ESC European Society of Cardiology

European Journal of Preventive Cardiology (2023) **00**, 1–11
https://doi.org/10.1093/eurjpc/zwad364

FULL RESEARCH PAPER
Cardiovascular disease

Drinking patterns of alcohol and risk of major adverse cardiovascular events after an acute coronary syndrome

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Received 16 July 2023; revised 14 November 2023; accepted 19 November 2023; online publish-ahead-of-print 23 November 2023

Aims To evaluate the risk of alcohol consumption after acute coronary syndromes (ACS).

Methods and results A total of 6557 patients hospitalized for ACS at four Swiss centres were followed over 12 months. Weekly alcohol consumption was collected at baseline and 12 months. Binge drinking was defined as consumption of ≥6 units of alcohol on one occasion. Major adverse cardiovascular events (MACE) were defined as a composite of cardiac death, myocardial infarction, stroke, or clinically indicated target vessel coronary revascularization. Cox regression analysis was performed to assess the risk of MACE in patients with heavy (>14 standard units/week), moderate (7–14 standard units per week), light consumption (<1 standard unit/week), or abstinence, and with binge drinking episodes, adjusted for baseline differences. At baseline, 817 (13.4%) patients reported heavy weekly alcohol consumption. At 1-year follow-up, 695/1667 (41.6%) patients reported having at least one or more episodes of binge drinking per month. The risk for MACE was not significantly higher in those with heavy weekly consumption compared to abstinence [8.6% vs. 10.2%, hazard ratio (HR) 0.97, 95% confidence interval (CI) 0.69–1.36] or light consumption (8.6% vs. 8.5%, HR 1.41, 95% CI 0.97–2.06). Compared to patients with no binge drinking, the risk of MACE was dose-dependently higher in those with binge drinking with less than one episode per month (9.2% vs. 7.8%, HR 1.61, 95% CI 1.23–2.11) or one or more episodes per month (13.6% vs. 7.8%, HR 2.17, 95% CI 1.66–2.83).

Conclusion Binge drinking during the year following an ACS, even less than once per month, is associated with worse clinical outcomes.

Lay summary The cardiovascular risk of alcohol consumption and binge drinking episodes after acute coronary syndrome (ACS) has not been established. Our data suggested the following:

- After ACS, regular weekly alcohol consumption is not associated with the risk of major adverse cardiovascular events (MACE), except for patients reporting binge drinking who have a two-fold increased risk of MACE within 1 year of the index event.
- After ACS, episodes of binge drinking, even less than once per month, are associated with worse clinical outcomes.

It is not the frequency but rather the quantity of alcohol intake in a binge drinking episode that is associated with worse prognosis in patients after an ACS.

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Graphical Abstract

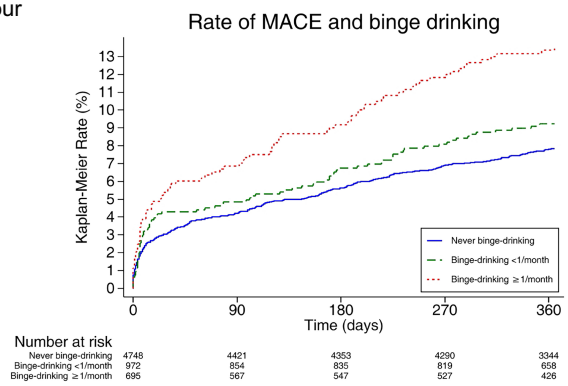
Drinking patterns of alcohol and risk of major adverse cardiovascular events after an acute coronary syndrome

Logistic regression model with the association between binge drinking behaviour and MACE, after an acute coronary syndrome

MACE are defined as: a composite of cardiac death, MI, stroke or clinically indicated target vessel coronary revascularization

Binge drinking group	Adj. HR (95%-CI)
Never binge drinking	Ref.
<1 per month binge-drinking	1.61 (1.23 to 2.11)
≥1 per month binge-drinking	2.17 (1.66 to 2.83)

Kaplan-Meier rates of the primary endpoint of MACE after an acute coronary syndrome by categories of alcohol binge drinking behaviour



Binge drinking during the year following an ACS, even less than once per month, is associated with worse clinical outcomes

Keywords Cardiovascular prevention • Secondary cardiovascular prevention • Alcohol consumption • Binge drinking • Acute coronary syndromes • Lifestyle

Introduction

Alcohol consumption is a well-known risk factor for causing disability and death in both men and women across all age groups, particularly when consumed in excess.[1] Nonetheless, it remains the most widely consumed psychoactive substance worldwide, with over 2 billion current drinkers.[2]

The European Society of Cardiology (ESC) 2016 guidelines recommend that alcohol consumption should be limited to two glasses per day (20 g/day) for men and one glass per day (10 g/day) for women independently of the presence of cardiovascular disease (CVD).[3]

Alcohol consumption represents a more complex construct than many other modifiable risk factors because of its multidimensional nature. As captured in the AUDIT[4] and similar alcohol assessment instruments, drinking patterns include drinking frequency (i.e. days per week in which alcohol is consumed), quantity per drinking day, and heavy episodic or binge drinking.

Although some beneficial effects of moderate alcohol intake have been described, mainly in case–control studies,[5,6] alcohol can become a risk factor for cardiovascular (CV) mortality if consumption is excessive.[7,8] Binge drinking is a particularly high-risk behaviour, but data reporting any association with CVD outcomes remain scant.[9,10] In addition, gender differences have been described: the effects of alcohol consumption can be even more deleterious in women already at lower dosages (>7 units/week) compared to men (>14 units/week); predictors and consequences of binge drinking also differ according to age and environment.[11]

Previous observational studies have attempted to relate alcohol consumption to prognosis following myocardial infarction (MI), but these studies occurred prior to the modern era of treatment for MI,[12] where current antiplatelet drugs and newer stenting techniques have improved clinical outcomes after acute coronary syndromes (ACS). Although limited alcohol intake has been associated with lower mortality among patients after MI, a finding bolstered by limited experimental evidence,[13] binge drinking, even among light drinkers, appears to be associated with a two-fold increase in mortality in this population.[14]

In secondary prevention among survivors of MI, no large recent study has investigated the risk of alcohol consumption on CV outcomes,[15,16] and there are still no clear recommendations on the quantity of alcohol consumption allowed after MI.

After a CV event, patients are more motivated to change their lifestyle, and CV rehabilitation programmes are implemented to improve adherence to a healthy lifestyle.[17] However, the question of alcohol consumption seems generally not to be considered a priority by cardiologists, in contrast to smoking or other CV risk factors, where target goals are well established. Notably, alcohol is not listed as a traditional CV risk factor but it might have a potential effect on the CV system besides atherogenesis.[18] Therefore, we lack clear directives and scientific evidence for secondary CV prevention on this topic in patients after ACS; in fact, risk thresholds for alcohol consumption seem to be the same in both primary and secondary prevention.[19]

To address the association between drinking patterns, including frequency, quantity, and binge drinking, and CV prognosis among patients with established coronary heart disease, we examined data from an inception cohort study of patients with ACS in Switzerland.

Methods

Study population

We extracted data of 6557 patients enrolled prospectively from 2009 to the end of 2018 in 'Special Program University Medicine Acute Coronary Syndromes and Inflammation' (SPUM-ACS) cohort, which included patients

with a primary diagnosis of ACS referred for angiography to one of four Swiss academic centres (Bern, Geneva, Lausanne, and Zürich; NCT01000701).[20]

We included men and women aged 18 years and older presenting within 5 days (preferably within 72 h) after pain onset, associated with ST-elevation myocardial infarction (STEMI), non–ST-elevation myocardial infarction (NSTEMI), or unstable angina. Patients had to present with symptoms compatible with angina pectoris (chest pain and dyspnoea) and fulfil at least one of the following criteria: (i) persistent ST-segment elevation or depression, T-inversion, or dynamic electrocardiogram changes, new left bundle branch abnormality; (ii) evidence of positive troponin by local laboratory reference values (with a rise and/or fall in serial troponin levels); or (iii) known coronary artery disease, specified as status after MI, coronary artery bypass grafting, or percutaneous coronary intervention (PCI) or newly documented ≥50% stenosis of an epicardial coronary artery during initial catheterization.[20] Exclusion criteria comprised severe physical disability, inability to comprehend the study, or <1 year of life expectancy (for non-cardiac reasons). Follow-up was performed at 12 months (clinical visit) with events adjudicated by three independent experts using pre-specified adjudication forms.

Measurement of alcohol consumption

Patient-reported alcohol consumption was collected at baseline and at the 1-year follow-up. We first asked patients to evaluate their frequency of consumption of alcoholic beverages during the last 12 months, with response options of never in the last 12 months, less than once a month, one to three times a month, once or twice a week, three or four times a week, every day, or nearly every day. We next asked patients to evaluate the number of standard drinks on the days when they had any beverage containing alcohol. A standard drink was defined as a glass of wine of 1 dL, a glass of beer of 2.5 dL, and a glass of spirit of 0.2 dL, corresponding to 10 g of alcohol as in previous studies[21] and defined by the 2021 ESC guidelines on CVD prevention in clinical practice.[22]

Based on these two questions, we classified patients according to the number of standard drinks of alcohol per week: 0, <1 standard unit drink per week, between 1 and 6 standard drinks per week, between 7 and 14 standard drinks per week, and >14 standard drinks per week, as in previous publications.[23]

At the 1-year follow-up, we also evaluated any binge drinking episodes in the last 12 months according to the following frequencies: never in the last 12 months, less than once a month, once a month, once a week, every day, or nearly every day. Binge drinking was defined as the consumption of ≥6 units of alcohol on one occasion as classified in previous cohort studies[24] and corresponding to 60 g of ethanol on one occasion. Data on binge drinking were available only at 1-year follow-up. The episodes of binge drinking were evaluated considering the period immediately following the index ACS event starting from baseline to 1 year.

Definition of study endpoints

We defined the primary endpoint as the risk of major adverse CV events (MACE) at 1-year follow-up post ACS. We defined MACE as a composite of cardiac death (defined as any death to proximal cardiac cause, e.g. MI, low-output failure, fatal arrhythmia, unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment), MI, stroke, or clinically indicated target vessel coronary revascularization.[25] As secondary endpoints, we analysed individually the components of the primary endpoints, as well as all-cause death, any coronary revascularization, any bleeding using the Bleeding Academic Research Consortium (BARC) classification, gastrointestinal bleeding, or intracranial bleeding.[26] All clinical events were adjudicated by a central committee of independent clinicians.

Statistical analysis

The types of consumed alcohol were described by weekly consumption categories at baseline and at 1-year follow-up. Baseline characteristics according to the quantity of weekly alcohol consumption are presented using descriptive analysis with frequencies and percentages for categorical variables and mean (±SD) or median [interquartile range (IQR)] for continuous variables. Cumulative failure rates for the primary endpoints were presented by alcohol weekly consumption categories and binge drinking categories. The *P*-values comparing the heavy alcohol consumption (>14 standard units/week) vs. abstinence were calculated using the log-rank test for equality and the *P*-value for linear trend across categories. We applied the Cox regression model to assess the risk of MACE associated with heavy alcohol weekly consumption categories. The proportionality assumption was tested based on Schoenfeld residuals after fitting the Cox regression model. In the case that the proportionality was not entirely satisfied, a parametric survival model with the Weibull distribution was applied. Hazard ratios (HR) were unadjusted and adjusted for baseline differences [age, sex, education level, body mass index (BMI), smoking, diabetes, peripheral artery disease (PAD), previous stroke, hypertension, LDL cholesterol (LDL-C) level, use of aspirin, anticoagulation, statin, beta-blocker, Angiotensin-converting enzyme (ACE)-inhibitor, or Angiotensin II (ATII) receptor blocker]. We examined two different referent categories: patients with abstinence and those consuming <1 standard unit/week. We performed several sensitivity analyses: (i) we added an interaction term that coded changes in weekly alcohol consumption categories from baseline to 1 year (as no change, a decrease, or an increase); (ii) we removed baseline hypertension from the multivariate model because hypertension may lie on the causal pathway between weekly alcohol consumption and clinical outcome[27]; (iii) we included the binge drinking categorization in the model; and (iv) we tested a competing risk model adding non-cardiac death as a competitor outcome. For the Cox regression model evaluating binge drinking behaviour, we compared those who reported episodes of binge drinking (≥1 episode per month or <1 episode per month) to those who did not report any episode of binge drinking adjusting for the same baseline differences. Stratified analyses in men vs. women were conducted as prespecified for both baseline weekly alcohol consumption categories and binge drinking categories. For binge drinking, we also performed a sensitivity analysis stratifying according to baseline smoking habits. Cubic splines were used to model the relationship between the probability of MACE and baseline alcohol consumption. As sensitivity analysis, we also performed a logistic regression to the model to assess the association between binge drinking and risk of MACE.

All hypothesis tests were two sided, and the significance level was set at 5%. Statistical analyses were performed using STATA software VR (Version 17, STATA Corp, College Station, TX, USA).

Missing values

In sensitivity analysis, 362 missing values on the quantity of alcohol consumption at baseline were imputed with values collected at 1 year follow-up (total sample size of 6415 patients). A total of 822 participants had missing information for binge drinking at 1 year follow-up. Among the 822 patients, 815 patients were imputed using baseline values of weekly consumption, with the following assumption: (i) 'no binge drinking' if baseline information was 'no alcohol consumption in the last 12 months' or '<1 standard unit/week'; (ii) 'binge drinking <1/month' if baseline information was between '1 and 6 standard unit drinks/week'; and (iii) 'binge drinking ≥1/month' if baseline information was either '7–14 standard unit drinks/week' or '>14 standard unit drinks/week' (the imputation was done in a single simple step, based on the baseline value). Finally, seven participants were imputed using 1-year follow-up values of weekly consumption using the same assumption as baseline.

Results

We prospectively enrolled 6557 patients from 2009 to 2018. Of those, 142 patients were excluded because of missing data at baseline and at 1 year follow-up, and 362 were excluded due to missing data on alcohol consumption at baseline only (but with information available at 1 year follow-up), yielding 6053 patients for the primary analysis (see Supplementary material online, *Figure S1A*). In the sensitivity analysis, the 362 missing values on the quantity of alcohol consumption at baseline were imputed with values collected at 1 year follow-up. Of notice, 289 patients withdrew consent or were lost at 1 year follow-up and 179 died within 365 days. Binge drinking behaviour was analysed in data from 6415 patients, and among those, 822 patients had imputation using baseline values (because of missing information), whereas 5593 patients had available data at 1 year follow-up (see Supplementary material online, *Figure S1B*).

Patient characteristics at baseline

Mean age was 63 ± 12.3 years, and 1242 of the 6053 included patients were female (21%). At baseline, 817 (13%) reported heavy alcohol consumption (>14 units of drinks per week), 1333 (22%) reported moderate alcohol consumption (between 7 and 14 standard units of drinks per week), 1857 (31%) reported 1–6 standard units drink per week, 933 (15%) reported <1 standard unit per week, and 1113 (18%) reported no alcohol consumption in the last 12 months.

Those with heavy alcohol consumption were more likely to be male, highly educated, active smokers, presenting high HDL-C values at baseline, and were less likely to have diabetes. Left ventricular ejection fraction at discharge did not differ across categories (*Table 1*).

A total of 1667 (25.9%) patients reported binge drinking behaviour, of whom 972 (58.3%) reported less than one episode per month and 695 (41.6%) reported at least one or more episodes per month. The latter were more likely to be younger males, highly educated, active smokers, and less likely to have hypertension or diabetes (see Supplementary material online, *Table S1*).

Patterns of alcohol consumption

Regarding the types of alcohol consumed, wine was the most common type at baseline, respectively, in those drinking <1 standard unit/week (67.8%), 1–6 standard units/week (50.8%), 7–14 standard units/week (60.8%), and >14 standard units/week (34.3%). Similarly, wine remained the most common type of alcohol consumed at 1 year follow-up (see Supplementary material online, *Table S2A and B*). Comparison between baseline and 1-year follow-up alcohol consumption showed that 72.3% of those who were abstinent at baseline remained in the same categories at 1 year follow-up. Similarly, 82.4% of patients who reported heavy consumption (7–14 standard units/week and >14 standard units/week) at baseline continued to consume at least seven drinks per week at follow-up. Furthermore, among heavy drinkers at 1 year (>14 standard unit drinks per week), 68% were already heavy drinkers at baseline and 24% were drinking between 7 and 14 standard unit drinks per week. Only 2% of patients were drinking less than once a week (see Supplementary material online, *Table S2C*).

Weekly alcohol consumption and clinical outcomes at 1-year follow-up after acute coronary syndrome

At 1-year follow-up, 506 patients with a MACE (8.4%) were identified. The cumulative failure rates of the primary endpoint of MACE were similar across all alcohol categories: 8.7% for heavy weekly consumption, 9.5% for 7–14 standard drinks per week, 7.4% for 1–6 standard drinks per week, 8.5% for <1 standard drinks per week, and 10.3% for no alcohol consumption (log-rank test for equality $P = 0.09$, P for trend = 0.39; see Supplementary material online, *Table S3A*). (A Kaplan–Meier curve is shown in Supplementary material online, *Figure S2*.) Sensitivity analysis, with missing values at baseline that were imputed with values collected at 1 year follow-up, also showed similar results (see Supplementary material online, *Table S3B*).

Regarding individual endpoints of the composite outcome, and other secondary endpoints, we observed no significant increased risk associated with weekly alcohol consumption, except for all-cause death and trend for cerebrovascular events (stroke or transitory ischaemic attack). In the multivariable model, the adjusted HR for MACE was similar in those with heavy weekly consumption compared to no alcohol consumption [8.6% vs. 10.2%, adjusted HR 0.97, 95% confidence interval (CI) 0.69–1.36, $P = 0.80$] or compared to light consumption (8.6% vs. 8.5%, adjusted HR 1.41, 95% CI 0.97–2.06, $P = 0.074$; *Table 2*). The results were consistent, to the multivariate model, even when adding the interaction term in alcohol changes from baseline to 1 year, and the adjusted HR for heavy consumption was 0.97 (95% CI 0.69–1.36, $P = 0.857$) when compared to abstinence and 1.41 (95% CI 0.97–2.06, $P = 0.074$) when compared to light alcohol consumption (*Table 2*). The risk for MACE among patients with heavy weekly consumption (>14 standard units/week) compared to no alcohol consumption did not show any difference when considering sex (HR 1.45, 95% CI 0.54–3.88 in women, see Supplementary material online, *Table S4*; HR 0.87, 95% CI 0.61–1.26 in men, see Supplementary material online, *Table S5*), with no significant interaction between gender and categories (P-value for interaction = 0.735). The risk in men and women was consistent when comparing those with <1 standard unit drink per week or adding the interaction term in alcohol changes, as increased or decreased alcohol consumption (see Supplementary material online, *Tables S4A–C* and *S5A–C*). Sensitivity analysis, with missing values at baseline that were imputed with values collected at 1 year follow-up, also showed similar results, respectively, when the reference was no alcohol consumption and when the reference was 1–6 standard unit drinks per week (see Supplementary material online, *Table S6A and B*).

Results were also similar when removing hypertension from the model or adding binge drinking in the model and considering the competitive risk of non-cardiac death (see Supplementary material online, *Table S7A–C*).

In the sensitivity analysis, after excluding those with binge drinking behaviour, those who reported > 14 standard unit drinks per week tended to have a lower risk of MACE compared to those who are abstinent (adj HR 0.93, 95% CI 0.63–1.04) but not compared to those with light consumption (<1 standard unit drink per week; adj HR 0.98, 95% CI 0.57–1.66) or other remaining categories (see Supplementary material online, *Table S8A and B*).

In a cubic spline model, the probability of the primary endpoint showed a pattern suggestive of a positive linear trend with risk starting to increase from 10 units of alcohol per week, whereas, for those between 0 and 10 units per week, the relationship was largely null or potentially inverse (*Figure 1*). When considering the quantity of alcohol intake per day, the pattern was similar, with a lower risk for values between 1 and 5 units of alcohol per day and no clear harm beyond 5 units per day (*Figure 2*).

Binge drinking behaviour and clinical outcomes at 1-year follow-up after acute coronary syndrome

Binge drinking behaviour was collected at 1 year follow-up only. Only complete cases were considered for the analysis ($n = 6415$ patients). The proportion of binge drinking was more prevalent in those reporting alcohol consumption between 7 and 14 units per week and >14 units per week as reported in Supplementary material online, *Figure S3*. At 1-year follow-up, a total of 531 patients had a non-fatal MACE (8.3%). The cumulative failure rate of MACE increased from 7.8% in those with no binge drinking behaviour to 9.2% with binge drinking behaviour less than once per month and 13.6% with binge drinking behaviour at least once or more per month, with a significant trend ($P < 0.001$, *Table 3*). A Kaplan–Meier curve is shown in *Figure 3*. The cumulative failure rate of cardiac death, MI, or stroke increased from 5.9% in those with no binge drinking behaviour, to 7.0% with binge drinking behaviour less than one per month, and up to 11.5% with binge drinking behaviour at least once or more per month, with a significant trend ($P < 0.001$). Similar differences were found for all cause death and cardiac death ($P < 0.001$) and a pattern of risk for MI and cerebrovascular events (*Table 3*). Compared to no binge drinking behaviour, the multivariable-adjusted HR were higher in those reporting less than one binge drinking episode a month (9.2% vs. 7.8%, adjusted HR 1.61, 95% CI 1.23–2.11, $P < 0.001$), as well as in those with at least one episode per month (13.6% vs. 7.8%, adjusted HR 2.17, 95% CI 1.66–2.83, $P < 0.001$; *Figure 4*). When stratifying analyses by sex and

Table 1 Baseline characteristics according to quantity of weekly alcohol consumption

	No alcohol in the last 12 months	<1 standard unit drinks per week	1–6 standard unit drinks per week	7–14 standard unit drinks per week	>14 standard unit drinks per week	*P*-value
	***n* = 1113**	***n* = 933**	***n* = 1857**	***n* = 1333**	***n* = 817**	
Baseline characteristics						
Age, years	63.7 ± 13.0	63.8 ± 13.5	61.4 ± 11.9	64.6 ± 12.4	62.5 ± 11.2	<0.001
Gender (female), *n (%)*	383 (34%)	311 (33%)	301 (16%)	199 (15%)	48 (6%)	<0.001
Indicate the highest level of education	*n* = 1056	*n* = 914	*n* = 1824	*n* = 1293	*n* = 798	<0.001
Lower than apprenticeship or vocational school, *n* (%)	252 (24%)	187 (20%)	227 (12%)	193 (15%)	139 (17%)	<0.001
Apprenticeship or vocational school, *n* (%)	569 (54%)	476 (52%)	1022 (56%)	695 (54%)	362 (45%)	<0.001
High school graduation (matura), *n* (%)	111 (11%)	117 (13%)	263 (14%)	165 (13%)	121 (15%)	0.017
University graduation (including applied sciences), *n* (%)	124 (12%)	134 (15%)	312 (17%)	240 (19%)	176 (22%)	<0.001
BMI, kg/m^2	27.1 ± 4.8	27.2 ± 4.7	27.2 ± 4.2	26.6 ± 3.9	27.2 ± 4.2	0.001
Current smoker, *n/N* (%)	432/1112 (39%)	344/932 (37%)	720/1857 (39%)	496/1331 (37%)	385/816 (47%)	<0.001
Diabetes mellitus, *n/N* (%)	262/1113 (24%)	198/932 (21%)	264/1857 (14%)	180/1333 (14%)	110/817 (13%)	<0.001
of congestive heart failure, *n/N* (%)	24/1113 (2%)	14/932 (2%)	26/1857 (1%)	17/1332 (1%)	9/817 (1%)	0.316
Peripheral arterial disease, *n/N* (%)	68/1113 (6%)	49/932 (5%)	83/1857 (4%)	78/1333 (6%)	53/817 (6%)	0.161
History of stroke, *n/N* (%)	39/1113 (4%)	31/932 (3%)	42/1857 (2%)	32/1332 (2%)	17/817 (2%)	0.126
Hypertension, *n/N* (%)	625/1113 (56%)	540/932 (58%)	965/1856 (52%)	726/1333 (54%)	441/817 (54%)	0.033
Hypercholesterolaemia[a], *n/N* (%)	682/1113 (61%)	575/931 (62%)	1152/1856 (62%)	859/1329 (65%)	500/815 (61%)	0.399
Previous myocardial infarction, *n/N* (%)	140/1112 (13%)	118/931 (13%)	213/1855 (11%)	169/1330 (13%)	107/816 (13%)	0.730
History of PCI or CABG, *n/N* (%)	184/1113 (17%)	156/932 (17%)	288/1857 (16%)	225/1332 (17%)	123/817 (15%)	0.701
Liver cirrhosis or chronic hepatitis, *n/N* (%)	11/1113 (1%)	5/932 (1%)	10/1857 (1%)	8/1332 (1%)	4/817 (0%)	0.567
Aspirin, *n/N* (%)	320/1108 (29%)	276/923 (30%)	462/1850 (25%)	372/1325 (28%)	203/814 (25%)	0.016
Oral anticoagulation, *n/N* (%)	51/1108 (5%)	26/923 (3%)	52/1850 (3%)	39/1324 (3%)	31/814 (4%)	0.058
Statin, *n/N* (%)	293/1106 (26%)	248/923 (27%)	450/1847 (24%)	363/1322 (27%)	230/813 (28%)	0.177
ACE-inhibitor, *n/N* (%)	176/1102 (16%)	144/920 (16%)	245/1844 (13%)	171/1317 (13%)	99/810 (12%)	0.046
ATII antagonist, *n/N* (%)	235/1102 (21%)	189/920 (21%)	340/1845 (18%)	262/1317 (20%)	182/811 (22%)	0.129
Beta-blocker, *n/N* (%)	273/1103 (25%)	200/922 (22%)	354/1844 (19%)	285/1321 (22%)	166/812 (20%)	0.010
Acute coronary syndrome	*n* = 1113	*n* = 933	*n* = 1857	*n* = 1333,	*n* = 817	0.319
Unstable angina, *n/N* (%)	45 (4%)	23 (2%)	79 (4%)	57 (4%)	30 (4%)	0.167
NSTEMI, *n/N* (%)	458(41%)	392 (42%)	775 (42%)	571 (43%)	355 (43%)	0.841
STEMI, *n/N* (%)	610 (55%)	518 (56%)	1003 (54%)	703 (53%)	431 (53%)	0.642
Undetermined ACS, *n/N* (%)	0 (0%)	0 (0%)	0 (0%)	2 (0%)	1 (0%)	0.237
Left ventricular function, (%)	51.7 ± 11.7	51.6 ± 11.0	52.0 ± 10.4	51.6 ± 10.7	51.1 ± 11.8	0.762
Congestive heart failure	*n* = 1071	*n* = 897	*n* = 1814	*n* = 1307	*n* = 795	0.005
Killip I; no clinical signs or symptoms of congestive heart failure, *n* (%)	937 (87%)	764 (85%)	1631 (90%)	1160 (89%)	709 (89%)	0.005
Killip II; third heart sound, rales, or radiographic evidence of CHF, *n* (%)	77 (7%)	94 (10%)	120 (7%)	98 (7%)	56 (7%)	0.008
Killip III; pulmonary oedema, *n* (%)	26 (2%)	25 (3%)	29 (2%)	22 (2%)	10 (1%)	0.080
Killip IV; cardiogenic shock, *n* (%)	31 (3%)	14 (2%)	34 (2%)	27 (2%)	20 (3%)	0.237
Cholesterol (mmol/L)	4.9 ± 1.2	4.9 ± 1.2	5.0 ± 1.2	5.0 ± 1.3	5.1 ± 1.2	0.001
HDL-C (mmol/L)	1.1 ± 0.4	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.4	1.3 ± 0.4	<0.001
LDL-C (mmol/L)	3.1 ± 1.1	3.1 ± 1.1	3.2 ± 1.1	3.2 ± 1.1	3.1 ± 1.1	0.035
Triglyceride (mmol/L)	1.4 ± 1.1	1.4 ± 1.2	1.4 ± 1.2	1.3 ± 0.9	1.5 ± 1.2	0.008
HbA1c (%) (if diabetic patient)	6.3 ± 1.5	6.4 ± 1.6	6.1 ± 1.2	6.0 ± 1.2	6.0 ± 1.2	<0.001

Continued

Table 1 *Continued*

	No alcohol in the last 12 months	<1 standard unit drinks per week	1–6 standard unit drinks per week	7–14 standard unit drinks per week	>14 standard unit drinks per week	*P*-value
	n = 1113	*n* = 933	*n* = 1857	*n* = 1333	*n* = 817	
NT-proBNP (ng/L)	1284.2 ± 3116.5	1380.6 ± 112.2	906.1 ± 3393.8	931.5 ± 541.8	643.6 ± 143.1	<0.001
Haemoglobin (g/L)	134.8 ± 19.4	137.6 ± 32.4	141.1 ± 25.9	140.1 ± 17.3	142.7 ± 16.8	<0.001
Did patient had a cardiovascular rehabilitation after your hospital stay, *n/N* (%)	667/1098 (61%)	622/929 (67%)	1333/1841 (72%)	881/1327 (66%)	517/812 (64%)	<0.001

Data are expressed as mean ± standard deviation or number (*n/N*) and percentages (%).
BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; STEMI, ST-elevation myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; CHF, congestive heart failure; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; HbA1c, haemoglobin A1c; NT-proBNP, N-terminal pro B-type natriuretic peptide.
[a]Hypercholesterolaemia defined as follows: total cholesterol >5.0 mmol or 190 mg/dL or requiring treatment.

compared with no binge drinking, the risk of MACE was higher in those reporting binge drinking at least one or more than once/month, both in men (HR 1.95, 95% CI 1.46–2.60, $P < 0.001$) and in women (HR 4.49, 95% CI 2.33–8.66, $P < 0.001$; *P*-value for interaction = 0.026). There was also a significant association between those reporting less than one binge drinking episode/month, independently of sex (men: HR 1.48, 95% CI 1.11–1.98, $P = 0.001$, and women: HR 2.49 95% CI 1.25–4.99, $P = 0.006$), compared to no binge drinking (*Figure 4*).

In sensitivity analysis, after removing hypertension as a covariate from the model, the risk for MACE at 1 year after ACS persisted in those who reported binge drinking less than once per month (adjusted HR 1.61, 95% CI 1.23–2.11, $P < 0.001$), as well as in those with at least one episode of binge drinking per month (adjusted HR 2.17, 95% CI 1.66–2.83, $P < 0.001$) compared to no binge drinking (see Supplementary material online, *Table S9A*). After controlling for baseline weekly alcohol consumption, the risk of MACE also persisted, in the group with a binge drinking behaviour of less than one episode a month (adjusted HR 1.77, 95% CI 1.34–2.35, $P < 0.001$) and in those with at least one episode per month (adjusted HR 2.48, 95% CI 1.83–3.34, $P < 0.001$) compared to no binge drinking (see Supplementary material online, *Table S9B*).

The risk of MACE remained significant using a competing risk model for non-cardiac death in the group with a binge drinking behaviour of less than one episode a month (adjusted HR 1.60, 95% CI 1.22–2.10, $P < 0.001$), as well as in those with at least one episode of binge drinking per month (adjusted HR 2.12, 95% CI 1.63–2.77, $P < 0.001$), compared to no binge drinking (see Supplementary material online, *Table S9C*).

The mean or median smoking daily quantity consumption did not increase over time in any of the binge drinking categories (see Supplementary material online, *Table 10A*). The association between binge drinking and the risk of MACE was not modified by smoking habit (*P*-value for interaction = 0.53). In those who reported at least one or more episode of binge drinking per month, the risk of MACE was similar between smokers (HR 2.30, 95% CI 1.51–3.49, $P < 0.001$) and non-smokers (HR 2.09, 95% CI 1.50–2.91, $P < 0.001$; see Supplementary material online, *Table 10B*).

A stratified analysis according to educational level was also performed (see Supplementary material online, *Table S11*), which showed an association between binge drinking and a low level of education with the risk of MACE.

When using logistic regression, the results were consistent with time-to-event analysis (see Supplementary material online, *Table S12*).

It was not possible to evaluate whether alcohol habits were discussed or not during cardiac rehabilitation after an ACS due to lack of data granularity; however, results did show that for patients who attended a cardiac rehabilitation programme, the risk of MACE associated with binge drinking was comparable to those who did not attend a programme (see Supplementary material online, *Table S13*; *P*-value for interaction = 0.22).

Medication compliance at 1 year after acute coronary syndrome

Finally, considering the compliance of CV medications, we observed that they were continued at 1 year follow-up in most of the patients (above 90% for both statin and aspirin in all categories of patients; see Supplementary material online, *Tables S14* and *S15*).

Discussion

In this large prospective contemporary cohort of ACS patients, weekly alcohol consumption was not associated with the risk of MACE, but patients reporting binge drinking had a two-fold increased risk of MACE within 1 year of the index event. Our data suggest that it is not the frequency but rather the quantity of alcohol intake on one occasion, or per day, that is associated with a worse prognosis.

Our findings add new evidence to the perception that regular, moderate, and non–binge-like alcohol consumption might be safe, up to a maximum of 100 g/week, as recommended by the last 2021 ESC guidelines for CV prevention.[22] In patients with previous coronary ischaemic accidents, moderate consumption of red wine, associated with a 'healthy western diet' and physical exercise, improves various blood parameters, such as total cholesterol and LDL-C levels, and it increases anti-oxidant status.[16] Similarly, the benefits of reducing oxidative stress and pro-inflammatory cytokines induced by moderate red alcohol intake have been reported after MI in patients with type II diabetes.[13] Nonetheless, the benefit on total mortality remains controversial, as recently demonstrated in a prospective cohort study from the UK where the risk of mortality in patients with CVD who consistently drank ≤ 14 units/week was similar to that reported for long-term abstainers.[28]

The relationship between weekly alcohol consumption and CVD was traditionally described as U-shaped in previous cohort studies, and based on a meta-analysis that stated that in patients with CVD, light-to-moderate alcohol consumption (5–25 g/day) was significantly associated with a lower risk of CV events and all-cause mortality.[12] But this U-shaped relationship was challenged when integrating genetic data from the UK Biobank study, where no protective effect of

Table 2 Hazard ratios of major adverse cardiovascular events at 1 year by baseline weekly alcohol consumption categories

Group at baseline	Model 1		Model 2	
	Crude HR (95% CI)	*P*-value	Crude HR (95% CI)	*P*-value
Unadjusted				
Reference (no alcohol)	1		NA	
<1 standard unit drinks per week	0.81 (0.60–1.09)	0.163	1	
1–6 standard unit drinks per week	0.71 (0.55–0.92)[a]	0.008	0.88 (0.66–1.16)	0.358
7–14 standard unit drinks per week	0.91 (0.70–1.17)	0.457	1.12 (0.84–1.49)	0.448
>14 standard unit drinks per week	0.83 (0.61–1.12)	0.229	1.02 (0.74–1.42)	0.889
Adjusted[a]	Adj HR[a] (95% CI)		Adj HR[a] (95% CI)	
Reference (no alcohol)	1		NA	
<1 standard unit drinks per week	0.70 (0.50–0.98)	0.040	1	
1–6 standard unit drinks per week	0.86 (0.65–1.13)	0.275	1.23 (0.89–1.71)	0.205
7–14 standard unit drinks per week	0.97 (0.73–1.30)	0.860	1.41 (1.01–1.97)	0.044
>14 standard unit drinks per week	0.97 (0.69–1.36)	0.857	1.41 (0.97–2.06)	0.074
Including interaction with increase/decrease of alcohol consumption at 1 year follow-up	**Model 1**		**Model 2**	
	Crude HR (95% CI)	***P*-value**	**Crude HR (95% CI)**	***P*-value**
Unadjusted				
Reference (no alcohol)	1		1.27 (0.83–1.96)	
<1 standard unit drinks per week	0.78 (0.51–1.21)	0.270	1	0.270
1–6 standard unit drinks per week	0.71 (0.50–1.01)	0.057	0.91 (0.61–1.36)	0.643
7–14 standard unit drinks per week	0.93 (0.66–1.32)	0.691	1.19 (0.79–1.78)	0.404
>14 standard unit drinks per week	0.78 (0.52–1.16)	0.214	0.99 (0.63–1.55)	0.961
Adjusted[a]	Adj HR[a] (95% CI)		Adj HR[a] (95% CI)	
Reference (no alcohol)	1		1.60 (0.99–2.60)	0.056
<1 standard unit drinks per week	0.62 (0.46–1.01)	0.056	1	
1–6 standard unit drinks per week	0.79 (0.54–1.14)	0.202	1.26 (0.80–1.99)	0.320
7–14 standard unit drinks per week	0.97 (0.67–1.42)	0.892	1.56 (0.98–2.49)	0.060
>14 standard unit drinks per week	0.81 (0.52–1.25)	0.336	1.29 (0.77–2.16)	0.326

Only complete cases are considered at baseline and 1 year follow-up for this analysis. Model 1 is defined as no alcohol consumption as reference. Model 2 is defined as <1 standard unit drinks per week as reference.
[a]Adjusted for age, sex, education, BMI, smoking, diabetes, peripheral artery disease, previous stroke, hypertension, LDL-C level, aspirin, anticoagulation, statin, ATII, ACE-inhibitor, and beta-blocker.

mild-to-moderate alcohol consumption could be shown compared with abstinence.[29] According to a large Chinese genetical study, drinking alcohol can raise blood pressure and increase the risk of stroke.[30] Interestingly, no significant association was found between genotype-predicted mean alcohol intake and risk of MI, showing that there is little net effect of variants of alcohol metabolism on the risk of MI. Of note, contrary to men, in women, there was no correlation between the analysed genetic traits and an increased risk of high blood pressure, stroke, or heart attack.

Considering binge drinking behaviour, although the episodes of binge drinking prior ACS were not collected in our study, the weekly consumption at baseline and 1 year after ACS remained mostly stable over time. Our findings align with the fact that consuming large amounts of alcohol in a short period of time can be a safety concern for CV events. In particular, we report that adverse effects associated with binge drinking were independent of other traditional CV risk factors. The importance of avoiding heavy alcohol consumption and binge drinking in patients with CVD has already been reported, underlining the danger of quantity of alcohol intake on one occasion.[12] In the INTERHEART study from 52 countries, patients who reported an episode of heavy drinking (≥6 drinks) showed an increased risk of acute MI

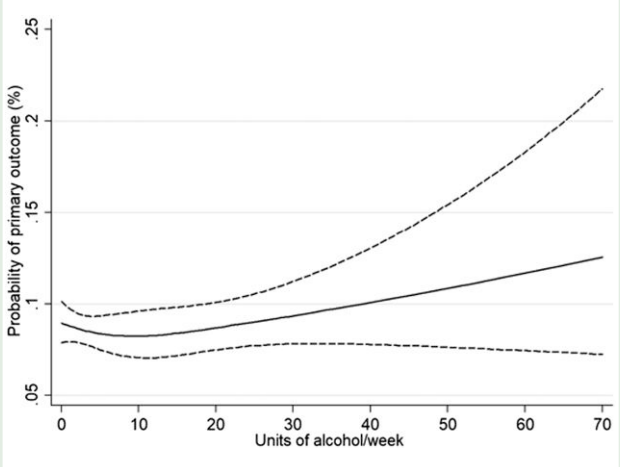


Figure 1 Alcohol splines for the probability of major adverse cardiovascular events based on the quantity of alcohol consumed per week.

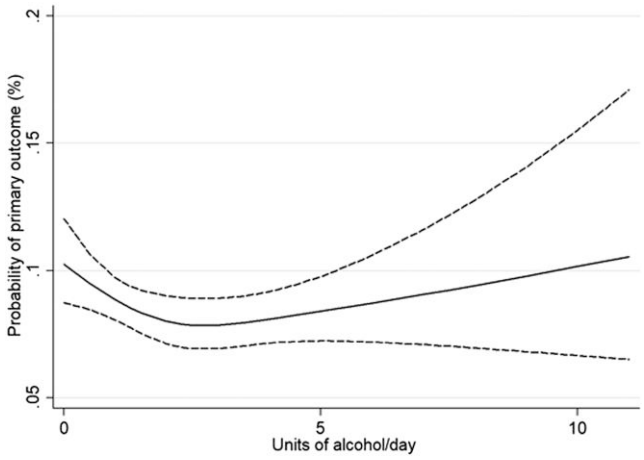


Figure 2 Alcohol splines for the probability of major adverse cardiovascular events based on the quantity of alcohol consumed per day.

Table 3 Cumulative failure risk of major adverse cardiovascular events at 1 year after acute coronary syndrome, by binge drinking behaviour categories

	Never binge drinking	<1 per month binge drinking	≥1 per month binge drinking	*P*-value[a]	*P*-value for trend
	n = 4748	*n* = 972	*n* = 695		
MACE (cardiac death, MI, clinically indicated TVR, stroke)	363 (7.8)	84 (9.2)	84 (13.6)	<0.001	<0.001
Cardiac death, MI, or stroke	273 (5.9)	64 (7.0)	71 (11.5)	<0.001	<0.001
All-cause death	76 (1.7)	40 (4.4)	63 (10.3)	<0.001	<0.001
Cardiac death	56 (1.2)	28 (3.1)	42 (6.9)	<0.001	<0.001
Myocardial infarction	165 (3.6)	27 (3.0)	31 (5.1)	0.097	0.228
CVE (stroke or TIA)	80 (1.7)	19 (2.1)	15 (2.5)	0.369	0.158
Stroke (any)	60 (1.3)	13 (1.4)	12 (2.0)	0.396	0.195
Revascularization (any)	313 (6.8)	56 (6.4)	42 (7.0)	0.811	0.952
Bleeding (any)	392 (8.5)	66 (7.3)	58 (9.5)	0.327	0.941
Gastrointestinal bleeding	112 (2.4)	18 (2.0)	16 (2.8)	0.675	0.998
Intracranial bleeding	10 (0.2)	3 (0.3)	3 (0.5)	0.376	0.164

ACS, acute coronary syndrome; MI, myocardial infarction; TVR, target vessel revascularization; CVE, cerebrovascular event; TIA, transitory ischaemic attack.
[a]Log-rank test of equality.

in the subsequent 24 h, particularly among older individuals (aged >65 years).[7] Even in studies where limited alcohol consumption after MI was associated with lower mortality, binge drinking appears to be clearly associated with a higher risk of death.[14] In the PRIME study, binge drinking was associated with an increased risk of MI,[14] as well as increased mortality after MI.[31] Although the mechanisms are not fully understood, binge drinking can induce vascular injury, exert proatherogenic effects, provoke adverse changes in endothelial and smooth cell function, and also cause haemostatic/coagulation vulnerability of the myocardium by affecting cellular electrophysiological properties.[32] A systematic review and dose–response meta-analysis showed how heavy alcohol drinking with an acute intake of ≥ 6 units is associated with higher CV risk on the following day and even in the following week.[33] Considering cardiac death, the arrhythmogenic potential of binge drinking may arise from several factors, including concomitant tachycardia-induced ischaemia, alcohol's negative inotropic effect, sympathetic activation, and cardiotoxic effects as myocardial fibrosis.[34,35] Nevertheless, few experimental human and animal models have studied the precise mechanisms associated with one or recurrent episodes of binge drinking and their time relation with adverse events.

Another important finding of our study is the similarity in the pattern of alcohol consumption in the year following the index ACS event, especially among those patients reporting heavy alcohol consumption, suggesting that patients after ACS received no effective intervention to promote changes in their alcohol-related behaviours in a secondary CV prevention setting.

Considering gender, although women were less likely to report heavy alcohol consumption or binge drinking episodes, this should not preclude inquiring about their alcohol consumption since the risk on clinical outcomes is described to be similar to that of men.[36] In the stratified analysis, our results showed that in the binge drinking group only, the effect is even stronger in women compared to men. Due to differences

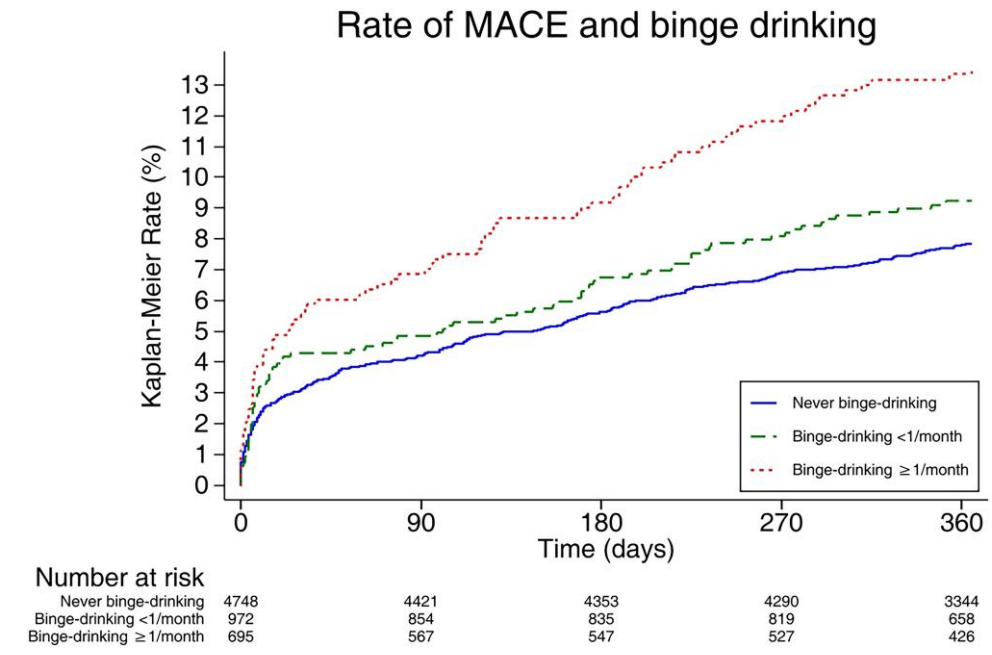


Figure 3 Kaplan–Meier rates of the primary endpoint of major adverse cardiovascular events (composite of cardiac death, myocardial infarction, stroke, or clinically indicated target lesion revascularization) after acute coronary syndromes by categories of alcohol binge drinking behaviour. MACE, major adverse cardiovascular events.

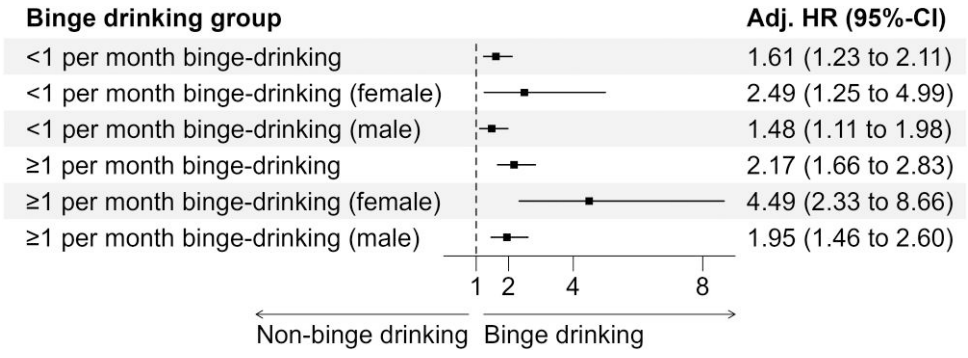


Figure 4 Adjusted hazard ratio of the primary endpoint of major adverse cardiovascular events by categories of alcohol binge drinking behaviour and stratified in men and women (*P*-value for interaction = 0.026). Adjusted for age, sex, education, body mass index, smoking, diabetes, peripheral artery disease, previous stroke, hypertension, LDL cholesterol level, aspirin, anticoagulation, statin, Angiotensin II, Angiotensin-converting enzyme inhibitor, and beta-blocker. Only complete cases are considered. The reference group is 'no binge drinking'.

in body structure, the effect of alcohol in women can even be greater and persist over a longer duration of time compared to men, mostly because women produce less alcohol dehydrogenase.[37]

Finally, we found that education has a strong association with alcohol consumption. In particular, we report how a low level of education and binge drinking are associated with higher CV risk. This could be a possible effect modifier for MACE, with a higher risk in those with low educational status. Although alcohol is not traditionally considered a direct risk factor for atherosclerosis in CVD, it is important for healthcare professionals to inquire about patients' drinking habits and record this information, especially in a secondary CV prevention setting, for both men and women.

At this stage of knowledge, randomized controlled trials among ACS patients are needed to evaluate the effectiveness of interventions to prevent high-risk behaviours, such as binge drinking, and the impact on clinical outcomes. We have designed a study (ClinicalTrial.Gov identifier: NCT05920629)[38] in which we will be investigating the effect of moderate alcohol consumption vs. abstinence on heart function in patients with a recent MI.

Limitations

Our study has several limitations. First, our main limitation is that we do not have information on binge drinking at baseline, but we used the

information collected at 1 year to estimate the pattern over the last 12 months. For those patients with missing values at 1 year, we imputed values based on the quantity reported at baseline. Of note, we did not collect the exact date of the binge drinking episodes to evaluate whether it preceded or not the CVD event. In addition, we corroborated our findings by analysing the baseline reported quantity per one occasion. Given the observational design, any statement regarding the causality between binge drinking and MACE after an ACS should be avoided.

Second, we used patient-reported alcohol consumption as an exposure and did not validate the responses with a specific biological biomarker, although we observed an association with higher HDL-C that has previously been confirmed in formal feeding studies.[39] Also, we did not validate the results according to genetic variants known to influence drinking patterns. Third, although we used a multivariate model to adjust for potential confounding factors, we cannot exclude residual confounding, especially for unmeasured clinical or health behaviours. The analysis for weekly alcohol consumption can be confounded by reverse causality since those who are abstinent have more comorbidities. However, results for heavy drinkers were similar when comparing the risk of MACE with abstinent or light drinkers. Since there was no dose–response association by weekly alcohol consumption categories, but only a trend for a lower risk compared to abstinence, the hypothesis of a protective effect seems not plausible. Reverse causality bias can potentially explain the findings in abstinence. To definitively clarify any potential protective effect of moderate alcohol consumption after ACS, we would need a randomized controlled trial comparing moderate alcohol consumption vs. abstinence and the impact on MACE. However, this trial is unlikely to be conducted for different reasons including the ethical aspect and feasibility of recruitment. Fourth, we did not collect all CV outcomes of interest, such as atrial fibrillation or heart failure. Fifth, our study population might not be representative of all individuals who survive an ACS, although there were no stringent exclusion criteria in this study. Sixth, the findings of our study do not allow for causal inference, given its non-randomized design. Finally, we might have limited statistical power due to the low number of patients with excessive alcohol consumption.

Conclusions

In contrast to regular weekly alcohol consumption, episodes of binge drinking reported during the year following an ACS, even less than once per month, are associated with worse clinical outcomes. Healthcare providers should consider recording this high-risk behaviour in both men and women, particularly after ACS, and offer adequate counselling that also addresses CV prognosis.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Acknowledgements

The authors wish to thank the two adjudication committees (Cohort I: Profs. Lukas Kappenberger, Mathias Pfisterer, and Tiziano Moccetti; Cohort II: David Carballo, René Lerch, Ulrich Sigwart, Pascal Meier, and Philippe Meyer) and the study nurses involved in the project. The authors are also grateful to all other members of the SPUM-ACS consortium.

Author contributions

B.G. and E.T. conceived the study; M.B. performed the statistical analysis; E.T., B.G., M.B., G.G., N.R., and K.J.M. interpreted the data; E.T. wrote the first draft of the manuscript. B.G., D.N., D.C., S.C., R.A., G.G., C.M.M., R.K., L.R., S.W., D.H., F.M., T.F.L., and N.R. contributed to the acquisition of data. All co-authors revisited the work critically for important intellectual content and approved the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the integrity of any part of the work presented are appropriately investigated and resolved.

Funding

This study was partly supported by a grant from the Swiss National Science Foundation to Dr. B. Gencer (SNSF 32003B_207881, 'Moderate alcohol consumption and heart function in patients with a recent myocardial infarction: a multicenter randomized controlled trial'). B.G.'s research on cardiovascular prevention is supported by the Swiss National Science Foundation (SNSF 325130_204361) and Swiss Heart Foundation. The SPUM-ACS cohort was supported by the Swiss National Science Foundation (SPUM 33CM30-124112 and 32473B_163271), the Swiss Heart Foundation (both Bern and Switzerland to T.F.L.), the Theodor-Ida Herzog Stiftung, Zurich, Switzerland (to S.K.), and the Foundation for Cardiovascular Research–Zurich Heart House, Zurich, Switzerland (T.F.L.). The SPUM consortium was further supported by unrestricted grants of Roche Diagnostics (Rotkreuz, Switzerland), Eli Lilly (Indianapolis, IN, USA; AstraZeneca Baar, Switzerland), Medtronic (Münchenbuchsee, Switzerland), and Merck Sharpe and Dome (Lucerne, Switzerland).

Conflict of interest: Conflicts of interest are detailed in the Declarations Form, and all authors have filled out the ICJME disclosure form.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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