*Alcohol & Alcoholism* Vol. 41, No. 6, pp. 664–671, 2006
Advance Access publication 18 October 2006
doi:10.1093/alcalc/agl087

# AVERAGE VOLUME OF ALCOHOL CONSUMED, TYPE OF BEVERAGE, DRINKING PATTERN AND THE RISK OF DEATH FROM ALL CAUSES

LAURA BAGLIETTO[1,2], DALLAS R. ENGLISH[1,2], JOHN L. HOPPER[2], JOHN POWLES[3] and GRAHAM G. GILES[1,2]*

[1]Cancer Epidemiology Centre, The Cancer Council of Victoria, [2]Centre for Molecular, Environmental, Genetic and Analytical Epidemiology, The University of Melbourne, Melbourne, Australia and [3]Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge, UK

(*Received* 28 *August* 2006; *in revised form* 28 *August* 2006; *accepted* 5 *September* 2006; *advance access publication* 18 *October* 2006)

**Abstract — Background:** The objective was to investigate associations between average volume of alcohol consumption, type of beverage and drinking pattern and all-cause mortality in the Melbourne Collaborative Cohort Study. **Methods:** Average consumption, including type of beverage, was estimated from beverage-specific questions on quantity and frequency of consumption. Pattern of consumption was estimated from a 7-day diary. During an average of 10.5 years of follow-up of 36 984 participants, 1971 deaths occurred. **Results:** For both men and women, mortality curves were J-shaped (nadir at 9–12 g/day of alcohol consumption; upper protective dose of 42–76 g/day). Wine consumption was associated with lower mortality (for men, minimum hazard ratio (HR) at 20–39 g/day of wine consumption: 0.69; 95% confidence interval (CI): 0.54–0.87; for women, minimum HR at 1–19 g/day: 0.82; 95% CI: 0.70–0.98). Beer was associated with an increased risk for men (test for trend, $P = 0.05$), but not for women. After adjustment for total amount of alcohol consumed, the number of drinking-days was inversely associated with the risk of dying in men ($P$-trend = 0.04). **Conclusions:** These results confirm previous findings about the effect of average volume of alcohol and type of beverage and suggest that drinking pattern is an independent risk factor for all-cause mortality.

## INTRODUCTION

The U- or J-shaped relationship between alcohol consumption and all-cause mortality, whereby light to moderate drinkers have reduced mortality and heavy drinkers have increased mortality, is well established (Shaper *et al*., 1988; Boffetta and Garfinkel, 1990; Klatsky *et al*., 1992; Doll *et al*., 1994; Gronbaek *et al*., 1994; Fuchs *et al*., 1995; Thun *et al*., 1997; Yuan *et al*., 1997). A recent meta-analysis of 29 studies (16 conducted in the USA, 9 in European countries, 2 in Japan, 1 in China and 1 in Australia) found the nadir (the level of alcohol consumption at which all-cause mortality rate ratio is lowest) and the upper protective dose to be 6–7 and 60 g/day, respectively for men and 5–6 and 47–51 g/day, respectively for women (Bagnardi *et al*., 2004). It has been suggested that the protective effect at low doses of alcohol consumption is due to its influence on coronary artery disease that accounts for a large proportion of total mortality (Di Castelnuovo *et al*., 2002; Klatsky, 1999), but not all authors agree. Higher mortality rates among people who stopped drinking because of illness ('sick quitters') was proposed as an explanation for the apparent protective effect of low to moderate consumption (Shaper *et al*., 1988). In a meta-analysis conducted on 54 studies on alcohol and all-cause mortality, the authors 'tested the extent to which a systematic misclassification error was committed by including as abstainers many people who had reduced or stopped drinking' (Fillmore *et al*., 2006). Among the seven studies judged to be error free, they found a small but non-significant protective effect of alcohol. However some authors argued that the 'sick quitters' hypothesis is unlikely to account for the whole observed protection given by low consumption of alcohol (Mukamal and Rimm, 2001), as shown by studies in which former drinkers have been separated from lifetime abstainers (Di Castelnuovo *et al*., 2002) and in which the first few years of follow-up were excluded (Fuchs *et al*., 1995). Confounding by socio-economic and lifestyle factors has also been proposed as a possible explanation (Fillmore *et al*., 1998), but most studies have adjusted for the relevant potential confounding variables and a meta-analysis showed that the protective effect of light to moderate alcohol consumption was still present when the analysis was restricted to those studies (Di Castelnuovo *et al*., 2002).

What is not established with certainty is whether, in middle-aged and older adults, the pattern of consumption has a role beyond that of the amount consumed alone. Only a few analytical studies have examined associations with pattern of consumption and interpretation of their reported findings is hampered by the diversity of measures of drinking pattern, which have varied from proportion of drinking-days to measures of 'binge drinking' or of drinking apart from meals (Rehm *et al*., 2001; Trevisan *et al*., 2001; Malyutina *et al*., 2002; Murray *et al*., 2002; Mukamal *et al*., 2003; Laatikainen *et al*., 2003; Tolstrup *et al*., 2004). Possible reasons for an association between heavy, infrequent drinking and all-cause mortality include increased risk of associated acute causes of death (Rehm *et al*., 2003), higher concentrations of alcohol in the gastrointestinal tract, enhancing the risk of liver disease and gastrointestinal cancers (Wetterling *et al*., 1999), and effects such as increases in blood pressure and effects on the ability of platelet aggregation that could reverse the protective effects on risk of coronary heart disease observed for moderate and regular drinking (Mukamal *et al*., 2003).

Whether different types of beverages confer different risks is also uncertain. Some studies have found that the protective effect of low alcohol consumption was common to any type of alcoholic beverage (Stampfer *et al*., 1988; Rimm *et al*.,

*Author to whom correspondence should be addressed at: Cancer Epidemiology Centre, The Cancer Council of Victoria, 100 Drummond Street, Carlton Vic 3053, Melbourne, Australia; Tel.: +61 3 9635 5155; Fax: +61 3 9635 5330; E-mail: graham.giles@cancervic.org.au

1991; Keil *et al*., 1997; Di Castelnuovo *et al*., 2002), whereas others have found the protective effect of beer and spirits to be smaller than the effect of wine (Gronbaek *et al*., 2000; Klatsky *et al*., 2003). Wine, and particularly red wine, differs from other alcoholic beverages in its high content of phenolic acids and polyphenols that act as antioxidants and which may prevent atherosclerotic cardiovascular disease (German and Walzem, 2000).

Much of the global variation in drinking patterns and beverage type occurs between rather than within populations. Analytical epidemiological studies, conducted on study populations relatively homogeneous for pattern and beverage type, would be expected to find that variations in the volume dimension of alcohol exposure should account for most of the variations in risk. Because the Melbourne Collaborative Study (MCCS) is ethnically diverse, and shows substantial variation in alcohol exposure, it provides a valuable opportunity to explore their joint associations with the risk of death from all causes.

## METHODS

### *Study population*

The MCCS is a prospective cohort study of 41 528 people (24 479 women) aged between 27 and 75 years at baseline (99% of whom were aged 40–69). Recruitment occurred between 1990 and 1994 in Melbourne, Australia. Subjects were recruited via the electoral rolls (registration to vote is compulsory for adults in Australia), advertisements and community announcements in local media (e.g. television, radio, newspapers). Southern European migrants to Australia (including 5425 Italian and 4535 Greek born people) were deliberately recruited to extend the range of lifestyle exposures. The Cancer Council Victoria's Human Research Ethics Committee approved the study protocol. Subjects gave written consent to participate and for the investigators to obtain access to their medical records.

Subjects with missing data on alcohol, smoking, fruit and vegetable consumption, saturated fat, and total energy intake were excluded, as were those who reported extreme values of total energy intake (< 1st percentile of > 99th percentile). We also excluded subjects who had a previous diagnosis of angina, myocardial infarction or diabetes, because their diets were not representative of the whole cohort, and we could not exclude the possibility that they had changed their diet after a recent diagnosis.

### *Assessment of alcohol intake*

At baseline, participants were first asked if they had ever drunk at least 12 alcoholic drinks in a year; those that had not were considered lifetime abstainers. Non-lifetime abstainers were asked about their current average quantity and frequency of intakes of beer, wine and spirits. Then they were asked about the intake of alcoholic beverages on each day during the week before the interview (this method will be referred to as the diary). All analyses except those for pattern of consumption are based on the beverage-specific frequency-quantity questions. Analyses of pattern of consumption are based upon the diary because the quantity-frequency questions did not ask about the frequency of consumption of all alcoholic beverages combined.

Australian food composition tables were used to calculate alcohol consumption from alcoholic beverages and consumption of beverage types is expressed in terms of the alcohol they supplied (Lewis *et al*., 1995). Subjects who were not lifetime abstainers, but did not consume alcohol at baseline, were classified as ex-drinkers.

### *Assessment of other risk factors*

A structured interview schedule was used to obtain information on potential risk factors, which included age, sex, country of birth, education, smoking habits, physical activity, household size, and previous medical conditions.

Subjects completed a dietary questionnaire that included a 121-item food frequency questionnaire (FFQ) without portion sizes, specifically developed for the MCCS (Ireland *et al*., 1994). The questionnaire had 26 items on intake of vegetables including fresh and cooked vegetables. Nutrient intakes were calculated using mean sex-specific portion sizes from weighed food records and Australian food composition tables (Lewis *et al*., 1995). Total energy intake included energy from the FFQ and energy from alcoholic beverages.

Body mass index was calculated from measured height and weight. Subjects were classified according to their smoking habits as never smokers, former smokers, and current smokers. Previous medical history items collected included angina, myocardial infarction, diabetes, cancer, and stroke.

### *Cohort follow-up and ascertainment of deaths*

Victorian deaths were identified through the Victorian Registry of Births, Deaths and Marriages and deaths outside Victoria from the National Death Index. Deaths were complete to 31 December 2003 for Victoria and to the end of 2002 for other states. Residential addresses were determined by record linkage to electoral rolls, from electronic phone books and from responses to mailed questionnaires and newsletters. By the end of follow-up on 31 December 2003, 48 (0.1%) of the subjects included in this analysis were known to have left Australia and were considered lost to follow-up; 617 (1.7%) were known to have left Victoria by the end of 2002 and 28 (0.1%) left in 2003.

### *Statistical analysis*

Follow-up began at baseline attendance and ended at death, date left Australia or 31 December 2003, whichever came first. The 28 subjects who left Victoria in 2003 were assumed to be alive at the end of 2003. Cox regression with age as the time axis was used to derive adjusted mortality hazard ratios (HRs) for alcohol consumption compared with lifetime abstention. Separate analyses were performed for men and women.

The models were stratified by the presence or absence of a history of cancer or stroke at baseline since for this variable the hazards were not proportional. Country of birth, smoking, intake of fruit and vegetables, physical activity, education, body mass index, total energy, and saturated fat were included as covariates (see Table 1 for details). Another potential confounder was household size, but it was not included in final analyses because it did not change the estimated HRs for alcohol by >5%. Interactions were tested for level of education and country of birth.

For the analyses of total amount of alcohol and type of beverage, intake was analyzed in categories (lifetime abstainers, ex-drinkers, occasional drinkers (defined as those who drank ⩽0.5 g/day), 0.6–19, 20–39 , 40–59 and ⩾60 g/day following the guidelines of the Australian National Health and Medical Research Council (NHMRC) (Pols and Hawks, 1992)) and as a continuous variable using second-order fractional polynomials (Bagnardi *et al.*, 2004). Fractional polynomials are a method of analyzing dose–response curves that make no *a priori* hypothesis about their shape (Altman and Royston, 1994). Second-order fractional polynomials describe the logarithm of the HR (HR) as a function of power transformation of the exposure variable $x$: $log\ (\mathrm{HR}) = \beta_1 x^{p1} + \beta_2 x^{p2}$.

Ex-drinkers were excluded from the analysis of type of beverage. Consumption of each beverage was categorized as above, but for males, the last two categories of spirits were merged and for females the last three categories of wine were merged and beer and spirits were categorized as none or any. Associations for each beverage were evaluated by including consumption of wine, beer and spirits in the same model.

For analyses of pattern of consumption, we first analyzed the number of drinking-days during the week grouped as 1–3, 4–6, and 7 days within separate categories of total consumption for the week (<140, 140–279 and 280+ g for males and <140 and 140+ g for females). Second, we applied

Table 1. Characteristics of participants in the Melbourne Collaborative Cohort Study

| | Males $N$ = 14 557 | | Females $N$ = 22 427 | |
|---|---|---|---|---|
| | Deaths [$n$ (%)] | Total | Deaths [$n$ (%)] | Total |
| Age at baseline (years) | | | | |
| <50 | 82 (2) | 4876 | 93 (1) | 7665 |
| 50–59 | 218 (5) | 4594 | 246 (3) | 7626 |
| 60+ | 790 (16) | 5087 | 542 (8) | 7136 |
| Country of birth | | | | |
| Australia/New Zealand | 709 (7) | 9706 | 654 (4) | 16 150 |
| UK | 79 (6) | 1218 | 55 (4) | 1500 |
| Italy | 169 (9) | 1980 | 100 (4) | 2608 |
| Greece | 133 (8) | 1653 | 72 (3) | 2169 |
| Smoking | | | | |
| never | 325 (5) | 6219 | 519 (3) | 15 485 |
| former | 539 (9) | 6225 | 225 (6) | 4959 |
| current | 226 (11) | 2113 | 137 (7) | 1983 |
| Fruit intake (times per day) | | | | |
| 0–1 | 237 (8) | 2844 | 123 (5) | 2486 |
| 2–3 | 456 (8) | 5687 | 292 (4) | 7617 |
| 4–5 | 227 (7) | 3419 | 235 (4) | 6387 |
| 6 or more | 170 (7) | 2607 | 231 (4) | 5937 |
| Vegetables intake (times per day) | | | | |
| 0–2 | 249 (9) | 2678 | 103 (5) | 1990 |
| 3–4 | 363 (7) | 5067 | 262 (4) | 6173 |
| 5–6 | 259 (7) | 3820 | 276 (4) | 6999 |
| 7 or more | 219 (7) | 2992 | 240 (3) | 7265 |
| Physical activity* | | | | |
| none | 245 (8) | 3260 | 197 (4) | 4870 |
| low | 185 (7) | 2714 | 193 (4) | 4764 |
| moderate | 468 (10) | 4842 | 349 (4) | 8131 |
| high | 192 (5) | 3741 | 142 (3) | 4662 |
| Education | | | | |
| primary school | 279 (11) | 2496 | 195 (5) | 4197 |
| some high/technical school | 361 (8) | 4450 | 409 (4) | 9680 |
| completed high/technical school | 261 (7) | 3650 | 157 (4) | 4042 |
| completed tertiary degree/diploma | 189 (5) | 3961 | 120 (3) | 4508 |
| Previous cancer or stroke | | | | |
| No | 872 (6) | 13 435 | 654 (3) | 20 488 |
| Yes | 218 (19) | 1122 | 227 (12) | 1939 |
| Total alcohol intake** | | | | |
| Lifetime abstainers | 160 (8) | 1917 | 381 (4) | 8488 |
| Ex-drinkers | 69 (11) | 629 | 28 (4) | 706 |
| 1–19 g/day | 442 (7) | 6618 | 362 (3) | 10 690 |
| 20–39 g/day | 199 (7) | 3034 | 85 (4) | 1974 |
| 40–59 g/day | 123 (9) | 1324 | 14 (4) | 383 |
| 60+ g/day | 97 (9) | 1035 | 11 (6) | 186 |
| BMI (kg/m$^2$)*** | 27.3 ± 4.0 | 27.0 ± 3.6 | 26.9 ± 5.3 | 26.6 ± 4.8 |
| Total Energy (MJ/day)*** | 10.3 ± 3.5 | 10.3 ± 3.3 | 8.4 ± 2.9 | 8.5 ± 2.8 |
| Daily percent energy from saturated fat (%)*** | 13 ± 3 | 13 ± 3 | 13 ± 3 | 13 ± 3 |

*See reference MacInnis *et al.*, 2004, for more details.
**Average daily intake estimated from beverage-specific questions about average quantity and frequency of consumption.
***Mean ± SD.

the multiple fractional polynomial algorithm to the number of drinking-days and total alcohol consumption, forcing both variables and covariates into the model (Royston and Sauerbrei, 2004). Subjects with no intake of alcohol during the week before baseline were excluded from the analysis of pattern with fractional polynomials.

Sensitivity analysis was performed to investigate the effect of pre-attendance illnesses on the association between alcohol and mortality in different ways: (i) excluding those with pre-attendance life-threatening medical conditions; (ii) excluding the first 2 years of follow-up; (iii) including a time-dependent covariate in the Cox regression model that tests if the association between alcohol and mortality differs with time since baseline (Korn *et al*., 1997).

Statistical analyses were computed using Stata 8.2 (Stata Corporation, College Station, TX).

## RESULTS

The main characteristics of the study participants are described in Table 1. Among the 36 984 eligible subjects (89% of the original cohort), 14 557 (39%) were male and 22 427 (61%) female. Approximately 23% of the cohort was born in Greece or Italy; the others were born in Australia, New Zealand, or the UK. Of the men, 17% were abstainers (lifetime abstainers or ex-drinkers) and 7% consumed at least 60 g/day of alcohol. Of the women, 41% were abstainers (lifetime abstainers or ex-drinkers) and 2% drank at least 40 g/day of alcohol or more. Over an average of 10.5 years of follow-up per person, we identified 1971 deaths, 179 of which occurred within 2 years from baseline.

### *Average volume of alcohol*

Table 2 parts A and B show the association between the average daily alcohol intake at baseline and all-cause mortality. When all eligible subjects were included, for men, the HR for former drinkers compared with lifetime abstainers was 1.26, the minimum HR was 0.86 for those consuming between 20 and 39 g/day of alcohol and the highest was 1.10 for the second highest category. For women, former drinkers were not at higher risk of dying than lifetime abstainers, the minimum HR was 0.90 for women consuming <20 g/day of alcohol and the highest was 1.02 in the second highest category of consumption. The level of education and country of birth did not significantly modify the associations between alcohol intake and all-cause mortality (interaction, $P = 0.30$ for men and $P = 0.49$ for women for education; $P = 0.29$ for men and $P = 0.59$ for women for country of birth). The exclusion of those with pre-attendance life-threatening medical conditions did not change materially the results and for both men and women, occasional drinkers had risk similar to ex-drinkers (Table 2 B). When modeling alcohol as a continuous variable using fractional polynomials, we first included ex-drinkers (Fig. 1). For males, the best fitting second-order fractional polynomial model had $p1 = p2 = 0.5$. The nadir was reached at 11.4 g/day [HR: 0.83; 95% confidence interval (CI): 0.71–0.96] and the HRs were greater than unity above 76 g/day. For females, when three overly influential observations with total alcohol intake >150 g/day were excluded, the best fitting second-order fractional polynomial model had $p1 = 0.5$ and $p2 = 1$. The nadir was reached at 10.9 g/day (HR: 0.91; 95% CI: 0.77–1.06) and the HRs were greater than unity above 42 g/day.

The analyses were repeated after excluding ex-drinkers. For males, the best fitting second-order fractional polynomial model ($p1 = 0.5$ $p2 = 0.5$) gave the nadir at 9.1 g/day (HR: 0.87; 95% CI: 0.74–1.02) and the HRs were greater than unity above 60 g/day. For females, the best fitting second-order fractional polynomial model ($p1 = 0.5$, $p2 = 1$) gave the nadir at 11.6 g/day (HR 0.90, 95% CI: 0.76–1.06) and the HRs were greater than unity above 45 g/day.

### *Type of beverage*

Table 3 shows the association between consumption of beer, wine and spirits and all-cause mortality after excluding ex-drinkers. The HRs for wine were U-shaped: the nadirs were at 20–39 g/day of alcohol from this source with a HR of 0.69 for males and 1–19 g/day with a HR of 0.82 for females. For both sexes, the HRs were never higher than one. For males, the HRs for beer increased with the amount consumed (test for trend, $P = 0.05$) to a maximum of 1.56 for those who consumed 60 g/day or more; for spirits, the highest

Table 2. HRs for the associations between alcohol consumption at baseline and all-cause mortality

| Alcohol intake* | Person years | No. of deaths | HR** | 95% CI |
|---|---|---|---|---|
| A. All subjects | | | | |
| *Males* | | | | |
| Lifetime abstainers | 20 164 | 160 | 1.00 | |
| Ex-drinkers | 6388 | 69 | 1.26 | 0.94–1.68 |
| 0.01–19 g/day | 68 237 | 442 | 0.95 | 0.79–1.15 |
| 20–39 g/day | 31 603 | 199 | 0.86 | 0.69–1.07 |
| 40–59 g/day | 13 614 | 123 | 1.10 | 0.86–1.41 |
| 60+ g/day | 10 749 | 97 | 1.05 | 0.80–1.40 |
| *Females* | | | | |
| Lifetime abstainers | 91 848 | 381 | 1.00 | |
| Ex-drinkers | 7418 | 28 | 0.89 | 0.61–1.32 |
| 0.01–19 g/day | 111 321 | 362 | 0.90 | 0.77–1.05 |
| 20–39 g/day | 20 252 | 85 | 1.02 | 0.79–1.31 |
| 40+ g/day | 5841 | 25 | 0.94 | 0.62–1.43 |
| B. Subjects with pre-attendance life-threatening medical conditions have been excluded | | | | |
| *Males* | | | | |
| Lifetime abstainers | 18 759 | 133 | 1.00 | |
| Ex-drinkers | 5750 | 50 | 1.24 | 0.89–1.73 |
| Occasional drinkers*** | 2611 | 23 | 1.24 | 0.79–1.94 |
| 0.6–19 g/day | 60 910 | 325 | 0.94 | 0.77–1.16 |
| 20–39 g/day | 29 243 | 162 | 0.91 | 0.71–1.15 |
| 40–59 g/day | 12 666 | 95 | 1.10 | 0.84–1.46 |
| 60+ g/day | 9928 | 84 | 1.20 | 0.88–1.63 |
| *Females* | | | | |
| Lifetime abstainers | 84 525 | 297 | 1.00 | |
| Ex-drinkers | 6787 | 19 | 0.76 | 0.48–1.22 |
| Occasional drinkers*** | 8092 | 19 | 0.67 | 0.42–1.07 |
| 0.6–19 g/day | 94 038 | 247 | 0.91 | 0.76–1.09 |
| 20–39 g/day | 18 391 | 56 | 0.92 | 0.68–1.24 |
| 40+ g/day | 5315 | 16 | 0.81 | 0.48–1.36 |

*Average daily intake estimated from beverage-specific questions about average quantity and frequency of consumption.
**HR and 95% CI, adjusted for country of birth, smoking, fruit and vegetable intake, total energy intake, saturated fat, physical activity, education, BMI, and in part A, previous cancer or stroke.
***Occasional drinkers are those drinking one glass of wine a month or less (≤0.5 g/day).

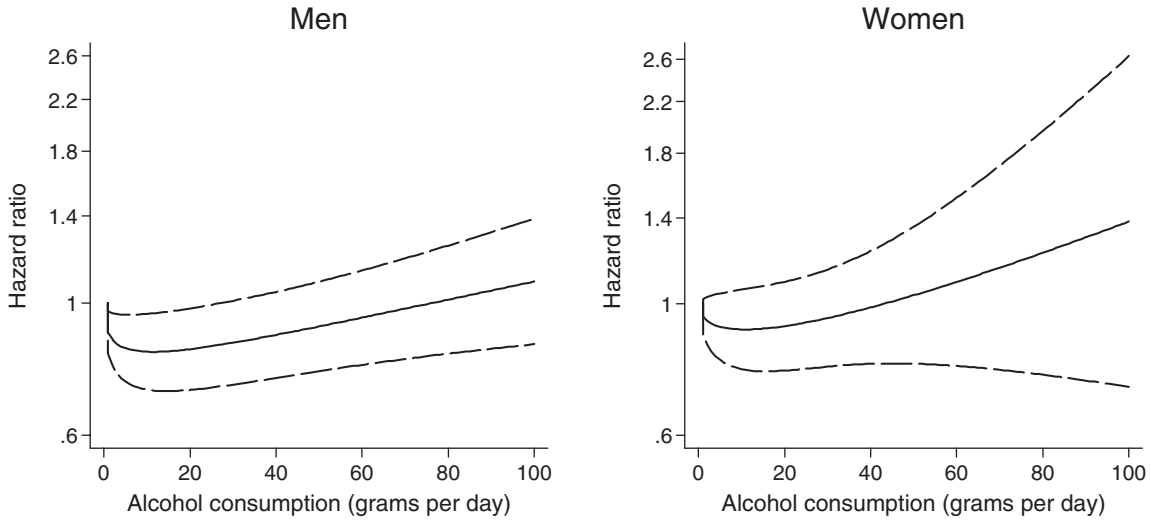


Fig. 1. Relation between the HR of all-cause mortality (continuous lines) and alcohol consumption for men and women. The relation is modeled by the best fitting second-order fractional polynomial, including ex-drinkers. Baseline category is 0 g/day. Dashed lines represent the 95% CIs.

Table 3. HRs for the association between consumption of alcohol from wine, beer and spirits at baseline and all-cause mortality

| Alcohol intake* | Person years | No. of deaths | HR** | 95% CI |
|---|---|---|---|---|
| *Males* | | | | |
| Wine (g/day) | | | | |
| 0 | 44 976 | 426 | 1.00 | |
| 1–19 | 71 938 | 418 | 0.83 | 0.71–0.96 |
| 20–39 | 17 965 | 99 | 0.69 | 0.54–0.87 |
| 40–59 | 5395 | 42 | 0.93 | 0.67–1.30 |
| 60+ | 4093 | 36 | 0.90 | 0.62–1.30 |
| Beer (g/day) | | | | |
| 0 | 39 494 | 290 | 1.00 | |
| 1–19 | 84 886 | 539 | 1.05 | 0.90–1.22 |
| 20–39 | 12 441 | 109 | 1.18 | 0.93–1.48 |
| 40–59 | 4564 | 43 | 1.04 | 0.75–1.46 |
| 60+ | 2982 | 40 | 1.56 | 1.08–2.26 |
| Spirits (g/day) | | | | |
| 0 | 83 739 | 644 | 1.00 | |
| 1–19 | 59 199 | 359 | 0.97 | 0.84–1.13 |
| 20+ | 1429 | 18 | 1.45 | 0.90–2.34 |
| *Females* | | | | |
| Wine (g/day) | | | | |
| 0 | 1103 925 | 457 | 1.00 | |
| 1–19 | 106 555 | 324 | 0.82 | 0.70–0.98 |
| 20+ | 18 782 | 72 | 0.91 | 0.69–1.20 |
| Beer (g/day) | | | | |
| 0 | 180 927 | 659 | 1.00 | |
| 1+ | 48 335 | 194 | 1.09 | 0.92–1.3 |
| Spirits (g/day) | | | | |
| 0 | 161 122 | 638 | 1.00 | |
| 1+ | 68 140 | 215 | 1.00 | 0.84–1.19 |

*Average daily intake at baseline of alcohol from each beverage type. Ex-drinkers were excluded.
**HRs and 95% CIs adjusted for all beverage types in the table plus country of birth, smoking, fruit and vegetable intake, total energy intake, saturated fat, physical activity, education, BMI and previous cancer or stroke.

HR was 1.45 for the highest category of consumption. For females, no increased risk was observed for beer and spirits consumption, but insufficient deaths were observed to investigate trends with consumption. Similar results were obtained when the analyses were adjusted for number of days of drinking in the week before interview (results not shown).

No significant interaction between beverage-specific hazards ratios and level of education or country of birth was observed (results not shown).

### *Drinking pattern*

The total alcohol intake during the week before interview was highly correlated with the average daily intake from the quantity-frequency questions (Spearman's correlation, 0.87). In the week before baseline, 4123 (28%) men and 11 842 (53%) women did not drink alcoholic beverages and were, thus, excluded from the analysis of pattern using fractional polynomials. Table 4 shows the HRs in relation to number of drinking-days within categories of total weekly alcohol intake estimated from the diary. For men, compared with regular drinkers, the HRs were 1.80 for those who consumed at least 280 g of alcohol in 1–3 days and 1.05 for those who consumed the same amount in 4–6 days. The best model selected using the multiple fractional polynomial algorithm included both variables as linear and showed a decrease in all-cause mortality rates with increasing number of drinking-days (HR per additional drinking-day: 0.96; 95% CI: 0.92–1.00; test for trend, $P = 0.04$) and an increase in HR with the amount of alcohol consumed (HR per 70 additional g/week: 1.04; 95% CI: 1.00–1.08; test for trend, $P = 0.06$). The interaction between the amount of alcohol consumed and the number of drinking-days was not significant ($P = 0.23$). For females, compared with regular drinkers, the HR for those who consumed at least 140 g of alcohol in a week was 1.42 if they drank on 1–3 days and 0.67 if they drank on 4–6 days of the week. The best model selected using the multiple fractional polynomial algorithm included alcohol as linear but not statistically significant and number of drinking-days with $p1 = 2$ and $p2 = 2$, corresponding to a U-shaped curve by number of drinking-days with a minimum mortality rate at 4 drinking-days/week and a maximum at 7 days/week (HR at 4 versus 7 drinking-days: 0.65; 95% CI: 0.47–0.90). The interaction between the total amount of alcohol consumed and the number of drinking-days was not significant ($P = 0.40$).

Table 4. HRs for the association between all-cause mortality and the consumption of alcohol during the week before baseline interview and the number of days in the week that alcohol was consumed

| | Number of drinking-days* | | |
|---|---|---|---|
| | 1–3 days | 4–6 days | 7 days |
| Total alcohol intake* | PY/deaths HR** (95% CI) | PY/deaths HR (95% CI) | PY/deaths |
| *Males* | | | |
| 1–139 g | 41 699/243 | 13 378/95 | 7921/66 |
| | 1.01 (0.77–1.33) | 1.11 (0.81–1.52) | 1 |
| 140–279 g | 3009/12 | 11 190/53 | 13 460/100 |
| | 1.09 (0.60–2.00) | 0.85 (0.61–1.18) | 1 |
| 280+ g | 444/3 | 4545/33 | 12 460/112 |
| | 1.80 (0.57–5.70) | 1.05 (0.71–1.55) | 1 |
| *Females* | | | |
| 1–139 g | 59 811/185 | 16 743/45 | 12 529/64 |
| | 0.84 (0.63–1.11) | 0.66 (0.45–0.97) | 1 |
| 140+ g | 1453/6 | 7780/18 | 11 344/56 |
| | 1.42 (0.61–3.31) | 0.67 (0.39–1.14) | 1 |

PY, Person years.
*Total alcohol intake and number of drinking-days during the week before interview calculated from the diary.
**HR and 95% CI, adjusted for country of birth, smoking, fruit and vegetable intake, total energy intake, saturated fat, physical activity, education, BMI, and previous cancer or stroke.

### *Effect of pre-attendance illnesses*

Sensitivity analyses, as described in the method section, were conducted to test for a different impact of total amount of alcohol, type of beverage and drinking pattern on early events. The results did not change after the exclusion of those subjects with pre-attendance illness or after the exclusion of the first 2 years of follow-up and no statistically significant differences in HRs were observed by duration of follow-up (results not shown).

## DISCUSSION

Our analysis of alcohol and all-cause mortality in the MCCS has shown that light drinkers had a lower mortality than lifetime abstainers. Only at high levels of consumption was there evidence of higher mortality. The upper protective dose of alcohol we found for men (76 and 60 g/day with and without former drinkers, respectively) and women (42 and 45 g/day with and without former drinkers, respectively) were comparable with those reported by the meta-analysis of Bagnardi *et al*. (2004). Wine-drinkers had a lower risk of dying; beer drinking was associated with increased mortality in males but not females and no significant associations were observed with the consumption of spirits. Although our ability to explore associations with drinking pattern was limited by the small proportion of person time characterized by infrequent heavy drinking, the results suggest that for the same weekly consumption of alcohol, men who drank less frequently had higher mortality than men who drank daily, whereas women experienced the minimum risk of dying from all causes at 4 drinking-days per week.

The strengths of our study include the large number of deaths, almost complete follow-up of participants and detailed measurements of alcohol consumption that allowed us to separate lifetime abstainers from former drinkers and to examine patterns of consumption. The participants were heterogeneous in terms of age and ethnic origin and, hence, in their amount and, to some extent, pattern of alcoholic beverage consumption. Men, but not women, were also heterogeneous with respect to the types of beverages they consumed.

A limitation of our study, as with all studies of alcohol consumption, is the inaccuracy of self-reported intake at baseline, both for average consumption and for consumption during the past week, which will tend to attenuate associations (World Health Organization, 2000). If recent consumption is a determinant of mortality, and if people changed their consumption during follow-up, then having a single measurement at baseline might also give biased estimates of the true association. In the absence of Australian longitudinal data on patterns of changes in alcohol consumption, we have no means of determining the likely effect of any change in alcohol consumption on the dose–response relationships. Because of the small proportion of heavy drinkers, especially among women, our results are not applicable to people with high levels of consumption and we had no information on preference for red or white wine. Although we measured several potential confounding variables, residual confounding due to their imprecise measurement, or to other unmeasured confounders, remains a possibility.

We found that men, but not women, who drank formerly had higher mortality than those who never drank. The mortality rate of men at the nadir was significantly lower than the mortality rate of lifetime abstainers and former drinkers pooled together and the relative risk similar to that found by Bagnardi *et al*. (2004) in their meta-analysis. After excluding former drinkers from the referent group, the minimum relative risk was slightly higher and no longer significant. Among females, where the average alcohol consumption was lower, the relative risk was never significantly different from unity regardless of whether former drinkers were included. Klatsky *et al*. (2003) found an increased mortality rate among former drinkers of both sexes. Our finding suggests that the reason why men and women in our cohort stopped drinking were different: men may have stopped drinking for important health problems, whereas this does not appear likely for women.

Many authors investigated the effect of alcohol on all-cause mortality, but only few studies have been judged free from the systematic misclassification of including ex-drinkers and long-term abstainers (those who drink once a month or less) among complete abstainers (Fillmore *et al*., 2006). In our study, the mortality rates for both men and women remained J-shaped after removing ex-drinkers from the analysis, and after excluding those subjects with pre-attendance life-threatening medical conditions or after excluding the first 2 years of follow-up when events related to recent changes in alcohol consumption may have occurred. Occasional drinkers defined as those who drank one glass of wine or less in a month had a risk as high as ex-drinkers and the protective effect of alcohol happened for consumption of alcohol around 10 g/day. Then our results, free from misclassification biases (Fillmore *et al*., 2006), support the theory that the 'sick-quitter' hypothesis (Shaper *et al*., 1988) can only partially explain the lower risk of death for all causes in those consuming light to moderate amount of alcohol.

The association between type of beverages and mortality may differ according to socio-economic levels (Nielsen *et al*.,

2004). We did not find any difference in the association between total amount of alcohol or type of beverage and mortality by level of education, but it is also possible that other measures of socio-economic status could have some influence.

It has been suggested that the protective effect of wine compared with beer and spirits could be due to confounding or could be partially explained by the fact that wine-drinkers drink more regularly compared with beer and spirit drinkers (Gronbaek *et al*., 2000). We had no data on pattern of alcohol consumption with respect to meals (Trevisan *et al*., 2001), but the protective effect of wine we observed was still evident after controlling for the number of drinking-days. A consensus about the benefits of phenolic acids and polyphenols, generally accepted for fruit and vegetables, is now slowly developing for wine (German and Walzem, 2000) and our study provides evidence that at least some of the protective effect of alcohol at low doses may be due to wine rather than to alcohol per se.

For men, a pattern of drinking involving consumption on only a few days in a week was associated with a higher mortality after adjusting for the total amount of alcohol consumed in the week. The different association for drinking pattern for women compared with men could be due to inadequate study power or their lower total consumption of alcohol, even if other mechanisms cannot be excluded. Other authors report that regular drinking has a less adverse association with mortality than occasional drinking. However, the definition of pattern differs substantially between studies, making direct comparisons of the findings difficult: some authors use heavy drinking or binge drinking as indicators of drinking pattern (Rehm *et al*., 2001; Malyutina *et al*., 2002; Murray *et al*., 2002; Laatikainen *et al*., 2003), others drinking with or without meals (Trevisan *et al*., 2001), and some the number of days of drinking per week (Mukamal *et al*., 2003; Tolstrup *et al*., 2004). One difficulty of studying the effect of drinking pattern is its positive correlation with the total amount of alcohol consumed. Any analysis of pattern within categories of total consumption is, thus, likely to suffer from residual confounding. We attempted to overcome this by modeling both the pattern and total amount as continuous variables using fractional polynomials.

In summary, our study shows that the amount of alcohol consumed and the drinking pattern are independent risk factors for all-cause mortality for men. Further studies based on valid and replicable measures of drinking pattern need to be conducted in order to confirm these results and to clarify the role that pattern of consumption may have on specific causes of death.

*Acknowledgements* — This study was made possible by the contribution of many people, including the original investigators and the diligent team who recruited the participants and who continue working on follow-up. Finally, we would like to express our gratitude to the many thousands of Melbourne residents who continue to participate in the study. Cohort recruitment was funded by VicHealth and The Cancer Council Victoria. This analysis was partly funded by grants from the National Health and Medical Research Council (Grants No: 209057 and 251533) and the Australian Brewers' Foundation.

## REFERENCES

Altman, D. G. and Royston, P. (1994) Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. *Applied Statistics* **43**, 429–467.

Bagnardi, V., Zambon, A., Quatto, P. *et al*. (2004) Flexible meta-regression functions for modeling aggregate dose–response data, with an application to alcohol and mortality. *Am J Epidemiol* **159**, 1077–1086.

Boffetta, P. and Garfinkel, L. (1990) Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. *Epidemiology* **1**, 342–348.

Di Castelnuovo, A., Rotondo, S., Iacoviello, L. *et al*. (2002) Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation* **105**, 2836–2844.

Doll, R., Peto, R., Hall, E. *et al*. (1994) Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *British Medical Journal* **309**, 911–8.

Fillmore, K., Kerr, W., Stockwell, T. *et al*. (2006) Moderate alcohol use and reduced mortality risk: systematic error inprospective studies. *Addiction Research and Theory* **14**, 101–132.

Fillmore, K. M., Golding, J. M., Graves, K. L. *et al*. (1998) Alcohol consumption and mortality. I. Characteristics of drinking groups. *Addiction* **93**, 183–203.

Fuchs, C. S., Stampfer, M. J., Colditz, G. A. *et al*. (1995) Alcohol consumption and mortality among women. *New England Journal of Medicine* **332**, 1245–1250.

German, J. B. and Walzem, R. L. (2000) The health benefits of wine. *Annual Review of Nutrition* **20**, 561–593.

Gronbaek, M., Becker, U., Johansen, D. *et al*. (2000) Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer. *Annals of Internal Medicine* **133**, 411–419.

Gronbaek, M., Deis, A., Sorensen, T. I. *et al*. (1994) Influence of sex, age, body mass index, and smoking on alcohol intake and mortality. *British Medical Journal* **308**, 302–306.

Ireland, P., Jolley, D., Giles, G. *et al*. (1994) Development of the Melbourne FFQ: a food frequency questionnaire for use in an Australian prosepctive study involving an ethnically diverse cohort. *Asia Pacific Journal of Clinical Nutrition* **3**, 19–31.

Keil, U., Chambless, L. E., Doring, A. *et al*. (1997) The relation of alcohol intake to coronary heart disease and all-cause mortality in a beer-drinking population. *Epidemiology* **8**, 150–156.

Klatsky, A. L. (1999) Moderate drinking and reduced risk of heart disease. *Alcohol Research and Health* **23**, 15–23.

Klatsky, A. L., Armstrong, M. A. and Friedman, G. D. (1992) Alcohol and mortality. *Annals of Internal Medicine* **117**, 646–54.

Klatsky, A. L., Friedman, G. D., Armstrong, M. A. *et al*. (2003) Wine, liquor, beer, and mortality. *American Journal of Epidemiology* **158**, 585–595.

Korn, E. L., Graubard, B. I. and Midthune, D. (1997) Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *American Journal of Epidemiology* **145**, 72–80.

Laatikainen, T., Manninen, L., Poikolainen, K. *et al*. (2003) Increased mortality related to heavy alcohol intake pattern. *Journal of Epidemiology and Community Health* **57**, 379–384.

Lewis, J., Milligan, G. and Hunt, A. (1995) *NUTTAB95 Nutrient Data Table for Use in Australia*. Australian Government Publishing Service, Canberra.

MacInnis, R. J., English, D. R., Hopper, J. L. *et al*. (2004) Body size and composition and colon cancer risk in men. *Cancer Epidemiology Biomarkers and Prevention* **13**, 553–559.

Malyutina, S., Bobak, M., Kurilovitch, S. *et al*. (2002) Relation between heavy and binge drinking and all-cause and cardiovascular mortality in Novosibirsk, Russia: a prospective cohort study. *Lancet* **360**, 1448–1454.

Mukamal, K. J. and Rimm, E. B. (2001) Alcohol's effects on the risk for coronary heart disease. *Alcohol Research and Health* **25**, 255–261.

Mukamal, K. J., Conigrave, K. M., Mittleman, M. A. *et al*. (2003) Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *New England Journal of Medicine* **348**, 109–118.

Murray, R. P., Connett, J. E., Tyas, S. L. *et al*. (2002) Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? *American Journal of Epidemiology* **155**, 242–248.

Nielsen, N. R., Schnohr, P., Jensen, G. *et al*. (2004) Is the relationship between type of alcohol and mortality influenced by socioeconomic status? *Journal of Internal Medicine* **255**, 280–288.

Pols, R. G. and Hawks, D. V. (1992) *Is There a Safe Level of Daily Consumption of Alcohol for Men and Women? Recommendations Regarding Responsible Drinking Behaviour*. National Health and Medical Research Council, Canberra.

Rehm, J., Gmel, G., Sempos, C. T. *et al*. (2003) Alcohol-related morbidity and mortality. *Alcohol Research and Health* **27**, 39–51.

Rehm, J., Greenfield, T. K. and Rogers, J. D. (2001) Average volume of alcohol consumption, patterns of drinking, and all-cause mortality: results from the US National Alcohol Survey. *American Journal of Epidemiology* **153**, 64–71.

Rimm, E. B., Giovannucci, E. L., Willett, W. C. *et al*. (1991) Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* **338**, 464–468.

Royston, P. and Sauerbrei, W. (2004) A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Statatistics in Medicine* **23**, 2509–2525.

Shaper, A. G., Wannamethee, G. and Walker, M. (1988) Alcohol and mortality in British men: explaining the U-shaped curve. *Lancet* **2**, 1267–1273.

Stampfer, M. J., Colditz, G. A., Willett, W. C. *et al*. (1988) A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *New England Journal of Medicine* **319**, 267–273.

Thun, M. J., Peto, R., Lopez, A. D. *et al*. (1997) Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *New England Journal of Medicine* **337**, 1705–1714.

Tolstrup, J. S., Jensen, M. K., Tjonneland, A. *et al*. (2004) Drinking pattern and mortality in middle-aged men and women. *Addiction* **99**, 323–330.

Trevisan, M., Schisterman, E., Mennotti, A. *et al*. (2001) Drinking pattern and mortality: the Italian Risk Factor and Life Expectancy pooling project. *Annals of Epidemiology* **11**, 312–319.

Wetterling, T., Veltrup, C., Driessen, M. *et al*. (1999) Drinking pattern and alcohol-related medical disorders. *Alcohol Alcohol* **34**, 330–336.

World Health Organization. (2000) *International Guide for Monitoring Alcohol Consumption and Related Harm*. Report No.: WHO/MSD/MSB/00.4. Department of Mental Health and Substance Dependence, Noncommunicable Diseases and Mental Health Cluster, World Health Organization, Geneva.

Yuan, J. M., Ross, R. K., Gao, Y. T. *et al*. (1997) Follow up study of moderate alcohol intake and mortality among middle-aged men in Shanghai, China. *British Medical Journal* **314**, 18–23.