Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a prospective cohort study

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Summary

Background **Alcohol consumption is proposed to be the third most important modifiable risk factor for death and disability. However, alcohol consumption has been associated with both benefits and harms, and previous studies were mostly done in high-income countries. We investigated associations between alcohol consumption and outcomes in a prospective cohort of countries at different economic levels in five continents.**

Methods **We included information from 12 countries participating in the Prospective Urban Rural Epidemiological (PURE) study, a prospective cohort study of individuals aged 35–70 years. We used Cox proportional hazards regression to study associations with mortality (n=2723), cardiovascular disease (n=2742), myocardial infarction (n=979), stroke (n=817), alcohol-related cancer (n=764), injury (n=824), admission to hospital (n=8786), and for a composite of these outcomes (n=11 963).**

Findings **We included 114 970 adults, of whom 12 904 (11%) were from high-income countries (HICs), 24 408 (21%) were from upper-middle-income countries (UMICs), 48 845 (43%) were from lower-middle-income countries (LMICs), and 28 813 (25%) were from low-income countries (LICs). Median follow-up was 4·3 years (IQR 3·0–6·0). Current drinking was reported by 36 030 (31%) individuals, and was associated with reduced myocardial infarction (hazard ratio [HR] 0·76 [95% CI 0·63–0·93]), but increased alcohol-related cancers (HR 1·51 [1·22–1·89]) and injury (HR 1·29 [1·04–1·61]). High intake was associated with increased mortality (HR 1·31 [1·04–1·66]). Compared with never drinkers, we identified significantly reduced hazards for the composite outcome for current drinkers in HICs and UMICs (HR 0·84 [0·77–0·92]), but not in LMICs and LICs, for which we identified no reductions in this outcome (HR 1·07 [0·95–1·21];** $p_{interaction}$**<0·0001).**

Interpretation **Current alcohol consumption had differing associations by clinical outcome, and differing associations by income region. However, we identified sufficient commonalities to support global health strategies and national initiatives to reduce harmful alcohol use.**

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Introduction

Alcohol consumption is estimated to be the third most important modifiable risk factor for death and disability worldwide.[1] However, the association between alcohol consumption and health is complex, since beneficial effects on some diseases might mitigate some of the harms on others,[2] and regional differences might exist.[3,4] The amount, type, and pattern of alcohol consumption can have differing associations with health outcomes. For example, low–moderate regular intake of alcohol is associated with reduced risk of myocardial infarction,[5] whereas heavy episodic drinking is associated with sudden cardiac death.[6] Risk of injury increases with extent of intoxication,[7] whereas risk of cancer is related to the amount consumed over time.[8] So far, most epidemiological studies have been done in high-income countries (HICs), or upper-middle-income countries (UMICs), including Russia,[9,10] but data from middle-income countries (MICs) and low-income countries (LICs), where patterns of alcohol consumption might differ, are sparse. Large international studies are needed to document regional variations in patterns and types of alcohol consumption, and their relation to a range of health outcomes. We describe here the association between alcohol consumption, cardiovascular disease, cancer, injury, admission to hospital, and mortality in 114 970 individuals from 12 countries in the Prospective Urban Rural Epidemiology (PURE) study.

Methods

Population

The design and methods of the PURE study have been described previously.[11] Briefly, 155 875 adults aged 35–70 years were enrolled into a prospective cohort

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See Online for appendix

study from 628 (348 urban and 280 rural) communities from 17 LICs, MICs, and HICs. Although not designed to be nationally representative, the main participant characteristics were sufficiently similar to the sampled populations and unlikely to distort exposure–disease associations or estimates of event rates.[12] We used standardised approaches to enumerate households, identify individuals, and collect data (including food frequency questionnaires to assess dietary intake). At each follow-up visit (completed every 3 years), participants or family members were asked about incident events, and standardised event forms and verbal autopsies were completed, as appropriate. Supporting documents were submitted with event reports to the country's lead investigator sites whenever possible. Deaths, cardiovascular events, and cancers were adjudicated with standardised criteria (appendix).[4]

For these analyses, we included 114 970 participants without a baseline history of heart disease, stroke, or cancer. We excluded participants from countries in which more than 95% of the population never drink alcohol (Iran, Bangladesh, Pakistan, Malaysia, and United Arab Emirates) because responses to the alcohol questionnaire might not be reliable, owing to cultural beliefs and social desirability bias. For the cross-sectional analysis, we categorised countries into four groups on the basis of World Bank classification at the time of enrolment into the study: HICs were Sweden and Canada; UMICs were Argentina, Brazil, Chile, Poland, South Africa, and Turkey; lower-middle-income countries (LMICs) were China and Colombia; and LICs were India and Zimbabwe. For analyses of prospective outcomes, we divided countries into two groups: HICs or UMICs (HICs/UMICs); and LICs or LMICs (LICs/LMICs). Analyses are based on follow-up data as of Oct 1, 2014.

Self-reported alcohol intake was recorded at baseline, when participants were asked about alcohol use, types of alcohol consumed (beer, wine, spirits or liquors, or other [including home spirits and arrack]), and number and frequency of drinks (appendix). Participants were also asked about alcohol use (never, former, or current drinking) during follow-up, but no further questions were asked; as such, we were unable to adjust for regression dilution bias. Never drinking was defined as self-reported abstinence, former drinking was defined as having ceased alcohol consumption for 1 year or more, and current drinking was defined as consumption of alcohol in the past year. Among current alcohol consumers, low intake was defined as up to seven drinks per week; moderate intake was defined as 7–14 drinks per week for women or 7–21 drinks per week for men; and high intake was defined as more than 14 drinks per week for women or more than 21 drinks per week for men. Heavy episodic drinking was defined as consumption of more than five drinks in one episode at least once per month.[13] For each current drinker, the number of drinks of each alcohol type (spirits or liquors, wine, and beer) consumed per week was expressed as a proportion of the total number of drinks; the drinker was included in the group for the type of drink that they consumed most often.

Outcomes included mortality, incident cardiovascular disease, alcohol-related cancer, injury, and admission to hospital. Major cardiovascular disease included cardiovascular death, myocardial infarction, stroke, or admission to hospital for heart failure. Cancers included those of sites known to be related to alcohol consumption (mouth, oesophagus, stomach, colorectal, liver, breast, ovary, and head and neck cancer).[8] We included injuries if they were fatal or resulted in admission to hospital. We used a binary composite outcome including the first event of mortality, cardiovascular disease, cancer, injury, or admission to hospital to investigate the net associations of alcohol with health outcomes. We assessed adequacy of the sample size with the assumption that, for analysis of binary outcomes with Cox regression, we needed at least ten events for each degree of freedom to produce stable models. In this study, we have 11 963 patients with the primary composite outcome, and 27 predictors to investigate, with a total of 35 degrees of freedom.[14,15] Thus, we could fit up to 340 predictors for the composite outcome before adversely affecting model stability.

Statistical analysis

We present categorical variables as proportions and continuous variables as median with range (presented as the 1st and 3rd quartiles), and we did comparisons with χ^2 and ANOVA, as appropriate. Event rates were standardised by age and sex and reported per 1000 person-years. With never drinkers as the reference category, we used Cox proportional hazards regression (Schoenfeld residuals verified the proportionality of hazards assumption)[16] to measure the association between alcohol and outcomes with multivariable adjustment. Covariates were prespecified[14,15] and included in all models. Continuous variables included age and body-mass index. Ethnicity was categorised as South Asian, Chinese or Japanese, Malay, Persian, Arabian, African, European, Latin American, and other. Education was categorised as none or primary school; secondary or high school; or trade, college, or university. Comorbidities, including diabetes, hypertension, hepatitis, and jaundice, were self-reported. Self-reported medication use included angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), β blockers, calcium channel blockers, diuretics, α blockers, lipid-lowering therapy (statins and other lipid-lowering drugs), and anti-thrombotic therapy (aspirin, clopidogrel, warfarin, and other anti-platelet agents). Physical activity was categorised on the basis of metabolic equivalent task (MET) minutes per week, including low (<600 MET min per week), moderate (600–3000 MET min per week), or

	All current drinkers (n=36 030)	High-income countries (n=10 348)	Upper-middle-income countries (n=10 435)	Lower-middle-income countries (n=11 328)	Low-income countries (n=3919)
Age (years [IQR])	50 (41–58)	53 (46–60)	50 (43–58)	51 (43–58)	47 (40–56)
Sex					
Men	23 611 (66%)	4993 (48%)	5469 (52%)	9381 (83%)	3768 (96%)
Women	12 419 (34%)	5355 (52%)	4966 (48%)	1947 (17%)	151 (4%)
Education					
None, primary, or unknown	11 265 (31%)	621 (6%)	5199 (50%)	3831 (34%)	1614 (41%)
Secondary or high school	13 175 (37%)	2976 (29%)	3023 (29%)	5423 (48%)	1753 (45%)
Trade, college, or university	11 530 (32%)	6743 (65%)	2196 (21%)	2057 (18%)	534 (14%)
BMI (kg/m²)	24·9 (21·9–28·4)	26·5 (23·6–30·4)	29·4 (25·4–34·4)	24·5 (22·1–27·1)	23·6 (19·9–27·5)
Systolic blood pressure (mm Hg)	128 (115–145)	128 (16–141)	131 (117–148)	129 (117–145)	125 (113–142)
Smoking status					
Never smoker	14 213 (39%)	4886 (47%)	4338 (42%)	3899 (34%)	1090 (28%)
Former smoker	8285 (23%)	3914 (38%)	2589 (25%)	1308 (12%)	474 (12%)
Current smoker	13 458 (37%)	1535 (15%)	3484 (33%)	6085 (54%)	2354 (60%)
Prevalent diabetes	1659 (5%)	389 (4%)	565 (5%)	300 (3%)	405 (10%)
Prevalent hypertension	6529 (18%)	1745 (17%)	2499 (24%)	1734 (15%)	551 (14%)
History of hepatitis or jaundice	1310 (4%)	364 (4%)	748 (7%)	163 (1%)	35 (1%)
Baseline medications					
ACE inhibitor or ARB	2517 (7%)	943 (9%)	1256 (12%)	294 (3%)	24 (1%)
β blocker	1123 (3%)	397 (4%)	592 (6%)	71 (1%)	63 (2%)
Calcium channel blocker	918 (3%)	319 (3%)	228 (2%)	305 (3%)	66 (2%)
Diuretic	1482 (4%)	494 (5%)	575 (6%)	401 (4%)	12 (0·3%)
α blocker	37 (0·1%)	0	31 (0·3%)	1 (0·01%)	5 (0·1%)
Lipid-lowering therapy	1403 (4%)	912 (9%)	415 (4%)	64 (1%)	12 (0·3%)
Anti-thrombotic	1571 (4%)	836 (8%)	485 (5%)	228 (2%)	22 (1%)

BMI=body-mass index. ACE=angiotensin-converting enzyme. ARB=Angiotensin receptor blocker.

***Table 1:* Characteristics of current drinkers by income region**

high (>3000 MET min per week) activity. Smoking was categorised as never, former, or current smoking, and we adjusted for pack-years of cigarette smoking. Dietary variables included servings per day of dairy, fruits, vegetables, meats, fish, soft drinks, processed foods, nuts, and trans fats. Additionally, all models included adjustment for clustering effects at the community level, specified as a random effect. We did three sensitivity analyses: including serum HDL (mol/L), available in 95 202 (82·8%) participants, because HDL concentrations might mediate the association between alcohol consumption and health outcomes; excluding participants with hypertension at baseline; and excluding admission to hospital from the composite outcome. To investigate whether drinking behaviours (drinks per day, heavy episodic drinking pattern, and predominant alcohol type) affected associations, we added these variables to the multivariable adjusted models. To investigate differences between HICs/UMICs and LICs/LMICs, we tested for interactions between alcohol consumption and the regional variable. We present results as hazard ratio (HR; 95% CI and associated p values). We use forest plots to display results. In view of the many comparisons done, we only considered persuasive p values of less than 0·001. We did analyses with Stata/MP version 13.1 for Windows.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 114 970 participants, 12 904 (11%) lived in HICs, 24 408 (21%) lived in UMICs, 48 845 (43%) lived in LMICs, and 28 813 (25%) lived in LICs. 47 695 (42%) were men, median age was 50 years (IQR 42–58), and median follow-up was 4·3 years (IQR 3·0–6·0).

Overall, 74 685 (65%) participants were never drinkers, 4255 (4%) were former drinkers, and 36 030 (31%) were current drinkers. Of current drinkers, 26 025 (72%) had low intake, 6114 (17%) had moderate intake, and 2931 (8%) had high intake. Current drinkers were younger and more educated than never drinkers or former drinkers. Male current drinkers had higher blood pressure than never drinkers, but female current

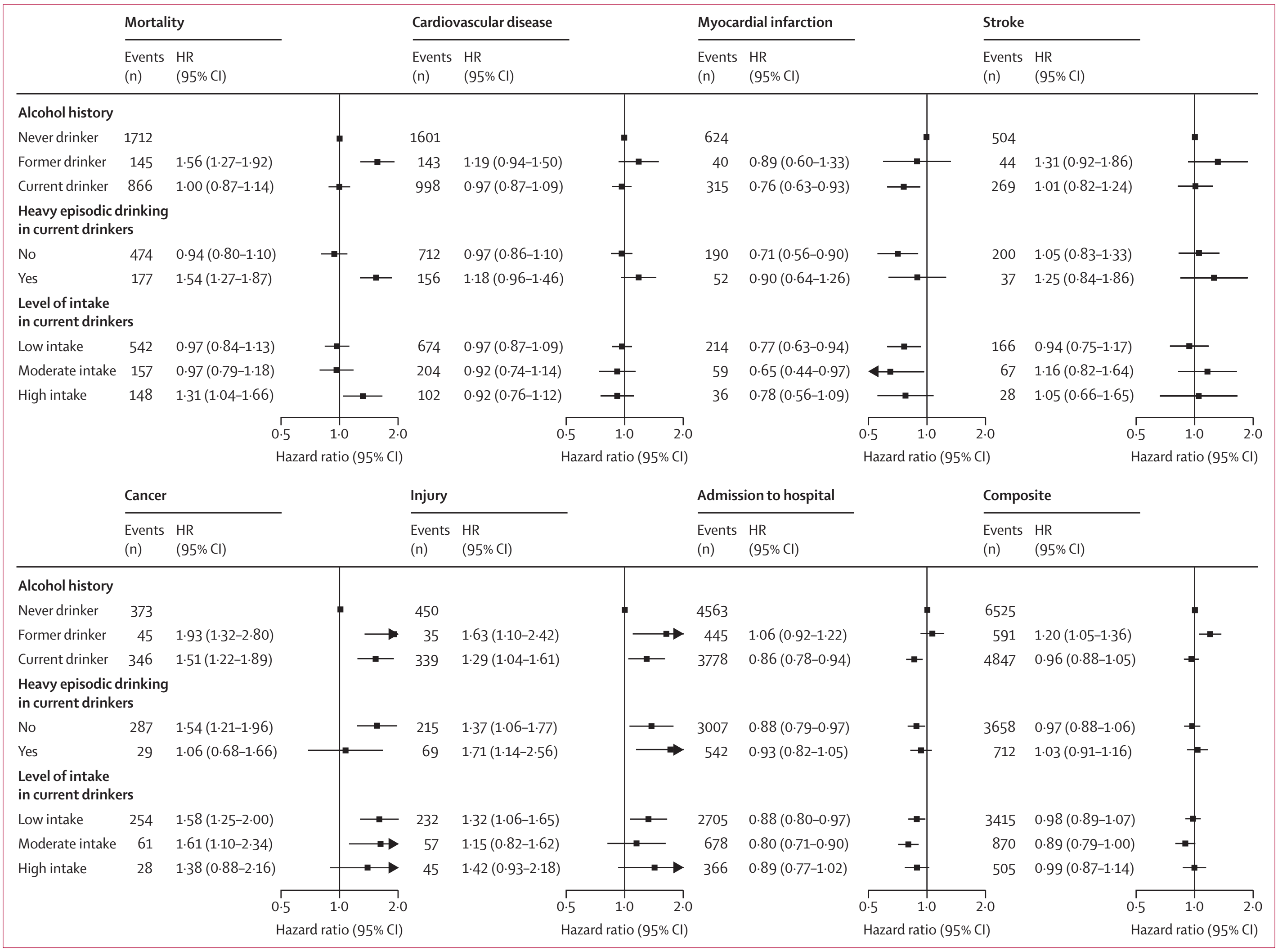


***Figure 1:* Association between alcohol consumption and incident outcomes**
Adjusted for age, sex, smoking, ethnicity, education, body-mass index, diabetes, hypertension, jaundice or hepatitis, physical activity, diet (dairy, fruits, vegetables, meats, fish, soft drinks, processed foods, nuts, and trans fats), medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β blockers, calcium channel blockers, diuretics, α blockers, lipid-lowering therapy, and anti-thrombotic therapy), and wealth index. Additional adjustment for clustering effects at the community level is specified as a random effect.

drinkers had lower blood pressure than never drinkers (appendix). People with high or moderate intake were older, and more likely to be male, less educated, and have high blood pressure than were those with low intake. A heavy episodic drinking pattern was reported by 4711 (13%) of 31 336 current drinkers; these individuals were younger, and more likely to be male and have high blood pressure than were those without a heavy episodic drinking pattern (appendix).

Frequency of current drinking varied by geographical and income region (appendix). Current drinkers in LICs were younger, more likely to be male, less educated, and more likely to be current smokers, and have lower body-mass index and blood pressure than current drinkers in higher income regions (table 1). In all regions, alcohol consumption was more common in men than in women, but the gap between men and women varied substantially across income countries (HICs 84% *vs* 77%, UMICs 58% *vs* 33%, LMICs 47% *vs* 7%, LICs 30% *vs* 1%, for men *vs* women [appendix]). In current drinkers, the highest prevalence of high-intake and heavy episodic drinking was in LICs, despite these countries having the lowest prevalence of current drinking. The highest proportion of wine consumers was in HICs (61%) and the lowest proportion of wine consumers was in LICs (3%), but the highest proportion of spirit or liquor consumers was in LICs (89%) and the lowest proportion of spirit or liquor consumers was in HICs (10%; appendix).

In multivariable analyses, current drinkers were at increased hazard of incident cancer and injury, and reduced hazard of myocardial infarction and admission to hospital, but we identified no association with mortality, cardiovascular disease, or stroke (figure 1, table 2). Heavy episodic drinking was associated with increased hazard of mortality and injury (figure 1). Compared with never drinking, there seemed to be a non-linear association between level of intake and myocardial infarction (low or moderate intake was associated with a reduction in risk of myocardial infarction, but there was no reduction in risk of myocardial infarction in those with high intake), and only high intake was associated with increased hazard

	Alcohol history			Heavy episodic drinking in current drinkers		Level of intake in current drinkers		
	Never drinker (n=74 685)	Former drinker (n=4255)	Current drinker (n=36 030)	No (n=26 625)	Yes (n=4711)	Low intake (n=26 025)	Moderate intake (n=6114)	High intake (n=2931)
Mortality								
Events	1712	145	866	474	177	542	157	148
Event rate	5·7 (5·4–6·0)	6·6 (5·3–7·9)	4·6 (4·3–5·0)	3·7 (3·3–4·0)	6·6 (5·3–7·9)	4·2 (3·9–4·6)	4·9 (3·7–6·1)	9·6 (7·5–11·7)
Unadjusted	1·00	1·68 (1·36–2·07)	0·98 (0·86–1·13)	0·75 (0·63–0·88)	1·53 (1·21–1·93)	0·87 (0·75–1·01)	1·01 (0·82–1·24)	1·84 (1·42–2·37)
Adjusted*	1·00	1·56 (1·27–1·92)	1·00 (0·87–1·14)	0·94 (0·80–1·10)	1·54 (1·27–1·87)	0·97 (0·84–1·13)	0·97 (0·79–1·18)	1·31 (1·04–1·66)
Cardiovascular disease								
Events	1601	143	998	712	156	674	204	102
Event rate	5·3 (5·1–5·6)	6·2 (5·0–7·4)	5·7 (5·3–6·1)	5·6 (5·1–6·0)	7·4 (5·6–9·2)	5·5 (5·1–6·0)	7·1 (5·4–8·8)	7·3 (4·9–9·8)
Unadjusted	1·00	1·75 (1·41–2·18)	1·24 (1·12–1·37)	1·22 (1·08–1·37)	1·47 (1·24–1·75)	1·18 (1·05–1·32)	1·44 (1·20–1·72)	1·39 (1·16–1·67)
Adjusted*	1·00	1·19 (0·94–1·50)	0·97 (0·87–1·09)	0·97 (0·86–1·10)	1·18 (0·96–1·46)	0·97 (0·87–1·09)	0·92 (0·74–1·14)	0·92 (0·76–1·12)
Myocardial infarction								
Events	624	40	315	190	52	214	59	36
Event rate	2·1 (2·0–2·3)	1·7 (1·1–2·2)	1·5 (1·3–1·7)	1·3 (1·1–1·5)	2·1 (1·4–2·9)	1·5 (1·3–1·7)	1·4 (0·8–2·1)	3·1 (1·1–5·0)
Unadjusted	1·00	1·30 (0·92–1·84)	1·01 (0·87–1·16)	0·84 (0·70–1·02)	1·26 (0·97–1·64)	0·97 (0·83–1·13)	1·06 (0·77–1·46)	1·24 (0·93–1·67)
Adjusted*	1·00	0·89 (0·60–1·33)	0·76 (0·63–0·93)	0·71 (0·56–0·90)	0·90 (0·64–1·26)	0·77 (0·63–0·94)	0·65 (0·44–0·97)	0·78 (0·56–1·09)
Stroke								
Events	504	44	269	200	37	166	67	28
Event rate	1·6 (1·5–1·8)	1·7 (1·1–2·2)	1·4 (1·2–1·6)	1·4 (1·2–1·6)	1·6 (0·9–2·2)	1·3 (1·1–1·5)	2·0 (1·3–2·8)	1·4 (0·8–2·1)
Unadjusted	1·00	1·65 (1·20–2·27)	1·04 (0·87–1·24)	1·07 (0·87–1·30)	1·09 (0·77–1·55)	0·90 (0·75–1·10)	1·48 (1·11–1·97)	1·21 (0·82–1·78)
Adjusted*	1·00	1·31 (0·92–1·86)	1·01 (0·82–1·24)	1·05 (0·83–1·33)	1·25 (0·84–1·86)	0·94 (0·75–1·17)	1·16 (0·82–1·64)	1·05 (0·66–1·65)
Cancer								
Events	373	45	346	287	29	254	61	28
Event rate	1·1 (1·0–1·3)	2·5 (1·7–3·3)	2·5 (2·2–2·8)	2·6 (2·3–3·0)	1·8 (1·0–2·5)	2·5 (2·2–2·9)	2·8 (1·9–3·7)	3·0 (1·6–4·4)
Unadjusted	1·00	2·25 (1·62–3·12)	1·82 (1·53–2·16)	2·06 (1·70–2·49)	1·16 (0·78–1·74)	1·87 (1·56–2·24)	1·84 (1·33–2·54)	1·67 (1·12–2·49)
Adjusted*	1·00	1·93 (1·32–2·80)	1·51 (1·22–1·89)	1·54 (1·21–1·96)	1·06 (0·68–1·66)	1·58 (1·25–2·00)	1·61 (1·10–2·34)	1·38 (0·88–2·16)
Injury								
Events	450	35	339	215	69	232	57	45
Event rate	1·5 (1·4–1·6)	1·8 (1·1–2·5)	1·9 (1·7–2·2)	1·8 (1·5–2·0)	3·1 (1·8–4·3)	1·9 (1·6–2·2)	2·0 (1·2–2·8)	2·2 (1·4–3·0)
Unadjusted	1·00	1·57 (1·06–2·33)	1·57 (1·33–1·86)	1·37 (1·11–1·69)	2·46 (1·88–3·22)	1·51 (1·25–1·83)	1·51 (1·14–2·02)	2·32 (1·69–3·18)
Adjusted*	1·00	1·63 (1·10–2·42)	1·29 (1·04–1·61)	1·37 (1·06–1·77)	1·71 (1·14–2·56)	1·32 (1·06–1·65)	1·15 (0·82–1·62)	1·42 (0·93–2·18)

(Table 2 continues on next page)

	Alcohol history			Heavy episodic drinking in current drinkers		Level of intake in current drinkers		
	Never drinker (n=74 685)	Former drinker (n=4255)	Current drinker (n=36 030)	No (n=26 625)	Yes (n=4711)	Low intake (n=26 025)	Moderate intake (n=6114)	High intake (n=2931)
(Continued from previous page)								
Admission to hospital								
Events	4563	445	3778	3007	542	2705	678	366
Event rate	14·7 (14·3–15·1)	26·5 (23·7–29·3)	27·1 (26·1–28·0)	28·1 (27·0–29·1)	32·1 (27·8–36·4)	27·2 (26·0–28·3)	27·5 (24·4–30·6)	30·6 (26·3–34·8)
Unadjusted	1·00	1·94 (1·60–2·35)	1·68 (1·47–1·92)	1·85 (1·60–2·15)	1·84 (1·56–2·17)	1·70 (1·47–1·96)	1·72 (1·49–1·99)	1·82 (1·53–2·16)
Adjusted*	1·00	1·06 (0·92–1·22)	0·86 (0·78–0·94)	0·88 (0·79–0·97)	0·93 (0·82–1·05)	0·88 (0·80–0·97)	0·80 (0·71–0·90)	0·89 (0·77–1·02)
Composite								
Events	6525	591	4847	3658	712	3415	870	505
Event rate	21·4 (20·9–21·9)	33·8 (30·7–36·9)	33·6 (32·6–34·7)	33·9 (32·7–35·1)	40·0 (35·4–44·7)	33·5 (32·3–34·7)	34·9 (31·4–38·4)	40·4 (35·6–45·2)
Unadjusted	1·00	1·82 (1·54–2·15)	1·52 (1·36–1·70)	1·59 (1·40–1·80)	1·71 (1·48–1·97)	1·51 (1·33–1·70)	1·56 (1·38–1·78)	1·77 (1·53–2·06)
Adjusted*	1·00	1·20 (1·05–1·36)	0·96 (0·88–1·05)	0·97 (0·88–1·06)	1·03 (0·91–1·16)	0·98 (0·89–1·07)	0·89 (0·79–1·00)	0·99 (0·87–1·14)

Age-standardised and sex-standardised event rates per 1000 person-years. *Adjusted for age, sex, smoking, ethnicity, education, body-mass index, diabetes, hypertension, jaundice and hepatitis, physical activity, diet (dairy, fruits, vegetables, meats, fish, soft drinks, processed foods, nuts, and trans fats), medications (angiotensin-converting enzyme or angiotensin receptor blocker, β blockers, calcium channel blockers, diuretics, α blockers, lipid-lowering therapy, and anti-thrombotic therapy), wealth index, total alcohol consumption (drinks per day), and heavy episodic drinking pattern. Additional adjustment for clustering effects at the community level specified as a random effect. Data are hazard ratio (95% CI), except for events, which are n, and event rates, which are per 1000 person-years.

Table 2: **Association between alcohol consumption and outcomes**

of mortality. Sensitivity analyses excluding admissions to hospital from the composite measure showed an increased hazard with alcohol consumption, but inclusion of HDL as a covariate or exclusion of participants with hypertension at baseline did not modify associations (appendix). Spirit or liquor drinkers seemed to have higher hazards for mortality, stroke, cancer, injury, admission to hospital, and the composite than did wine or beer drinkers (figure 2). Wine drinkers generally had the lowest hazards for cardiovascular disease, including a significantly reduced risk of myocardial infarction, compared with never drinkers (HR 0·55 [0·39–0·77]).

We identified important differences in the association between current drinking and outcomes between participants living in HICs/UMICs and LICs/LMICs (figure 3). In HICs/UMICs, current drinking was associated with reduced hazard of myocardial infarction (HR 0·53 [0·40–0·73]), which we did not see in LICs/LMICs (HR 0·97 [0·76–1·25]; $p_{interaction}$=0·02); this difference increased (HR 0·21 [0·10–0·44] in HICs/UMICs compared with HR 0·54 [0·31–0·94] in LICs/LMICs, $p_{interaction}$<0·0001) after additional adjustment (drinks per day, heavy episodic drinking pattern, and predominant alcohol type). Current drinking was associated with reduced hazard of the composite outcome in HICs/UMICs (HR 0·84 [0·77–0·92]) but not in LICs/LMICs (1·07 [0·95–1·21]) ($p_{interaction}$<0·0001). After adjustment for drinking behaviours, current drinking was associated with an increased hazard for the composite outcome in LICs/LMICs (0·84 [0·75–0·95] in HICs/UMICs *vs* 1·38 [1·04–1·84] in LICs/LMICs; $p_{interaction}$<0·0001).

Discussion

In our study of 114 970 participants from 12 countries, 36 030 (31%) individuals reported current consumption of alcohol, with substantial variations by country economic level: more than three-quarters of participants in HICs consumed alcohol compared with one-eighth of people in LICs, and we identified significant differences in the predominant alcohol type consumed. In view of these substantial differences and varying associations with outcomes, the population-attributable risks associated with alcohol differ substantially in countries by economic status. Although alcohol consumption has been associated with more than 60 medical disorders, associations are complex. Association of alcohol consumption with outcomes at the individual level varies on the basis of baseline risk—eg, any association with reduced risk of myocardial infarction is of little importance in young people at very low absolute risk, which might be outweighed by association with increased risks of alcohol-related injuries and breast cancer, but the opposite might be true in post-menopausal women.[17]

Although we report no association between current drinking and mortality, high intake was associated with increased risk of mortality, consistent with previous studies.[18,19] Similarly, we report no association between alcohol consumption and cardiovascular disease, but current drinking was associated with reduced risk of myocardial infarction. Results of previous studies are inconsistent,[20,21] probably owing to opposing mechanisms—ie, changes in HDL, fibrinolysis, platelet aggregation, and coagulation factors might reduce risk of thrombotic disease, but increased blood pressure and other coagulation changes might increase risk of haemorrhagic stroke. In our large study, done mostly in MICs and LICs, we were not able to reliably classify stroke subtype in many cases, because neuroimaging was not routinely done. Finally, former drinking was associated with increased risks of mortality, cancer, injury, and the composite outcome, consistent with the so-called sick quitters hypothesis, whereby individuals might stop consuming alcohol for health reasons.[22]

Current drinking was associated with increased risk of alcohol-related cancers, consistent with results of a previous study.[20] However, our study was underpowered to detect a significant association and dose response, owing to the low proportion of high-intake consumers and heavy episodic drinkers, the fairly small number of events in these groups, and the short duration of follow-up (inadequate to capture the time lag between chronic alcohol consumption and cancer). Although alcohol consumption is associated with injuries,[20] our study might have underestimated the association, because of the importance of alcohol consumption immediately before injury. We report that current drinking was associated with increased risk of injury, consistent with a previous study that excluded former drinkers.[23] Current drinking was associated with reduced risk of admission to hospital, but this outcome is heterogeneous, and reasons for admission to hospital might differ between countries of differing income levels.

Associations seemed to differ when current drinkers were stratified by predominant beverage type, although our study was underpowered to detect significant differences. Although wine drinking seemed to be associated with lower hazards of cardiovascular disease, injury, admission to hospital, and the composite outcome compared with spirit or beer drinkers, this result could also reflect characteristics of the drinker (eg, wine drinkers might be healthier individuals of higher socioeconomic status, be more educated, or might consume healthier diets than spirit or beer drinkers) rather than the exposure of drinking wine itself.[24] Although we adjusted for these factors, statistical adjustments cannot guarantee that biases do not exist.

A widely cited estimate of the associations between alcohol intake, death, and disability is the Global Burden of Disease Study,[25] which reported alcohol as a significant cause of adult chronic disease with a rising global risk factor ranking. However, in this previous study much of the estimate of alcohol intake was based on alcohol sales (per capita consumption). Further, these estimates were mostly based on extrapolation from studies in HICs, because few longitudinal studies have been done in MICs and LICs. Our study provides new information for many regions of the world (especially LICs and MICs), in which data for the association between alcohol consumption and outcomes are sparse (panel).

When countries were stratified by income region, current drinking was associated with lower hazards for the composite outcome in people living in HICs/UMICs

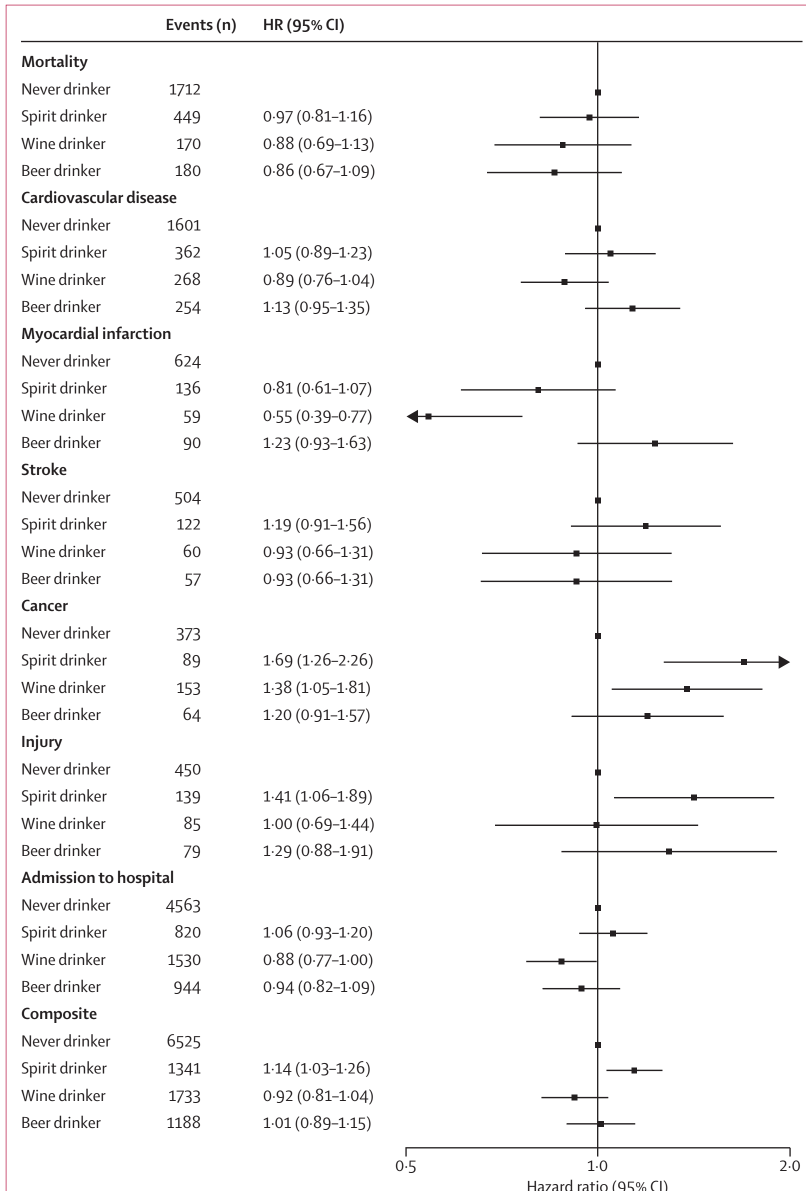
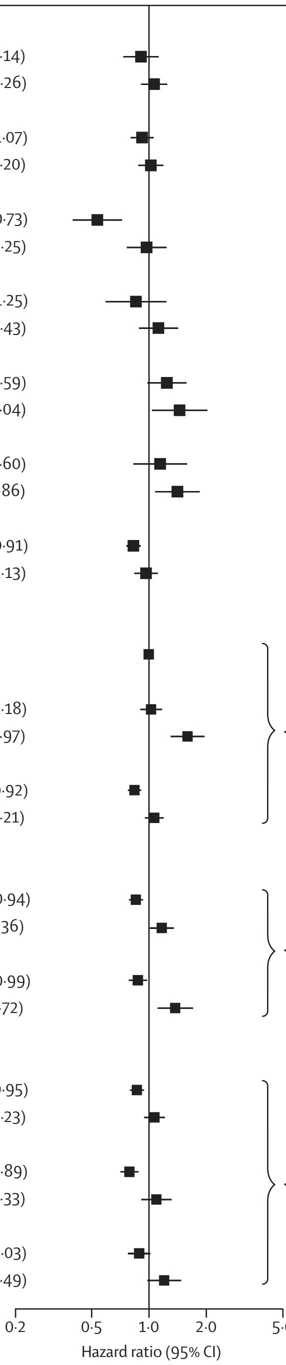


Figure 2: **Association between alcohol types and incident outcomes**
Reference category is never drinker for each outcome. Adjusted for age, sex, smoking, ethnicity, education, body-mass index, diabetes, hypertension, jaundice or hepatitis, physical activity, diet (dairy, fruits, vegetables, meats, fish, soft drinks, processed foods, nuts, and trans fats), medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β blockers, calcium channel blockers, diuretics, α blockers, lipid-lowering therapy, and anti-thrombotic therapy), wealth index, total alcohol consumption (drinks per day), and heavy episodic drinking pattern. Additional adjustment for clustering effects at the community level is specified as a random effect.

	Events (n)	Fully adjusted model HR (95% CI)	Fully adjusted model p value	Additional adjustment for drinking behaviours HR (95% CI)	Additional adjustment for drinking behaviours p value
Mortality			0·48		0·70
HICs/UMICs	410	0·91 (0·73–1·14)		1·33 (0·76–2·30)	
LICs/LMICs	456	1·07 (0·90–1·26)		0·94 (0·68–1·30)	
Cardiovascular disease			0·20		0·22
HICs/UMICs	641	0·92 (0·80–1·07)		0·97 (0·65–1·44)	
LICs/LMICs	357	1·02 (0·87–1·20)		0·98 (0·69–1·38)	
Myocardial infarction			0·02		0·0001
HICs/UMICs	156	0·54 (0·40–0·73)		0·21 (0·10–0·44)	
LICs/LMICs	159	0·97 (0·76–1·25)		0·54 (0·31–0·94)	
Stroke			0·15		0·13
HICs/UMICs	139	0·86 (0·59–1·25)		1·28 (0·59–2·79)	
LICs/LMICs	130	1·12 (0·88–1·43)		1·62 (0·97–2·72)	
Cancer			0·20		0·87
HICs/UMICs	267	1·24 (0·97–1·59)		2·09 (1·19–3·69)	
LICs/LMICs	79	1·45 (1·03–2·04)		3·06 (1·37–6·85)	
Injury			0·10		0·70
HICs/UMICs	196	1·15 (0·82–1·60)		1·17 (0·67–2·03)	
LICs/LMICs	143	1·41 (1·07–1·86)		1·23 (0·57–2·68)	
Admission to hospital			0·27		0·68
HICs/UMICs	3292	0·83 (0·76–0·91)		0·95 (0·77–1·18)	
LICs/LMICs	486	0·97 (0·83–1·13)		1·11 (0·72–1·73)	
Composite outcome					
Never drinker	6525				
Former drinker			<0·0001		<0·0001
HICs/UMICs	435	1·03 (0·89–1·18)		1·03 (0·90–1·19)	
LICs/LMICs	156	1·59 (1·29–1·97)		1·61 (1·30–1·99)	
Current drinker					
HICs/UMICs	3771	0·84 (0·77–0·92)		0·84 (0·75–0·95)	
LICs/LMICs	1076	1·07 (0·95–1·21)		1·38 (1·04–1·84)	
Heavy episodic drinking in current drinkers					
No			<0·0001		<0·0001
HICs/UMICs	3151	0·86 (0·78–0·94)		0·86 (0·76–0·97)	
LICs/LMICs	507	1·17 (1·00–1·36)		1·40 (1·05–1·85)	
Yes					
HICs/UMICs	527	0·88 (0·78–0·99)		0·87 (0·74–1·02)	
LICs/LMICs	185	1·38 (1·10–1·72)		1·68 (1·14–2·49)	
Level of intake in current drinkers					
Low intake			<0·0001		<0·0001
HICs/UMICs	2686	0·87 (0·79–0·95)		0·87 (0·77–0·98)	
LICs/LMICs	729	1·07 (0·94–1·23)		1·39 (1·04–1·86)	
Moderate intake					
HICs/UMICs	683	0·79 (0·71–0·89)		0·79 (0·68–0·93)	
LICs/LMICs	187	1·10 (0·90–1·33)		1·42 (1·01–1·99)	
High intake					
HICs/UMICs	374	0·89 (0·77–1·03)		0·89 (0·71–1·11)	
LICs/LMICs	131	1·20 (0·97–1·49)		1·48 (0·90–2·43)	



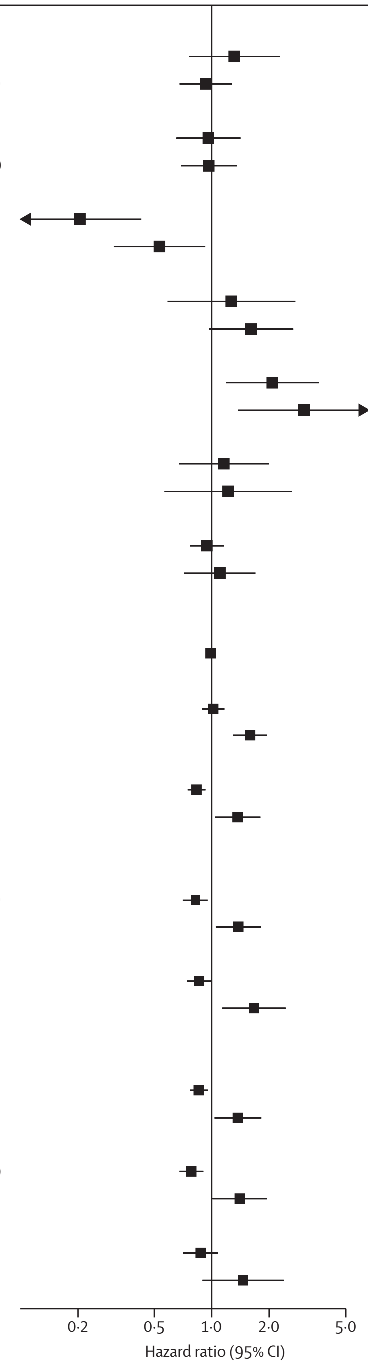


Figure 3: **Association between current drinking and outcomes by income region**

Reference category is never drinker. p values for interaction between alcohol history and income region. High-income and upper-middle-income countries (HICs/UMICs) include Canada, Sweden, Argentina, Brazil, Chile, Poland, South Africa, and Turkey; low-income and lower-middle-income countries (LICs/LMICs) include China, Colombia, India, and Zimbabwe. Data are adjusted for age, sex, smoking, ethnicity, education, body-mass index, diabetes, hypertension, jaundice or hepatitis, physical activity, diet (dairy, fruits, vegetables, meats, fish, soft drinks, processed foods, nuts, and trans fats), medications (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β blockers, calcium channel blockers, diuretics, α blockers, lipid-lowering therapy, and anti-thrombotic therapy), and wealth index. Additional adjustment for clustering effects at the community level is specified as a random effect. Drinking behaviours include total alcohol consumption (drinks per day), heavy episodic drinking pattern, and predominant alcohol type consumed. Interaction for alcohol consumption and income region with p<0·001 is considered persuasive.

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than for those living in LICs/LMICs. These differences were statistically significant (figure 3), and became more pronounced after adjustment for drinking behaviours, suggesting that the difference is not entirely explained by drinking behaviours and might show differences at the country level. Our data support the call to increase global awareness of the harmful effects of alcohol and the need for health policy interventions (including national strategies and legal frameworks) to reduce these harms,[26] especially in LICs/LMICs. Importantly, although alcohol consumption was associated with lower hazards than never drinking in HICs/UMICs, people who do not drink should not be advised to consume alcohol, because of the unknown risk of progression to high intake or development of a heavy episodic drinking pattern.[27]

The strengths of our study include representation of several geographical and income regions, availability of individual-level data for alcohol consumption and covariates, and prospective and careful assessment of outcomes. Unlike some studies, which rely on aggregate sales data, we used individual-level consumption data. Sales data might underestimate an individual's consumption by not including imported or homemade alcohol, or overestimate consumption by including purchased alcohol that is not consumed. Our questionnaire addresses these issues by recording an individual's consumption, including homemade or undeclared, imported alcohol, although we could not adjust for regression dilution bias. We chose never drinkers as our reference group, because many former drinkers abstain for health reasons (sick quitters hypothesis),[22] and their inclusion in the reference group might distort results.[28] Our data confirm this hypothesis because former drinkers were at increased risk of mortality, cancer, injury, and the composite outcome. We categorised current drinkers into sex-specific levels of intake because women might have less alcohol dehydrogenase, resulting in higher blood alcohol concentrations in women than in men for the same volume of intake.[29]

The main limitation of our study is the fairly short duration of follow-up (median 4·3 years), resulting in a moderate number of outcome events. Although our overall data are likely to be robust, analyses by country or geographical region are less stable. As such, we were unable to analyse by country. However, additional analyses including an interaction term for country and number of drinks consumed did not detect a significant difference (data not shown). Similarly, we were unable to use non-linear approaches (such as fractional polynomials) to further investigate disease associations. However, as follow-up continues and events accrue, we will be better placed to investigate the consistency of associations. Second, detailed assessment of alcohol consumption was self-reported and completed at baseline only, whereas, for several outcomes, consumption immediately before events is more important than consumption at baseline. During follow-up, 2310 (3%) never drinkers started to consume alcohol, 419 (10%) former drinkers restarted consuming alcohol, and 5990 (17%) current drinkers stopped consuming alcohol. Therefore, the hazards we report might be slight underestimates. Third, our composite outcome, generated to investigate the net effect of alcohol, includes outcomes with differing incidence and levels of association with alcohol consumption. When we excluded admission to hospital from the composite outcome, alcohol consumption was associated with increased hazards. Overall, we are likely to have underestimated the hazards of alcohol. Fourth, although we adjusted for important confounders, residual confounding cannot be excluded. Sensitivity analyses including HDL and excluding hypertension in statistical adjustment did not change the results. Further investigation of associations of alcohol consumption with health outcomes, especially in LICs and LMICs, is needed.

In summary, our study shows that current drinking is not associated with a net health benefit. We confirm that high intake is associated with increased risk of mortality, cancer, and injury. Importantly, the hazards of alcohol consumption differed between HICs/UMICs and LICs/LMICs. Because alcohol consumption is increasing in many countries, especially in LICs/LMICs, the importance of alcohol as a risk factor for disease might be underestimated.[30] Therefore, global strategies to reduce harmful use of alcohol are essential.

***Panel*: Research in context**

Systematic review

The association between alcohol consumption and health outcomes is complex. We searched PubMed with the search terms "alcohol", "health", "cardiovascular disease", "myocardial infarction", "stroke", "cancer", "injury", or "hospitalisation" for articles in English published before Oct 1, 2014. Many previous studies reported associations between alcohol and several health outcomes (eg, low–moderate intake associated with reduced risk of myocardial infarction[5] but increased risk of sudden death,[6] injury,[7] and cancer[8]).

Interpretation

We studied the net association between alcohol consumption and health outcomes (measured with a composite outcome of death, cardiovascular disease, cancer, injury, and hospital admission) in a large international cohort and report no net health benefit associated with alcohol consumption. Our study confirms that high alcohol consumption is associated with increased risk of mortality,[18,19] cancer,[20] and injury,[23] and a non-significantly reduced risk of myocardial infarction. Our study extends previous work to include participants from low-income and middle-income countries. Importantly, we observed differences in associations between participants living in high-income or upper-middle-income countries and those living in low-income or lower-middle-income countries. The observed differences in associations increased after adjustment for drinking behaviours (drinks per day, predominant alcohol type consumed, and heavy episodic drinking pattern). Although we adjusted for individual-level sociodemographic factors, other country-level factors might modify the association between alcohol consumption and health outcomes. Such factors could include health policies, including regulation and legislation of alcohol.

Contributors
ASm, SY, MO'D, and MM developed this research question and designed these analyses, and ASm had primary responsibility for the writing of this report. SY conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct and data analysis. KKT was the co-principal investigator of the study. SR coordinated the worldwide study. ASm and XZ completed all data analyses. PR, DPL, GD, PS, AR, AES, PL-J, AO, JC, RD, SL, AA, RK, VM, ASz, LW, WY, and BJ were involved in the coordination of the PURE study at the project office or in the included countries and provided comments during the writing and editing of the manuscript.

Declaration of interests
We declare no competing interests.

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