

Supplementary Table 1. Sex-specific study characteristics¹ of the random sub-cohort from the EPIC-CVD study by categories of baseline alcohol intake and smoking status (n=16,244).

Men	Alcohol intake at baseline				Smoking status		
	Non-drinkers	0.1-29.9 g/day	30-59.9 g/day	≥ 60 g/day	Never	Former	Current
Characteristics (Unit of measure)							
N	528	4,081	1,206	481	1,992	2,261	2,043
Age at recruitment (years)	53 (40, 68)	53 (37, 67)	53 (41, 64)	52 (41, 64)	52 (31, 66)	55 (41, 69)	51.5 (38, 65)
Alcohol intake at baseline (g/day)	-	11 (0.7, 27)	43 (31, 57)	81 (61, 130)	16 (0, 56)	22 (0, 68)	26 (0, 80)
Alcohol non consumers at baseline (%)	100	-	-	-	9.8	8.2	7.2
Never smokers (%)	37.1	34.8	24.6	16.6	100	-	-
Former smokers (%)	35.1	35.7	37.7	34.1	-	100	-
Current smokers (%)	27.8	29.5	37.7	49.3	-	-	100
Body mass index (kg/m ²)	27 (21, 34)	27 (21, 33)	27 (22, 33)	28 (23, 34)	26 (21, 33)	27 (22, 34)	27 (21, 33)
Height (cm)	172 (159, 185)	174 (162, 187)	173 (161, 186)	173 (162, 185)	174 (161, 187)	174 (162, 186)	173 (161, 186)
PA index moderately active (%)	22.4	26.3	26.1	27.2	26.6	25.2	26.2
Women	Alcohol intake at baseline				Smoking status		
	Non-drinkers	0.1-29.9 g/day	30-59.9 g/day	≥ 60 g/day	Never	Never	Former
Characteristics (Unit of measure)							
N	2,401	7,033	465	49	5,687	1,989	2,272
Age at recruitment (years)	52 (36, 67)	52 (36, 67)	52 (378, 64)	52 (41, 63)	53 (37, 67)	52 (36, 67)	49 (35, 64)
Alcohol intake at baseline (g/day)	-	7 (0.3, 24)	42 (30, 70)	76 (61, 108)	6 (0, 24)	10 (0, 33)	10 (0, 37)
Alcohol non consumers at baseline (%)	100	-	-	-	29.5	14.3	19.4
Never smokers (%)	69.8	54.6	34.2	20.4	100	-	-
Former smokers (%)	11.8	22.2	27.5	28.6	-	100	-
Current smokers (%)	18.4	23.2	38.3	51.0	-	-	100
Body mass index (kg/m ²)	28 (21, 37)	26 (20, 34)	25 (20, 32)	26 (21, 35)	27 (20, 36)	26 (20, 34)	25 (19, 33)
Height (cm)	158 (148, 170)	162 (151, 173)	164 (153, 175)	164 (152, 173)	160 (149, 172)	163 (152, 174)	162 (151, 173)
PA index moderately active (%)	14.0	21.5	23.7	18.4	17.9	23.2	21.5
Postmenopausal status ² (%)	55.0	49.8	52.3	46.9	55.1	49.4	42.8

¹Continuous variables were reported by means and 5th and 95th percentiles. Physical activity was measured by the Cambridge physical activity index; ²Comprehensive of women that underwent bilateral ovariectomy.

Supplementary Table 2. Frequencies of events, and hazard ratios (HR)¹ and 95% confidence intervals for non-fatal CHD and stroke by levels of **baseline alcohol consumption** (g/day), separately in current and never smokers.

Non-fatal CHD		Never smokers		Current smokers		P_{Interaction}⁴
	Events	HR (95% CI)	Events	HR (95% CI)		
Non-drinkers	757	1.20 (1.04, 1.38)	485	1.21 (0.99, 1.47)		
0.1-4.9	1,073	1 (ref.)	887	1 (ref.)		
5-14.9	668	0.84 (0.73, 0.97)	746	0.81 (0.69, 0.95)		
15-29.9	281	0.85 (0.71, 1.02)	545	0.77 (0.64, 0.91)		
30-59.9	190	0.88 (0.71, 1.10)	487	0.70 (0.58, 0.84)		
≥ 60	39	0.77 (0.51, 1.16)	218	0.68 (0.53, 0.87)		
p _{Wald} ²		0.106		9.0 E ⁻⁰⁴		0.464
p _{trend} ³		0.095		2.2 E ⁻⁰⁴		
Non-fatal stroke		Never smokers		Current smokers		P_{Interaction}⁴
	Events	HR (95% CI)	Events	HR (95% CI)		
Non-drinkers	490	1.20 (1.02, 1.41)	243	1.33 (1.05, 1.69)		
0.1-4.9	690	1 (ref.)	491	1 (ref.)		
5-14.9	575	1.11 (0.95, 1.28)	481	1.01 (0.83, 1.21)		
15-29.9	234	1.15 (0.94, 1.41)	330	1.07 (0.87, 1.32)		
30-59.9	149	1.19 (0.94, 1.52)	314	1.07 (0.86, 1.33)		
≥ 30	49	2.07 (1.34, 3.21)	145	1.19 (0.89, 1.59)		
p _{Wald} ²		0.016		0.784		0.019
p _{trend} ³		1.1 E ⁻⁰⁴		0.100		

¹Models were stratified by centre and sex, systematic adjustment was undertaken for age at recruitment, BMI, height, smoking status, history of hypertension. Models included interaction terms between baseline alcohol consumption and smoking indicators (0=never smokers, 1=current smokers). Moderate alcohol consumption (0.1-4.9 g/day) at baseline and never smokers were the reference category; ²p_{Wald} computed with a linear test for contrast with 4 degrees of freedom, not including the category of alcohol non-consumers (<0.1 g/day); ³p_{trend} associated to alcohol at baseline modelled as a linear variable, with the inclusion in the model of an indicator variable expressing alcohol consumption; ⁴p_{Interaction}: p-value for multiplicative interaction computed with a Wald test of the interaction term with 1 degree of freedom.

Supplementary Table 3. Frequencies of events, hazard ratios (HR)¹ and 95% confidence intervals by levels of **baseline alcohol consumption** (g/day) for heamorrhagic and ischaemic strokes.

	Heamorrhagic stroke		Ischaemic stroke	
	Events	HR (95% CI)	Events	HR (95% CI)
Non-consumers	146	1.42 (1.12, 1.80)	664	1.28 (1.11, 1.47)
0.1-4.9	201	1 (ref.)	1,102	1 (ref.)
5-14.9	208	1.13 (0.91, 1.39)	1,016	1.04 (0.92, 1.17)
15-29.9	117	1.15 (0.88, 1.49)	597	1.14 (0.99, 1.31)
30-59.9	102	1.40 (1.06, 1.85)	432	1.17 (0.99, 1.37)
≥ 60	39	1.78 (1.20, 2.69)	161	1.34 (1.06, 1.69)
p _{Wald} ²		0.034		0.079
12 g/day increase		1.10 (1.04, 1.15)		1.05 (1.02, 1.09)
p _{trend} ³		0.001		0.001

¹Models were stratified by centre and systematic adjustment was undertaken for age at recruitment, BMI, height, smoking status, history of hypertension. Analyses were conducted among participants with available information on lifetime alcohol intake; ²p_{Wald} computed with a linear test for contrast with 4 degrees of freedom, not including the category of alcoholic subtype non-consumers (<0.1 g/day); ³p_{trend} associated to alcohol at baseline modelled as a linear variable, with inclusion in the model of an indicator variable expressing alcohol subtype consumption.

Supplementary Table 4. Sensitivity analyses: frequencies of events, hazard ratios (HR)¹ and 95% confidence intervals by levels of baseline alcohol consumption (g/day), after exclusions of the first 2-years of follow-up for non-fatal coronary heart disease (CHD) and non-fatal stroke, on non-fatal and overall myocardial infarction (MI), and non-fatal CHD by recruitment centers that completed (or not) assessment of incident angina during follow-up.

Exclusion first 2 years	Non-fatal CHD		Non-fatal stroke	
	Events	HR (95% CI)	Events	HR (95% CI)
<0.1	1,425	1.13 (1.01, 1.26)	912	1.27 (1.12, 1.43)
0.1-4.9	2,548	1 (ref.)	1,559	1 (ref.)
5-14.9	2,008	0.82 (0.75, 0.90)	1,498	1.06 (0.96, 1.18)
15-29.9	1,183	0.78 (0.70, 0.87)	863	1.11 (0.98, 1.26)
30-59.9	905	0.72 (0.64, 0.82)	700	1.12 (0.97, 1.29)
≥ 60	320	0.68 (0.57, 0.82)	273	1.36 (1.11, 1.68)
pWald ²		4.85 E-05		0.052
12 g/day increase		0.94 (0.92, 0.96)		1.05 (1.02, 1.08)
Ptrend ³		4.9 E-07		0.001

	Non-fatal MI		Overall MI	
	Events	HR (95% CI)	Events	HR (95% CI)
<0.1	856	1.14 (1.01, 1.29)	1,077	1.18 (1.05, 1.33)
0.1-4.9	1,697	1 (ref.)	2,039	1 (ref.)
5-14.9	1,462	0.81 (0.73, 0.90)	1,739	0.81 (0.73, 0.89)
15-29.9	904	0.76 (0.67, 0.86)	1,049	0.75 (0.66, 0.84)
30-59.9	700	0.69 (0.60, 0.78)	838	0.71 (0.62, 0.81)
≥ 60	261	0.63 (0.52, 0.77)	328	0.68 (0.57, 0.83)
pWald ²		9.7 E-09		3.3 E-08
12 g/day increase		0.93 (0.91, 0.95)		0.94 (0.92, 0.97)
Ptrend ³		8.3 E-08		4.9 E-06

Non-fatal MI	Centers with angina ⁴		Centers without angina ⁴	
	Events	HR (95% CI)	Events	HR (95% CI)
<0.1	429	1.22 (1.03, 1.46)	427	1.09 (0.92, 1.29)
0.1-4.9	469	1 (ref.)	1,228	1 (ref.)
5-14.9	345	0.81 (0.68, 0.96)	1,117	0.81 (0.71, 0.91)
15-29.9	214	0.70 (0.57, 0.86)	690	0.77 (0.67, 0.90)
30-59.9	214	0.74 (0.59, 0.92)	486	0.66 (0.56, 0.78)
≥ 60	95	0.78 (0.58, 1.05)	166	0.57 (0.44, 0.74)
pWald ²		0.006		8.6 E-07
12 g/day increase		0.97 (0.93, 1.01)		0.91 (0.88, 0.94)
Ptrend ³		0.100		1.4 E-07

	Ischaemic stroke		Hemorrhagic stroke	
	Events	HR (95% CI)	Events	HR (95% CI)
<0.1	664	1.28 (1.11, 1.47)	146	1.42 (1.12, 1.80)
0.1-4.9	1,102	1 (ref.)	201	1 (ref.)
5-14.9	1,016	1.04 (0.92, 1.17)	208	1.13 (0.91, 1.39)
15-29.9	597	1.14 (0.99, 1.31)	117	1.15 (0.88, 1.49)
30-59.9	432	1.17 (0.99, 1.37)	102	1.40 (1.06, 1.85)
≥ 60	161	1.34 (1.06, 1.70)	39	1.78 (1.20, 2.65)
pWald ²		0.079		0.034
12 g/day increase		1.05 (1.02, 1.09)		1.10 (1.04, 1.15)
Ptrend ³		0.001		3.4 E-04

¹Models were stratified by centre and systematic adjustment was undertaken for age at recruitment, BMI, height, smoking status, history of hypertension; ² p_{Wald} computed with a linear test for contrast with 4 degrees of freedom, not including the category of alcohol non-consumers (<0.1 g/day); ³ p_{trend} associated to alcohol at baseline modelled as a linear variable, with inclusion in the model of an indicator variable expressing alcohol consumption; ⁴Incident angina events were assessed in Florence, Ragusa, Naples (Italy), Spain, UK, The Netherlands, Greece.

Supplementary Table 5. Validity of ascertainment for non-fatal and fatal coronary heart disease (CHD) and stroke events.

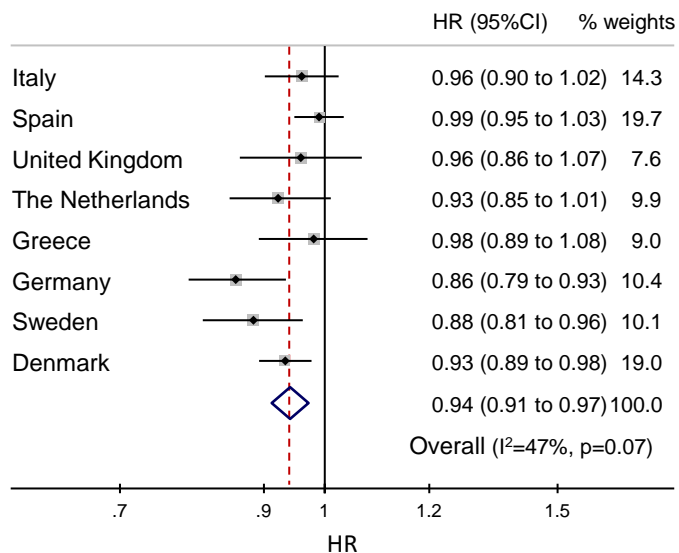
		Non-fatal CHD	Fatal CHD	Non-fatal stroke	Fatal stroke
Validity	Low	2,514 (27%)	126 (7%)	1,406 (24%)	383 (52%)
	Medium/High	6,793 (73%)	1,573 (93%)	4,449 (76%)	350 (48%)
	Total	9,307 (100%)	1,699 (100%)	5,855 (100%)	733 (100%)

Supplementary Figure 1. Country-specific random effects meta-analysis displaying HR for non-fatal and fatal coronary heart disease (CHD), fatal CHD, non-fatal and fatal stroke with respect to alcohol intake at baseline (for 12 g/day). For fatal CHD both a linear and a quadratic term were fitted, consistently with HR estimates in Table 2 and dose-response relationship in Figure 1.

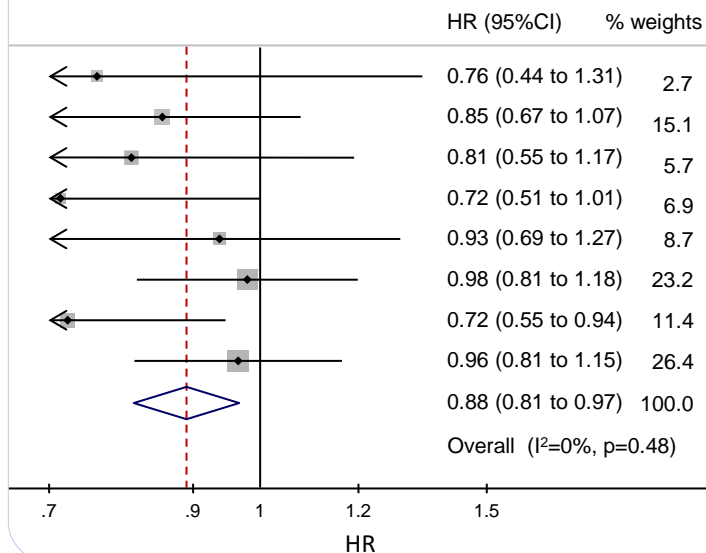
(Please refer to file Supplementary Figure1.pdf)

Alcohol consumption at baseline (g/day)

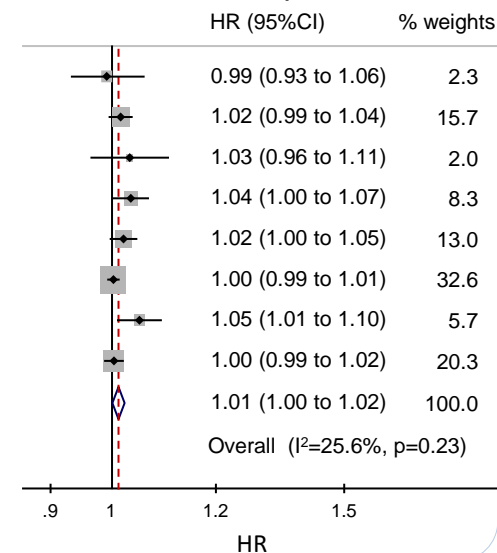
Non-fatal CHD



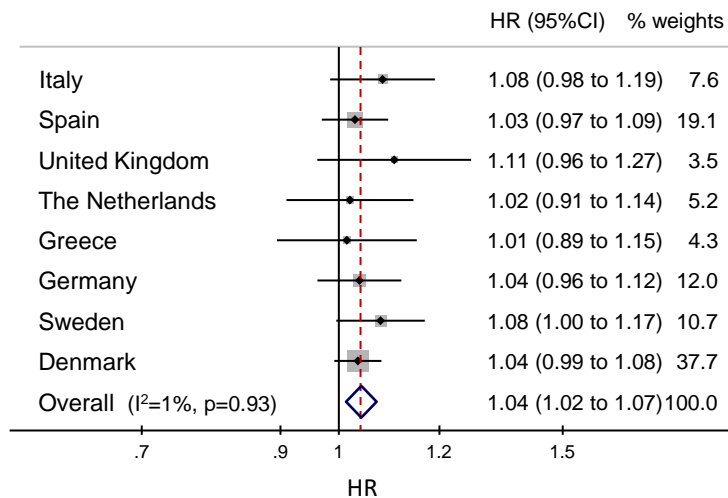
Fatal CHD linear



Fatal CHD quadratic



Non-fatal stroke



Fatal stroke

