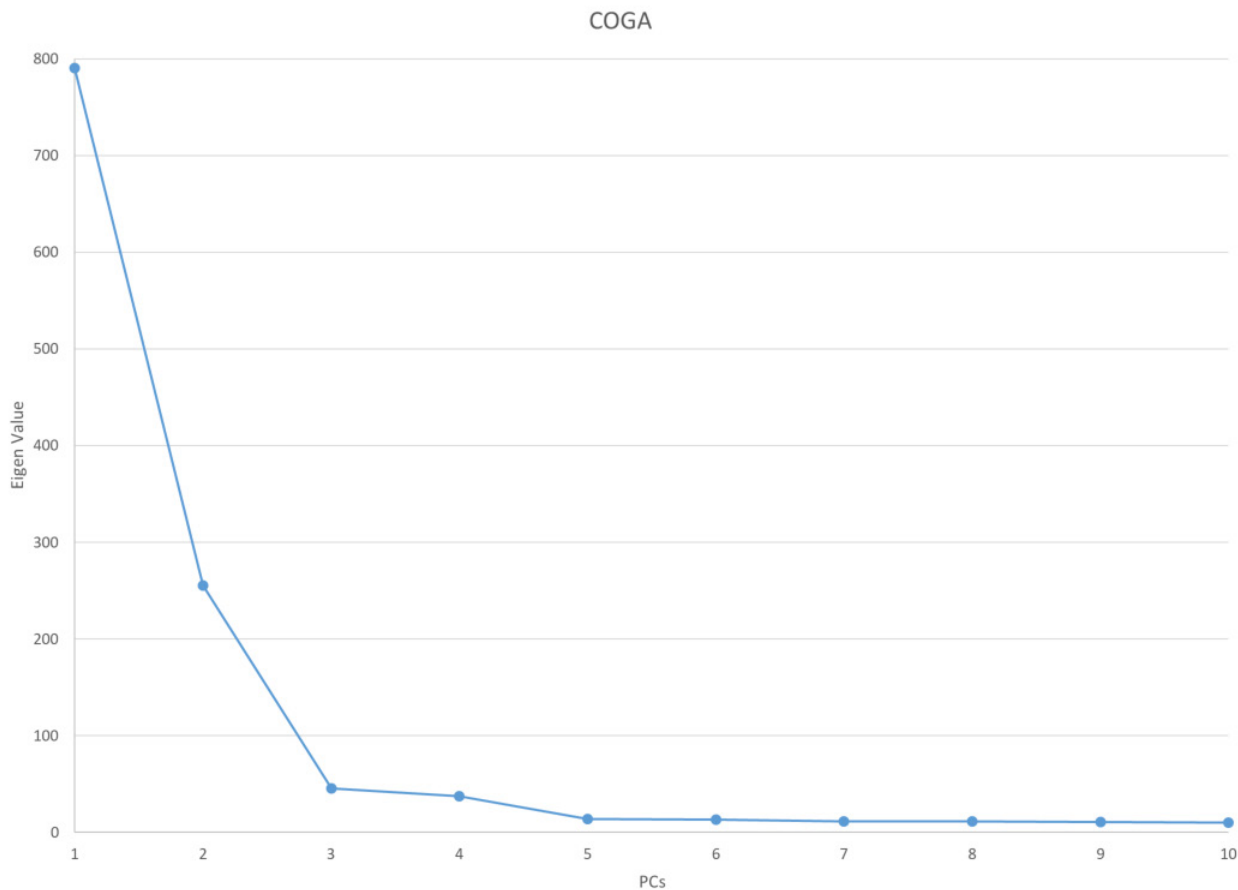


High Polygenic Risk Scores Are Associated With Age of Onset Of Alcohol Use Disorder in Adolescents and Young Adults at Risk

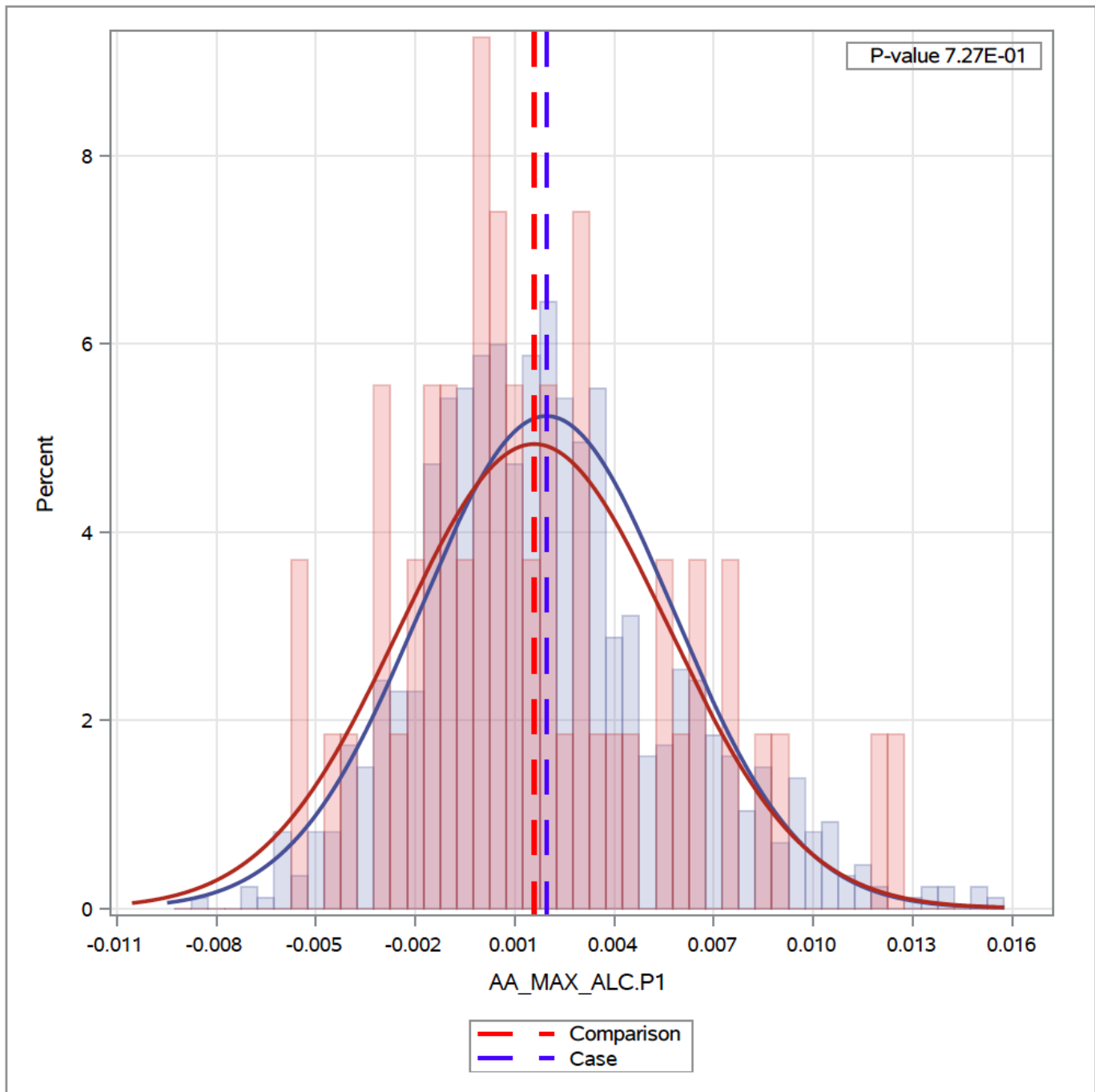
SUPPLEMENT

Supplementary Figure S1. Scree plot for ancestry assignment
Supplementary Figures S2-S5. PRS in the African Ancestry Subsample
Supplementary Table S1. Cox Proportional Hazards Analysis in EA and AA Subjects
Supplementary Table S2. Results of AUC analysis in EA and AA subjects

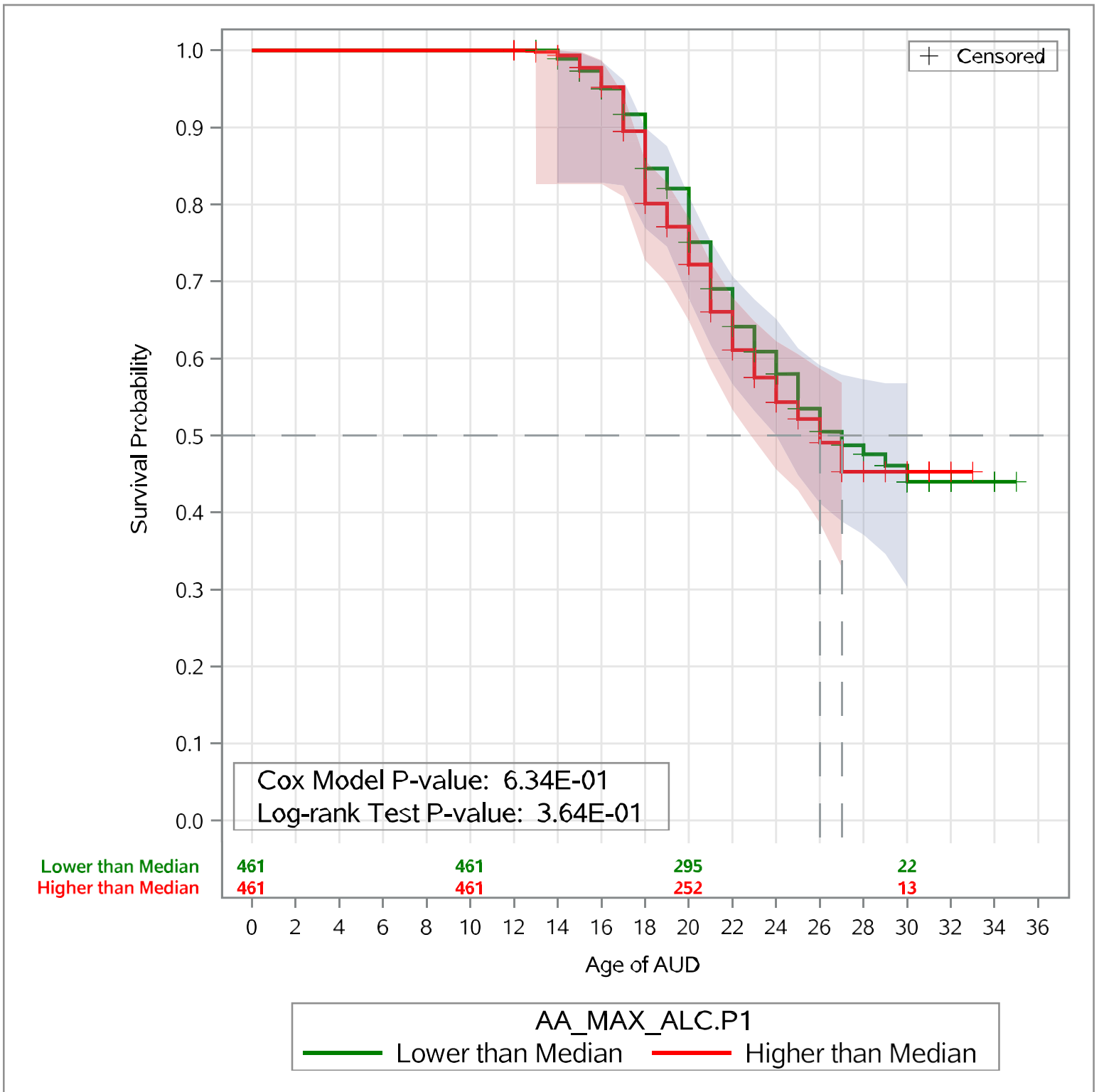


Supplementary Figure S1. Results of a principal components (PCs) analysis of the COGA sample for genetic polymorphisms related to ancestry are illustrated here. The first four PCs were used for ancestry assignment in the present analysis.

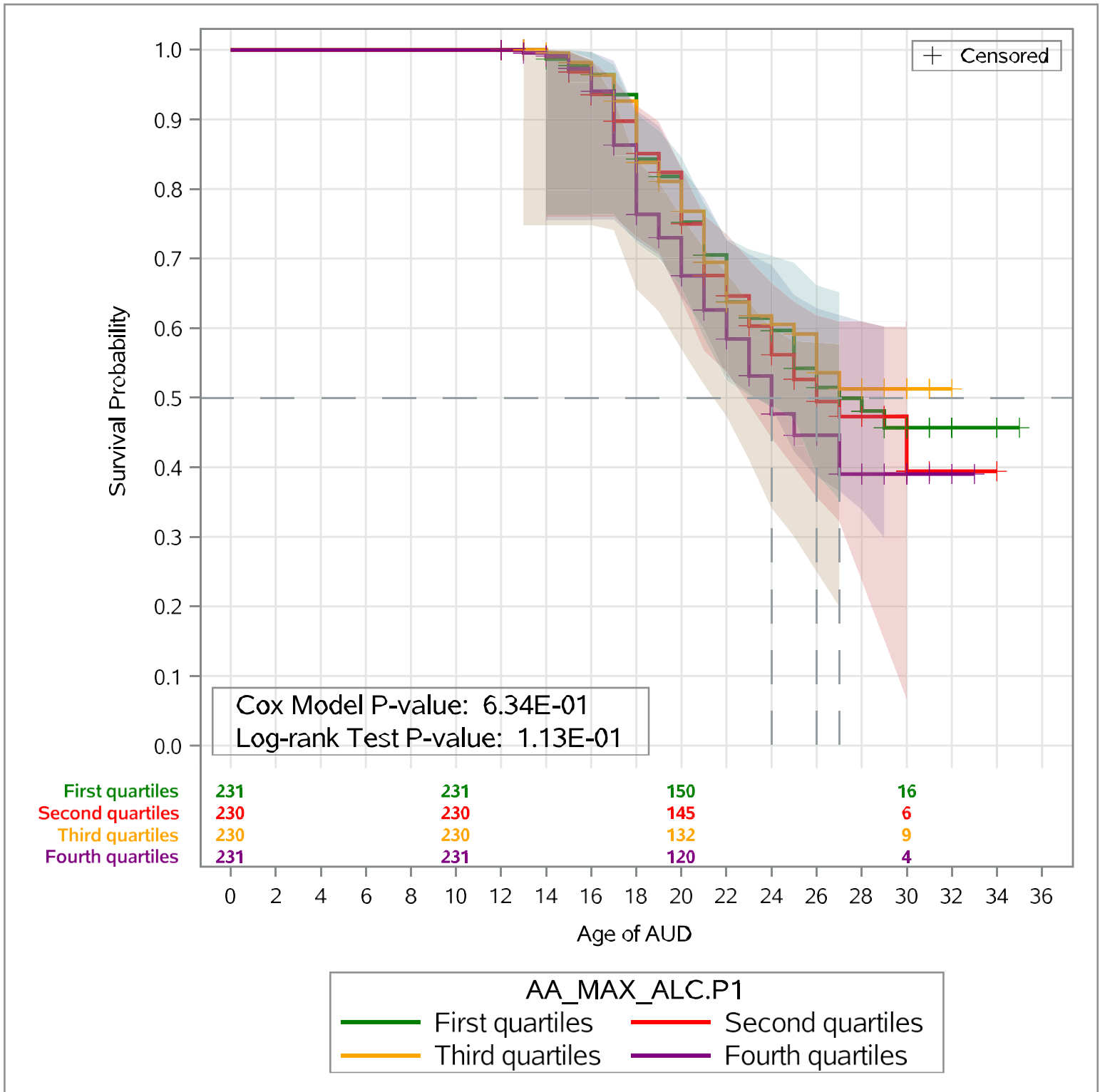
Supplementary Figures S2-S5 PRS in the African Ancestry Subsample



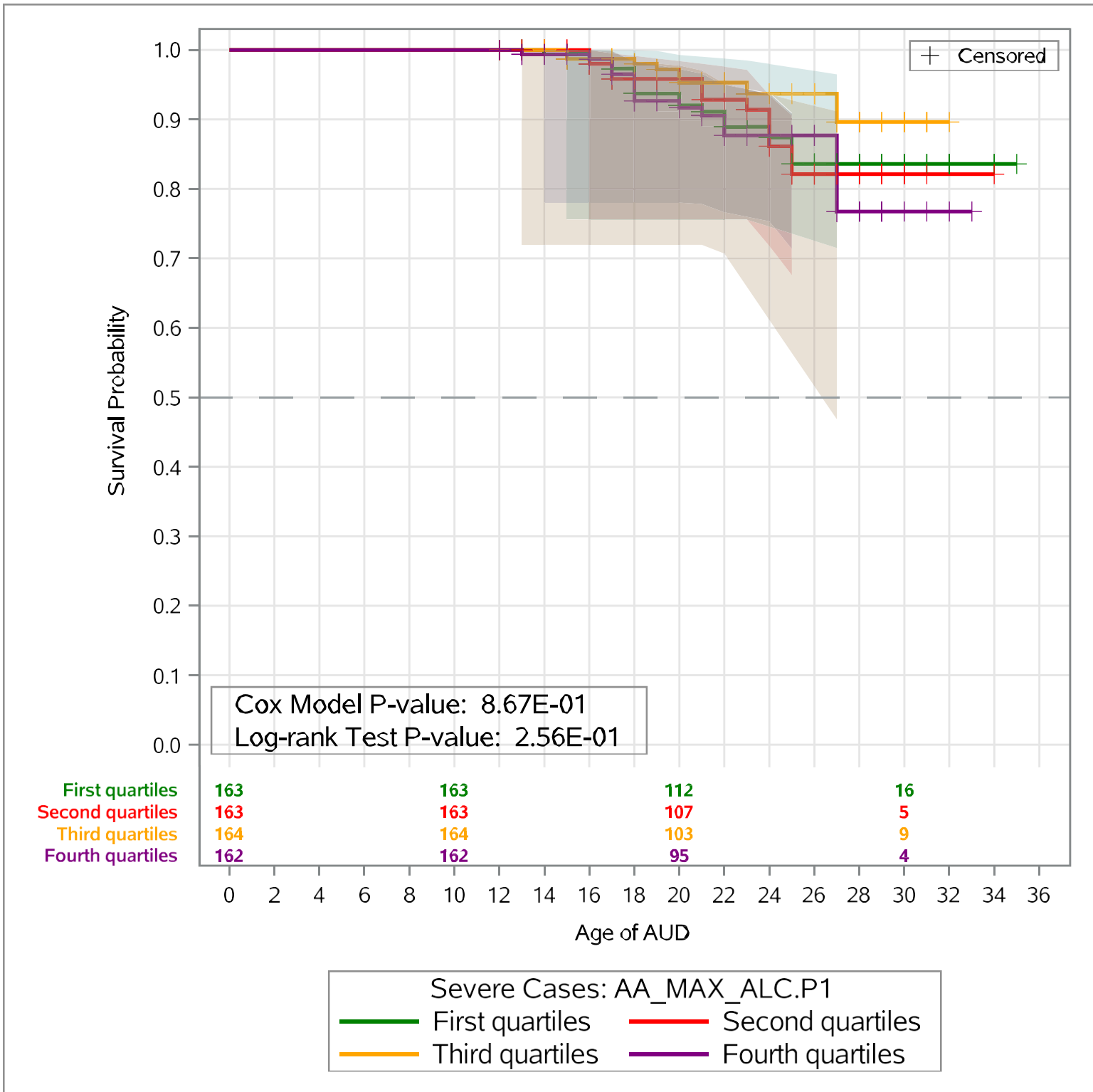
Supplementary Fig. S2. PRS (AA_MAX_ALC.P1) distribution in subjects from AA case families (blue) and comparison families (red). The PRS distribution is not shifted significantly in the case families, adjusting for gender and PC1-PC4. It is also not significant when calculated by PRS-CSx ($p=7.27e-1$).



Supplementary Fig. S3. Kaplan-Meier curve showing the AOO for AUD in African ancestry subjects using a median split in the PRS distribution. No significant difference is seen between the two groups.



Supplementary Fig. S4. Kaplan-Meier curve showing the AOO for AUD in African ancestry subjects divided by quartiles of the PRS distribution. No significant difference is seen between the four groups.



Supplementary Fig. S5. Kaplan-Meier curve showing the AOO for Severe AUD in African ancestry subjects divided by quartiles of the PRS distribution. No significant difference is seen between the four groups.

Supplementary Table S1. Cox proportional hazards models for AA subjects

Analysis of Maximum Likelihood Estimates AA								
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Sex	1	-0.53854	0.11760	20.9723	4.66E-06	0.584	0.463	0.735
AA_MAX_ALC.P1(with PC1 – PC4)	1	0.03633	0.07623	0.2271	6.34E-01	1.037	0.893	1.204
Family Type	1	0.04227	0.29567	0.0204	8.86E-01	1.043	0.584	1.862

Sup. Table S1A. Cox proportional hazards model for Sex, Family Type (Case/comparison) and PRS (AA_MAX_ALC>P1) in AA subjects. The model is also adjusted for ancestry using the first four principal components of population stratification (PC1-PC4). All hazard ratios show the effect of a particular variable after accounting for the effects of all other variables. The PRS effect is not significant (and remains non-significant after recalculation with PRS-CSx).

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Sex		1	-0.43121	0.11851	13.2382	2.74E-04	0.650	0.515	0.820
AA_MAX_ALC_P1(with PC1-PC4)		1	-0.00963	0.07646	0.0159	9.00E-01	0.990	0.853	1.151
Age of first drink		1	-0.13620	0.01863	53.4425	2.66E-13	0.873	0.841	0.905
Peer drink		1	0.89579	0.12376	52.3920	4.55E-13	2.449	1.922	3.122
Family Type		1	-0.01492	0.28410	0.0028	9.58E-01	0.985	0.565	1.719
Comorbidity	Both	1	0.56521	0.18406	9.4297	2.13E-03	1.760	1.227	2.524
Comorbidity	External	1	0.36410	0.12863	8.0127	4.65E-03	1.439	1.119	1.852
Comorbidity	Internal	1	0.15823	0.36115	0.1919	6.61E-01	1.171	0.577	2.378

Sup. Table S1B. Cox proportional hazards model for Sex, PRS (with PCs), Family type (Case/comparison), Age of first drink, Peer Drinking, and Comorbidity in AA subjects. The model is also adjusted for ancestry using the first four principal components of population stratification (PC1-PC4). All hazard ratios show the effect of a particular variable after accounting for the effects of all other variables. The PRS effect is not significant (and remains non-significant after recalculation with PRS-CSx).

Supplementary Table S2. Results of AUC analysis in EA and AA subjects

The following tables show Area under the Receiver Operating Characteristics Curve for All AUD in EA subjects (2A), Severe AUD in EA subjects (2B), All AUD in AA subjects (2C), and Severe AUD in AA subjects (2D). In each table the first group of rows shows PRS added as the last variable, the second group adds PRS as the first variable, and the third group adds PRS in the middle of the model. Columns reflect predictive accuracy at specific ages (e.g. the first column shows accuracy for all onsets up to the age of 15) and the last column shows integrated accuracy for all onsets at any time.

In general (though not always) peak accuracy is attained when all variables are included in the model. It may be observed that power is generally driven by the single variable Age of first drink. Other variables (including PRS) add little by themselves but together are contributory to optimal accuracy. Overall accuracy tends to be better for Severe AUD than All AUD. Accuracy tends to be better at earlier ages than later ages. The accuracy of these models is within the range generally thought to be potentially useful for genetic counseling.¹

A. EA Overall															
	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Integrated
age of first drink	0.8538	0.8236	0.8138	0.7801	0.7396	0.7304	0.7246	0.7136	0.7307	0.7530	0.7673	0.7497	0.7385	0.7022	0.7727
age of first drink sex	0.8439	0.8112	0.7966	0.7786	0.7423	0.7370	0.7282	0.7233	0.7396	0.7714	0.7908	0.7778	0.7639	0.7172	0.7723
age of first drink sex case/control	0.8517	0.8131	0.8025	0.7809	0.7464	0.7381	0.7297	0.7227	0.7357	0.7693	0.7795	0.7651	0.7520	0.7016	0.7734
age of first drink sex case/control comorbidity	0.8678	0.8304	0.8145	0.7782	0.7398	0.7384	0.7450	0.7384	0.7507	0.7868	0.7827	0.7704	0.7499	0.6891	0.7792
age of first drink sex case/control comorbidity peer drinking	0.8451	0.8304	0.8260	0.7957	0.7624	0.7454	0.7595	0.7604	0.7738	0.8012	0.7911	0.7712	0.7473	0.7203	0.7889
age of first drink sex case/control comorbidity peer drinking PRS(PC1-PC4)	0.8566	0.8402	0.8297	0.8069	0.7714	0.7577	0.7632	0.7662	0.7802	0.8055	0.7894	0.7648	0.7432	0.7230	0.7957
	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Integrated
PRS(PC1-PC4)	0.6359	0.5869	0.5889	0.6032	0.5877	0.6013	0.5649	0.5762	0.5859	0.5829	0.5528	0.5494	0.5561	0.6139	0.5863
PRS(PC1-PC4) age of first drink	0.8728	0.8342	0.8169	0.7946	0.7531	0.7496	0.7332	0.7247	0.7434	0.7631	0.7594	0.7374	0.7271	0.6939	0.7818
PRS(PC1-PC4) age of first drink sex	0.8634	0.8265	0.8054	0.7962	0.7575	0.7565	0.7376	0.7357	0.7516	0.7791	0.7859	0.7687	0.7579	0.7168	0.7841
PRS(PC1-PC4) age of first drink sex case/control	0.8679	0.8272	0.8105	0.7973	0.7597	0.7561	0.7380	0.7332	0.7462	0.7765	0.7771	0.7590	0.7483	0.7009	0.7841
PRS(PC1-PC4) age of first drink sex case/control comorbidity	0.8792	0.8401	0.8178	0.7887	0.7481	0.7508	0.7495	0.7455	0.7589	0.7924	0.7794	0.7628	0.7444	0.6883	0.7859
PRS(PC1-PC4) age of first drink sex case/control comorbidity peer drinking	0.8566	0.8402	0.8297	0.8069	0.7714	0.7577	0.7632	0.7662	0.7802	0.8055	0.7894	0.7648	0.7432	0.7230	0.7957
	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Integrated
sex	0.5382	0.5295	0.5025	0.5378	0.5520	0.5546	0.5489	0.5683	0.5662	0.5935	0.6198	0.6247	0.6319	0.5975	0.5494
sex case/control	0.6110	0.5864	0.5761	0.5873	0.6008	0.5946	0.5940	0.5946	0.5856	0.6111	0.6152	0.6165	0.6147	0.5696	0.5933
sex case/control comorbidity	0.7440	0.6982	0.6930	0.6500	0.6269	0.6449	0.6623	0.6649	0.6633	0.6891	0.6748	0.6955	0.6697	0.6170	0.6675
sex case/control comorbidity PRS(PC1-PC4)	0.7769	0.7184	0.7036	0.6711	0.6467	0.6694	0.6669	0.6717	0.6720	0.6946	0.6713	0.6846	0.6673	0.6356	0.6820
sex case/control comorbidity PRS(PC1-PC4) age of first drink	0.8792	0.8401	0.8178	0.7887	0.7481	0.7508	0.7495	0.7455	0.7589	0.7924	0.7794	0.7628	0.7444	0.6883	0.7859
sex case/control comorbidity PRS(PC1-PC4) age of first drink peer drinking	0.8566	0.8402	0.8297	0.8069	0.7714	0.7577	0.7632	0.7662	0.7802	0.8055	0.7894	0.7648	0.7432	0.7230	0.7957

B. EA Severe														
	15	16	17	18	19	20	21	22	23	24	25	26	27	integrated
age of first drink	0.873	0.890	0.902	0.886	0.865	0.847	0.833	0.835	0.859	0.884	0.850	0.854	0.837	0.870
age of first drink sex	0.847	0.873	0.873	0.867	0.849	0.838	0.821	0.826	0.847	0.881	0.858	0.861	0.841	0.857
age of first drink sex case/control	0.833	0.872	0.880	0.878	0.862	0.844	0.825	0.825	0.850	0.885	0.846	0.845	0.826	0.857
age of first drink sex case/control comorbidity	0.896	0.888	0.908	0.904	0.892	0.895	0.896	0.891	0.900	0.924	0.889	0.891	0.860	0.897
age of first drink sex case/control comorbidity peer drinking	0.939	0.918	0.939	0.929	0.919	0.902	0.900	0.898	0.913	0.934	0.898	0.889	0.868	0.917
age of first drink sex case/control comorbidity peer drinking PRS(PC1-PC4)	0.950	0.918	0.940	0.935	0.922	0.905	0.897	0.893	0.906	0.920	0.878	0.864	0.854	0.916
	15	16	17	18	19	20	21	22	23	24	25	26	27	integrated
PRS(PC1-PC4)	0.736	0.599	0.608	0.610	0.614	0.602	0.572	0.564	0.560	0.542	0.521	0.528	0.561	0.604
PRS(PC1-PC4) age of first drink	0.891	0.880	0.896	0.892	0.875	0.864	0.837	0.834	0.850	0.866	0.813	0.815	0.807	0.868
PRS(PC1-PC4) age of first drink sex	0.877	0.871	0.883	0.888	0.872	0.862	0.834	0.833	0.847	0.869	0.829	0.835	0.824	0.865
PRS(PC1-PC4) age of first drink sex case/control	0.872	0.878	0.895	0.902	0.887	0.868	0.837	0.835	0.851	0.875	0.820	0.822	0.813	0.869
PRS(PC1-PC4) age of first drink sex case/control comorbidity	0.909	0.880	0.904	0.903	0.893	0.899	0.892	0.884	0.891	0.910	0.866	0.865	0.845	0.894
PRS(PC1-PC4) age of first drink sex case/control comorbidity peer drinking	0.950	0.918	0.940	0.935	0.922	0.905	0.897	0.893	0.906	0.920	0.878	0.864	0.854	0.916
	15	16	17	18	19	20	21	22	23	24	25	26	27	integrated
sex	0.459	0.506	0.458	0.503	0.518	0.524	0.526	0.536	0.539	0.564	0.613	0.614	0.606	0.520
sex case/control	0.511	0.582	0.562	0.602	0.624	0.611	0.589	0.589	0.602	0.627	0.639	0.632	0.622	0.592
sex case/control comorbidity	0.777	0.751	0.781	0.792	0.799	0.814	0.814	0.800	0.797	0.809	0.805	0.816	0.768	0.791
sex case/control comorbidity PRS(PC1-PC4)	0.866	0.771	0.808	0.801	0.807	0.831	0.816	0.793	0.787	0.787	0.764	0.777	0.765	0.805
sex case/control comorbidity PRS(PC1-PC4) age of first drink	0.909	0.880	0.904	0.903	0.893	0.899	0.892	0.884	0.891	0.910	0.866	0.865	0.845	0.894
sex case/control comorbidity PRS(PC1-PC4) age of first drink peer drinking	0.950	0.918	0.940	0.935	0.922	0.905	0.897	0.893	0.906	0.920	0.878	0.864	0.854	0.916

C. AA Overall															
	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Integrated
age of first drink	0.805	0.754	0.766	0.752	0.761	0.739	0.682	0.688	0.704	0.771	0.832	0.825	0.805	0.770	0.770
age of first drink sex	0.854	0.724	0.751	0.748	0.768	0.736	0.705	0.684	0.700	0.786	0.847	0.836	0.796	0.776	0.766
age of first drink sex case/control	0.863	0.715	0.750	0.737	0.760	0.738	0.692	0.664	0.682	0.766	0.822	0.809	0.778	0.758	0.754
age of first drink sex case/control comorbidity	0.811	0.726	0.743	0.737	0.746	0.735	0.698	0.687	0.693	0.767	0.826	0.782	0.733	0.700	0.747
age of first drink sex case/control comorbidity peer drinking	0.885	0.810	0.838	0.812	0.812	0.786	0.759	0.729	0.749	0.794	0.823	0.750	0.730	0.691	0.780
age of first drink sex case/control comorbidity peer drinking PRS(PC1-PC4)	0.871	0.832	0.854	0.826	0.823	0.791	0.761	0.735	0.747	0.785	0.812	0.733	0.738	0.712	0.786
	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Integrated
PRS(PC1-PC4)	0.493	0.504	0.500	0.548	0.560	0.535	0.532	0.574	0.561	0.551	0.534	0.519	0.637	0.657	0.554
PRS(PC1-PC4) age of first drink	0.780	0.739	0.759	0.756	0.769	0.737	0.676	0.697	0.695	0.748	0.803	0.767	0.801	0.783	0.766
PRS(PC1-PC4) age of first drink sex	0.840	0.747	0.770	0.765	0.786	0.748	0.707	0.700	0.702	0.785	0.848	0.818	0.801	0.803	0.777
PRS(PC1-PC4) age of first drink sex case/control	0.846	0.745	0.773	0.758	0.780	0.749	0.697	0.680	0.686	0.769	0.827	0.803	0.787	0.786	0.767
PRS(PC1-PC4) age of first drink sex case/control comorbidity	0.791	0.744	0.749	0.746	0.756	0.738	0.700	0.696	0.692	0.757	0.816	0.753	0.738	0.720	0.749
PRS(PC1-PC4) age of first drink sex case/control comorbidity peer drinking	0.871	0.832	0.854	0.826	0.823	0.791	0.761	0.735	0.747	0.785	0.812	0.733	0.738	0.712	0.786
	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Integrated
sex	0.686	0.571	0.590	0.598	0.613	0.585	0.599	0.567	0.571	0.605	0.642	0.643	0.601	0.615	0.597
sex case/control	0.703	0.569	0.596	0.598	0.616	0.595	0.601	0.561	0.569	0.605	0.639	0.640	0.603	0.620	0.597
sex case/control comorbidity	0.634	0.631	0.615	0.629	0.622	0.620	0.632	0.618	0.611	0.623	0.639	0.588	0.538	0.510	0.609
sex case/control comorbidity PRS(PC1-PC4)	0.619	0.629	0.619	0.643	0.645	0.631	0.636	0.624	0.610	0.620	0.637	0.578	0.577	0.575	0.618
sex case/control comorbidity PRS(PC1-PC4) age of first drink	0.791	0.744	0.749	0.746	0.756	0.738	0.700	0.696	0.692	0.757	0.816	0.753	0.738	0.720	0.749
sex case/control comorbidity PRS(PC1-PC4) age of first drink peer drinking	0.871	0.832	0.854	0.826	0.823	0.791	0.761	0.735	0.747	0.785	0.812	0.733	0.738	0.712	0.786

D. AA Severe														
	15	16	17	18	19	20	21	22	23	24	25	26	27	integrated
age of first drink	0.807	0.847	0.848	0.815	0.837	0.783	0.753	0.779	0.757	0.848	0.911	0.924	0.894	0.847
age of first drink sex	0.872	0.901	0.902	0.899	0.899	0.821	0.813	0.789	0.743	0.844	0.917	0.928	0.852	0.853
age of first drink sex case/control	0.877	0.905	0.906	0.905	0.907	0.831	0.822	0.791	0.747	0.844	0.918	0.928	0.852	0.855
age of first drink sex case/control comorbidity	0.884	0.906	0.906	0.922	0.899	0.827	0.823	0.756	0.722	0.789	0.864	0.877	0.772	0.813
age of first drink sex case/control comorbidity peer drinking	0.918	0.938	0.938	0.918	0.917	0.838	0.839	0.774	0.723	0.797	0.834	0.830	0.857	0.846
age of first drink sex case/control comorbidity peer drinking PRS(PC1-PC4)	0.912	0.896	0.910	0.923	0.925	0.843	0.842	0.782	0.715	0.785	0.830	0.826	0.888	0.853
	15	16	17	18	19	20	21	22	23	24	25	26	27	integrated
PRS(PC1-PC4)	0.412	0.475	0.553	0.648	0.683	0.638	0.632	0.681	0.600	0.600	0.613	0.558	0.706	0.635
PRS(PC1-PC4) age of first drink	0.788	0.816	0.847	0.833	0.855	0.789	0.752	0.761	0.713	0.809	0.858	0.830	0.880	0.830
PRS(PC1-PC4) age of first drink sex	0.850	0.875	0.892	0.890	0.909	0.825	0.804	0.781	0.717	0.823	0.888	0.879	0.867	0.848
PRS(PC1-PC4) age of first drink sex case/control	0.862	0.879	0.895	0.899	0.919	0.837	0.820	0.785	0.726	0.829	0.897	0.891	0.845	0.845
PRS(PC1-PC4) age of first drink sex case/control comorbidity	0.856	0.859	0.880	0.929	0.926	0.842	0.830	0.758	0.705	0.776	0.863	0.867	0.883	0.847
PRS(PC1-PC4) age of first drink sex case/control comorbidity peer drinking	0.912	0.896	0.910	0.923	0.925	0.843	0.842	0.782	0.715	0.785	0.830	0.826	0.888	0.853
	15	16	17	18	19	20	21	22	23	24	25	26	27	integrated
sex	0.760	0.766	0.767	0.788	0.742	0.685	0.704	0.619	0.582	0.616	0.662	0.687	0.577	0.649
sex case/control	0.773	0.777	0.778	0.801	0.759	0.707	0.725	0.633	0.601	0.624	0.674	0.695	0.594	0.663
sex case/control comorbidity	0.823	0.820	0.823	0.870	0.799	0.743	0.755	0.704	0.688	0.646	0.670	0.677	0.595	0.693
sex case/control comorbidity PRS(PC1-PC4)	0.794	0.788	0.814	0.900	0.843	0.769	0.773	0.715	0.667	0.650	0.682	0.679	0.657	0.717
sex case/control comorbidity PRS(PC1-PC4) age of first drink	0.856	0.859	0.880	0.929	0.926	0.842	0.830	0.758	0.705	0.776	0.863	0.867	0.883	0.847
sex case/control comorbidity PRS(PC1-PC4) age of first drink peer drinking	0.912	0.896	0.910	0.923	0.925	0.843	0.842	0.782	0.715	0.785	0.830	0.826	0.888	0.853

Supplemental Reference

1. Eeltink E, van der Horst MZ, Zinkstok JR, Aalfs CM, Luykx JJ. Polygenic Risk Scores for Genetic Counseling in Psychiatry: Lessons Learned from other Fields of Medicine, Neuroscience and Biobehavioral Reviews (2020),doi: <https://doi.org/10.1016/j.neubiorev.2020.11.021>