Clinical Nutrition

Alcohol – the myth of cardiovascular protection

Short title: Alcohol and cardiovascular protection

Rudolph Schutte, PhD;[1] Lee Smith, PhD;[2] Goya Wannamethee, PhD[3]

[1]School of Allied Health, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Chelmsford, UK; [2]The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK; [3]UCL Department of Primary Care & Population Health, UCL Medical School, Rowland Hill Street, London, UK.

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Correspondence:
Rudolph Schutte, PhD
Faculty of Health, Education, Medicine and Social Care
Anglia Ruskin University
Chelmsford
CM1 1SQ
United Kingdom
Telephone: +44 (0)1245 493 053
e-mail: rudolph.schutte@aru.ac.uk

SUMMARY

Background & Aims: To investigate potential biases that exist in available epidemiological evidence resulting in negative associations or underestimation of cardiovascular (CV) risk associated with alcohol consumption.

Methods: UK Biobank involved baseline data collection from 22 assessment centres across the United Kingdom. The cohort consisted of 333 259 alcohol consumers and 21 710 never drinkers. Participants were followed up for a median 6.9 years capturing incident fatal and non-fatal CV events, ischemic heart disease and cerebrovascular disease. Alcohol intake was reported as grams/week.

Results: Using never drinkers as reference, alcohol from all drink types combined (hazard ratios ranging between 0.61 to 0.74), beer/cider (0.70 to 0.80) and spirits combined, and all wines combined (0.66 to 0.77) associated with a reduced risk for all outcome measures (all CV events, ischaemic heart disease, cerebrovascular disease). In continuous analysis, alcohol captured from all drink types combined (hazard ratio, 1.08, 95% confidence interval, 1.01–1.14), and beer/cider and spirits combined (1.24, 1.17–1.31) associated with an increased risk for overall CV events, however hazard ratios were stronger for beer/cider and spirits ($P<0.0001$). Wine associated with a reduced risk for overall CV events (0.92, 0.86–0.98) and ischemic heart disease (0.75, 0.67–0.84). This negative relationship with overall CV events was lost after excluding ischemic heart disease events (1.00, 0.93–1.08), while the positive association of alcohol captured from beer/cider and spirits remained significant (1.30, 1.22–1.40). This positive association with overall CV events was present even when consuming less than 14 units per week.

Conclusions: Avoiding potential biases prevents underestimation of cardiovascular risk and indicates that consuming up to 14 units per week also associated with increased CV risk in the general population.

Keywords: ■ alcohol ■ biases ■ cardiovascular risk ■ general population

Introduction

There is no doubt that high alcohol consumption is harmful to health [1-3]. However, uncertainty still exists whether consuming low to moderate levels is harmful or beneficial to cardiovascular (CV) health [2,4]. The trough of the J- or U-shaped association lies at the root of this uncertainty, which is potentially driven by biases embedded in available epidemiological evidence. First, it has been shown that a reference group of non-drinkers is likely to contain a high proportion of abstainers abstaining due to health reasons [5,6]. Yet, this strategy of using a high-risk group as reference is still used in epidemiological studies [7-9] and the main driver of the trough. Second, and still unexplained, evidence for CV protection mostly involve ischemic heart disease as outcome measure and could be the main driver when assessing overall CV risk seen in survival analysis. Third, combining drink types is problematic as directions of associations with different cardiovascular outcome measures are not comparable and may lead to underestimation of risk. We recently showed that when considering the four broad alcoholic drink categories separately, both beer/cider (hazard ratio, 1.25; 95% confidence interval, 1.17–1.33) and spirits (1.25; 1.16–1.36) intake associated with increased overall CV risk while no associations existed for white wine/sparkling wine (0.97; 0.90–1.05) and red wine (0.98; 0.92–1.05) [10]. Instead, both white wine/sparkling wine (0.84; 0.72–0.98) and red wine (0.88; 0.77–0.99) associated with a reduced risk for ischaemic heart disease events [10]. Consequently, we analysed and compared the prognostic significance when combining alcohol from (1) all drink types, (2) beer/cider and spirits, and (3) all wines. We performed these analyses in the total group when using never drinkers as reference, and then solely in drinkers in both categorical and continuous analysis. In addition, the statistical influence of ischaemic heart disease and above combinations of drink types when investigating alcohol and overall CV risk were investigated. Lastly, taking the above potential biases into consideration, we showed the cardiovascular risk associated with consuming 14 units or less per week, which is the current recommended limit for the United Kingdom [11].

Methods

Study population

UK Biobank involves a cohort of over half a million participants aged 40-69 years identified from National Health Service primary care registers. The participants attended one of 22 assessment centres across the United Kingdom located in accessible and convenient locations with a large surrounding population between 2006 and 2010. Participants provided sociodemographic, lifestyle and health information before undergoing physical and medical assessments. The UK Biobank protocol complied with the World Medical Association Declaration of Helsinki and was approved by the North West Multi-Centre Research Ethics Committee. Participants provided informed consent on a touchscreen before taking part. The UK Biobank protocol is available online (http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf). Additional details of the UK Biobank study have been published elsewhere [12]. For the present analysis, we excluded participants that had a previous CV event, former drinkers, or lacked information on alcohol intake (n=169 376).

Measurements at baseline

Participants completed a touchscreen questionnaire including questions on sociodemographic characteristics, health status and lifestyle habits. Intake of alcohol type was recorded as (1) average weekly pints of beer plus cider intake also including bitter, larger, stout, ale and/or Guinness; (2) average weekly glasses of white wine and sparkling wine intake with six glasses per bottle as reference; (3) average weekly glasses of red wine intake with six glasses per bottle as reference; and (4) average weekly measures of spirits such as whiskey, gin, rum, vodka or brandy and with 25 (30 ml) measures per normal 750 ml bottle as reference. Using 4.5%, 40%, 11.5% and 13% alcohol by volume for beer/cider, spirits, white wine/sparkling wine, and red wine, respectively, the amount of ethanol consumed in grams per week (g/wk) was calculated by multiplying the volume (litres) of ethanol consumed per week by the

specific gravity of ethanol (0.789). We combined the weekly intake of alcohol from (1) all drink types, (2) beer/cider and spirits, and (3) white wine/sparkling wine and red wine. A Townsend deprivation score as a measure of socioeconomic deprivation was computed for all participants using information about employment, car and home ownership and household overcrowding [13]. A higher Townsend deprivation score is indicative of greater levels of an area's socioeconomic deprivation.

Data on physical activity including frequency (number of days in a typical week that participants performed 10 minutes or more of walking, moderate and vigorous physical activity) and duration (minutes spent on each activity category on a typical day) were collected by asking questions similar to those included in the International Physical Activity Questionnaire [14]. For each activity category, the frequency was multiplied by the duration and the metabolic equivalent (MET) value (3.3 for walking, 4.0 for moderate physical activity and 8.0 for vigorous physical activity), which were then summed to generate a score of MET-minutes of physical activity per week for each participant. Participants were interviewed by a trained research nurse to determine whether they have previously been diagnosed with any medical conditions.

Height was measured using the SECA 240 height measure (SECA, Hamburg, Germany). Participants removed their socks and footwear and stood flat footed with their heels against a back plate. Body mass was measured to the nearest 0.1 kg using a segmental body composition analyser (Tanita BC-418MA, Tokyo, Japan). Height and weight were used to calculate body mass index as weight (kg) divided by height squared (m^2).

Blood pressure was measured in duplicate, one minute apart, using the OMRON hem-7015IT digital blood pressure monitor.

Assessment of outcome

We obtained the health outcomes of each participant through linkage with the Health and Social Care Information Centre for English and Welsh participants and the Information Services Department for Scottish participants and ascertained the diagnosis of incident fatal and non-fatal CV events (ICD10: I00-I99), ischemic heart disease (ICD10: I20-I25) and cerebrovascular disease (ICD10: I60-I69) until 31 January 2016 for England and Wales and 30 November 2015 for Scotland. The first event from baseline was used in the survival analysis. Primary care physicians confirmed the diagnosis of events.

Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute Inc., Cary, NC). We compared means and proportions by the standard normal z-test and the χ^2 statistic, respectively, and survival curves by Kaplan-Meier survival function estimates and the log-rank test. Statistical significance was set at a level of 0.05 on 2-sided tests.

We analysed the prognostic significance of alcohol intake by means of both categorical and continuous analysis using the PROC PHREG procedure of the SAS package. In categorical analysis using Cox proportional hazard regression analyses, alcohol consumption in g/wk were categorised into quintiles using either never drinkers or the first quintile as reference and associated P-values for trend reported. All models included baseline age, body mass index, sex, smoking, systolic blood pressure, physical activity, diabetes and Townsend deprivation index as covariables and/or potential confounders. We checked the proportional hazards assumption by the Kolmogorov-type supremum test, as implemented in the PROC PHREG procedure of the SAS package. We tested heterogeneity in the hazard ratios across gender and age by introducing the appropriate interaction term in the Cox models. Lastly, we compared hazard ratios using the Wald test as implemented in the TEST statement of the PROC PHREG procedure of the SAS software.

Role of the funding source

There was no funding for this study. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the participants. The cohort consisted of 333 259 alcohol consumers and 21 710 never drinkers. A larger proportion (71.6%) of never drinkers were women (P<0.0001). Never drinkers were older (P<0.0001), had a higher body mass index (P<0.0001), higher systolic and diastolic blood pressure (both P<0.0001), were less physically active (P<0.0001), had a higher prevalence of diabetes (P<0.0001) and higher incidence of overall CV events (P<0.0001), ischaemic heart disease (P<0.0001) and cerebrovascular disease events (P<0.0001). The incidence of overall CV events, ischaemic heart disease and cerebrovascular disease were comparable between never drinkers and drinkers consuming more than 14 units per week (Supplemental Table 1).

Of the 234 577 beer/cider and spirits consumers, 150 917 (64.3%) participants were men, while 149 199 (53.6%) of the 278 289 wine consumers were women. When combining alcohol from all drink types, beer/cider intake (73.3; 5th to 95th percentile interval, 20.2–403.2 g/wk) was the biggest contributor to mean weekly alcohol consumption, followed by red wine (62.5, 12.8–256.4 g/wk), white wine (49.5, 11.3–226.8 g/wk) and spirits (28.1, 9.5–151.5 g/wk).

Incidence of CV events

After a median of 6.9 years (5th to 95th percentile interval, 5.7 to 8.4 years) and 2 308 520 person-years of follow up, 11 512 (3.5%) fatal and non-fatal CV events occurred of which 3384 (29.4%) were due to ischaemic heart disease and 1154 (10.0%) due to cerebrovascular disease. The unadjusted incidence rates

of overall CV events when consuming alcohol from beer/cider and spirits combined increased by quintiles (2.82%, 2.92%, 3.58%, 4.30% and 5.28%; P<0.0001). Similarly, the incidence rate of ischaemic heart disease (0.69%, 0.85%, 1.15%, 1.40%, 1.81%; P<0.0001) and cerebrovascular disease (0.27%, 0.28%, 0.32%, 0.40%, 0.59%; P<0.0001) increased with increased alcohol consumption from these drink types. On the contrary, wine consumption associated wi+th a decreased incidence rate of overall CV events (3.32%, 3.04%, 2.99%, 3.00%, 3.26%; P=0.001) and ischaemic heart disease (1.03%, 0.83%, 0.80%, 0.81%, 0.90%; P<0.0001), however no relationship existed with cerebrovascular disease (0.33%, 0.30%, 0.30%, 0.27%, 0.32%; P=0.29).

Risk analysis

In analyses of Kaplan-Meier estimates, the log-rank test was significant for overall CV events when capturing alcohol from all drink types (Figure 1a, P<0.0001), beer/cider and spirits (Figure 1b, P<0.0001) and wine (Figure 1c, P=0.0008).

Alcohol from all drink types combined (overall CV events, P=0.15; ischaemic heart disease, P=0.91; cerebrovascular disease, P=0.46), beer/cider and spirits (overall CV events, P=0.15; ischaemic heart disease, P=0.67; cerebrovascular disease, P=0.52) and wine (overall CV events, P=0.61; ischaemic heart disease, P=0.14; cerebrovascular disease, P=0.37) fulfilled the proportional hazard assumption. No interaction existed between sex (P≥0.077 to P≤0.98) or age (P≥0.11 to P≤0.60) and alcohol captured from all drink types combined, beer/cider and spirits, or wine in association with overall CV events, ischaemic heart disease, and cerebrovascular disease.

Categorical analysis

Compared to current drinkers in adjusted models, never drinkers were at higher risk for overall CV events (hazard ratio, 1.31; 95% confidence interval, 1.20–1.42; P<0.0001), ischaemic heart disease (hazard ratio, 1.51; 95% confidence interval, 1.29–1.76; P<0.0001) and cerebrovascular disease (hazard ratio, 1.46;

95% confidence interval, 1.14–1.87; P<0.0001). Consequently, using never drinkers as reference resulted in alcohol from all drink types combined exhibiting protection in relation to all outcome measures, as shown in Figures 2a-4a, Supplemental Table 2 and Supplemental Fig. 1.

Performing analyses in drinkers only and using the first quintile as reference (Supplemental Table 3), all drink types combined (Figure 2a, P trend=0.10) and beer/cider and spirits combined (Figure 2b, P trend=0.12) were not associated with ischaemic heart disease, however wine was associated with a reduced risk (Figure 2c, P trend<0.0001). The risk of cerebrovascular events (Supplemental Table 3) increased with beer/cider and spirits consumption (Figure 3b, P trend<0.0001), but was not the case for all drink types combined (Figure 3a, P trend=0.24) or wine (Figure 3c, P trend=0.26).

The risk of overall CV events (Supplemental Table 3) in relation to all drink types combined was absent (Figure 4a, P trend=0.33), while risk increased with beer/cider and spirits consumption (Figure 4b, P trend<0.0001), but decreased with wine consumption (Figure 4c, P trend=0.006). When excluding events from ischaemic heart disease (Supplemental Table 3), the negative protective relationship between overall CV events and wine was lost (Figure 4c, P trend=0.72), while the association with beer/cider and spirits remained (Figure 4b, P trend<0.0001). These findings remained consistent when additionally excluding events from cerebrovascular disease (wine, P trend=0.62; beer/cider and spirits, P trend<0.0001; Supplemental Table 3).

Continuous analysis

In continuous analysis (Table 2), the above findings were confirmed, except for alcohol from all drink types combined predicting overall CV events (P=0.024). However, this relationship was weaker when compared to beer/cider and spirits (hazard ratio, 1.08; 95% confidence interval, 1.01–1.14 vs 1.24, 1.17–1.31; P<0.0001). Wine consumption remained protective for overall CV events (P=0.008).

Alcohol from all drink types (P=0.14) and beer/cider and spirits (P=0.11) were not associated with ischaemic heart disease, while wine was associated with a reduced risk (P<0.0001). On the other hand, alcohol from all drink types (P=0.011) and beer/cider and spirits (P<0.0001) were associated with an increased risk for cerebrovascular disease, but again the associations were stronger for beer/cider and spirits (hazard ratio, 1.30; 95% confidence interval, 1.06–1.58 vs 1.86, 1.57–2.21; P<0.0001), while no association existed with wine (P=0.34).

The inverse association between overall CV events and wine seemed driven by ischaemic heart disease, supported by the complete loss of significance (P=0.95) after excluding events from ischaemic heart disease. However, alcohol from all drink types (P=0.0003) and beer/cider and spirits (P<0.0001) remained associated with CV events and relationships again stronger for beer/cider and spirits (hazard ratio, 1.15; 95% confidence interval, 1.07–1.24 vs 1.30, 1.22–1.40; P<0.0001). These findings were consistent when additionally excluding cerebrovascular events and repeating the analyses in men and women (Supplemental Table 4).

When stratifying the groups into consuming up to and more than 14 units per week (Table 2), results for beer/cider and spirits in relation to overall CV events (P<0.0001) and cerebrovascular disease (P<0.0001) remained consistent when consuming more than 14 units. However, this was also the case when consuming 14 units or less (overall CV events, P=0.006; cerebrovascular disease, P<0.027). This low-level consumption remained associated with overall CV events even after excluding both ischaemic heart disease and cerebrovascular events (P=0.026).

Discussion

We investigated potential biases embedded in epidemiological evidence when assessing CV risk associated with alcohol intake, i.e., the use of abstainers as reference group, combining all drink types

when capturing alcohol consumption, and the inclusion of the protective relationship between ischaemic heart disease and wine in general CV risk stratification. Compared to drinkers, we confirm never drinkers to be at higher CV risk, and when used as reference, suggests alcohol is protective. In addition, combining all drink types and including ischaemic heart disease events in general CV risk analysis embeds coronary artery protection from wine, resulting in underestimation of risk and even suggests overall CV protection from alcohol. We showed that when considering these biases in general CV risk analysis, there is no overall CV protection from alcohol and instead associates with increased CV risk even when consuming 14 units or less per week.

The controversial J- or U-shaped relationship between CV disease and alcohol spans decades with the trough leading to confusion and opportunity [15-17]. The error created when using non-drinkers or never drinkers as reference is known and the main driver of the trough [5,6,18,19]. Ng Fat et al. [20] demonstrated that those with a persistent long-standing illness since the age of 23 years associated with remaining a non-drinker across adulthood. In our cohort, never drinkers were older, less physically active, had a higher body mass index and socioeconomically less affluent. Even after adjusting for these CV risk factors, never drinkers had a 31%, 51% and 46% higher risk of suffering an overall CV-, ischemic heart disease- or cerebrovascular disease event, respectively. Using never drinkers as reference consistently drove the inverse protective relationship with all outcome measures and overrode more subtle associations with different drink types. Using this overriding analytical strategy enables authors to report overall CV protection from alcohol. In addition, some authors also emphasise the protective relationships of alcohol by showing no differences in associations by drink type, therefore dismissing any alternative mechanistic explanations [7,9,21,22].

Our results lays emphasis on the importance of distinguishing between drink types [23]. Associations between overall CV events and alcohol captured from beer/cider and spirits combined and wine were in

opposite direction and resulted in statistically significant weaker hazard ratios when pooling all drink types. The ischemic heart disease-wine association seemed to drive this overall CV protection observed with wine as evidenced by the complete disappearance of any association when excluding ischemic heart disease events, while beer/cider and spirits remained associated with an increased risk for overall CV events, even after additionally excluding cerebrovascular events. Combining of drink types and embedment of this protective relationship can be observed in the study by Bell et al. [3] from the CALIBER cohort involving 1.937 360 participants. Using moderate drinkers as reference (up to 14 units per week), heavy drinkers had an increased risk of experiencing a multitude of CV outcome measures, however alcohol consumption was associated with a reduced risk for coronary heart disease [3]. In addition, Ricci et al. [24] as part of the EPIC-CVD study, used the first quintile as reference and showed that alcohol consumption from all drink types combined associated with an increased risk of non-fatal stroke, while the association with non-fatal coronary heart disease was in the opposite direction. However, when stratified by wine and beer consumption, a protective relationship was evident only between wine and non-fatal coronary heart disease, while these associations were absent for beer which instead was associated with increased risk of non-fatal stroke [24]. Two recent studies involving conventional and genetic epidemiology [25,26] further supports the impact of including the above biases by providing evidence from two populations with a distinct difference in drink type preference. In 599 912 participants from 83 prospective studies involving 19 mostly European countries in which wine consumption is common [27], Wood et al. reported the J-shaped association between alcohol and overall CV events using 0 to 25 grams per week as reference and therefore included abstainers [26]. Disaggregation of this association resulted in a positive relationship with stroke and negative protective relationship with myocardial infarction. The authors confirmed the above relationships when pooling separate study-specific estimates by random-effects meta-analysis [26] but did not report the risk associated with overall CV events, possibly due to weakening of the association or loss of significance. The prominent wine consumption in this cohort most likely explains the protective relationship observed with myocardial infarction. Conversely, in 512 715 Chinese participants where

consumption of spirits is more common [27], a strong positive association with stroke and a weak but positive relationship with coronary heart disease, but not with acute myocardial infarction were reported in conventional analysis when using low-level alcohol consumers as reference [25]. Our results support these findings in continuous analysis by observing a positive relationship with ischaemic heart disease when consuming more than 14 units alcohol per week when captured from beer/cider and spirits.

Evidence for CV protection versus harm attributable to alcohol comes mostly from *in vitro* [28,29], *in vivo* [30] and observational studies [4,31-33]. Regarding protection, current evidence tilts the balance towards polyphenols rather than alcohol [28,29,34,35] as investigators also observe CV protection from alcohol-free wine [33,36,37]. The evidence seems convincing and the most likely explains the generally observed inverse relationship between coronary events and wine [24,31]. Polyphenols are potent antioxidants, reduce platelet aggregation, has antithrombotic properties, and enhances endothelial and platelet-derived nitric oxide biosynthesis and biologic activity [35,37,38]. The latest experimental evidence comes from a randomised cross-over controlled trial involving 38 high-risk male volunteers aged 55-80 years receiving 30g ethanol daily from either aged white wine or gin for three weeks. Compared to consuming gin, wine consumption resulted in lower blood pressure, higher plasma nitric oxide and endothelial progenitor cells and lower pro-inflammatory markers [39,40].

Even low-level alcohol consumption may be hazardous to health [2]. We showed previously that consuming one to two pints of beer/cider or six measures of spirits per week associated with CV events [10] and that alcohol consumption may promote iron loading [41]. Even moderate alcohol consumption attenuates liver hepcidin production leading to uncontrolled iron absorption and accumulation [42-44], placing the body in a state of oxidative stress as iron induces free radical production through the Fenton reaction [45]. This likely explains our current findings of alcohol captured from beer/cider and spirits already associated with increased risk for overall CV events and cerebrovascular disease when consuming

14 units or less per week. Further supporting the iron loading hypothesis is that our findings were independent of potential mediators such as blood pressure [46] and body mass index [47].

The current study must be interpreted within the context of its potential strengths and limitations. Strengths include the prospective study design and the large sample size. The analysis included many incident fatal and non-fatal CV events and we controlled for various covariables and potential confounders. However, the possibility of residual confounding still exists such as measures of iron loading and oxidative stress as mediators of observed associations. The response rate of the UK Biobank was 5.5% and may not be representative of the UK population. In addition, our findings may not be transferable to all countries as different populations have different drink preferences. Alcohol consumption was self-reported as average weekly intake and we cannot exclude the possibility of recall bias; however, underreporting rather than overreporting is more likely. Analyses were not strictly limited to wine drinkers or beer/cider and spirits drinkers only as this would result in loss of information and not reflect the real-life scenario. Rather, associations with increased or reduced risk for cardiovascular events were reported if one does consume these drink type groupings, irrespective of consuming the other or not. However, this overlapping would rather lead to underestimation instead of overestimation of the risks associated with alcohol intake.

In conclusion, biases embedded in epidemiological evidence masks the hazards associated with alcohol consumption and when accounted for unveils adverse effects of even low-level alcohol consumption. Our results do not support the current alcohol consumption guidelines for the United Kingdom of up to 14 units per week in relation to CV risk in the general population.

Sources of funding

The UK Biobank is an independent data resource; there was no funding for the current study.

Statement of authorship

All authors have made substantial contributions to all of the following: (1) analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Conflicts of interest

None.

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Tables

Table 1 | Participant characteristics for never and current drinkers

Characteristics	Never drinkers	Current drinkers	P
n	21710	333259	
Women n (%)	15542 (71.6)	163662 (49.1)	<0.0001
Age (years)	56.8±8.6	56.5±8.0	<0.0001
Body mass index (kg/m^2)	28.1±5.6	27.0±4.4	<0.0001
Systolic blood pressure (mmHg)	139.1±20.4	140.4±19.6	<0.0001
Diastolic blood pressure (mmHg)	81.4±10.8	82.6±10.7	<0.0001
Physical Activity (MET-minutes/week)	914 (99-6929)	1064 (148-6132)	<0.0001
Current smoking n (%)	1402 (6.5)	34289 (10.3)	<0.0001
Townsend deprivation index	–0.17±3.49	–1.61±2.91	<0.0001
Diabetes n (%)	2239 (10.3)	12973 (3.9)	<0.0001
Overall events n (%)	881 (4.1)	11512 (3.5)	<0.0001
Ischemic heart disease n (%)	256 (1.2)	3384 (1.0)	0.020
Cerebrovascular disease n (%)	101 (0.47)	1154 (0.35)	0.004

Values are arithmetic mean ± standard deviation, geometric mean (5th to 95th percentile interval), or number of subjects (%). MET, metabolic equivalent of task. P denotes significance of the difference between groups.

Table 2 | Adjusted standardized hazard ratios in continuous analysis for alcohol from all drink types, beer/cider plus spirits, and all wines

	Hazard ratio (95% confidence interval)					
	All drink types	**Events**	**Beer/cider+spirits**	**Events**	**All wines**	**Events**
Overall CV events						
All drinkers (unadjusted for BMI, SBP)	1.11 (1.05–1.18)†	11512	1.28 (1.21–1.36)§	9063	0.93 (0.87–0.98)*	8697
All drinkers (fully adjusted)	1.08 (1.01–1.14)*	11512	1.24 (11.7–1.31)§	9063	0.92 (0.86–0.98)†	8697
Consuming ≤14 units/wk	0.95 (0.82–1.10)	4719	1.23 (1.06–1.43)†	3070	0.86 (0.75–0.99)*	3636
Consuming >14 units/wk	1.28 (1.13–1.46)‡	6793	1.35 (1.25–1.47)§	5993	0.87 (0.80–0.95)†	5061
Ischaemic heart disease (IHD						
All drinkers (unadjusted for BMI, SBP)	1.01 (0.91–1.13)	3384	1.20 (1.09–1.32)§	2869	0.77 (0.69–0.86)§	2440
All drinkers (fully adjusted)	0.92 (0.82–1.03)	3384	1.09 (0.98–1.21)	2869	0.75 (0.67–0.84)§	2440
Consuming ≤14 units/wk	0.86 (0.64–1.14)	1265	1.14 (0.87–1.50)	926	0.58 (0.44–0.86)§	934
Consuming >14 units/wk	0.99 (0.79–1.25)	2119	1.2.5 (1.09–1.44)†	1943	0.76 (0.65–0.89)‡	1506
Cerebrovascular disease (CBVD)						
All drinkers (unadjusted for BMI, SBP)	1.34 (1.11–1.62)§	1154	1.89 (1.61–2.22)§	892	0.91 (0.75–1.11)	853
All drinkers (fully adjusted)	1.30 (1.06–1.58)*	1154	1.86 (1.57–2.21)§	892	0.91 (0.74–1.11)	853
Consuming ≤14 units/wk	1.19 (0.75–1.89)	483	1.71 (1.06–2.74)*	307	1.00 (0.64–1.55)	369
Consuming >14 units/wk	2.52 (1.68–3.77)§	671	2.39 (1.87–3.05)§	585	0.85 (0.64–1.13)	484
CV events (excl. IHD)						
All drinkers (unadjusted for BMI, SBP)	1.16 (1.08–1.24)§	8128	1.33 (1.24–1.42)§	6194	1.00 (0.93–1.07)	6257
All drinkers (fully adjusted)	1.15 (1.07–1.24)‡	8128	1.30 (1.22–1.40)§	6194	1.00 (0.93–1.08)	6257
Consuming ≤14 units/wk	0.99 (0.83–1.17)	3454	1.30 (1.09–1.55)†	2144	0.99 (0.84–1.17)	2702
Consuming >14 units/wk	1.44 (1.24–1.68)§	4674	1.40 (1.27–1.54)§	405 0	0.92 (0.83–1.02)	3555
CV events (excl. IHD&CBVD)						
All drinkers (excl. BMI, SBP)	1.13 (1.05–1.22)†	6984	1.27 (1.18–1.37)§	5312	1.01 (0.94–1.10)	5409
All drinkers (fully adjusted)	1.12 (1.04–1.22)†	6984	1.26 (1.16–1.36)§	5312	1.01 (0.93–1.09)	5409
Consuming ≤14 units/wk	0.96 (0.80–1.15)	2973	1.24 (1.03–1.50)*	1839	0.99 (0.83–1.18)	2334
Consuming >14 units/wk	1.30 (1.10–1.54)†	4011	1.29 (1.17–1.43)§	3473	0.92 (0.83–1.04)	3075

Continuous analyses were performed in all drinkers, drinkers consuming up to 14 units, and more than 14 units per week. Standardised hazard ratios presented with 95% confidence intervals express the risk associated with a 1-standard deviation increase in alcohol consumption in grams/week. The Cox models included baseline age, body mass index (BMI), sex, smoking, systolic blood pressure (SBP), diagnosis of diabetes and Townsend deprivation index. Significance of the hazard ratios: * $p<0.05$; † $p<0.01$; ‡ $p<0.001$; and § $p<0.0001$.

Legends to figures

Figure 1 Kaplan-Meier survival function estimates in all drinkers for overall cardiovascular events by quintiles of alcohol intake (g/wk) from **(a)** all drink types, **(b)** beer/cider+spirits and **(c)** all wines. P values refer to the significance of the log-rank test.

Figure 2 Ischaemic heart disease. Hazard ratios for alcohol from **(a)** all drink types, **(b)** beer/cider and spirits, and **(c)** all wines, in relation to ischaemic heart disease. Hazard ratios were adjusted for baseline age, body mass index, sex, smoking, systolic blood pressure, physical activity, diabetes and Townsend deprivation index by quintiles of the distribution of weekly alcohol intake in grams per week with never drinkers (■) or the first quintile as reference (■). Hazard ratios are given with 95% confidence intervals. P denotes significance for trend.

Figure 3 Cerebrovascular disease. Hazard ratios for alcohol from **(a)** all drink types, **(b)** beer/cider and spirits, and **(c)** all wines, in relation to cerebrovascular disease. Hazard ratios were adjusted for baseline age, body mass index, sex, smoking, systolic blood pressure, physical activity, diabetes and Townsend deprivation index by quintiles of the distribution of weekly alcohol intake in grams per week with never drinkers (■) or the first quintile as reference (■). Hazard ratios are given with 95% confidence intervals. P denotes significance for trend.

Figure 4 Overall cardiovascular events. Hazard ratios for alcohol from **(a)** all drink types, **(c)** beer/cider and spirits, and **(c)** all wines, in relation to overall cardiovascular events. Hazard ratios were adjusted for baseline age, body mass index, sex, smoking, systolic blood pressure, physical activity, diabetes and Townsend deprivation index by quintiles of the distribution of weekly alcohol intake in grams per week with never drinkers as reference (■), the first quintile as reference (■), or the first quintile as reference with cardiovascular events from ischaemic heart

disease excluded (■). Hazard ratios are given with 95% confidence intervals. P denotes significance for trend.

Figures

Figure 1

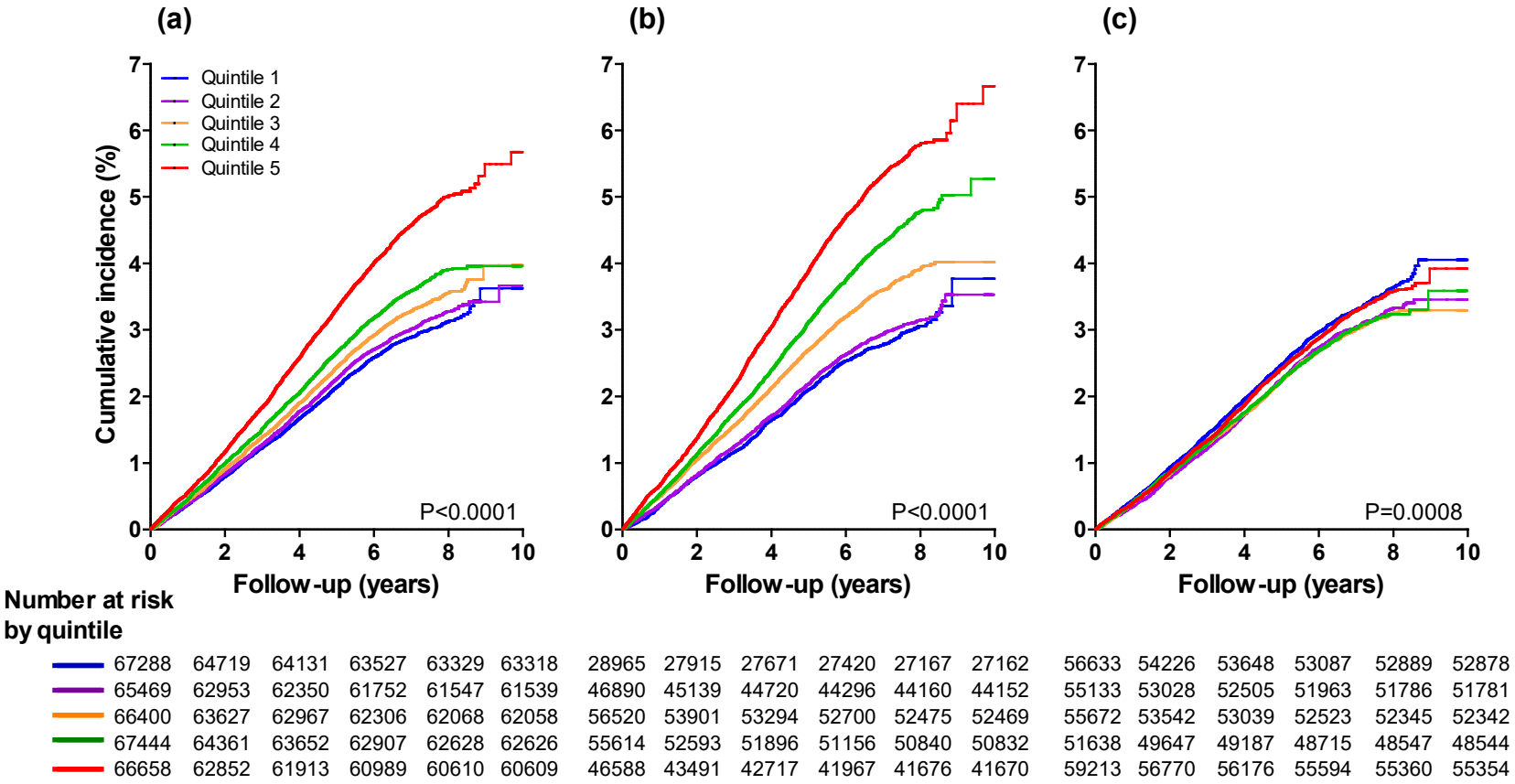


Figure 2

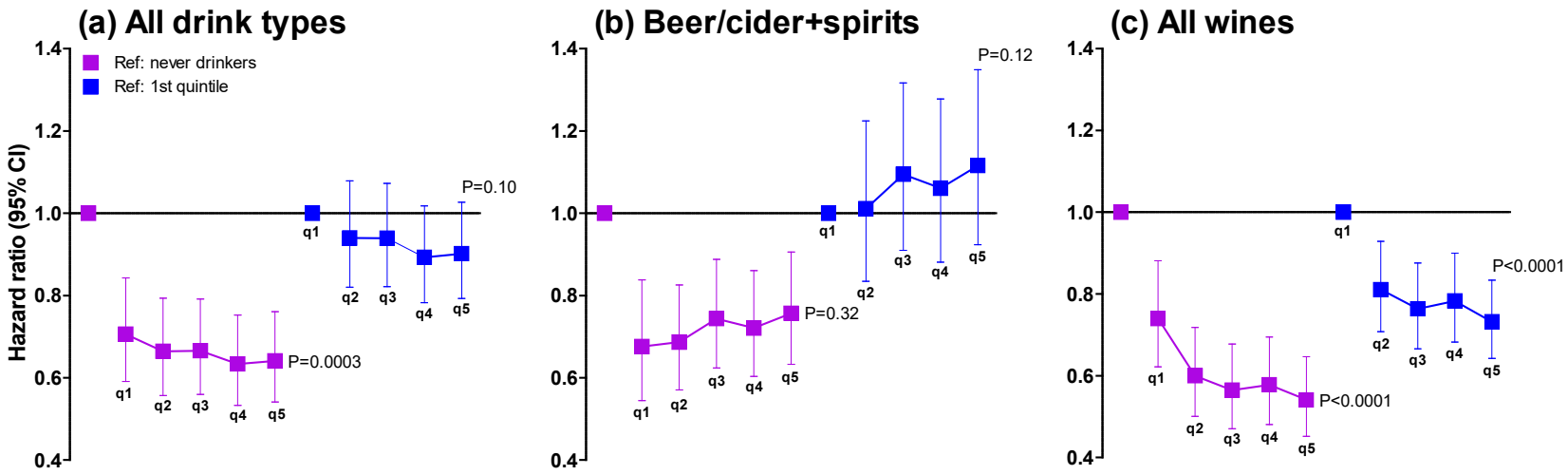

(a) All drink types
(b) Beer/cider+spirits
(c) All wines
Ref: never drinkers
Ref: 1st quintile
Hazard ratio (95% CI)
1.4
1.2
1.0
0.8
0.6
0.4
P=0.10
P=0.0003
P=0.12
P=0.32
P<0.0001
P<0.0001
q1
q2
q3
q4
q5

Figure 3

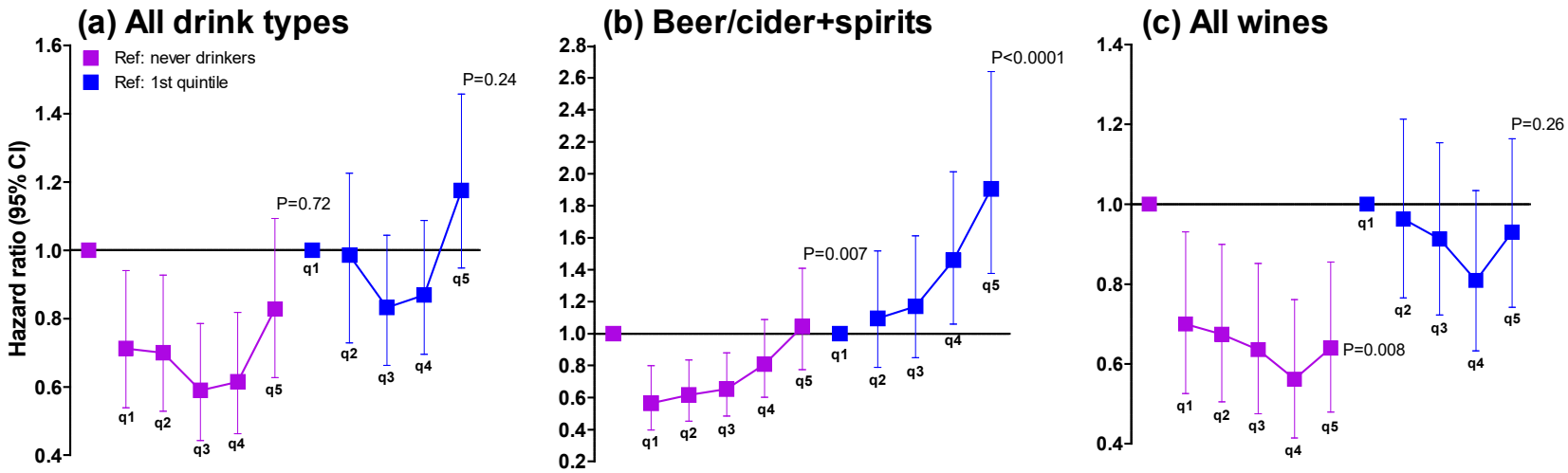
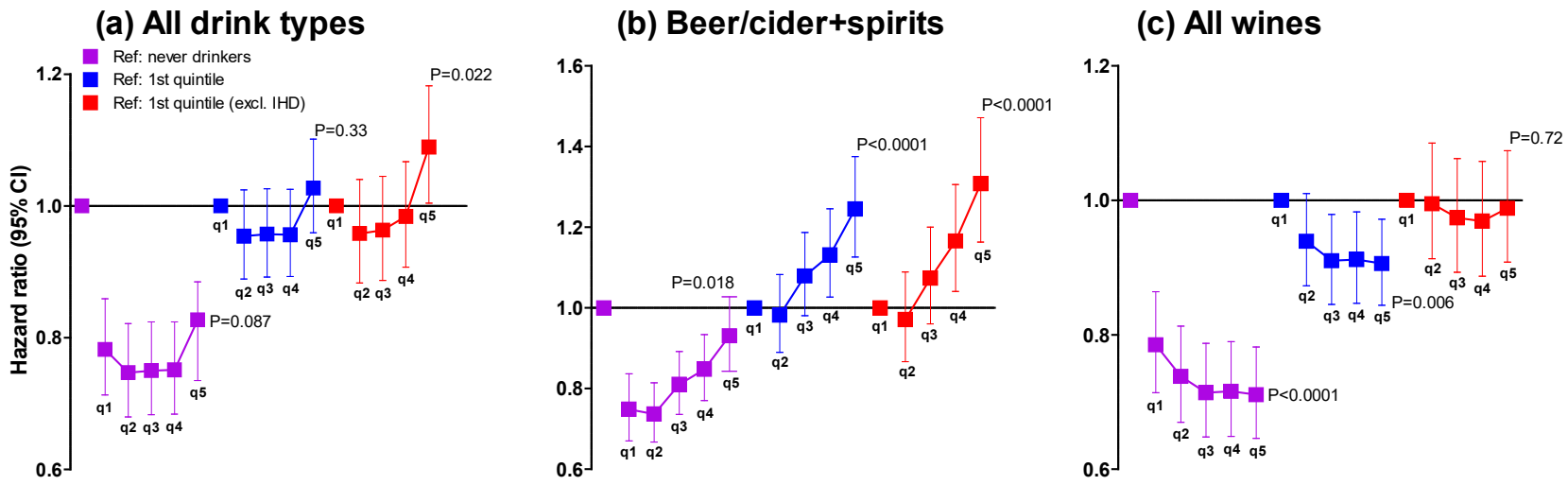

(a) All drink types
Ref: never drinkers
Ref: 1st quintile
Hazard ratio (95% CI)
P=0.72
P=0.24
(b) Beer/cider+spirits
P=0.007
P<0.0001
(c) All wines
P=0.008
P=0.26
q1
q2
q3
q4
q5

Figure 4


(a) All drink types
Ref: never drinkers
Ref: 1st quintile
Ref: 1st quintile (excl. IHD)
Hazard ratio (95% CI)
1.2
1.0
0.8
0.6
P=0.022
P=0.33
P=0.087
q1
q2
q3
q4
q5
(b) Beer/cider+spirits
1.6
1.4
1.2
1.0
0.8
0.6
P<0.0001
P<0.0001
P=0.018
(c) All wines
P=0.72
P=0.006
P<0.0001

Supplementary Data

Alcohol – the myth of cardiovascular protection

Short title: Alcohol and cardiovascular protection

Rudolph Schutte, PhD;[1] Lee Smith, PhD;[2] Goya Wannamethee, PhD[3]

[1]School of Allied Health, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Chelmsford, UK; [2]The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK; [3]UCL Department of Primary Care & Population Health, UCL Medical School, Rowland Hill Street, London, UK.

Online Supplemental Material: Tables 4, Figures 1

Correspondence:
Rudolph Schutte, PhD
Faculty of Health, Education, Medicine and Social Care
Anglia Ruskin University
Chelmsford
CM1 1SQ
United Kingdom
Telephone: +44 (0)1245 493 053
e-mail: rudolph.schutte@aru.ac.uk

Table 1 | Participant characteristics for never drinkers and current drinkers

Characteristics	Never drinkers	Drinkers (≤14 units/wk)	Drinkers (>14 units/wk)
n	21710	158526	174733
Women n (%)	15542 (71.6)	104699 (66.1)	58963 (33.7)
Age (years)	56.8±8.6[a]	56.8±8.0[a]	53.3±8.0
Body mass index (kg/m^2)	28.1±5.6	26.7±4.5	27.4±4.3
Systolic blood pressure (mmHg)	139.1±20.4	138.4±19.7	142.2±19.2
Diastolic blood pressure (mmHg)	81.4±10.8	81.2±10.6	8.3.9±10.6
Physical Activity (MET-min/wk)	914 (99-6929)	1011 (148-5649)	1116 (148-6717)
Current smoking n (%)	1402 (6.5)	10084 (6.4)	24205 (13.9)
Townsend deprivation index	–0.17±3.49	–1.80±2.80	–1.43 (3.00)
Diabetes n (%)	2239 (10.3)	5676 (3.6)	7297 (4.2)
Fatal and non-fatal CV events n (%)	881 (4.1)[a]	4719 (3.0)	6793 (3.9)[a]
Ischemic heart disease n (%)	256 (1.2)[a]	1265 (0.80)	2119 (1.2)[a]
Cerebrovascular disease n (%)	101 (0.47)[a]	483 (0.30)	671 (0.38)[a]

Values are arithmetic mean ± standard deviation, geometric mean (5th to 95th percentile interval), or number of subjects (%). MET, metabolic equivalent of task. 110.5 g/wk corresponds to 14 units/wk. All comparisons differ significantly ($p<0.05$) except between groups with similar superscript ([a]).

Table 2 | Adjusted standardized hazard ratios for alcohol from all drink types, beer/cider plus spirits, and white wine/champagne plus red wine

		CV events	IHD	CBVD
		HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
All drink types (g/wk)				
Never drinkers (Ref)		1.00	1.00	1.00
Q1	34.3 (12.8–55.7)	0.78 (0.71–0.86)§	0.71 (0.59–0.84)‡	0.71 (0.54–0.94)*
Q2	73.9 (59.3–90.4)	0.75 (0.68–0.82)§	0.67 (0.56–0.79)§	0.70 (0.53–0.93)*
Q3	115.5 (94.7–141.2)	0.75 (0.68–0.82)§	0.67 (0.56–0.79)§	0.59 (0.44–0.79)‡
Q4	181.9 (147.2–229.7)	0.75 (0.68–0.82)§	0.63 (0.53–0.75)§	0.62 (0.46–0.82)‡
Q5	357.4 (242.0–703.6)	0.83 (0.74–0.89)§	0.64 (0.54–0.76)	0.83 (0.63–1.09)
P-trend		0.087	0.0003	0.72
Beer/cider+spirits (g/wk)				
Never drinkers (Ref)		1.00	1.00	1.00
Q1	13.4 (9.5–18.9)	0.75 (0.67–0.84)§	0.68 (0.55–0.84)‡	0.56 (0.40–0.80)†
Q2	25.4 (20.2–39.1)	0.74 (0.67–0.81)§	0.69 (0.57–0.83)§	0.62 (0.45–0.84)†
Q3	52.6 (40.3–78.2)	0.81 (0.74–0.89)§	0.74 (0.62–0.89)†	0.65 (0.49–0.88)†
Q4	111.5 (80.7–161.3)	0.85 (0.77–0.93)‡	0.72 (0.60–0.86)‡	0.81 (0.60–1.09)
Q5	292.4 (179.0–635.5)	0.93 (0.84–1.03)	0.76 (0.63–0.91)†	1.04 (0.77–1.41)
P-trend		0.018	0.32	0.007
All wines (g/wk)				
Never drinkers (Ref)		1.00	1.00	1.00
Q1	20.8 (11.3–34.0)	0.79 (0.71–0.86)§	0.74 (0.62–0.88)‡	0.70 (0.53–0.93)*
Q2	44.5 (35.5–56.7)	0.74 (0.67–0.81)§	0.60 (0.50–0.72)§	0.67 (0.51–0.90)†
Q3	71.6 (61.2–80.9)	0.71 (0.65–0.79)§	0.57 (0.47–0.68)§	0.64 (0.48–0.85)†
Q4	107.9 (88.3–136.1)	0.72 (0.65–0.79)§	0.58 (0.48–0.70)§	0.56 (0.42–0.76)†
Q5	212.8 (145.0–434.9)	0.71 (0.65–0.78)§	0.54 (0.45–0.65)§	0.64 (0.48–0.86)†
P-trend		<0.0001	<0.0001	0.008

The Cox models included baseline age, body mass index, sex, smoking, systolic blood pressure, diagnosis of diabetes and Townsend deprivation index. Hazard ratios are given with 95% confidence intervals. Significance of the hazard ratios: * $p<0.05$; † $p<0.01$; ‡ $p<0.001$; and § $p<0.0001$. CV, cardiovascular; IHD, ischaemic heart disease; CBVD, cerebrovascular disease.

Table 3 | Adjusted standardized hazard ratios for alcohol from all drink types, beer/cider plus spirits, and white wine/champagne plus red wine						
		CV events	IHD	CBVD	CV events (excl. IHD)	CV events (excl. IHD&CBVD)
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
All drink types (g/wk)						
Q1	34.3 (12.8–55.7)	1.00	1.00	1.00	1.00	1.00
Q2	73.9 (59.3–90.4)	0.95 (0.89–1.02)	0.94 (0.82–1.08)	0.99 (0.79–1.23)	0.96 (0.88–1.04)	0.96 (0.87–1.04)
Q3	115.5 (94.7–141.2)	0.96 (0.89–1.03)	0.94 (0.82–1.07)	0.83 (0.66–1.04)	0.96 (0.89–1.05)	0.98 (0.90–1.07)
Q4	181.9 (147.2–229.7)	0.96 (0.89–1.03)	0.89 (0.78–1.02)	0.87 (0.70–1.09)	0.98 (0.91–1.07)	1.00 (0.92–1.09)
Q5	357.4 (242.0–703.6)	1.03 (0.96–1.10)	0.90 (0.79–1.03)	1.18 (0.95–1.46)	1.09 (1.00–1.18)*	1.07 (0.98–1.17)
P-trend		0.33	0.10	0.24	0.022	0.054
Beer/cider+spirits (g/wk)						
Q1	13.4 (9.5–18.9)	1.00	1.00	1.00	1.00	1.00
Q2	25.4 (20.2–39.1)	0.98 (0.89–1.08)	1.01 (0.84–1.23)	1.10 (0.79–1.52)	0.97 (0.87–1.09)	0.95 (0.84–1.08)
Q3	52.6 (40.3–78.2)	1.08 (0.98–1.19)	1.10 (0.91–1.32)	1.17 (0.85–1.61)	1.07 (0.96–1.20)	1.06 (0.94–1.19)
Q4	111.5 (80.7–161.3)	1.13 (1.03–1.25)*	1.06 (0.88–1.28)	1.46 (1.06–2.01)*	1.17 (1.04–1.31)†	1.13 (1.00–1.28)*
Q5	292.4 (179.0–635.5)	1.25 (1.13–1.38)§	1.12 (0.92–1.35)	1.91 (1.38–2.64)‡	1.31 (1.16–1.47)§	1.23 (1.09–1.40)†
P-trend		<0.0001	0.19	<0.0001	<0.0001	<0.0001
All wines (g/wk)						
Q1	20.8 (11.3–34.0)	1.00	1.00	1.00	1.00	1.00
Q2	44.5 (35.5–56.7)	0.94 (0.87–1.01)	0.81 (0.71–0.93)†	0.96 (0.77–1.21)	1.00 (0.91–1.09)	1.00 (0.91–1.10)
Q3	71.6 (61.2–80.9)	0.91 (0.85–0.98)*	0.76 (0.67–0.88)‡	0.91 (0.72–1.15)	0.97 (0.89–1.06)	0.98 (0.90–1.08)
Q4	107.9 (88.3–136.1)	0.91 (0.85–0.98)*	0.78 (0.68–0.90)‡	0.81 (0.63–1.03)	0.97 (0.89–1.06)	0.99 (0.90–1.09)
Q5	212.8 (145.0–434.9)	0.91 (0.84–0.97)†	0.73 (0.64–0.83)§	0.93 (0.74–1.16)	0.99 (0.91–1.07)	0.99 (0.91–1.09)
P-trend		0.006	<0.0001	0.26	0.72	0.62

The Cox models included baseline age, body mass index, sex, smoking, systolic blood pressure, diagnosis of diabetes and Townsend deprivation index. Hazard ratios are given with 95% confidence intervals. Significance of the hazard ratios: * $p<0.05$; † $p<0.01$; ‡ $p<0.001$; and § $p<0.0001$. CV, cardiovascular; IHD, ischaemic heart disease; CBVD, cerebrovascular disease.

Table 4 | Adjusted standardized hazard ratios in men and women for alcohol from all drink types, beer/cider plus spirits, and all wines						
	Hazard ratio (95% confidence interval)					
	All drink types	Events	Beer/cider+spirits	Events	All wines	Events
CV events						
Men	1.11 (1.03–1.20)†	7850	1.24 (1.16–1.32)§	7058	0.92 (0.86–0.99)*	5493
Women	0.99 (0.88–1.11)	3662	1.29 (1.12–1.47)‡	2005	0.91 (0.81–1.02)	3204
Ischaemic heart disease (IHD)						
Men	0.94 (0.83–1.07)	2722	1.08 (0.97–1.21)	2477	0.75 (0.66–0.85)§	1876
Women	0.85 (0.65–1.10)	662	1.14 (0.84–1.55)	392	0.74 (0.57–0.98)*	564
Cerebrovascular disease (CBVD)						
Men	1.48 (1.16–1.90)†	754	1.77 (1.43–2.19)§	671	0.93 (0.73–1.19)	512
Women	0.97 (0.68–1.37)	400	1.64 (1.09–2.46)*	221	0.85 (0.60–1.21)	341
CV events (excl. IHD)						
Men	1.21 (1.10–1.32)§	5128	1.30 (1.20–1.41)§	4581	1.01 (0.92–1.11)	3617
Women	1.02 (0.90–1.16)	3000	1.33 (1.15–1.55)‡	1613	0.95 (0.84–1.08)	2640
CV events (excl. IHD&CBVD)						
Men	1.18 (1.07–1.31)†	4384	1.27 (1.17–1.38)§	3920	1.03 (0.93–1.14)	3110
Women	1.04 (0.91–1.19)	2600	1.29 (1.09–1.51)†	1392	0.97 (0.85–1.11)	2299

The Cox models included baseline age, body mass index, sex, smoking, systolic blood pressure, diagnosis of diabetes and Townsend deprivation index. Hazard ratios are given with 95% confidence intervals. Significance of the hazard ratios: * $p<0.05$; † $p<0.01$; ‡ $p<0.001$; and § $p<0.0001$. CV, cardiovascular; IHD, ischaemic heart disease; CBVD, cerebrovascular disease.

Table 5 | Baseline characteristics of never drinkers and weekly beer/cider, champagne/white wine, red wine and spirits drinkers from the general population					
Characteristics	**Never drinkers**	**Beer/cider**	**Champ/w.wine**	**Red wine**	**Spirits**
n	21710	31396	24324	29486	8669
Women n (%)	15542 (71.6)	5043 (16.1)	22228 (91.4)	21917 (74.3)	6595 (76.1)
Age (years)	56.8±8.6	55.5±8.3	56.3±7.9	57.1±7.8	57.1±7.9
Body mass index (kg/m^2)	28.1±5.6	27.9±4.6	26.3±4.5	26.2±4.3	27.9±5.0
Systolic blood pressure (mmHg)	139.1±20.4	142.8±19.2	137.4±20.0	139.4±20.0	139.7±20.1
Diastolic blood pressure (mmHg)	81.4±10.8	84.1±10.8	80.8±10.5	81.5±10.6	81.7±10.7
Physical Activity (MET)	914 (99-6929)	1271 (148-9333)	984 (146-5544)	1025 (149-5598)	1021 (132-6930)
Current smoking n (%)	1402 (6.5)	589 (18.8)	1839 (7.6)	2182 (7.4)	1764 (20.4)
Diabetes n (%)	2239 (10.3)	1873 (6.0)	502 (2.1)	943 (3.2)	480 (5.5)
Overall CV events n (%)	881 (4.1)	1564 (5.0)	567 (2.3)	808 (2.7)	395 (4.6)
Ischaemic heart disease n (%)	256 (1.2)	530 (1.7)	103 (0.4)	183 (0.6)	104 (1.2)
Cerebrovascular disease n (%)	101 (0.5)	154 (0.5)	59 (0.2)	81 (0.3)	55 (0.6)
Values are arithmetic mean ± standard deviation, geometric mean (5th to 95th percentile interval), or number of subjects (%). MET, metabolic equivalent of task.					

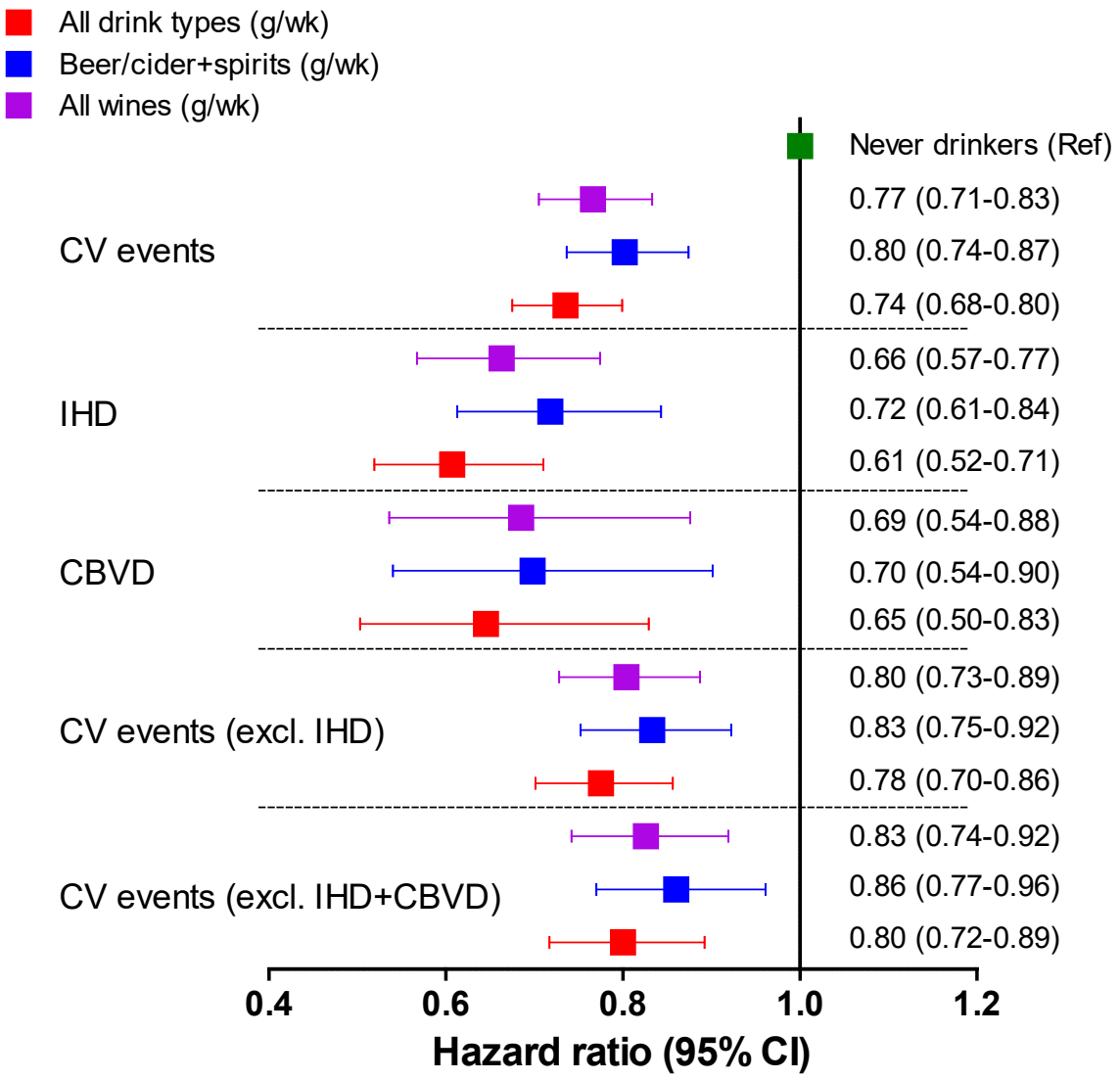


Figure 1 | Standardised hazard ratios for cardiovascular (CV) events, ischaemic heart disease (IHD), cerebrovascular disease (CBVD), CV events with IHD events excluded, and CV events with IHD and CBVD events excluded in all participants. Standardised hazard ratios presented with 95% confidence intervals express the risk associated with a 1-standard deviation increase in alcohol consumption in grams/week. Hazard ratios were adjusted for baseline age, body mass index, sex, smoking, systolic blood pressure, physical activity, diabetes and Townsend deprivation index by weekly alcohol intake in grams per week from all drink types (■), beer/cider and spirits (■), and all wines (■). Never drinkers served as reference. All hazard ratios were significant (P≤0.0004).