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Bassett Julie Karen (Orcid ID: 0000-0003-0799-4821)
Yang Yi (Orcid ID: 0000-0002-7594-6373)
Hodge Allison (Orcid ID: 0000-0001-5464-2197)
Lynch Brigid (Orcid ID: 0000-0001-8060-547X)
Jayasekara Harindra (Orcid ID: 0000-0002-2453-0183)

Alcohol intake trajectories during the life course and risk of alcohol-related cancer: a prospective cohort study

Running title: Alcohol intake trajectories and alcohol-related cancer

Julie K. Bassett[1], Robert J. MacInnis[1,2], Yi Yang[2], Allison M. Hodge[1,2], Brigid M. Lynch[1,2,3], Dallas R. English[1,2], Graham G. Giles[1,2,4], Roger L. Milne[1,2,4], Harindra Jayasekara[1,2,5]

[1] Cancer Epidemiology Division, Cancer Council Victoria, 615 St Kilda Road, Melbourne, Victoria 3004, Australia
[2] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Victoria 3010, Australia
[3] Physical Activity Laboratory, Baker IDI Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Victoria 3004, Australia
[4] Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria 3168, Australia
[5] School of Public Health and Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria 3168, Australia

Correspondence to:
Dr Julie K. Bassett
Cancer Epidemiology Division
Cancer Council Victoria
615 St Kilda Road
Melbourne, Victoria 3004
Australia
E-mail: julie.bassett@cancervic.org.au

Keywords: Cancer risk; cohort study; group-based trajectory modelling; lifetime alcohol intake

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD-O-3, International Classification of Diseases for Oncology; MCCS, Melbourne Collaborative Cohort Study; NHMRC, National Health and Medical Research Council; TR, trajectory; UADT, upper aero-digestive tract

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Novelty and Impact

Unlike most previous studies of alcohol intake and cancer risk, here the authors examined associations of longitudinal drinking trajectories across the lifespan. They observed an increased cancer risk associated with heavy drinking during early adulthood, even when the intake had ceased by middle age, and with drinking that increased during the life-course,

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compared with lifelong non-drinking. These findings point to critical timelines related to alcohol-related cancer etiology and prevention during the adult lifespan.

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Abstract

We examined associations between sex-specific alcohol intake trajectories and alcohol-related cancer risk using data from 22,756 women and 15,701 men aged 40-69 years at baseline in the Melbourne Collaborative Cohort Study. Alcohol intake for 10-year periods from age 20 until the decade encompassing recruitment, calculated using recalled beverage-specific frequency and quantity, was used to estimate group-based sex-specific intake trajectories. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated for primary invasive alcohol-related cancer (upper aerodigestive tract, breast, liver and colorectum). Three distinct alcohol intake trajectories for women (*lifetime abstention*, *stable light*, *increasing moderate*) and six for men (*lifetime abstention*, *stable light*, *stable moderate*, *increasing heavy*, *early decreasing heavy*, *late decreasing heavy*) were identified. 2,303 incident alcohol-related cancers were diagnosed during 485,525 person-years in women and 789 during 303,218 person-years in men. For men, compared with *lifetime abstention*, heavy intake (mean≥60 g/day) at age 20-39 followed by either an early (from age 40-49) (*early decreasing heavy;* HR=1.75, 95% CI: 1.25-2.44) or late decrease (from age 60-69) (*late decreasing heavy;* HR=1.94, 95% CI: 1.28-2.93), and moderate intake (mean<60 g/day) at age 20-39 increasing to heavy intake in middle-age (*increasing heavy;* HR=1.45, 95% CI: 1.06-1.97) were associated with increased risk of alcohol-related cancer. For women, compared with *lifetime abstention*, increasing intake from age 20 (*increasing moderate*) was associated with increased alcohol-related cancer risk (HR=1.25, 95% CI: 1.06-1.48). Similar associations were observed for colorectal (men) and breast cancer. Heavy drinking during early adulthood might increase cancer risk later in life.

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Introduction

Alcohol use caused an estimated 3 million deaths (5.3% of all deaths) including 400,000 deaths from cancer (4.2% of all cancer deaths) globally in 2016.[1] Ethanol in alcoholic beverages, and its toxic metabolite acetaldehyde, are both known to cause cancers in the oral cavity, pharynx, larynx, esophagus (squamous cell carcinoma), liver, colorectum and female breast.[2, 3] Cancer was the leading cause of disease burden in Australia in 2011 ahead of cardiovascular disease,[4] and colorectal and breast cancer, two of the most common cancers globally,[5] were among five cancers that accounted for nearly half of the total cancer burden.[4]

In Australia, the per-capita alcohol intake increased markedly post-World War II, peaked and plateaued during the late 70s, decreased in the 80s and early 90s, and since then has stabilized with mild fluctuations.[6] Alcohol intake in individuals is also likely to vary over time,[7, 8] and intake over time is likely to predict chronic outcomes better than intake at a single timepoint.[9] Despite this, most evidence on cancer risk from prospective studies is based on a single measure of alcohol intake close to study enrolment, usually during middle age, which might not be representative of participants' consumption during earlier age periods, particularly for heavy drinkers who had reduced alcohol intake.[10] Using average or cumulative lifetime alcohol intake overcomes some deficiencies inherent in studies using baseline intake alone but may still miss the effects of more complex patterns of change in alcohol intake over time.

In the present study, we assessed associations for lifetime alcohol intake trajectories with risk of alcohol-related cancer using retrospective information on consumption at various age periods before enrolment in a large prospective study.

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Materials and methods

Participants

The Melbourne Collaborative Cohort Study is a prospective study of 41,513 people (58.9% women; 99.2% aged 40-69 years) recruited during 1990-94 in Melbourne, Australia. Details of the cohort have been published previously.[11] For this analysis, we excluded participants if they were aged <40 or ≥70 years (n=325) or had a previous diagnosis of an invasive cancer at enrolment (n= 1,524), had reported extreme values of total energy intake (<1st percentile and >99th percentile) (n=796), were missing lifetime alcohol intake data (n=372) or data on any of the covariates modelled (n=37), or if they had alcohol intake reported for fewer than three decades of life (n=2), leaving 38,457 (92.6% of the total cohort; 22,756 women and 15,701 men) participants for analysis (Figure 1).

Collection of data

At study entry in 1990-94, structured questionnaires were used to obtain information on potential risk factors including age, sex, country of birth, education, previous medical conditions, and lifestyle behaviors (including cigarette smoking, physical activity, and alcohol intake). A 121-item food frequency questionnaire was used to collect dietary information,[12] and height and weight were measured.

Assessment of alcohol intake

Participants were asked at baseline if they had ever drunk at least 12 alcoholic drinks in a year. Those who had ('non-lifetime abstainers') were then asked about their usual frequency of consumption and usual quantity consumed per drinking occasion for beer, wine and spirits separately during 10-year age periods commencing at age 20, up to the decade of their age at baseline attendance. Usual intake within each age period in grams per day for each beverage

type was calculated by multiplying intake frequency by quantity and standard amount of alcohol per container using data from Australian food composition tables.[13] The alcohol intake for each age period in grams per day was calculated as the sum of intake from the three beverage types. The alcohol intake at baseline age in grams per day was obtained from intake for the age decade encompassing baseline. The average lifetime alcohol intake in grams per day was derived by dividing the total lifetime intake by the total number of days within the age intervals up to study enrolment.

Ascertainment of cancers and deaths

Cancers and vital status were ascertained through the Victorian Cancer Registry, the Australian Cancer Database, the Victorian Registry of Births, Deaths and Marriages and the National Death Index. Alcohol-related cancers were defined as a histopathological diagnosis of primary invasive cancer of the oral cavity, pharynx, larynx and esophagus (squamous cell carcinoma) (collectively referred to as upper aero-digestive tract [UADT] cancer) (codes C01–C06, C09–C10, C13–C15, C32), breast (code C50), liver (code C22) and colorectum (codes C180, C182-189, C199, C209, adenocarcinoma),[2] coded following the 3rd Revision of the International Classification of Diseases for Oncology (ICD-O-3). We further excluded any cancers unrelated to alcohol based on morphology (e.g. lymphomas).

Alcohol intake trajectories

We used a group-based trajectory model to identify clusters of individuals following similar long-term sex-specific alcohol intake trajectories from age 20 years to baseline. This semiparametric group-based trajectory model is an application of finite mixture modelling which assumes the study sample is composed of a mixture of groups following homogenous courses.[14] Sex-specific longitudinal alcohol intake data were fitted as a mixture of several

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latent trajectories in a censored normal model, allowing for the lower (zero g/day) and upper intake (capped at 100 g/day; <2% of men and <0.2% of women had intakes of >100 g/day at each age decade) limits, with a polynomial function for age.[14, 15] We used a two-step modelling process where we first selected the optimal number of trajectories and then we determined the optimal shape of these trajectories using the Bayesian information criterion (BIC) and the log Bayes factor.[14, 16] As approximately 30% of MCCS participants had never drunk alcohol or had very low intakes (<0.5 grams per day) over the observation period, in the first step we included a zero-order (or constant) trajectory and the remaining groups as quadratic functions of age to determine the number of groups. We also set a maximum of six trajectory groups to be investigated. Next, we determined the preferred order of the polynomial (i.e. constant, linear, quadratic or cubic) for each trajectory. Participants were assigned to the group for which their posterior predicted probability calculated from the final model was highest. We evaluated the adequacy of the fit of the final model using recommended diagnostic measures: average posterior probability of assignment for each group of 0.7 or higher; odds of correct classification of 5.0 or higher; the proportion of a sample assigned to a certain group close to the proportion estimated from the model; and a reasonably narrow confidence interval around each trajectory.[14] In trajectory models, alcohol intakes reported by each participant for each 10-year age period preceding their age decade at baseline attendance were considered intakes at the start of those age decades and intake reported for the decade of age at baseline attendance was used as their intake at baseline age.

Statistical analysis

Cox regression[17] was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) with age as the time scale. Follow-up started at baseline attendance and ended at the earliest of date of diagnosis of any first invasive primary cancer, death, emigration, or end of follow-

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up (31 December 2017). To maximize statistical power, the primary analysis was specified *a priori* to be risk of any alcohol-related cancer. A causal diagram (directed acyclic graph) and existing evidence[10] guided the inclusion of confounding variables (all measured at baseline, at the last alcohol assessment) in multivariable models. Alcohol intake was modelled as sex-specific trajectories in models adjusted for education (primary school, technical school, secondary school, university), cigarette smoking status (never, former, current), physical activity (none, low, moderate, high), Mediterranean diet score (0-3, 4-6, 7-9) and total energy from food not including alcoholic beverages (Kcal/day), and stratified by birth cohort (year of birth <1925, 5-year categories for 1925 to 1964, ≥1965) and country of birth (Australia/New Zealand/United Kingdom or Italy/Greece). Because excess body fatness might be a consequence rather than a cause of alcohol consumption, we fitted models with and without adjustment for body mass index (BMI). We considered the model without adjustment for BMI to be the primary analysis. We also examined associations between alcohol intake trajectories and risk of colorectal and breast cancer, the two alcohol-related cancers which had accrued enough cases to be examined individually. Sensitivity analyses were performed (i) excluding the first 2 years of follow-up to account for potential reverse causation; (ii) excluding current smokers to limit the possibility of residual confounding; (iii) further adjusting models for potential site-specific confounders: dietary folate, fiber and red meat intake for colorectal cancer and age at menarche (≤12, 13-14, ≥15 years), parity (0, 1, 2, 3, ≥4), oral contraceptive use (never, past, current), age at first pregnancy with gestation >24 weeks (nulliparous, <20, 20-24, 25-29, ≥30 years), and dietary folate intake for breast cancer. We also compared findings for alcohol intake trajectories with the HRs obtained from a one time-point assessment (at baseline 1990-94) of alcohol intake (men: abstention; >0-19; 20-39; 40-59; 60-79; ≥80 grams/day; women: abstention; >0-19; 20-39; ≥40 grams/day). Tests based on Schoenfeld residuals and graphical methods were used to examine the proportional

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hazards assumption and the Cox models were stratified on covariates that violated the proportional hazard assumption. For women, alcohol intake at baseline (sensitivity analysis) had non-proportional hazards for the highest intake category (≥40 grams/day), and therefore in this model we included a two-way interaction term between alcohol intake and attained age, and for the highest intake category, HRs were predicted separately for ages 62, 69 and 76 years. These ages were the 25th, 50th and 75th percentiles of the distribution of age at diagnosis of an alcohol-related cancer in women. All statistical tests were two-sided, and statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX).

Results

In women, 2,303 alcohol-related cancers were diagnosed during 485,525 person-years of follow-up (mean 21.3 person-years) while 789 alcohol-related cancers over 303,218 person-years (mean 19.3 person-years) were diagnosed in men. Breast cancer comprised nearly two-thirds (n=1,472) and colorectal cancer one-third (n=719) of the alcohol-related cancers in women whereas colorectal cancer accounted for over 80% (n=652) of the alcohol-related cancers in men.

We identified 6 lifetime alcohol intake trajectories for men and 3 for women (Figure 2). Most men (>85%; TR1 *lifetime abstention*, TR2 *stable light*, TR3 *stable moderate*) and women (>93%; TR1 *lifetime abstention*, TR2 *stable light*) either abstained from drinking or had relatively stable alcohol intake over their lifetime. Only 14% of men were lifetime abstainers (classified as TR1 *lifetime abstention;* 99.7% of whom had never consumed alcohol over their lifetime and maximum <0.5 g/day at each data point for the other 0.3%), compared with nearly 40% of women (99.5% of whom had never consumed alcohol over their lifetime and maximum <2.2 g/day at each data point for the other 0.5%). The heavy drinkers among men at age 20-39 (mean intake ≥60 g/day) tended to either cut down their

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intake from age 40-49 and were similar to TR2 *stable light* drinkers by age 60-69 (5.1%; TR5 *early decreasing heavy*) or continued to drink heavily until age 60-69 before cutting down their intake, but still remained heavy drinkers at age 60-69 (2.2%; TR6 *late decreasing heavy*). For both men and women there was a substantial group of drinkers who tended to increase their alcohol intake across the lifespan: 6.6% of men were classified as TR4 *increasing heavy* who consumed a moderate amount of alcohol (mean intake=30-59 g/day) at age 20-39 but increased their alcohol intake markedly over time, consuming over 60 g/day from age 40-49 before reducing their intake by age 60-69; while 6.9% of women were classified as TR3 *increasing moderate* who tended to consume around 20 g/day at age 20-29 but gradually increased their alcohol intake over time to consume close to 40 g/day at age 50-59. Sex-specific model adequacy diagnostics are presented in Supplementary Table 1.

Characteristics of participants by alcohol intake trajectories are given in Table 1. The mean lifetime alcohol intake in men was highest for TR6 *late decreasing heavy* (95 g/day, standard deviation: 19 g/day), well above the 55 g/day reported for TR4 *increasing heavy* (standard deviation: 11 g/day) and 58 g/day reported for TR5 *early decreasing heavy* (standard deviation: 18 g/day). A striking difference between mean baseline and lifetime alcohol intakes in men was observed for TR5 *early decreasing heavy* where the baseline mean intake was 13 g/day (standard deviation: 17 g/day). Approximately 63% of the women of southern European descent were included in TR1 *lifetime abstention* trajectory compared with 32% of women born in Australia/New Zealand/United Kingdom; the corresponding figures for men in the TR1 *lifetime abstention* were much lower and did not differ appreciably by country of birth (i.e. 17% of southern European descent and 13% of others were included in TR1 *lifetime abstention* trajectory).

For men, relative to TR1 *lifetime abstention*, heavy intake trajectories were associated with increased risk of alcohol-related cancer overall with the strongest associations observed

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for TR5 *early decreasing heavy* (HR = 1.75, 95% CI: 1.25-2.44) and TR6 *late decreasing heavy* (HR = 1.94, 95% CI: 1.28-2.93) (Table 2). The HR for TR4 *increasing heavy* was 1.45 (95% CI: 1.06-1.97) (Table 2). We observed the following results when HRs were compared: $p = 0.001$ comparing TR5 *early decreasing heavy* and TR2 *stable light*; $p = 0.18$ comparing TR6 *late decreasing heavy* and TR4 *increasing heavy*; $p = 0.65$ comparing TR6 *late decreasing heavy* and TR5 *early decreasing heavy*; and $p = 0.29$ comparing TR5 *early decreasing heavy* and TR4 *increasing heavy*. The strength of these associations did not change appreciably when current smokers at baseline were excluded (Table 2). TR5 *early decreasing heavy* and TR6 *late decreasing* heavy intake trajectories were similarly associated with increased risk of colorectal cancer in men: HR = 1.56 (95% CI: 1.07-2.27) and HR = 1.74 (95% CI: 1.09-2.77), respectively; the corresponding HR for TR4 *increasing heavy trajectory* was 1.36 (95% CI: 0.96-1.91) (Table 3).

For women, the intake trajectory classified as TR3 *increasing moderate* was associated with increased risk of alcohol-related cancer overall (HR = 1.25, 95% CI: 1.06-1.48), compared with TR1 *lifetime abstention* (Table 2). The strength of the association attenuated slightly when current smokers were excluded (Table 2). TR3 *increasing moderate* trajectory in women, compared with TR1 *lifetime abstention*, was similarly associated with increased risk of breast cancer (HR = 1.30, 95% CI: 1.06-1.59); the corresponding HR for colorectal cancer risk in women was 1.23 (95% CI: 0.90-1.69) (Table 3).

The sex-specific results from the sensitivity analysis excluding the first two years of follow-up were not materially different from the main results (Supplementary Table 2) except for the attenuation of the strength of the associations for TR5 *early decreasing heavy* trajectory in men, more so with colorectal cancer risk (Supplementary Table 2). HRs did not change appreciably when models were further adjusted for BMI (Supplementary Table 3) but

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attenuated when models assessing colorectal cancer for men and breast cancer were further adjusted for additional dietary and female reproductive factors (Supplementary Table 4).

Models including alcohol-intake trajectories showed slight differences to those with alcohol intake at baseline for men and women in terms of the Akaike information criterion (AIC) and BIC; for men the model fit was slightly better with the additional information provided by the trajectories while it was inconclusive for women (Supplementary Table 5). For men, the highest category of alcohol intake at baseline was associated with increased risk of alcohol-related cancer overall (HR = 1.90, 95% CI: 1.33-2.71) compared with abstention (Table 4), consistent with the HR observed for the TR6 *late decreasing heavy* trajectory. For women, the HRs for the highest baseline alcohol intake category (≥40 grams/day), compared with abstention, varied by attained age, and there was a stronger association for younger women (HR = 1.73, 95% CI: 1.34-2.23, age 62 years) compared with older women (HR = 1.20, 95% CI: 0.87-1.64, age 76 years) (Table 4).

Discussion

We observed marked heterogeneity in alcohol consumption over the life course in men, with heavy drinkers in early adulthood either cutting down their intake markedly after age 40 or continuing to be heavy drinkers well into their middle age. Although women were relatively more stable with their drinking habits over time, some continued to increase their alcohol intake with advancing age. Heavy drinking in early adulthood in men irrespective of whether the intake reduced or not in later life and increasing intake over time leading to heavy (men) or moderate (women) consumption in middle age were associated with increased risk of alcohol-related cancer, compared with lifelong abstention. These associations remained largely consistent for men and women in analyses for colorectal (men) and breast cancer.

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Colorectal and breast cancer accounted for most of the alcohol-related cancers in men and women, respectively.

Group-based trajectory modelling has been widely used in estimating growth trajectories in children to predict obesity in adulthood.[18] It has also been used in assessing body size or shape over the life course in relation to cancer risk.[19-22] While a few observational studies have previously modelled alcohol intake patterns over a short period of time, often modelling frequency of drinking over a week or number of drinks consumed in one day, or a combination of these,[23-25] to our knowledge associations between longitudinal group-based drinking trajectories from early adulthood and cancer risk have rarely been studied. For instance, a recent study assigned participants into common drinking patterns using alcohol intake at five waves between 1985-2012 and found consistent regular lifetime drinkers had higher rates of cancer mortality compared with occasional drinkers (HR=2.05; 95% CI: 1.31-3.74).[26] These findings were based on only 89 cancer deaths, risks for men and women were not assessed separately and the drinking patterns did not take into account the exact amount of alcohol consumed.[26] We have previously shown associations for heavy alcohol intake over the lifetime with subtypes of stomach cancer using semiparametric group-based trajectory modelling.[27] Although most cohort studies have relied upon baseline alcohol intake (i.e. intake closer to study enrolment) for their exposure variable,[10] we have demonstrated that baseline alcohol intake could be low for male former heavy drinkers. Our analyses using intake trajectories during the life course have also shown that using baseline intake alone is likely to miss risky drinking behaviors in early adult life especially in men (for example TR5 *early decreasing heavy* and TR2 *stable light* trajectories had similar baseline alcohol intakes but contrasting intakes in early adulthood) for whom the model fit was also slightly better with the additional information provided by the trajectories.

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The precise mechanisms leading to alcohol-associated carcinogenesis are not known, but include the production of lipid peroxidation and the generation of oxygen free radicals[3] and interference with estrogen metabolism influencing hormone levels and estrogen receptors[28, 29] leading to an increase in total estrogen levels and the amount of bioavailable estrogen.[30] Ethanol and acetaldehyde are carcinogens that can also induce DNA damage and defective repair, and cause direct cellular injury and gene mutation,[31, 32] but the precise timing of exposure that leads to the acquisition of a mutator phenotype that triggers a cascade of cellular mutations leading to a diagnosis of cancer is unknown. It has been posited that alcohol consumption in young adulthood contributes to breast[33] and colorectal cancer[34] risk in later life although evidence from prospective studies using long-term drinking trajectories was previously lacking. Increased cancer risk linked to heavy alcohol use during early adulthood (e.g. TR5 *early decreasing heavy* trajectory in men) is likely to suggest early initiation and chronic progression of carcinogenesis linked to alcohol and its metabolites ('cumulative carcinogen hypothesis').[35] The time lag between exposure to a carcinogen and clinical diagnosis of cancer is estimated to be around 20 years.[36] It has also been postulated that it would take between 8 and 16 years or longer for a single breast cancer cell to grow into a clinically detectable tumor, based on tumor volume doubling times and assuming continuous exponential growth.[35] Some authors speculate that the increased cancer risk linked to heavy alcohol use later in life (e.g. TR3 *increasing moderate* trajectory and risk of breast cancer) is due to alcohol accelerating tumor growth, leading to the diagnosis of an existing cancer, rather than a causal effect ('tumor-promoter hypothesis').[35] The present study was not intended to identify the mechanistic basis of disease, hence we are unable to either confirm or disprove hypotheses around the precise timing of initiation and progression of tumorigenesis.

Strengths of the present study include the comprehensive assessment of alcohol intake over the life course based on intakes at different ages and approximately 20 years of follow-

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up on average. In addition, using latent class trajectory modelling enabled us to avoid bias that is introduced when participants are grouped into categories of change between two time points.[14] Nonetheless, there are several limitations. First, the use of self-reported alcohol intake and exposure misclassification may have influenced estimates of association. Measurement error due to participants having to summarize their frequency and quantity of alcoholic beverage intake for 10-year age intervals into single 'usual' values and the potential for present intake to influence recall of past intake and under-reporting of past intake also cannot be ruled out. The present study did not assess cancer risk related to heavy episodic drinking (sometimes referred to as 'binge' drinking). Second, confounding variables such as cigarette smoking, physical activity and diet were not measured prior to baseline hence we controlled for variables assessed at baseline using them as 'proxies'.[37] Additionally, unmeasured residual confounding may also be present. Third, alcohol intake could have changed between the baseline assessment and the diagnosis of cancer. Finally, cautious interpretation of findings such as that for TR6 *late decreasing heavy* intake with colorectal cancer risk, is also warranted when analyses involve relatively small number of cases.

Alcohol intake in early adulthood is an important public health concern worldwide.[1] In Australia, where nearly 80% of the population aged ≥14 years had consumed alcohol in the previous 12 months according to recent population-based surveys, those aged 18-24 years were most likely to exceed the National Health and Medical Research Council (NHMRC) guideline on drinking during a single occasion (≤4 standard drinks; standard drink = 10 g of ethanol).[38] In comparison, those aged 40-59 years were most likely to exceed the NHMRC guideline on drinking during lifetime, current at the time (on average, ≤2 standard drinks per day).[38] In summary, we observed in the present study an increased risk of alcohol-related cancer for men with heavy alcohol intake (≥60 g/day) during early adulthood that either ceased or continued in middle age and in moderate drinkers (30-59 g/day) in early adulthood

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with heavy intake in middle age, and for women with increasing alcohol intake from early adulthood to middle age relative to lifetime abstention. It was evident that the potential extra information from using trajectories is important in people who were heavy drinkers and particularly when the intake was heavy during early adulthood. Our findings suggest that heavy drinking during early adulthood alone might be related to cancer risk and that limiting alcohol intake during early adulthood might be as important as adhering to low-risk drinking guidelines[39] in later life to prevent cancer.

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Author Contributions
JKB and HJ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JKB, HJ, RJM and RLM conceived and designed the study. JKB and HJ extracted the data. JKB carried out the statistical analysis with support from HJ. JKB produced an initial draft of the manuscript and subsequent revisions to it. All the authors critically revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript. GGG obtained funding. JKB and HJ were responsible for administrative, technical, and material support. HJ was responsible for study supervision. JKB and HJ are guarantors. The authors assume full responsibility for analyses and interpretation of these data. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict of Interest
All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

Ethics Statement
The MCCS study protocol was approved by the Cancer Council Victoria Human Research Ethics Committee. Participants gave written informed consent to participate and for investigators to obtain access to their medical records.

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Data Availability Statement
Statistical code is available from the lead/corresponding author. The MCCS data can be made available on request to pedigree@cancervic.org.au.

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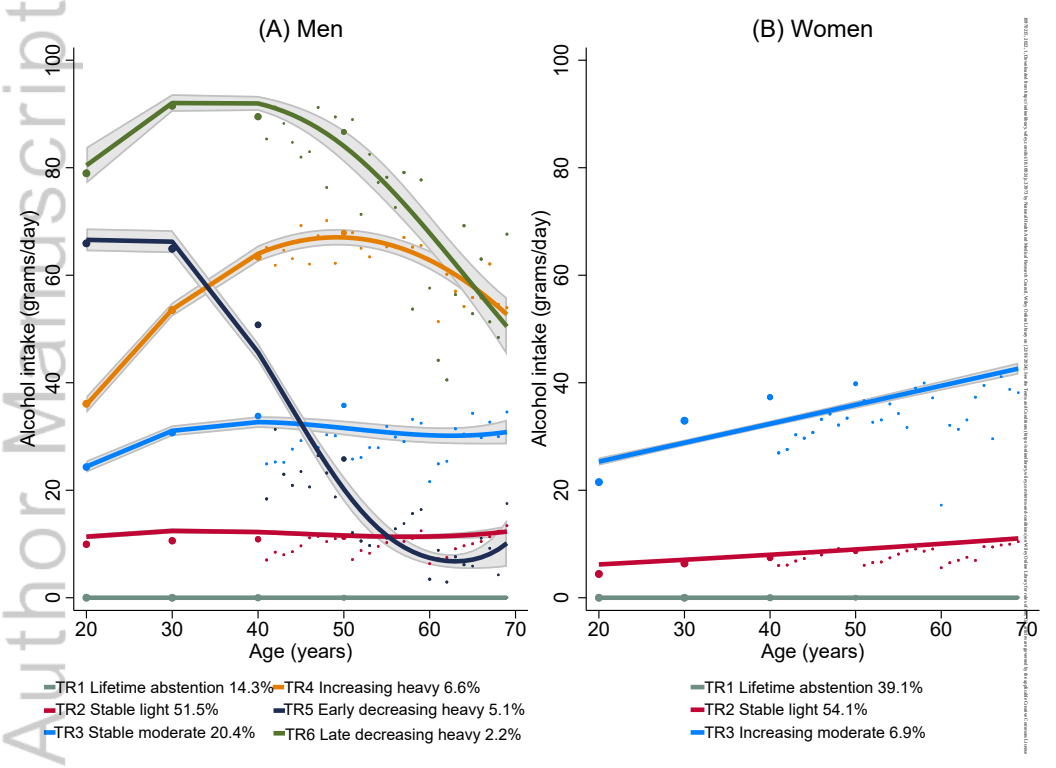
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Figure legends

Figure 1. Flowchart showing selection of participants in the Melbourne Collaborative Cohort Study

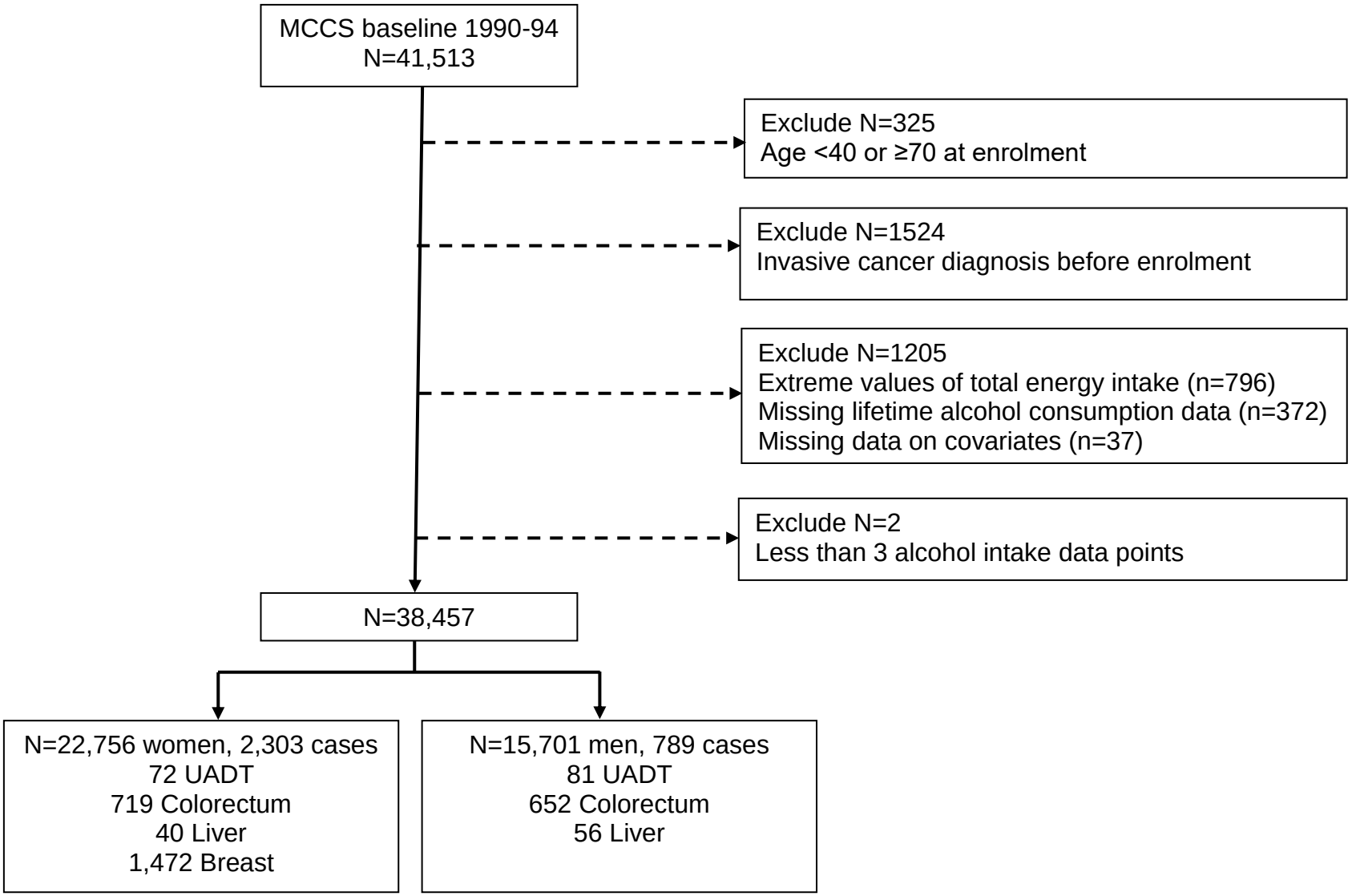
Figure 2. Sex-specific alcohol intake trajectories estimated in the Melbourne Collaborative Cohort Study using a latent class trajectory model. Dots represent weighted observed mean intakes and shaded areas represent 95% confidence intervals.

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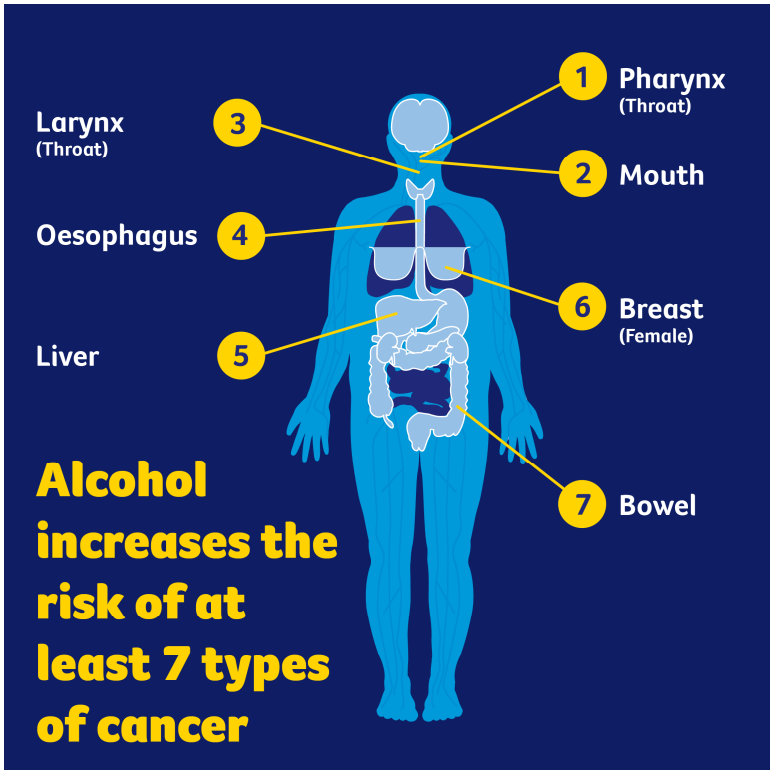


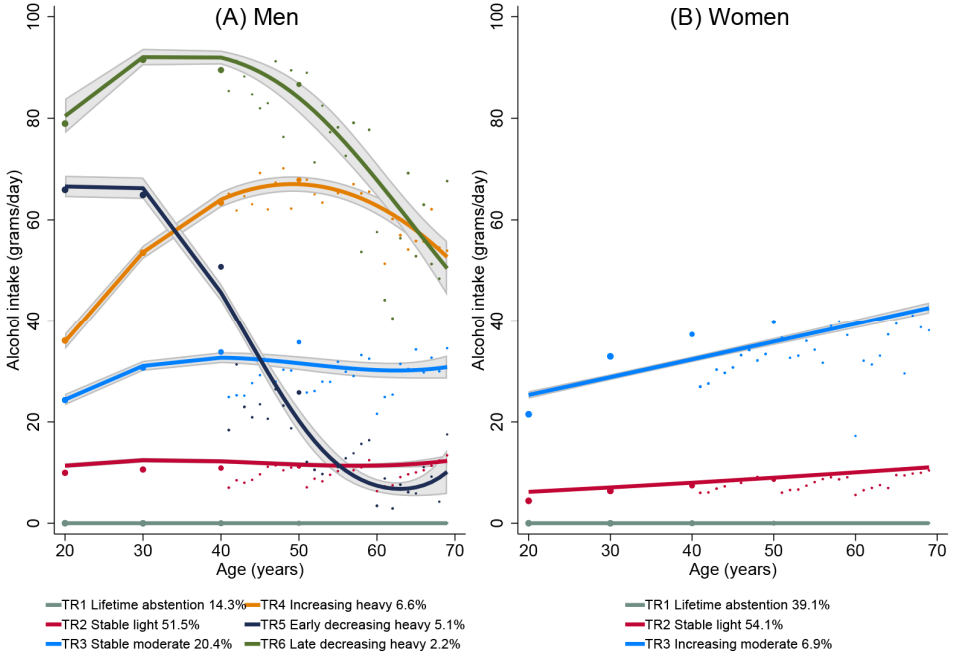
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- The association between alcohol intake trajectories during the life course and risk of cancer is still inconclusive

- Melbourne Collaborative Cohort Study recorded participants' alcohol intake for 10-year periods from age 20 at enrollment





- Six distinct alcohol intake trajectories for men and three for women were identified

- Heavy drinking during early adulthood, even when intake ceased by middle age (men TR5, TR6), and drinking that increased over the life course (men TR4, women TR3) increased cancer risk compared with lifetime abstention

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Table 1. Characteristics of participants by alcohol intake trajectory groups in the Melbourne Collaborative Cohort Study

	Alcohol intake trajectory groups Men (N=15,701)						Alcohol intake trajectory groups Women (N=22,756)		
	TR1 lifetime abstention	TR2 stable light	TR3 stable moderate	TR4 increasing heavy	TR5 early decreasing heavy	TR6 late decreasing heavy	TR1 lifetime abstention	TR2 stable light	TR3 increasing moderate
N (%)	2,239 (14.3)	8,079 (51.5)	3,205 (20.4)	1,044 (6.6)	793 (5.1)	341 (2.2)	8,893 (39.1)	12,301 (54.1)	1,562 (6.9)
Age at recruitment (years)[1]	57.2 (8.4)	55.0 (8.9)	55.5 (8.6)	57.5 (8.1)	54.2 (8.2)	57.9 (7.9)	56.7 (8.1)	54.0 (8.6)	52.2 (8.4)
Alcohol intake (g/day)[1]									
Age 20-29	0 (0)	9.9 (11.1)	25.3 (15.9)	36.4 (20.7)	66.9 (22.8)	79.5 (21.4)	0 (0)	4.5 (6.6)	22.1 (20.0)
Age 30-39	0 (0)	10.4 (9.5)	32.2 (14.0)	54.3 (19.3)	66.1 (22.8)	91.9 (11.6)	0 (0)	6.5 (7.6)	33.7 (20.4)
Age 40-49	0 (0)	10.2 (9.2)	33.7 (14.5)	65.0 (18.0)	41.7 (28.2)	89.1 (14.2)	0 (0)	7.6 (8.3)	35.1 (19.7)
Age 50-59	0 (0)	10.5 (9.8)	34.4 (16.8)	67.7 (19.0)	19.3 (21.4)	82.3 (22.8)	0 (0)	8.3 (9.3)	38.2 (21.6)
Age 60-69	0 (0)	9.6 (10.9)	30.2 (19.3)	57.4 (26.6)	6.1 (10.8)	55.6 (35.6)	0 (0)	8.2 (9.9)	33.7 (23.5)
Baseline 1990-94	0 (0)	9.3 (9.6)	30.2 (17.1)	63.0 (23.1)	13.4 (16.6)	69.1 (31.7)	0 (0)	7.8 (8.9)	33.3 (21.2)
Lifetime 1990-94	0 (0)	10.7 (7.1)	31.6 (7.2)	55.0 (10.6)	57.6 (17.6)	94.8 (19.0)	0 (0)	6.8 (5.7)	32.1 (14.2)
Country of birth, n (%)									
Australia/New Zealand/United Kingdom	1,546 (13.4)	6,337 (54.8)	2,260 (19.5)	719 (6.2)	513 (4.4)	194 (1.7)	5,719 (32.3)	10,569 (59.7)	1,410 (8.0)
Italy/Greece	693 (16.8)	1,742 (42.2)	945 (22.9)	325 (7.9)	280 (6.8)	147 (3.6)	3,174 (62.8)	1,732 (34.2)	152 (3.0)
Education, n (%)									
Primary school	512 (17.8)	1,124 (39.2)	649 (22.6)	251 (8.7)	217 (7.6)	117 (4.1)	2,917 (64.4)	1,493 (33.0)	116 (2.6)
Technical school	692 (14.4)	2,398 (49.7)	969 (20.1)	341 (7.1)	294 (6.1)	128 (2.7)	3,953 (40.3)	5,333 (54.4)	513 (5.2)
Secondary school	551 (14.0)	2,118 (54.0)	763 (19.4)	243 (6.2)	185 (4.7)	63 (1.6)	1,219 (30.3)	2,490 (61.8)	319 (7.9)
University	484 (11.8)	2,439 (59.7)	824 (20.2)	209 (5.1)	97 (2.4)	33 (0.8)	804 (18.3)	2,985 (67.8)	614 (13.9)
Cigarette smoking status, n (%)									
Never	1,320 (20.2)	3,684 (56.4)	1,039 (15.9)	238 (3.6)	189 (2.9)	66 (1.0)	7,320 (46.5)	7,802 (49.6)	621 (3.9)
Former	610 (8.8)	3,437 (49.5)	1,681 (24.2)	592 (8.5)	429 (6.2)	195 (2.8)	964 (19.3)	3,359 (67.4)	662 (13.3)
Current	309 (13.9)	958 (43.1)	485 (21.8)	214 (9.6)	175 (7.9)	80 (3.6)	609 (30.0)	1,140 (56.2)	279 (13.8)
Mediterranean Diet Score, n (%)									
0-3	959 (17.0)	2,842 (50.4)	939 (16.6)	456 (8.1)	286 (5.1)	158 (2.8)	3,364 (45.7)	3,488 (47.4)	508 (6.9)
4-6	1,136 (13.7)	4,288 (51.7)	1,777 (21.4)	521 (6.3)	413 (5.0)	162 (2.0)	4,824 (38.5)	6,859 (54.7)	859 (6.8)
7-9	144 (8.2)	949 (53.8)	489 (27.7)	67 (3.8)	94 (5.3)	21 (1.2)	705 (24.7)	1,954 (68.5)	195 (6.8)
Physical activity score, n (%)									
0	520 (14.8)	1,726 (49.0)	711 (20.2)	252 (7.2)	227 (6.4)	85 (2.4)	2262 (45.4)	2412 (48.4)	305 (6.1)
>0 and <4	385 (13.3)	1,581 (54.5)	546 (18.8)	184 (6.3)	141 (4.9)	62 (2.1)	1906 (39.2)	2675 (55.0)	286 (5.9)
≥4 and <6	802 (15.0)	2,680 (50.3)	1,093 (20.5)	364 (6.8)	260 (4.9)	134 (2.5)	3299 (40.0)	4415 (53.5)	540 (6.5)
≥6	532 (13.5)	2,092 (53.0)	855 (21.7)	244 (6.2)	165 (4.2)	60 (1.5)	1426 (30.6)	2799 (60.1)	431 (9.3)
Body mass index (kg/m^2)[1]	27.0 (3.8)	26.9 (3.5)	27.3 (3.5)	27.7 (3.5)	28.5 (4.1)	28.4 (3.7)	27.9 (5.3)	26.1 (4.5)	25.5 (4.3)
Energy intake from food (Kcal/day)[1]	2,398 (822)	2,316 (760)	2,215 (743)	2,158 (756)	2,280 (799)	2,120 (772)	1,972 (693)	1,966 (645)	1,885 (624)

[1]mean (standard deviation). Percentages add to 100% across the rows.

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Table 2. Sex-specific hazard ratios for associations between alcohol intake trajectory groups and risk of alcohol-related cancers in the Melbourne Collaborative Cohort Study

Alcohol intake trajectory groups	All participants (Women n=22,756; Men n=15,701)				Excluding current smokers (Women n=20,728; Men n=13,480)			
	Person-years	Cases	HR	95% CI	Person-years	Cases	HR	95% CI
Women	485,525	2303			443,803	2114		
TR1: lifetime abstention	189,493	904	1.00		177,090	846	1.00	
TR2: stable light	263,329	1212	0.96	(0.88, 1.05)	239,605	1119	0.97	(0.88, 1.07)
TR3: increasing moderate	32,703	187	1.25	(1.06, 1.48)	27,108	149	1.20	(1.00, 1.44)
Men	303,218	789			261,415	682		
TR1: lifetime abstention	42,529	104	1.00		36,666	93	1.00	
TR2: stable light	158,465	368	1.08	(0.87, 1.35)	140,059	327	1.04	(0.82, 1.31)
TR3: stable moderate	62,149	163	1.18	(0.92, 1.52)	52,991	135	1.10	(0.83, 1.44)
TR4: increasing heavy	18,922	69	1.45	(1.06, 1.97)	15,217	57	1.41	(1.01, 1.98)
TR5: early decreasing heavy	15,134	55	1.75	(1.25, 2.44)	11,897	45	1.68	(1.17, 2.42)
TR6: late decreasing heavy	6,020	30	1.94	(1.28, 2.93)	4,584	25	1.95	(1.25, 3.06)

HR, hazard ratio; CI, confidence interval.

Adjusted for education (primary school, technical school, secondary school, university), cigarette smoking status (never, former, current), physical activity (none, low, moderate, high), Mediterranean diet score (0-3, 4-6, 7-9) and total energy from food not including alcoholic beverages (Kcal/day), and stratified by birth cohort (year of birth <1925, 5-year categories for 1925 to 1964, ≥1965) and country of birth (Australia/New Zealand/United Kingdom or Italy/Greece), and with attained age as the time scale.

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Table 3. Sex-specific hazard ratios for associations between alcohol intake trajectory groups and risk of colorectal and breast cancer in the Melbourne Collaborative Cohort Study

Alcohol intake trajectory groups	Colorectal cancer				Breast cancer			
	Person-years	Cases	HR	95% CI	Person-years	Cases	HR	95% CI
Women (n=22,756)	485,525	719			485,525	1472		
TR1: lifetime abstention	189,493	297	1.00		189,493	555	1.00	
TR2: stable light	263,329	372	1.01	(0.86, 1.19)	263,329	786	0.95	(0.84, 1.06)
TR3: increasing moderate	32,703	50	1.23	(0.90, 1.69)	32,703	131	1.30	(1.06, 1.59)
Men (n=15,701)	303,218	652						
TR1: lifetime abstention	42,529	88	1.00					
TR2: stable light	158,465	311	1.08	(0.85, 1.37)				
TR3: stable moderate	62,149	133	1.12	(0.85, 1.48)				
TR4: increasing heavy	18,922	55	1.36	(0.96, 1.91)				
TR5: early decreasing heavy	15,134	42	1.56	(1.07, 2.27)				
TR6: late decreasing heavy	6,020	23	1.74	(1.09, 2.77)				

HR, hazard ratio; CI, confidence interval.

Adjusted for education (primary school, technical school, secondary school, university), cigarette smoking status (never, former, current), physical activity (none, low, moderate, high), Mediterranean diet score (0-3, 4-6, 7-9) and total energy from food not including alcoholic beverages (Kcal/day), and stratified by birth cohort (year of birth <1925, 5-year categories for 1925 to 1964, ≥1965) and country of birth (Australia/New Zealand/United Kingdom or Italy/Greece), and with attained age as the time scale.

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Table 4. Sex-specific hazard ratios for associations between alcohol intake at baseline and risk of alcohol-related cancers in the Melbourne Collaborative Cohort Study

Alcohol intake groups at baseline	Alcohol-related cancer			
	Person-years	Cases	HR[1]	95% CI
Women (N=22,756)	485,525	2303		
Abstention	233,008	1100	1.00	
>0–19 g/day	205,021	928	0.95	(0.87, 1.04)
20-39 g/day	36,448	194	1.08	(0.92, 1.27)
≥40 g/day[2]	11,048	81		
Age 62			1.73	(1.34, 2.23)
Age 69			1.44	(1,14, 1.82)
Age 76			1.20	(0.87, 1.64)
Men (N=15,701)	303,218	789		
Abstention	81,577	202	1.00	
>0–19 g/day	125,842	295	1.05	(0.87, 1.26)
20-39 g/day	55,061	149	1.18	(0.95, 1.47)
40-59 g/day	22,769	72	1.27	(0.97, 1.67)
60-79 g/day	10,466	34	1.31	(0.91, 1.90)
≥80 g/day	7,503	37	1.90	(1.33, 2.71)

HR, hazard ratio; CI, confidence interval.

[1]Adjusted for education (primary school, technical school, secondary school, university), cigarette smoking status (never, former, current), physical activity (none, low, moderate, high), Mediterranean diet score (0-3, 4-6, 7-9) and total energy from food not including alcoholic beverages (Kcal/day), and stratified by birth cohort (year of birth <1925, 5-year categories for 1925 to 1964, ≥1965) and country of birth (Australia/New Zealand/United Kingdom or Italy/Greece), and with attained age as the time scale.

[2] For women, HRs (95% CIs) estimated from Cox regression model with interaction between alcohol intake group and attained age, presented for the 25th, 50th and 75th percentile of age at diagnosis of an alcohol-related cancer.

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Alcoholic beverages are a known risk factor for oral cavity, pharynx, larynx, oesophagus, liver, colorectal, and breast cancers. Unlike most previous studies of alcohol intake and cancer risk, here the authors examined associations of longitudinal drinking trajectories across the lifespan. Compared with lifelong non-drinking, they observed an increased cancer risk associated with heavy drinking during early adulthood, even when the intake had ceased by middle age, and with drinking that increased during the life-course. The findings of this large prospective study point to critical timelines related to alcohol-related cancer aetiology and prevention during the adult lifespan.

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