

**EFFECTS OF HIGH ALCOHOL INTAKE, ALCOHOL-RELATED
SYMPTOMS, AND SMOKING ON MORTALITY**

Supplementary Material

Supplementary Note

Information on predictor variables: alcohol intake, alcohol-related symptoms and smoking.

Estimates of alcohol intake were based on self-report, with three approaches based on the number of alcoholic drinks taken in the past week; the number of alcoholic drinks taken in a typical week; and a combination of the usual frequency and quantity per occasion of drinking over the previous 12 months. For the number of drinks in the past week, study participants filled in a table of days of the week by beverage type (beer, wine, spirits, fortified wines and other). The total number of drinks was calculated. For typical number of drinks, participants endorsed a category and a quantitative measure was obtained from the mid-point of that category. Frequency and quantity were also categorical questions; we calculated the number of drinking occasions in the past year from the frequency, and the number of drinks on a day when alcohol was used from the quantity, again using the mid-point for each category. Multiplying the quantity and frequency and dividing by 52 gave an estimate of the usual number of drinks per week in units which were comparable to the other estimates. Amounts of beer, wine or spirits were derived from the past-week drinking diary by summing the number of drinks of each type across the seven days. For comparisons of beverage types, the small numbers of drinks not categorised as beer, wine or spirits (such as fortified wines) were ignored. Participants also reported the maximum number of drinks ever consumed within a 24-hour period.

For the earlier studies on the two cohorts of twins, and on their relatives, a list of 15 events or symptoms (Supplementary Table S1) was presented and participants endorsed each as having occurred or not. For later studies, a longer symptom list based on DSM III-R or DSM IV alcohol abuse or dependence criteria was presented. To keep the number of possible symptom endorsements at 15 and maximise comparability with earlier studies, we selected similar questions as far as possible (see Table S1). Symptom count was the number of symptoms endorsed as ever occurring.

We have previously reported (1) on the repeatability of alcohol intake estimates across occasions and across assessment methods. The current dataset includes additional studies, and the the ranges and medians for correlations between pairs of studies are 0.45 to 0.74 (median 0.61) for drinks in past week; 0.43 to 0.86,

(median 0.67) for the quantity x frequency drinks estimate, and 0.53 to 0.77 (median 0.61) for alcohol symptom count. The correlations across different measures of alcohol intake (past week, typical week, quantity x frequency, each averaged across all available times for each subject) were around 0.75 (Supplementary Table 2).

A score for lifetime smoking was calculated from questions on whether a person had ever smoked, whether they were a former smoker, and (for current smokers) whether they used fewer than 10, or 10 or more, cigarettes per day. For each study, never-smoker was scored 0, former smoker = 1, current smoker < 10 cigarettes/day = 2 and current smoker \geq 10 cigarettes/day = 3.

Two studies collected information from which we could derive DSM-III-R or DSM-IV lifetime alcohol dependence status. In the 1992-93 twin study (2) the SSAGA questionnaire (3) was administered by telephone interview, and in the 2001-05 twin-family study (4) the interview included questions about occurrence and timing of the DSM-IV diagnostic criteria. In order to explore the relationships between alcohol intake, symptom count and dependence, we classified participants as alcohol dependent if they met either or both of the DSM-III-R and DSM-IV criteria at any time. Because of smaller numbers of participants with assessment of dependence, this was handled as a separate analysis.

Body mass index (BMI, [weight in kilograms/(height in metres)²]) was calculated for each subject from the study-specific data on height and weight.

1. Whitfield JB, Zhu G, Madden PA, Neale MC, Heath AC, Martin NG. The genetics of alcohol intake and of alcohol dependence. *Alcohol Clin Exp Res.* 2004;28:1153-60.
2. Heath AC, Bucholz KK, Madden PA, Dinwiddie SH, Slutske WS, Bierut LJ, et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychol Med.* 1997;27:1381-96.
3. Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI, Jr., et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *J Stud Alcohol.* 1994;55:149-58.
4. Heath AC, Whitfield JB, Martin NG, Pergadia ML, Goate AM, Lind PA, et al. A quantitative-trait genome-wide association study of alcoholism risk in the community: findings and implications. *Biol Psychiatry.* 2011;70:513-8.

Table S1. Questions related to alcohol symptoms, used to compile the alcohol symptom count. See Table 1 for information on the constituent studies. Questions about symptoms or alcohol-related events were not included in the earlier ‘Canberra’ questionnaire or in the Alcohol Challenge Twin Study (ACTS).

Questionnaire studies on Cohorts 1 and 2, Twins and Relatives, and ACTS Follow-up study	Interview studies using SSAGA	Interviews for Nicotine/Alcohol studies
Was there ever a time when you drank too much?	Have you wanted to stop or cut down on drinking 3 or more times?	Have you ever felt that you were an excessive drinker?
Was there ever a time when you felt guilty about drinking?		
Was there ever a time when someone else objected to your drinking?		
Was there ever a time when you were treated for a drinking problem?	Have you ever discussed any problem you might have had with drinking with any professional?	Have you ever discussed any problem you may have had with drinking with any professional?
Was there ever a time when you deliberately tried to cut down on your drinking, but were unable to do so?	Have you ever started drinking at times you promised yourself that you wouldn't, or have you ever drunk more than you intended to?	Have there been 3 or more times in your life when you wanted to stop or cut down on drinking?
Was there ever a time when you planned to stop drinking completely, but then failed to stick to your plan?	Have you ever started drinking and become drunk when you didn't want to?	Has there been a time when you often started drinking and became drunk when you didn't want to?
Was there ever a time when you got into physical fights while drinking?		On 3 or more separate occasions, did you get into physical fights while drinking?
Was there ever a time when you went on binges where you kept drinking for a couple of days or more without sobering up?	Have you ever gone on binges or benders when you kept drinking for 2 days or more without sobering up, except for sleeping?	Have you ever gone on binges when you kept drinking for 2 days or more without sobering up, except for sleeping?
Was there ever a time when you went on drinking binges and neglected some of your usual responsibilities?	Has there ever been a period of several days or more when you spent so much time drinking or recovering from the effects of alcohol that you had little time for anything else?	Has there ever been a period of several days or more when you spent so much time drinking or recovering from the effects of alcohol that you had little time or anything else?
Was there ever a time when you got into trouble driving an automobile after drinking?	Have you ever been arrested for drunk driving?	Have you ever been arrested for drunk driving?
Was there ever a time when your drinking had harmful effects on your friendships and social life?	Did your drinking ever cause you to have problems with your family or friends?	On 3 or more separate occasions, did your drinking cause you to have problems with other family or friends?
Was there ever a time when your drinking had harmful effects on your health?		
Was there ever a time when your drinking had harmful effects on your marriage or home life?	Did your drinking cause serious or repeated problems in any marriage/romantic relationship?	Did your drinking ever cause serious or repeated problems in any marriage or romantic relationship?

Questionnaire studies on Cohorts 1 and 2, Twins and Relatives, and ACTS Follow-up study

Interview studies using SSAGA

Interviews for Nicotine/Alcohol studies

Was there ever a time when your drinking had harmful effects on your work, or employment opportunities?

Did your drinking ever cause you to have problems at work, school or college because of poor work performance or repeated absences?

Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?

Have you ever had blackouts when you didn't pass out while drinking, that is, you drank enough so that the next day you couldn't remember things you had said or done?

Now I'm going to ask you about blackouts. A blackout, which should not be confused with passing out, is when you drank enough so that you could not remember things you had said or done. Have you ever had blackouts, not just passing out from drinking?

Have you ever given up or greatly reduced important activities while drinking -- like sports, work, or associating with friends or relatives?

Have you ever given up or greatly reduced important activities while drinking -- like sports, work or spending time with friends, family or relatives?

Has your drinking or being drunk or hung over often interfered with your working or taking care of school or household responsibilities?

Has your drinking or being drunk or hung over often made it difficult for you to work or study or take care of household responsibilities?

Have you accidentally injured yourself when you were drinking, that is, had a bad fall or cut yourself badly, been hurt in a traffic accident, or anything like that?

Have you ever accidentally injured yourself when you were drinking, that is, had a bad fall or cut yourself badly, been hurt in a traffic accident, or anything like that?

When you were (very) drunk did you ever drive a car, motorbike or boat, use a knife, power equipment or gun, cross against traffic, climb or swim, or put yourself in any other situation where you might have been hurt?

Have you often been under the effects of alcohol or feeling its after-effects in a situation which increased your chances of getting hurt -- like when driving a car or riding a bike in traffic, swimming or diving, or putting yourself into any other situation where drinking increased your chances of getting hurt?

Table S2. Rank correlations between alcohol, smoking and BMI variables. Female correlations above the diagonal, male correlations below.

		Alcohol overall	Alcohol: past week	Alcohol: typical week	Alcohol: quantity x frequency	Alcohol: as Beer	Alcohol: as wine	Alcohol: as spirits	Maximum drinks ever	Symptom Count	Smoking Score	BMI
Alcohol overall	rho		0.925	0.848	0.942	0.463	0.694	0.454	0.399	0.340	0.272	-0.110
	N		14971	12255	15211	13348	14154	13470	14374	14140	17270	16949
Alcohol: past week	rho	0.924		0.744	0.754	0.475	0.734	0.485	0.388	0.319	0.254	-0.113
	N	12008		10510	12493	13351	14155	13470	12452	11963	14251	14367
Alcohol: typical week	rho	0.856	0.774		0.740	0.338	0.519	0.325	0.380	0.335	0.244	-0.063
	N	9403	8545		10737	10307	10363	10326	10238	11455	12165	11719
Alcohol: quantity x frequency	rho	0.941	0.749	0.739		0.389	0.582	0.357	0.372	0.309	0.249	-0.111
	N	12292	10240	8309		11312	11851	11424	13176	12592	14985	14377
Alcohol: as Beer	rho	0.761	0.820	0.614	0.610		0.154	0.139	0.307	0.256	0.220	-0.063
	N	11510	11531	8509	9883		13083	12942	11401	11108	12866	12794
Alcohol: as Wine	rho	0.375	0.388	0.233	0.324	0.061		0.190	0.214	0.169	0.106	-0.081
	N	10937	10944	8465	9399	10652		13164	11921	11514	13510	13578
Alcohol: as Spirits	rho	0.299	0.324	0.196	0.229	0.097	0.180		0.299	0.201	0.166	-0.053
	N	10547	10550	8439	9142	10373	10299		11468	11172	12972	12909
Maximum number of drinks, ever	rho	0.372	0.390	0.374	0.321	0.436	-0.015	0.177		0.563	0.369	-0.031
	N	11698	10024	7988	10900	9707	9342	9080		12875	14378	13742
Symptom Count	rho	0.383	0.388	0.403	0.337	0.402	-0.011	0.121	0.574		0.312	-0.083
	N	11937	10143	8921	10840	9876	9536	9306	11119		14108	13531
Smoking Score	rho	0.275	0.260	0.266	0.253	0.248	-0.037	0.111	0.308	0.293		-0.030
	N	13573	11406	9316	12067	11008	10455	10171	11680	11913		16703
BMI	rho	0.058	0.068	0.069	0.026	0.069	0.013	0.016	0.140	0.058	0.070	
	N	13074	11462	8880	11359	10987	10423	10036	10967	11238	12773	

Table S3. Effects on all-cause mortality by sex. Cox proportional hazards analysis, with adjustment within-family similarity.

	B	robust_se	p	HR	95% confidence Interval
Women					
	Univariate				
BMI ^a	0.00698	0.00607	0.250	1.00701	0.99509 to 1.01906
Alcohol ^b	0.00847	0.00172	8.10 x 10 ⁻⁷	1.00851	1.00511 to 1.01191
Alcohol, Past Week ^b	0.01425	0.00385	0.00022	1.01435	1.00673 to 1.02204
Alcohol, Typical Week ^b	0.0029	0.00485	0.550	1.0029	0.99342 to 1.01248
Alcohol QxF ^b	0.0066	0.00137	1.30 x 10 ⁻⁶	1.00663	1.00392 to 1.00933
Beer ^b	0.0341	0.00502	1.10 x 10 ⁻¹¹	1.03469	1.02456 to 1.04492
Wine ^b	0.0063	0.00653	0.330	1.00632	0.99352 to 1.01928
Spirits ^b	0.00932	0.01092	0.390	1.00936	0.98799 to 1.03120
Max Drinks Ever ^c	0.03067	0.00385	1.70 x 10 ⁻¹⁵	1.03115	1.02339 to 1.03896
Symptom Count ^d	0.0916	0.023	6.60 x 10 ⁻⁵	1.0959	1.04762 to 1.14646
Smoking Score ^e	0.3154	0.0251	<2 x 10 ⁻¹⁶	1.3708	1.30500 to 1.43993
	Multivariate				
BMI	0.0047	0.00985	0.630	1.00471	0.98550 to 1.02430
Alcohol	-0.002	0.0038	0.610	0.99805	0.99064 to 1.00550
Max Drinks Ever	0.00794	0.007	0.260	1.00797	0.99424 to 1.02190
Symptom Count	0.09285	0.0219	2.20 x 10 ⁻⁵	1.0973	1.05119 to 1.14542
Smoking Score	0.30061	0.03887	1.00 x 10 ⁻¹⁴	1.35069	1.25160 to 1.45761
Men					
	Univariate				
BMI ^a	0.02161	0.00758	0.0044	1.02184	1.00678 to 1.03714
Alcohol ^b	0.00798	0.00123	7.60 x 10 ⁻¹¹	1.00801	1.00558 to 1.01044
Alcohol, Past Week ^b	0.01107	0.00166	2.80 x 10 ⁻¹¹	1.01113	1.00785 to 1.01443
Alcohol, Typical Week ^b	0.00942	0.00254	0.00021	1.00947	1.00445 to 1.01450
Alcohol QxF ^b	0.00727	0.00114	2.10 x 10 ⁻¹⁰	1.0073	1.00505 to 1.00955
Beer ^b	0.01392	0.0019	2.20 x 10 ⁻¹³	1.01402	1.01025 to 1.01780

Table S4. Effects on all-cause mortality in never-smokers (Smoking Score = 0). Cox proportional hazards analysis, with adjustment within-family similarity. Hazard Ratios (HR) are per BMI unit, per drink per week, per drink, and per symptom, as appropriate.

	N total	N Deaths	B	robust_se	p	HR	95% Confidence Interval
Univariate							
Sex	14807	1541	0.2667	0.0553	1.40 x 10 ⁻⁶	1.3056	1.17153 to 1.45512
BMI	13886	1454	0.0223	0.0073	0.0022	1.0225	1.00802 to 1.03729
Alcohol	14256	1435	0.0079	0.0023	6.40 x 10 ⁻⁴	1.0079	1.0034 to 1.01249
Beer	10825	990	0.0174	0.0045	9.40 x 10 ⁻⁵	1.0175	1.00862 to 1.02657
Wine	10997	1000	0.0000	0.0101	0.996	1.0000	0.9804 to 1.01999
Spirits	10630	972	-0.0025	0.016	0.88	0.9976	0.96671 to 1.02928
Max Drinks Ever	11569	869	0.0082	0.0055	0.134	1.0083	0.99742 to 1.01916
Symptom Count	11556	903	0.0502	0.0264	0.057	1.0515	0.99846 to 1.10732
Multivariate							
			B	robust_se	p	HR	
Sex	9778	665	0.1824	0.0932	0.05	1.2001	0.99973 to 1.44062
BMI	9778	665	0.0248	0.0113	0.028	1.0251	1.00266 to 1.04807
Alcohol	9778	665	0.0037	0.0053	0.486	1.0037	0.99333 to 1.01419
Max Drinks Ever	9778	665	-0.0012	0.0078	0.883	0.9989	0.98365 to 1.01419
Symptom Count	9778	665	0.0667	0.0278	0.016	1.0690	1.01229 to 1.12884

Table S5. Effects on all-cause mortality in younger people, born in 1940 or later. Cox proportional hazards analysis, with adjustment within-family similarity. Hazard Ratios (HR) are per BMI unit, per drink per week, per drink, and per symptom, as appropriate. Hazard ratio for smoking score is per unit on the scale Never = 0, Ex = 1, Current < 10/day = 2, Current 10+/day = 3.

	N Total	N Deaths	B	robust_se	p	HR	95% Confidence Interval
Univariate							
Sex	25110	765	0.406	0.0742	4.40 x 10 ⁻⁸	1.5008	1.2977 to 1.7357
BMI	23091	707	0.0136	0.0099	0.170	1.0137	0.9942 to 1.0336
Alcohol	24452	740	0.011	0.0018	7.00 x 10 ⁻¹⁰	1.0110	1.0075 to 1.0146
Beer	18820	590	0.0164	0.0026	1.30 x 10 ⁻¹⁰	1.0166	1.0114 to 1.0217
Wine	18985	579	-0.0108	0.0094	0.250	0.9893	0.9712 to 1.0077
Spirits	18195	559	0.0194	0.0064	0.0025	1.0196	1.0069 to 1.0325
Max Drinks Ever	21552	583	0.0159	0.003	1.50 x 10 ⁻⁷	1.0160	1.0101 to 1.0220
Symptom Count	21727	585	0.105	0.0161	6.10 x 10 ⁻¹¹	1.1107	1.0762 to 1.1463
Smoking Score	24448	742	0.3149	0.034	<2.00 x 10 ⁻¹⁶	1.3701	1.2818 to 1.4645
Multivariate							
Sex	18438	480	0.1132	0.1071	0.291	1.1198	0.9078 to 1.3814
BMI	18438	480	0.0200	0.0116	0.083	1.0202	0.9973 to 1.0437
Alcohol	18438	480	0.0009	0.003	0.757	1.0009	0.9950 to 1.0068
Max Drinks Ever	18438	480	0.0002	0.0045	0.970	1.0002	0.9914 to 1.0091
Symptom Count	18438	480	0.0872	0.0203	1.70 x 10 ⁻⁵	1.0911	1.0486 to 1.1354
Smoking Score	18438	480	0.2916	0.0452	1.10 x 10 ⁻¹⁰	1.3386	1.2251 to 1.4626

Figure S1. Cumulative frequencies for number of drinks per week, assessed from questions on number of drinks in the past week, number of drinks in a typical week, and usual quantity x frequency, for men and women.

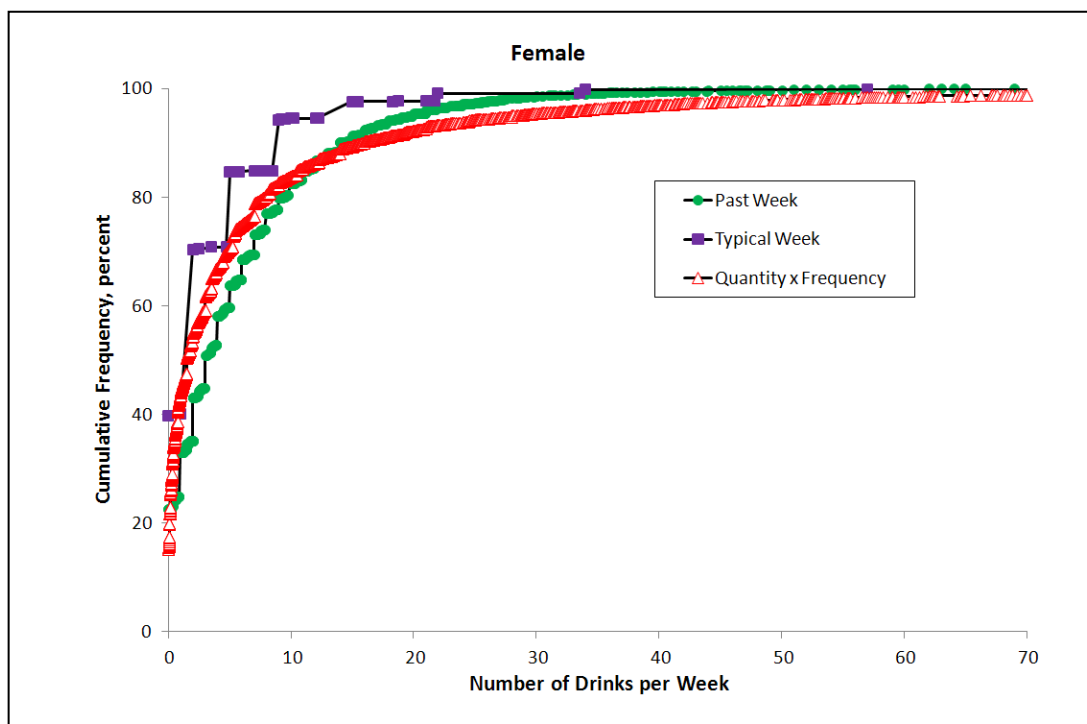
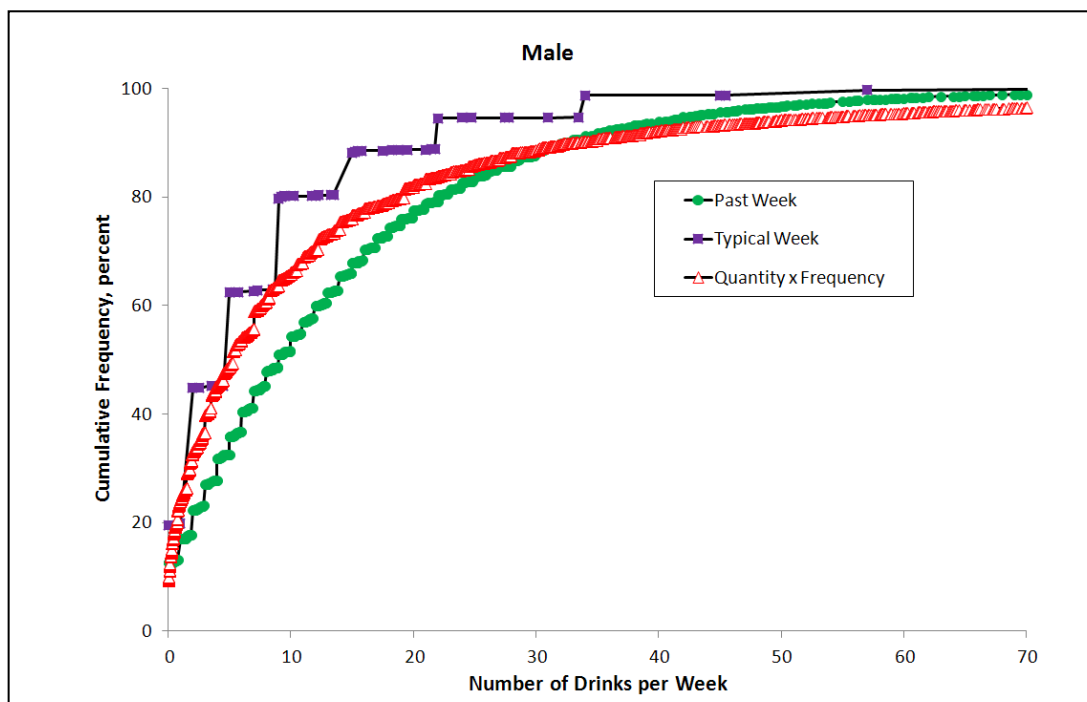


Figure S2. Kaplan-Meier plots. Observed survival for men and women by (a) alcohol intake group (0 = none, 1 = Less than 14, 2 = 14 to less than 28, 3 = 28 to less than 56, 4 = 56 or more drinks per week), (b) symptom count group (0 = No symptoms reported, 1 = any to < 2, 2 = 2 to < 4, 3 = 4 to < 8, 4 = 8 or more), and (c) by smoking group (0 = never smokers, 1 = former smokers, 2 = current smokers < 10/day, 3 = Current smoker \geq 10/day).

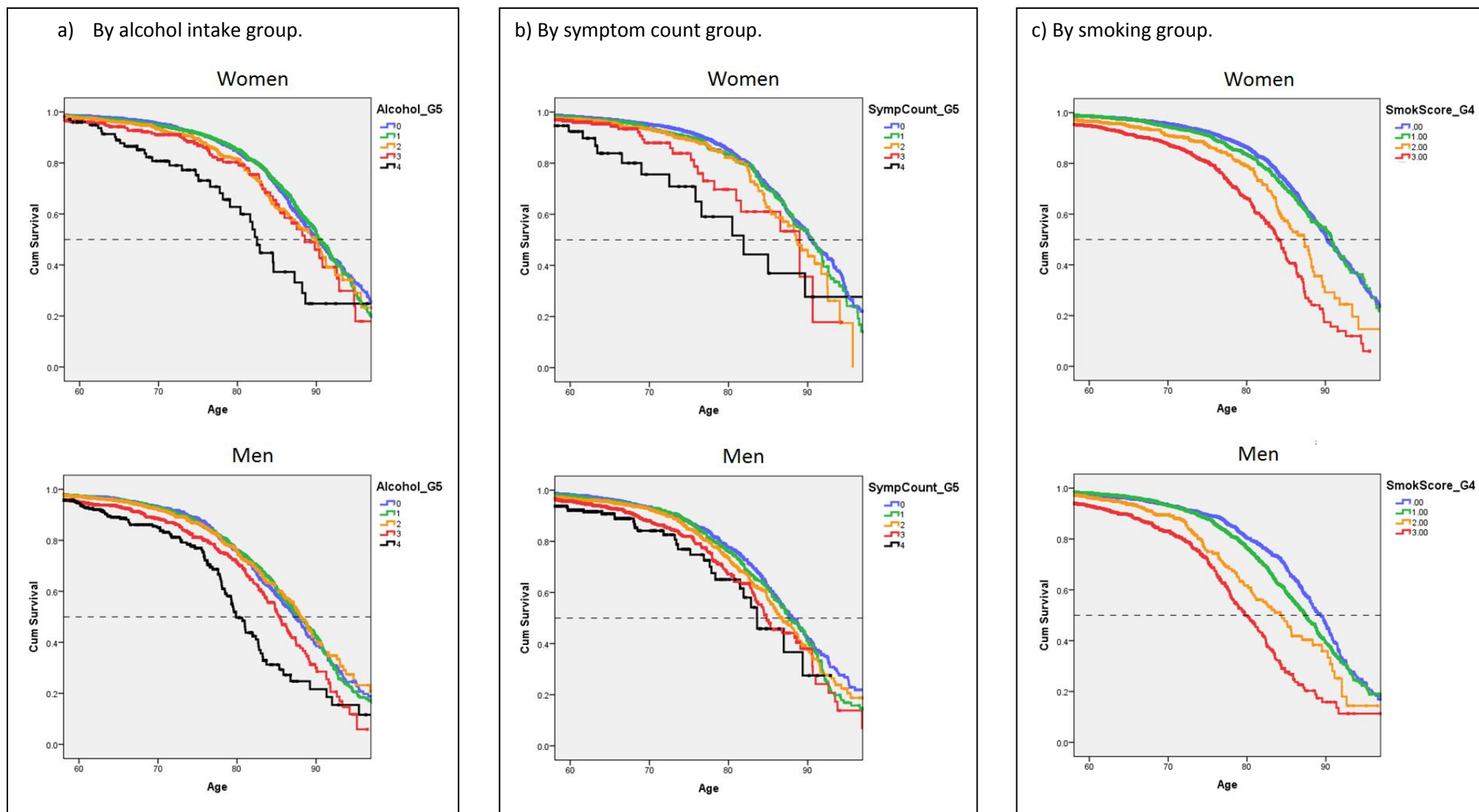


Figure S3. Relationships between total weekly number of drinks (grouped, on x-axis) and individual beverage types (drinks per week), maximum number of drinks in one day (lifetime), symptom count (lifetime) and smoking score (on the scale 0 = Never smoker, 1 = Ex-smoker, 2 = Current smoker < 10/day, 3 = Current smoker \geq 10/day). Shown separately for men and women.

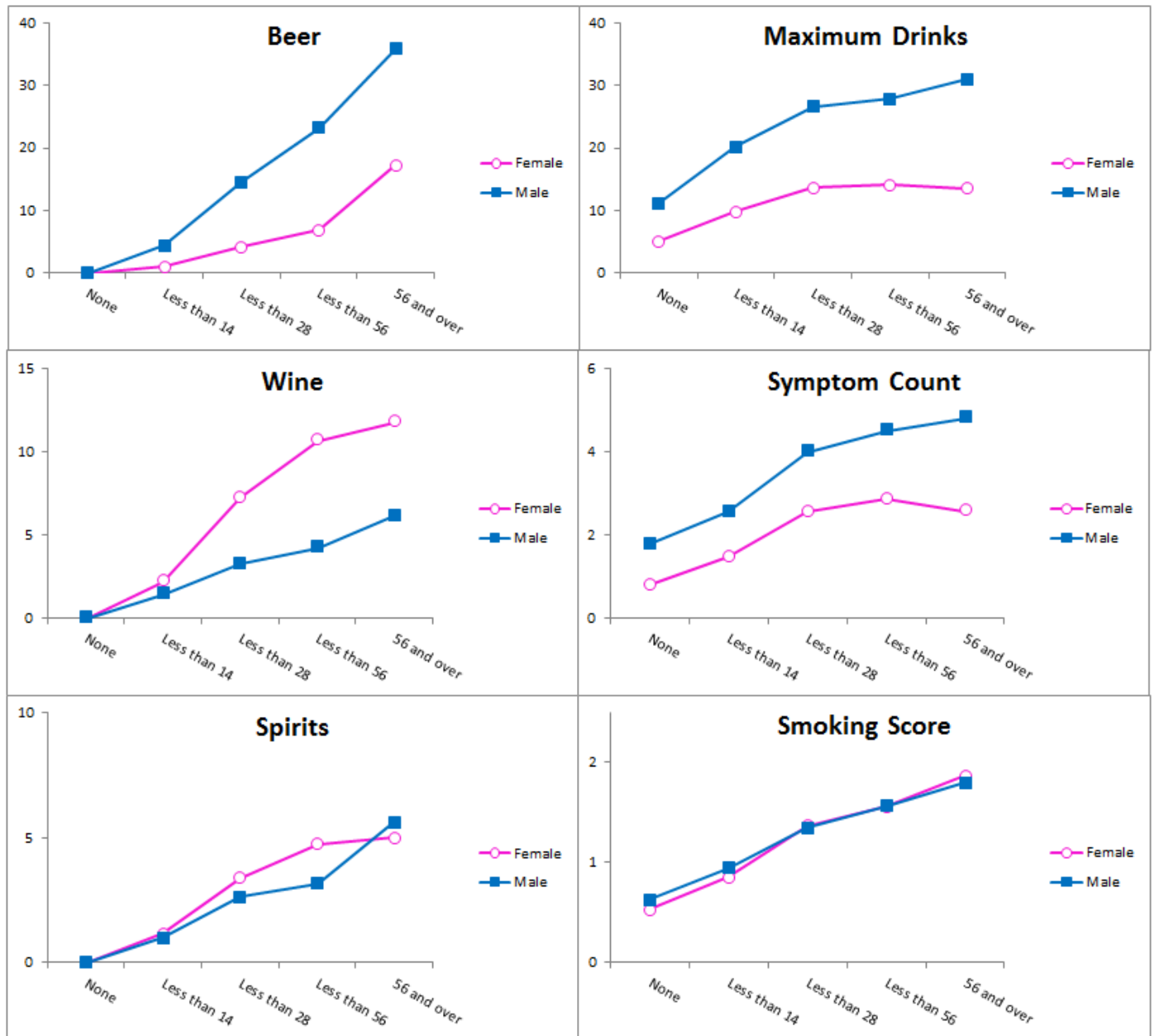


Figure S4. Associations between symptom score (grouped, on x-axis) and alcohol intake (overall and by beverage, in drinks per week), maximum lifetime daily drinks (number of drinks), and smoking score (on the scale 0 = Never smoker, 1 = Ex-smoker, 2 = Current smoker < 10/day, 3 = Current smoker ≥ 10/day). Shown separately for men and women.

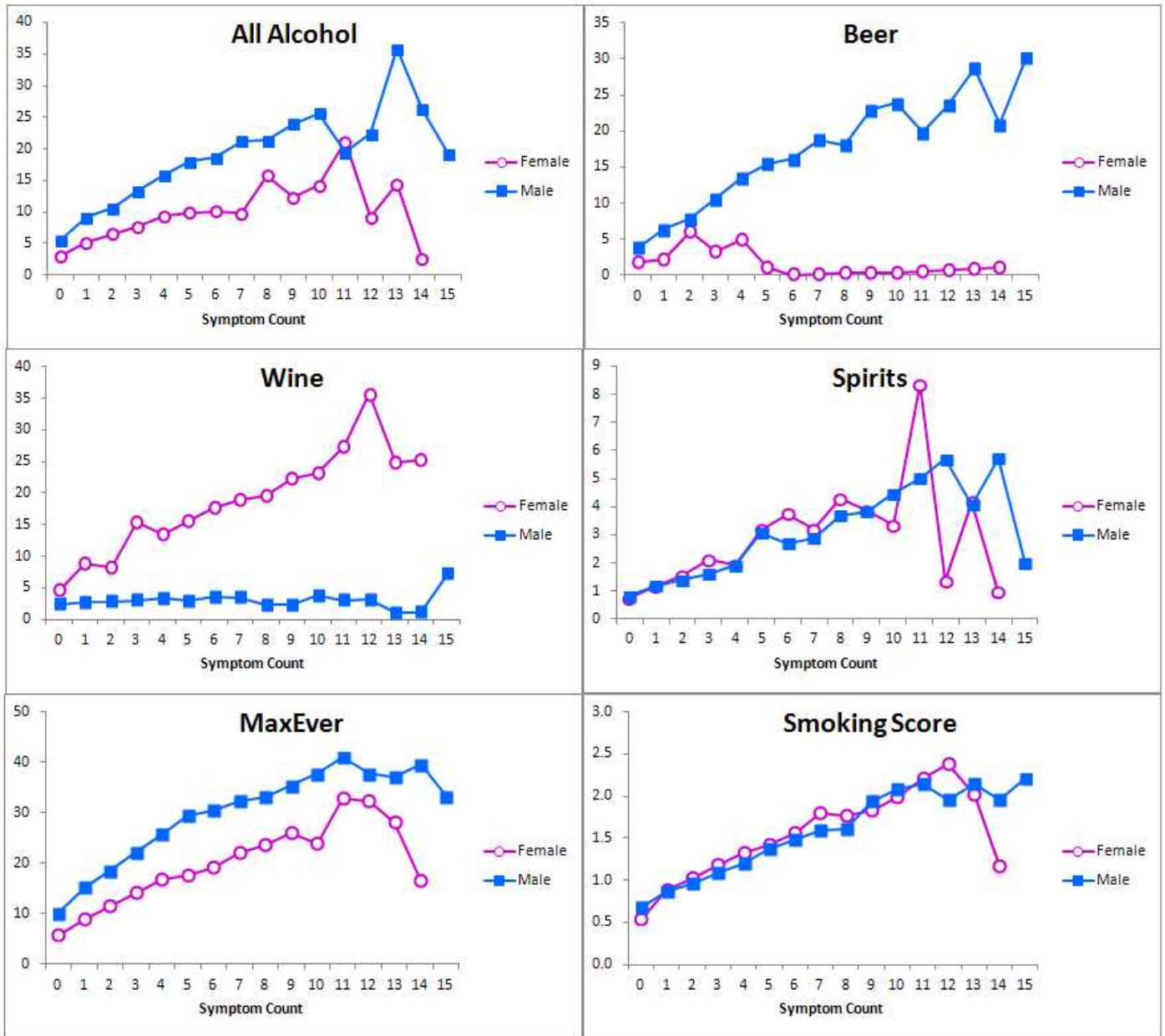


Figure S5. Relationship between calculated average symptom count, and alcohol dependence (AD) by DSM-IV criteria, in 5863 study participants for whom both were available.

