

**Supplementary Table 1.** Characteristics of genetic variants associated with amounts of alcohol consumed in the UK Biobank.

Chromosome	Rs number	Gene	EA	NA	Beta value	SE
4	rs10004020	Intergenic	A	G	0.009052333	0.001623231
4	rs10028756	Intergenic	A	G	-0.018574761	0.002171039
2	rs1004787	Intron:LINC01833	A	G	0.008442835	0.001465275
7	rs10085696	Intron:AUTS2	G	A	-0.011408902	0.001873083
7	rs10236149	Intron:ARPC1B	G	A	-0.013498145	0.002219081
17	rs10438820	Intron:RPTOR	T	C	0.008971778	0.001593488
12	rs10506274	Intron:ACSS3	T	G	-0.009037403	0.001458405
11	rs10750025	Intergenic	T	C	0.010321447	0.001570358
1	rs10753661	Intergenic	A	G	-0.008638128	0.001569272
12	rs10876188	Intron:SLC4A8	T	C	-0.007986853	0.001463078
9	rs10978550	Intergenic	C	T	-0.011748331	0.001802112
11	rs11030084	Intron:BDNF- AS LINC00678	T	C	-0.010606819	0.001880926
16	rs1104608	Intergenic	C	G	-0.010974988	0.001475848
14	rs1123285	Intron:OTX2	G	C	-0.008897365	0.00154416
16	rs113443718	Intron:SEZ6L2	A	G	-0.010208258	0.001584629
4	rs1154414	Intron:ADH5	C	T	0.017630373	0.002093815
14	rs11625650	Intron:KIF26A	A	G	-0.009568091	0.00172405
2	rs11692435	Nonsynonymous:ACTR1B	A	G	0.017449894	0.00261585
5	rs11739827	Intron:TENM2	T	G	-0.008375229	0.001469112
4	rs11940694	Intron:KLB	G	A	0.025949908	0.001485887
1	rs12088813	Intron:PDE4B	C	A	-0.009329047	0.001649158

8	rs1217091	Intergenic	C	T	0.012160827	0.001865386
4	rs12499107	Intergenic	G	A	0.012661209	0.002158718
2	rs1260326	Nonsynonymous:GCKR	C	T	0.020889835	0.001488339
4	rs12651313	Intergenic	G	C	-0.008642927	0.001467223
5	rs12655091	Intergenic	A	G	-0.008312109	0.001460289
11	rs12795042	Intron:LOC646522	C	A	-0.008319009	0.001503872
15	rs12907323	Intron:AGBL1	G	A	0.008496596	0.001481314
2	rs13024996	Intron:ARHGAP15	A	C	-0.010912645	0.001514769
2	rs13032049	Intron:WDPCP	G	A	0.01019455	0.001617979
3	rs13066454	Intergenic	T	C	-0.008775946	0.001491956
3	rs13094887	Intergenic	T	A	-0.010309671	0.001588926
4	rs13107325	Nonsynonymous:SLC39A8	T	C	-0.027504515	0.002815982
8	rs13250583	Intergenic	T	C	-0.009717545	0.001780116
2	rs13383034	Intron:LINC01833	T	C	0.014926977	0.001551195
11	rs1713676	Intergenic	G	A	-0.007991984	0.00145913
16	rs17177078	Intron:TNRC6A	T	C	-0.02231549	0.003011759
10	rs17665139	Intergenic	T	C	-0.011560138	0.002046764
3	rs2011092	Intron:ZBTB38	C	T	-0.008900405	0.001540056
4	rs2165670	Intergenic	A	G	0.02308038	0.002364267
2	rs2178197	Intron:GPN1	G	A	-0.008781445	0.001471773
14	rs2180870	Intron:ARID4A	C	T	-0.012177537	0.002132803
15	rs2472297	Intergenic	T	C	0.010606047	0.001685411
16	rs2764771	Intergenic	A	G	0.009890596	0.001581736
19	rs281379	Intergenic	A	G	0.013722336	0.001457844
17	rs2854334	Intergenic	G	A	0.009220984	0.001497813

8	rs28601761	Intergenic	G	C	0.009102878	0.001476682
1	rs28680958	Intron:ZBTB37	A	G	-0.010996457	0.001769942
7	rs35034355	Intron:ORC5	A	G	-0.008096817	0.001458945
4	rs35538052	Intron:KLB	A	G	-0.008524877	0.001502312
4	rs36052336	Intron:ADH1C	G	A	-0.018428809	0.00303378
4	rs3748034	Nonsynonymous:HGFAC	T	G	-0.011740341	0.002081935
16	rs378421	Intergenic	A	G	-0.011205474	0.001486812
17	rs3803800	Nonsynonymous:TNFSF12- TNFSF13 TNFSF13	G	A	0.011378876	0.001777082
12	rs3809162	Intergenic	G	A	0.009060925	0.001489607
18	rs4092465	Intergenic	G	A	-0.008291878	0.001513883
4	rs4501255	Intron:BEND4	G	C	0.010693415	0.001718941
17	rs4548913	Intron:SRR	A	G	-0.008359953	0.001511274
4	rs4690727	Intron:INPP4B	G	C	0.010816985	0.001619716
4	rs4699791	Intergenic	A	G	0.018570721	0.002477197
20	rs4815364	Intron:ACSS1	A	G	0.008582356	0.001498544
12	rs4842786	Intergenic	A	G	-0.008797801	0.001478674
5	rs4916723	Intron:LINC00461	C	A	-0.009952257	0.001478674
11	rs4938230	Intergenic	A	C	0.012810377	0.001998209
13	rs500321	Intergenic	T	A	-0.009669361	0.001653426
1	rs5024204	Intron:PTGER3	T	A	0.009702711	0.001628467
5	rs55872084	Intron:SGCD	T	G	0.009978744	0.001718941
9	rs55932213	Intergenic	G	A	0.009488271	0.001654204
11	rs56030824	Intron:SPI1	A	G	-0.011601888	0.001562978
2	rs56337305	Intergenic	C	T	-0.009588381	0.001499283

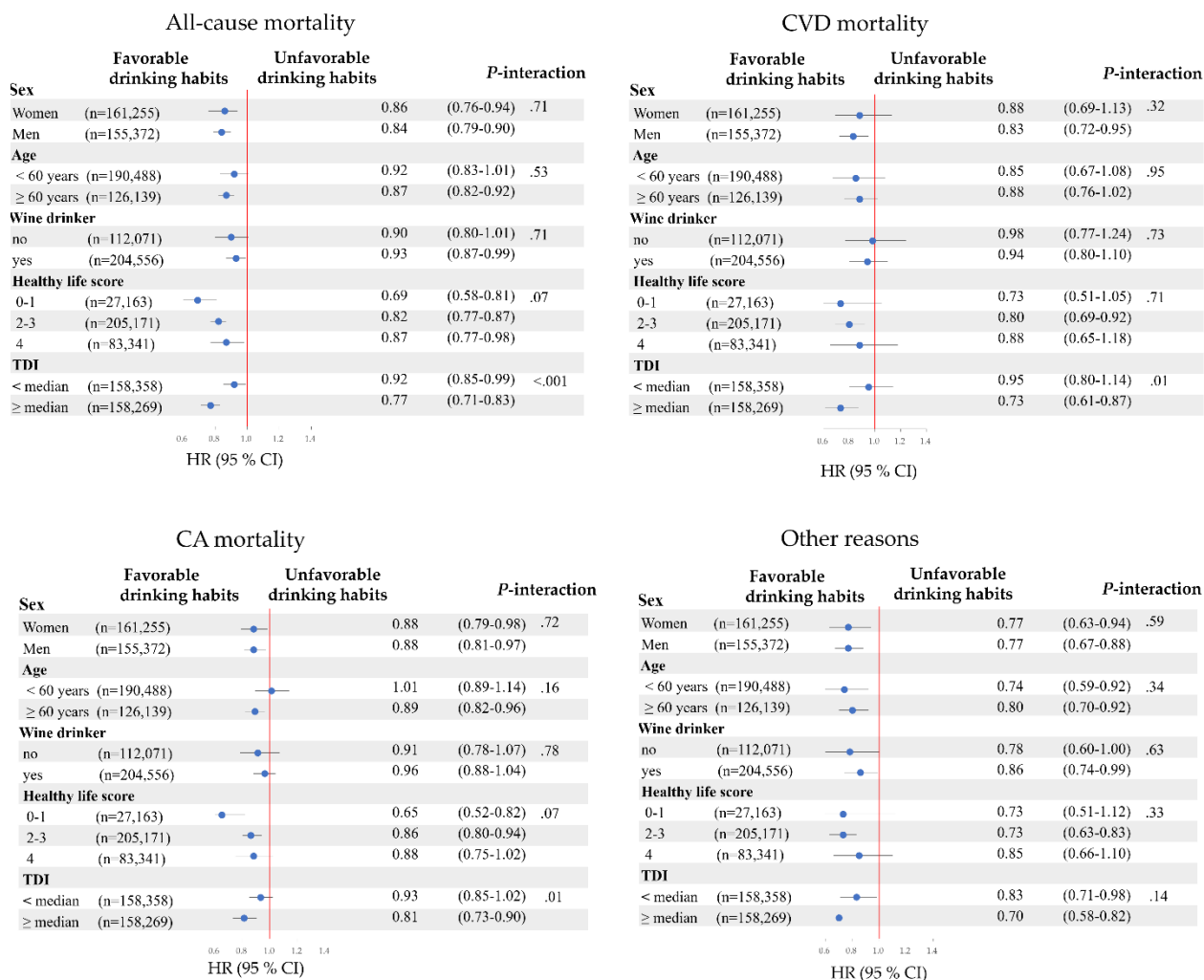
1	rs58107686	Intron:PHC2	A	C	-0.009747126	0.00158537
3	rs60654199	Intron:RASA2	A	C	-0.016660294	0.003001977
16	rs62044525	Intergenic	G	C	-0.01217318	0.001882851
3	rs62250685	Intron:CADM2	G	A	-0.014357061	0.001500092
7	rs6460047	Intergenic	C	T	0.011623538	0.00179569
3	rs6787172	Intron:RSRC1	G	T	-0.008030894	0.001466234
11	rs682011	Intergenic	C	T	0.008212447	0.001467913
7	rs6951574	Intergenic	C	T	0.013222216	0.001462828
1	rs705687	Intergenic	G	A	-0.010904017	0.001775889
10	rs7074871	Intergenic	A	G	-0.00939985	0.001672158
16	rs7185555	Intergenic	C	G	-0.011100514	0.002026667
2	rs72859280	Intergenic	T	G	0.022885324	0.003901915
2	rs77165542	Intergenic	T	C	-0.026010899	0.003971245
11	rs7950166	Intron:TRIM66	T	C	-0.009799202	0.001515663
16	rs79616692	Intron:LINC01572	C	G	0.016302272	0.002350583
1	rs823114	Intergenic	A	G	0.00876774	0.001467417
2	rs828867	Utr3:TET3	A	G	0.008757157	0.001463597
22	rs9607814	Intergenic	A	C	-0.010181001	0.001858788
3	rs9838144	Intron:CPNE4	C	G	-0.009964223	0.001792521
18	rs9950000	Intron:TCF4	T	C	-0.009117697	0.001490903

**Supplementary Table 2.** The association between drinking habits score (DHS) and all-cause mortality and cause specific mortality in the original analysis and 10-fold cross-validation analysis.

	Original analysis		Cross-validation analysis	
	HR (95% CI)	<i>P</i> -trend	HR (95% CI)	<i>P</i> -trend
<b>All-cause mortality</b>				
Multivariable adjusted	0.90 (0.87-0.93)	<.001	0.90 (0.87-0.93)	<.001
<b>CVD mortality</b>		<i>P</i> -trend		<i>P</i> -trend
Multivariable adjusted	0.92 (0.85-0.99)	0.03	0.92 (0.85-0.99)	0.03
<b>CA mortality</b>		<i>P</i> -trend		<i>P</i> -trend
Multivariable adjusted	0.91 (0.87-0.95)	<.001	0.91 (0.87-0.95)	<.001
<b>Other reason</b>		<i>P</i> -trend		<i>P</i> -trend
Multivariable adjusted	0.88 (0.82-0.94)	<.001	0.88 (0.82-0.94)	<.001

Results adjusted for age, sex, race, assessment centres, BMI, physical activity, smoking (never, past, current), healthy diet, Townsend deprivation index, diabetes, hypertension, high cholesterol and levels of alcohol intake.

**Supplementary Figure 1.** Stratified analyses for association of drinking habits score (DHS)\* and risk of all-cause mortality and cause-specific mortality.

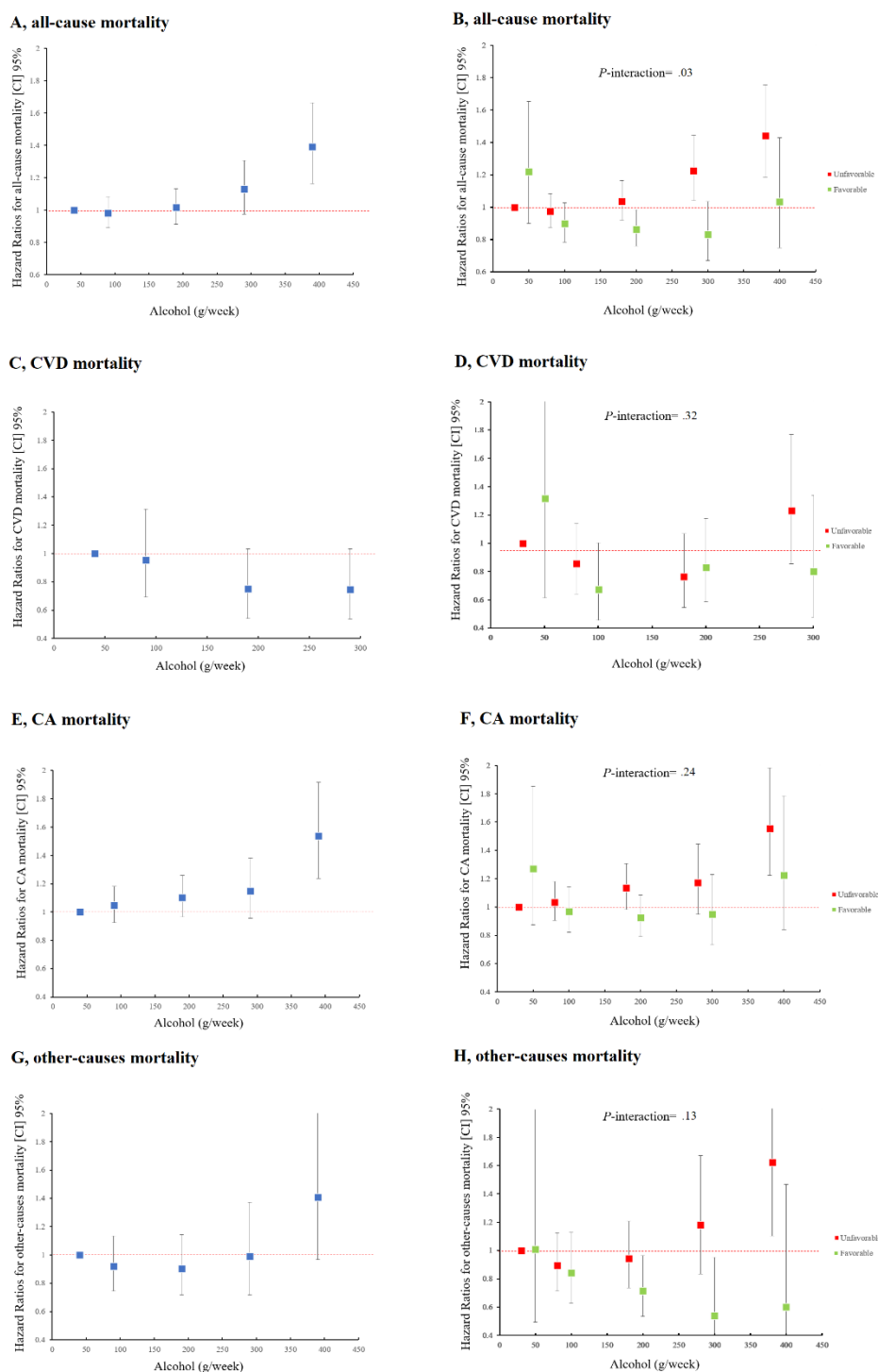


Results were adjusted by adjusted for age, sex, race, assessment centres, BMI, physical activity, smoking (never, past, current), healthy diet, Townsend deprivation index, diabetes, hypertension, high cholesterol and alcohol intake level.

For the stratified analyses by HLS, results were adjusted by adjusted for age, sex, race, Townsend deprivation index, diabetes, hypertension, high cholesterol and alcohol intake level.

\* Because the intermediate DHS (DHS=1) group had similar risk of mortality to the unhealthy DHS (DHS=0) group, we combined these two groups to maximize statistical power. Favorable drinking habits was defined as DHS=2 and unfavorable drinking habits was defined as DHS=0 or 1.

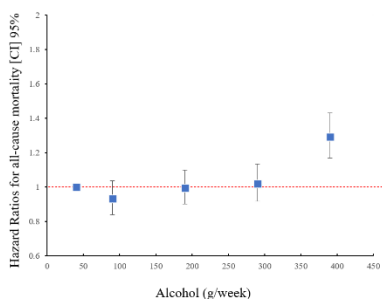
**Supplementary Figure 2.** The joint association of amount of alcohol intake and drinking habits score in relation to risks of all-cause mortality and cause-specific mortality in women.



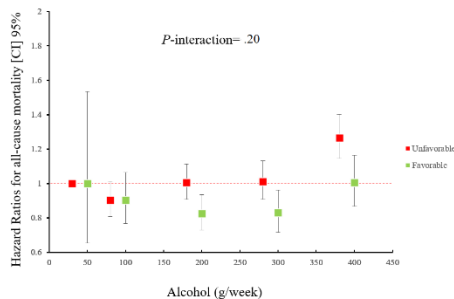
Results were adjusted age, race, assessment centres, BMI, physical activity, smoking (never, past, current), healthy diet, Townsend deprivation index, diabetes, hypertension, high cholesterol and DHS (for A, C, E and G). For CVD mortality, because the limited cases of CVD mortality in the high levels of amount of alcohol consumed, we combined two groups ( $\geq 200$ – $<300$  and  $\geq 300$ ) to maximize statistical power.

**Supplementary Figure 3.** The joint association of amount of alcohol intake and drinking habits score in relation to risks of all-cause mortality and cause-specific mortality in men.

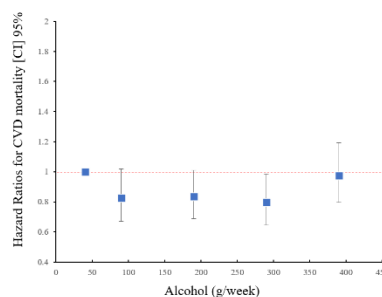
**A, all-cause mortality**



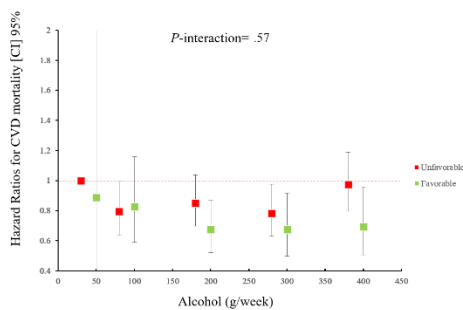
**B, all-cause mortality**



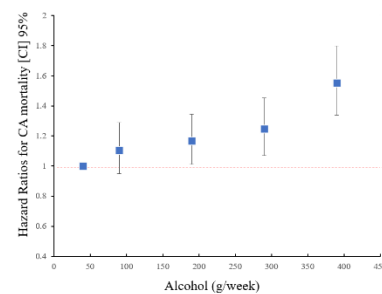
**C, CVD mortality**



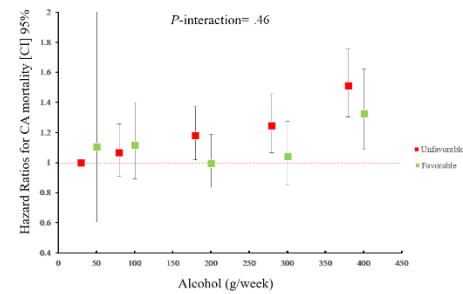
**D, CVD mortality**



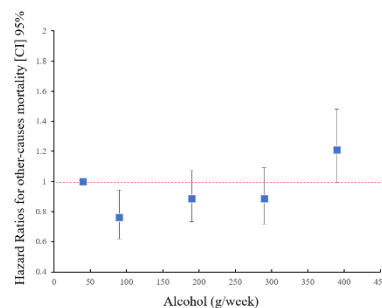
**E, CA mortality**



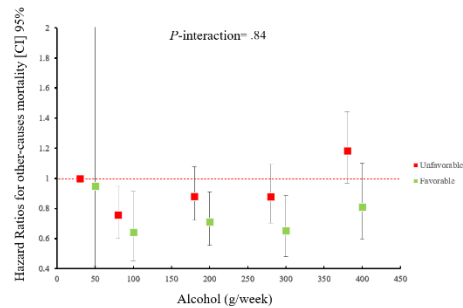
**F, CA mortality**



**G, other-causes mortality**



**H, other-causes mortality**

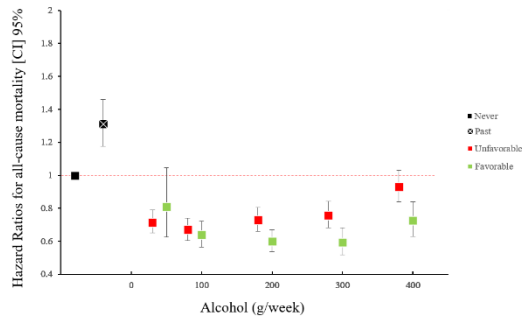


Results were adjusted age, race, assessment centres, BMI, physical activity, smoking (never, past, current), healthy diet, Townsend deprivation index, diabetes, hypertension, high cholesterol and DHS (for A, C, E and G).

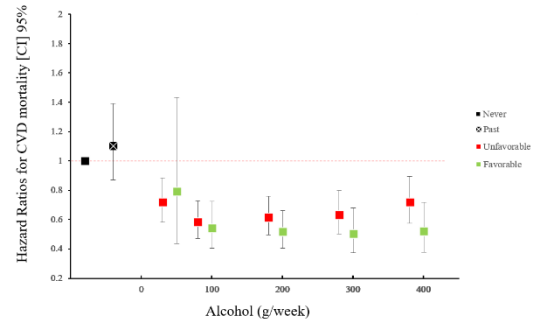


**Supplementary Figure 4.** The joint association of amount of alcohol intake and drinking habits score in relation to risks of all-cause mortality and cause-specific mortality in men (including never drinkers and past drinkers).

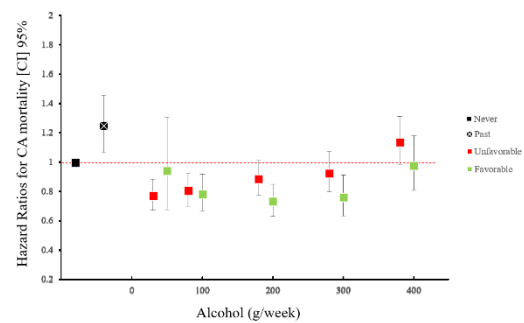
**A, All-cause mortality**



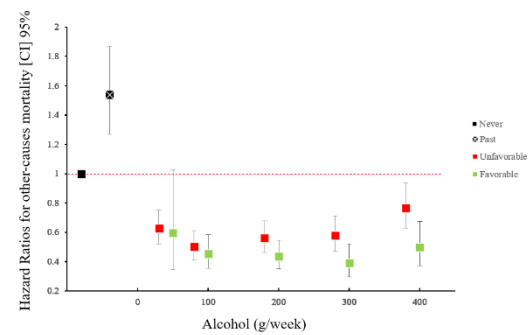
**B, CVD mortality**



**C, CA mortality**

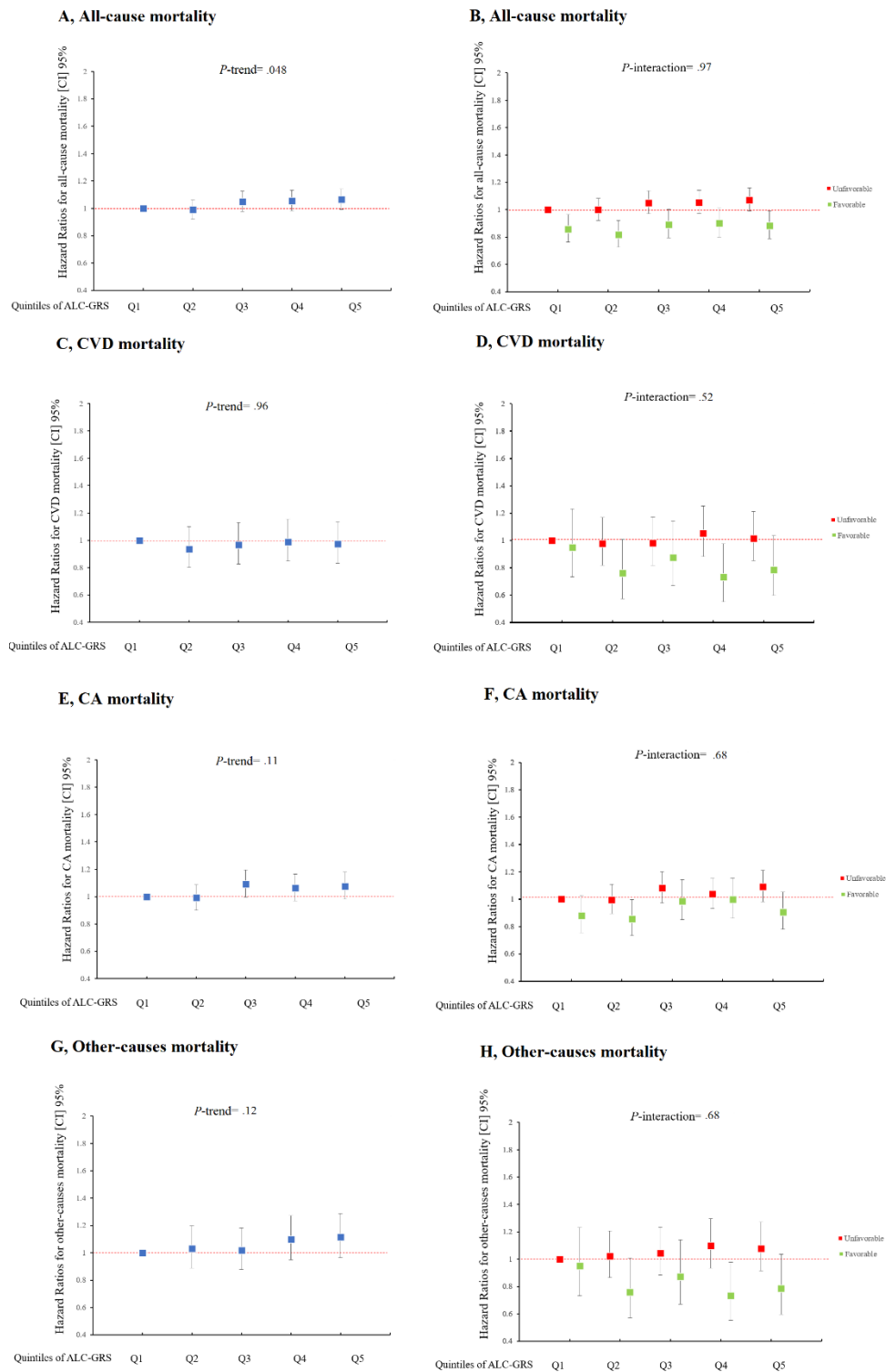


**D, Other-causes mortality**



Results were adjusted age, sex, race, assessment centres, BMI, physical activity, smoking (never, past, current), healthy diet, Townsend deprivation index, diabetes, hypertension and high cholesterol.

**Supplementary Figure 5.** The joint association of ALC-GRS and drinking habits score in relation to risk of all-cause mortality and cause-specific mortality.



Results were adjusted age, sex, assessment centres, BMI, physical activity, smoking (never, past, current), healthy diet, Townsend deprivation index, diabetes, hypertension, high cholesterol, DHS (for A, C, E and H), the first 10 genetic principal components, genotyping array and the third-degree relatedness.

## Supplemental Materials

### Genotyping and calculation of genetic risk score

Detailed information about genotyping and imputation in the UK Biobank study has have been described previously<sup>1</sup>. A weighted method was used to calculate the alcohol intake-GRS<sup>2</sup>. Each SNP was recoded as 0, 1, or 2 according to the number of risk alleles, and each SNP was weighted by its relative effect size ( $\beta$  coefficient) on alcohol consumption obtained from the previous genome-wide association study<sup>3</sup>. The ALC-GRS was calculated by the following equation:  $GRS=(\beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \dots + \beta_{90} \times SNP_{90}) \times (90 / \text{sum of the } \beta \text{ coefficients})$ , where  $SNP_i$  is the risk allele number of each SNP.

### Details of covariates

The baseline touch-screen questionnaire was used to assesses potential confounders, including age, sex, ethnicity, assessment centres, Townsend deprivation index, smoking status and dietary intakes (red meat, vegetables, fruits and fish). Healthy diet score was evaluated by red meat < median, vegetable intake  $\geq$  median, fruit intake  $\geq$  median, fish intake  $\geq$  median; One point was given for each favorable diet factor and the total diet score ranges from 0 to 4<sup>4,5</sup>; a healthy diet was defined as a healthy diet score  $\geq$  2. Height was measured by a Seca 202 height measure. Weight was measured to the nearest 0.1 kg by the Tanita BC-418 MA body composition analyzer. Body mass index (BMI) (calculated as weight (kg) divided by height in meters squared ( $m^2$ )). Total physical activity was computed as the sum of walking and moderate and vigorous activity, measured as metabolic equivalent (MET, minutes/week) according to the IPAQ scoring protocol<sup>6</sup>. Hypertension was defined as a self-reported history of hypertension or a systolic blood pressure  $\geq$  140 mmHg or a diastolic blood pressure  $\geq$  90 mm Hg or self-reported or taking antihypertensive medications. High cholesterol was defined as a self-reported history of high cholesterol or taking cholesterol lowering medication. Diabetes was evaluated by UK biobank algorithm for the diagnosis of diabetes<sup>7</sup>.

We also calculated a healthy lifestyle score based on BMI (<30 kg/ $m^2$ ), smoking (never smoking), healthy diet and physical activity ( $\geq$  600 MET minutes/week). One point was given for each favorable lifestyle factor (range, 0–4)<sup>8</sup>.

## References

1. Bycroft C, Freeman C, Petkova D, et al. Genome-wide genetic data on~ 500,000 UK Biobank participants. *BioRxiv*. 2017:166298.
2. Ripatti S, Tikkanen E, Orho-Melander M, et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *The Lancet*. 2010;376(9750):1393.
3. Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet*. 2019;51(2):237.
4. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction. The American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010:-.
5. Pazoki R, Dehghan A, Evangelou E, et al. Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. *Circulation*. 2018;137(7):653-661.
6. Committee IR. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)-short and long forms. <http://www.ipaq.ki.se/scoring.pdf>. 2005:-.
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8. Lloyd-Jones DM. American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's Strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586.