SUPPLEMENTAL MATERIAL

Appendix S1. Supplementary methods for *de novo* cohort analyses

Study cohorts

Data were obtained from participants in the Health Survey for England (HSE) [65], the Scottish Health Survey (SHeSs) [66], and UK Biobank [67]. Complete cohort profiles are available via the above citations. Briefly, HSE/SHeSs is a series of surveys which use a multistage stratified design to draw a nationally representative sample of the general population living in England/Scottish households. Each survey year consists of a new sample of private residential addresses and participants and entails a household interview followed by a nurse visit to collect baseline information on demographics, anthropometry, self-reported health, and health-related behaviours. Participants have been asked for consent to follow-up through data linkage, thus converting cross-sectional survey data into a longitudinal study with samples from different survey years with a range of health outcomes. The present analyses combined data from the 1994–2008 HSE datasets and the 1995, 1998 and 2003 SHeSs datasets and were restricted to participants aged ≥16 years reporting to have been diagnosed with myocardial infarction (MI)/angina (not recorded separately) or stroke prior to baseline.

UK Biobank is a prospective study of more than 500000 participants, aged 40–69 years when recruited in 2006–2010. Participants were invited to attend one of 22 centres across England, Scotland, and Wales, where a touchscreen questionnaire was completed, a nurse-led interview was performed, and physical measurements were taken. We identified participants with MI, angina, or stroke before recruitment based on record linkage to the Hospital Episode Statistics (HES, 2 December 1980 onwards). Participants who had self-reported events at baseline assessment but without evidence from HES data were excluded from analyses. Algorithmic definitions developed by the UK Biobank Outcome Adjudication Group were applied for MI [68] and stroke [69]. We developed classification algorithms for angina using the process and data fields (diagnoses in the primary or any secondary position) recommended by the Group [70] with relevant codes from the International Classification of Diseases (ICD) Edition 9 and Edition 10 (Table S1) [71].

Alcohol assessment

At baseline of each cohort, participants were asked about their drinking status and were asked to report their average weekly or monthly consumption of different types of alcoholic beverages. These measures were then converted into standard UK units and summed to obtain an average alcohol consumption in units per week, where one unit contains 8g of ethanol [15] and is equivalent to half a pint of beer/lager/cider, half a glass of wine/champagne, one measure of spirits, or one glass of fortified wine [16]. Alcopops and other forms of alcohol count as 1.5 units [72]. We separated former drinkers from never drinkers and used never drinkers as the reference group to provide additional data for meta-analyses on different non-drinking reference group. Current drinkers were categorized into three groups in line with the UK guidelines: low-level drinkers (≤ 14 units per week), medium-level drinkers (>14 to ≤50 units per week for men, >14 to ≤35 units per week for women), and high-level drinkers (>50 units per week for men, >35 units per week for women) [17].

Outcomes

We assessed alcohol consumption in relation to three outcomes: all-cause mortality, cardiovascular mortality (ICD-10 codes I00–I99) [73] and major cardiovascular events (as defined below). Date and underlying cause of death (coded with ICD-10) were ascertained by national death registries and all cohorts contributed to the mortality analyses. We censored participants at their date of death, the date they left the UK or the end of follow-up (until 14 February 2011 in HSE, 31 December 2009 in SHeSs or 9 February 2018 in UK Biobank), whichever came first.

Cardiovascular events were a composite of angina, fatal and non-fatal MI and stroke, revascularization procedures (angioplasty or coronary artery bypass graft), death from heart failure, and sudden cardiac death, and only UK Biobank contributed data to this analysis. Non-fatal events were identified from linked HES records using primary diagnoses coded with ICD-10 and procedures coded with OPCS4 (the Office of Population Censuses and Surveys' Classification of Interventions and Procedures Version 4), as given in Table S1. Any hospital or death records that occurred within 28 days of the date for a detected event were considered to relate to the same event [74]. Participants were followed up until the date of their first detected event or were censored on the date they left the UK or the last date of data linkage (31 March 2017).

Covariates

Covariates considered in analyses were assessed at baseline and included age, sex, smoking status (never, ex-, or current smoker), self-reported history of diabetes and hypertension, socioeconomic position/education, body mass index, and regular medications (cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, and warfarin). In HSE/SHeSs, socioeconomic position was defined using the participant's occupational classification, categorised as low (semi-skilled or unskilled manual), intermediate (skilled non-manual or manual) or high (professional or managerial technical) [75]. For UK Biobank participants, highest educational qualification was used and categorised into four levels: None; O levels/GCSEs, CSEs or equivalent; A/AS levels, NVQ or HND or HNC or equivalent, or other professional qualification; College or university degree [76].

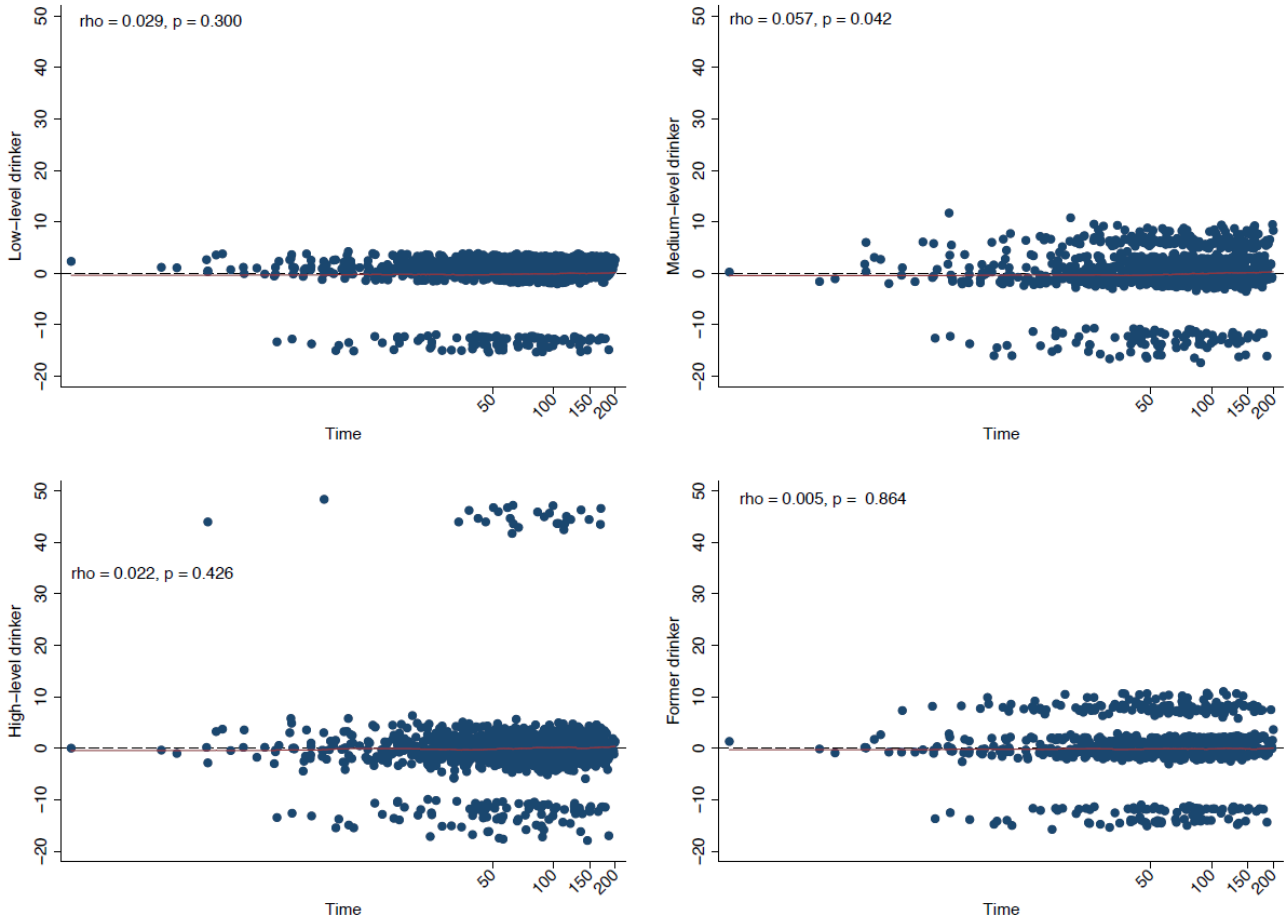
Table S1. ICD and OPCS codes used in analyses of UK Biobank and HSE/SHeSs

Angina [71]		
ICD-9	411, 4119, 413, 4139	
ICD-10	I20, I20.0, I20.1, I20.8, I20.9	
MI [68]		
ICD-10	MI, unclassified	I21, I22, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.1, I25.2
ICD-10	ST elevation MI	I21.0, I21.1, I21.2, I21.3, I22.0, I22.1, I22.8
ICD-10	Non-ST elevation MI	I21.4, I21.9, I22.9
Stroke [69]		
ICD-10	Ischaemic stroke	I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64.X
ICD-10	Intracerebral haemorrhage	I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9
ICD-10	Subarachnoid haemorrhage	I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9
Heart failure [77]		
ICD-10	I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.8, I42.9, I50.0, I50.1, I50.9	
Sudden death [78]		
ICD-10	I46.1, I49.9, R96, R96.0, R96.1	
Revascularization procedures [79]		
OPCS4	Coronary artery bypass graft	K40, K41, K42, K43, K44, K45, K46
OPCS4	Percutaneous transluminal coronary angioplasty	K49, K50, K75

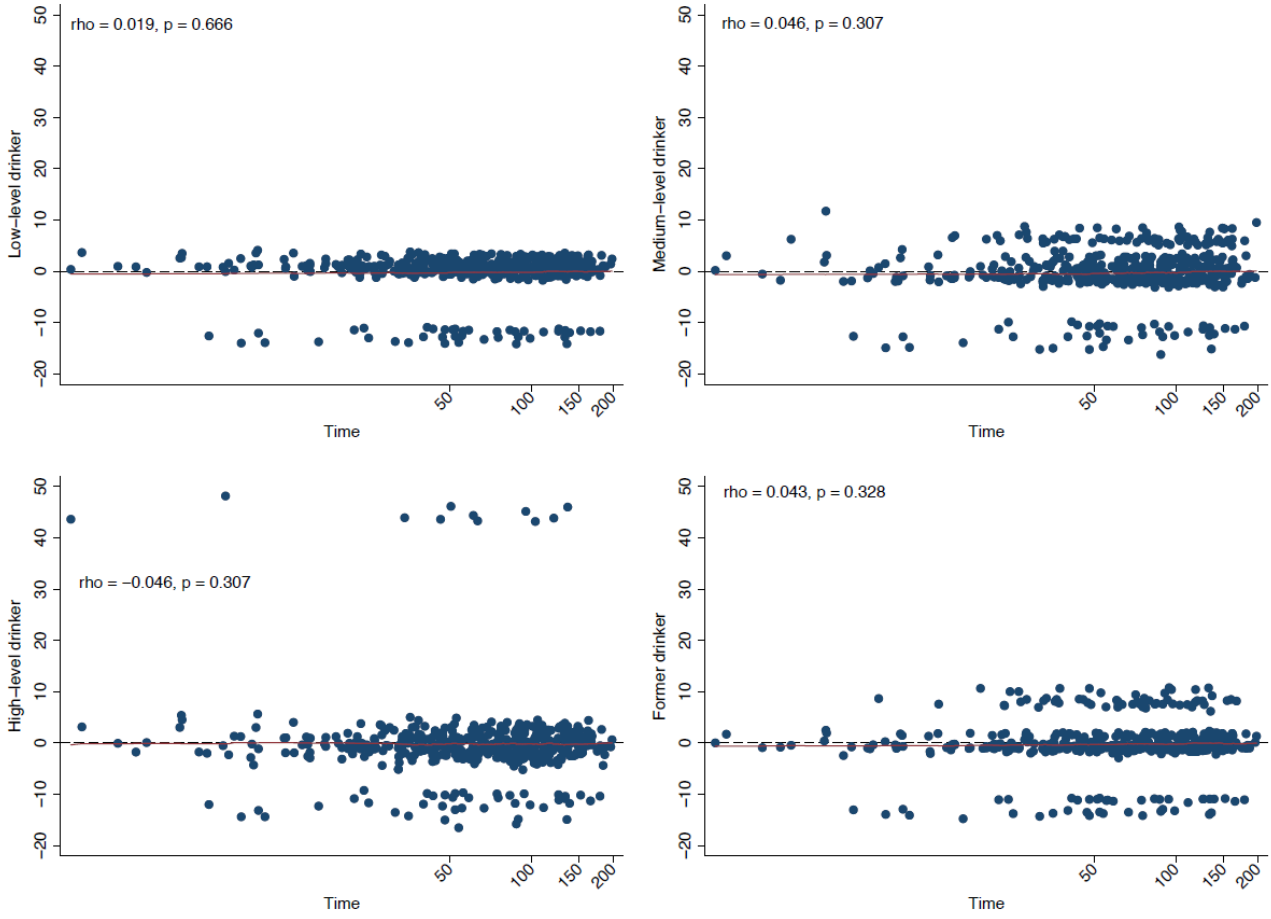
ICD=the International Classification of Diseases, MI=myocardial infarction, OPCS=OPCS Classification of Interventions and Procedures

Figure S1. Schoenfeld residuals

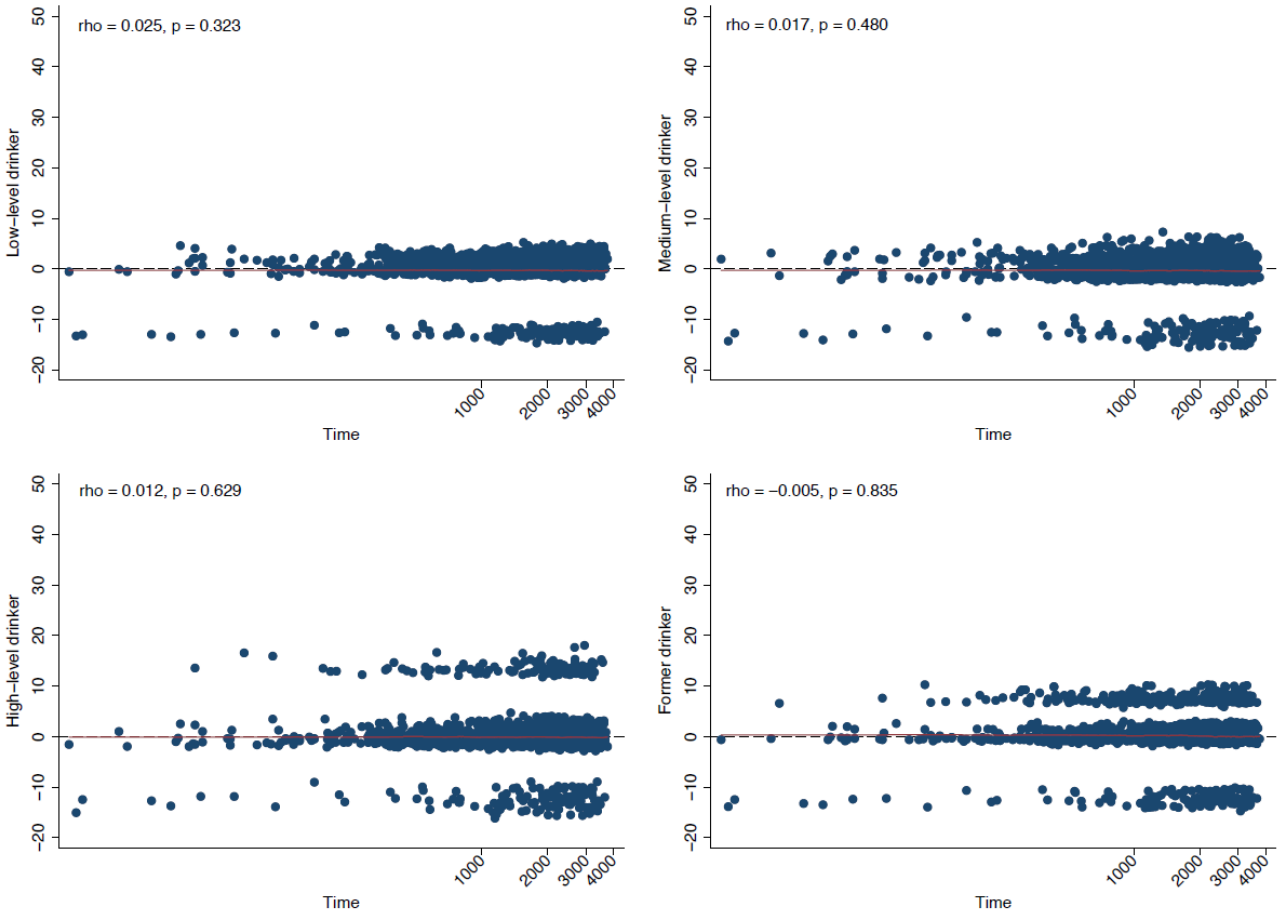
a. All-cause mortality for Health Survey for England/Scottish Health Survey models



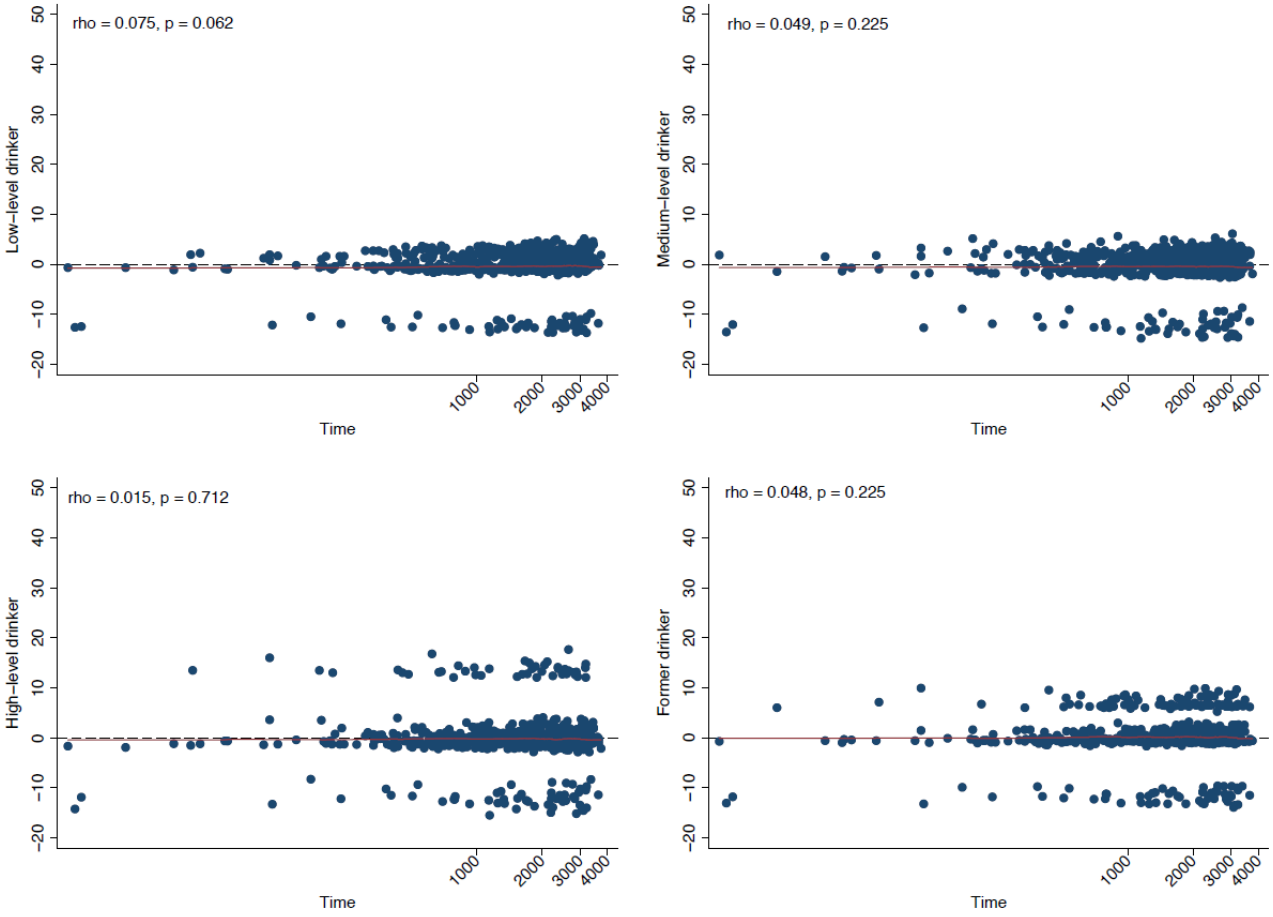
b. Cardiovascular mortality for Health Survey for England/Scottish Health Survey models



c. All-cause mortality for UK Biobank models



d. Cardiovascular mortality for UK Biobank models



e. Cardiovascular events for UK Biobank models

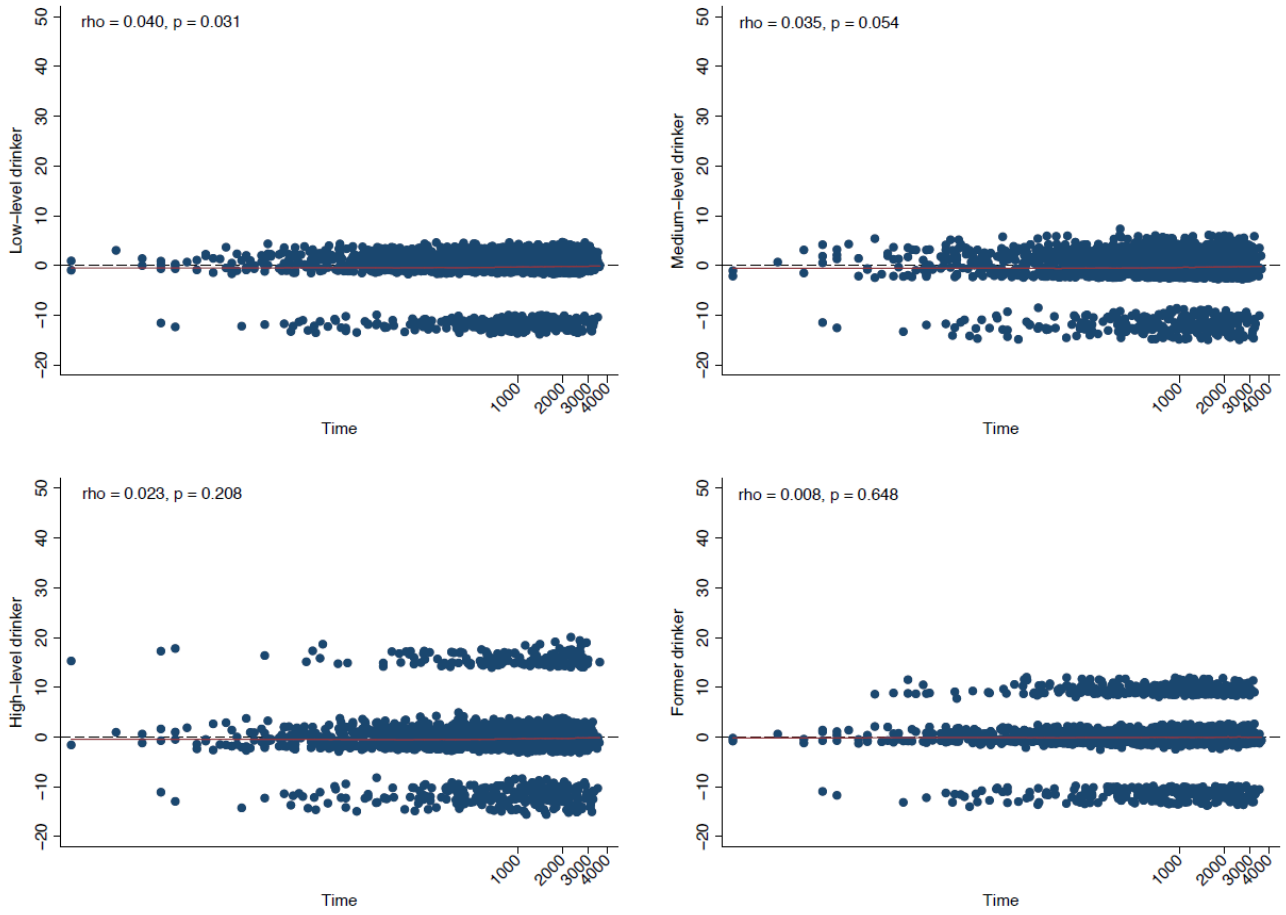


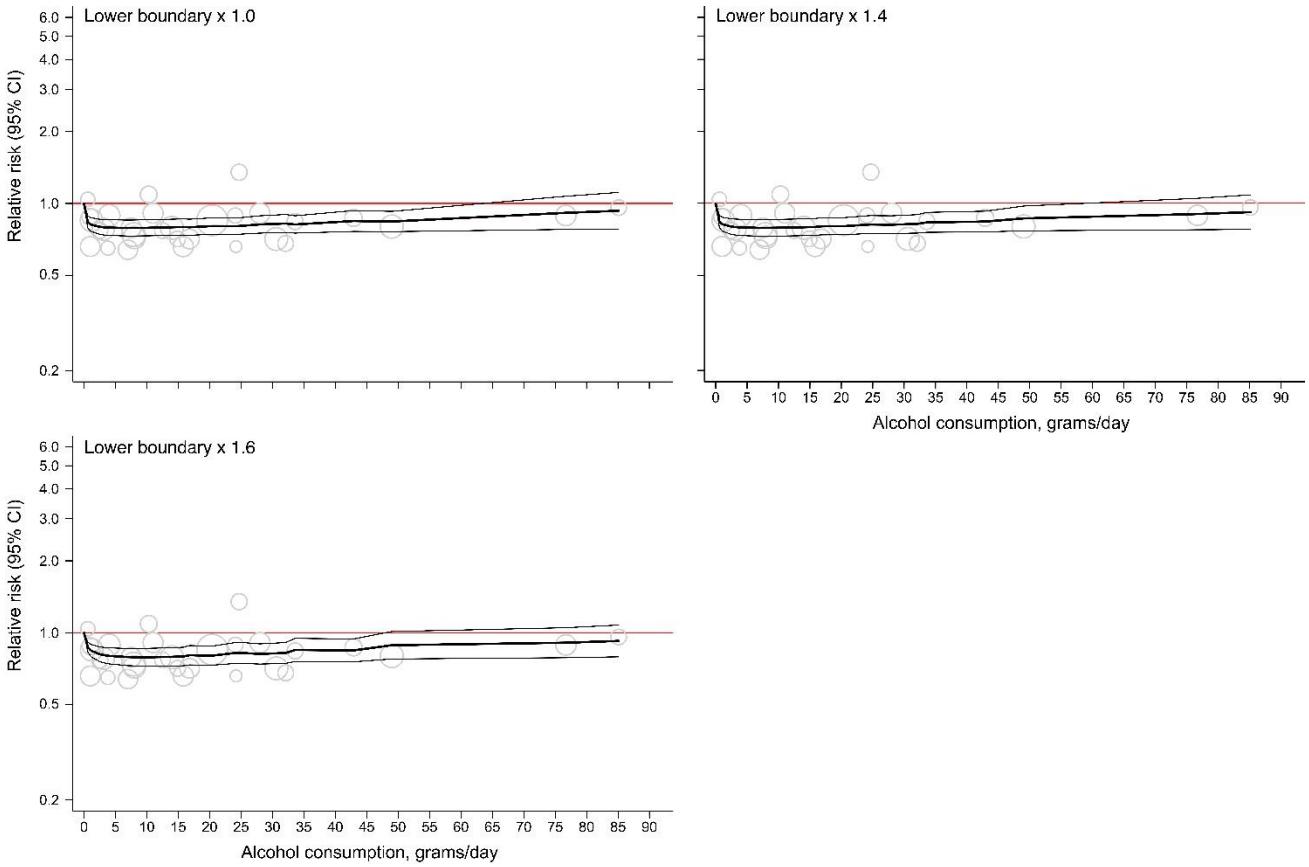
Table S2. Literature search strategy

#	Medline (Ovid)	Results
1	Alcohol Drinking/	66993
2	((alcohol or beer$1 or wine$1 or spirit or spirits or liquor$1 or liqueur$1) adj2 (intake$1 or consum$ or drink$)).ab,ti.	68862
3	exp myocardial infarction/ or exp coronary disease/	363351
4	((isch?emic heart disease$1 or IHD or myocardial isch?emia or myocardial infarct$ or MI or acute myocardial infarct$ or MI or coronary disease$1 or coronary artery disease$1 or CAD or coronary heart disease$1 or CHD or heart disease$1 or cardiovascular disease$1 or CVD or angina) adj2 (patients or people or women or men)).ab,ti.	78580
5	((myocardial infarct$ or MI or acute myocardial infarct$ or MI) adj2 (surviv$ or after or following)).ab,ti.	31387
6	exp STROKE/	134621
7	((stroke or strokes or acute cerebrovascular accident$1 or cerebrovascular accident$1 or CVA$1 or apoplexy or brain vascular accident$1) adj2 (patients or people or women or men or surviv$ or after or following)).ab,ti.	67330
8	exp cohort studies/ or exp follow-up studies/ or longitudinal studies/	2014690
9	(comment or editorial or letter or case reports or news or review or meta analysis).pt.	6532171
10	1 or 2	106345
11	3 or 4 or 5 or 6 or 7	551960
12	8 and 10 and 11	1128
13	limit 12 to humans	1128
14	13 not 9	1070
#	**Embase (Ovid)**	**Results**
1	exp drinking behavior/	47562
2	((alcohol or beer$1 or wine$1 or spirit or spirits or liquor$1 or liqueur$1) adj2 (intake$1 or consum$ or drink$)).ab,ti.	94229
3	exp heart infarction/ or exp coronary artery disease/	593221
4	((isch?emic heart disease$1 or IHD or myocardial isch?emia or myocardial infarct$ or MI or acute myocardial infarct$ or MI or coronary disease$1 or coronary artery disease$1 or CAD or coronary heart disease$1 or CHD or heart disease$1 or cardiovascular disease$1 or CVD or angina) adj2 (patients or people or women or men)).ab,ti.	115149
5	((myocardial infarct$ or MI or acute myocardial infarct$ or MI) adj2 (surviv$ or after or following)).ab,ti.	42351
6	exp cerebrovascular accident/	209214
7	((stroke or strokes or acute cerebrovascular accident$1 or cerebrovascular accident$1 or CVA$1 or apoplexy or brain vascular accident$1) adj2 (patients or people or women or men or surviv$ or after or following)).ab,ti.	111595
8	exp follow up/ or longitudinal study/	1663997
9	(Patent or Tombstone or Note or Editorial or Letter or Erratum or Books or Chapter or Review).pt.	5351012
10	1 or 2	122144
11	3 or 4 or 5 or 6 or 7	859770
12	8 and 10 and 11	1039
13	limit 12 to human	996
14	13 not 9	960

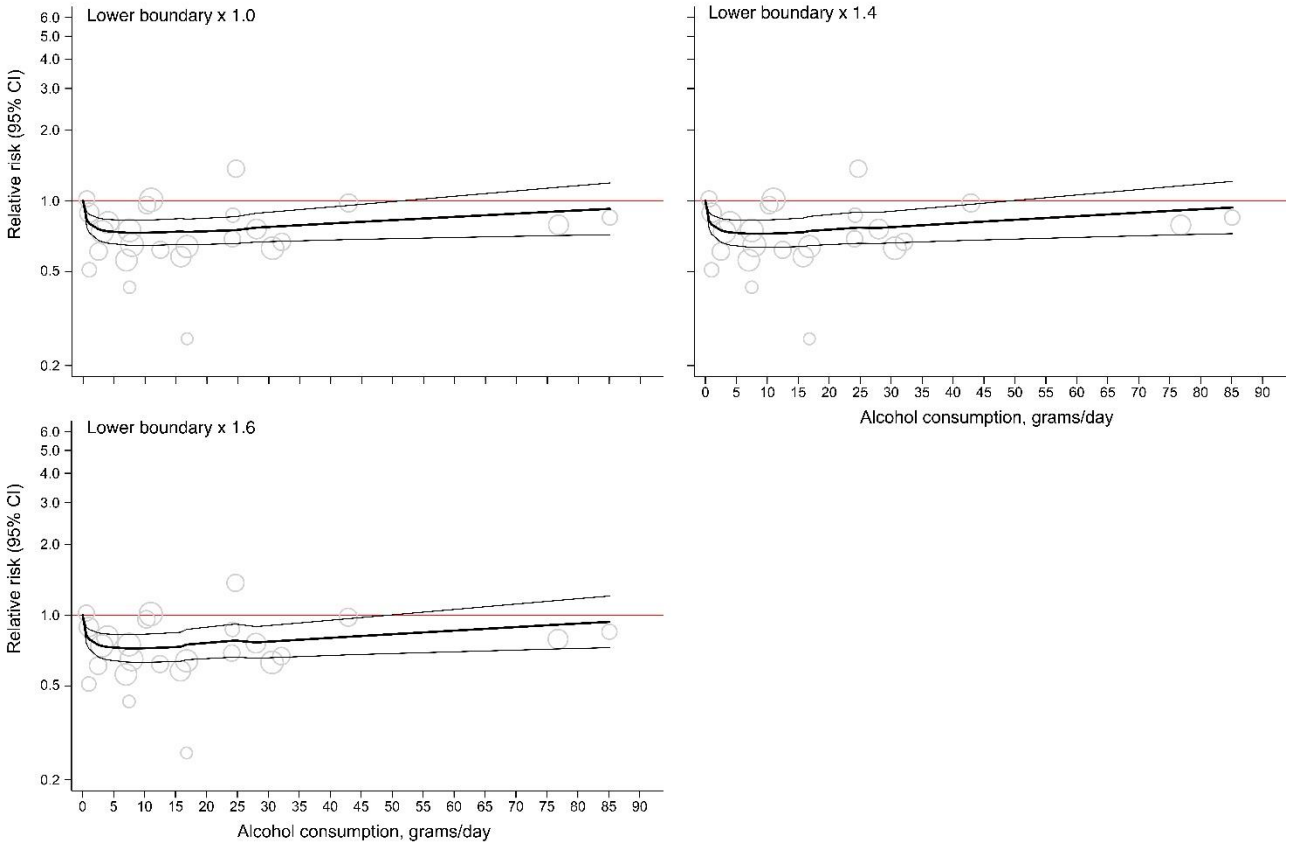
Figure S2. Dose-response relationship between alcohol consumption and risk of all-cause mortality, cardiovascular mortality, and cardiovascular events. For open-ended upper categories, mean values were defined as lower boundary×1, lower boundary×1.4, and lower boundary×1.6

Best-fitting second-degree fractional polynomial models (with 95% CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk.

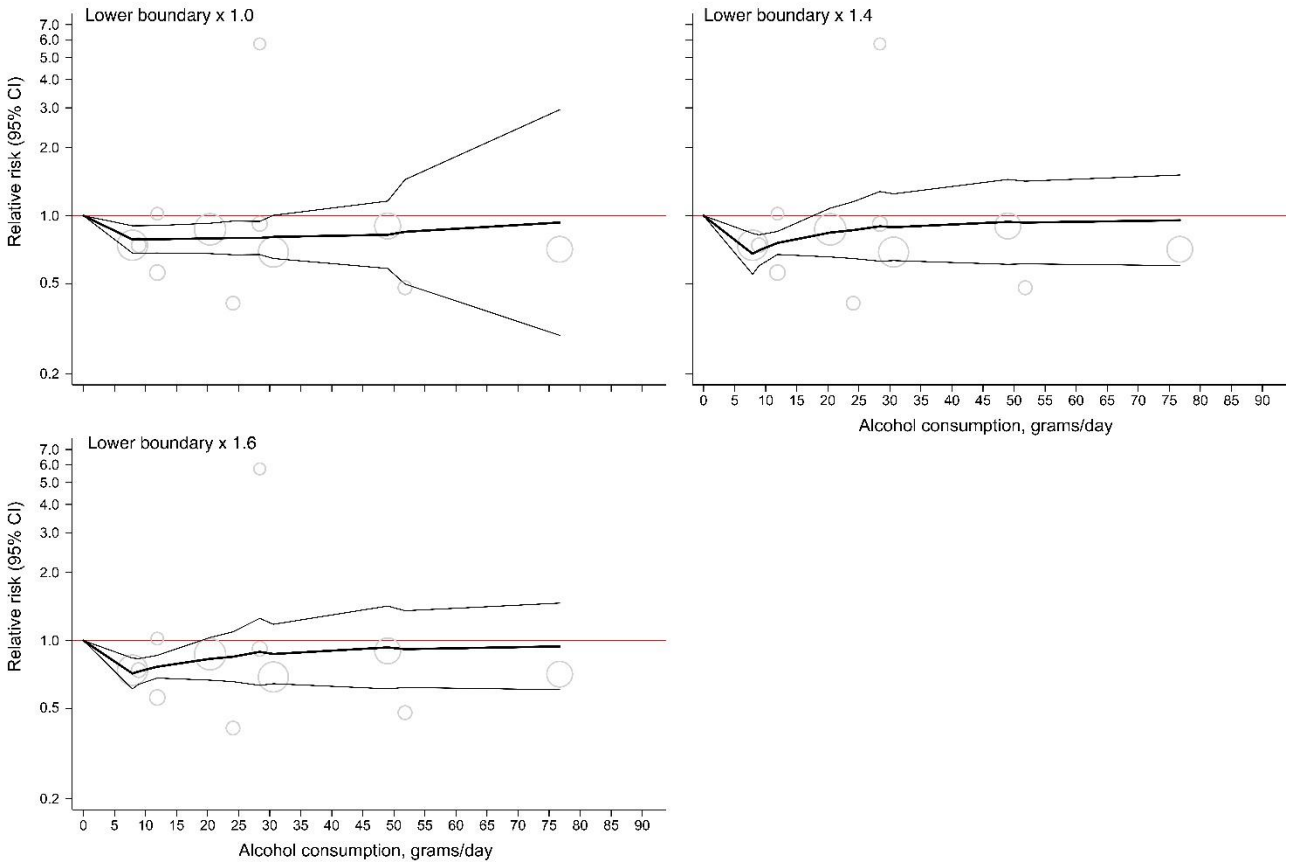
a. All-cause mortality



b. Cardiovascular mortality



c. Cardiovascular events



Appendix S2. Quality assessment checklist

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average *current drinkers* in the community *****
   b) somewhat representative of the average *current drinkers* in the community *****
   c) selected group of users (e.g. nurses, volunteers)
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort *****
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g. surgical records) *****
   b) structured interview *****
   c) written self-report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes *****
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for *smoking status* *****
   b) study controls for any additional factor *****

Outcome

1) Assessment of outcome
   a) independent blind assessment *****
   b) record linkage *****
   c) self-report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes, *at least six years duration* *****
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up: all subjects accounted for *****
   b) subjects lost to follow up unlikely to introduce bias:
      small number lost (> *95*% follow up) or description provided of those lost *****
   c) follow up rate < *95*% and no description of those lost
   d) no statement

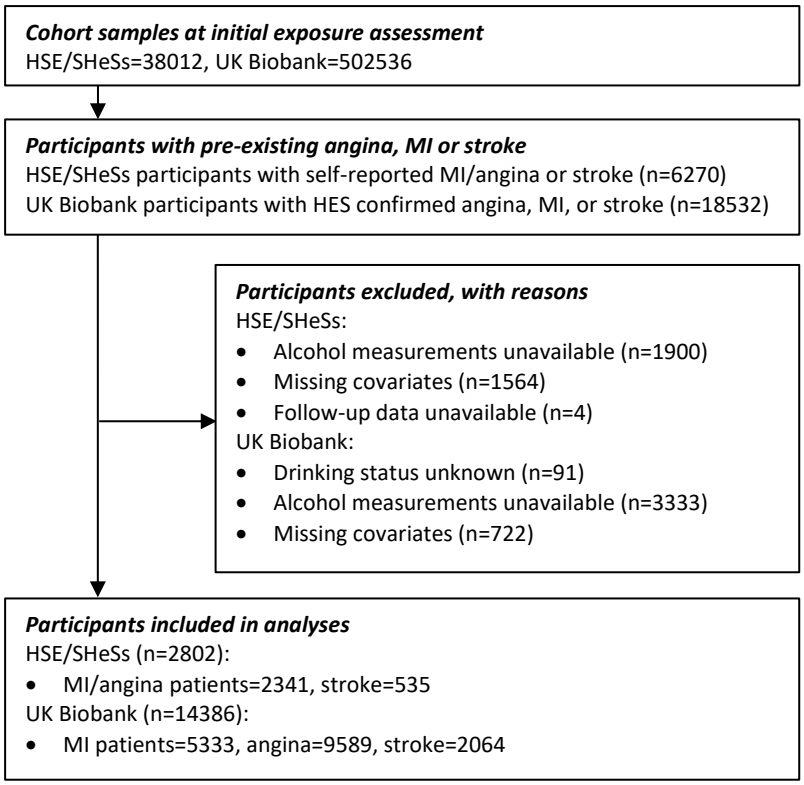


Figure S3. Patients inclusion flowchart for HSE/SHeSs and UK Biobank

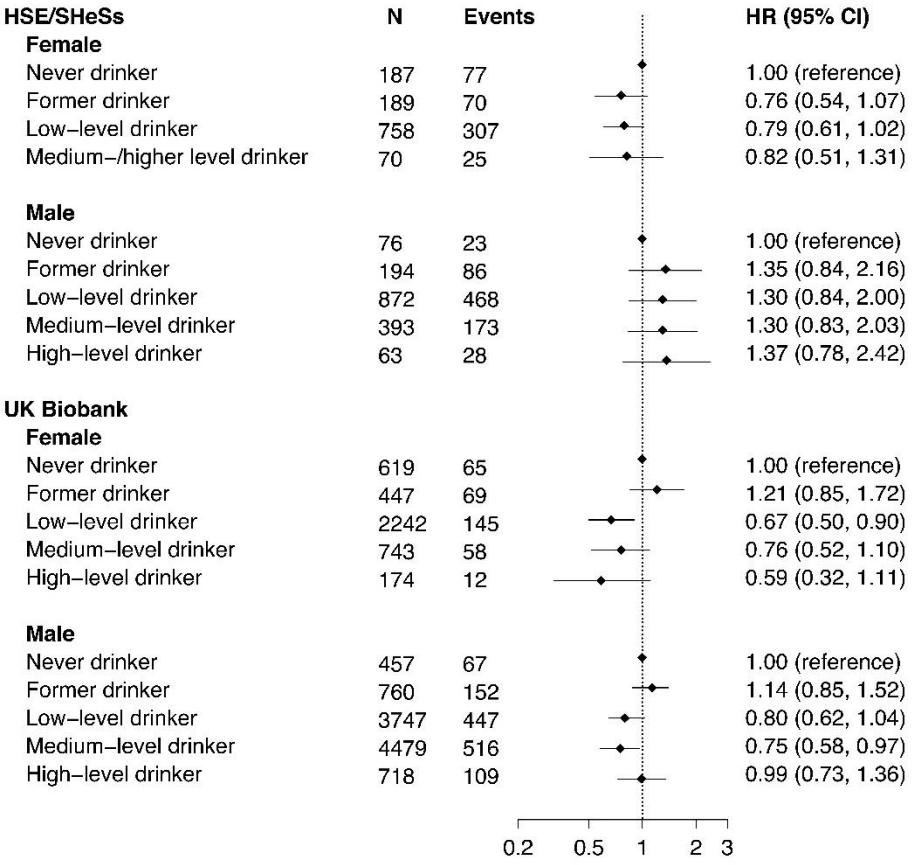
HES=hospital episode statistics, HSE=the Health Survey for England, MI= myocardial infarction, SHeSs=the Scottish Health Survey

Figure S4. Association of drinking categories with all-cause mortality, cardiovascular mortality, and cardiovascular events by cohort and sex

All models were adjusted for age, smoking status, diabetes, hypertension, socioeconomic position or education, body mass index, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, and warfarin.

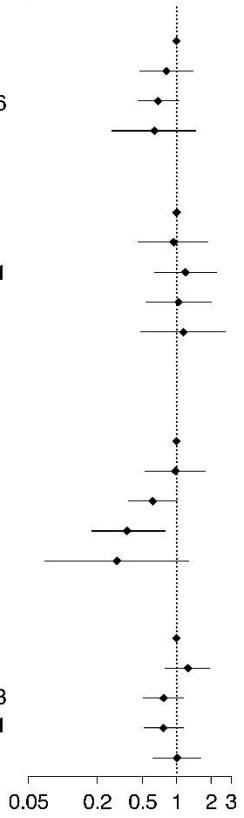
CI=confidence interval, HR=hazard ratio, HSE=the Health Survey for England, SHeSs= the Scottish Health Survey

a. All-cause mortality



b. Cardiovascular mortality

HSE/SHeSs	N	Events	HR (95% CI)
Female			
Never drinker	187	31	1.00 (reference)
Former drinker	189	30	0.82 (0.48, 1.39)
Low–level drinker	758	106	0.69 (0.46, 1.05)
Medium–/higher level drinker	70	7	0.64 (0.27, 1.48)
Male			
Never drinker	76	11	1.00 (reference)
Former drinker	194	29	0.94 (0.46, 1.90)
Low–level drinker	872	201	1.20 (0.64, 2.24)
Medium–level drinker	393	66	1.04 (0.54, 2.01)
High–level drinker	63	11	1.15 (0.49, 2.70)
UK Biobank			
Female			
Never drinker	619	26	1.00 (reference)
Former drinker	447	21	0.98 (0.53, 1.79)
Low–level drinker	2242	46	0.62 (0.38, 1.02)
Medium–level drinker	740	10	0.37 (0.18, 0.80)
High–level drinker	174	2	0.30 (0.07, 1.29)
Male			
Never drinker	457	28	1.00 (reference)
Former drinker	760	70	1.26 (0.80, 1.96)
Low–level drinker	3746	173	0.77 (0.51, 1.15)
Medium–level drinker	4478	211	0.77 (0.52, 1.15)
High–level drinker	717	44	1.01 (0.62, 1.62)



c. Cardiovascular events

UK Biobank	N	Events	HR (95% CI)
Female			
Never drinker	619	119	1.00 (reference)
Former drinker	447	87	0.98 (0.74, 1.30)
Low–level drinker	2242	323	0.78 (0.63, 0.97)
Medium–level drinker	740	117	0.84 (0.64, 1.10)
High–level drinker	174	20	0.61 (0.38, 0.99)
Male			
Never drinker	457	139	1.00 (reference)
Former drinker	760	217	0.92 (0.74, 1.14)
Low–level drinker	3747	832	0.71 (0.59, 0.85)
Medium–level drinker	4478	933	0.65 (0.54, 0.78)
High–level drinker	718	163	0.70 (0.56, 0.88)

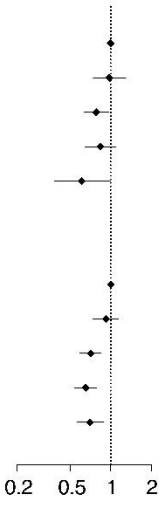
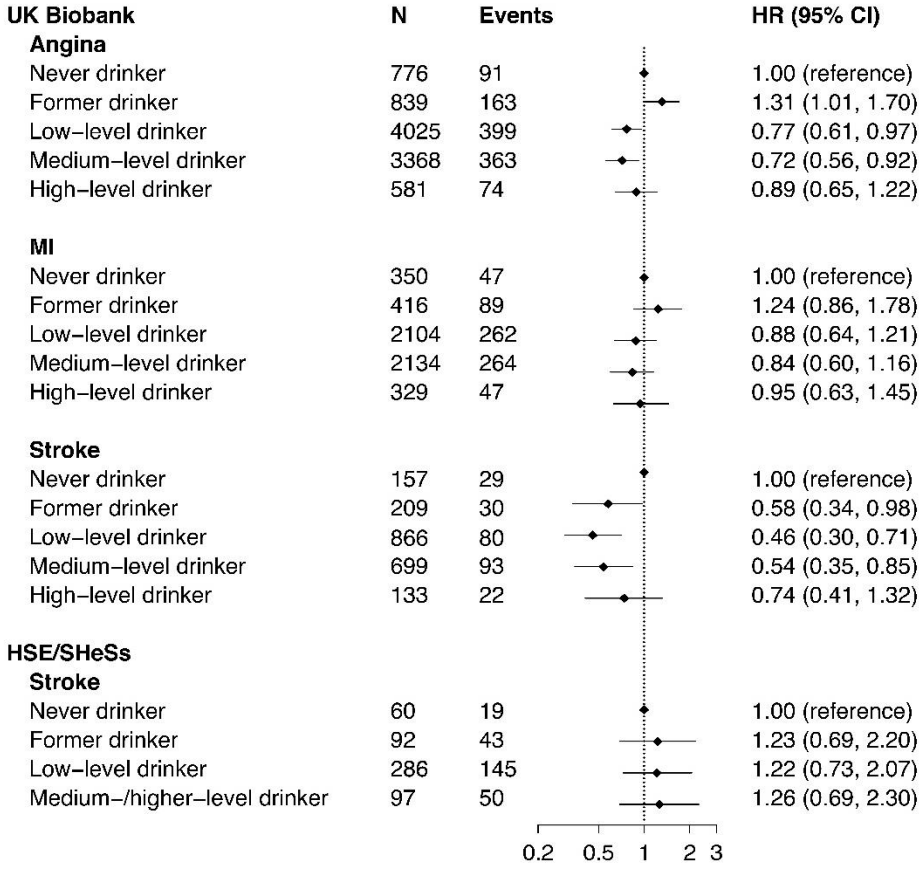


Figure S5. Association of drinking categories with all-cause mortality, cardiovascular mortality, and cardiovascular events by cohort and primary cardiovascular events

Models for MI, angina, and stroke as primary event were adjusted for each other as well as age, sex, smoking status, diabetes, hypertension, socioeconomic position or education, body mass index, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, and warfarin.

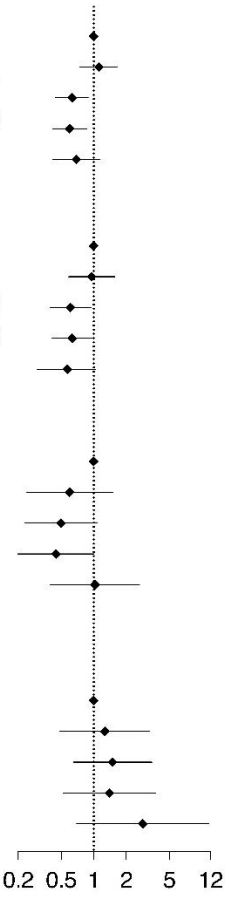
CI=confidence interval, HR=hazard ratio, HSE=the Health Survey for England, MI= myocardial infarction, SHeSs= the Scottish Health Survey

a. All-cause mortality



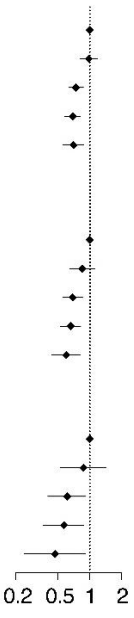
b. Cardiovascular mortality

UK Biobank	N	Events	HR (95% CI)
Angina			
Never drinker	776	42	1.00 (reference)
Former drinker	839	67	1.12 (0.75, 1.66)
Low−level drinker	4025	151	0.63 (0.44, 0.89)
Medium−level drinker	3365	145	0.60 (0.42, 0.87)
High−level drinker	580	27	0.69 (0.42, 1.14)
MI			
Never drinker	350	28	1.00 (reference)
Former drinker	416	42	0.96 (0.59, 1.57)
Low−level drinker	2104	108	0.61 (0.40, 0.94)
Medium−level drinker	2132	119	0.63 (0.41, 0.98)
High−level drinker	329	17	0.57 (0.30, 1.05)
Stroke			
Never drinker	157	9	1.00 (reference)
Former drinker	209	11	0.60 (0.24, 1.51)
Low−level drinker	865	29	0.50 (0.23, 1.08)
Medium−level drinker	699	26	0.45 (0.20, 1.01)
High−level drinker	133	10	1.03 (0.40, 2.65)
HSE/SHeSs			
Stroke			
Never drinker	60	7	1.00 (reference)
Former drinker	92	15	1.27 (0.49, 3.26)
Low−level drinker	286	56	1.49 (0.65, 3.45)
Medium−level drinker	87	15	1.40 (0.52, 3.75)
High−level drinker	10	4	2.84 (0.70, 11.51)



c. Cardiovascular events

UK Biobank	N	Events	HR (95% CI)
Angina			
Never drinker	776	200	1.00 (reference)
Former drinker	839	236	0.98 (0.81, 1.18)
Low−level drinker	4025	862	0.74 (0.63, 0.87)
Medium−level drinker	3365	757	0.69 (0.58, 0.81)
High−level drinker	581	132	0.70 (0.56, 0.88)
MI			
Never drinker	350	111	1.00 (reference)
Former drinker	416	119	0.85 (0.65, 1.11)
Low−level drinker	2104	483	0.69 (0.56, 0.86)
Medium−level drinker	2132	483	0.66 (0.53, 0.82)
High−level drinker	329	73	0.60 (0.44, 0.81)
Stroke			
Never drinker	157	30	1.00 (reference)
Former drinker	209	41	0.87 (0.53, 1.41)
Low−level drinker	866	107	0.61 (0.40, 0.92)
Medium−level drinker	699	90	0.57 (0.36, 0.88)
High−level drinker	133	13	0.47 (0.24, 0.91)



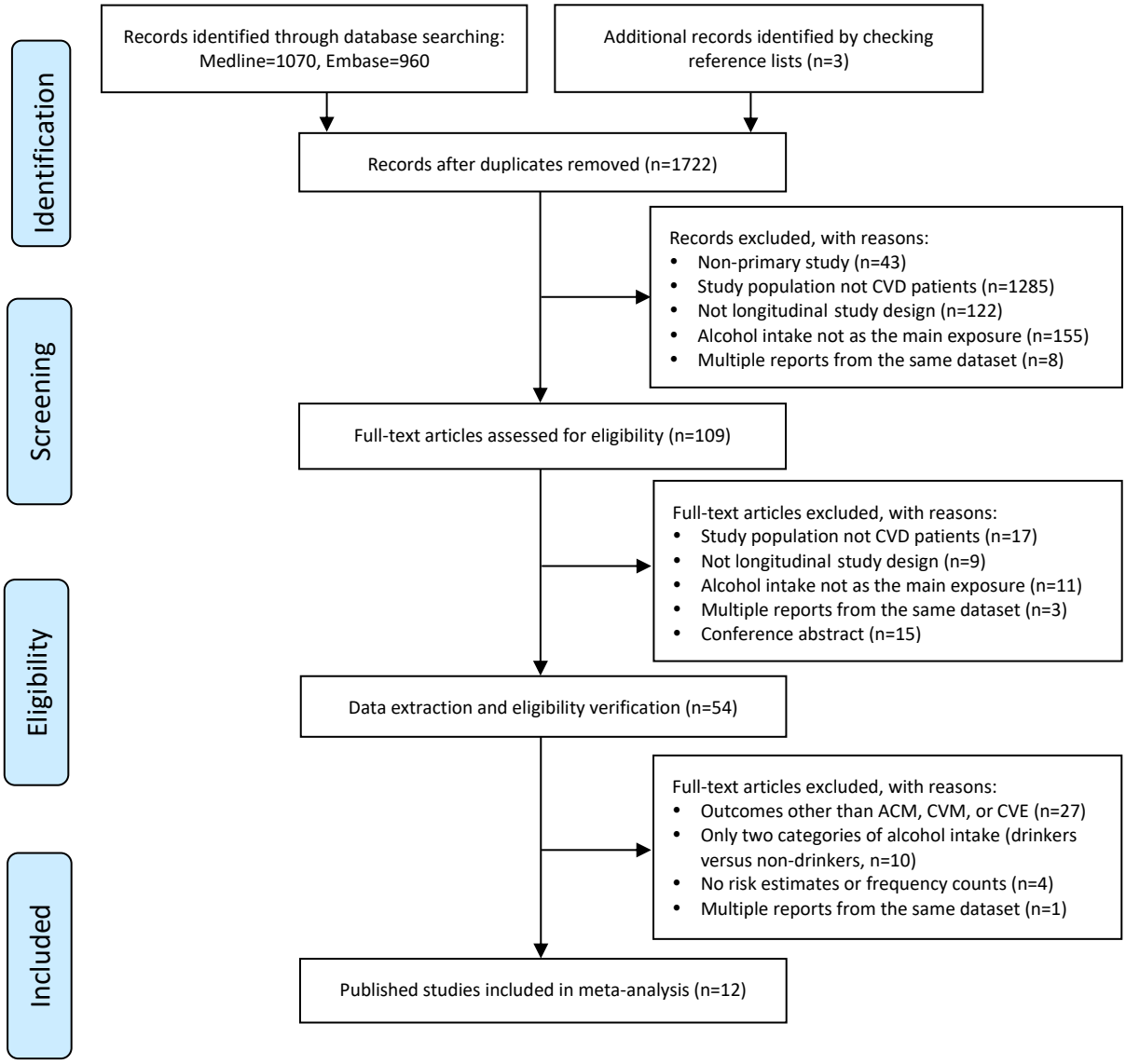


Figure S6. Study flow diagram

ACM=all-cause mortality, CVD=cardiovascular disease, CVE=cardiovascular events, CVM=cardiovascular mortality

Table S3. Alcohol consumption, effect estimates, and confounder adjustment reported by studies on all-cause mortality

First author, year	Alcohol consumption		Risk of all-cause mortality				
	Reported exposure categories	Estimated g/day *†	Total (N)	Cases (n)	Measure of association	Effect estimates	Confounder adjustment
Levantesi, 2013	Never/almost never	0.0	3713	645	HR	1.00 (reference)	Age, gender, BMI, smoking, prior MI, history of hypertension, DM, peripheral vascular disease, electrical instability, exercise, LVEF, NYHA class, revascularization procedures, intakes of cooked vegetables, raw vegetables, fruit, fish, olive oil, other oil, butter, cheese, and coffee, use of n−3 PUFA, vitamin-E, antiplatelet agents, angiotensin-converting-enzyme inhibitor, lipid-lowering medication , beta-blockers
	≤0.5 L/day	20.4	5821	874		0.85 (0.76–0.95)	
	>0.5 L/day	49.0	985	137		0.80 (0.66–0.98)	
Pai, 2012	0 g/day	0.0	515	168	HR	1.00 (reference)	Age at diagnosis, questionnaire follow-up cycle, smoking, BMI, physical activity, diabetes, hypertension, lipid-lowering medication, aspirin use, heart failure at MI
	0.1-9.9 g/day	3.1	719	161		0.78 (0.62–0.97)	
	10.0-29.9 g/day	15.8	420	97		0.66 (0.51–0.86)	
	≥30.0 g/day	42.9	164	42		0.87 (0.61–1.25)	
Rosenbloom, 2012	None	0.0	761	331	HR	1.00 (reference)	Age, BMI, previous MI, congestive HF, angina, DM, hypertension, non-cardiac co-morbidity, previous medication use, smoking, physical activity, income, education, marital status, race, peak creatine kinase level, receipt of thrombolytic therapy, congestive HF and ventricular tachycardia during hospitalization
	<1 serving/week	1.0	280	70		0.66 (0.50–0.86)	
	≥1 to <3 servings/week	3.8	75	15		0.65 (0.38–1.11)	
	≥3 servings/week	14.9	137	25		0.71 (0.46–1.09)	
Janszky, 2008	Longer-term abstainers	0.0	140	35	HR	1.00 (reference)	Age, sex, smoking, obesity, self-reported physical activity, history of DM, education
	>0 to <5 g/day	2.5	437	84		0.77 (0.51–1.15)	
	5–20 g/day	12.5	447	80		0.77 (0.50–1.18)	
	over 20 g/day	24.1	308	60		0.89 (0.56–1.40)	
Aguilar, 2004	0 drink/week	0.0	1437	274	HR	1.00 (reference)	Age, gender, LVEF, prior MI, history of hypertension, history of DM, BMI, tobacco use, New York Heart Association classification, Killip class, beta-blocker use at the time of randomization, thrombolytic therapy with the qualifying MI, treatment (captopril) assignment
	1 to 10 drinks/week	11	532	74		0.91 (0.70–1.19)	
	>10 drinks/week	24.2	67	7		0.66 (0.31–1.41)	
Jackson, 2003	Rarely/never	0.0	361	128	RR	1.00 (reference)	Age, smoking, diabetes mellitus, body mass index, exercise, angina, MI
	<1 drink/week	1.0	133	39		0.88 (0.60-1.28)	
	1–6 drinks/week	7.0	417	93		0.64 (0.48-0.85)	
	≥1 drink/day	16.8	409	109		0.71 (0.54-0.94)	

(continued)

First author, year	Alcohol consumption		Risk of all-cause mortality				
	Reported exposure categories	Estimated g/day *†	Total (N)	Cases (n)	Measure of association	Effect estimates	Confounder adjustment
Mukamal, 2001	Abstainers	0.0	896	196	HR	1.00 (reference)	Age, sex, use of thrombolytic therapy, peak creatine kinase level, congestive heart failure during index hospitalization, ventricular tachycardia during index hospitalization, and propensity score
	<7 drinks/week	7.5	696	91		0.79 (0.60-1.03)	
	≥7 drinks/week	32.1	321	30		0.68 (0.45-1.05)	
Shaper, 2000	Teetotallers	0.0	43	18	RR ‡	0.96 (0.57–1.62)	Age, smoking, social class, BMI, pre-existing diabetes, stroke, and regular medication
	< 1 unit/week	0.6	199	85		1.00 (reference)	
	1–15 units/week	10.3	230	94		1.05 (0.78–1.42)	
	> 16 units/week	24.7	124	61		1.30 (0.93–1.83)	
Muntwyler, 1998	Rarely/never	0.0	1125	240	RR	1.00 (reference)	Age, smoking, diabetes, physical activity, BMI
	1–4 drinks/month	1.2	1227	211		0.85 (0.69–1.05)	
	2–6 drinks/week	8.0	1390	187		0.72 (0.58–0.89)	
	1 drinks/day	14.0	1424	249		0.79 (0.64–0.96)	
	≥2 drinks/day	33.6	192	33		0.84 (0.55–1.26)	
HSE/SHeSs §	Never drinker	0.0	263	100	HR	1.00 (reference)	Age, sex, smoking, socioeconomic position, history of DM, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin
	Low-level drinker	4.0	1630	775		0.89 (0.71–1.11)	
	Medium-level drinker	28.0	458	198		0.91 (0.70–1.18)	
	High-level drinker	85.1	68	28		0.96 (0.62–1.49)	
UK Biobank §	Never drinker	0.0	1076	132	HR	1.00 (reference)	Age, sex, smoking, education, history of DM, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, warfarin
	Low-level drinker	7.9	5989	592		0.74 (0.61–0.89)	
	Medium-level drinker	30.6	5222	574		0.71 (0.58–0.87)	
	High-level drinker	76.7	892	121		0.89 (0.69–1.15)	

* The upper limit of the highest exposure category defined as the lower bound multiplied by 1.2, unless explicitly defined within each publication
† Average intake in each consumption category. Where unreported, the median of the upper and lower bounds was used
‡ Effect estimates re-calculated according to a reference group other than that originally reported. This was undertaken using the Hamling method, as described in text
§ Measures of usual weekly consumption are presented in line with the current UK guidelines, categorized as never drinker, low-level drinker (≤ 14 units/week), medium-level drinker (>14 to ≤50 units/week for men, >14 to ≤35 units/week for women), or high-level drinker (>50 units/week for men, >35 units/week for women)

Table S4. Alcohol consumption, effect estimates, and confounder adjustment reported by studies on cardiovascular mortality

First author, year	Alcohol consumption		Risk of cardiovascular mortality				
	Reported exposure categories	Estimated g/day *†	Total (N)	Cases (n)	Measure of association	Effect estimates	Confounder adjustment
Pai, 2012	0 g/day	0.0	515	92	HR	1.00 (reference)	Age at diagnosis, questionnaire follow-up cycle, smoking, BMI, physical activity, diabetes, hypertension, lipid-lowering medication, aspirin use, heart failure at MI
	0.1-9.9 g/day	3.1	719	81		0.74 (0.54–1.02)	
	10.0-29.9 g/day	15.8	420	47		0.58 (0.39–0.84)	
	≥30.0 g/day	42.9	164	23		0.98 (0.60–1.60)	
Janszky, 2008	Longer-term abstainers	0	140	23	HR	1.00 (reference)	Age, sex, smoking, obesity, self-reported physical activity, history of DM, education
	>0 to <5 g	2.5	437	44		0.61 (0.36–1.02)	
	5–20 g	12.5	447	42		0.62 (0.36–1.07)	
	over 20 g	24.1	308	31		0.69 (0.38–1.25)	
Aguilar, 2004	0 drink/week	0	1437	215	HR	1.00 (reference)	Age, gender, LVEF, prior MI, history of hypertension, history of DM, BMI, tobacco use, New York Heart Association classification, Killip class, beta-blocker use at the time of randomization, thrombolytic therapy with the qualifying MI, treatment (captopril) assignment
	1 to 10 drinks/week	11	532	62		1.00 (0.75–1.34)	
	>10 drinks/week	24.2	67	7		0.87 (0.40–1.87)	
Jackson, 2003	Rarely/never	0.0	361	101	RR	1.00 (reference)	Age, smoking, diabetes mellitus, body mass index, exercise, angina, MI
	<1 drink/week	1.0	133	29		0.89 (0.58-1.36)	
	1–6 drinks/week	7.0	417	62		0.56 (0.40-0.79)	
	≥1 drink/day	16.8	409	75		0.64 (0.46-0.88)	
Mukamal, 2001	Abstainers	0	896	153	HR	1.00 (reference)	Age, sex, use of thrombolytic therapy, peak creatine kinase level, congestive heart failure during index hospitalization, ventricular tachycardia during index hospitalization, and propensity score
	<7 drinks/week	7.5	696	64		0.75 (0.55-1.02)	
	≥7 drinks/week	32.1	321	21		0.67 (0.41-1.17)	
Shaper, 2000	Teetotallers	0	43	13	RR ‡	0.98 (0.53–1.82)	Age, smoking, social class, BMI, pre-existing diabetes, stroke, and regular medication
	< 1 unit/week	0.6	199	62		1.00 (reference)	
	1–15 units/week	10.3	230	62		0.94 (0.65–1.35)	
	> 16 units/week	24.7	124	47		1.34 (0.91–1.98)	
Valmadrid, 1999	Never drinkers	0	31	12	RR	1.00 (reference)	Age, sex, cigarette smoking, insulin use, glycosylated hemoglobin level, plasma C-peptide level, digoxin use, the presence and severity of diabetic retinopathy
	<2 g/day	1	87	27		0.51 (0.24-1.12)	
	2-13 g/day	7.5	20	8		0.43 (0.15-1.22)	
	≥14 g/day	16.8	25	5		0.26 (0.08-0.81)	
HSE/SHeSs §	Never drinker	0.0	263	42	HR	1.00 (reference)	Age, sex, smoking, socioeconomic position, history of DM, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin
	Low-level drinker	4.0	1630	307		0.81 (0.58–1.14)	
	Medium-level drinker	28.0	458	73		0.76 (0.50–1.14)	
	High-level drinker	85.1	68	11		0.85 (0.43–1.70)	

(continued)

First author, year	Alcohol consumption		Risk of cardiovascular mortality				
	Reported exposure categories	**Estimated g/day *†**	**Total (N)**	**Cases (n)**	**Measure of association**	**Effect estimates**	**Confounder adjustment**
UK Biobank §	Never drinker	0.0	1076	54	HR	1.00 (reference)	Age, sex, smoking, education, history of DM, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, warfarin
	Low-level drinker	7.9	5988	219		0.65 (0.48–0.88)	
	Medium-level drinker	30.6	5218	221		0.63 (0.46–0.86)	
	High-level drinker	76.8	891	46		0.79 (0.53–1.19)	

* The upper limit of the highest exposure category defined as the lower bound multiplied by 1.2, unless explicitly defined within each publication
† Average intake in each consumption category. Where unreported, the median of the upper and lower bounds was used
‡ Effect estimates re-calculated according to a reference group other than that originally reported. This was undertaken using the Hamling method, as described in text
§ Measures of usual weekly consumption are presented in line with the current UK guidelines, categorized as never drinker, low-level drinker (≤ 14 units/week), medium-level drinker (>14 to ≤50 units/week for men, >14 to ≤35 units/week for women), or high-level drinker (>50 units/week for men, >35 units/week for women)

Table S5. Alcohol consumption, effect estimates, and confounder adjustment reported by studies on cardiovascular events

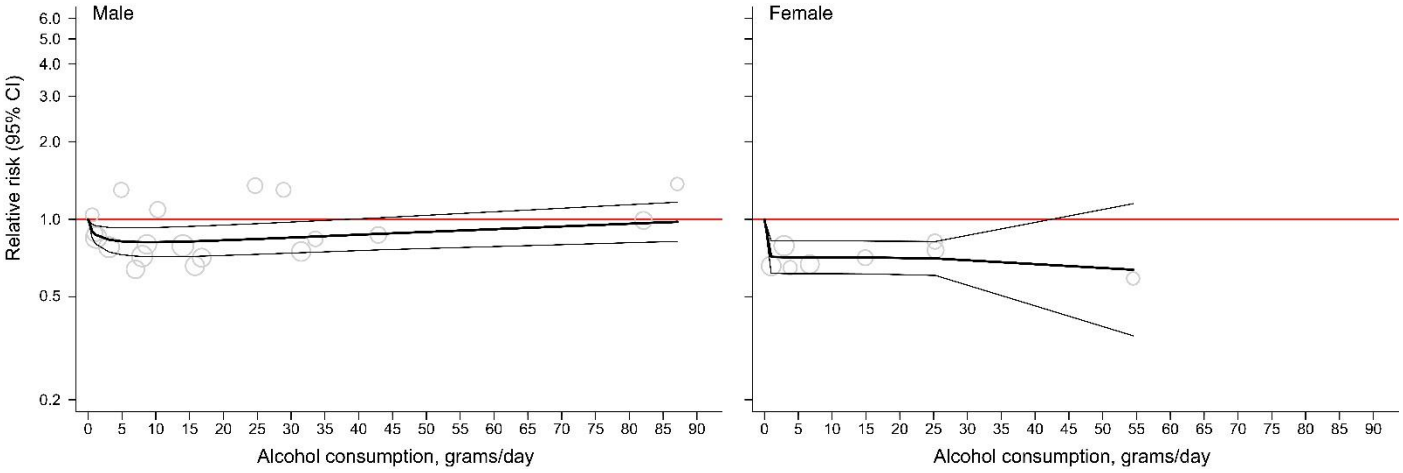
First author, year		Alcohol consumption		Risk of cardiovascular events				
		Reported exposure categories	Estimated g/day *†	Total (N)	Cases (n)	Measure of association	Effect estimates	Confounder adjustment
Levantesi, 2013		Never/almost never	0.0	4108	458		1.00 (reference)	Age, gender, BMI, smoking, prior MI, history of hypertension, DM, peripheral vascular disease, electrical instability, exercise, LVEF, NYHA class, revascularization procedures, intakes of cooked vegetables, raw vegetables, fruit, fish, olive oil, other oil, butter, cheese, and coffee, use of n−3 PUFA, vitamin-E, antiplatelet agents, angiotensin-converting-enzyme inhibitor, lipid-lowering medication , beta-blockers
		≤0.5 L/day	20.4	5446	551	HR	0.87 (0.76–0.99)	
		>0.5 L/day	49.0	1694	159		0.90 (0.74–1.09)	
Masunaga, 2006	Age < 65 years	Abstainers	0.0	1385	54		1.00 (reference)	CABG, atrial fibrillation, PCI, cholesterol-lowering agents, obesity, antiplatelet agents, β-blockers, warfarin, Forrester class, nitrates, coronary thrombolysis, calcium antagonists, DM, smoking, PVC, Gout, Killip class, ACE inhibitors, vasospastic angina, hyperlipidemia, multi-vessel disease, hypertension, positive exercise ECG, antiarrhythmic agents, angina pectoris
		<30 ml/day	11.9	1053	20	HR	0.56 (0.32–0.97)	
		≥30 ml/day	28.4	563	18		0.92 (0.51–1.66)	
	Age ≥65 years	Abstainers	0.0	533	24		1.00 (reference)	Same as above
		<30 ml/day	11.9	250	14	HR	1.02 (0.44–2.35)	
		≥30 ml/day	28.4	61	12		5.75 (2.21–14.90)	
de Lorgeril, 2002		Non-drinkers	0.0	96	36		1.00 (reference)	Diet group, age, current smoking, serum total cholesterol, and systolic blood pressure
		<5.41% of total energy intake/day	8.9	83	34	RR	0.74 (0.40–1.38)	
		>5.41 but <9.84%	24.1	89	18		0.41 (0.20–0.83)	
		>9.84%	51.8	85	16		0.48 (0.24–0.96)	
UK Biobank ‡		Never drinker	0.0	1076	258		1.00 (reference)	Age, sex, smoking, education, history of DM, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, warfarin
		Low-level drinker	7.9	5989	1155	HR	0.74 (0.64–0.85)	
		Medium-level drinker	30.6	5218	1050		0.69 (0.60–0.80)	
		High-level drinker	76.7	892	183		0.71 (0.58–0.86)	

* The upper limit of the highest exposure category defined as the lower bound multiplied by 1.2, unless explicitly defined within each publication
† Average intake in each consumption category. Where unreported, the median of the upper and lower bounds was used
‡ Measures of usual weekly consumption are presented in line with the current UK guidelines, categorized as never drinker, low-level drinker (≤ 14 units/week), medium-level drinker (>14 to ≤50 units/week for men, >14 to ≤35 units/week for women), or high-level drinker (>50 units/week for men, >35 units/week for women)

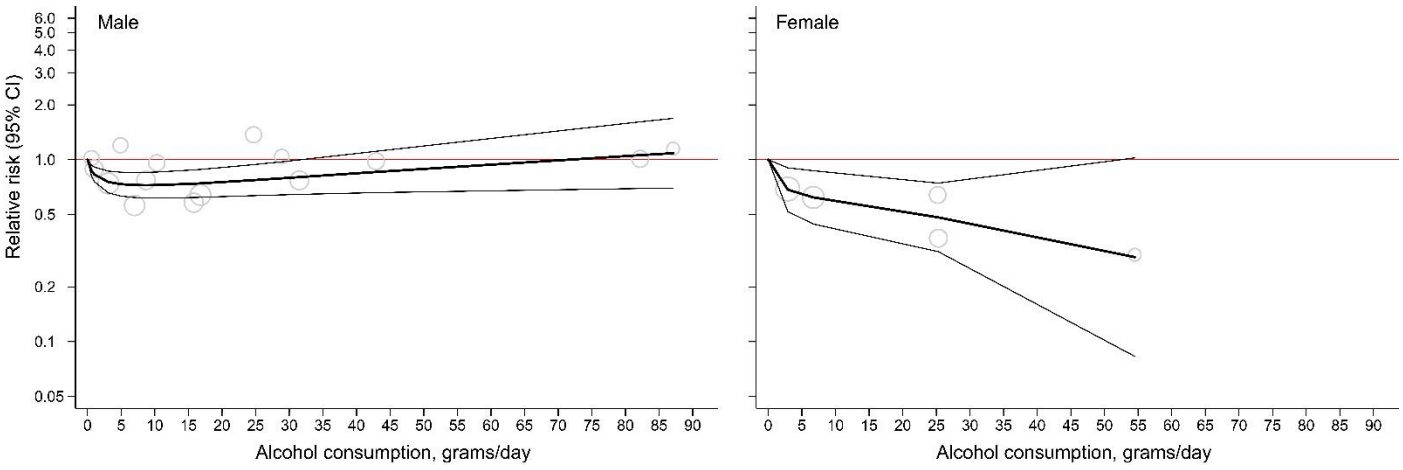
Figure S7. Dose-response relationship between alcohol consumption and risk of all-cause mortality, cardiovascular mortality, and cardiovascular events, stratified by sex

Best-fitting second-degree fractional polynomial models (with 95% CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk.

a. All-cause mortality



b. Cardiovascular mortality



c. Cardiovascular events

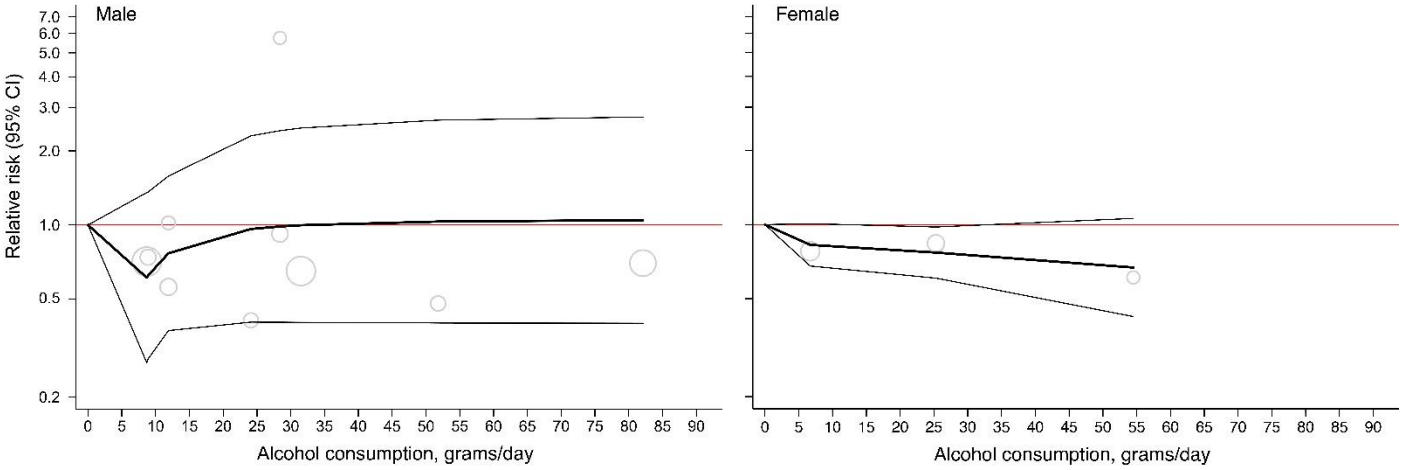
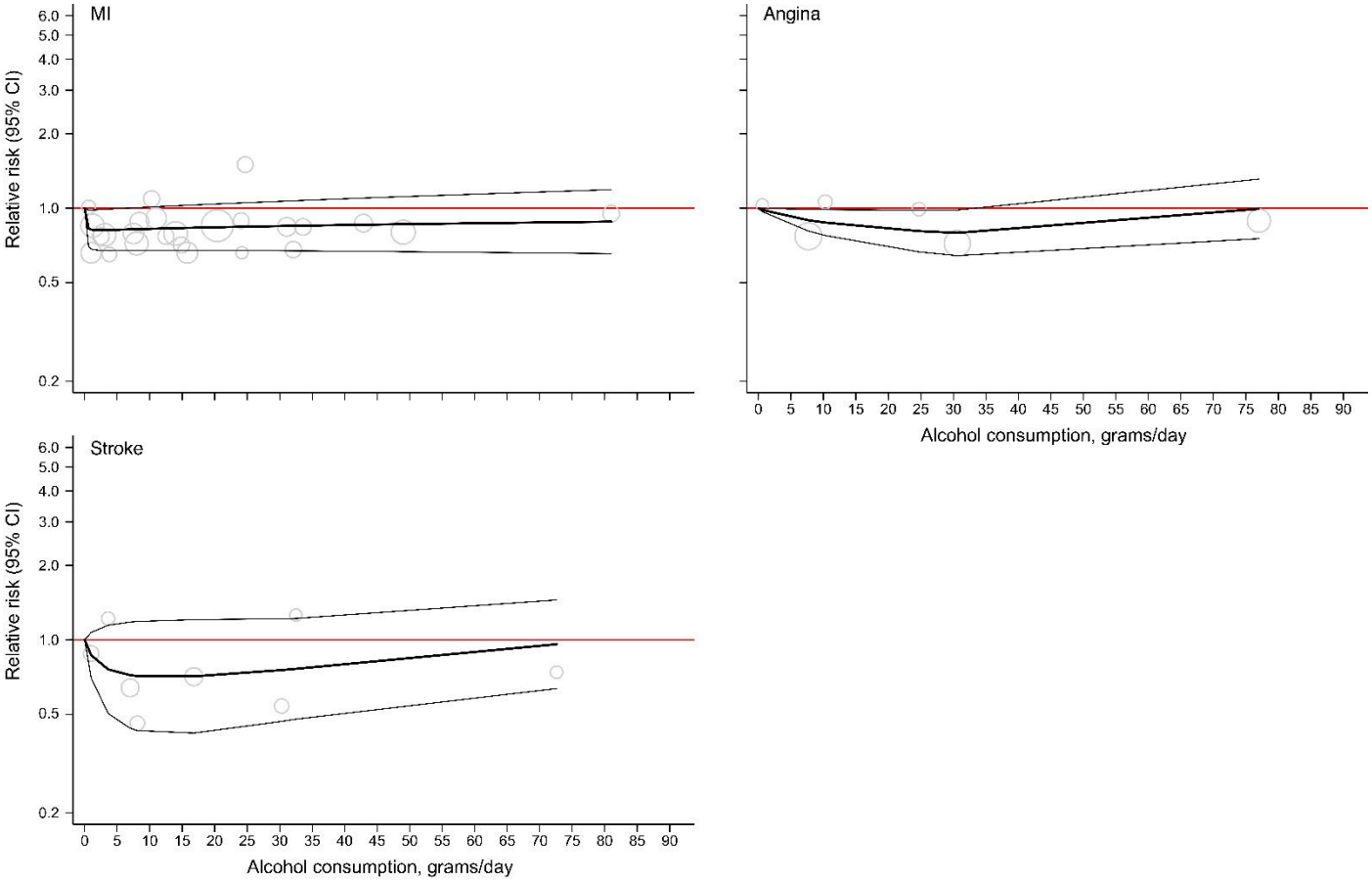


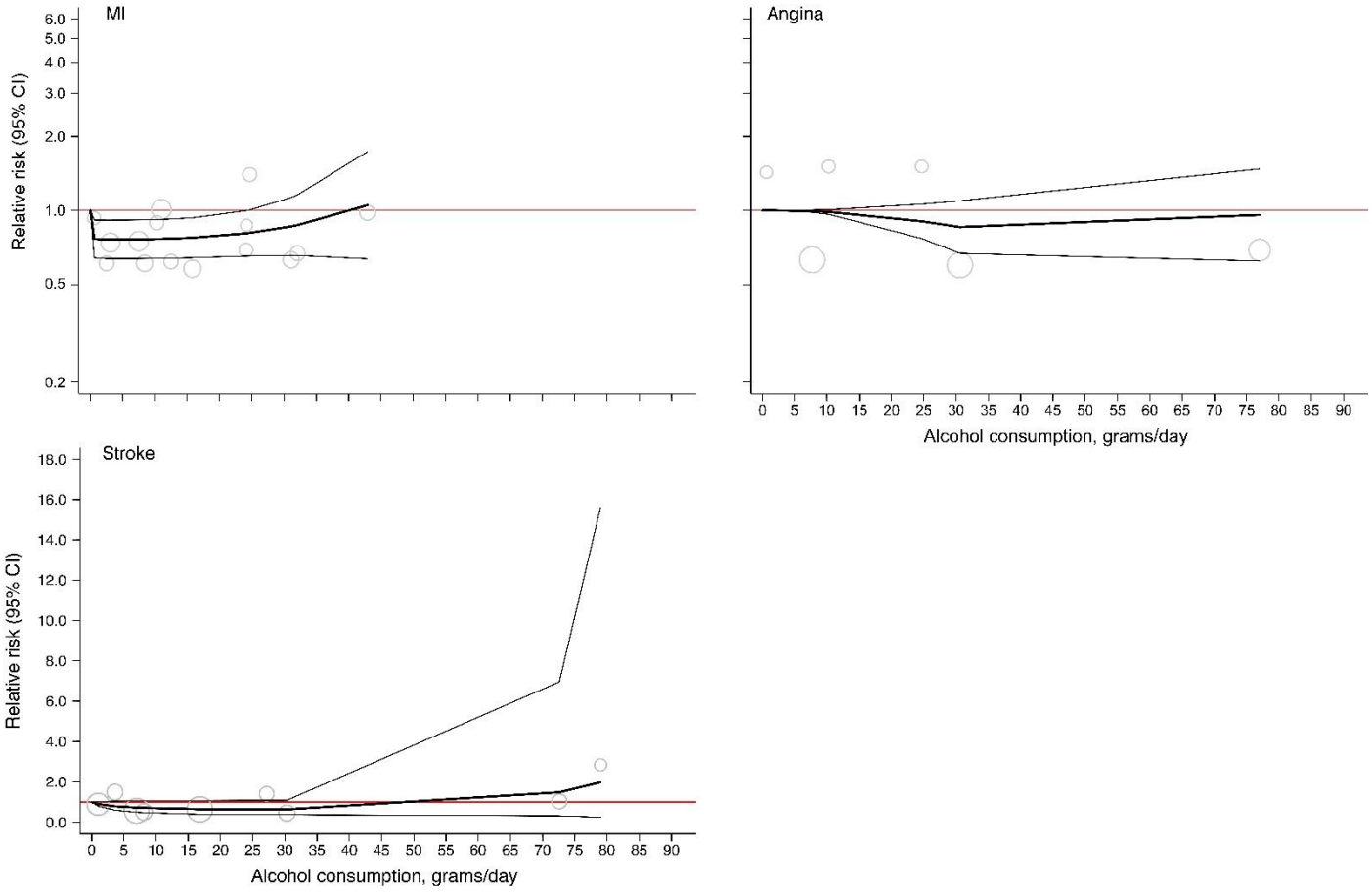
Figure S8. Dose-response relationship between alcohol consumption and risk of all-cause mortality, cardiovascular mortality, and cardiovascular events, stratified by primary cardiovascular event

Best-fitting second-degree fractional polynomial models (with 95% CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk.

a. All-cause mortality



b. Cardiovascular mortality



c. Cardiovascular events

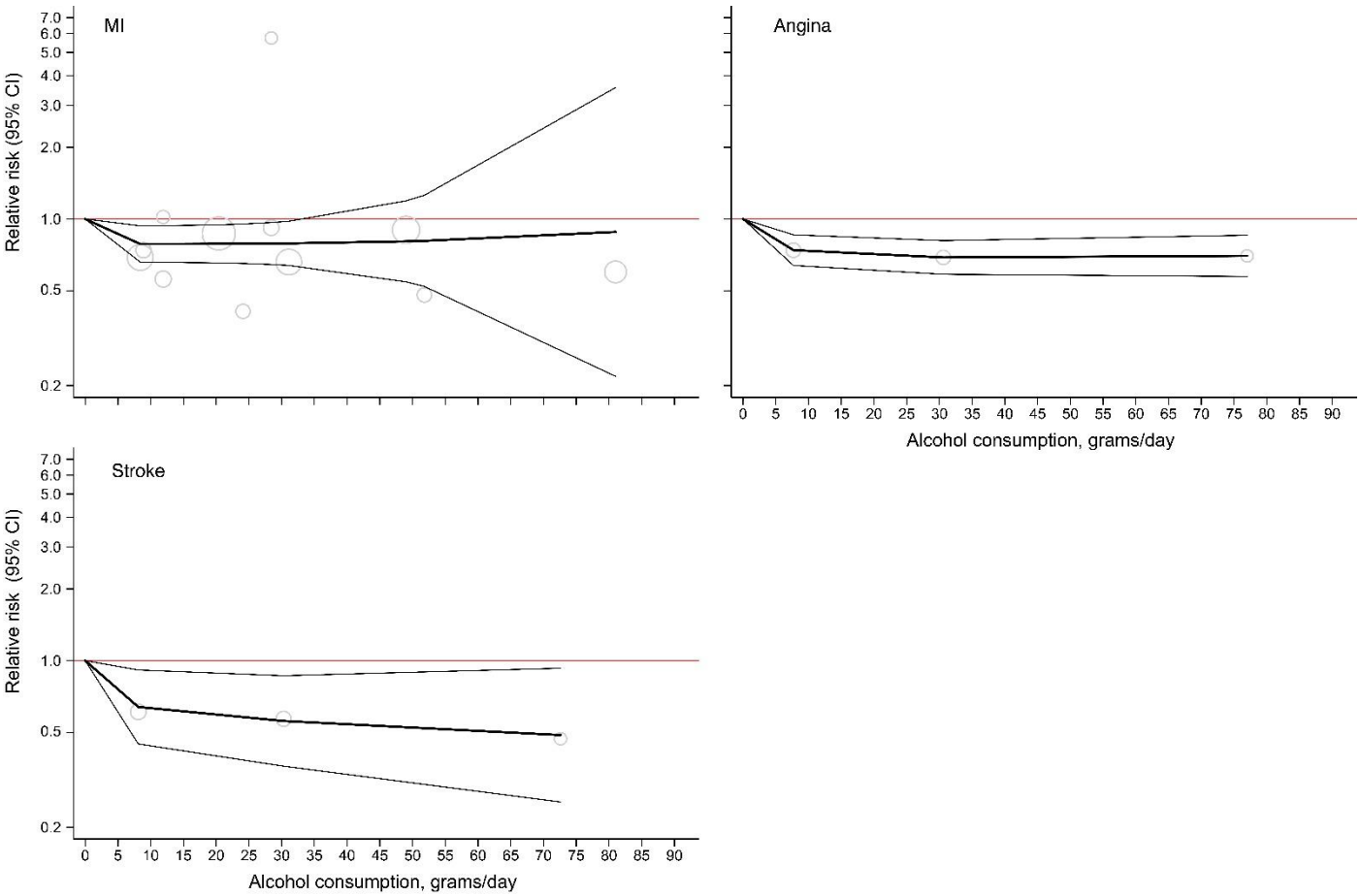
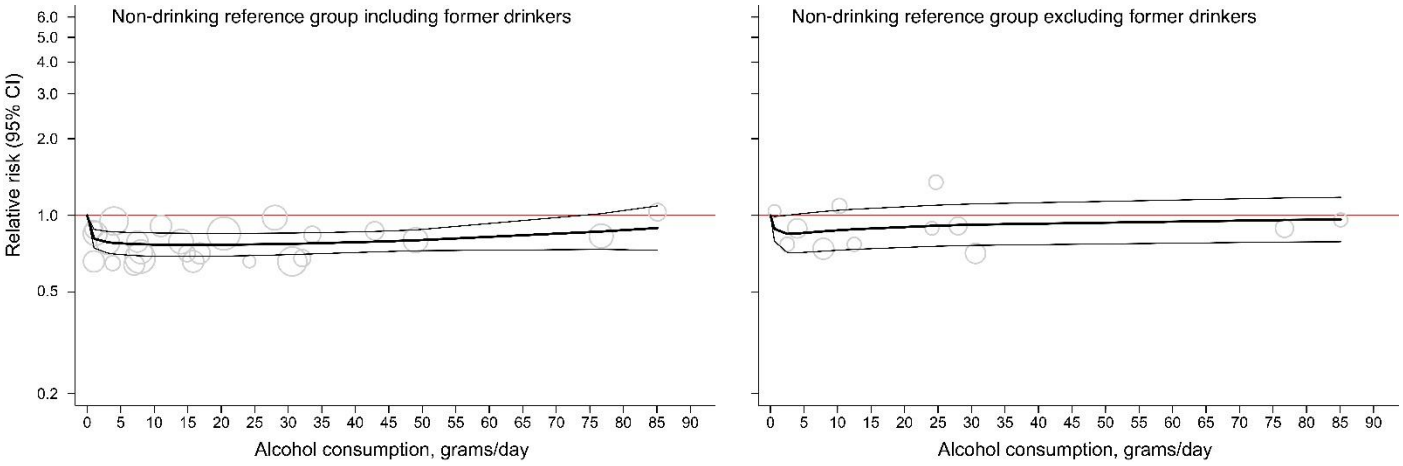


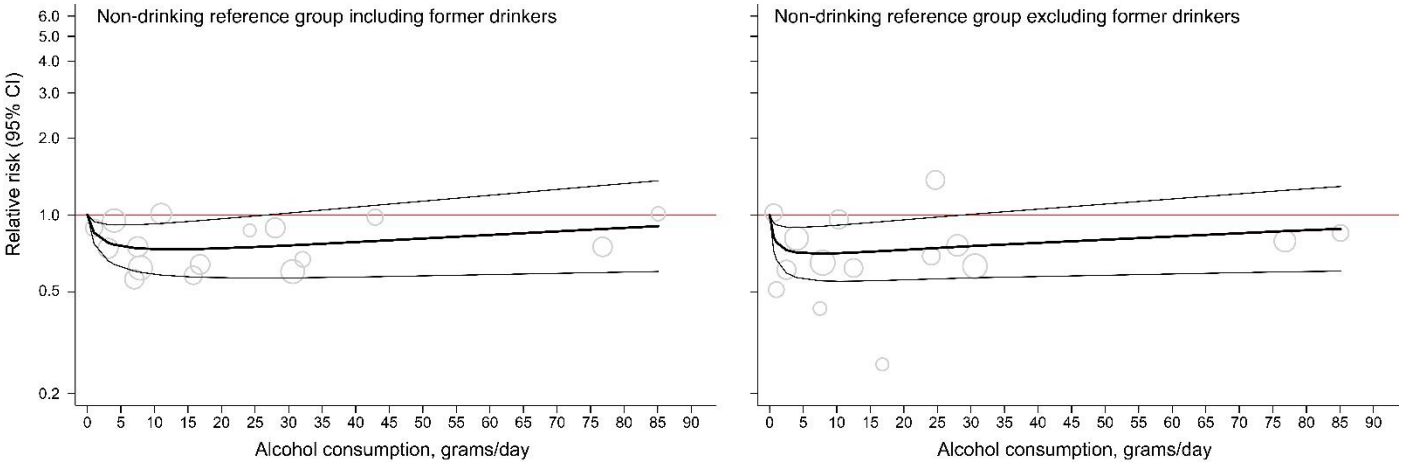
Figure S9. Dose-response relationship between alcohol consumption and risk of all-cause mortality, cardiovascular mortality, and cardiovascular events, relative to different non-drinking reference group

Best-fitting second-degree fractional polynomial models (with 95% CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk.

a. All-cause mortality



b. Cardiovascular mortality



c. Cardiovascular events

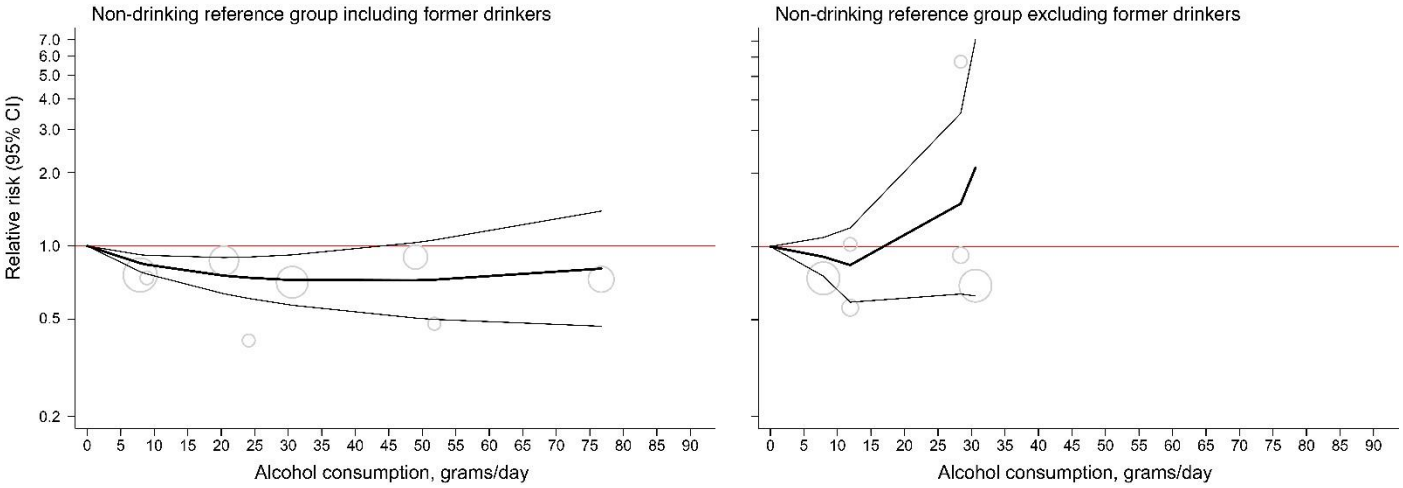
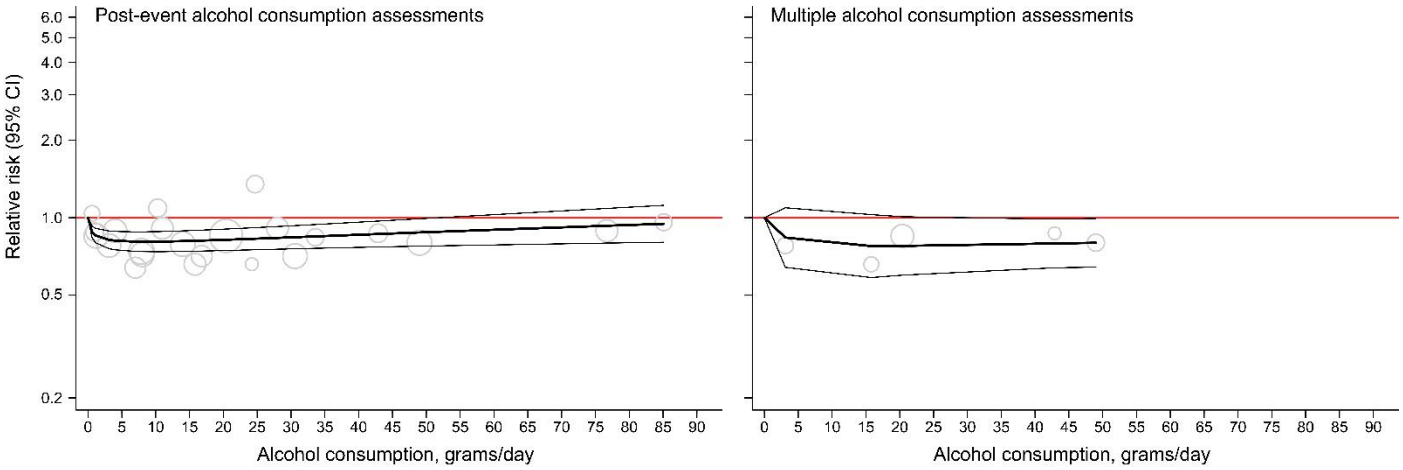


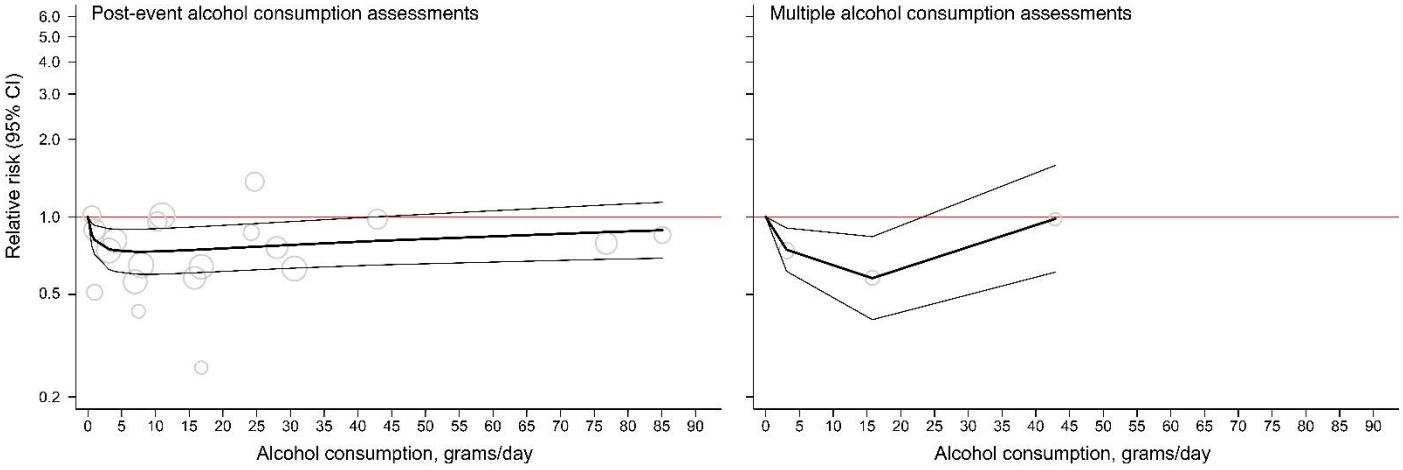
Figure S10. Dose-response relationship between alcohol consumption and risk of all-cause mortality, cardiovascular mortality and cardiovascular events, using different method of assessing alcohol consumption

Best-fitting second-degree fractional polynomial models (with 95% CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk.

a. All-cause mortality



b. Cardiovascular mortality



c. Cardiovascular events

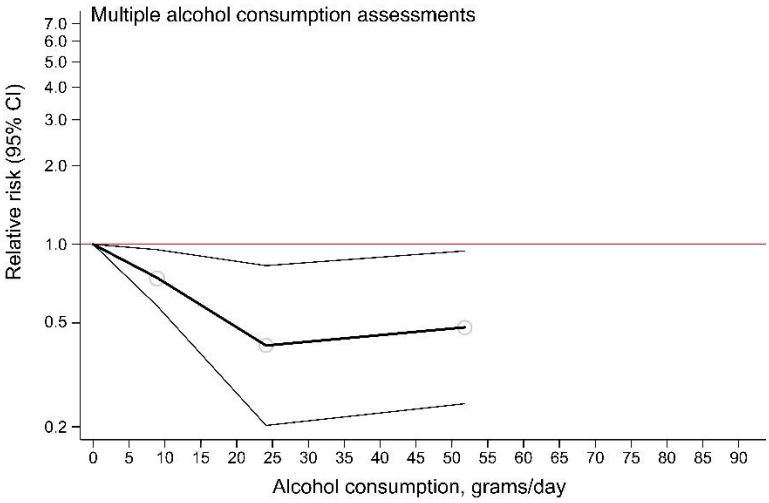


Figure S11. Overall dose-response relationship between alcohol consumption and risk of all-cause and cardiovascular mortality after excluding studies with a quality assessment score <7

Best-fitting second-degree fractional polynomial models (with 95% CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk.

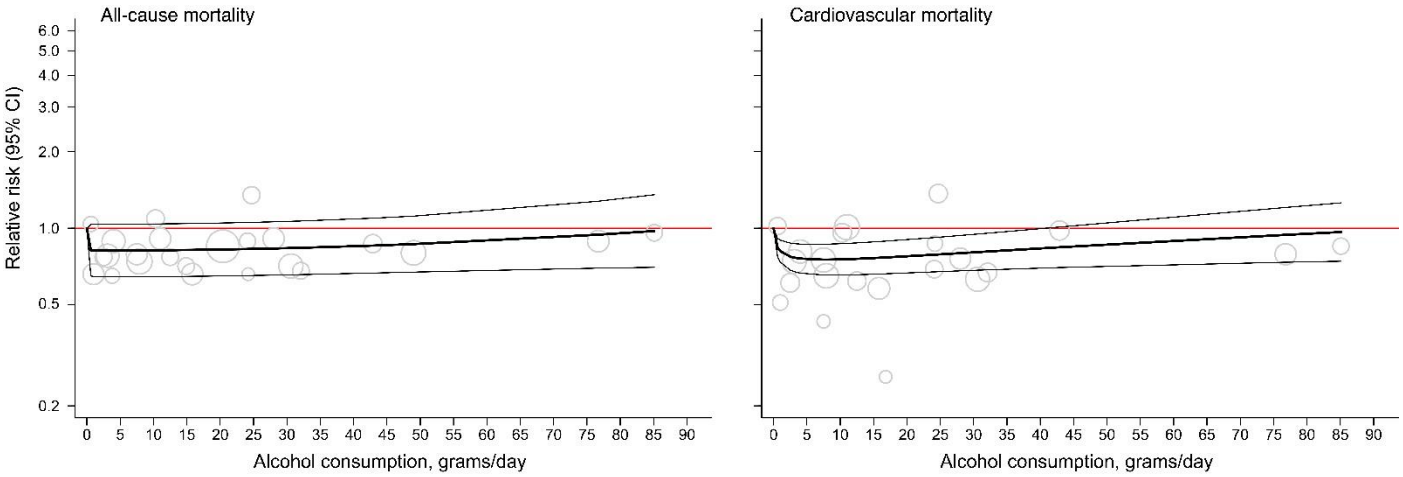


Figure S12. Overall dose-response relationship between alcohol consumption and risk of all-cause mortality, cardiovascular mortality, and cardiovascular events, using least adjusted estimates (adjusted for age, sex, and smoking status only)

Best-fitting second-degree fractional polynomial models (with 95% CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk.

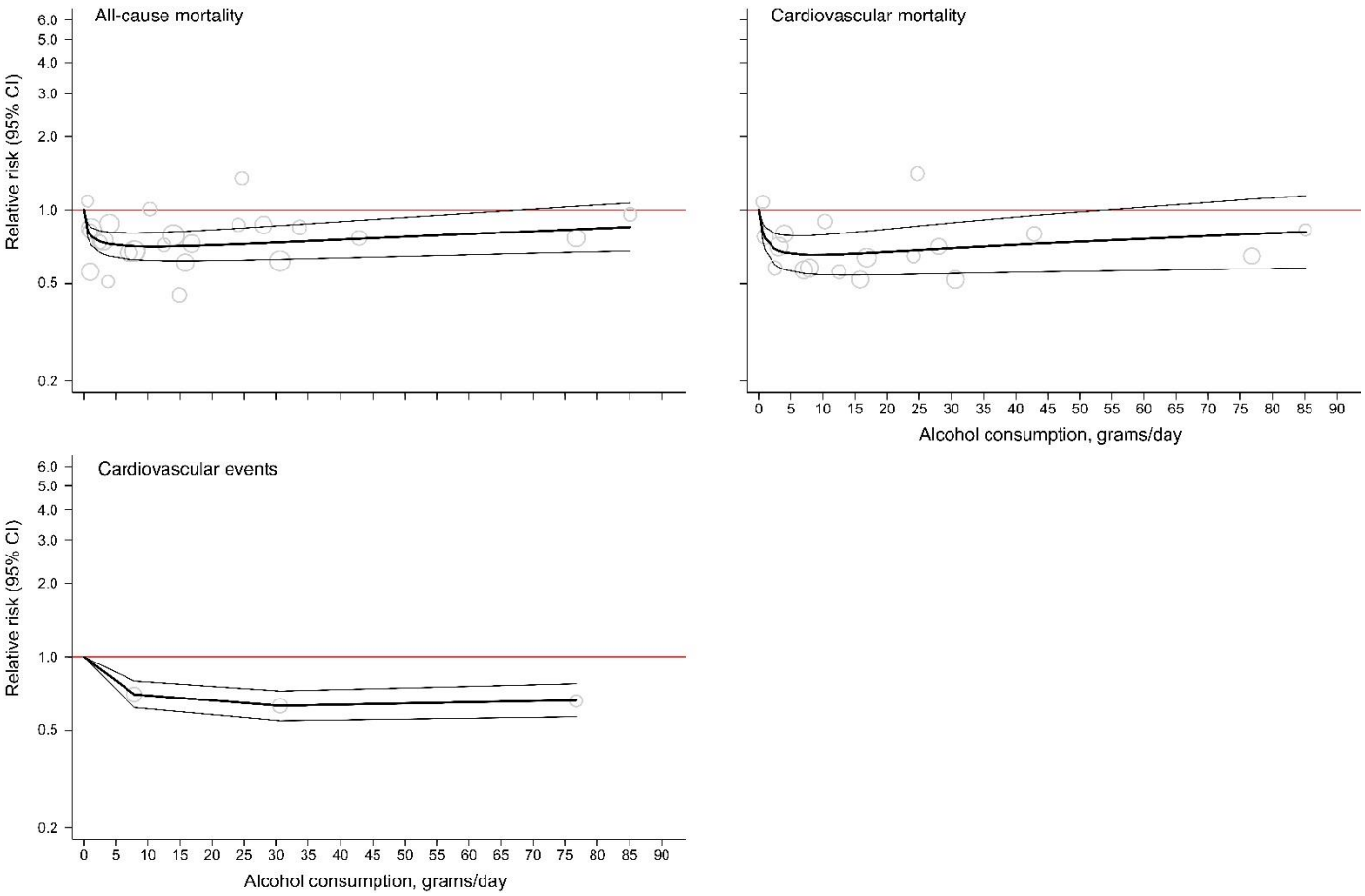
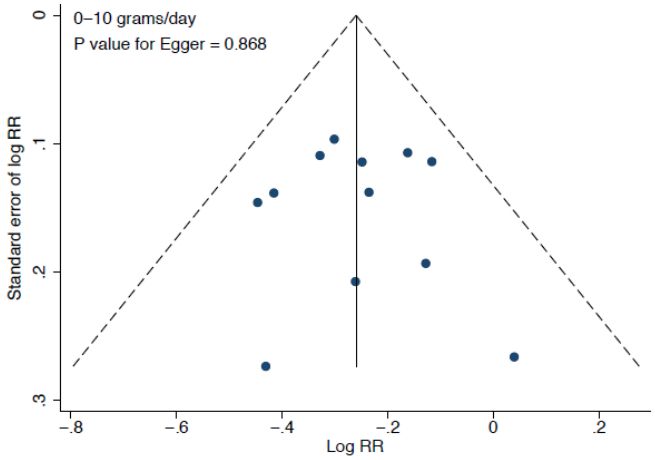
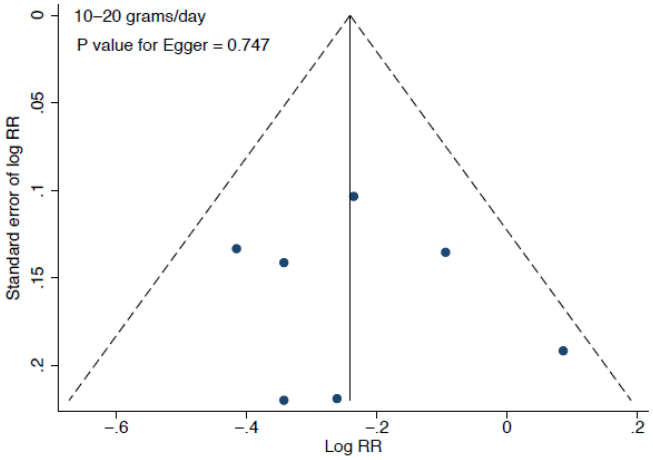


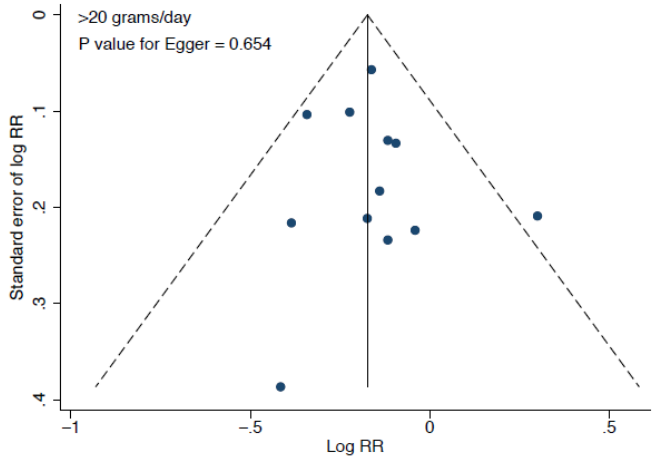
Figure S13. Funnel plots

As asymmetry cannot be examined using continuous dose-response data, alcohol consumption in each study was reclassified into three groups (0-10 g/day, 10-20 g/day and >20 g/day) according to its averages of the reported categories. For each outcome, we then repeated our analysis for each drinking group.

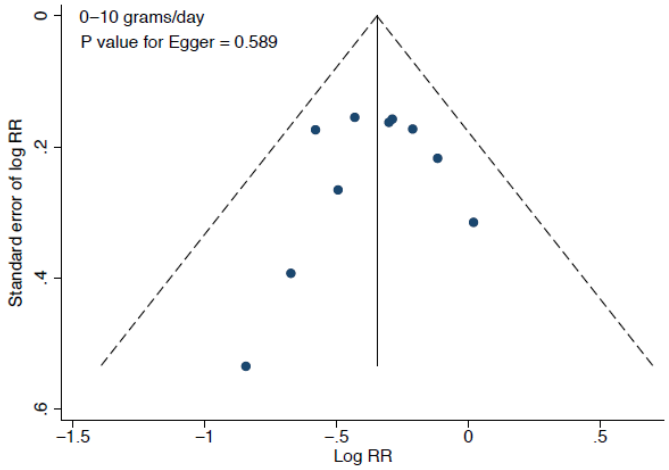
a. All-cause mortality

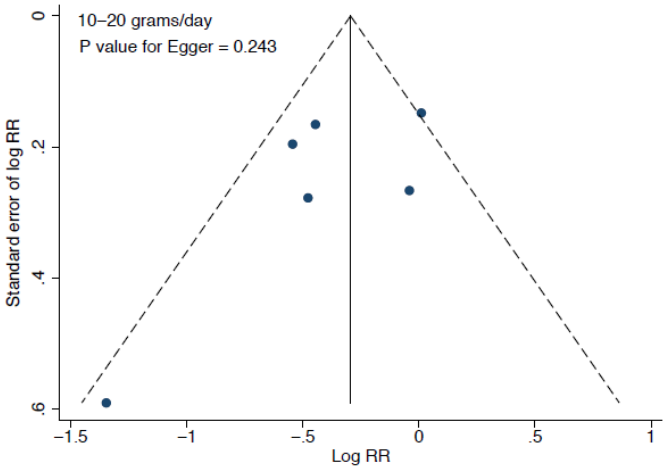


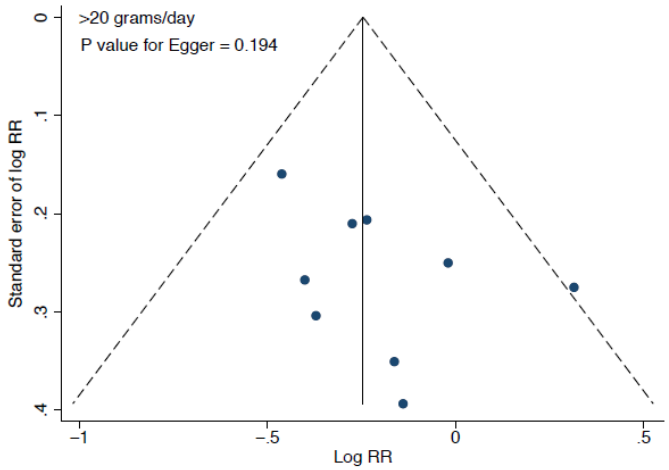




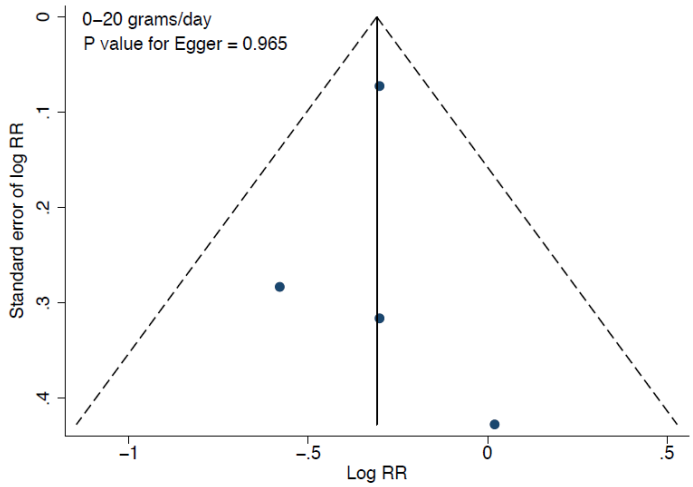
b. Cardiovascular mortality







c. Cardiovascular events



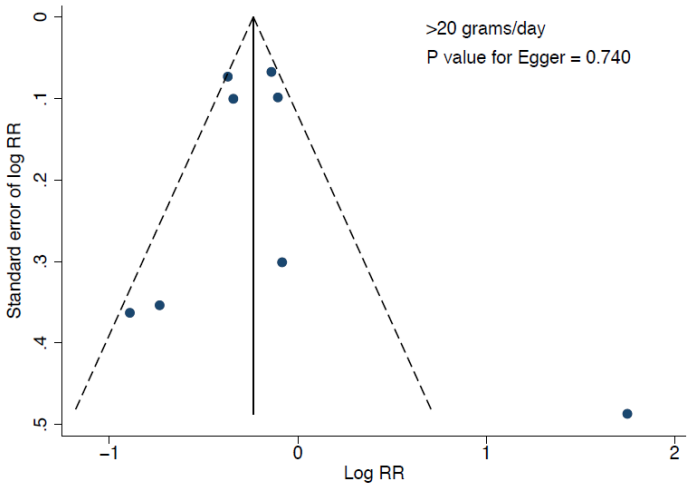


Table S6. Associations of alcohol intake with HDL-cholesterol and gamma-glutamyl transferase in UK Biobank and HSE/SHeSs

Study cohort	Alcohol consumption category					Alcohol intake (per 100 g/day) *	
	Never drinker	Low-level drinker	Medium-level drinker	High-level drinker	Former drinker	β (95% CI)	*P*-value
UK Biobank							
Gamma-glutamyl transferase (U/L) (N=13477)							
n	1000	5611	4908	836	1122		
Mean (95% CI) †	40.09 (36.46–43.72)	41.79 (40.10–43.49)	53.08 (51.16–54.99)	79.75 (75.83–83.66)	38.87 (35.46–42.27)	59.11 (54.40–63.82)	<0.001
UK Biobank							
HDL-cholesterol (mmol/L) (N=12334)							
n	917	5123	4481	766	1047		
Mean (95% CI) †	1.19 (1.17–1.21)	1.26 (1.25–1.27)	1.35 (1.34–1.36)	1.49 (1.47–1.51)	1.20 (1.18–1.22)	0.39 (0.36–0.41)	<0.001
HSE/SHeSs							
HDL-cholesterol (mmol/L) (N=385)							
n	60	196	55	6	68		
Mean (95% CI) †	1.24 (1.15–1.34)	1.31 (1.26–1.37)	1.43 (1.33–1.53)	1.54 (1.25–1.83)	1.26 (1.17–1.34)	0.40 (0.14–0.67)	0.003

* β (95% CI) and *P*-values were derived from multivariable linear regression models by treating alcohol intake as a continuous variable
† Means (95% CI) were derived from multivariable linear regression models by treating alcohol consumption as a categorical variable
All models were adjusted for age, sex, smoking status, diabetes, hypertension, socioeconomic position or education, body mass index, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, and warfarin
CI=confidence interval, HDL=high-density lipoprotein, HSE=the Health Survey for England, SHeSs=the Scottish Health Survey