.8
Physical functioning score < 50%	207,003 (79.1)	15.7	11.5	7.4	0.4	0.2	1.6
Ever had cancer or CVD	190,272 (72.7)	0.0	0.0	7.1	0.4	0.4	2.0
Death within 3 years of baseline	253,935 (97.0)	16.1	13.2	8.6	0.6	0.4	2.3
Age ≥ 65 years	161,527 (71.7)	11.7	7.1	6.4	0.3	0.2	2.0

CVD, Cardiovascular Disease.

Table 7.5. Odds of having illness by alcohol consumption at baseline by exclusion scenario in the 45 and Up Study (2006-2009), New South Wales, Australia.

	OR of having illness by drinks/week (95% CI)							
Exclusion scenario	**Non-drinker[a]**	**≥ 1, ≤ 3.5**	**> 3.5, ≤ 7**	**> 7, ≤ 14**	**> 14, ≤ 28**	**> 28**	p_{all}	$p_{drinkers}$
No exclusion								
Ever had cancer	1.00 (0.97-1.03)	1.00	0.99 (0.95-1.03)	1.02 (0.99-1.06)	0.99 (0.95-1.03)	0.93 (0.88-0.99)	0.07	0.07
Ever had cardiovascular disease	1.13 (1.09-1.18)	1.00	0.93 (0.89-0.97)	0.94 (0.90-0.98)	0.85 (0.81-0.90)	0.78 (0.81-0.90)	< 0.001	< 0.001
Ever had diabetes	1.40 (1.34-1.46)	1.00	0.78 (0.74-0.82)	0.68 (0.65-0.72)	0.67 (0.63-0.71)	0.62 (0.57-0.68)	< 0.001	< 0.001
Ever had Parkinson's disease	1.22 (1.04-1.42)	1.00	1.07 (0.90-1.27)	0.81 (0.67-0.99)	0.73 (0.58-0.92)	0.50 (0.34-0.74)	< 0.001	< 0.001
Hip fracture in past 5 years	1.06 (0.89-1.25)	1.00	0.96 (0.79-1.17)	0.79 (0.63-0.99)	0.84 (0.64-1.10)	1.04 (0.72-1.51)	0.06	0.21
Poor memory	1.10 (1.02-1.18)	1.00	0.91 (0.83-1.00)	0.79 (0.71-0.87)	0.84 (0.75-0.94)	0.90 (0.78-1.03)	< 0.001	< 0.001
Poor overall health excluded								
Ever had cancer	0.99 (0.96-1.02)	1.00	0.99 (0.95-1.03)	1.02 (0.98-1.06)	1.00 (0.95-1.04)	0.94 (0.89-1.01)	0.17	0.12
Ever had cardiovascular disease	1.14 (1.09-1.18)	1.00	0.94 (0.90-0.98)	0.96 (0.92-1.00)	0.87 (0.83-0.92)	0.80 (0.75-0.86)	< 0.001	< 0.001
Ever had diabetes	1.38 (1.32-1.44)	1.00	0.77 (0.73-0.82)	0.67 (0.64-0.71)	0.66 (0.62-0.71)	0.61 (0.56-0.67)	< 0.001	< 0.001
Ever had Parkinson's disease	1.19 (1.01-1.40)	1.00	1.06 (0.88-1.28)	0.84 (0.68-1.03)	0.75 (0.58-0.96)	0.50 (0.33-0.76)	< 0.001	0.001
Hip fracture in past 5 years	1.11 (0.92-1.33)	1.00	1.04 (0.84-1.28)	0.86 (0.68-1.09)	0.89 (0.67-1.19)	0.98 (0.65-1.47)	0.21	0.52
Poor memory	1.04 (0.96-1.14)	1.00	0.89 (0.81-0.99)	0.79 (0.71-0.88)	0.85 (0.75-0.96)	0.92 (0.79-1.07)	< 0.001	< 0.001
Poor quality of life excluded								
Ever had cancer	1.00 (0.97-1.04)	1.00	0.98 (0.95-1.02)	1.01 (0.98-1.05)	0.99 (0.94-1.03)	0.93 (0.88-1.00)	0.11	0.12
Ever had cardiovascular disease	1.13 (1.09-1.17)	1.00	0.93 (0.89-0.97)	0.95 (0.90-0.99)	0.87 (0.82-0.91)	0.79 (0.74-0.85)	< 0.001	< 0.001
Ever had diabetes	1.39 (1.33-1.45)	1.00	0.78 (0.74-0.82)	0.68 (0.64-0.72)	0.67 (0.62-0.71)	0.62 (0.57-0.68)	< 0.001	< 0.001
Ever had Parkinson's disease	1.17 (1.00-1.38)	1.00	0.99 (0.83-1.19)	0.78 (0.64-0.96)	0.73 (0.57-0.93)	0.50 (0.33-0.75)	< 0.001	0.002
Hip fracture in past 5 years	1.08 (0.90-1.30)	1.00	1.02 (0.82-1.26)	0.80 (0.63-1.01)	0.85 (0.63-1.13)	1.00 (0.67-1.51)	0.08	0.23
Poor memory	1.10 (1.01-1.20)	1.00	0.94 (0.85-1.04)	0.78 (0.70-0.87)	0.88 (0.78-0.99)	0.92 (0.79-1.07)	< 0.001	< 0.001
Need help with daily tasks excluded								
Ever had cancer	0.99 (0.96-1.03)	1.00	1.00 (0.96-1.04)	1.03 (0.99-1.07)	0.99 (0.94-1.03)	0.96 (0.90-1.03)	0.19	0.18
Ever had cardiovascular disease	1.11 (1.07-1.16)	1.00	0.95 (0.91-0.99)	0.96 (0.91-1.00)	0.88 (0.83-0.93)	0.80 (0.75-0.87)	< 0.001	< 0.001
Ever had diabetes	1.36 (1.30-1.42)	1.00	0.76 (0.72-1.81)	0.67 (0.63-0.71)	0.66 (0.62-0.70)	0.60 (0.55-0.66)	< 0.001	< 0.001
Ever had Parkinson's disease	1.21 (1.00-1.47)	1.00	1.09 (0.88-1.35)	0.88 (0.70-1.11)	0.86 (0.66-1.13)	0.60 (0.38-0.93)	< 0.001	0.08
Hip fracture in past 5 years	1.15 (0.92-1.44)	1.00	1.15 (0.90-1.48)	0.90 (0.68-1.18)	0.97 (0.69-1.35)	1.04 (0.65-1.68)	0.28	0.31
Poor memory	1.09 (0.99-1.19)	1.00	0.92 (0.82-1.03)	0.82 (0.73-0.92)	0.85 (0.75-0.97)	0.93 (0.80-1.10)	< 0.001	0.15

Models adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]< 1 drink per week. OR, Odds Ratio. CI, Confidence Interval. CVD, Cardiovascular Disease.

Table 7.5. (Continued)

Exclusion scenario	OR of having illness by drinks/week (95% CI)						p_{all}	$p_{drinkers}$
	Non-drinker[a]	≥ 1, ≤ 3.5	> 3.5, ≤ 7	> 7, ≤ 14	> 14, ≤ 28	> 28		
Physical functioning score < 50% excluded								
Ever had cancer	1.00 (0.96-1.04)	1.00	0.99 (0.95-1.04)	1.04 (1.00-1.09)	1.00 (0.95-1.05)	0.97 (0.91-1.04)	0.13	0.07
Ever had cardiovascular disease	1.10 (1.05-1.15)	1.00	0.95 (0.91-1.00)	0.96 (0.91-1.01)	0.88 (0.83-0.93)	0.80 (0.74-0.87)	< 0.001	< 0.001
Ever had diabetes	1.32 (1.26-1.39)	1.00	0.78 (0.74-0.83)	0.66 (0.62-0.71)	0.65 (0.61-0.70)	0.60 (0.54-0.66)	< 0.001	< 0.001
Ever had Parkinson's disease	1.09 (0.89-1.34)	1.00	1.00 (0.80-1.25)	0.74 (0.58-0.95)	0.77 (0.58-1.03)	0.44 (0.26-0.74)	< 0.001	0.005
Hip fracture in past 5 years	1.18 (0.89-1.55)	1.00	1.17 (0.86-1.58)	0.96 (0.69-1.34)	0.98 (0.66-1.46)	0.94 (0.52-1.69)	0.60	0.64
Poor memory	1.06 (0.95-1.18)	1.00	0.90 (0.79-1.01)	0.79 (0.69-0.89)	0.83 (0.72-0.96)	0.94 (0.78-1.12)	< 0.001	0.003
Ever had cancer or CVD excluded								
Ever had cancer	-	-	-	-	-	-	-	-
Ever had cardiovascular disease	-	-	-	-	-	-	-	-
Ever had diabetes	1.41 (1.33-1.49)	1.00	0.77 (0.72-0.82)	0.67 (0.63-0.72)	0.69 (0.63-0.74)	0.65 (0.58-0.72)	< 0.001	< 0.001
Ever had Parkinson's disease	1.23 (0.98-1.54)	1.00	1.18 (0.92-1.52)	0.79 (0.59-1.05)	0.64 (0.45-0.92)	0.41 (0.22-0.79)	< 0.001	< 0.001
Hip fracture in past 5 years	1.12 (0.89-1.41)	1.00	1.08 (0.83-1.40)	0.90 (0.67-1.20)	0.96 (0.67-1.36)	1.10 (0.69-1.78)	0.57	0.76
Poor memory	1.18 (1.07-1.31)	1.00	0.89 (0.78-1.00)	0.86 (0.76-0.98)	0.88 (0.76-1.02)	0.98 (0.82-1.17)	< 0.001	0.07
Death within 3 years of baseline excluded								
Ever had cancer	1.00 (0.96-1.03)	1.00	0.99 (0.95-1.03)	1.03 (0.99-1.07)	0.99 (0.94-1.03)	0.94 (0.88-1.00)	0.07	0.07
Ever had cardiovascular disease	1.13 (1.08-1.17)	1.00	0.93 (0.89-0.97)	0.94 (0.90-0.98)	0.86 (0.92-0.90)	0.78 (0.73-0.84)	< 0.001	< 0.001
Ever had diabetes	1.40 (1.34-1.46)	1.00	0.78 (0.74-0.82)	0.68 (0.65-0.72)	0.66 (0.62-0.71)	0.62 (0.57-0.68)	< 0.001	< 0.001
Ever had Parkinson's disease	1.20 (1.02-1.42)	1.00	1.06 (0.88-1.27)	0.79 (0.65-0.97)	0.76 (0.59-0.96)	0.44 (0.29-0.68)	< 0.001	< 0.001
Hip fracture in past 5 years	1.12 (0.93-1.35)	1.00	1.07 (0.86-1.32)	0.87 (0.69-1.11)	0.89 (0.67-1.20)	0.94 (0.61-1.44)	0.21	0.43
Poor memory	1.09 (1.00-1.18)	1.00	0.90 (0.82-0.99)	0.78 (0.70-0.86)	0.82 (0.73-0.92)	0.90 (0.78-1.04)	< 0.001	< 0.001
Age ≥ 65 years excluded								
Ever had cancer	1.00 (0.96-1.05)	1.00	0.97 (0.92-1.02)	1.02 (0.97-1.07)	0.99 (0.93-1.05)	0.99 (0.91-1.08)	0.60	0.45
Ever had cardiovascular disease	1.15 (1.08-1.22)	1.00	0.92 (0.86-0.99)	0.95 (0.89-1.02)	0.91 (0.85-0.99)	0.79 (0.72-0.88)	< 0.001	< 0.001
Ever had diabetes	1.41 (1.32-1.49)	1.00	0.73 (0.68-0.79)	0.63 (0.58-0.68)	0.65 (0.59-0.71)	0.59 (0.52-0.66)	< 0.001	< 0.001
Ever had Parkinson's disease	1.34 (0.99-1.82)	1.00	1.12 (0.79-1.57)	1.21 (0.86-1.71)	1.11 (0.74-1.66)	0.74 (0.40-1.35)	0.21	0.55
Hip fracture in past 5 years	1.25 (0.88-1.77)	1.00	0.91 (0.60-1.38)	0.97 (0.64-1.46)	0.85 (0.52-1.39)	0.72 (0.38-1.37)	0.23	0.94
Poor memory	1.17 (1.05-1.30)	1.00	0.89 (0.78-1.02)	0.75 (0.65-0.86)	0.84 (0.73-0.98)	0.96 (0.80-1.14)	< 0.001	< 0.001

Table 7.6. Odds of having illness by drinking pattern among drinkers at baseline by exclusion scenario in the 45 and Up Study (2006-2009), New South Wales, Australia.

	OR of having illness by drinking-days per week - adjusted for total alcohol consumption (95% CI)				OR of having illness by drinks per drinking-day - adjusted for total alcohol consumption (95% CI)			
Exclusion scenario	**1-2**	**3-5**	**6-7**	***p***	**≤ 2**	**> 2, ≤ 4**	**> 4**	***p***
No exclusion								
Ever had cancer	1.00	0.99 (0.96-1.03)	1.01 (0.97-1.05)	0.52	1.00	1.03 (1.00-1.07)	0.99 (0.93-1.06)	0.10
Ever had cardiovascular disease	1.00	0.98 (0.94-1.02)	0.99 (0.94-1.03)	0.70	1.00	0.93 (0.90-0.97)	0.93 (0.87-1.01)	0.004
Ever had diabetes	1.00	0.77 (0.74-0.81)	0.63 (0.59-0.67)	< 0.001	1.00	1.03 (0.98-1.09)	1.34 (1.23-1.46)	< 0.001
Ever had Parkinson's disease	1.00	1.19 (0.99-1.45)	1.26 (1.03-1.56)	0.07	1.00	0.78 (0.64-0.96)	0.71 (0.49-1.03)	0.04
Hip fracture in past 5 years	1.00	1.05 (0.85-1.30)	0.95 (0.75-1.19)	0.62	1.00	1.09 (0.87-1.37)	1.59 (1.10-2.30)	0.04
Poor memory	1.00	0.85 (0.77-0.93)	0.88 (0.80-0.98)	0.002	1.00	0.90 (0.82-0.99)	1.09 (0.94-1.26)	0.006
Poor overall health excluded								
Ever had cancer	1.00	1.00 (0.96-1.03)	1.01 (0.97-1.06)	0.59	1.00	1.03 (1.00-1.07)	0.99 (0.93-1.06)	0.08
Ever had cardiovascular disease	1.00	0.99 (0.95-1.03)	1.00 (0.95-1.05)	0.87	1.00	0.94 (0.90-0.98)	0.94 (0.87-1.02)	0.01
Ever had diabetes	1.00	0.77 (0.73-0.81)	0.63 (0.59-0.67)	< 0.001	1.00	1.03 (0.98-1.09)	1.31 (1.20-1.43)	< 0.001
Ever had Parkinson's disease	1.00	1.23 (1.01-1.51)	1.31 (1.04-1.63)	0.048	1.00	0.81 (0.66-1.01)	0.70 (0.47-1.04)	0.09
Hip fracture in past 5 years	1.00	1.04 (0.83-1.31)	1.00 (0.78-1.27)	0.90	1.00	1.02 (0.80-1.30)	1.48 (1.00-2.19)	0.10
Poor memory	1.00	0.84 (0.76-0.93)	0.90 (0.80-1.00)	0.004	1.00	0.90 (0.81-0.99)	1.08 (0.92-1.26)	0.01
Poor quality of life excluded								
Ever had cancer	1.00	1.00 (0.96-1.04)	1.02 (0.97-1.06)	0.60	1.00	1.04 (1.00-1.08)	1.01 (0.95-1.08)	0.07
Ever had cardiovascular disease	1.00	0.99 (0.94-1.03)	1.00 (0.95-1.05)	0.82	1.00	0.94 (0.90-0.98)	0.93 (0.87-1.01)	0.01
Ever had diabetes	1.00	0.79 (0.74-0.83)	0.64 (0.60-0.69)	< 0.001	1.00	1.04 (0.98-1.10)	1.34 (1.23-1.47)	< 0.001
Ever had Parkinson's disease	1.00	1.19 (0.95-1.50)	1.37 (1.06-1.77)	0.06	1.00	0.81 (0.66-1.01)	0.70 (0.47-1.04)	0.09
Hip fracture in past 5 years	1.00	1.05 (0.81-1.37)	1.00 (0.75-1.34)	0.91	1.00	1.10 (0.86-1.41)	1.77 (1.20-2.61)	0.01
Poor memory	1.00	0.84 (0.74-0.95)	0.91 (0.79-1.04)	0.02	1.00	0.92 (0.83-1.02)	1.17 (1.00-1.37)	0.003
Need help with daily tasks excluded								
Ever had cancer	1.00	0.99 (0.96-1.03)	1.01 (0.97-1.06)	0.58	1.00	1.03 (0.99-1.07)	1.00 (0.94-1.08)	0.32
Ever had cardiovascular disease	1.00	0.99 (0.95-1.04)	1.00 (0.95-1.05)	0.97	1.00	0.93 (0.89-0.98)	0.92 (0.85-0.99)	0.007
Ever had diabetes	1.00	0.76 (0.72-0.80)	0.62 (0.58-0.66)	< 0.001	1.00	1.05 (1.00-1.11)	1.34 (1.22-1.47)	< 0.001
Ever had Parkinson's disease	1.00	1.27 (1.01-1.58)	1.21 (0.94-1.56)	0.12	1.00	0.93 (0.74-1.17)	0.77 (0.49-1.19)	0.49
Hip fracture in past 5 years	1.00	1.03 (0.80-1.34)	0.94 (0.70-1.25)	0.74	1.00	1.08 (0.82-1.43)	1.63 (1.04-2.55)	0.09
Poor memory	1.00	0.85 (0.76-0.94)	0.88 (0.78-0.99)	0.008	1.00	0.92 (0.83-1.02)	1.11 (0.94-1.31)	0.03

Models adjusted for total alcohol consumption, sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. OR, Odds Ratio. CI, Confidence Interval. CVD, Cardiovascular Disease.

Table 7.6. (Continued)

Exclusion scenario	OR of having illness by drinking-days per week - adjusted for total alcohol consumption (95% CI)			*p*	OR of having illness by drinks per drinking-day - adjusted for total alcohol consumption (95% CI)			*p*
	1-2	**3-5**	**6-7**		**≤ 2**	**> 2, ≤ 4**	**> 4**	
Physical functioning score < 50% excluded								
Ever had cancer	1.00	0.99 (0.95-1.03)	1.01 (0.97-1.06)	0.55	1.00	1.03 (0.99-1.07)	1.00 (0.93-1.07)	0.26
Ever had cardiovascular disease	1.00	0.99 (0.94-1.03)	0.99 (0.93-1.04)	0.82	1.00	0.95 (0.90-0.99)	0.97 (0.89-1.05)	0.08
Ever had diabetes	1.00	0.76 (0.72-0.81)	0.60 (0.56-0.64)	< 0.001	1.00	1.06 (1.00-1.13)	1.38 (1.25-1.53)	< 0.001
Ever had Parkinson's disease	1.00	1.21 (0.96-1.53)	1.15 (0.88-1.51)	0.28	1.00	0.91 (0.71-1.16)	0.74 (0.46-1.20)	0.46
Hip fracture in past 5 years	1.00	1.03 (0.75-1.40)	0.94 (0.67-1.33)	0.84	1.00	1.00 (0.72-1.39)	1.34 (0.76-2.35)	0.53
Poor memory	1.00	0.85 (0.76-0.96)	0.90 (0.78-1.02)	0.03	1.00	0.84 (0.74-0.94)	1.06 (0.88-1.28)	< 0.001
Ever had cancer or CVD excluded								
Ever had cancer	-	-	-	-	-	-	-	-
Ever had cardiovascular disease	-	-	-	-	-	-	-	-
Ever had diabetes	1.00	0.76 (0.71-0.81)	0.60 (0.55-0.65)	< 0.001	1.00	1.07 (1.00-1.14)	1.44 (1.29-1.60)	< 0.001
Ever had Parkinson's disease	1.00	1.30 (0.98-1.72)	1.67 (1.23-2.28)	0.005	1.00	0.56 (0.41-0.76)	0.29 (0.14-0.57)	< 0.001
Hip fracture in past 5 years	1.00	1.13 (0.86-1.50)	1.06 (0.78-1.44)	0.67	1.00	1.07 (0.80-1.43)	1.20 (0.73-1.97)	0.77
Poor memory	1.00	0.88 (0.78-0.99)	0.94 (0.82-1.07)	0.09	1.00	0.88 (0.78-0.99)	1.05 (0.87-1.26)	0.03
Death within 3 years of baseline excluded								
Ever had cancer	1.00	0.99 (0.96-1.03)	1.01 (0.97-1.06)	0.49	1.00	1.03 (0.99-1.07)	1.00 (0.93-1.06)	0.16
Ever had cardiovascular disease	1.00	0.99 (0.94-1.03)	0.98 (0.94-1.03)	0.68	1.00	0.94 (0.90-0.98)	0.94 (0.88-1.02)	0.01
Ever had diabetes	1.00	0.78 (0.74-0.82)	0.62 (0.59-0.66)	< 0.001	1.00	1.04 (0.98-1.10)	1.35 (1.24-1.47)	< 0.001
Ever had Parkinson's disease	1.00	1.18 (0.97-1.43)	1.21 (0.97-1.51)	0.17	1.00	0.84 (0.68-1.04)	0.73 (0.49-1.08)	0.17
Hip fracture in past 5 years	1.00	1.06 (0.84-1.33)	1.05 (0.81-1.35)	0.90	1.00	1.10 (0.86-1.40)	1.42 (0.94-2.13)	0.24
Poor memory	1.00	0.85 (0.78-0.94)	0.87 (0.78-0.96)	0.003	1.00	0.88 (0.80-0.97)	1.12 (0.96-1.30)	< 0.001
Age ≥ 65 years excluded								
Ever had cancer	1.00	0.99 (0.94-1.03)	1.00 (0.94-1.06)	0.76	1.00	1.03 (0.98-1.08)	1.00 (0.92-1.09)	0.46
Ever had cardiovascular disease	1.00	0.99 (0.93-1.05)	1.01 (0.93-1.09)	0.81	1.00	0.96 (0.91-1.02)	0.96 (0.87-1.07)	0.48
Ever had diabetes	1.00	0.73 (0.68-0.78)	0.60 (0.55-0.66)	< 0.001	1.00	1.01 (0.94-1.09)	1.29 (1.15-1.45)	< 0.001
Ever had Parkinson's disease	1.00	1.45 (1.05-2.01)	1.74 (1.19-2.56)	0.02	1.00	0.68 (0.49-0.94)	0.58 (0.32-1.03)	0.045
Hip fracture in past 5 years	1.00	1.18 (0.81-1.74)	1.16 (0.73-1.85)	0.68	1.00	1.01 (0.70-1.48)	0.83 (0.43-1.63)	0.81
Poor memory	1.00	0.83 (0.73-0.94)	0.83 (0.72-0.96)	0.007	1.00	0.85 (0.75-0.97)	1.13 (0.94-1.35)	0.001

7.3 – Discussion and Conclusions

Chapter 7 demonstrated that the occurrence of a large number of health conditions were associated with drinking cessation, and that indicators of general health were associated with higher odds of quitting than specific diseases. The highest odds were found for the general health indicators of poor overall health and poor quality of life, and the specific diseases of diabetes, Parkinson's disease, poor memory and hip fracture. It was shown that accounting for cancer and cardiovascular disease alone will only address a small portion of the 'sick-quitter effect', while accounting for all associated diseases using a method such as exclusion is impractical due to a substantial decrease in sample size. Further, accounting for general indicators of health is likely to be a more effective approach than accounting for specific diseases, yet it was also shown that this is unlikely to address the 'sick-quitter effect' entirely. Further, limitation of excluding participants based on health status is the potential for selection bias. There were few differences in quitting by sex, age or smoking status, and the results appeared to be robust to sensitivity analyses.

A key implication of the results is that the exclusion of participants with specific diseases or poor indicators of general health is likely to only partially address the 'sick-quitter effect', and other methods (preferably those without the potential for selection bias) may also need to be considered. Alternative methods of addressing the 'sick-quitter effect' include the use of lifetime abstainers or light drinkers (or both) as the reference group, calculating a log-linear trend in risk for drinkers only, assigning ex-drinkers to their former levels of drinking at analysis, ascertaining alcohol consumption at multiple time points (either retrospectively or prospectively from baseline), excluding outcomes that occur early in the period of follow-up and restricting the study to younger participants who have had fewer health events causing them to reduce or quit drinking. It is possible to perform most of these methods using the 45 and Up Study, with the exception of the use of lifetime abstainers as the reference group and assigning ex-drinkers to their former levels of drinking. The first wave of

follow-up was completed in 2016, which is after the date of the cancer (2010) and mortality (2014) ascertainment. Thus, while it was not possible to ascertain alcohol consumption at multiple time points for these analyses this could be conducted in the future. Therefore, to examine associations between alcohol consumption and cancer and mortality in Chapters 8 and 9 with reduced risk of bias from the 'sick-quitter effect', risks were estimated where possible using very light drinkers as the reference group, calculating a log-linear trend in risk for drinkers only, excluding outcomes that occur early in the period of follow-up and restricting the study to younger participants.

The additional results showed that the odds of a disease in relation to quitting is not necessarily a good indicator of the potential for that disease to induce bias from the sick-quitter effect on its own. Accounting for the prevalence of each health variable is also important. For example, diseases that are highly related to quitting but are very uncommon would have a relatively small impact on the sick-quitter effect. Low physical functioning score and diabetes appeared to be health variables with both a relatively high prevalence and odds ratio. Thus, for any health condition potentially related to the 'sick-quitter effect', when determining exclusion criteria to reduce bias, it is important to consider both its association with drinking cessation and its prevalence in the cohort.

It was then shown that illness is also related to reductions in alcohol consumption and changes in drinking pattern, however fewer health conditions were significantly associated with a decline to very light drinking compared to those associated with drinking cessation, and the odds ratios were generally smaller. There were associations with a decline in drinking frequency in relation to some diseases (e.g. diabetes, breast cancer and poor memory). Overall, participants with low physical functioning score were significantly more likely to quit or reduce intake, reduce their number of drinking-days, and increase the number of drinks per drinking-day.

The odds of having poor indicators of general health also varied by total alcohol consumption, with higher odds of poor health outcomes observed among non-drinkers. There was generally a U-shaped association for the prevalence of poor health status by total alcohol consumption, and an inverse

association with drinking frequency. The odds of having selected diseases also varied by total alcohol consumption and drinking pattern, except for cancer. This means that despite the finding that cancer is associated with drinking behaviour change, potential confounding by prior cancer status may not bias risk estimates in the 45 and Up Study, unless there remain important differences in the distribution of cancer type or stage not examined here.

The results suggest that when examining alcohol consumption as a log-linear variable, a sensitivity test restricting the calculation to participants consuming ≥ 7 drinks per week may be effective in reducing bias caused by participants decreasing their alcohol consumption to light drinking in response to ill-health. This is because light drinkers had poorer health status compared to moderate drinkers, with the odds of having poor general health indicators appearing to reach a minimum after approximately 7 drinks per week. This sensitivity test should therefore provide an estimate of the log-linear association between alcohol consumption and outcomes less biased by ill-health, under the assumption that any association between moderate drinking and better health status compared to light and non-drinking is not causal and is instead entirely attributable to confounding.

Consistent with the analysis examining changes in drinking frequency in association with the occurrence of disease, frequent drinkers generally had lower odds of poor general health indicators at baseline, as well as diabetes and poor memory compared to infrequent drinkers. Persons consuming > 4 drinks per drinking-day were found to have higher odds of a low physical functioning score, diabetes and hip fracture, but no difference in odds for the other health variables. There were also lower odds of a number of health variables in participants consuming > 2 and ≤ 4 drinks per day compared to those consuming ≤ 2 drinks per day. It was found that the exclusion of participants with low physical functioning score performed best at reducing the uneven distribution of disease between categories of total alcohol consumption and drinks per drinking-day, however the improvements were only modest. For example, the odds of having cardiovascular disease and diabetes associated with non-drinking compared to very light drinking were only attenuated by 20 to

25%. No method of exclusion appeared to make a material difference to the uneven distribution of disease between categories of drinking frequency. The implication of these results is again that the exclusion of participants with low a physical functioning score may be an effective method to test for bias from the 'sick-quitter effect' when examining total alcohol consumption and drinks per drinking-day (but cannot be expected to remove the bias entirely), while it may not be effective when examining drinking frequency.

Taken together, these additional results suggest the exclusion of participants with a low physical functioning score is likely to be the most effective method examined here to assess bias from the 'sick-quitter effect' when using an exposure of total alcohol consumption or drinks per drinking-day, while no method appeared to be effective when using drinking frequency. The potential for selection bias however is a disadvantage of exclusion by physical functioning score. Another method identified as likely to reduce bias when analysing alcohol consumption as a log-linear variable was restriction to participants consuming ≥ 7 drinks per week, as this removes the potential for bias from any participants who may have decreased their alcohol consumption to light drinking in response to poor health status. Further, restriction to participants aged less than 65 years is also likely to be effective due to the resulting decrease in overall prevalence of disease, limiting the potential for confounding by health status. One disadvantage of using this method in the 45 and Up Study is that it results in the exclusion of the majority of outcomes (cancer and mortality) as these are associated with greater age, thereby greatly reducing statistical power. The exclusion of participants who died within three years of baseline was generally not as effective in reducing the uneven distribution of baseline disease by measures of drinking at baseline, but has the advantages of excluding the least participants and a low likelihood of introducing selection bias. Therefore, in Chapters 8 and 9 all four methods were examined where possible to test for the possibility of bias due to the 'sick-quitter effect' and other changes in drinking amount and pattern in relation to ill-health. This enabled the investigation of the robustness of associations between moderate and frequent alcohol

consumption and decreased risk of health outcomes, and between non-drinking, heavy drinking and drinks per drinking-day and increased risk of health outcomes.

The next chapter investigated the association between alcohol consumption, drinking pattern and cancer risk, with an examination of the likelihood that effect estimates may be over or underestimated due to bias from changes in drinking behaviours in response to ill-health.

7.4 – References

1. Banks, E., *Commentary: lifetime alcohol consumption and mortality: have some, but not too much.* Int J Epidemiol, 2013. **42**(6): p. 1790-2.
2. Naimi, T.S., et al., *Confounding and studies of 'moderate' alcohol consumption: the case of drinking frequency and implications for low-risk drinking guidelines.* Addiction, 2013. **108**(9): p. 1534-43.

Chapter 8 – Alcohol Consumption and Cancer Risk

Chapter summary

This chapter contains an article prepared for publication, which investigated the association between alcohol consumption and risk of various cancer types, with a focus on the effect of pattern of drinking. This was achieved by using baseline data from the 45 and Up Study linked to the NSW Central Cancer Registry to December 2010. The hazard of a cancer diagnosis was calculated for overall weekly alcohol intake assessed in three ways: as a categorical variable, a continuous log-linear variable and a continuous restricted cubic spline variable. After adjusting for total alcohol consumption, the independent effect on cancer risk of two measures of drinking pattern, drinking-days per week and mean drinks per drinking-day, was examined, along with an analysis accounting for both measures simultaneously. Interaction tests were performed to test for effect modification by sex and smoking status. Cancer types for which there was evidence of an independent effect of drinking pattern were identified. The findings of the article were presented at the University of Sydney Public Health Research Showcase 2017 (Sydney), the Australasian Epidemiological Association Annual Scientific Meeting 2017 (Sydney), the 45 and Up Study Annual Forum 2017 (Sydney) and the Dietitians Association of Australia National Conference 2018 (Sydney).

In additional analyses, sensitivity analyses examined possible bias in risk estimates due to the sick-quitter effect. Risk estimates were then used to calculate population attributable fractions, estimates of absolute risk and number of persons needed to quit or reduce drinking to prevent one cancer case.

8.1 – Journal Article (Prepared for Publication)

The following article is prepared for publication. The results of the proportional hazards assumption tests (Table E.1), the p-values for the interaction tests (Table E.2), and the Akaike information criterion results (Table E.3) are shown in Appendix E.1. The results of additional interaction tests for body mass index and hormone replacement therapy status are shown in Table E.2 in Appendix E.1 and Table E.4 in Appendix E.2.

Title

Alcohol consumption, drinking patterns and cancer incidence in the 45 and Up Study.

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Keywords

Alcohol consumption, cancer, drinking pattern, heavy episodic drinking.

7092 words.

Abstract

Background: Although alcohol has been associated with increased risk of incidence of a number of cancers, the particular role of patterns of drinking, has not been quantified in detail. We quantified these associations in the 45 and Up Study, a prospective cohort study in New South Wales (NSW).

Methods: Cox proportional hazards were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk associated with alcohol consumption (drinks/week) and pattern of drinking among 217,568 participants aged ≥ 45 years (2006-2009). Incident cancer cases were ascertained by linkage to the NSW Cancer Registry to December 2010.

Results: In a median follow-up of 2.4 years, 7733 cancers occurred. Increasing total alcohol consumption was associated with increased risk of any cancer (HR/one drink increase in mean daily alcohol consumption: 1.02; 95% CI: 1.00-1.04), and cancers of the colorectum (1.07; 1.02-1.12), colon (1.10; 1.04-1.17), larynx (1.18; 1.02-1.36) and female breast (1.09; 1.01-1.18); inverse associations were observed for non-Hodgkin lymphoma, bladder and thyroid cancer. People consuming > 28 drinks per week had over 5 times the risk of liver cancer. After adjusting for overall weekly alcohol intake, the average number of drinks consumed on drinking-days was independently associated with risk of any cancer (1.17; 1.04-1.33 for > 4 drinks per drinking-day), mouth and pharynx cancer (2.45; 1.22-4.92), oesophageal squamous cell carcinoma (9.04; 1.71-47.7) and kidney cancer (2.61; 1.24-5.47). Risk of kidney cancer and all cancers combined was increased when more than 4 drinks were consumed per drinking-day on only one or two days in a week (i.e. heavy episodic drinking), while risk of colorectal and colon cancer was increased with heavy frequent drinking.

Conclusions: Higher numbers of drinks per drinking-day, including both heavy episodic drinking and heavy frequent drinking, increased cancer risk independent of the risk associated with total alcohol consumption.

Word count: 300

Introduction

Alcohol consumption is an important risk factor for cancer, and has been estimated to account for 2.8% of cancer incidence in Australia and 5.5% of cancer incidence globally[1, 2]. The International Agency for Research on Cancer (IARC) has determined that seven types of cancer are causally related to alcohol consumption: mouth, pharynx, oesophagus, colorectal, liver, larynx and female breast[3, 4]. In addition, the World Cancer Research Fund (WCRF) concluded it is probable that heavy drinking increases risk of stomach cancer and low-volume drinking decreases risk of kidney cancer[5]. Both organisations conclude that evidence is suggestive of an association of heavy drinking with pancreatic cancer, with recent meta-analyses supporting this conclusion [6-9]. The evidence for other cancer types is less clear, although meta-analyses have found a positive association with gallbladder[6], lung[6] (but not in never-smokers[10]), melanoma[6] and prostate cancer[6, 11], and an inverse association with thyroid cancer[6, 12], Hodgkin lymphoma[6, 13] and non-Hodgkin lymphoma (NHL)[6, 14].

One aspect of the alcohol-cancer risk relationship that is unclear is the influence of pattern of drinking[15, 16]. In general, there have been two patterns of interest in relation to disease outcomes: 1) low-volume frequent intake and 2) heavy infrequent intake, which is commonly referred to as either 'binge drinking' or 'heavy episodic drinking'. Prospective studies have found that compared to non-drinking, daily low-volume drinking has been associated with lower risk of cardiovascular disease while heavy episodic drinking has been associated with higher risk[17, 18]. The many different ways in which drinking patterns are defined, the strong relationship between patterns and overall consumption levels and the diversity in the methods used to assess drinking patterns[19, 20] makes comparisons between studies difficult. Some studies report frequency of drinking occasions, for example, daily vs. weekly[15]. Other studies have reported the average number of drinks consumed per day that drinking occurs (i.e., mean drinks per drinking-day)[21]; and others, the highest number of drinks consumed in one day in a typical month[15, 22]. Higher

drinking frequency has also been reported to be inversely related to both drinks per drinking-day and the proportion of days with heavy episodic drinking[23]. Consequently, failure to account for drinks per drinking-day when examining the effect of drinking frequency (and vice versa) could potentially result in confounding of effect estimates for either of the two individual measures of drinking pattern alone.

A recent analysis of two prospective, United States cohorts examined the influence of two measures of drinking pattern on cancer risk and found that risk of alcohol-related cancers was increased for men who consumed alcohol on more days of the week compared to those who consumed alcohol less frequently, even when accounting for total intake. For women, risk of alcohol-related cancer was increased among those who reported higher number of drinks consumed in one day in a typical month, a finding that was also reported in the same cohort study for breast cancer[22]. Other studies of drinking pattern and cancer risk have used differing measures of drinking pattern, levels of adjustment for confounding factors, study populations, sample sizes and cancer types under examination[21, 24-36]. Most of these studies did not, or only partially, adjusted the effects of drinking patterns for total alcohol consumption[21, 24-32]. That is, it was not possible to determine whether drinking pattern had an independent effect on risk or whether the effect was primarily mediated through total alcohol consumption. Furthermore, large prospective studies of drinking pattern and cancer risk are few, especially those which have examined multiple cancer types and have included adjustment for total alcohol consumption.

The aim of our investigation was to use a large prospective Australian cohort study to quantify the risk of cancer in relation to total alcohol consumption and the independent effects of drinking frequency (number of alcohol drinking-days per week) and drinks per drinking-day. We directly compared the effects of low-volume infrequent drinking with low-volume daily drinking and heavy infrequent (episodic) drinking.

Methods

Study sample

The Sax Institute's 45 and Up Study is a prospective cohort study of 266,794 participants, with methods previously described[37]. In summary, men and women aged ≥ 45 years were randomly sampled from the general population of New South Wales (NSW) between 2006 and 2009 using the Department of Human Services enrolment database. The database has records for all Australian citizens and permanents residents, as well as some temporary residents and refugees. Oversampling by a factor of two was performed for persons aged ≥ 80 years and persons living in rural and remote areas. Participants completed a health and lifestyle questionnaire, with an estimated response rate of 18%. Ethics approval for the 45 and Up Study was provided by the University of NSW Human Research Ethics Committee and the NSW Population Health Services Research Ethics Committee.

Data linkage

The 45 and Up Study questionnaire data were probabilistically linked to the NSW Cancer Registry (NSWCR) and the NSW Registry of Births Deaths and Marriages by the NSW Ministry of Health's Centre for Health Record Linkage (CHeReL). The CHeReL used a best practice approach in privacy preserving record linkage[38] along with the open source probabilistic record linkage software Choice Maker[39]. The probabilistic matching process is highly accurate (false-positive and false-negative rates < 0.4%) and a detailed explanation of the linkage process has been published elsewhere[40].

Cancer and mortality data

Cancer incidence was ascertained from the NSWCR, which captures all primary cancers diagnosed in all NSW residents apart from non-melanoma skin cancer. Cancer diagnoses were available from January 1994 to December 2010 and were classified according to the International Classification of Diseases, version 10[41]. All cancers stated by IARC to be causally related to alcohol consumption

were examined separately, along with any cancer type examined in the IARC alcohol monographs or the WCRF reports[3-5] that had least 50 cases in the current study. Female breast cancer was examined separately from male breast cancer. All other cancer types were combined into an 'other' cancer group. All cancers combined, IARC-determined alcohol-related cancers combined (mouth and pharynx, oesophagus, colorectum, liver, larynx and female breast), and non-alcohol related cancers combined (all other cancer types) were also examined. Where subtype data was available, cancer of the oesophagus was subdivided by the histological subtypes adenocarcinoma (AC) and squamous cell carcinoma (SCC), due to evidence of a stronger association of alcohol with risk for SCC compared to AC[3, 4]. Cancer of the colorectum was subdivided into colon and rectum, due to evidence that the risk relationship may differ between these two sites[4]. Date of diagnosis was only available to the month, so all diagnosis dates were set to the 15th day of the month. The source of death data for censoring was via linkage to the NSW Registry of Births, Deaths and Marriages to December 2010.

Alcohol consumption

The question used to determine total alcohol consumption was "*About how many alcoholic drinks do you have each week? One drink = a glass of wine, middy of beer or nip of spirits (put "0" if you do not drink, or have less than one drink each week)*". Responses were categorised into six values: 'Non-drinker (< 1 drink/week)', '≥ 1 and ≤ 3.5 drinks/week', '> 3.5 and ≤ 7 drinks/week', '> 7 and ≤ 14 drinks/week', '> 14 and ≤ 28 drinks/week' and '> 28 drinks/week'. The cut-points of 14 and 28 drinks/week were chosen because they correspond with the Australian alcohol guidelines to minimise risk of long-term harm (≤ 2 drinks/day) and short-term harm (≤ 4 drinks/day)[42].

An additional question, "*On how many days each week do you usually drink alcohol?*", was used to make three categorical drinking pattern variables which applied to drinkers only. Firstly, drinking-days per week (drinking frequency) was coded with three values: '1-2 days per week', '3-5 days per week' and '6-7 days per week'. Secondly, mean drinks per drinking-day (with drinking-day being any day in a week where at least one alcoholic drink was consumed) was calculated by dividing the

number of drinks consumed per week by the number of days of alcohol consumption per week, giving the mean number of drinks per drinking-day. This variable was coded with three values: '≤ 2 drinks per drinking-day', '> 2 and ≤ 4 drinks per drinking-day' and '> 4 drinks per drinking-day'.

Finally, an 'overall drinking pattern' variable with nine categories was constructed by combining the drinking-days per week and drinks per drinking-day variables. This variable allowed for more specific drinking patterns to be examined, such as daily low-volume intake and heavy episodic drinking.

Statistical analyses

Participants with missing alcohol consumption data, a prior diagnosis of cancer (either self-reported or in the cancer registry dataset from January 1994) or had a date of death earlier than their questionnaire completion date were excluded from analysis.

Hazard ratios (HR) and 95% confidence intervals (CI) of being diagnosed with cancer were calculated using Cox proportional hazards regression models using age as the underlying time variable[43]. Censoring occurred if a participant died, was diagnosed with a cancer type different to the type being analysed, or was not diagnosed with a cancer by the end of study period (December 2010). If a participant was diagnosed with more than one primary cancers in the same month, they were counted as a case in the analysis of each cancer type. If a participant reported a hysterectomy, bilateral oophorectomy or radical prostatectomy at baseline, they were excluded respectively from the analysis for endometrium, ovary and prostate cancer, but still included in the analysis of all cancers combined.

For each cancer type, three analyses of total weekly alcohol consumption were performed. 1) Categorical levels of alcohol consumption were estimated. Light drinkers (≥ 1 and ≤ 3.5 drinks/week) were used as the reference group rather than non-drinkers to minimise bias from the 'sick-quitter effect', whereby 'non-drinkers' may have quit drinking due to cancer-related symptoms[44]. Tests for linear trend excluding non-drinkers were conducted by replacing the categorical alcohol

consumption variable with a continuous variable where the median level of alcohol consumption was assigned to participants within each category (to limit the impact of outliers). Two-way statistical interaction tests between alcohol consumption categories and sex, and between alcohol consumption categories and smoking status (never-smoking vs. ever-smoking) were conducted and the results stratified where relevant. This is because sex differences have been reported for alcohol and colorectal cancer risk, and differences between never- and ever-smokers for alcohol and cancers of the mouth, pharynx, oesophagus, liver and larynx[3, 4, 6]. 2) Total number of drinks/week was analysed as a continuous variable in log-linear Cox models with hazard ratios representing the change in risk per one drink increase in mean daily alcohol consumption, excluding non-drinkers. 3) To assess non-linearity, a restricted cubic spline was fitted with three knots at the 25^{th}, 50^{th} and 75^{th} percentiles of alcohol consumption (excluding non-drinkers). The reference quantity of alcohol consumption was 1 drink per week. When graphed, the x-axis was truncated at 56 drinks per week for presentation purposes, but the model included participants up to the maximum quantity of drinking: 140 drinks per week. The Akaike Information Criterion (AIC) was used to compare the log-linear and cubic spline models for best fit.

Three drinking patterns were assessed in separate models. To prevent bias from the 'sick-quitter effect' these analyses were restricted to drinkers. All three drinking patterns were analysed separately using categorical and continuous covariate counterparts (the continuous version was coded as the median number of drinks in each category): 1) Drinking frequency with 3 levels: those who reported consuming alcohol on '1-2 days per week' (reference), '3-5 days', '6-7 days' per week. 2) Mean drinks per drinking-day, where '≤ 2 drinks per drinking-day' was the reference category, compared to '> 2 and ≤ 4 drinks per drinking-day', and '> 4 drinks per drinking-day'. These models were calculated both without adjustment for total alcohol consumption and adjusted for total alcohol consumption (as a continuous log-linear variable). Statistical interaction tests for drinking pattern as a categorical variable (after adjusting for total alcohol consumption) and sex and smoking status were performed for each of the first two drinking patterns and the results stratified where

appropriate. 3) An interaction test between the drinking frequency and drinks per drinking-day variables was performed for all cancer types. Where significant, drinking frequency stratified by levels of drinks per drinking-day and vice versa was examined, along with an overall drinking pattern. The overall drinking pattern combined drinking frequency and mean drinks per drinking-day into a 3x3 matrix resulting in 9 categories ('overall drinking pattern'). The reference group was the category with the lowest total alcohol consumption: '≤ 2 drinks per drinking-day' consumed on '1-2 days per week'. The matrix captured low-volume episodic drinking, heavy episodic 'binge' drinking (defined here as > 4 drinks per drinking-day on 1-2 days per week), low-volume daily drinking and heavy daily drinking. Overall drinking pattern was also examined for all cancers combined.

All analyses were adjusted for a range of potential confounders as self-reported in the baseline questionnaire, including sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and intensity, body mass index and physical activity (see Supplementary Table 1). Remoteness categories were based on the 2006 ARIA (Accessibility/Remoteness Index of Australia) index[45]. Melanoma risk was additionally adjusted for time spent outdoors and skin tone. Dietary related variables (fruit, vegetable, fibre, red meat and processed meat consumption) were included as potential confounders in regression models for cancer types where the WCRF has found convincing or probable evidence of a causal relationship[5]. Analyses of colorectal cancer were additionally adjusted for fruit and vegetable consumption because these foods contain dietary fibre. Parity and age of first birth, breastfeeding time, menopausal status, hormonal contraceptive use, hormone replacement therapy (HRT) use were included as potential confounders in Cox models analysing cancers of the breast, endometrium and ovary. Hormonal contraceptive use was also included in regression models for liver cancer[46], and HRT use for colorectal cancer models[47]. Adjustment for aspirin use was made for oesophageal and colorectal cancer[48]. Finally, adjustment for history of bowel, breast and prostate screening was made for colorectum, breast and prostate cancer regression models.

A test of the proportional hazards assumption was performed for all Cox models. If significant violations were detected then log-log survival curves stratified by the variables in violation were plotted. If the lines were considerably non-parallel upon visual inspection, the model was stratified by the variable in violation.

Analyses were performed using SAS 9.4.

Results

217,568 of 266,794 participants (81.5%) were included for analysis after excluding 5,041 (1.9%) participants with missing information on total alcohol consumption, a further 13 (0.005%) who died before the questionnaire date and 44,172 (16.6%) participants who had previously been diagnosed with cancer. Of included participants, 7,733 (3.6%) had at least one incident diagnosis of cancer by December 2010 in a median follow-up of 2.4 years.

Overall, 145,605 (66.9%) participants consumed at least one alcoholic drink per week, including 31,148 (14.3%) who consumed > 14 drinks per week. Of drinkers, 1,711 (1.2%) were excluded from the drinking pattern analyses due to missing information on number of drinking-days per week. Of the 143,894 drinkers included in the drinking pattern analyses, 51,957 (36.1%) consumed alcohol 6 or 7 days per week and 15,286 (10.6%) reported an average of > 4 drinks per drinking-day. Very few women drinkers in the cohort (1.2%) were frequent heavy drinkers. Overall, 28,035 (19.5%) were low-volume daily drinkers, and 3452 (2.4%) reported infrequent (1-2 days) heavy (> 4 drinks) consumption and could be considered binge drinkers.

Participants consuming higher numbers of drinks per week were, on average, more likely to be men, Australian-born, consumed processed meat > 1 time per week and spent ≥ 2 hours outdoors per day (Table 1). Drinkers tended to be younger than non-drinkers. Among women, participants consuming higher numbers of drinks per week were more likely to be nulliparous, had never breastfed and had

ever used hormonal contraceptives. Non-drinkers were more likely to be current smokers, physically inactive and aspirin users compared to light drinkers, and less likely to have had a university degree, a household income ≥ $70,000 per year, private health insurance or be married or living with a partner. Among women, a greater proportion of non-drinkers had never breastfed compared to those who consumed up to 14 drink per week. For most baseline characteristics, there was greater variation by drinks per drinking-day than by drinking frequency. Participants consuming more than 4 drinks per drinking-day were more likely to be in lower socio-demographic categories and have unhealthy behavioural risk factors than those who consumed less than 4. Participants with higher drinking frequency were more likely to have private health insurance and a history of cancer screening, and less likely to be overweight or obese, while the reverse was true for participants with higher drinks per drinking-day.

Among drinkers, a greater number of drinks per week was significantly associated with increased risk of cancers of the colorectum, colon alone, larynx and breast, alcohol-related cancer and all cancer, and decreased risk of NHL (Table 2). For liver cancer, there was evidence of greater risk in non-drinkers and in those consuming > 28 drinks per week compared to those consuming ≥ 1 and ≤ 3.5 drinks per week. Significant interactions between total alcohol consumption and sex were detected for alcohol-related cancers (p = 0.01) and all cancers combined (p = 0.04) and between total alcohol consumption and smoking status for cancers of the pancreas (p = 0.04) and kidney (p = 0.02), non-alcohol-related cancer (p = 0.005) and all cancers combined (p = 0.004). When stratified by sex, risk of both alcohol-related cancer and all cancers combined was elevated in women compared to men for > 14 and ≤ 28 drinks per week, and in men compared to women for > 28 drinks per week (Supplementary Tables 2 and 3). When stratified by smoking status, risk of pancreatic cancer was most elevated in never-smokers compared to ever-smokers for > 7 and ≤ 14 drinks per week. For kidney cancer, risk was elevated in heavy drinking (> 28 drinks per day) never-smokers but not heavy drinking ever-smokers (Supplementary Tables 4 and 5). For both non-alcohol-related and all cancer

there were no large differences in hazard ratios by smoking status, except perhaps elevated risk in the non-drinking category among ever-smokers.

Figure 1 shows the results of the log-linear models in which the risk associated with each additional drink per day was plotted for each cancer type. The direction and statistical significance of effect estimates were similar to the corresponding categorical models, but with an additional inverse association for thyroid cancer.

Figure 2 shows the results of the restricted cubic spline models in which the risk associated with each additional drink per week was plotted by cancer type, accounting for a non-linear relationship with intake. The AIC was lower in the cubic spline model compared to the log-linear model for cancers of the colorectum, colon, breast, ovary and bladder (results not shown), suggesting non-linear relationships between these cancer types and overall alcohol consumption among drinkers.

After adjusting for total alcohol consumption, drinking frequency (drinking-days per week) was not significantly associated with any one cancer type, but more drinking-days per week was inversely associated with risk of any cancer (p_{trend} = 0.03; Table 3). A statistical interaction with sex was detected for alcohol-related cancers (p = 0.004) and with smoking status for breast cancer (p = 0.04). For alcohol-related cancer, the HR for 3-5 drinking-days per week was higher in women (HR: 1.10; 95% CI: 0.92-1.31) than men (0.80; 0.63-1.01) (Supplementary Table 6). For breast cancer, the HRs for 3-5 and 6-7 drinking-days per week were higher for non-smokers ((1.26; 0.97-1.65) and (1.14; 0.82-1.59) respectively) than for smokers ((0.97; 0.70-1.34) and (0.71; 0.47-1.08) respectively) (Supplementary Table 7).

Table 4 shows the risk of cancer by mean drinks per drinking-day. After adjustment for total alcohol consumption, drinks per drinking-day was positively associated with risk of mouth and pharynx (p_{trend} = 0.01), oesophagus (SCC) (p_{trend} = 0.009), kidney (p_{trend} = 0.02), alcohol-related (p_{trend} = 0.04), non-alcohol-related (p_{trend} = 0.04) and all cancer (p_{trend} = 0.007). For persons consuming > 2 and ≤ 4 drinks per drinking-day, there was evidence of decreased risk of colon cancer (HR: 0.75; 95% CI: 0.57-0.99)

and increased risk of ovarian cancer (3.54; 1.51-8.32). There was also evidence that risk differed by drinking category for colorectal cancer, which appeared to be due to elevated risk in persons consuming > 4 drinks per drinking-day compared to those consuming > 2 and ≤ 4 drinks. Statistical interactions with sex were detected for alcohol-related cancer (p = 0.02), and with smoking status for kidney cancer (p = 0.02) and multiple myeloma (p = 0.03). For alcohol-related cancer, the HR for > 4 drinks per drinking-day was higher in men (1.42; 1.05-1.92) than women (1.08; 0.70-1.66) (Supplementary Table 8). For kidney cancer, the HR for > 2 and ≤ 4 drinks per drinking-day was higher in ever-smokers (1.87; 1.01-3.46) than never-smokers (0.20; 0.05-0.89) (Supplementary Table 9). For multiple myeloma, the HR for ≥ 2 and < 4 drinks per drinking-day was higher in ever-smokers (3.07; 1.02-9.29) than never-smokers (0.45; 0.12-1.70).

A significant interaction was found between drinking-days per week and drinks per drinking-day for cancers of the colorectum (p = 0.04), colon (p = 0.03) and kidney (p = 0.02). Stratified results are presented in Supplementary Tables 10 and 11. For colorectal and colon cancer, more drinking-days per week was positively associated with risk (p_{trend} = 0.04 and 0.03 respectively) in persons consuming > 4 drinks per drinking-day, while drinks per drinking-day was positively associated with risk (p_{trend} = 0.006 and < 0.001 respectively) in persons with 6-7 drinking-days per week. For kidney cancer, more drinking-days per week was inversely associated with risk (p_{trend} = 0.003) in persons consuming > 4 drinks per drinking-day, while drinks per drinking-day was positively associated with risk (p_{trend} = 0.009) in persons with 1-2 drinking-days per week.

Table 5 shows the results of the overall drinking pattern analysis. For all cancers combined, there was a significantly elevated HR in those consuming > 4 drinks on 1-2 days per week (i.e. heavy episodic 'binge' drinkers) compared to those in the lowest consumption group (≤ 2 drinks on 1-2 days/week). For colorectal and colon cancer there was a significantly elevated HR in those consuming > 4 drinks on 6-7 days per week, with a significantly lowered HR in those consuming > 2

and ≤ 4 drinks on 1-2 days per week for colorectal cancer only. For kidney cancer, there was a significantly elevated HR in those consuming > 4 drinks on 1-2 and 3-5 days per week.

There were no violations of the proportional hazards assumption detected for the main exposure in any model. Violations were detected for some covariates in the total alcohol consumption models for colorectal cancer (partner status, fruit consumption, $p = 0.02$), thyroid cancer (health insurance status, $p = 0.03$), multiple myeloma (household income, health insurance status, $p = 0.01$) and alcohol-related cancers combined (partner status, physical activity, fruit consumption, $p = 0.04$). In each of the drinking pattern models violations were detected for colorectal cancer ($p = 0.02$ in drinking frequency and drinks per drinking-day models and 0.01 in overall drinking pattern model; partner status, BMI group). A violation was also detected for thyroid cancer in the mean drinks/day model (health insurance status, $p = 0.048$). Plotting the log-log graphs revealed non-parallel partner status strata for colorectal cancer (in both the total alcohol and drinking pattern models), but not for the other cancer types and variable strata (results not shown). A stratified Cox model was therefore used for colorectal cancer.

Discussion

Consistent with the IARC monographs, we found that increasing numbers of alcoholic drinks per week was associated with increased risk of cancers of the colorectum, colon, larynx and female breast, alcohol-related cancers combined and all cancers combined. Consuming > 28 drinks per week was also associated with increased risk of liver cancer. The HR point estimates for > 28 drinks per week were elevated (> 1) for cancers of the mouth and pharynx, oesophagus and rectum but not to the point of statistical significance. For other cancers not considered to be alcohol-related by IARC but reported to be positively associated with alcohol intake in meta-analyses (stomach, pancreas, lung, melanoma and prostate) we found no significant effects. For cancers where alcohol is reported to be associated with decreased risk, such as thyroid cancer and NHL, we also found an inverse association, but not kidney cancer. A U-shaped association with alcohol among drinkers was found for bladder cancer, where low to medium volume drinking (between 1 and 29 drinks per week) was associated with lower risk and heavier drinking with no difference in risk compared to those consuming 1 drink per week. Our results also suggest that cancers of the colorectum, colon, breast and bladder have a non-linear relationship with alcohol consumption, meaning that the relationship with alcohol may be more complex than a simple dose-response relationship. Regarding drinking patterns, drinking frequency was positively associated with risk of colorectal and colon cancer in persons consuming > 4 drinks per drinking-day, inversely associated with risk of kidney cancer in persons consuming > 4 drinks per drinking-day, and inversely associated with risk of all cancers combined. Mean number of drinks per drinking-day was positively associated with risk of mouth and pharynx, oesophageal (SCC), colorectal (in those with 6-7 drinking-days per week), colon (in those with 6-7 drinking-days per week), kidney (in those with 1-2 drinking-days per week), alcohol-related, non-alcohol-related and all cancer.

Our results for total weekly alcohol consumption and cancer risk are broadly consistent with previous research. Specifically, the positive associations with cancers of the colorectum, colon, liver,

larynx and breast, alcohol-related cancer combined and all cancer, and inverse associations for thyroid cancer and NHL. Alcohol is considered to be causally related to cancers of the mouth and pharynx, oesophagus and rectum. These cancers were not significantly associated with alcohol in our study, although the HR point estimates for consuming > 28 drinks per week were all above 1. Owing to the short follow-up period, it is possible that our analysis was underpowered for cancer types with fewer cases. The confidence intervals for consuming > 28 drinks per week were consistent with increased risk, particularly for mouth and pharynx and oesophageal cancer, which were consistent with a 3-fold increase in risk. Our confidence intervals are also consistent for some other cancer types which are possibly related to alcohol consumption, particularly for increased risk with stomach cancer and with decreased risk for kidney cancer.

The functional form of the relationship between total alcohol consumption and cancer risk has been reported as largely log-linear[16], apart from colorectal cancer[5]. In addition to colorectal cancer, we found non-linear relationships for cancers of the colon, breast, ovary and bladder. According to the WCRF, there is evidence of a non-linear relationship for colorectal cancer with increased risk at high levels of alcohol intake (i.e. > 30 g ethanol per day, i.e. 3 Australian standard drinks per day). The shape of the risk curve for colorectal and colon cancer in our study was consistent with the WCRF conclusion. Our finding of a non-linear relationship for breast cancer is inconsistent with the WCRF report. The WCRF systematic literature review and meta-analyses for cancers of the breast and bladder found no evidence for a non-linear relationship, while for ovarian cancer a test of non-linearity was not reported[5].

For bladder cancer, while there was no linear relationship with total alcohol intake, we observed a notable U-shaped association, whereby decreased risk was associated with moderate levels of weekly alcohol consumption in comparison to light drinking. This U-shaped relationship appears to be a novel finding, as both IARC and a recent meta-analysis reported no association[4, 6]. It is possible that the diuretic effect of alcohol could cause the bladder epithelium to be less subjected to

carcinogens[49]. Alternatively, there may be a role of the 'sick-quitter effect'[44, 50], although our analysis accounted for this by excluding non-drinkers. Perhaps a similar effect applies to decreasing alcohol consumption as well as quitting[51], in which light drinkers may have previously reduced their drinking in response to early symptoms of bladder cancer.

The 'sick-quitter effect' has also been suggested as an explanation for the protective associations seen for other cancer types[6, 12, 14]. For example, it has been reported that subtypes of NHL which characteristically produce symptoms before diagnosis (and may therefore cause a decrease in alcohol consumption prior to diagnosis) have an inverse association with alcohol consumption, while other subtypes without early symptoms do not[14]. If causal however, some of the proposed mechanisms for the association between alcohol and reduced risk for NHL are improved insulin sensitivity or an immunomodulatory effect[14], for thyroid cancer improved insulin sensitivity or altered thyroid or sex steroid hormone levels[12, 52], and for kidney cancer the antioxidant content of alcoholic beverages, the diuretic effect of alcohol reducing carcinogen exposure time or again improved insulin sensitivity[8]. The 'sick-quitter effect' may also explain our finding of elevated risk of liver cancer for non-drinkers in comparison to light drinkers.

Our results for the independent effect of drinking pattern on risk of cancer are only partially consistent with previous research. This is not surprising given that we assessed drinking patterns in three different ways and observed different outcomes for each. Almost every study to date has used a unique method to assess the impact of drinking pattern on cancer outcomes. This demonstrates the difficulty of comparing outcomes for patterns of interest including 'binge drinking' and 'moderate drinking' both within and across studies. Variation in study outcomes likely reflect the diversity of methods that have been used to assess drinking pattern. The patterns we compared directly to the literature were drinking frequency and drinks per drinking-day (including heavy episodic drinking).

For drinking frequency, more drinking-days per week was not independently associated with risk of any individual cancer type after accounting for total weekly consumption, consistent with a number of prior studies (i.e. breast cancer[22, 25, 33], stomach cancer (positive *H. pylori* status)[21], and mortality from 14 cancer types[31]). However, there are reports of increased risks of a number of cancer types associated with greater drinking frequency (i.e. mouth and pharynx cancer[29], mouth cancer[30], stomach cancer (negative *H. pylori* status)[21], prostate cancer[26], and mortality from oesophageal cancer in men[31]). Of the six studies which found a positive association between drinking frequency and risk of cancer[15, 21, 26, 29-31] where we did not, all except one ([15]) did not, or only partially, adjusted for total alcohol consumption. It is therefore not clear whether the observed associations between drinking frequency and increased risk were due to the impact of drinking frequency per se, or whether the results can simply be explained by more frequent drinkers consuming greater quantities of alcohol overall.

More drinks per drinking-day was independently associated with increased risk of cancers of the mouth and pharynx, oesophagus (SCC) and kidney after adjusting for total alcohol consumption, with between 2.5 to 9 times increased risk observed among those reporting > 4 drinks per day. As far as we are aware, this is the first study to report an increased risk of these cancer types with pattern of drinking. Previous studies have found increased risks with increasing drinks per drinking-day or heavy episodic drinking for breast cancer[22, 24], stomach cancer (negative *H. pylori* status)[21], lung cancer (in smokers)[28], pancreatic cancer[34] and prostate cancer[26, 27], however we did not. However, our estimates may be underpowered for some of these cancer types (e.g. stomach and pancreatic cancer), and the confidence intervals for > 4 drinks per drinking-day in our analyses are consistent with a hazard ratio of 2 or more for many cancer types including stomach, liver, larynx and breast. Nevertheless, our results are consistent with studies reporting no association with stomach cancer (positive *H. pylori* status)[21] or lung cancer (non-smokers)[28]. Of the seven studies which found an association between greater drinks per drinking-day and risk of cancer where we did not[21, 22, 24, 26-28, 34], six did not, or only partially, adjusted for total alcohol consumption[21,

24, 26-28, 32]. Similar to drinking frequency, it therefore cannot be determined from these studies whether there was an independent effect of drinks per drinking-day. Previous studies found increased risk of both breast[24] and prostate cancer[26, 27] without adjusting for total alcohol intake, similar to our estimates unadjusted for total alcohol intake.

For colorectal, colon and kidney cancer there was an interaction between drinking frequency and drinks per drinking-day. More drinking-days per week was positively associated with risk of colorectal and colon cancer and inversely associated with risk of kidney cancer in persons consuming > 4 drinks per drinking-day. Drinks per drinking-day was positively associated with risk in persons with 1-2 drinking-days per week for kidney cancer and in only in persons with 6-7 drinking-days per week for colorectal and colon cancer. When we analysed drinking frequency and drinks per drinking-day simultaneously, we were able to compare patterns such as heavy episodic, or 'binge', drinking and low-volume 'moderate' daily drinking. In this analysis we found a significant independent effect for drinking pattern on all three cancers. Specifically, kidney cancer risk was 3.5 times higher among those consuming > 4 drinks per drinking-day within 1-2 days per week compared to low-volume 'moderate' episodic drinkers (i.e. those averaging no more than 2 drinks on only 1-2 days in a week). This finding indicates an increased risk of kidney cancer in relation to heavy episodic binge drinking, which has not been reported previously. IARC concluded there is no causal association between alcohol consumption and kidney cancer[4], but reviews have found an inverse association with moderate drinking but not heavy drinking for kidney cancer[5, 6]. Thus, our findings could be interpreted as consistent with a slight decrease in risk associated with greater total alcohol consumption, except where heavy episodic drinking causes increased risk in heavy drinkers. Compared to light drinkers, the risk of colorectal and colon cancer was significantly higher among regular heavy drinkers, and for colorectal cancer only, lower risk among intermediate drinkers (those averaging > 2 and ≤ 4 drinks on 1-2 days). This is consistent with the WCRF report, which found evidence of increased risk only at high levels of alcohol intake.

For all cancers combined, we observed an independent inverse association with drinking frequency and an independent positive association with more drinks per drinking-day. Our results differ from studies which found positive associations between drinking frequency and all cancer mortality[31, 36], and another study which reported no association after adjusting for total alcohol consumption[15]. Our findings for drinks per drinking-day are consistent with the confidence intervals of one study, which reported a positive association between drinks per drinking-day and all cancer mortality in men but not women[36], but differ from a second study, which found no association with highest number of drinks consumed in one day in a typical month and risk of all cancer[15]. When analysing drinking frequency and drinks per drinking-day simultaneously, the only individual drinking category associated with significant elevated risk was consuming alcohol 1-2 days per week and with > 4 drinks per drinking-day (i.e. heavy episodic drinking), however the interaction was not significant. An association of increased risk with heavy episodic drinking has also been reported in a previous study examining all cancer mortality[32]. While combining all cancers together has the advantage of providing more cancer cases, the overall hazard ratio understates the role of alcohol in many individual cancers. Overall, these results suggest there is an independent effect of drinks per drinking-day including heavy episodic drinking on all cancer risk.

For alcohol-related cancers combined, we observed increased risk with more drinks per drinking-day, and no association with drinking frequency. An interaction with sex was detected for drinks per drinking-day, which when stratified appeared to show the association with increased risk was limited to men who drink > 4 drinks per drinking-day. The results for drinks per drinking-day are inconsistent with one report which showed no association for heavy episodic drinking and alcohol-related cancer, although the authors state the analysis was underpowered for this outcome[35]. They are also inconsistent with a previous study finding no association with highest number of drinks consumed in one day in a typical month for alcohol-related cancer in men but an association with increased risk in women[15]. This study also examined drinking frequency, and our results are consistent with the finding of no association in women, but differed from the finding of an association with increased

risk in men[15]. Therefore, we have found new evidence of an independent effect of drinks per drinking-day for risk of alcohol-related cancer.

One issue which may also explain the differences in results across studies is the inconsistent choice of potential confounders included. In an analysis of an American population survey, it was reported that infrequent drinkers had a higher prevalence of 13 of 15 measured risk factors compared to more frequent drinkers, including health insurance status, being physically inactive and having fair or poor overall health[23]. To a lesser extent these factors were also associated with heavy episodic drinking. Therefore, there is the potential for bias from confounding between studies due to unmeasured, or poorly measured, covariates that influence cancer risk.

Our study has several strengths. It is a prospective cohort study with a large number of participants, and examined multiple cancer types using a consistent methodology. We directly compared drinking pattern measured in three different ways and adjusted for a large number of potential confounders. We used age as the underlying time variable to minimise potential confounding by age. We used a reference group of very light drinkers as opposed to 'non-drinkers' to mitigate bias from the 'sick-quitter effect' and to ensure that any effect of drinking pattern is relative to other drinkers. The adjustment for total alcohol consumption enabled the independent effect of drinking pattern on cancer risk to be examined as separate from overall consumption. Adjusting for total alcohol consumption as a continuous (rather than a categorical variable, as in previous studies) should also have minimised bias from residual confounding by total alcohol consumption between drinking pattern groups.

The limitations of our study include the possibility of being underpowered for cancer types with a low number of cases, which can be addressed by a longer period of follow-up. For breast cancer in particular, the drinking pattern analysis may be underpowered due to the small number of women with a high number of drinks per drinking-day. Due to the use of very light drinkers as the reference group instead of lifetime abstainers, the risk associated with total alcohol consumption may be

slightly underestimated (or overestimated, where hazard ratios were less than 1). For example, even very light drinking (≤ 0.5 drinks per day) has been associated with elevated risk for breast cancer[53]. Also, due to the questionnaire design our drinks per drinking-day variable was based on the mean level of alcohol consumption. Some participants who were in fact heavy episodic drinkers will therefore have been grouped with less intense drinkers. For example, a participant who consumes alcohol 2 days per week, with 5 drinks on one day and 1 on the other, would have been grouped with a participant who consumed alcohol 2 days per week, with 3 drinks on both days. It is possible that the risk profile of these two participants is different but we were unable to differentiate between them. Further, because heavy episodic drinking was found to be independently associated with increased cancer risk, averaging the total number of drinks across days of drinking may have resulted in risk estimates for the drinks per drinking-day variable to be underestimated. In addition, our drinking pattern analysis only included participants who usually consume at least one alcoholic drink per week, meaning that participants who engage in heavy episodic drinking less frequently than once per week were excluded (such as once a month, as has been captured previously[15]). However, a possible advantage of using mean drinks per drinking-day may be that it is more representative of a person's usual exposure to alcohol than highest number of drinks consumed in one day over a period of time.

A potential problem common to all observational studies measuring alcohol consumption is the tendency for participants to underreport intake[54]. This could bias findings if underreporting differs by drinking patterns and consumption levels. In both Australian and a Canadian studies, low-risk and non-heavy episodic drinkers were found to underreport their drinking to a greater extent than higher-risk and heavy episodic drinkers[55, 56]. On the other hand, an English study found underreporting to be disproportionately associated with heavy drinking, frequent drinking and non-routine drinking compared to participants without these drinking behaviours[57]. If for example participants consuming alcohol 1-2 days per week underreported their total alcohol consumption to a greater extent than daily drinkers, this could result in conservative estimates of risk for total

alcohol consumption. Finally, despite our best efforts to control for covariates, confounding by unmeasured factors associated with drinking pattern and cancer risk could be responsible for at least part of our associations. For example, it was shown in a prospective study that declining health results in a reduction in drinking frequency[58], meaning that poorer health at baseline could bias estimates.

Conclusion

In conclusion, we used a large prospective study to examine the influence of total alcohol consumption on cancer risk, finding results largely consistent with those of prior research. Our robust investigation of the influence of drinking pattern on cancer risk suggests that number of drinks per drinking-day is independently associated with risk of cancers of the mouth, pharynx, oesophagus (SCC), colorectum, colon and kidney, as well as alcohol-related cancers combined and all cancer. More drinking-days per week was positively associated with risk of colorectal and colon cancer and inversely associated with risk of kidney cancer among persons consuming > 4 drinks per drinking-day. Heavy episodic 'binge' drinking was significantly related to kidney cancer and all cancer, while frequent heavy drinking was related to colorectal and colon cancer risk. These results have implications for burden of disease calculations, alcohol guidelines and government policies and programs aimed at reducing alcohol-related disease. Further, well-designed studies using a similar methodology to assess drinking pattern are needed to examine the effect of drinks per drinking-day, including heavy episodic drinking, on risk of cancer types for which our study may have been underpowered, such as cancers of the liver, stomach and pancreas. We provide evidence that limiting drinks per drinking-day, including both heavy episodic drinking and heavy frequent drinking, should be regarded as an approach to reduce cancer risk independent of and in addition to limiting total alcohol consumption.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Tables and figures

Table 1. Socio-demographic and other characteristics by alcohol consumption in the 45 and Up Study (2006-2010), New South Wales, Australia.

	Alcoholic drinks per week						Drinking frequency (days per week)			Drinks per drinking-day		
Characteristic at baseline	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	**1-2**	**3-5**	**6-7**	**≤ 2**	**> 2, ≤ 4**	**> 4**
n	71,963	34,093	42,083	38,281	22,598	8550	41,371	50,566	51,957	90,730	37,878	15,286
Male (%)	32.1	41.0	43.4	52.8	71.8	89.5	46.8	49.9	59.3	42.2	63.8	84.7
Mean age in years (SD)	63.2 (11.6)	60.5 (10.6)	61.6 (10.9)	60.8 (10.2)	60.6 (9.7)	59.8 (9.0)	59.3 (10.1)	59.2 (9.6)	63.7 (10.6)	61.8 (10.8)	59.4 (9.5)	58.7 (9.1)
Major city resident (%)	53.3	54.2	52.2	51.3	48.8	45.2	53.8	52.2	49.0	52.5	50.9	46.7
University degree (%)	18.0	26.7	27.3	28.7	27.2	19.4	25.1	29.6	26.4	28.2	28.0	18.5
Household income ≥ $70,000[b] (%)	14.5	27.0	28.9	33.7	35.2	29.2	29.1	35.3	27.8	28.5	36.4	30.6
Private health insurance[c] (%)	55.3	69.2	72.2	73.2	70.6	59.4	67.9	73.2	71.0	72.5	71.5	59.6
Married or living with partner (%)	68.7	76.3	78.8	80.6	80.5	73.7	75.7	80.2	79.7	78.9	80.2	73.8
Born in Australia (%)	71.9	72.0	75.1	76.8	78.2	81.3	74.3	76.7	76.0	73.9	78.1	80.5
Current smoker (%)	7.7	5.7	5.3	6.9	10.1	18.8	7.7	6.1	8.3	5.0	8.6	17.9
Overweight or obese[d] (%)	56.5	58.0	53.7	56.4	62.9	68.6	61.5	57.7	54.7	53.6	62.8	69.8
Physically inactive[e] (%)	8.3	4.3	3.7	3.4	3.9	6.1	4.2	3.2	4.3	3.6	3.8	5.3
< 2 fruit serves per day[f] (%)	37.8	37.2	38.7	44.4	52.9	63.5	39.7	41.1	49.0	39.0	48.5	58.4
< 5 vegetable serves per day (%)	64.6	66.4	65.3	67.1	70.0	73.1	67.4	66.6	67.8	65.6	69.4	72.0
< 7 fibre serves per week[g] (%)	15.2	13.6	11.2	13.6	17.1	27.4	14.9	13.2	14.8	11.9	16.0	24.3
Red meat > 5 times per week (%)	9.7	8.4	9.0	10.6	14.2	21.5	8.8	9.3	13.9	9.3	11.8	17.9
Processed meat > 1 time per week (%)	27.2	29.5	30.3	34.0	41.7	51.3	31.9	33.7	36.3	30.0	38.1	48.6
≥ 2 hours spent outdoors per day (%)	63.9	67.1	70.3	72.8	76.9	80.6	68.9	71.5	74.7	69.5	74.8	79.1
Fair skin tone (%)	68.9	68.1	69.6	69.8	70.1	70.1	67.5	69.7	70.8	69.6	69.4	69.1
Nulliparous (women) (%)	10.0	9.7	10.5	12.3	16.5	22.1	10.0	11.4	13.1	10.6	14.0	16.8
Never breastfed (women) (%)	24.2	18.8	19.6	21.0	26.2	33.4	19.6	19.6	22.6	19.4	23.5	28.9
Post-menopausal (women) (%)	65.4	61.9	64.0	62.2	60.6	52.5	59.2	59.9	68.9	64.5	56.6	51.2
Ever used HC (women) (%)	70.3	81.9	83.4	87.1	89.0	88.7	84.2	86.9	82.3	83.2	89.7	87.8
Ever used HRT (women) (%)	34.3	36.0	38.6	38.4	38.8	35.8	34.3	36.9	42.4	38.7	35.4	31.6
Current aspirin use (%)	22.0	19.0	19.9	19.8	21.0	20.9	18.1	18.0	23.0	20.2	19.1	19.8
Ever had bowel screening (%)	43.9	46.2	49.2	50.3	50.8	46.8	44.7	48.6	52.6	49.5	49.3	44.8
Ever had breast screening (women) (%)	85.2	87.2	89.2	88.9	87.4	82.1	86.5	88.7	89.7	89.0	86.7	82.1
Ever had PSA test (men) (%)	65.3	67.7	69.9	70.6	69.7	64.5	66.3	68.8	71.2	70.8	69.4	63.9

Percentages include participants with missing or invalid responses. [a]< 1 alcoholic drink per week. [b]Pre-tax annual household income from all sources in Australian dollars. [c]Including Department of Veterans' Affairs white or gold card. [d]Body mass index ≥ 25 kgm^{-2}. [e]Weekly physical activity time = 0 minutes. [f]Excludes fruit juice. [g]Serves of breakfast cereal and brown or wholemeal bread. SD, Standard Deviation. HC, Hormonal Contraceptives. HRT, Hormone Replacement Therapy. PSA, Prostate Specific Antigen.

Table 2. Hazard ratios and 95% confidence intervals of cancer risk by alcohol consumption in the 45 and Up Study (2006-2010), New South Wales, Australia.

		Drinks/week							
Cancer type (ICD-10 code)	**n cases**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Mouth and pharynx (C00-14)	150	0.63 (0.37-1.08)	1.00	0.92 (0.53-1.61)	1.08 (0.62-1.88)	1.09 (0.59-2.03)	1.65 (0.83-3.30)	0.10	0.24
Oesophagus (C15)	76	1.00 (0.48-2.09)	1.00	0.91 (0.40-2.09)	0.68 (0.27-1.69)	1.01 (0.41-2.47)	1.68 (0.64-4.44)	0.64	0.21
- Adenocarcinoma (C15)	49	1.03 (0.42-2.53)	1.00	0.90 (0.33-2.43)	0.50 (0.16-1.60)	0.88 (0.30-2.56)	1.29 (0.39-4.21)	0.76	0.60
- Squamous cell carcinoma (C15)	24	1.40 (0.30-6.58)	1.00	1.49 (0.27-8.20)	1.40 (0.23-8.57)	2.32 (0.36-14.8)	5.40 (0.79-36.8)	0.53	0.08
Colorectum (C18-20)	985	0.98 (0.80-1.20)	1.00	0.86 (0.68-1.07)	0.97 (0.77-1.21)	0.97 (0.75-1.26)	1.34 (0.98-1.84)	0.13	0.03
- Colon (C18-19)	676	0.99 (0.78-1.26)	1.00	0.82 (0.62-1.08)	0.93 (0.71-1.23)	0.99 (0.72-1.36)	1.57 (1.07-2.29)	0.04	0.006
- Rectum (C20)	315	0.92 (0.64-1.32)	1.00	0.90 (0.61-1.33)	1.00 (0.68-1.48)	0.90 (0.58-1.40)	1.09 (0.65-1.85)	0.96	0.73
Liver (C22)	67	3.61 (1.27-10.2)	1.00	1.45 (0.42-4.98)	1.85 (0.55-6.20)	1.94 (0.54-6.97)	5.21 (1.51-17.9)	0.02	0.051
Larynx (C32)	38	1.43 (0.38-5.33)	1.00	0.47 (0.08-2.80)	1.49 (0.38-5.81)	2.61 (0.70-9.70)	3.45 (0.85-13.9)	0.12	0.03
Breast (C50[d])	1012	0.96 (0.79-1.16)	1.00	1.13 (0.92-1.39)	1.25 (1.01-1.55)	1.60 (1.22-2.10)	0.71 (0.29-1.73)	< 0.001	0.007
Alcohol-related (C00-15;18-20;22;32;50[d])	2325	0.97 (0.85-1.10)	1.00	0.98 (0.85-1.13)	1.09 (0.94-1.26)	1.17 (0.99-1.39)	1.49 (1.18-1.88)	0.002	< 0.001
Stomach (C16)	112	1.52 (0.80-2.91)	1.00	1.45 (0.71-2.93)	1.21 (0.57-2.57)	1.26 (0.54-2.90)	1.59 (0.58-4.36)	0.83	0.38
Pancreas (C25)	156	1.23 (0.73-2.08)	1.00	1.30 (0.74-2.28)	1.02 (0.55-1.90)	1.34 (0.70-2.57)	0.55 (0.16-1.87)	0.64	0.75
Lung (C33-34)	546	0.98 (0.74-1.30)	1.00	0.93 (0.68-1.27)	0.90 (0.66-1.24)	1.06 (0.76-1.48)	0.91 (0.59-1.41)	0.92	0.92
Melanoma (C43)	909	0.88 (0.71-1.09)	1.00	0.93 (0.74-1.17)	1.15 (0.92-1.43)	1.16 (0.90-1.49)	1.01 (0.70-1.45)	0.09	0.24
Endometrium (C54.1)	132	1.59 (0.92-2.74)	1.00	0.68 (0.32-1.45)	1.23 (0.61-2.49)	1.68 (0.71-3.99)	-[e]	0.11	0.40
Ovary (C56)	67	0.55 (0.30-1.01)	1.00	0.24 (0.09-0.64)	0.73 (0.34-1.56)	0.95 (0.34-2.62)	-[e]	0.08	0.82
Prostate (C61)	1946	0.92 (0.78-1.07)	1.00	1.02 (0.87-1.20)	1.01 (0.86-1.18)	1.12 (0.95-1.32)	1.10 (0.90-1.36)	0.14	0.15
Kidney (C64)	146	0.91 (0.53-1.58)	1.00	1.08 (0.61-1.92)	1.11 (0.62-1.97)	1.00 (0.53-1.89)	0.90 (0.39-2.08)	0.97	0.76
Bladder (C67)	128	0.82 (0.50-1.34)	1.00	0.45 (0.24-0.84)	0.66 (0.37-1.17)	0.40 (0.19-0.84)	0.56 (0.22-1.36)	0.06	0.14
Brain (C71)	91	0.91 (0.48-1.73)	1.00	0.96 (0.49-1.89)	0.79 (0.39-1.59)	0.51 (0.21-1.23)	0.76 (0.27-2.16)	0.73	0.39
Thyroid (C73)	98	1.02 (0.58-1.79)	1.00	1.06 (0.57-1.99)	0.67 (0.32-1.41)	0.21 (0.05-0.93)	0.30 (0.04-2.34)	0.20	0.051
Non-Hodgkin lymphoma (C82-85)	264	0.88 (0.61-1.27)	1.00	0.74 (0.49-1.12)	1.01 (0.68-1.51)	0.64 (0.38-1.08)	0.48 (0.20-1.14)	0.19	0.04
Multiple myeloma (C90.0)	85	1.67 (0.79-3.52)	1.00	1.40 (0.62-3.14)	0.79 (0.31-2.01)	1.51 (0.61-3.72)	1.77 (0.58-5.45)	0.40	0.31
Leukaemia (C91-95)	145	1.05 (0.63-1.75)	1.00	0.95 (0.54-1.66)	0.79 (0.44-1.43)	0.68 (0.34-1.35)	0.72 (0.29-1.81)	0.74	0.39
Other (Other C;D45-47)	575	1.05 (0.82-1.36)	1.00	0.73 (0.54-1.00)	1.00 (0.75-1.35)	1.04 (0.74-1.45)	0.84 (0.52-1.37)	0.13	0.56
Non-alcohol-related (Other C;D45-47)	5413	0.97 (0.89-1.06)	1.00	0.92 (0.84-1.01)	0.99 (0.90-1.09)	1.03 (0.93-1.14)	0.93 (0.81-1.07)	0.22	0.68
All cancer (C00-97;D45-47)	7733	0.97 (0.90-1.04)	1.00	0.94 (0.87-1.01)	1.02 (0.94-1.10)	1.06 (0.97-1.16)	1.03 (0.92-1.17)	0.052	0.03

Models were adjusted for covariates as shown in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Female breast cancer only. [e]Zero cases in cell. ICD-10, International Classification of Diseases, version 10.

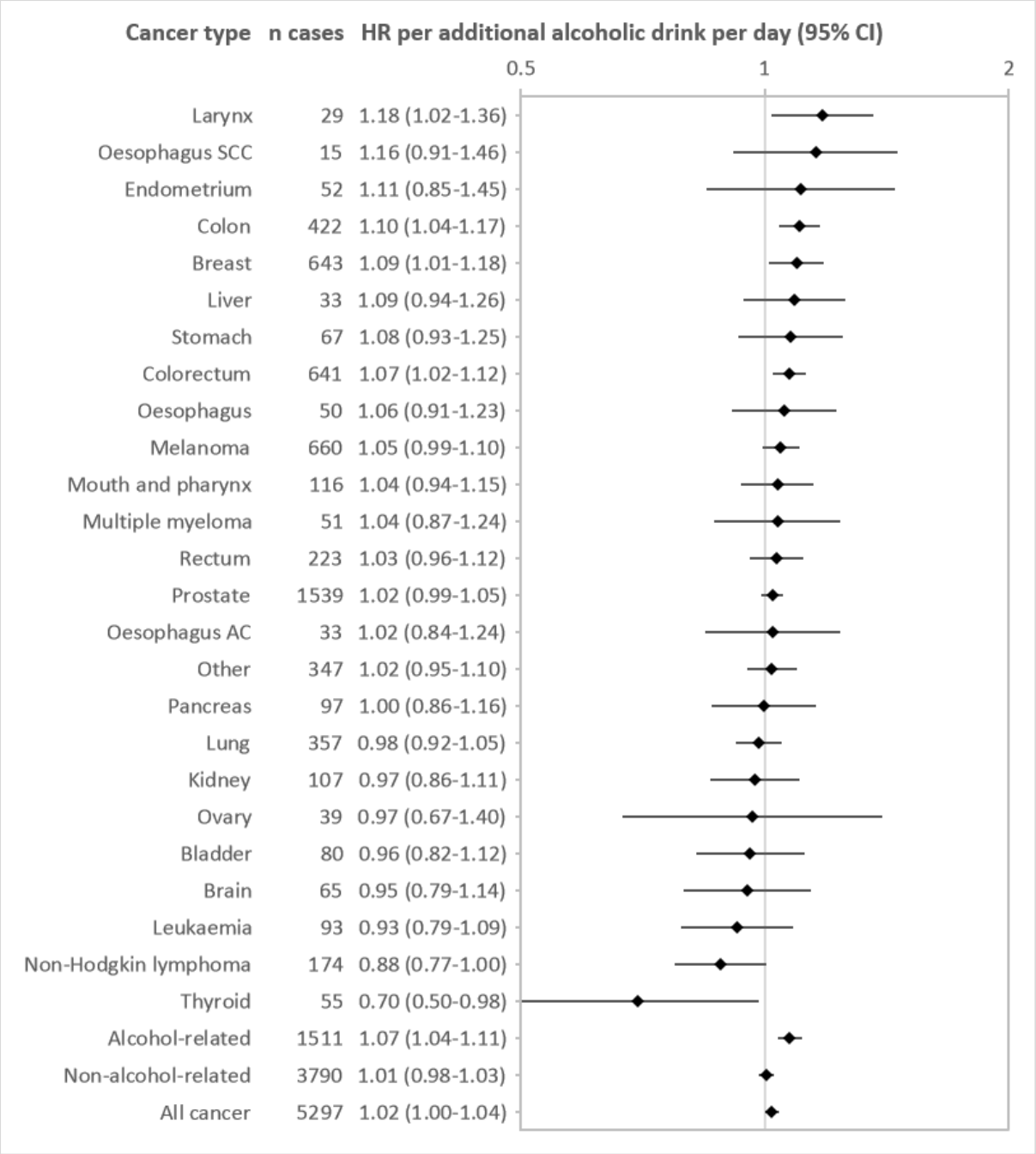

Figure 1. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk per one drink increase in mean daily alcohol consumption among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia. Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. Breast cancer in women only. SCC, Squamous Cell Carcinoma. AC, Adenocarcinoma.

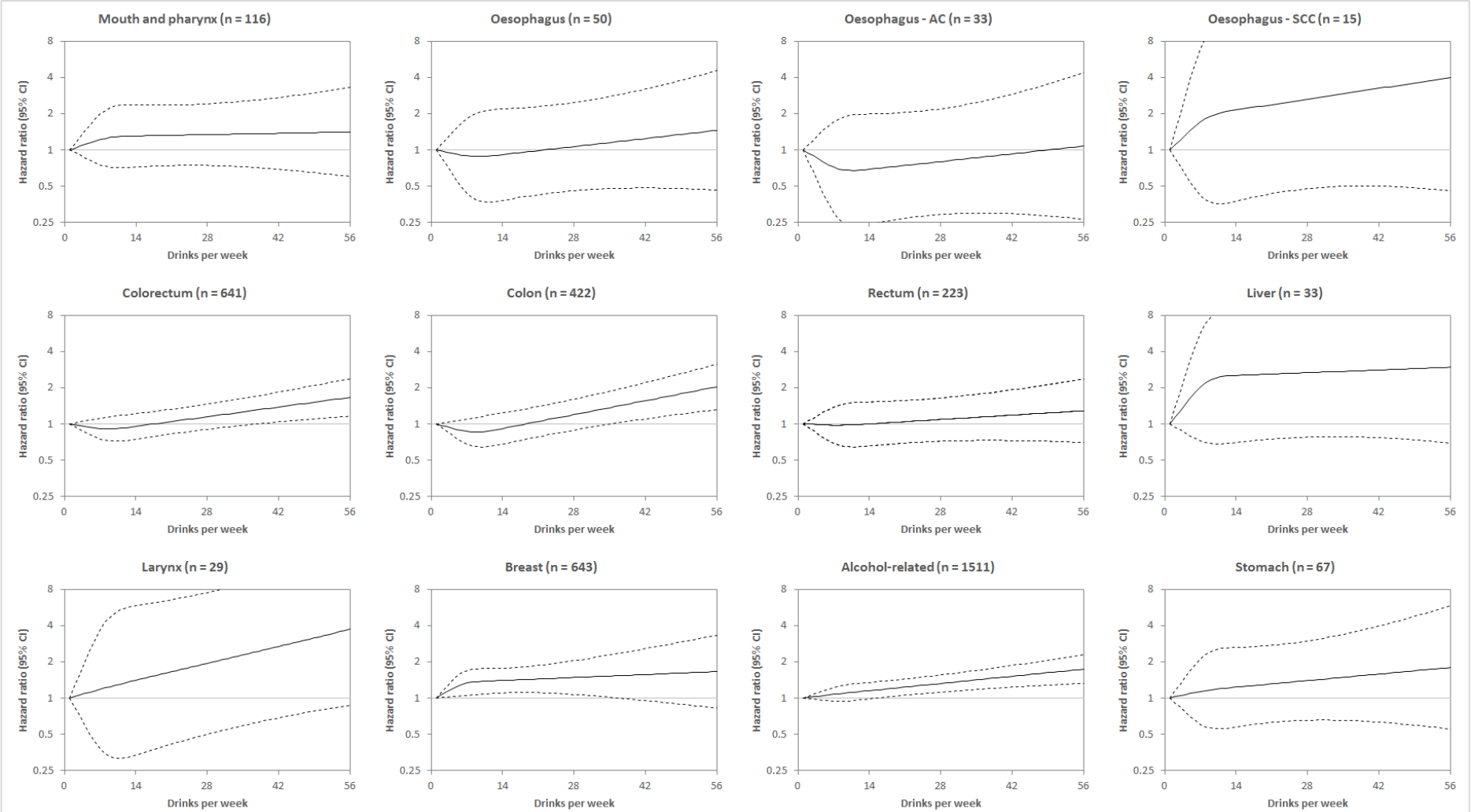

Figure 2. Hazard ratios and 95% confidence intervals (CI) of cancer risk by alcohol consumption using restricted cubic splines among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia. Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. Breast cancer in women only. AC, Adenocarcinoma. SCC, Squamous Cell Carcinoma.

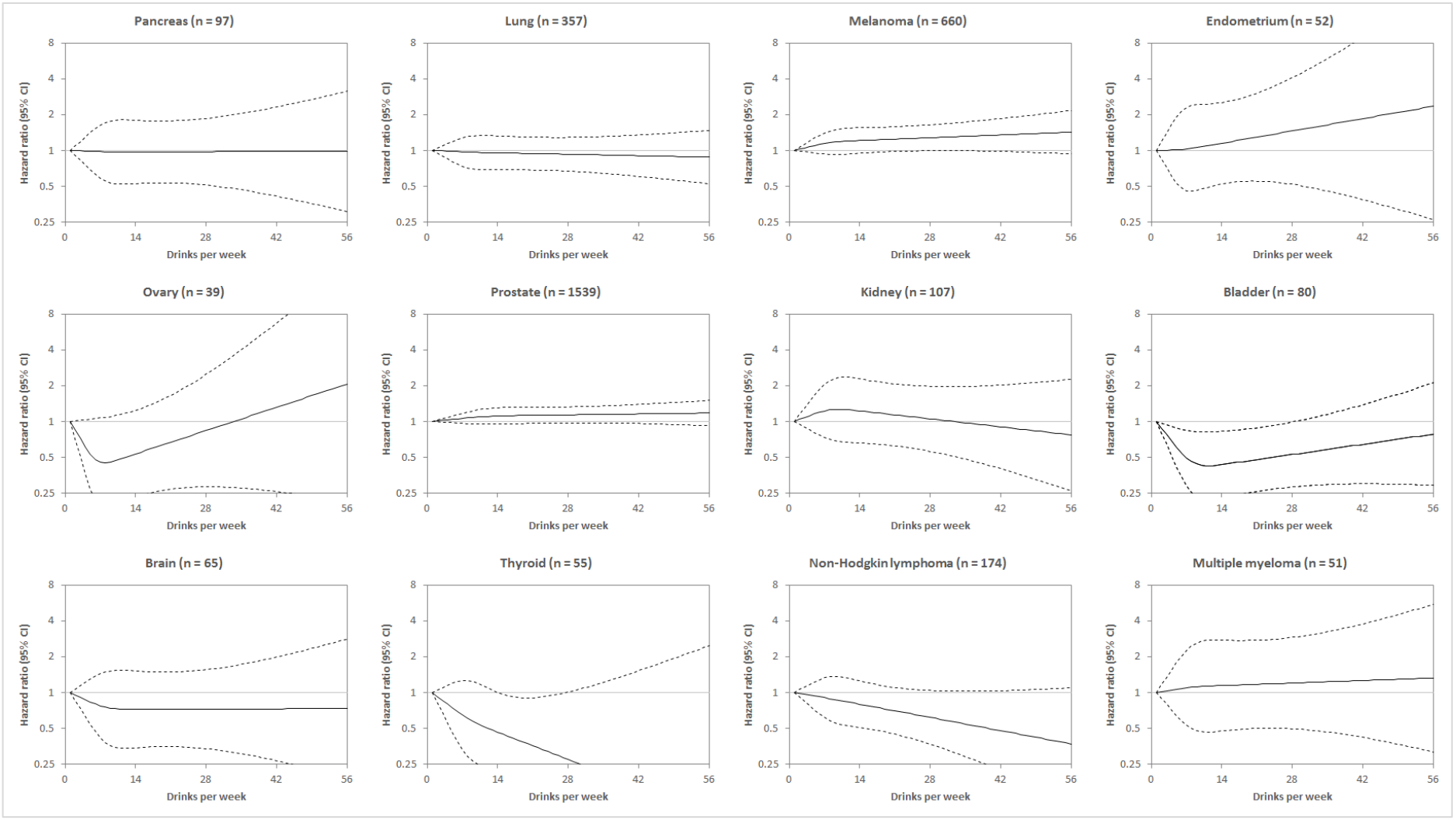

Figure 2. (Continued)

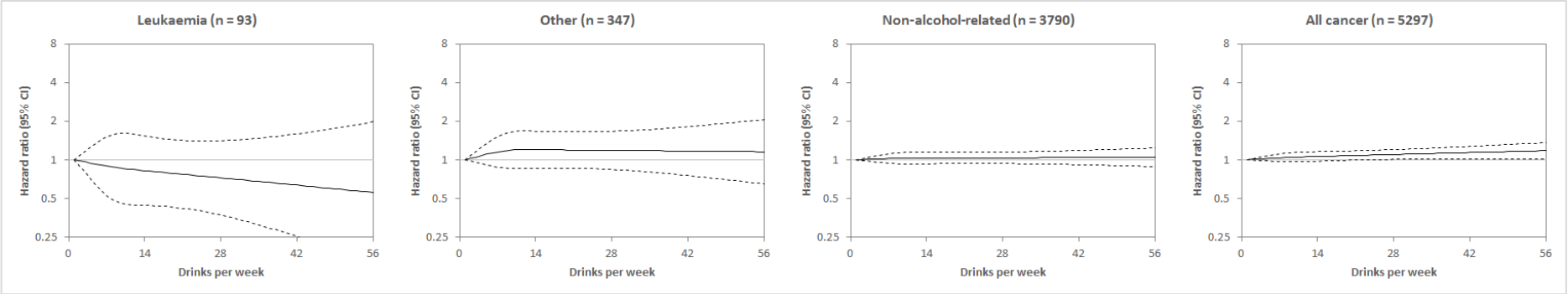

Figure 2. (Continued)

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by drinking-days per week among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

		HR drinking-days per week - unadjusted for total alcohol consumption (95% CI)					HR drinking-days per week - adjusted for total alcohol consumption (95% CI)				
Cancer type (ICD-10 code)	**n cases**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**
Mouth and pharynx (C00-14)	114	1.00	0.87 (0.54-1.41)	0.80 (0.50-1.27)	0.64	0.35	1.00	0.81 (0.50-1.32)	0.66 (0.38-1.14)	0.34	0.14
Oesophagus (C15)	50	1.00	0.84 (0.37-1.91)	1.17 (0.58-2.34)	0.66	0.57	1.00	0.81 (0.35-1.88)	1.07 (0.48-2.40)	0.77	0.81
- Adenocarcinoma (C15)	33	1.00	0.77 (0.28-2.14)	1.09 (0.46-2.56)	0.75	0.74	1.00	0.77 (0.27-2.19)	1.09 (0.40-2.99)	0.76	0.80
- Squamous cell carcinoma (C15)	15	1.00	1.47 (0.32-6.80)	1.92 (0.49-7.60)	0.64	0.34	1.00	1.36 (0.29-6.42)	1.49 (0.32-6.98)	0.87	0.62
Colorectum (C18-20)	630	1.00	0.94 (0.76-1.16)	1.02 (0.83-1.24)	0.69	0.78	1.00	0.87 (0.70-1.08)	0.84 (0.67-1.06)	0.31	0.16
- Colon (C18-19)	414	1.00	1.01 (0.77-1.31)	1.01 (0.79-1.30)	1.00	0.94	1.00	0.91 (0.69-1.19)	0.77 (0.58-1.03)	0.19	0.07
- Rectum (C20)	220	1.00	0.78 (0.54-1.13)	1.02 (0.73-1.42)	0.25	0.72	1.00	0.76 (0.52-1.11)	0.95 (0.64-1.40)	0.28	0.90
Liver (C22)	31	1.00	0.79 (0.27-2.37)	1.61 (0.66-3.95)	0.27	0.22	1.00	0.78 (0.26-2.38)	1.54 (0.54-4.33)	0.39	0.34
Larynx (C32)	29	1.00	1.58 (0.39-6.34)	2.80 (0.82-9.62)	0.17	0.06	1.00	1.37 (0.34-5.62)	2.01 (0.52-7.76)	0.53	0.26
Breast (C50[c])	630	1.00	1.25 (1.02-1.52)	1.13 (0.92-1.40)	0.09	0.26	1.00	1.16 (0.94-1.42)	0.95 (0.74-1.23)	0.12	0.73
Alcohol-related (C00-15;18-20;22;32;50[c])	1483	1.00	1.06 (0.92-1.21)	1.06 (0.93-1.21)	0.65	0.43	1.00	0.99 (0.86-1.13)	0.89 (0.76-1.04)	0.25	0.14
Stomach (C16)	66	1.00	0.87 (0.45-1.69)	0.90 (0.49-1.64)	0.91	0.75	1.00	0.80 (0.41-1.56)	0.71 (0.35-1.43)	0.62	0.34
Pancreas (C25)	93	1.00	1.03 (0.60-1.75)	0.82 (0.49-1.39)	0.63	0.41	1.00	0.97 (0.56-1.68)	0.71 (0.38-1.32)	0.45	0.26
Lung (C33-34)	348	1.00	0.78 (0.57-1.05)	0.91 (0.70-1.19)	0.26	0.69	1.00	0.78 (0.57-1.07)	0.94 (0.69-1.28)	0.27	0.82
Melanoma (C43)	651	1.00	1.10 (0.89-1.35)	1.05 (0.86-1.29)	0.68	0.70	1.00	1.05 (0.85-1.31)	0.95 (0.75-1.21)	0.59	0.63
Endometrium (C54.1)	52	1.00	0.93 (0.45-1.89)	1.36 (0.69-2.69)	0.49	0.36	1.00	0.91 (0.43-1.93)	1.30 (0.55-3.08)	0.64	0.55
Ovary (C56)	39	1.00	0.81 (0.38-1.72)	0.66 (0.29-1.50)	0.61	0.32	1.00	0.75 (0.33-1.67)	0.55 (0.19-1.57)	0.53	0.26
Prostate (C61)	1524	1.00	0.97 (0.84-1.12)	1.02 (0.90-1.17)	0.71	0.64	1.00	0.95 (0.82-1.09)	0.96 (0.82-1.12)	0.76	0.65
Kidney (C64)	105	1.00	0.86 (0.53-1.40)	0.69 (0.42-1.12)	0.31	0.12	1.00	0.83 (0.50-1.38)	0.63 (0.35-1.13)	0.30	0.12
Bladder (C67)	78	1.00	0.62 (0.34-1.15)	0.60 (0.36-1.02)	0.14	0.08	1.00	0.61 (0.33-1.15)	0.57 (0.30-1.08)	0.17	0.10
Brain (C71)	65	1.00	0.76 (0.41-1.41)	0.66 (0.36-1.22)	0.40	0.19	1.00	0.75 (0.40-1.41)	0.62 (0.29-1.33)	0.46	0.22
Thyroid (C73)	55	1.00	0.74 (0.41-1.34)	0.39 (0.18-0.84)	0.054	0.02	1.00	0.84 (0.43-1.62)	0.52 (0.20-1.37)	0.41	0.21
Non-Hodgkin lymphoma (C82-85)	174	1.00	1.06 (0.72-1.55)	0.79 (0.54-1.16)	0.24	0.19	1.00	1.15 (0.77-1.72)	0.97 (0.61-1.56)	0.61	0.88
Multiple myeloma (C90.0)	51	1.00	1.17 (0.54-2.54)	1.17 (0.56-2.45)	0.90	0.69	1.00	1.14 (0.52-2.52)	1.11 (0.47-2.61)	0.95	0.84
Leukaemia (C91-95)	91	1.00	0.66 (0.39-1.13)	0.58 (0.35-0.97)	0.09	0.04	1.00	0.67 (0.39-1.17)	0.61 (0.33-1.14)	0.24	0.12
Other (Other C;D45-47)	339	1.00	0.96 (0.72-1.29)	1.13 (0.86-1.48)	0.43	0.32	1.00	0.96 (0.71-1.30)	1.14 (0.83-1.57)	0.49	0.39
Non-alcohol-related (Other C;D45-47)	3738	1.00	0.94 (0.86-1.02)	0.95 (0.87-1.03)	0.31	0.27	1.00	0.92 (0.85-1.01)	0.92 (0.83-1.01)	0.15	0.09
All cancer (C00-97;D45-47)	5217	1.00	0.97 (0.90-1.04)	0.98 (0.91-1.05)	0.68	0.53	1.00	0.94 (0.87-1.02)	0.91 (0.84-0.99)	0.07	0.03

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Overall. [b]Linear trend using median number of drinking-days per week of each category. [c]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by mean drinks per drinking-day among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

		HR mean drinks per drinking-day - unadjusted for total alcohol consumption (95% CI)					HR mean drinks per drinking-day - adjusted for total alcohol consumption (95% CI)				
Cancer type (ICD-10 code)	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**
Mouth and pharynx (C00-14)	114	1.00	1.33 (0.84-2.09)	1.86 (1.09-3.19)	0.07	0.02	1.00	1.46 (0.90-2.37)	2.45 (1.22-4.92)	0.04	0.01
Oesophagus (C15)	50	1.00	0.98 (0.47-2.04)	2.12 (1.00-4.50)	0.10	0.06	1.00	1.08 (0.50-2.35)	2.76 (1.01-7.53)	0.09	0.054
- Adenocarcinoma (C15)	33	1.00	0.85 (0.36-2.01)	1.35 (0.52-3.52)	0.68	0.59	1.00	0.88 (0.35-2.23)	1.51 (0.40-5.71)	0.68	0.59
- Squamous cell carcinoma (C15)	15	1.00	1.68 (0.39-7.25)	6.69 (1.67-26.8)	0.02	0.007	1.00	1.88 (0.42-8.53)	9.04 (1.71-47.7)	0.03	0.009
Colorectum (C18-20)	630	1.00	0.87 (0.71-1.07)	1.42 (1.11-1.81)	0.002	0.02	1.00	0.81 (0.65-1.01)	1.15 (0.81-1.62)	0.03	0.74
- Colon (C18-19)	414	1.00	0.83 (0.64-1.08)	1.67 (1.23-2.25)	< 0.001	0.007	1.00	0.75 (0.57-0.99)	1.26 (0.83-1.94)	0.01	0.57
- Rectum (C20)	220	1.00	0.93 (0.67-1.29)	1.14 (0.76-1.71)	0.65	0.62	1.00	0.88 (0.62-1.26)	0.99 (0.56-1.75)	0.75	0.88
Liver (C22)	31	1.00	0.86 (0.34-2.18)	1.66 (0.67-4.11)	0.38	0.27	1.00	0.84 (0.32-2.21)	1.56 (0.47-5.14)	0.56	0.48
Larynx (C32)	29	1.00	1.72 (0.73-4.08)	1.47 (0.52-4.17)	0.46	0.46	1.00	1.23 (0.50-3.05)	0.48 (0.10-2.20)	0.33	0.37
Breast (C50[c])	630	1.00	1.32 (1.09-1.60)	1.38 (0.91-2.08)	0.01	0.006	1.00	1.26 (1.01-1.58)	1.24 (0.76-2.03)	0.13	0.11
Alcohol-related (C00-15;18-20;22;32;50[c])	1483	1.00	1.07 (0.94-1.21)	1.50 (1.26-1.80)	< 0.001	< 0.001	1.00	1.02 (0.89-1.17)	1.33 (1.04-1.69)	0.047	0.04
Stomach (C16)	66	1.00	1.18 (0.65-2.14)	1.65 (0.77-3.50)	0.43	0.20	1.00	1.15 (0.60-2.22)	1.55 (0.54-4.43)	0.72	0.42
Pancreas (C25)	93	1.00	1.14 (0.70-1.86)	0.78 (0.34-1.78)	0.67	0.74	1.00	1.03 (0.59-1.81)	0.60 (0.19-1.87)	0.56	0.48
Lung (C33-34)	348	1.00	1.27 (0.99-1.63)	1.14 (0.81-1.59)	0.16	0.29	1.00	1.40 (1.06-1.84)	1.46 (0.93-2.30)	0.051	0.06
Melanoma (C43)	651	1.00	1.14 (0.95-1.37)	1.16 (0.89-1.51)	0.30	0.19	1.00	1.10 (0.89-1.35)	1.05 (0.72-1.52)	0.65	0.68
Endometrium (C54.1)	52	1.00	1.41 (0.73-2.71)	-[d]	0.59	0.68	1.00	1.04 (0.45-2.39)	-[d]	1.00	0.27
Ovary (C56)	39	1.00	2.50 (1.24-5.04)	-[d]	0.04	0.33	1.00	3.54 (1.51-8.32)	-[d]	0.02	0.16
Prostate (C61)	1524	1.00	1.15 (1.03-1.29)	1.14 (0.98-1.32)	0.04	0.0497	1.00	1.14 (1.00-1.30)	1.12 (0.90-1.39)	0.13	0.22
Kidney (C64)	105	1.00	0.92 (0.57-1.48)	1.53 (0.88-2.67)	0.20	0.18	1.00	1.13 (0.67-1.90)	2.61 (1.24-5.47)	0.03	0.02
Bladder (C67)	78	1.00	0.70 (0.40-1.23)	0.59 (0.26-1.35)	0.29	0.14	1.00	0.64 (0.34-1.21)	0.46 (0.14-1.51)	0.30	0.15
Brain (C71)	65	1.00	0.73 (0.39-1.35)	0.88 (0.39-1.97)	0.60	0.59	1.00	0.75 (0.38-1.49)	0.97 (0.31-3.02)	0.67	0.82
Thyroid (C73)	55	1.00	0.66 (0.32-1.40)	0.94 (0.32-2.82)	0.56	0.59	1.00	1.04 (0.46-2.34)	2.52 (0.73-8.75)	0.31	0.23
Non-Hodgkin lymphoma (C82-85)	174	1.00	0.84 (0.58-1.22)	0.49 (0.25-0.95)	0.09	0.03	1.00	0.90 (0.59-1.38)	0.58 (0.24-1.38)	0.46	0.25
Multiple myeloma (C90.0)	51	1.00	1.24 (0.65-2.38)	1.20 (0.47-3.05)	0.80	0.61	1.00	1.22 (0.59-2.53)	1.15 (0.31-4.22)	0.87	0.76
Leukaemia (C91-95)	91	1.00	0.66 (0.38-1.14)	1.03 (0.53-2.00)	0.28	0.76	1.00	0.81 (0.44-1.47)	1.71 (0.70-4.15)	0.19	0.36
Other (Other C;D45-47)	339	1.00	1.03 (0.79-1.35)	1.33 (0.94-1.88)	0.26	0.13	1.00	1.08 (0.80-1.45)	1.50 (0.93-2.40)	0.23	0.11
Non-alcohol-related (Other C;D45-47)	3738	1.00	1.10 (1.02-1.19)	1.08 (0.97-1.20)	0.04	0.06	1.00	1.12 (1.03-1.22)	1.14 (0.98-1.32)	0.03	0.04
All cancer (C00-97;D45-47)	5217	1.00	1.10 (1.03-1.17)	1.16 (1.06-1.28)	0.001	< 0.001	1.00	1.10 (1.02-1.18)	1.17 (1.04-1.33)	0.01	0.007

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Overall. [b]Linear trend using median number of drinks per drinking-day of each category. [c]Female breast cancer only. [d]Zero cases in cell. ICD-10, International Classification of Diseases, version 10.

Table 5. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by drinking pattern among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

Cancer type	n cases	Drinking-days per week	HR mean drinks per drinking-day (95% CI)		
			≤ 2	> 2 and ≤ 4	> 4
Colorectum	630	1-2	1.00	0.54 (0.32-0.91)	0.99 (0.58-1.67)
		3-5	0.91 (0.71-1.16)	0.69 (0.47-1.01)	1.04 (0.62-1.75)
		6-7	0.81 (0.64-1.04)	0.92 (0.69-1.23)	1.47 (1.06-2.02)
Colon	414	1-2	1.00	0.50 (0.25-1.00)	0.97 (0.48-1.94)
		3-5	0.99 (0.74-1.34)	0.64 (0.39-1.05)	1.26 (0.66-2.40)
		6-7	0.77 (0.57-1.04)	0.89 (0.62-1.29)	1.82 (1.23-2.69)
Kidney	105	1-2	1.00	1.64 (0.67-4.03)	3.55 (1.49-8.48)
		3-5	0.91 (0.45-1.83)	1.29 (0.59-2.83)	2.59 (1.03-6.49)
		6-7	1.26 (0.67-2.38)	0.58 (0.24-1.38)	0.70 (0.25-1.95)
All cancer	5217	1-2	1.00	1.01 (0.88-1.17)	1.27 (1.07-1.52)
		3-5	0.96 (0.88-1.05)	1.08 (0.97-1.21)	1.02 (0.85-1.23)
		6-7	0.95 (0.87-1.03)	1.06 (0.96-1.17)	1.11 (0.98-1.26)

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1.

Supplementary data

Supplementary Table 1. Covariates in models by cancer type in the 45 and Up Study (2006-2010), New South Wales, Australia.

Cancer type (ICD-10 code)	Age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity	Sex	Fruit intake	Vegetable intake	Fibre and red meat intake	Processed meat intake	Time spent outdoors, skin tone	Parity and age of first birth, breastfeeding time, menopausal status	HC use	HRT use	Aspirin use	Bowel, breast and prostate screening history
Mouth and pharynx (C00-14)	Yes	Yes	Yes	Yes	-	-	-	-	-	-	-	-
Oesophagus (C15)	Yes	Yes	-	-	-	-	-	-	-	-	Yes	-
Colorectum (C18-20)	Yes	Yes	Yes	Yes	Yes	Yes	-	-	-	Yes	Yes	Bowel
Liver (C22)	Yes	Yes	-	-	-	-	-	-	Yes	-	-	-
Larynx (C32)	Yes	Yes	Yes	Yes	-	-	-	-	-	-	-	-
Breast (C50[a])	Yes	-	-	-	-	-	-	Yes	Yes	Yes	-	Breast
Alcohol-related (C00-15;18-20;22;32;50[a])	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes	Yes	Yes	Yes	Bowel/Breast
Stomach (C16)	Yes	Yes	-	-	-	Yes	-	-	-	-	-	-
Pancreas (C25)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Lung (C33-34)	Yes	Yes	Yes	-	-	-	-	-	-	-	-	-
Melanoma (C43)	Yes	Yes	-	-	-	-	Yes	-	-	-	-	-
Endometrium (C54.1)	Yes	-	-	-	-	-	-	Yes	Yes	Yes	-	-
Ovary (C56)	Yes	-	-	-	-	-	-	Yes	Yes	Yes	-	-
Prostate (C61)	Yes	-	-	-	-	-	-	-	-	-	-	Prostate
Kidney (C64)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Bladder (C67)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Brain (C71)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Thyroid (C73)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Non-Hodgkin lymphoma (C82-85)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Multiple myeloma (C90.0)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Leukaemia (C91-95)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Other (Other C;D45-47)	Yes	Yes	-	-	-	-	-	-	-	-	-	-
Non-alcohol-related (Other C;D45-47)	Yes	Yes	Yes	-	-	Yes	Yes	Yes	Yes	Yes	-	Prostate
All cancer (C00-97;D45-47)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	All three

[a]Female breast cancer only. ICD-10, International Classification of Diseases, version 10. HC, Hormonal Contraceptive. HRT, Hormone Replacement Therapy.

Supplementary Table 2. Hazard ratios and 95% confidence intervals of cancer risk by alcohol consumption in men in the 45 and Up Study (2006-2010), New South Wales, Australia.

		Drinks/week							
Cancer type (ICD-10 code)	**n cases**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Mouth and pharynx (C00-14)	96	0.45 (0.21-0.97)	1.00	0.85 (0.41-1.75)	0.96 (0.48-1.93)	1.18 (0.58-2.40)	1.58 (0.73-3.41)	0.053	0.17
Oesophagus (C15)	53	0.85 (0.35-2.04)	1.00	0.76 (0.29-1.98)	0.48 (0.17-1.39)	0.79 (0.30-2.09)	1.13 (0.40-3.22)	0.73	0.43
- Adenocarcinoma (C15)	41	1.17 (0.40-3.40)	1.00	1.11 (0.36-3.40)	0.66 (0.19-2.30)	1.04 (0.32-3.34)	1.43 (0.40-5.13)	0.89	0.51
- Squamous cell carcinoma (C15)	9	0.36 (0.05-2.75)	1.00	0.36 (0.03-4.30)	-[d]	0.61 (0.08-4.85)	0.82 (0.10-6.89)	0.93	0.34
Colorectum (C18-20)	555	0.92 (0.70-1.22)	1.00	0.84 (0.62-1.13)	0.94 (0.70-1.26)	0.94 (0.69-1.29)	1.39 (0.98-1.97)	0.09	0.03
- Colon (C18-19)	345	0.93 (0.65-1.32)	1.00	0.84 (0.57-1.23)	0.80 (0.54-1.18)	0.98 (0.65-1.46)	1.69 (1.10-2.61)	0.01	0.002
- Rectum (C20)	215	0.94 (0.59-1.49)	1.00	0.83 (0.50-1.37)	1.17 (0.74-1.86)	0.87 (0.52-1.46)	1.14 (0.64-2.03)	0.64	0.81
Liver (C22)	52	3.76 (1.12-12.7)	1.00	1.92 (0.49-7.46)	2.34 (0.62-8.92)	1.47 (0.32-6.66)	5.43 (1.39-21.2)	0.051	0.10
Larynx (C32)	-[e]	1.34 (0.35-5.09)	1.00	0.23 (0.02-2.21)	1.45 (0.37-5.68)	2.52 (0.68-9.39)	3.35 (0.83-13.6)	0.10	0.03
Alcohol-related (C00-15;18-20;22;32)	789	0.93 (0.73-1.18)	1.00	0.85 (0.65-1.10)	0.96 (0.74-1.23)	1.01 (0.78-1.32)	1.54 (1.15-2.05)	0.001	< 0.001
Stomach (C16)	76	1.57 (0.67-3.69)	1.00	1.84 (0.76-4.46)	1.53 (0.61-3.83)	1.40 (0.52-3.73)	1.74 (0.57-5.33)	0.84	0.44
Pancreas (C25)	89	1.14 (0.54-2.42)	1.00	1.80 (0.86-3.78)	1.32 (0.60-2.88)	1.25 (0.54-2.89)	0.43 (0.09-2.01)	0.31	0.23
Lung (C33-34)	308	1.08 (0.73-1.61)	1.00	0.97 (0.62-1.50)	1.08 (0.71-1.64)	1.16 (0.75-1.79)	1.05 (0.64-1.73)	0.96	0.70
Melanoma (C43)	558	0.95 (0.70-1.28)	1.00	0.99 (0.73-1.35)	1.19 (0.89-1.60)	1.20 (0.88-1.64)	1.10 (0.74-1.65)	0.42	0.34
Kidney (C64)	108	0.79 (0.41-1.50)	1.00	0.95 (0.49-1.83)	0.89 (0.47-1.72)	0.88 (0.44-1.75)	0.82 (0.35-1.97)	0.98	0.66
Bladder (C67)	99	0.69 (0.39-1.23)	1.00	0.45 (0.23-0.89)	0.63 (0.34-1.16)	0.35 (0.16-0.77)	0.42 (0.16-1.13)	0.08	0.08
Brain (C71)	60	1.71 (0.67-4.36)	1.00	1.31 (0.48-3.56)	1.41 (0.54-3.71)	0.80 (0.27-2.43)	1.18 (0.35-3.94)	0.65	0.72
Thyroid (C73)	24	3.04 (0.67-13.8)	1.00	2.10 (0.41-10.9)	1.49 (0.27-8.22)	0.43 (0.04-4.84)	0.70 (0.06-7.94)	0.27	0.40
Non-Hodgkin lymphoma (C82-85)	147	0.78 (0.47-1.28)	1.00	0.67 (0.39-1.16)	0.81 (0.48-1.36)	0.55 (0.30-1.02)	0.48 (0.20-1.19)	0.37	0.04
Multiple myeloma (C90.0)	56	2.42 (0.81-7.22)	1.00	2.12 (0.68-6.60)	0.99 (0.28-3.52)	2.39 (0.75-7.60)	2.64 (0.59-10.0)	0.28	0.14
Leukaemia (C91-95)	97	1.19 (0.62-2.26)	1.00	0.92 (0.46-1.86)	0.82 (0.41-1.66)	0.66 (0.30-1.45)	0.74 (0.28-1.96)	0.64	0.48
Other (Other C;D45-47)	331	0.97 (0.69-1.37)	1.00	0.68 (0.45-1.01)	0.95 (0.65-1.39)	1.00 (0.69-1.49)	0.86 (0.51-1.46)	0.37	0.51
Non-alcohol-related (Other C;D45-47[f])	3910	0.97 (0.87-1.08)	1.00	0.97 (0.87-1.09)	1.02 (0.91-1.14)	1.05 (0.93-1.18)	0.99 (0.85-1.15)	0.71	0.46
All cancer (C00-97;D45-47[f])	4696	0.96 (0.87-1.06)	1.00	0.95 (0.86-1.06)	1.01 (0.91-1.12)	1.04 (0.94-1.16)	1.09 (0.95-1.24)	0.24	0.04

Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Zero cases in cell. [e]Censored as this value would enable calculation of value for women (< 5 cases). [f]Includes prostate cancer, which is not shown. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 3. Hazard ratios and 95% confidence intervals of cancer risk by alcohol consumption in women the 45 and Up Study (2006-2010), New South Wales, Australia.

		Drinks/week							
Cancer type (ICD-10 code)	**n cases**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Mouth and pharynx (C00-14)	54	0.83 (0.38-1.84)	1.00	1.00 (0.42-2.38)	1.20 (0.49-2.95)	0.29 (0.04-2.32)	-[d]	0.79	0.31
Oesophagus (C15)	23	1.62 (0.36-7.37)	1.00	1.48 (0.27-8.14)	1.89 (0.21-11.7)	1.61 (0.14-19.0)	13.9 (1.13-172.2)	0.47	0.10
- Adenocarcinoma (C15)	8	0.57 (0.11-3.07)	1.00	0.35 (0.03-3.93)	-[d]	-[d]	-[d]	0.98	0.28
- Squamous cell carcinoma (C15)	15	-[e]	1.00	-[e]	-[e]	-[e]	-[e]	0.39	0.03
Colorectum (C18-20)	430	1.05 (0.79-1.39)	1.00	0.88 (0.63-1.24)	1.01 (0.71-1.44)	1.14 (0.71-1.86)	0.74 (0.18-3.05)	0.84	0.58
- Colon (C18-19)	331	1.07 (0.77-1.48)	1.00	0.80 (0.54-1.18)	1.12 (0.75-1.68)	1.05 (0.59-1.88)	0.50 (0.07-3.68)	0.50	0.81
- Rectum (C20)	100	0.87 (0.49-1.54)	1.00	1.03 (0.54-1.95)	0.58 (0.26-1.32)	1.26 (0.51-3.11)	1.24 (0.16-9.55)	0.68	0.50
Liver (C22)	15	2.86 (0.36-22.7)	1.00	-[d]	-[d]	7.60 (0.65-89.3)	-[d]	0.75	0.04
Larynx (C32)	< 5	-[f]	1.00	-[f]	-[f]	-[f]	-[f]	-[f]	-[f]
Alcohol-related (C00-15;18-20;22;32;50[g])	1536	1.00 (0.86-1.17)	1.00	1.05 (0.89-1.25)	1.18 (0.99-1.41)	1.42 (1.13-1.80)	0.75 (0.37-1.52)	0.02	0.01
Stomach (C16)	36	1.39 (0.52-3.74)	1.00	0.87 (0.25-3.03)	0.52 (0.10-2.72)	0.76 (0.09-6.68)	-[c]	0.80	0.61
Pancreas (C25)	67	1.28 (0.61-2.68)	1.00	0.75 (0.30-1.89)	0.60 (0.20-1.81)	2.01 (0.70-5.79)	2.74 (0.34-22.1)	0.23	0.049
Lung (C33-34)	238	0.93 (0.63-1.37)	1.00	0.92 (0.59-1.43)	0.72 (0.44-1.18)	1.02 (0.58-1.78)	0.28 (0.04-2.03)	0.60	0.28
Melanoma (C43)	351	0.84 (0.62-1.15)	1.00	0.87 (0.62-1.23)	1.11 (0.78-1.58)	1.25 (0.78-2.02)	0.88 (0.21-3.61)	0.38	0.38
Kidney (C64)	38	1.41 (0.47-4.27)	1.00	1.76 (0.53-5.89)	2.46 (0.73-8.32)	1.81 (0.32-10.2)	-[d]	0.78	0.42
Bladder (C67)	29	1.26 (0.42-3.78)	1.00	0.39 (0.07-2.13)	0.60 (0.11-3.33)	0.90 (0.10-8.30)	6.82 (0.71-65.7)	0.28	0.27
Brain (C71)	31	0.44 (0.17-1.14)	1.00	0.74 (0.29-1.87)	0.31 (0.08-1.18)	0.32 (0.04-2.62)	-[d]	0.41	0.11
Thyroid (C73)	74	0.79 (0.43-1.46)	1.00	0.93 (0.47-1.85)	0.56 (0.24-1.33)	0.20 (0.03-1.55)	-[d]	0.55	0.04
Non-Hodgkin lymphoma (C82-85)	117	1.02 (0.59-1.76)	1.00	0.84 (0.44-1.60)	1.42 (0.76-2.65)	0.85 (0.31-2.33)	-[d]	0.66	0.84
Multiple myeloma (C90.0)	29	1.10 (0.39-3.06)	1.00	0.77 (0.22-2.67)	0.71 (0.17-3.02)	-[d]	-[d]	0.98	0.16
Leukaemia (C91-95)	48	0.85 (0.37-1.93)	1.00	1.01 (0.40-2.58)	0.73 (0.24-2.28)	0.87 (0.18-4.19)	-[d]	0.99	0.73
Other (Other C;D45-47)	244	1.20 (0.81-1.76)	1.00	0.81 (0.51-1.31)	1.10 (0.68-1.78)	1.26 (0.66-2.40)	0.71 (0.10-5.23)	0.47	0.54
Non-alcohol-related (Other C;D45-47[h])	1503	0.95 (0.82-1.11)	1.00	0.80 (0.67-0.96)	0.93 (0.77-1.12)	1.04 (0.81-1.33)	0.48 (0.21-1.09)	0.06	0.73
All cancer (C00-97;D45-47[g,h])	3037	0.98 (0.88-1.09)	1.00	0.92 (0.82-1.04)	1.04 (0.92-1.19)	1.22 (1.03-1.44)	0.61 (0.36-1.03)	0.009	0.14

Models adjusted for covariates as shown in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Zero cases in cell. [e]Not possible to calculate due to zero deaths in reference group. [f]Model failed to converge. [g]Includes breast cancer, which is not shown. [h]Includes endometrium and ovary cancer, which are not shown. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 4. Hazard ratios and 95% confidence intervals of cancer risk by alcohol consumption in never-smokers in the 45 and Up Study (2006-2010), New South Wales, Australia.

		Drinks/week							
Cancer type (ICD-10 code)	**n cases**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Mouth and pharynx (C00-14)	67	0.60 (0.30-1.17)	1.00	0.81 (0.39-1.67)	0.53 (0.21-1.31)	0.90 (0.32-2.52)	2.88 (0.91-9.08)	0.09	0.27
Oesophagus (C15)	26	0.93 (0.29-2.95)	1.00	1.39 (0.40-4.78)	0.35 (0.04-3.20)	0.92 (0.10-8.49)	4.26 (0.44-41.4)	0.59	0.56
- Adenocarcinoma (C15)	14	0.59 (0.14-2.53)	1.00	1.36 (0.32-5.73)	-[d]	0.98 (0.10-9.96)	-[d]	0.89	0.49
- Squamous cell carcinoma (C15)	11	-[e]	1.00	-[e]	-[e]	-[e]	-[e]	0.01	0.01
Colorectum (C18-20)	484	0.96 (0.74-1.25)	1.00	0.92 (0.68-1.25)	0.78 (0.55-1.11)	0.96 (0.62-1.48)	1.52 (0.83-2.77)	0.40	0.24
- Colon (C18-19)	357	0.99 (0.73-1.33)	1.00	0.84 (0.59-1.20)	0.81 (0.54-1.22)	0.75 (0.43-1.32)	1.42 (0.67-3.02)	0.52	0.75
- Rectum (C20)	128	0.88 (0.52-1.49)	1.00	1.16 (0.66-2.04)	0.69 (0.34-1.40)	1.43 (0.70-2.90)	1.66 (0.61-4.53)	0.34	0.15
Liver (C22)	28	7.25 (0.96-54.5)	1.00	1.77 (0.16-19.6)	4.03 (0.41-39.3)	2.70 (0.17-44.2)	8.90 (0.53-149.2)	0.18	0.27
Larynx (C32)	< 5	-[f]	1.00	-[f]	-[f]	-[f]	-[f]	0.92	-[f]
Breast (C50[g])	632	0.85 (0.68-1.06)	1.00	1.11 (0.87-1.42)	1.25 (0.95-1.65)	1.52 (1.02-2.31)	1.64 (0.52-5.15)	0.005	0.01
Alcohol-related (C00-15;18-20;22;32;50[g])	1241	0.92 (0.78-1.08)	1.00	1.02 (0.85-1.22)	0.98 (0.80-1.21)	1.13 (0.85-1.50)	1.81 (1.16-2.81)	0.046	0.02
Stomach (C16)	56	0.68 (0.31-1.47)	1.00	1.15 (0.51-2.60)	0.90 (0.34-2.41)	1.10 (0.34-3.61)	-[d]	0.79	0.31
Pancreas (C25)	70	0.96 (0.46-2.01)	1.00	0.96 (0.41-2.23)	1.44 (0.62-3.32)	1.78 (0.66-4.79)	0.99 (0.13-7.90)	0.71	0.41
Lung (C33-34)	87	1.14 (0.61-2.12)	1.00	0.86 (0.40-1.83)	0.92 (0.39-2.18)	0.90 (0.25-3.21)	-[d]	0.96	0.48
Melanoma (C43)	521	0.78 (0.60-1.02)	1.00	0.87 (0.66-1.15)	1.12 (0.85-1.49)	1.09 (0.76-1.56)	0.99 (0.54-1.82)	0.09	0.53
Endometrium (C54.1)	91	2.15 (1.06-4.37)	1.00	0.77 (0.28-2.06)	2.01 (0.83-4.87)	1.43 (0.31-6.67)	-[d]	0.08	0.27
Ovary (C56)	47	0.61 (0.29-1.27)	1.00	0.32 (0.10-0.99)	0.98 (0.38-2.52)	1.61 (0.45-5.78)	-[d]	0.23	0.65
Prostate (C61)	975	0.88 (0.72-1.07)	1.00	0.95 (0.77-1.17)	0.96 (0.77-1.18)	1.12 (0.89-1.41)	1.06 (0.75-1.50)	0.36	0.27
Kidney (C64)	60	1.14 (0.50-2.61)	1.00	1.75 (0.75-4.10)	1.09 (0.41-2.94)	0.54 (0.11-2.56)	4.03 (1.28-12.7)	0.08	0.15
Bladder (C67)	39	0.72 (0.31-1.68)	1.00	0.58 (0.20-1.69)	0.29 (0.06-1.39)	0.96 (0.25-3.73)	1.01 (0.12-8.32)	0.69	0.96
Brain (C71)	39	0.56 (0.23-1.35)	1.00	0.89 (0.38-2.11)	0.58 (0.21-1.62)	-[d]	0.68 (0.08-5.48)	0.79	0.15
Thyroid (C73)	55	0.69 (0.36-1.32)	1.00	0.49 (0.21-1.17)	0.54 (0.21-1.42)	-[d]	-[d]	0.66	0.03
Non-Hodgkin lymphoma (C82-85)	141	0.99 (0.60-1.61)	1.00	1.04 (0.60-1.79)	1.28 (0.73-2.26)	0.54 (0.20-1.44)	-[d]	0.64	0.10
Multiple myeloma (C90.0)	55	1.35 (0.60-3.03)	1.00	1.33 (0.55-3.22)	0.52 (0.16-1.74)	0.81 (0.21-3.10)	0.84 (0.10-6.86)	0.58	0.63
Leukaemia (C91-95)	64	0.90 (0.43-1.85)	1.00	1.06 (0.48-2.35)	1.02 (0.43-2.43)	0.42 (0.09-1.93)	1.53 (0.33-7.10)	0.84	0.85
Other (Other C;D45-47)	299	1.01 (0.72-1.41)	1.00	0.76 (0.50-1.15)	0.95 (0.62-1.45)	1.17 (0.70-1.96)	1.43 (0.67-3.06)	0.45	0.16
Non-alcohol-related (Other C;D45-47)	2603	0.91 (0.81-1.03)	1.00	0.90 (0.79-1.02)	0.99 (0.87-1.13)	1.03 (0.88-1.21)	1.04 (0.80-1.33)	0.27	0.47
All cancer (C00-97;D45-47)	3842	0.91 (0.83-1.01)	1.00	0.94 (0.84-1.04)	0.99 (0.88-1.11)	1.06 (0.92-1.11)	1.16 (0.93-1.21)	0.07	0.08

Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Zero cases in cell. [e]Not possible to calculate due to zero deaths in reference group. [f]Model failed to converge. [g]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 5. Hazard ratios and 95% confidence intervals of cancer risk by alcohol consumption in ever-smokers in the 45 and Up Study (2006-2010), New South Wales, Australia.

		Drinks/week							
Cancer type (ICD-10 code)	**n cases**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Mouth and pharynx (C00-14)	83	0.69 (0.28-1.67)	1.00	1.12 (0.46-2.70)	1.77 (0.79-3.97)	1.39 (0.58-3.34)	1.60 (0.62-4.12)	0.15	0.56
Oesophagus (C15)	50	1.03 (0.39-2.71)	1.00	0.67 (0.22-2.09)	0.77 (0.27-2.24)	0.95 (0.33-2.71)	1.31 (0.43-4.01)	0.87	0.35
- Adenocarcinoma (C15)	35	1.35 (0.43-4.27)	1.00	0.65 (0.16-2.63)	0.69 (0.19-2.61)	0.90 (0.25-3.24)	1.40 (0.37-5.37)	0.73	0.55
- Squamous cell carcinoma (C15)	13	0.35 (0.05-2.57)	1.00	0.73 (0.10-5.30)	0.64 (0.09-4.64)	1.18 (0.19-7.37)	1.05 (0.14-8.08)	0.85	0.51
Colorectum (C18-20)	501	1.00 (0.73-1.35)	1.00	0.78 (0.56-1.10)	1.10 (0.81-1.51)	0.99 (0.71-1.40)	1.34 (0.90-1.97)	0.11	0.07
- Colon (C18-19)	319	1.01 (0.68-1.49)	1.00	0.81 (0.52-1.24)	1.06 (0.70-1.58)	1.15 (0.75-1.76)	1.72 (1.06-2.79)	0.06	0.003
- Rectum (C20)	187	0.94 (0.57-1.55)	1.00	0.71 (0.41-1.23)	1.12 (0.69-1.84)	0.73 (0.42-1.28)	0.98 (0.53-1.84)	0.39	0.72
Liver (C22)	39	2.16 (0.62-7.57)	1.00	1.22 (0.29-5.12)	1.18 (0.28-4.96)	1.38 (0.33-5.88)	3.25 (0.81-13.1)	0.35	0.13
Larynx (C32)	-[d]	0.96 (0.24-3.89)	1.00	0.46 (0.08-2.75)	1.35 (0.35-5.27)	2.22 (0.60-8.24)	2.35 (0.57-9.80)	0.25	0.08
Breast (C50[e])	380	1.26 (0.89-1.78)	1.00	1.19 (0.82-1.72)	1.33 (0.92-1.91)	1.76 (1.18-2.64)	0.42 (0.10-1.74)	0.06	0.19
Alcohol-related (C00-15;18-20;22;32;50[e])	1084	1.07 (0.87-1.32)	1.00	0.94 (0.74-1.18)	1.21 (0.97-1.50)	1.23 (0.97-1.56)	1.44 (1.08-1.92)	0.02	0.003
Stomach (C16)	56	5.60 (1.32-23.8)	1.00	2.80 (0.59-13.2)	2.92 (0.63-13.6)	2.72 (0.56-13.3)	4.54 (0.90-23.1)	0.11	0.13
Pancreas (C25)	86	1.56 (0.74-3.29)	1.00	1.59 (0.73-3.49)	0.76 (0.31-1.87)	1.30 (0.54-3.14)	0.51 (0.11-2.42)	0.22	0.40
Lung (C33-34)	459	0.94 (0.69-1.28)	1.00	0.95 (0.67-1.34)	0.91 (0.64-1.27)	1.07 (0.75-1.52)	0.90 (0.58-1.42)	0.93	0.95
Melanoma (C43)	388	1.15 (0.79-1.68)	1.00	1.04 (0.70-1.54)	1.22 (0.84-1.77)	1.31 (0.89-1.93)	1.15 (0.71-1.88)	0.73	0.27
Endometrium (C54.1)	41	0.92 (0.38-2.26)	1.00	0.60 (0.19-1.93)	0.59 (0.18-1.90)	1.43 (0.47-4.38)	-[f]	0.70	0.97
Ovary (C56)	20	0.43 (0.14-1.35)	1.00	0.11 (0.01-0.89)	0.38 (0.10-1.38)	0.34 (0.07-1.78)	-[f]	0.32	0.31
Prostate (C61)	971	0.98 (0.76-1.26)	1.00	1.14 (0.89-1.46)	1.09 (0.85-1.38)	1.17 (0.92-1.49)	1.17 (0.89-1.54)	0.50	0.34
Kidney (C64)	86	0.78 (0.37-1.63)	1.00	0.72 (0.33-1.57)	1.01 (0.50-2.06)	0.97 (0.46-2.04)	0.35 (0.10-1.26)	0.54	0.24
Bladder (C67)	89	0.86 (0.47-1.58)	1.00	0.39 (0.18-0.85)	0.72 (0.38-1.38)	0.31 (0.13-0.75)	0.49 (0.18-1.35)	0.04	0.09
Brain (C71)	52	1.70 (0.61-4.70)	1.00	1.15 (0.38-3.45)	1.17 (0.40-3.40)	1.00 (0.32-3.11)	1.18 (0.31-4.51)	0.85	0.88
Thyroid (C73)	43	2.73 (0.79-9.44)	1.00	3.91 (1.12-13.7)	1.56 (0.39-6.31)	0.81 (0.13-4.96)	1.01 (0.10-10.1)	0.08	0.43
Non-Hodgkin lymphoma (C82-85)	123	0.75 (0.43-1.30)	1.00	0.46 (0.24-0.87)	0.77 (0.44-1.34)	0.58 (0.30-1.10)	0.51 (0.20-1.28)	0.21	0.15
Multiple myeloma (C90.0)	30	4.08 (0.51-32.9)	1.00	2.37 (0.26-21.3)	2.41 (0.28-20.8)	4.35 (0.54-35.4)	4.96 (0.54-45.4)	0.58	0.10
Leukaemia (C91-95)	81	1.22 (0.60-2.47)	1.00	0.87 (0.39-1.92)	0.69 (0.31-1.54)	0.76 (0.33-1.75)	0.56 (0.18-1.78)	0.52	0.36
Other (Other C;D45-47)	276	1.17 (0.79-1.74)	1.00	0.71 (0.44-1.12)	1.07 (0.70-1.64)	1.03 (0.65-1.63)	0.74 (0.40-1.40)	0.15	0.85
Non-alcohol-related (Other C;D45-47)	2810	1.07 (0.93-1.22)	1.00	0.94 (0.81-1.08)	1.00 (0.87-1.15)	1.07 (0.92-1.23)	0.96 (0.81-1.15)	0.27	0.80
All cancer (C00-97;D45-47)	3891	1.06 (0.95-1.19)	1.00	0.94 (0.83-1.06)	1.05 (0.94-1.18)	1.10 (0.98-1.25)	1.06 (0.91-1.23)	0.07	0.10

Models were adjusted for cancers-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Censored as this value would enable calculation of value for never-smokers (< 5 cases). [e]Female breast cancer only. [f]Zero cases in cell. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 6. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by drinking-days per week among drinkers by sex in the 45 and Up Study (2006-2010), New South Wales, Australia.

		HR drinking-days per week in men - adjusted for total alcohol consumption (95% CI)						HR drinking-days per week in women - adjusted for total alcohol consumption (95% CI)				
Cancer type (ICD-10 code)	**n cases**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**	**n cases**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**
Mouth and pharynx (C00-14)	81	1.00	0.75 (0.42-1.35)	0.61 (0.32-1.18)	0.34	0.14	33	1.00	1.14 (0.45-2.88)	1.03 (0.33-3.17)	0.95	0.96
Oesophagus (C15)	39	1.00	0.58 (0.22-1.57)	0.97 (0.39-2.39)	0.47	0.93	11	1.00	1.91 (0.33-11.3)	1.21 (0.19-7.91)	0.72	0.92
- Adenocarcinoma (C15)	-[c]	1.00	0.62 (0.19-2.01)	1.25 (0.44-3.60)	0.43	0.56	-[c]	1.00	29.9 (0.17-5237.5)	-[d]	0.44	0.59
- Squamous cell carcinoma (C15)	-[c]	1.00	0.47 (0.05-4.61)	0.53 (0.06-5.00)	0.79	0.62	-[c]	1.00	1.83 (0.15-22.5)	2.30 (0.20-26.2)	0.80	0.51
Colorectum (C18-20)	409	1.00	0.82 (0.62-1.09)	0.87 (0.65-1.17)	0.40	0.44	221	1.00	0.92 (0.65-1.31)	0.75 (0.49-1.15)	0.38	0.21
- Colon (C18-19)	248	1.00	0.90 (0.63-1.30)	0.79 (0.54-1.15)	0.45	0.21	166	1.00	0.92 (0.61-1.39)	0.78 (0.48-1.28)	0.61	0.33
- Rectum (C20)	164	1.00	0.68 (0.43-1.09)	1.00 (0.63-1.58)	0.14	0.79	56	1.00	0.91 (0.46-1.81)	0.68 (0.30-1.57)	0.64	0.37
Liver (C22)	-[c]	1.00	0.90 (0.28-2.87)	1.63 (0.55-4.87)	0.46	0.32	-[c]	1.00	-[e]	-[e]	-[e]	-[e]
Larynx (C32)	-[c]	1.00	1.09 (0.25-4.67)	1.84 (0.47-7.12)	0.51	0.28	-[c]	1.00	-[e]	-[e]	-[e]	-[e]
Alcohol-related (C00-15;18-20;22;32;50[f])	585	1.00	0.80 (0.63-1.01)	0.88 (0.69-1.13)	0.17	0.44	898	1.00	1.10 (0.92-1.31)	0.90 (0.73-1.12)	0.08	0.36
Stomach (C16)	53	1.00	0.81 (0.37-1.77)	0.81 (0.36-1.78)	0.84	0.62	13	1.00	1.10 (0.24-5.06)	0.85 (0.12-6.23)	0.95	0.89
Pancreas (C25)	64	1.00	1.05 (0.53-2.06)	0.92 (0.43-1.95)	0.92	0.80	29	1.00	0.84 (0.32-2.19)	0.44 (0.15-1.29)	0.27	0.12
Lung (C33-34)	221	1.00	0.73 (0.48-1.10)	0.96 (0.65-1.42)	0.23	0.95	127	1.00	0.93 (0.57-1.51)	0.98 (0.57-1.70)	0.94	0.96
Melanoma (C43)	430	1.00	1.15 (0.87-1.52)	1.00 (0.74-1.35)	0.42	0.85	221	1.00	0.92 (0.65-1.31)	0.89 (0.58-1.36)	0.85	0.58
Kidney (C64)	83	1.00	0.75 (0.42-1.32)	0.48 (0.25-0.94)	0.10	0.03	22	1.00	1.29 (0.41-4.08)	1.55 (0.41-5.90)	0.81	0.52
Bladder (C67)	69	1.00	0.57 (0.29-1.13)	0.56 (0.29-1.11)	0.17	0.11	9	1.00	1.09 (0.19-6.10)	0.64 (0.08-5.30)	0.85	0.69
Brain (C71)	43	1.00	0.81 (0.36-1.82)	0.61 (0.24-1.56)	0.58	0.30	22	1.00	0.92 (0.30-2.86)	1.38 (0.30-6.47)	0.81	0.73
Thyroid (C73)	13	1.00	1.05 (0.29-3.86)	0.27 (0.04-2.03)	0.31	0.25	42	1.00	0.92 (0.41-2.04)	0.90 (0.28-2.88)	0.98	0.84
Non-Hodgkin lymphoma (C82-85)	109	1.00	1.05 (0.63-1.77)	1.01 (0.56-1.83)	0.98	0.97	65	1.00	1.26 (0.66-2.40)	0.83 (0.36-1.93)	0.41	0.68
Multiple myeloma (C90.0)	38	1.00	1.90 (0.66-5.53)	1.91 (0.63-5.79)	0.46	0.31	13	1.00	0.54 (0.12-2.37)	0.49 (0.05-4.52)	0.70	0.47
Leukaemia (C91-95)	66	1.00	0.63 (0.33-1.20)	0.51 (0.25-1.07)	0.18	0.08	25	1.00	0.78 (0.27-2.24)	0.89 (0.25-3.12)	0.90	0.84
Other (Other C;D45-47)	225	1.00	0.90 (0.62-1.32)	1.04 (0.70-1.54)	0.71	0.79	114	1.00	1.06 (0.64-1.77)	1.28 (0.71-2.31)	0.67	0.41
Non-alcohol-related (Other C;D45-47)	2941	1.00	0.94 (0.84-1.04)	0.93 (0.83-1.04)	0.35	0.20	797	1.00	0.91 (0.76-1.10)	0.88 (0.70-1.10)	0.48	0.25
All cancer (C00-97;D45-47)	3523	1.00	0.91 (0.85-1.00)	0.91 (0.82-1.01)	0.11	0.10	1694	1.00	1.00 (0.88-1.14)	0.88 (0.76-1.03)	0.13	0.12

Non-drinkers were excluded. Models were adjusted for cancers-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Overall. [b]Linear trend using median number of drinking-days per week of each category. [c]Censored due to < 5 cases in women, or if this value would enable calculation of value for another cell for which there is < 5 cases in women. [d]Zero cases in cell. [e]Model failed to converge. [f]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 7. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by drinking-days per week among drinkers by smoking status in the 45 and Up Study (2006-2010), New South Wales, Australia.

		HR drinking-days per week in never-smokers - adjusted for total alcohol consumption (95% CI)						HR drinking-days per week in ever-smokers - adjusted for total alcohol consumption (95% CI)				
Cancer type (ICD-10 code)	**n cases**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**	**n cases**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**
Mouth and pharynx (C00-14)	45	1.00	0.76 (0.37-1.57)	0.52 (0.21-1.28)	0.36	0.15	69	1.00	0.81 (0.42-1.58)	0.76 (0.37-1.55)	0.73	0.46
Oesophagus (C15)	14	1.00	1.15 (0.27-4.93)	0.95 (0.20-4.45)	0.96	0.94	36	1.00	0.71 (0.25-2.02)	1.19 (0.45-3.18)	0.55	0.61
- Adenocarcinoma (C15)	-[c]	1.00	1.54 (0.27-8.82)	1.09 (0.13-8.93)	0.87	0.92	-[c]	1.00	0.64 (0.17-2.45)	1.36 (0.40-4.61)	0.46	0.50
- Squamous cell carcinoma (C15)	-[c]	1.00	-[d]	-[d]	1.00	0.61	-[c]	1.00	0.79 (0.15-4.17)	0.80 (0.14-4.52)	0.96	0.81
Colorectum (C18-20)	261	1.00	0.93 (0.68-1.27)	0.70 (0.48-1.01)	0.13	0.06	369	1.00	0.82 (0.60-1.12)	0.95 (0.70-1.30)	0.39	0.93
- Colon (C18-19)	182	1.00	1.02 (0.71-1.48)	0.67 (0.43-1.05)	0.09	0.09	232	1.00	0.82 (0.55-1.22)	0.87 (0.59-1.29)	0.61	0.59
- Rectum (C20)	79	1.00	0.73 (0.41-1.30)	0.77 (0.40-1.47)	0.54	0.42	141	1.00	0.78 (0.47-1.30)	1.06 (0.64-1.76)	0.37	0.66
Liver (C22)	6	1.00	0.44 (0.04-5.42)	0.92 (0.09-9.57)	0.79	0.95	25	1.00	0.91 (0.25-3.24)	1.77 (0.54-5.79)	0.42	0.28
Larynx (C32)	-[c]	1.00	-[e]	-[e]	-[e]	-[e]	-[c]	1.00	1.44 (0.35-5.91)	2.11 (0.54-8.24)	0.51	0.25
Breast (C50[f])	373	1.00	1.26 (0.97-1.65)	1.14 (0.82-1.59)	0.21	0.42	257	1.00	0.97 (0.70-1.34)	0.71 (0.47-1.08)	0.16	0.10
Alcohol-related (C00-15;18-20;22;32;50[f])	700	1.00	1.07 (0.88-1.30)	0.88 (0.69-1.11)	0.14	0.28	783	1.00	0.89 (0.73-1.09)	0.89 (0.72-1.11)	0.48	0.35
Stomach (C16)	34	1.00	0.62 (0.24-1.57)	0.78 (0.28-2.15)	0.59	0.62	32	1.00	1.35 (0.45-4.05)	1.08 (0.35-3.32)	0.81	0.98
Pancreas (C25)	42	1.00	1.33 (0.58-3.04)	1.08 (0.42-2.82)	0.75	0.90	51	1.00	0.71 (0.34-1.52)	0.50 (0.22-1.10)	0.23	0.08
Lung (C33-34)	38	1.00	0.77 (0.31-1.91)	1.68 (0.62-4.55)	0.24	0.32	310	1.00	0.80 (0.57-1.12)	0.91 (0.65-1.26)	0.43	0.66
Melanoma (C43)	351	1.00	1.02 (0.77-1.34)	0.83 (0.59-1.15)	0.32	0.25	300	1.00	1.09 (0.77-1.55)	1.09 (0.76-1.57)	0.87	0.69
Endometrium (C54.1)	29	1.00	1.49 (0.56-3.93)	1.40 (0.40-4.87)	0.73	0.58	23	1.00	0.37 (0.09-1.54)	1.34 (0.36-4.91)	0.18	0.63
Ovary (C56)	26	1.00	0.74 (0.29-1.90)	0.48 (0.13-1.76)	0.54	0.27	13	1.00	0.73 (0.16-3.44)	0.70 (0.11-4.34)	0.91	0.70
Prostate (C61)	718	1.00	0.89 (0.73-1.09)	0.87 (0.69-1.08)	0.41	0.22	806	1.00	1.00 (0.81-1.24)	1.03 (0.83-1.29)	0.94	0.75
Kidney (C64)	39	1.00	1.34 (0.60-3.03)	0.78 (0.29-2.12)	0.39	0.61	66	1.00	0.58 (0.30-1.13)	0.54 (0.26-1.11)	0.17	0.10
Bladder (C67)	20	1.00	0.11 (0.01-0.87)	0.67 (0.22-2.00)	0.11	0.54	58	1.00	0.87 (0.43-1.76)	0.57 (0.26-1.24)	0.32	0.15
Brain (C71)	28	1.00	1.14 (0.43-2.98)	1.48 (0.41-5.41)	0.83	0.57	37	1.00	0.65 (0.27-1.59)	0.47 (0.18-1.25)	0.32	0.13
Thyroid (C73)	29	1.00	0.48 (0.19-1.22)	0.13 (0.02-0.81)	0.07	0.02	26	1.00	1.81 (0.64-5.10)	1.67 (0.45-6.18)	0.53	0.43
Non-Hodgkin lymphoma (C82-85)	83	1.00	1.42 (0.82-2.48)	0.98 (0.47-2.02)	0.27	0.98	91	1.00	0.95 (0.53-1.71)	0.99 (0.52-1.88)	0.98	0.98
Multiple myeloma (C90.0)	29	1.00	0.79 (0.29-2.15)	1.02 (0.34-3.11)	0.84	0.96	22	1.00	2.58 (0.53-12.5)	1.98 (0.38-10.3)	0.49	0.61
Leukaemia (C91-95)	38	1.00	0.59 (0.25-1.42)	0.87 (0.34-2.22)	0.47	0.75	53	1.00	0.71 (0.34-1.45)	0.47 (0.20-1.08)	0.20	0.07
Other (Other C;D45-47)	158	1.00	1.03 (0.68-1.56)	1.08 (0.67-1.73)	0.95	0.76	181	1.00	0.87 (0.56-1.36)	1.14 (0.73-1.77)	0.41	0.46
Non-alcohol-related (Other C;D45-47)	1663	1.00	0.92 (0.81-1.04)	0.86 (0.74-0.99)	0.12	0.04	2075	1.00	0.91 (0.80-1.04)	0.93 (0.81-1.06)	0.35	0.38
All cancer (C00-97;D45-47)	2362	1.00	0.96 (0.87-1.07)	0.87 (0.76-0.98)	0.054	0.02	2855	1.00	0.90 (0.81-1.01)	0.92 (0.82-1.03)	0.16	0.19

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Overall. [b]Linear trend using median number of drinking-days per week of each category. [c]Censored due to < 5 cases in never-smokers, or if this value would enable calculation of value for another cell for which there is < 5 cases in never-smokers. [d]Not possible to calculate due to zero deaths in reference group. [e]Model failed to converge. [f]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 8. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by mean drinks per drinking-day among drinkers by sex in the 45 and Up Study (2006-2010), New South Wales, Australia.

		HR mean drinks per drinking-day in men - adjusted for total alcohol consumption (95% CI)						HR mean drinks per drinking-day in women - adjusted for total alcohol consumption (95% CI)				
Cancer type (ICD-10 code)	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**
Mouth and pharynx (C00-14)	81	1.00	2.10 (1.19-3.71)	3.37 (1.57-7.21)	0.005	0.002	33	1.00	0.43 (0.11-1.77)	-[c]	0.50	0.13
Oesophagus (C15)	39	1.00	0.82 (0.34-2.00)	2.47 (0.84-7.23)	0.10	0.11	11	1.00	2.26 (0.44-11.8)	3.20 (0.21-49.3)	0.57	0.33
- Adenocarcinoma (C15)	-[d]	1.00	0.92 (0.36-2.38)	1.43 (0.37-5.56)	0.78	0.63	-[d]	1.00	-[c]	-[c]	1.00	1.00
- Squamous cell carcinoma (C15)	-[d]	1.00	-[c]	26.0 (1.73-392.7)	0.06	0.01	-[d]	1.00	3.14 (0.48-20.7)	4.96 (0.19-127.1)	0.46	0.26
Colorectum (C18-20)	409	1.00	0.78 (0.60-1.02)	1.19 (0.81-1.73)	0.02	0.52	221	1.00	0.98 (0.63-1.50)	0.82 (0.32-2.14)	0.92	0.73
- Colon (C18-19)	248	1.00	0.67 (0.48-0.95)	1.27 (0.78-2.05)	0.007	0.51	166	1.00	1.05 (0.64-1.73)	1.06 (0.38-2.98)	0.98	0.86
- Rectum (C20)	164	1.00	0.94 (0.63-1.40)	1.11 (0.61-2.03)	0.80	0.78	56	1.00	0.72 (0.30-1.70)	0.29 (0.03-3.22)	0.55	0.27
Liver (C22)	-[d]	1.00	0.75 (0.27-2.10)	1.61 (0.48-5.40)	0.44	0.45	-[d]	1.00	-[e]	-[e]	-[e]	-[e]
Larynx (C32)	-[d]	1.00	1.31 (0.52-3.33)	0.50 (0.11-2.36)	0.30	0.41	-[d]	1.00	-[e]	-[e]	-[e]	-[e]
Alcohol-related (C00-15;18-20;22;32;50[f])	585	1.00	0.92 (0.74-1.14)	1.42 (1.05-1.92)	0.007	0.04	898	1.00	1.16 (0.95-1.41)	1.08 (0.70-1.66)	0.33	0.34
Stomach (C16)	53	1.00	1.05 (0.52-2.12)	1.42 (0.48-4.24)	0.80	0.55	13	1.00	2.14 (0.30-15.2)	-[c]	0.75	0.77
Pancreas (C25)	64	1.00	0.97 (0.50-1.89)	0.72 (0.21-2.44)	0.85	0.64	29	1.00	1.11 (0.40-3.05)	0.34 (0.02-7.74)	0.69	0.73
Lung (C33-34)	221	1.00	1.35 (0.96-1.90)	1.76 (1.06-2.92)	0.08	0.03	127	1.00	1.73 (1.06-2.82)	0.22 (0.03-1.68)	0.01	0.97
Melanoma (C43)	430	1.00	1.05 (0.82-1.33)	0.91 (0.59-1.39)	0.71	0.74	221	1.00	1.14 (0.77-1.69)	1.98 (0.94-4.18)	0.20	0.11
Kidney (C64)	83	1.00	1.36 (0.77-2.40)	3.33 (1.52-7.26)	0.009	0.003	22	1.00	0.38 (0.08-1.82)	0.74 (0.05-10.3)	0.48	0.45
Bladder (C67)	69	1.00	0.56 (0.29-1.09)	0.29 (0.08-1.09)	0.12	0.046	9	1.00	1.63 (0.16-17.0)	10.4 (0.98-111.1)	0.15	0.07
Brain (C71)	43	1.00	0.53 (0.24-1.20)	0.68 (0.19-2.36)	0.31	0.44	22	1.00	2.78 (0.86-9.04)	-[c]	0.24	0.26
Thyroid (C73)	13	1.00	0.69 (0.17-2.76)	0.20 (0.01-4.13)	0.58	0.30	42	1.00	1.20 (0.43-3.37)	6.98 (1.85-26.3)	0.01	0.02
Non-Hodgkin lymphoma (C82-85)	109	1.00	0.89 (0.54-1.47)	0.46 (0.16-1.28)	0.32	0.17	65	1.00	0.89 (0.39-2.04)	1.41 (0.28-7.18)	0.84	0.88
Multiple myeloma (C90.0)	38	1.00	1.47 (0.66-3.29)	1.28 (0.32-5.06)	0.63	0.65	13	1.00	1.01 (0.11-9.49)	-[c]	1.00	0.89
Leukaemia (C91-95)	66	1.00	0.89 (0.46-1.74)	1.87 (0.71-4.93)	0.25	0.27	25	1.00	0.46 (0.09-2.29)	1.36 (0.13-14.8)	0.55	0.80
Other (Other C;D45-47)	225	1.00	1.14 (0.80-1.61)	1.71 (1.02-2.87)	0.12	0.048	114	1.00	0.89 (0.50-1.58)	1.04 (0.33-3.32)	0.89	0.90
Non-alcohol-related (Other C;D45-47)	2941	1.00	1.10 (1.02-1.21)	1.14 (0.97-1.33)	0.10	0.07	797	1.00	1.20 (0.97-1.48)	1.13 (0.72-1.79)	0.24	0.23
All cancer (C00-97;D45-47)	3523	1.00	1.07 (0.98-1.16)	1.18 (1.03-1.36)	0.06	0.02	1694	1.00	1.18 (1.03-1.37)	1.11 (0.82-1.52)	0.07	0.11

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Overall. [b]Linear trend using median number of drinks per drinking-day of each category. [c]Zero cases in cell. [d]Censored due to < 5 cases in women, or if this value would enable calculation of value for another cell for which there is < 5 cases in women. [e]Model failed to converge. [f]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 9. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by mean drinks per drinking-day among drinkers by smoking status in the 45 and Up Study (2006-2010), New South Wales, Australia.

		HR mean drinks per drinking-day in never-smokers - adjusted for total alcohol consumption (95% CI)						HR mean drinks per drinking-day in ever-smokers - adjusted for total alcohol consumption (95% CI)				
Cancer type (ICD-10 code)	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**
Mouth and pharynx (C00-14)	45	1.00	1.54 (0.67-3.53)	3.29 (0.92-11.8)	0.18	0.07	69	1.00	1.48 (0.80-2.73)	2.16 (0.93-5.03)	0.19	0.07
Oesophagus (C15)	14	1.00	0.72 (0.08-6.56)	4.99 (0.70-35.3)	0.20	0.14	36	1.00	1.13 (0.47-2.69)	2.09 (0.66-6.61)	0.41	0.21
- Adenocarcinoma (C15)	-[c]	1.00	1.69 (0.16-18.0)	5.67 (0.47-67.8)	0.39	0.18	-[c]	1.00	0.82 (0.29-2.29)	0.88 (0.19-4.02)	0.93	0.85
- Squamous cell carcinoma (C15)	-[c]	1.00	-[d]	1.85 (0.01-478.1)	0.98	0.82	-[c]	1.00	2.50 (0.45-13.8)	8.97 (1.29-62.2)	0.08	0.02
Colorectum (C18-20)	261	1.00	0.75 (0.51-1.10)	1.00 (0.52-1.91)	0.27	0.64	369	1.00	0.84 (0.64-1.10)	1.18 (0.78-1.78)	0.12	0.57
- Colon (C18-19)	182	1.00	0.59 (0.36-0.98)	1.16 (0.54-2.52)	0.06	0.75	232	1.00	0.85 (0.60-1.20)	1.32 (0.79-2.21)	0.14	0.39
- Rectum (C20)	79	1.00	1.08 (0.59-1.99)	0.71 (0.21-2.42)	0.74	0.71	141	1.00	0.78 (0.50-1.21)	1.01 (0.52-1.95)	0.43	0.93
Liver (C22)	6	1.00	-[d]	0.31 (0.01-17.8)	0.85	0.42	25	1.00	1.20 (0.41-3.46)	1.91 (0.51-7.18)	0.61	0.33
Larynx (C32)	-[c]	1.00	-[e]	-[e]	-[e]	-[e]	-[c]	1.00	1.22 (0.49-3.05)	0.41 (0.08-2.02)	0.26	0.31
Breast (C50[f])	373	1.00	0.88 (0.63-1.22)	0.51 (0.19-1.36)	0.38	0.19	257	1.00	1.74 (1.28-2.38)	2.21 (1.24-3.96)	< 0.001	< 0.001
Alcohol-related (C00-15;18-20;22;32;50[f])	700	1.00	0.84 (0.66-1.07)	0.94 (0.59-1.50)	0.34	0.44	783	1.00	1.15 (0.96-1.37)	1.52 (1.14-2.02)	0.02	0.005
Stomach (C16)	34	1.00	1.20 (0.42-3.45)	2.09 (0.37-11.7)	0.70	0.42	32	1.00	1.35 (0.55-3.28)	1.50 (0.40-5.71)	0.78	0.54
Pancreas (C25)	42	1.00	1.25 (0.53-2.94)	0.64 (0.10-4.29)	0.65	0.85	51	1.00	0.91 (0.43-1.91)	0.61 (0.15-2.47)	0.78	0.51
Lung (C33-34)	38	1.00	0.82 (0.27-2.50)	0.68 (0.07-6.92)	0.92	0.69	310	1.00	1.48 (1.11-1.97)	1.55 (0.98-2.47)	0.03	0.04
Melanoma (C43)	351	1.00	1.13 (0.84-1.52)	1.15 (0.66-2.01)	0.72	0.51	300	1.00	1.06 (0.79-1.42)	0.98 (0.59-1.63)	0.87	0.99
Endometrium (C54.1)	29	1.00	0.90 (0.26-3.13)	-[d]	0.99	0.47	23	1.00	1.10 (0.33-3.66)	-[d]	0.99	0.39
Ovary (C56)	26	1.00	2.79 (0.92-8.40)	-[d]	0.19	0.37	13	1.00	4.79 (1.08-21.2)	-[d]	0.12	0.34
Prostate (C61)	718	1.00	1.18 (0.98-1.43)	1.06 (0.74-1.50)	0.18	0.48	806	1.00	1.10 (0.92-1.31)	1.14 (0.86-1.52)	0.54	0.34
Kidney (C64)	39	1.00	0.20 (0.05-0.89)	2.13 (0.63-7.21)	0.02	0.51	66	1.00	1.87 (1.01-3.46)	3.20 (1.28-7.99)	0.04	0.01
Bladder (C67)	20	1.00	0.59 (0.16-2.21)	0.07 (0.00-3.70)	0.42	0.18	58	1.00	0.65 (0.31-1.36)	0.65 (0.18-2.33)	0.51	0.41
Brain (C71)	28	1.00	1.37 (0.45-4.20)	3.73 (0.66-21.2)	0.33	0.16	37	1.00	0.58 (0.25-1.35)	0.52 (0.12-2.19)	0.43	0.31
Thyroid (C73)	29	1.00	2.09 (0.69-6.31)	3.57 (0.41-31.2)	0.30	0.12	26	1.00	0.55 (0.17-1.80)	1.59 (0.31-8.11)	0.37	0.84
Non-Hodgkin lymphoma (C82-85)	83	1.00	0.78 (0.38-1.59)	1.01 (0.29-3.50)	0.76	0.81	91	1.00	0.90 (0.52-1.56)	0.38 (0.11-1.23)	0.23	0.15
Multiple myeloma (C90.0)	29	1.00	0.45 (0.12-1.70)	0.88 (0.11-7.14)	0.47	0.61	22	1.00	3.07 (1.02-9.29)	1.97 (0.33-11.8)	0.11	0.42
Leukaemia (C91-95)	38	1.00	0.52 (0.18-1.51)	0.59 (0.08-4.31)	0.48	0.38	53	1.00	1.01 (0.48-2.10)	2.58 (0.93-7.15)	0.12	0.09
Other (Other C;D45-47)	158	1.00	0.97 (0.61-1.55)	1.66 (0.80-3.43)	0.29	0.25	181	1.00	1.13 (0.77-1.66)	1.42 (0.77-2.62)	0.53	0.12
Non-alcohol-related (Other C;D45-47)	1663	1.00	1.08 (0.94-1.23)	1.14 (0.89-1.45)	0.46	0.24	2075	1.00	1.14 (1.02-1.28)	1.17 (0.97-1.41)	0.06	0.06
All cancer (C00-97;D45-47)	2362	1.00	1.02 (0.91-1.14)	1.08 (0.87-1.34)	0.79	0.51	2855	1.00	1.14 (1.04-1.26)	1.25 (1.07-1.46)	0.007	0.004

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Overall. [b]Linear trend using median number of drinks per drinking-day of each category. [c]Censored due to < 5 cases in never-smokers, or if this value would enable calculation of value for another cell for which there is < 5 cases in never-smokers. [d]Zero cases in cell. [e]Model failed to converge. [f]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 10. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by drinking-days per week stratified by mean drinks per drinking-day among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

Cancer type	Mean drinks per drinking-day	n cases	HR drinking-days per week (95% CI) 1-2	3-5	6-7	p^a	p_{trend}^b
Colorectum	≤ 2	397	1.00	0.90 (0.70-1.15)	0.80 (0.63-1.03)	0.21	0.08
	> 2 and ≤ 4	135	1.00	1.21 (0.67-2.19)	1.60 (0.92-2.78)	0.17	0.06
	> 4	98	1.00	1.05 (0.52-2.13)	1.70 (0.95-3.03)	0.09	0.04
Colon	≤ 2	270	1.00	1.00 (0.74-1.35)	0.78 (0.58-1.06)	0.19	0.11
	> 2 and ≤ 4	79	1.00	1.19 (0.54-2.62)	1.42 (0.68-2.95)	0.59	0.31
	> 4	65	1.00	1.20 (0.48-2.98)	2.13 (0.99-4.59)	0.07	0.03
Kidney	≤ 2	59	1.00	0.92 (0.46-1.84)	1.34 (0.71-2.55)	0.44	0.32
	> 2 and ≤ 4	26	1.00	0.70 (0.27-1.82)	0.30 (0.11-0.87)	0.07	0.82
	> 4	20	1.00	0.84 (0.29-2.43)	0.19 (0.06-0.60)	0.01	0.003

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Overall. [b]Linear trend using median number of drinking-days per week of each category.

Supplementary Table 11. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk by mean drinks per drinking-day stratified by drinking-days per week among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

Cancer type	Drinking-days per week	n cases	HR mean drinks per drinking-day (95% CI) ≤ 2	> 2 and ≤ 4	> 4	p^a	p_{trend}^b
Colorectum	1-2	161	1.00	0.52 (0.31-0.89)	1.02 (0.59-1.75)	0.053	0.50
	3-5	177	1.00	0.80 (0.54-1.19)	1.40 (0.80-2.44)	0.17	0.56
	6-7	292	1.00	1.09 (0.82-1.45)	1.64 (1.16-2.30)	0.01	0.006
Colon	1-2	104	1.00	0.47 (0.23-0.94)	0.93 (0.46-1.91)	0.10	0.38
	3-5	122	1.00	0.69 (0.41-1.15)	1.49 (0.75-2.96)	0.11	0.70
	6-7	188	1.00	1.17 (0.81-1.68)	2.29 (1.51-3.49)	< 0.001	< 0.001
Kidney	1-2	31	1.00	1.62 (0.65-4.08)	3.36 (1.35-8.34)	0.03	0.009
	3-5	34	1.00	1.38 (0.61-3.11)	2.36 (0.85-6.61)	0.26	0.10
	6-7	40	1.00	0.48 (0.21-1.09)	0.63 (0.23-1.75)	0.20	0.23

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Overall. [b]Linear trend using median number of drinks per drinking-day of each category.

8.2 – Additional Analyses

Additional research questions regarding the relationship between cancer incidence and alcohol consumption reported in the main analysis are reported here. The first set of analyses addressed the potential impact of the 'sick-quitter effect' and other biases on the main results. The second set used the cancer-specific risk estimates to calculate the population attributable fraction (PAF) of alcohol for the Australia, cumulative absolute cancer risk, and the number of persons needed to quit or reduce drinking to prevent one cancer case.

1. *The impact of the 'sick-quitter effect' and other changes in drinking behaviours in response to ill-health on risk estimates.*

Rationale and methods. A number of promising methods for mitigating bias from the 'sick-quitter effect' (and other changes in drinking behaviour) were identified in Chapter 7. Based on these findings, there are several exclusion scenarios that would be expected to decrease bias from the 'sick-quitter effect' in the cancer main analysis: exclusion of participants with a physical functioning score < 50%, exclusion of participants that consumed < 7 drinks per week, exclusion of cancer cases diagnosed within one year of baseline (analogous to the exclusion of deaths within three years of baseline when examining mortality as an outcome), and exclusion of participants aged ≥ 65 years at baseline. For analyses aimed at identifying a linear trend between alcohol and risk, a method that would be expected to *increase* bias from the 'sick-quitter effect' would be the inclusion of non-drinkers in the calculation. As some of these exclusion scenarios include a large proportion of cases, these analyses were only investigated for all cancers combined.

Fully adjusted HRs and 95% CIs for risk of all cancers combined were estimated from Cox Proportional Hazards models (as per the main results) under each 'exclusion scenario' noted above,

and directly compared with the main results. These models were conducted for total alcohol consumption as a log-linear variable.

Cancer-specific HRs and 95% CIs were then calculated for total alcohol consumption, drinking frequency, and drinks per drinking-day after exclusion of participants with a physical functioning score < 50%. Overall drinking pattern, incorporating both number of drinking-days and number of drinks per drinking-day was assessed for all cancers combined, and colorectal, colon, and kidney cancer. The low physical functioning score exclusion scenario was selected for these more detailed analyses based on the conclusion in Chapter 7 that it was likely the most effective exclusion scenario examined to assess bias from the 'sick-quitter effect'.

For the continuous log-linear analysis estimating the increase in risk per additional drink/day, the sensitivity tests excluding participants with a physical functioning score < 50% and restricting the calculation to participants consuming ≥ 7 drinks per week were performed (as this exclusion was intended to be applied to the log-linear analysis specifically).

Results. None of the sensitivity analyses materially altered the log-linear association between alcohol consumption and risk of all cancers combined (Figure 8.1).

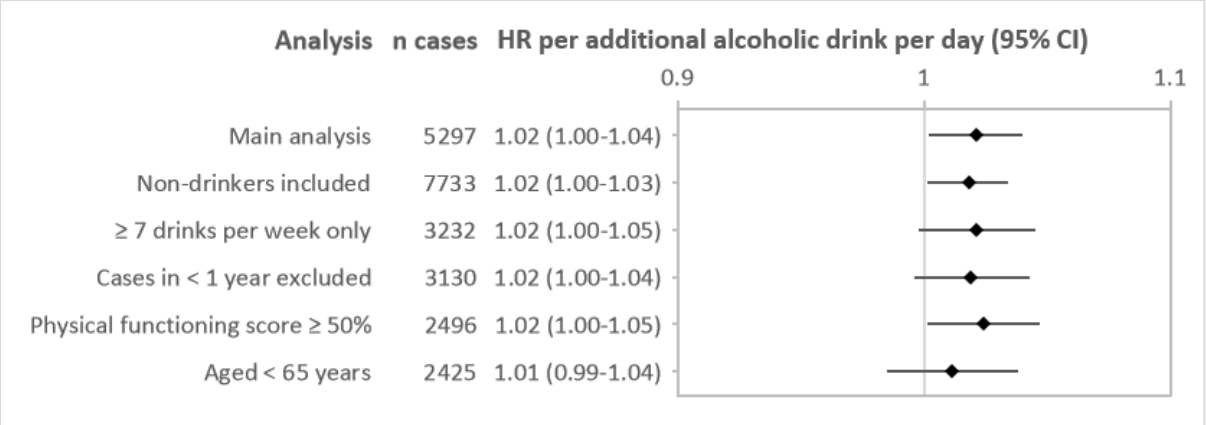

Figure 8.1. Hazard ratios (HR) and 95% confidence intervals (CI) of risk of all cancers combined per one drink increase in mean daily alcohol consumption among drinkers by different exclusion scenarios in the 45 and Up Study (2006-2010), New South Wales, Australia. Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, hormone replacement therapy use (women), aspirin use and bowel screening history.

The sensitivity analyses excluding participants with a low physical functioning score resulted in several risk estimates that differed from the main results and are presented in Tables 8.1-8.4. For categorical total alcohol consumption, there were significant trends of increased risk for cancers of the mouth and pharynx, oesophagus (squamous cell carcinoma) and liver (Table 8.1). The trends for laryngeal cancer, non-Hodgkin lymphoma (NHL) and all cancers combined were non-significant, however the hazard ratios were not materially different compared to the main analysis. There was also evidence of lower risk in those consuming '> 3.5 and ≤ 7' and '> 14 and ≤ 28' drinks per week for bladder cancer, and that those consuming '> 7 and ≤ 14' and '> 14 and ≤ 28' drinks per week had higher risk of melanoma compared to non-drinkers. For drinking-days per week, the inverse association of drinking frequency with all cancer risk was non-significant however the hazard ratio was not materially different compared to the main analysis (Table 8.2). There were no other changes in results.

For mean drinks per drinking-day, a significant trend of increased risk of cancer of the oesophagus was detected (Table 8.3). The associations for kidney cancer and non-alcohol-related cancer were non-significant, however the hazard ratios were not materially different compared to the main anlaysis. There was also evidence of higher risk in those consuming > 2 and ≤ 4 drinks per drinking-day for lung cancer. For the overall drinking pattern sensitivity analysis, consuming > 2 and ≤ 4 drinks on 1-2 days per week was associated with significant decreased risk for colon cancer, while consuming > 4 drinks on 1-2 days per week was non-significant for all cancers combined, but the hazard ratios were not materially different compared to the main analysis (Table 8.4). There were no other notable differences in results.

Table 8.1. Hazard ratios and 95% confidence intervals of cancer risk by alcohol consumption after excluding participants with physical functioning score < 50% at baseline in the 45 and Up Study (2006-2010), New South Wales, Australia.

		Drinks/week							
Cancer type (ICD-10 code)	**n cases**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Mouth and pharynx (C00-14)	107	0.70 (0.39-1.27)	1.00	0.47 (0.23-0.97)	0.89 (0.47-1.67)	1.03 (0.51-2.07)	2.06 (0.97-4.41)	0.02	0.01
Oesophagus (C15)	51	1.10 (0.45-2.67)	1.00	1.08 (0.42-2.79)	0.41 (0.12-1.41)	0.84 (0.27-2.55)	1.89 (0.61-5.92)	0.32	0.17
- Adenocarcinoma (C15)	32	0.75 (0.26-2.15)	1.00	0.96 (0.33-2.78)	0.23 (0.05-1.15)	0.61 (0.17-2.20)	0.94 (0.22-3.98)	0.54	0.94
- Squamous cell carcinoma (C15)	17	2.68 (0.33-22.1)	1.00	2.00 (0.21-19.3)	0.83 (0.05-13.4)	2.69 (0.23-31.5)	10.9 (1.01-117.9)	0.21	0.02
Colorectum (C18-20)	722	1.08 (0.86-1.37)	1.00	0.82 (0.63-1.08)	1.04 (0.80-1.35)	1.04 (0.77-1.39)	1.42 (1.00-2.04)	0.052	0.03
- Colon (C18-19)	476	1.14 (0.86-1.53)	1.00	0.83 (0.60-1.16)	0.99 (0.71-1.38)	1.10 (0.76-1.59)	1.67 (1.07-2.62)	0.04	0.01
- Rectum (C20)	252	0.94 (0.63-1.41)	1.00	0.78 (0.49-1.22)	1.08 (0.70-1.65)	0.90 (0.55-1.46)	1.18 (0.67-2.07)	0.63	0.51
Liver (C22)	42	1.96 (0.65-5.92)	1.00	0.97 (0.26-3.62)	0.80 (0.20-3.21)	1.65 (0.45-5.99)	3.76 (1.04-13.5)	0.11	0.03
Larynx (C32)	25	1.32 (0.25-6.88)	1.00	0.32 (0.03-3.53)	1.05 (0.19-5.79)	2.43 (0.50-11.8)	2.48 (0.46-13.4)	0.32	0.08
Breast (C50[e])	816	1.02 (0.83-1.27)	1.00	1.17 (0.94-1.47)	1.23 (0.97-1.56)	1.63 (1.21-2.20)	0.52 (0.16-1.63)	0.008	0.04
Alcohol-related (C00-15;18-20;22;32;50[d])	1,761	1.03 (0.89-1.19)	1.00	0.96 (0.81-1.13)	1.07 (0.91-1.27)	1.22 (1.01-1.49)	1.60 (1.24-2.08)	0.002	< 0.001
Stomach (C16)	77	1.51 (0.71-3.24)	1.00	1.19 (0.51-2.77)	1.22 (0.52-2.88)	1.28 (0.50-3.32)	1.69 (0.54-5.27)	0.89	0.30
Pancreas (C25)	107	1.35 (0.69-2.62)	1.00	1.56 (0.79-3.11)	1.04 (0.49-2.22)	1.74 (0.81-3.71)	0.55 (0.12-2.48)	0.37	0.89
Lung (C33-34)	339	0.88 (0.61-1.25)	1.00	1.00 (0.68-1.46)	0.91 (0.62-1.34)	1.18 (0.79-1.77)	0.80 (0.45-1.43)	0.58	0.69
Melanoma (C43)	711	0.80 (0.62-1.02)	1.00	0.88 (0.68-1.13)	1.13 (0.88-1.44)	1.19 (0.90-1.56)	0.95 (0.63-1.43)	0.01	0.30
Endometrium (C54.1)	95	1.51 (0.82-2.80)	1.00	0.69 (0.30-1.58)	1.32 (0.61-2.85)	1.37 (0.48-3.91)	-[e]	0.32	0.54
Ovary (C56)	52	0.67 (0.32-1.39)	1.00	0.33 (0.12-0.95)	0.93 (0.39-2.18)	1.29 (0.44-3.80)	-[e]	0.29	0.75
Prostate (C61)	1,636	0.88 (0.74-1.04)	1.00	0.98 (0.83-1.17)	0.98 (0.83-1.16)	1.06 (0.88-1.26)	1.03 (0.82-1.29)	0.37	0.49
Kidney (C64)	118	1.31 (0.69-2.52)	1.00	1.41 (0.72-2.75)	1.30 (0.66-2.57)	1.16 (0.55-2.46)	1.33 (0.54-3.29)	0.95	0.94
Bladder (C67)	92	0.76 (0.43-1.35)	1.00	0.33 (0.16-0.71)	0.61 (0.33-1.16)	0.32 (0.13-0.77)	0.52 (0.19-1.42)	0.03	0.15
Brain (C71)	71	1.02 (0.48-2.17)	1.00	1.14 (0.54-2.42)	0.81 (0.37-1.81)	0.39 (0.13-1.15)	0.75 (0.23-2.43)	0.44	0.30
Thyroid (C73)	79	1.01 (0.54-1.89)	1.00	1.08 (0.54-2.13)	0.66 (0.29-1.49)	0.26 (0.06-1.17)	0.42 (0.05-3.29)	0.38	0.09
Non-Hodgkin lymphoma (C82-85)	198	0.84 (0.55-1.28)	1.00	0.73 (0.46-1.16)	0.96 (0.61-1.50)	0.63 (0.36-1.13)	0.48 (0.18-1.23)	0.36	0.09
Multiple myeloma (C90.0)	64	2.07 (0.89-4.80)	1.00	1.03 (0.39-2.70)	0.74 (0.26-2.12)	1.47 (0.53-4.03)	1.83 (0.62-6.47)	0.14	0.19
Leukaemia (C91-95)	104	1.03 (0.58-1.83)	1.00	0.75 (0.39-1.43)	0.65 (0.33-1.27)	0.53 (0.24-1.17)	0.66 (0.24-1.83)	0.43	0.33
Other (Other C;D45-47)	377	1.16 (0.84-1.59)	1.00	0.72 (0.49-1.04)	1.06 (0.74-1.51)	1.04 (0.69-1.57)	0.84 (0.46-1.53)	0.09	0.71
Non-alcohol-related (Other C;D45-47)	4,125	0.95 (0.86-1.05)	1.00	0.91 (0.82-1.01)	0.99 (0.89-1.11)	1.02 (0.91-1.15)	0.91 (0.78-1.07)	0.22	0.99
All cancer (C00-97;D45-47)	5,883	0.98 (0.90-1.06)	1.00	0.92 (0.84-1.01)	1.02 (0.93-1.11)	1.07 (0.97-1.18)	1.03 (0.90-1.18)	0.06	0.06

Models were adjusted for cancers-specific covariates as shown in article Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Female breast cancer only. [e]Zero cases in cell. ICD-10, International Classification of Diseases, version 10.

Table 8.2. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk after excluding participants with physical functioning score < 50% by drinking-days per week among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

		HR drinking-days per week in main analysis - adjusted for total alcohol consumption (95% CI)						HR drinking-days per week in sensitivity analysis[a] - adjusted for total alcohol consumption (95% CI)				
Cancer type (ICD-10 code)	**n cases**	**1-2**	**3-5**	**6-7**	***p*[b]**	***p*$_{trend}$[c]**	**n cases**	**1-2**	**3-5**	**6-7**	***p*[b]**	***p*$_{trend}$[c]**
Mouth and pharynx (C00-14)	114	1.00	0.81 (0.50-1.32)	0.66 (0.38-1.14)	0.34	0.14	79	1.00	0.76 (0.42-1.38)	0.62 (0.32-1.21)	0.37	0.16
Oesophagus (C15)	50	1.00	0.81 (0.35-1.88)	1.07 (0.48-2.40)	0.77	0.81	34	1.00	0.78 (0.30-2.01)	0.64 (0.24-1.70)	0.67	0.37
- Adenocarcinoma (C15)	33	1.00	0.77 (0.27-2.19)	1.09 (0.40-2.99)	0.76	0.80	23	1.00	1.11 (0.35-3.47)	0.84 (0.24-2.96)	0.88	0.76
- Squamous cell carcinoma (C15)	15	1.00	1.36 (0.29-6.42)	1.49 (0.32-6.98)	0.87	0.62	10	1.00	0.45 (0.07-2.81)	0.45 (0.08-2.63)	0.60	0.39
Colorectum (C18-20)	630	1.00	0.87 (0.70-1.08)	0.84 (0.67-1.06)	0.31	0.16	480	1.00	0.94 (0.73-1.21)	0.92 (0.70-1.21)	0.83	0.58
- Colon (C18-19)	414	1.00	0.91 (0.69-1.19)	0.77 (0.58-1.03)	0.19	0.07	302	1.00	0.94 (0.68-1.29)	0.78 (0.55-1.11)	0.32	0.15
- Rectum (C20)	220	1.00	0.76 (0.52-1.11)	0.95 (0.64-1.40)	0.28	0.90	182	1.00	0.88 (0.57-1.35)	1.14 (0.73-1.78)	0.41	0.47
Liver (C22)	31	1.00	0.78 (0.26-2.38)	1.54 (0.54-4.33)	0.39	0.34	25	1.00	0.41 (0.10-1.68)	1.42 (0.46-4.37)	0.17	0.38
Larynx (C32)	29	1.00	1.37 (0.34-5.62)	2.01 (0.52-7.76)	0.53	0.26	20	1.00	0.58 (0.11-2.96)	1.25 (0.30-5.22)	0.53	0.54
Breast (C50[d])	630	1.00	1.16 (0.94-1.42)	0.95 (0.74-1.23)	0.12	0.73	528	1.00	1.18 (0.94-1.48)	0.95 (0.71-1.27)	0.11	0.76
Alcohol-related (C00-15;18-20;22;32;50[d])	1483	1.00	0.99 (0.86-1.13)	0.89 (0.76-1.04)	0.25	0.14	1166	1.00	1.00 (0.86-1.17)	0.89 (0.75-1.07)	0.28	0.20
Stomach (C16)	66	1.00	0.80 (0.41-1.56)	0.71 (0.35-1.43)	0.62	0.34	49	1.00	0.76 (0.34-1.67)	0.80 (0.35-1.85)	0.78	0.64
Pancreas (C25)	93	1.00	0.97 (0.56-1.68)	0.71 (0.38-1.32)	0.45	0.26	72	1.00	1.20 (0.62-2.29)	0.94 (0.45-1.93)	0.68	0.79
Lung (C33-34)	348	1.00	0.78 (0.57-1.07)	0.94 (0.69-1.28)	0.27	0.82	240	1.00	0.82 (0.56-1.19)	0.97 (0.66-1.42)	0.49	1.00
Melanoma (C43)	651	1.00	1.05 (0.85-1.31)	0.95 (0.75-1.21)	0.59	0.63	537	1.00	1.04 (0.82-1.31)	0.97 (0.74-1.27)	0.85	0.81
Endometrium (C54.1)	52	1.00	0.91 (0.43-1.93)	1.30 (0.55-3.08)	0.64	0.55	42	1.00	0.93 (0.41-2.13)	1.33 (0.50-3.57)	0.69	0.57
Ovary (C56)	39	1.00	0.75 (0.33-1.67)	0.55 (0.19-1.57)	0.53	0.26	32	1.00	0.95 (0.39-2.34)	0.73 (0.23-2.31)	0.83	0.59
Prostate (C61)	1524	1.00	0.95 (0.82-1.09)	0.96 (0.82-1.12)	0.76	0.65	1302	1.00	0.93 (0.79-1.08)	0.94 (0.79-1.11)	0.61	0.49
Kidney (C64)	105	1.00	0.83 (0.50-1.38)	0.63 (0.35-1.13)	0.30	0.12	85	1.00	1.08 (0.61-1.92)	0.79 (0.40-1.54)	0.52	0.45
Bladder (C67)	78	1.00	0.61 (0.33-1.15)	0.57 (0.30-1.08)	0.17	0.10	59	1.00	0.54 (0.26-1.12)	0.57 (0.27-1.18)	0.19	0.15
Brain (C71)	65	1.00	0.75 (0.40-1.41)	0.62 (0.29-1.33)	0.46	0.22	52	1.00	0.92 (0.46-1.84)	0.58 (0.24-1.42)	0.42	0.24
Thyroid (C73)	55	1.00	0.84 (0.43-1.62)	0.52 (0.20-1.37)	0.41	0.21	47	1.00	0.77 (0.38-1.58)	0.50 (0.18-1.40)	0.42	0.19
Non-Hodgkin lymphoma (C82-85)	174	1.00	1.15 (0.77-1.72)	0.97 (0.61-1.56)	0.61	0.88	140	1.00	0.98 (0.63-1.54)	0.90 (0.53-1.53)	0.91	0.70
Multiple myeloma (C90.0)	51	1.00	1.14 (0.52-2.52)	1.11 (0.47-2.61)	0.95	0.84	37	1.00	0.79 (0.30-2.10)	1.11 (0.41-3.00)	0.73	0.75
Leukaemia (C91-95)	91	1.00	0.67 (0.39-1.17)	0.61 (0.33-1.14)	0.24	0.12	68	1.00	0.63 (0.33-1.19)	0.59 (0.28-1.21)	0.26	0.15
Other (Other C;D45-47)	339	1.00	0.96 (0.71-1.30)	1.14 (0.83-1.57)	0.49	0.39	238	1.00	0.99 (0.68-1.42)	1.35 (0.91-1.99)	0.14	0.11
Non-alcohol-related (Other C;D45-47)	3738	1.00	0.92 (0.85-1.01)	0.92 (0.83-1.01)	0.15	0.09	3003	1.00	0.93 (0.84-1.03)	0.94 (0.84-1.05)	0.34	0.64
All cancer (C00-97;D45-47)	5217	1.00	0.94 (0.87-1.02)	0.91 (0.84-0.99)	0.07	0.03	4166	1.00	0.95 (0.87-1.03)	0.93 (0.85-1.02)	0.30	0.14

Non-drinkers were excluded. Models were adjusted for total alcohol consumption and cancer-specific covariates as listed in article Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Participants with physical functioning score < 50% excluded. [b]Overall. [c]Linear trend using median number of drinking-days per week of each category. [d]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Table 8.3. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk after excluding participants with physical functioning score < 50% by mean drinks per drinking-day among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

		HR mean drinks per drinking-day in main analysis - adjusted for total alcohol consumption (95% CI)						HR mean drinks per drinking-day in sensitivity analysis[a] - adjusted for total alcohol consumption (95% CI)				
Cancer type (ICD-10 code)	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[b]**	***p*$_{trend}$[c]**	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[b]**	***p*$_{trend}$[c]**
Mouth and pharynx (C00-14)	114	1.00	1.46 (0.90-2.37)	2.45 (1.22-4.92)	0.04	0.01	79	1.00	1.45 (0.80-2.60)	2.91 (1.26-6.74)	0.04	0.01
Oesophagus (C15)	50	1.00	1.08 (0.50-2.35)	2.76 (1.01-7.53)	0.09	0.054	34	1.00	1.18 (0.45-3.10)	4.55 (1.36-15.2)	0.03	0.02
- Adenocarcinoma (C15)	33	1.00	0.88 (0.35-2.23)	1.51 (0.40-5.71)	0.68	0.59	23	1.00	1.08 (0.34-3.45)	2.75 (0.55-13.7)	0.41	0.25
- Squamous cell carcinoma (C15)	15	1.00	1.88 (0.42-8.53)	9.04 (1.71-47.7)	0.03	0.009	10	1.00	2.28 (0.33-15.6)	19.4 (2.52-148.9)	0.01	0.003
Colorectum (C18-20)	630	1.00	0.81 (0.65-1.01)	1.15 (0.81-1.62)	0.03	0.74	480	1.00	0.85 (0.66-1.09)	1.36 (0.92-2.00)	0.02	0.25
- Colon (C18-19)	414	1.00	0.75 (0.57-0.99)	1.26 (0.83-1.94)	0.01	0.57	302	1.00	0.82 (0.59-1.14)	1.76 (1.09-2.86)	0.003	0.06
- Rectum (C20)	220	1.00	0.88 (0.62-1.26)	0.99 (0.56-1.75)	0.75	0.88	182	1.00	0.87 (0.59-1.28)	0.92 (0.49-1.72)	0.78	0.71
Liver (C22)	31	1.00	0.84 (0.32-2.21)	1.56 (0.47-5.14)	0.56	0.48	25	1.00	0.83 (0.29-2.40)	1.46 (0.38-5.55)	0.67	0.59
Larynx (C32)	29	1.00	1.23 (0.50-3.05)	0.48 (0.10-2.20)	0.33	0.37	20	1.00	1.20 (0.40-3.60)	0.39 (0.07-2.32)	0.33	0.30
Breast (C50[e])	630	1.00	1.26 (1.01-1.58)	1.24 (0.76-2.03)	0.13	0.11	528	1.00	1.25 (0.98-1.59)	1.08 (0.61-1.91)	0.19	0.29
Alcohol-related (C00-15;18-20;22;32;50[d])	1483	1.00	1.02 (0.89-1.17)	1.33 (1.04-1.69)	0.047	0.04	1166	1.00	1.04 (0.89-1.22)	1.42 (1.08-1.87)	0.03	0.02
Stomach (C16)	66	1.00	1.15 (0.60-2.22)	1.55 (0.54-4.43)	0.72	0.42	49	1.00	1.09 (0.51-2.35)	2.13 (0.68-6.68)	0.38	0.22
Pancreas (C25)	93	1.00	1.03 (0.59-1.81)	0.60 (0.19-1.87)	0.56	0.48	72	1.00	0.96 (0.51-1.81)	0.45 (0.12-1.77)	0.46	0.33
Lung (C33-34)	348	1.00	1.40 (1.06-1.84)	1.46 (0.93-2.30)	0.051	0.06	240	1.00	1.66 (1.19-2.30)	1.51 (0.86-2.67)	0.01	0.07
Melanoma (C43)	651	1.00	1.10 (0.89-1.35)	1.05 (0.72-1.52)	0.65	0.68	537	1.00	1.10 (0.88-1.38)	1.00 (0.66-1.52)	0.63	0.85
Endometrium (C54.1)	52	1.00	1.04 (0.45-2.39)	-[e]	1.00	0.27	42	1.00	0.92 (0.35-2.40)	-[e]	0.98	0.33
Ovary (C56)	39	1.00	3.54 (1.51-8.32)	-[e]	0.02	0.16	32	1.00	2.84 (1.08-7.42)	-[e]	0.11	0.41
Prostate (C61)	1524	1.00	1.14 (1.00-1.30)	1.12 (0.90-1.39)	0.13	0.22	1302	1.00	1.14 (0.99-1.31)	1.13 (0.89-1.44)	0.18	0.23
Kidney (C64)	105	1.00	1.13 (0.67-1.90)	2.61 (1.24-5.47)	0.03	0.02	85	1.00	0.97 (0.55-1.74)	2.15 (0.94-4.94)	0.10	0.09
Bladder (C67)	78	1.00	0.64 (0.34-1.21)	0.46 (0.14-1.51)	0.30	0.15	59	1.00	0.56 (0.27-1.15)	0.32 (0.08-1.34)	0.19	0.08
Brain (C71)	65	1.00	0.75 (0.38-1.49)	0.97 (0.31-3.02)	0.67	0.82	52	1.00	0.67 (0.30-1.48)	1.44 (0.43-4.79)	0.30	0.76
Thyroid (C73)	55	1.00	1.04 (0.46-2.34)	2.52 (0.73-8.75)	0.31	0.23	47	1.00	1.11 (0.46-2.63)	3.34 (0.93-12.0)	0.16	0.11
Non-Hodgkin lymphoma (C82-85)	174	1.00	0.90 (0.59-1.38)	0.58 (0.24-1.38)	0.46	0.25	140	1.00	0.86 (0.54-1.39)	0.66 (0.26-1.71)	0.68	0.38
Multiple myeloma (C90.0)	51	1.00	1.22 (0.59-2.53)	1.15 (0.31-4.22)	0.87	0.76	37	1.00	1.45 (0.62-3.40)	1.61 (0.36-7.27)	0.69	0.48
Leukaemia (C91-95)	91	1.00	0.81 (0.44-1.47)	1.71 (0.70-4.15)	0.19	0.36	68	1.00	0.69 (0.33-1.42)	2.04 (0.74-5.62)	0.07	0.30
Other (Other C;D45-47)	339	1.00	1.08 (0.80-1.45)	1.50 (0.93-2.40)	0.23	0.11	238	1.00	0.84 (0.59-1.19)	0.93 (0.51-1.72)	0.60	0.67
Non-alcohol-related (Other C;D45-47)	3738	1.00	1.12 (1.03-1.22)	1.14 (0.98-1.32)	0.03	0.04	3003	1.00	1.10 (1.00-1.21)	1.11 (0.94-1.31)	0.13	0.14
All cancer (C00-97;D45-47)	5217	1.00	1.10 (1.02-1.18)	1.17 (1.04-1.33)	0.01	0.007	4166	1.00	1.09 (1.00-1.18)	1.17 (1.02-1.35)	0.052	0.02

Non-drinkers were excluded. Models were adjusted for total alcohol consumption and cancer-specific covariates as listed in article Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Participants with physical functioning score < 50% excluded. [b]Overall. [c]Linear trend using median number of drinks per drinking-day of each category. [d]Female breast cancer only. [e]Zero cases in cell. ICD-10, International Classification of Diseases, version 10.

Table 8.4. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk after excluding participants with physical functioning score < 50% by drinking pattern among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

			HR mean drinks per drinking-day in main analysis (95% CI)				HR mean drinks per drinking-day in sensitivity analysis[a] (95% CI)		
Cancer type	**Drinking-days per week**	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	**n cases**	**≤ 2**	**> 2 and ≤ 4**	**> 4**
Colorectum	1-2	630	1.00	0.54 (0.32-0.91)	0.99 (0.58-1.67)	480	1.00	0.45 (0.23-0.87)	0.90 (0.47-1.75)
	3-5		0.91 (0.71-1.16)	0.69 (0.47-1.01)	1.04 (0.62-1.75)		0.87 (0.65-1.16)	0.81 (0.54-1.21)	1.35 (0.79-2.30)
	6-7		0.81 (0.64-1.04)	0.92 (0.69-1.23)	1.47 (1.06-2.02)		0.86 (0.64-1.14)	0.89 (0.64-1.25)	1.50 (1.04-2.17)
Colon	1-2	414	1.00	0.50 (0.25-1.00)	0.97 (0.48-1.94)	302	1.00	0.40 (0.16-0.99)	1.17 (0.53-2.60)
	3-5		0.99 (0.74-1.34)	0.64 (0.39-1.05)	1.26 (0.66-2.40)		0.95 (0.66-1.35)	0.75 (0.44-1.28)	1.75 (0.90-3.41)
	6-7		0.77 (0.57-1.04)	0.89 (0.62-1.29)	1.82 (1.23-2.69)		0.76 (0.53-1.09)	0.86 (0.56-1.32)	1.85 (1.17-2.92)
Kidney	1-2	105	1.00	1.64 (0.67-4.03)	3.55 (1.49-8.48)	85	1.00	1.75 (0.59-5.17)	4.06 (1.44-11.5)
	3-5		0.91 (0.45-1.83)	1.29 (0.59-2.83)	2.59 (1.03-6.49)		1.34 (0.60-2.98)	1.68 (0.69-4.11)	3.09 (1.08-8.81)
	6-7		1.26 (0.67-2.38)	0.58 (0.24-1.38)	0.70 (0.25-1.95)		1.73 (0.81-3.71)	0.65 (0.23-1.83)	1.02 (0.34-3.08)
All cancer	1-2	5217	1.00	1.01 (0.88-1.17)	1.27 (1.07-1.52)	4166	1.00	0.98 (0.83-1.15)	1.21 (0.99-1.49)
	3-5		0.96 (0.88-1.05)	1.08 (0.97-1.21)	1.02 (0.85-1.23)		0.94 (0.85-1.04)	1.07 (0.94-1.21)	1.09 (0.89-1.33)
	6-7		0.95 (0.87-1.03)	1.06 (0.96-1.17)	1.11 (0.98-1.26)		0.95 (0.86-1.05)	1.04 (0.93-1.16)	1.07 (0.92-1.23)

Non-drinkers were excluded. Models were adjusted for total alcohol consumption and cancer-specific covariates as listed in article Supplementary Table 1.

[a]Participants with physical functioning score < 50% excluded.

The sensitivity analyses for the continuous log-linear association between alcohol consumption and cancer risk for two exclusion scenarios (the exclusion of participants with a low physical functioning score and the exclusion of participants consuming < 7 drinks per week) are shown in Table 8.5. Both sensitivity analyses resulted in several risk estimates that differed from the main results. Specifically, the sensitivity analysis excluding participants with a low physical functioning score resulted in significant positive associations for mouth and pharynx and oesophageal cancer (squamous cell carcinoma), which were not observed in the main analysis. Associations for breast cancer, thyroid cancer and all cancers combined in men observed in the main analysis were non-significant, but there were no material differences in the hazard ratios compared to the main analysis. For the sensitivity analysis that excluded participants consuming < 7 drinks per week, the associations for breast and thyroid cancer observed in the main analysis were non-significant, and the hazard ratios moved closer toward the null in comparison to the main analysis. All cancers combined in men was also non-significant, but there was no material difference in hazard ratio compared to the main analysis. Risk estimates for cancer of the colorectum and colon were increased compared to the main analysis.

Table 8.5. Hazard ratios (HR) and 95% confidence intervals (CI) of cancer risk per one drink increase in mean daily alcohol consumption after excluding participants with physical functioning score < 50% or those consuming < 7 drinks per week among drinkers in the 45 and Up Study (2006-2010), New South Wales, Australia.

	Main analysis		Excluding MOS-PF < 50%		Excluding < 7 drinks/week	
Cancer type (ICD-10 code)	**n cases**	**HR (95% CI)**	**n cases**	**HR (95% CI)**	**n cases**	**HR (95% CI)**
Mouth and pharynx (C00-14)	116	1.04 (0.94-1.15)	80	1.13 (1.00-1.27)	75	0.99 (0.87-1.13)
Oesophagus (C15)	50	1.06 (0.91-1.23)	34	1.07 (0.89-1.30)	30	1.08 (0.92-1.27)
- Adenocarcinoma (C15)	33	1.02 (0.84-1.24)	23	0.93 (0.69-1.25)	19	1.05 (0.85-1.29)
- Squamous cell carcinoma (C15)	15	1.16 (0.91-1.46)	10	1.30 (1.02-1.67)	10	1.22 (0.92-1.60)
Colorectum (C18-20)	641	1.07 (1.02-1.12)	488	1.06 (1.01-1.12)	376	1.10 (1.04-1.16)
- Colon (C18-19)	422	1.10 (1.04-1.17)	308	1.09 (1.02-1.17)	242	1.15 (1.08-1.23)
- Rectum (C20)	223	1.03 (0.96-1.12)	184	1.04 (0.95-1.13)	137	1.03 (0.94-1.13)
Liver (C22)	33	1.09 (0.94-1.26)	26	1.12 (0.96-1.32)	24	1.05 (0.88-1.26)
Larynx (C32)	29	1.18 (1.02-1.36)	20	1.19 (1.01-1.40)	24	1.18 (1.00-1.39)
Breast (C50[a])	643	1.09 (1.01-1.18)	538	1.07 (0.98-1.17)	332	1.03 (0.92-1.16)
Alcohol-related (C00-15;18-20;22;32;50[a])	1,511	1.07 (1.04-1.11)	1,186	1.08 (1.04-1.12)	860	1.08 (1.04-1.13)
- Men	598	1.07 (1.03-1.12)	453	1.08 (1.03-1.13)	402	1.08 (1.03-1.13)
- Women	913	1.07 (1.00-1.14)	733	1.07 (0.99-1.15)	458	1.05 (0.95-1.15)
Stomach (C16)	67	1.08 (0.93-1.25)	50	1.08 (0.91-1.29)	39	1.07 (0.89-1.28)
Pancreas (C25)	97	1.00 (0.86-1.16)	73	1.03 (0.88-1.21)	53	1.12 (0.94-1.33)
Lung (C33-34)	357	0.98 (0.92-1.05)	243	0.97 (0.89-1.05)	230	0.97 (0.90-1.06)
Melanoma (C43)	660	1.05 (0.99-1.10)	544	1.05 (0.99-1.11)	411	1.04 (0.98-1.11)
Endometrium (C54.1)	52	1.11 (0.85-1.45)	42	1.07 (0.78-1.48)	25	1.24 (0.87-1.78)
Ovary (C56)	39	0.97 (0.67-1.40)	32	1.05 (0.73-1.52)	16	1.21 (0.80-1.84)
Prostate (C61)	1,539	1.02 (0.99-1.05)	1,315	1.01 (0.97-1.04)	1037	1.02 (0.98-1.06)
Kidney (C64)	107	0.97 (0.86-1.11)	86	0.99 (0.86-1.14)	67	0.95 (0.81-1.13)
Bladder (C67)	80	0.96 (0.82-1.12)	61	0.96 (0.81-1.15)	47	1.00 (0.83-1.19)
Brain (C71)	65	0.95 (0.79-1.14)	52	0.89 (0.71-1.12)	35	0.97 (0.77-1.21)
Thyroid (C73)	55	0.70 (0.50-0.98)	47	0.72 (0.51-1.04)	16	0.87 (0.54-1.39)
Non-Hodgkin lymphoma (C82-85)	174	0.88 (0.77-1.00)	140	0.89 (0.77-1.03)	94	0.98 (0.75-1.06)
Multiple myeloma (C90.0)	51	1.04 (0.87-1.24)	37	1.09 (0.89-1.34)	32	0.98 (0.77-1.25)
Leukaemia (C91-95)	93	0.93 (0.79-1.09)	69	0.93 (0.77-1.11)	53	0.93 (0.75-1.14)
Other (Other C;D45-47)	347	1.02 (0.95-1.10)	239	1.03 (0.94-1.12)	219	0.99 (0.90-1.08)
Non-alcohol-related (Other C;D45-47)	3,790	1.01 (0.98-1.03)	3,033	1.00 (0.98-1.02)	2,375	1.00 (0.98-1.03)
All cancer (C00-97;D45-47)	5,297	1.02 (1.00-1.04)	3,496	1.02 (1.00-1.05)	3,232	1.02 (1.00-1.05)
- Men	3,578	1.02 (1.00-1.04)	2,859	1.02 (1.00-1.04)	2,393	1.02 (1.00-1.05)
- Women	1,719	1.03 (0.98-1.08)	1,357	1.04 (0.98-1.10)	839	1.04 (0.97-1.12)

Non-drinkers were excluded. Models were adjusted for cancer-specific covariates as listed in article Supplementary Table 1. Cancer cases do not sum to totals as some participants were diagnosed with two primary cancers in the same month. [a]Female breast cancer only. ICD, International Classification of Diseases, version 10. MOS-PF, Medical Outcomes Study Physical Functioning score.

Conclusions. There was no material difference in the magnitude of the log-linear association between total alcohol consumption and risk of all cancers combined according to different exclusion scenarios aimed to assess the extent of bias from the 'sick-quitter effect'. This suggests that the results for all cancers combined were robust and unlikely to be impacted importantly by bias from the 'sick-quitter effect'.

Nevertheless, important differences were found for individual cancer types in two of the sensitivity analyses examined. That is, when participants with a physical functioning score < 50% or consuming < 7 drinks per week were excluded. In the majority of cases where trends were significant in the main analysis and non-significant in the sensitivity analyses there was no material change in hazard ratios, with the exception of breast and thyroid cancer.

The sensitivity test restricting the calculation to participants consuming ≥ 7 drinks per week suggested that the association between alcohol consumption and lower risk of thyroid cancer may be at least partially accounted for by bias from changes in drinking in response to ill-health. The finding that breast cancer risk may be overestimated was unexpected. For the sensitivity test restricting the calculation to participants consuming ≥ 7 drinks per week, this may be due to the fact that a non-linear relationship was found in the cubic spline analysis, with a plateauing of risk after approximately 7 drinks per week. The loss of significance may also reflect inadequate statistical power as the number of cases decreased by 48%. Therefore, further research is required to investigate the impact of confounding by the 'sick-quitter effect' on effect estimates for all cancer types, but for breast cancer risk in particular.

There were few changes when examining drinking pattern, suggesting these results were robust and unlikely to be impacted importantly by bias from the 'sick-quitter effect'. There was evidence of a positive association between with mean drinks per drinking-day and risk of cancer of the oesophagus (both subtypes combined). It should be noted however that the sensitivity test could not be expected to remove all bias, and so inverse associations for drinking frequency and all cancers

combined, and for colorectal and colon cancer in the overall drinking pattern analysis, are not necessarily causal.

2. *Population attributable fractions, cumulative absolute risk of cancer diagnosis and number of persons needed to quit or reduce drinking to prevent one cancer case.*

Rationale and methods. The population attributable fraction (PAF) for alcohol consumption and cancer in Australia has previously been estimated using internationally-derived relative risks[1]. It is possible that risk may differ between populations, and so it is of interest to investigate how the hazard ratios derived from the 45 and Up Study can be used to calculate estimates for population attributable fractions, as well as other outcomes which may have public health importance. Thus, the results of the continuous log-linear analysis in the main analysis were used to calculate three further results: PAF for cancer cases attributable to alcohol consumption in Australia in 2010, cumulative absolute risk of cancer diagnosis between the ages of 45 and 75 years by level of alcohol consumption, and number of persons needed to quit or reduce drinking by age 45 years to prevent one cancer case by age 75 years. Due to the significant interactions with sex for total alcohol consumption and risk of alcohol-related and all cancer observed in the main analysis, sex-specific hazard ratios were used in the calculations for these two cancer outcomes.

The PAF calculations were performed using the same method as Pandeya et al., (2015), which relied on log-linear conversions of international relative risks to estimate PAFs for Australia in 2010[1]. The exact lag time between alcohol consumption and the occurrence of cancer is unknown, however Pandeya et al., (2015) assumed a lag time of nine years, attributing cancer incidence in 2010 to sex- and age-specific alcohol consumption in the 2001 National Health Survey (2001 alcohol consumption data shown in Supplementary Table 2[1]). A full description of the methods used to calculate PAFs, cumulative absolute risk of cancer diagnosis and number of persons needed to quit or reduce drinking to prevent one cancer case are presented in Appendix E.3.

Results. The population attributable fraction calculations for alcohol consumption and cancer in Australia in 2010 are shown in Table 8.6. At 2.5%, the estimated PAF for all cancers combined was similar to that obtained by Pandeya et al., (2015) with international relative risks, and did not materially differ when using hazard ratios derived from either of the two sensitivity tests. Regarding individual cancer types, the estimates for the main analysis were lower for cancers of the mouth and pharynx and rectum, similar for cancers of the oesophagus, liver and breast, and higher for cancers of the colon and larynx. The highest PAF was found for larynx cancer and the greatest number of attributable cases for colon cancer. The sensitivity test excluding participants with a low physical functioning score resulted in an increase in the majority of PAF estimates, while the sensitivity test restricting the hazard ratio calculation to participants consuming ≥ 7 drinks per week resulted in a decrease in the majority of PAF estimates.

The estimated PAF for all cancers combined increased to 3.8% under the assumption that cancers of the stomach, pancreas and prostate and melanoma are causally related to alcohol consumption, and this estimate did not materially change in either of the two sensitivity tests. The highest PAF was found for stomach cancer and the greatest number of attributable cases for prostate cancer. The estimated PAF for all cancers combined decreased to net 1.6% under the assumption that cancers of the kidney and thyroid and NHL are causally related to alcohol consumption, with higher estimates obtained in the two sensitivity tests. The lowest PAF was found for thyroid cancer, with the estimate implying a 19% increase in thyroid cancer cases if the population consumed no alcohol. The estimated PAF for all cancers combined did not change materially under the assumption that both the positively and inversely associated cancers are causally related to alcohol consumption, except in the sensitivity test restricting the hazard ratio calculation to participants consuming ≥ 7 drinks per week, which resulted in a higher PAF for all cancers combined.

The cumulative absolute risk of cancer between the ages of 45 and 75 years by level of alcohol consumption is shown in Figure 8.2. The absolute risk difference between drinking groups was larger

in men for all individual cancer types, but was larger in women for alcohol-related cancer combined. For all cancers combined, cumulative absolute risk to age 75 years in men was 34.0% in those consuming > 14 drinks per week (median 21 drinks per week) and 32.1% in non-drinkers, while in women these values were 25.6% (median 20 drinks per week) and 23.9% respectively. For alcohol-related cancer risk by the age of 75 years, men and women consuming > 14 drinks per week 'brought forward' their risk of cancer by approximately 3.5 years, and those consuming > 0 and ≤ 14 drinks per week by approximately 1 year, compared to non-drinkers.

The estimated number of persons needed to quit or decrease drinking by age 45 years to prevent one cancer case by age 75 years is shown in Table 8.7. One cancer case was estimated to be prevented for every 42 men or 37 women quitting (or never starting) drinking at > 14 drinks per week (median 20 drinks per week in women and 21 in men). The largest values were found for persons quitting (or never starting) drinking at > 0 and ≤ 14 drinks per week (median 5 drinks per week in women and 6 in men). The smallest values among the individual cancer types were for colorectal cancer in men and breast cancer in women. The sensitivity tests did not materially change estimates for alcohol-related cancers combined in men, while in women the sensitivity test restricting the hazard ratio calculation to participants consuming ≥ 7 drinks per week resulted in higher values.

Conclusions. The PAF estimate for all cancers combined using log-linear hazard ratios from the 45 and Up Study was similar to that of a previous study using internationally-derived relative risks.

The estimates of cumulative absolute risk of cancer and number of persons needed to quit or reduce drinking to prevent one cancer case showed that colorectal and breast cancer contributed the most to the absolute cancer risk associated with alcohol consumption.

Table 8.6. Population attributable fractions for cancer caused by alcohol consumption in Australian persons in 2010 using international relative risks and hazard ratios from the 45 and Up Study (2006-2010), New South Wales, Australia.

		Pandeya et al., (2015)[1]		45 and Up Study: derived from main analysis		45 and Up Study: derived from sensitivity analysis 1[a]		45 and Up Study: derived from sensitivity analysis 2[b]	
Cancer type	**n cases**	**n excess cases**	**PAF (%)**	**n excess cases**	**PAF (%)**	**n excess cases**	**PAF (%)**	**n excess cases**	**PAF (%)**
Alcohol-related									
Mouth and pharynx[c]	1,996	613	30.6	102	5.1	397	19.9	0[d]	0.0
Oesophagus SCC	511	126	24.7	99	19.4	234	45.8	150	29.4
Colon[e]	10,865	868	8.0	1,258	11.6	1,105	10.2	1,996	18.4
Rectum[e]	3,967	470	11.8	165	4.2	175	4.4	150	3.8
Liver	1,389	175	12.7	175	12.6	260	18.7	92	6.6
Larynx	625	126	20.1	204	32.6	220	35.2	205	32.8
Breast (female)	14,174	830	5.8	822	5.8	618	4.4	274	1.9
All cancer	**115,118**	**3,208**	**2.8**	**2,824**	**2.5**	**3,009**	**2.6**	**2,867**	**2.5**
Alcohol-related and positively associated									
Stomach	1,993	-	-	184	9.3	198	9.9	160	8.0
Pancreas	2,712	-	-	0[d]	0.0	79	2.9	362	13.4
Melanoma	11,370	-	-	633	5.6	619	5.4	547	4.8
Prostate	20,093	-	-	710	3.5	221	1.1	544	2.7
All cancer	**115,118**	**-**	**-**	**4,352**	**3.8**	**4,125**	**3.6**	**4,482**	**3.9**
Alcohol-related and inversely associated									
Kidney	2,722	-	-	-86	-3.2	-32	-1.2	-138	-5.1
Thyroid	2,209	-	-	-419	-19.0	-390	-17.6	-215	-9.7
Non-Hodgkin lymphoma	4,429	-	-	-480	-10.8	-445	-10.0	-88	-2.0
All cancer	**115,118**	**-**	**-**	**1,839**	**1.6**	**2,143**	**1.9**	**2,426**	**2.1**
Alcohol-related and all associated									
All cancer	**115,118**	**-**	**-**	**3,367**	**2.9**	**3,259**	**2.8**	**4,040**	**3.5**

Hazard ratios used in calculations for the 45 and Up Study were derived from total alcohol consumption as a log-linear variable among participants consuming ≥ 1 drink per week. For each age group used in the calculation, cancer incidence was attributed to alcohol consumption nine years earlier in the 2001 National Health Survey. Pandeya et al., (2015) used international log-linear relative risks. 'n excess cases' refers to cancer cases attributable to alcohol consumption out of the total number of cases, 'n cases'. [a]Participants with physical functioning score < 50% excluded. [b]Among participants consuming ≥ 7 drinks per week. [c]ICD-10: C01-06;09-14 in Pandeya et al. 2015 and C00-14 for calculations in the 45 and Up Study. [d]Hazard ratio less than 1 (0.994 for mouth and pharynx cancer and 0.997 for pancreatic cancer). [e]Cancer of the Rectosigmoid junction (C19) was grouped with colon in Pandeya et al. 2015 and with rectum for calculations in the 45 and Up Study. PAF, Population Attributable Fraction. SCC, Squamous Cell Carcinoma. ICD-10: International Classification of Diseases, version 10.

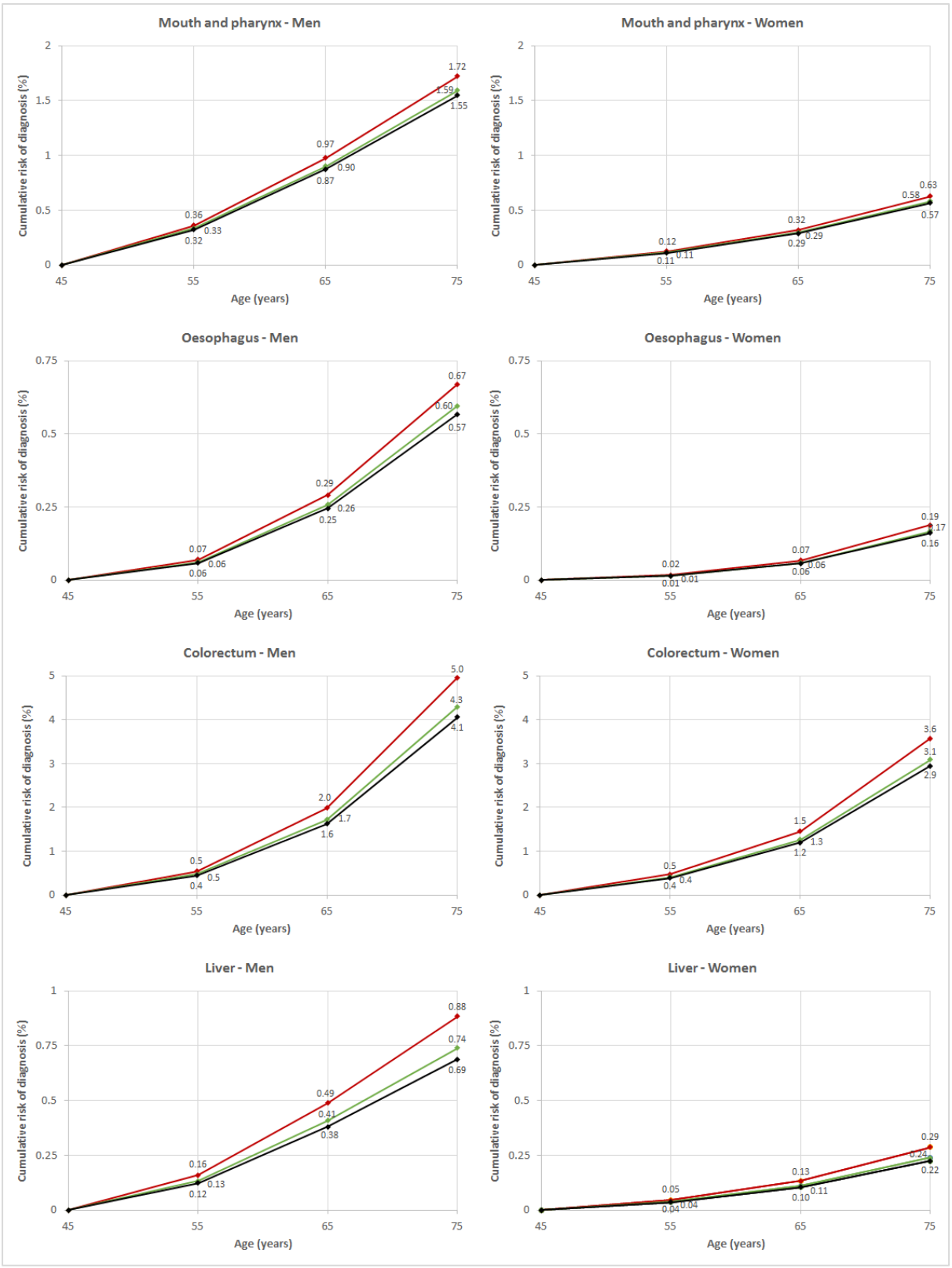

Figure 8.2. Cumulative absolute risk of cancer diagnosis between the ages of 45 and 75 years in Australia in 2013 using hazard ratios from the 45 and Up Study (2006-2010), New South Wales, Australia. Black line: 0 drinks per week; Green line: 5 drinks per week in women and 6 drinks per week in men; Red line: 20 drinks per week in women and 21 drinks per week in men. Results derived from total alcohol consumption as a log-linear variable among participants consuming ≥ 1 drink per week. International classification of diseases, version 10 codes for mouth and pharynx: C00-14;30-31 in incidence data and C00-14 as calculated in the 45 and Up Study.

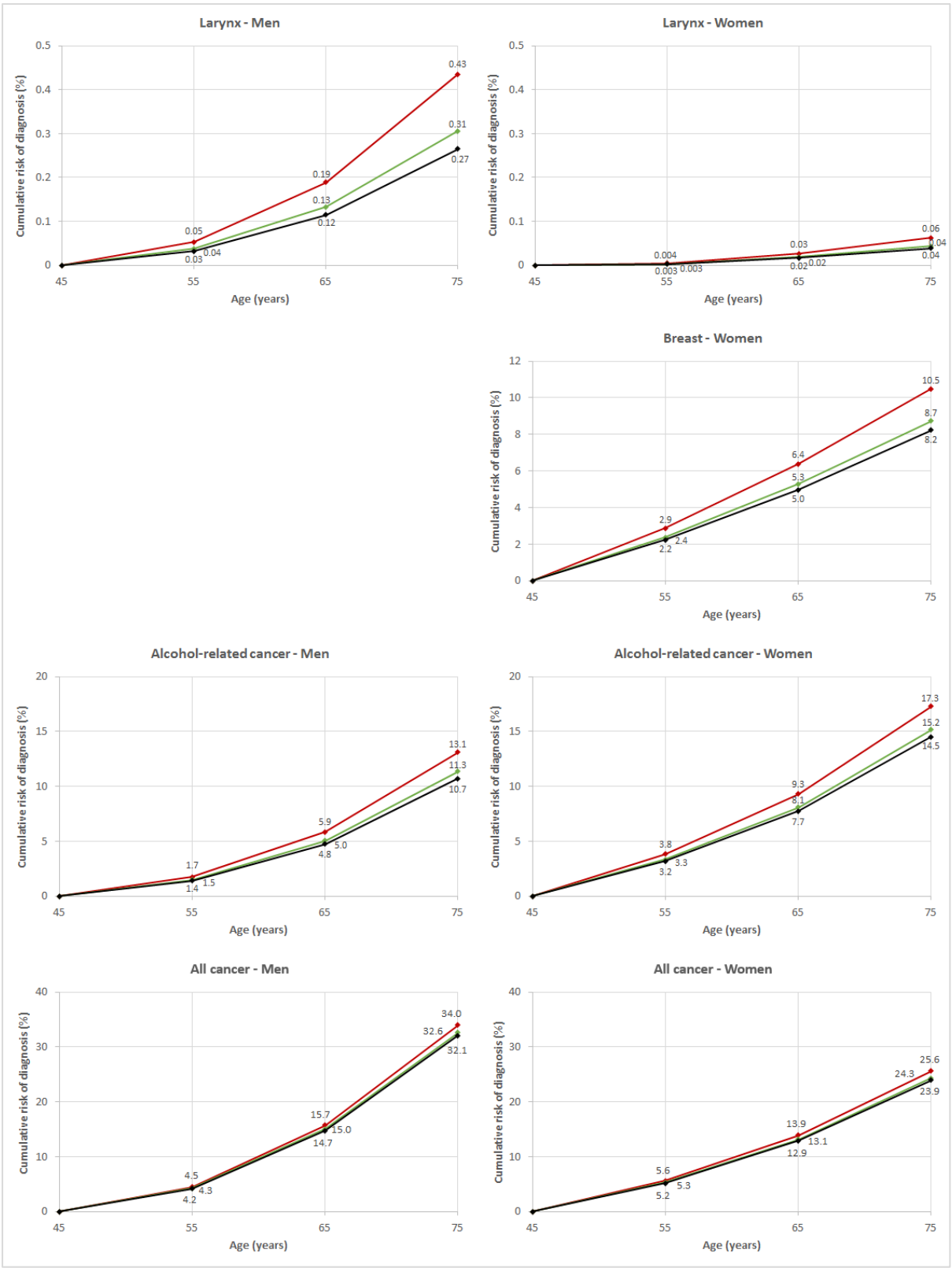

Figure 8.2. (Continued)

Table 8.7. Number of persons needed to quit or decrease drinking by age 45 years to prevent one cancer case by age 75 years in Australia in 2013.

	Men			Women		
Cancer type	**21 drinks/week → Quit**	**6 drinks/week → Quit**	**21 drinks/week → 6 drinks/week**	**20 drinks/week → Quit**	**5 drinks/week → Quit**	**20 drinks/week → 5 drinks/week**
Main analysis						
Mouth and pharynx[a]	567	2,063	782	1,622	6,744	2,133
Oesophagus	977	3,630	1,337	3,629	15,414	4,745
Colorectum	111	417	151	160	688	209
Liver	508	1,949	687	1,635	7,172	2,118
Larynx	591	2,490	775	4,287	20,632	5,412
Breast	-	-	-	44	193	57
Alcohol-related	42	158	58	37	154	48
Sensitivity analysis 1[b]						
Mouth and pharynx[a]	171	679	228	465	2,116	595
Oesophagus	756	2,858	1,027	2,781	12,024	3,617
Colorectum	127	472	173	184	783	240
Liver	364	1,448	486	1,149	5,229	1,472
Larynx	559	2,379	730	4,028	19,599	5,070
Breast	-	-	-	58	247	76
Alcohol-related	40	149	54	38	161	50
Sensitivity analysis 2[c]						
Mouth and pharynx[a]	-[d]	-[d]	-[d]	-[d]	-[d]	-[d]
Oesophagus	700	2,663	949	2,568	11,172	3,334
Colorectum	80	309	108	114	504	148
Liver	904	3,329	1,240	2,970	12,512	3,895
Larynx	588	2,479	771	4,263	20,533	5,379
Breast	-	-	-	127	524	168
Alcohol-related	40	150	55	54	222	70

Results derived from total alcohol consumption as a log-linear variable among participants consuming ≥ 1 drink per week. [a]International classification of diseases, version 10: C00-14;30-31 in incidence data and C00-14 as calculated in the 45 and Up Study. [b]Participants with physical functioning score < 50% excluded. [c]Among participants consuming ≥ 7 drinks per week. [d]Hazard ratio less than 1 (0.994 per drink per day).

8.3 – Discussion and Conclusions

The main findings of this chapter were that total alcohol consumption was associated with increased risk of several types of cancer, including colorectum, colon, larynx, female breast, alcohol-related and all cancer, along with decreased risk of bladder and thyroid cancer and NHL. The results for total alcohol consumption were largely consistent with prior research, and a summary of the results in comparison with the IARC and WCRF conclusions are present in Table 8.8. While light alcohol consumption (up to 1 drink per day) has been found in a meta-analyses to increase risk of oesophageal SCC, mouth, pharynx and breast cancer[2-4], we found no significant associations for light drinking (up to 7 drinks per week). Nevertheless, the confidence intervals for the ≥ 3.5 to ≤ 7 drinks per week category for most alcohol-related cancer types were consistent with a hazard ratio of at least 1.6, and so the analysis may have been underpowered to detect effects for light drinking. There was also evidence that the risk relationship between alcohol consumption and certain cancers may not be linear, including colorectum, colon and breast. This finding suggests that modelling cancer risk and estimating the burden of disease for these cancers may not be straightforward.

In analyses examining the effects of drinking pattern, there was an independent association of mean drinks per drinking-day with increased risk of mouth and pharynx, oesophagus (squamous cell carcinoma), colorectum, colon, kidney, alcohol-related, non-alcohol-related and all cancer. Frequent drinking was associated with a lower risk of all cancer combined compared to less frequent drinking. Among participants consuming > 4 drinks per drinking-day, frequent drinking was also positively associated with colorectal and colon cancer risk and inversely associated with kidney cancer risk. A key implication of these results was that a reduction in the number of drinks consumed per drinking occasion is likely to be an effective approach to reduce cancer risk, independent of and in addition to limiting the total amount of alcohol consumed. Another implication was that there was no evidence that alcohol consumption is associated with increased risk of five cancer types (stomach, pancreas,

lung, melanoma and prostate) or decreased risk of kidney cancer, for which there is prior evidence of an association but the IARC has not declared causality.

The additional analyses presented evidence that there was no material difference in the magnitude of the log-linear association between total alcohol consumption and risk of all cancers combined under a number of sensitivity tests aimed to test the extent of bias from the 'sick-quitter effect'. Similarly, there was no material change in the inverse association between drinking frequency and risk of all cancers combined or in the results for overall drinking pattern. These results suggest that the results for all cancers combined were robust and unlikely to be impacted importantly by bias from the 'sick-quitter effect'.

Table 8.8. Relationship between alcohol consumption and cancer according to the IARC[5, 6], the WCRF[7, 8] and the results for total alcohol consumption in the 45 and Up Study.

Cancer type (ICD-10 code)	IARC	WCRF	45 and Up Study
Mouth and pharynx (C00-14)	Increased risk (RR 3 at 50 g/day); interaction with smoking	Convincing increased risk	No significant association[a]
Oesophagus (C15)	Increased risk (RR 2 at 50 g/day); interaction with smoking[b]	Convincing increased risk[b]	No significant association[a]
Stomach (C16)	Inconsistent evidence (increased risk in some studies)	Probable increased risk[c]	No significant association
Colorectum (C18-20)	Increased risk (only at > 30 g/day; RR 1.4 at 50 g/day)	Convincing increased risk[d]	Positive association (colorectum and colon)
Liver (C22)	Increased risk, interaction with smoking	Convincing increased risk[c]	Increased risk at > 28 drinks/week[a]
Gallbladder (C23-24)	-	Limited - no conclusion	No significant association
Pancreas (C25)	Association with small increased risk (only at ≥ 30 g/day)	Suggestive increased risk[e]	No significant association; interaction with smoking
Larynx (C32)	Increased risk (RR 2 at 50 g/day); interaction with smoking	Convincing increased risk	Positive association
Lung (C33-34)	Inconsistent evidence (increased risk in some studies)	Limited - no conclusion	No significant association
Melanoma (C43)	Inconsistent evidence	Limited - no conclusion[f]	No significant association
Female breast (C50)	Increased risk (RR 1.5 at 50 g/day)	Convincing increased risk	Positive association[g]
Male breast (C50)	Inconsistent evidence	-	-
Vulva and vagina (C51-52)	Inconsistent evidence (increased risk in some studies)	-	-
Cervix (C53)	Inconsistent evidence (increased risk in some studies)	Limited - no conclusion[h]	-
Endometrium (C54.1)	Inconsistent evidence	Limited - no conclusion	No significant association
Ovary (C56)	Little evidence for association	Limited - no conclusion	No significant association
Prostate (C61)	Little evidence for association (increased risk in some studies)	Limited - no conclusion	No significant association
Testis (C62)	Inconsistent evidence	-	-
Kidney (C64)	No association (decreased risk in some studies)	Probable decreased risk[i]	No significant association; interaction with smoking
Bladder (C67)	No association	Limited - no conclusion	No significant association
Brain (C71)	Inconsistent evidence	-	No significant association
Thyroid (C73)	Inconsistent evidence (decreased risk in some studies)	-	Inverse association[g]
Hodgkin lymphoma (C81)	Inconsistent evidence (decreased risk in some studies)	-	-
Non-Hodgkin lymphoma (C82-85)	Inconsistent evidence (decreased risk in some studies)	-	Inverse association
Multiple myeloma (C90.0)	Inconsistent evidence	-	No significant association
Leukaemia (C91-95)	Inconsistent evidence	-	No significant association

[a]Positive association in sensitivity test aiming to mitigate bias from changes in drinking behaviours in response to ill-health. [b]Squamous cell carcinoma only; not enough evidence/no association for adenocarcinoma. [c]For alcohol consumption > 30 g/day. [d]For alcohol consumption > 45 g/day. [e]Limited-suggestive increased risk, for alcohol consumption > 3 drinks/day. [f]For all skin cancer. [g]No significant association and a material change in risk estimate in sensitivity test aiming to mitigate bias from changes in drinking behaviours in response to ill-health. [h]For alcoholism. [i]For alcohol consumption ≤ 30 g/day. IARC relative risks are compared to non-drinkers. IARC, International Agency for Cancer Research. WCRF, World Cancer Research Fund. ICD-10, International Classification of Diseases version 10. RR, Relative Risk.

Nevertheless, for a number of individual cancer types, the risk relationship with alcohol varied from that observed in the main analysis when either participants with poor physical functioning, or those who consumed < 7 drinks per week, were excluded. Specifically, for mouth and pharynx, oesophageal (SCC) and liver cancers, the risks associated with alcohol may have been underestimated in the main analyses due to bias from the 'sick-quitter effect', including the association between mean drinks per drinking-day and oesophageal cancer. The inverse association for thyroid cancer may also have been overestimated in the main analysis.

The PAF estimate for all cancers combined using log-linear hazard ratios from the 45 and Up Study was similar to that of a previous study using internationally-derived relative risks, while there was some variation by individual cancer type. The inclusion of cancers which have previously been associated with alcohol consumption made a material difference to the PAF estimate, increasing from 2.5% to 3.8% when including four positively associated cancers and decreasing to 1.6% when including three inversely associated cancers. This shows that determining whether the associations for the positively associated cancers are causal will make an important difference to burden of disease estimates for alcohol and cancer. It also follows that whether or not the associations for the inversely associated cancers are causal, the net impact of alcohol consumption on cancer PAFs will always be that of increased risk.

The estimates of cumulative absolute risk of cancer and number of persons needed to quit or reduce drinking to prevent one cancer case showed that colorectal and breast cancer contributed the most to the absolute cancer risk associated with alcohol consumption. It was largely found that the number of persons needed to quit or reduce drinking to prevent one cancer case for all cancers combined were not materially affected by bias from the 'sick-quitter effect'. One key finding was that the absolute risk difference between drinking groups was larger in men for all individual cancer types (excluding breast) due to the higher incidence of cancer in men. The absolute risk difference was larger in women for alcohol-related cancer combined due to the impact of breast cancer. It was

also shown that by age 75 years, persons consuming > 14 drinks per week 'brought forward' their risk of alcohol-related cancer by 3.5 years compared to non-drinkers. Other key findings included that one cancer case could be prevented by the age of 75 years for every 42 men or 37 women quitting (or never starting) drinking at > 14 drinks per week, and that targeting persons drinking > 14 drinks per week to decrease their drinking to > 0 and ≤ 14 drinks per week is likely to be a more efficient strategy to reduce cancer incidence than targeting persons drinking > 0 and ≤ 14 drinks per week to decrease their drinking to zero. These results may be useful for planning preventative public health interventions to reduce the burden of cancer.

The next chapter investigated the association between alcohol consumption, drinking pattern and risk of all-cause and cause-specific mortality.

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Chapter 9 – Alcohol Consumption and All-Cause and Cause-Specific Mortality Risk

Chapter summary

This chapter contains an article prepared for publication, which investigated the association between alcohol consumption and risk of all-cause and cause-specific mortality, with a focus on the effect of pattern of drinking. This was achieved by using baseline data from the 45 and Up Study linked to the NSW Registry of Births, Deaths and Marriages to December 2014 and cause of death data to December 2012. The hazard of death was calculated for overall weekly alcohol intake assessed in three ways: as a categorical variable, a continuous log-linear variable and a continuous restricted cubic spline variable. After adjusting for total alcohol consumption, the independent effect on mortality of two measures of drinking pattern, drinking-days per week and drinks per drinking-day, was examined, along with an analysis accounting for both measures simultaneously. Interaction tests were performed to test for effect modification by sex and smoking status. Causes of death for which there was evidence of an independent effect of drinking pattern were identified. The findings of the article were presented at the Australasian Epidemiological Association Annual Scientific Meeting 2017 (Sydney) and the 45 and Up Study Annual Forum 2017 (Sydney).

In additional analyses, sensitivity analyses examined possible bias in risk estimates due to the sick-quitter effect. Risk estimates were then used to calculate population attributable fractions, estimates of absolute risk and number of persons needed to quit or reduce drinking to prevent one death.

9.1 – Journal Article (Prepared for Publication)

The following article is prepared for publication. The results of the proportional hazards assumption tests (Table F.1), the p-values for the interaction tests (Table F.2), and the Akaike information criterion results (Table F.3) are shown in Appendix F.1. Using the all-cause mortality model reported in the main analysis, a further investigation of the exclusion scenarios assessed in Chapter 7 aiming to mitigate bias from the 'sick-quitter effect' by their effect on the association between disease and all-cause mortality is shown in Appendix F.2. This investigation differs from the analyses reported in Chapter 7 because it examined whether the exclusion scenarios attenuate the association between the confounding factor (ill-health) and the outcome (all-cause mortality), rather than whether the exclusion scenarios reduce differences in health status between drinking groups.

Title

Alcohol consumption, drinking patterns and cause-specific mortality in the 45 and Up Study.

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Keywords

Alcohol consumption, mortality, drinking pattern, heavy episodic drinking.

7325 words.

Abstract

Background: For many causes of death, the association of alcohol, and in particular pattern of drinking, with mortality remains unclear. We quantified these associations in the 45 and Up Study, a prospective cohort study in New South Wales (NSW).

Methods: Cox proportional hazards were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk associated with alcohol consumption (drinks/week) and pattern of drinking among 253,935 participants aged ≥ 45 years (2006-2009). Deaths were ascertained by linkage to NSW mortality data to December 2012 for cause-specific mortality and December 2014 for all-cause mortality. To prevent bias from reverse causation, deaths occurring within three years of baseline were excluded.

Results: In a median follow-up of 4.4 and 6.4 years, 6,254 and 13,988 deaths were captured to December 2012 and 2014, respectively. Increasing overall alcohol consumption increased risk of all-cause mortality (HR/one drink increase in mean daily alcohol consumption: 1.03; 95% CI: 1.02-1.05), death from alcohol-related cancers combined (1.08; 1.01-1.16) including liver cancer (1.17; 1.01-1.36), cardiovascular diseases other than ischaemic heart disease and stroke (1.13; 1.05-1.22), digestive system disease (1.15; 1.03-1.28) including liver disease (1.26; 1.11-1.43), and external causes (1.18; 1.07-1.31) including fall (1.34; 1.09-1.64) and other external causes (1.19; 1.00-1.41); J-shaped associations were found for all-cause mortality and death from cardiovascular disease; an inverse association was found for death from non-Hodgkin lymphoma (0.61; 0.42-0.88). After adjusting for overall weekly intake, the average number of drinks consumed on drinking-days was independently associated with risk of all-cause mortality (1.21; 1.08-1.34 for > 4 drinks per drinking-day) and death from cancer (1.38; 1.09-1.33) including oesophageal cancer (2.86; 1.08-7.56). More drinking-days per week was positively associated with risk of respiratory system disease mortality, and inversely associated with risk of all-cause mortality and death from all cancer combined, diabetes, cardiovascular disease and ischaemic heart disease after adjusting for overall intake. All-

cause mortality risk was increased when more than 4 drinks were consumed per drinking-day on only one or two days in a week (i.e. heavy episodic drinking; 1.24; 1.07-1.43).

Conclusions: Alcohol consumption increased the risk of death from many causes, although for some diseases, the relationship between quantity and risk was not linear. More drinks per drinking-day, including heavy episodic drinking, increased mortality risk independent of the additional risk associated with overall intake. Low-volume and more frequent drinking appeared to be protective but it is unclear whether these observations were causal or reflect methodological biases.

Word count: 403

Introduction

Alcohol consumption increases the risk of a variety of diseases, and was attributed to 5.9% of deaths and 5.1% of the burden of disease and injury globally in 2012[1]. Meta-analyses have identified a J-shaped relationship between alcohol and all-cause mortality, where low-volume 'moderate' drinking is associated with decreased risk and heavy drinking with increased risk[2-4]. It is unclear however whether the apparent protective relationship between low-volume drinking and all-cause mortality and diseases such as cardiovascular disease (CVD) is causal, or due to confounding by factors such as baseline health status, behavioural risk factors and/or socio-demographic characteristics[5, 6]. Indeed, meta-analyses that account for these study characteristics[7] and other factors including length of follow-up[7] and choice of reference group[7, 8] have failed to replicate the protective association between low-volume drinking and all-cause mortality. Thus, the evidence regarding the inverse relationship of low-volume drinking and mortality risk is inconsistent.

Moreover, it has been reported that pattern of drinking influences risk of mortality independent of the overall amount of alcohol consumed. There have largely been two patterns of interest in relation to health outcomes: 1) low-volume frequent intake and 2) heavy infrequent intake, which is commonly referred to as either 'binge drinking' or 'heavy episodic drinking'. Drinking frequency has been associated with differences in risk of all-cause mortality[9, 10], while a large number of drinks per drinking-day or heavy episodic 'binge' drinking have been found to increase risk[9, 11-14]. Relationships between drinking pattern and mortality are not straightforward, and there are several methodological issues which may cause spurious or biased associations. One is that higher drinking frequency is reported to be inversely related to both the number of drinks consumed per drinking-day as well as the proportion of days with heavy episodic drinking[15]. For example, people who drink daily are less likely to engage in heavy episodic drinking. Consequently, failure to account for drinks per drinking-day when examining the effect of drinking frequency (and vice versa) could potentially result in confounding for either of the two individual measures of drinking pattern alone.

In addition, analyses are not always adjusted for the total amount of alcohol consumed, making it impossible to determine whether drinking pattern has an effect on risk that is independent of overall intake. Furthermore, confounding by unmeasured, or poorly measured, covariates that influence mortality risk may explain inverse relationships between drinking frequency and mortality, as a number of risk factors including lack of health insurance, being physically inactive and having fair or poor overall health have been associated with infrequent drinking[15].

Variation in the direction and strength of the relationship between alcohol consumption and mortality from specific causes has also been reported. Positive associations have been reported for death from cancers of the upper-aerodigestive tract[16], oesophagus (squamous cell carcinoma)[17], colorectum (women only)[18] and liver[19], tuberculosis[20], digestive system disease[21], liver cirrhosis[20], external causes[20-22]. Inverse associations have been reported for death from cancers of the stomach[18], lung[18] and kidney[18] and CVD including ischaemic heart disease (IHD) and stroke[23], and J-shaped associations for death from colorectal cancer[24], breast cancer[18] and all cancers combined[25]. Pattern of drinking has been less studied than total alcohol consumption for cause-specific mortality, and largely for CVD and cancer. Drinking frequency has been associated with both increased and decreased CVD mortality[9, 10, 14], and with increased mortality from oesophageal cancer and all cancers combined[10, 14]. A large number of drinks per drinking-day or heavy episodic 'binge' drinking have been reported to increase risk of CVD mortality[9, 14, 26], all cancer mortality[11, 14], and suicide[27]. Overall, large prospective studies of drinking pattern and mortality are scarce, especially those which have examined multiple causes of death and have included adjustment for total alcohol consumption.

We used a large prospective Australian cohort study to quantify the risk of mortality in relation to total alcohol consumption and the independent effects of drinking frequency (number of alcohol drinking-days per week) and drinks per drinking-day. We directly compared the effects of low-volume infrequent drinking with low-volume daily drinking and heavy infrequent (episodic) drinking.

Methods

Study sample

The Sax Institute's 45 and Up Study is a prospective cohort study of 266,794 participants, with methods previously described[28]. In summary, men and women aged ≥ 45 years were randomly sampled from the general population of New South Wales (NSW) between 2006 and 2009 using the Department of Human Services enrolment database. The database includes all Australian citizens and permanents residents, and also some temporary residents and refugees. Oversampling by a factor of two was undertaken for persons living in rural and remote areas and those aged ≥ 80 years. Participants completed a health and lifestyle questionnaire, and the response rate was estimated to be 18%. Ethics approval for the 45 and Up Study was granted by the University of NSW Human Research Ethics Committee and the NSW Population Health Services Research Ethics Committee.

Data linkage

The 45 and Up Study questionnaire data were probabilistically linked to the NSW Registry of Births Deaths and Marriages (RBDM) and the Cause of Death Unit Record File (COD-URF) by the NSW Ministry of Health's Centre for Health Record Linkage (CHeReL). In order to conduct sensitivity analyses, questionnaire data were also linked probabilistically to data from the NSW Cancer Registry (1994-2010). The CHeReL used a best practice approach in privacy preserving record linkage[29] along with the open source probabilistic record linkage software Choice Maker[30]. The probabilistic matching process is highly accurate (false-positive and false-negative rates < 0.4%), with a detailed explanation of the linkage process published elsewhere[31].

Mortality data

Fact of death was derived from the NSW RBDM to December 2014 which captures deaths for all NSW residents. Cause of death from the COD-URF was available to December 2012 and was classified according to the International Classification of Diseases, version 10[32]. All causes of death

identified in a recent review of alcohol consumption and burden of disease[27], and two large analyses of alcohol consumption and cause-specific mortality[21, 22] were included. Relevant causes of death with less than 30 outcomes were combined with any other causes of death into an 'other' group, except for pancreatitis which was included in the other digestive system disease group.

Cancer deaths were subdivided into 'alcohol-related cancer', as defined by the International Agency for Research on Cancer: mouth, pharynx, and larynx (combined), oesophagus, colorectum, liver, and female breast[33, 34] and 'non-alcohol-related cancer'. Other cancer types of interest were those for which there is evidence of an association with alcohol and the number of deaths exceeded 30: stomach[35, 36], pancreas[36, 37], lung[36], melanoma[36], prostate[36, 38], kidney[36, 39], and non-Hodgkin lymphoma (NHL)[36, 40].

Death from CVD was subdivided into IHD, cerebrovascular disease and other. There is also evidence of increased risk of lower respiratory infection due to the immunosuppressive effects of alcohol consumption, so death from respiratory system disease was subdivided into lower respiratory infection and other[27]. Death from digestive system disease was subdivided into liver disease and other. Death from external causes was subdivided into transport accident, fall, suicide and other. Death from diabetes, dementia and cerebrovascular disease were not subdivided as for each of these outcomes 50% or more were missing subtype information.

Alcohol consumption

The question used to determine total alcohol consumption was "*About how many alcoholic drinks do you have each week? One drink = a glass of wine, middy of beer or nip of spirits (put "0" if you do not drink, or have less than one drink each week)*". Responses were categorised into six values: 'Non-drinker (< 1 drink/week)', '≥ 1 and ≤ 3.5 drinks/week', '> 3.5 and ≤ 7 drinks/week', '> 7 and ≤ 14 drinks/week', '> 14 and ≤ 28 drinks/week' and '> 28 drinks/week'. The cut-points of 14 and 28 drinks/week were chosen because they correspond with the Australian alcohol guidelines to minimise risk of long-term harm (≤ 2 drinks/day) and short-term harm (≤ 4 drinks/day)[41].

An additional question, "*On how many days each week do you usually drink alcohol?*", was used to make three categorical drinking pattern variables which applied to drinkers only. Firstly, drinking-days per week (drinking frequency) was coded with three values: '1-2 days per week', '3-5 days per week' and '6-7 days per week'. Secondly, mean drinks per drinking-day (with drinking-day being any day in a week where at least one alcoholic drink was consumed) was calculated by dividing the number of drinks consumed per week by the number of days of alcohol consumption per week, giving the mean number of drinks per drinking-day. This variable was coded with three values: '≤ 2 drinks per drinking-day', '> 2 and ≤ 4 drinks per drinking-day' and '> 4 drinks per drinking-day'.

Finally, an 'overall drinking pattern' variable with nine categories was constructed by combining the drinking-days per week and drinks per drinking-day variables. This variable allowed for more specific drinking patterns to be examined, such as daily low-volume intake and heavy episodic drinking.

Statistical analyses

Participants with missing alcohol consumption data, a date of death less than three years after baseline (to prevent bias from reverse causation as done in previous analyses[20-22]) or a date of death earlier than their questionnaire completion date were excluded from the analysis.

Hazard ratios (HR) and 95% confidence intervals (CI) of death were calculated using Cox proportional hazards regression models using age as the underlying time variable[42]. Censoring occurred if a participant died from a different cause to the cause being analysed or at the end of study period (December 2012 for cause-specific mortality and December 2014 for all-cause mortality).

For each cause of death, three analyses of total weekly alcohol consumption were performed. 1) Categorical levels of alcohol consumption where light drinkers (≥ 1 and ≤ 3.5 drinks/week) were used as the reference group rather than non-drinkers to minimise bias from the 'sick-quitter effect'. That is, 'non-drinkers' may have quit drinking due to ill-health and may be at higher risk of mortality[43]. Tests for linear trend excluding non-drinkers were conducted by replacing the categorical alcohol

consumption variable with a continuous variable where the median level of alcohol consumption was assigned to participants within each category (to limit the impact of outliers). Two-way statistical interaction tests between alcohol consumption and sex and smoking status (never-smoking vs. ever-smoking) were conducted and the results stratified where relevant. 2) Total number of drinks/week was analysed as a continuous variable in log-linear Cox models with hazard ratios representing the change in risk per one drink increase in mean daily alcohol consumption, excluding non-drinkers. 3) To assess non-linearity, a restricted cubic spline was fitted with three knots at the 25th, 50th and 75th percentiles of alcohol consumption (excluding non-drinkers). The reference quantity of alcohol consumption was 1 drink per week. When graphed, the x-axis was truncated at 56 drinks per week for presentation purposes, but the model included participants up to the maximum quantity of drinking: 140 drinks per week. The Akaike Information Criterion (AIC) was used to compare the log-linear and cubic spline models for best fit.

Three drinking patterns were assessed in separate models. To prevent bias from the 'sick-quitter effect' these analyses were restricted to drinkers. All three drinking patterns were analysed separately using categorical and continuous covariate counterparts (the continuous version was coded as the median number of drinks in each category): 1) Drinking frequency with 3 levels: those who reported consuming alcohol on '1-2 days per week' (reference), '3-5 days', '6-7 days' per week. 2) Mean drinks per drinking-day, where '≤ 2 drinks per drinking-day' was the reference category, compared to '> 2 and ≤ 4 drinks per drinking-day', and '> 4 drinks per drinking-day'. These models were calculated both without adjustment for total alcohol consumption and adjusted for total alcohol consumption (as a continuous log-linear variable). Statistical interaction tests for drinking pattern as a categorical variable (after adjusting for total alcohol consumption) and sex and smoking status were performed for each of the first two drinking patterns and the results stratified where appropriate. 3) An interaction test between the drinking frequency and drinks per drinking-day variables was performed for all causes of death. Where significant, drinking frequency stratified by levels of drinks per drinking-day and vice versa was examined, along with an overall drinking pattern.

The overall drinking pattern combined drinking frequency and mean drinks per drinking-day into a 3x3 matrix resulting in 9 categories ('overall drinking pattern'). The reference group was the category with the lowest total alcohol consumption: '≤ 2 drinks per drinking-day' consumed on '1-2 days per week'. The matrix captured low-volume episodic drinking, heavy episodic 'binge' drinking (defined here as > 4 drinks per drinking-day on 1-2 days per week), low-volume daily drinking and heavy daily drinking. Overall drinking pattern was also examined for all-cause mortality.

Sensitivity analyses were conducted to examine the impact of self-reported history of disease at baseline on the main results. Specifically, participants who had ever been diagnosed with cancer (ascertained from both the baseline questionnaire and the NSW Cancer Registry) were excluded from analysis of cancer mortality. Likewise, a history of heart disease or stroke were excluded for CVD mortality, pre-existing diabetes for diabetes mortality, fair/poor memory for dementia-related mortality, asthma for death from respiratory system disease, depression for suicide, and had ever had cancer, heart disease, stroke or diabetes for all-cause mortality. These exclusions were made, where relevant, for all models except the log-linear trends and cubic spline models.

All analyses were adjusted for covariates that are potentially related to mortality as self-reported in the baseline questionnaire, including sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and intensity, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women only), menopausal status (women only), hormone replacement therapy use (women only) and height. Remoteness categories were based on the 2006 ARIA (Accessibility/Remoteness Index of Australia) index[44].

A test of the proportional hazards assumption was performed for all Cox models. If significant violations were detected then log-log survival curves stratified by the variables in violation were plotted. If the lines were considerably non-parallel upon visual inspection, the model was stratified by the variable in violation.

Analyses were performed using SAS 9.4.

Results

253,935 of 266,794 participants (95.2%) were included in the analysis after excluding 5041 (1.9%) participants with missing information on total alcohol consumption and a further 13 (0.005%) participants who died before their self-reported questionnaire date and 7805 (2.9%) participants who died within the first three years of follow-up. Of included participants, 6254 (2.5%) had died by December 2012 in a median follow-up of 4.4 years and 13,988 (5.5%) had died by December 2014 in a median follow-up of 6.4 years.

Overall, 170,254 (67.0%) participants consumed at least one alcoholic drink per week, including 36,472 (14.4%) who consumed > 14 drinks per week. Of drinkers, 2006 (1.2%) were excluded from the drinking pattern analyses due to missing information on number of drinking-days per week. Of the 168,248 drinkers included in the drinking pattern analyses, 62,027 (36.9%) consumed alcohol 6 or 7 days per week and 17,643 (10.5%) reported an average of > 4 drinks per drinking-day. Overall, 33,724 (19.8%) were low-volume daily drinkers, and 3988 (2.3%) reported infrequent (1-2 days) heavy (> 4 drinks) consumption and could be considered 'binge' drinkers.

Participants consuming higher numbers of drinks per week were, on average, more likely to be men, Australian-born, consumed processed meat > 1 time per week and spent ≥ 2 hours outdoors per day (Table 1). Drinkers tended to be younger than non-drinkers. Among men, participants consuming higher numbers of drinks per week were more likely to be ≥ 180 cm tall. Among women, participants consuming higher numbers of drinks per week were more likely to be ≥ 165 cm tall, nulliparous and had ever used hormonal contraceptives. Non-drinkers were more likely to be current smokers and physically inactive compared to light drinkers, and less likely to have had a university degree, a household income ≥ $70,000 per year, private health insurance or be married or living with a

partner. For most baseline characteristics, there was greater variation by drinks per drinking-day than by drinking frequency. Participants consuming more than 4 drinks per drinking-day were more likely to be in lower socio-demographic categories and have unhealthy behavioural risk factors than those who consumed less than 4. Participants with higher drinking frequency were more likely to have private health insurance and less likely to be overweight or obese, while the reverse was true for participants with higher drinks per drinking-day.

Among drinkers, a greater number of drinks per week was significantly associated with increased risk of death from digestive system disease, liver disease, external causes, falls and suicide and all-cause mortality, and decreased risk of death from prostate cancer and NHL (Table 2). There was significant variation in the risk of death from non-alcohol-related cancers combined by total weekly alcohol consumption, however there was no evidence of a linear trend. There were no significant interactions between total alcohol consumption and sex, while significant interactions with smoking status were detected for death from lung cancer ($p = 0.02$) and all-cause mortality ($p = 0.01$). When stratified by smoking status, risk was elevated in never-smokers compared to ever-smokers for > 14 and ≤ 28 drinks per week for lung cancer mortality and for > 28 drinks per week for all-cause mortality (Supplementary Tables 1 and 2).

When excluding participants with disease at baseline, the positive linear trends for suicide and all-cause mortality remained significant, the inverse trend for prostate cancer was not significant, while the inverse trend for NHL was also not significant but the hazard ratios did not appear to differ materially. Furthermore, additional positive associations with drinking were detected for death from alcohol-related cancers combined, oesophageal cancer, kidney cancer, CVD and other CVD (Supplementary Table 3).

Figure 1 shows the results of the log-linear models in which the risk associated with each additional drink per day was plotted for each cause of death. The direction and statistical significance of effect estimates were similar to the corresponding categorical models, but with no significant association

for suicide, and additional positive associations for death from alcohol-related cancers combined, liver cancer, other CVD and other external causes.

Figure 2 shows the results of the restricted cubic spline models in which the risk associated with each additional drink per week was plotted by cause of death, accounting for a non-linear relationship with intake. The AIC was lower in the cubic spline model compared to the log-linear model for death from all cancers combined, liver cancer, breast cancer, non-alcohol-related cancers combined, CVD, IHD, respiratory system disease, fall, suicide, other external causes, other causes combined and all-cause mortality (results not shown), suggesting non-linear relationships between these causes of death and overall alcohol consumption among drinkers.

After adjusting for total alcohol consumption, drinking frequency (drinking-days per week) was positively associated with risk of death from respiratory system disease (p_{trend} = 0.03; Table 3) and inversely associated with risk of death from all cancers combined (p_{trend} < 0.001), non-alcohol-related cancers combined (p_{trend} < 0.001), CVD (p_{trend} = 0.02), IHD (p_{trend} = 0.01), and all-cause mortality (p_{trend} < 0.001). Death from pancreatic cancer varied significantly by drinking frequency, however there was no evidence of a linear trend. A statistical interaction with sex was detected for non-alcohol-related cancers combined (p = 0.03), with lower HRs for 3-5 and 6-7 drinking-days per week in men (Supplementary Table 4). There were no significant interactions by smoking status.

After excluding participants with disease at baseline in sensitivity analyses (see Supplementary Table 5), the inverse linear trends observed for death from all cancers combined, non-alcohol-related cancers combined, IHD and all-cause mortality remained unchanged. The inverse linear trend for CVD mortality and drinking frequency observed in the main analysis was not significant in sensitivity analyses, however the HRs were not materially different. Likewise, the positive linear trend for respiratory system disease in the main analysis was not significant in sensitivity analyses, however the HRs were consistent with the main effects. After exclusion of baseline diabetes, there was an inverse association with drinking frequency and death from diabetes (p_{trend} = 0.04). After exclusion of

participants with prior cancer, lung cancer mortality risk varied by drinking frequency, with lower risk in those consuming alcohol 3-7 days compared to 1-2 drinking-days per week, but the linear trend was not significant.

Table 4 shows mortality risk by mean drinks per drinking-day. After adjustment for total alcohol consumption, drinks per drinking-day was positively associated with risk of death from all cancers combined (p_{trend} = 0.006), oesophageal cancer (p_{trend} = 0.047), non-alcohol-related cancers combined (p_{trend} = 0.01), lung cancer (p_{trend} = 0.04), and all-cause mortality (p_{trend} = 0.001). A significant interaction with sex was detected for all-cause mortality (p = 0.02), with elevated HRs for '> 2 and ≤ 4' and '> 4' drinks per drinking-day in women (Supplementary Table 6). There were no statistical interactions between smoking status and mean drinks per drinking-day. When excluding participants with disease at baseline and adjusting for total alcohol consumption all significant trends observed in the main analysis remained significant, and an additional positive association with mean drinks per drinking-day was detected for death from kidney cancer (p_{trend} = 0.03) (Supplementary Table 7).

There were no significant interactions between drinking-days per week and drinks per drinking-day for any cause of death. Table 5 shows the results of the overall drinking pattern analysis for all-cause mortality. There were significantly elevated HRs in those consuming > 4 drinks on 6-7 days per week (i.e. heavy frequent drinkers), > 4 drinks on 1-2 days per week (i.e. heavy episodic 'binge' drinkers) and > 2 and ≤ 4 drinks on 1-2 days per week, compared to those in the lowest consumption group (≤ 2 drinks on 1-2 days/week). There was also a significantly lowered HR in those consuming ≤ 2 drinks on 3-5 days per week.

No violations of the proportional hazards assumption were detected.

Discussion

We found that increasing numbers of alcoholic drinks per week was associated with increased risk of death from oesophageal cancer, liver cancer, kidney cancer, alcohol-related cancers combined, CVD, digestive system disease, liver disease, external causes, falls, suicide, all other causes combined and all-cause mortality. CVD and all-cause mortality had a J-shaped relationship with total weekly intake, however there was no significant decrease in risk, and for all-cause mortality, risk was significantly increased with heavier consumption. Decreased risk in relation to increasing numbers of drinks per week was found for death from NHL. Death from causes previously reported to have an association with alcohol consumption[27], including all cancers combined, mouth, pharynx and larynx cancer, colorectal cancer, breast cancer, diabetes, dementia, IHD, cerebrovascular disease, lower respiratory infection, other digestive system disease and transport accident, were not associated with alcohol consumption in our study, possibly due to limited power. Many causes of death were found to have a non-linear relationship with alcohol consumption, suggesting that the risks of drinking may be more complex than a simple dose-response relationship. This was the case for all cancers combined, liver cancer, breast cancer, non-alcohol-related cancers combined, CVD, IHD, respiratory system disease, fall, suicide, other external causes, other causes combined and all-cause mortality. Drinking pattern was independently related to mortality from a number of causes. Specifically, drinking frequency was positively associated with risk of death from respiratory system disease and inversely associated with risk of death from all cancers combined, non-alcohol-related cancers combined, diabetes, CVD, IHD and all-cause mortality. Mean number of drinks per drinking-day was positively associated with risk of death from all cancers combined, oesophageal cancer, non-alcohol-related cancers combined, lung cancer, kidney cancer and all-cause mortality.

Our results for total weekly alcohol consumption are largely consistent with previous literature. As expected, we found that drinking was positively associated with a wide variety of mortality outcomes, including death from cancers, digestive system disease and external causes. For death from lower respiratory infection, diabetes, dementia and transport accident, we expected to find an association but did not. Most of these outcomes had a small number of deaths, especially in the

sensitivity analyses that excluded prior disease. It is possible these analyses were underpowered, as the confidence intervals for consuming > 28 drinks per week were often consistent with a substantial increased risk (e.g. greater than 5-fold increased risk for death from low respiratory infection) or decreased risk (e.g. approximately one tenth the risk for death from diabetes and dementia).

The potential benefits of 'moderate' drinking for reducing the risk of death from CVD has received much attention. Proposed causal mechanisms for the benefits of drinking for CVD have included increased high density lipoprotein cholesterol, decreased low density lipoprotein cholesterol, increased insulin sensitivity, reduced atherosclerotic plaque formations and possible anti-coagulant effects including reduced fibrinogen levels[45-47]. However, methodological considerations have also been put forward as an explanation for the apparent protective effect[8], and we attempted to account for some of these factors in a number of ways. Specifically, we used light drinkers as the reference group rather than non-drinkers to account for the 'sick-quitter effect'[43], we excluded participants who died within three years of baseline to mitigate the potential for reverse causation, and we excluded participants with prior CVD in a sensitivity analysis. Thus, even though we observed a J-shaped, non-linear association for risk of CVD mortality, we did not detect a significant decrease in risk for low levels of consumption. Indeed, it was noteworthy that the exclusion of participants with prior CVD resulted in a significant linear increase in risk for CVD mortality, indicating that reduction in alcohol consumption in response to CVD diagnosis is likely to have biased risk estimates for CVD mortality. That is, participants with pre-existing CVD may have reduced their level of drinking from higher levels down to low-volume drinking, and therefore may be included in the reference group. We also found non-linear relationships between alcohol consumption and all cancers combined, liver cancer, breast cancer, non-alcohol-related cancers combined, respiratory system disease, fall, suicide, other external causes, other causes combined and all-cause mortality, The reason for the non-linear relationships is unclear and requires further examination.

Of the seven cancer types known to be caused by alcohol[33, 34],we only observed a significant increased risk of death from oesophageal and liver cancer. In sensitivity analyses, the exclusion of participants with prior cancer tended to result in increased hazard ratios for heavy drinking (> 28 drinks per week) for most of these cancer types, and for all cancers combined, indicating that estimates in the main analysis may have been biased by changes in alcohol consumption in response to pre-existing cancer diagnoses. It is likely that the length of follow-up was not sufficient to detect an increased risk of death from many of these cancer types, although the risks were in the right direction.

We found that alcohol was related to a decreased risk of death from prostate cancer, which was not consistent with prior reports of increased risk[36, 38]. However, this effect disappeared when participants with prior cancer were excluded, indicating the main effect could be accounted for by reverse causation. We also observed a decreased risk of death from NHL, similar to other studies[36, 40]). After excluding prior cancers the association was not significant, however there was no material change in the hazard ratios, and the confidence intervals were consistent with a large decrease in risk. Two alternate explanations have been proposed for the inverse relationship of NHL and alcohol. Either 1) that alcohol decreases risk of NHL by improved insulin sensitivity or an immunomodulatory effect[40], or 2) reverse causation, because the subtypes of NHL that characteristically produce symptoms before diagnosis (and may therefore cause a decrease in alcohol consumption prior to diagnosis) are inversely associated with drinking, while other subtypes without early symptoms do not[40]. However, our choice of reference group, the exclusion of prior cancer and deaths within three years of baseline would reduce the impact of any bias from reverse causation, suggesting that alcohol may indeed be protective for risk of NHL mortality.

Our findings were suggestive of an increased risk of death from kidney cancer and were unexpected. Meta-analyses have reported a decreased risk with moderate drinking[18, 36] or an inverse association with drinking[39]. While the confidence intervals in our main analysis for the hazards of

kidney cancer mortality indicated the possibility for a protective association, the HRs were all greater than 1. We also observed a significant positive trend in risk after excluding prior cancer (although there were no deaths in the reference category so we were unable to report confidence intervals for individual categories of alcohol consumption). Our results indicate that the decreased risk of death from kidney cancer reported in meta-analyses may have been biased by methodological factors.

Our results for the independent effect of drinking pattern on risk of mortality are only partially consistent with the few previous studies. Variation in study outcomes likely reflect the diversity of methods that have been used to assess drinking pattern. Specifically, the varied ways in which drinking patterns are defined, the strong relationship between patterns and overall consumption levels and the diversity in the methods used to assess drinking patterns[48, 49] makes comparisons between studies difficult. Indeed, almost every study to date has used a unique method to assess the impact of drinking pattern, including the decision to adjust for total alcohol consumption or not. We examined drinking patterns in three different ways, and observed different results for each.

We found that more drinking-days per week was inversely associated with risk of all-cause mortality and several causes of death, including all cancers combined, non-alcohol-related cancers combined, CVD (including IHD) and diabetes. If causal, it is thought inverse associations for all-cause mortality are probably mediated through CVD mortality[8]. The suggested mechanism for reduced risk of diabetes with 'moderate' drinking is via decreased gluconeogenesis, decreased glycogenolysis and increased insulin sensitivity[26, 50]. Perhaps the mechanisms for reduced risk with 'moderate' drinking for CVD and diabetes also operate to lower risk with greater drinking frequency. The inverse associations between drinking frequency and death from all cancers combined and non-alcohol-related cancers combined were unexpected, with a recent analysis reporting no relationship with incidence of these two cancer outcomes[51]. As there is no mechanistic basis for alcohol consumption to lower cancer risk, these two outcomes may serve as 'negative controls'[52]. That is, the existence of inverse associations for cancer mortality may be evidence for residual reverse

causation, signifying that inverse associations with drinking frequency for other outcomes such as cardiovascular and all-cause mortality are overestimated. It is also possible that these inverse associations reflect bias from the potential methodological issues which can affect studies of drinking pattern, such as incomplete adjustment for confounding variables related to mortality risk.

More drinking-days per week was positively related to respiratory system disease mortality. It has previously been reported that total alcohol consumption has no association with respiratory system disease mortality[20, 21], and no studies, to our knowledge, have examined the impact of drinking frequency. This novel finding could possibly be mediated by increased risk of lower respiratory infections which have been reported to be related to alcohol consumption[27].

More drinks per drinking-day was independently associated with risk of all-cause mortality and death from several cancers, with between 1.2 to 8.7 times increased risk observed among those reporting > 4 drinks per day. Our results were largely consistent with prior research, including previous studies which found a positive association between drinks per drinking-day or heavy episodic drinking and all-cause mortality[9, 11-14]. We did not however detect an effect for risk of death from CVD or its subtypes. Meta-analyses have reported relative risks of 1.75 (95% CI 1.36-2.25) for heavy episodic drinking[53], and 1.10 (1.03-1.17) for 'heavy irregular or binge' drinking[54] for IHD incidence. The confidence intervals for an independent effect of CVD and its subtypes we observed were compatible with hazard ratios of up to 1.5 to 2, and therefore consistent with these findings. There is also evidence for an effect of heavy episodic drinking on risk of diabetes[27], but we did not detect an association with drinks per drinking-day. Our confidence intervals were compatible with a hazard ratio of up to 7 however, indicating that our analysis was likely underpowered for this outcome. There were no associations for death from digestive system disease and external causes, but the confidence intervals for > 4 drinks per drinking-day with these outcomes were consistent with hazard ratios of at least 2, so perhaps these analyses were also underpowered.

We found an increase in risk of mortality from all cancers combined with more drinks per drinking-day. Evidence for a relationship between drinking pattern and cancer risk is sparse. Previous cohort studies have reported a positive association with heavy episodic drinking for cancer mortality[11], but no association with the highest number of drinks consumed in one day in a typical month for incidence (although there was a positive association for alcohol-related cancers combined in women alone)[51]. We did not detect an effect of drinks per drinking-day for death from alcohol-related cancers combined over and above the increased risk that was observed for overall consumption. The relative risks we observed for those reporting > 4 drinks per drinking-day were elevated but not significant. Similar to the analyses of overall alcohol consumption, our study may have been underpowered to detect an effect of drinks per drinking-day for some cancer types, and for breast cancer mortality in particular, due to few women with a high number of drinks per drinking-day.

We did however observe an independent, increased risk of death from oesophageal and kidney cancer mortality (for kidney cancer, after excluding those with pre-existing cancer) in relation to drinks per drinking-day. We are the first, to our knowledge, to report these effects. For oesophageal cancer, the proposed causal mechanism is the carcinogenic effect of acetaldehyde[55]. This finding suggests that consumption of many drinks on one occasion may multiply the carcinogenic effect of acetaldehyde accumulation. It should be noted that while the > 28 drinks per week category of total alcohol consumption was not significant, the HR point estimate and 95% confidence interval were very similar to those of the > 4 drinks per drinking-day category (2.50, 0.92-6.77; 2.86, 1.08-7.56 respectively). This may indicate that our analysis was only powered to detect a HR of approximately 2.7 for this outcome, and also that the potential increased risk in those consuming > 28 drinks per week may be largely attributable to the independent increased risk associated with consuming many drinks on one day rather than the risk associated with total alcohol consumption, as all persons in this group consumed > 4 mean drinks per drinking-day. For kidney cancer mortality, our results suggest the apparent positive association for total alcohol consumption may be mediated through heavier drinkers consuming more drinks per drinking-day.

We also found increased risk of lung cancer mortality with more drinks per drinking-day, which is consistent with one cohort study reporting an effect for heavy episodic drinking on incidence[56]. That study found the effect was only present in smokers, but we did not detect an interaction with smoking status. As current smoking was positively associated with drinks per drinking-day in our study, residual confounding by smoking could be at least partially responsible for this result.

There were no significant interactions between drinking-days per week and drinks per drinking-day for any cause of death including all-cause mortality. This is in contrast to a study reporting that drinks per drinking-day modified the relationship between drinking frequency and all-cause mortality, with a J-shaped association between drinking-days per week and mortality among persons consuming < 5 drinks per drinking-day and a linear dose-response association among persons consuming ≥ 5 drinks per drinking-day[57]. When we analysed drinking frequency and drinks per drinking-day simultaneously, for those who drank on only 1-2 days of the week, all-cause mortality risk was higher for those consuming more than 2 drinks on each of those days, compared to those who had less than 2. The risk for > 4 drinks per drinking-day was similar whether the drinks were consumed on 1-2 days or on 6-7 days. This shows that both heavy frequent drinking and heavy episodic 'binge' drinking independently increase risk of death. Indeed, the lack of significant interactions between drinking frequency and drinks per drinking-day means that for many causes of death, consuming a high number of drinks per drinking-day increases mortality risk regardless of whether it is 1 or 7 days per week. Further, even after rigorous attempts to prevent bias in relation to reverse causation, those who were frequent (3-5 days/week), low-volume (≤ 2 drinks) drinkers had a lower risk of death than infrequent (1-2 days/week) low-volume drinkers. In an analysis of an American population survey, it was reported that infrequent drinkers had a higher prevalence of 13 of 15 measured risk factors compared to more frequent drinkers, including health insurance status, being physically inactive and having fair or poor overall health[15]. We adjusted for many of these factors in our analyses, however the possibility of residual confounding cannot be ruled out.

Our study has several strengths. It is a prospective cohort study with a large number of participants, and examined multiple causes of death using a consistent methodology. We directly compared drinking pattern measured in three different ways and comprehensively adjusted for a large number of potential confounders. We used age as the underlying time variable to minimise potential confounding by age. We used a reference group of very light drinkers as opposed to 'non-drinkers' to mitigate bias from the 'sick-quitter effect' and to ensure that any effect of drinking pattern is relative to other drinkers. The adjustment for total alcohol consumption allowed for investigation of the independent effect of drinking pattern as separate from overall consumption. Furthermore, adjusting for total alcohol consumption as a continuous (rather than a categorical variable, as in previous studies) should have minimised bias from residual confounding by total alcohol consumption between drinking pattern groups.

Limitations of our study include the possibility of being underpowered for causes of death with a relatively low number of outcomes, which can be addressed by a longer period of follow-up. Due to the use of light drinkers as the reference group instead of lifetime abstainers, our hazard ratios for the true effects of alcohol consumption may be slightly underestimated (or overestimated, where hazard ratios were less than 1). Further, due to the questionnaire design our drinks per drinking-day variable was based on mean level of alcohol consumption. Some participants who were in fact heavy episodic drinkers will therefore have been grouped with less intense drinkers. For example, a participant consuming alcohol 2 days per week, with 5 drinks on one day and 1 on the other, would have been grouped with a participant consuming alcohol 2 days per week, with 3 drinks on both days. The risk profile of these two participants is possibly different but we were unable to differentiate between them. In addition, our drinking pattern analysis only included participants who usually consume at least one alcoholic drink per week, meaning those engaging in heavy episodic drinking less frequently than once per week were excluded. However, a possible advantage of using mean drinks per drinking-day may be that it is more representative of a person's usual exposure to

alcohol than other measures such as highest number of drinks consumed in one day over a period of time.

A potential issue in any observational study measuring alcohol consumption is the tendency for participants to underreport intake[58]. Risk estimates could therefore be biased if underreporting differs by drinking patterns and consumption levels. In both Australian and a Canadian studies, low-risk and non-heavy episodic drinkers were found to underreport their alcohol consumption to a greater degree than higher-risk and heavy episodic drinkers[59, 60]. Conversely, an English study found underreporting was disproportionately associated with heavy drinking, frequent drinking and non-routine drinking compared to participants without these drinking behaviours[61]. If for example participants consuming alcohol 1-2 days per week underreported their total alcohol consumption to a greater degree than daily drinkers, this could result in conservative estimates of risk for total alcohol consumption. Additionally, despite our best efforts to control for covariates, confounding by unmeasured factors associated with both drinking pattern and risk of mortality could be responsible for at least part of our associations. For example, it was reported in a prospective study that declining health is associated with a reduction in drinking frequency[62], meaning estimates could be biased by poor baseline health. We attempted to account for this however by excluding outcomes within the first three years of follow-up. Perhaps this period was not long enough to capture potential changes in alcohol consumption in response to ill-health that may begin many years before death. Another limitation was that cause-specific mortality data was only available to 2012 and all-cause mortality to 2014. A longer follow-up period works to mitigate selection bias[7], and it has been shown in meta-analyses that longer follow-up attenuates the association between moderate drinking and lowered risk of all-cause mortality[2, 3]. For this reason, inverse associations of moderate drinking, and perhaps drinking frequency, with mortality risk may be overestimated in our analysis, especially for cause-specific mortality. The issue of competing risks, whereby death from disease and injury associated with alcohol consumption earlier in life may confound

associations with risk of death from other causes later in life, may also result in an overestimation of decreased risk in analyses of both cause-specific and all-cause mortality[7, 63].

Conclusion

In conclusion, we used a large prospective study to investigate the influence of total alcohol consumption on risk of all-cause and cause-specific mortality, finding mostly consistent results with previous research. Our robust examination of the influence of drinking pattern on mortality suggests that number of drinks per drinking-day is independently associated with risk of all-cause mortality and death from all cancers combined, oesophageal cancer, non-alcohol-related cancers combined, lung cancer and kidney cancer. More drinking-days per week was also positively associated with risk of respiratory system disease mortality and inversely associated with risk of all-cause mortality and death from all cancers combined, non-alcohol-related cancers combined, diabetes, CVD and IHD. There are however methodological limitations in this and prior studies which mean we cannot eliminate the possibility that the observed decreased mortality risk with both low-volume drinking and drinking frequency are overestimated. Both heavy frequent drinking and heavy episodic drinking were significantly related to all-cause mortality risk, and are likely to independently increase cancer mortality as well.

These findings have a number of implications. Alcohol guidelines should emphasise that a high number of drinks per drinking-day, including heavy episodic drinking, is independently associated with mortality risk in addition to the total amount consumed. Drinks per drinking-day and drinking frequency should also be incorporated into calculations of the burden of disease and injury attributable to alcohol consumption, so that more accurate estimates reflecting the influence of pattern of drinking can be obtained. Finally, these results show that government policies and programs aiming to lessen alcohol-related harm should target persons consuming a high number of drinks per drinking-day and heavy episodic drinkers as a priority, to ensure that interventions have

maximal health impact. Mass media campaigns for heavy episodic drinking often target younger people and in relation to immediate harms, whereas these findings show that older age groups are also relevant targets, especially in relation to long-term harm. According to the 2016 National Drug Strategy Household Survey, 17% of Australians aged 60-69 years and 7% aged ≥ 70 years consumed > 4 drinks per occasion at least monthly[64], meaning that a sizable portion of older Australians engage in heavy episodic drinking and are at increased mortality risk.

In the absence of a randomised controlled trials, further investigation of the possible role of confounding by health status on drinking patterns and mortality is required to be confident that independent associations of drinking frequency and other drinking patterns with risk are truly causal. Nevertheless, our study has provided evidence that limiting drinks per drinking-day, including heavy episodic drinking, is an important approach to prevent mortality independent of and in addition to limiting total alcohol consumption.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Tables and figures

Table 1. Socio-demographic and other characteristics by alcohol consumption in the 45 and Up Study (2006-2014), New South Wales, Australia.

	Alcoholic drinks per week						Drinking frequency (days per week)			Drinks per drinking-day		
Characteristic at baseline	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	**1-2**	**3-5**	**6-7**	**≤ 2**	**> 2, ≤ 4**	**> 4**
n	83,681	39,464	49,226	45,092	26,553	9919	47,700	58,521	62,027	106,345	44,260	17,643
Male (%)	32.5	41.0	43.9	53.4	72.3	89.6	46.8	50.0	60.0	42.8	64.2	84.5
Mean age in years (SD)	63.6 (11.4)	61.1 (10.7)	62.3 (10.9)	61.5 (10.4)	61.3 (9.9)	60.4 (9.1)	59.8 (10.2)	59.7 (9.7)	64.4 (10.7)	63.6 (11.4)	60.1 (9.7)	59.3 (9.2)
Major city resident (%)	52.9	54.0	52.0	51.2	49.0	44.8	53.5	52.1	48.9	52.3	50.9	46.4
University degree (%)	17.6	26.2	26.6	28.1	27.0	19.3	24.5	29.0	26.0	27.7	27.4	18.3
Household income ≥ $70,000[b] (%)	14.0	35.9	27.6	32.3	34.0	28.5	28.0	33.9	26.8	27.3	35.2	29.6
Private health insurance[c] (%)	55.8	69.3	72.2	73.3	71.0	60.4	67.9	73.2	71.5	72.7	71.6	60.2
Married or living with partner (%)	68.7	76.1	78.6	80.3	80.4	74.0	75.5	79.9	79.6	78.7	80.1	73.8
Born in Australia (%)	73.0	72.8	75.8	77.4	78.8	82.0	75.0	77.3	76.7	74.8	78.7	81.0
Current smoker (%)	7.4	5.6	5.1	6.6	9.6	17.7	7.5	5.9	7.8	4.8	8.4	17.0
Overweight or obese[d] (%)	57.1	58.2	53.9	56.4	63.0	68.8	61.7	57.8	55.0	53.8	63.0	69.7
Physically inactive[e] (%)	7.9	4.2	3.6	3.3	3.9	5.9	4.2	3.2	4.1	3.6	3.8	5.2
< 2 fruit serves per day[f] (%)	37.4	37.0	38.5	44.4	52.8	63.2	39.6	40.9	48.7	38.8	48.5	58.4
< 5 vegetable serves per day (%)	64.3	66.1	65.1	66.7	70.0	73.2	67.1	66.3	67.6	65.3	69.2	72.0
< 7 fibre serves per week[g] (%)	14.6	13.2	10.9	13.2	16.7	26.7	14.5	12.9	14.3	11.5	15.6	23.8
Red meat > 5 times per week (%)	9.9	8.6	9.3	10.8	14.5	21.7	9.0	9.5	14.1	9.5	12.1	18.1
Processed meat > 1 time per week (%)	27.4	29.4	30.3	34.0	41.7	51.1	31.9	33.7	36.1	29.9	38.2	48.7
Nulliparous (women) (%)	10.1	9.9	10.7	12.6	16.9	21.6	10.1	11.6	13.3	10.7	14.3	16.7
Post-menopausal (women) (%)	66.3	63.2	65.3	63.5	61.6	54.3	60.5	61.1	70.0	65.7	57.7	53.5
Ever used HRT (women) (%)	35.2	36.8	39.2	39.2	39.5	36.0	35.1	37.5	43.2	39.4	35.9	32.8
Height ≥ 180 cm (men) (%)	26.7	30.9	32.0	33.8	34.8	35.9	32.6	34.8	32.5	31.5	34.9	35.7
Height ≥ 165 cm (women) (%)	31.3	36.7	38.6	41.9	43.7	42.7	37.7	41.3	39.1	38.3	43.5	41.6

Percentages include participants with missing or invalid responses. [a]< 1 alcoholic drink per week. [b]Pre-tax annual household income from all sources in Australian dollars. [c]Including Department of Veterans' Affairs white or gold card. [d]Body mass index ≥ 25 kgm^{-2}. [e]Weekly physical activity time = 0 minutes. [f]Excludes fruit juice. [g]Serves of breakfast cereal and brown or wholemeal bread. SD, Standard Deviation. HRT, Hormone Replacement Therapy.

Table 2. Hazard ratios and 95% confidence intervals of cause-specific mortality risk by alcohol consumption in the 45 and Up Study (2006-2014), New South Wales, Australia.

		Drinks/week							
Cause of death (ICD-10 code)	**n deaths**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Cancer (C00-97;D45-47)	2391	1.04 (0.92-1.19)	1.00	0.93 (0.81-1.08)	0.90 (0.78-1.05)	0.87 (0.74-1.03)	0.95 (0.76-1.18)	0.13	0.68
- Alcohol-related (C00-15;18-20;22;32;50[d])	524	0.91 (0.70-1.20)	1.00	0.82 (0.60-1.12)	0.99 (0.73-1.36)	0.90 (0.62-1.30)	1.33 (0.85-2.08)	0.37	0.07
- Mouth, pharynx and larynx (C00-14;32)	38	1.03 (0.36-2.95)	1.00	-[e]	1.50 (0.51-4.42)	0.99 (0.29-3.36)	0.80 (0.18-3.54)	0.92	0.70
- Oesophagus (C15)	78	1.33 (0.59-2.99)	1.00	1.30 (0.55-3.09)	1.44 (0.61-3.39)	0.59 (0.19-1.84)	2.50 (0.92-6.77)	0.19	0.27
- Colorectum (C18-20)	205	1.01 (0.64-1.58)	1.00	0.98 (0.60-1.62)	0.98 (0.58-1.65)	1.34 (0.77-2.32)	1.25 (0.59-2.65)	0.84	0.16
- Liver (C22)	62	2.04 (0.69-6.03)	1.00	2.14 (0.69-6.65)	2.56 (0.82-7.95)	2.10 (0.60-7.37)	4.04 (1.09-15.1)	0.46	0.06
- Breast (C50[d])	141	0.62 (0.40-0.95)	1.00	0.55 (0.32-0.94)	0.60 (0.33-1.07)	0.47 (0.18-1.23)	0.78 (0.10-5.77)	0.20	0.19
- Non-alcohol-related (Other C;D45-47)	1867	1.08 (0.94-1.25)	1.00	0.97 (0.82-1.14)	0.88 (0.74-1.05)	0.87 (0.72-1.05)	0.86 (0.67-1.12)	0.04	0.17
- Stomach (C16)	55	1.24 (0.57-3.17)	1.00	1.16 (0.45-2.99)	0.63 (0.21-1.89)	0.87 (0.29-2.66)	0.59 (0.12-2.94)	0.63	0.66
- Pancreas (C25)	154	1.15 (0.69-1.93)	1.00	1.10 (0.62-1.94)	1.13 (0.63-2.04)	1.11 (0.57-2.17)	0.68 (0.23-2.04)	0.94	0.58
- Lung (C33-34)	416	1.50 (1.05-2.13)	1.00	1.26 (0.86-1.86)	1.10 (0.74-1.64)	1.21 (0.80-1.84)	1.21 (0.72-2.01)	0.20	0.63
- Melanoma (C43)	98	0.77 (0.42-1.42)	1.00	0.72 (0.38-1.40)	0.62 (0.31-1.24)	0.86 (0.42-1.76)	0.47 (0.13-1.66)	0.73	0.37
- Prostate (C61)	243	0.72 (0.50-1.05)	1.00	0.72 (0.48-1.08)	0.56 (0.36-0.87)	0.59 (0.36-0.96)	0.56 (0.28-1.12)	0.13	0.049
- Kidney (C64)	47	1.43 (0.52-3.88)	1.00	1.31 (0.44-3.94)	1.15 (0.36-3.68)	1.05 (0.27-4.04)	2.28 (0.52-10.1)	0.89	0.33
- Non-Hodgkin lymphoma (C82-85)	75	1.01 (0.54-1.91)	1.00	0.65 (0.31-1.39)	0.50 (0.22-1.17)	0.42 (0.15-1.20)	-[e]	0.29	0.02
Diabetes (E10-14)	115	1.47 (0.81-2.66)	1.00	0.84 (0.40-1.77)	1.24 (0.61-2.54)	0.92 (0.38-2.23)	0.52 (0.11-2.32)	0.31	0.72
Dementia (F00-03;G30)	218	0.90 (0.61-1.33)	1.00	0.79 (0.50-1.25)	0.80 (0.48-1.35)	0.62 (0.30-1.28)	0.39 (0.09-1.63)	0.64	0.29
Cardiovascular disease (G45-46;I00-99)	1926	1.00 (0.87-1.15)	1.00	0.86 (0.73-1.01)	0.86 (0.72-1.03)	0.89 (0.72-1.09)	1.00 (0.75-1.33)	0.13	0.52
- Ischaemic heart disease (I20-25)	915	1.02 (0.84-1.25)	1.00	0.90 (0.72-1.14)	0.80 (0.62-1.03)	0.90 (0.67-1.20)	0.80 (0.52-1.22)	0.29	0.46
- Cerebrovascular disease (G45-46;I60-69)	468	0.96 (0.73-1.27)	1.00	0.82 (0.59-1.14)	0.83 (0.58-1.18)	0.91 (0.59-1.40)	0.95 (0.50-1.83)	0.79	0.67
- Other cardiovascular disease (Other I)	543	1.00 (0.77-1.30)	1.00	0.82 (0.60-1.12)	1.00 (0.72-1.37)	0.82 (0.55-1.24)	1.45 (0.88-2.40)	0.22	0.08
Respiratory system disease (J00-99)	517	1.26 (0.94-1.69)	1.00	1.13 (0.81-1.57)	1.19 (0.85-1.68)	1.22 (0.83-1.79)	0.99 (0.56-1.75)	0.69	0.76
- Lower respiratory infection (J09-22)	87	1.27 (0.63-2.58)	1.00	0.96 (0.42-2.22)	1.41 (0.61-3.26)	1.75 (0.67-4.60)	0.73 (0.09-5.84)	0.75	0.63
- Other respiratory system disease (Other J)	430	1.27 (0.91-1.75)	1.00	1.16 (0.81-1.67)	1.16 (0.80-1.69)	1.13 (0.74-1.73)	1.00 (0.55-1.81)	0.79	0.94
Digestive system disease (K00-93)	175	1.33 (0.80-2.23)	1.00	1.20 (0.67-2.14)	1.13 (0.60-2.10)	1.40 (0.71-2.74)	2.41 (1.13-5.15)	0.30	0.04
- Liver disease (K70-77)	40	1.66 (0.55-5.06)	1.00	0.66 (0.15-2.96)	1.14 (0.30-4.29)	0.91 (0.20-4.16)	4.54 (1.30-15.9)	0.03	0.002
- Other digestive system disease (Other K)	135	1.24 (0.69-2.21)	1.00	1.32 (0.70-2.49)	1.11 (0.55-2.26)	1.59 (0.75-3.38)	1.01 (0.28-3.60)	0.86	0.80
External (V01-Y98)	208	1.81 (1.11-2.95)	1.00	1.06 (0.59-1.88)	1.38 (0.79-2.45)	1.74 (0.93-3.23)	1.99 (0.90-4.36)	0.0500[f]	0.005
- Transport accident (V00-99;Y85)	40	1.40 (0.49-3.96)	1.00	0.73 (0.21-2.55)	1.26 (0.40-3.93)	1.64 (0.50-5.40)	0.60 (0.07-5.35)	0.72	0.57
- Fall (W00-19)	48	2.28 (0.68-7.72)	1.00	1.35 (0.33-5.44)	2.93 (0.78-11.1)	2.75 (0.59-12.8)	9.03 (1.86-43.7)	0.07	0.002
- Suicide (X60-84;Y87.0)	39	8.72 (1.16-65.6)	1.00	2.40 (0.25-23.1)	5.98 (0.73-49.0)	7.55 (0.89-63.9)	5.49 (0.48-62.9)	0.15	0.04
- Other external (W20-X59;Y86;Y87.1-98)	81	1.31 (0.66-2.59)	1.00	0.99 (0.45-2.19)	0.56 (0.20-1.52)	0.84 (0.28-2.47)	1.28 (0.34-4.80)	0.52	0.84
Other (Other A00-R99)	704	1.11 (0.88-1.41)	1.00	1.08 (0.82-1.42)	0.95 (0.71-1.27)	0.86 (0.60-1.21)	1.29 (0.84-1.98)	0.37	0.67
All-cause mortality (A00-Y98)	13,988	1.11 (1.05-1.17)	1.00	0.95 (0.89-1.01)	0.97 (0.91-1.04)	0.96 (0.89-1.03)	1.10 (1.00-1.21)	< 0.001	0.02

Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Female breast cancer only. [e]Zero deaths in cell. [f]$p < 0.05$. ICD-10, International Classification of Diseases, version 10.

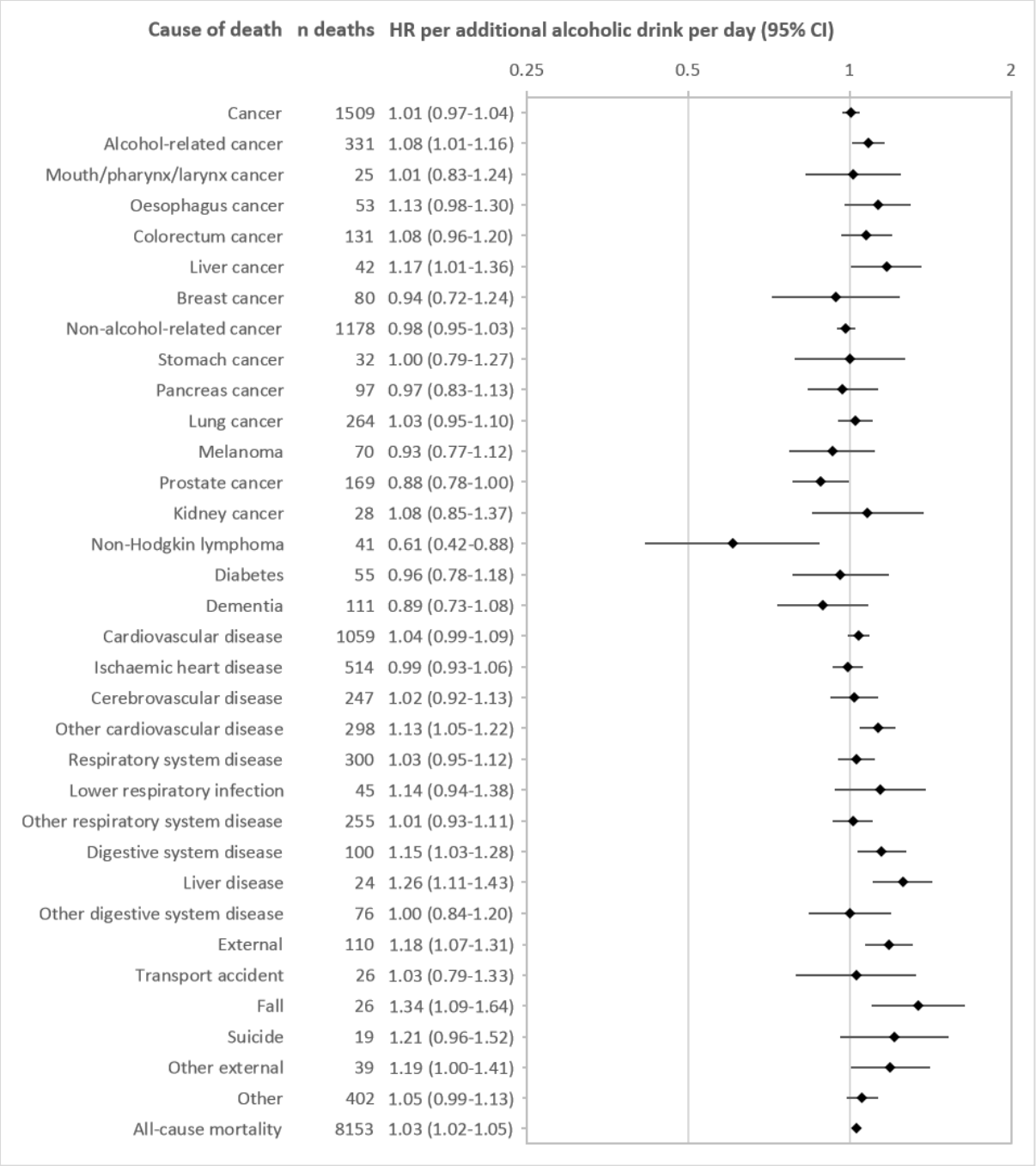

Figure 1. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk per one drink increase in mean daily alcohol consumption among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia. Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. Breast cancer in women only.

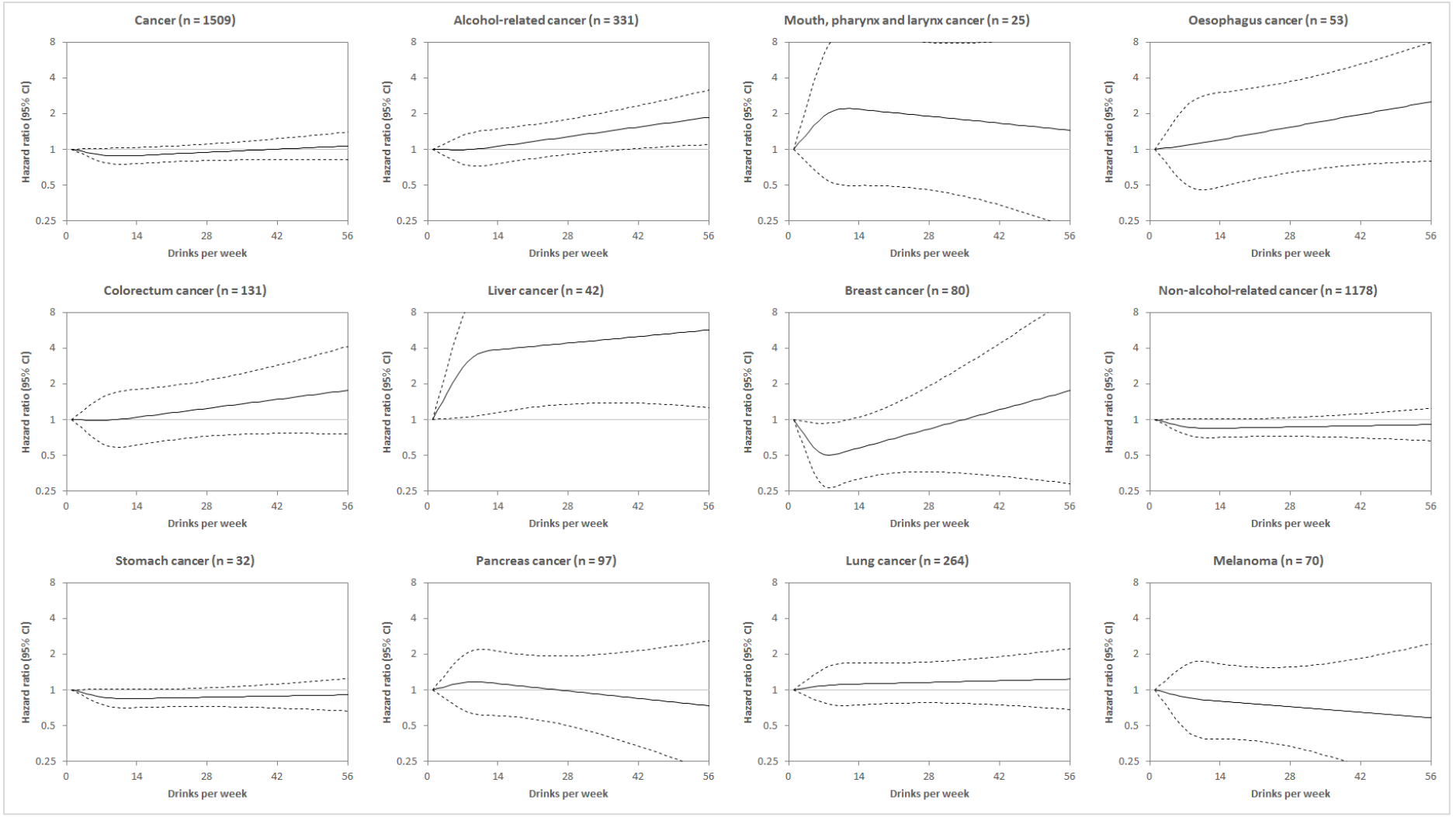

Figure 2. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk by alcohol consumption using restricted cubic splines among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia. Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. Brackets show n cases. Breast cancer in women only.

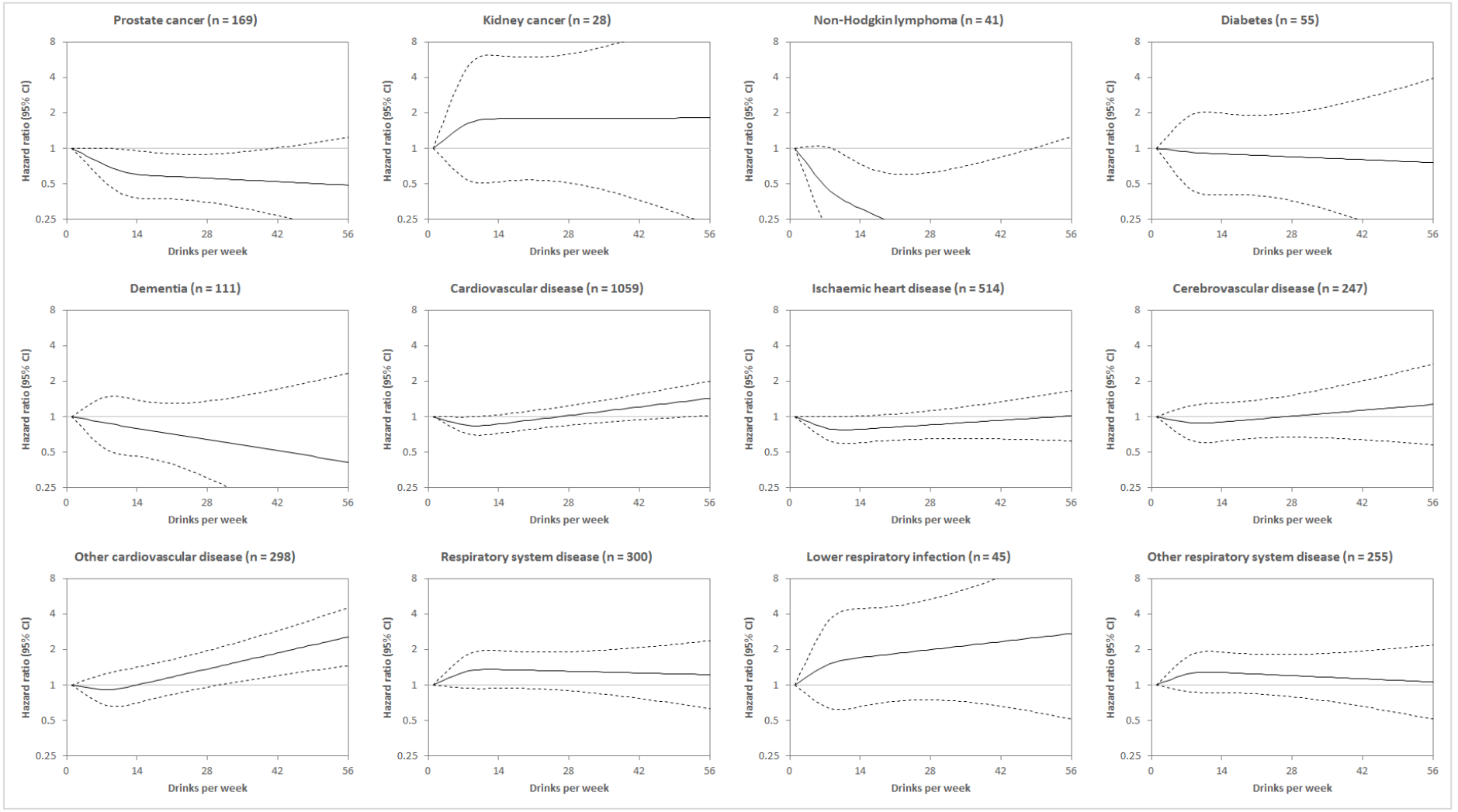

Figure 2. (Continued)

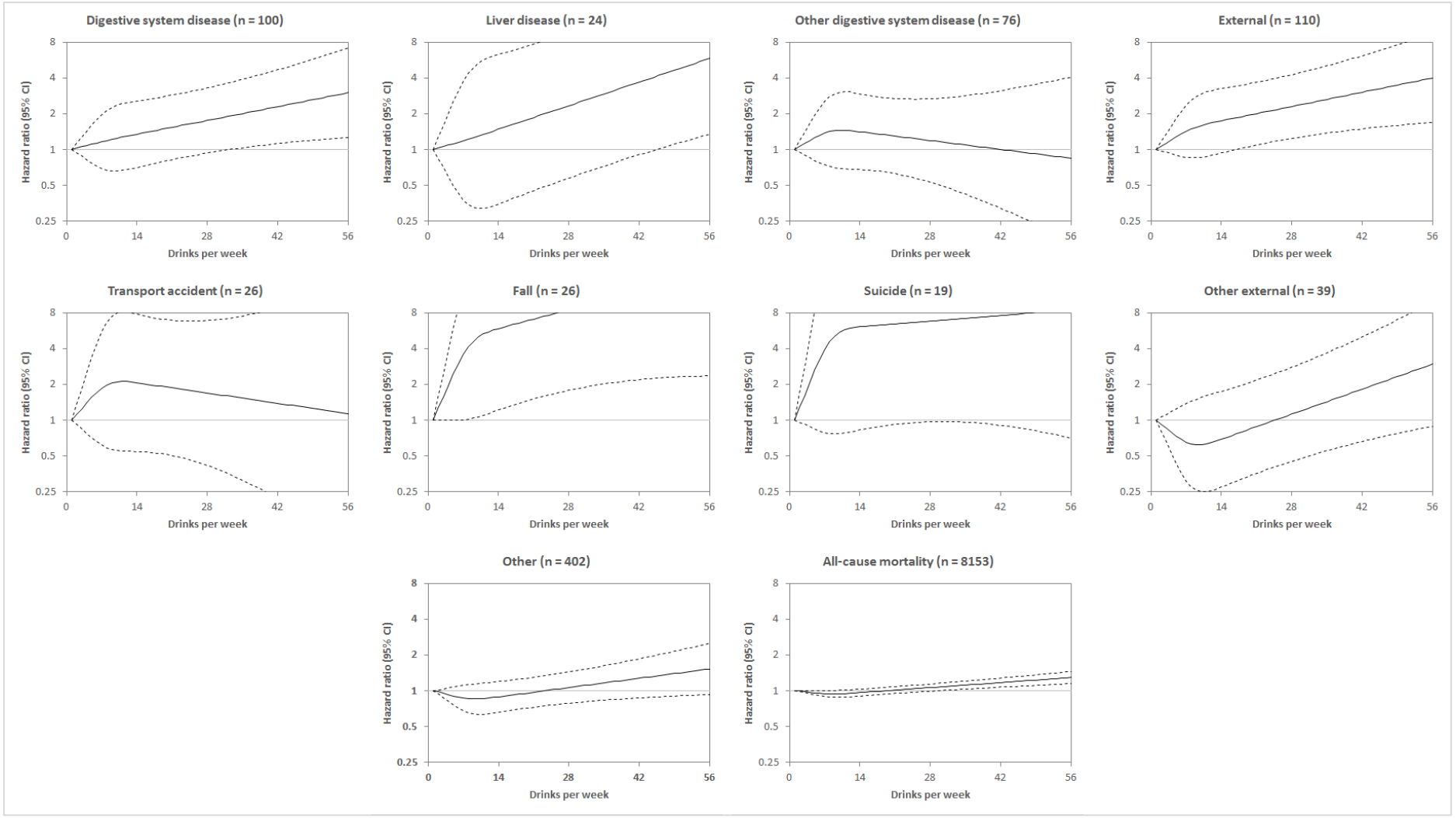

Figure 2. (Continued)

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk by drinking-days per week among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia.

		HR drinking-days per week - unadjusted for total alcohol consumption (95% CI)					HR drinking-days per week - adjusted for total alcohol consumption (95% CI)				
Cause of death (ICD-10 code)	**n deaths**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**
Cancer (C00-97;D45-47)	1470	1.00	0.82 (0.71-0.94)	0.80 (0.70-0.91)	0.001	0.001	1.00	0.79 (0.68-0.91)	0.73 (0.63-0.85)	< 0.001	< 0.001
- Alcohol-related (C00-15;18-20;22;32;50[c])	325	1.00	0.88 (0.65-1.19)	0.98 (0.75-1.29)	0.65	0.99	1.00	0.82 (0.60-1.12)	0.82 (0.60-1.12)	0.37	0.24
- Mouth, pharynx and larynx (C00-14;32)	25	1.00	3.00 (0.79-11.3)	2.49 (0.69-9.04)	0.27	0.25	1.00	3.23 (0.83-12.6)	2.97 (0.71-12.4)	0.23	0.19
- Oesophagus (C15)	53	1.00	0.89 (0.41-1.93)	0.85 (0.43-1.68)	0.90	0.65	1.00	0.77 (0.35-1.70)	0.58 (0.26-1.26)	0.38	0.16
- Colorectum (C18-20)	129	1.00	0.85 (0.52-1.40)	0.98 (0.63-1.50)	0.78	1.00	1.00	0.79 (0.48-1.31)	0.81 (0.49-1.36)	0.62	0.44
- Liver (C22)	41	1.00	1.05 (0.40-2.76)	1.81 (0.79-4.17)	0.23	0.12	1.00	0.94 (0.35-2.49)	1.36 (0.54-3.44)	0.65	0.45
- Breast (C50[c])	77	1.00	0.68 (0.39-1.20)	0.70 (0.40-1.22)	0.31	0.20	1.00	0.79 (0.43-1.45)	0.97 (0.46-2.05)	0.69	0.90
- Non-alcohol-related (Other C;D45-47)	1145	1.00	0.80 (0.68-0.94)	0.76 (0.65-0.87)	< 0.001	< 0.001	1.00	0.78 (0.66-0.92)	0.71 (0.60-0.84)	< 0.001	< 0.001
- Stomach (C16)	28	1.00	0.89 (0.31-2.56)	0.91 (0.36-2.33)	0.97	0.87	1.00	0.84 (0.28-2.47)	0.79 (0.27-2.35)	0.91	0.69
- Pancreas (C25)	91	1.00	1.35 (0.79-2.29)	0.75 (0.43-1.30)	0.06	0.21	1.00	1.27 (0.73-2.20)	0.65 (0.34-1.25)	0.048	0.15
- Lung (C33-34)	258	1.00	0.67 (0.46-0.96)	0.83 (0.62-1.13)	0.10	0.42	1.00	0.64 (0.44-0.93)	0.74 (0.52-1.06)	0.06	0.16
- Melanoma (C43)	68	1.00	0.75 (0.37-1.48)	0.87 (0.48-1.59)	0.70	0.76	1.00	0.79 (0.39-1.59)	1.00 (0.49-2.05)	0.71	0.93
- Prostate (C61)	166	1.00	0.56 (0.36-0.89)	0.71 (0.50-1.02)	0.04	0.13	1.00	0.61 (0.38-0.98)	0.90 (0.58-1.39)	0.10	0.75
- Kidney (C64)	26	1.00	0.69 (0.21-2.19)	1.06 (0.41-2.73)	0.70	0.79	1.00	0.64 (0.20-2.10)	0.91 (0.30-2.72)	0.73	0.95
- Non-Hodgkin lymphoma (C82-85)	41	1.00	1.05 (0.51-2.19)	0.34 (0.15-0.76)	0.009	0.006	1.00	1.30 (0.60-2.84)	0.56 (0.20-1.57)	0.15	0.30
Diabetes (E10-14)	54	1.00	0.71 (0.34-1.49)	0.70 (0.37-1.33)	0.50	0.30	1.00	0.69 (0.33-1.47)	0.66 (0.31-1.40)	0.49	0.28
Dementia (F00-03;G30)	104	1.00	1.05 (0.62-1.76)	0.76 (0.47-1.22)	0.34	0.22	1.00	1.08 (0.63-1.85)	0.84 (0.47-1.48)	0.62	0.52
Cardiovascular disease (G45-46;I00-99)	1031	1.00	0.99 (0.83-1.18)	0.91 (0.78-1.06)	0.37	0.19	1.00	0.95 (0.79-1.13)	0.81 (0.68-0.97)	0.04	0.02
- Ischaemic heart disease (I20-25)	501	1.00	0.90 (0.70-1.15)	0.78 (0.63-0.97)	0.08	0.02	1.00	0.88 (0.68-1.12)	0.72 (0.56-0.93)	0.04	0.01
- Cerebrovascular disease (G45-46;I60-69)	240	1.00	0.99 (0.69-1.42)	0.89 (0.65-1.22)	0.69	0.42	1.00	0.95 (0.66-1.38)	0.81 (0.56-1.17)	0.47	0.24
- Other cardiovascular disease (Other I)	290	1.00	1.21 (0.85-1.71)	1.23 (0.91-1.66)	0.40	0.22	1.00	1.13 (0.79-1.60)	1.02 (0.72-1.43)	0.74	0.97
Respiratory system disease (J00-99)	291	1.00	1.25 (0.86-1.80)	1.43 (1.04-1.95)	0.08	0.03	1.00	1.26 (0.87-1.83)	1.47 (1.03-2.09)	0.11	0.03
- Lower respiratory infection (J09-22)	44	1.00	1.32 (0.48-3.62)	1.86 (0.82-4.26)	0.29	0.12	1.00	1.27 (0.46-3.51)	1.67 (0.67-4.16)	0.53	0.26
- Other respiratory system disease (Other J)	247	1.00	1.24 (0.83-1.85)	1.36 (0.83-1.85)	0.22	0.09	1.00	1.27 (0.85-1.89)	1.43 (0.97-2.11)	0.20	0.07
Digestive system disease (K00-93)	100	1.00	1.12 (0.61-2.05)	1.39 (0.82-2.35)	0.42	0.20	1.00	1.02 (0.55-1.89)	1.07 (0.60-1.93)	0.97	0.81
- Liver disease (K70-77)	24	1.00	0.54 (0.16-1.86)	1.40 (0.53-3.70)	0.25	0.40	1.00	0.40 (0.11-1.41)	0.62 (0.19-1.99)	0.36	0.49
- Other digestive system disease (Other K)	76	1.00	1.46 (0.71-2.99)	1.43 (0.75-2.70)	0.51	0.33	1.00	1.50 (0.73-3.11)	1.56 (0.76-3.19)	0.44	0.26
External (V01-Y98)	107	1.00	0.91 (0.51-1.61)	1.38 (0.85-2.25)	0.18	0.14	1.00	0.82 (0.46-1.46)	1.05 (0.60-1.82)	0.62	0.77
- Transport accident (V00-99;Y85)	26	1.00	0.50 (0.14-1.75)	1.51 (0.57-3.96)	0.16	0.29	1.00	0.54 (0.15-1.93)	1.76 (0.57-5.49)	0.14	0.25
- Fall (W00-19)	25	1.00	1.54 (0.33-7.26)	3.57 (0.99-12.9)	0.08	0.03	1.00	1.44 (0.30-6.83)	2.88 (0.73-11.4)	0.23	0.09
- Suicide (X60-84;Y87.0)	18	1.00	1.93 (0.49-7.62)	1.27 (0.32-5.04)	0.58	0.89	1.00	1.57 (0.39-6.32)	0.71 (0.15-3.37)	0.40	0.52
- Other external (W20-X59;Y86;Y87.1-98)	38	1.00	0.75 (0.30-1.88)	0.87 (0.40-1.89)	0.83	0.77	1.00	0.62 (0.24-1.59)	0.55 (0.23-1.32)	0.38	0.19
Other (Other A00-R99)	392	1.00	1.07 (0.81-1.43)	1.05 (0.81-1.35)	0.88	0.76	1.00	1.02 (0.76-1.37)	0.92 (0.69-1.23)	0.71	0.52
All-cause mortality (A00-Y98)	7965	1.00	0.91 (0.85-0.97)	0.93 (0.88-0.98)	0.006	0.03	1.00	0.88 (0.82-0.93)	0.85 (0.80-0.90)	< 0.001	< 0.001

Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]Overall. [b]Linear trend using median number of drinking-days per week of each category. [c]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk by mean drinks per drinking-day among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia.

		HR mean drinks per drinking-day - unadjusted for total alcohol consumption (95% CI)					HR mean drinks per drinking-day - adjusted for total alcohol consumption (95% CI)				
Cause of death (ICD-10 code)	**n deaths**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**
Cancer (C00-97;D45-47)	1470	1.00	1.09 (0.96-1.24)	1.19 (1.00-1.42)	0.10	0.03	1.00	1.16 (1.00-1.33)	1.38 (1.09-1.33)	0.02	0.006
- Alcohol-related (C00-15;18-20;22;32;50[c])	325	1.00	0.94 (0.71-1.26)	1.58 (1.11-2.24)	0.02	0.03	1.00	0.91 (0.66-1.24)	1.42 (0.88-2.30)	0.13	0.24
- Mouth, pharynx and larynx (C00-14;32)	25	1.00	0.97 (0.38-2.47)	0.67 (0.20-2.28)	0.80	0.53	1.00	0.84 (0.31-2.29)	0.43 (0.31-2.29)	0.63	0.35
- Oesophagus (C15)	53	1.00	0.64 (0.29-1.44)	2.69 (1.33-5.46)	0.002	0.01	1.00	0.66 (0.28-1.53)	2.86 (1.08-7.56)	0.01	0.047
- Colorectum (C18-20)	129	1.00	1.09 (0.70-1.70)	1.67 (0.97-2.87)	0.18	0.08	1.00	1.07 (0.66-1.74)	1.60 (0.75-3.40)	0.44	0.25
- Liver (C22)	41	1.00	1.20 (0.54-2.66)	2.11 (0.89-5.03)	0.23	0.10	1.00	1.02 (0.44-2.34)	1.27 (0.38-4.27)	0.91	0.71
- Breast (C50[c])	77	1.00	0.83 (0.43-1.61)	-[d]	0.86	0.15	1.00	1.07 (0.50-2.29)	-[d]	0.98	0.47
- Non-alcohol-related (Other C;D45-47)	1145	1.00	1.13 (0.98-1.30)	1.10 (0.90-1.34)	0.21	0.20	1.00	1.24 (1.05-1.45)	1.37 (1.05-1.80)	0.02	0.01
- Stomach (C16)	28	1.00	1.26 (0.52-3.07)	1.02 (0.27-3.91)	0.87	0.87	1.00	1.16 (0.75-1.52)	0.81 (0.12-5.33)	0.88	0.90
- Pancreas (C25)	91	1.00	1.23 (0.74-2.03)	1.22 (0.60-2.45)	0.69	0.50	1.00	1.37 (0.78-2.40)	1.60 (0.63-4.06)	0.49	0.28
- Lung (C33-34)	258	1.00	1.42 (1.07-1.89)	1.40 (0.95-2.06)	0.04	0.047	1.00	1.51 (1.10-2.08)	1.66 (0.98-2.80)	0.03	0.04
- Melanoma (C43)	68	1.00	1.06 (0.61-1.84)	0.65 (0.25-1.72)	0.63	0.49	1.00	1.10 (0.57-2.12)	0.73 (0.20-2.73)	0.74	0.76
- Prostate (C61)	166	1.00	0.87 (0.60-1.26)	0.70 (0.39-1.91)	0.43	0.20	1.00	1.06 (0.69-1.62)	1.13 (0.53-2.40)	0.95	0.74
- Kidney (C64)	26	1.00	2.22 (0.89-5.54)	2.55 (0.75-8.62)	0.15	0.08	1.00	2.56 (0.94-6.98)	3.62 (0.76-17.2)	0.14	0.08
- Non-Hodgkin lymphoma (C82-85)	41	1.00	0.80 (0.37-1.73)	0.22 (0.03-1.63)	0.31	0.11	1.00	1.60 (0.65-3.94)	0.86 (0.10-7.31)	0.55	0.71
Diabetes (E10-14)	54	1.00	1.26 (0.64-2.46)	1.62 (0.68-3.89)	0.52	0.25	1.00	1.56 (0.74-3.27)	2.60 (0.88-7.67)	0.20	0.08
Dementia (F00-03;G30)	104	1.00	0.59 (0.31-1.13)	0.71 (0.28-1.80)	0.24	0.20	1.00	0.63 (0.31-1.29)	0.81 (0.27-2.45)	0.45	0.47
Cardiovascular disease (G45-46;I00-99)	1031	1.00	0.94 (0.80-1.11)	1.26 (1.00-1.57)	0.07	0.13	1.00	0.92 (0.76-1.10)	1.17 (0.86-1.59)	0.18	0.51
- Ischaemic heart disease (I20-25)	501	1.00	0.93 (0.74-1.18)	1.20 (0.87-1.63)	0.36	0.42	1.00	0.99 (0.76-1.29)	1.39 (0.92-2.10)	0.20	0.18
- Cerebrovascular disease (G45-46;I60-69)	240	1.00	1.16 (0.82-1.62)	1.16 (0.69-1.94)	0.65	0.44	1.00	1.18 (0.80-1.74)	1.21 (0.62-2.38)	0.69	0.49
- Other (Other I)	290	1.00	0.80 (0.57-1.12)	1.41 (0.93-2.15)	0.06	0.34	1.00	0.65 (0.45-0.94)	0.83 (0.46-1.50)	0.06	0.27
Respiratory system disease (J00-99)	291	1.00	1.10 (0.83-1.47)	0.80 (0.50-1.27)	0.41	0.54	1.00	0.95 (0.69-1.32)	0.54 (0.28-1.03)	0.13	0.09
- Lower respiratory infection (J09-22)	44	1.00	1.65 (0.80-3.38)	0.68 (0.15-3.02)	0.30	0.90	1.00	1.19 (0.52-2.72)	0.29 (0.04-2.17)	0.28	0.38
- Other respiratory system disease (Other J)	247	1.00	1.01 (0.74-1.38)	0.80 (0.49-1.30)	0.64	0.45	1.00	0.90 (0.63-1.29)	0.59 (0.29-1.17)	0.31	0.15
Digestive system disease (K00-93)	100	1.00	0.98 (0.58-1.66)	1.66 (0.90-3.06)	0.22	0.14	1.00	0.81 (0.46-1.42)	0.96 (0.40-2.32)	0.74	0.83
- Liver disease (K70-77)	24	1.00	0.43 (0.09-2.00)	3.81 (1.39-10.4)	0.004	0.005	1.00	0.37 (0.08-1.74)	2.17 (0.62-7.65)	0.10	0.21
- Other digestive system disease (Other K)	76	1.00	1.21 (0.69-2.13)	0.64 (0.22-1.87)	0.51	0.65	1.00	1.12 (0.57-2.20)	0.53 (0.13-2.21)	0.47	0.52
External (V01-Y98)	107	1.00	1.83 (1.17-2.86)	1.49 (0.77-2.91)	0.03	0.08	1.00	1.47 (0.90-2.40)	0.81 (0.32-2.06)	0.12	0.98
- Transport accident (V00-99;Y85)	26	1.00	1.58 (0.67-3.73)	0.35 (0.04-2.83)	0.27	0.59	1.00	1.24 (0.46-3.33)	0.16 (0.01-2.68)	0.22	0.37
- Fall (W00-19)	25	1.00	2.10 (0.75-5.89)	4.66 (1.42-15.3)	0.04	0.009	1.00	1.94 (0.64-5.86)	3.85 (0.81-18.2)	0.22	0.08
- Suicide (X60-84;Y87.0)	18	1.00	3.98 (1.33-11.9)	3.61 (0.80-16.4)	0.04	0.051	1.00	3.74 (1.13-12.4)	3.05 (0.39-23.7)	0.09	0.20
- Other external (W20-X59;Y86;Y87.1-98)	38	1.00	1.19 (0.53-2.68)	0.89 (0.25-3.18)	0.87	0.98	1.00	0.80 (0.34-1.89)	0.24 (0.04-1.59)	0.33	0.15
Other (Other A00-R99)	392	1.00	0.85 (0.65-1.11)	1.33 (0.96-1.86)	0.06	0.25	1.00	0.78 (0.58-1.05)	1.09 (0.68-1.74)	0.12	0.97
All-cause mortality (A00-Y98)	7965	1.00	1.04 (0.99-1.10)	1.22 (1.13-1.32)	< 0.001	< 0.001	1.00	1.04 (0.97-1.10)	1.21 (1.08-1.34)	0.002	0.001

Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]Overall. [b]Linear trend using median number of drinks per drinking-day of each category. [c]Female breast cancer only. [d]Zero deaths in cell. ICD-10, International Classification of Diseases, version 10.

Table 5. Hazard ratios (HR) and 95% confidence intervals (CI) of all-cause mortality risk by drinking pattern among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia.

Drinking-days per week	HR mean drinks per drinking-day (95% CI)		
	≤ 2	**> 2 and ≤ 4**	**> 4**
1-2	1.00	1.13 (1.00-1.28)	1.24 (1.07-1.43)
3-5	0.92 (0.85-0.99)	0.96 (0.86-1.08)	1.18 (1.00-1.40)
6-7	0.94 (0.88-1.01)	0.97 (0.90-1.05)	1.13 (1.02-1.26)

Non-drinkers were excluded. n deaths = 7965. Model was adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women only), menopausal status (women only), hormone replacement therapy use (women only) and height.

Supplementary data

Supplementary Table 1. Hazard ratios and 95% confidence intervals of cause-specific mortality risk by alcohol consumption in never-smokers in the 45 and Up Study (2006-2014), New South Wales, Australia.

		Drinks/week							
Cause of death (ICD-10 code)	**n deaths**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Cancer (C00-97;D45-47)	1019	1.00 (0.83-1.20)	1.00	0.96 (0.78-1.19)	0.84 (0.66-1.07)	0.96 (0.70-1.30)	1.01 (0.60-1.69)	0.73	0.89
- Alcohol-related (C00-15;18-20;22;32;50[d])	247	0.76 (0.53-1.07)	1.00	0.77 (0.51-1.16)	0.83 (0.52-1.32)	0.77 (0.40-1.51)	1.13 (0.40-3.20)	0.69	0.98
- Mouth, pharynx and larynx (C00-14;32)	9	3.71 (0.14-99.0)	1.00	-[e]	12.4 (0.47-329.4)	-[e]	14.1 (0.19-1061.6)	0.72	-[f]
- Oesophagus (C15)	25	1.52 (0.42-5.54)	1.00	1.33 (0.32-5.64)	1.49 (0.33-6.81)	-[e]	2.61 (0.25-26.9)	0.98	0.86
- Colorectum (C18-20)	105	0.80 (0.46-1.39)	1.00	0.96 (0.51-1.81)	0.89 (0.43-1.83)	1.16 (0.47-2.86)	-[e]	0.94	0.48
- Liver (C22)	24	1.45 (0.31-6.86)	1.00	1.74 (0.34-9.04)	2.85 (0.56-14.4)	1.11 (0.10-12.6)	5.32 (0.44-63.8)	0.63	0.30
- Breast (C50[d])	84	0.55 (0.32-0.93)	1.00	0.50 (0.25-1.00)	0.28 (0.10-0.83)	0.93 (0.28-3.13)	3.69 (0.49-27.9)	0.03	0.68
- Non-alcohol-related (Other C;D45-47)	772	1.10 (0.88-1.36)	1.00	1.04 (0.82-1.33)	0.86 (0.65-1.13)	1.03 (0.73-1.45)	1.00 (0.54-1.82)	0.52	0.86
- Stomach (C16)	23	0.77 (0.23-2.62)	1.00	1.41 (0.41-4.92)	0.47 (0.08-2.66)	0.43 (0.05-4.01)	-[e]	0.71	0.12
- Pancreas (C25)	81	1.26 (0.62-2.57)	1.00	1.43 (0.66-3.10)	1.36 (0.58-3.17)	1.33 (0.44-4.00)	1.02 (0.13-8.21)	0.97	0.61
- Lung (C33-34)	66	1.08 (0.48-2.39)	1.00	1.37 (0.57-3.28)	0.81 (0.26-2.50)	3.52 (1.31-9.46)	1.33 (0.16-11.0)	0.06	0.02
- Melanoma (C43)	53	0.65 (0.31-1.37)	1.00	0.55 (0.23-1.32)	0.47 (0.17-1.26)	1.17 (0.45-3.06)	0.70 (0.09-5.52)	0.44	0.68
- Prostate (C61)	104	0.85 (0.48-1.49)	1.00	0.92 (0.50-1.70)	0.61 (0.29-1.28)	0.46 (0.17-1.26)	1.04 (0.30-3.59)	0.59	0.24
- Kidney (C64)	23	0.76 (0.23-2.51)	1.00	0.89 (0.22-3.63)	1.07 (0.23-4.94)	0.83 (0.09-7.85)	3.72 (0.37-37.2)	0.84	0.37
- Non-Hodgkin lymphoma (C82-85)	40	1.13 (0.47-2.71)	1.00	0.67 (0.22-2.00)	0.46 (0.12-1.79)	1.03 (0.26-4.14)	-[e]	0.73	0.83
Diabetes (E10-14)	52	1.84 (0.71-4.78)	1.00	1.25 (0.39-3.97)	1.51 (0.43-5.32)	0.74 (0.09-6.47)	-[e]	0.77	0.62
Dementia (F00-03;G30)	131	0.80 (0.48-1.32)	1.00	0.88 (0.48-1.60)	0.89 (0.43-1.84)	0.64 (0.19-2.18)	-[e]	0.95	0.35
Cardiovascular disease (G45-46;I00-99)	1011	0.95 (0.79-1.14)	1.00	0.90 (0.72-1.13)	0.88 (0.67-1.14)	0.77 (0.53-1.13)	1.16 (0.64-2.10)	0.71	0.74
- Ischaemic heart disease (I20-25)	451	0.95 (0.72-1.25)	1.00	0.90 (0.65-1.25)	0.72 (0.48-1.09)	1.02 (0.62-1.68)	0.92 (0.37-2.32)	0.72	0.79
- Cerebrovascular disease (G45-46;I60-69)	276	0.94 (0.66-1.34)	1.00	0.84 (0.55-1.30)	0.99 (0.60-1.63)	0.50 (0.20-1.28)	1.36 (0.41-4.45)	0.69	0.88
- Other cardiovascular disease (Other I)	284	0.95 (0.66-1.35)	1.00	0.95 (0.63-1.46)	1.03 (0.64-1.68)	0.58 (0.25-1.30)	1.38 (0.49-3.94)	0.76	0.89
Respiratory system disease (J00-99)	153	1.72 (0.97-3.04)	1.00	1.42 (0.74-2.76)	1.56 (0.74-3.31)	1.16 (0.38-3.59)	3.95 (1.11-14.1)	0.26	0.13
- Lower respiratory infection (J09-22)	41	3.01 (0.70-12.9)	1.00	1.98 (0.38-10.4)	4.06 (0.73-22.7)	5.30 (0.69-40.7)	12.3 (1.02-148.6)	0.33	0.004
- Other respiratory system disease (Other J)	112	1.47 (0.78-2.75)	1.00	1.28 (0.62-2.64)	1.18 (0.51-2.77)	0.62 (0.14-2.82)	2.74 (0.60-12.6)	0.58	0.63
Digestive system disease (K00-93)	84	1.04 (0.54-2.01)	1.00	0.88 (0.40-1.94)	0.88 (0.34-2.26)	0.96 (0.26-3.48)	3.47 (0.92-12.1)	0.47	0.12
- Liver disease (K70-77)	16	1.44 (0.30-7.03)	1.00	1.03 (0.14-7.48)	0.67 (0.06-7.66)	1.35 (0.11-16.1)	6.87 (0.82-57.3)	0.42	0.053
- Other digestive system disease (Other K)	68	0.95 (0.46-1.95)	1.00	0.86 (0.36-2.04)	0.88 (0.31-2.47)	0.82 (0.17-3.85)	1.52 (0.18-13.1)	1.00	0.90
External (V01-Y98)	109	1.24 (0.70-2.21)	1.00	0.69 (0.33-1.46)	0.77 (0.34-1.79)	1.52 (0.61-3.80)	4.35 (1.52-12.5)	0.02	0.002
- Transport accident (V00-99;Y85)	21	1.13 (0.33-3.89)	1.00	0.77 (0.19-3.16)	0.25 (0.03-2.29)	1.56 (0.32-7.63)	-[e]	0.72	0.84
- Fall (W00-19)	27	1.73 (0.37-8.13)	1.00	1.66 (0.29-9.57)	3.71 (0.62-22.1)	4.70 (0.58-37.8)	37.5 (3.91-359.0)	0.02	0.001
- Suicide (X60-84;Y87.0)	15	4.65 (0.58-37.5)	1.00	0.85 (0.05-13.7)	0.99 (0.06-16.0)	1.77 (0.11-29.2)	7.34 (0.43-125.8)	0.27	0.32
- Other external (W20-X59;Y86;Y87.1-98)	46	1.01 (0.45-2.29)	1.00	0.43 (0.13-1.45)	0.60 (0.16-2.30)	0.47 (0.06-4.01)	4.19 (0.81-21.7)	0.17	0.16
Other (Other A00-R99)	371	1.07 (0.78-1.47)	1.00	1.20 (0.84-1.72)	0.90 (0.58-1.39)	0.84 (0.46-1.53)	1.37 (0.61-3.08)	0.64	0.98
All-cause mortality (A00-Y98)	6660	1.06 (0.99-1.15)	1.00	0.97 (0.89-1.06)	0.92 (0.84-1.02)	0.95 (0.83-1.09)	1.35 (1.10-1.65)	< 0.001	0.09

Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Female breast cancer only. [e]Zero deaths in cell. [f]Model failed to converge. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 2. Hazard ratios and 95% confidence intervals of cause-specific mortality risk by alcohol consumption in ever-smokers in the 45 and Up Study (2006-2014), New South Wales, Australia.

		Drinks/week							
Cause of death (ICD-10 code)	**n deaths**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Cancer (C00-97;D45-47)	1372	1.11 (0.92-1.32)	1.00	0.91 (0.74-1.10)	0.95 (0.78-1.15)	0.88 (0.71-1.08)	0.97 (0.74-1.25)	0.10	0.56
- Alcohol-related (C00-15;18-20;22;32;50[d])	277	1.19 (0.78-1.81)	1.00	0.93 (0.58-1.49)	1.25 (0.80-1.95)	1.11 (0.68-1.81)	1.60 (0.92-2.79)	0.37	0.051
- Mouth, pharynx and larynx (C00-14;32)	29	0.97 (0.29-3.24)	1.00	-[e]	1.18 (0.35-4.06)	0.98 (0.26-3.62)	0.46 (0.08-2.65)	0.93	0.84
- Oesophagus (C15)	53	1.30 (0.46-3.70)	1.00	1.30 (0.44-3.85)	1.43 (0.50-4.12)	0.71 (0.20-2.52)	2.58 (0.80-8.28)	0.34	0.31
- Colorectum (C18-20)	100	1.49 (0.70-3.19)	1.00	1.12 (0.49-2.56)	1.24 (0.55-2.79)	1.77 (0.79-3.97)	1.90 (0.75-4.82)	0.57	0.04
- Liver (C22)	38	2.56 (0.56-11.7)	1.00	2.47 (0.51-12.0)	2.49 (0.51-12.2)	2.85 (0.56-14.5)	4.57 (0.84-24.8)	0.67	0.11
- Breast (C50[d])	57	0.78 (0.36-1.69)	1.00	0.70 (0.29-1.69)	1.04 (0.45-2.38)	0.34 (0.07-1.58)	-[e]	0.70	0.24
- Non-alcohol-related (Other C;D45-47)	1095	1.09 (0.89-1.33)	1.00	0.90 (0.73-1.12)	0.89 (0.71-1.10)	0.83 (0.66-1.05)	0.84 (0.63-1.14)	0.06	0.11
- Stomach (C16)	32	2.56 (0.72-9.11)	1.00	1.00 (0.22-4.50)	0.89 (0.20-4.03)	1.50 (0.34-6.50)	1.23 (0.19-7.77)	0.34	0.52
- Pancreas (C25)	73	1.06 (0.50-2.26)	1.00	0.77 (0.32-1.81)	0.95 (0.42-2.14)	0.95 (0.40-2.25)	0.52 (0.14-1.96)	0.88	0.24
- Lung (C33-34)	350	1.59 (1.08-2.36)	1.00	1.24 (0.81-1.91)	1.14 (0.74-1.74)	1.08 (0.69-1.71)	1.21 (0.70-2.07)	0.10	0.84
- Melanoma (C43)	45	1.19 (0.40-3.57)	1.00	1.20 (0.40-3.58)	1.00 (0.33-2.99)	0.91 (0.29-2.90)	0.52 (0.10-2.81)	0.93	0.16
- Prostate (C61)	139	0.62 (0.37-1.03)	1.00	0.58 (0.33-0.99)	0.54 (0.31-0.93)	0.60 (0.34-1.06)	0.43 (0.18-1.00)	0.18	0.14
- Kidney (C64)	24	4.84 (0.60-38.7)	1.00	3.18 (0.37-27.7)	2.20 (0.24-20.1)	2.18 (0.22-21.6)	4.31 (0.37-50.1)	0.58	0.57
- Non-Hodgkin lymphoma (C82-85)	25	0.95 (0.37-2.43)	1.00	0.65 (0.23-1.88)	0.54 (0.18-1.62)	0.23 (0.05-1.15)	-[e]	0.48	0.01
Diabetes (E10-14)	63	1.20 (0.55-2.61)	1.00	0.65 (0.24-1.75)	1.12 (0.46-2.69)	0.87 (0.31-2.39)	0.44 (0.09-2.08)	0.60	0.78
Dementia (F00-03;G30)	87	1.03 (0.54-1.95)	1.00	0.67 (0.32-1.40)	0.71 (0.33-1.50)	0.62 (0.24-1.57)	0.49 (0.11-2.20)	0.57	0.56
Cardiovascular disease (G45-46;I00-99)	915	1.07 (0.86-1.31)	1.00	0.81 (0.64-1.03)	0.85 (0.67-1.08)	0.90 (0.70-1.17)	0.95 (0.67-1.34)	0.09	0.55
- Ischaemic heart disease (I20-25)	464	1.10 (0.81-1.47)	1.00	0.89 (0.64-1.24)	0.84 (0.60-1.17)	0.84 (0.58-1.21)	0.77 (0.47-1.28)	0.31	0.36
- Cerebrovascular disease (G45-46;I60-69)	192	1.00 (0.64-1.58)	1.00	0.79 (0.48-1.30)	0.71 (0.42-1.20)	1.02 (0.59-1.74)	0.80 (0.36-1.79)	0.59	0.65
- Other cardiovascular disease (Other I)	259	1.06 (0.72-1.57)	1.00	0.70 (0.44-1.10)	0.99 (0.64-1.53)	0.93 (0.56-1.53)	1.53 (0.84-2.78)	0.16	0.04
Respiratory system disease (J00-99)	364	1.11 (0.78-1.58)	1.00	1.02 (0.70-1.50)	1.08 (0.74-1.59)	1.13 (0.74-1.72)	0.74 (0.39-1.39)	0.80	0.77
- Lower respiratory infection (J09-22)	46	0.72 (0.29-1.77)	1.00	0.65 (0.24-1.75)	0.79 (0.30-2.13)	1.05 (0.35-3.17)	-[e]	0.93	0.46
- Other respiratory system disease (Other J)	318	1.20 (0.82-1.76)	1.00	1.11 (0.73-1.68)	1.14 (0.75-1.73)	1.16 (0.73-1.83)	0.86 (0.45-1.64)	0.87	0.90
Digestive system disease (K00-93)	90	1.80 (0.77-4.20)	1.00	1.81 (0.74-4.44)	1.55 (0.62-3.86)	1.88 (0.74-4.79)	2.65 (0.95-7.45)	0.58	0.10
- Liver disease (K70-77)	24	1.99 (0.40-9.91)	1.00	0.43 (0.04-4.87)	1.46 (0.26-8.20)	0.88 (0.12-6.56)	4.25 (0.81-22.4)	0.16	0.02
- Other digestive system disease (Other K)	66	1.83 (0.67-5.00)	1.00	2.28 (0.81-6.38)	1.61 (0.55-4.76)	2.45 (0.83-7.23)	1.15 (0.21-6.17)	0.55	0.69
External (V01-Y98)	99	3.55 (1.39-9.09)	1.00	2.10 (0.76-5.81)	2.91 (1.09-7.78)	2.91 (1.04-8.14)	2.11 (0.60-7.49)	0.11	0.21
- Transport accident (V00-99;Y85)	19	2.46 (0.27-22.3)	1.00	0.80 (0.05-13.1)	4.99 (0.60-41.8)	3.30 (0.35-31.2)	1.81 (0.11-31.1)	0.41	0.48
- Fall (W00-19)	21	4.54 (0.54-38.3)	1.00	1.68 (0.15-19.5)	4.15 (0.46-37.9)	2.85 (0.23-34.7)	8.02 (0.63-102.6)	0.50	0.15
- Suicide (X60-84;Y87.0)	24	-[f]	1.00	-[f]	-[f]	-[f]	-[f]	0.76	0.15
- Other external (W20-X59;Y86;Y87.1-98)	35	2.09 (0.59-7.43)	1.00	2.19 (0.59-8.12)	0.67 (0.13-3.35)	1.21 (0.26-5.56)	0.52 (0.05-5.25)	0.28	0.46
Other (Other A00-R99)	333	1.18 (0.82-1.69)	1.00	0.95 (0.64-1.42)	0.96 (0.64-1.43)	0.85 (0.54-1.34)	1.23 (0.73-2.09)	0.48	0.78
All-cause mortality (A00-Y98)	7326	1.16 (1.08-1.26)	1.00	0.93 (0.85-1.01)	1.00 (0.92-1.09)	0.97 (0.88-1.06)	1.05 (0.93-1.18)	< 0.001	0.19

Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Female breast cancer only. [e]Zero deaths in cell. [f]Not possible to calculate due to zero deaths in reference group. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 3. Hazard ratios and 95% confidence intervals of cause-specific mortality risk by alcohol consumption after excluding participants with disease at baseline in the 45 and Up Study (2006-2014), New South Wales, Australia.

		Drinks/week							
Cause of death (ICD-10 code)	**n deaths**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Cancer (C00-97;D45-47)	1313	1.18 (0.99-1.41)	1.00	1.08 (0.89-1.32)	0.96 (0.78-1.19)	1.02 (0.81-1.28)	1.22 (0.91-1.62)	0.14	0.26
- Alcohol-related (C00-15;18-20;22;32;50[d])	258	1.34 (0.87-2.06)	1.00	1.14 (0.70-1.86)	1.36 (0.84-2.22)	1.31 (0.76-2.25)	2.28 (1.26-4.12)	0.13	0.002
- Mouth, pharynx and larynx (C00-14;32)	20	1.04 (0.20-5.52)	1.00	-[e]	1.54 (0.29-8.20)	2.26 (0.43-11.8)	1.12 (0.15-8.54)	0.86	0.32
- Oesophagus (C15)	46	1.90 (0.54-6.71)	1.00	1.79 (0.46-6.98)	3.11 (0.86-11.3)	0.74 (0.12-4.55)	7.46 (1.89-29.4)	0.008	0.008
- Colorectum (C18-20)	118	1.15 (0.64-2.07)	1.00	1.08 (0.56-2.09)	0.86 (0.42-1.78)	1.12 (0.52-2.41)	1.02 (0.36-2.92)	0.97	0.42
- Liver (C22)	47	1.82 (0.52-6.41)	1.00	2.41 (0.66-8.84)	2.43 (0.65-9.12)	2.36 (0.57-9.76)	3.99 (0.90-17.7)	0.58	0.12
- Breast (C50[d])	27	1.29 (0.42-3.98)	1.00	0.43 (0.08-2.38)	0.91 (0.20-4.19)	0.76 (0.08-7.10)	5.08 (0.52-50.2)	0.48	0.21
- Non-alcohol-related (Other C;D45-47)	1055	1.15 (0.94-1.40)	1.00	1.07 (0.86-1.33)	0.89 (0.70-1.12)	0.96 (0.74-1.24)	1.02 (0.73-1.42)	0.17	0.76
- Stomach (C16)	40	1.49 (0.54-4.08)	1.00	1.35 (0.45-4.06)	0.44 (0.10-1.85)	0.75 (0.20-2.88)	0.32 (0.04-2.88)	0.30	0.41
- Pancreas (C25)	123	0.93 (0.52-1.66)	1.00	1.12 (0.61-2.09)	1.17 (0.62-2.22)	1.11 (0.53-2.31)	0.78 (0.26-2.41)	0.94	0.67
- Lung (C33-34)	291	1.44 (0.95-2.18)	1.00	1.27 (0.81-2.00)	0.94 (0.58-1.51)	1.08 (0.65-1.77)	1.26 (0.71-2.26)	0.22	0.98
- Melanoma (C43)	34	0.46 (0.17-1.24)	1.00	0.38 (0.12-1.16)	0.39 (0.13-1.23)	0.76 (0.26-2.22)	0.25 (0.03-2.09)	0.34	0.35
- Prostate (C61)	71	0.98 (0.49-1.98)	1.00	0.61 (0.27-1.40)	0.54 (0.22-1.29)	0.99 (0.43-2.30)	0.77 (0.21-2.81)	0.55	0.76
- Kidney (C64)	24	-[f]	1.00	-[f]	-[f]	-[f]	-[f]	0.67	0.03
- Non-Hodgkin lymphoma (C82-85)	33	1.06 (0.41-2.77)	1.00	0.94 (0.32-2.75)	0.29 (0.06-1.47)	0.21 (0.03-1.79)	-[e]	0.43	0.06
Diabetes (E10-14)	20	0.88 (0.22-3.57)	1.00	1.11 (0.26-4.83)	0.52 (0.08-3.29)	0.88 (0.13-5.77)	1.15 (0.11-12.2)	0.97	0.58
Dementia (F00-03;G30)	80	0.77 (0.40-1.48)	1.00	0.78 (0.40-1.48)	1.12 (0.51-2.46)	0.59 (0.16-2.14)	-[e]	0.84	0.24
Cardiovascular disease (G45-46;I00-99)	1018	0.99 (0.81-1.20)	1.00	0.88 (0.71-1.10)	0.93 (0.73-1.18)	0.99 (0.75-1.31)	1.34 (0.94-1.92)	0.29	0.047
- Ischaemic heart disease (I20-25)	429	1.07 (0.79-1.45)	1.00	0.85 (0.60-1.21)	0.88 (0.61-1.28)	1.01 (0.66-1.54)	1.10 (0.63-1.93)	0.62	0.85
- Cerebrovascular disease (G45-46;I60-69)	237	0.88 (0.61-1.27)	1.00	0.91 (0.60-1.38)	0.86 (0.54-1.37)	1.13 (0.66-1.92)	1.32 (0.63-2.80)	0.78	0.19
- Other cardiovascular disease (Other I)	316	0.96 (0.68-1.37)	1.00	0.90 (0.60-1.34)	1.06 (0.70-1.61)	0.83 (0.49-1.42)	1.72 (0.94-3.13)	0.32	0.04
Respiratory system disease (J00-99)	381	1.14 (0.81-1.59)	1.00	1.03 (0.70-1.50)	1.15 (0.78-1.69)	1.35 (0.88-2.08)	1.07 (0.57-2.02)	0.75	0.36
- Lower respiratory infection (J09-22)	73	1.05 (0.51-2.18)	1.00	0.61 (0.24-1.57)	1.35 (0.57-3.20)	2.06 (0.78-5.47)	0.85 (0.11-6.91)	0.29	0.36
- Other respiratory system disease (Other J)	308	1.17 (0.80-1.72)	1.00	1.15 (0.75-1.74)	1.12 (0.73-1.73)	1.25 (0.78-2.01)	1.08 (0.55-2.12)	0.96	0.60
Suicide (X60-84;Y87.0)	18	-[f]	1.00	-[f]	-[f]	-[f]	-[f]	0.81	0.04
All-cause mortality (A00-Y98)	5435	1.10 (1.01-1.20)	1.00	0.94 (0.86-1.04)	1.04 (0.94-1.16)	1.03 (0.91-1.15)	1.21 (1.04-1.40)	0.001	0.01

Participants who at baseline had ever had cancer were excluded from cancer analyses, ever had diabetes excluded from diabetes analysis, did not have good/very good/excellent memory excluded from dementia analysis, ever had heart disease or stroke excluded from cardiovascular disease analyses, ever had asthma excluded from respiratory system disease analyses, ever had depression excluded from suicide analysis and ever had cancer, heart disease, stroke or diabetes excluded from all-cause mortality analysis. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Female breast cancer only. [e]Zero deaths in cell. [f]Not possible to calculate due to zero deaths in reference group. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk by drinking-days per week among drinkers by sex in the 45 and Up Study (2006-2014), New South Wales, Australia.

		HR drinking-days per week in men - adjusted for total alcohol consumption (95% CI)						HR drinking-days per week in women - adjusted for total alcohol consumption (95% CI)				
Cause of death (ICD-10 code)	**n deaths**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**	**n deaths**	**1-2**	**3-5**	**6-7**	***p*[a]**	***p*$_{trend}$[b]**
Cancer (C00-97;D45-47)	1066	1.00	0.76 (0.64-0.91)	0.65 (0.55-0.78)	< 0.001	< 0.001	404	1.00	0.85 (0.64-1.11)	0.96 (0.71-1.31)	0.42	0.85
- Alcohol-related (C00-15;18-20;22;32)	196	1.00	0.86 (0.57-1.31)	0.84 (0.56-1.28)	0.69	0.01	129	1.00	0.79 (0.50-1.27)	0.84 (0.49-1.45)	0.63	0.53
- Mouth, pharynx and larynx (C00-14;32)	-[c]	1.00	2.80 (0.71-11.1)	2.80 (0.66-11.9)	0.31	0.21	-[c]	1.00	-[d]	-[d]	-[d]	-[d]
- Oesophagus (C15)	45	1.00	0.66 (0.28-1.53)	0.44 (0.19-1.02)	0.16	0.06	8	1.00	10.8 (0.13-918.1)	12.7 (0.14-1191.2)	0.52	0.31
- Colorectum (C18-20)	94	1.00	0.77 (0.42-1.42)	0.81 (0.45-1.47)	0.69	0.54	35	1.00	0.69 (0.28-1.71)	0.60 (0.23-1.58)	0.56	0.31
- Liver (C22)	-[c]	1.00	0.86 (0.29-2.54)	1.25 (0.45-3.45)	0.73	0.60	-[c]	1.00	0.76 (0.04-13.7)	2.11 (0.11-38.8)	0.65	0.48
- Non-alcohol-related (Other C;D45-47)	870	1.00	0.75 (0.62-0.90)	0.62 (0.51-0.75)	< 0.001	< 0.001	275	1.00	0.88 (0.62-1.23)	1.04 (0.72-1.50)	0.56	0.81
- Stomach (C16)	22	1.00	0.86 (0.26-2.80)	0.60 (0.18-2.00)	0.68	0.39	6	1.00	3.21 (0.07-148.1)	13.3 (0.22-792.5)	0.43	0.20
- Pancreas (C25)	64	1.00	1.22 (0.62-2.41)	0.70 (0.32-1.51)	0.21	0.29	27	1.00	1.46 (0.55-3.85)	0.58 (0.15-2.20)	0.22	0.48
- Lung (C33-34)	183	1.00	0.64 (0.41-0.99)	0.55 (0.36-0.85)	0.02	0.008	75	1.00	0.64 (0.30-1.38)	1.55 (0.77-3.13)	0.04	0.13
- Melanoma (C43)	59	1.00	0.85 (0.39-1.85)	0.99 (0.45-2.16)	0.89	0.97	9	1.00	0.98 (0.13-7.66)	3.16 (0.21-47.4)	0.61	0.48
- Kidney (C64)	20	1.00	0.78 (0.20-3.05)	1.08 (0.30-3.90)	0.87	0.85	6	1.00	-[d]	-[d]	-[d]	-[d]
- Non-Hodgkin lymphoma (C82-85)	32	1.00	1.68 (0.68-4.18)	0.62 (0.19-2.01)	0.08	0.41	9	1.00	0.85 (0.09-7.70)	1.83 (0.13-24.9)	0.83	0.70
Diabetes (E10-14)	40	1.00	0.59 (0.25-1.38)	0.42 (0.17-1.02)	0.15	0.06	14	1.00	1.40 (0.24-8.10)	3.57 (0.55-23.1)	0.34	0.17
Dementia (F00-03;G30)	70	1.00	1.31 (0.66-2.61)	1.12 (0.56-2.24)	0.73	0.79	34	1.00	0.96 (0.38-2.44)	0.59 (0.18-1.97)	0.62	0.41
Cardiovascular disease (G45-46;I00-99)	740	1.00	1.01 (0.81-1.25)	0.87 (0.70-1.07)	0.23	0.14	291	1.00	0.82 (0.59-1.13)	0.65 (0.46-0.93)	0.06	0.02
- Ischaemic heart disease (I20-25)	385	1.00	0.89 (0.66-1.20)	0.81 (0.60-1.08)	0.36	0.15	116	1.00	0.76 (0.47-1.25)	0.42 (0.24-0.74)	0.009	0.003
- Cerebrovascular disease (G45-46;I60-69)	160	1.00	1.14 (0.73-1.78)	0.80 (0.51-1.27)	0.24	0.27	80	1.00	0.60 (0.31-1.18)	0.71 (0.37-1.34)	0.31	0.33
- Other cardiovascular disease (Other I)	195	1.00	1.26 (0.80-2.00)	1.16 (0.75-1.80)	0.61	0.60	95	1.00	1.16 (0.65-2.07)	1.14 (0.59-2.20)	0.87	0.71
Respiratory system disease (J00-99)	222	1.00	1.20 (0.78-1.85)	1.50 (1.00-2.24)	0.13	0.045	69	1.00	1.67 (0.78-3.60)	1.64 (0.75-3.63)	0.37	0.26
- Lower respiratory infection (J09-22)	36	1.00	1.50 (0.46-4.93)	2.25 (0.78-6.44)	0.30	0.12	8	1.00	-[d]	-[d]	-[d]	-[d]
- Other respiratory system disease (Other J)	186	1.00	1.17 (0.73-1.87)	1.39 (0.89-2.17)	0.32	0.13	61	1.00	1.75 (0.76-4.00)	1.77 (0.75-4.14)	0.36	0.23
Digestive system disease (K00-93)	73	1.00	1.12 (0.53-2.37)	1.13 (0.55-2.31)	0.94	0.76	27	1.00	0.83 (0.26-2.65)	0.83 (0.26-2.68)	0.94	0.77
- Liver disease (K70-77)	18	1.00	0.87 (0.19-4.09)	1.02 (0.22-4.75)	0.97	0.93	6	1.00	-[e]	0.71 (0.02-21.7)	0.98	0.59
- Other digestive system disease (Other K)	55	1.00	1.38 (0.58-3.26)	1.54 (0.67-3.57)	0.60	0.32	21	1.00	1.74 (0.38-8.02)	1.23 (0.25-6.01)	0.74	0.90
External (V01-Y98)	79	1.00	0.88 (0.44-1.76)	1.11 (0.58-2.14)	0.75	0.67	28	1.00	0.70 (0.23-2.15)	0.95 (0.31-2.90)	0.79	0.96
- Transport accident (V00-99;Y85)	18	1.00	0.70 (0.15-3.38)	2.55 (0.62-10.5)	0.15	0.14	8	1.00	0.20 (0.02-2.60)	0.35 (0.03-4.07)	0.45	0.42
- Fall (W00-19)	16	1.00	1.52 (0.23-10.2)	2.91 (0.51-16.5)	0.41	0.19	9	1.00	1.13 (0.04-30.9)	2.02 (0.09-44.3)	0.87	0.62
- Suicide (X60-84;Y87.0)	-[c]	1.00	1.32 (0.23-7.49)	0.97 (0.16-5.84)	0.90	0.90	-[c]	1.00	-[d]	-[d]	-[d]	-[d]
- Other external (W20-X59;Y86;Y87.1-98)	-[c]	1.00	0.72 (0.25-2.01)	0.55 (0.20-1.49)	0.50	0.24	-[c]	1.00	-[d]	-[d]	-[d]	-[d]
Other (Other A00-R99)	297	1.00	1.03 (0.73-1.45)	0.87 (0.62-1.22)	0.49	0.34	95	1.00	1.13 (0.62-2.03)	1.34 (0.71-2.55)	0.66	0.37
All-cause mortality (A00-Y98)	5725	1.00	0.87 (0.81-0.95)	0.85 (0.78-0.91)	< 0.001	< 0.001	2240	1.00	0.87 (0.77-0.98)	0.83 (0.73-0.94)	0.01	0.005

Non-drinkers were excluded. Models were adjusted for age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]Overall. [b]Linear trend using median number of drinking-days per week of each category. [c]Censored due to < 5 deaths in women, or if this value would enable calculation of value for another cell for which there is < 5 deaths in women. [d]Model failed to converge. [e]Zero deaths in cell. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 5. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk by drinking-days per week among drinkers after excluding participants with disease at baseline in the 45 and Up Study (2006-2014), New South Wales, Australia.

		HR drinking-days per week in main analysis - adjusted for total alcohol consumption (95% CI)						HR drinking-days per week after disease exclusion[a] - adjusted for total alcohol consumption (95% CI)				
Cause of death (ICD-10 code)	**n deaths**	**1-2**	**3-5**	**6-7**	p^b	p_{trend}^c	**n deaths**	**1-2**	**3-5**	**6-7**	p^b	p_{trend}^c
Cancer (C00-97;D45-47)	1470	1.00	0.79 (0.68-0.91)	0.73 (0.63-0.85)	< 0.001	< 0.001	795	1.00	0.79 (0.64-0.96)	0.69 (0.56-0.84)	0.001	< 0.001
- Alcohol-related (C00-15;18-20;22;32;50[d])	325	1.00	0.82 (0.60-1.12)	0.82 (0.60-1.12)	0.37	0.24	157	1.00	0.98 (0.62-1.55)	0.90 (0.57-1.44)	0.89	0.64
- Mouth, pharynx and larynx (C00-14;32)	25	1.00	3.23 (0.83-12.6)	2.97 (0.71-12.4)	0.23	0.19	15	1.00	7.11 (0.82-61.3)	3.60 (0.37-34.9)	0.15	0.49
- Oesophagus (C15)	53	1.00	0.77 (0.35-1.70)	0.58 (0.26-1.26)	0.38	0.16	32	1.00	0.33 (0.10-1.10)	0.55 (0.21-1.41)	0.17	0.30
- Colorectum (C18-20)	129	1.00	0.79 (0.48-1.31)	0.81 (0.49-1.36)	0.62	0.44	69	1.00	1.04 (0.52-2.06)	0.95 (0.47-1.92)	0.96	0.86
- Liver (C22)	41	1.00	0.94 (0.35-2.49)	1.36 (0.54-3.44)	0.65	0.45	32	1.00	1.45 (0.47-4.46)	1.68 (0.54-5.23)	0.67	0.38
- Breast (C50[d])	77	1.00	0.79 (0.43-1.45)	0.97 (0.46-2.05)	0.69	0.90	9	1.00	0.53 (0.09-3.03)	0.13 (0.01-1.76)	0.31	0.13
- Non-alcohol-related (Other C;D45-47)	1145	1.00	0.78 (0.66-0.92)	0.71 (0.60-0.84)	< 0.001	< 0.001	638	1.00	0.75 (0.60-0.94)	0.65 (0.52-0.82)	0.001	< 0.001
- Stomach (C16)	28	1.00	0.84 (0.28-2.47)	0.79 (0.27-2.35)	0.91	0.69	18	1.00	0.87 (0.23-3.23)	0.68 (0.18-2.62)	0.85	0.57
- Pancreas (C25)	91	1.00	1.27 (0.73-2.20)	0.65 (0.34-1.25)	0.048	0.15	78	1.00	1.04 (0.58-1.86)	0.57 (0.28-1.13)	0.11	0.09
- Lung (C33-34)	258	1.00	0.64 (0.44-0.93)	0.74 (0.52-1.06)	0.06	0.16	181	1.00	0.51 (0.32-0.80)	0.65 (0.43-0.99)	0.01	0.08
- Melanoma (C43)	68	1.00	0.79 (0.39-1.59)	1.00 (0.49-2.05)	0.71	0.93	25	1.00	0.63 (0.19-2.07)	0.86 (0.27-2.78)	0.73	0.86
- Prostate (C61)	166	1.00	0.61 (0.38-0.98)	0.90 (0.58-1.39)	0.10	0.75	44	1.00	0.54 (0.21-1.40)	0.81 (0.34-1.90)	0.44	0.73
- Kidney (C64)	26	1.00	0.64 (0.20-2.10)	0.91 (0.30-2.72)	0.73	0.95	15	1.00	1.31 (0.23-7.60)	1.30 (0.22-7.59)	0.95	0.81
- Non-Hodgkin lymphoma (C82-85)	41	1.00	1.30 (0.60-2.84)	0.56 (0.20-1.57)	0.15	0.30	17	1.00	2.78 (0.76-10.2)	1.01 (0.16-6.26)	0.16	0.85
Diabetes (E10-14)	54	1.00	0.69 (0.33-1.47)	0.66 (0.31-1.40)	0.49	0.28	12	1.00	0.27 (0.04-1.67)	0.16 (0.03-0.87)	0.09	0.04
Dementia (F00-03;G30)	104	1.00	1.08 (0.63-1.85)	0.84 (0.47-1.48)	0.62	0.52	41	1.00	1.05 (0.44-2.50)	0.85 (0.33-2.21)	0.90	0.74
Cardiovascular disease (G45-46;I00-99)	1031	1.00	0.95 (0.79-1.13)	0.81 (0.68-0.97)	0.04	0.02	559	1.00	0.76 (0.60-0.98)	0.80 (0.63-1.01)	0.08	0.10
- Ischaemic heart disease (I20-25)	501	1.00	0.88 (0.68-1.12)	0.72 (0.56-0.93)	0.04	0.01	229	1.00	0.68 (0.46-0.99)	0.68 (0.47-0.98)	0.06	0.047
- Cerebrovascular disease (G45-46;I60-69)	240	1.00	0.95 (0.66-1.38)	0.81 (0.56-1.17)	0.47	0.24	153	1.00	0.62 (0.38-1.02)	0.76 (0.49-1.18)	0.16	0.29
- Other cardiovascular disease (Other I)	290	1.00	1.13 (0.79-1.60)	1.02 (0.72-1.43)	0.74	0.97	177	1.00	1.13 (0.72-1.79)	1.10 (0.71-1.72)	0.86	0.71
Respiratory system disease (J00-99)	291	1.00	1.26 (0.87-1.83)	1.47 (1.03-2.09)	0.11	0.03	224	1.00	1.48 (0.97-2.26)	1.42 (0.94-2.15)	0.16	0.14
- Lower respiratory infection (J09-22)	44	1.00	1.27 (0.46-3.51)	1.67 (0.67-4.16)	0.53	0.26	39	1.00	1.35 (0.47-3.91)	1.36 (0.51-3.60)	0.81	0.57
- Other respiratory system disease (Other J)	247	1.00	1.27 (0.85-1.89)	1.43 (0.97-2.11)	0.20	0.07	185	1.00	1.51 (0.95-2.40)	1.43 (0.91-2.26)	0.20	0.18
Suicide (X60-84;Y87.0)	18	1.00	1.57 (0.39-6.32)	0.71 (0.15-3.37)	0.40	0.52	10	1.00	2.34 (0.19-28.2)	1.62 (0.13-20.3)	0.78	0.87
All-cause mortality (A00-Y98)	7965	1.00	0.88 (0.82-0.93)	0.85 (0.80-0.90)	< 0.001	< 0.001	3172	1.00	0.87 (0.78-0.96)	0.88 (0.80-0.98)	0.01	0.03

Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]Participants who at baseline had ever had cancer were excluded from cancer analyses, ever had diabetes excluded from diabetes analysis, did not have good/very good/excellent memory excluded from dementia analysis, ever had heart disease or stroke excluded from cardiovascular disease analyses, ever had asthma excluded from respiratory system disease analyses, ever had depression excluded from suicide analysis and ever had cancer, heart disease, stroke or diabetes excluded from all-cause mortality analysis. [b]Overall. [c]Linear trend using median number of drinking-days per week of each category. [d]Female breast cancer only. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 6. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk by mean drinks per drinking-day among drinkers by sex in the 45 and Up Study (2006-2014), New South Wales, Australia.

		HR mean drinks per drinking-day in men - adjusted for total alcohol consumption (95% CI)						HR mean drinks per drinking-day in women - adjusted for total alcohol consumption (95% CI)				
Cause of death (ICD-10 code)	**n deaths**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**	**n deaths**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[a]**	***p*$_{trend}$[b]**
Cancer (C00-97;D45-47)	1066	1.00	1.17 (0.99-1.37)	1.52 (1.17-1.96)	0.006	0.001	404	1.00	1.13 (0.82-1.54)	0.85 (0.42-1.70)	0.57	0.99
- Alcohol-related (C00-15;18-20;22;32)	196	1.00	0.92 (0.62-1.34)	1.52 (0.88-2.61)	0.13	0.17	129	1.00	1.03 (0.58-1.83)	1.18 (0.38-3.68)	0.96	0.79
- Mouth, pharynx and larynx (C00-14;32)	-[c]	1.00	0.88 (0.31-2.48)	0.53 (0.09-3.09)	0.77	0.49	-[c]	1.00	-[d]	-[d]	-[d]	-[d]
- Oesophagus (C15)	45	1.00	0.50 (0.19-1.28)	2.58 (0.91-7.26)	0.01	0.10	8	1.00	3.86 (0.12-126.9)	82.3 (0.33-20716.9)	0.29	0.12
- Colorectum (C18-20)	94	1.00	1.07 (0.62-1.84)	1.47 (0.63-3.43)	0.65	0.39	35	1.00	0.95 (0.32-2.86)	2.75 (0.56-13.4)	0.38	0.31
- Liver (C22)	-[c]	1.00	0.91 (0.36-2.28)	1.30 (0.38-4.44)	0.82	0.69	-[c]	1.00	0.53 (0.03-9.41)	-[e]	0.91	0.33
- Non-alcohol-related (Other C;D45-47)	870	1.00	1.24 (1.04-1.48)	1.53 (1.14-2.04)	0.009	0.003	275	1.00	1.16 (0.80-1.70)	0.72 (0.30-1.73)	0.42	0.84
- Stomach (C16)	22	1.00	1.17 (0.39-3.46)	0.81 (0.11-5.81)	0.88	0.89	6	1.00	2.83 (0.08-107.5)	-[e]	0.85	0.77
- Pancreas (C25)	64	1.00	1.16 (0.60-2.21)	1.49 (0.54-4.10)	0.75	0.45	27	1.00	2.86 (0.86-9.51)	-[e]	0.23	0.67
- Lung (C33-34)	183	1.00	1.58 (1.09-2.29)	1.90 (1.07-3.39)	0.04	0.02	75	1.00	1.31 (0.68-2.51)	0.80 (0.19-3.37)	0.56	0.95
- Melanoma (C43)	59	1.00	1.15 (0.58-2.28)	0.79 (0.20-3.08)	0.75	0.86	9	1.00	1.04 (0.06-17.4)	-[e]	1.00	0.63
- Kidney (C64)	20	1.00	2.88 (0.94-8.79)	4.21 (0.83-21.2)	0.13	0.07	6	1.00	-[d]	-[d]	-[d]	-[d]
- Non-Hodgkin lymphoma (C82-85)	32	1.00	1.39 (0.52-3.71)	0.78 (0.09-7.21)	0.73	0.92	9	1.00	6.14 (0.31-121.7)	-[e]	0.49	0.62
Diabetes (E10-14)	40	1.00	1.77 (0.77-4.06)	3.31 (1.04-10.5)	0.12	0.17	14	1.00	1.55 (0.22-11.0)	-[e]	0.91	0.92
Dementia (F00-03;G30)	70	1.00	0.54 (0.25-1.17)	0.51 (0.13-1.96)	0.27	0.19	34	1.00	0.61 (0.07-5.34)	2.60 (0.32-21.1)	0.59	0.59
Cardiovascular disease (G45-46;I00-99)	740	1.00	0.86 (0.70-1.06)	1.13 (0.81-1.58)	0.10	0.72	291	1.00	1.32 (0.85-2.05)	1.08 (0.45-2.56)	0.46	0.48
- Ischaemic heart disease (I20-25)	385	1.00	0.88 (0.66-1.17)	1.27 (0.81-1.99)	0.18	0.46	116	1.00	1.91 (1.02-3.59)	2.08 (0.70-6.14)	0.09	0.06
- Cerebrovascular disease (G45-46;I60-69)	160	1.00	1.33 (0.86-2.06)	1.43 (0.69-2.98)	0.41	0.26	80	1.00	0.88 (0.37-2.10)	0.75 (0.14-4.01)	0.93	0.70
- Other (Other I)	195	1.00	0.61 (0.41-0.92)	0.83 (0.44-1.57)	0.055	0.31	95	1.00	1.19 (0.49-2.84)	-[e]	0.93	0.48
Respiratory system disease (J00-99)	222	1.00	0.94 (0.66-1.34)	0.50 (0.25-1.00)	0.11	0.07	69	1.00	1.08 (0.47-2.48)	0.53 (0.06-4.35)	0.80	0.71
- Lower respiratory infection (J09-22)	36	1.00	0.94 (0.38-2.34)	0.05 (0.00-1.10)	0.11	0.09	8	1.00	-[d]	-[d]	-[d]	-[d]
- Other respiratory system disease (Other J)	186	1.00	0.89 (0.60-1.32)	0.62 (0.30-1.29)	0.44	0.21	61	1.00	1.07 (0.45-2.57)	-[e]	0.99	0.36
Digestive system disease (K00-93)	73	1.00	0.76 (0.40-1.42)	0.84 (0.32-2.22)	0.69	0.65	27	1.00	1.08 (0.30-3.93)	2.67 (0.37-19.6)	0.59	0.40
- Liver disease (K70-77)	18	1.00	0.19 (0.02-1.64)	1.68 (0.42-6.82)	0.15	0.35	6	1.00	1.51 (0.05-48.7)	21.9 (0.47-1015.8)	0.28	0.14
- Other digestive system disease (Other K)	55	1.00	1.28 (0.59-2.75)	0.65 (0.14-3.07)	0.52	0.77	21	1.00	0.60 (0.10-3.59)	0.79 (0.03-24.8)	0.84	0.76
External (V01-Y98)	79	1.00	1.49 (0.86-2.58)	0.79 (0.30-2.13)	0.15	0.88	28	1.00	1.44 (0.45-4.58)	1.16 (0.09-15.6)	0.82	0.72
- Transport accident (V00-99;Y85)	18	1.00	1.01 (0.31-3.23)	0.15 (0.01-2.71)	0.33	0.25	8	1.00	2.38 (0.27-20.8)	-[e]	0.74	0.76
- Fall (W00-19)	16	1.00	2.04 (0.51-8.14)	4.33 (0.74-25.3)	0.26	0.10	9	1.00	2.14 (0.16-29.0)	4.51 (0.06-346.7)	0.74	0.44
- Suicide (X60-84;Y87.0)	-[c]	1.00	5.99 (1.38-26.1)	4.51 (0.48-42.3)	0.055	0.16	-[c]	1.00	-[d]	-[d]	-[d]	-[d]
- Other external (W20-X59;Y86;Y87.1-98)	-[c]	1.00	0.87 (0.35-2.16)	0.22 (0.03-1.64)	0.31	0.17	-[c]	1.00	-[d]	-[d]	-[d]	-[d]
Other (Other A00-R99)	297	1.00	0.66 (0.48-0.92)	0.97 (0.58-1.61)	0.03	0.56	95	1.00	1.51 (0.76-2.99)	1.48 (0.42-5.29)	0.48	0.33
All-cause mortality (A00-Y98)	5725	1.00	1.00 (0.93-1.07)	1.17 (1.04-1.31)	0.006	0.02	2240	1.00	1.22 (1.06-1.41)	1.34 (1.03-1.75)	0.009	0.004

Non-drinkers were excluded. Models were adjusted for age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]Overall. [b]Linear trend using median number of drinks per drinking-day of each category. [c]Censored due to < 5 deaths in women, or if this value would enable calculation of value for another cell for which there is < 5 deaths in women. [d]Model failed to converge. [e]Zero deaths in cell. ICD-10, International Classification of Diseases, version 10.

Supplementary Table 7. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk by mean drinks per drinking-day among drinkers after excluding participants with disease at baseline in the 45 and Up Study (2006-2014), New South Wales, Australia.

		HR mean drinks per drinking-day in main analysis - adjusted for total alcohol consumption (95% CI)						HR mean drinks per drinking-day after disease exclusion[a] - adjusted for total alcohol consumption (95% CI)				
Cause of death (ICD-10 code)	**n deaths**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[b]**	***p*$_{trend}$[c]**	**n deaths**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[b]**	***p*$_{trend}$[c]**
Cancer (C00-97;D45-47)	1470	1.00	1.16 (1.00-1.33)	1.38 (1.09-1.33)	0.02	0.006	795	1.00	1.21 (1.00-1.47)	1.52 (1.12-2.06)	0.02	0.006
- Alcohol-related (C00-15;18-20;22;32;50[d])	325	1.00	0.91 (0.66-1.24)	1.42 (0.88-2.30)	0.13	0.24	157	1.00	0.87 (0.56-1.34)	1.43 (0.76-2.66)	0.23	0.34
- Mouth, pharynx and larynx (C00-14;32)	25	1.00	0.84 (0.31-2.29)	0.43 (0.31-2.29)	0.63	0.35	15	1.00	2.06 (0.57-7.50)	0.87 (0.11-6.88)	0.37	0.94
- Oesophagus (C15)	53	1.00	0.66 (0.28-1.53)	2.86 (1.08-7.56)	0.01	0.047	32	1.00	0.69 (0.22-2.24)	4.50 (1.49-13.6)	0.004	0.006
- Colorectum (C18-20)	129	1.00	1.07 (0.66-1.74)	1.60 (0.75-3.40)	0.44	0.25	69	1.00	0.73 (0.36-1.48)	1.03 (0.35-3.10)	0.60	0.90
- Liver (C22)	41	1.00	1.02 (0.44-2.34)	1.27 (0.38-4.27)	0.91	0.71	32	1.00	0.97 (0.38-2.49)	0.93 (0.23-3.82)	0.99	0.92
- Breast (C50[d])	77	1.00	1.07 (0.50-2.29)	-[e]	0.98	0.47	9	1.00	0.44 (0.03-6.46)	-[e]	0.83	0.42
- Non-alcohol-related (Other C;D45-47)	1145	1.00	1.24 (1.05-1.45)	1.37 (1.05-1.80)	0.02	0.01	638	1.00	1.34 (1.08-1.65)	1.57 (1.11-2.23)	0.01	0.006
- Stomach (C16)	28	1.00	1.16 (0.75-1.52)	0.81 (0.12-5.33)	0.88	0.90	18	1.00	1.13 (0.33-3.93)	0.77 (0.08-7.41)	0.92	0.88
- Pancreas (C25)	91	1.00	1.37 (0.78-2.40)	1.60 (0.63-4.06)	0.49	0.28	78	1.00	1.26 (0.68-2.34)	1.54 (0.57-4.15)	0.66	0.37
- Lung (C33-34)	258	1.00	1.51 (1.10-2.08)	1.66 (0.98-2.80)	0.03	0.04	181	1.00	1.47 (1.01-2.16)	1.99 (1.09-3.64)	0.054	0.02
- Melanoma (C43)	68	1.00	1.10 (0.57-2.12)	0.73 (0.20-2.73)	0.74	0.76	25	1.00	0.68 (0.22-2.12)	0.42 (0.04-4.05)	0.71	0.42
- Prostate (C61)	166	1.00	1.06 (0.69-1.62)	1.13 (0.53-2.40)	0.95	0.74	44	1.00	1.62 (0.74-3.55)	0.85 (0.17-4.42)	0.31	0.85
- Kidney (C64)	26	1.00	2.56 (0.94-6.98)	3.62 (0.76-17.2)	0.14	0.08	15	1.00	5.85 (1.41-24.2)	8.68 (1.24-61.0)	0.04	0.03
- Non-Hodgkin lymphoma (C82-85)	41	1.00	1.60 (0.65-3.94)	0.86 (0.10-7.31)	0.55	0.71	17	1.00	1.82 (0.38-8.81)	2.17 (0.22-21.0)	0.67	0.41
Diabetes (E10-14)	54	1.00	1.56 (0.74-3.27)	2.60 (0.88-7.67)	0.20	0.08	12	1.00	1.58 (0.29-8.71)	0.67 (0.02-30.4)	0.71	0.99
Dementia (F00-03;G30)	104	1.00	0.63 (0.31-1.29)	0.81 (0.27-2.45)	0.45	0.47	41	1.00	0.88 (0.29-2.66)	0.55 (0.06-5.39)	0.87	0.61
Cardiovascular disease (G45-46;I00-99)	1031	1.00	0.92 (0.76-1.10)	1.17 (0.86-1.59)	0.18	0.51	559	1.00	0.97 (0.76-1.24)	1.11 (0.74-1.66)	0.77	0.70
- Ischaemic heart disease (I20-25)	501	1.00	0.99 (0.76-1.29)	1.39 (0.92-2.10)	0.20	0.18	229	1.00	1.01 (0.69-1.46)	1.20 (0.65-2.20)	0.82	0.60
- Cerebrovascular disease (G45-46;I60-69)	240	1.00	1.18 (0.80-1.74)	1.21 (0.62-2.38)	0.69	0.49	153	1.00	1.31 (0.83-2.08)	1.18 (0.52-2.67)	0.51	0.53
- Other (Other I)	290	1.00	0.65 (0.45-0.94)	0.83 (0.46-1.50)	0.06	0.27	177	1.00	0.69 (0.43-1.10)	0.93 (0.45-1.92)	0.25	0.60
Respiratory system disease (J00-99)	291	1.00	0.95 (0.69-1.32)	0.54 (0.28-1.03)	0.13	0.09	224	1.00	0.95 (0.66-1.37)	0.48 (0.22-1.01)	0.11	0.08
- Lower respiratory infection (J09-22)	44	1.00	1.19 (0.52-2.72)	0.29 (0.04-2.17)	0.28	0.38	39	1.00	1.32 (0.55-3.17)	0.30 (0.04-2.46)	0.24	0.46
- Other respiratory system disease (Other J)	247	1.00	0.90 (0.63-1.29)	0.59 (0.29-1.17)	0.31	0.15	185	1.00	0.88 (0.58-1.32)	0.51 (0.23-1.14)	0.25	0.12
Suicide (X60-84;Y87.0)	18	1.00	3.74 (1.13-12.4)	3.05 (0.39-23.7)	0.09	0.20	10	1.00	7.92 (1.12-56.0)	5.60 (0.29-109)	0.11	0.25
All-cause mortality (A00-Y98)	7965	1.00	1.04 (0.97-1.10)	1.21 (1.08-1.34)	0.002	0.001	3172	1.00	1.01 (0.92-1.12)	1.03 (0.87-1.22)	0.93	0.71

Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]Participants who at baseline had ever had cancer were excluded from cancer analyses, ever had diabetes excluded from diabetes analysis, did not have good/very good/excellent memory excluded from dementia analysis, ever had heart disease or stroke excluded from cardiovascular disease analyses, ever had asthma excluded from respiratory system disease analyses, ever had depression excluded from suicide analysis and ever had cancer, heart disease, stroke or diabetes excluded from all-cause mortality analysis. [b]Overall. [c]Linear trend using median number of drinks per drinking-day of each category. [d]Female breast cancer only. [e]Zero deaths in cell. ICD-10, International Classification of Diseases, version 10.

9.2 – Additional Analyses

Additional research questions regarding the relationship between alcohol consumption and mortality reported in the main analysis are reported here. The first set of analyses addressed the potential impact of the 'sick-quitter effect' and other biases on the main results. The second set used the mortality-specific risk estimates to calculate the population attributable fraction (PAF) of alcohol for the Australia, cumulative absolute risk of mortality, and the number of persons needed to quit or reduce drinking to prevent one death.

1. *The impact of the 'sick-quitter effect' and other changes in drinking behaviours in response to ill-health on risk estimates.*

Rationale and methods. A number of promising methods for mitigating bias from the 'sick-quitter effect' (and other changes in drinking behaviour) were identified in Chapter 7. Based on these findings, there are several exclusion scenarios that would be expected to decrease bias from the 'sick-quitter effect' in the mortality main analysis: exclusion of participants with a physical functioning score < 50%, exclusion of participants that consumed < 7 drinks per week, exclusion of deaths within five years of baseline (rather than three years as in the main analysis), exclusion of participants with prior disease (as this was performed in the article) and exclusion of participants aged ≥ 65 years at baseline. For analyses aimed at identifying a linear trend between alcohol and risk, methods that would be expected to *increase* bias from the 'sick-quitter effect' would be the inclusion of non-drinkers in the calculation and the inclusion of deaths within three years of baseline. As some of these exclusion scenarios include a large proportion of cases, these analyses were only investigated for all-cause mortality.

Fully adjusted HRs and 95% CIs for risk of all-cause mortality were estimated from Cox Proportional Hazards models (as per the main results) under each 'exclusion scenario' noted above, and directly

compared with the main results. These models were conducted for total alcohol consumption as a log-linear variable.

Mortality-specific HRs and 95% CIs were then calculated for total alcohol consumption, drinking frequency, and drinks per drinking-day after exclusion of participants with a physical functioning score < 50%. Overall drinking pattern, incorporating both number of drinking-days and number of drinks per drinking-day was assessed for all-cause mortality. The low physical functioning score exclusion scenario was selected for these more detailed analyses based on the conclusion in Chapter 7 that it was likely the most effective exclusion scenario examined to assess bias from the 'sick-quitter effect'.

For the continuous log-linear analysis estimating the increase in risk per additional drink/day, sensitivity tests excluding participants with prior disease (as this exclusion was performed for most results in the article), excluding participants with a physical functioning score < 50% and restricting the calculation to participants consuming ≥ 7 drinks per week (as this exclusion was intended to be applied to the log-linear analysis specifically) were performed.

Results. The log-linear association between alcohol consumption and risk of all-cause mortality was slightly altered under each exclusion scenario (Figure 9.1). Specifically, when non-drinkers were included in the calculation, the association between alcohol and mortality was not significant, and the HR was significantly lower than the main analysis (the confidence intervals did not overlap). Further, lower mortality HRs were observed when deaths within the first three years of follow-up were *included* in the calculation and separately, when participants aged ≥ 65 years were excluded. The remaining exclusion scenarios resulted in slightly higher risk estimates, however the confidence intervals overlapped with the main analysis.

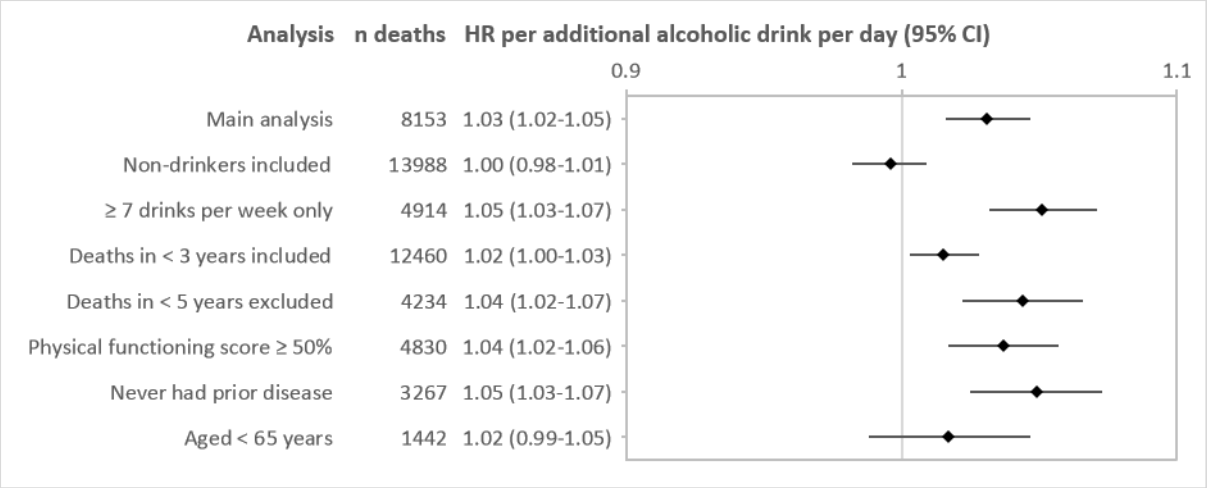

Figure 9.1. Hazard ratios (HR) and 95% confidence intervals (CI) of all-cause mortality risk per one drink increase in mean daily alcohol consumption among drinkers by different exclusion scenarios in the 45 and Up Study (2006-2014), New South Wales, Australia. Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. Prior disease refers to cancer, cardiovascular disease and diabetes.

The sensitivity analyses excluding participants with a low physical functioning score resulted in several risk estimates that differed from the main results and are presented in Tables 9.1-9.4. For categorical total alcohol consumption, there were significant trends of increased risk for death from liver cancer and other causes combined, and of decreased risk for death from breast cancer and dementia (Table 9.1). The trends for death from prostate cancer, non-Hodgkin lymphoma, external causes and suicide were non-significant, however there were no clear differences in hazard ratios compared to the main analysis. For drinking-days per week, the inverse associations of drinking frequency with death from cardiovascular disease and ischaemic heart disease were non-significant however the hazard ratios were not materially different compared to the main analysis (Table 9.2). There was also an inverse association for death from oesophageal cancer. There were no other changes in results.

For mean drinks per drinking-day, significant trends of increased risk of death from cardiovascular disease and fall were detected (Table 9.3). The associations for death from cancer, non-alcohol-

related cancer and lung cancer were non-significant, however there were no clear differences in hazard ratios compared to the main analysis. There was also evidence of higher risk in those consuming > 4 compared to > 2 and ≤ 4 drinks per drinking-day for death from cardiovascular disease. For the overall drinking pattern sensitivity analysis, the results were similar to the main analysis (Table 9.4).

Table 9.1. Hazard ratios and 95% confidence intervals of cause-specific mortality risk by alcohol consumption after excluding participants with physical functioning score < 50% at baseline in the 45 and Up Study (2006-2014), New South Wales, Australia.

		Drinks/week							
Cause of death (ICD-10 code)	**n deaths**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***p*[b]**	***p*$_{trend}$[c]**
Cancer (C00-97;D45-47)	1556	0.99 (0.84-1.16)	1.00	0.83 (0.70-0.99)	0.85 (0.71-1.01)	0.90 (0.74-1.10)	0.95 (0.73-1.24)	0.13	0.73
- Alcohol-related (C00-15;18-20;22;32;50[d])	355	0.83 (0.60-1.13)	1.00	0.64 (0.45-0.93)	0.77 (0.53-1.10)	0.79 (0.52-1.21)	1.31 (0.79-2.17)	0.06	0.08
- Mouth, pharynx and larynx (C00-14;32)	28	0.84 (0.24-2.87)	1.00	-[e]	1.19 (0.34-4.17)	1.21 (0.33-4.44)	1.02 (0.21-4.89)	0.99	0.35
- Oesophagus (C15)	52	1.45 (0.56-3.74)	1.00	1.15 (0.41-3.19)	0.99 (0.35-2.82)	0.55 (0.15-2.00)	2.01 (0.61-6.55)	0.42	0.44
- Colorectum (C18-20)	139	0.93 (0.54-1.58)	1.00	0.75 (0.41-1.37)	0.86 (0.47-1.58)	1.14 (0.59-2.19)	1.40 (0.62-3.19)	0.66	0.12
- Liver (C22)	38	1.41 (0.39-5.18)	1.00	1.34 (0.33-5.39)	2.27 (0.60-8.50)	1.59 (0.34-7.36)	4.87 (1.08-21.8)	0.27	0.04
- Breast (C50[d])	98	0.58 (0.35-0.96)	1.00	0.50 (0.27-0.91)	0.41 (0.20-0.83)	0.45 (0.16-1.32)	-[e]	0.10	0.04
- Non-alcohol-related (Other C;D45-47)	1201	1.05 (0.87-1.26)	1.00	0.90 (0.73-1.10)	0.88 (0.71-1.08)	0.94 (0.75-1.18)	0.86 (0.63-1.18)	0.30	0.62
- Stomach (C16)	32	1.14 (0.35-3.70)	1.00	1.41 (0.42-4.71)	0.67 (0.16-2.70)	0.89 (0.21-3.70)	0.91 (0.16-5.34)	0.90	0.94
- Pancreas (C25)	109	1.35 (0.69-2.64)	1.00	1.27 (0.63-2.58)	1.47 (0.73-2.97)	1.32 (0.59-2.91)	1.03 (0.32-3.30)	0.92	0.91
- Lung (C33-34)	266	1.44 (0.92-2.24)	1.00	1.11 (0.69-1.81)	1.08 (0.67-1.75)	1.38 (0.84-2.27)	1.03 (0.54-1.98)	0.37	0.59
- Melanoma (C43)	76	0.62 (0.31-1.22)	1.00	0.50 (0.24-1.03)	0.41 (0.19-0.90)	0.80 (0.38-1.67)	0.28 (0.06-1.27)	0.15	0.34
- Prostate (C61)	146	0.55 (0.33-0.92)	1.00	0.68 (0.41-1.12)	0.50 (0.29-0.87)	0.59 (0.33-1.06)	0.61 (0.27-1.37)	0.16	0.20
- Kidney (C64)	28	2.47 (0.54-11.3)	1.00	1.65 (0.32-8.54)	2.16 (0.43-10.9)	1.01 (0.14-7.44)	3.22 (0.43-24.4)	0.71	0.68
- Non-Hodgkin lymphoma (C82-85)	51	0.93 (0.42-2.09)	1.00	0.66 (0.26-1.66)	0.74 (0.29-1.88)	0.65 (0.21-2.01)	-[e]	0.93	0.19
Diabetes (E10-14)	35	1.79 (0.57-5.64)	1.00	1.42 (0.40-4.97)	1.63 (0.46-5.74)	0.75 (0.13-4.24)	0.79 (0.08-7.43)	0.80	0.74
Dementia (F00-03;G30)	90	0.96 (0.51-1.81)	1.00	0.93 (0.47-1.84)	0.89 (0.42-1.87)	0.25 (0.06-1.10)	-[e]	0.62	0.04
Cardiovascular disease (G45-46;I00-99)	815	1.05 (0.84-1.30)	1.00	0.92 (0.72-1.18)	0.94 (0.73-1.21)	0.90 (0.66-1.21)	1.08 (0.72-1.61)	0.75	0.85
- Ischaemic heart disease (I20-25)	405	1.10 (0.80-1.51)	1.00	1.02 (0.72-1.43)	0.92 (0.64-1.32)	0.84 (0.55-1.29)	1.04 (0.61-1.79)	0.76	0.51
- Cerebrovascular disease (G45-46;I60-69)	196	1.00 (0.64-1.56)	1.00	0.86 (0.52-1.42)	0.92 (0.54-1.57)	1.22 (0.68-2.19)	0.85 (0.32-2.25)	0.87	0.43
- Other cardiovascular disease (Other I)	214	0.98 (0.65-1.50)	1.00	0.82 (0.51-1.31)	0.98 (0.61-1.59)	0.76 (0.41-1.40)	1.28 (0.60-2.77)	0.75	0.64
Respiratory system disease (J00-99)	186	1.62 (0.96-2.73)	1.00	1.27 (0.72-2.25)	1.27 (0.70-2.29)	1.53 (0.81-2.91)	1.49 (0.63-3.51)	0.53	0.24
- Lower respiratory infection (J09-22)	28	0.81 (0.27-2.45)	1.00	0.38 (0.09-1.63)	0.93 (0.26-3.33)	0.89 (0.19-4.12)	0.72 (0.07-7.57)	0.84	0.84
- Other respiratory system disease (Other J)	158	1.93 (1.05-3.55)	1.00	1.62 (0.85-3.09)	1.43 (0.72-2.82)	1.73 (0.84-3.55)	1.69 (0.66-4.35)	0.41	0.33
Digestive system disease (K00-93)	90	1.89 (0.87-4.12)	1.00	1.40 (0.59-3.30)	1.14 (0.45-2.87)	1.68 (0.64-4.37)	3.34 (1.19-9.35)	0.15	0.04
- Liver disease (K70-77)	24	1.95 (0.41-9.38)	1.00	0.80 (0.11-5.72)	0.79 (0.11-5.67)	1.70 (0.27-10.6)	7.65 (1.46-40.2)	0.02	< 0.001
- Other digestive system disease (Other K)	66	1.84 (0.75-4.52)	1.00	1.52 (0.57-4.04)	1.21 (0.42-3.47)	1.56 (0.51-4.80)	0.70 (0.08-5.98)	0.72	0.82
External (V01-Y98)	109	1.74 (0.89-3.42)	1.00	1.01 (0.47-2.19)	1.35 (0.64-2.85)	1.74 (0.78-3.86)	1.69 (0.60-4.73)	0.35	0.15
- Transport accident (V00-99;Y85)	32	0.80 (0.25-2.52)	1.00	0.45 (0.11-1.88)	1.29 (0.41-4.02)	1.66 (0.50-5.53)	0.63 (0.07-5.72)	0.49	0.47
- Fall (W00-19)	16	2.79 (0.32-24.3)	1.00	1.02 (0.09-11.9)	1.81 (0.17-18.9)	1.25 (0.07-21.4)	11.1 (0.87-140.8)	0.26	0.04
- Suicide (X60-84;Y87.0)	23	-[f]	1.00	-[f]	-[f]	-[f]	-[f]	0.55	0.18
- Other external (W20-X59;Y86;Y87.1-98)	38	1.16 (0.41-3.26)	1.00	1.29 (0.43-3.89)	0.49 (0.12-2.08)	1.18 (0.31-4.59)	1.42 (0.25-7.88)	0.79	0.89
Other (Other A00-R99)	305	1.08 (0.74-1.59)	1.00	1.09 (0.72-1.64)	1.20 (0.79-1.82)	1.04 (0.64-1.70)	1.98 (1.14-3.43)	0.20	0.04
All-cause mortality (A00-Y98)	7401	1.12 (1.04-1.21)	1.00	0.96 (0.89-1.05)	0.99 (0.91-1.08)	0.98 (0.89-1.08)	1.19 (1.05-1.34)	< 0.001	0.008

Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. [d]Female breast cancer only. [e]Zero deaths in cell. [f]Not possible to calculate due to zero deaths in reference group. ICD-10, International Classification of Diseases, version 10.

Table 9.2. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk after excluding participants with physical functioning score < 50% by drinking-days per week among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia.

		HR drinking-days per week in main analysis - adjusted for total alcohol consumption (95% CI)						HR drinking-days per week in sensitivity analysis[a] - adjusted for total alcohol consumption (95% CI)				
Cause of death (ICD-10 code)	**n deaths**	**1-2**	**3-5**	**6-7**	***p*[b]**	***p*$_{trend}$[c]**	**n deaths**	**1-2**	**3-5**	**6-7**	***p*[b]**	***p*$_{trend}$[c]**
Cancer (C00-97;D45-47)	1470	1.00	0.79 (0.68-0.91)	0.73 (0.63-0.85)	< 0.001	< 0.001	1032	1.00	0.77 (0.64-0.91)	0.71 (0.59-0.86)	< 0.001	< 0.001
- Alcohol-related (C00-15;18-20;22;32;50[d])	325	1.00	0.82 (0.60-1.12)	0.82 (0.60-1.12)	0.37	0.24	232	1.00	0.70 (0.49-1.01)	0.69 (0.48-1.01)	0.10	0.07
- Mouth, pharynx and larynx (C00-14;32)	25	1.00	3.23 (0.83-12.6)	2.97 (0.71-12.4)	0.23	0.19	20	1.00	3.64 (0.72-18.5)	2.62 (0.47-14.7)	0.29	0.42
- Oesophagus (C15)	53	1.00	0.77 (0.35-1.70)	0.58 (0.26-1.26)	0.38	0.16	35	1.00	0.42 (0.16-1.14)	0.37 (0.14-0.95)	0.09	0.049
- Colorectum (C18-20)	129	1.00	0.79 (0.48-1.31)	0.81 (0.49-1.36)	0.62	0.44	92	1.00	0.78 (0.42-1.43)	0.83 (0.45-1.53)	0.71	0.61
- Liver (C22)	41	1.00	0.94 (0.35-2.49)	1.36 (0.54-3.44)	0.65	0.45	26	1.00	0.78 (0.22-2.76)	1.29 (0.40-4.11)	0.65	0.56
- Breast (C50[d])	77	1.00	0.79 (0.43-1.45)	0.97 (0.46-2.05)	0.69	0.90	59	1.00	0.71 (0.36-1.40)	0.77 (0.32-1.89)	0.61	0.52
- Non-alcohol-related (Other C;D45-47)	1145	1.00	0.78 (0.66-0.92)	0.71 (0.60-0.84)	< 0.001	< 0.001	800	1.00	0.79 (0.65-0.96)	0.72 (0.59-0.89)	0.007	0.003
- Stomach (C16)	28	1.00	0.84 (0.28-2.47)	0.79 (0.27-2.35)	0.91	0.69	19	1.00	1.06 (0.28-4.02)	0.65 (0.16-2.71)	0.69	0.49
- Pancreas (C25)	91	1.00	1.27 (0.73-2.20)	0.65 (0.34-1.25)	0.048	0.15	74	1.00	1.30 (0.69-2.45)	0.76 (0.36-1.57)	0.18	0.35
- Lung (C33-34)	258	1.00	0.64 (0.44-0.93)	0.74 (0.52-1.06)	0.06	0.16	176	1.00	0.58 (0.36-0.92)	0.79 (0.51-1.22)	0.07	0.45
- Melanoma (C43)	68	1.00	0.79 (0.39-1.59)	1.00 (0.49-2.05)	0.71	0.93	57	1.00	0.71 (0.34-1.50)	0.79 (0.36-1.73)	0.67	0.58
- Prostate (C61)	166	1.00	0.61 (0.38-0.98)	0.90 (0.58-1.39)	0.10	0.75	110	1.00	0.52 (0.29-0.92)	0.72 (0.42-1.24)	0.08	0.31
- Kidney (C64)	26	1.00	0.64 (0.20-2.10)	0.91 (0.30-2.72)	0.73	0.95	16	1.00	1.02 (0.25-4.13)	0.65 (0.14-3.08)	0.78	0.56
- Non-Hodgkin lymphoma (C82-85)	41	1.00	1.30 (0.60-2.84)	0.56 (0.20-1.57)	0.15	0.30	32	1.00	1.36 (0.55-3.37)	0.58 (0.18-1.84)	0.20	0.35
Diabetes (E10-14)	54	1.00	0.69 (0.33-1.47)	0.66 (0.31-1.40)	0.49	0.28	21	1.00	0.75 (0.23-2.37)	0.57 (0.15-2.08)	0.69	0.39
Dementia (F00-03;G30)	104	1.00	1.08 (0.63-1.85)	0.84 (0.47-1.48)	0.62	0.52	48	1.00	0.82 (0.35-1.90)	0.96 (0.41-2.26)	0.88	0.94
Cardiovascular disease (G45-46;I00-99)	1031	1.00	0.95 (0.79-1.13)	0.81 (0.68-0.97)	0.04	0.02	506	1.00	1.05 (0.81-1.35)	0.82 (0.63-1.06)	0.08	0.09
- Ischaemic heart disease (I20-25)	501	1.00	0.88 (0.68-1.12)	0.72 (0.56-0.93)	0.04	0.01	256	1.00	1.02 (0.72-1.45)	0.75 (0.52-1.09)	0.15	0.11
- Cerebrovascular disease (G45-46;I60-69)	240	1.00	0.95 (0.66-1.38)	0.81 (0.56-1.17)	0.47	0.24	117	1.00	0.89 (0.51-1.53)	0.90 (0.52-1.56)	0.90	0.74
- Other cardiovascular disease (Other I)	290	1.00	1.13 (0.79-1.60)	1.02 (0.72-1.43)	0.74	0.97	133	1.00	1.27 (0.77-2.12)	0.88 (0.51-1.49)	0.23	0.46
Respiratory system disease (J00-99)	291	1.00	1.26 (0.87-1.83)	1.47 (1.03-2.09)	0.11	0.03	112	1.00	1.39 (0.71-2.70)	1.85 (0.99-3.46)	0.71	0.047
- Lower respiratory infection (J09-22)	44	1.00	1.27 (0.46-3.51)	1.67 (0.67-4.16)	0.53	0.26	17	1.00	1.94 (0.26-14.4)	1.89 (0.30-11.7)	0.77	0.55
- Other respiratory system disease (Other J)	247	1.00	1.27 (0.85-1.89)	1.43 (0.97-2.11)	0.20	0.07	95	1.00	1.39 (0.68-2.84)	1.83 (0.93-3.60)	0.20	0.07
Digestive system disease (K00-93)	100	1.00	1.02 (0.55-1.89)	1.07 (0.60-1.93)	0.97	0.81	53	1.00	0.63 (0.26-1.52)	0.85 (0.39-1.90)	0.57	0.84
- Liver disease (K70-77)	24	1.00	0.40 (0.11-1.41)	0.62 (0.19-1.99)	0.36	0.49	16	1.00	0.19 (0.04-1.03)	0.30 (0.07-1.28)	0.11	0.14
- Other digestive system disease (Other K)	76	1.00	1.50 (0.73-3.11)	1.56 (0.76-3.19)	0.44	0.26	37	1.00	1.22 (0.41-3.65)	1.94 (0.68-5.55)	0.39	0.18
External (V01-Y98)	107	1.00	0.82 (0.46-1.46)	1.05 (0.60-1.82)	0.62	0.77	65	1.00	0.73 (0.35-1.50)	0.98 (0.48-2.03)	0.59	0.95
- Transport accident (V00-99;Y85)	26	1.00	0.54 (0.15-1.93)	1.76 (0.57-5.49)	0.14	0.25	24	1.00	0.49 (0.14-1.76)	1.34 (0.42-4.30)	0.26	0.55
- Fall (W00-19)	25	1.00	1.44 (0.30-6.83)	2.88 (0.73-11.4)	0.23	0.09	8	1.00	-[e]	-[e]	0.94	0.17
- Suicide (X60-84;Y87.0)	18	1.00	1.57 (0.39-6.32)	0.71 (0.15-3.37)	0.40	0.52	10	1.00	1.26 (0.21-7.51)	0.50 (0.06-4.04)	0.54	0.45
- Other external (W20-X59;Y86;Y87.1-98)	38	1.00	0.62 (0.24-1.59)	0.55 (0.23-1.32)	0.38	0.19	23	1.00	0.56 (0.17-1.86)	0.51 (0.15-1.69)	0.50	0.28
Other (Other A00-R99)	392	1.00	1.02 (0.76-1.37)	0.92 (0.69-1.23)	0.71	0.52	205	1.00	1.42 (0.92-2.19)	1.13 (0.72-1.76)	0.21	0.86
All-cause mortality (A00-Y98)	7965	1.00	0.88 (0.82-0.93)	0.85 (0.80-0.90)	< 0.001	< 0.001	4760	1.00	0.85 (0.78-0.93)	0.84 (0.77-0.91)	< 0.001	< 0.001

Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]Participants with physical functioning score < 50% excluded. [b]Overall. [c]Linear trend using median number of drinking-days per week of each category. [d]Female breast cancer only. [e]Not possible to calculate due to zero deaths in reference group. ICD-10, International Classification of Diseases, version 10.

Table 9.3. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk after excluding participants with physical functioning score < 50% by mean drinks per drinking-day among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia.

		HR mean drinks per drinking-day in main analysis - adjusted for total alcohol consumption (95% CI)						HR mean drinks per drinking-day in sensitivity analysis[a] - adjusted for total alcohol consumption (95% CI)				
Cause of death (ICD-10 code)	**n deaths**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[b]**	***p*$_{trend}$[c]**	**n deaths**	**≤ 2**	**> 2 and ≤ 4**	**> 4**	***p*[b]**	***p*$_{trend}$[c]**
Cancer (C00-97;D45-47)	1470	1.00	1.16 (1.00-1.33)	1.38 (1.09-1.33)	0.02	0.006	1032	1.00	1.16 (0.98-1.37)	1.28 (0.96-1.71)	0.16	0.07
- Alcohol-related (C00-15;18-20;22;32;50[d])	325	1.00	0.91 (0.66-1.24)	1.42 (0.88-2.30)	0.13	0.24	232	1.00	0.84 (0.58-1.22)	1.49 (0.85-2.64)	0.08	0.29
- Mouth, pharynx and larynx (C00-14;32)	25	1.00	0.84 (0.31-2.29)	0.43 (0.31-2.29)	0.63	0.35	20	1.00	1.42 (0.48-4.24)	0.86 (0.14-5.15)	0.69	0.92
- Oesophagus (C15)	53	1.00	0.66 (0.28-1.53)	2.86 (1.08-7.56)	0.01	0.047	35	1.00	0.49 (0.15-1.53)	3.89 (1.20-12.6)	0.005	0.03
- Colorectum (C18-20)	129	1.00	1.07 (0.66-1.74)	1.60 (0.75-3.40)	0.44	0.25	92	1.00	0.80 (0.45-1.44)	1.07 (0.42-2.74)	0.65	0.98
- Liver (C22)	41	1.00	1.02 (0.44-2.34)	1.27 (0.38-4.27)	0.91	0.71	26	1.00	1.03 (0.35-2.99)	1.66 (0.41-6.81)	0.74	0.49
- Breast (C50[d])	77	1.00	1.07 (0.50-2.29)	-[e]	0.98	0.47	59	1.00	1.20 (0.52-2.77)	-[e]	0.91	0.77
- Non-alcohol-related (Other C;D45-47)	1145	1.00	1.24 (1.05-1.45)	1.37 (1.05-1.80)	0.02	0.01	800	1.00	1.26 (1.04-1.52)	1.23 (0.88-1.72)	0.06	0.12
- Stomach (C16)	28	1.00	1.16 (0.75-1.52)	0.81 (0.12-5.33)	0.88	0.90	19	1.00	1.36 (0.41-4.51)	1.32 (0.17-10.6)	0.88	0.75
- Pancreas (C25)	91	1.00	1.37 (0.78-2.40)	1.60 (0.63-4.06)	0.49	0.28	74	1.00	1.08 (0.58-2.01)	1.11 (0.38-3.28)	0.97	0.83
- Lung (C33-34)	258	1.00	1.51 (1.10-2.08)	1.66 (0.98-2.80)	0.03	0.04	176	1.00	1.59 (1.08-2.34)	1.38 (0.70-2.72)	0.055	0.22
- Melanoma (C43)	68	1.00	1.10 (0.57-2.12)	0.73 (0.20-2.73)	0.74	0.76	57	1.00	1.37 (0.68-2.74)	0.86 (0.21-3.59)	0.50	0.93
- Prostate (C61)	166	1.00	1.06 (0.69-1.62)	1.13 (0.53-2.40)	0.95	0.74	110	1.00	1.45 (0.88-2.38)	1.44 (0.59-3.51)	0.34	0.29
- Kidney (C64)	26	1.00	2.56 (0.94-6.98)	3.62 (0.76-17.2)	0.14	0.08	16	1.00	3.27 (0.90-11.9)	4.05 (0.48-34.3)	0.19	0.15
- Non-Hodgkin lymphoma (C82-85)	41	1.00	1.60 (0.65-3.94)	0.86 (0.10-7.31)	0.55	0.71	32	1.00	1.99 (0.76-5.22)	1.17 (0.12-11.1)	0.36	0.47
Diabetes (E10-14)	54	1.00	1.56 (0.74-3.27)	2.60 (0.88-7.67)	0.20	0.08	21	1.00	1.22 (0.38-3.91)	1.11 (0.13-9.77)	0.94	0.86
Dementia (F00-03;G30)	104	1.00	0.63 (0.31-1.29)	0.81 (0.27-2.45)	0.45	0.47	48	1.00	0.64 (0.21-1.93)	0.46 (0.05-4.55)	0.66	0.39
Cardiovascular disease (G45-46;I00-99)	1031	1.00	0.92 (0.76-1.10)	1.17 (0.86-1.59)	0.18	0.51	506	1.00	0.90 (0.70-1.18)	1.69 (1.12-2.54)	0.004	0.04
- Ischaemic heart disease (I20-25)	501	1.00	0.99 (0.76-1.29)	1.39 (0.92-2.10)	0.20	0.18	256	1.00	0.80 (0.55-1.15)	1.71 (0.99-2.95)	0.01	0.15
- Cerebrovascular disease (G45-46;I60-69)	240	1.00	1.18 (0.80-1.74)	1.21 (0.62-2.38)	0.69	0.49	117	1.00	1.24 (0.73-2.12)	1.12 (0.40-3.09)	0.72	0.69
- Other (Other I)	290	1.00	0.65 (0.45-0.94)	0.83 (0.46-1.50)	0.06	0.27	133	1.00	0.82 (0.48-1.41)	2.04 (0.93-4.48)	0.0497	0.16
Respiratory system disease (J00-99)	291	1.00	0.95 (0.69-1.32)	0.54 (0.28-1.03)	0.13	0.09	112	1.00	0.95 (0.57-1.60)	0.55 (0.19-1.57)	0.48	0.32
- Lower respiratory infection (J09-22)	44	1.00	1.19 (0.52-2.72)	0.29 (0.04-2.17)	0.28	0.38	17	1.00	0.69 (0.14-3.50)	0.08 (0.00-4.33)	0.45	0.24
- Other respiratory system disease (Other J)	247	1.00	0.90 (0.63-1.29)	0.59 (0.29-1.17)	0.31	0.15	95	1.00	0.96 (0.55-1.69)	0.63 (0.21-1.88)	0.67	0.46
Digestive system disease (K00-93)	100	1.00	0.81 (0.46-1.42)	0.96 (0.40-2.32)	0.74	0.83	53	1.00	0.73 (0.34-1.54)	0.96 (0.31-2.95)	0.67	0.83
- Liver disease (K70-77)	24	1.00	0.37 (0.08-1.74)	2.17 (0.62-7.65)	0.10	0.21	16	1.00	0.33 (0.04-2.94)	3.58 (0.79-16.4)	0.06	0.07
- Other digestive system disease (Other K)	76	1.00	1.12 (0.57-2.20)	0.53 (0.13-2.21)	0.47	0.52	37	1.00	1.03 (0.39-2.72)	0.22 (0.02-3.02)	0.41	0.39
External (V01-Y98)	107	1.00	1.47 (0.90-2.40)	0.81 (0.32-2.06)	0.12	0.98	65	1.00	1.76 (0.95-3.27)	0.76 (0.21-2.73)	0.052	0.93
- Transport accident (V00-99;Y85)	26	1.00	1.24 (0.46-3.33)	0.16 (0.01-2.68)	0.22	0.37	24	1.00	1.38 (0.51-3.73)	0.20 (0.01-3.28)	0.22	0.49
- Fall (W00-19)	25	1.00	1.94 (0.64-5.86)	3.85 (0.81-18.2)	0.22	0.08	8	1.00	14.7 (1.76-127.4)	49.6 (1.34-1834.6)	0.04	0.02
- Suicide (X60-84;Y87.0)	18	1.00	3.74 (1.13-12.4)	3.05 (0.39-23.7)	0.09	0.20	10	1.00	1.86 (0.37-9.32)	2.14 (0.15-30.5)	0.74	0.54
- Other external (W20-X59;Y86;Y87.1-98)	38	1.00	0.80 (0.34-1.89)	0.24 (0.04-1.59)	0.33	0.15	23	1.00	1.31 (0.44-3.92)	0.51 (0.05-4.81)	0.53	0.69
Other (Other A00-R99)	392	1.00	0.78 (0.58-1.05)	1.09 (0.68-1.74)	0.12	0.97	205	1.00	0.80 (0.54-1.17)	0.95 (0.50-1.80)	0.47	0.70
All-cause mortality (A00-Y98)	7965	1.00	1.04 (0.97-1.10)	1.21 (1.08-1.34)	0.002	0.001	4760	1.00	1.03 (0.95-1.11)	1.24 (1.08-1.42)	0.006	0.005

Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women) and height. [a]Participants with physical functioning score < 50% excluded. [b]Overall. [c]Linear trend using median number of drinks per drinking-day of each category. [d]Female breast cancer only. [e]Zero deaths in cell. ICD-10, International Classification of Diseases, version 10.

Table 9.4. Hazard ratios (HR) and 95% confidence intervals (CI) of all-cause mortality risk after excluding participants with physical functioning score < 50% by drinking pattern among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia.

Drinking-days per week	n deaths	HR mean drinks per drinking-day in main analysis (95% CI)			n deaths	HR mean drinks per drinking-day of in sensitivity analysis[a] (95% CI)		
		≤ 2	> 2 and ≤ 4	> 4		≤ 2	> 2 and ≤ 4	> 4
1-2	7965	1.00	1.13 (1.00-1.28)	1.24 (1.07-1.43)	4760	1.00	1.16 (0.99-1.35)	1.27 (1.05-1.54)
3-5		0.92 (0.85-0.99)	0.96 (0.86-1.08)	1.18 (1.00-1.40)		0.90 (0.82-0.99)	0.93 (0.81-1.07)	1.25 (1.01-1.55)
6-7		0.94 (0.88-1.01)	0.97 (0.90-1.05)	1.13 (1.02-1.26)		0.95 (0.87-1.04)	0.96 (0.86-1.07)	1.16 (1.02-1.33)

Non-drinkers were excluded. Model was adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women only), menopausal status (women only), hormone replacement therapy use (women only) and height. [a]Participants with physical functioning score < 50% excluded.

The sensitivity analyses for the continuous log-linear association between alcohol consumption and mortality for three exclusion scenarios (the exclusion of participants with prior disease, the exclusion of participants with a low physical functioning score, and the exclusion of participants consuming < 7 drinks per week) are shown in Table 9.5. All three sensitivity analyses resulted in several risk estimates that differed from the main results. Specifically, the sensitivity analysis excluding participants with prior disease resulted in significant positive associations for death from oesophageal cancer, breast cancer and cardiovascular disease, which were not observed in the main analysis. The positive association with death from liver cancer and inverse association with death from prostate cancer observed in the main analysis were non-significant, with the hazard ratio for death from prostate cancer appearing to change the most compared to the main analysis. The sensitivity analysis excluding participants with a low physical functioning score resulted in significant positive associations for death from oesophageal cancer and other causes combined. The positive associations for death from other cardiovascular disease, external causes, fall and other external causes, and the inverse associations for death from prostate cancer and non-Hodgkin lymphoma (NHL), were non-significant, with the hazard ratio for death from NHL appearing to change the most compared to the main analysis. The sensitivity analysis that excluded participants consuming < 7 drinks per week resulted in significant positive associations for death from cardiovascular disease and other causes combined. The positive associations for death from liver cancer, digestive system disease, external causes and fall, and the inverse associations for death from prostate cancer and NHL observed in the main analysis, were non-significant, with the hazard ratios for death from fall and NHL appearing to change the most compared to the main analysis.

Table 9.5. Hazard ratios (HR) and 95% confidence intervals (CI) of cause-specific mortality risk per one drink increase in mean daily alcohol consumption after excluding participants with prior disease, a physical functioning score < 50% or those consuming < 7 drinks per week among drinkers in the 45 and Up Study (2006-2014), New South Wales, Australia.

	Main analysis		Excluding prior disease[a]		Excluding MOS-PF < 50%		Excluding < 7 drinks/week	
Cause of death (ICD-10 code)	**n deaths**	**HR (95% CI)**	**n deaths**	**HR (95% CI)**	**n deaths**	**HR (95% CI)**	**n deaths**	**HR (95% CI)**
Cancer (C00-97;D45-47)	1,509	1.01 (0.97-1.04)	824	1.04 (1.00-1.09)	1,052	1.02 (0.98-1.06)	909	1.03 (0.99-1.08)
- Alcohol-related (C00-15;18-20;22;32;50[b])	331	1.08 (1.01-1.16)	161	1.16 (1.07-1.25)	235	1.10 (1.02-1.20)	202	1.09 (1.00-1.18)
- Mouth, pharynx and larynx (C00-14;32)	25	1.01 (0.83-1.24)	15	1.06 (0.85-1.32)	20	1.07 (0.87-1.32)	20	0.93 (0.70-1.22)
- Oesophagus (C15)	53	1.13 (0.98-1.30)	32	1.25 (1.09-1.43)	35	1.18 (1.01-1.39)	38	1.14 (0.96-1.35)
- Colorectum (C18-20)	131	1.08 (0.96-1.20)	70	1.08 (0.92-1.26)	93	1.10 (0.97-1.25)	79	1.12 (0.99-1.28)
- Liver (C22)	42	1.17 (1.01-1.36)	33	1.15 (0.98-1.36)	27	1.22 (1.03-1.45)	33	1.08 (0.89-1.28)
- Breast (C50[b])	80	0.94 (0.72-1.24)	11	1.59 (1.10-2.29)	60	0.69 (0.47-1.02)	32	1.17 (0.86-1.59)
- Non-alcohol-related (Other C;D45-47)	1,178	0.98 (0.95-1.03)	663	1.01 (0.96-1.06)	817	1.00 (0.95-1.05)	707	1.02 (0.97-1.07)
- Stomach (C16)	32	1.00 (0.79-1.27)	22	0.98 (0.73-1.30)	22	1.08 (0.83-1.42)	18	1.09 (0.83-1.43)
- Pancreas (C25)	97	0.97 (0.83-1.13)	83	0.97 (0.82-1.14)	76	1.01 (0.86-1.18)	58	0.93 (0.76-1.13)
- Lung (C33-34)	264	1.03 (0.95-1.10)	185	1.02 (0.93-1.11)	179	1.02 (0.93-1.12)	179	1.01 (0.93-1.11)
- Melanoma (C43)	70	0.93 (0.77-1.12)	26	0.87 (0.65-1.17)	57	0.91 (0.74-1.11)	42	0.94 (0.74-1.20)
- Prostate (C61)	169	0.88 (0.78-1.00)	46	1.01 (0.82-1.25)	113	0.90 (0.77-1.04)	99	0.92 (0.79-1.08)
- Kidney (C64)	28	1.08 (0.85-1.37)	16	1.22 (0.96-1.56)	17	1.02 (0.74-1.41)	21	0.98 (0.65-1.32)
- Non-Hodgkin lymphoma (C82-85)	41	0.61 (0.42-0.88)	17	0.43 (0.20-0.92)	32	0.75 (0.52-1.09)	16	0.77 (0.45-1.29)
Diabetes (E10-14)	55	0.96 (0.78-1.18)	13	1.36 (0.96-1.93)	21	1.00 (0.73-1.37)	31	0.96 (0.74-1.26)
Dementia (F00-03;G30)	111	0.89 (0.73-1.08)	43	0.79 (0.55-1.13)	52	0.73 (0.52-1.03)	56	0.89 (0.68-1.17)
Cardiovascular disease (G45-46;I00-99)	1,059	1.04 (0.99-1.09)	577	1.09 (1.03-1.15)	511	1.01 (0.95-1.08)	603	1.08 (1.03-1.14)
- Ischaemic heart disease (I20-25)	514	0.99 (0.93-1.06)	237	1.03 (0.95-1.13)	258	0.98 (0.89-1.07)	286	1.05 (0.97-1.13)
- Cerebrovascular disease (G45-46;I60-69)	247	1.02 (0.92-1.13)	157	1.09 (0.97-1.22)	119	1.03 (0.89-1.19)	142	1.03 (0.90-1.17)
- Other (Other I)	298	1.13 (1.05-1.22)	183	1.15 (1.05-1.27)	134	1.06 (0.93-1.21)	175	1.17 (1.07-1.28)
Respiratory system disease (J00-99)	300	1.03 (0.95-1.12)	230	1.06 (0.98-1.16)	114	1.10 (0.97-1.23)	198	0.99 (0.90-1.10)
- Lower respiratory infection (J09-22)	45	1.14 (0.94-1.38)	39	1.19 (0.98-1.45)	17	1.27 (0.93-1.73)	30	1.10 (0.84-1.42)
- Other respiratory system disease (Other J)	255	1.01 (0.93-1.11)	191	1.04 (0.94-1.14)	97	1.07 (0.94-1.22)	168	0.98 (0.87-1.10)
Digestive system disease (K00-93)	100	1.15 (1.03-1.28)	-	-	53	1.22 (1.08-1.39)	64	1.13 (1.00-1.28)
- Liver disease (K70-77)	24	1.26 (1.11-1.43)	-	-	16	1.38 (1.20-1.59)	18	1.25 (1.08-1.45)
- Other digestive system disease (Other K)	76	1.00 (0.84-1.20)	-	-	37	0.94 (0.72-1.24)	46	0.94 (0.73-1.20)
External (V01-Y98)	110	1.18 (1.07-1.33)	-	-	67	1.10 (0.96-1.27)	76	1.12 (0.99-1.27)
- Transport accident (V00-99;Y85)	26	1.03 (0.79-1.33)	-	-	24	1.04 (0.81-1.34)	18	0.87 (0.59-1.29)
- Fall (W00-19)	26	1.34 (1.09-1.64)	-	-	9	1.29 (0.88-1.90)	21	1.14 (0.87-1.48)
- Suicide (X60-84;Y87.0)	19	1.21 (0.96-1.52)	10	1.31 (0.95-1.80)	11	1.22 (0.88-1.69)	16	1.07 (0.77-1.49)
- Other external (W20-X59;Y86;Y87.1-98)	39	1.19 (1.00-1.41)	-	-	23	1.07 (0.82-1.40)	21	1.21 (1.00-1.46)
Other (Other A00-R99)	402	1.05 (0.99-1.13)	-	-	210	1.12 (1.04-1.22)	238	1.10 (1.02-1.19)
All-cause mortality (A00-Y98)	8,153	1.03 (1.02-1.05)	3,267	1.05 (1.03-1.07)	4,830	1.04 (1.02-1.06)	4,914	1.05 (1.03-1.07)

Non-drinkers were excluded. Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women only), menopausal status (women only), hormone replacement therapy use (women only) and height. [a]Participants who at baseline had ever had cancer were excluded from cancer analyses, ever had diabetes excluded from diabetes analysis, did not have good/very good/excellent memory excluded from dementia analysis, ever had heart disease or stroke excluded from cardiovascular disease analyses, ever had asthma excluded from respiratory system disease analyses, ever had depression excluded from suicide analysis and ever had cancer, heart disease, stroke or diabetes excluded from all-cause mortality analysis. [b]Female breast cancer only. ICD, International Classification of Diseases, version 10. MOS-PF, Medical Outcomes Study Physical Functioning score.

Conclusions. The magnitude of the log-linear association between total alcohol consumption and all-cause mortality risk appeared to vary according to different exclusion scenarios aimed to assess the extent of bias from the 'sick-quitter effect'. The sensitivity analyses that would be expected to increase bias from the 'sick-quitter effect' (including non-drinkers in the calculation, including deaths within the first three years of follow-up) both resulted in lower effect estimates, while four of the five the sensitivity analyses that would be expected to reduce bias from the 'sick-quitter effect' (restricting the calculation to participants consuming ≥ 7 drinks per week, the exclusion of deaths occurring within the first five years of follow-up, the exclusion of participants with a physical functioning score of < 50% and the exclusion of participants ever diagnosed with cancer or cardiovascular disease, but not restriction to participants aged < 65 years at baseline) resulted in higher effect estimates. The restriction to participants aged < 65 years at baseline resulted in the exclusion of the majority of deaths, and so this sensitivity test was likely underpowered. The results suggest that while the methods used to limit bias in the main analysis (excluding non-drinkers and excluding deaths that occurred within the first three years of follow-up) were effective, it is probable that bias from the 'sick-quitter effect' has not been eliminated entirely.

Some important differences were found for individual causes of death in three of the sensitivity analyses examined. That is, when participants with a physical functioning score < 50%, consuming < 7 drinks per week or with prior disease were excluded. In the majority of cases where trends were significant in the main analysis and non-significant in the sensitivity analyses there was no material change in hazard ratios, with the exception of death from prostate cancer, NHL and fall.

The results suggest that the main analysis may have underestimated the association between alcohol consumption and risk of all-cause and cause-specific mortality due to participants decreasing their drinking in response to ill-health, in addition to quitting entirely. For death from prostate cancer and NHL, the loss of significance and increase in effect estimates suggests that the association between alcohol consumption and lower risk of these outcomes may be at least partially

accounted for by this bias. The risk of death from fall may also have been overestimated, but this may be due to the fact that a non-linear relationship was found in the cubic spline analysis, with a lower risk gradient associated with heavier drinking. In the categorical analysis, the finding that the exclusion of participants with a low physical functioning score resulted in a new association with decreased risk of death from dementia adds to the evidence that this association may be causal, however this was not found in all sensitivity analyses. In addition, the finding of an association with decreased risk of death from breast cancer for this sensitivity analysis was unexpected, and inconsistent with the analysis excluding participants with prior cancer which found a new association with increased risk. Therefore, further research involving a greater number of dementia and breast cancer deaths is required to investigate these alcohol-mortality relationships and the impact of confounding by the 'sick-quitter effect' on effect estimates.

Regarding drinking patterns, the lack of material change in associations for drinking frequency, drinks per drinking-day and overall drinking pattern suggests that these effect estimates are robust to changes in drinking pattern in response to ill-health. There was largely no evidence that these estimates were be biased. However, the inverse association between drinking frequency and death from oesophageal cancer was unexpected. Considering that there was a positive association with drinks per drinking-day for this outcome, this perhaps implies that infrequent heavy drinking (heavy episodic drinking) raises risk of death from oesophageal cancer more so than other drinking patterns. It should be noted however that the sensitivity test could not be expected to remove all bias, and so inverse associations for drinking frequency and all-cause and cause-specific mortality are not necessarily causal.

2. *Population attributable fractions, cumulative absolute risk of mortality and number of persons needed to quit or reduce drinking to prevent one death.*

Rationale and methods. As for alcohol consumption and cancer incidence, it is of interest to investigate how the hazard ratios derived from the 45 and Up Study can be used to calculate estimates for population attributable fractions, as well as other outcomes which may have public health importance. Thus, the results of the continuous log-linear analysis in the main analysis were used to calculate three further results: PAF for deaths attributable to alcohol consumption in Australia in 2010, cumulative absolute risk of mortality between the ages of 45 and 75 years by level of alcohol consumption, and number of persons needed to quit or reduce drinking by age 45 years to prevent one death by age 75 years. Due to finding no significant interactions with sex for total alcohol consumption and risk of any mortality outcome, sex-specific hazard ratios were not used

The PAF calculations were performed using the same method as Pandeya et al., (2015), which relied on log-linear conversions of international relative risks to estimate PAFs for cancer in Australia in 2010[1]. So that lag time would be consistent for each cause of death and to be consistent with the analyses for cancer incidence, a lag time of nine years was used, attributing mortality in 2010 to sex- and age-specific alcohol consumption in the 2001 National Health Survey (2001 alcohol consumption data shown in Supplementary Table 2[1]). A full description of the methods used to calculate PAFs, cumulative absolute risk of mortality and number of persons needed to quit or reduce drinking to prevent one death are presented in Appendix E.3.

Results. The population attributable fraction calculations for alcohol consumption and mortality in Australia in 2010 are shown in Table 9.6. In the calculation derived from the log-linear analysis hazard ratios, the PAF for all-cause mortality was 2.2% and 4.4% when calculated without and with the exclusion of participants with prior disease (cancer for the cancer mortality hazard ratio and cardiovascular disease for the cardiovascular disease mortality hazard ratio) at baseline respectively. The highest PAF was found for death from external causes. The sensitivity test excluding participants

with a low physical functioning score resulted in a decrease in the majority of PAF estimates, while the sensitivity test restricting the hazard ratio calculation to participants consuming ≥ 7 drinks per week resulted in an increase in the majority of PAF estimates. In the calculation derived from the restricted cubic spline hazard ratios, the net PAF for all-cause mortality was lower, at 0.3% and 1.8% when calculated without and with the exclusion of participants with prior disease at baseline respectively. The highest PAF remained death from external causes. The sensitivity test excluding participants with a low physical functioning score resulted in a decrease in the majority of PAF estimates, with the net PAF for all-cause mortality remaining above 0.

The cumulative absolute risk of mortality between the ages of 45 and 75 years by level of alcohol consumption is shown in Figure 9.2. The absolute risk difference between drinking groups was larger in men for all mortality outcomes. For all-cause mortality calculated from hazard ratios which excluded participants with prior disease at baseline, cumulative absolute risk to age 75 years in men was 23.5% in those consuming > 14 drinks per week (median 21 drinks per week) and 20.7% in non-drinkers, while in women these values were 15.2% (median 20 drinks per week) and 13.4% respectively. By the age of 75 years, men and women consuming > 14 drinks per week 'brought forward' their risk of all-cause mortality by approximately 2 years, and those consuming > 0 and ≤ 14 drinks per week by approximately 0.5 years, compared to non-drinkers.

The estimated number of persons needed to quit or decrease drinking by age 45 years to prevent one death by age 75 years is shown in Table 9.7. For all-cause mortality calculated from hazard ratios which excluded participants with prior disease at baseline, one death was estimated to be prevented for every 36 men or 56 women quitting (or never starting) drinking at > 14 drinks per week (median 20 drinks per week in women and 21 in men). The largest values were found for persons quitting (or never starting) drinking at > 0 and ≤ 14 drinks per week (median 5 drinks per week in women and 6 in men). The smallest values among the specific causes of death were for death from cancer and cardiovascular disease. The sensitivity test excluding participants with a low physical functioning

score did not materially change the values for all-cause mortality, while the sensitivity test restricting the hazard ratio calculation to participants consuming ≥ 7 drinks per week resulted in smaller values.

Regarding participants consuming ≤ 14 drinks per week, the cumulative absolute risk difference of all-cause mortality obtained from the analysis excluding participants with prior disease was 0.77% for men (for those consuming a median of 6 drinks per week compared to non-drinkers) and 0.43% for women (for those consuming a median of 5 drinks per week compared to non-drinkers) (Figure 9.2). Higher values of 0.94% and 0.53% respectively were obtained in the sensitivity analysis derived from hazard ratios when restricting to participants consuming ≥ 7 drinks per week (data not shown).

Conclusions. The PAF estimate for all-cause mortality using log-linear hazard ratios from the 45 and Up Study varied substantially depending on the assumptions made about whether linear or non-linear relationships should be modelled, whether the association of lower risk of some diseases with drinking is causal and whether participants with prior disease should be excluded from calculations, and also in the sensitivity tests aiming to detect bias from the 'sick-quitter effect'.

The estimates of cumulative absolute risk of mortality and number of persons needed to quit or reduce drinking to prevent one death showed that cancer and cardiovascular disease (when excluding participants with prior disease) were the largest contributing causes of death to the absolute cancer risk associated with alcohol consumption.

Table 9.6. Population attributable fractions for deaths caused and prevented by alcohol consumption in Australian persons aged ≥ 45 years in 2010 using hazard ratios from the 45 and Up Study (2006-2012), New South Wales, Australia.

		Derived from main analysis		Derived from sensitivity analysis 1[a]		Derived from sensitivity analysis 2[b]	
Cause of death	**n deaths**	**n excess deaths**	**PAF (%)**	**n excess deaths**	**PAF (%)**	**n excess deaths**	**PAF (%)**
Log-linear-derived calculation							
Cancer	41,979	229	0.5	779	1.9	1,267	3.0
Cancer (excluding prior cancer)	41,979	1,730	4.1	2,119	5.0	3,113	7.4
CVD	44,706	1,011	2.3	274	0.6	2,292	5.1
CVD (excluding prior CVD)	44,706	2,448	5.5	427	1.0	3,126	7.0
Digestive system disease	4,899	644	13.2	1,028	22.1	552	11.3
External causes	5,481	1,158	21.1	573	10.4	701	12.8
All-cause mortality method 1[c]	**135,214**	**3,042**	**2.2**	**2,708**	**2.0**	**4,812**	**3.6**
All-cause mortality method 2[d]	**135,214**	**5,980**	**4.4**	**4,201**	**3.1**	**7,492**	**5.5**
Cubic spline-derived calculation							
Cancer	41,979	-1,231	-2.9	-1,344	-3.2	-	-
Cancer (excluding prior cancer)	41,979	-495	-1.2	420	1.0	-	-
CVD	44,706	-577	-1.3	-542	-1.2	-	-
CVD (excluding prior CVD)	44,706	633	1.4	-1,251	-2.8	-	-
Digestive system disease	4,899	651	13.3	993	20.3	-	-
External causes	5,481	1,621	29.6	1,010	18.4	-	-
All-cause mortality method 1[c]	**135,214**	**465**	**0.3**	**116**	**0.1**	-	-
All-cause mortality method 2[d]	**135,214**	**2,411**	**1.8**	**1,172**	**0.9**	-	-

Hazard ratios used in calculations for the 45 and Up Study were derived from total alcohol consumption in linear and restricted cubic spline models among participants consuming ≥ 1 drink per week. For each age group used in the calculation, mortality was attributed to alcohol consumption nine years earlier in the 2001 National Health Survey. 'n excess deaths' refers to deaths attributable to alcohol consumption out of the total number of deaths, 'n deaths'. [a]Participants with physical functioning score < 50% excluded. [b]Among participants consuming ≥ 7 drinks per week. [c]Summation of the cancer, CVD, digestive system disease and external mortality. [d]Summation of cancer (excluding prior cancer), CVD (excluding prior CVD), digestive system disease and external mortality. PAF, Population Attributable Fraction. CVD, Cardiovascular Disease.

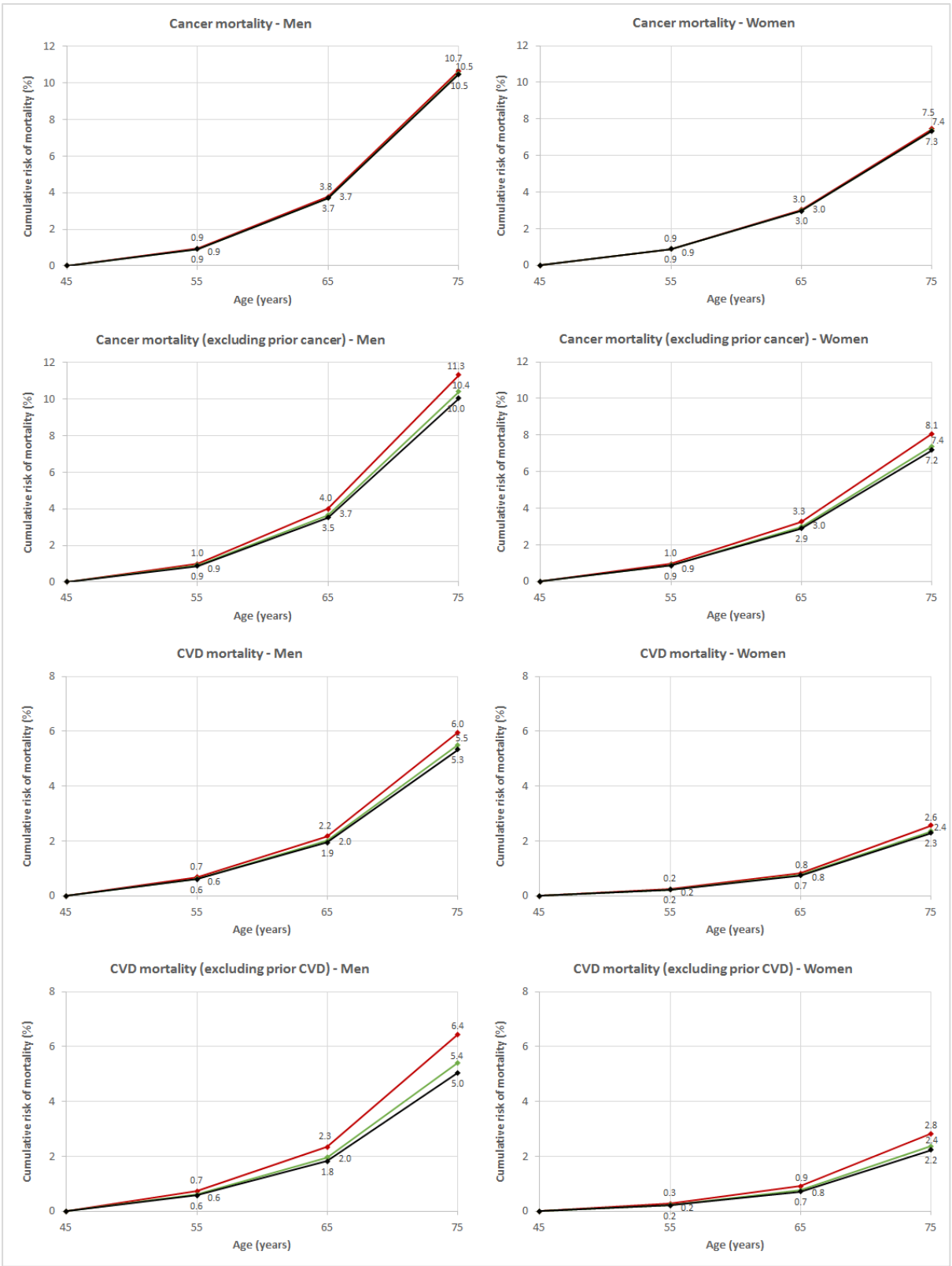

Figure 9.2. Cumulative absolute risk of mortality between the ages of 45 and 75 years in Australia in 2013 using hazard ratios from the 45 and Up Study (2006-2014), New South Wales, Australia. Black line: 0 drinks per week; Green line: 5 drinks per week in women and 6 drinks per week in men; Red line: 20 drinks per week in women and 21 drinks per week in men. Results derived from total alcohol consumption in a linear model among participants consuming ≥ 1 drink per week. The prior diseases excluded from the second all-cause mortality analysis were cancer, CVD and diabetes. CVD, Cardiovascular disease.

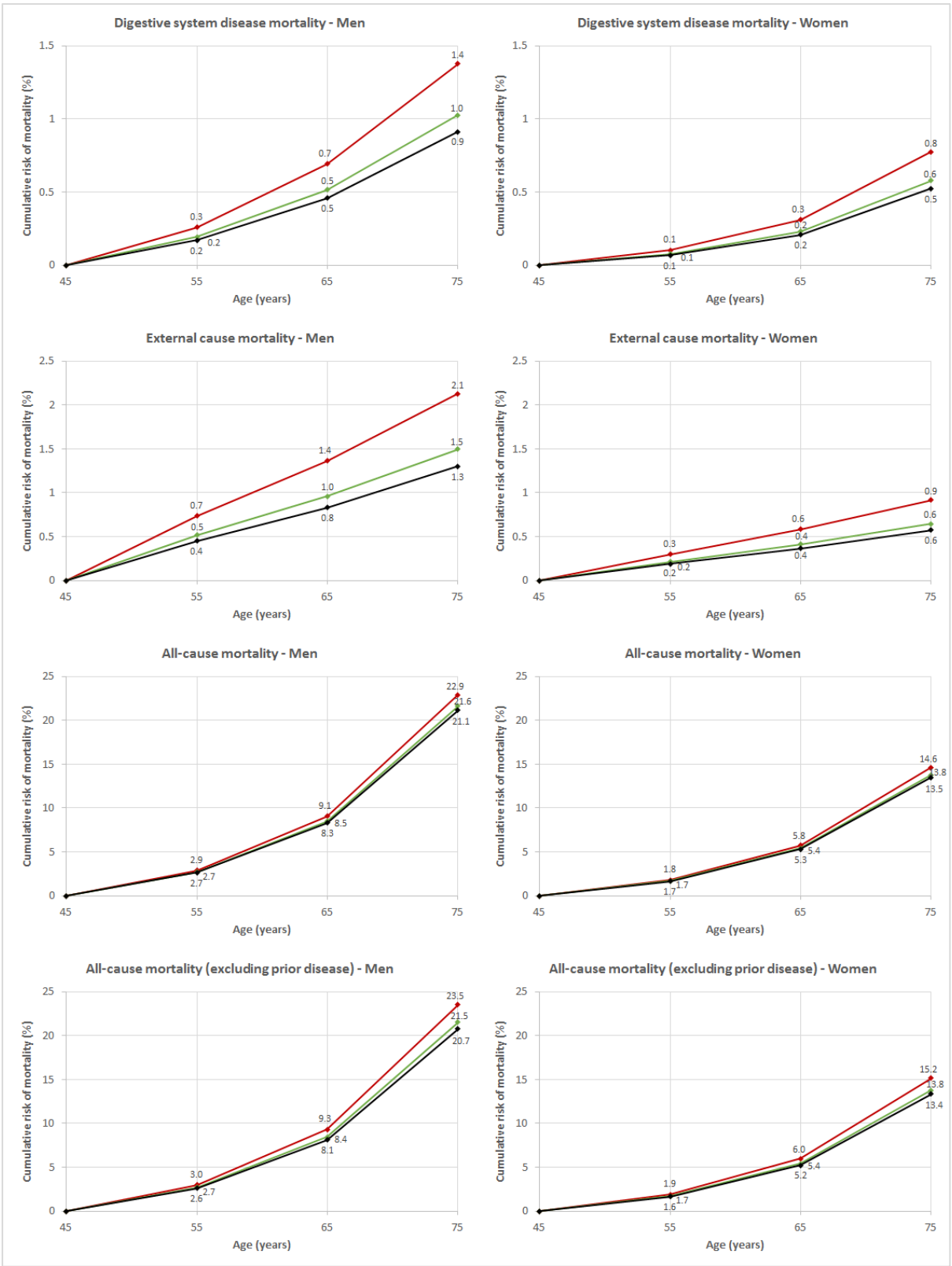

Figure 9.2. (Continued)

Table 9.7. Number of persons needed to quit or decrease drinking by age 45 years to prevent one death by age 75 years in Australia in 2013.

	Men			Women		
Cause of death	**21 drinks/week → Quit**	**6 drinks/week → Quit**	**21 drinks/week → 6 drinks/week**	**20 drinks/week → Quit**	**5 drinks/week → Quit**	**20 drinks/week → 5 drinks/week**
Main analysis						
Cancer	558	1,965	780	823	3,308	1,094
Cancer (excluding prior cancer)	79	287	109	114	475	150
CVD	159	579	220	382	1,590	503
CVD (excluding prior CVD)	72	273	97	167	731	217
Digestive system disease	216	877	285	397	1,849	505
External causes	121	509	159	291	1,397	367
All-cause mortality method 1[a]	57	203	79	89	363	117
All-cause mortality method 2[b]	36	131	50	56	233	74
Sensitivity analysis 1[c]						
Cancer	168	599	234	246	1,003	326
Cancer (excluding prior cancer)	66	240	90	94	395	123
CVD	561	1,983	781	1,365	5,521	1,813
CVD (excluding prior CVD)	363	1,293	505	882	3,588	1,169
Digestive system disease	146	639	188	258	1,293	322
External causes	213	827	287	534	2,369	689
All-cause mortality method 1[a]	48	171	66	74	305	98
All-cause mortality method 2[b]	36	128	49	55	228	72
Sensitivity analysis 2[d]						
Cancer	106	380	146	154	632	203
Cancer (excluding prior cancer)	46	173	63	66	282	86
CVD	76	287	103	178	772	230
CVD (excluding prior CVD)	58	226	78	134	599	173
Digestive system disease	244	976	325	454	2,076	581
External causes	180	712	241	446	2,019	573
All-cause mortality method 1[a]	35	126	48	54	224	71
All-cause mortality method 2[b]	29	107	40	45	189	59

Results were derived from total alcohol consumption in a linear model among participants consuming ≥ 1 drink per week. [a]Main analysis. [b]Participants with a prior diagnosis of cancer, CVD or diabetes excluded. [c]Participants with physical functioning score < 50% excluded. [d]Among participants consuming ≥ 7 drinks per week. CVD, Cardiovascular Disease.

9.3 – Discussion and Conclusions

The main findings of this chapter were that total alcohol consumption was associated with increased risk of all-cause mortality and many causes of death, including alcohol-related cancer, oesophageal cancer, liver cancer, kidney cancer, cardiovascular disease, digestive system disease, liver disease, external causes, fall, suicide, other external causes, other causes combined. There was an inverse association with death from NHL. The results for total alcohol consumption were largely consistent with prior research. There was also evidence that the inclusion or exclusion of participants with prior disease at baseline made a material difference to risk estimates for several causes of death. This was particularly important for cardiovascular disease mortality. Despite finding a J-shaped non-linear association between alcohol consumption and cardiovascular disease mortality in the main analyses, there was no significant protective effect. The evidence suggested that reduction in alcohol consumption in response to cardiovascular disease diagnosis is likely to have biased risk estimates for cardiovascular disease mortality, due to the appearance of the new significant linear trend of increased risk when excluding participants with prior cardiovascular disease.

In analyses examining the effects of drinking pattern, there was an independent association of mean drinks per drinking-day with increased risk of death from cancer, oesophageal cancer, non-alcohol-related cancer, lung cancer, kidney cancer and all-cause mortality. Frequent drinking was associated with higher risk of respiratory system disease mortality and lower risk of death from cancer, non-alcohol-related cancer, diabetes, cardiovascular disease, ischaemic heart disease and all-cause mortality compared to less frequent drinking. There is no mechanistic basis for alcohol consumption to lower cancer risk, and yet strong inverse associations with drinking frequency were observed for all cancers combined and non-alcohol-related cancers combined. These two outcomes may serve as 'negative controls'[2], indicating that inverse associations with drinking frequency for other outcomes including all-cause mortality and cardiovascular disease mortality may be attributable to

bias from reverse causation or incomplete adjustment from confounding. A key implication of these results was that a reduction in the number of drinks consumed per drinking occasion is likely to be an effective approach to prevent cancer and all-cause mortality, independent of and in addition to limiting the total amount of alcohol consumed. Increasing drinking frequency without changing total alcohol consumption may also be an effective approach, although it cannot be ruled out that the association with protection may be attributable to bias. Another important finding was that both heavy frequent drinking and heavy episodic drinking were significantly related to all-cause mortality risk. Altogether, these findings have implications for risk modelling, burden of disease estimates, alcohol health guidelines and government policies and programs aiming to lessen alcohol-related harm.

The additional analyses revealed several important findings. Firstly, there was evidence that bias from the 'sick-quitter effect' and decreased drinking in response to ill-health may have biased estimates between alcohol-consumption and all-cause mortality in the main analysis, resulting in an underestimation of the association. For a number of individual causes of death, the risk relationship with alcohol varied from that observed in the main analysis when either participants with poor physical functioning, those who consumed < 7 drinks per week, or those with prior disease, were excluded. Specifically, for death from oesophageal cancer, liver cancer, breast cancer, cardiovascular disease and other causes combined, the risks associated with alcohol may have been underestimated in the main analyses due to bias from the 'sick-quitter effect'. The inverse association for death from dementia may also have been underestimated. In addition, the inverse associations for death from prostate cancer and NHL may also have been overestimated in the main analysis, while the inverse association for death from dementia may have been underestimated. On the other hand, the drinking pattern results were largely unaffected by the sensitivity tests, providing evidence that these findings were robust to bias from changes in drinking patterns in response to ill-health.

The PAF estimate for all-cause mortality varied substantially depending on the assumptions made about whether linear or non-linear relationships should be modelled, whether the association of lower risk of some diseases with drinking is causal and whether participants with prior disease should be excluded from calculations. There were also material changes in the estimate in sensitivity tests aiming to detect bias from the 'sick-quitter effect'. The World Health Organisation estimated that 3.2% of deaths in Australia in 2012 were attributable to alcohol consumption[3], which is comparable to the range of estimates derived from the 45 and Up Study. In all cases the 45 and Up Study-derived PAF estimates were greater than zero, indicating that under all scenarios tested alcohol consumption caused more deaths than it prevented. It is possible that the value of 2.2% derived using continuous log-linear hazard ratios in the main analysis could be greatly underestimated, with the PAF doubling to 4.4% if participants with prior cancer and cardiovascular disease are excluded from the calculations, with a higher PAF still of up to 5.5% when taking into account the sensitivity analysis designed to reduce bias from the 'sick-quitter effect'. If a variable were available to exclude participants with prior digestive system disease, then the estimate for this outcome and all-cause mortality may have been higher still. On the other hand, if the relationship between alcohol consumption and reduced risk of cardiovascular disease and cancer mortality is assumed to be causal, then PAF estimates for all-cause mortality decrease by approximately 2% compared to their corresponding estimates derived from continuous log-linear hazard ratios. It should be noted that these PAF estimates applied to deaths in Australia among persons aged ≥ 45 years (94% of all deaths in 2010). If the proportion of alcohol-attributable deaths is higher in persons aged < 45 years than persons aged ≥ 45 years, these estimates may have been slightly higher if persons of all ages were included in the calculations. A limitation of this analysis was that lag time between alcohol consumption and mortality may differ for each cause of death, and for death from external causes current drinking is likely to be more relevant than past drinking.

The estimates of cumulative absolute risk of mortality and number of persons needed to quit or reduce drinking to prevent one death showed that cancer and cardiovascular disease (when

excluding participants with prior disease) contributed the most to the absolute cancer risk associated with alcohol consumption. One key finding was that when excluding participants with prior disease, by age 75 years, persons consuming > 14 drinks per week 'brought forward' their risk of all-cause mortality by 2 years compared to non-drinkers. Another key finding included that (when excluding participants with prior disease) one death could be prevented by the age of 75 years for every 36 men or 56 women quitting (or never starting) drinking at > 14 drinks per week, with even lower numbers in the sensitivity test designed to reduce bias from the 'sick-quitter effect'. As for cancer incidence, it was also found that targeting persons drinking > 14 drinks per week to decrease their drinking to > 0 and ≤ 14 drinks per week is likely to be a more efficient strategy to reduce alcohol-attributable mortality than targeting persons drinking > 0 and ≤ 14 drinks per week to decrease their drinking to zero. These results may be useful for planning preventative public health interventions to reduce the burden of alcohol-related mortality.

The results also have implications for the Australian alcohol guidelines. The guidelines recommend a cut-point value of ≤ 2 drinks per day (allowing for consumption up to 14 drinks per week) to reduce the risk of long-term harm. The cut-point was chosen to limit the risk of death to the arbitrary value of 1 in 100[4]. The cumulative absolute risk difference obtained from the analysis excluding participants with prior disease was 0.77% for men (for those consuming a median of 6 drinks per week compared to non-drinkers) and 0.43% for women (for those consuming a median of 5 drinks per week compared to non-drinkers). As the same hazard ratios were used in the calculation for men and women, the reason for the larger absolute risk difference in men is largely due to the higher underlying absolute mortality risk at any point in time for men compared to women. Extrapolating these values, the results imply that men and women could consume up to 7 and 11 drinks per week respectively and have an absolute risk of alcohol-attributable mortality less than 1%. As there was no interaction between sex and total alcohol consumption for all-cause mortality risk, it would be conservative to select the male value in the development of alcohol guidelines. Therefore, based on the results of the 45 and Up Study accounting for the 'sick-quitter effect', a conservative drinking

guideline could recommend an upper limit of 7 drinks per week to ensure that lifetime risk of alcohol-attributable mortality is less than 1%. This is before taking into account that the calculated values underestimate the true lifetime absolute mortality risk attributable to alcohol consumption due to only capturing the age period of 45 to 75 years, and so the guideline may need to be even lower. Further, the absolute risk difference estimate derived from the sensitivity test restricting to participants consuming ≥ 7 drinks per week suggested that values of the main analysis may be underestimated, meaning that a guideline of 7 drinks per week may still be too high. In summary, using the hazard ratios derived from the 45 and Up Study, there is evidence that the Australian alcohol guideline to limit the risk of long term harm could be lowered to 7 drinks per week, to limit lifetime risk of alcohol-attributable mortality to 1%.

The final chapter of this thesis is the discussion. This chapter summarises the findings of the first nine chapters and the strengths and weaknesses of the analyses, explores implications for government policy and outlines areas for further research.

9.4 – References

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2. Lipsitch, M., E. Tchetgen Tchetgen, and T. Cohen, *Negative controls: a tool for detecting confounding and bias in observational studies.* Epidemiology, 2010. **21**(3): p. 383-8.
3. World Health Organisation, *Global status report on alcohol and health 2014*. 2014, WHO: Geneva.
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Chapter 10 – Discussion and Conclusions

Chapter summary

This chapter summarises the key findings of each chapter, as well as the strengths and limitations of the analyses. The implications of the results for policy are examined, including recommendations for potential strategies to reduce alcohol-related harm in Australia, messaging concerning the harms of heavy episodic drinking, and modifications to the national alcohol guidelines. Finally, gaps in the research base regarding alcohol consumption and heavy episodic drinking are identified and recommendations for future research made.

10.1 – Discussion

Summary of findings

This thesis investigated several important topics related to alcohol consumption and its impact on burden of disease and injury in Australia. Alcohol consumption is commonplace in Australia, as is drinking at levels above health guidelines. Chapter 1 presented **an introduction to alcohol and the Australian context**. It was described how alcohol consumption affects the human body; the role of alcohol in Australian society, including the nature of the alcohol industry, how alcoholic beverages are classified, Australian alcohol health guidelines, the prevalence of drinking behaviours, and public health efforts to reduce alcohol-related harm.

Alcohol consumption is commonplace in Australia and is associated with substantial social and economic harm. Of adults, 81% are current consumers of alcohol, and 19% of adults (28% of men; 10% of women) consume greater than two standard drinks per day on average, exceeding the 2009

NHMRC guideline for risk of long-term harm. There is little variation by age, with 19% to 23% of persons exceeding this guideline in all adult age groups less than 70 years. Persons born in non-English speaking countries have a lower prevalence of exceeding the long-term risk guideline than persons born in English-speaking countries and in Australia. Population sub-groups with a higher prevalence of consuming alcohol at levels that put them at risk of long-term harm include Aboriginal and Torres Strait Islanders, persons living in regional and remote areas, those with higher socio-economic status, and those who are employed, and/or homosexual or bisexual. In addition, 27% of adults (36% of men and 17% of women) exceed the guideline for risk of short-term harm by consuming greater than four standard drinks on a single occasion at least monthly. The burden of disease and injury due to alcohol consumption may worsen over time, as adult per capita alcohol consumption in Australia is projected to increase by 11% between 2010 and 2025[1].

The chapter then discussed potential methodological issues for observational studies of alcohol consumption. One of the key issues identified was the 'sick-quitter effect', whereby former drinkers may have health conditions which caused them to quit drinking, and which may be related to increased morbidity and mortality when compared to lifetime abstainers. A reference group of non-drinkers may therefore result in an underestimate of the health risks associated with drinking, and therefore a reference group of 'light drinkers' might be more appropriate.

Finally, the aims of the thesis were specified:

1. Review of the association between alcohol consumption and disease and injury, with a focus on cancer.
2. Systematically review previous systematic reviews and meta-analyses of the association between alcohol consumption and all-cause mortality.
3. Investigate the clustering of alcohol consumption with other behavioural risk factors and assess potential variation by country of birth.

4. Quantify the relationship between a variety of incident health conditions and drinking cessation.
5. Quantify the relationship between alcohol consumption and cancer risk.
6. Quantify the relationship between alcohol consumption and risk of all-cause and cause-specific mortality.

Chapter 2 presented **a narrative review of the relationship between alcohol consumption and risk of disease and injury**. The burden of disease and injury attributable to alcohol consumption in Australia in 2011 was 5.1%[2]. Of all risk factors, alcohol contributed third-most to the burden of disease and injury, behind smoking (9.0%) and overweight and obesity (5.5%)[2]. Drinking is associated with increased risk of many conditions, including at least seven types of cancer (mouth, pharynx, oesophagus, colorectum, liver, larynx and female breast). The incidence of two alcohol-related cancers, breast and liver, has been increasing over time in Australia[3], although how much of this increase is attributable to alcohol consumption is unclear. Other diseases positively associated with alcohol consumption include certain infections, nutritional deficiencies, overweight and obesity, vascular dementia, alcohol-related dementia, Wernicke-Korsakoff syndrome, alcohol use disorder, epilepsy, neurodegeneration, liver disease, acute pancreatitis in men and chronic pancreatitis in both sexes, and other digestive system diseases such as alcoholic gastritis and intestinal malabsorption. Several external causes of morbidity and mortality are also related to alcohol, including injury, poisoning, drowning, self-harm and interpersonal violence. There is evidence of a J-shaped association, where lower volume drinking is associated with decreased risk and higher volume drinking with increased risk, for type 2 diabetes and certain types of cardiovascular disease (CVD) such as ischaemic heart disease and ischaemic stroke.

A key finding of Chapter 2 was that for 23 types of cancer, the evidence for a causal relationship with alcohol consumption remains inconsistent or unclear. For some cancer types there is evidence from meta-analyses of an association with alcohol intake, but the evidence is not sufficient for the IARC

and WCRF to declare these associations as causal. Another key finding was that there is a need for observational research to explore the impact of potential biases, such as the 'sick-quitter effect', on risk estimates for disease, especially those for which an inverse association was found. Finally, it was found that for many health outcomes, including cancer, the influence of pattern of drinking of drinking on risk has not been quantified.

Chapter 3 presented **a systematic review of systematic reviews that investigated the association between alcohol and all-cause mortality**, with a focus on methodological quality and risk of bias. The majority of the 18 included reviews reported a J- or U-shaped relationship with risk, with some finding only a positive association and some no association. The majority of reviews were considered to be at high risk of bias, or used a reference group of non-drinkers, which possibly biased results due to the 'sick-quitter effect'. Only one review both used a reference group of lifetime abstainers and was considered at low risk of bias[4], and this review reported only a positive association, with a 42% increased risk of all-cause mortality for > 6 drinks/day or ≥ 65 g/day.

The reviews examined the influence of many factors on the shape of the alcohol-mortality risk curve, but in most cases, the evidence was limited or inconsistent. The factors for which this applied included sex, age, population (region or ethnicity), current smoking, the exclusion of participants with pre-existing CVD, average cohort alcohol consumption, variability in cohort alcohol consumption, the proportion of non-drinkers in the cohort, per capita alcohol consumption in the population, length of follow-up, primary study year of publication, level of adjustment for confounders, modelling method, primary study methodological quality and choice of reference group. There was also limited evidence that the risk relationship was not influenced by primary study sample size or by evidence of industry funding. There was however good evidence that the alcohol-mortality relationship differs by choice of reference group and by adjustment for primary study characteristics (such as adjustment for smoking, adequacy of drinking measure and follow-up time) at the meta-analysis level. There was also good evidence that inverse relationships between

alcohol and mortality could be accounted for by adjustment for primary study characteristics at the meta-analysis level. Additionally, that observed decreases in mortality risk is attenuated when using a reference group of lifetime abstainers (instead of non-drinkers) and is eliminated when using a reference group of occasional drinkers. Evidence was lacking for whether certain populations (e.g. Africa, the Middle East, Latin America), ex-smoking, pattern of drinking (including drinking frequency and heavy episodic drinking, independent of total alcohol consumption), change in alcohol consumption over time, measurement of alcohol consumption at single or multiple time points, and beverage type affected mortality. Evidence was also lacking regarding whether risk is cumulative over the lifetime or if exposure during certain periods of life are more critical for risk.

The key findings of the systematic review were 1) potential factors that impact the relationship between alcohol and mortality remain unclear due to the low methodological quality of previous systematic reviews and meta-analyses, and 2) there is evidence that the apparent protective effect of moderate drinking on mortality may be accounted for by biases in primary study design including choice of reference choice of group, inadequate measures of alcohol consumption and differences in adjustment for confounding and inclusion criteria. These same factors may also be responsible for underestimating the harms of higher levels of drinking. It was concluded that there is a need for well-designed reviews and meta-analyses to examine the shape of the alcohol-mortality risk curve and how population subgroups, the distribution of alcohol consumption in the cohort or population, measures of alcohol exposure and primary study methodology may influence the relationship. The influence of drinking pattern on mortality risk was identified as a key evidence gap. Furthermore, given that the risk relationship may vary by population around the world, there is a need for local Australian data.

Chapters 4 and 5 **described the cohort, the 45 and Up Study, and the methods used to address the aims of this thesis**. This included the description of three drinking patterns and a comprehensive list of potential cancer and mortality-specific covariates. It was shown that the 45 and Up Study is

comparable to other contemporaneous population surveys in NSW and Australia, although there is a possibility that the cohort may have better health status and healthier behaviours than the general population. A higher proportion of participants in the 45 and Up Study consumed alcohol at least weekly compared to three population surveys. Overall, 32.7% of the cohort were non-drinkers at baseline and 3.8% had more than 28 drinks per week. The median number of drinks per week was 4. Of drinkers, 37.2% consumed alcohol 6-7 days per week, and 10.5% consumed > 4 drinks per drinking-day. The large number of participants in the study, the use of multiple measures of alcohol consumption and drinking pattern and the consideration of a large number of important covariates were identified as strengths of the study, and overall it was concluded that the 45 and Up Study was well-suited to investigate the influence of alcohol consumption on risk of cancer and mortality while ensuring that bias from confounding was minimised.

Chapter 6 considered **the co-occurrence of alcohol consumption with other modifiable risk factors** by combining them into a weighted chronic disease risk index (CDRI). Alcohol consumption contributed the most to CDRI scores among Australian-born participants and participants born in English-speaking countries. Participants born in Australia and English-speaking countries had higher odds of consuming > 14 drinks per week, having 6-7 drinking-days per week, and consuming > 4 drinks per drinking-day compared to participants born elsewhere, even when restricted to drinkers. For almost all regions of birth, the odds of consuming > 14 drinks per week increased with greater years lived in Australia, particularly for participants born in non-English speaking countries. Using the CDRI, the regions of birth with the highest potential risk of chronic disease due the combination of risk factors were the Middle East and North Africa, and Eastern and Central Europe, while the regions of birth with the lowest risk were East Asia, Southeast Asia and Central and South Asia. There was evidence that the differences in CDRI score between Australian-born participants and immigrants were largely attenuated with greater number of years since migration. Specifically, the risk profile of immigrants approximated that of the Australian-born participants the longer they had lived in Australia. Overall, a key finding was that lifestyle behaviours acculturate to those of the host

population over time. This particularly applied to alcohol consumption for participants born in non-English speaking countries. It was concluded that health interventions should be targeted not only at groups with the highest CDRI scores overall, but also at groups with low CDRI scores that may be at risk of worsening risk factors over time, including increased alcohol consumption.

Chapter 7 **investigated the relationship between a variety of incident health conditions and drinking cessation** using the 45 and Up Study baseline and follow-up questionnaires. A key finding was that many health conditions are associated with drinking cessation and therefore have the potential to bias risk estimates for alcohol consumption and outcomes such as mortality. Indicators of general health, such as self-rated overall health and physical functioning score were associated with the highest hazards of quitting, with those who reported a decline in self-rated health to poor 2.9 times more likely to quit drinking than those who maintained better health. Further, the persistence of associations between the general health indicator variables and drinking cessation after adjustment for all other health conditions suggested that there are other health conditions not diagnosed or not examined in the analysis that also lead to quitting. It was concluded that the exclusion of participants with specific health conditions (such as cancer and CVD as in some previous studies) is unlikely to be an adequate method of addressing the 'sick-quitter effect', and that accounting for indicators of general health, which capture most conditions associated with cessation, is preferable. It should be noted however that when the analysis was restricted to participants with good overall health or good general health indicators at follow-up, although the associations between quitting and health conditions were attenuated, many of the health conditions remained significant predictors of quitting. Thus, although preferable to excluding specific health conditions, accounting for general health indicators is not a completely adequate method of addressing the 'sick-quitter effect'. Alternative methods of addressing the 'sick-quitter effect' were suggested, including using lifetime abstainers or light drinkers (or both) as the reference group, calculating a log-linear trend in risk for drinkers only, and/or excluding outcomes that occur early in the period of follow-up.

Additional analyses examined the association between incident health conditions and other changes in drinking behaviour, and found that the occurrence of disease and a decline in indicators of general health were also observed in relation to 1) a reduction in alcohol consumption to very light drinking (i.e. from > 3.5 drinks per week to ≥ 1 and ≤ 3.5 drinks per week), 2) a reduction in drinking frequency to 1-2 days per week, and 3) an increase in number of drinks consumed per drinking-day to > 4 drinks per drinking-day. Thus, just as using non-drinkers as a reference group in studies of alcohol consumption and health outcomes may bias risk estimates, so too may the use of very light drinkers as the reference group (i.e. a 'sick-decreaser effect'). The results also suggested that frequent drinkers may have better health status than infrequent drinkers. In sensitivity analyses, the exclusion of participants with a low physical functioning score was shown to be the most effective method of addressing bias from persons changing drinking behaviours in response to ill-health, however studies would require that sufficient numbers of cases are retained for reliable estimates of risk. This method was used in sensitivity analyses in the analyses of cancer and mortality. As participants who consumed about 7 drinks per week appeared to have the best health status, a sensitivity test for the continuous linear analyses in later chapters limited to participants that consumed ≥ 7 drinks per week was performed to examine risk relationships under the assumption that the association between moderate drinking and better health status at baseline is entirely attributable to bias. Other methods used in later chapters to address bias from the 'sick-quitter effect' and other changes in drinking behaviours in response to ill-health included a restriction to participants aged less than 65 years and the exclusion of participants that died within 3 years of baseline.

Chapter 8 **quantified the relationship between alcohol consumption and cancer risk** using Cox proportional hazard models and 45 and Up Study baseline data linked to the NSW Cancer Registry. In a median follow-up of 2.4 years, 7,733 participants had at least one diagnosis of cancer. Analyses included total alcohol consumption, drinking frequency and drinks per drinking-day. The results for total alcohol consumption were largely consistent with prior research, with increasing numbers of

alcoholic drinks per week associated with increased risk of cancers of the colorectum, colon, larynx and female breast, alcohol-related cancers combined and all cancers combined. Consuming > 28 drinks per week was also associated with increased risk of liver cancer. For thyroid cancer and non-Hodgkin lymphoma (NHL), where alcohol is reported to be associated with decreased risk, inverse associations were found.

Of note was the independent association of drinking pattern on a number of cancer types. Specifically, drinks per day drinking-day and risk of cancers of the mouth and pharynx, oesophagus (squamous cell carcinoma), colorectum, colon, kidney, alcohol-related cancers combined and all cancer. There was also evidence of increased risk associated with heavy episodic drinking (> 4 drinks per drinking-day, 1-2 days per week) for kidney and all cancer, and with heavy frequent drinking (> 4 drinks, 6-7 days per week) for colorectal and colon cancer, when examining drinking frequency in conjunction with drinks per drinking-day.

The additional analyses in Chapter 8 examined the impact of strategies to mitigate potential bias from the 'sick-quitter effect' and changes in alcohol consumption related to ill-health on risk estimates for cancer. This included a restriction to participants with a physical functioning score ≥ 50% and separately, to participants consuming ≥ 7 drinks per week. Among those with ≥ 50% physical functioning, linear positive trends with total alcohol consumption for cancers of the mouth and pharynx, oesophagus (squamous cell carcinoma). When limited to participants who consumed ≥ 7 drinks per week, risk estimates were increased for colorectal and colon cancer, and were non-significant and materially increased for thyroid cancer and materially decreased for breast cancer compared to the main analysis. Taken together, this suggests that the 'sick-quitter effect' may result in an underestimation of risk for certain cancer types due to participants decreasing their drinking in response to ill-health, in addition to quitting entirely. The sensitivity tests also suggested that the inverse association between alcohol and risk of thyroid cancer may be attributable to this same bias. It is possible that the loss of significance for breast cancer in sensitivity analyses may reflect

inadequate statistical power because the number of cases decreased by 48%. While differences were found for individual cancer types, there was little difference across the results of sensitivity tests for the continuous log-linear analysis for all cancers combined. Specifically, the hazard ratio for all cancers combined was 1.02 (1.00-1.04) per additional drink per day in the main analysis (broadly similar to the findings in all sensitivity analyses). This provided evidence that the association between total alcohol consumption and all cancer was not materially biased due to changes in alcohol consumption in response to ill-health.

Restriction to participants with a physical functioning score ≥ 50% was also performed for the drinking pattern analyses. There was no material change to the inverse association between drinking frequency and risk of all cancers combined, however it should be noted it was shown in Chapter 7 that this sensitivity test was likely to be less effective at mitigating potential bias when examining drinking frequency compared to both total alcohol consumption and drinks per drinking-day. There was evidence however that changes in drinking behaviour in response to ill-health may be responsible for bias resulting in an underestimate of the association between mean drinks per drinking-day and oesophageal cancer.

Chapter 8 also reported estimates of population attributable fractions (PAF) for cancer and alcohol. The PAF estimate for Australia of 2.5% for all cancers combined was similar to a previous estimate of 2.8% that used internationally-derived relative risks[5], although there was some variation by individual cancer types. The sensitivity test that included cancers for which there is evidence of an association with alcohol consumption (but for which IARC has not declared a causal association) made a material difference to the PAF estimate, increasing from 2.5% to 3.8% (i.e. stomach, pancreas, melanoma, prostate), and decreasing to 1.6% when three inversely associated cancers (kidney, thyroid, NHL) were included. The variation in PAF estimates demonstrates that determining whether the associations for the positively associated cancers are causal will make an important difference to burden of disease estimates for alcohol and cancer. The overall PAF estimate did not

change materially in sensitivity analyses, indicating that the results are not likely to be substantially biased by the 'sick-quitter effect'.

Estimates of absolute risk and number of persons needed to quit or reduce drinking to prevent one cancer case were also calculated. One cancer case could be prevented by the age of 75 years for every 42 men or 37 women who consume > 14 drinks per week quitting (or never starting) drinking. Persons consuming > 14 drinks per week 'brought forward' their risk of alcohol-related cancer by 3.5 years compared to non-drinkers. The results for all cancer risk were in most cases not materially altered by the sensitivity analyses aiming to reduce bias from the 'sick-quitter effect', indicating little evidence that the results were biased due to confounding by baseline health status.

Chapter 9 **quantified the relationship of alcohol consumption and mortality** using Cox proportional hazard models and 45 and Up Study baseline data linked to the NSW Registry of Births, Deaths and Marriages. In 6.4 years follow-up, 13,988 deaths occurred that were included for analysis. The results for total alcohol consumption were largely consistent with prior research, with increasing numbers of alcoholic drinks per week associated with increased risk of all-cause mortality and death from alcohol-related cancer including oesophageal, liver and kidney cancer, CVD, digestive system disease including liver disease, external causes including fall and suicide, and other causes combined. There was an inverse association with death from NHL. J-shaped associations were found for all-cause mortality and death from CVD. Mortality estimates were affected by inclusion or exclusion of participants with prior disease at baseline, with the positive associations with risk for death from alcohol-related cancer, oesophageal cancer, kidney cancer, and CVD only significant when these participants were excluded.

There was an independent positive association between drinks per drinking-day and risk of death from all cancer, oesophageal cancer, non-alcohol-related cancer, lung cancer, kidney cancer and all-cause mortality. Frequent drinking was independently associated with higher risk of respiratory system disease mortality and lower risk of death from all cancer, non-alcohol-related cancer,

diabetes, CVD, ischaemic heart disease and all-cause mortality compared to less frequent drinking, although it is possible that these associations at least partially reflect residual confounding by baseline health status. There was evidence of increased risk associated with heavy episodic drinking (> 4 drinks per drinking-day, 1-2 days/week), heavy frequent drinking (> 4 drinks, 6-7 days/week), and decreased risk of frequent low-volume drinking (≤ 2 drinks on 3-5 days/week), for all-cause mortality risk.

There were some important conclusions regarding bias. Despite finding a J-shaped non-linear association between alcohol consumption and CVD mortality, there was no significant protective effect. The evidence suggested that reduction in alcohol consumption in response to CVD diagnosis is likely to have biased risk estimates for CVD mortality, due to a significant linear trend of increased risk when participants with prior CVD were excluded. This interpretation was supported by the empirical evidence from Chapter 7 that heart disease and stroke are both associated with drinking cessation and reduction. Another conclusion concerning the possibility of bias was for drinking frequency. Specifically, there is no mechanistic basis for alcohol consumption to lower cancer risk, and yet strong inverse associations with drinking frequency were observed for all cancers combined and non-alcohol-related cancers combined. These two outcomes may serve as 'negative controls'[6], indicating that inverse associations with drinking frequency for other outcomes including CVD and all-cause mortality may be attributable to bias from reverse causation or incomplete adjustment from confounding.

Additional analyses in Chapter 9 examined the impact of sensitivity analyses aimed to mitigate potential bias from the 'sick-quitter effect' and other changes in alcohol consumption related to ill-health. These sensitivity tests included restriction to participants with a physical functioning score ≥ 50% and to participants consuming ≥ 7 drinks per week. Many differences in risk estimates were found for individual causes of death when employing these sensitivity tests. There were trends of increased risk with total alcohol consumption for death from oesophageal cancer, liver cancer, CVD

and other causes combined, while there were trends of decreased risk for death from breast cancer and dementia. The trend of increased risk was non-significant and materially decreased for death from fall compared to the main analysis, while the trend of decreased risk was non-significant and materially increased for death from NHL, suggesting that these associations may be at least partially accounted for by changes in drinking behaviours in response to ill-health, in addition to quitting entirely. The finding that the exclusion of participants with a low physical functioning score resulted in an inverse association for dementia mortality also adds to the evidence that this association may be causal, however this was not found in all sensitivity analyses.

Furthermore, in a sensitivity test excluding participants with prior disease for the log-linear analysis, were significant positive associations for risk of death from oesophageal cancer, breast cancer, and CVD. The inverse association for death from prostate cancer was non-significant and materially increased compared to the main analysis. The results suggest that risk estimates for several cancer mortality outcomes in the main analysis may be underestimated due to participants decreasing their alcohol intake in response to ill-health. For breast cancer mortality, the results were inconsistent overall, with the sensitivity test restricting to participants consuming ≥ 7 drinks per week resulting in a significant positive association and the test restricting to participants with a physical functioning score ≥ 50% resulting in an inverse association. This suggests further research involving greater numbers of breast cancer deaths is required to investigate the role of bias from changes in drinking behaviours in response to ill-health on this association.

The possibility that mortality risk may be underestimated was supported by the sensitivity tests for the continuous log-linear analysis for all-cause mortality. Two sensitivity tests that would be expected to increase bias from the 'sick-quitter effect' (including non-drinkers and deaths occurring within three years of baseline) both resulted in lower effect estimates, while four sensitivity analyses that would be expected to reduce bias from the 'sick-quitter effect' (restricting to participants with a physical functioning score ≥ 50%, restricting to participants consuming ≥ 7 drinks per week,

excluding deaths occurring within 5 years of baseline, and excluding participants who had ever been diagnosed with cancer or CVD) resulted in higher effect estimates. This suggests that while the steps taken of restricting to drinkers only and excluding deaths occurring within the first three years of follow-up were effective in reducing bias from the 'sick-quitter effect' and decreased drinking in response to ill-health, it is probable that these biases was not eliminated entirely, meaning that the effect estimates in the main analysis are likely to be underestimated. Overall, there was evidence that bias induced by changes in drinking behaviours in response to ill-health is important to account for when interpreting the results.

Restriction to participants with a physical functioning score ≥ 50% was also performed for the drinking pattern analyses, and there was largely no evidence that these risk estimates may be biased due to changes in drinking behaviours in response to ill-health. It should again be noted however that this sensitivity test may not have been effective at mitigating potential bias when examining drinking frequency.

Chapter 9 also contained estimates of PAF for all-cause mortality, which varied appreciably depending on the assumptions made about whether linear or non-linear relationships were modelled, whether the association for some diseases of reduced risk with low-volume drinking is causal and whether participants with prior disease or a physical functioning score < 50% should be excluded from calculations. In all cases, the 45 and Up Study-derived PAF estimates were greater than zero, indicating that under all scenarios tested, alcohol consumption caused more deaths than it prevented. A PAF of 2.2% was derived using continuous log-linear hazard ratios in the main analysis, but this doubled to 4.4% if participants with prior cancer and CVD were excluded from the calculations, with a PAF of up to 5.5% when using the log-linear hazard ratios derived from the sensitivity analysis restricting to participants consuming ≥ 7 drinks per week. Thus, the main analysis may have substantially underestimated the association between alcohol consumption and mortality due to confounding by baseline health status.

Estimates of absolute risk and number of persons needed to quit or reduce drinking to prevent one death were calculated. One death could be prevented by the age of 75 years for every 36 men or 56 women who consume > 14 drinks per week quitting (or never starting) drinking. Persons consuming > 14 drinks per week 'brought forward' their risk of all-cause mortality by 2 years compared to non-drinkers. There was evidence that these values may be underestimated due to confounding by baseline health status. Finally, if the conservative assumption is made that the inverse association between alcohol consumption and risk of mortality is entirely attributable to bias, there was evidence that the Australian alcohol guideline to limit the risk of long-term harm should be lowered from ≤ 2 drinks per day (allowing up to 14 drinks per week) to ≤ 7 drinks per week to ensure that lifetime risk of alcohol-attributable mortality for all persons remains less than 1%.

Strengths and limitations of the thesis

One major strength of this thesis is the large sample size of the 45 and Up Study, which allowed for detailed analyses of drinking patterns on various health outcomes. Specifically, risk factor clustering for a dozen regions of birth including those which make up a relatively small proportion of the Australian population; the relation of 32 health conditions and indicators of general health to drinking cessation and other changes in drinking behaviour; and risk of a large range of cancer types and causes of death. Indeed, the analysis of factors related to drinking cessation is substantially larger than any previous study on the topic, with approximately 6.5 times more participants than the next largest study[7].

Another important strength of the thesis was the use of data linkage to obtain cancer incidence and mortality outcomes. As all cancer cases diagnosed and deaths occurring in NSW are recorded in the NSW Central Cancer Registry and NSW Registry of Births, Deaths and Marriages respectively, it is expected that almost all outcomes were captured. This eliminated bias from loss to follow-up, which if differential by level of alcohol consumption or drinking pattern may have resulted in an underestimate of cancer or mortality risk in certain drinking groups. This also avoided potential bias from alternative methods of outcome ascertainment, such as self-report which is less reliable.

The large number of key covariates available for adjustment was another strength of the thesis. Chapter 4 demonstrated the variation in alcohol consumption by each covariate, revealing that failure to adjust for these covariates may have biased risk estimates in prior studies. It has also been shown in prior research that a large number and variety of covariates are associated with alcohol consumption and patterns of drinking[8, 9]. The quantity and breadth of covariates adjusted for was comparable to other large previous studies of alcohol consumption and cancer and mortality risk[10-12].

The measures of alcohol consumption and drinking pattern used in the analyses were also a strength. When total alcohol consumption was examined categorically, a reference group of very

light drinkers was used rather than non-drinkers to mitigate bias from the 'sick-quitter effect'. Total alcohol consumption was also modelled as a continuous log-linear variable and a restricted cubic spline excluding non-drinkers, to limit the impact of this bias. Unlike the majority of prior studies investigating the effect of pattern of drinking, drinking frequency and drinks per drinking-day were adjusted for total alcohol consumption enabling the independent effect of these measures of drinking pattern to be evaluated. This was an important strength, as it is otherwise not possible to determine whether effects are due to drinking pattern itself or are simply attributable to total alcohol consumption. The test for interaction between drinking frequency and drinks per drinking-day and stratification into an overall drinking pattern variable enabled the impact of these measures of drinking pattern on risk to be explored concurrently, something few previous studies have examined.

A further strength of the thesis was the use of sensitivity tests aimed to systematically and comprehensively examine the impact of bias due to the 'sick-quitter effect' and other changes in drinking behaviours in response to ill-health (decreased drinking and changes in drinking frequency and drinks per drinking-day). In particular, the empirically-derived sensitivity test of restricting to participants with a physical functioning score of ≥ 50%, to test the robustness of the cancer and mortality risk estimates to these biases. This provided evidence that the effect estimates for all-cause mortality were likely to be higher than those reported in the main analysis due to the inclusion of those with impaired health status at baseline, who were more likely to have quit or decreased drinking. The observed estimates for all cancer risk however, appeared to be robust and not materially impacted by the 'sick-quitter effect'.

There were also several limitations. While the number of participants in the study was large, the length of follow-up and number of outcomes was limited. This was especially true for the cancer incidence data, which was only available for analysis to December 2010 at the time of thesis submission. This reduced the statistical power of the analyses.

Another limitation was the measure of alcohol consumption. In particular, the questionnaire item for number of drinks consumed per week had the instruction: "*Put "0" if you do not drink, or have less than once drink each week*". This meant the 'non-drinking' group was an amalgam of three distinct drinking groups – lifetime abstainers, former drinkers and occasional drinkers, which likely have different risk profiles. While it has been suggested that lifetime abstainers should be used as a reference group, there is evidence that lifetime abstainers have poorer health status in comparison to drinkers, and therefore using lifetime abstainers as the reference group may result in conservative estimates of the effects of drinking on health, which has been termed the 'sick non-starter effect'[13, 14]. Risks in relation to drinking cessation were also unable to be investigated, including the length of time following cessation that risk of alcohol-related cancer and mortality return to baseline, and whether there is a particular age by which one can cease heavy episodic drinking to obtain maximal health benefits.

Some prior studies have also recorded alcohol consumption at multiple time points (either retrospectively or prospectively from baseline)[12, 15] to enable estimates of lifetime alcohol consumption rather than consumption at a single time point. This also has the advantage of mitigating bias from regression dilution, which can occur in studies measuring alcohol consumption at a single time point[16]. While prospective alcohol consumption data was available with the first follow-up questionnaire, retrospective data would be required to investigate questions relating to drinking over the life course. One of these questions is whether cancer and mortality risk related to alcohol consumption and pattern of drinking is cumulative, or whether exposure at particular stages of life is important, such as during young adulthood. For example, there is evidence that ultraviolet light exposure during childhood and adolescence is associated with greater risk of skin cancer compared to exposure during adulthood[17].

A further questionnaire item which would have enabled comparison to some previous studies was the maximum number of drinks consumed on one occasion over a longer time period, such as one

month[18, 19]. This would have enabled heavy episodic drinking that occurs less frequently than once per week to be examined. As a result, future follow-up questionnaires may contain a question to identify lifetime abstainers, former drinkers and occasional drinkers, along with the question: "*In a typical month, what is the largest number of drinks you have in one day?*". Beverage type was also missing from the questionnaire, meaning that it was not possible to compare potential differences in risk relationships by this factor. For example, there is some evidence that beverage type may be important for CVD[20] and alcoholic liver disease risk[21], with lower risk associated with wine consumption compared to beer and spirit consumption.

Alcohol exposure was ascertained by self-report, which may be unreliable. Respondents may have had difficulty estimating (often underestimating) the quantity of alcohol they consume[22, 23], and may also under-report consumption due to concern that their drinking does not match societal norms[22, 24]. These issues typically result in an underestimate of consumption overall, which if differential could bias associations between total alcohol consumption and health outcomes towards or away from the null. Reports are inconsistent on whether underreporting differs by drinking pattern. Australian and Canadian studies found that low-risk and non-heavy episodic drinkers underreported their alcohol consumption to a greater degree than higher-risk and heavy episodic drinkers[25, 26], while an English study found underreporting was disproportionately associated with heavy drinking, frequent drinking and non-routine drinking[27]. Therefore, the risk estimates for drinking patterns may also be susceptible to bias from measurement error. Overall, if alcohol consumption is underreported in the 45 and Up Study, the extent of risk associated with each level of drinking would be an overestimate, as the risk ascribed to a specific level of consumption may actually represent the risk associated with higher levels of consumption. This means that extra caution should be applied when inferring thresholds of risk for alcohol consumption guidelines.

It was also shown in Chapter 5 (and has previously been reported[28]) that the participants of the 45 and Up Study are not representative of the general population of NSW. Participants generally had

more favourable socio-demographic, self-rated overall health and lifestyle risk factors than in population surveys, as well as a greater prevalence of weekly alcohol consumption. Further, those with more extreme drinking behaviours, such as those with mental illness and those who are institutionalised, are not likely to participate in surveys of this kind. This may have led to a 'healthy volunteer effect'[29, 30], causing the observed incidence of cancer, CVD and mortality to be lower than expected. A detailed comparison of the 45 and Up Study with the NSW Population Survey found consistent exposure-outcome relationships between the two studies however, meaning that the 45 and Up Study will most likely provide generalisable results when analyses are based on internal comparisons within the cohort[28].

Further, as the 45 and Up Study was based on middle-aged and older participants, survival bias cannot be ruled out[31]. Given those with a history of heavy drinking and heavy episodic drinking are at a higher risk of mortality and morbidity, they are less likely to be sampled. Thus heavy drinkers may be underrepresented in the 45 and Up Study, particularly those in older age groups. Indeed, there were few heavy drinkers among women, which reduced the reliability of risk estimates for heavy drinking and drinks per drinking-day for some female-specific outcomes, including risk of breast, endometrial and cervical cancer. The exclusion of persons aged < 45 years also meant that the harms of drinking in younger persons and interactions with age could not be examined. For example, the risk relationship between alcohol consumption and outcomes such as all-cause mortality and death from external causes may have differed if younger participants were included.

Lastly, despite efforts to use sensitivity tests to remove bias from the 'sick-quitter effect' and other changes in drinking behaviour caused by ill-health, these attempts could not be expected to remove all of the bias, as shown in Chapter 7. Therefore, the effect estimates for cancer and mortality risk may still be biased due to differing health status between groups of different consumption levels. Moreover, this bias makes interpretations about the association between low-volume drinking and frequent drinking with reduced mortality risk difficult, because sensitivity tests suggested that

excluding those with ill-health reduced inverse associations, but it was not possible to infer whether the effect could be wholly accounted for by bias. The use of a younger cohort with alcohol consumption ascertained at multiple time points may help to reduce the impact of this bias. A randomised controlled trial of low-volume drinking and drinking frequency would provide more conclusive evidence[32].

Research gaps and implications for future research

The relationship between alcohol consumption and health outcomes

For many health conditions, despite the work in this thesis, the precise relationship between alcohol consumption, drinking pattern, and risk of incidence and mortality remains to be determined. For outcomes which have been inversely associated with alcohol consumption in particular, such as type 2 diabetes, dementia and CVD, further studies are required with careful examination of bias from changes in drinking behaviours in response to ill-health to investigate whether these inverse associations are truly causal, and whether the risk of harm associated with heavy drinking and heavy episodic drinking is underestimated. This may also involve the use of measures of drinking pattern which were not available in this study but have been previously used in research, such as beverage type and maximum number of drinks consumed in one day in one month (to capture heavy episodic drinking that occurs less frequently than once per week). Additional research is also required for some female-specific outcomes such as drinking pattern and risk of breast, endometrial and ovarian cancer due to the small number of women with a high number of drinks per drinking-day in this study. Furthermore, as risk relationships may vary among populations around the world, it would be of interest to examine the association between alcohol consumption and health outcomes among immigrant groups in Australia as well as Indigenous Australians. There were not yet enough cancer cases and deaths to answer this question using the 45 and Up Study for the former, while Indigenous status data was not available and was outside the scope of this thesis for the latter. Indigenous Australians experience substantial burden from alcohol-related harm, and so epidemiological research in this group should be a priority.

In addition, for diseases other than cancer, associations were only able to be examined for mortality, rather than incidence. As well as potential bias from confounding due to differences in health status between drinking groups, there may be true underlying differences in the risk relationship for certain diseases for incidence compared to mortality. For example, it has been reported in a meta-

analysis that the relationship between alcohol consumption and liver cirrhosis differs whether the outcome is incidence or mortality, as alcohol consumption negatively influences the course of existing liver cirrhosis and accelerates liver cirrhosis mortality[33]. Risk relationships with alcohol consumption and drinking pattern for other diseases may similarly differ by choice of outcome, and so the impact of bias from changes in drinking behaviour in response to ill-health should be investigated for the incidence of disease as well as mortality. The use of incidence as an outcome for diseases such as type 2 diabetes and dementia may also have the advantage of providing greater statistical power, which may have been lacking in this study.

Furthermore, studies investigating the independent effect of drinking pattern on risk of disease incidence and mortality must include adjustment for total alcohol consumption, to determine whether drinking pattern has an independent effect on risk or whether the effect is primarily mediated through total alcohol consumption.

Recommendation: Further research is required to understand the relationship between alcohol consumption, drinking pattern and risk of disease incidence and mortality. Variation in the risk relationship by population subgroups such as immigrants and Indigenous Australians could be investigated. It is especially important that the role of bias from changes in drinking behaviours in response to ill-health be investigated for all associations, along with adjustment for total alcohol consumption when examining the influence of patterns of drinking on risk.

The systematic review of previous systematic reviews and meta-analyses also highlighted several opportunities to improve the evidence base regarding the association between alcohol consumption and all-cause mortality. As most prior systematic reviews were found to be at high risk of bias, the evidence was inconsistent for differences in the risk relationship by sex and age, and there was only limited evidence for differences by smoking status and duration of follow-up. Furthermore, there were some topics for which systematic review evidence was lacking entirely. These included

whether the risk relationship differed by certain populations (e.g. Africa, the Middle East, Latin America), smoking status when including an ex-smoking category, pattern of drinking (including drinking frequency and heavy episodic drinking), changes in alcohol consumption over time, and beverage type. One of the most important topics of research is whether the association between low-volume drinking and decreased risk may be accounted for by biases in primary study design, including choice of reference choice of group, inadequate measures of alcohol consumption, differences in adjustment for confounding and differences in inclusion criteria. Further carefully designed systematic reviews and meta-analyses with high methodological quality (such as the review by Stockwell et al., (2016)[4]) that capture primary studies that have been published since 2016 are required to investigate the influence of these factors, particularly pattern of drinking, on the association between drinking and all-cause mortality.

Recommendation: Systematic reviews and meta-analyses with high methodological quality are required to investigate factors influencing the association between alcohol consumption and all-cause mortality, including patterns of drinking such as drinking frequency and heavy episodic drinking. A research priority should be to continue to investigate whether the inverse association between low-volume drinking and mortality can be accounted for by bias.

One area of research relating to drinking pattern and alcohol consumption more broadly is the timing between exposure and outcome for risk of cancer, other disease and mortality. Firstly, it should be investigated whether the lag-time between drinking patterns (such as heavy episodic drinking) and cancer risk is the same as that for total alcohol consumption. That is, the length of time between exposure and outcome. Previous estimates for the lag-time between alcohol consumption and cancer mortality have ranged from 8 to 25 years[34, 35]. Another research gap is whether the risk associated with heavy episodic drinking while young persists throughout life, and whether risk is greater during certain age periods, such as in young adulthood. Does the cessation of heavy episodic

drinking cause a reduction in cancer and mortality over time and a return to the baseline level of risk, or only prevent further increased risk? Is there a particular age by which one can cease heavy episodic drinking to obtain maximal benefit to cancer and mortality risk? For example, there is evidence that increased risk of breast cancer with drinking begins in young adulthood[36], and in the Nurses' Health Study it was found that alcohol consumption in earlier and later life both independently increase risk[37]. Understanding risk lag-time and the relationship between changes in heavy episodic drinking behaviour (and more broadly, for total alcohol consumption) and health outcomes would enable population attributable fractions and burden of disease estimates for drinking, as well as individual risk assessments, to be modelled more accurately. The incorporation of heavy episodic drinking and possibly other patterns of drinking into these estimates would ensure that individual and population interventions involving alcohol consumption can be planned and targeted to achieve maximal health benefit.

Recommendation: Further research is required to understand the exact lag-time between exposure and outcomes, differences in risk by age and period of life, and the effect of changes in drinking behaviours on associations between total alcohol consumption and patterns of drinking (including heavy episodic drinking) on risk of cancer, other disease and mortality.

It was shown in Chapter 1 that there are no consistent definitions for terms such as 'occasional', 'light', 'low-volume', 'moderate' and 'heavy' drinking, as well as the term 'heavy episodic drinking'. These terms should be globally standardised so that the findings of studies can be more easily compared and translated into practice. For heavy episodic drinking, the occasional consumption of > 4 drinks per drinking-day could be adopted as a standardised definition, or alternatively the definition recommended in a review adapted from the United States National Institute on Alcohol Abuse and Alcoholism definition: "*A pattern of drinking alcohol that brings BAC to 0.08 gram percent or above (≥5/4 for men/women in 2 hr) on more than one occasion within the past 6 months*"[38].

Recommendation: Terms such as 'occasional', 'light', 'low-volume', 'moderate' and 'heavy' drinking, as well as the term 'heavy episodic drinking', could be globally standardised to enable the results of future studies to be more easily compared and translated into practice.

Causal mechanisms for differences in risk by pattern of drinking

It is also of importance to investigate evidence for causal mechanisms regarding the independent effect of drinks per drinking-day and heavy episodic drinking on cancer, other disease and mortality risk. For example, it was found there was an independent positive association between drinks per drinking-day and risk of mouth, pharynx and oesophageal cancer, but not breast cancer. Perhaps this implies that the accumulation of acetaldehyde in the upper aerodigestive tract on single drinking occasions has an exponential effect on cancer risk at this site, while the drinking-induced increase in levels of hormones associated with breast cancer risk depends only on total alcohol consumption. It may also be necessary to investigate causal mechanisms for drinking frequency if the association with decreased risk of cancer, other disease and mortality is truly causal.

Recommendation: Further research is required to understand the mechanistic evidence underlying the independent relationship between drinking patterns (especially drinks per drinking-day and heavy episodic drinking) and cancer, other disease and mortality risk.

Mitigating bias from the 'sick-quitter effect' and other changes in drinking behaviours in response to ill-health

This thesis also identified a number of methodological considerations for future studies of alcohol and its impact on health outcomes. It was shown in Chapter 7 that the exclusion of participants with health conditions or poor indicators of general health at baseline is likely to be an inadequate method of addressing bias from the 'sick-quitter effect' and other changes in drinking behaviours in

response to ill-health. Future studies should instead use a reference group of lifetime abstainers or light drinkers (or both), calculate a log-linear trend in risk for drinkers only, assign ex-drinkers to their former levels of drinking at analysis (if available), ascertain alcohol consumption at multiple time points (either retrospectively or prospectively from baseline), exclude outcomes that occur early in the period of follow-up, or restrict the study to younger participants. Ideally more than one of these methods would be performed, along with a sensitivity test to at least examine the possibility that changes in drinking behaviours in response to ill-health may have biased risk estimates. It would also be of interest for future studies to quantify the magnitude of potential bias from the 'sick non-starter effect'[13, 14] on risk estimates for cancer, other diseases and mortality.

Recommendation: Future studies using alcohol consumption as an exposure should use methods other than the exclusion of participants with health conditions or poor indicators of general health to address bias from the 'sick-quitter effect'. A sensitivity test examining the possibility of bias due to changes in drinking behaviours in response to ill-health should also be performed. The possibility of bias due to the 'sick non-starter effect' should also be investigated.

While it was shown that the exclusion of participants with a low physical functioning score (i.e. score < 50) was likely to be useful as a sensitivity test to assess whether the 'sick-quitter effect' and other changes in drinking behaviours in response to ill-health have biased risk estimates, this test did not eliminate all bias. In particular, this test was shown to be less effective at mitigating potential bias when examining drinking frequency compared to both total alcohol consumption and drinks per drinking-day. This sensitivity test could be refined by examining alternative cut-points for restriction. This comparison could be performed empirically using the same methods as in Chapter 7. Furthermore, only four indicators of general health were examined in this thesis. There are many other indicators of general health and health status in the literature, including the Medical Outcomes Study Short Form surveys (a portion of which appeared in the 45 and Up Study as the

physical functioning score), Nottingham Health Profile, Sickness Impact Profile, Health Utilities Index, the Quality of Well-being Scale, Assessment of Quality of Life, and the Charlson Comorbidity Index[39, 40]. It is possible that these may be better predictors of drinking cessation than the indicators of general health examined in this thesis, and therefore may be used to create a more effective sensitivity test.

Recommendation: Further research is required to refine the sensitivity test involving the exclusion of participants with low physical functioning score to examine possible bias due to changes in drinking behaviours in response to ill-health. The use of alternative indicators of general health as a sensitivity test should also be investigated.

Ill-health and changes in other behavioural risk factors

As it was shown that the development of a variety of health conditions is associated with changes in alcohol consumption, it would also be of interest to investigate how this may apply to other risk factors, including the co-occurrence of multiple risk factors. For example, one area of research may be to examine whether ill-health is associated with changes in CDRI score as well as changes in individual risk factors, to ascertain a more complete picture of how ill-health is associated with behaviour change, and how this may influence future chronic disease risk. Whether any changes persist in the long-term is also an area for further research. Furthermore, perhaps changes in other risk factors in response to ill-health may cause biased associations with health outcomes in the same way as the 'sick-quitter effect' for alcohol consumption.

Recommendation: The association between the development of health conditions and changes in behavioural risk factors other than alcohol consumption should be investigated, including changes in the co-occurrence of multiple risk factors.

Evidence for implementation of the findings for heavy episodic drinking to achieve public health benefit

Due to the finding of independent associations with risk, there is also a need for implementation research around interventions, both individual and population, targeting heavy episodic drinking for the prevention of cancer, other disease and mortality. One question which should be investigated is whether behaviour change can be facilitated by increasing awareness that heavy episodic drinking raises risk of cancer and other chronic disease in addition to acute events such as accidents and injuries. It is particularly important for this research to be performed in middle-aged and older persons, due to the ageing of the population and the higher risk of cancer in this group, and as anti-heavy episodic drinking campaigns have typically been targeted at younger persons in the past. As consuming > 4 drinks per drinking-day is more prevalent in men than women[41], targeting middle-aged and older men in particular could be a worthwhile strategy, especially if it can be determined whether cessation of heavy episodic drinking results in decreased cancer risk over time. There is also a need for further research on the effectiveness of primary healthcare brief alcohol interventions in ethnic minority groups[42], and it was found in this thesis that immigrants born in non-English speaking countries in particular were at potential risk of worsening alcohol consumption behaviours over time. Therefore research could also be performed in immigrants and Indigenous Australians.

Recommendation: There is a need for implementation research on individual and population interventions targeting heavy episodic drinking for the prevention of cancer, other disease and mortality. A research priority should be to investigate interventions for middle-aged and older persons, particularly men, immigrant groups and Indigenous Australians.

Implications for policy and action

The outcomes of this thesis have a number of implications for policy and actions aimed at reducing the burden of disease and injury from alcohol consumption in Australia, and in particular for informing future reviews and health guidelines. The NHMRC guidelines recommend:

1. "*For healthy men and women, drinking no more than two standard drinks on any day reduces the lifetime risk of harm from alcohol-related disease or injury.*"
2. "*For healthy men and women, drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion.*"[43]

The current NHMRC guideline to reduce the lifetime risk harm was designed to limit lifetime risk of alcohol-related mortality to 1%[43]. It should be noted however that the guidelines are based on international relative risks, and risk may differ between populations. The findings for alcohol and mortality observed in this thesis suggest that 2 drinks per day may be too many. Specifically, the association between alcohol consumption and all-cause mortality appeared to be substantially underestimated due to methodological factors such as changes in drinking behaviour caused by ill-health. In the main analysis, the risk of all-cause mortality per additional drink per day was 1.03 (95% confidence interval: 1.02-1.05) but up to 1.05 (1.03-1.07) in sensitivity analyses, while the PAF value for drinking and all-cause mortality was 2.2% in the main analysis and as high as 5.5% in sensitivity analyses. There was evidence presented that the NHMRC guideline to reduce the lifetime risk of harm could be lowered to 7 drinks per week, to ensure that lifetime risk of alcohol-attributable mortality remains less than 1%. The limitation should be noted that if alcohol consumption was underreported in the 45 and Up Study then the level of risk associated with 7 drinks per week may be an overestimate. Furthermore, it may be prudent for future guidelines to reassess whether a 1% lifetime risk of mortality is an appropriate cut-point, as this level of risk is higher than society accepts

for most other voluntary (such as driving) and involuntary exposures (such as contaminants in drinking water)[44].

It was also found that drinks per drinking-day, including heavy episodic drinking, is an independent risk factor for cancer incidence and all-cause mortality. A significant increased risk was detected for > 2 drinks per drinking-day for cancer incidence and > 4 drinks per drinking-day for all-cause mortality, however the exact threshold for harm is unknown. The guidelines could therefore emphasise that consuming many drinks in one occasion increases risk of long-term harm including cancer and all-cause mortality (not just injury as captured by the current guideline to limit risk of short-term harm), to a greater degree than the same quantity of alcohol consumed over several occasions. That is, in addition to a guideline of 7 drinks per week, risk of long-term harm will be lower if individuals limit their consumption on any one day as much as possible. If one were to consume 7 drinks per week, the safest drinking pattern would be one drink per day. As the threshold for increased risk associated with drinks per drinking-day is unknown but increased cancer risk was detected at > 2 drinks per drinking-day, the current recommendation of no more than 2 drinks on any day could be retained as a guideline for drinks per drinking-day.

The existence of two guidelines and two cut-points, one to limit risk of long-term harm and one to limit risk of short-term harm, is potentially confusing to individuals and sends mixed messages. The results support one clear guideline to limit risk of both long-term and short-term harm, addressing both a maximum number of drinks per week and a maximum number of drinks per day. Therefore, a potential future drinking guideline could recommend:

> *For healthy men and women, drinking no more than seven standard drinks per week and no more than two standard drinks on any day reduces the lifetime risk of harm from both alcohol-related disease and injury.*

The results also have implications for other aspects of the alcohol guidelines. There was formerly a recommendation to have one or two alcohol-free days per week, in the 2001 guidelines[45]. The rationale for this was that although the evidence for effect on health was limited, it may help people control their drinking habits and avoid alcohol dependency. This recommendation did not appear in the 2009 guidelines, although it is mentioned in the explanatory document that alcohol-free days can further reduce the lifetime risk of disease and injury[43]. The results of this thesis imply however that heavy episodic drinking, even 1-2 days per week, can cause a substantial increased risk of cancer incidence and all-cause mortality, similar to that of heavy frequent drinking. This suggests that a recommendation of 1-2 alcohol-free days per week (or even 5-6) would not importantly reduce alcohol-related harm.

Furthermore, it was shown in the alcohol and mortality analysis that despite observing a J-shaped non-linear association between alcohol consumption and CVD mortality, there was no significant protective effect. The use of light drinkers as the reference group rather than non-drinkers, the exclusion of participants who died within three years of baseline, and the exclusion of participants with prior CVD as a sensitivity analysis were used to account for potential methodological considerations which may have caused a spurious protective association in previous studies. Importantly, the exclusion of participants with prior CVD resulted in a significant positive linear trend of alcohol and risk for CVD mortality. It was also shown empirically in Chapter 7 that heart disease and stroke are associated with drinking consumption cessation and reduction. Therefore, this thesis provides evidence that alcohol guidelines should not regard the apparent protective association between 'moderate' drinking and CVD mortality as causal.

Finally, as it was shown that drinking pattern influences cancer and mortality risk, population health surveys designed to measure the prevalence of drinking behaviours could record frequency of alcohol consumption as well as total amount. This will enable the drinks per drinking-day and more complex patterns of drinking such as heavy episodic drinking and heavy frequent drinking to be

captured, so that the prevalence of drinking patterns in Australia can be monitored and linked to health outcomes. These estimates may also be used to calculate more accurate disease burden and population attributable fractions for alcohol consumption.

Recommendation: To develop guidelines that reduce the burden of alcohol-related harm in Australia, the national alcohol guidelines revision could consider the evidence presented in this thesis along with all previous evidence. Specifically, that the alcohol-mortality relationship may be underestimated due to bias from changes in alcohol consumption in response to ill-health and that a limit of 7 drinks per week may be required to ensure that lifetime risk of alcohol-attributable mortality remains below 1%, that individuals limit their consumption on any one day as much as possible, and that the apparent protective association between 'moderate' drinking and cardiovascular disease mortality should not be regarded as causal. A potential future drinking guideline could recommend: *For healthy men and women, drinking no more than seven standard drinks per week and no more than two standard drinks on any day reduces the lifetime risk of harm from both alcohol-related disease and injury.* Population health surveys could also be designed to capture drinking pattern so that the prevalence of harmful patterns of drinking can be estimated.

As well as alcohol guidelines, the findings of this thesis can also be considered in the alcohol policy debate. In Chapter 1, current public health efforts to reduce alcohol-related harm in Australia were discussed. The seven policy areas which can be used to reduce the burden of alcohol consumption were pricing and taxation, regulating physical availability, modifying the drinking environment, drink-driving countermeasures, education and persuasion, restrictions on marketing and treatment and early intervention[46]. Support for change to alcohol policy in Australia is high, with a 2017 Foundation for Alcohol Research and Education survey found that 81% of Australians wanted further action taken to reduce alcohol-related harm[47]. Ideally, all seven policy areas will continue to be researched, developed and expanded, but the findings of this thesis relate most directly to the policy

area of ‘education and persuasion’. That is, programs aiming to educate and inform Australians of the harms associated with alcohol consumption.

There is evidence that government alcohol harm reduction campaigns that focus on the long-term harms of alcohol (particularly cancer and stroke risk) and include drinking guidelines, promote behaviour change to a greater degree than campaigns without these features[48]. Of 83 English-language television advertisements evaluated in 2015 by over 2000 Australian participants who consumed alcohol at least weekly, an Australian advertisement focusing on cancer risk was the most effective in motivating a reduction in drinking[48]. In general, advertisements with a focus on long-term harms were more effective than those focusing on short-term harms including injury and violence. It was also reported in a Western Australian study that a 2010 mass media education campaign on alcohol and cancer risk was effective in increasing women’s knowledge of alcohol as a risk factor for cancer, knowledge of drinking guidelines, and intention to decrease alcohol consumption[49].

Altogether, this means the findings of this thesis that consuming more than 4 drinks per day on only 1 or 2 days per week increases risk of cancer by 27% and all-cause mortality by 24%, could be used as evidence for future mass media campaigns and other elements of ‘education and persuasion’ policy such as school-based education campaigns and on drink labelling. Namely, messaging surrounding alcohol consumption, particularly heavy episodic drinking, could be changed to promote greater awareness of the link between drinking and cancer risk and other long-term harms.

At present, mass media campaigns funded by state and federal governments often focus on themes relating to acute consequences of alcohol consumption, such as violence, injury and drink-driving[46]. Alcohol harm reduction is typically viewed by the government and public through the prism of policing and public safety rather than that of long-term harms such as cancer, liver disease and CVD. This is despite recent evidence that of all deaths in Australia caused by alcohol consumption, cancer deaths comprised 36% – more than any other disease or injury[50]. There is

great opportunity for an increase in public awareness regarding alcohol and cancer risk as a 2017 Foundation for Alcohol Research and Education national survey reported that only 15% and 25% of respondents were aware of the link between drinking and breast and mouth/throat cancer respectively[47]. This compares to 78% of respondents who were aware of the link with liver cirrhosis. In addition, in 2013 it was found that 56% of men and 42% of women believed there is a level of drinking which does not increase risk of lifetime harm[41]. The lack of existing public knowledge of the link between drinking and cancer, combined with the evidence that raising awareness of cancer risk is one of the most effective methods in motivating a reduction in drinking suggests there is a substantial public health opportunity to be gained in reframing the focus of government alcohol harm reduction campaigns, particularly those focusing on heavy episodic drinking, to cancer risk and other long-term harms.

A shift in focus to chronic disease prevention may also increase the relevance of anti-heavy episodic drinking campaigns to older Australians. In 2016, 17% of Australians aged 60-69 years and 7% aged ≥ 70 years consumed > 4 drinks per occasion at least monthly[51], meaning that a sizable portion of older Australians engage in heavy episodic drinking and are at increased risk of cancer and all-cause mortality. Harm reduction campaigns focusing on heavy episodic drinking could therefore consider middle-aged and older Australians as a key target constituent group.

Finally, in addition to media campaigns, there are also implications for alcoholic beverage labelling. Warning labels were voluntarily introduced by the alcohol industry in Australia in 2011, but are not mandatory[46]. The findings of this thesis suggest that mandatory warning labels could be introduced in Australia similar to tobacco products, with messaging focused on the harms of heavy episodic drinking for cancer risk and other long-term harms, and targeted at middle-aged and older drinkers. As only 38% of Australians are aware of the national guideline of 2 standard drinks per day to minimise risk of long-term harm[47], and that guideline promotion was found to be a component of advertisements which effectively motivate reductions in drinking behaviour[48], perhaps a

greater emphasis on standard drinks and the national guidelines could also feature on alcohol labelling. Another potential change for alcohol labelling could be to introduce plain packaging, which has been successfully implemented for tobacco products in Australia and has been associated with an increased rate of smoking cessation attempts[52]. Finally, although there is no precedent, standardised serving sizes for alcoholic beverages to ensure that all products contain a maximum of one standard drink per serve could also assist individuals to monitor their alcohol consumption more accurately, and if implemented globally would facilitate cancer control strategies by enabling comparisons between populations and the standardising of risk.

Recommendation: To reduce the burden of alcohol-related harm in Australia, mass media campaigns, education programs and alcoholic beverage labelling could emphasise the long-term harms of alcohol consumption and the national alcohol guidelines, especially regarding heavy episodic drinking and cancer and mortality risk. These campaigns could consider middle-aged and older Australians who are particularly at risk of these harms.

The findings in this thesis around illness as determinants for drinking cessation have implications for guidelines relating to 'treatment and early intervention'. That is, recommendations relating to screening patients for alcohol use in a medical setting and brief interventions. In Chapter 7, it was found that many health conditions were associated with drinking cessation. For these conditions, the occurrence of illness may have been a "teachable moment" for some participants to improve their health behaviours[53], including the reduction or cessation of alcohol consumption. While it was not possible to examine in this thesis, it would be informative to investigate whether participants were quitting drinking spontaneously or if they were informed to do so by their medical practitioners. For diseases which are caused by drinking (e.g. cancer, CVD, liver disease and bone fractures), diseases which are exacerbated by alcohol or where alcohol may interfere with treatment (e.g. cancer, osteoporosis, diabetes, depression and anxiety) and diseases for which alcohol

increases risk of recurrence (e.g. cancer), the clinical guidelines for the prevention and management of each disease could recommend the reduction or cessation of alcohol consumption. For example, the Royal Australian College of General Practitioners *Guidelines for preventive activities in general practice* recommends that practitioners advise patients with pancreatitis, diabetes, liver disease, sleep disorders, sexual dysfunction, other major organ disease and mental health problems that "*non-drinking is the safest option*"[54]. Patients with hypertension are advised to "*limit alcohol intake to no more than two (for men) or one (for women) standard drinks per day*". Based on the findings of the narrative review and the cancer and mortality analyses, diseases which could be added to this list include cancer, other CVD, infectious diseases, nutritional deficiencies, overweight and obesity, epilepsy and certain types of dementia, as drinking increases risk or exacerbates the condition, along with osteoporosis and Parkinson's disease as drinking increases fall risk. Patients who have been injured as a result of external causes would also be an appropriate target for drinking assessment and intervention if alcohol was a contributing factor.

These changes should improve health outcomes for patients, as there is consistent evidence in systematic reviews that primary healthcare brief alcohol interventions are effective in addressing 'hazardous and harmful' alcohol consumption[42]. As well as in general practice, screening and brief interventions could be considered by specialists and allied health practitioners such as dietitians who are in contact with patients for the management of their specific health conditions. There is also evidence that Australian oncologists could do more to provide cancer survivors with guidelines for healthy eating, including the reduction of alcohol consumption[55]. Unfortunately, some Australian general practitioners do not routinely assess the alcohol consumption of their patients or provide recommendations for their drinking[56, 57], with barriers including a lack of confidence in managing alcohol issues and a desire to avoid an adversarial patient-doctor relationship[57, 58].

Recommendation: To reduce the burden of alcohol-related harm in Australia, the occurrence of ill-health could be considered as an opportunity to screen the drinking behaviours of patients, educate them on the long-terms harms of alcohol consumption, and offer brief alcohol interventions in the primary care setting.

10.2 – Conclusions

In conclusion, this thesis has made several important contributions to the evidence base for the impact of alcohol on disease and mortality. The narrative review investigated the relationship between alcohol consumption and numerous health outcomes, identifying important gaps in the evidence such as the uncertain relationship for many types of cancer, lack of evidence for the effect of pattern of drinking for many outcomes, and the possibility that risk estimates may be biased due to the 'sick-quitter effect' and other biases. It was then shown that previous systematic reviews of the association between alcohol consumption and all-cause mortality were largely at high risk of bias, and that there is little evidence concerning the factors that may influence this relationship, and for some factors such as pattern of drinking no evidence at all. It was also concluded that the apparent protective effect of moderate drinking on mortality may be accounted for by biases in primary study design. The investigation of risk factor co-occurrence revealed that lifestyle behaviours, including drinking behaviours, acculturate to those of the host population over time. It was shown that immigrants to Australia from non-English-speaking countries in particular appeared to be at risk of worsening alcohol consumption behaviours over time. Investigation of the 'sick-quitter effect' resulted in the identification of a sensitivity test, restriction to participants with a physical functioning score ≥ 50%, to examine the potential for bias in associations between alcohol consumption and health outcomes. A systematic investigation of the effect of total alcohol consumption on cancer and mortality risk was performed, finding results that were largely consistent with prior research. There was also evidence for scepticism of the protective association between 'moderate' alcohol consumption and drinking frequency on risk of CVD and all-cause mortality, as these may be attributable to reverse causation or confounding. When the sensitivity test restricting to participants with a physical functioning score ≥ 50% was applied to mortality risk estimates, the risk of all-cause mortality in relation to alcohol consumption appeared to be

substantially underestimated when not accounted for. Finally, another important contribution to the evidence base was the systematic investigation of the independent effect of drinking pattern on cancer and mortality risk (with adjustment for total alcohol intake), with the key finding that drinks per drinking-day and heavy episodic drinking are independently associated with risk of cancers of the mouth, pharynx, oesophagus and kidney, and all-cause mortality.

Many areas for future research have been identified that will further understanding of the relationship between alcohol consumption to health, such as the risk relationship between alcohol consumption, pattern of drinking and health outcomes in key population subgroups such as immigrants and Indigenous Australians, mechanistic evidence for the effect of pattern of drinking on risk of cancer and other diseases, and further investigation into the nature of bias due to changes in drinking behaviours in response to ill-health.

While progress has been made in recent decades in enacting policy aiming to reduce the burden of alcohol-related harm in Australia, there is still great public health opportunity to be gained from actions that could yet be implemented. In particular, it was shown that national alcohol guidelines could be revised to decrease the recommended level of drinking to reduce the lifetime risk of harm from disease and injury, and to address the independent harms of drinks per drinking-day and heavy episodic drinking, such as cancer risk. Further, the occurrence of ill-health could be used as an opportunity to screen the drinking behaviours of patients and offer brief alcohol interventions in the primary care setting. Finally, mass media campaigns, education programs and alcoholic beverage labelling could emphasise the long-term harms of alcohol consumption and the national alcohol guidelines, especially regarding heavy episodic drinking and cancer and mortality risk. There is evidence that a focus on cancer risk especially is likely to be effective in motivating behaviour change. These campaigns could also consider middle-aged and older Australians who are at greater risk of these harms, but who are not the usual subject of anti-heavy episodic drinking campaigns.

There must be continued communication of research findings to the public, government and non-government organisations, along with sustained advocacy from public health stakeholders for policies and action to reduce the burden of alcohol-related harm, to create a healthier drinking culture for all Australians.

> *"Three cups do I mix for the temperate; one to health, which they empty first, the second to love and pleasure, the third to sleep. When this bowl is drunk up, wise guests go home. The fourth bowl is ours no longer, but belongs to violence; the fifth to uproar, the sixth to drunken revel, the seventh to black eyes, the eighth is the policeman's, the ninth belongs to biliousness, and the tenth to insanity and the hurling of furniture."*
>
> - Eubulus, 375 BC[59]

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Appendices

Appendix A – Narrative Review of Alcohol Consumption and Risk of Disease and Injury: Outcomes Other than Cancer

Scope

The diseases and injuries captured were those stated to be caused (or in some cases, prevented) by alcohol consumption in the 2009 Australian alcohol guidelines, the World Health Organisation Global Status Report on Alcohol and Health 2014, and a 2017 review of alcohol consumption and burden of disease[1-3]; namely, cancer, various infectious diseases, diabetes, nutritional deficiencies, overweight and obesity, dementia, neuropsychiatric conditions, cardiovascular disease, liver disease, pancreatitis, other digestive system diseases and external causes of morbidity and mortality. Psoriasis and pregnancy and birth complications such as foetal alcohol spectrum disorders which do not directly cause death in adults (and therefore could not be investigated using the 45 and Up Study with linkage to mortality data) were not considered.

Infections (ICD-10: A15-19; B20-24; J09-22)

Burden in Australia

Of all deaths in Australia in 2015, lower respiratory tract infections, tuberculosis and human immunodeficiency virus (HIV) were a contributing cause towards 20,403 (13%) deaths, including 3532 (2.2%) deaths where these infections were the underlying cause[4]. Alcohol consumption was attributed to 246 deaths from infection in 2010, including 232 (9%) lower respiratory infection deaths, 12 (23%) tuberculosis deaths and 3 (4%) HIV deaths[5, 6]. The most recent estimate of the disease burden from influenza and lower respiratory infections attributable to alcohol consumption in Australia was 6%[7].

Epidemiology

A systematic review and meta-analysis found that people who consume 60 g/day of alcohol had a 33% higher risk of community acquired pneumonia compared to abstainers, while those with alcohol use disorders had 8 times the risk[8]. A linear dose-response relationship was found with total alcohol consumption.

For tuberculosis, a systematic review and meta-analysis found that those consuming ≥ 40 g/day alcohol and/or with an alcohol use disorder had an odds ratio of 2.94 (95% confidence interval: 1.89-4.59) compared to non-drinkers/those without an alcohol use disorder[9]. However, there was significant heterogeneity between studies. Another systematic review found a threshold effect, where risk was significant at intakes > 60 g/day[10]. Heavy alcohol consumption also increases the risk of mortality in those diagnosed with tuberculosis[11].

In a recent meta-analysis, those consuming alcohol had double the risk of incident HIV infection compared to non-drinkers, while heavy episodic drinkers had 2.2 times the risk compared to non-heavy episodic drinkers[12]. There were no differences across developing and developed countries.

Causal mechanisms

Heavy drinking increases the risk of lower respiratory tract infections (in particular, pneumonia) and tuberculosis by inhibiting the action of the immune system, thereby increasing susceptibility to infection[2, 13]. The mechanisms by which alcohol consumption increases susceptibility to infectious disease include lessened innate immunity through decreased production of lysozyme and complement, and the damaging of gastrointestinal and respiratory tract immune barriers. Acquired immunity is also affected, through decreased ability to produce antibodies in response to antigens and a reduced lymphocyte proliferative response (via inhibition of the activities of dendritic cells, CD4+ and CD8+ T-lymphocytes). Various other mechanisms are involved, including inhibition of the activities of alveolar macrophages, polymorphonuclear leukocytes and bone marrow granulopoietic function[8, 14]. Nutritional deficiencies induced by heavy alcohol consumption may also play a role[8, 9].

There are two explanations for the association between drinking and HIV infection which are not necessarily mutually exclusive. Firstly, that alcohol consumption through its effects on judgement and disinhibition increases the likelihood of unsafe sex, or that people who take more risks in general are more likely to both consume more alcohol and partake in risky behaviours including unsafe sex and drug injection[15]. Another mechanism is the harmful effect of alcohol on the immune system increasing susceptibility to infection. Alcohol consumption has also been shown to negatively impact disease progression in those already infected with HIV, by interacting with antiretroviral therapies and other medications[14-16]. Heavy drinking is also associated with reduced treatment adherence[16].

Diabetes (ICD-10: E10-14)

Burden in Australia

Diabetes was responsible for 2.3% of the total burden of disease in Australia in 2011[7]. In 2011-12 it was estimated that 917,000 Australian adults (5.4%) were living with diabetes, of which 849,000 were cases of type 2 diabetes[17]. The prevalence of diabetes approximately tripled between 1989-90 and 2011-12. Diabetes was an underlying or associated cause of death in a total of 16,420 (10.3%) deaths in 2015[4]. It was estimated that 2.1% of the burden of diabetes in Australia in 2011 was attributable to alcohol consumption[7]. On the other hand, it was estimated that a net 208 deaths from diabetes were prevented due to alcohol consumption in Australia in 2010[5].

Epidemiology

Alcohol consumption has been associated with an approximate 30-40% reduced risk of incident type 2 diabetes in moderate drinkers[5, 18-20]. The relationship is either J-shaped or U-shaped, with heavy episodic drinking associated with increased risk[19]. Compared to lifetime abstainers, the maximum protective effect has been reported at approximately 25 g/day, while the relative risk is significantly increased above 1 at intakes ≥ 50 g/day in women and 60 g/day in men[20]. Women may gain greater benefit from moderate drinking than men[20].

A systematic review and meta-analysis found that in patients with type 2 diabetes, moderate alcohol consumption was associated with protection against coronary heart disease incidence, coronary heart disease mortality and all-cause mortality[21]. The reference group in that study was non-drinkers however, meaning that the point estimate for protection was possibly overestimated due to the presence of former drinkers in the reference group.

Other potential biases in cohort studies examining the relationship between alcohol consumption and diabetes include misclassification of alcohol consumption and the potential for incomplete control of confounding[19, 22]. For example, one study accounted for a variety of socio-

demographic and health-related variables which were found to cluster with heavy drinking, including employment status, marijuana use and depression, finding that accounting for these factors attenuated the apparent lowered odds of diabetes in moderate drinkers compared to lifetime abstainers[22]. There is also heterogeneity in relative risks in studies of both men and women, and it has been suggested that this may be due to confounding by patterns of alcohol consumption (e.g. heavy episodic drinking, drinking with meals)[20].

Causal mechanisms

The proposed mechanism for the protective effect on type 2 diabetes incidence is through decreased gluconeogenesis, decreased glycogenolysis and increased insulin sensitivity[19]. Insulin sensitivity is increased by inhibiting adipose tissue from releasing fatty acids, which in skeletal muscles are substrate competitors in the Krebs cycle[19]. This assists the rate of glucose metabolism. In non-diabetics, regular moderate alcohol consumption also decreases fasting and post-prandial insulin levels[19]. Alcohol may also play a role in prevention through altered lipid metabolism, lowered blood pressure or an anti-inflammatory effect[5, 13]. The mechanism for greater risk with heavy drinking may be through the association of heavy drinking with poor diet, contribution to excess bodyweight or a direct toxic effect on pancreatic islet cells[5, 23]. Alcohol consumption does not have a role in the aetiology of type 1 diabetes, which is primarily caused by genetic and epigenetic factors[24].

Nutritional deficiencies (ICD-10: E40-64)

Burden in Australia

Heavy alcohol consumption was found to be associated with a number of nutritional deficiencies, including vitamin A, vitamin B_1 (e.g. Wernicke-Korsakoff syndrome), vitamin B_2 (pellagra), folate, vitamin D, vitamin E, calcium, iron, zinc and magnesium deficiency[1, 25]. Nutritional deficiencies were an underlying or associated cause of death in a total of 942 (0.6%) deaths in Australia in 2015[4]. The most common causes were protein-energy malnutrition, vitamin B deficiency and vitamin D deficiency. In the 1980's Australia had the highest prevalence of Wernicke-Korsakoff syndrome in the world at 2.8%, however this decreased to approximately 1% following the fortification of bread with vitamin B_1 in 1991[26, 27].

Epidemiology

A study of alcoholics in Portugal found that over half had low folate and vitamin B_6 status, but none had low vitamin B_{12} status[28], however more moderate levels of alcohol consumption may also produce changes in vitamin status. For example, a randomised cross-over study found that 24 g/day of ethanol is enough to cause significant reductions in serum folate and vitamin B_{12}[29].

Causal mechanisms

The reason nutritional deficiencies are associated with alcohol consumption is two-fold. Specifically, alcohol displaces the consumption of other nutrient-rich foods while also altering the absorption and metabolism of nutrients[30]. The mechanisms by which heavy alcohol consumption can alter the absorption and metabolism of nutrients include the inhibition of pancreatic enzyme release, reducing the absorptive capacity of cells in the stomach and intestines, inhibiting fat absorption and therefore the absorption of fat-soluble vitamins A, D, E and K as well as calcium, impaired utilisation of vitamin B_1 due to impairment of the enzymes that process it, decreased storage of vitamin A in the liver with alcohol-induced liver damage, increased urinary excretion of magnesium and zinc,

nutrient loss with vomiting and diarrhoea, zinc malabsorption secondary to other nutrient deficiency diseases and gastrointestinal bleeding causing iron loss[25, 31].

Overweight and obesity (ICD-10: E66)

Burden in Australia

High body mass was responsible for 5.5% of the total burden of disease in Australia in 2011[7]. In 2014-15, 63% of Australian adults were overweight or obese, increasing from 56% in 1995[32]. The proportion overweight or obese in 2014-15 was 71% for men and 56% for women. Overweight and obesity are risk factors for many conditions, including hypertension, cardiovascular disease, stroke, diabetes, cancer (oesophagus, stomach, colorectum, liver, gallbladder, pancreas, breast, endometrium, ovary, prostate and kidney), osteoarthritis, sleep apnoea and infertility[33, 34]. Alcohol comprised 5.1% and 3.5% of total energy intake for adult men and women respectively in Australia in 2011-12[35].

Epidemiology

Studies examining the relationship between alcohol consumption and obesity often produce inconsistent results[36]. For moderate drinking, the majority of longitudinal and experimental studies find no association with weight gain over time, although both positive and negative associations have been reported. Heavy alcohol consumption and heavy episodic drinking are both associated with weight gain. In addition, those who increase their level of alcohol consumption over time are more likely to gain weight than those who consume alcohol at a constant level. The association between drinking and body weight is usually more apparent in studies of men than of women[36].

Causal mechanisms

The mechanism by which alcohol consumption causes overweight and obesity is by contribution to total energy intake. This occurs if there is no compensation of energy intake by a reduction in the consumption of other foods[36]. The ethanol in alcoholic beverages contains 29 kJ of energy per gram, or 290 kJ in an Australian standard drink[37]. The approximate energy requirements for

moderately active 76 kg men and 61 kg women aged 51-70 years are 12,100 kJ and 9600 kJ respectively[38]. Different types of alcoholic beverage contain various amounts of carbohydrates that also contribute to the total energy content of the beverage. The estimated average energy content of various alcoholic beverages consumed in Australia in 2011-13 is shown below in Table A.1. The energy content of alcoholic beverage varies by type, with a 'middy' of light beer and 'nip' of spirits having the lowest energy content and a ready-to-drink beverage, the highest.

In addition to the energy content of the drinks themselves, a majority of studies in a review found that alcohol consumption can promote appetite, increasing the consumption of food during a meal[39]. Further, alcohol may inhibit the action of hormones that control satiety including leptin and glucagon-like peptide-1, and also by effecting the regulation of neurotransmitters such as opioids, serotonin and gamma-aminobutyric acid within the appetite pathways in the brain[36]. Alcohol consumption may also impact fat storage in the body via its effect on inhibiting fat oxidation (the breakdown of fat as a source of energy), thereby leading to the long-term accumulation of body fat. Finally, there is evidence that genetic factors such as ADH1B polymorphism may modify the relationship between alcohol consumption and bodyweight among alcoholics, possibly by altering the utilisation of ethanol as a source of energy[36].

Table A.1. Estimated average energy content in alcoholic beverages consumed in Australia in 2011-13[37].

Beverage	Serving size (mL)	Energy per serve (kJ)
Full strength beer	285-425[a]	408-608
Light beer	285-425[a]	294-438
Red wine	150	486
White wine	150	444
Spirits	30	274
Cider	285-425[a]	530-791
Ready-to-drink[b]	375	923

[a]Common serving sizes for beer and cider range from a 285 mL 'middy' to a 425 mL 'schooner'. [b]Mean of commercial 'gin and tonic', 'rum and cola', 'vodka and soft drink' and 'whisky or scotch and cola' ready-to-drink beverages.

The finding that moderate alcohol consumption does not increase bodyweight has been attributed to increased energy expenditure caused by an inefficiency in ethanol metabolism by the liver microsomal ethanol oxidising system, but also to possible confounding by health and lifestyle factors such as physical activity which promote weight control and are associated with moderate drinking[30, 36].

Dementia (ICD-10: F00-03; G30)

Burden in Australia

Dementia is a disease associated with brain damage and causes a decline in memory and cognitive function. An estimated 354,000 people in Australia were living with dementia in 2016, comprising 9% of the population aged ≥ 65 years and approximately 30% of the population aged ≥ 85 years[40]. Of all deaths in Australia in 2015, dementia, of which Alzheimer's disease is the most common[41], was a contributing cause towards 25,921 (16%) deaths, including 12,625 (7.9%) deaths where dementia was the underlying cause[4].

Epidemiology

Moderate alcohol consumption has been reported to be associated with a lower risk of Alzheimer's disease[1, 18]. One systematic review and meta-analysis reported that drinkers had a lower risk of both dementia of any type (risk ratio: 0.63; 95% confidence interval: 0.53-0.75) and Alzheimer's disease (0.57; 0.44-0.74) when compared to non-drinkers, although there was significant heterogeneity between studies[42]. Few studies used lifetime abstainers as the reference group or accounted for the level of cognitive function at baseline. Another more recent systematic review of 19 cohort and case-control studies found 7 studies where alcohol consumption was protective, 9 studies where there was no association, and 3 studies where drinking was associated with increased risk, concluding that the evidence is inconsistent[43]. Some studies reported that heavy drinking was associated with increased risk, but the evidence overall was inconsistent. The authors of the review noted several methodological limitations in the literature. These included the possibility of bias in self-reported alcohol consumption, the use of caregivers to collect data from participants rather than the participants themselves, that drinking is only measured at baseline and may change, variation between studies in how alcohol consumption is quantified (e.g. drinks per week, grams of ethanol per day, drink type), the possibility of confounding by biological and behavioural factors that influence Alzheimer's disease risk, and variation in the quality of methods used to ascertain an

Alzheimer's disease diagnosis[43]. There is insufficient evidence to determine whether risk of Alzheimer's disease is modified by drinking pattern and beverage type[41].

Due to the hypothesis that low-volume drinking decreases risk of cardiovascular disease the possibility that drinking may reduce risk of vascular dementia has also been investigated. One systematic review and meta-analysis found no significant association of alcohol with risk of vascular dementia compared to non-drinkers (0.82; 0.50-1.35)[42], however a cohort study found that alcohol use disorders were associated with approximately triple the risk (along with increased risk of Alzheimer's disease and total dementia)[44]. Further research is needed to understand how alcohol consumption is associated with risk of dementia (including Alzheimer's disease and vascular dementia), whether risk is altered by drinking pattern or beverage type, and whether associations may be accounted for by confounding due to baseline level of cognitive function.

Heavy levels of alcohol consumption also cause dementia through two other diseases: alcohol-related dementia and Wernicke-Korsakoff syndrome[45]. The distinction between these conditions is not fully elucidated, and so they are sometimes grouped as 'alcohol-related brain damage'. An Australian autopsy study estimated a prevalence of Wernicke-Korsakoff syndrome of 1.1%, and most cases were in people with a history of alcoholism[26]. Only 16% of cases were diagnosed while the person was alive. Compared to dementia caused by Alzheimer's disease, patients with these conditions are more likely to be male and younger[46]. The level of alcohol consumption required to cause either condition remains unclear, but approximately 70-84 grams of ethanol per day or above over an extended period has been shown to be sufficient to cause cognitive deficits[45]. There is evidence that abstinence from alcohol halts or even partially reverses cognitive decline for both conditions[45]. Further areas for research include how risk is influenced by different patterns of drinking such as heavy episodic drinking, duration of alcohol abuse and withdrawal periods.

Causal mechanisms

The antioxidant action of flavonoids such as polyphenols and resveratrol present in red wine have been proposed to contribute to the potential protective mechanism of alcohol and dementia by inhibiting the aggregation of amyloid-β plaque in the brain and therefore preventing neurodegeneration[41]. Additionally, alcoholic beverages contain fulvic acid which may prevent τ protein aggregation, which is seen in Alzheimer's disease pathology[41]. Proposed mechanisms for the harmful effects of heavy alcohol consumption on Alzheimer's disease are via damage to cholinergic neurons, vascular changes or nutritional deficiencies which affect cognitive function[41]. The suggested mechanism for the association of heavy drinking with increased risk of vascular dementia is through an effect on cardiovascular disease, including increased risk of hypertension and haemorrhagic stroke[44]. Alcohol-related dementia is caused by the neurotoxic effects of heavy alcohol consumption while Wernicke-Korsakoff syndrome is caused by vitamin B_1 deficiency that often accompanies heavy alcohol consumption[45].

Neuropsychiatric conditions (ICD-10: F10; 32-33; 34.1; G31.2; 40-41)

Burden in Australia

A variety of neuropsychiatric conditions are associated with alcohol consumption, including mental and behavioural disorders, depression, degeneration of the nervous system and epilepsy[3, 13]. The prevalence of alcohol use disorders (comprising alcohol dependence and harmful use of alcohol) in Australia was estimated to be 5.0% for men and 2.1% for women in 2010[2]. It was estimated that 380 deaths from neuropsychiatric conditions in Australia in 2010 were caused by alcohol consumption, including 310 deaths due to mental and behavioural disorders due to use of alcohol and 66 (22%) of the 294 epilepsy deaths[5, 6]. It was estimated that 13% of the burden of epilepsy in Australia in 2011 was attributable to alcohol consumption[7].

Epidemiology

Alcohol use disorders occur when an individual displays characteristics of alcohol dependence such as withdrawal symptoms, or characteristics of alcohol abuse including interference with work, interference with interpersonal relationships, and engagement in risky activities such as drink driving or unsafe sex[47]. Prior to 2013, alcohol dependence and alcohol abuse were considered separate disorders. Alcohol use disorders are associated with many other mental health conditions, including substance abuse, depression, anxiety, phobias, panic disorder and lower social and emotional functioning[48]. There are also socio-demographic risk factors for alcohol use disorder, including younger age, being male, having lower household income and not being married or living with a partner[48]. In particular, heavy alcohol consumption is associated with major depressive disorder, however it remains unknown whether this is due to causation, reverse-causation and/or other factors such as genetic vulnerability[3, 49, 50]. When alcohol use disorder and major depressive disorder co-occur in an individual, there is a higher risk of low global functioning, alcohol dependence and suicide attempt than for either condition alone[51].

Heavy alcohol consumption has been shown to cause neurodegeneration at multiple sites in the brain, particularly the frontal lobes (responsible for memory, temporal ordering, attention and judgement), and in both grey and white matter[52]. A 30-year longitudinal study found that both moderate (≥ 7 and < 14 drinks per week) and heavier drinking were associated with decline in lexical fluency, a measure of cognitive ability[53]. This study also reported a significantly higher risk of hippocampal atrophy in those consuming ≥ 14 drinks per week. Further, a dose-response relationship has been demonstrated for alcohol consumption and risk of epilepsy, with an estimated lag time between exposure and outcome of ten years[3]. Importantly, abstinence from alcohol consumption can partially reverse neurodegeneration and improve cognitive deficits[52], and withdrawal from alcohol consumption is associated with non-epileptic seizures[49].

Causal mechanisms

Potential mechanisms by which heavy alcohol consumption causes depression include its adverse effects on interpersonal relationships and employment, genetic susceptibility for both alcohol use disorders and depression, and alcohol-induced biochemical changes, such as a disruption to folate metabolism which can lead to depression[50]. The mechanism by which alcohol consumption causes neurodegeneration is through cellular atrophy and death, and through inhibition of new cell generation caused primarily by oxidative stress in the brain associated with acute alcohol intoxication[52]. Finally, the proposed mechanisms by which alcohol consumption causes epilepsy are via a 'kindling' effect where repeated bouts of heavy drinking lower the threshold for epileptic seizures, as well as an increase in head trauma associated with drinking, cerebral atrophy, neurotransmitter changes, ionic balance disturbances, lesions and cerebrovascular infarctions[3, 49].

Cardiovascular disease (ICD-10: G45-46; I00-99)

Burden in Australia

Cardiovascular disease (CVD) was responsible for 15% of the total burden of disease in Australia in 2011[7], 5% of which was attributable to alcohol consumption in 2011[7]. Of all deaths in Australia in 2015, CVD was a contributing cause towards 87,385 (55%) deaths, including 45,446 (29%) deaths where CVD was the underlying cause[4] (including 19,777 ischaemic heart disease, 10,869 cerebrovascular disease, 14,800 other). It has been estimated that a net 356 (0.8%) of the 45,576 CVD deaths in 2010 were caused by alcohol consumption[5, 6].

Epidemiology

Alcohol consumption has a J-shaped association with prevalence of a range of cardiovascular risk factors (including hypertension, coronary calcification and triglyceride levels) and with outcomes, such as peripheral artery disease, ischaemic heart disease, myocardial infarction, congestive heart failure, Raynaud's phenomenon and ischaemic stroke[18, 54, 55]. This means that low-volume drinking is associated with lower risk and heavy drinking with higher risk compared to non-drinking. Relative risks from a systematic review and meta-analysis for drinking 2.5 to 14.9 grams of ethanol per day compared to non-drinking were 0.75 (0.65-0.88) for coronary heart disease and 0.80 (0.74-0.87) for stroke[54]. Heavy drinking (greater than 60 grams per day) was associated with relative risks of 0.76 (0.52-1.09) and 1.62 (1.32-1.98) for coronary heart disease and stroke respectively. The association of moderate drinking with dysrhythmia and haemorrhagic stroke is inconclusive, however heavier drinking is associated with increased risk[13, 56]. It has been reported that the protective effects of moderate drinking on CVD persist whether or not ex-drinkers are included in the reference group[13, 54]. The apparent cardiovascular benefits of moderate alcohol consumption are greater in those with existing coronary heart disease and/or diabetes, however there is still some evidence of protection for persons without these conditions[18].

Comparable findings have been observed regarding cardiovascular mortality. A systematic review and meta-analysis found that alcohol consumption reduced the risk of death from CVD (> 0 and ≤ 60 grams per day), coronary heart disease (≥ 2.5 grams per day) and stroke (≥ 2.5 and < 15 grams per day), when compared to non-drinkers[54]. When the analysis examined all drinkers combined compared to lifetime abstainers, the reduced risk for CVD and coronary heart disease remained, while an increased risk was found for stroke mortality. Systematic reviews and meta-analyses have also examined the effect of moderate alcohol consumption on all-cause mortality in patients with existing CVD, coronary artery disease and hypertension, finding reduced risk in each of these cases[57-59]. In all three reviews former drinkers were included in the control group, and so these estimates could be biased by the 'sick-quitter effect'.

Pattern of drinking (e.g. number of drinks per occasion) appears to have independent effects on CVD over and above the total amount of alcohol consumed. Specifically, regular daily alcohol consumption is associated with greater cardiovascular benefits compared to more occasional consumption, and consuming alcohol before or during a meal may increase the protective effects of moderate drinking[18]. Heavy episodic drinking (i.e. consuming many drinks on one occasion) is associated with increased risk of ischaemic heart disease, myocardial infarction, ischaemic stroke and haemorrhagic stroke compared to non-drinkers or to those who consume the same quantity of alcohol spread over a greater number of occasions[13, 18, 55]. A systematic review and meta-analysis found that among drinkers with an average daily alcohol consumption of less than 30 grams per day, heavy episodic drinkers had a relative risk of ischemic heart disease of 1.75 (1.36-2.25) compared to persons who did not engage in heavy episodic drinking[55].

The relationship between temporal changes in alcohol consumption and risk of CVD has also been investigated. A recent cohort study examined change in alcohol consumption over time and risk of coronary heart disease[60]. It found that postmenopausal women who increased their alcohol consumption over a five year period had a lower risk of coronary heart disease after adjusting for

total alcohol consumption at baseline, while those who decreased their alcohol consumption had no significant difference in risk.

However, there is controversy regarding the quantification of cardiovascular benefits related to low-volume alcohol consumption, and to what extent these apparent benefits may be explained by poorly selected control groups, misclassification of alcohol consumption, confounding or other factors[18, 19]. Of particular concern is the 'sick-quitter effect' and confounding by illness present at baseline, as illnesses can be strongly associated with both drinking habits and cardiovascular outcomes[61]. A large American study provided evidence that confounding by socio-demographic factors and health status may bias risk estimates for CVD, because low-volume drinkers were less likely to have a low household income, be unemployed, obese, have hypertension or poor general health status compared to non-drinkers[62]. As a result, studies that have used a reference group of non-drinkers may have overestimated the protective effects between low-volume drinking and CVD. An analysis of the same study accounted for a variety of socio-demographic and health-related variables, such as employment status, marijuana use, depression and distress, reported that accounting for these factors eliminated the protective association of low-volume drinking on "heart problems" and hypertension, when compared to lifetime abstainers[22].

Another factor which could explain protective associations for CVD is the exclusion of participants with health conditions at baseline. This may induce selection bias in studies of CVD (and other health outcomes), which can potentially create spurious J-shaped associations where the underlying relationship is linear[63, 64]. This is because the participants who remain in the cohort may have an uneven distribution of CVD risk factors other than alcohol consumption, which has the potential to cause confounding.

There is also evidence that measuring alcohol consumption over multiple time points results in higher estimates of the risk of arterial stiffness in relation to heavy drinking, compared to measuring only recent alcohol consumption[65]. In addition to mitigating bias from the 'sick-quitter effect', the

measurement of alcohol consumption over multiple time points prevents bias from regression dilution which can occur in studies measuring alcohol consumption at a single time point[65]. Regression dilution bias refers to a situation where measurement error in an exposure can cause a widened distribution of exposure values, resulting in a fitted regression line with a lower gradient and thereby biasing estimates of effect towards the null[66]. Averaging measurements of exposure at multiple time points reduces measurement error and therefore mitigates this bias.

Finally, the possibility that alcohol industry funding may have influenced estimates of effect for drinking and CVD has also been examined. A systematic review and meta-analysis found that studies with evidence of industry funding are more likely to report a protective effect of drinking on stroke incidence compared to studies without evidence of industry funding, but not for other types of CVD[67].

It is possible that bias may also influence risk estimates for pattern of drinking, particularly the apparent inverse association of frequent low-volume drinking with CVD. In the aforementioned large American study, among low-volume drinkers, infrequent drinkers were more likely to have 13 socio-demographic and health-related risk factors compared to frequent drinkers, including low household income, no health insurance, smoking, obesity and physical inactivity. This indicates that confounding may account for the apparent protective associations observed between frequent drinking and CVD, rather than alcohol consumption itself[68].

Overall, the Australian alcohol guidelines consider the evidence for a protective effect with low-volume drinking too uncertain to make specific claims about potential cardiovascular health benefits, and state that few persons below the age of 40 years would benefit[1]. There is a clear need for further research to clarify whether low-volume drinking and greater drinking frequency causally lower CVD risk, and whether past findings in prospective cohort studies are biased. A randomised controlled trial of low-volume drinking and risk of chronic disease could address this issue conclusively[69].

Causal mechanisms

If causal, the protective association with low-volume drinking is proposed to be primarily attributable to mechanisms known to reduce risk of heart disease such as, increased high density lipoprotein (HDL) cholesterol, decreased low density lipoprotein (LDL) cholesterol, increased insulin sensitivity, reduced atherosclerotic plaque formations and possible anti-coagulant effects including reduced fibrinogen levels[1, 18, 70, 71], while decreased inflammation perhaps has a minor role[18]. A systematic review and meta-analysis of randomised controlled trials examined the effect of moderate drinking on 13 biomarkers associated with CVD risk[71]. It found that alcohol consumption significantly raised HDL cholesterol, apolipoprotein A1 and adiponectin and lowered fibrinogen levels – all factors associated with lower risk of CVD. There was no significant association with LDL cholesterol or eight other cardiovascular risk markers[71]. Overall, for 9 of 13 cardiovascular risk markers examined there was no association, and there was significant heterogeneity in the HDL cholesterol and apolipoprotein A1 meta-analyses. Moderate alcohol consumption has also been associated with lowered homocysteine, a risk factor for CVD[72]. The potential cardiovascular benefits of alcohol are believed to be conferred by ethanol itself rather than other components within alcoholic beverages[18]. Red wine should theoretically offer additional cardiovascular benefit due to its relatively high levels of bioflavonoids (molecules with antioxidant, antiplatelet and other effects which protect against CVD) compared to other beverage types, however overall quantity and frequency of alcohol consumption appear to have a greater association with risk than type of beverage[18]. Increased clotting, hypertension, ventricular fibrillation and elevated homocysteine levels as well as cardiomyopathy caused by a direct toxic effect of alcohol on heart muscle are proposed as means for the harmful effects of heavy drinking[13, 72-74].

Liver disease (ICD-10: K70-77)

Burden in Australia

Of all deaths in Australia in 2015, liver disease was a contributing cause towards 4945 (3.1%) deaths, including 1857 (1.2%) deaths where liver disease was the underlying cause[4] (891 from alcoholic liver disease, 455 from fibrosis and cirrhosis of the liver, and 511 from other causes). This does not include the 1820 deaths due to liver cancer for which liver disease is a risk factor[75]. It was estimated that 24% of the burden of chronic liver disease in 2011 was attributable to alcohol consumption[7], while 746 (47%) of the 1592 liver disease deaths in 2010 were attributable to alcohol consumption[5, 6]. It is notable that there is a large difference in burden from liver disease by Indigenous status, as Indigenous Australians have a liver disease mortality rate approximately four times that of non-Indigenous Australians[75].

Epidemiology

Alcoholic liver disease is a spectrum of conditions progressing from alcoholic fatty liver to alcoholic hepatitis, liver fibrosis and ultimately liver cirrhosis[76, 77]. More than one condition may be present at once. Elevated risk is seen at levels of alcohol consumption greater than 60 g/day in men and greater than 20 g/day in women, however the precise threshold at which risk increases is unknown. It has been reported in a meta-analysis that the association between drinking and liver cirrhosis is stronger when the outcome is mortality rather than morbidity[78]. Beer and spirit consumption may promote alcoholic liver disease to a greater extent than wine[76]. Pattern of drinking is also important, as drinking outside of meal times as opposed to with meals, and heavy episodic drinking of at least five drinks in one occasion for men and four drinks for women also increase risk. A cohort study found that after adjusting for total alcohol consumption, a higher drinking frequency in days per week was associated with increased risk of alcoholic liver cirrhosis in men but not in women[79]. Continued alcohol consumption worsens already existing liver disease and reduces survival[13].

Although alcohol consumption is a necessary cause of alcoholic liver disease, the dose-response relationship is complex and is influenced by a number of confounding factors[76]. In the presence of alcohol consumption, other factors that increase risk include fat intake, excess body weight, smoking, genetic factors, haemochromatosis, HIV and viral hepatitis from hepatitis B and C viruses (HBV, HCV)[76, 77]. There appears to be a multiplicative effect on risk between alcohol consumption and HCV-induced hepatitis, and the threshold at which alcohol consumption begins to increase risk may be lower in those with HCV-induced hepatitis. There are also multiplicative effects on risk between alcohol consumption and obesity, HBV, HIV, haemochromatosis and non-alcoholic fatty liver disease[77]. More research is needed to better understand the interaction between alcohol consumption and these risk factors[77].

Causal mechanisms

There are several mechanisms by which alcohol consumption causes liver disease, acting at multiple stages along the spectrum from alcoholic fatty liver to liver cirrhosis. Drinking contributes to alcoholic fatty liver by increasing lipogenesis and decreasing fatty acid oxidation, through inhibiting enzyme activity and modifying transcription factors associated with lipid metabolism in the liver[77]. Regarding alcoholic hepatitis, alcohol contributes by increases the permeability of the intestines to lipopolysaccharides which promote inflammation in the liver, the infiltration of immune cells into the liver, and the metabolism of ethanol forms acetaldehyde and reactive oxygen species that injure hepatocytes[77]. The presence of inflammation stimulates hepatic stellate cells to produce excess extracellular matrix proteins, which cause fibrosis. Drinking also contributes to fibrosis directly by inhibiting anti-fibrotic factors. Over time fibrosis can develop into cirrhosis and ultimately hepatocellular carcinoma, and the continued consumption of alcohol after fibrosis has occurred, accelerates this process. Finally, alcohol consumption also prevents liver regeneration through the inhibition of hepatocyte proliferation.

Pancreatitis (ICD-10: K85-86.1)

Burden in Australia

Pancreatitis refers to inflammation of the pancreas. In 2015, acute pancreatitis was a contributing cause towards 369 (0.2%) Australian deaths, including 181 (0.1%) as an underlying cause of death[4]. The exact number of deaths due to chronic pancreatitis (ICD-10: 86.0-86.1) is not reported as Australian cause of death data is only available for integer ICD codes. Chronic pancreatic was therefore a contributing cause for up to 176 deaths, and an underlying cause for up to 35 deaths. It was estimated that 24% of the pancreatitis burden in 2011 was attributable to alcohol consumption[7], while 39 pancreatitis deaths in 2010 were attributable to alcohol consumption[5].

Epidemiology

Like liver disease, pancreatitis is considered to be a spectrum of conditions, with recurrent acute pancreatitis being a risk factor for chronic pancreatitis[80]. Chronic pancreatitis is in turn a risk factor for pancreatic cancer. A recent systematic review found that alcohol consumption is associated with risk of both acute and chronic pancreatitis, however the dose-response curves for acute pancreatitis differed by sex[81]. Alcohol consumption produced a linear increase in risk of acute pancreatitis in men with a relative risk of 1.89 (95% confidence interval: 1.25-2.86) at 50 g/day, but in women a J-shaped relationship was found with an association with decreased risk at levels of consumption below 40 g/day. There was a linear relationship for chronic pancreatitis for both sexes combined with a relative risk of 2.51 (1.74-3.61) at 50 g/day. For any pancreatitis, the relationship was linear increasing in men and J-shaped in women. There was low to moderate inter-study heterogeneity for acute pancreatitis in women, but moderate to high heterogeneity for chronic pancreatitis and acute pancreatitis in men. There is a possible interaction between alcohol consumption and choledocholithiasis (the presence of gallstones in the biliary tract) on risk of pancreatitis[81]. A smaller systematic review and meta-analysis found no effect for alcohol drinking overall vs non-drinking for either acute or chronic pancreatitis, but the one included primary study which examined

different levels of alcohol consumption found that heavy drinking was associated with a relative risk of 1.75 (1.11-2.75) for acute pancreatitis and 2.18 (1.19-3.98) for chronic pancreatitis[82]. Further research is needed to compare lifetime abstainers and ex-drinkers, and whether risk relationships differ by patterns of drinking[81].

Causal mechanisms

The hypothesised mechanism by which alcohol consumption causes acute pancreatitis is through oxidant stress, increased digestive and lysosomal enzyme synthesis, and the accumulation of cholesteryl esters and fatty acid ethyl esters (alcohol metabolites) in pancreatic acinar cells[83]. These materials destabilise lysosomes and zymogen granules, causing a decrease in digestive enzyme secretion and an increase in concentration of lysosomes and digestive enzymes in the cell. In this state the acinar cells are more susceptible to alcoholic acute pancreatitis however the specific trigger for this remains unknown, and may be related to genetic polymorphisms in enzymes that metabolise ethanol[83, 84]. During acute pancreatitis, acinar cells undergo necrosis and release cytokines that stimulate pancreatic stellate cells to overproduce extracellular matrix proteins, which cause pancreatic fibrosis[83]. Separate to this process, acetaldehyde from the metabolism of ethanol also stimulates the stellate cells directly through oxidant stress. The accumulation of pancreatic fibrosis with repeated episodes of acute pancreatitis then increases risk of chronic pancreatitis. Factors that may promote progression to chronic pancreatitis include continued alcohol consumption, smoking, number and severity of acute pancreatitis episodes, the hereditary pancreatitis gene PRSS1 and other genetic polymorphisms[84].

Other digestive system diseases (ICD-10: K00-69; 80-83; 86.2-93)

Burden in Australia

Apart from liver disease and pancreatitis, a range of other diseases of the digestive system are associated with alcohol consumption. Other digestive system diseases accounted for 3594 to 3629 (2.3%) deaths in Australia in 2015[4]. The exact number of deaths is not reported as Australian cause of death data is only available for integer ICD codes. The most common causes of death in this group were paralytic ileus/intestinal obstruction, vascular disorders of the intestine and diseases of the gallbladder/biliary tract.

Epidemiology

A diverse group of conditions is associated with alcohol consumption, comprising diseases of the oesophagus including gastro-oesophageal reflux disease, diseases of the stomach including ulceration and alcoholic gastritis, diseases of the appendix, diseases of the intestines including diverticular disease and irritable bowel syndrome, diseases of the anus and rectum including haemorrhoids, diseases of the peritoneum, and intestinal malabsorption[3, 85]. For most conditions alcohol is associated with increased risk, however there is a possible inverse association between alcohol consumption and gallbladder and biliary tract disease[3]. Despite previous reports of an inverse association between alcohol consumption and risk of gallstone formation, a recent meta-analysis found no significant association[86, 87].

Causal mechanisms

Some of the mechanisms by which alcohol consumption harms the digestive system (aside from harming the liver and pancreas) include ethanol and acetaldehyde causing mucosal inflammation and erosion in the oesophagus, stomach and intestines; reduced oesophageal motility; decreased lower oesophageal sphincter pressure resulting in reflux, changed gastric acid secretion; altered gut microflora and impaired gut mucosal immune system; and altered proliferation of epithelial cells in

the rectum and interference with the absorption of certain vitamins, monosaccharides, amino acids and lipids in the intestines[85]. A proposed mechanism for the protective effect of alcohol consumption on gallstone formation is via increased serum high-density lipoprotein cholesterol which is associated with lower risk[86].

External causes of morbidity and mortality (ICD10: V01-Y98)

Burden in Australia

A range of injuries and other external causes of morbidity and mortality are attributable to alcohol, including interpersonal violence, falls, motor vehicle accidents, self-harm and suicide, poisoning, suffocation, drownings and fires[1, 2]. Injuries were responsible for 9% of the total burden of disease in Australia in 2011[7]. Of all deaths in Australia in 2015, external causes were a contributing cause of 17,301 (11%) deaths, including 10,573 (6.6%) deaths where external causes were the underlying cause[4]. The most common causes were intentional self-harm (most common cause in men), accidental fall (most common cause in women), transport accident and accidental poisoning. It was estimated that 1495 injury deaths in 2010 were caused by alcohol consumption[5].

Alcohol contributed an estimated 21% of the burden from injury including 23% of the burden from suicide and self-inflicted injury in 2011[7]. Alcohol consumption has been attributed to 33% of male, and 11% of female, motor vehicle deaths in Australia, while the corresponding figures for male and female pedestrian deaths were 40% and 17% respectively[1]. Alcohol has also been attributed to 44% of fire deaths, 34% of drowning deaths and 27% of violence-related deaths in Australia[88]. There is also a significant burden in the form of hospitalisation for alcohol-related injury and assault. In Australia in 2013, 10% of men and 5% of women reported being hospitalised as a result of an alcohol-related injury during their lifetime[89].

Epidemiology

Men are at higher risk of alcohol-related injuries than women at all levels of alcohol consumption[1]. For both motor vehicle accident injuries (24% increase in odds per 10 grams) and non-motor vehicle injuries (30% increase in odds per 10 grams), there is an exponential dose-response relationship between acute alcohol consumption and risk of injury[90]. Alcohol is unique as a lifestyle risk factor in that it can impact the health of the user's family and friends[1]. It is known that alcohol

consumption increases the risk of domestic violence in men already predisposed to this behaviour. There is also serious harm to children who witness or experience alcohol-related domestic violence. Alcohol consumption can also injure persons other than the drinker through its effect on risk of non-domestic violence and motor vehicle accidents[13].

Methodological issues regarding alcohol consumption and injury have been reported in the literature. There is potential for the relationship between drinking and injury to be under- or overestimated due to study methodologies relying on self-reported alcohol consumption[1]. Further, unlike for the diseases discussed in the other sections of this chapter, studies that measure acute alcohol consumption provide better estimates of injury risk than studies measuring usual alcohol consumption[90].

Causal mechanisms

The mechanism by which alcohol consumption increases the risk of injury is through its depressant effect on the central nervous system, inhibiting coordination, balance, reaction time and the ability to resolve conflicts while promoting drowsiness, disinhibition, risk-taking and aggressive behaviour[1]. Engaging in risky activities while drinking is not uncommon in Australia. In 2013 12% of people reported driving a vehicle while under the influence of alcohol in the previous 12 months, 8% went swimming, and 2% operated a boat or heavy machinery[89]. Heavy alcohol consumption also decreases bone density which increases the likelihood of fractures when falls occur[91].

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Appendix B – Additional Tables for Chapter 4

Table B.1. Socio-demographic characteristics at baseline by alcohol consumption in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Alcoholic drinks per week				
Variable	**n**	**Mean (SD)**	**Median (Q1-Q3)**	**Non-drinker[a] (%)**	**≥ 1, ≤ 14 (%)**	**> 14 (%)**
Sex						
Men	123,769	9.9 (11.9)	6 (1-14)	23.3	51.8	23.4
Women	143,025	4.4 (6.2)	2 (0-7)	40.8	51.0	6.0
Age (years)						
≥ 45, < 55	77,852	7.1 (9.8)	4 (0-10)	29.5	54.9	14.4
≥ 55, < 65	85,822	7.6 (10.2)	4 (0-10)	30.0	52.8	15.8
≥ 65, < 75	58,018	7.1 (9.7)	4 (0-10)	34.3	49.0	14.6
≥ 75, < 85	36,853	5.8 (8.3)	2 (0-8)	39.7	46.7	10.2
≥ 85	8,249	4.0 (6.4)	0 (0-7)	48.7	41.1	5.2
Remoteness						
Major city	139,090	6.6 (9.2)	3 (0-10)	33.3	51.7	12.9
Inner regional	92,735	7.3 (9.9)	4 (0-10)	31.6	51.7	15.2
Outer regional	27,295	7.4 (10.7)	4 (0-10)	34.4	48.4	15.5
Remote	2,539	8.0 (11.4)	4 (0-10)	32.4	48.1	16.9
Missing	5,135	7.4 (9.9)	5 (0-10)	28.2	56.1	14.6
Annual household income[b]						
< $30,000	78,021	5.9 (9.9)	2 (0-8)	43.2	42.7	11.6
≥ $30,000, < $70,000	68,184	7.7 (10.0)	5 (0-10)	28.2	54.7	16.1
≥ $70,000	62,780	8.7 (9.7)	6 (2-12)	18.8	61.6	19.0
Missing	57,809	5.6 (8.5)	2 (0-8)	38.8	48.2	9.6
Highest level of education						
No school certificate	31,367	5.6 (9.9)	1 (0-7)	46.9	38.4	11.1
School certificate	58,700	6.2 (9.3)	3 (0-10)	38.1	48.1	11.9
Higher school certificate	26,059	7.4 (10.1)	4 (0-10)	31.4	51.3	15.3
Trade or apprenticeship	29,594	9.2 (12.0)	5 (0-14)	27.8	49.6	20.9
Certificate or diploma	55,188	6.7 (8.9)	4 (0-10)	30.9	55.0	13.0
University degree or higher	61,521	7.4 (8.8)	5 (1-10)	24.5	59.6	15.0
Missing	4,465	5.9 (10.1)	2 (0-7)	38.8	40.7	10.0
Health insurance status						
None	40,211	7.2 (10.9)	3 (0-10)	36.1	46.8	15.1
Health care concession card	47,654	5.8 (10.3)	1 (0-7)	46.7	38.5	11.4
DVA white or gold card	4,802	7.1 (10.6)	3 (0-10)	35.8	46.8	14.1
Private, no extras	130,810	7.3 (9.1)	5 (0-10)	26.8	57.2	14.8
Private, with extras	38,233	7.1 (9.1)	4 (0-10)	30.1	54.5	14.0
Missing	5,084	6.1 (10.7)	2 (0-8)	41.8	39.9	11.4
Married/living with partner						
No	66,548	6.1 (10.3)	2 (0-8)	41.2	44.1	11.8
Yes	198,625	7.2 (9.4)	4 (0-10)	29.9	53.9	14.8
Missing	1,621	8.2 (10.5)	5 (0-12)	28.2	47.8	17.9

[a]< 1 alcoholic drink per week. [b]Pre-tax annual household income from all sources in Australian dollars. [c]Cell contains < 5 participants. Missing alcohol data not shown. SD, Standard Deviation. Q1, 25th percentile. Q3, 75th percentile. DVA, Department of Veterans' Affairs. NZ, New Zealand. UK, United Kingdom. USA, United States of America.

Table B.1. (Continued)

		Alcoholic drinks per week				
Variable	**n**	**Mean (SD)**	**Median (Q1-Q3)**	**Non-drinker[a] (%)**	**≥ 1, ≤ 14 (%)**	**> 14 (%)**
Country of birth						
Australia	199,875	7.3 (9.9)	4 (0-10)	31.9	51.7	14.9
Canada/Ireland/NZ/UK/USA	33,149	7.8 (9.7)	5 (0-10)	26.2	56.6	15.8
Other country	31,427	4.2 (7.3)	1 (0-6)	44.5	44.4	6.8
Missing	2,343	6.5 (9.8)	3 (0-10)	34.9	43.8	12.0
Years lived in Australia						
< 10	3,063	4.8 (7.2)	2 (0-7)	41.9	46.5	8.8
≥ 10 and < 20	6,362	4.2 (7.3)	1 (0-6)	46.2	42.7	7.4
≥ 20 and < 30	10,029	5.5 (8.5)	2 (0-8)	38.6	48.4	10.2
≥ 30 and < 40	13,254	6.7 (9.3)	4 (0-10)	32.1	52.1	13.3
≥ 40	28,771	6.6 (9.1)	4 (0-10)	32.0	53.5	12.3
Born in Australia	199,875	7.3 (9.9)	4 (0-10)	31.9	51.7	14.9
Missing	5,440	6.0 (9.1)	2 (0-8)	35.5	45.4	10.7
Language spoken at home						
English only	241,352	7.3 (9.8)	4 (0-10)	31.2	52.3	14.9
Other language	25,439	3.9 (7.3)	1 (0-5)	46.8	42.4	6.1
Missing	< 5	-[c]	-[c]	-[c]	-[c]	-[c]
Total	266,794	7.0 (9.7)	4 (0-10)	32.7	51.4	14.0

Table B.2. Alcohol consumption by key behavioural and physical covariates at baseline in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Alcoholic drinks per week				
Variable	**n**	**Mean (SD)**	**Median (Q1-Q3)**	**Non-drinker[a] (%)**	**≥ 1, ≤ 14 (%)**	**> 14 (%)**
Smoking status and dose (cigarettes/day)						
Never smoker	152,066	5.0 (7.4)	2 (0-7)	38.1	51.8	7.9
Ex-smoker; ≤ 15	46,046	8.3 (9.2)	6 (1-12)	23.1	58.2	17.6
Ex-smoker; > 15	46,813	10.7 (12.5)	7 (1-15)	24.6	47.8	26.5
Ex-smoker; Missing	1,707	8.7 (10.2)	6 (1-14)	23.4	52.1	18.5
Current smoker; ≤ 15	9,273	8.1 (10.9)	4 (0-12)	32.9	46.3	18.8
Current smoker; > 15	9,612	11.6 (16.3)	5 (0-18)	34.0	36.1	27.6
Current smoker; Missing	419	8.3 (12.5)	4 (0-10)	32.9	40.8	16.2
Missing	858	7.5 (10.4)	4 (0-10)	32.3	47.0	16.6
Height (cm)						
Male; < 175	46,796	9.0 (11.5)	5 (0-14)	27.5	50.1	20.6
Male; ≥ 175, < 180	33,348	10.3 (11.9)	7 (1-15)	21.3	52.7	24.8
Male; ≥ 180	38,732	10.7 (12.3)	7 (2-15)	19.7	53.2	26.1
Female; < 160	45,606	3.8 (5.9)	1 (0-6)	46.8	45.6	4.7
Female; ≥ 160, < 165	38,797	4.5 (6.2)	2 (0-7)	39.8	52.4	6.0
Female; ≥ 165	50,927	5.1 (6.5)	2 (0-8)	35.5	55.6	7.3
Missing	12,588	5.8 (8.5)	2 (0-8)	37.5	47.8	10.4
Body mass index (kgm^{-2})						
Underweight (< 18.5)	3,406	5.4 (9.0)	4 (0-10)	31.5	54.7	12.0
Normal range (≥ 18.5, < 25.0)	90,787	6.6 (8.8)	2 (0-7)	43.8	44.3	9.0
Overweight (≥ 25.0, < 30.0)	97,404	7.8 (10.0)	5 (0-11)	28.8	52.9	16.7
Obese (≥ 30.0)	55,056	6.7 (10.6)	2 (0-10)	38.7	45.3	14.2
Missing	20,141	5.9 (9.0)	2 (0-8)	38.5	46.8	10.8
Physical activity (min/week[b])						
Inactive (0)	15,201	5.6 (10.5)	0 (0-7)	50.1	35.6	11.5
Insufficient (> 0, < 150)	43,843	6.1 (9.6)	2 (0-8)	38.2	47.4	11.8
Sufficient (≥ 150, < 300)	40,840	6.8 (9.5)	4 (0-10)	32.1	52.8	13.5
High (≥ 300)	160,024	7.4 (9.6)	5 (0-10)	29.4	54.1	15.2
Missing	6886	6.0 (9.6)	2 (0-8)	37.7	39.7	10.2
Total	266,794	7.0 (9.7)	4 (0-10)	32.7	51.4	14.0

[a]< 1 alcoholic drink per week. [b]Time spent in vigorous physical activity was given twice the weighting of lower intensity physical activity. Missing alcohol data not shown. SD, Standard Deviation. Q1, 25th percentile. Q3, 75th percentile.

Table B.3. Alcohol consumption by sun exposure covariates at baseline in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Alcoholic drinks per week				
Variable	**n**	**Mean (SD)**	**Median (Q1-Q3)**	**Non-drinker[a] (%)**	**≥ 1, ≤ 14 (%)**	**> 14 (%)**
Time outdoors (hours/day)						
< 2	70,154	5.5 (8.1)	2 (0-8)	38.1	50.5	9.7
≥ 2, < 4	98,123	6.7 (9.1)	4 (0-10)	32.1	53.2	13.1
≥ 4, < 6	46,526	7.9 (10.1)	5 (0-12)	29.2	52.4	16.9
≥ 6	40,587	9.3 (12.0)	6 (0-14)	27.1	49.9	21.2
Missing	11,404	6.5 (10.3)	2 (0-10)	38.7	42.2	12.7
Skin tone						
Fair	187,290	7.0 (9.7)	4 (0-10)	32.6	51.5	14.3
Olive	70,764	7.0 (9.6)	4 (0-10)	31.5	52.6	14.0
Brown or black	5,252	4.8 (9.5)	0 (0-6)	48.0	36.3	9.4
Missing	3,488	6.3 (10.3)	2 (0-9)	37.4	45.1	11.2
Total	266,794	7.0 (9.7)	4 (0-10)	32.7	51.4	14.0

[a]< 1 alcoholic drink per week. Missing alcohol data not shown. SD, Standard Deviation. Q1, 25th percentile. Q3, 75th percentile.

Table B.4. Alcohol consumption by dietary factors at baseline in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Alcoholic drinks per week				
Variable	**n**	**Mean (SD)**	**Median (Q1-Q3)**	**Non-drinker[a] (%)**	**≥ 1, ≤ 14 (%)**	**> 14 (%)**
Fruit consumption[b]						
< 1 serve/day	25,200	10.2 (13.6)	6 (0-14)	31.2	42.4	24.3
≥ 1, < 2 serves/day	85,431	8.0 (10.3)	5 (0-12)	29.2	51.9	17.3
≥ 2 serves/day	149,468	5.8 (8.2)	3 (0-8)	34.9	52.9	10.5
Missing	6,695	7.2 (10.5)	3 (0-10)	33.9	45.5	14.3
Vegetable consumption[c]						
< 3 serves/day	95,126	7.6 (10.6)	4 (0-10)	32.4	49.3	16.4
≥ 3, < 5 serves/day	81,074	6.8 (9.2)	4 (0-10)	31.2	53.7	13.5
≥ 5 serves/day	83,871	6.4 (9.0)	3 (0-10)	34.1	52.0	12.0
Missing	6,723	6.6 (10.0)	3 (0-10)	36.0	45.3	12.5
Fibre intake[d]						
< 7 serves/week	37,215	8.6 (12.4)	4 (0-12)	33.8	45.2	19.5
≥ 7, < 14 serves/week	74,569	6.7 (8.9)	4 (0-10)	31.4	54.3	12.9
≥ 14, < 21 serves/week	63,067	6.8 (8.8)	4 (0-10)	30.1	55.4	13.0
≥ 21 serves/week	66,427	6.6 (9.2)	3 (0-10)	34.8	50.3	13.4
Missing	25,516	6.8 (10.2)	3 (0-10)	35.5	45.1	13.6
Red meat consumption						
0 times/week	14,516	3.9 (7.5)	0 (0-6)	51.6	38.7	6.3
> 0, ≤ 2 times/week	80,151	5.9 (8.4)	3 (0-8)	34.7	52.6	10.7
> 2, ≤ 5 times/week	137,955	7.4 (9.7)	4 (0-10)	29.9	53.3	15.3
> 5 times/week	28,619	9.3 (12.5)	5 (0-14)	30.5	46.3	21.6
Missing	5,553	6.3 (9.4)	3 (0-10)	36.5	45.7	11.8
Processed meat consumption						
0 times/week	88,879	5.4 (8.1)	2 (0-7)	39.2	49.2	9.1
> 0, ≤ 1 times/week	87,548	7.0 (9.2)	4 (0-10)	30.1	54.7	13.9
> 1, ≤ 2 times/week	43,270	8.0 (10.4)	5 (0-12)	28.9	52.1	17.5
> 2 times/week	41,525	9.3 (12.1)	6 (0-14)	27.6	49.2	21.7
Missing	5,572	6.2 (9.3)	3 (0-10)	36.6	45.5	11.4
Total	266,794	7.0 (9.7)	4 (0-10)	32.7	51.4	14.0

[a]< 1 alcoholic drink per week. [b]Serve = one medium piece, two small pieces or one cup of diced or canned fruit, excluding fruit juice. [c]Serve = half cup of cooked vegetables or one cup of raw vegetables. [d]Serve = slice or piece of brown/wholemeal bread or bowl of breakfast cereal per week. Missing alcohol data not shown. SD, Standard Deviation. Q1, 25th percentile. Q3, 75th percentile.

Table B.5. Alcohol consumption by female reproductive characteristics at baseline among women in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Alcoholic drinks per week				
Variable	**n**	**Mean (SD)**	**Median (Q1-Q3)**	**Non-drinker[a] (%)**	**≥ 1, ≤ 14 (%)**	**> 14 (%)**
Parity and age at first birth						
No children	15,632	5.5 (7.3)	3 (0-8)	37.5	51.4	9.5
1 child, < 25 years	3,414	4.6 (6.9)	1 (0-7)	44.5	45.5	7.5
1 child, ≥ 25 years	8,498	4.8 (6.8)	2 (0-7)	39.8	50.7	7.5
2 children, < 25 years	19,787	4.5 (6.4)	2 (0-7)	41.2	50.6	6.1
2 children, ≥ 25 years	27,087	4.9 (6.1)	3 (0-7)	34.4	57.8	6.4
≥ 3 children, < 25 years	40,105	3.7 (5.8)	1 (0-6)	47.1	45.9	4.5
≥ 3 children, ≥ 25 years	21,966	4.4 (5.8)	2 (0-7)	37.0	55.9	5.2
Missing	6,536	3.7 (5.9)	0.5 (0-6)	46.7	42.3	4.4
Breastfeeding time (months)						
Never breastfed	31,763	4.6 (6.8)	1.5 (0-7)	44.6	46.2	7.4
> 0, ≤ 12	59,404	4.5 (6.2)	2 (0-7)	40.4	51.3	6.0
> 12, ≤ 24	27,997	4.5 (6.0)	2 (0-7)	37.6	55.3	5.6
> 24	20,954	4.1 (5.6)	2 (0-6)	40.4	53.2	4.7
Missing	2,907	3.8 (6.0)	1 (0-6)	40.6	41.7	4.0
Menopausal status						
Pre-menopausal	17,936	4.9 (6.5)	3 (0-7)	34.9	56.5	7.0
Irregular periods	8,153	5.2 (6.8)	3 (0-8)	33.7	57.3	8.0
Post-menopausal	93,140	4.4 (6.1)	2 (0-7)	41.7	50.4	5.6
Missing	23,796	4.3 (6.4)	1 (0-7)	43.8	47.3	5.9
Hormonal contraceptive use						
Never user	29,673	2.9 (5.2)	0 (0-4)	55.2	37.7	3.0
Ever user	110,745	4.9 (6.4)	3 (0-7)	36.7	54.9	6.8
Missing	2,607	3.4 (5.9)	0 (0-5)	49.3	37.2	3.7
HRT use						
Never used	86,852	4.3 (6.2)	2 (0-7)	41.7	50.2	5.9
Formerly used	38,254	4.6 (6.2)	2 (0-7)	39.9	52.2	6.1
Current user	14,257	5.1 (6.5)	3 (0-7)	35.2	56.1	7.1
Missing	3,662	3.4 (5.7)	0 (0-5)	48.0	38.8	3.4
Total	143,025	4.4 (6.2)	2 (0-7)	40.8	51.0	6.0

[a]< 1 alcoholic drink per week. Missing alcohol data not shown. SD, Standard Deviation. Q1, 25th percentile. Q3, 75th percentile. HRT, Hormone Replacement Therapy.

Table B.6. Alcohol consumption by medical and health-related factors at baseline in the 45 and Up Study (2006-2009), New South Wales, Australia.

		Alcoholic drinks per week				
Variable	**n**	**Mean (SD)**	**Median (Q1-Q3)**	**Non-drinker[a] (%)**	**≥ 1, ≤ 14 (%)**	**> 14 (%)**
Bowel screening history[b]						
Not in last 10 years	135,599	6.7 (9.8)	3 (0-10)	34.6	50.1	13.3
Yes; ≥ 2, ≤ 10 years ago	56,529	7.2 (9.5)	4 (0-10)	31.2	52.8	14.6
Yes; < 2 years ago	62,351	7.5 (9.6)	5 (0-10)	29.1	54.1	15.6
Missing	12,315	6.5 (9.7)	3 (0-10)	36.7	46.0	12.3
Breast screening history[c]						
Not in last 10 years	18,545	4.1 (6.7)	1 (0-6)	46.4	44.7	6.2
Yes; ≥ 2, ≤ 10 years ago	47,659	4.3 (6.1)	2 (0-7)	42.8	49.4	5.5
Yes; < 2 years ago	68,665	4.7 (6.2)	2 (0-7)	37.2	54.9	6.4
Missing	8,156	3.8 (6.1)	1 (0-6)	46.5	42.3	4.8
Prostate screening history[d]						
Never	34,570	10.0 (12.9)	6 (0-14)	25.2	49.6	23.6
Yes; ≥ 1, ≤ 3 times	41,874	10.0 (11.7)	7 (1-14)	21.5	53.3	24.1
Yes; > 3 times	32,244	9.9 (11.0)	7 (1-14)	21.5	53.8	23.7
Yes; times missing	4,868	8.6 (11.3)	5 (0-14)	29.2	48.2	19.6
Missing	10,213	9.1 (11.9)	5 (0-14)	27.6	48.3	20.6
Aspirin use[e]						
No	208,806	7.0 (9.7)	4 (0-10)	32.1	52.0	14.0
Yes	57,962	6.9 (9.7)	4 (0-10)	34.6	49.1	14.1
Missing	26	2.9 (5.2)	0 (0-5)	57.7	30.8	-[f]
Self-rated overall health						
Excellent	38,887	7.1 (8.3)	5 (0-10)	24.9	61.0	13.0
Very good	95,001	7.3 (9.1)	5 (0-10)	28.0	56.1	14.7
Good	86,936	7.1 (10.2)	3 (0-10)	34.9	48.4	14.8
Fair	30,893	6.2 (11.0)	1 (0-8)	44.7	39.5	12.9
Poor	5,656	5.2 (11.4)	0 (0-6)	54.7	30.6	10.2
Missing	9,421	5.8 (9.6)	2 (0-8)	39.0	43.5	10.6
Physical functioning score						
≥ 75%	181,837	7.5 (9.6)	0 (0-5)	27.9	55.6	15.4
≥ 50%, < 75%	23,571	6.2 (10.2)	1 (0-7)	41.5	44.5	12.4
≥ 25%, < 50%	12,867	5.5 (9.9)	2 (0-8)	47.7	38.9	11.1
< 25%	8,450	4.5 (9.7)	5 (0-10)	56.6	31.7	8.5
Missing	31,170	6.0 (9.2)	2 (0-8)	38.3	45.3	11.1
Total	266,794	7.0 (9.7)	4 (0-10)	32.7	51.4	14.0

[a]< 1 alcoholic drink per week. [b]Faecal occult blood test, sigmoidoscopy or colonoscopy. [c]Breast screening mammogram; women only. [d]Prostate specific antigen blood test; men only. [e]Use in most of the previous 4 weeks. [f]Cell contains < 5 participants. Missing alcohol data not shown. SD, Standard Deviation. Q1, 25th percentile. Q3, 75th percentile.

Appendix C – Additional Tables for Chapter 6

Table C.1. Number of participants included in the Chapter 6 analyses by country and region of birth.

Region of birth	Country of birth	n	% of region	% of total
Australia		**199 908**	**100.0**	**75.7**
	Australia	199 900	100.0	75.7
	Norfolk Island	8	0.0	0.0
New Zealand		**5 069**	**100.0**	**1.9**
	New Zealand	5 069	100.0	1.9
Oceania		**887**	**100.0**	**0.3**
	Cook Islands	19	2.1	0.0
	Fiji	503	56.7	0.2
	French Polynesia	5	0.6	0.0
	Kiribati	6	0.7	0.0
	Nauru	-[a]	-[a]	-[a]
	New Caledonia	17	1.9	0.0
	Niue	5	0.6	0.0
	Papua New Guinea	205	23.1	0.1
	Samoa	51	5.7	0.0
	Solomon Islands	6	0.7	0.0
	Tonga	53	6.0	0.0
	Vanuatu	14	1.6	0.0
	Wallis and Futuna	-[a]	-[a]	-[a]
East Asia		**3 231**	**100.0**	**1.2**
	China	1 868	57.8	0.7
	Hong Kong	707	21.9	0.3
	Japan	221	6.8	0.1
	Macau	20	0.6	0.0
	South Korea	315	9.7	0.1
	Taiwan	100	3.1	0.0
Southeast Asia		**4 487**	**100.0**	**1.7**
	Brunei Darussalam	7	0.2	0.0
	Burma (Myanmar)	109	2.4	0.0
	Cambodia	94	2.1	0.0
	East Timor	31	0.7	0.0
	Indonesia	495	11.0	0.2
	Laos	83	1.8	0.0
	Malaysia	669	14.9	0.3
	Philippines	1 253	27.9	0.5
	Singapore	254	5.7	0.1
	Sri Lanka	530	11.8	0.2
	Thailand	130	2.9	0.0
	Viet Nam	832	18.5	0.3

[a]Censored due to < 5 participants, or if this value would enable calculation of value for another cell with < 5 participants.

Table C.1. (Continued)

Region of birth	Country of birth	n	% of region	% of total
Central & South Asia		**1 357**	**100.0**	**0.5**
	Afghanistan	46	3.4	0.0
	Armenia	13	1.0	0.0
	Bangladesh	70	5.2	0.0
	Georgia	-[a]	-[a]	-[a]
	India	1 130	83.3	0.4
	Kyrgyz Republic	-[a]	-[a]	-[a]
	Mongolia	-[a]	-[a]	-[a]
	Nepal	12	0.9	0.0
	Pakistan	81	6.0	0.0
United Kingdom & Ireland		**26 282**	**100.0**	**10.0**
	Channel Islands	18	0.1	0.0
	Ireland	1 148	4.4	0.4
	Isle of Man	6	0.0	0.0
	Northern Ireland	24	0.1	0.0
	Scotland	319	1.2	0.1
	United Kingdom	24 669	93.9	9.3
	Wales	98	0.4	0.0
Western Europe		**11 534**	**100.0**	**4.4**
	Austria	552	4.8	0.2
	Belgium	94	0.8	0.0
	Cyprus	146	1.3	0.1
	Denmark	207	1.8	0.1
	Finland	190	1.6	0.1
	France	362	3.1	0.1
	Germany	2 786	24.2	1.1
	Gibraltar	8	0.1	0.0
	Greece	838	7.3	0.3
	Iceland	8	0.1	0.0
	Israel	52	0.5	0.0
	Italy	2 121	18.4	0.8
	Luxembourg	6	0.1	0.0
	Malta	656	5.7	0.2
	Netherlands	2 642	22.9	1.0
	Norway	60	0.5	0.0
	Portugal	161	1.4	0.1
	Spain	211	1.8	0.1
	Sweden	128	1.1	0.0
	Switzerland	306	2.7	0.1

Table C.1. (Continued)

Region of birth	Country of birth	n	% of region	% of total
Eastern & Central Europe		**3 940**	**100.0**	**1.5**
	Albania	5	0.1	0.0
	Belarus	..[a]	..[a]	..[a]
	Bosnia Herzegovina	80	2.0	0.0
	Bulgaria	27	0.7	0.0
	Croatia	442	11.2	0.2
	Czech Republic	308	7.8	0.1
	Estonia	106	2.7	0.0
	Hungary	574	14.6	0.2
	Latvia	165	4.2	0.1
	Lithuania	61	1.5	0.0
	Moldova	5	0.1	0.0
	Montenegro	..[a]	..[a]	..[a]
	Poland	925	23.5	0.4
	Republic of Macedonia	208	5.3	0.1
	Romania	138	3.5	0.1
	Russian Federation	147	3.7	0.1
	Serbia	115	2.9	0.0
	Slovakia	58	1.5	0.0
	Slovenia	114	2.9	0.0
	Ukraine	147	3.7	0.1
	Union of Soviet Socialist Republics	31	0.8	0.0
	Yugoslavia	279	7.1	0.1
Middle East & North Africa		**2 125**	**100.0**	**0.8**
	Algeria	10	0.5	0.0
	Bahrain	11	0.5	0.0
	Egypt	649	30.5	0.2
	Gaza Strip & West Bank	64	3.0	0.0
	Iran	189	8.9	0.1
	Iraq	220	10.4	0.1
	Jordan	45	2.1	0.0
	Lebanon	693	32.6	0.3
	Libya	5	0.2	0.0
	Morocco	10	0.5	0.0
	Syria	43	2.0	0.0
	Tunisia	..[a]	..[a]	..[a]
	Turkey	179	8.4	0.1
	Yemen	..[a]	..[a]	..[a]

Table C.1. (Continued)

Region of birth	Country of birth	n	% of region	% of total
Sub-Saharan Africa		**2 247**	**100.0**	**0.9**
	Africa Unspecified	32	1.4	0.0
	Botswana	..[a]	..[a]	..[a]
	Congo	..[a]	..[a]	..[a]
	East Africa	20	0.9	0.0
	Ethiopia	7	0.3	0.0
	Ghana	21	0.9	0.0
	Kenya	99	4.4	0.0
	Lesotho	..[a]	..[a]	..[a]
	Madagascar	5	0.2	0.0
	Malawi	11	0.5	0.0
	Mauritius	211	9.4	0.1
	Mozambique	..[a]	..[a]	..[a]
	Namibia	8	0.4	0.0
	Nigeria	18	0.8	0.0
	Senegal	..[a]	..[a]	..[a]
	Seychelles	6	0.3	0.0
	South Africa	1 444	64.3	0.5
	St Helena	..[a]	..[a]	..[a]
	Sudan	67	3.0	0.0
	Tanzania	32	1.4	0.0
	Uganda	27	1.2	0.0
	Zambia	53	2.4	0.0
	Zimbabwe	174	7.7	0.1
North America		**1 768**	**100.0**	**0.7**
	Bermuda	13	0.7	0.0
	Canada	576	32.6	0.2
	United States of America	1 179	66.7	0.4

Table C.1. (Continued)

Region of birth	Country of birth	n	% of region	% of total
Central & South America		**1 267**	**100.0**	**0.5**
	Argentina	179	14.1	0.1
	Bolivia	9	0.7	0.0
	Brazil	68	5.4	0.0
	Chile	386	30.5	0.1
	Colombia	69	5.4	0.0
	Costa Rica	5	0.4	0.0
	Cuba	6	0.5	0.0
	Dominican Republic	..[a]	..[a]	..[a]
	Dutch West Indies	10	0.8	0.0
	Ecuador	34	2.7	0.0
	El Salvador	30	2.4	0.0
	Falkland Islands	..[a]	..[a]	..[a]
	Guatemala	..[a]	..[a]	..[a]
	Guyana	5	0.4	0.0
	Jamaica	9	0.7	0.0
	Mexico	19	1.5	0.0
	Netherlands Antilles	..[a]	..[a]	..[a]
	Nicaragua	10	0.8	0.0
	Panama	..[a]	..[a]	..[a]
	Paraguay	6	0.5	0.0
	Peru	123	9.7	0.0
	South America Unspecified	7	0.6	0.0
	St Vincent and the Grenadines	..[a]	..[a]	..[a]
	Suriname	..[a]	..[a]	..[a]
	Trinidad and Tobago	21	1.7	0.0
	Uruguay	241	19.0	0.1
	Venezuela	17	1.3	0.0
Total born overseas		**64 194**		**24.3**
Total		**264 102**		**100.0**

Table C.2: Decade first migrated to Australia for at least one year by place of birth.

		Decade first migrated to Australia for at least one year (n [row %])										
Place of birth	**n**	**1910s**	**1920s**	**1930s**	**1940s**	**1950s**	**1960s**	**1970s**	**1980s**	**1990s**	**2000s**	**Unspecified**
New Zealand	5,069	5 [0.1]	57 [1.1]	78 [1.5]	102 [2.0]	334 [6.6]	923 [18.2]	1,454 [28.7]	1,147 [22.6]	469 [9.3]	300 [5.9]	200 [4.0]
Oceania	887	0 [0.0]	6 [0.7]	29 [3.3]	50 [5.6]	67 [7.6]	127 [14.3]	156 [17.6]	235 [26.5]	125 [14.1]	59 [6.7]	33 [3.7]
East Asia	3,231	-[a]	-[a]	20 [0.6]	83 [2.6]	154 [4.8]	192 [5.9]	356 [11.0]	1,024 [31.7]	1,032 [31.9]	280 [8.7]	86 [2.7]
Southeast Asia	4,487	-[a]	-[a]	8 [0.2]	48 [1.1]	201 [4.5]	304 [6.8]	892 [19.9]	1,758 [39.2]	871 [19.4]	256 [5.7]	146 [3.3]
Central & South Asia	1,357	-[a]	-[a]	6 [0.4]	63 [4.6]	71 [5.2]	192 [14.1]	266 [19.6]	250 [18.4]	330 [24.3]	139 [10.2]	38 [2.8]
UK & Ireland	26,282	20 [0.1]	387 [1.5]	138 [0.5]	1,426 [5.4]	5,017 [19.1]	8,755 [33.3]	4,828 [18.4]	2,927 [11.1]	1,095 [4.2]	660 [2.5]	1,029 [3.9]
Western Europe	11,534	0 [0.0]	26 [0.2]	159 [1.4]	535 [4.6]	4,753 [41.2]	2,805 [24.3]	1,147 [9.9]	984 [8.5]	314 [2.7]	140 [1.2]	671 [5.8]
Eastern & Central Europe	3,940	0 [0.0]	5 [0.1]	27 [0.7]	572 [14.5]	1,086 [27.6]	827 [21.0]	450 [11.4]	306 [7.8]	277 [7.0]	75 [1.9]	315 [8.0]
Middle East & North Africa	2,125	-[a]	-[a]	6 [0.3]	87 [4.1]	236 [11.1]	385 [18.1]	581 [27.3]	341 [16.0]	247 [11.6]	99 [4.7]	138 [6.5]
Sub-Saharan Africa	2,247	0 [0.0]	-[a]	6 [0.3]	-[a]	50 [2.2]	397 [17.7]	429 [19.1]	604 [26.9]	346 [15.4]	330 [14.7]	66 [2.9]
North America	1,768	0 [0.0]	8 [0.5]	10 [0.6]	47 [2.7]	71 [4.0]	338 [19.1]	573 [32.4]	375 [21.2]	211 [11.9]	96 [5.4]	39 [2.2]
Central & South America	1,267	0 [0.0]	-[a]	0 [0.0]	-[a]	13 [1.0]	92 [7.3]	611 [48.2]	280 [22.1]	136 [10.7]	43 [3.4]	88 [7.0]
Total born overseas	64,194	26 [0.0]	505 [0.8]	487 [0.8]	3,033 [4.7]	12,053 [18.8]	15,337 [23.9]	11,743 [18.3]	10,231 [15.9]	5,453 [8.5]	2,477 [3.9]	2,849 [4.4]

[a]Censored due to < 5 participants, or if this value would enable calculation of value for another cell with < 5 participants.

Appendix D – Additional Figure for Chapter 7 Journal Article

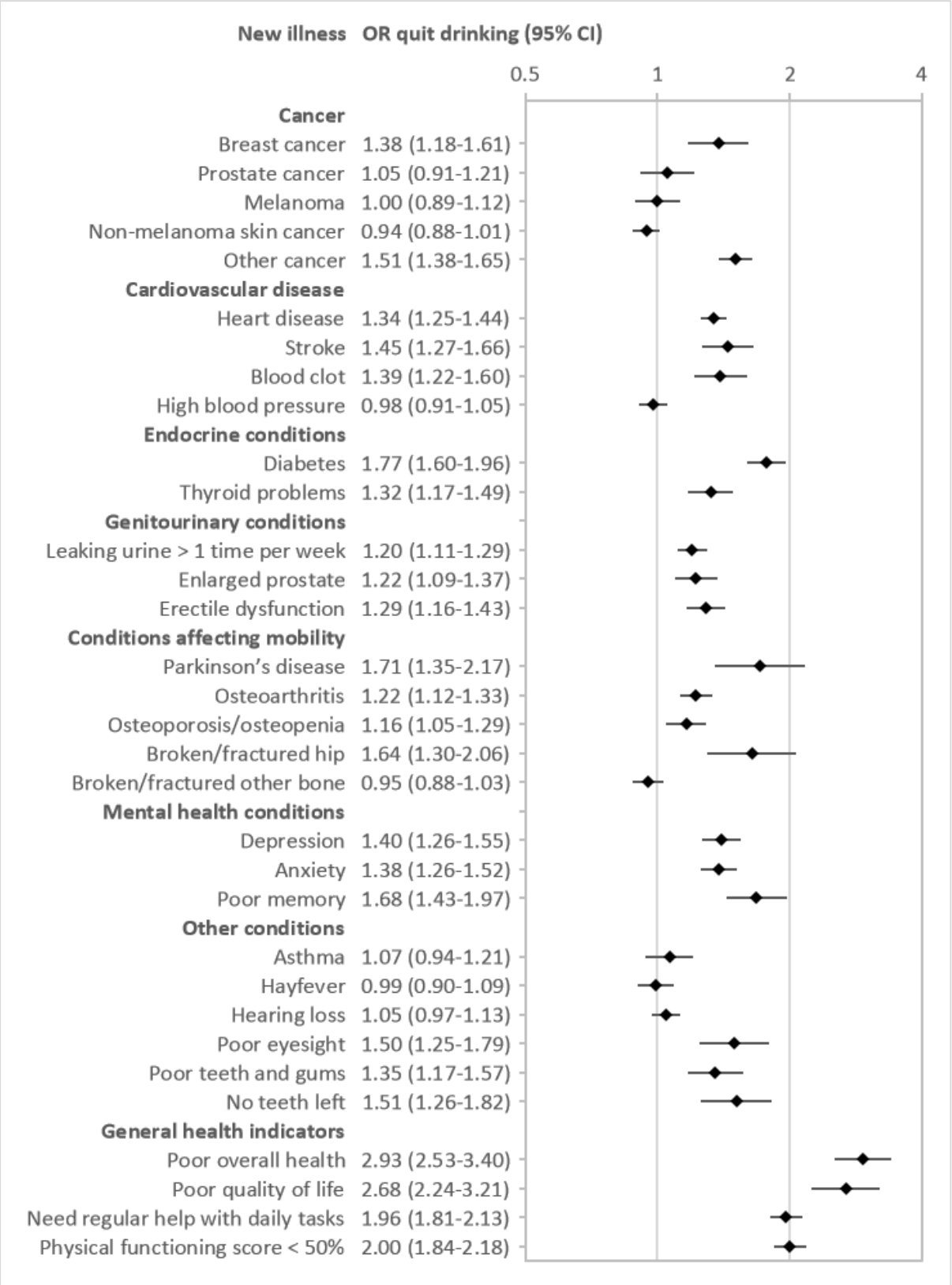

Figure D.1. Odds ratios (OR; 95% confidence intervals, CI) of quitting drinking at follow-up by health conditions newly acquired between baseline and follow-up in the 45 and Up Study (2006-2016), New South Wales, Australia. Adjusted for sex, age, remoteness, education, household income, health insurance status, partner status and country of birth.

Appendix E.1 – Additional Tables for Chapter 8 Journal Article

Table E.1. Proportional hazards assumption tests by cancer type in the 45 and Up Study (2006-2010), New South Wales, Australia.

	Total alcohol consumption model		Drinking-days per week model		Drinks per drinking-day model		Drinking pattern model	
Cancer type	**p**	**Variables in violation**	**p**	**Variables in violation**	**p**	**Variables in violation**	**p**	**Variables in violation**
Mouth and pharynx	0.73	-	0.81	-	0.80	-	-	-
Oesophagus	0.94	-	0.90	-	0.74	-	-	-
- Adenocarcinoma	0.45	-	0.30	-	0.19	-	-	-
- Squamous cell carcinoma	0.57	-	0.80	-	0.88	-	-	-
Colorectum	0.02	Partner status, fruit	0.02	Partner status, BMI	0.02	Partner status, BMI	0.01	Partner status, BMI
- Colon	0.26	-	0.12	-	0.11	-	0.13	-
- Rectum	0.10	-	0.10	-	0.33	-	-	-
Liver	0.72	-	0.81	-	0.94	-	-	-
Larynx	0.36	-	0.31	-	0.42	-	-	-
Breast	0.87	-	0.71	-	0.65	-	-	-
Alcohol-related	0.04	Partner status, PA, fruit	0.08	-	0.07	-	-	-
Stomach	0.54	-	0.66	-	0.65	-	-	-
Pancreas	0.09	-	0.26	-	0.32	-	-	-
Lung	0.39	-	0.27	-	0.27	-	-	-
Melanoma	0.43	-	0.09	-	0.11	-	-	-
Endometrium	0.76	-	0.69	-	0.72	-	-	-
Ovary	0.47	-	0.44	-	0.48	-	-	-
Prostate	0.49	-	0.61	-	0.73	-	-	-
Kidney	0.74	-	0.23	-	0.30	-	0.28	-
Bladder	0.74	-	0.44	-	0.43	-	-	-
Brain	0.34	-	0.11	-	0.29	-	-	-
Thyroid	0.03	Health insurance	0.08	-	0.048	Health insurance	-	-
Non-Hodgkin lymphoma	0.58	-	0.49	-	0.31	-	-	-
Multiple myeloma	0.01	Income, health insurance	0.59	-	0.49	-	-	-
Leukaemia	0.38	-	0.15	-	0.15	-	-	-
Other	0.15	-	0.18	-	0.14	-	-	-
Non-alcohol-related	0.23	-	0.12	-	0.10	-	-	-
All cancer	0.13	-	0.11	-	0.09	-	0.09	-

BMI, Body Mass Index. PA, physical activity.

Table E.2. Interaction tests by cancer type in the 45 and Up Study (2006-2010), New South Wales, Australia.

	Total alcohol consumption				Drinking-days per week				Mean drinks per drinking-day				
Cancer type	**Sex**	**Smoking[a]**	**BMI[b]**	**HRT[c]**	**Sex**	**Smoking[a]**	**BMI[b]**	**HRT[c]**	**Sex**	**Smoking[a]**	**BMI[b]**	**HRT[c]**	**Drinking pattern[d]**
Mouth and pharynx	0.64	0.34	-	-	0.14	0.95	-	-	0.06	0.95	-	-	0.22
Oesophagus	0.79	0.70	-	-	0.46	0.94	-	-	0.48	0.55	-	-	0.97
- Adenocarcinoma	0.99	0.71	-	-	0.70	0.72	-	-	1.00	0.74	-	-	0.99
- Squamous cell carcinoma	1.00	0.82	-	-	0.40	0.79	-	-	0.70	0.90	-	-	0.53
Colorectum	0.87	0.40	0.31	-	0.62	0.18	0.32	-	0.43	0.80	0.80	-	0.04
- Colon	0.31	0.84	0.36	-	0.95	0.12	0.27	-	0.25	0.36	0.87	-	0.03
- Rectum	0.39	0.10	0.01	-	0.41	0.96	0.32	-	0.71	0.51	0.81	-	0.74
Liver	0.58	0.85	-	-	0.95	0.90	-	-	0.60	0.90	-	-	0.88
Larynx	0.83	1.00	-	-	1.00	1.00	-	-	1.00	1.00	-	-	1.00
Breast	-	0.22	-	0.45	-	0.04	-	0.64	-	0.17	-	0.19	0.38
Alcohol-related	0.01	0.25	-	-	0.004	0.32	-	-	0.02	0.07	-	-	0.33
Stomach	0.69	0.09	-	-	0.86	0.37	-	-	1.00	0.30	-	-	0.78
Pancreas	0.07	0.04	0.97	-	0.86	0.27	0.96	-	0.35	0.52	0.80	-	0.97
Lung	0.64	0.97	-	-	0.50	0.88	-	-	0.055	0.52	-	-	0.98
Melanoma	0.77	0.50	-	-	0.71	0.71	-	-	0.07	0.67	-	-	0.10
Endometrium	-	0.46	-	-	-	0.14	-	-	-	1.00	-	-	0.82
Ovary	-	0.87	-	-	-	0.95	-	-	-	0.99	-	-	0.78
Prostate	-	0.89	-	-	-	0.88	-	-	-	0.52	-	-	0.73
Kidney	0.89	0.02	-	-	0.47	0.19	-	-	0.60	0.02	-	-	0.02
Bladder	0.29	0.44	-	-	0.80	0.06	-	-	0.20	0.79	-	-	0.34
Brain	0.31	0.58	-	-	0.91	0.93	-	-	0.59	0.97	-	-	0.59
Thyroid	0.56	0.23	-	-	0.63	0.08	-	-	0.45	0.60	-	-	0.97
Non-Hodgkin lymphoma	0.83	0.52	-	-	0.70	0.50	-	-	0.53	0.37	-	-	0.82
Multiple myeloma	0.88	0.45	-	-	0.14	0.33	-	-	0.62	0.03	-	-	0.83
Leukaemia	0.99	0.57	-	-	0.86	0.28	-	-	0.78	0.68	-	-	0.47
Other	0.95	0.31	-	-	0.70	0.74	-	-	0.88	0.30	-	-	0.35
Non-alcohol-related	0.15	0.005	-	-	0.77	0.70	-	-	0.37	0.09	-	-	0.40
All cancer	0.04	0.004	-	-	0.10	0.31	-	-	0.09	0.53	-	-	0.37

[a]Never-smokers vs. ever-smokers. [b]BMI ≥ 18.5 and < 25.0 kgm^{-2} vs. BMI ≥ 25.0 kgm^{-2}. [c]Never used vs ever used HRT. [d]Between drinking-days per week and mean drinks per drinking-day variables. BMI, Body Mass Index. HRT, Hormone Replacement Therapy.

Table E.3. Akaike information criterion of log-linear and restricted cubic spline models by cancer type in the 45 and Up Study (2006-2010), New South Wales, Australia.

	Akaike Information Criterion		
Cancer type	**Log-linear model**	**Restricted cubic spline model**	**Restricted cubic spline model lower?**
Mouth and pharynx	2,091.834	2093.365	No
Oesophagus	891.472	893.260	No
- Adenocarcinoma	602.395	603.760	No
- Squamous cell carcinoma	274.295	275.949	No
Colorectum	10,554.976	10,554.680	Yes
- Colon	7,484.087	7,482.533	Yes
- Rectum	3,975.444	3,977.341	No
Liver	591.859	592.262	No
Larynx	512.810	514.808	No
Breast	10,978.683	10,977.439	Yes
Alcohol-related	27,232.786	27,234.777	No
Stomach	1,170.473	1,172.437	No
Pancreas	1,712.732	1,714.724	No
Lung	5,858.493	5,860.479	No
Melanoma	11,812.321	11,813.465	No
Endometrium	892.079	894.053	No
Ovary	701.075	699.782	Yes
Prostate	26,018.802	26,020.101	No
Kidney	1,936.148	1,937.349	No
Bladder	1,342.390	1,338.259	Yes
Brain	1,233.330	1234.842	No
Thyroid	1,045.393	1047.214	No
Non-Hodgkin lymphoma	3,175.487	3,177.486	No
Multiple myeloma	931.169	933.144	No
Leukaemia	1,668.044	1670.009	No
Other	6,152.303	6,153.470	No
Non-alcohol-related	67,152.487	67,154.356	No
All cancer	94,977.104	94,978.883	No

Appendix E.2 – Additional Interaction Tests for Chapter 8

Rationale and Methods. It was identified in Chapter 2 that an area for further research is whether body mass index (BMI) modifies the relationship between alcohol consumption and risk of colorectal and pancreatic cancer, and whether hormone replacement therapy (HRT) use modifies the relationship between alcohol consumption and risk of breast cancer. Statistical interactions between these variables (BMI: ≥ 18.5 and < 25.0 kgm^{-2} vs. ≥ 25.0 kgm^{-2} for colorectal and pancreatic cancer; HRT use: never vs. ever for breast cancer) were examined for total alcohol consumption, drinking frequency and drinks per drinking-day.

Results. A significant interaction was found between total alcohol consumption and BMI for risk of cancer of the rectum, but not for any other measures of alcohol consumption or for other cancer types (Table E.2). Stratification of the relationship between total alcohol consumption and risk of cancer of the rectum by BMI is shown in Table E.4. In no stratum was the overall p-value or test for trend significant. The > 7 and ≤ 14 drinks per week category was associated with significantly lower risk in participants with a BMI ≥ 18.5 and < 25 kgm^{-2} and with significantly higher risk in participants with a BMI ≥ 25 kgm^{-2}. There were no significant interactions found between alcohol consumption and hormone replacement therapy for breast cancer risk.

Table E.4. Hazard ratios and 95% confidence intervals of rectum cancer risk by alcohol consumption and BMI status in the 45 and Up Study (2006-2010), New South Wales, Australia.

		Drinks/week (95% CI)							
Rectum cancer analysis	**n cases**	**Non-drinker[a]**	**≥ 1 and ≤ 3.5**	**> 3.5 and ≤ 7**	**> 7 and ≤ 14**	**> 14 and ≤ 28**	**> 28**	***P*[b]**	***p*$_{trend}$[c]**
Main analysis	315	0.92 (0.64-1.32)	1.00	0.90 (0.61-1.33)	1.00 (0.68-1.48)	0.90 (0.58-1.40)	1.09 (0.65-1.85)	0.96	0.73
- BMI ≥ 18.5 and < 25 kgm^{-2}	123	0.78 (0.46-1.33)	1.00	0.67 (0.37-1.22)	0.41 (0.21-0.82)	0.85 (0.44-1.63)	1.41 (0.65-3.03)	0.06	0.20
- BMI ≥ 25 kgm^{-2}	168	1.18 (0.69-2.03)	1.00	1.05 (0.58-1.91)	1.78 (1.03-3.08)	0.97 (0.51-1.87)	1.12 (0.53-2.36)	0.12	0.71

Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, hormone replacement therapy use (women), aspirin use and bowel screening history. [a]< 1 drink per week. [b]Overall. [c]Linear trend using median alcohol consumption of each category, excluding non-drinkers. BMI, Body Mass Index.

Conclusion. The results showed that the relationship between drinking and risk of rectum cancer was modified by bodyweight. When stratified, it appeared that participants with a BMI ≥ 18.5 and < 25 kgm^{-2} who consumed between > 7 and ≤ 14 drinks per week had a lower risk of rectal cancer than light drinkers, whereas those with a BMI ≥ 25 kgm^{-2} had increased risk. There were no significant trends overall however in either stratum, nor were there any interactions detected with drinking patterns or for colon or colorectal cancer. Therefore more research is required to determine whether persons with greater bodyweight have a higher risk of colorectum cancer associated with alcohol consumption compared to those with lesser bodyweight. In addition, the lack of significant interaction between drinking and bodyweight for pancreas cancer risk and between drinking and hormone replacement therapy for breast cancer risk adds to the evidence that the risk factors act independently for these cancer types.

Appendix E.3 – Detailed Description of Methods Used to Calculate Additional Results in Chapters 8 and 9

Population attributable fractions

Cancer

The survey data was categorised into 12 drinking groups by average alcohol consumption per day: None; > 0 to < 1 g; ≥ 1 to < 2 g; ≥ 2 to < 5; ≥ 5 to < 10 g; ≥ 10 to < 15 g; ≥ 15 to < 20 g; ≥ 20 to < 30 g; ≥ 30 to < 40 g; ≥ 40 to < 50 g; ≥ 50 to < 60 g; ≥ 60 g. The hazard ratio for each drinking group was calculated using the median level of intake within each category. For this analysis, like Pandeya et al., (2015), the sex-specific PAFs for cancer incidence in 2010 were attributed to alcohol consumption in 2001, but the log-linear hazard ratios obtained from the 45 and Up Study were used instead. Cancer cases in 2010 were ascertained from the Australian Cancer Incidence and Mortality books[1]. Cancer cases in each age group were attributed to the alcohol consumption of the age group ten years younger. For each sex, age and level of drinking group, the PAF was given by:

$$PAF = \frac{F(HR-1)}{F(HR-1)+1}$$

Where F = the proportion of the sex and age group in the drinking group and HR = the hazard ratio of the median alcohol consumption in grams per day of the drinking group. For this calculation it was assumed that each drink per week in the 45 and Up Study was equivalent to 10 grams of alcohol. After summing the PAFs for all drinking groups in a sex and age group, the summed PAF was multiplied by the number of cancer cases for the cancer type in question. This gave the number of excess cases due to alcohol. The excess cases were then summed for all sex and age groups to obtain the overall PAF. This was performed for cancers of the mouth and pharynx, oesophagus (squamous cell carcinoma), colorectum, liver, larynx, female breast, alcohol-related cancers combined. Hypothetical PAFs were also calculated for cancers of the stomach, pancreas, prostate, kidney and

thyroid, and melanoma and Non-Hodgkin lymphoma, under the assumption that the associations of these cancers with alcohol are causal. In addition to using the hazard ratios from the main analysis, the effect on PAF estimates of using the hazard ratios derived from the sensitivity tests excluding participants with a physical functioning score < 50% and restricting the calculation to participants consuming ≥ 7 drinks per week was also examined. A hypothetical PAF was not calculated for lung cancer due to the finding of a hazard ratio point estimate less than one in the main analysis and both sensitivity tests. The results were compared to the findings of Pandeya et al., (2015). As the distribution of drinks consumed per drinking-day by sex, age and total alcohol consumption was not available in the 2001 National Health Survey data, it was not possible to model an independent association of mean drinks per drinking-day on cancer risk for the PAF calculations.

Mortality

For the mortality PAF calculations, sex- and age-specific deaths in 2010 were ascertained from the General Record of Incidence of Mortality books[2]. It has previously been reported that the relationship between alcohol consumption and mortality may differ for persons aged < 40 or 45 years[3, 4], while the 45 and Up Study contains participants aged ≥ 45 years only. The PAFs were therefore calculated only for deaths in Australians aged ≥ 45 years (94% of all deaths in 2010), and using alcohol consumption in persons aged ≥ 35 years in 2001. PAFs were calculated for cancer, cardiovascular disease, digestive system disease, external and all-cause mortality. A sensitivity analysis was performed excluding participants with a prior diagnosis of cancer or cardiovascular disease from the calculation of the hazard ratio used to derive the cancer and cardiovascular disease mortality PAFs respectively. In addition to using the hazard ratios from the main analysis, the effect on PAF estimates of using the hazard ratios derived from the sensitivity tests excluding participants with a physical functioning score < 50% and restricting the calculation to participants consuming ≥ 7 drinks per week was also examined. Finally, as the relationship between alcohol consumption and

mortality may be non-linear, another sensitivity analysis was performed using hazard ratios derived from the restricted cubic spline analysis rather than the continuous log-linear analysis. As the restricted cubic splines used a reference group of 1 drink per week, it was assumed that the hazard ratio associated with non-drinking was also 1.00. The sensitivity analyses excluding participants with prior cancer, cardiovascular disease and a low physical functioning score were repeated for the restricted cubic spline derived analysis.

Cumulative absolute risk and number of persons needed to quit or reduce drinking to prevent one cancer case or death

Cancer

The hazard ratios obtained from the continuous log-linear analysis, the 2014-15 National Health Survey sex- and age-specific alcohol consumption prevalence data[5] and sex- and age-specific 2013 national cancer incidence data[1] were used to calculate the cumulative absolute risk of cancer in Australians between the ages of 45 and 75 years in 2013 by alcohol consumption status. This method was used in a previous study examining smoking status and cumulative risk of mortality in the 45 and Up Study[6]. Cancer incidence data was available in five-year increments while drinking data was available only in ten-year increments, so sex- and age-specific ten-year increments for cancer incidence were calculated using a mean weighted by the population in each sex and five-year age group in 2013[7]. Cumulative risk was calculated by sex for three drinking groups: Non-drinkers, drinkers consuming > 0 and ≤ 14 drinks per week, and drinkers consuming > 14 drinks per week. Three age groups were used: 45-54 years, 55-64 years and 65-74 years. In each sex and age group, the absolute rates of a specific cancer in drinkers consuming > 14 drinks per week ($A_{>14}$), non-drinkers (A_0) and drinkers consuming ≤ 14 drinks per week ($A_{\leq 14}$) were given by:

$$A_{>14} = A / (P_{>14} + P_{\leq 14} \times HR_{\leq 14} / HR_{>14} + P_0 / HR_{>14})$$

$$A_0 = A / (P_{>14} \times HR_{>14} + P_{\leq 14} \times HR_{\leq 14} + P_0)$$

$$A_{\leq 14} = A_0 \times HR_{\leq 14}$$

Where A = the Australian incidence rate for this cancer type in this sex and age group, P_0 = the national prevalence of non-drinkers for this sex and age group, $P_{\leq 14}$ = the national prevalence of drinkers consuming > 0 and ≤ 14 drinks per week for this sex and age group, $P_{>14}$ = the national prevalence of drinkers consuming > 14 drinks per week for this sex and age group, $HR_{\leq 14}$ = the sex-specific hazard ratio for this cancer type in persons consuming 1-14 drinks per week compared to

non-drinkers derived from the log-linear analysis of total alcohol consumption (calculated for the median drinker within this group from the 45 and Up Study: 6 drinks per week for men and 5 drinks per week for women), and $HR_{>14}$ = the sex-specific hazard ratio for this cancer type in persons consuming > 14 drinks per week compared to non-drinkers derived from the log-linear analysis of total alcohol consumption (calculated for the median drinker within this group from the 45 and Up Study: 21 drinks per week for men and 20 drinks per week for women). Absolute incidence for this cancer type was then calculated for each sex and ten-year age group (i), by:

$$1 - \exp(-10 \sum_{i=(45-54)}^{x} A_i)$$

Where x = age 55, 65 or 75 years, and $A_i = A_0$, $A_{\leq 14}$ or $A_{>14}$ for each ten-year age group. These were then summed to calculate the sex-specific cumulative absolute risk of cancer between the ages of 45 and x by drinking status. This was performed for cancers of the mouth and pharynx, oesophagus, colorectum, liver, larynx, female breast, alcohol-related cancers combined and all cancers combined. The results were graphed.

The absolute difference in risk of cancer by drinking group between the ages of 45 and 75 years was used to calculate sex-specific numbers of persons needed to quit or reduce drinking by age 45 years to prevent one cancer case by age 75 years, by:

$$n = \frac{1}{Absolute\ risk\ difference}$$

Three scenarios were calculated: a person consuming > 14 drinks per week becoming a non-drinker (or never starting drinking) by age 45, a person consuming > 0 and ≤ 14 drinks per week becoming a non-drinker (or never starting drinking) by age 45, and a person consuming > 14 drinks per week becoming a person consuming > 0 and ≤ 14 drinks per week by age 45. Again, for each of the drinking groups, the median drinker within this group from the 45 and Up Study was used (5 drinks for women and 6 drinks for men for persons consuming > 0 and ≤ 14 drinks per week; 20 drinks for women and 21 drinks for men for persons consuming > 14 drinks per week). It should be noted that

a limitation of this analysis is the lag time between alcohol consumption and the occurrence of cancer. If for example the lag time is 10 years, this would imply a person would need to quit or decrease drinking by age 35 years to obtain the complete reduction in risk presented here. The impact of using the hazard ratios derived from the sensitivity tests excluding participants with a physical functioning score < 50% and restricting the calculation to participants consuming ≥ 7 drinks per week was also examined.

Mortality

The hazard ratios obtained from the continuous log-linear analysis, the 2014-15 National Health Survey sex- and age-specific alcohol consumption prevalence data[5] and sex- and age-specific 2013 national mortality incidence data[2] were used to calculate the cumulative absolute risk of mortality in Australians between the ages of 45 and 75 years in 2013 by alcohol consumption status. Calculations were performed for cancer mortality (both with and without the exclusion of prior cancer), cardiovascular disease mortality (both with and without the exclusion of prior cardiovascular disease), digestive system disease mortality, external cause mortality and all-cause mortality (both with and without the exclusion of prior cancer, cardiovascular disease and diabetes). The results were graphed. As only two non-zero categories of alcohol consumption were available, a sensitivity analysis using the hazard ratios obtained from the restricted cubic spline analysis was not performed.

The absolute difference in risk of mortality by drinking group between the ages of 45 and 75 years was used to calculate sex-specific numbers of persons needed to quit or reduce drinking by age 45 years to prevent one death by age 75 years using the same method as in Chapter 8. It should be noted that a limitation of this analysis is the lag time between alcohol consumption and mortality. If for example the lag time is 10 years, this would imply a person would need to quit or decrease drinking by age 35 years to obtain the complete reduction in risk presented here. The impact of

using the hazard ratios derived from the sensitivity tests excluding participants with a physical functioning score < 50% and restricting the calculation to participants consuming ≥ 7 drinks per week was also examined.

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Appendix F.1 – Additional Tables for Chapter 9 Journal Article

Table F.1. Proportional hazards assumption tests by cause of death in the 45 and Up Study (2006-2014), New South Wales, Australia.

	Total alcohol consumption model		Drinking-days per week model		Drinks per drinking-day model		Drinking pattern model	
Cause of death	**p**	**Variables in violation**	**p**	**Variables in violation**	**p**	**Variables in violation**	**p**	**Variables in violation**
Cancer	0.89	-	0.81	-	0.78	-	-	-
- Alcohol-related	0.63	-	0.77	-	0.91	-	-	-
- Mouth, pharynx and larynx	0.52	-	0.62	-	0.64	-	-	-
- Oesophagus	0.41	-	0.81	-	0.81	-	-	-
- Colorectum	0.42	-	0.07	-	0.06	-	-	-
- Liver	0.53	-	0.87	-	0.89	-	-	-
- Breast	0.29	-	0.32	-	0.36	-	-	-
- Non-alcohol-related	0.90	-	0.77	-	0.75	-	-	-
- Stomach	0.74	-	0.43	-	0.52	-	-	-
- Pancreas	0.25	-	0.80	-	0.81	-	-	-
- Lung	0.72	-	0.60	-	0.58	-	-	-
- Melanoma	0.33	-	0.82	-	0.71	-	-	-
- Prostate	0.52	-	0.92	-	0.93	-	-	-
- Kidney	0.47	-	0.60	-	0.56	-	-	-
- Non-Hodgkin lymphoma	0.71	-	0.33	-	0.32	-	-	-
Diabetes	0.89	-	0.70	-	0.69	-	-	-
Dementia	0.71	-	0.57	-	0.47	-	-	-
Cardiovascular disease	0.71	-	0.86	-	0.86	-	-	-
- Ischaemic heart disease	0.20	-	0.86	-	0.84	-	-	-
- Cerebrovascular disease	0.65	-	0.43	-	0.26	-	-	-
- Other cardiovascular disease	0.48	-	0.43	-	0.42	-	-	-
Respiratory system disease	0.55	-	0.58	-	0.56	-	-	-
- Lower respiratory infection	0.64	-	0.72	-	0.86	-	-	-
- Other respiratory system disease	0.44	-	0.26	-	0.21	-	-	-
Digestive system disease	0.53	-	0.88	-	0.93	-	-	-
- Liver disease	0.21	-	0.43	-	0.48	-	-	-
- Other digestive system disease	0.70	-	0.67	-	0.68	-	-	-
External	0.54	-	0.88	-	0.93	-	-	-
- Transport accident	0.37	-	0.56	-	0.57	-	-	-
- Fall	0.79	-	0.85	-	0.86	-	-	-
- Suicide	0.50	-	0.47	-	0.46	-	-	-
- Other external	0.72	-	0.64	-	0.60	-	-	-
Other	0.051	-	0.53	-	0.52	-	-	-
All-cause mortality	0.26	-	0.68	-	0.79	-	0.82	-

Table F.2. Interaction tests by cause of death in the 45 and Up Study (2006-2014), New South Wales, Australia.

	Total alcohol consumption		Drinking-days per week		Mean drinks per drinking-day		
Cause of death	**Sex**	**Smoking[a]**	**Sex**	**Smoking[a]**	**Sex**	**Smoking[a]**	**Drinking pattern[b]**
Cancer	0.35	0.30	0.13	0.34	0.31	0.34	0.16
- Alcohol-related	0.91	0.58	0.86	0.84	0.63	0.36	0.60
- Mouth, pharynx and larynx	1.00	0.86	1.00	0.41	1.00	0.67	0.62
- Oesophagus	0.82	1.00	0.43	0.38	0.21	0.42	0.40
- Colorectum	0.66	0.82	0.93	0.26	0.32	0.08	0.47
- Liver	0.85	0.81	0.61	0.32	0.69	0.58	0.32
- Breast	-	0.33	-	0.48	-	0.40	0.89
- Non-alcohol-related	0.36	0.39	0.03	0.16	0.36	0.11	0.10
- Stomach	0.43	0.57	0.42	0.48	1.00	0.87	0.99
- Pancreas	0.86	0.89	0.86	0.15	0.77	0.89	0.16
- Lung	1.00	0.02	0.06	0.18	0.78	0.13	0.71
- Melanoma	0.85	0.65	0.68	0.61	0.88	0.53	0.08
- Prostate	-	0.59	-	0.80	-	0.58	0.91
- Kidney	0.78	0.71	0.96	0.87	0.96	0.86	0.39
- Non-Hodgkin lymphoma	0.78	0.73	0.37	0.34	1.00	0.26	0.82
Diabetes	0.69	0.93	0.18	0.88	0.99	0.92	0.63
Dementia	0.98	0.75	0.44	0.82	0.73	0.55	0.42
Cardiovascular disease	0.11	0.56	0.59	0.59	0.24	0.20	0.11
- Ischaemic heart disease	0.43	0.85	0.62	0.84	0.10	0.95	0.13
- Cerebrovascular disease	0.33	0.46	0.13	0.49	0.98	0.053	0.79
- Other cardiovascular disease	0.56	0.54	0.28	0.82	0.97	0.30	0.69
Respiratory system disease	0.29	0.47	0.78	0.22	0.97	0.43	0.96
- Lower respiratory infection	0.60	0.73	0.79	0.28	0.13	0.41	0.96
- Other respiratory system disease	0.63	0.76	0.72	0.55	0.91	0.33	0.92
Digestive system disease	0.92	0.81	0.87	0.69	0.63	0.39	0.99
- Liver disease	0.36	0.94	0.67	0.60	0.68	0.53	0.95
- Other digestive system disease	0.38	0.69	0.81	0.80	0.38	0.91	0.98
External	0.65	0.06	0.76	0.07	0.97	0.14	0.71
- Transport accident	0.80	0.44	0.87	0.43	0.74	0.97	0.95
- Fall	0.77	0.52	0.64	0.96	0.80	0.46	1.00
- Suicide	0.84	0.73	0.92	1.00	0.50	0.36	0.62
- Other external	0.71	0.16	0.65	0.91	1.00	0.17	0.98
Other	0.49	0.78	0.83	0.51	0.14	0.97	0.79
All-cause mortality	0.13[c]	0.01[c]	0.88	0.10	0.02	0.54	0.68

[a]Never-smokers vs. ever-smokers. [b]Between drinking-days per week and mean drinks per drinking-day variables. [c]Derived without using age as the underlying time variable due to insufficient computing power. [d]Between drinking-days per week and mean drinks per drinking-day variables.

Table F.3. Akaike information criterion of log-linear and restricted cubic spline models by cause of death in the 45 and Up Study (2006-2014), New South Wales, Australia.

	Akaike Information Criterion		
Cause of death	**Log-linear model**	**Restricted cubic spline model**	**Restricted cubic spline model lower?**
Cancer	27,686.821	27,685.452	Yes
- Alcohol-related	6,266.332	6,267.992	No
- Mouth, pharynx and larynx	506.702	507.520	No
- Oesophagus	1,025.705	1,027.698	No
- Colorectum	2,480.816	2,482.685	No
- Liver	821.884	820.264	Yes
- Breast	1,479.842	1,477.222	Yes
- Non-alcohol-related	21,456.564	21,455.663	Yes
- Stomach	645.681	647.378	No
- Pancreas	1,871.418	1,873.019	No
- Lung	4,709.746	4,711.634	No
- Melanoma	1,347.316	1,349.248	No
- Prostate	2,887.887	2,888.079	No
- Kidney	600.845	602.269	No
- Non-Hodgkin lymphoma	809.176	810.454	No
Diabetes	1,023.986	1,025.972	No
Dementia	1,817.869	1,819.865	No
Cardiovascular disease	17,872.181	17,867.379	Yes
- Ischaemic heart disease	8,745.425	8,743.522	Yes
- Cerebrovascular disease	4,177.548	4,178.791	No
- Other cardiovascular disease	5,081.479	5,081.601	No
Respiratory system disease	5,008.045	5,007.990	Yes
- Lower respiratory infection	761.654	763.220	No
- Other respiratory system disease	4,315.388	4,315.977	No
Digestive system disease	1,753.005	1,754.991	No
- Liver disease	531.124	533.122	No
- Other digestive system disease	1,299.644	1,300.534	No
External	2,003.013	2,004.321	No
- Transport accident	547.898	548.638	No
- Fall	510.690	509.738	Yes
- Suicide	427.543	426.857	Yes
- Other external	710.052	709.780	Yes
Other	6,955.119	6,954.727	Yes
All-cause mortality	149,183.27	149,175.88	Yes

Appendix F.2 – Further Investigation of the Exclusion Scenarios Assessed in Chapter 7 Aiming to Mitigate Bias from the 'Sick-Quitter Effect' by Effect on the Association between Disease and All-Cause Mortality

Using the all-cause mortality model reported in the main analysis of Chapter 9, it was possible to investigate the effect of the exclusion scenarios used in the additional analyses of Chapter 7 on the association between disease and all-cause mortality, to further assess their use as potential sensitivity tests to mitigate bias from the 'sick-quitter effect'. The following question was investigated:

1. *Whether the exclusion of participants with different types of health characteristics at baseline attenuates the association between prevalent disease and all-cause mortality for participants who remain in the cohort.*

Rationale and methods. If the exclusion of participants with poor health status can attenuate associations between disease and all-cause mortality for those who remain in the cohort, this may reduce bias from the 'sick-quitter effect'. This is because one of the criteria for confounding is that the potential confounder must be associated with risk of the outcome[1]. To examine the effect of the methods of restriction on the association between disease and all-cause mortality, the six diseases examined using the exclusion scenarios in Chapter 7 were added to the all-cause mortality model reported in the main analysis in Chapter 9. The 'no restriction' scenario included non-drinkers and deaths within the first three years of follow-up. The hazard ratio of all-cause mortality associated with the presence of each of the six diseases at baseline was examined by exclusion scenario.

Results. The fully adjusted hazard ratios of all-cause mortality by disease status at baseline and method of restriction is shown in Table E.4. For most exclusion scenarios there were no obvious

changes in the association between baseline disease and mortality. Exceptions were restriction to participants aged < 65 years, which resulted in non-significance for Parkinson's disease and poor memory (and material changes in the hazard ratio point estimates), and stronger associations for the remaining four diseases, and restriction to participants never diagnosed with cancer or cardiovascular disease, which resulted in higher effect estimates for the four remaining diseases. The exclusion of participants who died within three years of baseline also resulted in the largest attenuation of the association between mortality and baseline cancer diagnosis and hip fracture.

Conclusions. It was shown that most exclusion scenarios did not consistently change associations between baseline disease and mortality. The exclusion of participants with a baseline cancer or cardiovascular disease diagnosis resulted in stronger associations for the remaining diseases, suggesting that confounding from these diseases on the association between alcohol consumption and all-cause mortality may become stronger if this is performed. Restriction to participants aged less than 65 years resulted in non-significance for two diseases, but resulted in stronger associations for other diseases. Overall, this analysis showed that the exclusion of participants with poor health status is unlikely to mitigate bias from the 'sick-quitter effect' through attenuating the association between disease and all-cause mortality for participants remaining in the cohort. Rather, the mitigation of bias operates primarily through the reduction of differences in health status between drinking groups.

Table F.4. Hazard ratio of all-cause mortality by disease status at baseline by exclusion scenario in the 45 and Up Study (2006-2014), New South Wales, Australia.

	HR of all-cause mortality for presence of disease at baseline (95% CI)					
Exclusion scenario	**Ever had cancer**	**Ever had CVD**	**Ever had diabetes**	**Ever had Parkinson's disease**	**Hip fracture in past 5 years**	**Poor memory**
No exclusion	1.70 (1.65-1.75)	1.41 (1.37-1.45)	1.37 (1.32-1.42)	1.49 (1.36-1.63)	1.48 (1.35-1.62)	1.50 (1.42-1.59)
Poor overall health	1.68 (1.63-1.73)	1.38 (1.34-1.43)	1.36 (1.30-1.41)	1.52 (1.38-1.68)	1.45 (1.31-1.61)	1.45 (1.36-1.55)
Poor quality of life	1.71 (1.66-1.77)	1.41 (1.37-1.46)	1.38 (1.33-1.44)	1.50 (1.36-1.66)	1.43 (1.29-1.59)	1.48 (1.39-1.58)
Need help with daily tasks	1.74 (1.69-1.80)	1.38 (1.33-1.43)	1.37 (1.31-1.44)	1.27 (1.11-1.45)	1.47 (1.27-1.70)	1.34 (1.24-1.46)
Physical functioning score < 50%	1.92 (1.84-2.00)	1.32 (1.27-1.38)	1.38 (1.31-1.46)	1.47 (1.26-1.71)	1.37 (1.10-1.70)	1.47 (1.33-1.62)
Ever had cancer or CVD	-	-	1.51 (1.42-1.60)	2.49 (2.15-2.88)	1.62 (1.41-1.87)	1.60 (1.46-1.75)
Death within 3 years of baseline	1.44 (1.39-1.49)	1.39 (1.34-1.44)	1.39 (1.33-1.46)	1.70 (1.52-1.90)	1.32 (1.16-1.51)	1.51 (1.41-1.63)
Age ≥ 65 years	3.35 (3.12-3.59)	1.63 (1.49-1.79)	1.64 (1.49-1.81)	1.19 (0.84-1.69)	1.70 (1.12-2.56)	1.12 (0.96-1.32)

Models adjusted for total alcohol consumption (categorical), sex, age, remoteness, education, household income, health insurance status, partner status, country of birth, smoking status and dose, body mass index, physical activity, fruit consumption, vegetable consumption, fibre intake, red meat consumption, processed meat consumption, parity (women), menopausal status (women), hormone replacement therapy use (women), height and other five illnesses. Calculations derived without using age as the underlying time variable due to insufficient computing power. HR, Hazard Ratio. CI, Confidence Interval. CVD, Cardiovascular Disease.

References

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