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# Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke: EPIC-CVD case-cohort study

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## ABSTRACT

### OBJECTIVE

To investigate the association between alcohol consumption (at baseline and over lifetime) and non-fatal and fatal coronary heart disease (CHD) and stroke.

### DESIGN

Multicentre case-cohort study.

### SETTING

A study of cardiovascular disease aetiology within the European Prospective Investigation into Cancer and nutrition cohort (EPIC-CVD) from 10 European countries.

### PARTICIPANTS

A subcohort of 16 244 participants in the EPIC-CVD study without cardiovascular disease (CVD) and incident CVD events.

### MAIN OUTCOME MEASURES

Non-fatal and fatal CHD and stroke. Stroke included ischaemic and haemorrhagic stroke events.

### RESULTS

There were 9307 non-fatal CHD events, 1699 fatal CHD, 5855 non-fatal stroke, and 733 fatal stroke. Baseline alcohol intake was inversely associated with non-fatal CHD, with a hazard ratio of 0.94 (95% confidence interval 0.92 to 0.96,  $P < 0.001$  for trend) per 12 g/day increase. A J shaped association was observed for fatal CHD risk, with hazard ratios of 0.83 (95% confidence interval 0.70 to 0.98), 0.65 (0.53 to 0.81), and 0.82 (0.65 to 1.03) for participants drinking 5.0–14.9 g/day, 15.0–29.9 g/day, and 30.0–59.9 g/day total alcohol intake, respectively, compared with those drinking 0.1–4.9 g/day. Hazard ratio estimates for non-fatal and fatal stroke risk were 1.04 (95% confidence interval 1.02 to 1.07,  $P = 0.002$

for trend), and 1.05 (0.98 to 1.13,  $P = 0.14$  for trend) per 12 g/day increase in alcohol intake respectively. Hazard ratios for the association of alcohol with ischaemic and haemorrhagic stroke were similar. Wine consumption was inversely related to non-fatal CHD (hazard ratio of 0.94 per 12 g/day increase, 95% confidence interval 0.91 to 0.97,  $P < 0.001$  for trend), while beer was positively associated with non-fatal stroke (1.07, 1.03 to 1.12,  $P = 0.002$  for trend).

### CONCLUSIONS

Alcohol was inversely associated with non-fatal CHD risk, and positively related to stroke, for both baseline and lifetime intakes. Wine and beer consumption showed favourable risk patterns for CHD risk, whereas beer, but not wine, was positively associated with the risk of stroke.

### Introduction

Cardiovascular disease is a leading cause of mortality worldwide, and it is estimated that the overall number of cardiovascular disease deaths will rise to 20 million by 2030.<sup>1</sup> Coronary heart disease (CHD) and stroke are the most common forms of cardiovascular disease, as estimated by the Global Burden of Disease study.<sup>2</sup> CHD and stroke account for 20% and 12% respectively of overall mortality in Europe.<sup>3</sup> The association between alcohol consumption and cardiovascular disease risk has been investigated. A positive association with stroke has been established, but the shape of the dose-response relation for CHD has been the object of continuous research.<sup>4</sup>

Epidemiological studies have provided evidence supporting moderate alcohol consumption to lower the risk of CHD. The existence of a J shaped relation between alcohol intake and the risk of CHD was reported in a meta-regression study.<sup>5</sup> Lower risk of CHD in regular drinkers and higher risk of CHD in binge and heavy drinkers, compared with non-drinkers, was described in a subsequent meta-analysis.<sup>6</sup> Those results were recently confirmed in a meta-analysis of 11 cohort studies, which reported that baseline alcohol intake in the range of 15–30 g/day was inversely related to the risk of CHD, compared with non-drinkers.<sup>7</sup> It has also been suggested that non-fatal and fatal CHD might have different aetiology.<sup>8</sup> Investigations focusing on fatal CHD events tended to report positive associations with alcohol compared with studies that evaluated the relation between alcohol and both non-fatal and fatal CHD events.<sup>9</sup> A meta-analysis of cohort and case-control studies reported that alcohol intake was consistently associated with an increased risk of morbidity and mortality of ischaemic and haemorrhagic stroke, in both men and women.<sup>10</sup> In

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Moderate alcohol consumption has a beneficial role in reducing the risk of coronary heart disease (CHD)

The relation between alcohol consumption and CHD risk has been suggested to be J shaped, when using non-drinkers as a reference

Alcohol consumption at baseline is associated with an increased risk of stroke

## WHAT THIS STUDY ADDS

Baseline and lifetime alcohol consumption were inversely associated with the risk of non-fatal CHD, and were associated with fatal CHD through a J shaped dose-response relation

Baseline and lifetime alcohol consumption were consistently associated with an increased risk of non-fatal stroke

Despite the inverse association with risk of CHD, alcohol consumption should not be encouraged owing to the greater risk of cancer and all cause mortality

a recent study in the UK, heavy alcohol intake was positively associated with coronary death, heart failure, cardiac arrest, transient ischaemic attack, ischaemic stroke, intracerebral haemorrhage, and peripheral arterial disease, compared with moderate use, but inversely related to myocardial infarction or stable angina.<sup>4</sup>

The role of lifetime alcohol consumption on CHD and stroke incidence has not been widely investigated.<sup>11 12</sup> The association between consumption of alcohol subtypes and cardiovascular disease risk has not been thoroughly explored.<sup>13</sup> We evaluated the role of baseline and lifetime alcohol consumption, the association by alcohol subtype, and the dose-response relation of alcohol with the risk of cardiovascular disease in the EPIC-CVD study.

## Methods

### Study population and design

The European Prospective Investigation into Cancer and nutrition (EPIC) study enrolled 519 978 adults (366 521 women) aged mostly 35–70 from 23 centres in 10 countries between 1991 and 2000, as described elsewhere.<sup>14</sup> EPIC-CVD is a multi centre case-cohort study nested within the EPIC cohort designed to investigate the causes of cardiovascular disease.<sup>15</sup> The study included 17 594 incident cardiovascular disease cases identified between March 1991 and December 2010 in the EPIC cohort and a random subcohort of 17 634 EPIC participants was used as a reference group.<sup>16</sup> Effectively, participants in the case-cohort study belonged to one of the following categories: cases that arose outside the subcohort, cases that arose in the subcohort, and non-cases in the subcohort.

### Outcome assessment

The main coronary disease endpoints were defined as any coronary heart disease (CHD), comprised of myocardial infarction (ICD-10 (international classification of diseases, 10th revision) codes: I21, I22), angina (I20), or other CHD (I23-I25). Cerebrovascular events were ascertained and validated using the same methods as for coronary events and included haemorrhagic stroke (I60-I61), ischaemic stroke (I63), unclassified stroke (I64), and other acute cerebrovascular events (I62, I65-69, F01). Non-fatal coronary events were ascertained by different methods depending on the follow-up procedures used by each centre, using active follow-up through questionnaires or linkage with morbidity and hospital registries, or both.<sup>15</sup> Validation of suspected events was performed on all ascertained case events (Italy, Spain, Greece, Germany, and Denmark) or on a subset of events (UK, the Netherlands, and Sweden). Validation was performed by retrieving and assessing medical records or hospital notes, contact with medical professionals, retrieving and assessing death certificates, or verbal autopsy. Angina was not assessed as a CHD outcome in the Italian EPIC centres of Varese, Torino, and in Germany, Sweden, and Denmark. Each subgroup was classified as non-fatal or fatal with the exception

of angina, which is never fatal. To harmonise the definition of fatal cardiovascular disease across centres, non-fatal and fatal events occurring within 28 days of each other were considered to be a single fatal event, in accordance with commonly used definitions.<sup>17</sup> Information on cardiovascular disease and overall mortality were ascertained using boards of health and mortality registries (Italy, Spain, UK, the Netherlands, Sweden, and Denmark) or by active follow-up (Greece and Germany). In the EPIC study, loss to follow-up is less than 0.3%.

### Participant characteristics

We calculated alcohol consumption at baseline for the whole EPIC cohort from validated dietary questionnaires specific to each country which captured local dietary habits.<sup>14</sup> Participants reported the number of standard glasses of wine, beer, cider, sweet liquor, distilled spirits, or fortified wines they consumed daily or weekly during the 12 months before recruitment. Alcohol consumption was taken from highly standardised 24 hour dietary recall measurements from a subset of the cohort.<sup>18</sup> We calculated total alcohol intake using the estimated ethanol content in the alcohol subtype and information on average glass volumes for each country. Lifetime alcohol consumption, available for 76% of participants (395 183/519 978), was assessed as glasses of different beverages consumed weekly at age 20, 30, 40, and 50. Average lifetime alcohol consumption was determined as a weighted average of intake over lifetime, with weights equal to the time of individual exposure to alcohol at different ages.<sup>19</sup> Smoking status at baseline, age at starting and quitting smoking, and number of cigarettes smoked daily was collected by lifestyle questionnaires for each country. The following information was also collected: socioeconomic status, height and weight (self reported in the UK Oxford centre, measured elsewhere), physical activity, and history of previous illnesses (including myocardial infarction, angina, stroke, diabetes, and hypertension).

### Statistical analyses

After exclusion of participants with missing values for smoking variables ( $n=505$ ), baseline alcohol consumption (51), body mass index (273), physical activity (333), and history of hypertension (1112), 32 549 participants (52% women, 17 015/32 549), remained in the analysis. Predefined categories of baseline and lifetime alcohol intakes were defined as lower than 0.1 g/day (defined as non-drinkers at baseline and never drinkers at lifetime), 0.1–4.9 g/day (reference category), 5.0–14.9 g/day, 15.0–29.9 g/day, 30–59.9 g/day, and  $\geq 60$  g/day. Associations for wine and beer use (each grouped into non-drinkers, 0.1–2.9 g/day (reference), 3.0–9.9 g/day, 10.0–19.9 g/day, 20.0–39.9 g/day, and  $\geq 40$  g/day,  $\geq 20$  g/day in women) were assessed in mutually adjusted models, also accounting for spirits, liquors and fortified wine intake (linearly).

The first non-fatal and fatal CHD and stroke events were modelled in Prentice weighted Cox proportional

hazard models with age as the underlying time variable,<sup>16</sup> stratified by sex and centre. Participants within the subcohort contributed follow-up time until the point at which they had a non-fatal or fatal cardiovascular disease event, died of a non-cardiovascular disease cause, were lost to follow-up, or reached the end of a given centre's follow-up period. Robust standard errors were used since participants' contributions to the case-cohort pseudo-likelihood are not independent.<sup>20</sup> Models were adjusted for age at recruitment; body mass index; height; smoking status categorised as never (reference category), former, and current; history of hypertension (yes or no); physical activity as defined by the Cambridge Index (inactive, moderately inactive, moderately active, and active); and education level (no schooling, primary, secondary, and University or more). Adjustment for more extensive information on smoking frequency and duration, plasma levels of total cholesterol, high density lipoprotein cholesterol, and triglycerides at baseline did not alter the risk estimates and these results were not retained further.

Hazard ratios for overall cardiovascular disease and non-fatal and fatal CHD and stroke were computed in relation to baseline and lifetime alcohol consumption in categories per 12 g/day increase, and for mutually adjusted alcohol subtypes. In analyses for lifetime alcohol consumption, information on alcohol intake at different ages was used to separate non-drinkers at baseline into never drinkers and former drinkers. We conducted sensitivity analyses, in turn, for non-fatal CHD and stroke after exclusion of the first two years of follow-up (to address potential reverse causality), for non-fatal and overall myocardial infarction, separately in centres that collected information on incident angina, and by adjusting models for known history of cancer and diabetes. We conducted further analyses for ischaemic and haemorrhagic stroke.

The overall test of significance for the association of alcohol consumption with cardiovascular disease outcomes was assessed with Wald test statistics compared with a  $\chi^2$  distribution with degrees of freedom equal to the number of categories minus one, not including the non-drinker category. We performed trend tests by modelling alcohol consumption as a linear variable on the log hazard scale, after inclusion of an indicator variable expressing any alcohol consumption. A quadratic term for alcohol intake was also included in the model for fatal CHD to assess non-linearity. We investigated further the shape of the relation between alcohol consumption and non-fatal risk of CHD using restricted cubic splines with knots defined by the same cut offs described previously.

We evaluated potential heterogeneity of associations between alcohol consumption and the risk of non-fatal CHD and stroke according to smoking status by including an interaction term between alcohol consumption at baseline (linear) and smoking status (0=never, 1=current smokers). We did this by comparing the log-likelihood of models with and

without the interaction term to a one degree of freedom  $\chi^2$  distribution. We also evaluated the heterogeneity of associations by physical activity and education level, but the results were compatible with the hypothesis of homogeneous relations across levels of these variables. The assumption of proportionality of hazards was evaluated using the inclusion into the disease model of interaction terms between exposure and attained age (data not shown).

The quality of the validity of ascertainment of each non-fatal and fatal CHD and stroke event was assessed using available clinical information, and a score was developed to express low, medium, or high validation, as summarised in supplementary table 5. We excluded events with a low minimum level of validation when performing the sensitivity analyses and showed that hazard ratio estimates were minimally affected, even for fatal stroke.

Hazard ratios for association of non-fatal and fatal CHD and stroke with baseline alcohol consumption (per 12 g/day increase) were further estimated for each country and combined with random effects meta-analyses. A linear and a quadratic term were modelled for fatal CHD. Heterogeneity by country was assessed with the Cochran Q test, and estimated by the  $I^2$  index. We obtained the associated P value by comparing the Cochran Q statistics to a  $\chi^2$  distribution with degrees of freedom equal to the number of countries minus one. Statistical tests were two sided, and P values less than 0.05 were considered statistically significant. All analyses were performed using Stata version 12 (StataCorp, College Station, TX).<sup>21</sup>

### Patient involvement

No participants were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No participants were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

## Results

### Baseline characteristics

Table 1 shows the country specific frequencies of coronary heart disease (CHD) events, descriptive statistics of baseline and lifetime alcohol consumption, and alcohol subtype for the subcohort. A total of 11 006 CHD events were identified; 9307 were non-fatal and 1699 were fatal. A total of 6588 stroke events were identified; 5855 were non-fatal and 733 were fatal. The median age at recruitment in the subcohort was 52 years, and the average follow-up time in the study was 9.5 years.

Baseline and lifetime alcohol consumption averages among alcohol drinkers in the subcohort were, respectively, 24 g/day and 30 g/day in men, and 10 g/day and 8 g/day in women. Baseline alcohol consumption in men was higher in Italy, Spain, Germany, and Denmark than in other EPIC countries.

**Table 1 | Sex and country specific frequencies of total, non-fatal, and fatal coronary heart disease (CHD) and stroke events, percentages of alcohol non-drinkers or never drinkers and means (5th–95th centiles) of baseline and lifetime alcohol consumption (g/day), as well as baseline alcohol subtypes, in the EPIC-CVD subcohort (n=16 244)**

Country	All	CHD		Stroke		Baseline alcohol		Lifetime alcohol		Alcohol subtype		
		Non-fatal	Fatal	Non-fatal	Fatal	Non-drinkers (%)	Drinkers*	Never drinkers (%)	Drinkers*	Wine	Beer	Spirits†
<b>Men</b>												
Italy	622	472	25	115	10	5	26 (1-65)	3	24 (2-60)	22 (0-59)	1 (0-5)	2 (0-11)
Spain	1265	797	93	343	32	13	33 (2-88)	3	46 (3-111)	26 (0-73)	3 (0-16)	4 (0-17)
UK	1568	1042	292	161	73	11	11 (1-39)	1	14 (1-38)	5 (0-29)	4 (0-22)	2 (0-8)
The Netherlands	498	385	31	75	7	10	18 (1-55)	NA	NA	3 (0-14)	9 (0-35)	3 (0-22)
Greece	399	177	62	104	56	9	20 (1-67)	5	32 (0-96)	10 (0-43)	4 (0-19)	6 (0-28)
Germany	761	383	93	263	22	4	26 (2-68)	1	29 (3-76)	8 (0-44)	15 (0-60)	2 (0-7)
Sweden	2763	1220	407	1,057	79	11	11 (1-36)	NA	NA	3 (0-12)	4 (0-12)	4 (0-16)
Denmark	2158	1055	154	922	27	2	29 (2-78)	1	21 (3-51)	11 (0-30)	14 (0-55)	4 (0-11)
All	10 034	5531	1157	3040	306	8	24 (1-70)	2	30 (2-87)	13 (0-51)	7 (0-32)	3 (0-15)
<b>Women</b>												
Italy	596	403	10	160	23	22.7	11 (0-36)	16	8 (1-23)	9 (0-35)	1 (0-3)	1 (0-11)
Spain	630	311	23	260	36	49.8	9 (0-30)	37	7 (0-22)	7 (0-30)	1 (0-8)	0 (0-17)
UK	1233	780	142	203	108	15.9	7 (0-29)	6	7 (0-22)	5 (0-12)	1 (0-4)	2 (0-8)
The Netherlands	1444	986	67	321	70	19.8	11 (0-37)	11	9 (1-24)	6 (0-24)	1 (0-3)	4 (0-22)
Greece	271	87	30	91	63	36.0	6 (1-18)	34	5 (0-17)	3 (0-12)	1 (0-6)	1 (0-28)
Germany	318	112	23	172	11	4.6	10 (0-36)	3	7 (1-23)	7 (0-26)	2 (0-14)	1 (0-7)
Sweden	1866	641	187	950	88	17.8	7 (0-21)	NA	NA	3 (0-12)	1 (0-5)	2 (0-16)
Denmark	1202	456	60	658	28	2.2	14 (1-41)	6	9 (1-24)	6 (0-30)	3 (0-12)	2 (0-11)
All	7560	3776	542	2815	427	24.1	10 (0-33)	15	8 (0-23)	6 (0-27)	2 (0-7)	2 (0-7)

NA=Information on lifetime consumption not available in Bilthoven (The Netherlands), Naples (Italy), and Sweden.

\*Mean and 5th-95th centile values calculated among drinkers only.

†Spirits, liquors, and fortified wine.

Danish women displayed the largest baseline and lifetime alcohol intakes. Wine represented more than 50% of total alcohol intake, while beer represented around 30% and 20% of total intake, in men and women respectively. This pattern of consumption was

relatively homogenous across countries for women. In Italy and Spain men mainly consumed wine, but in Germany they mainly consumed beer. The subcohort is described by categories of alcohol intake and smoking status in supplementary table 1. Average baseline alcohol consumption was consistently higher, for men and women, in former and current smokers than never smokers.

**Table 2 | Number of events and hazard ratios for coronary heart disease and stroke by levels of baseline alcohol consumption (g/day)**

Characteristic	Non-fatal		Fatal	
	Events	Hazard ratio (95% CI)	Events	Hazard ratio (95% CI)
<b>Coronary heart disease</b>				
Non-drinkers	1592	1.15 (1.03 to 1.28)	332	1.25 (1.01 to 1.53)
0.1-4.9	2797	1 (ref)	497	1 (ref)
5.0-14.9	2207	0.82 (0.75 to 0.90)	418	0.83 (0.70 to 0.98)
15.0-29.9	1324	0.78 (0.70 to 0.87)	198	0.65 (0.53 to 0.81)
30.0-59.9	1027	0.73 (0.65 to 0.83)	174	0.82 (0.65 to 1.03)
≥60.0	360	0.68 (0.57 to 0.81)	80	0.98 (0.70 to 1.37)
P value*		<0.001		0.002
12 g/day increase	Linear	0.94 (0.92 to 0.96)	Linear	0.92 (0.85 to 0.99)
			Quadratic	1.01 (1.00 to 1.02)
P value for trend†		<0.001	P value‡	0.003
<b>Stroke</b>				
Non-drinkers	924	1.26 (1.12 to 1.43)	187	1.41 (1.12 to 1.79)
0.1-4.9	1573	1 (ref)	214	1 (ref)
5.0-14.9	1508	1.03 (0.93 to 1.14)	167	1.04 (0.83 to 1.31)
15.0-29.9	872	1.08 (0.96 to 1.22)	88	1.07 (0.81 to 1.42)
30.0-59.9	704	1.10 (0.96 to 1.26)	61	1.20 (0.87 to 1.67)
≥60.0	274	1.31 (1.07 to 1.60)	16	1.14 (0.65 to 2.01)
P value*		0.109		0.863
12 g/day increase	Linear	1.04 (1.02 to 1.07)	Linear	1.05 (0.98 to 1.13)
P value for trend†		0.002		0.136

Models were stratified by centre and sex, and systematic adjustment was undertaken for age at recruitment, body mass index, height, smoking status, and history of hypertension.

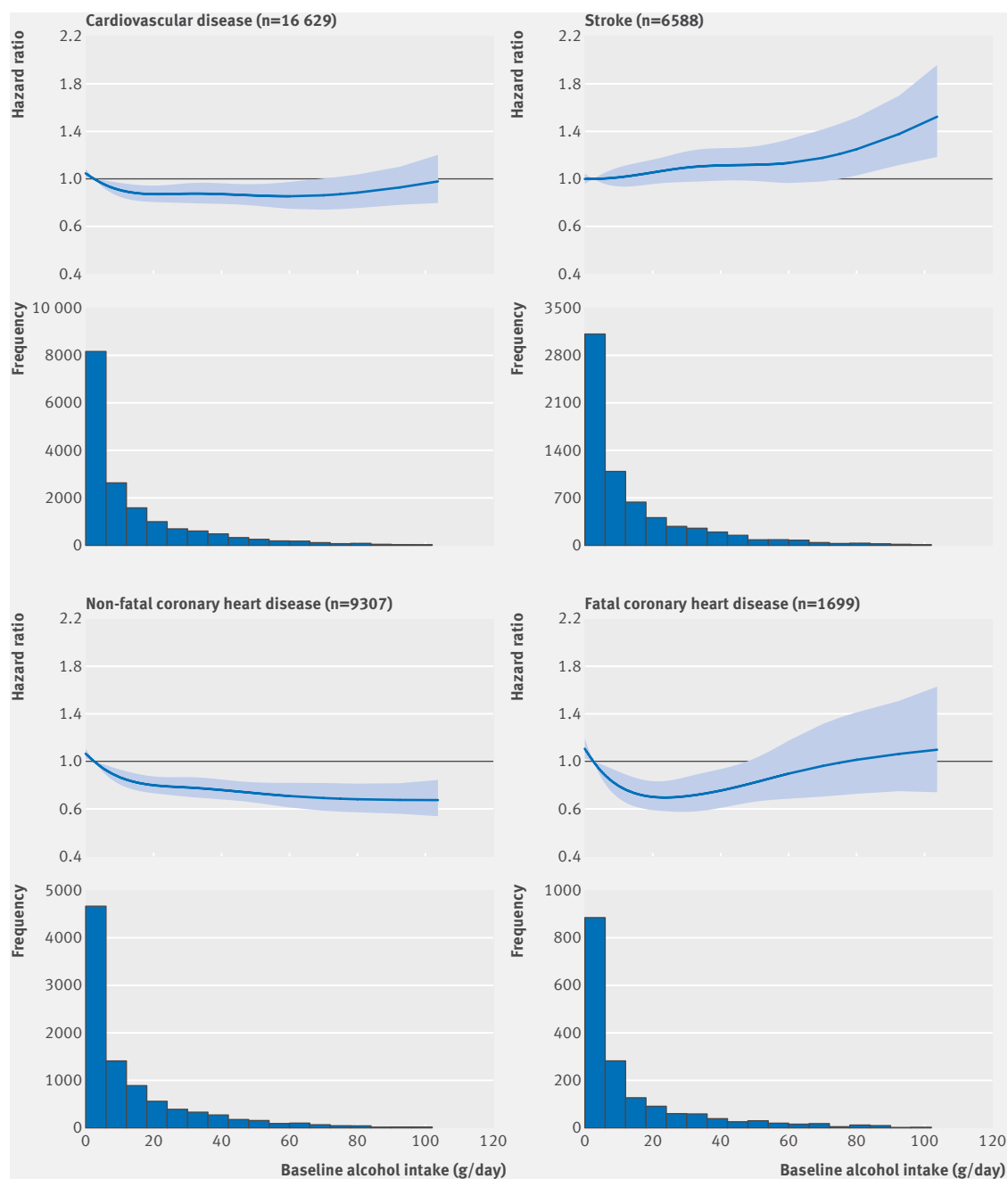
\*P value for the Wald test statistics compared with a  $\chi^2$  distribution with four degrees of freedom, not including the category of non-drinkers (<0.1 g/day).

†Associated to baseline alcohol consumption modelled as a linear variable, with inclusion in the model of an indicator variable expressing alcohol consumption.

‡P value for non-linearity associated to the quadratic term of baseline alcohol consumption modelled as a linear variable.

### Alcohol consumption, coronary heart disease, and stroke

Alcohol consumption was inversely associated with non-fatal CHD (hazard ratio of 0.94 per 12 g/day increase, 95% confidence interval 0.91 to 0.97,  $P<0.001$  for trend). Table 2 shows that compared with the reference group (0.1-4.9 g/day), alcohol drinkers of 30.0-59.9 g/day and 60.0 g/day and more displayed hazard ratio estimates equal to 0.73 (95% confidence interval 0.65 to 0.83) and 0.68 (0.57 to 0.81) for non-fatal CHD. Alcohol was non-linearly associated with fatal CHD, with hazard ratios for the 15.0-29.9 g/day group as low as 0.65 (0.53 to 0.81), and up to 0.98 (0.70 to 1.37) for intakes greater than 60.0 g/day. The non-linear relation between alcohol intake and fatal CHD was described by a quadratic model with hazard ratio per 12 g/day increase indicating first and second degree terms equal to, respectively, 0.92 (0.85 to 0.99) and 1.01 (1.00 to 1.02). Figure 1 shows the non-linear trends with restricted cubic splines analysis. Baseline alcohol consumption was positively associated with non-fatal stroke (hazard ratio of 1.04 per 12 g/day increase, 95% confidence interval 1.02 to 1.07), while the association with fatal stroke was of similar magnitude but not statistically significant (1.05, 0.98 to 1.13). Consistent positive associations



**Fig 1 | Relation between baseline alcohol consumption (g/day) and risk of cardiovascular disease, stroke, non-fatal coronary heart disease, and fatal coronary heart disease**

were observed for ischaemic and haemorrhagic stroke, with hazard ratio of 1.05 per 12 g/day increase (95% confidence interval 1.02 to 1.09,  $P=0.001$  for trend) and 1.10 (1.04 to 1.15,  $P<0.001$  for trend), respectively (see supplementary table 3).

Table 3 shows that lifetime alcohol consumption was inversely related to non-fatal CHD, with hazard ratios of 0.74 (95% confidence interval 0.64 to 0.86) and 0.75 (0.62 to 0.91) for alcohol consumption of 30.0–59.9 g/day and 60.0 g/day and more, respectively, compared with the reference category. The associations of lifetime alcohol consumption with non-fatal or fatal stroke were not statistically significant. Never and

former drinkers had similar non-fatal CHD and stroke risks, showing on average a 20% higher risk compared with light drinkers (0.1–5.0 g/day).

#### Alcohol subtype

Table 4 shows that wine and beer intake were inversely related to non-fatal CHD, with hazard ratio of 0.94 per 12 g/day increase (95% confidence interval 0.91 to 0.97,  $P<0.001$  for trend) and 0.94 (0.89 to 0.99,  $P=0.013$  for trend), respectively. Beer intake was positively associated with non-fatal stroke with a 7% higher risk associated per 12 g/day (3% to 12%,  $P=0.002$  for trend) but wine showed no evidence of association. Spirits,



**Table 3 | Number of events and hazard ratios for non-fatal coronary heart disease (CHD) and non-fatal stroke by levels of lifetime alcohol consumption (g/day), accounting for former drinkers**

Characteristic	Non-fatal CHD		Non-fatal stroke	
	Events	Hazard ratio (95% CI)	Events	Hazard ratio (95% CI)
Former drinkers*	615	1.24 (1.05 to 1.46)	253	1.27 (1.04 to 1.54)
Never drinkers	580	1.17 (1.00 to 1.38)	305	1.14 (0.95 to 1.37)
0.1-4.9	1571	1 (ref)	791	1 (ref)
5.0-14.9	1800	0.89 (0.80 to 1.00)	1024	0.98 (0.86 to 1.11)
15.0-29.9	1102	0.79 (0.69 to 0.90)	685	1.01 (0.87 to 1.17)
30.0-59.9	698	0.74 (0.64 to 0.86)	428	1.08 (0.90 to 1.30)
≥60.0	331	0.75 (0.62 to 0.91)	179	1.12 (0.88 to 1.44)
P value†		<0.001		0.736
12 g/day increase		0.97 (0.94 to 0.99)		1.03 (1.00 to 1.06)
P value for trend‡		0.008		0.034

Models were stratified by centre and systematic adjustment was undertaken for age at recruitment, body mass index, height, smoking status, and history of hypertension. Analyses were conducted among participants with available information on lifetime alcohol consumption.

\*Defined as lifetime drinkers who were non-drinkers at baseline.

†P value for the Wald test statistics compared with a  $\chi^2$  distribution with four degrees of freedom, not including the category of alcohol subtype non-drinkers (<0.1 g/day).

‡Associated to baseline alcohol consumption modelled as linear variable, with inclusion in the model of an indicator variable expressing alcohol subtype.

liquors, and fortified wine intakes were not associated with CHD or stroke (data not shown).

#### Interaction with smoking

Smoking was associated with all cardiovascular disease events, with stronger hazard ratio estimates comparing current to never smokers observed for fatal CHD (hazard ratio 2.97, 95% confidence interval 2.53 to 3.50) and non-fatal CHD (2.24, 2.05 to 2.45) than stroke (1.76, 1.61 to 1.92). Alcohol and smoking displayed a weak interaction for non-

fatal stroke (P=0.019 for interaction), but seemed to act independently for non-fatal CHD (P=0.464 for interaction), as reported in supplementary table 2.

#### Sensitivity analyses

After exclusion of the first two years of follow-up, the associations between baseline alcohol consumption and non-fatal CHD and stroke were virtually unchanged, as shown in supplementary table 4. Alcohol consumption had inverse relations of similar magnitude with non-fatal and overall myocardial infarction. The inverse relation for non-fatal myocardial infarction was confirmed in centres that did not assess incident angina, with a hazard ratio of 0.91 per 12 g/day increase (95% confidence interval 0.88 to 0.94, P<0.001 for trend). In centres that assessed angina the relations were weaker, with a hazard ratio of 0.97 per 12 g/day increase (0.93 to 1.01, P=0.100 for trend). Further adjustment for known history of cancer and diabetes at baseline did not appreciably change the results (data not shown). Analyses by country indicated that the associations between baseline alcohol consumption and risk of non-fatal and fatal CHD and stroke were homogenous across countries (see supplementary figure 1).

#### Discussion

The association between alcohol consumption and the risk of incident non-fatal and fatal coronary heart disease (CHD) and stroke was evaluated in eight European countries in the EPIC-CVD study among individuals without cardiovascular disease, cancer, or diabetes at baseline. While baseline and lifetime alcohol consumption were strongly inversely associated with non-fatal CHD risk, alcohol drinking was positively associated with non-fatal stroke, but not with fatal stroke.

In this study, wine intake was strongly inversely related to non-fatal CHD, with weaker evidence for beer intake. In contrast, wine intake was not associated to the risk of non-fatal stroke while beer intake was positively linked to it. Country specific hazard ratio estimates for risk of stroke in predominantly wine consuming countries (Italy) were similar to hazard ratios in beer consuming countries (Germany and Denmark). This could suggest that the positive association between beer intake and risk of stroke was not driven by an ecologic association. These findings are consistent with evidence from a meta-analysis evaluating the relation between alcohol subtypes and non-fatal and fatal cardiovascular outcomes.<sup>13</sup> Wine intake has been associated with a reduction in oxidative stress levels, putatively through the activity of antioxidants found in wine such as polyphenols.<sup>22-23</sup> Polyphenols may be beneficial for cardiovascular outcomes because of anti-platelet and anti-inflammatory effects, as enhancers of high-density lipoprotein cholesterol concentrations, and because they are associated with improved endothelial functions.<sup>24</sup> In the EPIC study, information on the type of wine consumed (ie, red or white) is not available.

**Table 4 | Number of events and hazard ratios for non-fatal coronary heart disease (CHD) and non-fatal stroke by levels of baseline alcohol consumption (g/day)**

Characteristic	Wine intake		Beer intake	
	Events	Hazard ratio (95% CI)	Events	Hazard ratio (95% CI)
<b>Non-fatal CHD</b>				
Non-drinkers	2932	1.14 (1.03 to 1.25)	4021	1.08 (0.98 to 1.18)
0.1-2.9	2823	1 (ref)	2733	1 (ref)
3.0-9.9	1869	0.86 (0.77 to 0.93)	1611	1.07 (0.97 to 1.19)
10.0-19.9	649	0.86 (0.75 to 0.98)	473	0.98 (0.84 to 1.15)
20.0-39.9	686	0.76 (0.66 to 0.86)	317	0.86 (0.71 to 1.04)
≥40.0	348	0.73 (0.61 to 0.87)	152	0.79 (0.59 to 1.05)
P value*		<0.001		0.069
12 g/day increase		0.94 (0.91 to 0.97)		0.94 (0.89 to 0.99)
P value for trend†		<0.001		0.013
<b>Non-fatal stroke</b>				
Non-drinkers	1764	1.13 (1.01 to 1.25)	2,094	1.14 (1.03 to 1.26)
0.1-2.9	1671	1 (ref)	1829	1 (ref)
3.0-9.9	1398	0.95 (0.85 to 1.05)	1167	1.21 (1.08 to 1.35)
10.0-19.9	391	1.00 (0.85 to 1.16)	369	1.16 (0.98 to 1.37)
20.0-39.9	436	1.01 (0.87 to 1.17)	248	1.31 (1.07 to 1.60)
≥40.0	195	1.05 (0.84 to 1.30)	148	1.40 (1.06 to 1.84)
P value*		0.762		0.002
12 g/day increase		1.03 (0.99 to 1.07)		1.07 (1.03 to 1.12)
P value for trend†		0.204		0.002

Models were mutually adjusted for wine, beer, spirits, and fortified wine, and stratified by centre and sex, and systematic adjustment was undertaken for age at recruitment, body mass index, height, smoking status, and history of hypertension. Models on wine and beer consumptions were mutually adjusted, and also included spirits and fortified wine.

\*P value for the Wald test statistics compared with a  $\chi^2$  distribution with four degrees of freedom, not including the category of alcohol subtype non-drinkers (<0.1 g/day).

†Associated to baseline alcohol consumption modelled as a linear variable, with inclusion in the model of an indicator variable expressing alcohol subtype.

In our analysis, smoking was strongly positively associated with the risk of CHD and stroke, which is consistent with existing evidence.<sup>25-27</sup> In current smokers, continual accumulation of favourable conditions for atheroma formation increases the chance of experiencing cardiovascular disease events.<sup>28</sup> In the absence of clear a priori knowledge on the synergism of alcohol and tobacco, interaction analyses were conducted in this study. In line with previous observations,<sup>29-30</sup> our findings suggested that alcohol consumption and smoking act independently on the occurrence of non-fatal CHD. The borderline interaction observed for non-fatal stroke may indicate that the detrimental effect of alcohol is detectable in the absence of smoking.

### Strengths and weaknesses of this study

To our knowledge, this is the first population based study assessing the relation between baseline and lifetime alcohol consumption and the risk of non-fatal and fatal CHD and stroke in a large prospective investigation of Europeans. Our findings reinforce previous evidence of the association between alcohol consumption and the risk of CHD in the Spanish population.<sup>31</sup> Analyses were performed based on robust methods, relied on a large number of incident CHD and stroke events (after exclusion of prevalent cardiovascular disease conditions at baseline), and controlled for numerous potential confounding factors. The evidence provided in the study was based on validated cardiovascular disease outcomes and on harmonised exposure data across participating countries on alcohol consumption, smoking status, and other lifestyle characteristics. A number of sensitivity analyses were undertaken, including the exclusion of the first two years of follow-up to limit potential reverse causation.

Among the limitations of this study it is important to note that the assessment of the relation between alcohol consumption and the risk of CHD and stroke could be biased by the misclassification of alcohol exposure and by the presence of prevalent morbid conditions at baseline that possibly led to diminished alcohol consumption during the assessment. Assuming that such conditions were precursors of coronary events, this could explain the inverse association between alcohol consumption and non-fatal CHD and motivated our choice to widen the focus on lifetime alcohol consumption (available for 76% of study participants). Statistical adjustment for baseline blood pressure was systematically undertaken. Sensitivity analyses based on additional adjustment for history of cancer and diabetes showed consistent results after exclusion of subjects with a history of angina. However, even if statistical models controlled for many potential confounding factors, residual confounding may still affect the observed associations. In the EPIC study, alcohol measurements at baseline showed relatively high validity,<sup>32</sup> but exposure misclassification could have biased our findings. Moreover, specific drinking patterns during life such as binge drinking or regular

drinking during meals were not investigated because this information was not available in the study. Therefore, we were not able to exhaustively investigate key components of the association between alcohol consumption and the risk of cardiovascular disease subtypes.

### Comparison with other studies

In a recent meta-analysis, regular alcohol consumption as high as 72 g/day was inversely related to CHD risk compared with non-drinkers, with relative risk estimates equal to 0.75 (95% confidence interval 0.64 to 0.89).<sup>6</sup> The association was positive in irregular and binge drinkers compared with non-drinkers, with relative risk estimates equal to 1.10 (1.03 to 1.17).<sup>6</sup> A study in the EPIC cohort evaluated the role of lifetime alcohol consumption on overall and cause specific mortality consistently found no association between lifetime alcohol intake and CHD mortality, in men and women.<sup>29</sup> In a meta-analysis of 26 epidemiological studies (17 cohort and 9 case-control) on stroke morbidity and mortality, alcohol intake was positively associated with the risk of haemorrhagic and ischaemic stroke, consistently in men and women.<sup>10</sup> In a large recent study conducted in the UK, heavy drinkers (defined as participants exceeding current UK guidelines for alcohol of 24 g/day and 16 g/day, for men and women respectively) compared with moderate drinkers (within the UK alcohol guidelines) showed hazard ratio estimates of 1.21 (1.08 to 1.35) for coronary heart death, 1.22 (1.08 to 1.37) for heart failure, 1.50 (1.26 to 1.77) for cardiac arrest, 1.11 (1.02 to 1.37) for transient ischaemic attack, 1.33 (1.09 to 1.63) for ischaemic stroke, 1.37 (1.16 to 1.62) for intracerebral haemorrhage, 1.35 (1.23 to 1.48) for peripheral arterial disease, and 0.88 (0.79 to 1.00) for myocardial infarction.<sup>4</sup> However, the value of using clinically deployed surveys for public health investigations has recently been questioned in a commentary on the use of clinical data to study aetiology.<sup>33</sup>

A controversial element in the evaluation of the relation between alcohol consumption and cardiovascular disease has been the observation that non-drinkers (<0.1 g/day) have greater cardiovascular disease risks than moderate drinkers.<sup>4,29</sup> As non-drinkers were often used as the reference category in analyses of alcohol consumption and risk of cardiovascular disease, this has produced evidence of a J-shaped dose-response relation between alcohol consumption and cardiovascular disease outcomes. It has been suggested that misclassification of alcohol use and inaccuracy in reporting prevalent morbid conditions in the group of non-drinkers could explain the excess cardiovascular disease risks observed.<sup>34-35</sup> For these reasons we undertook our analysis with several important points in mind. Firstly, light alcohol drinkers (0.1-4.9 g/day) were set as the reference category. Throughout the analysis, statistical tests and dose-response relations were evaluated among drinkers only, to rule out the possibility that including non-drinkers could introduce

bias. Secondly, a proportion of baseline non-drinkers were former drinkers, who were possibly heavy drinkers and had quit drinking before recruitment. This motivated our choice to analyse lifetime alcohol consumption, which confirmed that average amounts of alcohol consumed throughout adulthood, in addition to recent intakes, have a noticeable impact on the risk of CHD, though less on stroke. Thirdly, information on lifetime alcohol consumption was instrumental in separating out former and never drinkers, and to estimate that these two groups display similar non-fatal CHD and stroke risks compared with baseline light drinkers (see supplementary table 2). Our findings suggest that the impact of reverse causality in explaining an increased risk of CHD among baseline non-drinkers due to former drinking was probably limited, and that the inverse association between alcohol consumption and the risk of CHD is likely robust.

### Conclusions

This study indicated positive associations between alcohol consumption and non-fatal and fatal stroke, consistently for ischaemic and haemorrhagic stroke. An inverse relation between baseline and lifetime alcohol consumption and risk of non-fatal CHD was observed. It remains challenging to translate this evidence into public health recommendations since alcohol consumption has been consistently positively associated with the risk of cancer and to all cause and cause specific mortality. For these reasons, alcohol consumption should not be encouraged.

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**Contributors:** AA, HB, AT, EW, RK, MS, SP, DP, RT, TJK, RCT, KO, WMMV, JRQ, AT, RS, ER, PF and JD collected, stored, and administered study participants' information on lifestyle exposure within the EPIC study. ASB, MS, ER, and JD designed the case-cohort study, and assessed and validated the cardiovascular disease (CVD) events within the EPIC-CVD study. CR, AW, DM, MS, ASB, and PF performed the statistical analyses. CR, AW, DM, MS, ASB, PF, RS, MJG, PB, and HF interpreted the results and prepared the first versions of the manuscript. All authors actively contributed to the final manuscript. PF is the guarantor.

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**Data sharing:** Access to EPIC data and biospecimens can be found at <http://epic.iarc.fr/access/index.php>.

**Transparency:** The manuscripts' guarantor (PF) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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#### Appendix: Supplementary materials