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Original Research

Alcohol consumption, drinking patterns and cause-specific mortality in an Australian cohort of 181,607 participants aged 45 years and over

Peter Sarich [a,*], Karen Canfell [b], Sam Egger [a], Emily Banks [c], Grace Joshy [c], Paul Grogan [a], Marianne F. Weber [a]

[a] The Daffodil Centre, The University of Sydney, a Joint Venture with Cancer Council NSW, Postal Address: PO Box 572, KINGS CROSS, NSW, 1340, Australia
[b] Sydney School of Public Health, Faculty of Medicine and Health, The University of Sydney, Postal Address: Edward Ford Building (A27), NSW, 2006, Australia
[c] National Centre for Epidemiology and Population Health, Australian National University, Postal Address: Building 62, THE AUSTRALIAN NATIONAL UNIVERSITY, ACT, 2601, Australia

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ABSTRACT

Objectives: Despite relatively high alcohol consumption in Australia, local evidence regarding drinking and cause-specific mortality is limited. We aimed to quantify the risk of alcohol-related causes of death and to calculate contemporary estimates of absolute risk and population attributable fractions for deaths caused by alcohol consumption in Australia.

Study design: Prospective cohort study.

Methods: Cox proportional hazards regressions were used to calculate hazard ratios (HR) for cause-specific mortality in relation to overall alcohol consumption and pattern of drinking among 181,607 of 267,357 participants aged ≥45 years (2005–2009) in the New South Wales 45 and Up Study, with linkage to death records to December 24, 2019. Cumulative absolute risks and population attributable fractions were estimated.

Results: Over a median 11.4 years, there were 18,193 deaths. Every additional seven drinks/week increased risk of death from: alcohol-related cancers combined by 12 % (HR = 1.12; 95%CI = 1.05–1.18); digestive system disease by 32 % (1.33; 1.22–1.44); falls by 23 % (1.23; 1.03–1.46); cardiovascular disease by 7 % (1.07; 1.03–1.11); alcohol-related causes combined by 10 % (1.10; 1.07–1.12); and from all-cause mortality by 6 % (1.06; 1.04–1.08). By age 85 years, men and women who consumed >10 drinks/week were estimated to have 8.5 % and 4.1 % higher cumulative absolute risk of mortality from alcohol-related causes, respectively, compared to those consuming 0 to <1 drink/week. An estimated 9029 deaths (5.3 % of all deaths) were attributable to alcohol consumption in Australia in 2021.

Conclusions: Excess risk of death from alcohol consumption in Australia is substantial. Given relatively high alcohol intake, interventions aimed at reducing consumption may translate into significant public health gains.

1. Introduction

Alcohol consumption increases the risk of a range of diseases and causes of death, and 5.3 % of deaths and 5.1 % of the burden of disease and injury globally were attributed to alcohol in 2016,[1] as well as 4.6 % of deaths in Australia.[1] Variation in the direction and strength of the relationship between alcohol consumption and mortality from specific causes has also been reported in prospective cohort studies. Positive associations between alcohol and death from cancers of the upper-aerodigestive tract,[2] oesophagus (squamous cell carcinoma),[3] colorectum (women only)[4] and liver[5] have been reported, as well as death from tuberculosis,[6] digestive system disease,[7] liver cirrhosis,[6] and external causes.[6–8] Inverse associations have been reported for death from cancers of the stomach,[4] lung[4] and kidney,[4] and ischaemic heart disease (IHD),[9] and J- or U-shaped associations for death from cardiovascular disease (CVD; including stroke[9]), colorectal cancer,[10] breast cancer,[4] and all cancers combined,[11] although many of these associations are not likely to be causal.

Furthermore, it has been reported that pattern of drinking influences risk of mortality independent of the overall amount of alcohol consumed. Two main drinking patterns have been reported in relation to health outcomes: 1) frequency of drinking and 2) consumption of a large

* Corresponding author. PO Box 572, KINGS CROSS, NSW, 1340, Australia.
E-mail address: peter.sarich@sydney.edu.au (P. Sarich).

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number of drinks on drinking occasions, which is commonly referred to as 'heavy episodic' drinking and/or 'binge' drinking. Differences in drinking frequency have been associated with differences in risk for all-cause mortality,[12–14] and a large number of drinks per drinking occasion or heavy episodic drinking has been found to increase all-cause mortality risk.[12,14–18] Relatively few studies have explored pattern of drinking in relation to death from specific diseases, and these have largely focused on CVD and cancer mortality.

Several older meta-analyses of observational studies reported a J-shaped association between alcohol and all-cause mortality, where low-volume 'moderate' drinking is associated with decreased mortality risk, and heavy drinking with increased risk.[19–21] However, more recent large-scale individual participant meta-analyses and Mendelian randomisation studies have suggested that the underlying relationship is linear,[22] with the inverse relationship between low-volume drinking and mortality possibly affected by reverse causation and confounding by factors such as baseline health status, behavioural risk factors and/or socio-demographic characteristics.[23–25] Studies that account for these study factors and other factors, including length of follow-up and choice of reference group,[26–28] have not found an inverse association between low-volume drinking and all-cause mortality. It has also been argued that it is not possible to determine the true relationship between alcohol consumption and all-cause mortality or coronary heart disease using cohort studies,[29,30] with Mendelian randomisation studies put forward as an alternative approach.[25,31–33] These studies have not observed protective effects of alcohol consumption on risk of all-cause mortality and CVD outcomes, and instead have found risk relationships that are either monotonically increasing or null.[25,31–33] It should be noted however that Mendelian randomisation studies have limitations, including that the genetic instrument used may not be robustly associated with the exposure (i.e., a violation of the relevance assumption), may be associated with other confounding factors (a violation of the independence assumption), may influence risk of the outcome through means other than the exposure being studied (e.g., pleiotropic effects; a violation of the exclusion restriction assumption), or that the direction of the effect of the exposure may not be consistent between study subjects (a violation of the monotonicity assumption).[32,34] The evidence on the overall mortality risks associated with alcohol consumption from prospective cohort studies may also be limited by differences between populations and/or differences in study design. For example, the relationship between alcohol consumption and mortality risk is likely to vary across different regions of the world,[20,29] in part because the distribution of alcohol-related causes of death vary from country to country.[29]

In Australia, levels of alcohol consumption are relatively high (10.6 L per capita in 2016, substantially higher than the global average of 6.4 L), and over a third of Australians have a 30-day history of heavy episodic drinking.[1] The relationship between alcohol consumption and several causes of death has been investigated previously in Australia,[35–37] however there are few population-based, prospective studies that quantify the risk of many causes of death in a single study, and few that investigate the impact of drinking pattern on mortality risk. We aimed to use the 45 and Up Study, a prospective cohort study in Australia, to quantify the risk of death from causes known to have a positive association with alcohol in relation to both self-reported weekly intake and pattern of drinking, and to calculate contemporary estimates of absolute risk and population attributable fractions for deaths caused by alcohol consumption in Australia. Due to the evidence from multiple study types that inverse associations between drinking and CVD may not be causal, we presented results both with and without CVD mortality.

2. Methods

2.1. Study sample

The Sax Institute's 45 and Up Study is a prospective cohort study of 267,357 participants, with recruitment methods previously described.[38,39] In summary, men and women aged ≥45 years were randomly sampled from the general population of New South Wales (NSW), Australia, between 2005 and 2009 using the Services Australia Medicare enrolment database. The database includes all Australian citizens and permanent residents, and also some temporary residents and refugees. Oversampling was performed for persons aged ≥80 years and persons living in rural and remote areas. Participants completed a postal questionnaire (available at: https://www.saxinstitute.org.au/solutions/45-and-up-study/use-the-45-and-up-study/data-and-technical-information/) which contained items on demographic factors, health-behaviours (such as smoking, physical activity, and diet), and medical history (including presence of chronic disease and quality of life). Approximately 19 % of persons invited participated, and those that participated comprised approximately 11 % of the NSW population aged ≥45 years. Participants completed a 5-year follow-up questionnaire (wave 2 questionnaire; 2012–2015; median 5.3 years after baseline; response rate 53 %).

Participants with a history of cancer in the NSW Cancer Registry (from 1994), or self-reported cancer, heart disease, stroke, diabetes, Parkinson's disease or a broken/fractured hip (in the last five years) on the baseline questionnaire were excluded from analysis to minimise bias from the 'sick-quitter effect'. Those with self-reported non-melanoma skin cancer/melanoma only were not excluded because skin lesions are common in Australia and skin cancers are often reported inaccurately.[40,41] Participants with missing alcohol consumption data or linkage errors were excluded.

Ethics approval for the 45 and Up Study was granted by the University of New South Wales Human Research Ethics Committee (reference: HC210602), and for this specific analysis by the NSW Population Health Services Research Ethics Committee (reference: 2014/08/551). Written informed consent was obtained from all participants in the study.

2.2. Record linkage

The 45 and Up Study questionnaire data were probabilistically linked to the NSW Cancer Registry, the NSW Registry of Births Deaths and Marriages (RBDM) and the Australian Bureau of Statistics Cause of Death Unit Record File (COD URF)[42] by the NSW Ministry of Health's Centre for Health Record Linkage (CHeReL; http://www.cherel.org.au/). The CHeReL used a best practice approach in privacy preserving record linkage[43] along with the open source probabilistic record linkage software Choice Maker.[44] 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.[45]

2.3. Mortality data

Date of death was ascertained from the NSW RBDM and cause of death from the COD URF to December 24, 2019. Cause of death was classified according to the International Classification of Diseases, version 10 (ICD-10).[46] Causes of death identified as being significantly increased by alcohol consumption in a recent review of the burden of alcohol-related disease[47] and where there were at least 100 deaths in the 45 and Up Study (based on underlying cause) were included for analyses (detailed in Table 2 and Supplementary Information p.3). Due to evidence that associations between alcohol consumption and CVD in cohort studies are more likely to be affected by bias than other outcomes, deaths from CVD were combined as, '*Outcomes considered more prone to bias*'. Death from all-cause mortality and all alcohol-related causes combined were also assessed, both with and without CVD.

2.4. Alcohol consumption

Alcohol consumption was ascertained from two questionnaire items

Table 1
Socio-demographic and other characteristics by alcohol consumption in the 45 and Up Study (2005–2019).

	Alcohol consumption (drinks per week)						Drinking-days per week[a]	
	0 to <1	≥1 to ≤3.5	>3.5 to ≤10	>10 to ≤20	>20 to ≤30	>30	1–3	4–7
Characteristic at baseline								
Participants (n)	56,261	28,860	55,957	26,438	9638	4453	23,295	72,272
Participants (%)	31.0	15.9	30.8	14.6	5.3	2.5	24.4	75.6
Male (%)	29.4	37.5	43.3	58.8	75.4	89.9	52.3	53.1
Mean age in years (SD)	61.6 (11.1)	59.1 (9.9)	59.7 (10.0)	60.0 (9.7)	60.2 (9.5)	58.9 (8.6)	56.6 (8.4)	60.8 (10.0)
Major city resident (%)	52.6	53.7	52.0	49.9	46.6	43.2	53.0	49.7
University degree (%)	19.5	28.0	29.5	28.8	24.7	17.7	26.1	29.1
Household income ≥$70,000[b] (%)	16.6	29.3	33.6	36.7	33.6	29.0	37.3	33.3
Private health insurance[c] (%)	57.3	70.9	73.8	73.3	68.1	56.7	69.6	73.3
Married or living with partner (%)	70.3	77.1	79.8	81.5	79.5	72.6	78.3	80.5
Born in Australia (%)	72.3	73.0	76.2	78.2	80.4	81.3	77.9	77.3
Ever smoked (%)	31.4	32.8	41.1	56.1	67.9	76.1	47.3	50.2
Overweight or obese[d] (%)	54.7	56.4	53.5	57.8	62.6	66.8	62.2	54.3
Inadequate physical activity[e] (%)	24.1	20.0	16.1	15.0	16.7	20.8	16.7	15.7
<2 fruit serves per day[f] (%)	38.2	37.3	40.2	49.2	56.6	66.6	42.6	46.4
<5 vegetable serves per day (%)	64.8	66.4	65.9	68.8	70.1	73.1	67.8	67.4
<7 fibre serves per week[g] (%)	16.2	14.1	12.7	15.5	20.3	30.8	16.2	14.7
Red meat >5 times per week (%)	9.3	8.1	9.0	12.0	16.1	22.7	8.9	11.9
Processed meat >1 time per week (%)	26.4	28.8	31.0	37.4	44.3	53.2	34.8	35.3
Nulliparous (women) (%)	10.2	10.0	11.1	14.4	18.6	23.6	11.6	12.6
Post-menopausal (women) (%)	63.5	60.5	61.4	62.1	63.0	53.7	53.0	64.4
Ever used MHT (women) (%)	33.8	35.4	37.3	39.4	39.6	35.6	31.3	40.0
Height in tallest tertile (men) (%)	28.6	33.6	35.7	37.3	36.1	37.1	37.2	36.2
Height in tallest tertile (women) (%)	28.9	33.4	36.4	38.3	38.9	37.9	37.6	36.9
Follow-up period								
Person-years of follow-up (thousands)	629.0	330.1	638.3	300.4	109.1	49.9	267.7	819.7
n deaths	7137	2290	4630	2493	1050	593	1386	7216

Denominators in calculated percentages include participants with missing or invalid responses. BMI, Body Mass Index. MHT, Menopausal Hormone Therapy. SD, Standard Deviation.

[a] Among participants consuming ≥4 drinks 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 <150 min, with each minute of walking or moderate physical activity counted as 1 min, and each minute of vigorous physical activity counted as 2 min, according to the Australian physical activity guidelines.[82]

[f] Excludes fruit juice.

[g] Serves of breakfast cereal and brown or wholemeal bread.

at both baseline and follow-up: "*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)*" and, "*On how many days each week do you usually drink alcohol?*".[48] As the questionnaire items asked about usual consumption there was no reference time frame. Responses were used to derive two independent variables: (1) to assess the total amount of alcohol consumed in a week, and (2) to assess pattern of consumption across the week.

The following categories and stratification criteria were defined for each of the independent variables at baseline:

(1) Number of drinks per week, ('Weekly alcohol consumption'): '0 to <1 drink', '≥1 to ≤3.5 drinks', '>3.5 to ≤10 drinks', '>10 to ≤20 drinks', '>20 to ≤30 drinks' and '>30 drinks'. For breast cancer mortality and in models among women only, '>20 drinks/week' was used as the maximum category as there were few heavy drinkers among women. Low-volume drinkers (≥1 to ≤3.5 drinks/week) were used as the reference group rather than those reporting 0 to <1 drink per week due to the potential for bias from the 'sick-quitter effect', whereby non-drinkers may have quit drinking due to ill-health, potentially resulting in underestimated hazard ratios in relation to heavier drinking.[49,50] The cut-point of 3.5 drinks per week was chosen as it corresponds to 0.5 drinks per day, which has been described as the upper limit of 'very light drinking'.[4] The variable was otherwise categorised with cut-points aimed to align with multiples of the Australian alcohol consumption guideline of ≤10 standard drinks per week to reduce the risk of alcohol-related harm, where a standard drink contains 10 g of ethanol.[51]

(2) Pattern of drinking: A cut-point of 1–3 vs. 4–7 days per week was chosen to classify participants as consuming alcohol on more or less than half of the week and to capture participants who may only be weekend and Friday evening drinkers, versus those who drink across the week. We also used this classification in a previous analysis.[52] Participants who consumed <4 drinks/week were excluded from this analysis because they could not be divided into two levels of drinking frequency since they could not have consumed alcohol on more than 1–3 days/week. Three categories of drinks per week were used, with an upper cut-point of 10 drinks/week. This created a six category variable (detailed in Supplementary Information p.3).

The risk for each cause of death in relation to weekly alcohol consumption was also assessed as a continuous variable in log-linear Cox regressions with hazard ratios representing the change in risk per seven-drink increase in weekly alcohol consumption (among drinkers only). For the continuous variable, participants within each category of alcohol consumption at baseline were assigned the mean level of alcohol consumption reported by these same participants at the 5-year follow-up questionnaire (participants who did not complete the follow-up questionnaire were excluded from this calculation). This was to allow for regression dilution,[53] to reduce the potential for misclassification, and to mitigate the impact of outliers on the linear trend.

Restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentiles of alcohol consumption among drinkers were modelled, and

Table 2
Hazard ratios (HR) and 95 % confidence intervals (CI) of cause-specific mortality risk by overall alcohol consumption in the 45 and Up Study (2005–2019).

Cause of death (ICD-10 code)	n deaths	Age- and sex-standardised rate[a]	HR drinks per week (95 % CI)						p^b
			0 to <1	≥1 to ≤3.5	>3.5 to ≤10	>10 to ≤20	>20 to ≤30	>30	
Outcomes considered less prone to bias									
Alcohol-related cancer (C00–15;18–20;22;26.0;32;50[c])	1560	99.7	1.07 (0.91–1.26)	1.00	0.95 (0.80–1.12)	1.07 (0.88–1.30)	1.05 (0.82–1.36)	1.75 (1.32–2.31)	<0.001
Mouth, pharynx and larynx cancer (C00-14; 32)	103	6.6	0.90 (0.44–1.85)	1.00	1.11 (0.54–2.26)	1.53 (0.72–3.25)	0.96 (0.35–2.67)	3.77 (1.64–8.70)	0.003
Oesophageal cancer (C15)	192	11.7	1.67 (0.97–2.87)	1.00	1.27 (0.73–2.21)	1.07 (0.58–1.99)	1.65 (0.85–3.20)	2.29 (1.12–4.68)	0.08
Colorectal cancer (C18-20; 26.0)	761	51.8	0.99 (0.79–1.24)	1.00	0.91 (0.72–1.15)	1.06 (0.81–1.39)	1.08 (0.76–1.53)	1.03 (0.64–1.66)	0.81
Liver cancer (C22)	227	13.2	1.02 (0.67–1.57)	1.00	0.88 (0.56–1.37)	1.05 (0.64–1.72)	0.98 (0.51–1.87)	2.38 (1.29–4.36)	0.02
Breast cancer (C50[c])	277	31.1	1.11 (0.78–1.58)	1.00	0.94 (0.64–1.38)	1.07 (0.66–1.73)	0.52 (0.18–1.46)[d]	–	0.55
Diabetes (E10–14)	134	11.1	1.72 (0.95–3.09)	1.00	1.25 (0.67–2.36)	0.59 (0.25–1.43)	1.13 (0.45–2.86)	1.44 (0.50–4.15)	0.09
Dementia (F00–03;05.1; G30–31.1;31.8–31.9)	1399	133.1	1.05 (0.88–1.24)	1.00	0.98 (0.82–1.17)	0.98 (0.79–1.23)	1.23 (0.92–1.64)	1.06 (0.65–1.74)	0.62
Vascular dementia (F01)	128	12.3	0.71 (0.40–1.26)	1.00	1.03 (0.58–1.85)	1.42 (0.73–2.74)	1.23 (0.47–3.21)	2.60 (0.84–8.09)	0.11
Alzheimer's disease (F00; G30)	369	30.7	1.10 (0.79–1.52)	1.00	1.03 (0.73–1.46)	0.97 (0.64–1.48)	1.28 (0.74–2.22)	0.40 (0.10–1.69)	0.67
Other and unspecified dementia (Other)	902	90.1	1.07 (0.87–1.32)	1.00	0.94 (0.75–1.18)	0.92 (0.70–1.22)	1.21 (0.84–1.75)	1.14 (0.62–2.09)	0.48
Lower respiratory infection (J09–22)	330	35.4	1.63 (1.10–2.40)	1.00	1.32 (0.87–1.99)	1.36 (0.84–2.21)	1.57 (0.85–2.92)	1.35 (0.52–3.55)	0.22
Digestive system disease (K00–93)	596	49.8	1.08 (0.82–1.44)	1.00	1.13 (0.84–1.52)	1.73 (1.25–2.39)	1.64 (1.08–2.48)	3.86 (2.55–5.84)	<0.001
Liver disease (K70-77)	147	8.0	1.97 (0.82–4.73)	1.00	2.54 (1.05–6.15)	4.99 (2.05–12.2)	7.21 (2.84–18.4)	15.8 (6.33–39.5)	<0.001
Other digestive system disease (K00-67; 80–93)	449	41.8	0.97 (0.72–1.31)	1.00	0.97 (0.70–1.34)	1.35 (0.94–1.94)	0.90 (0.53–1.55)	1.52 (0.80–2.91)	0.19
External cause (V01-Y98)	785	60.9	1.12 (0.89–1.41)	1.00	1.06 (0.84–1.34)	1.16 (0.88–1.52)	1.10 (0.77–1.59)	1.13 (0.69–1.83)	0.91
Accident (V01-X59; Y85-86)	607	50.6	1.08 (0.83–1.41)	1.00	1.02 (0.78–1.34)	1.13 (0.83–1.55)	1.09 (0.71–1.66)	1.16 (0.66–2.06)	0.93
Transport accident (V00-99; Y85)	122	7.4	0.56 (0.32–0.98)	1.00	0.84 (0.50–1.42)	0.90 (0.49–1.65)	0.73 (0.32–1.69)	0.33 (0.08–1.45)	0.27
Fall (W00-19)	203	18.7	1.26 (0.78–2.04)	1.00	1.17 (0.71–1.94)	1.66 (0.95–2.89)	1.98 (0.99–3.95)	2.17 (0.80–5.94)	0.24
Other accident (W20-X59; Y86)	282	24.5	1.30 (0.89–1.92)	1.00	1.02 (0.68–1.53)	0.92 (0.56–1.51)	0.84 (0.42–1.68)	1.33 (0.60–2.95)	0.37
Suicide (X60-84; Y87.0)	136	7.8	1.20 (0.66–2.16)	1.00	1.39 (0.78–2.47)	1.36 (0.71–2.59)	1.02 (0.43–2.44)	1.12 (0.40–3.16)	0.87
Other alcohol-related causes combined ([e])	66	4.6	1.26 (0.54–2.94)	1.00	0.62 (0.23–1.67)	1.53 (0.58–4.06)	1.59 (0.49–5.22)	3.64 (1.17–11.3)	0.04
Outcomes considered more prone to bias									
Cardiovascular disease (G45-46;I00-99)	4942	464.9	1.12 (1.02–1.22)	1.00	0.96 (0.87–1.06)	1.05 (0.94–1.18)	1.16 (1.00–1.35)	1.29 (1.06–1.58)	<0.001
Hypertensive heart disease (I11)	147	14.5	1.58 (0.87–2.89)	1.00	1.25 (0.65–2.39)	1.29 (0.60–2.79)	2.16 (0.90–5.18)	2.75 (0.94–8.11)	0.28
Ischaemic heart disease (I20-25)	1925	178.7	1.07 (0.93–1.24)	1.00	0.81 (0.70–0.95)	0.84 (0.70–1.00)	0.90 (0.71–1.14)	1.16 (0.86–1.55)	<0.001
Atrial fibrillation and flutter (I48)	243	23.5	0.95 (0.63–1.44)	1.00	1.07 (0.69–1.65)	1.22 (0.74–2.03)	2.02 (1.10–3.69)	0.64 (0.15–2.74)	0.14
Cerebrovascular disease (G45-46; I60-69)	1316	125.3	1.13 (0.94–1.35)	1.00	1.11 (0.92–1.34)	1.15 (0.92–1.44)	1.22 (0.90–1.65)	1.16 (0.73–1.85)	0.77
Ischaemic stroke (G45-46; I63;65–66;67.2-67.3;67.5-67.6;69.3)	172	16.7	0.77 (0.48–1.25)	1.00	1.01 (0.62–1.65)	1.25 (0.71–2.20)	0.79 (0.32–1.96)	1.29 (0.43–3.90)	0.47
Haemorrhagic stroke (I60-62.0;67.0-67.1;68.1-68.2;69.0-69.2)	325	24.8	1.37 (0.94–1.98)	1.00	1.26 (0.85–1.86)	1.14 (0.72–1.83)	1.19 (0.64–2.21)	0.38 (0.09–1.60)	0.33
Other and unspecified stroke (Other I62.1-69.8)	819	83.8	1.13 (0.90–1.42)	1.00	1.08 (0.85–1.37)	1.13 (0.85–1.51)	1.36 (0.93–1.97)	1.52 (0.87–2.66)	0.52
Other cardiovascular disease (I00-10;12–15;26-47;49–52;70-99)	1311	122.9	1.17 (0.97–1.40)	1.00	1.01 (0.84–1.23)	1.28 (1.03–1.60)	1.37 (1.03–1.81)	1.50 (1.03–2.19)	0.02
Combined outcomes									
Alcohol-related causes combined (All of the above)	9812	859.5	1.12 (1.05–1.19)	1.00	0.99 (0.92–1.06)	1.10 (1.01–1.19)	1.18 (1.06–1.31)	1.53 (1.34–1.75)	<0.001
Alcohol-related causes combined except CVD ([f])	4870	394.6	1.11 (1.01–1.22)	1.00	1.01 (0.92–1.12)	1.14 (1.01–1.27)	1.19 (1.02–1.38)	1.78 (1.49–2.13)	<0.001
Non-alcohol-related causes combined (Other A00-Y98)	8381	597.4	1.12 (1.05–1.21)	1.00	0.97 (0.90–1.05)	1.03 (0.95–1.12)	0.98 (0.88–1.09)	1.16 (1.02–1.33)	<0.001

(*continued on next page*)

Table 2 (*continued*)

Cause of death (ICD-10 code)	n deaths	Age- and sex-standardised rate[a]	HR drinks per week (95 % CI)						p^b
			0 to <1	≥1 to ≤3.5	>3.5 to ≤10	>10 to ≤20	>20 to ≤30	>30	
All-cause mortality (A00-Y98)	18,193	1456.9	1.12 (1.07–1.18)	1.00	0.98 (0.93–1.03)	1.06 (1.00–1.12)	1.08 (1.00–1.16)	1.33 (1.22–1.47)	<0.001
All-cause mortality except CVD ([g])	13,251	992.0	1.12 (1.06–1.19)	1.00	0.99 (0.93–1.05)	1.07 (1.00–1.14)	1.05 (0.97–1.15)	1.35 (1.21–1.50)	<0.001

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), menopausal hormone therapy use (women) and height. CVD, Cardiovascular Disease. ICD-10, International Classification of Diseases, version 10.

[a] Standardised rate per 100,000 person-years, standardised by age and sex to the 2006 New South Wales population aged ≥45 years.

[b] *p* heterogeneity.

[c] Breast cancer in women only.

[d] > 20 drinks per week for women.

[e] Tuberculosis (8 deaths; ICD-10: A15-19; B90; M49.0; P37.0), sexually transmitted infections (<5 deaths; ICD10: A50-64; B20-24; M03.1; 73.0–73.1; N70-71; 73–74), mental and behavioural disorders due to use of alcohol (23 deaths; ICD-10: F10), depression (9 deaths; ICD-10: F32-33; 34.1), degeneration of nervous system due to alcohol (<5 deaths, ICD-10: G31.2), and epilepsy (21 deaths; ICD-10: G40-41).

[f] All of the above except G45-46; I00-99.

[g] A00-Y98 except G45-46; I00-99.

a test for non-linearity performed.[54] One drink per week was used as the reference amount. For each outcome, where there was evidence for non-linearity, restricted cubic spline models were presented, otherwise log-linear models were presented. The restricted cubic spline models were not corrected for regression dilution.

2.5. Covariates

Covariates that were self-reported in the baseline questionnaire are listed in Supplementary Table 1. Remoteness of place of residence was derived from postcode in the Services Australia Medicare enrolment database, and categories were based on the Accessibility/Remoteness Index of Australia (ARIA+ 2006).[55] All categorical covariates except sex had a missing indicator category. The selection of covariates was based on those used in previous large cohort studies investigating alcohol consumption and cause-specific mortality.[7,8,15]

2.6. Statistical analyses

Hazard ratios (HR) and 95 % confidence intervals (CI) of death were calculated for each cause of death using Cox proportional hazard regressions using age as the underlying time variable.[56] Censoring occurred at death from the cause in question, death from other causes, or at the end of study period (December 24, 2019), whichever occurred first. A test of the proportional hazards assumption was performed for all Cox regressions. If significant violations were detected, then log-log survival curves stratified by the variables in violation were plotted. If, upon visual inspection the lines were non-parallel for a covariate, a stratified Cox model was fitted to examine whether the HRs deviated. If the lines were non-parallel for the exposure variable (alcohol consumption), the model was divided into two age groups with equal person-years of follow-up (<58 and ≥ 58 years) to investigate differences in HRs.

As sex[57] and smoking status[26] differences have been reported for alcohol and all-cause mortality risk, two-way statistical interaction tests between alcohol consumption as a continuous variable (per seven drink increase in weekly alcohol consumption) among drinkers and both sex and smoking status (never-smoking vs. ever-smoking) were conducted, with the inclusion of alcohol consumption as a main-effects categorical variable. The results were stratified where relevant.

A *p*-value for interaction by pattern of drinking was calculated, defined as the test of interaction between days per week and drinks per week (both categorical variables). The pattern of drinking analysis was only performed for outcomes with at least 1000 deaths.

The cumulative absolute risk of cause-specific mortality from age 25–85 years in Australia in 2021 by sex and level of alcohol consumption was estimated for mortality where possible (methods detailed in Supplementary Information p.3).

Population attributable fractions (PAFs) for alcohol consumption and cause-specific mortality in Australia in 2021 by sex were estimated for the same set of causes of death as for cumulative absolute risk, along with mortality from all cancers combined, all-cause mortality and all-cause mortality except CVD. This calculation was based on the results of the continuous variable analysis, and 14 categories of drinking were used. The methods used to calculate PAFs are detailed in the Supplementary Information (p.5).

All analyses were adjusted for potential confounders, including sex, age (underlying time variable), 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), menopausal hormone therapy use (women) and height. Minimally adjusted regressions (including only sex and age as the underlying time variable) are also included in the Supplementary Information. Analyses were performed using SAS 9.4 and STATA 16.0. Secure data access was provided through the Sax Institute's Secure Unified Research Environment (SURE).

A sensitivity analysis examined the impact of excluding the first three years of follow-up to assess the possibility of reverse causation. For the analysis of drinks per week as a continuous variable, sensitivity analyses examined the effect of using the mean number of drinks per week of each alcohol consumption category reported at baseline rather than at 5-year follow-up (to assess any impact of regression dilution), and the effect of using the actual number of drinks per week reported by participants rather than the mean of each alcohol consumption category. As body mass may be on the causal pathway between alcohol consumption and cause-specific mortality, sensitivity analyses including all covariates except for BMI in regression models were also performed.

The funding source of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. Results

181,607 of 267,153 participants (67.6 %) were included for analysis after excluding 640 participants (0.2 %) who withdrew from the study after baseline, 175 (0.07 %) from a pilot study, 5 (0.002 %) aged <45 years at baseline, 81,512 (30.5 %) with a history of cancer, CVD,

diabetes, Parkinson's disease or hip fracture at baseline, 3149 (1.2 %) with missing information on overall alcohol consumption, and 65 (0.02 %) with record linkage errors. The percentage of missing data for each covariate is shown in Supplementary Table 1.

Of all included participants, the median follow-up period was 11.4 years. 18,193 (10.0 %) participants had died by December 24, 2019. Overall, 125,346 (69.0 %) participants consumed at least one alcoholic drink per week, of whom 40,529 (32.3 %) consumed >10 drinks per week. Of the 96,485 participants who consumed ≥4 drinks per week, 918 (1.0 %) were excluded from the drinking pattern analyses due to missing information on number of drinking-days per week. Of the 95,567 drinkers included in the drinking pattern analyses, 72,272 (75.6 %) consumed alcohol 4–7 days per week, including 31,816 (33.3 %) who consumed alcohol every day. There was variation in the distribution of covariates by level of alcohol consumption, particularly by socio-demographic characteristics and smoking status (Table 1).

Table 2 shows the risk of each cause of death in relation to weekly alcohol consumption. Deaths from liver disease (among participants consuming >3.5 drinks/week), digestive system disease (>10 drinks per week), CVD (>20 drinks/week), and cancers of the mouth, pharynx and larynx, oesophagus, and liver (>30 drinks/week) were significantly greater compared to those among participants with low-volume consumption (≥1 to ≤3.5 drinks/week). Participants with 0 to <1 drinks/week had significantly increased risk of death from CVD and lower respiratory infection compared to low-volume drinkers. All-cause mortality risk (both with and without CVD deaths) was significantly increased for participants who consumed >10 drinks/week and was also increased for non-drinkers compared to low-volume drinkers.

Among drinkers, risk of death increased with increased levels of alcohol consumption for mouth, pharynx and larynx cancer, oesophageal cancer, liver cancer, digestive system disease, liver disease, falls, and CVD (Fig. 1). For every additional seven drinks per week, the risk of

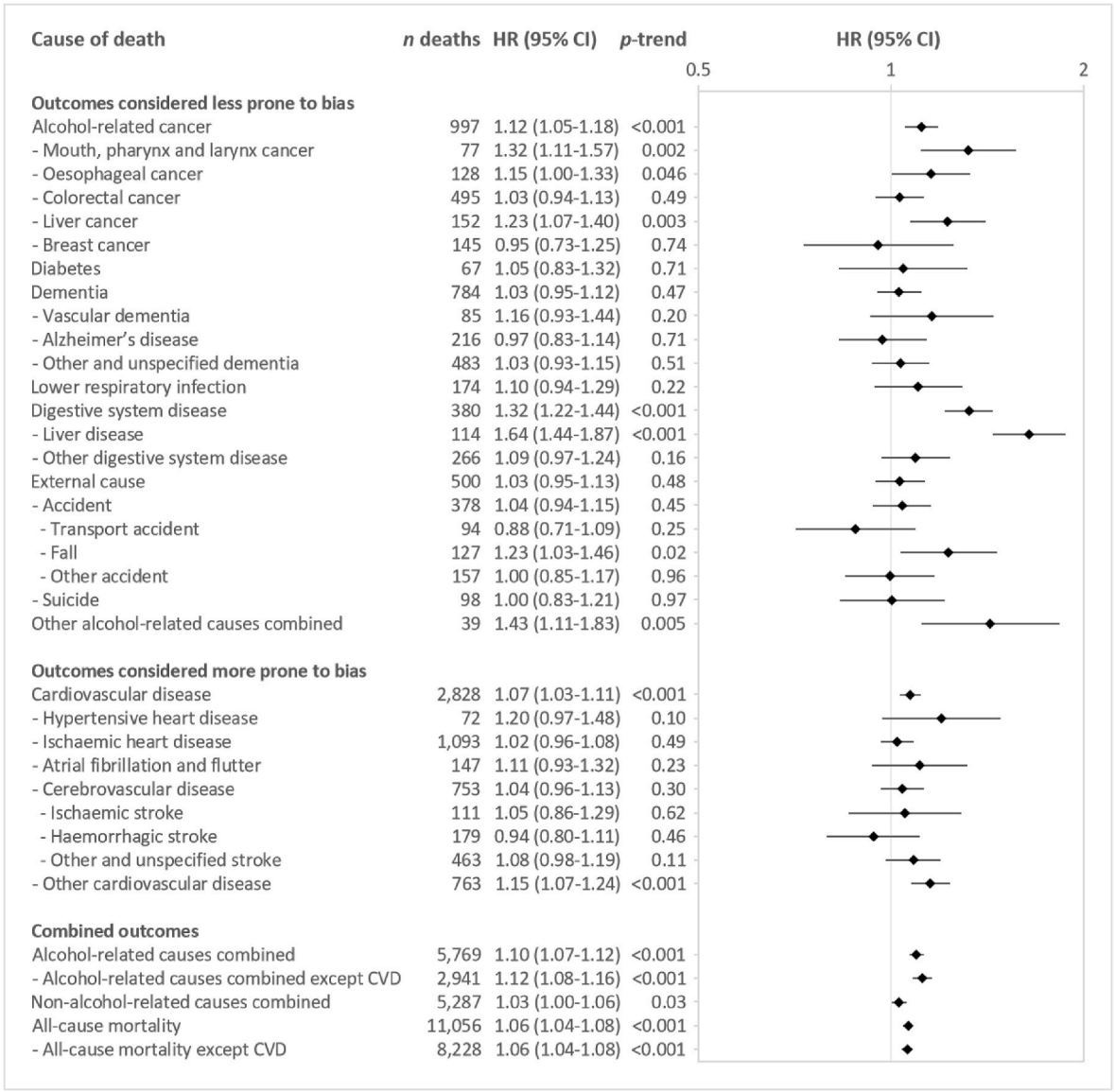

Fig. 1. Hazard ratios (HR) and 95 % confidence intervals (CI) of cause-specific mortality risk per seven drink increase in weekly alcohol consumption among drinkers in the 45 and Up Study (2005–2019). Linear trend calculated among drinkers only, where participants within each category of alcohol consumption at baseline were assigned the mean level of alcohol consumption they reported at first wave follow-up (median 5.3 years after baseline). 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), menopausal hormone therapy use (women) and height. Breast cancer in women only for the outcomes of mortality from alcohol-related cancer, breast cancer, alcohol-related causes combined, and alcohol-related causes combined except CVD. CVD, Cardiovascular Disease.

death from alcohol-related cancers combined increased by 11 %, from alcohol-related causes combined by 10 %, and from any cause by 6 %.

There was evidence of non-linearity for the relationship between alcohol consumption and liver disease mortality ($p = 0.001$) and IHD mortality ($p = 0.006$). Liver disease mortality risk increased monotonically with increasing levels of alcohol, with significantly elevated risk from ≥8 drinks per week. For IHD mortality the risk relationship was J-shaped, with decreased risk from ≥4 to ≤20 drinks/week, and increased risk from ≥117 drinks/week. The restricted cubic spline models for these outcomes are shown in Supplementary Fig. 1.

Mortality risk did not vary significantly in relation to drinking pattern. Specifically, there were no statistically significant interactions between days per week of drinking and number of drinks per week for any of the mortality outcomes examined (Fig. 2 and Supplementary Table 2).

Significant statistical interactions were observed for mortality risk per seven drink increase in weekly alcohol consumption by sex: other and unspecified dementia ($p = 0.02$; HR women 0.77, 95 % CI: 0.60–0.97; HR men 1.12, 1.00–1.25), external causes ($p = 0.04$; HR women 1.25, 1.04–1.51; HR men 0.98, 0.88–1.08), accidents ($p = 0.03$; HR women 1.28, 1.04–1.58; HR men 0.97, 0.86–1.10), and other accidents ($p = 0.04$; HR women 1.22, 0.88–1.69; HR men 0.92, 0.76–1.11); and with smoking status in relation to death from atrial fibrillation and flutter ($p = 0.03$; smoking history HR 1.19, 0.97–1.46; no smoking history HR 0.91, 0.65–1.28), cerebrovascular disease ($p = 0.006$; smoking history HR 0.96, 0.86–1.06; no smoking history HR 1.18; 1.05–1.32), other and unspecified stroke ($p < 0.001$; smoking history HR 0.94; 0.82–1.07; no smoking history HR 1.33, 1.15–1.53), and suicide ($p = 0.047$; smoking history HR 0.89, 0.69–1.14; no smoking history HR 1.20, 0.91–1.59).

Fig. 3 shows the cumulative absolute risk of mortality from alcohol-related causes combined between the ages of 25–85 years, by sex and level of alcohol consumption. By age 85 years, the absolute risk of mortality from alcohol-related causes combined was 38.2 % in men and 25.3 % in women for those consuming >10 drinks per week, compared to 29.7 % in men and 21.2 % in women for those consuming 0 to <1 drink per week. This represented an absolute risk increase of 8.5 % in men and 4.1 % in women. Cumulative risk for each cause of death is provided in Supplementary Table 3. In sensitivity analyses, using drinking categories based on the 2009 National Health and Medical Research Council (NHMRC) alcohol health guidelines, the absolute risk of mortality from alcohol-related causes combined by age 85 years was 38.9 % in men and 27.4 % in women for those consuming >14 drinks per week, compared to 29.8 % in men and 21.3 % in women for those consuming 0 to <1 drink per week. This represented an absolute risk increase of 9.0 % in men and 6.1 % in women (Supplementary Fig. 2 and Supplementary Table 4).

The population attributable fractions for alcohol consumption and cause-specific mortality in the Australian population in 2021 are shown in Supplementary Table 5. Of 171,469 deaths in Australia in 2021, 9029 (5.3 %) were estimated to be attributable to alcohol consumption, with a higher proportion in men (7.3 %) than in women (3.0 %). Of 49,528 cancer deaths in Australia in 2021, 1680 (3.4 %) were estimated to be attributable to alcohol consumption (4.2 % for men; 2.4 % for women).

Generally, results did not materially differ when the first three years of follow-up were excluded (Supplementary Tables 6, 7 and 8). Using the

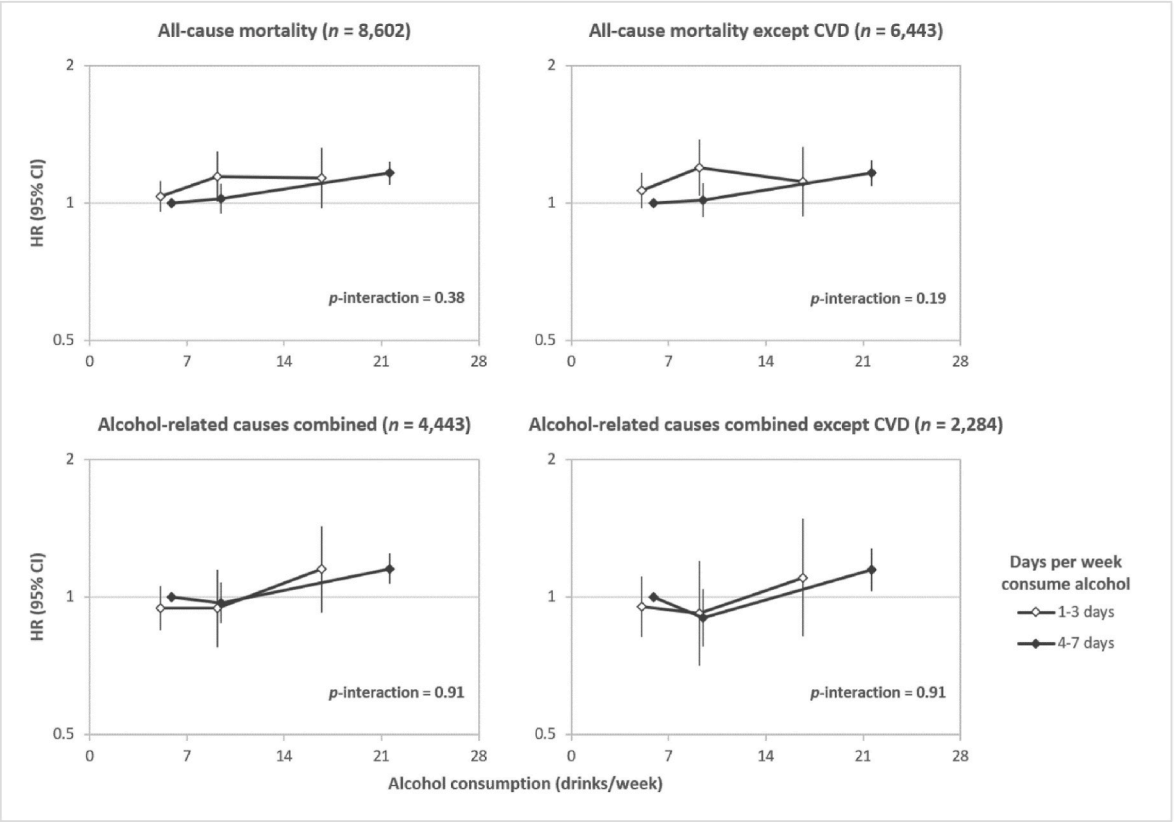

Fig. 2. Hazard ratios (HR) and 95 % confidence intervals (CI) of cause-specific mortality risk by drinking pattern among participants consuming ≥4 drinks per week in the 45 and Up Study (2005–2019). Models were adjusted for sex, age, remoteness, education, household income, health insurance status, partner 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), menopausal hormone therapy use (women) and height. Reference category: ≥4 to 7 to ≤10 drinks per week, and >10 drinks per week). $p_{interaction}$ is for test of interaction between days per week and drinks per week. CVD, Cardiovascular Disease.

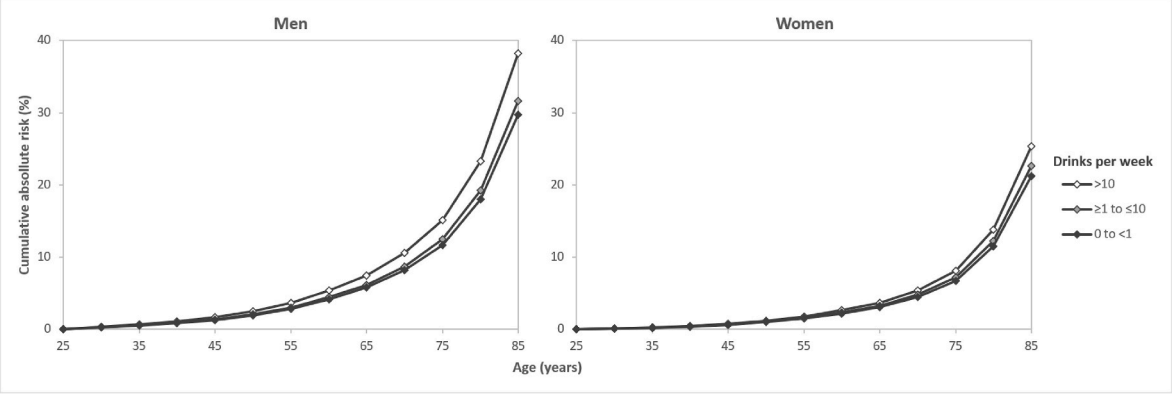

Fig. 3. Cumulative absolute risk (%) of mortality from alcohol-related causes combined from age 25–85 years in Australia in 2021 by sex and level of alcohol consumption using hazard ratios from the 45 and Up Study (2005–2019). Cumulative absolute risk estimate does not include deaths from the alcohol-related causes of death of tuberculosis (ICD-10: A15-19; B90; M49.0; P37.0), sexually transmitted infections (ICD10: A50-64; B20-24; M03.1; 73.0–73.1; N70-71; 73–74), mental and behavioural disorders due to use of alcohol (ICD-10: F10), depression (ICD-10: F32-33; 34.1), degeneration of nervous system due to alcohol (ICD-10: G31.2), and epilepsy (ICD-10: G40-41). ICD-10, International Classification of Diseases, version 10.

mean number of drinks per week of each alcohol consumption category reported at baseline (rather than at 5-year follow up) and using the actual number of drinks per week reported by participants (rather than the mean of each drinking category) both appeared to attenuate hazard ratios for some outcomes, particularly for death from liver disease (Supplementary Table 7). Minimally adjusted hazard ratios are presented in Supplementary Tables 9, 10 and 11. Results did not materially differ when BMI was not included in regressions as a covariate (Supplementary Tables 10, 12 and 13).

Statistically significant violations of the proportional hazards assumption were detected in models for several causes of death. For some covariates, plotting the log-log graphs did not reveal clear proportional hazards violations (Supplementary Table 14). Stratified Cox models for the remaining covariates with a statistically significant proportional hazards assumption violation were calculated (results not shown). For models with a statistically significant proportional hazards assumption violation for alcohol consumption, Cox models stratified by age are presented in Supplementary Table 15. Models without stratification were reported in the manuscript for ease of interpretation.

4. Discussion

In this large, population-based cohort study in Australia, we found that increasing numbers of alcoholic drinks per week were associated with increased risk of death from cancers of the mouth, pharynx, larynx, oesophagus, liver and alcohol-related cancers combined, digestive system disease, liver disease, falls, other alcohol-related causes combined, and CVD. Overall, we estimated that approximately 1 in 12 Australian men (8.5 %) and approximately 1 in 24 Australian women (4.1 %) who consume more than 10 alcoholic drinks per week, will die from their drinking by age 85 years. Relative risk of alcohol-related mortality in our study did not vary significantly by sex or smoking status for most causes of death. We found no evidence that mortality risk varied by pattern of drinking.

Our results are largely consistent with previous studies,[47] and where we observed null results, the confidence intervals for many of these causes of death were consistent with previous estimates[4,10,36,58,59] (apart from dementia, where risk estimates were closer to the null than those reported previously[60]). Our absolute risk estimates for mortality in relation to total weekly alcohol consumption differed slightly to previous reports, however each study has used different methods, making direct comparisons challenging. In the modelling report used to inform the Australian alcohol guidelines, men and women who consumed 21 drinks per week (over three days per week, the Australian average frequency of consumption[51]), had an absolute lifetime risk of alcohol-attributable mortality of 6.9 % and 9.8 % to age 90 years, respectively.[61] In a European study, 30 g of ethanol per day (approximately equivalent to the amount used in the calculation in our study) was associated with a lifetime risk of death due to alcohol use of 1.4 % in men and 4.7 % in women to age 75 years, respectively.[62] These findings are lower than the result for men in our study, and higher than or similar to the result for women in our study. It is also notable that our study found that risk was higher in men than in women, while the reverse was found in these two studies. Reasons for these differences may include that our hazard ratios differed from those used in prior calculations, differences in the conditions included as alcohol-attributable conditions, and differences in the age range used for the definition of lifetime risk.

Previous studies have found that heavy episodic 'binge' drinking (defined in several different ways) increases mortality risk independent of the overall amount of alcohol consumed.[12,14,17,18] We did not observe an independent effect of drinking pattern on risk of death from alcohol-related causes combined or all-cause mortality. However, our drinking pattern analyses relied on a quantity-frequency construct rather than specific drinking patterns that were ascertained directly, and was likely underpowered, especially among heavier drinkers. We examined whether participants who concentrated intake on 1–3 days per week had a different risk profile to those who consumed the same amount of alcohol on average over 4–7 days of the week. Because this quantity-frequency construct used the average number of drinks consumed over the week, it could not differentiate participants by daily variation in intake. For example, participants who consumed a low volume of alcohol every day were grouped with those who drink heavily on the weekend and also consumed small amounts during the week, yet the risk profile of these participants may differ. Previous studies have reported significant variation in mortality outcomes for drinking patterns defined in other ways, including the average number of drinks consumed on drinking-days,[18] and heavy episodic drinking frequency.[12,14] Significant differences in all-cause mortality risk[12–14] and death from cancer[13,18] and CVD[12,13,18] have also been reported in relation to drinking frequency. Studies of drinking pattern that did not account for overall alcohol consumption are difficult to interpret, given it is impossible to differentiate the effects of overall alcohol consumption from the impact of drinking pattern itself.[13,15,16] An effect of drinking pattern on mortality risk would be evidence of a mechanism where acute, heavy alcohol exposure impacts health differently than chronic exposure, and that the true extent of risk relationships may be occluded if overall alcohol consumption is examined alone. Ultimately, further well-designed and adequately powered studies that account for overall alcohol consumption are needed to address this research question.

We estimated that 9029 deaths (5.3 % of all deaths) and 1680 cancer

deaths (3.4 % of all cancer deaths) were attributable to alcohol consumption in Australia in 2021. These estimates are slightly higher than the range of results that have been reported for all-cause mortality in Australia, which include 3.9 % in 2010,[63] 4.6 % in 2016,[1] 4.1 % in 2018,[64] a net 4734 deaths in 2020,[65] and a net 1697 deaths (net 1.6 %) annually in 2012–2016.[61] For cancer mortality, our estimate of 3.4 % is within the range of results that have been reported for Australia, which include 1503 deaths in 2010,[63] 2.4 % in 2013,[66] 2577 deaths (men: 7.1 %; women: 3.7 %) in 2018,[1] and 2214 deaths in 2020.[65] Our estimate used hazard ratios derived from the Australian population and accounted for regression dilution, which may explain differences between our findings and those of other studies, which are largely based on relative risks derived from international populations. As our estimate was for a more recent year (2021) than estimates in other studies, population growth and ageing could also account for differences.

The strengths of our study include: the use of linked health records to obtain complete follow-up of registered death notifications; regressions that could be adjusted for a large number of potential confounders; the use of a reference group of low-volume drinkers as opposed to a reference group that included non-drinkers to calculate relative risk, thereby minimising potential bias from the 'sick-quitter effect'; and the exclusion of participants with a history of chronic disease at baseline to account for the possibility that declining health was associated with a reduction in drinking.[67]

A limitation of our study was that we were unable to differentiate between never-drinking, former drinking and occasional drinking (<1 drink/week), nor could we investigate differences in mortality risk by beverage type. In the 2007–2008 National Health Survey, 33.4 % of persons aged 55–64 consumed alcohol less than weekly, including 9.6 % who were never-drinkers, 7.2 % who were former drinkers (12 months or more since drinking) and 16.6 % who consumed alcohol less than 12 months ago.[68] It is unclear whether the distribution would be similar for participants consuming <1 drink per week in the 45 and Up Study.

There are also some limitations to using a reference group of low-volume drinkers. These include that similar to the 'sick-quitter effect', some participants may have cut down their drinking to low levels in response to ill-health,[26,27] and also that the removal of former drinkers who have quit drinking in response to ill-health (alcohol-related or otherwise) from drinking groups can create a systematic bias towards the remaining drinkers appearing more healthy.[7,69] To address this bias, it has been proposed that former drinkers should be assigned to the drinking group of their former level of alcohol consumption.[69] Both of these limitations would cause mortality attributable to drinking to be underestimated. Furthermore, if there are any health benefits attributable to low-volume drinking, the use of low-volume drinkers as the reference group could cause risks for higher-volume drinking to be overestimated, and for any health benefits of low-volume drinking to be underestimated, should these exist. This could be mitigated by using a lower drinking cut-point for the reference group, such as occasional drinkers who consume <1 drink per week. In our study, hazard ratio point estimates for consuming <1 drink per week relative to low-volume drinking were higher for some outcomes (e.g. CVD mortality) than others (e.g. mouth, pharynx and larynx cancer mortality), which may suggest that lower risk associations for low-volume drinking are not entirely attributable to the 'sick-quitter effect' for all outcomes.

Heavier drinkers may be underrepresented in our study, as cohort study participants may have more health-conscious behaviours than the general population compared to those who do not participate. Despite not being directly representative of the general population, it has been shown however that exposure-outcome relationships based on internal comparisons in the 45 and Up Study are likely to be generalisable and reliable.[70] Nevertheless, there remains the possibility that non-response bias due the underrepresentation of heavier drinkers in the 45 and Up Study may have resulted in an underestimate of mortality risk within each category of alcohol consumption examined here, as well as for risk overall. Similarly, the population health surveys used in the calculations for cumulative absolute risk and population attributable fractions may also be subject to non-response bias due to the underrepresentation of heavier drinkers. Importantly, the direction of bias for these absolute risk measures will depend on the relative degree of non-response bias between the 45 and Up Study and the respective population health surveys, which, based on current data, remains unknown.

Participants may underreport their level of alcohol consumption in observational studies, which could bias risk estimates.[72] Lower-risk drinkers have been found to underreport alcohol consumption to a greater degree than higher-risk drinkers in Australia and Canada.[73,74] Conversely, underreporting was associated with heavy drinking, frequent drinking and non-routine drinking in a study in England.[75] The extent to which underreporting occurred in the 45 and Up Study is unknown. We were also not able to ascertain alcohol consumption and drinking patterns over the life-course, and rather, were limited to consumption at one point in time. Another limitation may have been the length of the follow-up period in our study (median 11.4 years). Longer follow-up periods are likely to mitigate selection bias,[27] and result in higher risk estimates for drinking vs. non-drinking,[28] as well as attenuated inverse associations between low- and medium-volume drinking and risk of all-cause mortality.[19,20] 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 underestimates of mortality risk.[27,71] While there were no appreciable changes in the widths of the 95 % confidence intervals between the minimally adjusted and fully adjusted models (e.g. Supplementary Table 10), it remains possible that adjustment for approximately twenty covariates may have led to reductions in statistical power. Finally, there were limitations to the cumulative absolute risk and population attributable fraction calculations, which are detailed in the Supplementary Information (p.3-7).

In Australia, interventions aimed at reducing the health risks of alcohol consumption have tended to focus on short-term harm minimisation, and have also involved industry engagement and a degree of self-regulation.[76,77] Our study highlights the importance of targeting alcohol minimisation interventions at older people, especially given evidence that more than half of risky drinkers aged ≥50 years in Australia do not perceive their level of drinking to be harmful, and identify as light, occasional or social drinkers.[78] An Australian mass media campaign conducted in 2010, which emphasised cancer risk rather than risk of injury or other short-term harms, evaluated comparatively well among persons aged 18–64 years.[79] Furthermore, interventions focusing on long-term harms such as cancer and digestive system disease risk may be especially important since the onset of the COVID-19 pandemic, given findings that a portion of Australians have reported an increase in alcohol consumption,[80] and the possibility that these drinking behaviour changes may persist into the long term.

The Australian alcohol consumption guidelines were last updated in 2020,[51] and our results support the guideline for healthy adults of no more than ten standard drinks per week and no more than four standard drinks on any one day to reduce the risk of alcohol-related harm. The Australian Government has also developed a National Alcohol Strategy (2019–2028), designed to reduce alcohol-related harm through agreed national priority areas and multisector partnerships, with the overall target of a 10 % reduction in harmful alcohol consumption.[81] Implementation of the strategy is a matter for all nine Australian federal, state and territory governments. Our findings reinforce the case, as documented in the National Alcohol Strategy, for adding health-related warning labels such as chronic disease and mortality risk information to alcoholic beverage labelling, structural measures including those regulating the pricing (e.g., minimum unit pricing), availability (e.g., outlet density and trading hours) and promotion of alcohol, targeted education programs, and for updating national health guidelines to promote public understanding about alcohol-related harms, especially in relation to chronic disease. Moreover, increasing awareness in the community of the relationship between alcohol consumption and

chronic disease may help to reduce risky consumption across the life course. Our results strengthen the evidence on the adverse health effects of alcohol consumption and can be used to support public health interventions aimed at minimising risky levels of alcohol consumption.

Author statements

Ethical approval

Ethics approval for the 45 and Up Study was granted by the University of New South Wales Human Research Ethics Committee (reference: HC210602), and for this specific analysis by the NSW Population Health Services Research Ethics Committee (reference: 2014/08/551). Written informed consent was obtained from all participants in the study.

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Competing interests

PS was funded by a postgraduate research scholarship from Cancer Council NSW, the 45 and Up PhD Scholarship in Cancer Research. KC is co-principal investigator of an unrelated investigator-initiated trial of cervical screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the VCS Foundation (VCS), a government-funded health promotion charity. KC is also an investigator of Compass New Zealand (ACTRN12614000714684), which was conducted and funded by Diagnostic Medlab (DML), now Auckland District Health Board. The VCS Foundation received equipment and a funding contribution from Roche Molecular Systems and Ventana USA and DML received equipment and a funding contribution for Compass from Roche Molecular Systems. However, neither KC nor her institution on her behalf receives direct funding from industry for this trial or any other project. EB is supported by the National Health and Medical Research Council of Australia (reference: 1136128) and the Government of Australia. The other authors have no interests to declare.

Data statement

The data that support the findings of this study are available from the Sax Institute (https://www.saxinstitute.org.au/solutions/45-and-up-study/).

Contributors

PS and MFW contributed to the conceptualisation of the study. PS, MFW, EB, GJ and SE contributed to the design of the study. PS performed the analyses and wrote the initial draft of the manuscript. PS and MW have accessed and verified the data. All authors contributed to interpreting the data and reviewing the manuscript. All authors have approved the final article. All authors confirm that they had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2024.12.022.

References

1. World Health Organisation. *Global Status Report on Alcohol and Health 2018*. Geneva: WHO; 2018.
2. Li Y, Mao Y, Zhang Y, et al. Alcohol drinking and upper aerodigestive tract cancer mortality: a systematic review and meta-analysis. *Oral Oncol*. 2014;50:269–275.
3. Fahey PP, Mallitt KA, Astell-Burt T, Stone G, Whiteman DC. Impact of pre-diagnosis behavior on risk of death from esophageal cancer: a systematic review and meta-analysis. *Cancer Causes Control*. 2015;26:1365–1373.
4. Choi YJ, Myung SK, Lee JH. *Light Alcohol Drinking and Risk of Cancer: A Meta-Analysis of Cohort Studies*. Cancer Res Treat; 2017.
5. Turati F, Galeone C, Rota M, et al. Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. *Ann Oncol*. 2014;25:1526–1535.
6. Yang L, Zhou M, Sherliker P, et al. Alcohol drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220,000 men with 15 years of follow-up. *Int J Epidemiol*. 2012;41:1101–1113.
7. Bergmann MM, Rehm J, Klipstein-Grobusch K, et al. The association of pattern of lifetime alcohol use and cause of death in the European prospective investigation into cancer and nutrition (EPIC) study. *Int J Epidemiol*. 2013;42:1772–1790.
8. Ferrari P, Licaj I, Muller DC, et al. Lifetime alcohol use and overall and cause-specific mortality in the European Prospective Investigation into Cancer and nutrition (EPIC) study. *BMJ Open*. 2014;4, e005245.

9. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ*. 2011;342, d671.
10. Cai S, Li Y, Ding Y, Chen K, Jin M. Alcohol drinking and the risk of colorectal cancer death: a meta-analysis. *Eur J Cancer Prev*. 2014;23:532–539.
11. Jin M, Cai S, Guo J, et al. Alcohol drinking and all cancer mortality: a meta-analysis. *Ann Oncol*. 2013;24:807–816.
12. Graff-Iversen S, Jansen MD, Hoff DA, et al. Divergent associations of drinking frequency and binge consumption of alcohol with mortality within the same cohort. *J Epidemiol Community Health*. 2013;67:350–357.
13. Ozasa K. Alcohol use and mortality in the Japan collaborative cohort study for evaluation of cancer (JACC). *Asian Pac J Cancer Prev APJCP*. 2007;8(Suppl):81–88.
14. Plunk AD, Syed-Mohammed H, Cavazos-Rehg P, Bierut LJ, Grucza RA. Alcohol consumption, heavy drinking, and mortality: rethinking the j-shaped curve. *Alcohol Clin Exp Res*. 2014;38:471–478.
15. Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. Relationship of alcohol consumption to all-cause, cardiovascular, and cancer-related mortality in U.S. Adults. *J Am Coll Cardiol*. 2017;70:913–922.
16. Smyth A, Teo KK, Rangarajan S, et al. Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a prospective cohort study. *Lancet*. 2015;386:1945–1954.
17. Rehm J, Greenfield TK, Rogers JD. Average volume of alcohol consumption, patterns of drinking, and all-cause mortality: results from the US National Alcohol Survey. *Am J Epidemiol*. 2001;153:64–71.
18. Breslow RA, Graubard BI. Prospective study of alcohol consumption in the United States: quantity, frequency, and cause-specific mortality. *Alcohol Clin Exp Res*. 2008; 32:513–521.
19. Gmel G, Gutjahr E, Rehm J. How stable is the risk curve between alcohol and all-cause mortality and what factors influence the shape? A precision-weighted hierarchical meta-analysis. *Eur J Epidemiol*. 2003;18:631–642.
20. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L, de Gaetano G. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med*. 2006;166:2437–2445.
21. Bagnardi V, Zambon A, Quatto P, Corrao G. Flexible meta-regression functions for modeling aggregate dose-response data, with an application to alcohol and mortality. *Am J Epidemiol*. 2004;159:1077–1086.
22. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet*. 2018;391:1513–1523.
23. Naimi TS, Brown DW, Brewer RD, et al. Cardiovascular risk factors and confounders among nondrinking and moderate-drinking U.S. adults. *Am J Prev Med*. 2005;28: 369–373.
24. Fekjaer HO. Alcohol-a universal preventive agent? A critical analysis. *Addiction*. 2013;108:2051–2057.
25. Millwood IY, Walters RG, Mei XW, et al. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. *Lancet*. 2019;393:1831–1842.
26. Fillmore KM, Kerr WC, Stockwell T, Chikritzhs T, Bostrom A. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies. *Addiction Res Theor*. 2006;14:101–132.
27. Stockwell T, Zhao J, Panwar S, Roemer A, Naimi T, Chikritzhs T. Do "moderate" drinkers have reduced mortality risk? A systematic review and meta-analysis of alcohol consumption and all-cause mortality. *J Stud Alcohol Drugs*. 2016;77: 185–198.
28. Zhao J, Stockwell T, Naimi T, Churchill S, Clay J, Sherk A. Association between daily alcohol intake and risk of all-cause mortality: a systematic review and meta-analyses. *JAMA Netw Open*. 2023;6, e236185.
29. Rehm J. Why the relationship between level of alcohol-use and all-cause mortality cannot be addressed with meta-analyses of cohort studies. *Drug Alcohol Rev*. 2019; 38:3–4.
30. Naimi TS. Comment on Rehm: alcohol, cohort studies and all-cause mortality: where to from here? *Drug Alcohol Rev*. 2019;38:9–10.
31. Lankester J, Zanetti D, Ingelsson E, Assimes TL. Alcohol use and cardiometabolic risk in the UK Biobank: a Mendelian randomization study. *PLoS One*. 2021;16, e0255801.
32. van de Luitgaarden IAT, van Oort S, Bouman EJ, et al. Alcohol consumption in relation to cardiovascular diseases and mortality: a systematic review of Mendelian randomization studies. *Eur J Epidemiol*. 2022;37:655–669.
33. Biddinger KJ, Emdin CA, Haas ME, et al. Association of habitual alcohol intake with risk of cardiovascular disease. *JAMA Netw Open*. 2022;5, e223849.
34. Islam SN, Ahammed T, Anjum A, Albalawi O, Uddin MJ. Reporting methodological issues of the mendelian randomization studies in health and medical research: a systematic review. *BMC Med Res Methodol*. 2022;22:21.
35. Cullen KJ, Knuiman MW, Ward NJ. Alcohol and mortality in busselton, western Australia. *Am J Epidemiol*. 1993;137:242–248.
36. Gun RT, Pratt N, Ryan P, Gordon I, Roder D. Tobacco and alcohol-related mortality in men: estimates from the Australian cohort of petroleum industry workers. *Aust N Z J Publ Health*. 2006;30:318–324.
37. Nelson MR, Alkhateeb AN, Ryan P, et al. Physical activity, alcohol and tobacco use and associated cardiovascular morbidity and mortality in the Second Australian National Blood Pressure study cohort. *Age Ageing*. 2010;39:112–116.
38. Banks E, Redman S, Jorm L, et al. Cohort profile: the 45 and up study. *Int J Epidemiol*. 2008;37:941–947.
39. Bleicher K, Summerhayes R, Baynes S, et al. Cohort profile update: the 45 and up study. *Int J Epidemiol*. 2023;52(1):e92–e101.
40. Bergmann MM, Calle EE, Mervis CA, Miracle-McMahill HL, Thun MJ, Heath CW. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. *Am J Epidemiol*. 1998;147:556–562.
41. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust*. 2006;184:6–10.
42. Source Cause of Death Unit Record File Held by the NSW Ministry of Health Secure Analytics for Population. Health Research and Intelligence.
43. Kelman CW, Bass AJ, Holman CD. Research use of linked health data–a best practice protocol. *Aust N Z J Publ Health*. 2002;26:251–255.
44. Open Source ChoiceMaker Technology. *ChoiceMaker*. Open Source ChoiceMaker Technology; 2018 [cited 2023 Jun 14]; Available from: http://oscmt.sourceforge.net/.
45. Bentley JP, Ford JB, Taylor LK, Irvine KA, Roberts CL. Investigating linkage rates among probabilistically linked birth and hospitalization records. *BMC Med Res Methodol*. 2012;12:149.
46. World Health Organisation. *ICD-10 Version:2019*. Geneva: WHO; 2019 [cited 2023 Jun 14]; Available from: https://icd.who.int/browse10/2019/en#/.
47. Rehm J, Gmel Sr GE, Gmel G, et al. The relationship between different dimensions of alcohol use and the burden of disease-an update. *Addiction*. 2017;112:968–1001.
48. Sax Institute. *Data and Technical Information*. Sydney: Sax Institute; 2023 [cited 2023 Nov 27]; Available from: https://www.saxinstitute.org.au/solutions/45-and-up-study/use-the-45-and-up-study/data-and-technical-information/.
49. Rehm J, Irving H, Ye Y, Kerr WC, Bond J, Greenfield TK. Are lifetime abstainers the best control group in alcohol epidemiology? On the stability and validity of reported lifetime abstention. *Am J Epidemiol*. 2008;168:866–871.
50. Sarich P, Canfell K, Banks E, et al. A prospective study of health conditions related to alcohol consumption cessation among 97,852 drinkers aged 45 and over in Australia. *Alcohol Clin Exp Res*. 2019;43:710–721.
51. National Health and Medical Research Council. *Australian Guidelines to Reduce Health Risks from Drinking Alcohol*. Canberra: NHMRC; 2020 [cited 2023 Feb 24]; Available from: https://www.nhmrc.gov.au/health-advice/alcohol.
52. Sarich P, Canfell K, Egger S, et al. Alcohol consumption, drinking patterns and cancer incidence in an Australian cohort of 226,162 participants aged 45 years and over. *Br J Cancer*. 2021;124:513–523.
53. Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst*. 2009;101:296–305.
54. Dupont WD, Plummer D. *Using Stata V9 to Model Complex Non-linear Relationships with Restricted Cubic Splines*. Nashville: Department of Biostatistics, Vanderbilt University Medical School; 2005.
55. Glover JD, Tennant SK. Remote areas statistical geography in Australia: notes on the accessibility/remoteness index for Australia (ARIA+ version). In: *Working Paper Series No. 9. Adelaide: Public Health Information Development Unit*. University of Adelaide; 2003. Report No.: 0730892301.
56. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol*. 1997;145:72–80.
57. Wang C, Xue H, Wang Q, et al. Effect of drinking on all-cause mortality in women compared with men: a meta-analysis. *J Womens Health (Larchmt)*. 2014;23:373–381.
58. Baliunas DO, Taylor BJ, Irving H, et al. Alcohol as a risk factor for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2009;32:2123–2132.
59. Simou E, Britton J, Leonardi-Bee J. Alcohol and the risk of pneumonia: a systematic review and meta-analysis. *BMJ Open*. 2018;8, e022344.
60. Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing*. 2008;37:505–512.
61. Angus C, Henney M, Meier P, Brennan A, Holmes J. *Mortality and Morbidity Risks from Alcohol Consumption in Australia: Analyses Using an Australian Adaptation of the Sheffield Alcohol Policy Model (v2.7) to Inform the Development of New Alcohol Guidelines. Final Report*. Sheffield: ScHARR, University of Sheffield; 2019.
62. Rehm J, Gmel G, Probst C, Shield KD. Lifetime-risk of alcohol-attributable mortality based on different levels of alcohol consumption in seven European countries. In: *Implications for Low-Risk Drinking Guidelines*. Toronto: Centre for Addiction and Mental Health; 2015.
63. Gao C, Ogeil RP, Lloyd B. Alcohol's burden of disease in Australia. In: *Canberra: FARE and VicHealth in Collaboration with Turning Point*. 2014.
64. Australian Institute of Health and Welfare. *Australian Burden of Disease Study: Impact and Causes of Illness and Death in Australia 2018*. Canberra: AIHW; 2021. Contract No.: BOD 29.
65. Gilmore W, Lensvelt E, Jones P, et al. *Australian Alcohol-Attributable Harm Visualisation Tool Version 2.1: National Drug Research Institute*. Curtin University and Canadian Institute for Substance Use Research, University of Victoria; 2023.
66. Wilson LF, Antonsson A, Green AC, et al. How many cancer cases and deaths are potentially preventable? Estimates for Australia in 2013. *Int J Cancer*. 2018;142(4): 691–701.
67. Holdsworth C, Mendonca M, Pikhart H, Frisher M, de Oliveira C, Shelton N. Is regular drinking in later life an indicator of good health? Evidence from the English Longitudinal Study of Ageing. *J Epidemiol Community Health*. 2016;70:764–770.
68. Australian Bureau of Statistics. *National Health Survey: Summary of Results, 2007-2008 (Reissue). Canberra: ABS*. 2009. Contract No. 4364.0.
69. Liang W, Chikritzhs T. The association between alcohol exposure and self-reported health status: the effect of separating former and current drinkers. *PLoS One*. 2013;8, e55881.
70. Mealing NM, Banks E, Jorm LR, Steel DG, Clements MS, Rogers KD. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. *BMC Med Res Methodol*. 2010;10:26.
71. Delgado-Rodriguez M, Llorca J. Bias. *J Epidemiol Community Health*. 2004;58: 635–641.

72. Davis CG, Thake J, Vilhena N. Social desirability biases in self-reported alcohol consumption and harms. *Addict Behav*. 2010;35:302–311.
73. Livingston M, Callinan S. Underreporting in alcohol surveys: whose drinking is underestimated? *J Stud Alcohol Drugs*. 2015;76:158–164.
74. Stockwell T, Zhao J, Macdonald S. Who under-reports their alcohol consumption in telephone surveys and by how much? An application of the 'yesterday method' in a national Canadian substance use survey. *Addiction*. 2014;109:1657–1666.
75. Boniface S, Kneale J, Shelton N. Drinking pattern is more strongly associated with under-reporting of alcohol consumption than socio-demographic factors: evidence from a mixed-methods study. *BMC Publ Health*. 2014;14:1297.
76. Howard SJ, Gordon R, Jones SC. Australian alcohol policy 2001-2013 and implications for public health. *BMC Publ Health*. 2014;14:848.
77. Stafford J, Chikritzhs T, Pierce H, Pettigrew S. An evaluation of the evidence submitted to Australian alcohol advertising policy consultations. *PLoS One*. 2021;16, e0261280.
78. Chapman J, Harrison N, Kostadinov V, Skinner N, Roche A. Older Australians' perceptions of alcohol-related harms and low-risk alcohol guidelines. *Drug Alcohol Rev*. 2020;39:44–54.
79. Wakefield MA, Brennan E, Dunstone K, et al. Features of alcohol harm reduction advertisements that most motivate reduced drinking among adults: an advertisement response study. *BMJ Open*. 2017;7, e014193.
80. Foundation for Alcohol Research & Education. *Alcohol Use and Harms during the COVID-19 Pandemic*. Canberra: FARE; 2022.
81. Australian Government Department of Health. *National Alcohol Strategy 2019-2028*. Canberra: Australian Government Department of Health; 2019. Contract No.: 12045.
82. Australian Government Department of Health. *Make Your Move - Sit Less - Be Active for Life*. Canberra: Australian Government Department of Health; 2014.