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Table S2-1. Number of complete MZ and DZ twin pairs whose twin members are cases (1) or controls (0) for each of the binary psychiatric diagnoses of affective disorders (AD) or substance use (SU). (0,0) means both twin 1 and twin 2 are controls. (0,1) means twin 1 is a control and twin 2 is a case. (1,0) means twin 1 is a case and twin 2 is a control. (1,1) means both twins are cases.

Scale	Diagnosis	MZ twin pairs (twin1, twin2)				DZ twin pairs (twin1, twin2)				Total twin pairs	Total twin individuals
		(0, 0)	(0, 1)	(1, 0)	(1, 1)	(0, 0)	(0, 1)	(1, 0)	(1, 1)		
AD	major depressive disorder	258	46	39	27	328	67	60	20	845	2132
	agoraphobia	361	6	3	0	467	4	4	0	845	2132
	depressive episodes	252	49	40	29	324	69	61	21	845	2132
	panic attack	283	33	35	19	362	55	49	9	845	2132
	panic disorder	355	8	6	1	447	11	17	0	845	2132
	social anxiety	275	39	34	22	341	55	63	16	845	2132
SU	alcohol use	41	24	32	273	29	43	35	368	845	2132
	drug use ever	131	44	32	163	133	89	79	174	845	2132
	cannabis use ever	117	28	22	74	138	75	59	83	596	1663
	tobacco use ever	103	49	43	175	130	76	80	189	845	2132

Table S2-2. Tests concerning thresholds (t) and covariances (c) for binary diagnoses in affective disorders (AD) or substance use (SU). The tests compare the fit between the base model and a submodel (H1t- H4c). Modelling results shown are the difference in log-likelihoods. Superscript a indicates p value between 0.001 and 0.01. Superscript b indicates p value < 0.001. NC: not calculable.

Scale	Diagnosis	Homogeneity of thresholds				Homogeneity of covariances			
		H1t	H2t	H3t	H4t	H1c	H2c	H3c	H4c
AD	major depressive disorder	2.87	0.61	1.11	4.65	0.59	0.06	3.74	27.14 ^b
	agoraphobia	1.72	1.09	NC	NC	0.66	0	0.00	NC
	depressive episodes	2.89	0.69	0.89	4.59	0.37	0	3.98	26.90 ^b
	panic attack	1.8	1.13	0.64	0.03	0.73	2.01	5.90	17.42 ^a
	panic disorder	8.42	0.26	2.36	0.01	0.22	0	2.45	2.83
	social anxiety	2.95	4.73	1.29	0.01	3.83	0.05	4.24	23.20 ^b
SU	alcohol use	6.44	9.24 ^a	2.10	0.01	1.78	4.11	2.54	113.58 ^b
	drug use ever	6.02	2.89	2.65	0.02	2.74	0.67	20.22 ^b	167.30 ^b
	cannabis use ever	5.81	1.79	1.61	0.06	5.29	0.87	16.66 ^b	104.91 ^b
	tobacco use ever	0.43	1.17	2.83	0.03	1.97	1.43	3.47	128.77 ^b

Table S2-3. Tests concerning means (m), variances (v) and covariances (c) for affective disorder IRT (AD-IRT), psychological (PSYCH6) and somatic distress (SOMA6) subscale, and substance use IRT (SU-IRT). The tests compare the fit between the base model and a submodel (H1m- H4c). Modelling results shown are the difference in log-likelihoods. Superscript a indicates p value between 0.001 and 0.01. Superscript b indicates p value < 0.001.

Scale	Phenotype	Phenotype	Homogeneity of means				Homogeneity of variances				Homogeneity of covariances			
			H1m	H2m	H3m	H4m	H1v	H2v	H3v	H4v	H1c	H2c	H3c	H4c
AD	AD-IRT	AD-IRT	5.22	6.49	0.02	2.96	2.66	0.5	0.16	16.75 ^b	1.07	0.58	14.19 ^b	38.22 ^b
PSYCH6	IRT score	IRT score	1.29	1.67	3.54	0	0.81	0.79	0.19	0.01	0.22	1.85	6.71 ^a	13.46 ^b
SOMA6	IRT score	IRT score	5.09	5.11	4.4	0	1.72	0.01	0.75	0.02	4.46	0.12	10.60 ^a	15.01 ^b
SU	SU-IRT	SU-IRT	1.33	1.5	2.97	0.03	0.97	0.28	0.07	0.15	3.94	3.09	16.32 ^b	111.96 ^b

Table S2-4. Model-fitting results for univariate ACE or ADE models for diagnoses in affective disorders (AD), substance use (SU), psychological (PSYCH6) and somatic distress (SOMA6) subscale. The univariate ADE models and their nested sub-models are shown in blue. Model-fitting statistics are (1) -2LL: twice negative log-likelihood, (2) DF: degrees of freedom, (3) diff DF: difference in degrees of freedom to previous submodel, (4) diffLL: difference in log-likelihood, (5) AIC: Akaike's information criterion, (6) p: p value, (7) CI: confidence interval, (8) A: additive genetic factors, (9) C: common environmental factors, (10) E: unique environmental factors.

Scale	Diagnosis	Model	Goodness-of-fit statistics				Parameter estimates (95% CI)		
			-2LL	DF	AIC	diff DF	diff LL	p	A
AD	agoraphobia	ACE	206.61	2069	-3931.4			0.00 (0.00-0.66)	0.00 (0.00-0.00)
		AE	206.61	2070	-3933.4	1	0	0.999	0.00 (0.00-0.00)
		CE	206.61	2070	-3933.4	1	0	1	0.00 (0.00-0.00)
		E	206.61	2071	-3935.4	2	0	1	1.00 (1.00-1.00)
AD-IRT	AD-IRT	ADE	8934.85	2068	4798.85			0.06 (0.00-0.37)	0.28 (0.00-0.42)
		AE	8936.8	2069	4798.8	1	1.95	0.162	0.32 (0.23-0.39)
		E	8987.26	2070	4847.26	2	52.41	0	0.66 (0.58-0.75) 0.68 (0.61-0.77) 1.00 (1.00-1.00)
depressive episodes	depressive episodes	ADE	1986.5	2069	-2151.5			0.23 (0.00-0.55)	0.20 (0.00-0.59)
		AE	1986.72	2070	-2153.3	1	0.23	0.635	0.41 (0.24-0.56)
		E	2008.43	2071	-2133.6	2	21.93	0	0.57 (0.41-0.75) 0.59 (0.44-0.76) 1.00 (1.00-1.00)
major depressive disorder	major depressive disorder	ADE	1941.69	2069	-2196.3			0.26 (0.00-0.56)	0.17 (0.00-0.59)
		AE	1941.86	2070	-2198.1	1	0.16	0.685	0.41 (0.24-0.57)
		E	1963.53	2071	-2178.5	2	21.84	0	0.59 (0.43-0.76) 1.00 (1.00-1.00)
panic attack	panic attack	ADE	1608.7	2069	-2529.3			0.00 (0.00-0.00)	0.42 (0.00-0.60)
		AE	1610.19	2070	-2529.8	1	1.5	0.221	0.37 (0.17-0.55)
		E	1623.07	2071	-2518.9	2	14.38	0.001	0.58 (0.40-0.79) 0.63 (0.45-0.83) 1.00 (1.00-1.00)
panic disorder	panic disorder	ADE	471.43	2069	-3666.6			0.00 (0.00-0.00)	0.32 (0.00-0.76)
		AE	471.93	2070	-3668.1	1	0.49	0.483	0.23 (0.00-0.68)
		E	472.61	2071	-3669.4	2	1.17	0.556	0.68 (0.24-1.00) 0.77 (0.32-1.00) 1.00 (1.00-1.00)
social anxiety	social anxiety	ADE	1817.56	2069	-2320.4			0.16 (0.00-0.57)	0.28 (0.00-0.62)
		AE	1817.96	2070	-2322	1	0.4	0.528	0.42 (0.23-0.58)
		E	1836.87	2071	-2305.1	2	19.31	0	0.56 (0.38-0.76) 0.58 (0.42-0.77) 1.00 (1.00-1.00)

Table S2-4. Model-fitting results for univariate ACE or ADE models for diagnoses in affective disorders (AD), substance use (SU), psychological (PSYCH6) and somatic distress (SOMA6) subscale. The univariate ADE models and their nested sub-models are shown in blue. Model-fitting statistics are (1) -2LL: twice negative log-likelihood, (2) DF: degrees of freedom, (3) diff DF: difference in degrees of freedom to previous submodel, (4) diffLL: difference in log-likelihood, (5) AIC: Akaike's information criterion, (6) p: p value, (7) CI: confidence interval, (8) A: additive genetic factors, (9) C: common environmental factors, (10) E: unique environmental factors.

Scale	Diagnosis	Model	Goodness-of-fit statistics				Parameter estimates (95% CI)		
			-2LL	DF	AIC	diff DF	diff LL	p	A
SU	SU-IRT	ACE	8660.64	2068	4524.64			0.46 (0.24-0.56)	0.03 (0.00-0.20)
		AE	8660.75	2069	4522.75	1	0.12	0.731	0.49 (0.42-0.56)
		CE	8676.96	2069	4538.96	1	16.32	0	0.36 (0.30-0.41)
		E	8788.91	2070	4648.91	2	128.28	0	0.64 (0.59-0.70) 1.00 (1.00-1.00)
	alcohol use	ACE	1655.59	2069	-2482.4			0.31 (0.00-0.69)	0.41 (0.07-0.69)
		AE	1660.98	2070	-2479	1	5.39	0.02	0.75 (0.64-0.84) 0.25 (0.16-0.36)
		CE	1658.13	2070	-2481.9	1	2.54	0.111	0.64 (0.54-0.73) 0.36 (0.27-0.46)
		E	1763.27	2071	-2378.7	2	107.68	0	1.00 (1.00-1.00)
	alcohol use disorder	ACE	4769.05	2067	635.05			0.36 (0.05-0.58)	0.12 (0.00-0.36)
		AE	4769.96	2068	633.96	1	0.91	0.341	0.50 (0.40-0.59) 0.50 (0.41-0.60)
		CE	4774.13	2068	638.13	1	5.08	0.024	0.38 (0.30-0.46) 0.62 (0.54-0.70)
		E	4846.92	2069	708.92	2	77.87	0	1.00 (1.00-1.00)
	cannabis use disorder	ACE	1985.18	2067	-2148.8			0.60 (0.16-0.83)	0.13 (0.00-0.49)
		AE	1985.54	2068	-2150.5	1	0.36	0.548	0.74 (0.61-0.83) 0.26 (0.17-0.39)
		CE	1992.43	2068	-2143.6	1	7.26	0.007	0.59 (0.46-0.69) 0.41 (0.31-0.54)
		E	2057.34	2069	-2080.7	2	72.16	0	1.00 (1.00-1.00)
	drug use ever	ACE	2640.27	2069	-1497.7			0.69 (0.40-0.85)	0.09 (0.00-0.34)
		AE	2640.73	2070	-1499.3	1	0.46	0.5	0.79 (0.71-0.86) 0.21 (0.14-0.29)
		CE	2660.5	2070	-1479.5	1	20.22	0	0.60 (0.52-0.67) 0.40 (0.33-0.48)
		E	2804.15	2071	-1337.9	2	163.87	0	1.00 (1.00-1.00)
	tobacco use ever	ACE	2618.87	2069	-1519.1			0.31 (0.00-0.63)	0.34 (0.07-0.59)
		AE	2625.05	2070	-1514.9	1	6.18	0.013	0.70 (0.60-0.78) 0.30 (0.22-0.40)
		CE	2622.34	2070	-1517.7	1	3.47	0.062	0.57 (0.48-0.65) 0.43 (0.35-0.52)
		E	2744.2	2071	-1397.8	2	125.34	0	1.00 (1.00-1.00)

Table S2-4. Model-fitting results for univariate ACE or ADE models for diagnoses in affective disorders (AD), substance use (SU), psychological (PSYCH6) and somatic distress (SOMA6) subscale. The univariate ADE models and their nested sub-models are shown in blue. Model-fitting statistics are (1) -2LL: twice negative log-likelihood, (2) DF: degrees of freedom, (3) diff DF: difference in degrees of freedom to previous submodel, (4) diffLL: difference in log-likelihood, (5) AIC: Akaike's information criterion, (6) p: p value, (7) CI: confidence interval, (8) A: additive genetic factors, (9) C: common environmental factors, (10) E: unique environmental factors.

Scale	Diagnosis	Model	Goodness-of-fit statistics				Parameter estimates (95% CI)		
			-2LL	DF	AIC	diff	p	A	C/D
						DF			
PSYCH6	IRT score	ADE	2076.43	1611	-1145.6			0.74 (0.09-0.86)	0.04 (0.00-0.71)
		AE	2076.44	1612	-1147.6	1	0.02	0.902	0.78 (0.66-0.86)
		E	2175.12	1613	-1050.9	2	98.69	0	0.22 (0.13-0.34) 0.22 (0.14-0.34) 1.00 (1.00-1.00)
SOMA6	IRT score	ADE	6500.77	1499	3502.77			0.00 (0.00-0.31)	0.27 (0.00-0.37)
		AE	6502.19	1500	3502.19	1	1.42	0.233	0.23 (0.13-0.33)
		E	6520.93	1501	3518.93	2	20.16	0	0.73 (0.63-0.85) 0.77 (0.67-0.87) 1.00 (1.00-1.00)
SOMA6	cannabis use ever	ADE	6116.77	1499	3118.77			0.00 (0.00-0.30)	0.29 (0.00-0.38)
		AE	6119.51	1500	3119.51	1	2.74	0.098	0.25 (0.15-0.35)
		E	6141.97	1501	3139.97	2	25.2	0	0.71 (0.62-0.82) 0.75 (0.65-0.85) 1.00 (1.00-1.00)

Table S2-5. Model-fitting results for multivariate models of (1) psychological (PSYCH6r) and (2) somatic (SOMA6-r) distress subscales of the SPHERE12 and (3) affective disorders (ADr) and (4) substance use (SUR) scales. The models included the Cholesky decomposition (Cholesky ACE) and its submodels (Cholesky AE, Cholesky CE and Cholesky E), Independent pathway (IP), IP with 2 common A factors (IP2A), IP with 3 common A factors (IP3A), common pathway (CP), and eight submodels of the IP. Model-fitting statistics are (1) -2LL: twice negative log-likelihood, (2) DF: degrees of freedom, (3) diff DF: difference in degrees of freedom to previous submodel. Best-fitting models (in boldface type) are selected based on AIC.

Model	Base model	Compare	DF	diff DF	-2LL	diff LL	AIC	p
1	Cholesky ACE		6,354		26388		13680	
2	Cholesky ACE	Cholesky AE	6,364	10	26389	0.94	13661	0.9999
3	Cholesky ACE	Cholesky CE	6,364	10	26418	30.04	13690	0.0008
4	Cholesky ACE	Cholesky E	6,374	20	26536	148.11	13788	<.0001
5	Cholesky ACE	IP	6,360	6	26391	3.51	13671	0.7422
6	Cholesky ACE	IP2A	6,358	4	26390	1.75	13674	0.7818
7	Cholesky ACE	IP3A	6,356	2	26391	3.44	13679	0.1795
8	Cholesky ACE	CP	6,366	12	26397	9.34	13665	0.6737
9	IP		6,360		26391		13671	
10	IP	IP_CE_ACE	6,364	4	26402	10.93	13674	0.0274
11	IP	IP_AE_ACE	6,364	4	26393	1.56	13665	0.8151
12	IP	IP_AC_ACE	6,364	4	26514	122.94	13786	<.0001
13	IP	IP_E_ACE	6,368	8	26423	31.32	13687	0.0001
14	IP	IP_ACE_CE	6,364	4	26408	16.31	13680	0.0026
15	IP	IP_ACE_AE	6,364	4	26391	0	13663	1.0000
16	IP	IP_ACE_E	6,368	8	26420	29.08	13684	0.0003
17	IP	IP_AE_AE	6,368	8	26393	1.56	13657	0.9916
18	IP_ACE_AE		6,364		26391		13663	
19	IP_ACE_AE	IP_AE_AE	6,368	4	26393	1.56	13657	0.8151
20	IP2A		6,358		26390		13674	
21	IP2A	IP2A_CE_ACE	6,364	6	26402	12.69	13674	0.0482
22	IP2A	IP2A_AE_ACE	6,362	4	26391	1.1	13667	0.8946
23	IP2A	IP2A_AC_ACE	6,362	4	26520	130.67	13796	<.0001
24	IP2A	IP2A_E_ACE	6,368	10	26423	33.08	13687	0.0003
25	IP2A	IP2A_ACE_CE	6,362	4	26393	3.04	13669	0.5511
26	IP2A	IP2A_ACE_AE	6,362	4	26390	0	13666	1.0000
27	IP2A	IP2A_ACE_E	6,366	8	26393	3.58	13661	0.8931
28	IP2A	IP2A_AE_AE	6,366	8	26391	1.1	13659	0.9976
29	IP2A_ACE_AE		6,362		26390		13666	
30	IP2A_ACE_AE	IP2A_AE_AE	6,366	4	26391	1.1	13659	0.8946
31	Cholesky AE		6,364		26389		13661	

Table S2-5. Model-fitting results for multivariate models of (1) psychological (PSYCH6r) and (2) somatic (SOMA6-r) distress subscales of the SPHERE12 and (3) affective disorders (ADr) and (4) substance use (SUR) scales. The models included the Cholesky decomposition (Cholesky ACE) and its submodels (Cholesky AE, Cholesky CE and Cholesky E), Independent pathway (IP), IP with 2 common A factors (IP2A), IP with 3 common A factors (IP3A), common pathway (CP), and eight submodels of the IP. Model-fitting statistics are (1) -2LL: twice negative log-likelihood, (2) DF: degrees of freedom, (3) diff DF: difference in degrees of freedom to previous submodel. Best-fitting models (in boldface type) are selected based on AIC.

Model	Base model	Compare	DF	diff DF	-2LL	diff LL	AIC	p
32	Cholesky AE	CP	6,366	2	26397	8.4	13665	0.0150
33	Cholesky AE	IP_AE_AE	6,368	4	26393	4.14	13657	0.3872
34	Cholesky AE	IP2A_AE_AE	6,366	2	26391	1.91	13659	0.3848

Table S3-1. Number of SNPs with p values lower than a p value threshold in the GSCAN GWAS files on which quality control was performed (QC) and number of SNPs that were selected by LD-based clumping (LD, blue) according to eight significance thresholds. The SNP numbers are shown for each autosome (1-22) and summed (Total). The discovery sample phenotypes are SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per day).

Trait	Chromosome	p < 5e-08		p < 1e-05		p < 1e-03		p < 1e-02		p < 5e-02		p < 0.1		p < 0.5		p < 1	
		QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD
SI	1	898	16	2,507	56	9,637	385	29,653	1,445	83,964	4,431	141,855	7,268	548,730	22,221	1,031,901	31,511
	2	1,062	18	2,350	77	12,770	497	38,716	1,739	102,030	4,798	166,533	7,759	597,005	22,418	1,096,596	31,710
	3	787	11	2,432	63	11,111	413	32,428	1,391	85,107	3,965	139,860	6,465	502,468	19,331	920,128	27,345
	4	480	8	1,279	31	6,737	252	24,226	1,099	74,822	3,492	128,761	5,847	498,374	18,148	941,095	25,912
	5	485	10	1,687	52	6,963	298	22,884	1,102	67,678	3,316	114,412	5,551	447,450	17,327	839,031	24,823
	6	450	12	1,764	44	8,194	281	27,756	1,157	79,125	3,420	131,576	5,592	471,630	16,525	864,068	23,436
	7	443	10	1,582	42	6,974	291	22,366	1,117	63,462	3,243	106,713	5,309	412,380	15,879	761,980	22,564
	8	181	7	823	22	4,772	221	19,019	1,000	59,410	3,006	100,544	4,931	380,885	14,750	707,512	21,000
	9	25	5	725	24	4,062	186	14,584	827	45,120	2,538	77,229	4,207	299,858	12,864	557,645	18,478
	10	652	11	1,449	33	5,101	213	16,852	959	52,736	2,851	90,862	4,685	351,798	14,367	659,810	20,472
	11	505	11	971	34	5,947	256	19,608	974	58,134	2,797	96,946	4,659	355,736	13,917	644,268	19,722
	12	34	4	401	18	3,465	189	14,901	819	48,160	2,584	84,966	4,357	334,258	13,678	628,572	19,789
	13	60	3	346	23	3,757	161	12,204	637	37,300	2,054	65,015	3,377	251,847	10,445	475,016	14,957
	14	5	1	498	15	2,571	141	10,748	597	34,267	1,887	60,091	3,099	230,514	9,317	427,053	13,312
	15	358	6	769	22	2,575	124	9,186	503	29,171	1,596	50,830	2,694	197,740	8,375	375,590	12,248
	16	30	4	540	21	3,132	183	11,415	712	33,790	1,945	57,023	3,196	219,586	9,705	403,863	13,935
	17	23	3	399	13	3,121	101	11,620	480	31,230	1,541	51,999	2,606	194,845	8,458	365,677	12,489
	18	14	4	498	20	2,921	143	9,828	574	30,505	1,701	52,152	2,858	198,609	9,101	370,903	13,055
	19	2	1	71	6	821	75	5,826	390	21,403	1,319	38,653	2,258	160,102	7,028	306,515	10,152
	20	67	3	336	10	1,751	80	7,250	399	21,845	1,364	37,647	2,269	152,996	7,670	289,784	11,081
	21	2	1	40	5	1,328	52	4,210	231	13,143	790	23,159	1,367	94,073	4,470	179,287	6,502
	22	2	1	179	7	815	40	3,366	223	12,741	786	22,380	1,352	94,814	4,370	181,222	6,523
	Total	6,565	150	21,646	638	108,52	4,582	368,64	18,375	1,085,143	55,424	1,839,206	91,706	6,995,698	280,36	13,027,516	401,01
						5		6					4			6	
AI	1	0	0	68	7	2,818	166	15,819	1,031	62,236	3,880	117,897	6,783	541,484	22,128	1,050,270	31,418
	2	292	3	537	10	3,836	225	19,709	1,239	74,185	4,369	135,960	7,286	587,465	22,382	1,115,507	31,636
	3	63	1	247	10	2,526	183	15,588	1,030	62,825	3,646	116,909	6,208	494,184	19,238	936,996	27,354
	4	3	1	326	10	2,198	129	13,533	892	55,773	3,279	107,540	5,708	491,591	18,138	956,626	25,980
	5	0	0	6	4	1,738	132	12,989	859	52,873	3,178	99,707	5,481	443,467	17,458	853,872	24,775
	6	0	0	181	6	1,921	143	12,521	822	52,480	2,973	98,889	5,130	450,587	16,459	880,787	23,540

Table S3-1. Number of SNPs with p values lower than a p value threshold in the GSCAN GWAS files on which quality control was performed (QC) and number of SNPs that were selected by LD-based clumping (LD, blue) according to eight significance thresholds. The SNP numbers are shown for each autosome (1-22) and summed (Total). The discovery sample phenotypes are SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per day).

Trait	Chromosome	p < 5e-08		p < 1e-05		p < 1e-03		p < 1e-02		p < 5e-02		p < 0.1		p < 0.5		p < 1	
		QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD
	7	0	0	25	6	2,064	151	11,482	846	46,972	2,922	89,346	5,028	399,541	15,803	776,785	22,554
	8	5	1	140	6	1,432	99	9,109	672	41,057	2,601	78,212	4,463	366,426	14,616	721,727	20,960
	9	0	0	11	5	946	101	7,709	657	34,679	2,346	65,735	4,008	294,334	12,932	571,355	18,380
	10	0	0	43	4	870	102	8,315	687	38,073	2,544	73,469	4,445	343,299	14,222	672,512	20,440
	11	0	0	20	3	1,237	116	10,428	718	40,624	2,590	77,857	4,416	342,300	13,834	655,648	19,710
	12	0	0	39	5	1,496	107	9,383	697	38,687	2,556	73,221	4,293	332,207	13,892	641,757	19,805
	13	0	0	26	3	1,277	85	7,253	499	29,547	1,838	54,725	3,230	247,726	10,360	482,755	14,908
	14	0	0	2	0	642	72	6,314	512	26,812	1,684	50,511	2,963	224,494	9,293	434,252	13,349
	15	1	1	14	5	775	64	5,570	426	23,412	1,574	44,040	2,663	197,850	8,600	383,523	12,310
	16	0	0	1	1	721	85	6,088	532	25,844	1,853	49,076	3,181	212,632	9,833	409,997	14,002
	17	20	1	57	2	927	82	6,025	461	22,674	1,534	42,427	2,647	191,982	8,735	370,824	12,502
	18	0	0	57	3	1,211	90	5,989	431	23,213	1,588	43,524	2,788	194,387	9,131	377,969	13,036
	19	0	0	46	1	438	44	3,459	299	16,797	1,136	32,823	1,982	155,737	6,975	310,173	10,178
	20	0	0	11	1	479	43	4,050	355	17,555	1,279	33,468	2,290	152,207	7,593	294,245	11,059
	21	0	0	0	0	138	23	1,818	188	9,650	775	19,370	1,351	93,359	4,542	183,504	6,483
	22	0	0	1	0	372	28	2,571	199	10,280	739	19,663	1,302	93,653	4,418	185,085	6,517
	Total	384	8	1,858	92	30,062	2,270	195,72	14,052	806,248	50,884	1,524,369	87,646	6,850,912	280,58	13,266,169	400,89
								2						2		6	
CPD	1	2	1	232	10	3,077	184	17,085	1,110	67,428	3,979	125,772	6,759	547,876	21,944	1,050,545	31,418
	2	0	0	43	10	3,090	205	17,304	1,114	68,028	4,092	129,636	7,145	577,958	22,188	1,116,431	31,678
	3	89	2	367	10	4,027	199	17,955	1,096	61,264	3,587	111,653	6,112	485,697	19,258	937,783	27,330
	4	25	2	477	12	2,941	156	14,949	892	58,589	3,195	109,107	5,536	494,742	18,223	957,180	25,954
	5	0	0	17	4	1,858	134	12,848	910	54,077	3,175	102,045	5,481	447,601	17,319	854,960	24,672
	6	7	1	85	7	2,355	126	13,233	865	55,471	3,108	103,830	5,238	457,377	16,566	881,810	23,502
	7	129	1	222	9	2,114	148	14,282	798	53,127	2,864	96,356	4,963	405,495	15,880	777,421	22,540
	8	251	7	403	12	2,275	140	13,139	774	47,533	2,768	87,903	4,696	379,379	14,788	722,369	21,059
	9	30	4	69	11	1,796	131	8,688	649	33,985	2,359	64,445	4,010	294,154	12,912	571,707	18,434
	10	0	0	92	2	1,542	112	10,529	731	41,126	2,561	76,819	4,432	348,031	14,266	672,911	20,503
	11	47	5	319	12	2,078	130	10,295	723	41,868	2,529	77,677	4,342	339,509	13,844	655,999	19,707
	12	0	0	48	5	1,382	116	8,913	661	38,181	2,404	73,270	4,156	330,203	13,763	642,649	19,843

Table S3-1. Number of SNPs with p values lower than a p value threshold in the GSCAN GWAS files on which quality control was performed (QC) and number of SNPs that were selected by LD-based clumping (LD, blue) according to eight significance thresholds. The SNP numbers are shown for each autosome (1-22) and summed (Total). The discovery sample phenotypes are SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per day).

Trait	Chromosome	p < 5e-08		p < 1e-05		p < 1e-03		p < 1e-02		p < 5e-02		p < 0.1		p < 0.5		p < 1	
		QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD
	13	0	0	91	5	927	86	7,096	529	30,124	1,861	56,973	3,202	251,728	10,343	483,335	14,863
	14	0	0	33	4	1,322	74	6,631	458	26,579	1,668	50,070	2,913	222,474	9,368	434,826	13,397
	15	1,031	36	1,171	46	2,354	136	7,395	504	25,938	1,630	47,119	2,734	201,092	8,533	384,214	12,313
	16	47	2	188	9	1,879	100	7,639	513	27,182	1,764	49,765	3,078	215,040	9,772	410,070	14,045
	17	0	0	11	2	859	57	4,673	387	21,239	1,457	40,395	2,519	188,638	8,519	371,174	12,476
	18	0	0	53	5	1,172	89	6,211	498	24,804	1,679	44,936	2,845	195,940	9,097	378,367	13,019
	19	394	21	737	33	2,150	104	6,668	433	21,807	1,331	38,430	2,247	160,876	7,102	310,344	10,198
	20	14	2	150	6	876	67	4,664	379	18,663	1,299	34,563	2,258	151,783	7,556	294,441	11,077
	21	0	0	2	1	493	35	2,350	167	10,279	676	19,231	1,231	91,600	4,475	183,808	6,510
	22	0	0	0	0	303	19	2,414	187	10,367	704	20,089	1,273	93,900	4,401	185,105	6,513
Total		2,066	84	4,810	215	40,870	2,548	214,96	14,378	837,659	50,690	1,560,084	87,170	6,881,093	280,11	13,277,449	401,05
								1						7			1
SC	1	0	0	29	4	2,278	151	13,591	977	59,250	3,914	112,211	6,795	511,618	22,074	990,550	31,573
	2	0	0	22	5	2,610	201	16,161	1,150	65,613	4,075	124,818	7,068	549,857	22,480	1,056,808	31,852
	3	0	0	61	4	1,522	132	11,207	961	51,506	3,484	99,464	6,031	455,146	19,292	890,512	27,465
	4	0	0	378	1	1,451	99	11,292	839	52,385	3,265	100,419	5,793	468,492	18,360	910,375	26,097
	5	0	0	19	2	1,552	143	11,294	846	48,865	3,115	93,079	5,441	416,619	17,429	813,216	24,835
	6	0	0	55	5	1,172	115	11,622	792	49,944	2,976	94,808	5,096	431,955	16,639	837,392	23,679
	7	0	0	2	2	1,262	125	9,551	741	41,860	2,747	79,668	4,794	374,725	15,856	736,810	22,784
	8	0	0	18	5	1,358	112	8,479	741	39,193	2,742	75,795	4,668	350,454	14,772	686,535	21,031
	9	49	6	340	13	1,377	96	7,158	613	30,319	2,334	59,738	3,995	276,404	12,935	540,025	18,466
	10	0	0	0	0	1,144	106	8,407	707	36,516	2,545	69,946	4,427	320,633	14,432	635,982	20,630
	11	6	1	78	6	1,342	90	8,813	605	34,238	2,344	66,639	4,137	318,192	13,858	621,285	19,878
	12	0	0	10	1	758	93	7,355	654	34,240	2,500	67,226	4,346	311,368	13,881	606,311	19,878
	13	0	0	0	0	470	62	5,289	472	25,132	1,816	49,686	3,200	233,780	10,443	457,816	15,003
	14	0	0	130	1	792	60	5,527	405	24,180	1,584	46,376	2,811	209,990	9,379	409,609	13,508
	15	59	3	292	6	1,414	67	5,640	419	20,947	1,508	39,247	2,600	181,998	8,572	360,453	12,373
	16	0	0	1	1	495	73	4,833	432	21,715	1,672	42,158	2,922	196,129	9,687	387,105	14,020
	17	0	0	2	2	598	53	4,939	383	22,937	1,495	41,048	2,616	177,202	8,654	346,068	12,547
	18	0	0	4	0	542	56	4,441	417	20,828	1,603	40,192	2,769	183,443	9,134	358,537	13,094

Table S3-1. Number of SNPs with p values lower than a p value threshold in the GSCAN GWAS files on which quality control was performed (QC) and number of SNPs that were selected by LD-based clumping (LD, blue) according to eight significance thresholds. The SNP numbers are shown for each autosome (1-22) and summed (Total). The discovery sample phenotypes are SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per day).

Trait	Chromosome	p < 5e-08		p < 1e-05		p < 1e-03		p < 1e-02		p < 5e-02		p < 0.1		p < 0.5		p < 1	
		QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD
	19	57	5	149	17	840	74	3,934	348	16,381	1,239	31,153	2,150	146,820	7,005	289,386	10,240
	20	20	3	108	8	684	48	3,422	338	15,098	1,273	28,404	2,211	141,271	7,529	279,408	11,193
	21	0	0	1	0	208	36	1,745	197	9,260	783	18,095	1,350	87,310	4,493	173,767	6,602
	22	10	1	265	5	1,627	49	3,653	246	11,756	820	21,356	1,393	89,644	4,496	174,076	6,534
Total		201	19	1,964	88	25,496	2,041	168,35	13,283	732,163	49,834	1,401,526	86,613	6,433,050	281,40	12,562,026	403,28
							3								0		2
DPW	1	2	1	297	19	4,481	188	18,634	1,147	65,086	3,919	119,936	6,791	534,222	21,930	1,045,907	31,459
	2	217	9	1,111	41	6,932	315	24,214	1,351	78,440	4,247	139,223	7,180	577,570	22,381	1,107,792	31,752
	3	528	3	946	18	4,134	193	18,768	1,009	64,841	3,461	113,984	5,950	481,918	19,173	929,662	27,327
	4	744	21	1,437	41	4,872	259	21,466	1,164	68,285	3,584	120,599	5,914	494,305	18,280	949,852	26,037
	5	3	2	374	15	3,201	179	15,492	955	57,168	3,213	102,507	5,403	436,366	17,343	847,271	24,792
	6	0	0	19	6	2,559	131	16,068	864	57,512	2,984	103,991	5,150	448,522	16,490	873,169	23,456
	7	309	2	827	16	3,513	193	14,235	919	50,971	2,959	92,583	5,038	399,787	15,874	772,182	22,559
	8	0	0	367	13	2,831	148	13,223	834	47,612	2,876	87,285	4,767	372,220	14,745	718,035	20,987
	9	1	1	247	9	2,240	146	11,131	696	38,853	2,364	68,459	3,928	290,281	12,754	566,063	18,341
	10	0	0	260	4	1,587	119	10,030	711	42,603	2,584	79,402	4,425	343,282	14,287	667,947	20,577
	11	334	6	1,019	22	3,608	152	14,578	751	46,956	2,510	81,502	4,318	336,772	13,783	651,833	19,654
	12	32	1	346	21	2,673	153	12,603	731	43,666	2,443	77,677	4,207	328,450	13,755	637,249	19,803
	13	0	0	77	5	1,486	103	7,801	554	29,898	1,891	56,063	3,192	244,663	10,376	478,164	14,968
	14	69	3	163	7	1,116	83	7,103	464	28,673	1,636	52,199	2,921	223,680	9,324	432,097	13,427
	15	0	0	130	8	2,182	82	7,122	459	24,361	1,528	43,798	2,614	194,266	8,478	380,216	12,327
	16	305	8	629	23	2,690	149	9,392	603	30,114	1,897	53,104	3,168	213,666	9,856	410,772	14,035
	17	2,198	3	3,201	13	6,070	96	11,559	451	28,756	1,574	48,234	2,624	192,684	8,669	372,508	12,518
	18	0	0	196	9	1,726	87	6,413	404	23,521	1,550	43,131	2,728	190,791	9,061	374,843	13,098
	19	104	1	138	4	772	55	4,081	372	17,087	1,243	32,851	2,146	155,420	6,969	314,998	10,171
	20	1	1	76	3	1,093	65	5,778	406	20,989	1,352	37,056	2,367	153,692	7,623	293,686	11,047
	21	0	0	2	1	313	27	2,151	183	9,471	750	18,533	1,309	90,283	4,483	182,071	6,530
	22	0	0	62	4	849	51	3,016	213	11,552	748	21,060	1,331	94,228	4,460	186,676	6,522

Table S3-1. Number of SNPs with p values lower than a p value threshold in the GSCAN GWAS files on which quality control was performed (QC) and number of SNPs that were selected by LD-based clumping (LD, blue) according to eight significance thresholds. The SNP numbers are shown for each autosome (1-22) and summed (Total). The discovery sample phenotypes are SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per day).

Trait	Chromosome	p < 5e-08		p < 1e-05		p < 1e-03		p < 1e-02		p < 5e-02		p < 0.1		p < 0.5		p < 1	
		QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD	QC	LD
Total		4,847	62	11,924	302	60,928	2,974	254,85	15,241	886,415	51,313	1,593,177	87,471	6,797,068	280,09	13,192,993	401,38

Table S3-2. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5) in females (F), males (M) or both sexes (F+M). PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3 is 3.607512e-03 for females, 3.622416e-03 for males, and 3.633203e-03 for both sexes. T4 is 7.142857e-04 for all the sex groups. T5 is 5.681818e-05 for all the sex groups.

Target phenotype	Sex	SI					AI					CPD					SC					DPW				
		T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
Ever used cocaine	F+M	8	6	6	1	0	8	3	0	0	0	8	0	0	0	0	8	0	0	0	0	8	6	5	3	0
	F	8	6	5	1	0	8	1	0	0	0	8	0	0	0	0	8	4	0	0	0	8	3	0	0	0
	M	8	6	5	1	0	8	1	0	0	0	8	0	0	0	0	8	4	0	0	0	8	3	0	0	0
Ever used amphetamine	F+M	8	7	6	5	4	8	5	2	0	0	8	0	0	0	0	8	0	0	0	0	8	5	1	1	0
	F	8	6	5	5	4	8	4	1	0	0	8	0	0	0	0	8	0	0	0	0	8	5	0	0	0
	M	8	6	5	5	4	8	4	1	0	0	8	0	0	0	0	8	0	0	0	0	8	5	0	0	0
Ever used inhalants	F+M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0
	F	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0
	M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0
Ever used sedatives	F+M	8	5	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0	8	5	3	0	0
	F	8	2	1	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	5	2	0	0
	M	8	2	1	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	5	2	0	0
Ever used hallucinogens	F+M	8	6	4	3	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0	8	5	1	0	0
	F	8	6	5	5	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	3	0	0	0
	M	8	6	5	5	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	3	0	0	0
Ever used opioids	F+M	8	5	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	2	0	0	0
	F	8	6	5	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	5	1	0	0
	M	8	6	5	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	5	1	0	0
Ever used ecstasy	F+M	8	7	6	6	5	8	4	0	0	0	8	0	0	0	0	8	0	0	0	0	8	7	5	5	3
	F	8	6	6	5	5	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	7	5	5	0
	M	8	6	6	5	5	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	7	5	5	0

Table S3-2. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5) in females (F), males (M) or both sexes (F+M). PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3 is 3.607512e-03 for females, 3.622416e-03 for males, and 3.633203e-03 for both sexes. T4 is 7.142857e-04 for all the sex groups. T5 is 5.681818e-05 for all the sex groups.

Target phenotype	Sex	SI					AI					CPD					SC					DPW				
		T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
Ever used prescription pain killers	F+M	8	4	0	0	0	8	2	0	0	0	8	1	0	0	0	8	2	1	0	0	8	1	0	0	0
	F	8	7	1	0	0	8	2	0	0	0	8	3	0	0	0	8	2	0	0	0	8	2	0	0	0
	M	8	7	1	0	0	8	2	0	0	0	8	3	0	0	0	8	2	0	0	0	8	2	0	0	0
Ever used prescription stimulants	F+M	8	2	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	2	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	2	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Ever used cannabis	F+M	8	7	6	6	1	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	5	1	0	0
	F	8	7	6	1	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0
	M	8	6	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0	8	2	0	0	0
Age at onset of cannabis initiation	F+M	8	0	0	0	0	8	0	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Alcohol abuse	F+M	8	7	1	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	6	0	0	0	8	0	0	0	0	8	0	0	0	0	8	5	0	0	0	8	0	0	0	0
	M	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Alcohol dependence	F+M	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	3	0	0	0	8	0	0	0	0	8	0	0	0	0	8	4	0	0	0	8	1	0	0	0
	M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0
DSM5 AUD (4 point scale)	F+M	8	6	5	1	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	6	0	0	0
	F	8	6	0	0	0	8	4	0	0	0	8	0	0	0	0	8	4	1	0	0	8	1	0	0	0
	M	8	5	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	4	0	0	0

Table S3-2. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5) in females (F), males (M) or both sexes (F+M). PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3 is 3.607512e-03 for females, 3.622416e-03 for males, and 3.633203e-03 for both sexes. T4 is 7.142857e-04 for all the sex groups. T5 is 5.681818e-05 for all the sex groups.

Target phenotype	Sex	SI					AI					CPD					SC					DPW				
		T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
DSM5 AUD (ctrl mild vs moderate severe)	F+M	8	6	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	8	0	0	0
	F	8	1	0	0	0	8	1	0	0	0	8	0	0	0	0	8	4	0	0	0	8	1	0	0	0
	M	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	6	0	0	0
Cannabis abuse	F+M	8	0	0	0	0	8	1	0	0	0	8	2	0	0	0	8	0	0	0	0	8	3	0	0	0
	F	8	3	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	1	0	0	0	8	3	0	0	0	8	0	0	0	0	8	2	0	0	0
Age at onset of cannabis abuse	F+M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	2	0	0	0
	F	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0
Cannabis dependence	F+M	8	5	0	0	0	8	1	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	5	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0
	M	8	0	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Age at onset of cannabis dependence	F+M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0
	F	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0
DSM5 CUD (4 point scale)	F+M	8	5	0	0	0	8	4	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	6	5	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	1	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0
DSM5 CUD (ctrl mild vs moderate severe)	F+M	8	5	1	0	0	8	4	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	5	4	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	2	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0

Table S3-2. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5) in females (F), males (M) or both sexes (F+M). PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3 is 3.607512e-03 for females, 3.622416e-03 for males, and 3.633203e-03 for both sexes. T4 is 7.142857e-04 for all the sex groups. T5 is 5.681818e-05 for all the sex groups.

Target phenotype	Sex	SI					AI					CPD					SC					DPW				
		T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
Age at onset of DSM5 CUD	F+M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	2	0	0	0
	F	8	0	0	0	0	8	0	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0	8	1	0	0	0
Number target phenotypes predicted	F+M	22	16	8	6	3	22	12	1	0	0	22	6	0	0	0	22	2	1	0	0	22	14	6	3	1
	F	22	17	10	5	2	22	8	1	0	0	22	2	0	0	0	22	8	1	0	0	22	13	3	1	0
	M	22	12	7	4	2	22	9	1	0	0	22	6	0	0	0	22	4	0	0	0	22	14	3	1	0

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
Ever used cocaine	S1	F+M	0.012	0.01	0.1764	0.09	-0.014	0.01	0.1051	0.13	-0.014	0.01	0.1078	0.13	-0.005	0.01	0.5479	0.02	0.005	0.01	0.5376	0.02
	S1	F	0.011	0.01	0.2884	0.10	-0.014	0.01	0.1524	0.18	-0.012	0.01	0.2453	0.12	-0.013	0.01	0.2187	0.13	0.007	0.01	0.4717	0.05
	S1	M	0.011	0.01	0.2884	0.06	-0.014	0.01	0.1524	0.12	-0.012	0.01	0.2453	0.08	-0.013	0.01	0.2187	0.10	0.007	0.01	0.4717	0.03
	S2	F+M	0.014	0.01	0.1066	0.13	0.004	0.01	0.6417	0.01	-0.014	0.01	0.1219	0.12	-0.012	0.01	0.1804	0.09	0.008	0.01	0.3823	0.04
	S2	F	0.011	0.01	0.2581	0.11	-0.001	0.01	0.8977	0.00	-0.010	0.01	0.3593	0.07	-0.004	0.01	0.7061	0.01	0.016	0.01	0.1085	0.22
	S2	M	0.011	0.01	0.2581	0.07	-0.001	0.01	0.8977	0.00	-0.010	0.01	0.3593	0.05	-0.004	0.01	0.7061	0.01	0.016	0.01	0.1085	0.14
	S3	F+M	0.025	0.01	0.0032	0.44	0.002	0.01	0.8087	0.00	-0.017	0.01	0.0518	0.19	-0.005	0.01	0.5678	0.02	0.018	0.01	0.0405	0.21
	S3	F	0.022	0.01	0.0246	0.44	0.003	0.01	0.7393	0.01	-0.012	0.01	0.2639	0.11	-0.013	0.01	0.2008	0.15	0.017	0.01	0.1120	0.22
	S3	M	0.022	0.01	0.0246	0.28	0.003	0.01	0.7393	0.01	-0.012	0.01	0.2639	0.07	-0.013	0.01	0.2008	0.09	0.017	0.01	0.1120	0.15
	S4	F+M	0.026	0.01	0.0032	0.44	-0.008	0.01	0.3759	0.04	-0.016	0.01	0.0780	0.16	0.006	0.01	0.4964	0.02	0.029	0.01	0.0008	0.56
	S4	F	0.032	0.01	0.0018	0.83	0.004	0.01	0.6961	0.01	-0.006	0.01	0.5918	0.03	-0.018	0.01	0.0951	0.25	0.018	0.01	0.0798	0.26
	S4	M	0.032	0.01	0.0018	0.51	0.004	0.01	0.6961	0.01	-0.006	0.01	0.5918	0.02	-0.018	0.01	0.0951	0.17	0.018	0.01	0.0798	0.19
	S5	F+M	0.029	0.01	0.0010	0.54	-0.019	0.01	0.0368	0.22	-0.006	0.01	0.4995	0.02	0.001	0.01	0.8899	0.00	0.028	0.01	0.0014	0.51
	S5	F	0.034	0.01	0.0010	0.95	-0.011	0.01	0.2599	0.11	-0.006	0.01	0.5849	0.03	-0.029	0.01	0.0127	0.56	0.020	0.01	0.0555	0.32
	S5	M	0.034	0.01	0.0010	0.61	-0.011	0.01	0.2599	0.06	-0.006	0.01	0.5849	0.02	-0.029	0.01	0.0127	0.42	0.020	0.01	0.0555	0.21
	S6	F+M	0.032	0.01	0.0003	0.67	-0.017	0.01	0.0541	0.19	-0.007	0.01	0.4071	0.04	0.000	0.01	0.9667	0.00	0.033	0.01	0.0001	0.75
	S6	F	0.037	0.01	0.0003	1.15	-0.012	0.01	0.2244	0.13	-0.011	0.01	0.3074	0.09	-0.027	0.01	0.0225	0.48	0.026	0.01	0.0120	0.55
	S6	M	0.037	0.01	0.0003	0.75	-0.012	0.01	0.2244	0.07	-0.011	0.01	0.3074	0.06	-0.027	0.01	0.0225	0.35	0.026	0.01	0.0120	0.36
	S7	F+M	0.027	0.01	0.0020	0.48	-0.020	0.01	0.0271	0.26	-0.002	0.01	0.8344	0.00	-0.003	0.01	0.7450	0.01	0.032	0.01	0.0001	0.71
	S7	F	0.032	0.01	0.0015	0.87	-0.019	0.01	0.0685	0.30	-0.004	0.01	0.6857	0.01	-0.028	0.01	0.0150	0.55	0.029	0.01	0.0041	0.70
	S7	M	0.032	0.01	0.0015	0.55	-0.019	0.01	0.0685	0.16	-0.004	0.01	0.6857	0.01	-0.028	0.01	0.0150	0.40	0.029	0.01	0.0041	0.46
	S8	F+M	0.028	0.01	0.0017	0.50	-0.021	0.01	0.0229	0.27	-0.002	0.01	0.7922	0.00	-0.004	0.01	0.6526	0.01	0.032	0.01	0.0002	0.70
	S8	F	0.034	0.01	0.0010	0.94	-0.021	0.01	0.0448	0.36	-0.005	0.01	0.6266	0.02	-0.029	0.01	0.0133	0.58	0.029	0.01	0.0037	0.72
	S8	M	0.034	0.01	0.0010	0.59	-0.021	0.01	0.0448	0.20	-0.005	0.01	0.6266	0.01	-0.029	0.01	0.0133	0.41	0.029	0.01	0.0037	0.46
Ever used amphetamine	S1	F+M	0.012	0.01	0.1676	0.10	-0.002	0.01	0.8247	0.00	-0.001	0.01	0.8995	0.00	-0.006	0.01	0.5262	0.02	0.008	0.01	0.3802	0.04
	S1	F	0.012	0.01	0.2981	0.10	-0.002	0.01	0.8795	0.00	-0.003	0.01	0.8198	0.00	-0.015	0.01	0.2046	0.14	0.009	0.01	0.3975	0.06

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
S1	M	0.012	0.01	0.2981	0.08	-0.002	0.01	0.8795	0.00	-0.003	0.01	0.8198	0.00	-0.015	0.01	0.2046	0.13	0.009	0.01	0.3975	0.05	
S2	F+M	0.021	0.01	0.0158	0.30	-0.000	0.01	0.9930	0.00	-0.001	0.01	0.9035	0.00	-0.007	0.01	0.4647	0.03	0.011	0.01	0.2380	0.07	
S2	F	0.019	0.01	0.0831	0.27	-0.005	0.01	0.6563	0.02	-0.004	0.01	0.7589	0.01	-0.009	0.01	0.4316	0.05	0.016	0.01	0.1582	0.17	
S2	M	0.019	0.01	0.0831	0.22	-0.005	0.01	0.6563	0.01	-0.004	0.01	0.7589	0.01	-0.009	0.01	0.4316	0.05	0.016	0.01	0.1582	0.14	
S3	F+M	0.028	0.01	0.0016	0.51	-0.011	0.01	0.2070	0.08	0.001	0.01	0.8710	0.00	0.002	0.01	0.7870	0.00	0.014	0.01	0.1142	0.13	
S3	F	0.029	0.01	0.0076	0.61	-0.004	0.01	0.7519	0.01	0.008	0.01	0.4706	0.05	-0.005	0.01	0.6931	0.01	0.019	0.01	0.0986	0.24	
S3	M	0.029	0.01	0.0076	0.51	-0.004	0.01	0.7519	0.01	0.008	0.01	0.4706	0.04	-0.005	0.01	0.6931	0.01	0.019	0.01	0.0986	0.21	
S4	F+M	0.034	0.01	0.0002	0.70	-0.023	0.01	0.0122	0.32	0.001	0.01	0.8721	0.00	0.007	0.01	0.4581	0.03	0.031	0.01	0.0006	0.59	
S4	F	0.039	0.01	0.0005	1.05	-0.018	0.01	0.1170	0.22	0.012	0.01	0.2867	0.10	-0.002	0.01	0.9007	0.00	0.031	0.01	0.0067	0.64	
S4	M	0.039	0.01	0.0005	0.82	-0.018	0.01	0.1170	0.15	0.012	0.01	0.2867	0.08	-0.002	0.01	0.9007	0.00	0.031	0.01	0.0067	0.57	
S5	F+M	0.048	0.01	<.0001	1.40	-0.030	0.01	0.0011	0.54	0.007	0.01	0.4326	0.03	0.008	0.01	0.4000	0.04	0.021	0.01	0.0179	0.28	
S5	F	0.050	0.01	<.0001	1.70	-0.028	0.01	0.0141	0.53	0.007	0.01	0.5445	0.03	-0.004	0.01	0.7752	0.01	0.023	0.01	0.0408	0.36	
S5	M	0.050	0.01	<.0001	1.39	-0.028	0.01	0.0141	0.36	0.007	0.01	0.5445	0.03	-0.004	0.01	0.7752	0.01	0.023	0.01	0.0408	0.31	
S6	F+M	0.050	0.01	<.0001	1.54	-0.028	0.01	0.0033	0.44	0.009	0.01	0.3007	0.06	0.008	0.01	0.4256	0.03	0.026	0.01	0.0039	0.42	
S6	F	0.052	0.01	<.0001	1.79	-0.030	0.01	0.0086	0.61	0.005	0.01	0.6497	0.02	-0.005	0.01	0.6845	0.02	0.027	0.01	0.0169	0.50	
S6	M	0.052	0.01	<.0001	1.49	-0.030	0.01	0.0086	0.41	0.005	0.01	0.6497	0.02	-0.005	0.01	0.6845	0.01	0.027	0.01	0.0169	0.42	
S7	F+M	0.041	0.01	<.0001	1.05	-0.023	0.01	0.0175	0.30	0.013	0.01	0.1442	0.11	0.004	0.01	0.6826	0.01	0.020	0.01	0.0250	0.25	
S7	F	0.047	0.01	<.0001	1.51	-0.033	0.01	0.0040	0.74	0.013	0.01	0.2626	0.11	-0.011	0.01	0.4119	0.06	0.025	0.01	0.0256	0.43	
S7	M	0.047	0.01	<.0001	1.22	-0.033	0.01	0.0040	0.52	0.013	0.01	0.2626	0.10	-0.011	0.01	0.4119	0.06	0.025	0.01	0.0256	0.36	
S8	F+M	0.042	0.01	<.0001	1.07	-0.025	0.01	0.0079	0.37	0.014	0.01	0.1346	0.12	0.003	0.01	0.7848	0.00	0.019	0.01	0.0297	0.24	
S8	F	0.048	0.01	<.0001	1.57	-0.037	0.01	0.0011	0.95	0.012	0.01	0.2880	0.10	-0.012	0.01	0.3704	0.08	0.024	0.01	0.0299	0.40	
S8	M	0.048	0.01	<.0001	1.27	-0.037	0.01	0.0011	0.66	0.012	0.01	0.2880	0.09	-0.012	0.01	0.3704	0.07	0.024	0.01	0.0299	0.33	
Ever used inhalants	S1	F+M	0.007	0.00	0.1254	0.11	0.001	0.00	0.8193	0.00	-0.007	0.00	0.1619	0.09	0.006	0.00	0.2380	0.07	-0.002	0.00	0.6173	0.01
	S1	F	0.005	0.01	0.2989	0.10	0.002	0.01	0.6353	0.02	-0.003	0.01	0.5602	0.03	-0.000	0.01	0.9313	0.00	0.003	0.01	0.6349	0.02
	S1	M	0.005	0.01	0.2989	0.04	0.002	0.01	0.6353	0.01	-0.003	0.01	0.5602	0.02	-0.000	0.01	0.9313	0.00	0.003	0.01	0.6349	0.01
	S2	F+M	0.006	0.00	0.1899	0.08	0.007	0.00	0.1247	0.11	-0.004	0.00	0.3663	0.04	0.002	0.00	0.6338	0.01	0.005	0.00	0.3216	0.05
	S2	F	0.002	0.01	0.6779	0.02	0.008	0.01	0.1446	0.19	-0.002	0.01	0.6622	0.02	0.004	0.01	0.4937	0.04	0.011	0.01	0.0444	0.35

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW				
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²				
S2	M	0.002	0.01	0.6779	0.01	0.008	0.01	0.1446	0.09	-0.002	0.01	0.6622	0.01	0.004	0.01	0.4937	0.02	0.011	0.01	0.0444	0.16					
S3	F+M	0.006	0.00	0.1664	0.09	-0.003	0.00	0.5505	0.02	-0.005	0.00	0.3542	0.04	-0.002	0.00	0.6385	0.01	0.002	0.00	0.6454	0.01					
S3	F	0.006	0.01	0.2841	0.10	-0.002	0.01	0.6858	0.01	-0.002	0.01	0.7594	0.01	-0.006	0.01	0.2925	0.10	0.009	0.01	0.1013	0.23					
S3	M	0.006	0.01	0.2841	0.05	-0.002	0.01	0.6858	0.01	-0.002	0.01	0.7594	0.00	-0.006	0.01	0.2925	0.05	0.009	0.01	0.1013	0.12					
S4	F+M	0.008	0.00	0.0992	0.13	-0.000	0.00	0.9678	0.00	-0.003	0.00	0.5980	0.01	0.002	0.01	0.6901	0.01	0.008	0.00	0.0858	0.14					
S4	F	0.010	0.01	0.0704	0.28	-0.007	0.01	0.2092	0.14	0.001	0.01	0.8958	0.00	-0.006	0.01	0.3320	0.08	0.006	0.01	0.2492	0.11					
S4	M	0.010	0.01	0.0704	0.13	-0.007	0.01	0.2092	0.06	0.001	0.01	0.8958	0.00	-0.006	0.01	0.3320	0.04	0.006	0.01	0.2492	0.06					
S5	F+M	0.008	0.00	0.1146	0.12	-0.006	0.00	0.2037	0.08	0.001	0.00	0.9058	0.00	0.002	0.01	0.6793	0.01	0.009	0.00	0.0663	0.16					
S5	F	0.005	0.01	0.3365	0.08	-0.007	0.01	0.1715	0.16	0.002	0.01	0.7203	0.01	-0.003	0.01	0.5959	0.03	0.006	0.01	0.2289	0.12					
S5	M	0.005	0.01	0.3365	0.04	-0.007	0.01	0.1715	0.06	0.002	0.01	0.7203	0.01	-0.003	0.01	0.5959	0.01	0.006	0.01	0.2289	0.06					
S6	F+M	0.007	0.00	0.1499	0.10	-0.005	0.00	0.3273	0.05	0.002	0.00	0.6281	0.01	0.001	0.01	0.8288	0.00	0.010	0.00	0.0353	0.21					
S6	F	0.005	0.01	0.3322	0.08	-0.007	0.01	0.2133	0.14	0.004	0.01	0.5182	0.04	-0.002	0.01	0.8043	0.01	0.005	0.01	0.3730	0.07					
S6	M	0.005	0.01	0.3322	0.04	-0.007	0.01	0.2133	0.05	0.004	0.01	0.5182	0.02	-0.002	0.01	0.8043	0.00	0.005	0.01	0.3730	0.03					
S7	F+M	0.006	0.00	0.2197	0.07	0.000	0.01	0.9595	0.00	0.004	0.00	0.3640	0.04	0.001	0.01	0.8912	0.00	0.007	0.00	0.1592	0.09					
S7	F	0.009	0.01	0.0843	0.26	-0.006	0.01	0.2577	0.11	0.005	0.01	0.3454	0.08	-0.004	0.01	0.5507	0.03	0.001	0.01	0.9113	0.00					
S7	M	0.009	0.01	0.0843	0.12	-0.006	0.01	0.2577	0.05	0.005	0.01	0.3454	0.04	-0.004	0.01	0.5507	0.02	0.001	0.01	0.9113	0.00					
S8	F+M	0.006	0.00	0.2035	0.08	0.000	0.01	0.9512	0.00	0.004	0.00	0.3998	0.03	0.001	0.01	0.8465	0.00	0.006	0.00	0.1854	0.08					
S8	F	0.010	0.01	0.0692	0.28	-0.007	0.01	0.2236	0.13	0.005	0.01	0.3242	0.09	-0.004	0.01	0.5520	0.03	0.000	0.01	0.9535	0.00					
S8	M	0.010	0.01	0.0692	0.13	-0.007	0.01	0.2236	0.05	0.005	0.01	0.3242	0.04	-0.004	0.01	0.5520	0.02	0.000	0.01	0.9535	0.00					
Ever used sedatives	S1	F+M	0.021	0.01	0.0056	0.37	0.008	0.01	0.3054	0.05	0.001	0.01	0.9406	0.00	0.001	0.01	0.9149	0.00	0.005	0.01	0.5096	0.02				
	S1	F	0.032	0.01	0.0008	0.92	0.014	0.01	0.1442	0.17	0.009	0.01	0.3476	0.07	-0.005	0.01	0.6092	0.02	0.000	0.01	0.9782	0.00				
	S1	M	0.032	0.01	0.0008	0.78	0.014	0.01	0.1442	0.16	0.009	0.01	0.3476	0.07	-0.005	0.01	0.6092	0.02	0.000	0.01	0.9782	0.00				
	S2	F+M	0.019	0.01	0.0095	0.32	0.007	0.01	0.3476	0.04	0.001	0.01	0.9220	0.00	-0.004	0.01	0.6254	0.01	0.008	0.01	0.2867	0.05				
	S2	F	0.024	0.01	0.0125	0.51	0.007	0.01	0.4687	0.04	0.009	0.01	0.3654	0.07	-0.001	0.01	0.8879	0.00	0.013	0.01	0.1785	0.14				
	S2	M	0.024	0.01	0.0125	0.45	0.007	0.01	0.4687	0.04	0.009	0.01	0.3654	0.06	-0.001	0.01	0.8879	0.00	0.013	0.01	0.1785	0.12				
	S3	F+M	0.016	0.01	0.0398	0.20	-0.010	0.01	0.1879	0.08	0.001	0.01	0.9418	0.00	0.003	0.01	0.6718	0.01	0.009	0.01	0.2377	0.07				
	S3	F	0.015	0.01	0.1037	0.21	-0.003	0.01	0.7612	0.01	0.008	0.01	0.4392	0.05	0.008	0.01	0.4056	0.06	0.018	0.01	0.0607	0.28				

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	
S3	M	0.015	0.01	0.1037	0.19	-0.003	0.01	0.7612	0.01	0.008	0.01	0.4392	0.04	0.008	0.01	0.4056	0.05	0.018	0.01	0.0607	0.27						
S4	F+M	0.014	0.01	0.0635	0.17	-0.012	0.01	0.1429	0.10	-0.002	0.01	0.8160	0.00	0.006	0.01	0.4394	0.03	0.023	0.01	0.0026	0.44						
S4	F	0.018	0.01	0.0639	0.28	-0.010	0.01	0.2932	0.09	0.005	0.01	0.5754	0.03	-0.006	0.01	0.5483	0.03	0.032	0.01	0.0011	0.85						
S4	M	0.018	0.01	0.0639	0.23	-0.010	0.01	0.2932	0.07	0.005	0.01	0.5754	0.02	-0.006	0.01	0.5483	0.03	0.032	0.01	0.0011	0.82						
S5	F+M	0.018	0.01	0.0217	0.25	-0.016	0.01	0.0480	0.19	0.000	0.01	0.9918	0.00	0.003	0.01	0.7646	0.00	0.025	0.01	0.0012	0.50						
S5	F	0.017	0.01	0.0873	0.24	-0.016	0.01	0.1017	0.22	-0.002	0.01	0.8416	0.00	-0.013	0.01	0.2143	0.13	0.030	0.01	0.0022	0.75						
S5	M	0.017	0.01	0.0873	0.21	-0.016	0.01	0.1017	0.16	-0.002	0.01	0.8416	0.00	-0.013	0.01	0.2143	0.13	0.030	0.01	0.0022	0.68						
S6	F+M	0.017	0.01	0.0323	0.22	-0.012	0.01	0.1455	0.10	0.000	0.01	0.9620	0.00	0.004	0.01	0.6248	0.01	0.024	0.01	0.0018	0.47						
S6	F	0.013	0.01	0.1843	0.14	-0.014	0.01	0.1442	0.17	-0.005	0.01	0.5825	0.03	-0.012	0.01	0.2793	0.10	0.026	0.01	0.0071	0.58						
S6	M	0.013	0.01	0.1843	0.13	-0.014	0.01	0.1442	0.12	-0.005	0.01	0.5825	0.02	-0.012	0.01	0.2793	0.10	0.026	0.01	0.0071	0.52						
S7	F+M	0.014	0.01	0.0764	0.15	-0.008	0.01	0.3031	0.05	0.003	0.01	0.6615	0.01	-0.003	0.01	0.7557	0.00	0.021	0.01	0.0058	0.36						
S7	F	0.016	0.01	0.1033	0.21	-0.014	0.01	0.1586	0.17	-0.003	0.01	0.7408	0.01	-0.021	0.01	0.0535	0.31	0.026	0.01	0.0061	0.60						
S7	M	0.016	0.01	0.1033	0.18	-0.014	0.01	0.1586	0.12	-0.003	0.01	0.7408	0.01	-0.021	0.01	0.0535	0.30	0.026	0.01	0.0061	0.53						
S8	F+M	0.014	0.01	0.0795	0.15	-0.010	0.01	0.2358	0.07	0.003	0.01	0.6770	0.01	-0.003	0.01	0.6912	0.01	0.020	0.01	0.0075	0.34						
S8	F	0.016	0.01	0.1039	0.21	-0.017	0.01	0.0931	0.24	-0.004	0.01	0.7178	0.01	-0.021	0.01	0.0578	0.30	0.025	0.01	0.0096	0.53						
S8	M	0.016	0.01	0.1039	0.18	-0.017	0.01	0.0931	0.17	-0.004	0.01	0.7178	0.01	-0.021	0.01	0.0578	0.29	0.025	0.01	0.0096	0.46						
Ever used hallucinogens	S1	F+M	-0.001	0.01	0.9383	0.00	-0.002	0.01	0.7513	0.01	-0.004	0.01	0.6165	0.01	-0.000	0.01	0.9570	0.00	0.012	0.01	0.1410	0.11					
	S1	F	-0.004	0.01	0.6592	0.02	0.002	0.01	0.8391	0.00	-0.002	0.01	0.8414	0.00	-0.003	0.01	0.7693	0.01	0.001	0.01	0.9438	0.00					
	S1	M	-0.004	0.01	0.6592	0.01	0.002	0.01	0.8391	0.00	-0.002	0.01	0.8414	0.00	-0.003	0.01	0.7693	0.01	0.001	0.01	0.9438	0.00					
	S2	F+M	0.010	0.01	0.2121	0.08	0.011	0.01	0.1658	0.10	-0.003	0.01	0.6744	0.01	-0.008	0.01	0.3125	0.05	0.012	0.01	0.1310	0.12					
	S2	F	0.012	0.01	0.1659	0.18	0.003	0.01	0.7300	0.01	-0.002	0.01	0.8105	0.01	-0.001	0.01	0.9439	0.00	0.009	0.01	0.3245	0.09					
	S2	M	0.012	0.01	0.1659	0.10	0.003	0.01	0.7300	0.01	-0.002	0.01	0.8105	0.00	-0.001	0.01	0.9439	0.00	0.009	0.01	0.3245	0.05					
	S3	F+M	0.019	0.01	0.0196	0.28	-0.014	0.01	0.0762	0.16	-0.012	0.01	0.1552	0.10	-0.007	0.01	0.4095	0.04	0.015	0.01	0.0633	0.18					
	S3	F	0.025	0.01	0.0049	0.70	-0.007	0.01	0.4541	0.05	-0.004	0.01	0.6711	0.02	-0.013	0.01	0.1667	0.18	0.006	0.01	0.5321	0.04					
	S3	M	0.025	0.01	0.0049	0.40	-0.007	0.01	0.4541	0.03	-0.004	0.01	0.6711	0.01	-0.013	0.01	0.1667	0.10	0.006	0.01	0.5321	0.02					
	S4	F+M	0.022	0.01	0.0066	0.38	-0.011	0.01	0.1706	0.10	-0.004	0.01	0.6148	0.01	0.000	0.01	0.9786	0.00	0.022	0.01	0.0056	0.39					
	S4	F	0.033	0.01	0.0003	1.17	-0.005	0.01	0.5660	0.03	0.002	0.01	0.8002	0.01	-0.010	0.01	0.3064	0.10	0.012	0.01	0.1885	0.15					

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
S4	M	0.033 0.01 0.0003 0.63	-0.005	0.01	0.5660	0.01	0.002	0.01	0.8002	0.00	-0.010	0.01	0.3064	0.06	0.012	0.01	0.1885	0.10				
S5	F+M	0.027	0.01	0.0007	0.58	-0.014	0.01	0.0884	0.15	0.005	0.01	0.5021	0.02	0.001	0.01	0.9334	0.00	0.021	0.01	0.0081	0.36	
S5	F	0.033 0.01 0.0003 1.16	-0.009	0.01	0.3096	0.09	0.007	0.01	0.4856	0.05	-0.015	0.01	0.1587	0.19	0.016	0.01	0.0961	0.25				
S5	M	0.033 0.01 0.0003 0.66	-0.009	0.01	0.3096	0.04	0.007	0.01	0.4856	0.03	-0.015	0.01	0.1587	0.12	0.016	0.01	0.0961	0.15				
S6	F+M	0.029 0.01 0.0003 0.67	-0.017	0.01	0.0473	0.21	0.011	0.01	0.1793	0.10	0.001	0.01	0.8905	0.00	0.024	0.01	0.0022	0.48				
S6	F	0.032 0.01 0.0006 1.06	-0.012	0.01	0.1943	0.15	0.006	0.01	0.5273	0.04	-0.015	0.01	0.1598	0.19	0.020	0.01	0.0334	0.41				
S6	M	0.032 0.01 0.0006 0.61	-0.012	0.01	0.1943	0.07	0.006	0.01	0.5273	0.02	-0.015	0.01	0.1598	0.12	0.020	0.01	0.0334	0.24				
S7	F+M	0.030 0.01 0.0002 0.70	-0.015	0.01	0.0807	0.16	0.016	0.01	0.0534	0.20	-0.000	0.01	0.9901	0.00	0.022	0.01	0.0057	0.39				
S7	F	0.031 0.01 0.0007 1.03	-0.013	0.01	0.1561	0.19	0.010	0.01	0.2767	0.11	-0.016	0.01	0.1363	0.21	0.021	0.01	0.0178	0.50				
S7	M	0.031 0.01 0.0007 0.58	-0.013	0.01	0.1561	0.09	0.010	0.01	0.2767	0.06	-0.016	0.01	0.1363	0.14	0.021	0.01	0.0178	0.29				
S8	F+M	0.030 0.01 0.0002 0.72	-0.016	0.01	0.0546	0.20	0.015	0.01	0.0660	0.18	-0.001	0.01	0.9478	0.00	0.023	0.01	0.0040	0.42				
S8	F	0.032 0.01 0.0004 1.10	-0.016	0.01	0.0919	0.26	0.009	0.01	0.3281	0.09	-0.016	0.01	0.1245	0.23	0.022	0.01	0.0151	0.52				
S8	M	0.032 0.01 0.0004 0.62	-0.016	0.01	0.0919	0.13	0.009	0.01	0.3281	0.05	-0.016	0.01	0.1245	0.14	0.022	0.01	0.0151	0.29				
Ever used opioids	S1	F+M	0.005	0.00	0.3244	0.04	0.005	0.00	0.3112	0.05	-0.001	0.01	0.9173	0.00	-0.003	0.00	0.5800	0.01	0.003	0.01	0.5631	0.02
	S1	F	0.006	0.01	0.3389	0.08	0.003	0.01	0.5871	0.02	-0.005	0.01	0.4545	0.05	-0.003	0.01	0.6620	0.02	0.006	0.01	0.3220	0.08
	S1	M	0.006	0.01	0.3389	0.06	0.003	0.01	0.5871	0.02	-0.005	0.01	0.4545	0.04	-0.003	0.01	0.6620	0.01	0.006	0.01	0.3220	0.06
	S2	F+M	0.006	0.00	0.2330	0.07	0.004	0.00	0.4063	0.03	0.002	0.01	0.6421	0.01	-0.004	0.01	0.3806	0.04	0.004	0.01	0.3901	0.03
	S2	F	0.012	0.01	0.0605	0.29	-0.001	0.01	0.8783	0.00	-0.003	0.01	0.6312	0.02	-0.005	0.01	0.4661	0.04	0.012	0.01	0.0720	0.26
	S2	M	0.012	0.01	0.0605	0.24	-0.001	0.01	0.8783	0.00	-0.003	0.01	0.6312	0.02	-0.005	0.01	0.4661	0.04	0.012	0.01	0.0720	0.21
	S3	F+M	0.006	0.00	0.2142	0.07	-0.004	0.01	0.3886	0.03	0.001	0.01	0.7970	0.00	0.003	0.01	0.6021	0.01	0.000	0.01	0.9889	0.00
	S3	F	0.015	0.01	0.0178	0.46	-0.005	0.01	0.4744	0.04	-0.002	0.01	0.8053	0.01	0.003	0.01	0.6264	0.02	0.011	0.01	0.1042	0.21
	S3	M	0.015	0.01	0.0178	0.38	-0.005	0.01	0.4744	0.04	-0.002	0.01	0.8053	0.00	0.003	0.01	0.6264	0.02	0.011	0.01	0.1042	0.19
	S4	F+M	0.013	0.01	0.0140	0.28	-0.008	0.01	0.1144	0.12	0.000	0.01	0.9304	0.00	0.001	0.01	0.9146	0.00	0.012	0.01	0.0165	0.26
	S4	F	0.022	0.01	0.0008	0.90	-0.003	0.01	0.6006	0.02	-0.004	0.01	0.5787	0.03	-0.006	0.01	0.3999	0.06	0.020	0.01	0.0023	0.75
	S4	M	0.022	0.01	0.0008	0.71	-0.003	0.01	0.6006	0.02	-0.004	0.01	0.5787	0.02	-0.006	0.01	0.3999	0.05	0.020	0.01	0.0023	0.68
	S5	F+M	0.014	0.01	0.0054	0.36	-0.006	0.01	0.2374	0.07	0.001	0.01	0.8650	0.00	-0.001	0.01	0.8650	0.00	0.009	0.01	0.0782	0.14
	S5	F	0.022	0.01	0.0008	0.91	-0.002	0.01	0.8001	0.01	0.001	0.01	0.9186	0.00	-0.007	0.01	0.3392	0.08	0.018	0.01	0.0062	0.61

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW				
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²				
	S5	M	0.022	0.01	0.0008	0.75	-0.002	0.01	0.8001	0.00	0.001	0.01	0.9186	0.00	-0.007	0.01	0.3392	0.07	0.018	0.01	0.0062	0.52				
	S6	F+M	0.012	0.01	0.0150	0.27	-0.006	0.01	0.2465	0.06	-0.001	0.01	0.7921	0.00	-0.002	0.01	0.7672	0.00	0.010	0.01	0.0553	0.17				
	S6	F	0.019	0.01	0.0031	0.71	-0.003	0.01	0.6179	0.02	-0.004	0.01	0.4991	0.04	-0.009	0.01	0.2227	0.13	0.018	0.01	0.0058	0.62				
	S6	M	0.019	0.01	0.0031	0.60	-0.003	0.01	0.6179	0.01	-0.004	0.01	0.4991	0.03	-0.009	0.01	0.2227	0.12	0.018	0.01	0.0058	0.53				
	S7	F+M	0.015	0.01	0.0041	0.38	-0.006	0.01	0.3032	0.05	-0.000	0.01	0.9279	0.00	-0.001	0.01	0.9075	0.00	0.010	0.00	0.0447	0.18				
	S7	F	0.020	0.01	0.0020	0.77	-0.005	0.01	0.4927	0.04	-0.003	0.01	0.6161	0.02	-0.009	0.01	0.2158	0.13	0.016	0.01	0.0109	0.52				
	S7	M	0.020	0.01	0.0020	0.63	-0.005	0.01	0.4927	0.03	-0.003	0.01	0.6161	0.02	-0.009	0.01	0.2158	0.12	0.016	0.01	0.0109	0.44				
	S8	F+M	0.014	0.01	0.0048	0.36	-0.006	0.01	0.2879	0.05	-0.000	0.01	0.9413	0.00	-0.001	0.01	0.8305	0.00	0.010	0.01	0.0554	0.17				
	S8	F	0.020	0.01	0.0022	0.76	-0.006	0.01	0.3892	0.06	-0.003	0.01	0.6159	0.02	-0.009	0.01	0.2042	0.14	0.015	0.01	0.0155	0.47				
	S8	M	0.020	0.01	0.0022	0.62	-0.006	0.01	0.3892	0.04	-0.003	0.01	0.6159	0.02	-0.009	0.01	0.2042	0.13	0.015	0.01	0.0155	0.39				
Ever used ecstasy	S1	F+M	0.007	0.01	0.4974	0.02	0.000	0.01	0.9849	0.00	-0.009	0.01	0.3809	0.04	0.013	0.01	0.1953	0.09	0.008	0.01	0.4247	0.03				
	S1	F	0.004	0.01	0.7750	0.01	0.005	0.01	0.6765	0.02	-0.014	0.01	0.2736	0.11	0.012	0.01	0.3504	0.08	0.010	0.01	0.4212	0.06				
	S1	M	0.004	0.01	0.7750	0.01	0.005	0.01	0.6765	0.01	-0.014	0.01	0.2736	0.09	0.012	0.01	0.3504	0.07	0.010	0.01	0.4212	0.04				
	S2	F+M	0.021	0.01	0.0335	0.23	0.010	0.01	0.3066	0.05	-0.005	0.01	0.6191	0.01	0.004	0.01	0.7268	0.01	0.022	0.01	0.0338	0.23				
	S2	F	0.016	0.01	0.1876	0.16	-0.002	0.01	0.8718	0.00	-0.008	0.01	0.5221	0.04	0.014	0.01	0.2831	0.10	0.031	0.01	0.0152	0.51				
	S2	M	0.016	0.01	0.1876	0.13	-0.002	0.01	0.8718	0.00	-0.008	0.01	0.5221	0.03	0.014	0.01	0.2831	0.09	0.031	0.01	0.0152	0.40				
	S3	F+M	0.037	0.01	0.0002	0.71	-0.004	0.01	0.6847	0.01	-0.009	0.01	0.3587	0.04	-0.002	0.01	0.8142	0.00	0.020	0.01	0.0463	0.20				
	S3	F	0.037	0.01	0.0027	0.78	0.005	0.01	0.6807	0.01	-0.015	0.01	0.2620	0.11	-0.011	0.01	0.3996	0.06	0.031	0.01	0.0160	0.51				
	S3	M	0.037	0.01	0.0027	0.63	0.005	0.01	0.6807	0.01	-0.015	0.01	0.2620	0.09	-0.011	0.01	0.3996	0.05	0.031	0.01	0.0160	0.45				
	S4	F+M	0.048	0.01	<.0001	1.12	-0.017	0.01	0.1081	0.13	-0.010	0.01	0.3543	0.04	0.005	0.01	0.6327	0.01	0.043	0.01	<.0001	0.90				
	S4	F	0.054	0.01	<.0001	1.57	-0.009	0.01	0.5010	0.04	-0.000	0.01	0.9890	0.00	-0.006	0.01	0.6467	0.02	0.048	0.01	0.0002	1.22				
	S4	M	0.054	0.01	<.0001	1.20	-0.009	0.01	0.5010	0.03	-0.000	0.01	0.9890	0.00	-0.006	0.01	0.6467	0.02	0.048	0.01	0.0002	1.08				
	S5	F+M	0.054	0.01	<.0001	1.40	-0.026	0.01	0.0144	0.31	0.001	0.01	0.8941	0.00	-0.002	0.01	0.8648	0.00	0.043	0.01	<.0001	0.87				
	S5	F	0.057	0.01	<.0001	1.76	-0.017	0.01	0.1807	0.16	-0.003	0.01	0.8406	0.00	-0.020	0.01	0.1615	0.18	0.049	0.01	0.0001	1.27				
	S5	M	0.057	0.01	<.0001	1.41	-0.017	0.01	0.1807	0.11	-0.003	0.01	0.8406	0.00	-0.020	0.01	0.1615	0.17	0.049	0.01	0.0001	1.06				
	S6	F+M	0.059	0.01	<.0001	1.66	-0.026	0.01	0.0150	0.31	0.003	0.01	0.7348	0.01	-0.002	0.01	0.8699	0.00	0.042	0.01	<.0001	0.90				
	S6	F	0.064	0.01	<.0001	2.21	-0.021	0.01	0.0958	0.25	-0.001	0.01	0.9278	0.00	-0.015	0.01	0.2904	0.10	0.050	0.01	<.0001	1.37				

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
S6	M	0.064	0.01	<.0001	1.80	-0.021	0.01	0.0958	0.16	-0.001	0.01	0.9278	0.00	-0.015	0.01	0.2904	0.09	0.050	0.01	<.0001	1.13	
S7	F+M	0.052	0.01	<.0001	1.34	-0.026	0.01	0.0148	0.31	0.012	0.01	0.2555	0.07	-0.005	0.01	0.6465	0.01	0.038	0.01	0.0001	0.74	
S7	F	0.062	0.01	<.0001	2.08	-0.032	0.01	0.0144	0.54	0.008	0.01	0.5302	0.04	-0.017	0.01	0.2355	0.13	0.049	0.01	<.0001	1.36	
S7	M	0.062	0.01	<.0001	1.65	-0.032	0.01	0.0144	0.37	0.008	0.01	0.5302	0.03	-0.017	0.01	0.2355	0.12	0.049	0.01	<.0001	1.12	
S8	F+M	0.052	0.01	<.0001	1.32	-0.028	0.01	0.0093	0.36	0.011	0.01	0.2747	0.06	-0.007	0.01	0.5573	0.02	0.039	0.01	<.0001	0.76	
S8	F	0.062	0.01	<.0001	2.08	-0.034	0.01	0.0082	0.63	0.007	0.01	0.5747	0.03	-0.018	0.01	0.2145	0.15	0.049	0.01	<.0001	1.37	
S8	M	0.062	0.01	<.0001	1.65	-0.034	0.01	0.0082	0.43	0.007	0.01	0.5747	0.02	-0.018	0.01	0.2145	0.13	0.049	0.01	<.0001	1.09	
Ever used prescription pain killers	S1	F+M	0.018	0.01	0.0317	0.23	-0.002	0.01	0.8297	0.00	0.012	0.01	0.1741	0.09	-0.002	0.01	0.7750	0.00	-0.011	0.01	0.1953	0.08
	S1	F	0.019	0.01	0.0812	0.26	-0.009	0.01	0.4276	0.05	0.010	0.01	0.4029	0.06	-0.003	0.01	0.8280	0.00	-0.022	0.01	0.0496	0.33
	S1	M	0.019	0.01	0.0812	0.25	-0.009	0.01	0.4276	0.06	0.010	0.01	0.4029	0.06	-0.003	0.01	0.8280	0.00	-0.022	0.01	0.0496	0.30
	S2	F+M	0.022	0.01	0.0085	0.34	0.003	0.01	0.7482	0.01	0.014	0.01	0.0991	0.13	0.001	0.01	0.9481	0.00	-0.001	0.01	0.9172	0.00
	S2	F	0.022	0.01	0.0459	0.34	-0.004	0.01	0.7238	0.01	0.011	0.01	0.3477	0.07	0.000	0.01	0.9993	0.00	-0.015	0.01	0.1784	0.15
	S2	M	0.022	0.01	0.0459	0.34	-0.004	0.01	0.7238	0.01	0.011	0.01	0.3477	0.08	0.000	0.01	0.9993	0.00	-0.015	0.01	0.1784	0.15
	S3	F+M	0.021	0.01	0.0118	0.31	-0.003	0.01	0.7364	0.01	0.017	0.01	0.0467	0.20	0.026	0.01	0.0030	0.44	-0.018	0.01	0.0364	0.22
	S3	F	0.034	0.01	0.0021	0.79	-0.004	0.01	0.6912	0.01	0.029	0.01	0.0131	0.52	0.029	0.01	0.0105	0.57	-0.029	0.01	0.0114	0.54
	S3	M	0.034	0.01	0.0021	0.80	-0.004	0.01	0.6912	0.01	0.029	0.01	0.0131	0.55	0.029	0.01	0.0105	0.56	-0.029	0.01	0.0114	0.59
	S4	F+M	0.019	0.01	0.0321	0.23	-0.016	0.01	0.0737	0.16	0.015	0.01	0.0833	0.15	0.022	0.01	0.0156	0.29	-0.007	0.01	0.4373	0.03
	S4	F	0.031	0.01	0.0056	0.64	-0.020	0.01	0.0757	0.27	0.024	0.01	0.0393	0.38	0.028	0.01	0.0200	0.47	-0.018	0.01	0.1151	0.21
	S4	M	0.031	0.01	0.0056	0.61	-0.020	0.01	0.0757	0.23	0.024	0.01	0.0393	0.35	0.028	0.01	0.0200	0.49	-0.018	0.01	0.1151	0.23
	S5	F+M	0.016	0.01	0.0627	0.17	-0.019	0.01	0.0326	0.23	0.014	0.01	0.1094	0.13	0.014	0.01	0.1285	0.12	-0.006	0.01	0.5142	0.02
	S5	F	0.029	0.01	0.0120	0.54	-0.023	0.01	0.0411	0.35	0.023	0.01	0.0450	0.35	0.021	0.01	0.1017	0.23	-0.018	0.01	0.1277	0.20
	S5	M	0.029	0.01	0.0120	0.54	-0.023	0.01	0.0411	0.29	0.023	0.01	0.0450	0.35	0.021	0.01	0.1017	0.27	-0.018	0.01	0.1277	0.20
	S6	F+M	0.015	0.01	0.0909	0.14	-0.023	0.01	0.0112	0.32	0.010	0.01	0.2452	0.07	0.012	0.01	0.1954	0.09	-0.004	0.01	0.6245	0.01
	S6	F	0.025	0.01	0.0292	0.40	-0.030	0.01	0.0075	0.61	0.017	0.01	0.1443	0.19	0.021	0.01	0.1047	0.23	-0.013	0.01	0.2671	0.10
	S6	M	0.025	0.01	0.0292	0.41	-0.030	0.01	0.0075	0.50	0.017	0.01	0.1443	0.19	0.021	0.01	0.1047	0.26	-0.013	0.01	0.2671	0.11
	S7	F+M	0.017	0.01	0.0560	0.18	-0.016	0.01	0.0750	0.16	0.007	0.01	0.3939	0.04	0.010	0.01	0.2924	0.06	-0.001	0.01	0.8879	0.00

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
	S7	F	0.023	0.01	0.0453	0.34	-0.022	0.01	0.0624	0.30	0.012	0.01	0.3136	0.09	0.018	0.01	0.1553	0.18	-0.011	0.01	0.3086	0.09
	S7	M	0.023	0.01	0.0453	0.33	-0.022	0.01	0.0624	0.26	0.012	0.01	0.3136	0.09	0.018	0.01	0.1553	0.20	-0.011	0.01	0.3086	0.09
	S8	F+M	0.017	0.01	0.0533	0.18	-0.015	0.01	0.1034	0.14	0.007	0.01	0.4422	0.03	0.009	0.01	0.3563	0.05	-0.001	0.01	0.9471	0.00
	S8	F	0.023	0.01	0.0434	0.34	-0.021	0.01	0.0652	0.30	0.011	0.01	0.3232	0.08	0.017	0.01	0.1779	0.16	-0.011	0.01	0.3394	0.08
	S8	M	0.023	0.01	0.0434	0.34	-0.021	0.01	0.0652	0.25	0.011	0.01	0.3232	0.09	0.017	0.01	0.1779	0.18	-0.011	0.01	0.3394	0.08
Ever used prescription stimulants	S1	F+M	0.009	0.01	0.2385	0.07	-0.001	0.01	0.8601	0.00	0.007	0.01	0.3772	0.04	0.005	0.01	0.4759	0.02	-0.007	0.01	0.3823	0.04
	S1	F	0.003	0.01	0.7300	0.01	-0.005	0.01	0.5590	0.03	0.001	0.01	0.8983	0.00	-0.001	0.01	0.9135	0.00	0.003	0.01	0.7104	0.01
	S1	M	0.003	0.01	0.7300	0.01	-0.005	0.01	0.5590	0.02	0.001	0.01	0.8983	0.00	-0.001	0.01	0.9135	0.00	0.003	0.01	0.7104	0.01
	S2	F+M	0.010	0.01	0.1612	0.09	0.008	0.01	0.2520	0.06	0.006	0.01	0.3963	0.03	0.002	0.01	0.7466	0.01	-0.001	0.01	0.8928	0.00
	S2	F	0.010	0.01	0.2844	0.09	0.002	0.01	0.8475	0.00	0.000	0.01	0.9804	0.00	0.004	0.01	0.6273	0.02	0.005	0.01	0.5622	0.03
	S2	M	0.010	0.01	0.2844	0.07	0.002	0.01	0.8475	0.00	0.000	0.01	0.9804	0.00	0.004	0.01	0.6273	0.01	0.005	0.01	0.5622	0.02
	S3	F+M	0.010	0.01	0.1651	0.09	-0.005	0.01	0.4663	0.02	0.006	0.01	0.4323	0.03	0.007	0.01	0.3908	0.04	-0.008	0.01	0.2864	0.05
	S3	F	0.013	0.01	0.1606	0.16	-0.000	0.01	0.9731	0.00	0.009	0.01	0.3452	0.07	0.010	0.01	0.2758	0.10	-0.007	0.01	0.4675	0.04
	S3	M	0.013	0.01	0.1606	0.12	-0.000	0.01	0.9731	0.00	0.009	0.01	0.3452	0.06	0.010	0.01	0.2758	0.07	-0.007	0.01	0.4675	0.03
	S4	F+M	0.014	0.01	0.0616	0.17	-0.011	0.01	0.1420	0.10	-0.000	0.01	0.9533	0.00	-0.002	0.01	0.8417	0.00	0.000	0.01	0.9609	0.00
	S4	F	0.019	0.01	0.0337	0.37	-0.015	0.01	0.1056	0.22	0.006	0.01	0.5012	0.04	-0.004	0.01	0.7109	0.01	-0.004	0.01	0.6862	0.01
	S4	M	0.019	0.01	0.0337	0.25	-0.015	0.01	0.1056	0.13	0.006	0.01	0.5012	0.03	-0.004	0.01	0.7109	0.01	-0.004	0.01	0.6862	0.01
	S5	F+M	0.018	0.01	0.0180	0.27	-0.016	0.01	0.0424	0.20	0.007	0.01	0.3696	0.04	-0.006	0.01	0.4448	0.03	0.007	0.01	0.3561	0.04
	S5	F	0.018	0.01	0.0499	0.32	-0.015	0.01	0.1048	0.22	0.006	0.01	0.5270	0.03	-0.016	0.01	0.1106	0.21	-0.003	0.01	0.7775	0.01
	S5	M	0.018	0.01	0.0499	0.23	-0.015	0.01	0.1048	0.13	0.006	0.01	0.5270	0.02	-0.016	0.01	0.1106	0.18	-0.003	0.01	0.7775	0.00
	S6	F+M	0.015	0.01	0.0404	0.20	-0.016	0.01	0.0360	0.21	0.006	0.01	0.4135	0.03	-0.003	0.01	0.7152	0.01	0.009	0.01	0.2404	0.07
	S6	F	0.016	0.01	0.0868	0.24	-0.018	0.01	0.0485	0.32	0.001	0.01	0.9383	0.00	-0.012	0.01	0.2371	0.12	0.002	0.01	0.8193	0.00
	S6	M	0.016	0.01	0.0868	0.18	-0.018	0.01	0.0485	0.19	0.001	0.01	0.9383	0.00	-0.012	0.01	0.2371	0.10	0.002	0.01	0.8193	0.00
	S7	F+M	0.014	0.01	0.0715	0.15	-0.013	0.01	0.1015	0.13	0.005	0.01	0.4977	0.02	-0.006	0.01	0.4535	0.03	0.012	0.01	0.0904	0.14
	S7	F	0.012	0.01	0.2032	0.13	-0.015	0.01	0.1000	0.23	-0.003	0.01	0.7130	0.01	-0.014	0.01	0.1797	0.16	0.005	0.01	0.6051	0.02
	S7	M	0.012	0.01	0.2032	0.09	-0.015	0.01	0.1000	0.14	-0.003	0.01	0.7130	0.01	-0.014	0.01	0.1797	0.12	0.005	0.01	0.6051	0.02

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
	S8	F+M	0.014	0.01	0.0737	0.15	-0.012	0.01	0.1229	0.12	0.006	0.01	0.4375	0.03	-0.006	0.01	0.4687	0.03	0.013	0.01	0.0897	0.14
	S8	F	0.012	0.01	0.1936	0.14	-0.015	0.01	0.1039	0.22	-0.003	0.01	0.7639	0.01	-0.014	0.01	0.1788	0.16	0.004	0.01	0.6317	0.02
	S8	M	0.012	0.01	0.1936	0.10	-0.015	0.01	0.1039	0.14	-0.003	0.01	0.7639	0.01	-0.014	0.01	0.1788	0.12	0.004	0.01	0.6317	0.01
Ever used cannabis	S1	F+M	0.015	0.01	0.2084	0.09	0.001	0.01	0.9153	0.00	-0.002	0.01	0.8994	0.00	-0.007	0.01	0.5563	0.02	-0.010	0.01	0.4332	0.04
	S1	F	0.018	0.02	0.2394	0.00	-0.005	0.02	0.7595	0.00	-0.004	0.02	0.8222	0.00	-0.014	0.02	0.3812	0.00	-0.006	0.02	0.6804	0.00
	S1	M	0.012	0.02	0.5124	0.00	0.008	0.02	0.6384	0.00	0.003	0.02	0.8788	0.00	0.003	0.02	0.8566	0.00	-0.018	0.02	0.3424	0.00
	S2	F+M	0.030	0.01	0.0098	0.39	0.012	0.01	0.3147	0.06	0.000	0.01	0.9673	0.00	-0.006	0.01	0.6447	0.01	-0.001	0.01	0.9203	0.00
	S2	F	0.037	0.02	0.0142	0.00	-0.006	0.02	0.7111	0.00	-0.003	0.02	0.8638	0.00	-0.004	0.02	0.7931	0.00	0.002	0.02	0.8888	0.00
	S2	M	0.025	0.02	0.1672	0.00	0.031	0.02	0.0927	0.00	0.001	0.02	0.9412	0.00	-0.005	0.02	0.7850	0.00	-0.008	0.02	0.6874	0.00
	S3	F+M	0.048	0.01	<.0001	0.97	-0.002	0.01	0.8350	0.00	-0.005	0.01	0.6820	0.01	-0.002	0.01	0.8746	0.00	0.003	0.01	0.8040	0.00
	S3	F	0.056	0.02	0.0002	0.00	-0.014	0.02	0.3567	0.00	-0.016	0.02	0.3101	0.00	-0.007	0.02	0.6380	0.00	0.008	0.02	0.5977	0.00
	S3	M	0.038	0.02	0.0356	0.00	0.014	0.02	0.4324	0.00	0.004	0.02	0.8190	0.00	0.020	0.02	0.2935	0.00	-0.002	0.02	0.9273	0.00
	S4	F+M	0.045	0.01	0.0002	0.78	-0.004	0.01	0.7432	0.01	-0.011	0.01	0.3574	0.05	0.005	0.01	0.6925	0.01	0.029	0.01	0.0149	0.35
	S4	F	0.047	0.02	0.0025	0.00	-0.008	0.02	0.6172	0.00	-0.013	0.02	0.4029	0.00	0.006	0.02	0.7190	0.00	0.026	0.02	0.1155	0.00
	S4	M	0.043	0.02	0.0226	0.00	0.009	0.02	0.6311	0.00	-0.015	0.02	0.4295	0.00	0.007	0.02	0.7346	0.00	0.035	0.02	0.0526	0.00
	S5	F+M	0.046	0.01	0.0001	0.86	-0.007	0.01	0.5625	0.02	-0.019	0.01	0.1251	0.14	-0.004	0.01	0.7908	0.00	0.038	0.01	0.0017	0.58
	S5	F	0.053	0.02	0.0009	0.00	-0.016	0.02	0.3140	0.00	-0.021	0.02	0.1870	0.00	-0.010	0.02	0.5687	0.00	0.030	0.02	0.0625	0.00
	S5	M	0.039	0.02	0.0355	0.00	0.009	0.02	0.6440	0.00	-0.024	0.02	0.1905	0.00	0.002	0.02	0.9183	0.00	0.048	0.02	0.0090	0.00
	S6	F+M	0.044	0.01	0.0003	0.77	-0.001	0.01	0.9246	0.00	-0.017	0.01	0.1676	0.11	-0.005	0.01	0.6890	0.01	0.034	0.01	0.0052	0.46
	S6	F	0.050	0.02	0.0016	0.00	-0.007	0.02	0.6498	0.00	-0.020	0.02	0.2025	0.00	-0.013	0.02	0.4774	0.00	0.028	0.02	0.0798	0.00
	S6	M	0.037	0.02	0.0483	0.00	0.010	0.02	0.6128	0.00	-0.024	0.02	0.2053	0.00	-0.001	0.02	0.9529	0.00	0.041	0.02	0.0262	0.00
	S7	F+M	0.047	0.01	0.0001	0.88	0.012	0.01	0.3445	0.05	-0.023	0.01	0.0607	0.21	-0.003	0.01	0.8235	0.00	0.033	0.01	0.0046	0.46
	S7	F	0.049	0.02	0.0016	0.00	0.006	0.02	0.7128	0.00	-0.022	0.02	0.1782	0.00	-0.011	0.02	0.5465	0.00	0.031	0.02	0.0484	0.00
	S7	M	0.046	0.02	0.0152	0.00	0.018	0.02	0.3886	0.00	-0.035	0.02	0.0596	0.00	0.003	0.02	0.8950	0.00	0.034	0.02	0.0541	0.00
	S8	F+M	0.046	0.01	0.0001	0.85	0.011	0.01	0.4009	0.04	-0.023	0.01	0.0585	0.21	-0.006	0.01	0.6751	0.01	0.033	0.01	0.0057	0.44
	S8	F	0.050	0.02	0.0015	0.00	0.004	0.02	0.7940	0.00	-0.020	0.02	0.2046	0.00	-0.014	0.02	0.4480	0.00	0.030	0.02	0.0525	0.00
	S8	M	0.045	0.02	0.0181	0.00	0.017	0.02	0.4083	0.00	-0.037	0.02	0.0452	0.00	-0.000	0.02	0.9962	0.00	0.034	0.02	0.0561	0.00

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	
Age at onset of cannabis initiation	S1	F+M	0.038	0.13	0.7634	0.02	0.010	0.12	0.9363	0.00	-0.174	0.12	0.1640	0.29	0.055	0.12	0.6443	0.03	-0.044	0.12	0.7152	0.02					
	S1	F	0.006	0.21	0.9759	0.00	0.052	0.21	0.8059	0.00	-0.102	0.21	0.6214	0.00	0.351	0.21	0.0963	0.00	0.203	0.20	0.3224	0.00					
	S1	M	0.094	0.16	0.5555	0.00	-0.018	0.15	0.9047	0.00	-0.209	0.16	0.1827	0.00	-0.088	0.15	0.5454	0.00	-0.204	0.15	0.1741	0.00					
	S2	F+M	-0.190	0.13	0.1398	0.38	0.244	0.12	0.0509	0.59	-0.150	0.12	0.2250	0.22	0.040	0.13	0.7482	0.02	0.032	0.13	0.7965	0.01					
	S2	F	-0.169	0.21	0.4245	0.00	0.338	0.20	0.0937	0.00	-0.095	0.20	0.6434	0.00	0.331	0.22	0.1266	0.00	0.248	0.21	0.2413	0.00					
	S2	M	-0.157	0.17	0.3420	0.00	0.142	0.16	0.3818	0.00	-0.175	0.15	0.2586	0.00	-0.119	0.15	0.4380	0.00	-0.104	0.16	0.5050	0.00					
	S3	F+M	-0.126	0.13	0.3354	0.16	-0.034	0.13	0.7847	0.01	-0.264	0.12	0.0318	0.68	-0.083	0.13	0.5210	0.07	0.170	0.12	0.1567	0.29					
	S3	F	-0.029	0.21	0.8899	0.00	0.125	0.21	0.5470	0.00	-0.255	0.20	0.1972	0.00	0.151	0.22	0.4913	0.00	0.270	0.20	0.1844	0.00					
	S3	M	-0.102	0.17	0.5463	0.00	-0.221	0.16	0.1653	0.00	-0.289	0.16	0.0649	0.00	-0.208	0.16	0.1996	0.00	0.105	0.15	0.4760	0.00					
	S4	F+M	-0.161	0.14	0.2525	0.25	0.011	0.13	0.9366	0.00	-0.254	0.13	0.0468	0.64	-0.043	0.13	0.7379	0.02	0.129	0.12	0.2985	0.17					
	S4	F	-0.032	0.22	0.8855	0.00	-0.017	0.22	0.9398	0.00	-0.325	0.20	0.1117	0.00	0.015	0.21	0.9436	0.00	0.245	0.21	0.2477	0.00					
	S4	M	-0.221	0.18	0.2259	0.00	-0.004	0.17	0.9828	0.00	-0.177	0.17	0.2896	0.00	-0.059	0.16	0.7168	0.00	0.059	0.15	0.6976	0.00					
	S5	F+M	-0.217	0.13	0.1079	0.46	0.064	0.14	0.6457	0.04	-0.100	0.13	0.4354	0.10	-0.053	0.14	0.6954	0.02	-0.038	0.12	0.7590	0.01					
	S5	F	-0.217	0.22	0.3274	0.00	-0.039	0.22	0.8632	0.00	-0.109	0.21	0.5996	0.00	0.090	0.23	0.6947	0.00	0.147	0.21	0.4823	0.00					
	S5	M	-0.208	0.17	0.2269	0.00	0.103	0.18	0.5640	0.00	-0.118	0.16	0.4679	0.00	-0.107	0.17	0.5270	0.00	-0.089	0.16	0.5678	0.00					
	S6	F+M	-0.189	0.14	0.1632	0.35	0.115	0.14	0.4190	0.12	-0.092	0.13	0.4665	0.08	-0.147	0.14	0.2945	0.18	0.028	0.12	0.8216	0.01					
	S6	F	-0.200	0.22	0.3582	0.00	0.072	0.23	0.7513	0.00	-0.040	0.20	0.8447	0.00	-0.006	0.23	0.9794	0.00	0.209	0.21	0.3159	0.00					
	S6	M	-0.168	0.18	0.3387	0.00	0.147	0.19	0.4295	0.00	-0.161	0.16	0.3167	0.00	-0.197	0.18	0.2633	0.00	-0.035	0.15	0.8189	0.00					
	S7	F+M	-0.105	0.14	0.4407	0.11	-0.004	0.15	0.9766	0.00	-0.107	0.13	0.4003	0.11	-0.144	0.14	0.3094	0.18	0.021	0.12	0.8621	0.00					
	S7	F	-0.069	0.22	0.7523	0.00	-0.152	0.23	0.5180	0.00	-0.068	0.21	0.7421	0.00	0.118	0.24	0.6215	0.00	0.180	0.20	0.3606	0.00					
	S7	M	-0.095	0.18	0.5895	0.00	0.116	0.19	0.5348	0.00	-0.170	0.16	0.2946	0.00	-0.274	0.18	0.1213	0.00	-0.034	0.15	0.8260	0.00					
	S8	F+M	-0.108	0.14	0.4308	0.11	0.027	0.15	0.8509	0.01	-0.104	0.13	0.4078	0.11	-0.128	0.14	0.3715	0.14	0.032	0.12	0.7922	0.01					
	S8	F	-0.060	0.22	0.7858	0.00	-0.109	0.24	0.6470	0.00	-0.084	0.21	0.6853	0.00	0.140	0.24	0.5605	0.00	0.172	0.20	0.3838	0.00					
	S8	M	-0.109	0.18	0.5399	0.00	0.137	0.19	0.4616	0.00	-0.150	0.16	0.3505	0.00	-0.263	0.18	0.1397	0.00	-0.008	0.15	0.9589	0.00					
Alcohol abuse	S1	F+M	0.006	0.01	0.5574	0.02	-0.004	0.01	0.6884	0.01	-0.011	0.01	0.2799	0.05	-0.008	0.01	0.4482	0.03	0.003	0.01	0.8073	0.00					

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
	S1	F	0.005	0.01	0.6644	0.00	0.004	0.01	0.7467	0.00	-0.010	0.01	0.4275	0.00	-0.005	0.01	0.7074	0.00	0.006	0.01	0.6486	0.00
	S1	M	0.012	0.02	0.4575	0.00	-0.016	0.02	0.3177	0.00	-0.014	0.02	0.3869	0.00	-0.015	0.02	0.3359	0.00	-0.000	0.02	0.9839	0.00
	S2	F+M	0.022	0.01	0.0302	0.22	0.010	0.01	0.3164	0.05	-0.013	0.01	0.2206	0.07	-0.011	0.01	0.2905	0.05	0.006	0.01	0.5553	0.02
	S2	F	0.021	0.01	0.0882	0.00	0.008	0.01	0.5282	0.00	-0.013	0.01	0.3233	0.00	-0.006	0.01	0.6578	0.00	0.002	0.01	0.8586	0.00
	S2	M	0.026	0.02	0.0999	0.00	0.008	0.02	0.6499	0.00	-0.016	0.02	0.3248	0.00	-0.022	0.02	0.1740	0.00	0.016	0.02	0.3328	0.00
	S3	F+M	0.030	0.01	0.0034	0.41	-0.010	0.01	0.3060	0.05	-0.012	0.01	0.2658	0.06	-0.015	0.01	0.1551	0.10	0.005	0.01	0.6528	0.01
	S3	F	0.025	0.01	0.0440	0.00	-0.001	0.01	0.9457	0.00	-0.003	0.01	0.7971	0.00	-0.020	0.01	0.1323	0.00	0.013	0.01	0.3238	0.00
	S3	M	0.040	0.02	0.0141	0.00	-0.021	0.02	0.2060	0.00	-0.027	0.02	0.1009	0.00	-0.008	0.02	0.6370	0.00	-0.002	0.02	0.8834	0.00
	S4	F+M	0.026	0.01	0.0128	0.29	-0.014	0.01	0.1904	0.08	-0.000	0.01	0.9696	0.00	-0.009	0.01	0.3987	0.03	0.015	0.01	0.1326	0.11
	S4	F	0.029	0.01	0.0256	0.00	-0.011	0.01	0.3840	0.00	0.012	0.01	0.3455	0.00	-0.028	0.01	0.0405	0.00	0.016	0.01	0.2180	0.00
	S4	M	0.024	0.02	0.1546	0.00	-0.014	0.02	0.4434	0.00	-0.026	0.02	0.1172	0.00	0.014	0.02	0.4166	0.00	0.015	0.02	0.3621	0.00
	S5	F+M	0.029	0.01	0.0056	0.36	-0.011	0.01	0.3185	0.05	-0.010	0.01	0.3373	0.04	-0.021	0.01	0.0641	0.17	0.015	0.01	0.1397	0.10
	S5	F	0.031	0.01	0.0166	0.00	-0.014	0.01	0.2638	0.00	-0.004	0.01	0.7854	0.00	-0.042	0.01	0.0038	0.00	0.015	0.01	0.2533	0.00
	S5	M	0.027	0.02	0.1006	0.00	-0.001	0.02	0.9449	0.00	-0.028	0.02	0.0974	0.00	0.001	0.02	0.9724	0.00	0.015	0.02	0.3579	0.00
	S6	F+M	0.028	0.01	0.0063	0.35	-0.008	0.01	0.4420	0.03	-0.009	0.01	0.3938	0.03	-0.018	0.01	0.1221	0.12	0.014	0.01	0.1656	0.09
	S6	F	0.030	0.01	0.0202	0.00	-0.020	0.01	0.1283	0.00	-0.003	0.01	0.7949	0.00	-0.036	0.01	0.0124	0.00	0.016	0.01	0.2124	0.00
	S6	M	0.027	0.02	0.1058	0.00	0.013	0.02	0.4806	0.00	-0.028	0.02	0.0950	0.00	0.001	0.02	0.9705	0.00	0.010	0.02	0.5488	0.00
	S7	F+M	0.028	0.01	0.0060	0.36	-0.002	0.01	0.8447	0.00	-0.012	0.01	0.2651	0.06	-0.021	0.01	0.0685	0.17	0.012	0.01	0.2486	0.06
	S7	F	0.037	0.01	0.0037	0.00	-0.012	0.01	0.3652	0.00	-0.004	0.01	0.7814	0.00	-0.040	0.01	0.0060	0.00	0.016	0.01	0.2073	0.00
	S7	M	0.018	0.02	0.2868	0.00	0.014	0.02	0.4457	0.00	-0.032	0.02	0.0531	0.00	-0.001	0.02	0.9648	0.00	0.004	0.02	0.8064	0.00
	S8	F+M	0.028	0.01	0.0066	0.35	-0.004	0.01	0.7227	0.01	-0.011	0.01	0.3003	0.05	-0.021	0.01	0.0706	0.16	0.013	0.01	0.1932	0.08
	S8	F	0.036	0.01	0.0055	0.00	-0.015	0.01	0.2435	0.00	-0.003	0.01	0.8082	0.00	-0.038	0.01	0.0081	0.00	0.019	0.01	0.1334	0.00
	S8	M	0.019	0.02	0.2564	0.00	0.015	0.02	0.4118	0.00	-0.031	0.02	0.0642	0.00	-0.002	0.02	0.8939	0.00	0.003	0.02	0.8527	0.00
Alcohol dependence	S1	F+M	0.003	0.01	0.7635	0.00	0.003	0.01	0.7776	0.00	-0.012	0.01	0.2320	0.07	0.004	0.01	0.6418	0.01	0.016	0.01	0.0980	0.13
	S1	F	0.011	0.01	0.3337	0.00	0.012	0.01	0.3164	0.00	-0.009	0.01	0.4433	0.00	0.011	0.01	0.3774	0.00	0.024	0.01	0.0414	0.00
	S1	M	-0.005	0.02	0.7462	0.00	-0.010	0.02	0.5136	0.00	-0.016	0.02	0.3062	0.00	-0.007	0.02	0.6524	0.00	0.004	0.02	0.7892	0.00
	S2	F+M	0.006	0.01	0.5385	0.02	0.003	0.01	0.7199	0.01	-0.010	0.01	0.2974	0.05	-0.011	0.01	0.2581	0.06	0.019	0.01	0.0576	0.17

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p	R ²	Sex	Beta	SE	p	R ²	Sex	Beta	SE	p	R ²	Sex	Beta	SE	p	R ²	Sex	Beta	SE	p	R ²	
S2	F	0.024	0.01	0.0366	0.00	0.003	0.01	0.7763	0.00	-0.012	0.01	0.3338	0.00	0.002	0.01	0.8871	0.00	0.021	0.01	0.0762	0.00						
S2	M	-0.015	0.02	0.3340	0.00	0.003	0.02	0.8747	0.00	-0.012	0.02	0.4631	0.00	-0.033	0.02	0.0394	0.00	0.017	0.02	0.3134	0.00						
S3	F+M	0.019	0.01	0.0465	0.19	0.000	0.01	0.9760	0.00	-0.011	0.01	0.2582	0.06	-0.003	0.01	0.7975	0.00	0.011	0.01	0.2456	0.06						
S3	F	0.024	0.01	0.0394	0.00	-0.006	0.01	0.6404	0.00	-0.008	0.01	0.5171	0.00	-0.001	0.01	0.9338	0.00	0.013	0.01	0.3003	0.00						
S3	M	0.017	0.02	0.2962	0.00	0.004	0.02	0.7863	0.00	-0.021	0.02	0.2001	0.00	-0.006	0.02	0.7373	0.00	0.012	0.02	0.4335	0.00						
S4	F+M	0.019	0.01	0.0577	0.17	-0.012	0.01	0.2159	0.07	-0.006	0.01	0.5658	0.02	-0.009	0.01	0.4001	0.03	0.010	0.01	0.2868	0.05						
S4	F	0.026	0.01	0.0263	0.00	-0.013	0.01	0.2667	0.00	0.002	0.01	0.8606	0.00	-0.019	0.01	0.1407	0.00	0.007	0.01	0.5623	0.00						
S4	M	0.010	0.02	0.5456	0.00	-0.013	0.02	0.4562	0.00	-0.023	0.02	0.1609	0.00	0.002	0.02	0.9002	0.00	0.017	0.02	0.2748	0.00						
S5	F+M	0.018	0.01	0.0684	0.16	-0.017	0.01	0.0982	0.13	-0.010	0.01	0.2919	0.05	-0.018	0.01	0.0881	0.14	0.012	0.01	0.2350	0.07						
S5	F	0.020	0.01	0.1026	0.00	-0.022	0.01	0.0658	0.00	-0.017	0.01	0.1577	0.00	-0.034	0.01	0.0109	0.00	0.003	0.01	0.7791	0.00						
S5	M	0.019	0.02	0.2325	0.00	-0.010	0.02	0.5735	0.00	-0.004	0.02	0.7839	0.00	-0.004	0.02	0.8146	0.00	0.026	0.02	0.1061	0.00						
S6	F+M	0.020	0.01	0.0447	0.19	-0.015	0.01	0.1523	0.10	-0.008	0.01	0.4174	0.03	-0.014	0.01	0.1934	0.08	0.011	0.01	0.2690	0.06						
S6	F	0.023	0.01	0.0515	0.00	-0.023	0.01	0.0530	0.00	-0.015	0.01	0.2002	0.00	-0.031	0.01	0.0208	0.00	0.002	0.01	0.8453	0.00						
S6	M	0.018	0.02	0.2830	0.00	-0.004	0.02	0.8341	0.00	-0.003	0.02	0.8442	0.00	0.002	0.02	0.9009	0.00	0.025	0.02	0.1159	0.00						
S7	F+M	0.012	0.01	0.2336	0.07	-0.007	0.01	0.4787	0.02	-0.010	0.01	0.3058	0.05	-0.016	0.01	0.1377	0.11	0.008	0.01	0.3776	0.04						
S7	F	0.016	0.01	0.1886	0.00	-0.016	0.01	0.2000	0.00	-0.018	0.01	0.1291	0.00	-0.030	0.01	0.0241	0.00	0.001	0.01	0.9351	0.00						
S7	M	0.009	0.02	0.5639	0.00	0.003	0.02	0.8739	0.00	-0.005	0.02	0.7827	0.00	-0.004	0.02	0.8078	0.00	0.022	0.02	0.1635	0.00						
S8	F+M	0.013	0.01	0.1995	0.08	-0.008	0.01	0.4522	0.03	-0.009	0.01	0.3854	0.04	-0.017	0.01	0.1165	0.13	0.008	0.01	0.3782	0.04						
S8	F	0.015	0.01	0.2158	0.00	-0.016	0.01	0.1875	0.00	-0.018	0.01	0.1432	0.00	-0.032	0.01	0.0193	0.00	0.002	0.01	0.8764	0.00						
S8	M	0.012	0.02	0.4484	0.00	0.003	0.02	0.8820	0.00	-0.002	0.02	0.9012	0.00	-0.005	0.02	0.7719	0.00	0.021	0.02	0.1842	0.00						
DSM5 AUD (4 point scale)	S1	F+M	0.025	0.02	0.2906	0.05	0.002	0.02	0.9374	0.00	-0.030	0.02	0.2098	0.07	0.000	0.02	0.9854	0.00	0.044	0.02	0.0688	0.16					
	S1	F	0.020	0.03	0.4941	0.00	0.021	0.03	0.4813	0.00	-0.018	0.03	0.5559	0.00	0.012	0.03	0.6829	0.00	0.057	0.03	0.0547	0.00					
	S1	M	0.048	0.04	0.2136	0.00	-0.028	0.04	0.4557	0.00	-0.052	0.04	0.1742	0.00	-0.023	0.04	0.5362	0.00	0.027	0.04	0.5012	0.00					
	S2	F+M	0.043	0.02	0.0681	0.16	0.000	0.02	0.9880	0.00	-0.024	0.02	0.3111	0.05	-0.028	0.02	0.2460	0.06	0.045	0.02	0.0643	0.16					
	S2	F	0.051	0.03	0.0764	0.00	0.001	0.03	0.9753	0.00	-0.020	0.03	0.5034	0.00	0.001	0.03	0.9651	0.00	0.037	0.03	0.2095	0.00					
	S2	M	0.044	0.04	0.2474	0.00	-0.012	0.04	0.7615	0.00	-0.039	0.04	0.3087	0.00	-0.074	0.04	0.0547	0.00	0.068	0.04	0.0876	0.00					
	S3	F+M	0.069	0.02	0.0035	0.41	-0.030	0.02	0.2033	0.08	-0.017	0.02	0.4814	0.02	-0.023	0.02	0.3345	0.04	0.048	0.02	0.0480	0.19					

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
S3	F	0.058	0.03	0.0449	0.00	-0.013	0.03	0.6607	0.00	0.001	0.03	0.9737	0.00	-0.009	0.03	0.7576	0.00	0.049	0.03	0.1088	0.00	
S3	M	0.100	0.04	0.0085	0.00	-0.058	0.04	0.1327	0.00	-0.051	0.04	0.1882	0.00	-0.041	0.04	0.3060	0.00	0.059	0.04	0.1231	0.00	
S4	F+M	0.065	0.02	0.0076	0.34	-0.048	0.02	0.0537	0.18	0.008	0.02	0.7330	0.01	-0.019	0.03	0.4519	0.03	0.062	0.02	0.0094	0.32	
S4	F	0.067	0.03	0.0237	0.00	-0.054	0.03	0.0713	0.00	0.034	0.03	0.2448	0.00	-0.054	0.03	0.0884	0.00	0.061	0.03	0.0417	0.00	
S4	M	0.071	0.04	0.0765	0.00	-0.037	0.04	0.3764	0.00	-0.040	0.04	0.3166	0.00	0.017	0.04	0.6711	0.00	0.071	0.04	0.0585	0.00	
S5	F+M	0.077	0.02	0.0014	0.49	-0.054	0.02	0.0316	0.22	-0.017	0.02	0.4872	0.02	-0.049	0.03	0.0644	0.17	0.056	0.02	0.0208	0.25	
S5	F	0.067	0.03	0.0247	0.00	-0.069	0.03	0.0203	0.00	-0.016	0.03	0.5998	0.00	-0.101	0.03	0.0025	0.00	0.041	0.03	0.1755	0.00	
S5	M	0.101	0.04	0.0097	0.00	-0.027	0.04	0.5367	0.00	-0.025	0.04	0.5274	0.00	-0.001	0.04	0.9799	0.00	0.085	0.04	0.0273	0.00	
S6	F+M	0.085	0.02	0.0005	0.58	-0.052	0.03	0.0375	0.21	-0.009	0.02	0.7030	0.01	-0.032	0.03	0.2359	0.07	0.054	0.02	0.0226	0.25	
S6	F	0.078	0.03	0.0092	0.00	-0.081	0.03	0.0063	0.00	-0.009	0.03	0.7621	0.00	-0.080	0.03	0.0185	0.00	0.042	0.03	0.1611	0.00	
S6	M	0.099	0.04	0.0111	0.00	-0.008	0.04	0.8490	0.00	-0.023	0.04	0.5522	0.00	0.010	0.04	0.8160	0.00	0.078	0.04	0.0397	0.00	
S7	F+M	0.074	0.02	0.0021	0.45	-0.036	0.03	0.1532	0.10	-0.009	0.02	0.7251	0.01	-0.042	0.03	0.1239	0.12	0.051	0.02	0.0291	0.22	
S7	F	0.073	0.03	0.0141	0.00	-0.071	0.03	0.0192	0.00	-0.002	0.03	0.9419	0.00	-0.087	0.03	0.0102	0.00	0.037	0.03	0.2113	0.00	
S7	M	0.086	0.04	0.0280	0.00	0.014	0.04	0.7529	0.00	-0.031	0.04	0.4330	0.00	-0.002	0.04	0.9539	0.00	0.078	0.04	0.0394	0.00	
S8	F+M	0.076	0.02	0.0017	0.47	-0.037	0.03	0.1497	0.10	-0.004	0.02	0.8595	0.00	-0.043	0.03	0.1130	0.13	0.052	0.02	0.0268	0.23	
S8	F	0.072	0.03	0.0158	0.00	-0.072	0.03	0.0170	0.00	-0.000	0.03	0.9951	0.00	-0.087	0.03	0.0097	0.00	0.041	0.03	0.1657	0.00	
S8	M	0.090	0.04	0.0223	0.00	0.015	0.04	0.7264	0.00	-0.023	0.04	0.5496	0.00	-0.004	0.04	0.9161	0.00	0.075	0.04	0.0492	0.00	
DSM5 AUD (ctrl mild vs moderate severe)	S1	F+M	0.010	0.01	0.3088	0.05	0.000	0.01	0.9762	0.00	-0.013	0.01	0.1888	0.08	0.006	0.01	0.5587	0.02	0.021	0.01	0.0303	0.22
	S1	F	0.012	0.01	0.3026	0.00	0.005	0.01	0.6632	0.00	-0.007	0.01	0.5936	0.00	0.014	0.01	0.2626	0.00	0.028	0.01	0.0163	0.00
	S1	M	0.010	0.02	0.5160	0.00	-0.008	0.02	0.6130	0.00	-0.022	0.02	0.1628	0.00	-0.008	0.02	0.6062	0.00	0.011	0.02	0.5058	0.00
	S2	F+M	0.011	0.01	0.2488	0.06	-0.002	0.01	0.8571	0.00	-0.011	0.01	0.2509	0.06	-0.006	0.01	0.5221	0.02	0.020	0.01	0.0384	0.20
	S2	F	0.021	0.01	0.0713	0.00	-0.003	0.01	0.7716	0.00	-0.007	0.01	0.5878	0.00	0.010	0.01	0.4143	0.00	0.021	0.01	0.0765	0.00
	S2	M	0.001	0.02	0.9665	0.00	-0.002	0.02	0.8875	0.00	-0.019	0.02	0.2184	0.00	-0.031	0.02	0.0537	0.00	0.021	0.02	0.2023	0.00
	S3	F+M	0.021	0.01	0.0273	0.23	-0.005	0.01	0.6219	0.01	-0.008	0.01	0.4087	0.03	-0.008	0.01	0.4128	0.03	0.026	0.01	0.0089	0.32
	S3	F	0.019	0.01	0.1040	0.00	0.000	0.01	0.9878	0.00	-0.000	0.01	0.9866	0.00	-0.001	0.01	0.9372	0.00	0.022	0.01	0.0720	0.00

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	
	S3	M	0.030	0.02	0.0615	0.00	-0.015	0.02	0.3556	0.00	-0.022	0.02	0.1797	0.00	-0.018	0.02	0.2632	0.00	0.033	0.02	0.0398	0.00					
	S4	F+M	0.020	0.01	0.0445	0.19	-0.014	0.01	0.1481	0.10	-0.003	0.01	0.7726	0.00	-0.003	0.01	0.7567	0.00	0.025	0.01	0.0085	0.32					
	S4	F	0.022	0.01	0.0673	0.00	-0.014	0.01	0.2428	0.00	0.009	0.01	0.4303	0.00	-0.018	0.01	0.1581	0.00	0.021	0.01	0.0848	0.00					
	S4	M	0.020	0.02	0.2266	0.00	-0.017	0.02	0.3152	0.00	-0.024	0.02	0.1462	0.00	0.013	0.02	0.4351	0.00	0.033	0.02	0.0327	0.00					
	S5	F+M	0.025	0.01	0.0122	0.29	-0.015	0.01	0.1501	0.10	-0.010	0.01	0.3282	0.04	-0.013	0.01	0.2256	0.07	0.024	0.01	0.0137	0.28					
	S5	F	0.019	0.01	0.1065	0.00	-0.023	0.01	0.0547	0.00	-0.010	0.01	0.3881	0.00	-0.037	0.01	0.0066	0.00	0.017	0.01	0.1532	0.00					
	S5	M	0.035	0.02	0.0290	0.00	-0.002	0.02	0.9101	0.00	-0.011	0.02	0.5098	0.00	0.011	0.02	0.5186	0.00	0.035	0.02	0.0262	0.00					
	S6	F+M	0.028	0.01	0.0051	0.37	-0.015	0.01	0.1369	0.10	-0.008	0.01	0.3878	0.04	-0.005	0.01	0.6498	0.01	0.025	0.01	0.0091	0.31					
	S6	F	0.024	0.01	0.0458	0.00	-0.028	0.01	0.0208	0.00	-0.007	0.01	0.5476	0.00	-0.029	0.01	0.0340	0.00	0.018	0.01	0.1312	0.00					
	S6	M	0.035	0.02	0.0326	0.00	0.003	0.02	0.8736	0.00	-0.014	0.02	0.3769	0.00	0.019	0.02	0.2633	0.00	0.037	0.02	0.0201	0.00					
	S7	F+M	0.023	0.01	0.0176	0.26	-0.011	0.01	0.3029	0.05	-0.003	0.01	0.7578	0.00	-0.009	0.01	0.3959	0.04	0.021	0.01	0.0244	0.23					
	S7	F	0.021	0.01	0.0772	0.00	-0.021	0.01	0.0812	0.00	-0.001	0.01	0.9082	0.00	-0.030	0.01	0.0270	0.00	0.015	0.01	0.2044	0.00					
	S7	M	0.030	0.02	0.0702	0.00	0.004	0.02	0.8242	0.00	-0.009	0.02	0.5808	0.00	0.011	0.02	0.5151	0.00	0.032	0.02	0.0405	0.00					
	S8	F+M	0.025	0.01	0.0124	0.29	-0.010	0.01	0.3166	0.05	-0.001	0.01	0.9011	0.00	-0.009	0.01	0.3890	0.04	0.022	0.01	0.0215	0.24					
	S8	F	0.021	0.01	0.0764	0.00	-0.022	0.01	0.0788	0.00	-0.001	0.01	0.9584	0.00	-0.030	0.01	0.0268	0.00	0.017	0.01	0.1572	0.00					
	S8	M	0.032	0.02	0.0501	0.00	0.005	0.02	0.7838	0.00	-0.006	0.02	0.7251	0.00	0.011	0.02	0.5171	0.00	0.031	0.02	0.0478	0.00					
Cannabis abuse	S1	F+M	-0.002	0.01	0.7909	0.00	-0.009	0.01	0.2141	0.08	0.017	0.01	0.0152	0.29	0.003	0.01	0.6402	0.01	-0.007	0.01	0.3647	0.04					
	S1	F	-0.004	0.01	0.6531	0.00	-0.002	0.01	0.7887	0.00	0.010	0.01	0.2263	0.00	0.007	0.01	0.4086	0.00	-0.011	0.01	0.1566	0.00					
	S1	M	0.003	0.01	0.8003	0.00	-0.013	0.01	0.2848	0.00	0.025	0.01	0.0437	0.00	-0.006	0.01	0.5941	0.00	-0.003	0.01	0.7904	0.00					
	S2	F+M	0.013	0.01	0.0702	0.16	0.006	0.01	0.3640	0.04	0.018	0.01	0.0128	0.30	-0.002	0.01	0.7340	0.01	-0.000	0.01	0.9912	0.00					
	S2	F	0.015	0.01	0.0588	0.00	-0.008	0.01	0.3230	0.00	0.007	0.01	0.3974	0.00	0.011	0.01	0.1810	0.00	-0.003	0.01	0.6871	0.00					
	S2	M	0.012	0.01	0.3327	0.00	0.024	0.01	0.0613	0.00	0.030	0.01	0.0137	0.00	-0.024	0.01	0.0561	0.00	0.002	0.01	0.8915	0.00					
	S3	F+M	0.007	0.01	0.2923	0.06	0.001	0.01	0.8471	0.00	0.010	0.01	0.1449	0.11	-0.005	0.01	0.4564	0.03	0.004	0.01	0.5405	0.02					
	S3	F	0.014	0.01	0.0781	0.00	0.005	0.01	0.5224	0.00	0.000	0.01	0.9624	0.00	-0.006	0.01	0.4666	0.00	0.003	0.01	0.7140	0.00					
	S3	M	0.004	0.01	0.7199	0.00	-0.002	0.01	0.8836	0.00	0.029	0.01	0.0203	0.00	-0.005	0.01	0.7264	0.00	0.007	0.01	0.5743	0.00					
S4	F+M	0.013	0.01	0.0685	0.17	-0.010	0.01	0.1607	0.10	0.008	0.01	0.2482	0.07	0.000	0.01	0.9696	0.00	0.010	0.01	0.1593	0.10						
	F	0.017	0.01	0.0376	0.00	0.002	0.01	0.7866	0.00	-0.002	0.01	0.8209	0.00	-0.002	0.01	0.8223	0.00	0.004	0.01	0.5849	0.00						

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	
S4	M	0.010	0.01	0.4445	0.00	-0.025	0.01	0.0696	0.00	0.024	0.01	0.0583	0.00	0.006	0.01	0.6389	0.00	0.020	0.01	0.0998	0.00						
S5	F+M	0.010	0.01	0.1476	0.11	-0.016	0.01	0.0309	0.24	0.005	0.01	0.4586	0.03	-0.003	0.01	0.7098	0.01	0.012	0.01	0.1024	0.13						
S5	F	0.013	0.01	0.0979	0.00	-0.004	0.01	0.6247	0.00	-0.007	0.01	0.3976	0.00	-0.005	0.01	0.6000	0.00	0.005	0.01	0.5765	0.00						
S5	M	0.006	0.01	0.6328	0.00	-0.029	0.01	0.0367	0.00	0.021	0.01	0.0982	0.00	0.003	0.01	0.8203	0.00	0.026	0.01	0.0380	0.00						
S6	F+M	0.012	0.01	0.0857	0.15	-0.013	0.01	0.0788	0.16	0.003	0.01	0.6435	0.01	-0.005	0.01	0.5297	0.02	0.016	0.01	0.0263	0.24						
S6	F	0.015	0.01	0.0718	0.00	-0.002	0.01	0.8092	0.00	-0.008	0.01	0.3179	0.00	-0.006	0.01	0.4877	0.00	0.009	0.01	0.2644	0.00						
S6	M	0.009	0.01	0.4840	0.00	-0.026	0.01	0.0657	0.00	0.019	0.01	0.1327	0.00	-0.000	0.01	0.9966	0.00	0.029	0.01	0.0188	0.00						
S7	F+M	0.012	0.01	0.0886	0.15	-0.013	0.01	0.1002	0.14	0.001	0.01	0.9444	0.00	-0.011	0.01	0.1821	0.10	0.015	0.01	0.0296	0.23						
S7	F	0.016	0.01	0.0437	0.00	-0.002	0.01	0.7628	0.00	-0.009	0.01	0.2964	0.00	-0.013	0.01	0.1559	0.00	0.012	0.01	0.1150	0.00						
S7	M	0.007	0.01	0.5716	0.00	-0.025	0.01	0.0861	0.00	0.011	0.01	0.3801	0.00	-0.005	0.01	0.6971	0.00	0.021	0.01	0.0874	0.00						
S8	F+M	0.012	0.01	0.0883	0.15	-0.013	0.01	0.0872	0.15	0.000	0.01	0.9915	0.00	-0.011	0.01	0.1720	0.10	0.015	0.01	0.0323	0.23						
S8	F	0.016	0.01	0.0398	0.00	-0.003	0.01	0.7255	0.00	-0.008	0.01	0.3056	0.00	-0.012	0.01	0.1905	0.00	0.012	0.01	0.1217	0.00						
S8	M	0.006	0.01	0.6257	0.00	-0.025	0.01	0.0787	0.00	0.010	0.01	0.4342	0.00	-0.007	0.01	0.5858	0.00	0.021	0.01	0.0939	0.00						
Age at onset of cannabis abuse	S1	F+M	-0.407	0.21	0.0538	1.69	-0.077	0.20	0.7015	0.06	-0.066	0.22	0.7636	0.04	0.014	0.21	0.9440	0.00	0.142	0.19	0.4465	0.20					
	S1	F	-0.710	0.38	0.0646	0.00	-0.254	0.35	0.4654	0.00	0.554	0.39	0.1564	0.00	0.352	0.41	0.3941	0.00	0.169	0.32	0.5961	0.00					
	S1	M	-0.257	0.26	0.3240	0.00	0.089	0.26	0.7348	0.00	-0.417	0.27	0.1311	0.00	-0.170	0.25	0.4924	0.00	0.084	0.25	0.7350	0.00					
	S2	F+M	-0.312	0.21	0.1412	1.01	0.013	0.20	0.9452	0.00	0.021	0.21	0.9198	0.00	0.028	0.22	0.9004	0.01	0.170	0.21	0.4102	0.29					
	S2	F	-0.424	0.38	0.2683	0.00	0.325	0.32	0.3116	0.00	0.561	0.37	0.1357	0.00	0.318	0.45	0.4850	0.00	0.168	0.36	0.6457	0.00					
	S2	M	-0.273	0.27	0.3176	0.00	-0.199	0.26	0.4464	0.00	-0.272	0.27	0.3141	0.00	-0.134	0.27	0.6176	0.00	0.172	0.27	0.5225	0.00					
	S3	F+M	-0.155	0.22	0.4844	0.24	-0.044	0.21	0.8293	0.02	-0.089	0.21	0.6757	0.08	-0.038	0.22	0.8634	0.01	0.415	0.20	0.0440	1.69					
	S3	F	-0.003	0.41	0.9943	0.00	0.638	0.36	0.0784	0.00	0.547	0.38	0.1516	0.00	0.678	0.44	0.1227	0.00	0.434	0.35	0.2192	0.00					
	S3	M	-0.166	0.28	0.5555	0.00	-0.389	0.26	0.1300	0.00	-0.493	0.26	0.0635	0.00	-0.364	0.27	0.1832	0.00	0.472	0.26	0.0746	0.00					
	S4	F+M	-0.194	0.24	0.4277	0.36	0.113	0.23	0.6209	0.12	-0.007	0.22	0.9749	0.00	0.222	0.21	0.2966	0.43	0.583	0.21	0.0051	3.37					
	S4	F	-0.314	0.44	0.4731	0.00	0.648	0.40	0.1098	0.00	0.239	0.42	0.5691	0.00	0.484	0.39	0.2219	0.00	0.635	0.35	0.0711	0.00					
	S4	M	-0.139	0.32	0.6650	0.00	-0.222	0.29	0.4455	0.00	-0.240	0.27	0.3827	0.00	0.061	0.28	0.8271	0.00	0.585	0.26	0.0280	0.00					
	S5	F+M	-0.103	0.23	0.6501	0.10	0.224	0.25	0.3657	0.46	0.147	0.22	0.5063	0.21	0.247	0.22	0.2668	0.51	0.267	0.20	0.1897	0.69					

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW				
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²				
	S5	F	-0.332	0.42	0.4295	0.00	0.963	0.43	0.0263	0.00	0.198	0.40	0.6237	0.00	0.768	0.40	0.0590	0.00	0.055	0.34	0.8706	0.00				
	S5	M	-0.011	0.28	0.9681	0.00	-0.223	0.31	0.4701	0.00	-0.012	0.28	0.9667	0.00	-0.066	0.29	0.8238	0.00	0.453	0.27	0.0958	0.00				
	S6	F+M	0.044	0.24	0.8533	0.02	0.179	0.24	0.4652	0.29	0.192	0.22	0.3796	0.36	0.308	0.23	0.1871	0.78	0.249	0.20	0.2253	0.62				
	S6	F	-0.405	0.42	0.3389	0.00	0.715	0.39	0.0683	0.00	0.260	0.39	0.5027	0.00	0.806	0.41	0.0529	0.00	0.039	0.33	0.9057	0.00				
	S6	M	0.205	0.30	0.4960	0.00	-0.238	0.32	0.4594	0.00	0.058	0.28	0.8364	0.00	-0.025	0.32	0.9357	0.00	0.455	0.27	0.0968	0.00				
	S7	F+M	0.153	0.24	0.5259	0.23	0.058	0.24	0.8103	0.03	0.124	0.22	0.5718	0.15	0.277	0.24	0.2480	0.64	0.136	0.20	0.4933	0.19				
	S7	F	-0.191	0.44	0.6626	0.00	0.440	0.41	0.2813	0.00	0.100	0.40	0.8010	0.00	0.777	0.40	0.0532	0.00	-0.132	0.33	0.6873	0.00				
	S7	M	0.274	0.30	0.3624	0.00	-0.139	0.31	0.6523	0.00	0.012	0.28	0.9648	0.00	-0.148	0.33	0.6521	0.00	0.404	0.26	0.1263	0.00				
	S8	F+M	0.153	0.24	0.5262	0.23	0.087	0.24	0.7196	0.07	0.119	0.22	0.5872	0.14	0.309	0.24	0.1989	0.79	0.127	0.20	0.5274	0.16				
	S8	F	-0.153	0.43	0.7238	0.00	0.419	0.41	0.3038	0.00	0.051	0.40	0.8979	0.00	0.843	0.40	0.0362	0.00	-0.150	0.33	0.6492	0.00				
	S8	M	0.272	0.30	0.3680	0.00	-0.095	0.30	0.7556	0.00	0.051	0.28	0.8557	0.00	-0.125	0.33	0.7039	0.00	0.408	0.27	0.1295	0.00				
Cannabis dependence	S1	F+M	0.002	0.01	0.7197	0.01	-0.006	0.01	0.2566	0.06	0.011	0.01	0.0440	0.20	0.003	0.01	0.6180	0.01	-0.006	0.01	0.2834	0.06				
	S1	F	0.002	0.01	0.7764	0.00	-0.002	0.01	0.6764	0.00	0.007	0.01	0.2529	0.00	0.005	0.01	0.4556	0.00	-0.012	0.01	0.0471	0.00				
	S1	M	0.007	0.01	0.4511	0.00	-0.009	0.01	0.3756	0.00	0.015	0.01	0.1331	0.00	-0.000	0.01	0.9823	0.00	0.001	0.01	0.8844	0.00				
	S2	F+M	0.005	0.01	0.3880	0.04	0.008	0.01	0.1220	0.12	0.010	0.01	0.0637	0.17	-0.000	0.01	0.9524	0.00	-0.008	0.01	0.1716	0.09				
	S2	F	0.009	0.01	0.1163	0.00	-0.002	0.01	0.7556	0.00	0.002	0.01	0.6920	0.00	0.006	0.01	0.2983	0.00	-0.006	0.01	0.2816	0.00				
	S2	M	0.004	0.01	0.7014	0.00	0.020	0.01	0.0405	0.00	0.018	0.01	0.0685	0.00	-0.010	0.01	0.3207	0.00	-0.010	0.01	0.3278	0.00				
	S3	F+M	0.005	0.01	0.3533	0.04	-0.005	0.01	0.3863	0.04	0.003	0.01	0.6007	0.01	-0.004	0.01	0.4377	0.03	-0.004	0.01	0.4325	0.03				
	S3	F	0.011	0.01	0.0534	0.00	-0.003	0.01	0.6553	0.00	-0.002	0.01	0.7907	0.00	-0.005	0.01	0.3886	0.00	0.000	0.01	0.9971	0.00				
	S3	M	0.002	0.01	0.8688	0.00	-0.010	0.01	0.3287	0.00	0.010	0.01	0.3362	0.00	-0.002	0.01	0.8502	0.00	-0.008	0.01	0.4110	0.00				
	S4	F+M	0.011	0.01	0.0470	0.20	-0.012	0.01	0.0325	0.23	-0.001	0.01	0.8101	0.00	-0.001	0.01	0.8074	0.00	0.006	0.01	0.2739	0.06				
	S4	F	0.014	0.01	0.0159	0.00	-0.004	0.01	0.4907	0.00	-0.004	0.01	0.4736	0.00	-0.001	0.01	0.9288	0.00	0.005	0.01	0.4143	0.00				
	S4	M	0.012	0.01	0.2403	0.00	-0.024	0.01	0.0265	0.00	0.004	0.01	0.6643	0.00	-0.000	0.01	0.9933	0.00	0.008	0.01	0.3870	0.00				
	S5	F+M	0.013	0.01	0.0162	0.29	-0.009	0.01	0.1013	0.13	0.000	0.01	0.9924	0.00	0.001	0.01	0.9098	0.00	-0.001	0.01	0.7975	0.00				
	S5	F	0.016	0.01	0.0067	0.00	-0.005	0.01	0.3980	0.00	-0.006	0.01	0.3333	0.00	-0.001	0.01	0.8323	0.00	-0.002	0.01	0.7454	0.00				
	S5	M	0.013	0.01	0.1750	0.00	-0.017	0.01	0.1177	0.00	0.007	0.01	0.4661	0.00	0.003	0.01	0.7456	0.00	0.001	0.01	0.9568	0.00				
	S6	F+M	0.014	0.01	0.0123	0.31	-0.008	0.01	0.1784	0.09	-0.001	0.01	0.9002	0.00	0.001	0.01	0.8276	0.00	0.000	0.01	0.9821	0.00				

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	
S6	F	0.017	0.01	0.0047	0.00	-0.003	0.01	0.6004	0.00	-0.009	0.01	0.1383	0.00	-0.003	0.01	0.6385	0.00	-0.000	0.01	0.9489	0.00						
	M	0.013	0.01	0.1767	0.00	-0.016	0.01	0.1446	0.00	0.009	0.01	0.3762	0.00	0.006	0.01	0.5500	0.00	0.001	0.01	0.8869	0.00						
	F+M	0.012	0.01	0.0274	0.24	-0.008	0.01	0.1599	0.10	-0.003	0.01	0.5964	0.01	-0.005	0.01	0.4342	0.03	0.001	0.01	0.8941	0.00						
	F	0.017	0.01	0.0056	0.00	-0.003	0.01	0.6162	0.00	-0.011	0.01	0.0747	0.00	-0.010	0.01	0.1432	0.00	-0.001	0.01	0.9302	0.00						
	M	0.011	0.01	0.2610	0.00	-0.018	0.01	0.1175	0.00	0.007	0.01	0.4614	0.00	0.002	0.01	0.8760	0.00	0.003	0.01	0.7866	0.00						
	F+M	0.012	0.01	0.0319	0.23	-0.008	0.01	0.1597	0.10	-0.003	0.01	0.5792	0.02	-0.005	0.01	0.4596	0.03	0.001	0.01	0.8620	0.00						
	F	0.016	0.01	0.0075	0.00	-0.004	0.01	0.5364	0.00	-0.011	0.01	0.0752	0.00	-0.010	0.01	0.1657	0.00	-0.000	0.01	0.9900	0.00						
	M	0.011	0.01	0.2665	0.00	-0.016	0.01	0.1477	0.00	0.007	0.01	0.4931	0.00	0.001	0.01	0.8935	0.00	0.002	0.01	0.8256	0.00						
Age at onset of cannabis dependence	S1	F+M	-0.145	0.26	0.5743	0.25	-0.205	0.25	0.4130	0.49	0.285	0.28	0.3052	0.89	-0.558	0.26	0.0325	3.63	-0.034	0.21	0.8697	0.01					
	S1	F	0.450	0.47	0.3422	0.00	-0.449	0.43	0.3073	0.00	0.754	0.45	0.1001	0.00	-1.119	0.52	0.0358	0.00	0.541	0.32	0.0954	0.00					
	S1	M	-0.293	0.31	0.3555	0.00	0.224	0.32	0.4829	0.00	0.048	0.35	0.8920	0.00	-0.445	0.30	0.1421	0.00	-0.351	0.28	0.2123	0.00					
	S2	F+M	-0.366	0.27	0.1846	1.59	0.167	0.25	0.5002	0.32	0.276	0.27	0.3046	0.83	-0.367	0.28	0.1857	1.51	0.013	0.25	0.9595	0.00					
	S2	F	0.161	0.45	0.7198	0.00	0.508	0.38	0.1837	0.00	0.650	0.42	0.1298	0.00	-0.347	0.53	0.5157	0.00	0.506	0.43	0.2500	0.00					
	S2	M	-0.609	0.37	0.1029	0.00	-0.073	0.33	0.8243	0.00	0.051	0.35	0.8839	0.00	-0.445	0.33	0.1750	0.00	-0.199	0.32	0.5369	0.00					
	S3	F+M	-0.187	0.27	0.4935	0.40	-0.149	0.26	0.5645	0.25	0.171	0.27	0.5301	0.32	-0.329	0.26	0.2153	1.19	0.239	0.25	0.3359	0.64					
	S3	F	0.153	0.46	0.7436	0.00	0.160	0.37	0.6682	0.00	0.429	0.47	0.3658	0.00	0.184	0.51	0.7183	0.00	0.215	0.43	0.6223	0.00					
	S3	M	-0.410	0.36	0.2555	0.00	-0.466	0.36	0.2007	0.00	-0.226	0.34	0.5039	0.00	-0.775	0.32	0.0167	0.00	0.268	0.32	0.4042	0.00					
	S4	F+M	-0.182	0.30	0.5431	0.36	0.005	0.28	0.9851	0.00	-0.196	0.31	0.5220	0.43	0.130	0.26	0.6125	0.17	0.343	0.27	0.2114	1.34					
	S4	F	0.322	0.50	0.5231	0.00	0.112	0.43	0.7943	0.00	-0.087	0.51	0.8662	0.00	-0.058	0.45	0.8987	0.00	0.325	0.42	0.4384	0.00					
	S4	M	-0.481	0.40	0.2371	0.00	-0.096	0.40	0.8105	0.00	-0.452	0.38	0.2355	0.00	-0.011	0.34	0.9755	0.00	0.322	0.38	0.3931	0.00					
	S5	F+M	-0.111	0.28	0.6939	0.14	0.145	0.31	0.6359	0.22	-0.223	0.30	0.4587	0.56	0.308	0.27	0.2594	0.91	0.095	0.28	0.7322	0.10					
	S5	F	-0.161	0.46	0.7296	0.00	0.347	0.45	0.4475	0.00	0.046	0.50	0.9263	0.00	0.273	0.46	0.5550	0.00	-0.108	0.42	0.7984	0.00					
	S5	M	-0.219	0.38	0.5674	0.00	-0.026	0.44	0.9534	0.00	-0.494	0.38	0.1992	0.00	0.066	0.37	0.8609	0.00	0.103	0.40	0.7996	0.00					
	S6	F+M	-0.031	0.30	0.9185	0.01	0.260	0.32	0.4194	0.71	-0.178	0.31	0.5684	0.35	0.402	0.28	0.1528	1.52	0.087	0.28	0.7568	0.09					
	S6	F	-0.298	0.47	0.5322	0.00	0.237	0.47	0.6179	0.00	0.093	0.51	0.8572	0.00	0.334	0.49	0.4964	0.00	-0.009	0.41	0.9833	0.00					
	S6	M	0.119	0.41	0.7738	0.00	0.243	0.47	0.6095	0.00	-0.470	0.41	0.2548	0.00	0.182	0.39	0.6428	0.00	-0.021	0.42	0.9605	0.00					

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
	S7	F+M	0.332	0.29	0.2558	1.23	0.147	0.32	0.6504	0.22	-0.154	0.29	0.6003	0.26	0.344	0.29	0.2406	1.13	0.063	0.26	0.8086	0.05
	S7	F	0.093	0.48	0.8469	0.00	0.338	0.51	0.5126	0.00	-0.193	0.49	0.6979	0.00	0.497	0.50	0.3233	0.00	-0.215	0.38	0.5732	0.00
	S7	M	0.401	0.39	0.3115	0.00	0.132	0.45	0.7712	0.00	-0.304	0.38	0.4205	0.00	-0.052	0.40	0.8973	0.00	0.266	0.38	0.4873	0.00
	S8	F+M	0.369	0.29	0.2095	1.51	0.157	0.32	0.6275	0.26	-0.153	0.29	0.6027	0.26	0.367	0.29	0.2091	1.28	0.069	0.26	0.7940	0.05
	S8	F	0.169	0.49	0.7298	0.00	0.330	0.52	0.5269	0.00	-0.239	0.50	0.6373	0.00	0.577	0.50	0.2513	0.00	-0.223	0.38	0.5616	0.00
	S8	M	0.396	0.40	0.3209	0.00	0.156	0.45	0.7297	0.00	-0.261	0.37	0.4816	0.00	-0.029	0.40	0.9428	0.00	0.287	0.38	0.4564	0.00
DSM5 CUD (4 point scale)	S1	F+M	-0.002	0.02	0.8849	0.00	-0.029	0.02	0.0825	0.15	0.040	0.02	0.0191	0.28	0.014	0.02	0.3917	0.04	-0.013	0.02	0.4406	0.03
	S1	F	0.003	0.02	0.8754	0.00	-0.011	0.02	0.5286	0.00	0.017	0.02	0.3562	0.00	0.023	0.02	0.2226	0.00	-0.029	0.02	0.1166	0.00
	S1	M	0.002	0.03	0.9581	0.00	-0.044	0.03	0.1303	0.00	0.061	0.03	0.0404	0.00	-0.003	0.03	0.9047	0.00	0.003	0.03	0.9298	0.00
	S2	F+M	0.022	0.02	0.1768	0.09	0.021	0.02	0.2049	0.08	0.041	0.02	0.0145	0.30	-0.001	0.02	0.9707	0.00	-0.007	0.02	0.6968	0.01
	S2	F	0.032	0.02	0.0769	0.00	-0.006	0.02	0.7399	0.00	0.008	0.02	0.6556	0.00	0.032	0.02	0.0856	0.00	-0.009	0.02	0.6042	0.00
	S2	M	0.019	0.03	0.5121	0.00	0.049	0.03	0.1059	0.00	0.074	0.03	0.0115	0.00	-0.050	0.03	0.0914	0.00	-0.006	0.03	0.8364	0.00
	S3	F+M	0.022	0.02	0.1932	0.09	-0.005	0.02	0.7578	0.00	0.019	0.02	0.2709	0.06	-0.010	0.02	0.5414	0.02	-0.002	0.02	0.9264	0.00
	S3	F	0.042	0.02	0.0195	0.00	0.001	0.02	0.9466	0.00	-0.005	0.02	0.8090	0.00	-0.002	0.02	0.9106	0.00	0.005	0.02	0.8023	0.00
	S3	M	0.008	0.03	0.7983	0.00	-0.014	0.03	0.6408	0.00	0.054	0.03	0.0730	0.00	-0.015	0.03	0.6331	0.00	-0.007	0.03	0.8227	0.00
	S4	F+M	0.039	0.02	0.0217	0.27	-0.029	0.02	0.0936	0.14	0.011	0.02	0.5150	0.02	0.005	0.02	0.7814	0.00	0.029	0.02	0.0874	0.15
	S4	F	0.054	0.02	0.0034	0.00	-0.007	0.02	0.6882	0.00	-0.012	0.02	0.5278	0.00	0.012	0.02	0.5436	0.00	0.015	0.02	0.4355	0.00
	S4	M	0.027	0.03	0.3875	0.00	-0.061	0.03	0.0588	0.00	0.049	0.03	0.1129	0.00	0.005	0.03	0.8781	0.00	0.047	0.03	0.1085	0.00
	S5	F+M	0.040	0.02	0.0179	0.29	-0.039	0.02	0.0268	0.25	0.012	0.02	0.4848	0.02	0.010	0.02	0.5995	0.01	0.019	0.02	0.2495	0.07
	S5	F	0.056	0.02	0.0026	0.00	-0.022	0.02	0.2223	0.00	-0.021	0.02	0.2481	0.00	0.009	0.02	0.6588	0.00	0.004	0.02	0.8184	0.00
	S5	M	0.023	0.03	0.4538	0.00	-0.067	0.03	0.0457	0.00	0.052	0.03	0.0845	0.00	0.014	0.03	0.6519	0.00	0.040	0.03	0.1735	0.00
	S6	F+M	0.046	0.02	0.0070	0.37	-0.037	0.02	0.0353	0.23	0.009	0.02	0.5929	0.01	0.009	0.02	0.6210	0.01	0.025	0.02	0.1410	0.11
	S6	F	0.059	0.02	0.0014	0.00	-0.022	0.02	0.2360	0.00	-0.026	0.02	0.1691	0.00	0.006	0.02	0.7769	0.00	0.012	0.02	0.5042	0.00
	S6	M	0.031	0.03	0.3016	0.00	-0.063	0.03	0.0597	0.00	0.052	0.03	0.0874	0.00	0.017	0.03	0.6037	0.00	0.039	0.03	0.1821	0.00
	S7	F+M	0.041	0.02	0.0158	0.30	-0.039	0.02	0.0277	0.26	0.001	0.02	0.9710	0.00	-0.009	0.02	0.6509	0.01	0.022	0.02	0.1778	0.09
	S7	F	0.059	0.02	0.0014	0.00	-0.030	0.02	0.1154	0.00	-0.031	0.02	0.0940	0.00	-0.016	0.02	0.4515	0.00	0.013	0.02	0.4656	0.00
	S7	M	0.022	0.03	0.4774	0.00	-0.056	0.03	0.1001	0.00	0.042	0.03	0.1687	0.00	0.004	0.03	0.8975	0.00	0.029	0.03	0.3129	0.00

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	Sex	SI				AI				CPD				SC				DPW			
			Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
	S8	F+M	0.041	0.02	0.0167	0.29	-0.039	0.02	0.0298	0.25	-0.000	0.02	0.9898	0.00	-0.008	0.02	0.6719	0.01	0.023	0.02	0.1701	0.09
	S8	F	0.058	0.02	0.0015	0.00	-0.030	0.02	0.1070	0.00	-0.031	0.02	0.0999	0.00	-0.015	0.02	0.4791	0.00	0.014	0.02	0.4363	0.00
	S8	M	0.021	0.03	0.5012	0.00	-0.053	0.03	0.1206	0.00	0.039	0.03	0.1967	0.00	0.003	0.03	0.9229	0.00	0.029	0.03	0.3347	0.00
DSM5 CUD (ctrl mild vs moderate severe)	S1	F+M	-0.002	0.01	0.7235	0.01	-0.011	0.01	0.0817	0.15	0.012	0.01	0.0634	0.17	0.004	0.01	0.5500	0.02	-0.000	0.01	0.9567	0.00
	S1	F	-0.000	0.01	0.9469	0.00	-0.005	0.01	0.4286	0.00	0.005	0.01	0.4472	0.00	0.007	0.01	0.3063	0.00	-0.006	0.01	0.3538	0.00
	S1	M	0.000	0.01	0.9873	0.00	-0.015	0.01	0.1729	0.00	0.018	0.01	0.1121	0.00	-0.002	0.01	0.8390	0.00	0.006	0.01	0.6146	0.00
	S2	F+M	0.005	0.01	0.3882	0.04	0.007	0.01	0.2747	0.06	0.012	0.01	0.0488	0.19	-0.002	0.01	0.7154	0.01	-0.002	0.01	0.7514	0.01
	S2	F	0.008	0.01	0.2259	0.00	-0.002	0.01	0.7690	0.00	0.001	0.01	0.9105	0.00	0.008	0.01	0.2049	0.00	-0.002	0.01	0.7272	0.00
	S2	M	0.006	0.01	0.5948	0.00	0.018	0.01	0.1239	0.00	0.024	0.01	0.0310	0.00	-0.020	0.01	0.0852	0.00	-0.002	0.01	0.8642	0.00
	S3	F+M	0.006	0.01	0.2980	0.05	-0.003	0.01	0.5895	0.01	0.004	0.01	0.5414	0.02	-0.004	0.01	0.5713	0.02	-0.001	0.01	0.8625	0.00
	S3	F	0.012	0.01	0.0535	0.00	0.001	0.01	0.8966	0.00	-0.004	0.01	0.5319	0.00	-0.002	0.01	0.8121	0.00	0.004	0.01	0.5463	0.00
	S3	M	0.003	0.01	0.7833	0.00	-0.008	0.01	0.4914	0.00	0.015	0.01	0.1796	0.00	-0.005	0.01	0.6441	0.00	-0.006	0.01	0.6070	0.00
	S4	F+M	0.014	0.01	0.0293	0.24	-0.012	0.01	0.0582	0.18	0.003	0.01	0.6677	0.01	-0.000	0.01	0.9628	0.00	0.008	0.01	0.1729	0.09
	S4	F	0.017	0.01	0.0106	0.00	-0.005	0.01	0.4381	0.00	-0.005	0.01	0.4250	0.00	0.004	0.01	0.5956	0.00	0.007	0.01	0.3065	0.00
	S4	M	0.014	0.01	0.2414	0.00	-0.023	0.01	0.0653	0.00	0.015	0.01	0.1888	0.00	-0.003	0.01	0.7805	0.00	0.010	0.01	0.3676	0.00
	S5	F+M	0.015	0.01	0.0139	0.31	-0.015	0.01	0.0184	0.28	0.005	0.01	0.4686	0.03	0.001	0.01	0.8444	0.00	0.003	0.01	0.6125	0.01
	S5	F	0.019	0.01	0.0035	0.00	-0.010	0.01	0.1137	0.00	-0.008	0.01	0.2390	0.00	0.002	0.01	0.7723	0.00	0.001	0.01	0.9095	0.00
	S5	M	0.013	0.01	0.2574	0.00	-0.026	0.01	0.0440	0.00	0.020	0.01	0.0801	0.00	0.001	0.01	0.9151	0.00	0.006	0.01	0.5810	0.00
	S6	F+M	0.018	0.01	0.0034	0.43	-0.016	0.01	0.0175	0.29	0.005	0.01	0.4664	0.03	0.000	0.01	0.9877	0.00	0.006	0.01	0.3712	0.04
	S6	F	0.022	0.01	0.0011	0.00	-0.010	0.01	0.1313	0.00	-0.009	0.01	0.1822	0.00	-0.001	0.01	0.8826	0.00	0.003	0.01	0.6406	0.00
	S6	M	0.017	0.01	0.1430	0.00	-0.026	0.01	0.0408	0.00	0.022	0.01	0.0596	0.00	0.002	0.01	0.8678	0.00	0.008	0.01	0.4875	0.00
	S7	F+M	0.015	0.01	0.0150	0.30	-0.016	0.01	0.0143	0.31	0.001	0.01	0.8602	0.00	-0.006	0.01	0.4179	0.04	0.003	0.01	0.5693	0.02
	S7	F	0.020	0.01	0.0019	0.00	-0.012	0.01	0.0686	0.00	-0.012	0.01	0.0698	0.00	-0.009	0.01	0.2513	0.00	0.002	0.01	0.8168	0.00
	S7	M	0.011	0.01	0.3340	0.00	-0.024	0.01	0.0692	0.00	0.019	0.01	0.0986	0.00	-0.001	0.01	0.9167	0.00	0.004	0.01	0.6925	0.00
	S8	F+M	0.015	0.01	0.0192	0.28	-0.016	0.01	0.0191	0.29	0.001	0.01	0.8909	0.00	-0.005	0.01	0.4459	0.03	0.004	0.01	0.5571	0.02

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	PT	SI					AI					CPD					SC					DPW				
		Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²				
			F	0.020	0.01	0.0026	0.00	-0.013	0.01	0.0620	0.00	-0.012	0.01	0.0708	0.00	-0.008	0.01	0.2698	0.00	0.002	0.01	0.7719	0.00			
	S8	M	0.010	0.01	0.3663	0.00	-0.021	0.01	0.1024	0.00	0.018	0.01	0.1108	0.00	-0.001	0.01	0.9158	0.00	0.004	0.01	0.7464	0.00				
Age at onset of DSM5 CUD	S1	F+M	-0.301	0.19	0.1078	0.98	0.047	0.18	0.7988	0.02	-0.041	0.20	0.8367	0.02	-0.046	0.18	0.7975	0.02	0.115	0.16	0.4816	0.14				
	S1	F	-0.349	0.32	0.2792	0.00	0.006	0.31	0.9837	0.00	0.676	0.32	0.0385	0.00	0.325	0.33	0.3197	0.00	0.502	0.28	0.0723	0.00				
	S1	M	-0.294	0.23	0.1938	0.00	0.141	0.24	0.5517	0.00	-0.404	0.25	0.1032	0.00	-0.179	0.21	0.4014	0.00	-0.049	0.20	0.8107	0.00				
	S2	F+M	-0.356	0.20	0.0721	1.41	0.135	0.19	0.4753	0.19	0.032	0.19	0.8674	0.01	-0.006	0.20	0.9759	0.00	0.241	0.18	0.1861	0.61				
	S2	F	-0.337	0.33	0.3085	0.00	0.295	0.28	0.2902	0.00	0.665	0.31	0.0345	0.00	0.268	0.37	0.4689	0.00	0.577	0.31	0.0632	0.00				
	S2	M	-0.304	0.25	0.2309	0.00	-0.032	0.26	0.9027	0.00	-0.311	0.24	0.2013	0.00	-0.071	0.23	0.7588	0.00	0.095	0.23	0.6761	0.00				
	S3	F+M	-0.320	0.19	0.0992	1.11	-0.122	0.19	0.5133	0.16	-0.233	0.18	0.2077	0.56	-0.107	0.19	0.5814	0.12	0.387	0.18	0.0315	1.57				
	S3	F	-0.295	0.31	0.3458	0.00	0.211	0.30	0.4866	0.00	0.149	0.29	0.6090	0.00	0.353	0.36	0.3233	0.00	0.477	0.29	0.1060	0.00				
	S3	M	-0.229	0.25	0.3651	0.00	-0.327	0.24	0.1680	0.00	-0.534	0.24	0.0245	0.00	-0.384	0.24	0.1105	0.00	0.336	0.23	0.1453	0.00				
	S4	F+M	-0.244	0.21	0.2373	0.61	-0.057	0.20	0.7810	0.03	-0.167	0.18	0.3648	0.29	0.082	0.19	0.6629	0.06	0.516	0.19	0.0059	2.83				
	S4	F	-0.283	0.32	0.3845	0.00	0.091	0.33	0.7839	0.00	0.064	0.29	0.8256	0.00	0.239	0.33	0.4662	0.00	0.472	0.30	0.1229	0.00				
	S4	M	-0.203	0.27	0.4595	0.00	-0.208	0.28	0.4507	0.00	-0.341	0.25	0.1692	0.00	0.029	0.24	0.9043	0.00	0.516	0.24	0.0306	0.00				
	S5	F+M	-0.176	0.19	0.3640	0.32	-0.020	0.22	0.9277	0.00	0.021	0.19	0.9128	0.00	0.109	0.20	0.5791	0.11	0.103	0.18	0.5638	0.11				
	S5	F	-0.188	0.31	0.5503	0.00	0.026	0.34	0.9404	0.00	0.307	0.31	0.3304	0.00	0.460	0.33	0.1673	0.00	-0.192	0.28	0.4998	0.00				
	S5	M	-0.153	0.25	0.5371	0.00	-0.119	0.29	0.6850	0.00	-0.228	0.24	0.3534	0.00	-0.160	0.26	0.5374	0.00	0.356	0.23	0.1283	0.00				
	S6	F+M	-0.117	0.20	0.5584	0.14	-0.026	0.22	0.9066	0.01	0.113	0.19	0.5541	0.13	0.151	0.21	0.4660	0.20	0.072	0.18	0.6887	0.06				
	S6	F	-0.234	0.31	0.4530	0.00	0.045	0.32	0.8862	0.00	0.360	0.31	0.2419	0.00	0.517	0.33	0.1243	0.00	-0.161	0.28	0.5688	0.00				
	S6	M	-0.032	0.26	0.9038	0.00	-0.071	0.31	0.8179	0.00	-0.125	0.25	0.6197	0.00	-0.135	0.28	0.6272	0.00	0.337	0.24	0.1597	0.00				
	S7	F+M	0.057	0.20	0.7767	0.03	-0.103	0.22	0.6431	0.10	0.064	0.19	0.7404	0.04	0.115	0.21	0.5840	0.12	-0.047	0.17	0.7868	0.02				
	S7	F	-0.066	0.32	0.8365	0.00	-0.119	0.34	0.7280	0.00	0.360	0.31	0.2542	0.00	0.460	0.33	0.1691	0.00	-0.328	0.27	0.2286	0.00				
	S7	M	0.080	0.26	0.7636	0.00	-0.004	0.29	0.9896	0.00	-0.203	0.25	0.4140	0.00	-0.198	0.28	0.4839	0.00	0.266	0.23	0.2424	0.00				
	S8	F+M	0.060	0.20	0.7663	0.04	-0.054	0.22	0.8069	0.03	0.079	0.19	0.6799	0.06	0.134	0.21	0.5267	0.16	-0.054	0.17	0.7562	0.03				
	S8	F	-0.046	0.32	0.8849	0.00	-0.055	0.35	0.8747	0.00	0.347	0.31	0.2691	0.00	0.498	0.33	0.1398	0.00	-0.350	0.27	0.2020	0.00				

Table S3-3. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to initiation of illicit substance, alcohol-related disorders, and cannabis-related disorders for females (F), males (M), and both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.14e-4.

Target phenotype	SI					AI					CPD					SC					DPW					
	PT	Sex	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²	Beta	SE	p	R ²
S8	M	0.081	0.27	0.7613	0.00	0.034	0.29	0.9044	0.00	-0.151	0.25	0.5400	0.00	-0.187	0.28	0.5093	0.00	0.266	0.23	0.2476	0.00					

Table S3-4. Phenotypic correlation between illicit substance use or substance use disorders and polygenic risk scores (PRS) for licit substance use in females, males or both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08, 1e-05, 1e-03, 1e-02, 5e-02, 1e-01, 5e-01, and 1.

Target phenotype	PT	Females					Males					F+M				
		SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW
Ever used cocaine	p < 5e-08	0.04	-0.04	-0.05	-0.03	0.04	0.06	-0.03	-0.02	-0.00	-0.01	0.04	-0.03	-0.04	-0.02	0.02
	p < 1e-05	0.02	-0.01	-0.03	-0.01	0.04	0.05	0.01	-0.03	-0.06	-0.00	0.03	0.00	-0.03	-0.03	0.02
	p < 1e-03	0.06	-0.02	-0.04	-0.04	0.04	0.09	-0.02	-0.03	0.00	0.05	0.07	-0.02	-0.05	-0.02	0.04
	p < 0.01	0.08	0.00	-0.01	-0.05	0.04	0.05	-0.08	-0.07	0.04	0.11	0.06	-0.03	-0.04	-0.01	0.07
	p < 0.05	0.09	-0.05	-0.01	-0.07	0.04	0.07	-0.07	-0.01	0.04	0.11	0.07	-0.05	-0.02	-0.03	0.07
	p < 0.1	0.09	-0.04	-0.02	-0.07	0.05	0.07	-0.06	-0.00	0.03	0.11	0.08	-0.05	-0.02	-0.03	0.08
	p < 0.5	0.09	-0.06	-0.01	-0.07	0.07	0.04	-0.07	0.00	0.02	0.11	0.06	-0.06	-0.01	-0.04	0.08
	p < 1	0.09	-0.06	-0.02	-0.07	0.07	0.04	-0.06	0.00	0.01	0.10	0.06	-0.06	-0.02	-0.04	0.08
Ever used amphetamine	p < 5e-08	0.03	-0.01	-0.02	-0.03	0.05	0.06	-0.01	-0.00	0.03	-0.00	0.04	-0.01	-0.01	-0.01	0.03
	p < 1e-05	0.03	-0.02	-0.02	-0.02	0.05	0.09	-0.02	0.01	-0.00	0.01	0.06	-0.02	-0.01	-0.01	0.03
	p < 1e-03	0.06	-0.02	0.01	-0.04	0.06	0.09	-0.07	-0.01	-0.01	0.03	0.07	-0.04	-0.00	-0.02	0.05
	p < 0.01	0.08	-0.04	0.02	-0.00	0.07	0.08	-0.10	-0.03	0.02	0.08	0.08	-0.06	-0.00	0.00	0.07
	p < 0.05	0.12	-0.07	0.01	-0.01	0.05	0.13	-0.09	0.02	0.02	0.05	0.12	-0.07	0.01	0.00	0.05
	p < 0.1	0.12	-0.07	0.00	-0.01	0.05	0.12	-0.07	0.03	0.02	0.06	0.12	-0.07	0.01	0.00	0.06
	p < 0.5	0.11	-0.07	0.02	-0.02	0.06	0.08	-0.04	0.03	0.02	0.05	0.09	-0.06	0.02	-0.01	0.05
	p < 1	0.11	-0.08	0.02	-0.02	0.05	0.08	-0.04	0.03	0.01	0.04	0.09	-0.06	0.02	-0.01	0.05
Ever used inhalants	p < 5e-08	0.02	0.01	-0.01	0.01	0.00	0.05	-0.00	-0.04	0.05	-0.02	0.03	0.01	-0.03	0.03	-0.01
	p < 1e-05	0.00	0.03	-0.01	0.03	0.04	0.05	0.03	-0.01	0.00	0.00	0.03	0.03	-0.01	0.02	0.02
	p < 1e-03	0.02	-0.01	-0.01	-0.02	0.02	0.03	-0.02	-0.02	-0.02	-0.01	0.02	-0.01	-0.02	-0.01	0.01
	p < 0.01	0.04	-0.04	0.01	-0.01	0.02	0.01	0.01	-0.03	0.03	0.05	0.02	-0.01	-0.01	0.00	0.03
	p < 0.05	0.02	-0.04	0.02	-0.01	0.02	0.04	-0.02	0.01	0.01	0.05	0.03	-0.03	0.01	-0.00	0.03
	p < 0.1	0.03	-0.03	0.02	-0.00	0.01	0.03	-0.01	0.01	0.00	0.07	0.03	-0.02	0.01	-0.01	0.04
	p < 0.5	0.05	-0.03	0.03	-0.02	-0.01	0.01	0.02	0.02	0.01	0.06	0.03	-0.00	0.02	-0.01	0.02
	p < 1	0.05	-0.03	0.03	-0.02	-0.01	0.01	0.03	0.01	0.01	0.06	0.03	-0.00	0.02	-0.01	0.02
Ever used sedatives	p < 5e-08	0.10	0.04	0.02	0.00	0.02	0.04	-0.01	-0.02	0.01	0.03	0.07	0.02	0.00	0.01	0.03
	p < 1e-05	0.06	0.02	0.02	0.01	0.04	0.04	-0.00	-0.02	-0.02	0.00	0.05	0.01	0.00	-0.00	0.02
	p < 1e-03	0.04	-0.01	0.02	0.01	0.04	0.05	-0.07	-0.02	-0.04	-0.00	0.04	-0.03	0.00	-0.01	0.02
	p < 0.01	0.05	-0.04	0.01	-0.01	0.08	0.02	-0.06	-0.04	0.01	0.04	0.03	-0.04	-0.01	-0.00	0.06

Table S3-4. Phenotypic correlation between illicit substance use or substance use disorders and polygenic risk scores (PRS) for licit substance use in females, males or both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08, 1e-05, 1e-03, 1e-02, 5e-02, 1e-01, 5e-01, and 1.

Target phenotype	PT	Females					Males					F+M				
		SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW
Ever used hallucinogens	p < 0.05	0.04	-0.05	0.01	-0.03	0.07	0.04	-0.06	0.01	0.01	0.05	0.04	-0.05	0.01	-0.01	0.06
	p < 0.1	0.03	-0.04	-0.00	-0.03	0.06	0.05	-0.04	0.02	0.02	0.06	0.03	-0.04	0.01	-0.01	0.06
	p < 0.5	0.04	-0.05	-0.01	-0.05	0.07	0.01	-0.02	0.03	0.01	0.04	0.02	-0.03	0.01	-0.03	0.05
	p < 1	0.04	-0.05	-0.01	-0.05	0.06	0.01	-0.02	0.03	0.00	0.04	0.03	-0.04	0.01	-0.03	0.05
	p < 5e-08	-0.02	0.01	-0.01	0.02	0.01	0.03	-0.04	0.00	0.02	0.08	0.00	-0.01	-0.01	0.02	0.05
	p < 1e-05	0.02	0.01	-0.01	0.02	0.03	0.03	0.02	0.01	-0.04	0.06	0.02	0.02	-0.00	-0.01	0.04
	p < 1e-03	0.06	-0.02	-0.01	-0.04	0.02	0.03	-0.08	-0.03	-0.01	0.08	0.04	-0.05	-0.03	-0.02	0.05
	p < 0.01	0.08	-0.02	0.02	-0.03	0.03	0.01	-0.08	-0.03	0.00	0.09	0.03	-0.04	-0.01	-0.02	0.05
Ever used opioids	p < 0.05	0.10	-0.04	0.02	-0.05	0.03	0.04	-0.07	0.01	0.02	0.07	0.07	-0.05	0.01	-0.02	0.05
	p < 0.1	0.09	-0.04	0.02	-0.05	0.04	0.05	-0.06	0.04	0.03	0.08	0.07	-0.05	0.02	-0.02	0.06
	p < 0.5	0.09	-0.05	0.03	-0.05	0.05	0.05	-0.05	0.05	0.02	0.06	0.06	-0.05	0.03	-0.02	0.05
	p < 1	0.09	-0.06	0.02	-0.05	0.05	0.05	-0.05	0.05	0.02	0.06	0.06	-0.05	0.03	-0.03	0.06
	p < 5e-08	0.03	0.02	-0.02	-0.01	0.05	0.03	0.03	0.02	-0.00	-0.01	0.03	0.02	-0.00	-0.01	0.02
	p < 1e-05	0.06	0.00	-0.02	-0.02	0.05	-0.00	0.03	0.04	-0.02	-0.01	0.03	0.01	0.01	-0.02	0.02
	p < 1e-03	0.06	-0.02	-0.01	0.01	0.04	-0.02	-0.02	0.01	-0.01	-0.03	0.02	-0.02	-0.00	0.00	0.01
	p < 0.01	0.09	-0.01	-0.02	-0.01	0.07	-0.01	-0.08	0.01	0.01	0.02	0.04	-0.04	-0.00	-0.00	0.05
Ever used ecstasy	p < 0.05	0.09	-0.00	0.01	-0.02	0.06	0.01	-0.05	0.01	0.00	-0.01	0.06	-0.02	0.01	-0.01	0.03
	p < 0.1	0.08	-0.01	-0.02	-0.02	0.06	0.01	-0.04	0.02	0.01	0.00	0.05	-0.02	-0.00	-0.01	0.03
	p < 0.5	0.08	-0.01	-0.02	-0.02	0.06	0.02	-0.03	0.01	0.02	0.00	0.05	-0.02	-0.00	-0.01	0.03
	p < 1	0.08	-0.02	-0.01	-0.02	0.05	0.02	-0.02	0.01	0.01	0.00	0.05	-0.02	-0.00	-0.01	0.03
	p < 5e-08	0.00	0.01	-0.04	0.03	0.03	0.05	-0.02	-0.00	0.05	0.01	0.02	-0.00	-0.02	0.04	0.02
	p < 1e-05	0.03	-0.01	-0.03	0.03	0.06	0.07	0.03	-0.00	-0.01	0.04	0.05	0.01	-0.02	0.01	0.05
	p < 1e-03	0.08	0.01	-0.03	-0.03	0.06	0.10	-0.05	-0.01	-0.02	0.04	0.08	-0.02	-0.03	-0.02	0.05
	p < 0.01	0.12	-0.01	0.00	-0.01	0.09	0.09	-0.08	-0.06	0.01	0.10	0.10	-0.04	-0.03	-0.01	0.09
Ever used tobacco	p < 0.05	0.13	-0.04	-0.01	-0.04	0.09	0.11	-0.07	0.00	0.00	0.09	0.12	-0.05	-0.01	-0.03	0.09
	p < 0.1	0.14	-0.05	-0.01	-0.03	0.09	0.11	-0.05	0.01	-0.00	0.08	0.12	-0.05	-0.01	-0.03	0.08
	p < 0.5	0.13	-0.07	0.01	-0.03	0.09	0.07	-0.03	0.01	-0.02	0.08	0.10	-0.05	0.00	-0.04	0.08
	p < 1	0.13	-0.08	0.00	-0.03	0.09	0.07	-0.03	0.01	-0.03	0.08	0.10	-0.06	-0.00	-0.04	0.08

Table S3-4. Phenotypic correlation between illicit substance use or substance use disorders and polygenic risk scores (PRS) for licit substance use in females, males or both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08, 1e-05, 1e-03, 1e-02, 5e-02, 1e-01, 5e-01, and 1.

Target phenotype	PT	Females					Males					F+M				
		SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW
Ever used prescription pain killers	p < 5e-08	0.04	-0.01	0.02	-0.01	-0.05	0.06	0.02	0.04	-0.00	0.00	0.05	0.00	0.03	-0.01	-0.02
	p < 1e-05	0.06	0.01	0.03	-0.00	-0.04	0.07	0.02	0.05	0.03	0.05	0.07	0.01	0.04	0.01	-0.00
	p < 1e-03	0.08	-0.02	0.08	0.07	-0.08	0.03	-0.01	0.01	0.06	0.01	0.06	-0.01	0.05	0.06	-0.04
	p < 0.01	0.07	-0.05	0.06	0.07	-0.06	0.01	-0.03	0.01	0.06	0.02	0.05	-0.04	0.04	0.06	-0.02
	p < 0.05	0.06	-0.06	0.06	0.06	-0.05	0.01	-0.03	0.03	0.02	0.01	0.04	-0.05	0.05	0.04	-0.02
	p < 0.1	0.05	-0.07	0.04	0.05	-0.04	0.01	-0.02	0.02	0.01	0.01	0.04	-0.05	0.03	0.04	-0.02
	p < 0.5	0.06	-0.05	0.04	0.05	-0.03	0.02	-0.01	0.03	-0.00	0.03	0.04	-0.03	0.04	0.03	-0.01
	p < 1	0.06	-0.05	0.04	0.05	-0.03	0.02	-0.00	0.03	-0.01	0.03	0.04	-0.03	0.04	0.03	-0.00
Ever used prescription stimulants	p < 5e-08	0.00	-0.01	0.00	0.00	0.03	0.05	0.00	0.04	0.03	-0.04	0.02	-0.00	0.02	0.02	-0.00
	p < 1e-05	0.02	0.02	-0.00	0.02	0.03	0.03	0.04	0.04	0.01	-0.01	0.02	0.03	0.01	0.01	0.01
	p < 1e-03	0.02	-0.00	0.02	0.02	-0.02	0.03	-0.05	0.01	-0.01	-0.00	0.02	-0.02	0.01	0.01	-0.01
	p < 0.01	0.04	-0.05	0.02	-0.01	-0.01	0.02	-0.04	-0.02	-0.02	0.03	0.03	-0.04	-0.00	-0.02	0.01
	p < 0.05	0.04	-0.05	0.02	-0.04	-0.01	0.05	-0.04	0.03	-0.00	0.05	0.04	-0.04	0.02	-0.03	0.02
	p < 0.1	0.03	-0.06	0.00	-0.04	-0.01	0.04	-0.04	0.04	-0.00	0.05	0.04	-0.05	0.01	-0.03	0.02
	p < 0.5	0.03	-0.05	0.00	-0.03	0.01	0.04	-0.02	0.05	-0.02	0.07	0.03	-0.03	0.02	-0.03	0.03
	p < 1	0.03	-0.05	0.00	-0.03	0.01	0.03	-0.02	0.05	-0.02	0.07	0.03	-0.03	0.02	-0.03	0.03
Alcohol abuse	p < 5e-08	0.02	-0.00	-0.02	-0.02	0.03	0.03	-0.03	-0.02	-0.04	-0.01	0.02	-0.01	-0.03	-0.03	0.01
	p < 1e-05	0.05	0.02	-0.03	-0.01	0.01	0.05	0.03	-0.02	-0.05	0.04	0.05	0.02	-0.03	-0.03	0.02
	p < 1e-03	0.05	-0.01	-0.00	-0.04	0.03	0.07	-0.04	-0.07	-0.03	-0.00	0.06	-0.02	-0.04	-0.03	0.01
	p < 0.01	0.05	-0.03	0.04	-0.07	0.03	0.04	-0.04	-0.06	0.01	0.04	0.04	-0.03	-0.01	-0.04	0.03
	p < 0.05	0.06	-0.03	0.00	-0.08	0.02	0.06	0.00	-0.06	-0.02	0.03	0.06	-0.01	-0.03	-0.06	0.03
	p < 0.1	0.06	-0.04	-0.00	-0.07	0.03	0.07	0.03	-0.05	-0.01	0.02	0.06	-0.01	-0.03	-0.06	0.03
	p < 0.5	0.08	-0.02	-0.00	-0.08	0.02	0.05	0.02	-0.07	-0.02	0.01	0.06	-0.00	-0.04	-0.06	0.02
	p < 1	0.07	-0.03	-0.00	-0.07	0.03	0.04	0.03	-0.06	-0.03	0.01	0.05	-0.00	-0.04	-0.06	0.02
Alcohol dependence	p < 5e-08	0.04	0.02	-0.03	0.02	0.06	-0.01	-0.01	-0.03	-0.02	-0.01	0.01	0.01	-0.03	0.00	0.03
	p < 1e-05	0.06	0.00	-0.03	0.01	0.05	-0.04	0.01	-0.03	-0.06	0.05	0.02	0.01	-0.03	-0.02	0.04

Table S3-4. Phenotypic correlation between illicit substance use or substance use disorders and polygenic risk scores (PRS) for licit substance use in females, males or both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08, 1e-05, 1e-03, 1e-02, 5e-02, 1e-01, 5e-01, and 1.

Target phenotype	PT	Females					Males					F+M				
		SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW
Cannabis abuse	p < 1e-03	0.06	-0.02	-0.01	0.01	0.03	0.03	0.01	-0.05	-0.03	0.02	0.04	-0.01	-0.04	-0.00	0.03
	p < 0.01	0.07	-0.03	0.01	-0.03	0.02	0.02	-0.04	-0.05	-0.02	0.03	0.04	-0.03	-0.02	-0.03	0.02
	p < 0.05	0.05	-0.05	-0.03	-0.06	0.00	0.04	-0.02	-0.03	-0.03	0.05	0.04	-0.03	-0.04	-0.06	0.02
	p < 0.1	0.06	-0.05	-0.02	-0.06	0.00	0.05	-0.01	-0.02	-0.01	0.05	0.05	-0.03	-0.03	-0.05	0.02
	p < 0.5	0.03	-0.03	-0.03	-0.06	-0.00	0.02	-0.00	-0.01	-0.02	0.06	0.02	-0.02	-0.03	-0.05	0.02
	p < 1	0.03	-0.04	-0.03	-0.06	0.00	0.03	-0.00	-0.01	-0.02	0.05	0.02	-0.02	-0.03	-0.06	0.02
	p < 5e-08	-0.01	-0.02	0.03	0.05	0.01	0.02	-0.04	0.07	-0.02	0.03	0.01	-0.02	0.05	0.01	0.02
	p < 1e-05	0.06	-0.03	0.02	0.05	0.02	0.03	0.04	0.09	-0.07	0.02	0.04	0.01	0.05	-0.01	0.02
Cannabis dependence	p < 1e-03	0.05	0.03	-0.01	-0.01	0.02	0.02	-0.02	0.07	-0.03	0.04	0.03	0.00	0.02	-0.02	0.03
	p < 0.01	0.06	0.02	-0.01	0.00	-0.00	0.03	-0.08	0.06	0.00	0.06	0.04	-0.02	0.01	-0.00	0.02
	p < 0.05	0.06	-0.01	-0.03	-0.00	0.00	0.03	-0.08	0.06	-0.01	0.06	0.04	-0.04	0.01	-0.02	0.03
	p < 0.1	0.07	-0.00	-0.03	-0.01	0.01	0.04	-0.06	0.06	-0.02	0.08	0.05	-0.03	0.01	-0.02	0.04
	p < 0.5	0.07	-0.00	-0.02	-0.03	0.02	0.04	-0.05	0.04	-0.02	0.07	0.05	-0.03	0.00	-0.04	0.05
	p < 1	0.07	-0.01	-0.02	-0.03	0.02	0.03	-0.06	0.04	-0.03	0.07	0.05	-0.03	-0.00	-0.04	0.05
	p < 5e-08	0.00	-0.01	0.03	0.02	-0.03	0.03	-0.03	0.05	0.01	0.03	0.02	-0.02	0.03	0.01	0.00
	p < 1e-05	0.05	-0.01	0.01	0.03	-0.02	0.00	0.06	0.06	-0.03	-0.01	0.02	0.02	0.03	0.00	-0.02
DSM5 AUD (4 point scale)	p < 1e-03	0.05	-0.01	-0.01	-0.01	0.01	-0.01	-0.04	0.02	-0.03	-0.01	0.02	-0.02	-0.00	-0.02	-0.00
	p < 0.01	0.07	-0.01	-0.02	0.01	0.01	0.02	-0.10	0.01	-0.01	0.03	0.04	-0.05	-0.01	-0.01	0.02
	p < 0.05	0.08	-0.02	-0.02	0.02	-0.01	0.05	-0.07	0.02	-0.01	0.00	0.06	-0.04	-0.00	-0.00	-0.01
	p < 0.1	0.08	-0.01	-0.03	0.01	-0.01	0.06	-0.06	0.04	0.00	0.01	0.07	-0.03	-0.00	-0.00	0.00
	p < 0.5	0.08	-0.00	-0.03	-0.02	-0.01	0.05	-0.07	0.02	-0.01	0.03	0.06	-0.04	-0.01	-0.02	0.01
	p < 1	0.08	-0.01	-0.03	-0.02	-0.01	0.05	-0.07	0.02	-0.01	0.03	0.06	-0.04	-0.01	-0.02	0.01
	p < 5e-08	0.04	0.00	-0.02	0.00	0.05	0.04	-0.02	-0.03	-0.03	0.01	0.04	-0.00	-0.03	-0.01	0.04
	p < 1e-05	0.06	-0.01	-0.02	0.01	0.03	0.05	0.00	-0.02	-0.06	0.07	0.05	-0.00	-0.03	-0.02	0.05
	p < 1e-03	0.07	-0.04	0.01	-0.01	0.04	0.09	-0.05	-0.04	-0.05	0.04	0.07	-0.04	-0.02	-0.02	0.04
	p < 0.01	0.07	-0.05	0.04	-0.05	0.05	0.07	-0.05	-0.04	-0.01	0.06	0.06	-0.04	0.00	-0.04	0.05
	p < 0.05	0.07	-0.07	0.01	-0.08	0.03	0.10	-0.03	-0.03	-0.03	0.07	0.08	-0.04	-0.02	-0.07	0.04
	p < 0.1	0.08	-0.08	0.01	-0.07	0.03	0.11	-0.01	-0.02	-0.02	0.07	0.09	-0.04	-0.01	-0.06	0.05
	p < 0.5	0.08	-0.08	0.01	-0.07	0.03	0.11	-0.01	-0.02	-0.02	0.07	0.09	-0.04	-0.01	-0.06	0.05

Table S3-4. Phenotypic correlation between illicit substance use or substance use disorders and polygenic risk scores (PRS) for licit substance use in females, males or both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08, 1e-05, 1e-03, 1e-02, 5e-02, 1e-01, 5e-01, and 1.

Target phenotype	PT	Females					Males					F+M				
		SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW
	p < 0.5	0.07	-0.06	0.01	-0.07	0.03	0.09	0.01	-0.02	-0.02	0.08	0.07	-0.03	-0.01	-0.07	0.04
	p < 1	0.07	-0.07	0.01	-0.08	0.03	0.09	0.01	-0.02	-0.03	0.07	0.07	-0.03	-0.01	-0.07	0.05
DSM5 AUD (ctrl mild vs moderate severe)	p < 5e-08	0.04	0.00	-0.02	0.02	0.07	0.02	0.00	-0.04	-0.03	0.01	0.03	0.01	-0.03	0.00	0.05
	p < 1e-05	0.06	-0.01	-0.02	0.03	0.06	-0.00	0.01	-0.03	-0.06	0.06	0.03	0.00	-0.03	-0.01	0.06
	p < 1e-03	0.04	-0.00	-0.00	-0.00	0.06	0.06	-0.03	-0.05	-0.06	0.06	0.04	-0.02	-0.03	-0.02	0.06
	p < 0.01	0.04	-0.04	0.03	-0.04	0.05	0.04	-0.06	-0.06	0.00	0.07	0.03	-0.04	-0.01	-0.03	0.05
	p < 0.05	0.04	-0.05	-0.01	-0.06	0.03	0.08	-0.02	-0.03	0.00	0.07	0.05	-0.03	-0.03	-0.04	0.05
	p < 0.1	0.05	-0.06	-0.00	-0.05	0.04	0.09	-0.01	-0.03	0.02	0.08	0.06	-0.03	-0.02	-0.03	0.06
	p < 0.5	0.04	-0.05	0.01	-0.06	0.03	0.07	-0.01	-0.02	0.00	0.08	0.05	-0.03	-0.01	-0.04	0.05
	p < 1	0.04	-0.05	0.01	-0.06	0.04	0.07	-0.01	-0.02	0.00	0.08	0.05	-0.03	-0.01	-0.05	0.05
DSM5 CUD (4 point scale)	p < 5e-08	0.01	-0.02	0.03	0.06	-0.00	0.03	-0.05	0.07	0.01	0.03	0.02	-0.03	0.05	0.03	0.02
	p < 1e-05	0.06	-0.00	0.02	0.07	0.01	0.03	0.03	0.09	-0.05	0.01	0.04	0.02	0.05	0.01	0.01
	p < 1e-03	0.06	0.02	-0.02	0.00	0.02	0.00	-0.04	0.06	-0.05	0.03	0.03	-0.01	0.01	-0.02	0.03
	p < 0.01	0.08	0.02	-0.03	0.02	0.02	0.01	-0.10	0.04	-0.01	0.08	0.04	-0.03	0.00	-0.00	0.04
	p < 0.05	0.09	-0.03	-0.05	0.02	0.01	0.03	-0.09	0.06	-0.01	0.06	0.05	-0.05	-0.01	-0.00	0.03
	p < 0.1	0.09	-0.02	-0.05	0.03	0.02	0.04	-0.08	0.06	-0.01	0.07	0.06	-0.05	-0.00	-0.01	0.04
	p < 0.5	0.10	-0.03	-0.04	-0.00	0.02	0.03	-0.07	0.04	-0.02	0.07	0.06	-0.05	-0.01	-0.02	0.04
	p < 1	0.10	-0.04	-0.04	-0.00	0.02	0.03	-0.08	0.04	-0.02	0.07	0.06	-0.05	-0.01	-0.03	0.04
DSM5 CUD (ctrl mild vs moderate severe)	p < 5e-08	-0.00	-0.02	0.02	0.03	0.00	0.02	-0.05	0.06	-0.00	0.05	0.00	-0.03	0.04	0.01	0.03
	p < 1e-05	0.04	-0.01	0.01	0.04	0.00	0.01	0.04	0.08	-0.06	0.01	0.02	0.02	0.04	-0.01	0.01
	p < 1e-03	0.05	0.01	-0.02	0.01	0.02	0.00	-0.04	0.04	-0.04	-0.00	0.02	-0.02	0.00	-0.01	0.01
	p < 0.01	0.08	-0.02	-0.02	0.02	0.02	0.03	-0.09	0.04	-0.02	0.04	0.04	-0.05	0.00	-0.00	0.03
	p < 0.05	0.10	-0.04	-0.03	0.02	-0.01	0.04	-0.09	0.06	-0.01	0.03	0.06	-0.06	0.01	-0.00	0.01
	p < 0.1	0.10	-0.04	-0.03	0.01	0.00	0.06	-0.08	0.07	-0.01	0.04	0.07	-0.06	0.01	-0.01	0.02
	p < 0.5	0.10	-0.05	-0.03	-0.01	-0.00	0.04	-0.08	0.05	-0.01	0.04	0.06	-0.06	0.00	-0.02	0.02
	p < 1	0.10	-0.05	-0.04	-0.01	-0.00	0.04	-0.08	0.05	-0.01	0.04	0.06	-0.06	0.00	-0.03	0.02

Table S3-4. Phenotypic correlation between illicit substance use or substance use disorders and polygenic risk scores (PRS) for licit substance use in females, males or both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08, 1e-05, 1e-03, 1e-02, 5e-02, 1e-01, 5e-01, and 1.

Target phenotype	PT	Females					Males					F+M				
		SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW
Ever used cannabis	p < 5e-08	0.03	-0.02	0.01	-0.01	-0.01	0.04	0.03	-0.00	0.00	-0.03	0.04	0.01	-0.00	-0.01	-0.01
	p < 1e-05	0.08	-0.02	0.02	0.01	0.01	0.05	0.07	-0.01	0.00	-0.00	0.07	0.02	-0.00	0.01	-0.00
	p < 1e-03	0.11	-0.04	-0.02	-0.02	0.02	0.06	0.01	-0.02	-0.00	0.02	0.09	-0.02	-0.03	-0.01	0.02
	p < 0.01	0.09	-0.03	-0.01	0.00	0.03	0.07	0.01	-0.06	-0.02	0.08	0.07	-0.01	-0.03	-0.01	0.05
	p < 0.05	0.10	-0.05	-0.03	-0.03	0.04	0.08	0.03	-0.06	-0.04	0.10	0.08	-0.01	-0.05	-0.04	0.07
	p < 0.1	0.09	-0.03	-0.04	-0.03	0.03	0.08	0.02	-0.05	-0.04	0.09	0.08	-0.00	-0.05	-0.04	0.06
	p < 0.5	0.09	-0.01	-0.04	-0.02	0.04	0.09	0.02	-0.06	-0.03	0.10	0.08	0.00	-0.06	-0.03	0.06
	p < 1	0.09	-0.01	-0.04	-0.02	0.03	0.08	0.02	-0.07	-0.04	0.09	0.08	0.00	-0.07	-0.04	0.06
Age at onset of cannabis initiation	p < 5e-08	-0.01	-0.01	-0.01	0.06	0.04	0.02	-0.02	-0.05	0.02	-0.06	0.01	-0.01	-0.03	0.04	-0.01
	p < 1e-05	-0.06	0.04	-0.02	0.07	0.04	-0.08	0.03	-0.03	-0.00	-0.02	-0.07	0.04	-0.03	0.02	0.01
	p < 1e-03	-0.05	0.06	-0.05	0.07	0.11	-0.05	-0.07	-0.06	-0.07	0.08	-0.06	-0.01	-0.06	-0.01	0.09
	p < 0.01	-0.04	-0.02	-0.09	0.02	0.03	-0.06	-0.00	-0.03	-0.00	0.09	-0.06	-0.01	-0.06	-0.00	0.06
	p < 0.05	-0.05	-0.01	-0.04	0.02	-0.02	-0.08	-0.01	-0.00	-0.02	0.05	-0.08	-0.00	-0.03	-0.01	0.02
	p < 0.1	-0.06	0.01	-0.01	-0.00	0.00	-0.06	0.03	-0.03	-0.03	0.07	-0.07	0.02	-0.02	-0.03	0.04
	p < 0.5	-0.03	-0.01	-0.02	0.02	0.00	-0.06	-0.00	-0.04	-0.04	0.08	-0.06	-0.00	-0.04	-0.03	0.04
	p < 1	-0.02	0.00	-0.02	0.03	0.00	-0.05	0.00	-0.03	-0.04	0.08	-0.05	0.01	-0.03	-0.02	0.05
Age at onset of cannabis abuse	p < 5e-08	-0.09	-0.24	0.11	0.01	0.09	-0.13	0.04	-0.09	-0.01	0.02	-0.12	-0.07	-0.01	0.00	0.04
	p < 1e-05	-0.07	-0.01	0.11	0.08	0.02	-0.17	-0.01	-0.05	-0.00	0.08	-0.13	0.01	0.01	0.02	0.06
	p < 1e-03	-0.06	0.19	0.13	0.17	0.13	-0.10	-0.10	-0.10	-0.09	0.16	-0.08	0.01	-0.01	0.01	0.15
	p < 0.01	-0.11	0.13	0.04	0.06	0.15	-0.09	-0.03	-0.03	0.01	0.25	-0.10	0.03	0.00	0.03	0.21
	p < 0.05	-0.09	0.20	0.07	0.09	-0.03	-0.08	-0.05	0.05	-0.05	0.22	-0.09	0.05	0.06	0.01	0.12
	p < 0.1	-0.12	0.15	0.07	0.11	-0.03	-0.03	-0.05	0.03	-0.04	0.20	-0.07	0.03	0.05	0.02	0.10
	p < 0.5	-0.06	0.12	-0.00	0.11	-0.08	-0.03	-0.07	0.02	-0.06	0.21	-0.05	0.01	0.01	0.01	0.08
	p < 1	-0.05	0.13	-0.03	0.14	-0.10	-0.02	-0.06	0.04	-0.06	0.20	-0.04	0.02	0.01	0.02	0.08
Age at onset of cannabis dependence	p < 5e-08	0.23	-0.30	0.15	-0.26	0.37	-0.11	0.14	-0.01	-0.06	-0.17	0.03	-0.03	0.05	-0.14	0.03

Table S3-4. Phenotypic correlation between illicit substance use or substance use disorders and polygenic risk scores (PRS) for licit substance use in females, males or both sexes (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08, 1e-05, 1e-03, 1e-02, 5e-02, 1e-01, 5e-01, and 1.

Target phenotype	PT	Females					Males					F+M				
		SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW	SI	AI	CPD	SC	DPW
	p < 1e-05	0.15	-0.00	0.15	0.00	0.15	-0.23	0.02	0.01	-0.03	-0.05	-0.07	0.03	0.06	-0.02	0.03
	p < 1e-03	0.09	0.13	0.17	0.02	0.15	-0.20	-0.09	-0.04	-0.02	0.13	-0.10	-0.00	0.03	-0.01	0.13
	p < 0.01	0.06	0.04	-0.02	-0.07	0.10	-0.17	-0.05	-0.15	0.12	0.17	-0.09	-0.03	-0.10	0.04	0.14
	p < 0.05	-0.05	0.09	-0.01	0.01	0.00	-0.09	-0.02	-0.12	0.07	0.15	-0.09	0.03	-0.07	0.05	0.08
	p < 0.1	-0.14	0.06	0.00	0.04	0.06	-0.06	0.03	-0.19	0.11	0.09	-0.10	0.04	-0.11	0.07	0.07
	p < 0.5	-0.00	0.11	-0.05	0.06	-0.02	-0.00	0.01	-0.19	0.01	0.18	-0.02	0.05	-0.12	0.04	0.09
	p < 1	0.02	0.07	-0.06	0.08	-0.02	0.02	0.01	-0.17	0.01	0.17	0.00	0.04	-0.12	0.04	0.09
Age at onset of DSM5 CUD	p < 5e-08	-0.01	-0.14	0.14	0.02	0.22	-0.14	0.04	-0.10	0.03	-0.03	-0.09	-0.03	-0.00	0.03	0.07
	p < 1e-05	-0.05	0.02	0.13	0.05	0.16	-0.17	0.02	-0.07	0.03	0.08	-0.12	0.02	0.01	0.03	0.12
	p < 1e-03	-0.08	0.12	0.09	0.12	0.18	-0.12	-0.07	-0.14	-0.06	0.13	-0.10	0.01	-0.04	0.01	0.16
	p < 0.01	-0.05	-0.01	0.02	0.02	0.15	-0.09	-0.02	-0.12	0.02	0.23	-0.09	-0.02	-0.05	0.02	0.19
	p < 0.05	-0.07	0.02	0.10	0.08	-0.07	-0.12	-0.01	-0.06	-0.06	0.19	-0.11	0.01	0.02	-0.00	0.08
	p < 0.1	-0.08	-0.01	0.11	0.08	-0.05	-0.08	0.01	-0.07	-0.06	0.16	-0.09	0.00	0.01	0.00	0.06
	p < 0.5	-0.02	-0.01	0.11	0.09	-0.10	-0.05	-0.01	-0.12	-0.09	0.15	-0.05	-0.01	-0.02	-0.01	0.04
	p < 1	-0.01	-0.00	0.10	0.11	-0.11	-0.05	-0.01	-0.10	-0.09	0.14	-0.04	-0.00	-0.01	-0.00	0.03

Table S4-1. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5). Modelling in these associations contained a sex*PRS interaction term. PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3, T4 and T5 are 3.657103e-03, 7.142857e-04, and 8.333333e-05 respectively.

Target phenotype	SI					AI					CPD					SC					DPW				
	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
Smoking initiation	8	7	6	6	6	8	4	0	0	0	8	5	0	0	0	8	0	0	0	0	8	4	1	0	0
Age at starting regular smoking	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Cigarettes per day	8	1	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Smoking cessation	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0
Drinking initiation	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Drinks per week	8	8	8	8	8	8	8	7	1	1	8	0	0	0	0	8	7	0	0	0	8	8	8	7	7
DSM-IV alcohol dependence	8	1	0	0	0	8	4	3	0	0	8	0	0	0	0	8	2	0	0	0	8	5	0	0	0
DSM-IV nicotine dependence	8	7	5	5	2	8	0	0	0	0	8	5	3	1	0	8	4	1	0	0	8	4	1	0	0
FTND-based nicotine dependence	8	8	7	5	5	8	6	4	0	0	8	7	1	0	0	8	4	3	1	0	8	0	0	0	0
DSM-IV antisocial personality disorder	8	4	0	0	0	8	6	5	0	0	8	6	0	0	0	8	3	0	0	0	8	0	0	0	0
DSM-IV major depressive disorder	8	0	0	0	0	8	0	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0
DSM-IV conduct disorder	8	6	5	5	2	8	6	1	0	0	8	6	5	1	0	8	0	0	0	0	8	1	0	0	0
Mania screen	8	4	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	6	3	0	0
DSM-IV panic disorder	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0

Table S4-1. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5). Modelling in these associations contained a sex*PRS interaction term. PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3, T4 and T5 are $3.657103e-03$, $7.142857e-04$, and $8.333333e-05$ respectively.

Target phenotype	SI					AI					CPD					SC					DPW				
	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
DSM-IV social anxiety disorder	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Numb_target_pheno_predic	15	10	5	5	5	15	8	5	1	1	15	6	3	2	0	15	6	2	1	0	15	6	4	1	1

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.
 PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW			
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
Smoking initiation	S1	PRS	0.014	0.02	0.43969	0.08	0.003	0.02	0.87911	0.00	0.002	0.02	0.89326	0.00	0.017	0.02	0.36152	0.12
	S1 sexPRS		0.007	0.01	0.49253	0.06	-0.008	0.01	0.48107	0.07	-0.001	0.01	0.89741	0.00	-0.009	0.01	0.41462	0.09
	S2	PRS	0.049	0.02	0.00685	0.99	0.010	0.02	0.57063	0.04	-0.002	0.02	0.93254	0.00	0.027	0.02	0.14007	0.31
	S2 sexPRS		0.003	0.01	0.78101	0.01	-0.014	0.01	0.20571	0.21	0.003	0.01	0.79660	0.01	-0.014	0.01	0.20715	0.22
	S3	PRS	0.088	0.02	<0.0001	3.15	-0.007	0.02	0.71469	0.02	0.015	0.02	0.39889	0.10	0.014	0.02	0.44406	0.08
	S3 sexPRS		-0.006	0.01	0.54910	0.05	-0.012	0.01	0.27495	0.16	-0.005	0.01	0.67667	0.02	-0.003	0.01	0.77762	0.01
	S4	PRS	0.094	0.02	<0.0001	3.63	-0.034	0.02	0.05849	0.48	0.043	0.02	0.02089	0.74	0.017	0.02	0.35770	0.12
	S4 sexPRS		-0.007	0.01	0.50585	0.06	0.005	0.01	0.65655	0.03	-0.018	0.01	0.10955	0.35	-0.004	0.01	0.68848	0.02
	S5	PRS	0.109	0.02	<0.0001	4.85	-0.049	0.02	0.00681	1.01	0.039	0.02	0.03327	0.62	0.019	0.02	0.29246	0.16
	S5 sexPRS		-0.012	0.01	0.25290	0.17	0.011	0.01	0.33098	0.13	-0.016	0.01	0.13196	0.30	-0.012	0.01	0.27146	0.16
Age at starting regular smoking	S6	PRS	0.112	0.02	<0.0001	5.09	-0.050	0.02	0.00627	1.05	0.041	0.02	0.02486	0.68	0.017	0.02	0.35710	0.13
	S6 sexPRS		-0.013	0.01	0.21892	0.20	0.010	0.01	0.36786	0.11	-0.019	0.01	0.08712	0.39	-0.007	0.01	0.49446	0.06
	S7	PRS	0.104	0.02	<0.0001	4.43	-0.044	0.02	0.01567	0.82	0.045	0.02	0.01308	0.85	0.021	0.02	0.25218	0.19
	S7 sexPRS		-0.012	0.01	0.26287	0.16	0.004	0.01	0.69749	0.02	-0.021	0.01	0.05160	0.51	-0.007	0.01	0.49792	0.06
	S8	PRS	0.103	0.02	<0.0001	4.37	-0.043	0.02	0.01995	0.76	0.047	0.02	0.01038	0.91	0.019	0.02	0.29149	0.16
	S8 sexPRS		-0.012	0.01	0.25377	0.17	0.003	0.01	0.78016	0.01	-0.022	0.01	0.04248	0.56	-0.007	0.01	0.51094	0.06
	S1	PRS	0.292	0.25	0.24079	0.64	0.165	0.26	0.51971	0.20	-0.115	0.26	0.65401	0.10	0.344	0.25	0.17048	0.89
	S1 sexPRS		-0.223	0.15	0.13575	1.04	0.012	0.15	0.93994	0.00	0.056	0.15	0.71231	0.07	-0.172	0.15	0.25309	0.62

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.
 PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI				AI				CPD				SC				DPW			
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
S5	PRS	-0.318	0.26	0.22244	0.75	0.339	0.26	0.18701	0.86	-0.178	0.26	0.49492	0.24	-0.037	0.25	0.88458	0.01	-0.332	0.27	0.21078	0.82	
S5	sexPRS	0.066	0.16	0.67357	0.09	-0.097	0.15	0.52357	0.20	0.158	0.16	0.30947	0.51	-0.038	0.15	0.80009	0.03	0.114	0.16	0.46721	0.27	
S6	PRS	-0.178	0.26	0.49306	0.24	0.168	0.26	0.51462	0.21	-0.101	0.26	0.69682	0.08	-0.026	0.26	0.91839	0.01	-0.079	0.26	0.76321	0.05	
S6	sexPRS	0.007	0.16	0.96574	0.00	0.015	0.15	0.92112	0.00	0.090	0.15	0.55696	0.17	-0.035	0.15	0.81964	0.03	-0.056	0.15	0.71868	0.06	
S7	PRS	-0.149	0.26	0.56762	0.16	0.170	0.25	0.50598	0.22	0.015	0.26	0.95244	0.00	-0.036	0.26	0.88967	0.01	-0.047	0.27	0.86364	0.02	
S7	sexPRS	-0.016	0.16	0.91771	0.01	-0.016	0.15	0.91758	0.01	0.009	0.15	0.95104	0.00	-0.010	0.15	0.94826	0.00	-0.032	0.16	0.84269	0.02	
S8	PRS	-0.149	0.26	0.56733	0.17	0.128	0.25	0.61559	0.12	0.038	0.26	0.88470	0.01	-0.041	0.26	0.87265	0.01	-0.025	0.27	0.92589	0.00	
S8	sexPRS	-0.012	0.16	0.93772	0.00	-0.003	0.15	0.98307	0.00	0.002	0.15	0.99158	0.00	-0.005	0.15	0.97485	0.00	-0.042	0.16	0.79209	0.04	
Cigarettes per day	SI	PRS	0.170	0.08	0.02629	2.50	-0.227	0.08	0.00385	4.43	0.037	0.08	0.63596	0.12	0.042	0.08	0.58548	0.15	0.073	0.08	0.33592	0.47
	S1	sexPRS	-0.080	0.05	0.08059	1.53	0.139	0.05	0.00299	4.60	0.029	0.05	0.53444	0.20	-0.008	0.05	0.86364	0.01	-0.042	0.04	0.34083	0.44
	S2	PRS	0.114	0.08	0.14263	1.13	-0.080	0.08	0.31076	0.54	0.056	0.08	0.47470	0.27	0.042	0.08	0.59654	0.15	0.121	0.08	0.12050	1.29
	S2	sexPRS	-0.023	0.05	0.61659	0.13	0.039	0.05	0.40482	0.36	0.023	0.05	0.61806	0.13	-0.005	0.05	0.91407	0.01	-0.062	0.05	0.17969	0.92
	S3	PRS	0.015	0.08	0.84597	0.02	0.061	0.08	0.43915	0.32	0.121	0.08	0.11912	1.26	-0.001	0.08	0.99055	0.00	0.039	0.08	0.61199	0.14
	S3	sexPRS	0.059	0.05	0.21278	0.83	-0.065	0.05	0.16776	0.99	-0.004	0.05	0.93535	0.00	0.027	0.05	0.56909	0.18	-0.023	0.05	0.62200	0.12
	S4	PRS	0.037	0.08	0.63788	0.12	-0.034	0.08	0.65434	0.10	0.129	0.08	0.09822	1.43	-0.099	0.08	0.21359	0.86	0.087	0.08	0.27445	0.65
	S4	sexPRS	0.035	0.05	0.45827	0.29	-0.019	0.05	0.66934	0.09	0.002	0.05	0.96855	0.00	0.086	0.05	0.06658	1.81	-0.048	0.05	0.30627	0.54
	S5	PRS	0.078	0.08	0.32155	0.52	-0.017	0.08	0.82699	0.03	0.126	0.08	0.11302	1.36	-0.114	0.08	0.14468	1.16	0.103	0.08	0.20611	0.92
	S5	sexPRS	0.025	0.05	0.58953	0.15	-0.035	0.05	0.45411	0.29	0.016	0.05	0.73332	0.06	0.101	0.05	0.02936	2.51	-0.057	0.05	0.23342	0.78
	S6	PRS	0.089	0.08	0.26114	0.68	-0.000	0.08	0.99660	0.00	0.112	0.08	0.15615	1.08	-0.094	0.08	0.24035	0.79	0.115	0.08	0.15813	1.13
	S6	sexPRS	0.009	0.05	0.85450	0.02	-0.049	0.05	0.29465	0.58	0.023	0.05	0.61665	0.13	0.093	0.05	0.04911	2.12	-0.071	0.05	0.13848	1.19
	S7	PRS	0.060	0.08	0.44431	0.31	-0.054	0.08	0.49066	0.26	0.107	0.08	0.17524	0.99	-0.090	0.08	0.26068	0.72	0.140	0.08	0.09668	1.67
	S7	sexPRS	0.022	0.05	0.63366	0.12	-0.017	0.05	0.71714	0.07	0.015	0.05	0.74883	0.05	0.081	0.05	0.08369	1.62	-0.089	0.05	0.06999	1.87
	S8	PRS	0.072	0.08	0.36405	0.44	-0.050	0.08	0.52683	0.22	0.102	0.08	0.19902	0.90	-0.088	0.08	0.26837	0.70	0.136	0.08	0.10388	1.58
	S8	sexPRS	0.016	0.05	0.73415	0.06	-0.017	0.05	0.70930	0.07	0.018	0.05	0.70400	0.08	0.079	0.05	0.08996	1.55	-0.086	0.05	0.07684	1.77
Smoking cessation	S1	PRS	0.008	0.03	0.74262	0.03	-0.048	0.03	0.06608	0.93	0.037	0.03	0.14863	0.56	0.049	0.03	0.05816	0.98	0.011	0.03	0.65826	0.05

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.
 PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW			
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
S1 sexPRS			0.003	0.02	0.86657	0.01	0.030	0.02	0.06696	1.01	-0.009	0.02	0.56368	0.10	-0.021	0.02	0.19526	0.49
S2 PRS			0.004	0.03	0.87815	0.01	-0.007	0.03	0.79555	0.02	0.040	0.03	0.10942	0.67	0.043	0.03	0.09933	0.77
S2 sexPRS			0.015	0.02	0.35258	0.24	0.005	0.02	0.74439	0.03	-0.012	0.02	0.46251	0.15	-0.026	0.02	0.11175	0.77
S3 PRS			0.008	0.03	0.76910	0.02	0.009	0.03	0.71789	0.03	0.033	0.03	0.18918	0.45	0.057	0.03	0.02841	1.34
S3 sexPRS			0.014	0.02	0.39669	0.21	-0.006	0.02	0.69153	0.04	-0.008	0.02	0.62510	0.07	-0.027	0.02	0.08979	0.86
S4 PRS			0.044	0.03	0.09055	0.79	-0.001	0.02	0.95626	0.00	0.039	0.03	0.12433	0.64	0.020	0.03	0.43205	0.17
S4 sexPRS			-0.003	0.02	0.84570	0.01	-0.006	0.02	0.67767	0.05	-0.010	0.02	0.52843	0.12	-0.004	0.02	0.79267	0.02
S5 PRS			0.033	0.03	0.21090	0.43	-0.002	0.03	0.94786	0.00	0.009	0.03	0.71977	0.03	0.015	0.03	0.56181	0.09
S5 sexPRS			0.001	0.02	0.96630	0.00	-0.010	0.02	0.54380	0.10	0.004	0.02	0.77725	0.02	0.002	0.02	0.90212	0.00
S6 PRS			0.020	0.03	0.44389	0.16	0.008	0.03	0.75656	0.03	0.005	0.03	0.84756	0.01	0.016	0.03	0.53764	0.11
S6 sexPRS			0.006	0.02	0.73144	0.04	-0.015	0.02	0.35071	0.25	0.005	0.02	0.72928	0.03	-0.001	0.02	0.95269	0.00
S7 PRS			0.009	0.03	0.71890	0.04	-0.001	0.03	0.95441	0.00	0.002	0.03	0.94832	0.00	0.010	0.03	0.69713	0.04
S7 sexPRS			0.009	0.02	0.58337	0.09	-0.008	0.02	0.60413	0.08	0.003	0.02	0.82951	0.01	-0.000	0.02	0.98193	0.00
S8 PRS			0.011	0.03	0.66494	0.05	-0.002	0.03	0.94097	0.00	0.002	0.03	0.94767	0.00	0.012	0.03	0.64333	0.06
S8 sexPRS			0.007	0.02	0.66495	0.05	-0.008	0.02	0.62909	0.07	0.004	0.02	0.78097	0.02	-0.001	0.02	0.94949	0.00
Drinking initiation	S1	PRS	0.022	0.02	0.13818	0.32	-0.009	0.02	0.57203	0.05	0.023	0.02	0.13514	0.33	-0.000	0.02	0.98252	0.00
	S1	sexPRS	-0.013	0.01	0.14890	0.30	-0.003	0.01	0.74921	0.02	-0.013	0.01	0.14932	0.31	-0.003	0.01	0.74926	0.02
	S2	PRS	0.025	0.02	0.10132	0.39	0.014	0.02	0.37133	0.12	0.029	0.02	0.05775	0.53	0.005	0.02	0.72471	0.02
	S2	sexPRS	-0.017	0.01	0.06517	0.49	-0.007	0.01	0.44218	0.09	-0.017	0.01	0.06090	0.52	-0.006	0.01	0.54928	0.05
	S3	PRS	0.034	0.02	0.02386	0.75	0.003	0.02	0.85638	0.00	0.020	0.02	0.18630	0.26	0.019	0.02	0.21506	0.23
	S3	sexPRS	-0.017	0.01	0.05712	0.52	0.002	0.01	0.83336	0.01	-0.016	0.01	0.07352	0.47	-0.016	0.01	0.08518	0.44
	S4	PRS	0.028	0.02	0.06404	0.50	0.003	0.02	0.81604	0.01	0.015	0.02	0.33317	0.14	0.020	0.02	0.17641	0.27
	S4	sexPRS	-0.012	0.01	0.18913	0.25	0.004	0.01	0.64750	0.03	-0.015	0.01	0.11422	0.37	-0.019	0.01	0.03583	0.64
	S5	PRS	0.013	0.02	0.39618	0.10	-0.001	0.02	0.97213	0.00	0.003	0.02	0.84763	0.01	0.013	0.01	0.37086	0.12
	S5	sexPRS	-0.001	0.01	0.92183	0.00	0.006	0.01	0.48110	0.07	-0.010	0.01	0.27892	0.17	-0.013	0.01	0.13167	0.32
	S6	PRS	0.015	0.02	0.31309	0.15	-0.003	0.02	0.86924	0.00	0.008	0.02	0.59220	0.04	0.013	0.01	0.39695	0.11
	S6	sexPRS	-0.001	0.01	0.87915	0.00	0.006	0.01	0.52054	0.06	-0.013	0.01	0.14273	0.31	-0.013	0.01	0.15007	0.29

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.
 PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW			
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
	S7	PRS	0.012	0.02	0.42961	0.09	-0.003	0.02	0.85970	0.00	0.013	0.02	0.37037	0.12	0.011	0.01	0.46425	0.08
	S7 sexPRS		-0.000	0.01	0.99868	0.00	0.003	0.01	0.76821	0.01	-0.017	0.01	0.06135	0.50	-0.013	0.01	0.12358	0.33
	S8	PRS	0.011	0.02	0.45221	0.08	-0.002	0.02	0.88505	0.00	0.015	0.02	0.33364	0.14	0.011	0.01	0.45096	0.08
	S8 sexPRS		-0.000	0.01	0.98807	0.00	0.002	0.01	0.84869	0.01	-0.018	0.01	0.05088	0.55	-0.014	0.01	0.12163	0.33
Drinks per week	S1	PRS	2.419	0.57	<0.00003	3.21	-1.739	0.59	0.00317	1.63	1.047	0.59	0.07450	0.60	-1.357	0.59	0.02188	1.01
	S1 sexPRS		-1.260	0.35	<0.00036	2.40	0.830	0.36	0.02189	1.03	-0.472	0.36	0.18863	0.34	0.718	0.36	0.04895	0.78
	S2	PRS	2.840	0.58	<0.00001	4.39	-2.714	0.58	<0.00001	3.91	0.884	0.58	0.12992	0.42	-1.170	0.59	0.04858	0.75
	S2 sexPRS		-1.361	0.35	0.00013	2.77	1.307	0.36	<0.00029	2.48	-0.400	0.36	0.26459	0.24	0.497	0.36	0.17175	0.37
	S3	PRS	2.360	0.58	0.00005	3.01	-1.280	0.58	0.02807	0.89	0.438	0.58	0.44985	0.10	-1.197	0.59	0.04299	0.78
	S3 sexPRS		-0.976	0.36	0.00605	1.42	0.539	0.36	0.13347	0.43	-0.126	0.36	0.72421	0.02	0.591	0.36	0.10061	0.53
	S4	PRS	2.593	0.58	<0.00001	3.67	-1.756	0.57	0.00215	1.69	0.826	0.58	0.15507	0.37	-1.222	0.58	0.03556	0.83
	S4 sexPRS		-1.093	0.35	0.00202	1.78	0.790	0.35	0.02571	0.94	-0.350	0.36	0.32791	0.18	0.654	0.35	0.06387	0.66
	S5	PRS	2.811	0.58	<0.00001	4.27	-1.826	0.58	0.00178	1.82	-0.493	0.57	0.38758	0.13	-0.929	0.57	0.10286	0.49
	S5 sexPRS		-1.182	0.36	0.00094	2.07	0.817	0.36	0.02277	1.00	0.364	0.35	0.30251	0.20	0.557	0.35	0.10726	0.48
	S6	PRS	2.403	0.58	0.00004	3.11	-1.770	0.58	0.00245	1.73	-0.538	0.57	0.34653	0.16	-1.168	0.57	0.04114	0.77
	S6 sexPRS		-0.960	0.36	0.00740	1.36	0.774	0.36	0.03104	0.91	0.388	0.35	0.27064	0.23	0.662	0.35	0.05538	0.68
	S7	PRS	2.402	0.58	0.00003	3.12	-1.937	0.59	0.00095	2.07	-1.045	0.57	0.06720	0.60	-1.413	0.57	0.01276	1.13
	S7 sexPRS		-1.020	0.36	0.00418	1.54	0.901	0.36	0.01220	1.24	0.639	0.35	0.06894	0.62	0.784	0.34	0.02174	0.96
	S8	PRS	2.488	0.57	0.00002	3.35	-1.976	0.59	0.00074	2.16	-1.081	0.57	0.05875	0.64	-1.420	0.57	0.01220	1.15
	S8 sexPRS		-1.068	0.36	0.00265	1.69	0.930	0.36	0.00956	1.32	0.650	0.35	0.06447	0.64	0.778	0.34	0.02257	0.95
DSM-IV alcohol dependence	S1	PRS	-0.007	0.02	0.65923	0.03	0.014	0.02	0.34355	0.11	-0.009	0.02	0.56722	0.04	-0.009	0.02	0.55151	0.05
	S1 sexPRS		0.016	0.01	0.08969	0.37	-0.011	0.01	0.22614	0.19	0.007	0.01	0.44717	0.07	0.002	0.01	0.85396	0.00
	S2	PRS	-0.016	0.02	0.29971	0.14	0.007	0.02	0.66042	0.02	-0.015	0.02	0.33038	0.12	-0.005	0.02	0.74023	0.01
	S2 sexPRS		0.022	0.01	0.01535	0.75	-0.004	0.01	0.64421	0.03	0.013	0.01	0.18230	0.23	-0.002	0.01	0.83555	0.01

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.
 PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW							
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²				
S3	PRS	0.008	0.02	0.57656	0.04	-0.022	0.02	0.14999	0.27	-0.017	0.02	0.26870	0.16	-0.021	0.02	0.17997	0.24	0.033	0.02	0.02975	0.61	
S3 sexPRS		0.011	0.01	0.24893	0.17	0.008	0.01	0.42294	0.08	0.013	0.01	0.15630	0.26	0.010	0.01	0.30385	0.14	-0.002	0.01	0.84042	0.01	
S4	PRS	0.024	0.02	0.10395	0.34	-0.021	0.02	0.16186	0.26	-0.011	0.02	0.47384	0.07	-0.016	0.02	0.28829	0.15	0.029	0.02	0.05403	0.47	
S4 sexPRS		-0.000	0.01	0.99584	0.00	0.008	0.01	0.40569	0.09	0.008	0.01	0.37752	0.10	0.007	0.01	0.46072	0.07	-0.001	0.01	0.91876	0.00	
S5	PRS	0.032	0.02	0.03394	0.58	-0.041	0.02	0.00741	0.94	-0.010	0.02	0.50489	0.06	-0.027	0.01	0.06690	0.45	0.040	0.02	0.00898	0.87	
S5 sexPRS		-0.004	0.01	0.63879	0.03	0.017	0.01	0.07092	0.42	0.008	0.01	0.38488	0.10	0.016	0.01	0.07766	0.40	-0.007	0.01	0.44394	0.07	
S6	PRS	0.027	0.02	0.07638	0.41	-0.050	0.02	0.00110	1.41	-0.006	0.02	0.68708	0.02	-0.025	0.01	0.09296	0.38	0.034	0.02	0.02599	0.63	
S6 sexPRS		-0.001	0.01	0.87447	0.00	0.023	0.01	0.01314	0.81	0.005	0.01	0.59467	0.04	0.014	0.01	0.12224	0.31	-0.005	0.01	0.63133	0.03	
S7	PRS	0.024	0.02	0.11549	0.32	-0.049	0.02	0.00145	1.35	-0.009	0.02	0.54468	0.05	-0.036	0.01	0.01675	0.77	0.038	0.02	0.01458	0.77	
S7 sexPRS		-0.001	0.01	0.94803	0.00	0.022	0.01	0.02035	0.71	0.007	0.01	0.43513	0.08	0.020	0.01	0.02409	0.65	-0.006	0.01	0.51652	0.05	
S8	PRS	0.024	0.02	0.10790	0.34	-0.049	0.02	0.00146	1.35	-0.004	0.02	0.76661	0.01	-0.037	0.01	0.01225	0.84	0.041	0.02	0.00724	0.93	
S8 sexPRS		-0.001	0.01	0.92388	0.00	0.021	0.01	0.02219	0.69	0.005	0.01	0.61118	0.03	0.021	0.01	0.01866	0.71	-0.008	0.01	0.38223	0.10	
DSM-IV nicotine dependence	S1	PRS	0.029	0.02	0.10419	0.36	0.005	0.02	0.79538	0.01	0.018	0.02	0.32815	0.13	0.038	0.02	0.03707	0.60	0.010	0.02	0.55738	0.05
	S1 sexPRS		0.002	0.01	0.86158	0.00	-0.009	0.01	0.38545	0.10	-0.001	0.01	0.91628	0.00	-0.016	0.01	0.14344	0.29	-0.010	0.01	0.36531	0.11
	S2	PRS	0.037	0.02	0.03552	0.60	-0.006	0.02	0.71665	0.02	0.018	0.02	0.32932	0.13	0.036	0.02	0.04484	0.55	0.017	0.02	0.32440	0.13
	S2 sexPRS		0.008	0.01	0.48534	0.07	-0.002	0.01	0.83046	0.01	0.001	0.01	0.91966	0.00	-0.017	0.01	0.11762	0.34	-0.015	0.01	0.15526	0.27
	S3	PRS	0.045	0.02	0.01191	0.86	-0.017	0.02	0.33409	0.13	0.014	0.02	0.42873	0.09	0.056	0.02	0.00184	1.34	0.016	0.02	0.35633	0.11
	S3 sexPRS		0.009	0.01	0.38648	0.10	-0.002	0.01	0.84566	0.01	0.006	0.01	0.61898	0.03	-0.024	0.01	0.03081	0.64	-0.015	0.01	0.16106	0.26
	S4	PRS	0.068	0.02	0.00011	1.99	-0.026	0.02	0.14385	0.29	0.036	0.02	0.04011	0.57	0.043	0.02	0.01437	0.84	0.025	0.02	0.16241	0.26
	S4 sexPRS		-0.003	0.01	0.80344	0.01	-0.000	0.01	0.97966	0.00	-0.004	0.01	0.68448	0.02	-0.018	0.01	0.10205	0.36	-0.012	0.01	0.26262	0.17
	S5	PRS	0.070	0.02	0.00008	2.12	-0.011	0.02	0.54712	0.05	0.054	0.02	0.00232	1.25	0.023	0.02	0.19781	0.23	0.044	0.02	0.01261	0.84
	S5 sexPRS		-0.001	0.01	0.89600	0.00	-0.015	0.01	0.17476	0.25	-0.014	0.01	0.21178	0.21	-0.002	0.01	0.84104	0.01	-0.024	0.01	0.03127	0.62
S6	PRS	0.075	0.02	0.00003	2.39	-0.022	0.02	0.22808	0.20	0.048	0.02	0.00643	1.00	0.027	0.02	0.12812	0.33	0.053	0.02	0.00321	1.16	
	S6 sexPRS		-0.003	0.01	0.77672	0.01	-0.011	0.01	0.32560	0.13	-0.008	0.01	0.46022	0.07	-0.004	0.01	0.73825	0.02	-0.028	0.01	0.01168	0.85
	S7	PRS	0.067	0.02	0.00013	1.98	-0.032	0.02	0.07861	0.43	0.056	0.02	0.00152	1.36	0.018	0.02	0.30859	0.15	0.050	0.02	0.00558	1.04
	S7 sexPRS		0.000	0.01	0.98468	0.00	-0.005	0.01	0.63007	0.03	-0.015	0.01	0.16877	0.25	0.000	0.01	0.97084	0.00	-0.024	0.01	0.02989	0.64

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.

PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW				
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	
	S8	PRS	0.068 0.02 0.00012 2.00	-0.029	0.02	0.10466	0.36	0.060 0.02 0.00068 1.56	0.018	0.02	0.31632	0.14	0.049	0.02	0.00680	0.99			
	S8 sexPRS		-0.000	0.01	0.96544	0.00	-0.007	0.01	0.53665	0.05	-0.017	0.01	0.12254	0.32	0.000	0.01	0.96514	0.00	
FTND-based nicotine dependence	S1	PRS	0.040	0.02	0.01361	0.82	-0.015	0.02	0.36542	0.11	0.029	0.02	0.08548	0.41	0.054	0.02	0.00118	1.44	
	S1 sexPRS		-0.009	0.01	0.37315	0.11	0.004	0.01	0.67674	0.02	-0.001	0.01	0.95520	0.00	-0.020	0.01	0.05187	0.52	
	S2	PRS	0.053	0.02	0.00129	1.41	-0.029	0.02	0.08107	0.40	0.034	0.02	0.04320	0.56	0.059 0.02 0.00044 1.70	0.009	0.02	0.59909	0.04
	S2 sexPRS		-0.006	0.01	0.55456	0.05	0.011	0.01	0.30011	0.14	-0.002	0.01	0.86182	0.00	-0.027	0.01	0.00926	0.93	
	S3	PRS	0.053	0.02	0.00122	1.42	-0.039	0.02	0.01940	0.74	0.036	0.02	0.02754	0.66	0.055	0.02	0.00103	1.49	
	S3 sexPRS		0.000	0.01	0.96289	0.00	0.014	0.01	0.15966	0.27	-0.002	0.01	0.81109	0.01	-0.020	0.01	0.05212	0.52	
	S4	PRS	0.068 0.02 0.00003 2.35	-0.046	0.02	0.00504	1.07	0.041	0.02	0.01173	0.86	0.040	0.02	0.01407	0.84	-0.003	0.02	0.84042	0.01
	S4 sexPRS		-0.005	0.01	0.60739	0.03	0.013	0.01	0.20802	0.21	-0.001	0.01	0.94445	0.00	-0.008	0.01	0.40501	0.09	
	S5	PRS	0.077 0.02 < <0.0001 2.99	-0.050	0.02	0.00233	1.27	0.050	0.02	0.00213	1.26	0.024	0.02	0.14383	0.30	0.010	0.02	0.55407	0.05
	S5 sexPRS		-0.010	0.01	0.31188	0.14	0.011	0.01	0.26740	0.17	-0.004	0.01	0.69216	0.02	0.004	0.01	0.70090	0.02	
	S6	PRS	0.084 0.02 < <0.0001 3.57	-0.050	0.02	0.00275	1.24	0.039	0.02	0.01692	0.77	0.024	0.02	0.14402	0.30	0.010	0.02	0.55014	0.05
	S6 sexPRS		-0.015	0.01	0.14955	0.28	0.009	0.01	0.38882	0.10	0.005	0.01	0.63986	0.03	0.004	0.01	0.65557	0.03	
	S7	PRS	0.077 0.02 < <0.0001 2.99	-0.053	0.02	0.00144	1.40	0.039	0.02	0.01643	0.78	0.022	0.02	0.17960	0.26	0.014	0.02	0.38787	0.10
	S7 sexPRS		-0.010	0.01	0.33506	0.12	0.010	0.01	0.33713	0.13	0.001	0.01	0.94836	0.00	0.002	0.01	0.82264	0.01	
	S8	PRS	0.078 0.02 < <0.0001 3.10	-0.053	0.02	0.00135	1.42	0.043	0.02	0.00793	0.95	0.022	0.02	0.17792	0.26	0.014	0.02	0.40943	0.09
	S8 sexPRS		-0.011	0.01	0.28726	0.15	0.011	0.01	0.29014	0.15	-0.001	0.01	0.89461	0.00	0.002	0.01	0.84147	0.01	
DSM-IV conduct disorder	S1	PRS	0.001	0.01	0.91085	0.00	-0.013	0.01	0.05780	0.53	0.011	0.01	0.09754	0.41	0.004	0.01	0.60459	0.04	
	S1 sexPRS		0.003	0.00	0.52801	0.06	0.006	0.00	0.13250	0.33	-0.006	0.00	0.14826	0.31	-0.003	0.00	0.52788	0.06	
	S2	PRS	0.011	0.01	0.08766	0.43	0.004	0.01	0.55982	0.05	0.010	0.01	0.14303	0.32	0.005	0.01	0.42622	0.10	
	S2 sexPRS		-0.003	0.00	0.39656	0.11	-0.004	0.00	0.32487	0.14	-0.005	0.00	0.24525	0.20	-0.004	0.00	0.30863	0.16	
	S3	PRS	0.013	0.01	0.04490	0.59	-0.015	0.01	0.02884	0.71	0.020	0.01	0.00224	1.37	-0.001	0.01	0.85267	0.01	
	S3 sexPRS		-0.012	0.00	0.28726	0.15	-0.011	0.01	0.29014	0.15	-0.001	0.01	0.89461	0.00	-0.002	0.01	0.84147	0.01	

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.
 PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW							
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²				
S3 sexPRS		-0.005	0.00	0.25442	0.19	0.007	0.00	0.10623	0.39	-0.011	0.00	0.01056	0.96	-0.000	0.00	0.95790	0.00	0.006	0.00	0.15930	0.29	
S4 PRS		0.022 0.01 0.00071 1.67	-0.020	0.01	0.00325	1.30	0.019	0.01	0.00471	1.18	0.003	0.01	0.62698	0.04	-0.007	0.01	0.28398	0.17				
S4 sexPRS		-0.009	0.00	0.02196	0.76	0.008	0.00	0.06761	0.50	-0.010	0.00	0.01571	0.86	-0.001	0.00	0.74626	0.02	0.004	0.00	0.36382	0.12	
S5 PRS		0.025 0.01 0.00020 2.06	-0.014	0.01	0.04399	0.61	0.021	0.01	0.00166	1.47	0.006	0.01	0.36048	0.13	-0.001	0.01	0.83593	0.01				
S5 sexPRS		-0.010	0.00	0.01326	0.90	0.004	0.00	0.36934	0.12	-0.011	0.00	0.00741	1.06	-0.002	0.00	0.64598	0.03	0.000	0.00	0.95353	0.00	
S6 PRS		0.023 0.01 0.00054 1.77	-0.016	0.01	0.02129	0.80	0.021	0.01	0.00146	1.51	0.010	0.01	0.13153	0.35	-0.001	0.01	0.82426	0.01				
S6 sexPRS		-0.010	0.00	0.02068	0.79	0.005	0.00	0.23308	0.21	-0.011	0.00	0.00777	1.05	-0.004	0.00	0.27304	0.18	0.000	0.00	0.97770	0.00	
S7 PRS		0.027 0.01 0.00005 2.42	-0.016	0.01	0.02004	0.82	0.023 0.01 0.00057 1.77	0.006	0.01	0.33579	0.14	-0.002	0.01	0.78815	0.01							
S7 sexPRS		-0.012	0.00	0.00407	1.21	0.005	0.00	0.27058	0.18	-0.011	0.00	0.00482	1.18	-0.002	0.00	0.53255	0.06	0.000	0.00	0.98364	0.00	
S8 PRS		0.027 0.01 0.00005 2.45	-0.015	0.01	0.02205	0.80	0.022	0.01	0.00074	1.71	0.006	0.01	0.33593	0.14	-0.000	0.01	0.95989	0.00				
S8 sexPRS		-0.012	0.00	0.00404	1.22	0.004	0.00	0.29952	0.16	-0.011	0.00	0.00553	1.15	-0.002	0.00	0.52988	0.06	-0.001	0.00	0.90204	0.00	
DSM-IV antisocial personality disorder	S1	PRS	0.005	0.01	0.31935	0.14	-0.009	0.01	0.08088	0.44	0.005	0.01	0.32430	0.14	-0.007	0.01	0.19770	0.24	-0.008	0.01	0.12620	0.34
S1 sexPRS		-0.001	0.00	0.68680	0.02	0.005	0.00	0.13369	0.32	-0.002	0.00	0.53688	0.06	0.004	0.00	0.27093	0.18	0.005	0.00	0.17869	0.26	
S2 PRS		0.009	0.01	0.08933	0.42	-0.004	0.01	0.45059	0.08	0.006	0.01	0.30310	0.15	-0.007	0.01	0.20429	0.24	-0.003	0.01	0.60479	0.04	
S2 sexPRS		-0.003	0.00	0.36327	0.12	0.002	0.00	0.58623	0.04	-0.002	0.00	0.61719	0.04	0.004	0.00	0.29110	0.16	0.002	0.00	0.49872	0.06	
S3 PRS		0.011	0.01	0.05093	0.55	-0.014	0.01	0.01167	0.93	0.015	0.01	0.00779	1.02	0.004	0.01	0.46149	0.08	-0.004	0.01	0.41437	0.10	
S3 sexPRS		-0.004	0.00	0.24055	0.20	0.006	0.00	0.07743	0.46	-0.007	0.00	0.04504	0.58	-0.001	0.00	0.66436	0.03	0.003	0.00	0.41321	0.10	
S4 PRS		0.008	0.01	0.14240	0.31	-0.017	0.01	0.00158	1.47	0.015	0.01	0.00528	1.12	0.013	0.01	0.01567	0.86	-0.002	0.01	0.76116	0.01	
S4 sexPRS		-0.002	0.00	0.50849	0.06	0.007	0.00	0.03911	0.62	-0.007	0.00	0.02616	0.71	-0.006	0.00	0.08295	0.44	0.001	0.00	0.73415	0.02	
S5 PRS		0.012	0.01	0.03173	0.67	-0.018	0.01	0.00113	1.55	0.015	0.01	0.00751	1.03	0.011	0.01	0.03094	0.68	0.002	0.01	0.69473	0.02	
S5 sexPRS		-0.004	0.00	0.18053	0.26	0.007	0.00	0.03557	0.65	-0.007	0.00	0.03160	0.67	-0.005	0.00	0.15263	0.29	-0.001	0.00	0.81864	0.01	
S6 PRS		0.011	0.01	0.04451	0.58	-0.016	0.01	0.00329	1.27	0.011	0.01	0.03850	0.62	0.011	0.01	0.04619	0.58	0.005	0.01	0.34578	0.13	
S6 sexPRS		-0.004	0.00	0.23582	0.20	0.006	0.00	0.05739	0.53	-0.005	0.00	0.10715	0.38	-0.004	0.00	0.17691	0.26	-0.002	0.00	0.52821	0.06	
S7 PRS		0.014	0.01	0.01066	0.94	-0.017	0.01	0.00199	1.41	0.013	0.01	0.01784	0.81	0.009	0.01	0.07942	0.45	0.010	0.01	0.08032	0.45	
S7 sexPRS		-0.005	0.00	0.11433	0.36	0.007	0.00	0.05148	0.56	-0.007	0.00	0.04797	0.57	-0.003	0.00	0.28544	0.17	-0.005	0.00	0.15947	0.29	

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.
 PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW			
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
	S8	PRS	0.015	0.01	0.00606	1.09	-0.017	0.01	0.00180	1.44	0.013	0.01	0.01702	0.83	0.009	0.01	0.09995	0.40
	S8 sexPRS		-0.006	0.00	0.08193	0.44	0.007	0.00	0.04730	0.58	-0.007	0.00	0.04389	0.59	-0.003	0.00	0.32200	0.14
DSM-IV major depressive disorder	S1	PRS	-0.004	0.02	0.83915	0.01	0.007	0.02	0.68379	0.02	0.020	0.02	0.24901	0.19	-0.029	0.02	0.10041	0.39
	S1 sexPRS		0.008	0.01	0.43815	0.09	0.001	0.01	0.91408	0.00	-0.005	0.01	0.66984	0.03	0.021	0.01	0.05273	0.54
	S2	PRS	-0.009	0.02	0.60891	0.04	0.016	0.02	0.35126	0.12	0.025	0.02	0.15109	0.30	-0.028	0.02	0.11291	0.36
	S2 sexPRS		0.007	0.01	0.49794	0.07	-0.002	0.01	0.84083	0.01	-0.007	0.01	0.49563	0.07	0.018	0.01	0.08729	0.42
	S3	PRS	0.006	0.02	0.74828	0.01	-0.024	0.02	0.17251	0.27	0.021	0.02	0.23565	0.20	-0.031	0.02	0.07813	0.45
	S3 sexPRS		0.003	0.01	0.80679	0.01	0.014	0.01	0.17779	0.26	-0.006	0.01	0.59178	0.04	0.019	0.01	0.08311	0.43
	S4	PRS	0.012	0.02	0.50068	0.06	-0.021	0.02	0.22150	0.22	0.029	0.02	0.08901	0.41	0.003	0.02	0.88396	0.00
	S4 sexPRS		0.001	0.01	0.88935	0.00	0.009	0.01	0.39586	0.10	-0.013	0.01	0.22723	0.21	-0.004	0.01	0.72648	0.02
	S5	PRS	0.005	0.02	0.76799	0.01	-0.028	0.02	0.10789	0.38	0.041	0.02	0.01772	0.81	-0.004	0.02	0.82216	0.01
	S5 sexPRS		0.006	0.01	0.60000	0.04	0.014	0.01	0.20413	0.23	-0.016	0.01	0.13356	0.32	0.004	0.01	0.66626	0.03
	S6	PRS	-0.003	0.02	0.87358	0.00	-0.027	0.02	0.12617	0.34	0.033	0.02	0.05272	0.54	-0.003	0.02	0.87507	0.00
	S6 sexPRS		0.010	0.01	0.32856	0.14	0.013	0.01	0.20922	0.23	-0.013	0.01	0.22576	0.21	0.005	0.01	0.63089	0.03
	S7	PRS	-0.004	0.02	0.80775	0.01	-0.023	0.02	0.18941	0.25	0.031	0.02	0.07187	0.47	-0.005	0.02	0.76737	0.01
	S7 sexPRS		0.013	0.01	0.21749	0.22	0.010	0.01	0.35749	0.12	-0.012	0.01	0.25875	0.18	0.006	0.01	0.53956	0.05
	S8	PRS	-0.003	0.02	0.86304	0.00	-0.017	0.02	0.33987	0.13	0.034	0.02	0.04936	0.56	-0.007	0.02	0.69575	0.02
	S8 sexPRS		0.012	0.01	0.24847	0.19	0.007	0.01	0.51411	0.06	-0.014	0.01	0.18964	0.25	0.007	0.01	0.50011	0.07
DSM-IV panic disorder	S1	PRS	-0.013	0.01	0.09118	0.42	-0.007	0.01	0.39481	0.11	0.008	0.01	0.32881	0.14	-0.004	0.01	0.63342	0.03
	S1 sexPRS		0.011	0.00	0.02992	0.70	0.006	0.00	0.23232	0.21	-0.004	0.00	0.37561	0.12	0.003	0.00	0.56034	0.05
	S2	PRS	-0.005	0.01	0.53468	0.06	0.013	0.01	0.09561	0.41	0.004	0.01	0.62871	0.03	-0.001	0.01	0.94460	0.00
	S2 sexPRS		0.007	0.00	0.17696	0.27	-0.008	0.00	0.10728	0.38	-0.002	0.00	0.70560	0.02	0.001	0.00	0.82497	0.01
															0.003	0.00	0.59415	0.04

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.

PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW								
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²					
S3	PRS	-0.008	0.01	0.28828	0.16	-0.000	0.01	0.98213	0.00	0.002	0.01	0.78170	0.01	0.009	0.01	0.27520	0.18	0.002	0.01	0.76982	0.01		
S3	sexPRS	0.009	0.00	0.07177	0.47	-0.001	0.00	0.85954	0.00	0.001	0.00	0.82645	0.01	-0.004	0.00	0.41739	0.10	-0.000	0.00	0.99369	0.00		
S4	PRS	-0.002	0.01	0.80587	0.01	-0.007	0.01	0.38105	0.12	0.009	0.01	0.27331	0.18	0.009	0.01	0.24452	0.20	0.005	0.01	0.51678	0.06		
S4	sexPRS	0.005	0.00	0.33087	0.14	0.004	0.00	0.43606	0.09	-0.002	0.00	0.64567	0.03	-0.003	0.00	0.56315	0.05	-0.004	0.00	0.41128	0.10		
S5	PRS	-0.001	0.01	0.85628	0.00	-0.000	0.01	0.98555	0.00	0.002	0.01	0.80493	0.01	0.004	0.01	0.61751	0.04	0.004	0.01	0.65046	0.03		
S5	sexPRS	0.004	0.00	0.38541	0.11	-0.001	0.00	0.81780	0.01	0.003	0.00	0.60333	0.04	0.002	0.00	0.72321	0.02	-0.001	0.00	0.81911	0.01		
S6	PRS	-0.002	0.01	0.82368	0.01	-0.004	0.01	0.60752	0.04	0.002	0.01	0.84624	0.01	0.001	0.01	0.86434	0.00	0.002	0.01	0.78610	0.01		
S6	sexPRS	0.005	0.00	0.33245	0.14	0.001	0.00	0.84175	0.01	0.002	0.00	0.67086	0.03	0.003	0.00	0.49561	0.07	-0.000	0.00	0.94475	0.00		
S7	PRS	-0.005	0.01	0.54731	0.05	-0.007	0.01	0.38167	0.12	-0.002	0.01	0.75362	0.01	-0.001	0.01	0.92759	0.00	-0.001	0.01	0.86352	0.00		
S7	sexPRS	0.007	0.00	0.13394	0.33	0.002	0.00	0.74378	0.02	0.004	0.00	0.36425	0.12	0.004	0.00	0.38710	0.11	0.002	0.00	0.72033	0.02		
S8	PRS	-0.005	0.01	0.54152	0.05	-0.008	0.01	0.31903	0.15	-0.003	0.01	0.70217	0.02	-0.002	0.01	0.81628	0.01	-0.000	0.01	0.97750	0.00		
S8	sexPRS	0.007	0.00	0.13359	0.33	0.002	0.00	0.62102	0.04	0.005	0.00	0.33740	0.14	0.005	0.00	0.30576	0.15	0.001	0.00	0.85070	0.01		
DSM-IV social anxiety disorder	S1	PRS	-0.014	0.01	0.33970	0.13	-0.015	0.01	0.29501	0.16	0.007	0.02	0.65796	0.03	-0.010	0.02	0.52370	0.06	-0.007	0.01	0.63897	0.03	
		S1 sexPRS	0.017	0.01	0.06904	0.49	0.010	0.01	0.28930	0.16	-0.003	0.01	0.72293	0.02	0.004	0.01	0.65002	0.03	0.003	0.01	0.70395	0.02	
		S2	PRS	-0.018	0.01	0.21756	0.22	0.011	0.01	0.48120	0.07	0.002	0.01	0.88550	0.00	-0.012	0.02	0.42557	0.10	-0.008	0.01	0.58780	0.04
		S2	sexPRS	0.017	0.01	0.06591	0.49	-0.004	0.01	0.67626	0.03	-0.001	0.01	0.95082	0.00	0.005	0.01	0.62025	0.04	0.004	0.01	0.62636	0.03
		S3	PRS	-0.018	0.01	0.21939	0.22	0.013	0.02	0.38104	0.11	-0.005	0.01	0.71574	0.02	-0.019	0.01	0.21270	0.23	0.005	0.01	0.74688	0.02
		S3	sexPRS	0.020	0.01	0.03205	0.67	-0.008	0.01	0.38285	0.11	0.005	0.01	0.55391	0.05	0.015	0.01	0.10373	0.39	-0.002	0.01	0.83035	0.01
		S4	PRS	-0.019	0.01	0.18814	0.25	0.024	0.01	0.11480	0.37	0.008	0.01	0.58377	0.04	-0.016	0.01	0.27570	0.18	0.008	0.01	0.59121	0.04
		S4	sexPRS	0.019	0.01	0.03367	0.65	-0.016	0.01	0.08213	0.45	-0.001	0.01	0.90311	0.00	0.012	0.01	0.19510	0.25	-0.006	0.01	0.51988	0.06
		S5	PRS	-0.022	0.01	0.13357	0.33	0.009	0.01	0.55946	0.05	0.012	0.01	0.42180	0.10	-0.020	0.01	0.16944	0.28	0.002	0.01	0.91180	0.00
		S5	sexPRS	0.021	0.01	0.02358	0.75	-0.007	0.01	0.41688	0.10	-0.001	0.01	0.92819	0.00	0.015	0.01	0.09990	0.40	-0.001	0.01	0.94642	0.00
		S6	PRS	-0.023	0.01	0.12538	0.35	0.008	0.01	0.59182	0.04	0.010	0.01	0.51261	0.06	-0.023	0.01	0.11750	0.37	-0.002	0.01	0.89445	0.00
		S6	sexPRS	0.020	0.01	0.02871	0.70	-0.006	0.01	0.52095	0.06	-0.000	0.01	0.97368	0.00	0.015	0.01	0.08435	0.44	0.003	0.01	0.75225	0.01
		S7	PRS	-0.016	0.01	0.28645	0.17	0.007	0.01	0.64677	0.03	0.007	0.01	0.63780	0.03	-0.020	0.01	0.17527	0.28	-0.004	0.02	0.80595	0.01
		S7	sexPRS	0.017	0.01	0.05357	0.55	-0.008	0.01	0.38642	0.11	0.001	0.01	0.88392	0.00	0.014	0.01	0.10576	0.39	0.001	0.01	0.90008	0.00

Table S4-2. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores (PRS in Predictor column) and the interaction between sex and PRS (sexPRS in Predictor column) on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders.
 PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Effect	SI			AI			CPD			SC			DPW			
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
	S8	PRS	-0.015	0.01	0.29318	0.16	0.009	0.01	0.53667	0.06	0.007	0.01	0.61251	0.04	-0.019	0.01	0.19027	0.26
	S8	sexPRS	0.018	0.01	0.04885	0.57	-0.009	0.01	0.33233	0.14	0.001	0.01	0.89316	0.00	0.013	0.01	0.12861	0.34
Mania screen	S1	PRS	-0.003	0.00	0.51252	0.08	-0.004	0.00	0.39567	0.13	0.005	0.00	0.26271	0.24	0.002	0.00	0.68155	0.03
	S1	sexPRS	0.002	0.00	0.51353	0.08	0.003	0.00	0.27916	0.22	-0.002	0.00	0.40393	0.13	-0.003	0.00	0.35903	0.16
	S2	PRS	0.001	0.00	0.90721	0.00	-0.001	0.00	0.86701	0.01	0.001	0.00	0.77240	0.02	-0.001	0.00	0.90805	0.00
	S2	sexPRS	-0.000	0.00	0.92806	0.00	-0.000	0.00	0.92712	0.00	-0.000	0.00	0.97592	0.00	-0.001	0.00	0.63364	0.04
	S3	PRS	0.003	0.00	0.43324	0.11	-0.001	0.00	0.88969	0.00	-0.002	0.00	0.59767	0.05	-0.003	0.00	0.53901	0.07
	S3	sexPRS	-0.001	0.00	0.68646	0.03	0.000	0.00	0.88486	0.00	0.001	0.00	0.59626	0.05	0.001	0.00	0.83704	0.01
	S4	PRS	0.006	0.00	0.13896	0.41	0.000	0.00	0.98442	0.00	0.001	0.00	0.86712	0.01	-0.001	0.00	0.78884	0.01
	S4	sexPRS	-0.003	0.00	0.28950	0.21	-0.001	0.00	0.81488	0.01	0.001	0.00	0.73676	0.02	-0.000	0.00	0.95216	0.00
	S5	PRS	0.009	0.00	0.03656	0.83	0.000	0.00	0.95688	0.00	-0.000	0.00	0.96119	0.00	0.000	0.00	0.91630	0.00
	S5	sexPRS	-0.005	0.00	0.07388	0.60	-0.000	0.00	0.88019	0.00	0.001	0.00	0.63437	0.04	-0.000	0.00	0.85516	0.01
	S6	PRS	0.010	0.00	0.01946	1.03	-0.002	0.00	0.65739	0.04	0.001	0.00	0.87520	0.00	0.001	0.00	0.77351	0.02
	S6	sexPRS	-0.006	0.00	0.03454	0.84	0.001	0.00	0.70734	0.03	0.001	0.00	0.84867	0.01	-0.001	0.00	0.76829	0.02
	S7	PRS	0.010	0.00	0.02386	0.96	-0.002	0.00	0.67496	0.03	0.001	0.00	0.85260	0.01	-0.000	0.00	0.96118	0.00
	S7	sexPRS	-0.006	0.00	0.03742	0.81	-0.000	0.00	0.98277	0.00	0.000	0.00	0.95091	0.00	-0.000	0.00	0.94231	0.00
	S8	PRS	0.011	0.00	0.01250	1.17	-0.001	0.00	0.75633	0.02	0.000	0.00	0.91579	0.00	-0.000	0.00	0.98777	0.00
	S8	sexPRS	-0.006	0.00	0.01971	1.02	-0.000	0.00	0.92365	0.00	0.000	0.00	0.90158	0.00	-0.000	0.00	0.90145	0.00

Table S4-3. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5). Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3, T4 and T5 are 3.657103e-03, 7.142857e-04, and 8.333333e-05 respectively.

Target phenotype	Sex	SI					AI					CPD					SC					DPW				
		T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
Smoking initiation	F+M	8	8	8	8	8	8	6	6	6	6	8	2	0	0	0	8	0	0	0	0	8	7	6	5	0
	F	8	8	8	8	7	8	7	6	5	2	8	0	0	0	0	8	0	0	0	0	8	7	0	0	0
	M	8	8	7	7	7	8	6	5	4	4	8	5	0	0	0	8	0	0	0	0	8	5	3	1	0
Age at starting regular smoking	F+M	8	6	0	0	0	8	4	0	0	0	8	0	0	0	0	8	0	0	0	0	8	3	0	0	0
	F	8	1	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	2	0	0	0
	M	8	1	0	0	0	8	1	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0
Cigarettes per day	F+M	8	7	7	6	3	8	5	3	0	0	8	8	8	8	6	8	1	0	0	0	8	0	0	0	0
	F	8	7	6	6	2	8	6	4	1	0	8	8	8	6	5	8	3	0	0	0	8	0	0	0	0
	M	8	4	0	0	0	8	1	0	0	0	8	7	6	3	0	8	0	0	0	0	8	0	0	0	0
Smoking cessation	F+M	8	7	5	2	1	8	0	0	0	0	8	4	0	0	0	8	2	0	0	0	8	0	0	0	0
	F	8	7	1	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	3	1	1	0	8	0	0	0	0	8	4	0	0	0	8	2	0	0	0	8	0	0	0	0
Drinking initiation	F+M	8	4	0	0	0	8	2	0	0	0	8	4	0	0	0	8	0	0	0	0	8	7	6	6	6
	F	8	0	0	0	0	8	1	0	0	0	8	6	2	0	0	8	6	0	0	0	8	7	6	6	1
	M	8	3	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	6	3	3	0
Drinks per week	F+M	8	8	7	7	7	8	8	3	1	0	8	0	0	0	0	8	1	0	0	0	8	8	8	8	7
	F	8	6	0	0	0	8	2	0	0	0	8	0	0	0	0	8	0	0	0	0	8	8	8	7	7
	M	8	8	8	7	3	8	7	1	1	0	8	0	0	0	0	8	0	0	0	0	8	8	7	7	6
DSM-IV alcohol dependence	F+M	8	8	8	8	6	8	5	3	0	0	8	0	0	0	0	8	0	0	0	0	8	8	8	8	8
	F	8	8	8	8	6	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	8	8	8	8
	M	8	6	3	0	0	8	4	3	0	0	8	0	0	0	0	8	0	0	0	0	8	8	6	6	2

Table S4-3. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5). Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3, T4 and T5 are $3.657103e-03$, $7.142857e-04$, and $8.333333e-05$ respectively.

Target phenotype	Sex	SI					AI					CPD					SC					DPW				
		T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
DSM-IV nicotine dependence	F+M	8	8	8	8	8	8	6	6	5	5	8	8	7	6	5	8	7	2	0	0	8	2	0	0	0
	F	8	8	8	8	8	8	7	5	4	4	8	8	6	3	1	8	4	0	0	0	8	0	0	0	0
	M	8	8	8	8	7	8	6	3	2	0	8	8	5	5	4	8	5	2	1	0	8	4	3	0	0
FTND-based nicotine dependence	F+M	8	8	8	8	8	8	7	6	5	5	8	8	8	8	8	8	8	7	6	8	2	0	0	0	
	F	8	8	7	7	7	8	5	5	4	3	8	8	8	8	8	8	5	4	2	1	8	0	0	0	0
	M	8	8	8	8	7	8	7	6	5	5	8	8	8	8	7	8	8	6	4	3	8	0	0	0	0
DSM-IV conduct disorder	F+M	8	8	5	5	3	8	6	5	5	1	8	4	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	6	0	0	0	8	5	1	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	6	5	3	0	8	6	1	0	0	8	6	0	0	0	8	0	0	0	0	8	0	0	0	0
DSM-IV antisocial personality disorder	F+M	8	7	2	1	0	8	6	5	5	1	8	3	0	0	0	8	5	0	0	0	8	0	0	0	0
	F	8	8	0	0	0	8	5	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	4	0	0	0	8	6	5	0	0	8	3	0	0	0	8	2	0	0	0	8	0	0	0	0
DSM-IV major depressive disorder	F+M	8	5	0	0	0	8	1	0	0	0	8	7	1	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	4	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	0	0	0	0	8	8	2	1	0	8	0	0	0	0	8	0	0	0	0
DSM-IV panic disorder	F+M	8	7	0	0	0	8	0	0	0	0	8	2	0	0	0	8	4	0	0	0	8	0	0	0	0
	F	8	7	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	0	0	0	0	8	0	0	0	0	8	1	0	0	0	8	2	0	0	0	8	0	0	0	0
DSM-IV social anxiety disorder	F+M	8	6	0	0	0	8	0	0	0	0	8	1	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	8	3	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0

Table S4-3. Number of phenotype-PRS associations with observed p values lower than various significance thresholds (T1- T5). Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS for SI (smoking initiation), AI (age of initiation of regular smoking), CPD (number of cigarettes per day), SC (smoking cessation) and DPW (drinks per week). The significance threshold was (1) $p < 1$ (T1), (2) nominal $p < 0.05$ (T2), (3) $p < T3$ with the adjustment for number of independent target phenotypes, (4) $p < T4$ with the adjustment for number of both independent target phenotypes and discovery traits, and (5) $p < T5$ with the adjustment by Bonferroni procedure. T3, T4 and T5 are $3.657103e-03$, $7.142857e-04$, and $8.333333e-05$ respectively.

Target phenotype	Sex	SI					AI					CPD					SC					DPW				
		T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5	T1	T2	T3	T4	T5
	M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
Mania screen	F+M	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	F	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0
	M	8	4	0	0	0	8	0	0	0	0	8	0	0	0	0	8	0	0	0	0	8	4	3	0	0
Number target phenotypes predicted	F+M	15	14	9	9	8	15	11	8	6	5	15	11	4	3	3	15	7	2	1	1	15	7	4	4	3
	F	15	13	7	5	5	15	10	5	4	3	15	4	4	3	3	15	4	1	1	1	15	5	3	3	3
	M	15	12	7	6	4	15	9	7	4	2	15	9	4	4	2	15	6	2	1	15	6	6	4	2	

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Sex	SI			AI			CPD			SC			DPW			
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
Smoking initiation	S1	F+M	0.026	0.01	<0.00004	0.27	-0.009	0.01	0.13554	0.04	0.000	0.01	0.96961	0.00	0.003	0.01	0.66828	0.00
	S1	F	0.030	0.01	<0.00021	0.38	-0.016	0.01	0.05160	0.11	-0.001	0.01	0.88210	0.00	0.000	0.01	0.95702	0.00
	S1	M	0.023	0.01	0.01045	0.21	-0.004	0.01	0.66816	0.01	0.001	0.01	0.94865	0.00	0.009	0.01	0.31827	0.03
	S2	F+M	0.054	0.01	<0.00001	1.19	-0.012	0.01	0.06671	0.05	0.003	0.01	0.64634	0.00	0.005	0.01	0.39236	0.01
	S2	F	0.057	0.01	<0.00001	1.35	-0.020	0.01	0.01383	0.17	0.002	0.01	0.76841	0.00	0.002	0.01	0.84031	0.00
	S2	M	0.053	0.01	<0.00001	1.17	0.000	0.01	0.98119	0.00	0.002	0.01	0.84502	0.00	0.011	0.01	0.21030	0.05
	S3	F+M	0.078	0.01	<0.00001	2.45	-0.026	0.01	<0.00003	0.27	0.008	0.01	0.18642	0.03	0.009	0.01	0.14374	0.04
	S3	F	0.078	0.01	<0.00001	2.50	-0.029	0.01	<0.00039	0.34	0.005	0.01	0.56391	0.01	0.011	0.01	0.17921	0.05
	S3	M	0.079	0.01	<0.00001	2.57	-0.021	0.01	0.01778	0.18	0.009	0.01	0.32536	0.03	0.007	0.01	0.47581	0.02
	S4	F+M	0.082	0.01	<0.00001	2.81	-0.027	0.01	<0.00002	0.29	0.015	0.01	0.01790	0.09	0.010	0.01	0.12765	0.04
	S4	F	0.082	0.01	<0.00001	2.79	-0.025	0.01	0.00239	0.25	0.007	0.01	0.39451	0.02	0.011	0.01	0.19929	0.05
	S4	M	0.083	0.01	<0.00001	2.87	-0.028	0.01	0.00163	0.32	0.025	0.01	0.00617	0.25	0.011	0.01	0.23775	0.05
	S5	F+M	0.089	0.01	<0.00001	3.27	-0.033	0.01	<0.00001	0.44	0.013	0.01	0.03794	0.07	0.001	0.01	0.92750	0.00
	S5	F	0.085	0.01	<0.00001	2.97	-0.029	0.01	<0.00049	0.34	0.006	0.01	0.49831	0.01	-0.004	0.01	0.63333	0.01
	S5	M	0.094	0.01	<0.00001	3.60	-0.041	0.01	<0.00001	0.71	0.022	0.01	0.01133	0.21	0.010	0.01	0.31892	0.04
	S6	F+M	0.091	0.01	<0.00001	3.35	-0.035	0.01	<0.00001	0.50	0.012	0.01	0.06466	0.06	0.005	0.01	0.44759	0.01
	S6	F	0.085	0.01	<0.00001	2.94	-0.032	0.01	<0.00011	0.42	0.002	0.01	0.77864	0.00	0.002	0.01	0.84531	0.00
	S6	M	0.095	0.01	<0.00001	3.69	-0.043	0.01	<0.00001	0.79	0.024	0.01	0.00763	0.23	0.012	0.01	0.22976	0.06
	S7	F+M	0.085	0.01	<0.00001	2.96	-0.038	0.01	<0.00001	0.59	0.012	0.01	0.05905	0.06	0.010	0.01	0.17958	0.04
	S7	F	0.080	0.01	<0.00001	2.64	-0.038	0.01	<0.00001	0.60	0.002	0.01	0.81969	0.00	0.006	0.01	0.53091	0.01
	S7	M	0.090	0.01	<0.00001	3.29	-0.043	0.01	<0.00001	0.77	0.025	0.01	0.00529	0.26	0.016	0.01	0.11324	0.11
	S8	F+M	0.084	0.01	<0.00001	2.88	-0.038	0.01	<0.00001	0.60	0.012	0.01	0.05726	0.06	0.008	0.01	0.24763	0.03
	S8	F	0.079	0.01	<0.00001	2.54	-0.038	0.01	<0.00001	0.62	0.002	0.01	0.85354	0.00	0.005	0.01	0.61759	0.01
	S8	M	0.089	0.01	<0.00001	3.23	-0.042	0.01	<0.00001	0.75	0.026	0.01	0.00376	0.29	0.015	0.01	0.13239	0.10

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI					AI					CPD					SC					DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²				
Age at starting regular smoking	S1	F+M	-0.061	0.08	0.43783	0.03	0.183	0.08	0.02102	0.25	-0.025	0.08	0.75089	0.00	0.071	0.08	0.35818	0.04	-0.048	0.08	0.54487	0.02				
	S1	F	-0.150	0.10	0.14991	0.17	0.209	0.11	0.04722	0.32	-0.008	0.10	0.93543	0.00	-0.009	0.10	0.92785	0.00	-0.035	0.10	0.73317	0.01				
	S1	M	0.056	0.12	0.62724	0.02	0.172	0.12	0.14540	0.22	-0.082	0.12	0.49566	0.05	0.163	0.12	0.15831	0.20	-0.002	0.12	0.98573	0.00				
	S2	F+M	-0.159	0.08	0.04729	0.19	0.144	0.08	0.06838	0.15	-0.056	0.08	0.47693	0.02	0.113	0.08	0.14643	0.10	-0.173	0.08	0.02907	0.23				
	S2	F	-0.184	0.11	0.08064	0.25	0.163	0.11	0.12165	0.19	-0.067	0.10	0.51577	0.03	0.036	0.10	0.72862	0.01	-0.150	0.10	0.15088	0.17				
	S2	M	-0.151	0.12	0.20526	0.17	0.158	0.12	0.17891	0.18	-0.054	0.12	0.64645	0.02	0.234	0.12	0.04970	0.41	-0.153	0.12	0.20265	0.18				
	S3	F+M	-0.139	0.08	0.08321	0.14	0.029	0.08	0.71135	0.01	0.038	0.08	0.63161	0.01	0.068	0.08	0.40873	0.03	-0.181	0.08	0.02158	0.25				
	S3	F	-0.158	0.11	0.13575	0.19	0.042	0.10	0.68907	0.01	0.049	0.10	0.63627	0.02	0.069	0.11	0.52342	0.04	-0.255	0.10	0.01249	0.49				
	S3	M	-0.102	0.12	0.39988	0.08	0.001	0.12	0.99404	0.00	0.021	0.12	0.85353	0.00	0.107	0.12	0.39188	0.09	-0.045	0.12	0.70963	0.02				
	S4	F+M	-0.177	0.08	0.02805	0.24	0.153	0.08	0.04864	0.18	0.009	0.08	0.90482	0.00	0.025	0.08	0.75729	0.00	-0.111	0.08	0.15602	0.09				
	S4	F	-0.214	0.11	0.04677	0.34	0.064	0.10	0.52818	0.03	0.104	0.11	0.32649	0.08	0.048	0.11	0.65495	0.02	-0.113	0.10	0.26361	0.09				
	S4	M	-0.136	0.12	0.25357	0.14	0.282	0.12	0.01604	0.60	-0.100	0.12	0.39615	0.07	0.013	0.12	0.91776	0.00	-0.127	0.12	0.29360	0.12				
	S5	F+M	-0.214	0.08	0.00823	0.34	0.184	0.08	0.02314	0.25	0.074	0.08	0.35368	0.04	-0.097	0.08	0.24228	0.07	-0.148	0.08	0.06155	0.16				
	S5	F	-0.176	0.11	0.09991	0.23	0.153	0.11	0.14857	0.17	0.165	0.11	0.11683	0.20	-0.049	0.11	0.65746	0.02	-0.113	0.10	0.26817	0.10				
	S5	M	-0.272	0.12	0.02450	0.55	0.206	0.12	0.09320	0.32	-0.023	0.12	0.84852	0.00	-0.132	0.12	0.27524	0.14	-0.229	0.12	0.06371	0.39				
	S6	F+M	-0.168	0.08	0.03705	0.21	0.192	0.08	0.01791	0.28	0.044	0.08	0.57931	0.01	-0.082	0.08	0.33010	0.05	-0.170	0.08	0.03031	0.21				
	S6	F	-0.149	0.11	0.16362	0.16	0.215	0.11	0.04273	0.35	0.099	0.10	0.33698	0.07	-0.026	0.11	0.81807	0.01	-0.203	0.10	0.04391	0.30				
	S6	M	-0.201	0.12	0.09410	0.30	0.161	0.12	0.19108	0.20	-0.006	0.12	0.95819	0.00	-0.132	0.12	0.28856	0.14	-0.139	0.12	0.25860	0.14				
	S7	F+M	-0.175	0.08	0.03012	0.23	0.145	0.08	0.07743	0.16	0.030	0.08	0.70348	0.01	-0.051	0.08	0.54096	0.02	-0.099	0.08	0.21406	0.07				
	S7	F	-0.163	0.11	0.12436	0.20	0.156	0.11	0.14981	0.18	0.057	0.10	0.58284	0.02	0.019	0.11	0.86471	0.00	-0.133	0.10	0.18980	0.13				
	S7	M	-0.196	0.12	0.10481	0.28	0.128	0.12	0.29644	0.12	0.007	0.12	0.95522	0.00	-0.129	0.12	0.29826	0.13	-0.075	0.13	0.55441	0.04				
	S8	F+M	-0.169	0.08	0.03644	0.21	0.123	0.08	0.13301	0.11	0.040	0.08	0.61561	0.01	-0.049	0.08	0.56146	0.02	-0.094	0.08	0.23758	0.06				
	S8	F	-0.153	0.11	0.14974	0.17	0.141	0.11	0.19189	0.15	0.064	0.10	0.53964	0.03	0.025	0.11	0.82296	0.00	-0.131	0.10	0.19555	0.13				
	S8	M	-0.194	0.12	0.10890	0.28	0.102	0.12	0.40516	0.08	0.017	0.12	0.89115	0.00	-0.127	0.12	0.30374	0.13	-0.063	0.13	0.61666	0.03				

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI				AI				CPD				SC				DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
Cigarettes per day	S1	F+M	0.043	0.02	0.07710	0.16	-0.006	0.02	0.81879	0.00	0.084	0.02	0.00068	0.60	0.029	0.02	0.22519	0.07	0.005	0.02	0.85094	0.00
	S1	F	0.023	0.03	0.45801	0.05	0.045	0.03	0.15712	0.17	0.095	0.03	0.00215	0.77	0.020	0.03	0.52098	0.03	-0.020	0.03	0.51922	0.03
	S1	M	0.079	0.04	0.03750	0.54	-0.095	0.04	0.01440	0.77	0.061	0.04	0.12161	0.32	0.039	0.04	0.29504	0.13	0.028	0.04	0.46987	0.07
	S2	F+M	0.077	0.02	0.00189	0.52	-0.018	0.02	0.47827	0.03	0.093	0.02	0.00017	0.74	0.034	0.02	0.16785	0.10	0.022	0.02	0.37654	0.04
	S2	F	0.081	0.03	0.01025	0.57	0.000	0.03	0.98824	0.00	0.103	0.03	0.00092	0.91	0.025	0.03	0.42388	0.05	-0.010	0.03	0.74578	0.01
	S2	M	0.082	0.04	0.03583	0.57	-0.043	0.04	0.27056	0.15	0.077	0.04	0.04724	0.51	0.042	0.04	0.28063	0.15	0.056	0.04	0.14795	0.28
	S3	F+M	0.110	0.02	0.00001	1.03	-0.042	0.02	0.08442	0.16	0.115	0.02	<0.0001	1.14	0.043	0.03	0.09489	0.16	0.003	0.02	0.90087	0.00
	S3	F	0.140	0.03	<0.0001	1.69	-0.079	0.03	0.01098	0.54	0.113	0.03	0.00031	1.09	0.047	0.03	0.14569	0.19	-0.016	0.03	0.60217	0.02
	S3	M	0.053	0.04	0.18468	0.24	0.005	0.04	0.89007	0.00	0.116	0.04	0.00245	1.15	0.021	0.04	0.60086	0.04	0.019	0.04	0.62607	0.03
	S4	F+M	0.092	0.02	0.00024	0.73	-0.065	0.02	0.00759	0.37	0.132	0.02	<0.0001	1.49	0.039	0.03	0.12732	0.14	0.009	0.02	0.69762	0.01
	S4	F	0.113	0.03	0.00038	1.11	-0.084	0.03	0.00620	0.61	0.133	0.03	0.00003	1.51	0.068	0.03	0.03420	0.41	-0.019	0.03	0.52670	0.03
	S4	M	0.053	0.04	0.17197	0.24	-0.047	0.04	0.22531	0.19	0.134	0.04	0.00052	1.53	-0.017	0.04	0.67031	0.03	0.040	0.04	0.31775	0.14
	S5	F+M	0.119	0.03	<0.0001	1.20	-0.073	0.03	0.00372	0.46	0.151	0.02	<0.0001	1.97	0.046	0.03	0.07917	0.19	0.010	0.02	0.67073	0.01
	S5	F	0.139	0.03	0.00001	1.65	-0.100	0.03	0.00152	0.86	0.147	0.03	<0.0001	1.87	0.079	0.03	0.01726	0.56	-0.013	0.03	0.66083	0.02
	S5	M	0.085	0.04	0.03066	0.62	-0.043	0.04	0.27933	0.16	0.151	0.04	0.00013	1.95	-0.016	0.04	0.68281	0.02	0.043	0.04	0.29277	0.16
	S6	F+M	0.103	0.02	0.00004	0.90	-0.079	0.03	0.00185	0.54	0.150	0.02	<0.0001	1.93	0.054	0.03	0.04239	0.26	-0.000	0.02	0.99802	0.00
	S6	F	0.115	0.03	0.00030	1.13	-0.113	0.03	0.00039	1.11	0.145	0.03	<0.0001	1.81	0.083	0.03	0.01258	0.63	-0.029	0.03	0.33690	0.07
	S6	M	0.083	0.04	0.03497	0.59	-0.039	0.04	0.33847	0.13	0.146	0.04	0.00022	1.84	-0.005	0.04	0.90957	0.00	0.039	0.04	0.33248	0.13
	S7	F+M	0.096	0.03	0.00013	0.79	-0.081	0.03	0.00153	0.57	0.131	0.02	<0.0001	1.48	0.040	0.03	0.13369	0.15	-0.006	0.02	0.81478	0.00
	S7	F	0.112	0.03	0.00040	1.08	-0.102	0.03	0.00161	0.91	0.126	0.03	0.00006	1.38	0.065	0.03	0.05090	0.38	-0.040	0.03	0.19005	0.14
	S7	M	0.069	0.04	0.07786	0.41	-0.064	0.04	0.11651	0.35	0.132	0.04	0.00088	1.51	-0.009	0.04	0.83405	0.01	0.041	0.04	0.32849	0.14
	S8	F+M	0.097	0.03	0.00011	0.81	-0.077	0.03	0.00245	0.52	0.130	0.02	<0.0001	1.47	0.039	0.03	0.14580	0.14	-0.005	0.02	0.83268	0.00
	S8	F	0.111	0.03	0.00050	1.05	-0.100	0.03	0.00197	0.88	0.127	0.03	0.00005	1.40	0.063	0.03	0.05979	0.36	-0.038	0.03	0.21594	0.12
	S8	M	0.074	0.04	0.05937	0.47	-0.059	0.04	0.14577	0.30	0.130	0.04	0.00114	1.46	-0.009	0.04	0.83527	0.01	0.040	0.04	0.33558	0.14
Smoking cessation	S1	F+M	0.012	0.01	0.13754	0.06	-0.003	0.01	0.74252	0.00	0.023	0.01	0.00631	0.22	0.017	0.01	0.04243	0.12	-0.006	0.01	0.47528	0.02
	S1	F	0.011	0.01	0.33059	0.05	0.011	0.01	0.35155	0.05	0.017	0.01	0.16313	0.11	0.008	0.01	0.52711	0.02	-0.013	0.01	0.27221	0.07

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI				AI				CPD				SC				DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
S1	M	0.013	0.01	0.27197	0.07	-0.020	0.01	0.08479	0.17	0.028	0.01	0.01700	0.32	0.026	0.01	0.02539	0.28	0.002	0.01	0.85166	0.00	
S2	F+M	0.026	0.01	0.00173	0.28	0.001	0.01	0.88218	0.00	0.023	0.01	0.00621	0.22	0.004	0.01	0.65683	0.01	0.000	0.01	0.95997	0.00	
S2	F	0.032	0.01	0.00539	0.43	0.004	0.01	0.73787	0.01	0.015	0.01	0.20737	0.09	-0.009	0.01	0.46311	0.03	-0.007	0.01	0.56946	0.02	
S2	M	0.019	0.01	0.09462	0.15	-0.004	0.01	0.71112	0.01	0.028	0.01	0.01371	0.33	0.016	0.01	0.17525	0.11	0.010	0.01	0.38100	0.05	
S3	F+M	0.028	0.01	0.00084	0.33	-0.000	0.01	0.96785	0.00	0.021	0.01	0.01026	0.19	0.015	0.01	0.07699	0.10	-0.006	0.01	0.48071	0.01	
S3	F	0.033	0.01	0.00627	0.44	-0.004	0.01	0.72371	0.01	0.018	0.01	0.13854	0.13	0.000	0.01	0.99988	0.00	-0.015	0.01	0.21796	0.09	
S3	M	0.022	0.01	0.06789	0.19	0.002	0.01	0.86441	0.00	0.023	0.01	0.04039	0.22	0.028	0.01	0.02128	0.31	0.002	0.01	0.86508	0.00	
S4	F+M	0.039	0.01	<0.00001	0.63	-0.011	0.01	0.18258	0.05	0.024	0.01	0.00464	0.24	0.014	0.01	0.11386	0.08	0.006	0.01	0.44662	0.02	
S4	F	0.037	0.01	0.00256	0.56	-0.017	0.01	0.14555	0.12	0.019	0.01	0.11594	0.15	0.008	0.01	0.49739	0.03	0.011	0.01	0.35528	0.05	
S4	M	0.040	0.01	0.00056	0.68	-0.009	0.01	0.42348	0.04	0.029	0.01	0.01214	0.35	0.015	0.01	0.21366	0.09	-0.002	0.01	0.89713	0.00	
S5	F+M	0.034	0.01	0.00010	0.46	-0.016	0.01	0.05709	0.11	0.016	0.01	0.06023	0.10	0.018	0.01	0.04775	0.13	0.008	0.01	0.33607	0.03	
S5	F	0.034	0.01	0.00595	0.46	-0.024	0.01	0.04248	0.24	0.018	0.01	0.13970	0.13	0.016	0.01	0.21339	0.10	0.014	0.01	0.23020	0.08	
S5	M	0.032	0.01	0.00660	0.42	-0.011	0.01	0.34588	0.05	0.014	0.01	0.22480	0.08	0.016	0.01	0.18550	0.11	-0.000	0.01	0.98112	0.00	
S6	F+M	0.029	0.01	0.00097	0.33	-0.014	0.01	0.09223	0.09	0.013	0.01	0.11967	0.07	0.014	0.01	0.11117	0.09	0.004	0.01	0.60335	0.01	
S6	F	0.030	0.01	0.01547	0.36	-0.025	0.01	0.03632	0.26	0.016	0.01	0.19018	0.10	0.012	0.01	0.35852	0.06	0.006	0.01	0.62677	0.01	
S6	M	0.025	0.01	0.03293	0.26	-0.007	0.01	0.58295	0.02	0.011	0.01	0.35334	0.05	0.015	0.01	0.22359	0.09	0.002	0.01	0.85260	0.00	
S7	F+M	0.023	0.01	0.00785	0.21	-0.014	0.01	0.11193	0.08	0.007	0.01	0.42467	0.02	0.009	0.01	0.29990	0.04	0.003	0.01	0.71436	0.00	
S7	F	0.026	0.01	0.03082	0.28	-0.023	0.01	0.06238	0.22	0.008	0.01	0.49075	0.03	0.007	0.01	0.58083	0.02	0.004	0.01	0.74221	0.01	
S7	M	0.018	0.01	0.13157	0.13	-0.007	0.01	0.53947	0.02	0.006	0.01	0.61071	0.01	0.010	0.01	0.41453	0.04	0.001	0.01	0.93854	0.00	
S8	F+M	0.022	0.01	0.01070	0.19	-0.013	0.01	0.12391	0.08	0.008	0.01	0.32746	0.03	0.010	0.01	0.25591	0.04	0.003	0.01	0.70796	0.00	
S8	F	0.024	0.01	0.04597	0.24	-0.022	0.01	0.06864	0.21	0.010	0.01	0.40151	0.04	0.007	0.01	0.56486	0.02	0.004	0.01	0.73572	0.01	
S8	M	0.018	0.01	0.13477	0.13	-0.007	0.01	0.54154	0.02	0.007	0.01	0.53492	0.02	0.011	0.01	0.35633	0.05	0.002	0.01	0.89747	0.00	
Drinking initiation	S1	F+M	0.002	0.00	0.71817	0.00	-0.013	0.00	0.00707	0.11	0.002	0.00	0.68884	0.00	-0.005	0.00	0.30665	0.02	0.008	0.00	0.08922	0.04
	S1	F	-0.004	0.01	0.51542	0.01	-0.014	0.01	0.03863	0.13	-0.005	0.01	0.49172	0.01	-0.008	0.01	0.25125	0.04	0.010	0.01	0.14197	0.06
	S1	M	0.010	0.01	0.13000	0.06	-0.011	0.01	0.10291	0.08	0.009	0.01	0.18305	0.05	-0.002	0.01	0.72548	0.00	0.006	0.01	0.39526	0.02
	S2	F+M	-0.002	0.00	0.74151	0.00	0.003	0.00	0.60566	0.00	0.002	0.00	0.70182	0.00	-0.003	0.00	0.49633	0.01	0.013	0.00	0.00728	0.11
	S2	F	-0.010	0.01	0.15161	0.06	-0.000	0.01	0.95941	0.00	-0.006	0.01	0.35186	0.03	-0.006	0.01	0.36186	0.02	0.016	0.01	0.01878	0.17

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	
S2	M	0.006	0.01	0.39690	0.02	0.008	0.01	0.24545	0.04	0.011	0.01	0.09985	0.08	-0.001	0.01	0.92833	0.00	0.010	0.01	0.12455	0.07						
S3	F+M	0.007	0.00	0.15414	0.03	0.006	0.00	0.23219	0.02	-0.006	0.00	0.24603	0.02	-0.006	0.00	0.23581	0.02	0.022	0.00	<0.00001	0.30						
S3	F	-0.001	0.01	0.84883	0.00	0.007	0.01	0.33271	0.03	-0.014	0.01	0.04589	0.12	-0.014	0.01	0.04588	0.12	0.028	0.01	0.00004	0.49						
S3	M	0.015	0.01	0.02591	0.14	0.004	0.01	0.57913	0.01	0.002	0.01	0.72343	0.00	0.002	0.01	0.72478	0.00	0.015	0.01	0.02827	0.14						
S4	F+M	0.009	0.00	0.05985	0.05	0.010	0.00	0.04018	0.06	-0.008	0.00	0.10336	0.04	-0.009	0.01	0.06576	0.06	0.022	0.00	<0.00001	0.30						
S4	F	0.004	0.01	0.60265	0.01	0.012	0.01	0.06862	0.10	-0.016	0.01	0.02147	0.16	-0.020	0.01	0.00471	0.26	0.025	0.01	0.00018	0.41						
S4	M	0.015	0.01	0.02356	0.14	0.007	0.01	0.28730	0.03	-0.002	0.01	0.71261	0.00	0.002	0.01	0.72318	0.00	0.018	0.01	0.00767	0.21						
S5	F+M	0.011	0.00	0.01981	0.08	0.010	0.00	0.05220	0.06	-0.012	0.00	0.01107	0.10	-0.008	0.01	0.14496	0.04	0.023	0.00	<0.00001	0.34						
S5	F	0.011	0.01	0.11467	0.07	0.013	0.01	0.05743	0.11	-0.018	0.01	0.00929	0.20	-0.016	0.01	0.02612	0.17	0.026	0.01	0.00010	0.43						
S5	M	0.011	0.01	0.09758	0.08	0.004	0.01	0.55886	0.01	-0.010	0.01	0.15122	0.06	0.001	0.01	0.87068	0.00	0.019	0.01	0.00514	0.23						
S6	F+M	0.013	0.00	0.00746	0.11	0.007	0.00	0.17417	0.03	-0.013	0.00	0.00954	0.10	-0.007	0.01	0.16117	0.04	0.024	0.00	<0.00001	0.38						
S6	F	0.012	0.01	0.06995	0.10	0.010	0.01	0.14730	0.06	-0.020	0.01	0.00397	0.25	-0.016	0.01	0.03001	0.17	0.025	0.01	0.00015	0.40						
S6	M	0.013	0.01	0.04568	0.11	0.001	0.01	0.89115	0.00	-0.008	0.01	0.23022	0.04	0.000	0.01	0.95952	0.00	0.024	0.01	0.00037	0.37						
S7	F+M	0.012	0.00	0.01534	0.09	0.002	0.01	0.75941	0.00	-0.013	0.00	0.00864	0.11	-0.010	0.01	0.05017	0.07	0.024	0.00	<0.00001	0.36						
S7	F	0.012	0.01	0.08670	0.09	0.004	0.01	0.57965	0.01	-0.022	0.01	0.00146	0.31	-0.019	0.01	0.00863	0.24	0.024	0.01	0.00039	0.35						
S7	M	0.011	0.01	0.09840	0.08	-0.003	0.01	0.67876	0.01	-0.007	0.01	0.31180	0.03	-0.002	0.01	0.75638	0.00	0.026	0.01	0.00021	0.41						
S8	F+M	0.011	0.00	0.02334	0.08	0.001	0.01	0.91490	0.00	-0.013	0.00	0.00807	0.11	-0.010	0.01	0.05528	0.07	0.023	0.00	<0.00001	0.33						
S8	F	0.011	0.01	0.11228	0.07	0.002	0.01	0.73337	0.00	-0.022	0.01	0.00125	0.32	-0.019	0.01	0.00918	0.24	0.023	0.01	0.00065	0.32						
S8	M	0.010	0.01	0.12305	0.07	-0.003	0.01	0.65552	0.01	-0.006	0.01	0.34589	0.03	-0.002	0.01	0.79317	0.00	0.025	0.01	0.00033	0.38						
Drinks per week	S1	F+M	0.488	0.19	0.01100	0.13	-0.464	0.19	0.01704	0.12	0.319	0.19	0.10085	0.06	-0.256	0.19	0.18760	0.04	0.721	0.19	0.00016	0.29					
	S1	F	-0.124	0.15	0.41003	0.01	-0.120	0.15	0.42944	0.01	0.033	0.15	0.82628	0.00	0.056	0.15	0.71490	0.00	0.497	0.15	0.00086	0.14					
	S1	M	1.171	0.36	0.00130	0.75	-0.896	0.37	0.01590	0.43	0.594	0.37	0.11021	0.19	-0.650	0.37	0.07998	0.23	0.909	0.37	0.01305	0.46					
	S2	F+M	0.756	0.19	0.00008	0.31	-0.719	0.19	0.00020	0.27	0.270	0.19	0.16435	0.04	-0.404	0.19	0.03694	0.09	1.028	0.19	<0.00001	0.59					
	S2	F	0.117	0.15	0.43986	0.01	-0.103	0.15	0.49991	0.01	0.016	0.15	0.91551	0.00	-0.272	0.15	0.07207	0.04	0.642	0.15	0.00002	0.23					
	S2	M	1.469	0.36	0.00005	1.17	-1.387	0.37	0.00015	1.02	0.503	0.37	0.17255	0.14	-0.654	0.37	0.07992	0.23	1.393	0.37	0.00016	1.08					
	S3	F+M	0.853	0.19	<0.00001	0.39	-0.454	0.19	0.01764	0.11	0.245	0.19	0.20174	0.03	-0.282	0.20	0.15363	0.04	1.235	0.19	<0.00001	0.84					
	S3	F	0.369	0.15	0.01351	0.07	-0.247	0.15	0.10226	0.03	0.101	0.15	0.50250	0.01	-0.168	0.15	0.27215	0.02	0.668	0.15	<0.00001	0.24					

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	
	S3	M	1.337	0.37	<0.00001	0.96	-0.633	0.37	0.08466	0.22	0.363	0.36	0.31850	0.07	-0.460	0.38	0.22835	0.12	1.854	0.36	<0.00001	1.88					
	S4	F+M	0.915	0.19	<0.00001	0.46	-0.553	0.19	0.00387	0.17	0.290	0.19	0.13421	0.05	-0.211	0.20	0.29478	0.02	1.268	0.19	<0.00001	0.88					
	S4	F	0.368	0.15	0.01442	0.07	-0.235	0.15	0.12300	0.03	0.033	0.15	0.83062	0.00	-0.168	0.16	0.28246	0.02	0.855	0.15	<0.00001	0.40					
	S4	M	1.455	0.36	<0.00001	1.16	-0.843	0.36	0.01974	0.39	0.582	0.37	0.11368	0.18	-0.436	0.38	0.25550	0.11	1.770	0.37	<0.00001	1.71					
	S5	F+M	1.009	0.19	<0.00001	0.55	-0.571	0.19	0.00341	0.18	0.061	0.19	0.75227	0.00	-0.074	0.21	0.72096	0.00	1.179	0.19	<0.00001	0.76					
	S5	F	0.397	0.15	0.00952	0.09	-0.298	0.15	0.05233	0.05	0.097	0.15	0.52566	0.01	-0.059	0.16	0.71000	0.00	0.802	0.15	<0.00001	0.35					
	S5	M	1.589	0.36	<0.00001	1.36	-0.871	0.37	0.01983	0.41	-0.026	0.36	0.94182	0.00	-0.240	0.38	0.53190	0.03	1.653	0.37	<0.00001	1.49					
	S6	F+M	0.935	0.19	<0.00001	0.47	-0.583	0.20	0.00297	0.19	0.055	0.19	0.77752	0.00	-0.147	0.21	0.47932	0.01	1.160	0.19	<0.00001	0.73					
	S6	F	0.444	0.15	0.00372	0.11	-0.346	0.15	0.02504	0.07	0.104	0.15	0.49537	0.01	-0.072	0.16	0.65189	0.00	0.760	0.15	<0.00001	0.31					
	S6	M	1.394	0.37	<0.00001	1.05	-0.842	0.38	0.02498	0.39	-0.049	0.36	0.89245	0.00	-0.382	0.39	0.32605	0.08	1.673	0.37	<0.00001	1.51					
	S7	F+M	0.846	0.19	<0.00001	0.39	-0.554	0.20	0.00530	0.17	-0.069	0.20	0.72332	0.00	-0.202	0.21	0.33249	0.02	1.055	0.19	<0.00001	0.60					
	S7	F	0.342	0.15	0.02580	0.06	-0.314	0.16	0.04471	0.05	0.100	0.15	0.51738	0.01	-0.059	0.16	0.71164	0.00	0.685	0.15	<0.00001	0.25					
	S7	M	1.356	0.36	<0.00001	0.99	-0.846	0.38	0.02610	0.40	-0.313	0.37	0.39333	0.05	-0.527	0.39	0.17544	0.16	1.537	0.38	0.00004	1.27					
	S8	F+M	0.860	0.19	<0.00001	0.40	-0.548	0.20	0.00588	0.17	-0.087	0.20	0.65590	0.00	-0.219	0.21	0.29442	0.03	1.066	0.19	<0.00001	0.61					
	S8	F	0.327	0.15	0.03278	0.06	-0.299	0.16	0.05613	0.05	0.094	0.15	0.54151	0.00	-0.075	0.16	0.64076	0.00	0.657	0.15	0.00001	0.23					
	S8	M	1.398	0.36	<0.00001	1.06	-0.856	0.38	0.02451	0.41	-0.335	0.37	0.36173	0.06	-0.537	0.39	0.16676	0.16	1.603	0.38	0.00002	1.38					
DSM-IV alcohol dependence	S1	F+M	0.018	0.01	<0.00001	0.17	-0.003	0.00	0.55218	0.00	0.002	0.01	0.65362	0.00	-0.006	0.00	0.19433	0.02	0.022	0.01	0.00002	0.26					
	S1	F	0.024	0.01	<0.00001	0.32	-0.007	0.01	0.20562	0.03	0.003	0.01	0.56236	0.01	-0.006	0.01	0.33193	0.02	0.025	0.01	0.00004	0.34					
	S1	M	0.008	0.01	0.30071	0.04	0.002	0.01	0.82559	0.00	-0.003	0.01	0.75244	0.00	-0.007	0.01	0.39208	0.03	0.018	0.01	0.02918	0.17					
	S2	F+M	0.019	0.00	<0.00001	0.20	0.000	0.01	0.99246	0.00	0.004	0.01	0.38057	0.01	-0.008	0.01	0.10440	0.04	0.027	0.00	<0.00001	0.40					
	S2	F	0.028	0.01	<0.00001	0.45	-0.002	0.01	0.79602	0.00	0.008	0.01	0.17090	0.04	-0.010	0.01	0.10547	0.05	0.030	0.01	<0.00001	0.50					
	S2	M	0.008	0.01	0.33015	0.03	0.002	0.01	0.77649	0.00	-0.003	0.01	0.68595	0.01	-0.006	0.01	0.44885	0.02	0.023	0.01	0.00419	0.29					
	S3	F+M	0.025	0.00	<0.00001	0.35	-0.010	0.00	0.03614	0.06	0.004	0.01	0.47743	0.01	-0.006	0.01	0.26443	0.02	0.030	0.01	<0.00001	0.51					
	S3	F	0.029	0.01	<0.00001	0.48	-0.009	0.01	0.15046	0.04	0.008	0.01	0.16650	0.04	-0.004	0.01	0.50130	0.01	0.030	0.01	<0.00001	0.51					
	S3	M	0.018	0.01	0.02290	0.18	-0.014	0.01	0.07939	0.11	-0.003	0.01	0.72768	0.00	-0.009	0.01	0.27928	0.04	0.031	0.01	0.00016	0.52					
	S4	F+M	0.024	0.00	<0.00001	0.33	-0.009	0.01	0.06104	0.05	0.002	0.00	0.72080	0.00	-0.006	0.01	0.28204	0.02	0.028	0.00	<0.00001	0.43					

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI					AI					CPD					SC					DPW					
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	
S4	F	0.024	0.01	<0.00001	0.33	-0.008	0.01	0.17459	0.04	0.003	0.01	0.57329	0.01	-0.005	0.01	0.37043	0.02	0.029	0.01	<0.00001	0.47						
S4	M	0.024	0.01	0.00272	0.32	-0.012	0.01	0.14300	0.08	-0.001	0.01	0.89819	0.00	-0.004	0.01	0.59937	0.01	0.029	0.01	0.00035	0.46						
S5	F+M	0.025	0.00	<0.00001	0.36	-0.015	0.01	0.00334	0.12	0.002	0.01	0.64348	0.00	-0.003	0.01	0.60686	0.00	0.029	0.00	<0.00001	0.45						
S5	F	0.024	0.01	<0.00007	0.31	-0.010	0.01	0.09607	0.06	0.003	0.01	0.59016	0.01	0.002	0.01	0.73496	0.00	0.027	0.01	<0.00001	0.42						
S5	M	0.027	0.01	0.00072	0.42	-0.023	0.01	0.00603	0.28	0.000	0.01	0.96543	0.00	-0.007	0.01	0.39203	0.03	0.033	0.01	0.00004	0.59						
S6	F+M	0.025	0.00	<0.00001	0.34	-0.014	0.01	0.00537	0.11	0.002	0.01	0.76494	0.00	-0.004	0.01	0.50793	0.01	0.027	0.00	<0.00001	0.40						
S6	F	0.024	0.01	<0.00006	0.32	-0.007	0.01	0.22028	0.03	0.001	0.01	0.91047	0.00	0.000	0.01	0.96973	0.00	0.027	0.01	<0.00001	0.41						
S6	M	0.025	0.01	0.00181	0.35	-0.025	0.01	0.00247	0.35	0.001	0.01	0.86472	0.00	-0.006	0.01	0.44913	0.02	0.030	0.01	0.00024	0.48						
S7	F+M	0.023	0.00	<0.00001	0.30	-0.015	0.01	0.00277	0.13	0.002	0.01	0.69849	0.00	-0.004	0.01	0.42429	0.01	0.028	0.01	<0.00001	0.43						
S7	F	0.022	0.01	<0.00014	0.29	-0.010	0.01	0.10751	0.05	0.002	0.01	0.73193	0.00	0.003	0.01	0.61745	0.01	0.028	0.01	<0.00001	0.41						
S7	M	0.022	0.01	0.00536	0.28	-0.025	0.01	0.00255	0.35	0.000	0.01	0.95633	0.00	-0.012	0.01	0.16811	0.08	0.032	0.01	0.00008	0.55						
S8	F+M	0.023	0.00	<0.00001	0.30	-0.016	0.01	0.00207	0.14	0.003	0.01	0.58523	0.00	-0.005	0.01	0.38854	0.01	0.029	0.01	<0.00001	0.45						
S8	F	0.022	0.01	<0.00015	0.28	-0.010	0.01	0.08334	0.06	0.002	0.01	0.79795	0.00	0.003	0.01	0.58031	0.01	0.027	0.01	<0.00001	0.39						
S8	M	0.023	0.01	0.00468	0.29	-0.025	0.01	0.00241	0.36	0.003	0.01	0.72759	0.00	-0.013	0.01	0.13713	0.10	0.034	0.01	0.00004	0.61						
DSM-IV nicotine dependence	S1	F+M	0.032	0.01	<0.00001	0.43	-0.010	0.01	0.11018	0.04	0.016	0.01	0.01089	0.11	0.013	0.01	0.03791	0.07	-0.005	0.01	0.45254	0.01					
	S1	F	0.033	0.01	<0.00004	0.47	-0.019	0.01	0.02186	0.15	0.017	0.01	0.03507	0.12	0.004	0.01	0.59619	0.01	-0.007	0.01	0.38900	0.02					
	S1	M	0.031	0.01	<0.00051	0.40	-0.007	0.01	0.40447	0.02	0.018	0.01	0.04329	0.14	0.021	0.01	0.01832	0.18	0.000	0.01	0.99755	0.00					
	S2	F+M	0.049	0.01	<0.00001	1.04	-0.010	0.01	0.10446	0.04	0.019	0.01	0.00193	0.16	0.010	0.01	0.11715	0.04	-0.006	0.01	0.32305	0.02					
	S2	F	0.054	0.01	<0.00001	1.24	-0.013	0.01	0.12697	0.07	0.022	0.01	0.00795	0.20	0.002	0.01	0.84089	0.00	-0.013	0.01	0.12326	0.07					
	S2	M	0.047	0.01	<0.00001	0.95	-0.009	0.01	0.28559	0.04	0.020	0.01	0.02235	0.18	0.017	0.01	0.05381	0.12	0.004	0.01	0.65732	0.01					
	S3	F+M	0.059	0.01	<0.00001	1.50	-0.021	0.01	0.00074	0.18	0.023	0.01	0.00027	0.22	0.020	0.01	0.00183	0.17	-0.007	0.01	0.26045	0.02					
	S3	F	0.067	0.01	<0.00001	1.90	-0.021	0.01	0.00983	0.18	0.027	0.01	0.00090	0.32	0.006	0.01	0.44423	0.02	-0.014	0.01	0.08508	0.08					
	S3	M	0.052	0.01	<0.00001	1.17	-0.019	0.01	0.02971	0.15	0.021	0.01	0.01766	0.18	0.031	0.01	0.00062	0.41	0.003	0.01	0.74417	0.00					
	S4	F+M	0.064	0.01	<0.00001	1.76	-0.026	0.01	<0.00001	0.30	0.030	0.01	<0.00001	0.38	0.016	0.01	0.01134	0.12	0.006	0.01	0.31799	0.02					
	S4	F	0.066	0.01	<0.00001	1.89	-0.027	0.01	0.00075	0.32	0.030	0.01	0.00021	0.39	0.007	0.01	0.43661	0.02	0.000	0.01	0.96862	0.00					
	S4	M	0.063	0.01	<0.00001	1.70	-0.026	0.01	0.00385	0.28	0.034	0.01	0.00011	0.50	0.027	0.01	0.00347	0.32	0.014	0.01	0.12133	0.08					

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	Sex	SI			AI			CPD			SC			DPW			
			Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
S5	F+M		0.068	0.01	<.00001	1.99	-0.034	0.01	<.00001	0.48	0.033	0.01	<.00001	0.47	0.019	0.01	0.00388	0.17
S5	F		0.069	0.01	<.00001	2.05	-0.042	0.01	<.00001	0.76	0.029	0.01	0.00045	0.35	0.017	0.01	0.04365	0.14
S5	M		0.067	0.01	<.00001	1.93	-0.023	0.01	0.00935	0.23	0.043	0.01	<.00001	0.78	0.020	0.01	0.03458	0.18
S6	F+M		0.070	0.01	<.00001	2.10	-0.038	0.01	<.00001	0.62	0.036	0.01	<.00001	0.56	0.021	0.01	0.00170	0.21
S6	F		0.069	0.01	<.00001	2.06	-0.045	0.01	<.00001	0.87	0.034	0.01	0.00003	0.50	0.019	0.01	0.03158	0.16
S6	M		0.070	0.01	<.00001	2.13	-0.030	0.01	0.00093	0.39	0.042	0.01	<.00001	0.77	0.023	0.01	0.01570	0.24
S7	F+M		0.068	0.01	<.00001	1.99	-0.040	0.01	<.00001	0.68	0.033	0.01	<.00001	0.48	0.018	0.01	0.00712	0.16
S7	F		0.070	0.01	<.00001	2.11	-0.044	0.01	<.00001	0.85	0.028	0.01	0.00080	0.33	0.019	0.01	0.02970	0.17
S7	M		0.066	0.01	<.00001	1.89	-0.034	0.01	0.00018	0.50	0.042	0.01	<.00001	0.78	0.017	0.01	0.07255	0.14
S8	F+M		0.067	0.01	<.00001	1.96	-0.039	0.01	<.00001	0.67	0.034	0.01	<.00001	0.52	0.018	0.01	0.00777	0.16
S8	F		0.069	0.01	<.00001	2.05	-0.045	0.01	<.00001	0.88	0.028	0.01	0.00072	0.34	0.019	0.01	0.03268	0.16
S8	M		0.066	0.01	<.00001	1.88	-0.033	0.01	0.00026	0.48	0.045	0.01	<.00001	0.88	0.017	0.01	0.07738	0.13
FTND-based nicotine dependence	S1	F+M	0.027	0.01	<.00001	0.36	-0.008	0.01	0.13978	0.04	0.028	0.01	<.00001	0.38	0.024	0.01	0.00004	0.27
	S1	F	0.021	0.01	0.00373	0.23	-0.010	0.01	0.19663	0.05	0.030	0.01	0.00004	0.45	0.014	0.01	0.05759	0.10
	S1	M	0.030	0.01	0.00028	0.47	-0.012	0.01	0.14799	0.07	0.029	0.01	0.00054	0.43	0.035	0.01	0.00003	0.60
	S2	F+M	0.044	0.01	<.00001	0.97	-0.013	0.01	0.02645	0.08	0.031	0.01	<.00001	0.47	0.018	0.01	0.00184	0.16
	S2	F	0.040	0.01	<.00001	0.83	-0.009	0.01	0.25205	0.04	0.033	0.01	<.00001	0.53	0.006	0.01	0.45526	0.02
	S2	M	0.045	0.01	<.00001	1.02	-0.018	0.01	0.03030	0.16	0.033	0.01	0.00008	0.55	0.031	0.01	0.00020	0.48
	S3	F+M	0.054	0.01	<.00001	1.45	-0.017	0.01	0.00293	0.14	0.033	0.01	<.00001	0.53	0.024	0.01	0.00003	0.30
	S3	F	0.055	0.01	<.00001	1.50	-0.009	0.01	0.24309	0.04	0.034	0.01	<.00001	0.56	0.014	0.01	0.06084	0.10
	S3	M	0.051	0.01	<.00001	1.32	-0.027	0.01	0.00142	0.35	0.035	0.01	0.00002	0.62	0.038	0.01	0.00001	0.71
	S4	F+M	0.060	0.01	<.00001	1.84	-0.027	0.01	<.00001	0.36	0.040	0.01	<.00001	0.81	0.027	0.01	<.00001	0.39
S4	S4	F	0.059	0.01	<.00001	1.77	-0.021	0.01	0.00326	0.23	0.042	0.01	<.00001	0.90	0.021	0.01	0.00597	0.23
	S4	M	0.061	0.01	<.00001	1.87	-0.034	0.01	0.00006	0.57	0.039	0.01	<.00001	0.78	0.035	0.01	0.00005	0.65
	S5	F+M	0.061	0.01	<.00001	1.90	-0.033	0.01	<.00001	0.55	0.044	0.01	<.00001	0.98	0.029	0.01	<.00001	0.46
	S5	F	0.056	0.01	<.00001	1.58	-0.029	0.01	0.00011	0.41	0.046	0.01	<.00001	1.07	0.029	0.01	0.00017	0.47

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI				AI				CPD				SC				DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
	S5	M	0.066	0.01	<.00001	2.19	-0.038	0.01	<.00001	0.71	0.045	0.01	<.00001	1.04	0.028	0.01	0.00180	0.41	0.010	0.01	0.24925	0.05
	S6	F+M	0.062	0.01	<.00001	1.94	-0.036	0.01	<.00001	0.66	0.046	0.01	<.00001	1.07	0.030	0.01	<.00001	0.49	0.011	0.01	0.06104	0.06
	S6	F	0.054	0.01	<.00001	1.48	-0.034	0.01	<.00001	0.59	0.051	0.01	<.00001	1.30	0.032	0.01	0.00006	0.55	0.010	0.01	0.19645	0.04
	S6	M	0.069	0.01	<.00001	2.38	-0.039	0.01	<.00001	0.78	0.043	0.01	<.00001	0.93	0.028	0.01	0.00145	0.43	0.010	0.01	0.22451	0.05
	S7	F+M	0.062	0.01	<.00001	1.95	-0.038	0.01	<.00001	0.72	0.040	0.01	<.00001	0.81	0.025	0.01	0.00008	0.34	0.012	0.01	0.04442	0.06
	S7	F	0.057	0.01	<.00001	1.65	-0.036	0.01	<.00001	0.65	0.042	0.01	<.00001	0.92	0.026	0.01	0.00108	0.37	0.010	0.01	0.17434	0.05
	S7	M	0.065	0.01	<.00001	2.18	-0.041	0.01	<.00001	0.84	0.040	0.01	<.00001	0.81	0.024	0.01	0.00732	0.32	0.011	0.01	0.17761	0.06
	S8	F+M	0.062	0.01	<.00001	1.95	-0.037	0.01	<.00001	0.68	0.041	0.01	<.00001	0.86	0.025	0.01	0.00010	0.34	0.011	0.01	0.04677	0.06
	S8	F	0.056	0.01	<.00001	1.62	-0.034	0.01	<.00001	0.58	0.042	0.01	<.00001	0.92	0.026	0.01	0.00135	0.36	0.010	0.01	0.17678	0.05
	S8	M	0.066	0.01	<.00001	2.22	-0.040	0.01	<.00001	0.83	0.042	0.01	<.00001	0.90	0.024	0.01	0.00725	0.32	0.011	0.01	0.18882	0.06
DSM-IV conduct disorder	S1	F+M	0.005	0.00	0.02898	0.07	-0.003	0.00	0.14325	0.03	0.002	0.00	0.37017	0.01	-0.001	0.00	0.80221	0.00	-0.003	0.00	0.20667	0.03
	S1	F	0.006	0.00	0.00451	0.13	-0.000	0.00	0.93572	0.00	-0.001	0.00	0.51380	0.01	-0.002	0.00	0.43279	0.01	0.001	0.00	0.55181	0.01
	S1	M	0.003	0.00	0.50967	0.02	-0.007	0.00	0.07643	0.16	0.006	0.00	0.14313	0.11	0.001	0.00	0.84914	0.00	-0.008	0.00	0.05136	0.19
	S2	F+M	0.006	0.00	0.00525	0.12	-0.002	0.00	0.28024	0.02	0.002	0.00	0.25792	0.02	-0.001	0.00	0.59957	0.00	-0.001	0.00	0.58732	0.00
	S2	F	0.005	0.00	0.01770	0.09	-0.004	0.00	0.06414	0.06	-0.000	0.00	0.91085	0.00	-0.003	0.00	0.18867	0.03	0.002	0.00	0.31804	0.02
	S2	M	0.007	0.00	0.07003	0.16	-0.001	0.00	0.85648	0.00	0.005	0.00	0.16167	0.10	0.001	0.00	0.84255	0.00	-0.005	0.00	0.19768	0.08
	S3	F+M	0.006	0.00	0.00415	0.13	-0.004	0.00	0.04107	0.06	0.004	0.00	0.04899	0.06	-0.002	0.00	0.47147	0.01	-0.003	0.00	0.14431	0.03
	S3	F	0.005	0.00	0.03093	0.07	-0.001	0.00	0.81974	0.00	-0.000	0.00	0.85751	0.00	-0.001	0.00	0.72636	0.00	-0.001	0.00	0.72908	0.00
	S3	M	0.008	0.00	0.04538	0.20	-0.008	0.00	0.03368	0.23	0.010	0.00	0.01275	0.31	-0.002	0.00	0.53327	0.02	-0.006	0.00	0.13340	0.11
	S4	F+M	0.008	0.00	0.00018	0.22	-0.008	0.00	0.00017	0.22	0.004	0.00	0.09431	0.04	0.001	0.00	0.58891	0.01	-0.001	0.00	0.51131	0.01
	S4	F	0.004	0.00	0.04716	0.06	-0.004	0.00	0.04977	0.06	-0.000	0.00	0.97892	0.00	0.001	0.00	0.62557	0.00	-0.000	0.00	0.98607	0.00
	S4	M	0.012	0.00	0.00119	0.52	-0.013	0.00	0.00129	0.53	0.009	0.00	0.02479	0.25	0.001	0.00	0.80582	0.00	-0.003	0.00	0.48257	0.02
	S5	F+M	0.009	0.00	0.00002	0.28	-0.008	0.00	0.00037	0.20	0.004	0.00	0.05900	0.06	0.003	0.00	0.15994	0.04	-0.001	0.00	0.63803	0.00
	S5	F	0.005	0.00	0.01815	0.09	-0.006	0.00	0.01377	0.10	-0.000	0.00	0.97824	0.00	0.003	0.00	0.17529	0.03	-0.001	0.00	0.65555	0.00
	S5	M	0.014	0.00	0.00036	0.64	-0.010	0.00	0.00853	0.36	0.010	0.00	0.01107	0.33	0.003	0.00	0.49874	0.03	-0.001	0.00	0.88312	0.00
	S6	F+M	0.008	0.00	0.00009	0.24	-0.008	0.00	0.00032	0.21	0.004	0.00	0.04067	0.07	0.003	0.00	0.16633	0.04	-0.001	0.00	0.54417	0.01

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI				AI				CPD				SC				DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
S6	F	0.005	0.00	0.03567	0.07	-0.005	0.00	0.01983	0.09	0.001	0.00	0.82177	0.00	0.002	0.00	0.40818	0.01	-0.001	0.00	0.53206	0.01	
	M	0.013	0.00	0.00097	0.55	-0.011	0.00	0.00600	0.40	0.010	0.00	0.01001	0.34	0.004	0.00	0.27786	0.07	-0.001	0.00	0.85046	0.00	
	F+M	0.009	0.00	0.00005	0.26	-0.009	0.00	0.00009	0.25	0.005	0.00	0.01655	0.09	0.002	0.00	0.27980	0.02	-0.002	0.00	0.43710	0.01	
	F	0.004	0.00	0.06332	0.06	-0.006	0.00	0.00512	0.13	0.001	0.00	0.58825	0.00	0.002	0.00	0.30920	0.02	-0.002	0.00	0.46742	0.01	
	M	0.014	0.00	0.00020	0.70	-0.011	0.00	0.00445	0.44	0.011	0.00	0.00539	0.40	0.002	0.00	0.55221	0.02	-0.001	0.00	0.74694	0.01	
	F+M	0.009	0.00	0.00003	0.27	-0.009	0.00	0.00007	0.26	0.005	0.00	0.02145	0.09	0.002	0.00	0.28555	0.02	-0.001	0.00	0.60272	0.00	
	F	0.004	0.00	0.05347	0.06	-0.007	0.00	0.00338	0.15	0.001	0.00	0.60395	0.00	0.002	0.00	0.32747	0.02	-0.001	0.00	0.55565	0.01	
	M	0.015	0.00	0.00017	0.72	-0.011	0.00	0.00422	0.44	0.011	0.00	0.00664	0.39	0.002	0.00	0.54648	0.02	-0.000	0.00	0.92530	0.00	
DSM-IV antisocial personality disorder	S1	F+M	0.003	0.00	0.05078	0.05	-0.002	0.00	0.30521	0.01	0.002	0.00	0.19952	0.02	-0.001	0.00	0.43661	0.01	-0.001	0.00	0.42508	0.01
	S1	F	0.003	0.00	0.02264	0.05	0.001	0.00	0.70393	0.00	0.001	0.00	0.42945	0.01	0.000	0.00	0.80213	0.00	0.001	0.00	0.70435	0.00
	S1	M	0.004	0.00	0.28032	0.06	-0.004	0.00	0.17715	0.10	0.003	0.00	0.31650	0.06	-0.003	0.00	0.30530	0.06	-0.004	0.00	0.24583	0.07
	S2	F+M	0.005	0.00	0.00771	0.10	-0.001	0.00	0.44954	0.01	0.003	0.00	0.07565	0.04	-0.001	0.00	0.39203	0.01	0.001	0.00	0.69642	0.00
	S2	F	0.004	0.00	0.00981	0.07	-0.001	0.00	0.67049	0.00	0.002	0.00	0.13894	0.02	0.000	0.00	0.97637	0.00	0.002	0.00	0.28224	0.01
	S2	M	0.006	0.00	0.08134	0.16	-0.002	0.00	0.46236	0.03	0.004	0.00	0.22950	0.08	-0.004	0.00	0.29571	0.06	-0.001	0.00	0.84380	0.00
	S3	F+M	0.005	0.00	0.00758	0.10	-0.005	0.00	0.00691	0.10	0.004	0.00	0.01577	0.08	0.002	0.00	0.30450	0.02	-0.000	0.00	0.90000	0.00
	S3	F	0.003	0.00	0.03254	0.05	-0.002	0.00	0.14776	0.02	0.001	0.00	0.43002	0.01	0.001	0.00	0.40810	0.01	0.001	0.00	0.59620	0.00
	S3	M	0.006	0.00	0.05909	0.19	-0.008	0.00	0.01781	0.30	0.008	0.00	0.02060	0.29	0.002	0.00	0.47083	0.03	-0.002	0.00	0.59960	0.01
	S4	F+M	0.005	0.00	0.00779	0.10	-0.007	0.00	0.00013	0.21	0.004	0.00	0.03077	0.07	0.004	0.00	0.01591	0.09	0.000	0.00	0.95270	0.00
	S4	F	0.004	0.00	0.00942	0.07	-0.004	0.00	0.01354	0.06	0.000	0.00	0.79115	0.00	0.001	0.00	0.37712	0.01	0.000	0.00	0.89981	0.00
	S4	M	0.005	0.00	0.10275	0.14	-0.010	0.00	0.00185	0.54	0.008	0.00	0.02173	0.28	0.007	0.00	0.03293	0.26	-0.001	0.00	0.88066	0.00
	S5	F+M	0.005	0.00	0.00519	0.11	-0.007	0.00	0.00007	0.23	0.003	0.00	0.04446	0.06	0.004	0.00	0.01364	0.09	0.001	0.00	0.57714	0.00
	S5	F	0.003	0.00	0.04239	0.04	-0.004	0.00	0.01239	0.07	0.000	0.00	0.82645	0.00	0.002	0.00	0.15849	0.02	0.000	0.00	0.88514	0.00
	S5	M	0.007	0.00	0.03941	0.23	-0.011	0.00	0.00109	0.60	0.007	0.00	0.02954	0.26	0.007	0.00	0.04672	0.23	0.001	0.00	0.67850	0.01
	S6	F+M	0.005	0.00	0.00489	0.11	-0.006	0.00	0.00034	0.19	0.003	0.00	0.08656	0.04	0.004	0.00	0.02870	0.08	0.002	0.00	0.27244	0.02
	S6	F	0.003	0.00	0.02697	0.05	-0.004	0.00	0.01678	0.06	0.001	0.00	0.64435	0.00	0.002	0.00	0.21880	0.02	0.000	0.00	0.73398	0.00

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI					AI					CPD					SC					DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²				
S6	M	0.007	0.00	0.04373	0.22	-0.010	0.00	0.00365	0.48	0.006	0.00	0.08564	0.16	0.006	0.00	0.07272	0.19	0.003	0.00	0.35641	0.05					
	F+M	0.006	0.00	0.00079	0.16	-0.007	0.00	0.00009	0.23	0.003	0.00	0.12018	0.04	0.004	0.00	0.02358	0.08	0.002	0.00	0.18621	0.02					
	F	0.003	0.00	0.01581	0.06	-0.004	0.00	0.00694	0.08	-0.000	0.00	0.89638	0.00	0.002	0.00	0.09748	0.03	-0.000	0.00	0.85843	0.00					
	M	0.008	0.00	0.01135	0.35	-0.011	0.00	0.00174	0.57	0.006	0.00	0.06689	0.19	0.006	0.00	0.09643	0.17	0.005	0.00	0.14130	0.12					
	F+M	0.006	0.00	0.00050	0.17	-0.007	0.00	0.00010	0.23	0.003	0.00	0.13401	0.03	0.004	0.00	0.03119	0.07	0.002	0.00	0.16498	0.03					
	F	0.003	0.00	0.01655	0.06	-0.004	0.00	0.00835	0.07	-0.000	0.00	0.83647	0.00	0.002	0.00	0.10875	0.03	-0.000	0.00	0.97039	0.00					
	M	0.009	0.00	0.00726	0.39	-0.011	0.00	0.00163	0.58	0.006	0.00	0.06819	0.19	0.005	0.00	0.11779	0.15	0.005	0.00	0.14256	0.12					
	S1	F+M	0.009	0.01	0.10310	0.04	0.009	0.01	0.11668	0.04	0.013	0.01	0.02005	0.08	0.003	0.01	0.55008	0.01	-0.003	0.01	0.64580	0.00				
DSM-IV major depressive disorder	S1	F	0.013	0.01	0.09203	0.08	0.009	0.01	0.25457	0.04	0.011	0.01	0.15252	0.06	0.012	0.01	0.11584	0.07	0.004	0.01	0.58688	0.01				
	S1	M	0.005	0.01	0.55035	0.01	0.007	0.01	0.35870	0.02	0.017	0.01	0.02796	0.14	-0.007	0.01	0.35961	0.02	-0.010	0.01	0.17394	0.05				
	S2	F+M	0.002	0.01	0.69179	0.00	0.013	0.01	0.02220	0.08	0.014	0.01	0.01443	0.09	0.001	0.01	0.91561	0.00	-0.002	0.01	0.76142	0.00				
	S2	F	0.005	0.01	0.48914	0.01	0.012	0.01	0.12337	0.07	0.010	0.01	0.17887	0.05	0.009	0.01	0.25834	0.04	-0.001	0.01	0.85602	0.00				
	S2	M	-0.001	0.01	0.89736	0.00	0.013	0.01	0.09179	0.08	0.019	0.01	0.01222	0.18	-0.008	0.01	0.30547	0.03	-0.001	0.01	0.84865	0.00				
	S3	F+M	0.010	0.01	0.08863	0.04	-0.002	0.01	0.78339	0.00	0.012	0.01	0.03636	0.07	-0.002	0.01	0.70417	0.00	0.004	0.01	0.44005	0.01				
	S3	F	0.011	0.01	0.14964	0.06	0.005	0.01	0.53070	0.01	0.010	0.01	0.22360	0.04	0.006	0.01	0.46856	0.02	0.002	0.01	0.74974	0.00				
	S3	M	0.009	0.01	0.26160	0.04	-0.010	0.01	0.19834	0.05	0.017	0.01	0.03130	0.13	-0.010	0.01	0.18576	0.05	0.006	0.01	0.47103	0.01				
	S4	F+M	0.014	0.01	0.01372	0.09	-0.007	0.01	0.19525	0.03	0.010	0.01	0.08500	0.04	-0.003	0.01	0.58640	0.00	-0.002	0.01	0.74893	0.00				
	S4	F	0.014	0.01	0.07163	0.10	-0.004	0.01	0.62067	0.01	0.003	0.01	0.74150	0.00	-0.007	0.01	0.40690	0.02	-0.007	0.01	0.34226	0.03				
	S4	M	0.013	0.01	0.08752	0.08	-0.012	0.01	0.13530	0.06	0.018	0.01	0.01586	0.16	0.001	0.01	0.88957	0.00	0.004	0.01	0.56950	0.01				
	S5	F+M	0.014	0.01	0.01480	0.09	-0.007	0.01	0.21369	0.02	0.016	0.01	0.00346	0.13	0.003	0.01	0.60310	0.00	0.004	0.01	0.44839	0.01				
	S5	F	0.016	0.01	0.03398	0.13	-0.002	0.01	0.81274	0.00	0.008	0.01	0.32955	0.03	0.003	0.01	0.71578	0.00	-0.000	0.01	0.97631	0.00				
	S5	M	0.010	0.01	0.18191	0.05	-0.013	0.01	0.08917	0.09	0.027	0.01	0.00048	0.35	0.003	0.01	0.66647	0.01	0.009	0.01	0.26110	0.04				
	S6	F+M	0.013	0.01	0.01869	0.08	-0.006	0.01	0.29495	0.02	0.014	0.01	0.01533	0.09	0.005	0.01	0.40134	0.01	0.008	0.01	0.18245	0.03				
	S6	F	0.018	0.01	0.02231	0.15	-0.001	0.01	0.86336	0.00	0.006	0.01	0.45002	0.02	0.004	0.01	0.58261	0.01	0.004	0.01	0.61064	0.01				
	S6	M	0.008	0.01	0.31494	0.03	-0.012	0.01	0.13602	0.07	0.023	0.01	0.00352	0.25	0.005	0.01	0.52431	0.01	0.011	0.01	0.17076	0.05				

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI				AI				CPD				SC				DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
	S7	F+M	0.016	0.01	0.00463	0.12	-0.008	0.01	0.17798	0.03	0.013	0.01	0.02603	0.08	0.005	0.01	0.42882	0.01	0.010	0.01	0.08189	0.05
	S7	F	0.021	0.01	0.00565	0.22	-0.005	0.01	0.49596	0.01	0.005	0.01	0.53223	0.01	0.005	0.01	0.54593	0.01	0.008	0.01	0.32957	0.03
	S7	M	0.009	0.01	0.26421	0.04	-0.011	0.01	0.16244	0.06	0.021	0.01	0.00709	0.21	0.004	0.01	0.64081	0.01	0.012	0.01	0.11247	0.07
	S8	F+M	0.016	0.01	0.00480	0.12	-0.006	0.01	0.30453	0.02	0.013	0.01	0.02717	0.08	0.004	0.01	0.49589	0.01	0.010	0.01	0.06373	0.05
	S8	F	0.021	0.01	0.00681	0.21	-0.005	0.01	0.52977	0.01	0.004	0.01	0.61612	0.01	0.004	0.01	0.57435	0.01	0.008	0.01	0.30113	0.03
	S8	M	0.009	0.01	0.23435	0.04	-0.008	0.01	0.33992	0.03	0.022	0.01	0.00468	0.23	0.003	0.01	0.73679	0.00	0.013	0.01	0.08955	0.08
DSM-IV panic disorder	S1	F+M	0.003	0.00	0.23253	0.02	0.002	0.00	0.36353	0.01	0.001	0.00	0.66509	0.00	0.001	0.00	0.80411	0.00	0.003	0.00	0.21020	0.02
	S1	F	0.008	0.00	0.03769	0.14	0.005	0.00	0.19666	0.05	-0.001	0.00	0.81492	0.00	0.002	0.00	0.54021	0.01	0.006	0.00	0.08449	0.10
	S1	M	-0.003	0.00	0.37904	0.02	-0.001	0.00	0.75492	0.00	0.003	0.00	0.29865	0.03	-0.001	0.00	0.74042	0.00	-0.001	0.00	0.78542	0.00
	S2	F+M	0.005	0.00	0.03415	0.06	0.001	0.00	0.66206	0.00	0.001	0.00	0.68913	0.00	0.001	0.00	0.64930	0.00	0.001	0.00	0.69215	0.00
	S2	F	0.008	0.00	0.02999	0.15	-0.002	0.00	0.56231	0.01	0.000	0.00	0.98416	0.00	0.002	0.00	0.63649	0.01	0.002	0.00	0.52118	0.01
	S2	M	0.001	0.00	0.63940	0.01	0.005	0.00	0.09521	0.07	0.002	0.00	0.56011	0.01	0.001	0.00	0.85728	0.00	-0.001	0.00	0.76206	0.00
	S3	F+M	0.005	0.00	0.03801	0.06	-0.002	0.00	0.54091	0.01	0.004	0.00	0.12099	0.03	0.003	0.00	0.30712	0.02	0.002	0.00	0.36302	0.01
	S3	F	0.009	0.00	0.01490	0.19	-0.002	0.00	0.58181	0.01	0.004	0.00	0.26971	0.04	0.000	0.00	0.94897	0.00	0.002	0.00	0.53449	0.01
	S3	M	0.000	0.00	0.94549	0.00	-0.000	0.00	0.90504	0.00	0.003	0.00	0.27444	0.03	0.005	0.00	0.10204	0.07	0.002	0.00	0.55879	0.01
	S4	F+M	0.005	0.00	0.03107	0.07	-0.001	0.00	0.66378	0.00	0.005	0.00	0.03538	0.06	0.005	0.00	0.05365	0.06	-0.001	0.00	0.67109	0.00
	S4	F	0.008	0.00	0.03938	0.14	0.000	0.00	0.99524	0.00	0.003	0.00	0.35173	0.03	0.002	0.00	0.50142	0.02	-0.003	0.00	0.44727	0.02
	S4	M	0.002	0.00	0.42890	0.01	-0.002	0.00	0.51195	0.01	0.007	0.00	0.03072	0.11	0.007	0.00	0.02648	0.13	0.001	0.00	0.74813	0.00
	S5	F+M	0.005	0.00	0.03929	0.06	-0.002	0.00	0.45716	0.01	0.006	0.00	0.01848	0.08	0.006	0.00	0.01000	0.10	0.002	0.00	0.44998	0.01
	S5	F	0.007	0.00	0.05573	0.12	-0.003	0.00	0.38097	0.03	0.006	0.00	0.09259	0.09	0.006	0.00	0.10830	0.09	0.001	0.00	0.70255	0.00
	S5	M	0.002	0.00	0.46093	0.01	-0.000	0.00	0.99720	0.00	0.005	0.00	0.11602	0.06	0.007	0.00	0.03935	0.11	0.002	0.00	0.45017	0.01
	S6	F+M	0.006	0.00	0.02562	0.07	-0.003	0.00	0.30583	0.02	0.005	0.00	0.05746	0.05	0.006	0.00	0.01223	0.10	0.002	0.00	0.51029	0.01
	S6	F	0.008	0.00	0.03780	0.14	-0.003	0.00	0.41981	0.02	0.005	0.00	0.17694	0.06	0.007	0.00	0.07751	0.11	0.002	0.00	0.67133	0.01
	S6	M	0.003	0.00	0.41713	0.02	-0.002	0.00	0.57820	0.01	0.004	0.00	0.20507	0.04	0.005	0.00	0.08973	0.08	0.002	0.00	0.58529	0.01
	S7	F+M	0.006	0.00	0.00857	0.10	-0.005	0.00	0.07580	0.05	0.004	0.00	0.08416	0.04	0.006	0.00	0.02585	0.08	0.001	0.00	0.58802	0.00
	S7	F	0.010	0.00	0.00746	0.23	-0.005	0.00	0.19761	0.06	0.005	0.00	0.14351	0.07	0.006	0.00	0.09293	0.10	0.002	0.00	0.53211	0.01

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI					AI					CPD					SC					DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²				
	S7	M	0.002	0.00	0.50069	0.01	-0.004	0.00	0.22700	0.04	0.002	0.00	0.44933	0.01	0.004	0.00	0.19445	0.05	0.000	0.00	0.89487	0.00				
	S8	F+M	0.006	0.00	0.00916	0.10	-0.004	0.00	0.09747	0.04	0.004	0.00	0.09486	0.04	0.006	0.00	0.02418	0.08	0.001	0.00	0.62785	0.00				
	S8	F	0.010	0.00	0.00812	0.22	-0.004	0.00	0.26369	0.04	0.005	0.00	0.14554	0.07	0.007	0.00	0.07176	0.11	0.002	0.00	0.62599	0.01				
	S8	M	0.002	0.00	0.50433	0.01	-0.004	0.00	0.21358	0.04	0.002	0.00	0.50296	0.01	0.004	0.00	0.24055	0.04	0.001	0.00	0.83340	0.00				
DSM-IV social anxiety disorder	S1	F+M	0.011	0.00	0.01710	0.09	-0.001	0.00	0.89228	0.00	0.002	0.00	0.73759	0.00	-0.003	0.00	0.51364	0.01	-0.002	0.00	0.73594	0.00				
	S1	F	0.019	0.01	0.00327	0.25	0.003	0.01	0.66321	0.01	-0.000	0.01	0.98909	0.00	-0.001	0.01	0.82725	0.00	0.001	0.01	0.89127	0.00				
	S1	M	0.003	0.01	0.67071	0.01	-0.005	0.01	0.42819	0.02	0.004	0.01	0.53059	0.01	-0.004	0.01	0.53398	0.01	-0.004	0.01	0.57116	0.01				
	S2	F+M	0.007	0.00	0.11421	0.04	0.005	0.00	0.33593	0.01	0.001	0.00	0.78883	0.00	-0.005	0.00	0.30352	0.02	-0.001	0.00	0.80165	0.00				
	S2	F	0.015	0.01	0.02491	0.15	0.002	0.01	0.75329	0.00	0.001	0.01	0.91035	0.00	-0.002	0.01	0.73685	0.00	0.002	0.01	0.79798	0.00				
	S2	M	-0.001	0.01	0.90451	0.00	0.007	0.01	0.29587	0.03	0.003	0.01	0.69606	0.00	-0.006	0.01	0.33403	0.03	-0.004	0.01	0.52535	0.01				
	S3	F+M	0.012	0.00	0.01245	0.09	0.001	0.00	0.87812	0.00	0.003	0.00	0.53970	0.01	0.004	0.00	0.36632	0.01	0.002	0.00	0.70918	0.00				
	S3	F	0.021	0.01	0.00167	0.29	-0.003	0.01	0.65529	0.01	0.006	0.01	0.37097	0.02	0.012	0.01	0.06452	0.10	0.000	0.01	0.94469	0.00				
	S3	M	0.001	0.01	0.83031	0.00	0.005	0.01	0.48058	0.01	0.001	0.01	0.83905	0.00	-0.004	0.01	0.59492	0.01	0.002	0.01	0.73000	0.00				
	S4	F+M	0.010	0.00	0.03170	0.07	-0.001	0.00	0.82820	0.00	0.006	0.00	0.17776	0.03	0.002	0.00	0.69101	0.00	-0.001	0.00	0.82039	0.00				
	S4	F	0.019	0.01	0.00381	0.25	-0.009	0.01	0.18650	0.05	0.006	0.01	0.37490	0.02	0.008	0.01	0.22961	0.05	-0.004	0.01	0.56555	0.01				
	S4	M	-0.000	0.01	0.94450	0.00	0.007	0.01	0.27556	0.04	0.008	0.01	0.22668	0.04	-0.004	0.01	0.50487	0.01	0.002	0.01	0.77807	0.00				
	S5	F+M	0.010	0.00	0.04484	0.06	-0.003	0.00	0.57191	0.01	0.011	0.00	0.02618	0.08	0.003	0.00	0.61101	0.00	0.001	0.00	0.88315	0.00				
	S5	F	0.019	0.01	0.00454	0.24	-0.007	0.01	0.33015	0.03	0.010	0.01	0.12710	0.07	0.010	0.01	0.12870	0.08	-0.000	0.01	0.99576	0.00				
	S5	M	-0.002	0.01	0.73475	0.00	0.001	0.01	0.91951	0.00	0.012	0.01	0.07043	0.10	-0.006	0.01	0.38166	0.02	0.001	0.01	0.86829	0.00				
	S6	F+M	0.008	0.00	0.09374	0.04	-0.001	0.00	0.82700	0.00	0.009	0.00	0.05385	0.06	0.001	0.00	0.87083	0.00	0.002	0.00	0.60345	0.00				
	S6	F	0.017	0.01	0.01081	0.19	-0.004	0.01	0.53146	0.01	0.009	0.01	0.19040	0.05	0.009	0.01	0.17690	0.06	0.003	0.01	0.62256	0.01				
	S6	M	-0.003	0.01	0.60615	0.01	0.002	0.01	0.78901	0.00	0.010	0.01	0.11789	0.07	-0.008	0.01	0.23063	0.05	0.001	0.01	0.89256	0.00				
	S7	F+M	0.011	0.00	0.01797	0.09	-0.005	0.00	0.26910	0.02	0.009	0.00	0.06201	0.05	0.002	0.00	0.63776	0.00	-0.002	0.00	0.69096	0.00				
	S7	F	0.019	0.01	0.00417	0.24	-0.009	0.01	0.17059	0.06	0.010	0.01	0.15438	0.06	0.010	0.01	0.12973	0.08	-0.002	0.01	0.78022	0.00				
	S7	M	0.001	0.01	0.86890	0.00	-0.001	0.01	0.84143	0.00	0.009	0.01	0.18122	0.05	-0.006	0.01	0.35850	0.03	-0.002	0.01	0.71924	0.00				
	S8	F+M	0.012	0.00	0.01143	0.10	-0.004	0.00	0.36081	0.01	0.009	0.00	0.05173	0.06	0.002	0.00	0.73700	0.00	-0.002	0.00	0.72863	0.00				

Table S4-4. Effect estimates (Beta, SE, two-sided p value, and R² as percentage) of polygenic risk scores on target phenotypes related to lifetime use of licit substance, substance use disorders, and psychiatric disorders. Modelling in these associations stratified the target sample by sex into females (F), males (M) and both sexes together (F+M). PRS was calculated for five discovery phenotypes smoking initiation (SI), age of initiation of regular smoking (AI), number of cigarettes per day (CPD), smoking cessation (SC) and drinks per week (DPW) at eight p value thresholds (PT): 5e-08 (S1), 1e-05 (S2), 1e-03 (S3), 1e-02 (S4), 5e-02 (S5), 1e-01 (S6), 5e-01 (S7), and 1 (S8). Associations that survive multiple testing are presented in bold-face blue. The corrected significance threshold is 7.142857e-04.

Target phenotype	PT	SI				AI				CPD				SC				DPW				
		Sex	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²	Beta	SE	p-value	R ²
		S8	F	0.020	0.01	0.00267	0.27	-0.009	0.01	0.19304	0.05	0.010	0.01	0.14049	0.07	0.009	0.01	0.17828	0.06	-0.001	0.01	0.82477
	S8	M	0.002	0.01	0.80047	0.00	-0.000	0.01	0.99842	0.00	0.009	0.01	0.16656	0.06	-0.006	0.01	0.35344	0.03	-0.002	0.01	0.72247	0.00
Mania screen	S1	F+M	-0.000	0.00	0.91319	0.00	0.001	0.00	0.56380	0.01	0.001	0.00	0.29092	0.02	-0.002	0.00	0.13222	0.04	0.001	0.00	0.44826	0.01
	S1	F	0.001	0.00	0.71875	0.00	0.002	0.00	0.28019	0.04	0.000	0.00	0.88202	0.00	-0.003	0.00	0.12167	0.09	0.000	0.00	0.96650	0.00
	S1	M	-0.001	0.00	0.52663	0.01	-0.001	0.00	0.70251	0.01	0.003	0.00	0.19344	0.06	-0.001	0.00	0.70034	0.01	0.002	0.00	0.27004	0.04
	S2	F+M	0.000	0.00	0.92064	0.00	-0.001	0.00	0.41171	0.01	0.001	0.00	0.40140	0.01	-0.003	0.00	0.06460	0.06	0.001	0.00	0.50705	0.01
	S2	F	-0.000	0.00	0.98809	0.00	-0.001	0.00	0.49902	0.02	0.001	0.00	0.61487	0.01	-0.003	0.00	0.12664	0.08	-0.001	0.00	0.61296	0.01
	S2	M	0.000	0.00	0.91627	0.00	-0.001	0.00	0.63576	0.01	0.001	0.00	0.58913	0.01	-0.002	0.00	0.35243	0.03	0.003	0.00	0.10600	0.09
	S3	F+M	0.002	0.00	0.19539	0.03	-0.000	0.00	0.99738	0.00	-0.000	0.00	0.93804	0.00	-0.002	0.00	0.18006	0.03	0.001	0.00	0.32777	0.02
	S3	F	0.001	0.00	0.48921	0.02	0.000	0.00	0.95368	0.00	0.000	0.00	0.82207	0.00	-0.002	0.00	0.36628	0.03	-0.003	0.00	0.15823	0.07
	S3	M	0.002	0.00	0.21001	0.06	-0.000	0.00	0.90868	0.00	-0.001	0.00	0.61216	0.01	-0.002	0.00	0.31475	0.04	0.006	0.00	0.00146	0.36
	S4	F+M	0.002	0.00	0.12662	0.04	-0.001	0.00	0.51281	0.01	0.002	0.00	0.11676	0.04	-0.001	0.00	0.30491	0.02	-0.001	0.00	0.57855	0.01
	S4	F	0.001	0.00	0.72458	0.00	-0.001	0.00	0.47981	0.02	0.002	0.00	0.20604	0.06	-0.002	0.00	0.39763	0.03	-0.004	0.00	0.05656	0.13
	S4	M	0.004	0.00	0.05070	0.13	-0.000	0.00	0.81874	0.00	0.002	0.00	0.40327	0.03	-0.001	0.00	0.51835	0.02	0.003	0.00	0.13921	0.08
	S5	F+M	0.002	0.00	0.20539	0.03	-0.000	0.00	0.77781	0.00	0.002	0.00	0.19635	0.03	-0.000	0.00	0.83201	0.00	0.000	0.00	0.79025	0.00
	S5	F	-0.001	0.00	0.74928	0.00	-0.001	0.00	0.64227	0.01	0.002	0.00	0.24592	0.05	-0.001	0.00	0.65033	0.01	-0.002	0.00	0.21029	0.06
	S5	M	0.004	0.00	0.02110	0.19	0.000	0.00	0.95359	0.00	0.001	0.00	0.57014	0.01	0.000	0.00	0.93994	0.00	0.004	0.00	0.05413	0.13
	S6	F+M	0.001	0.00	0.29121	0.02	-0.000	0.00	0.78113	0.00	0.001	0.00	0.27937	0.02	0.000	0.00	0.97868	0.00	0.001	0.00	0.48798	0.01
	S6	F	-0.001	0.00	0.47072	0.02	-0.000	0.00	0.87107	0.00	0.002	0.00	0.40504	0.03	-0.001	0.00	0.72014	0.00	-0.002	0.00	0.39172	0.03
	S6	M	0.005	0.00	0.01502	0.21	-0.001	0.00	0.76403	0.00	0.001	0.00	0.50714	0.02	0.001	0.00	0.75854	0.00	0.004	0.00	0.03835	0.15
	S7	F+M	0.001	0.00	0.36458	0.01	-0.002	0.00	0.16249	0.04	0.001	0.00	0.43806	0.01	-0.000	0.00	0.71432	0.00	0.001	0.00	0.47610	0.01
	S7	F	-0.002	0.00	0.42552	0.02	-0.003	0.00	0.19666	0.06	0.001	0.00	0.62333	0.01	-0.001	0.00	0.60195	0.01	-0.003	0.00	0.11011	0.09
	S7	M	0.004	0.00	0.02311	0.18	-0.002	0.00	0.44117	0.02	0.001	0.00	0.56782	0.01	-0.000	0.00	0.88872	0.00	0.006	0.00	0.00310	0.31
	S8	F+M	0.001	0.00	0.36463	0.01	-0.002	0.00	0.20311	0.03	0.001	0.00	0.47753	0.01	-0.001	0.00	0.67904	0.00	0.001	0.00	0.43103	0.01
	S8	F	-0.002	0.00	0.33391	0.03	-0.002	0.00	0.20692	0.06	0.001	0.00	0.62442	0.01	-0.001	0.00	0.55449	0.01	-0.003	0.00	0.11344	0.09
	S8	M	0.005	0.00	0.01351	0.22	-0.001	0.00	0.53586	0.01	0.001	0.00	0.63649	0.01	-0.000	0.00	0.89300	0.00	0.006	0.00	0.00242	0.33

Table S5-1. SNP heritability estimated for use of different substances analysed using LD score correlation. Heritability in liability scale was used for binary trait and observed scale was used for continuous traits. Z scores were derived by dividing the heritability estimates by the standard errors (SE), assuming that these quotients follow a Z distribution. Two-tailed p values were calculated in R using the equation: $2 * \text{pnorm}(\text{abs}(z), \text{lower.tail} = F)$.

Sample	Substance	Trait	Type	Sample size	Prevalence	SNP heritability					
						Lambda	Mean	Chisq	Intercept		
						GC	Intercept	SE			
GSCAN	alcohol	Drinks consumed per week	continuous	185,828	NA	0.042	0.003	1.108	1.132	0.980	0.007
GSCAN	nicotine	Age of initiation of regular smoking	continuous	119,239	NA	0.033	0.004	1.068	1.074	0.998	0.007
GSCAN	nicotine	Cigarettes smoked per day	continuous	122,027	NA	0.062	0.008	1.096	1.123	0.975	0.008
GSCAN	nicotine	Smoking cessation	binary	125,361	0.659	0.063	0.007	1.053	1.065	0.964	0.007
GSCAN	nicotine	Regular smoking initiation	binary	207,726	0.539	0.109	0.006	1.204	1.236	0.957	0.008
ICC	cannabis	Cannabis initiation	binary	164,741	0.267	0.065	0.004	1.184	1.213	0.996	0.007
UKB	alcohol	Estimated standard drinks per week	continuous	296,735	NA	0.068	0.004	1.369	1.432	1.034	0.009
UKB	caffeine	Caffeine consumed per day	continuous	168,919	NA	0.057	0.006	1.146	1.206	1.013	0.008
UKB	nicotine	Cigarettes smoked per day	continuous	25,153	NA	0.088	0.023	1.047	1.057	1.014	0.007
UKB	nicotine	Pack years of smoking	continuous	186,411	NA	0.093	0.005	1.310	1.357	1.015	0.008

Table S5-2. Genetic correlations (rG) between the initiation or use of different substances analysed by LD score correlation analysis. The significance threshold was 0.00111111 (0.05/45). Analyses that survived multiple testing are shown in blue and boldface. Details of multiple testing correction was provided in the method section.

No.	Trait 1			Trait 2			Genetic correlations			
	Sample	Substance	Trait	Sample	Substance	Trait	rG	SE	Z score	p value
1	UKB	alcohol	Estimated standard drinks per week	UKB	tobacco	Pack years of smoking	0.222	0.028	7.981	1.4E-15
2	UKB	tobacco	Cigarettes smoked per day	UKB	tobacco	Pack years of smoking	0.534	0.077	6.977	3.0E-12
3	UKB	tobacco	Cigarettes smoked per day	UKB	alcohol	Estimated standard drinks per week	0.025	0.068	0.368	7.1E-01
4	UKB	caffeine	Caffeine consumed per day	UKB	tobacco	Pack years of smoking	0.383	0.050	7.639	2.2E-14
5	UKB	caffeine	Caffeine consumed per day	UKB	alcohol	Estimated standard drinks per week	0.157	0.041	3.799	1.0E-04
6	UKB	caffeine	Caffeine consumed per day	UKB	tobacco	Cigarettes smoked per day	0.475	0.094	5.059	4.2E-07
7	ICC	cannabis	Cannabis initiation	UKB	tobacco	Pack years of smoking	0.392	0.035	11.28	1.6E-29
8	ICC	cannabis	Cannabis initiation	UKB	alcohol	Estimated standard drinks per week	0.382	0.035	10.87	1.6E-27
9	ICC	cannabis	Cannabis initiation	UKB	tobacco	Cigarettes smoked per day	-0.225	0.077	-2.94	3.2E-03
10	ICC	cannabis	Cannabis initiation	UKB	coffee	Caffeine consumed per day	-.017	0.046	-.375	7.1E-01
11	GSCAN	tobacco	Regular smoking initiation	UKB	tobacco	Pack years of smoking	0.874	0.031	28.66	1.E-180
12	GSCAN	tobacco	Regular smoking initiation	UKB	alcohol	Estimated standard drinks per week	0.270	0.028	9.760	1.7E-22
13	GSCAN	tobacco	Regular smoking initiation	UKB	tobacco	Cigarettes smoked per day	0.153	0.074	2.069	3.9E-02
14	GSCAN	tobacco	Regular smoking initiation	UKB	coffee	Caffeine consumed per day	0.280	0.039	7.136	9.6E-13
15	GSCAN	tobacco	Regular smoking initiation	ICC	cannabis	Cannabis initiation	0.402	0.033	12.17	4.8E-34
16	GSCAN	tobacco	Smoking cessation	UKB	tobacco	Pack years of smoking	0.462	0.045	10.28	8.3E-25
17	GSCAN	tobacco	Smoking cessation	UKB	alcohol	Estimated standard drinks per week	0.112	0.043	2.592	9.5E-03
18	GSCAN	tobacco	Smoking cessation	UKB	tobacco	Cigarettes smoked per day	0.533	0.116	4.595	4.3E-06
19	GSCAN	tobacco	Smoking cessation	UKB	coffee	Caffeine consumed per day	0.279	0.062	4.468	7.9E-06
20	GSCAN	tobacco	Smoking cessation	ICC	cannabis	Cannabis initiation	-.061	0.052	-1.17	2.4E-01
21	GSCAN	tobacco	Smoking cessation	GSCAN	tobacco	Regular smoking initiation	0.421	0.047	8.937	4.0E-19
22	GSCAN	alcohol	Drinks consumed per week	UKB	tobacco	Pack years of smoking	0.256	0.038	6.818	9.2E-12
23	GSCAN	alcohol	Drinks consumed per week	UKB	alcohol	Estimated standard drinks per week	0.911	0.042	21.91	2.E-106
24	GSCAN	alcohol	Drinks consumed per week	UKB	tobacco	Cigarettes smoked per day	0.143	0.081	1.774	7.6E-02
25	GSCAN	alcohol	Drinks consumed per week	UKB	coffee	Caffeine consumed per day	0.143	0.047	3.037	2.4E-03
26	GSCAN	alcohol	Drinks consumed per week	ICC	cannabis	Cannabis initiation	0.382	0.046	8.348	7.0E-17
27	GSCAN	alcohol	Drinks consumed per week	GSCAN	tobacco	Regular smoking initiation	0.359	0.038	9.358	8.1E-21

Table S5-2. Genetic correlations (rG) between the initiation or use of different substances analysed by LD score correlation analysis. The significance threshold was 0.00111111 (0.05/45). Analyses that survived multiple testing are shown in blue and boldface. Details of multiple testing correction was provided in the method section.

No.	Trait 1			Trait 2			Genetic correlations			
	Sample	Substance	Trait	Sample	Substance	Trait	rG	SE	Z score	p value
28	GSCAN alcohol	Drinks consumed per week		GSCAN tobacco	tobacco	Smoking cessation	0.052	0.058	0.900	3.7E-01
29	GSCAN tobacco	Cigarettes smoked per day		UKB	tobacco	Pack years of smoking	0.696	0.041	16.84	1.3E-63
30	GSCAN tobacco	Cigarettes smoked per day		UKB	alcohol	Estimated standard drinks per week	0.006	0.040	0.162	8.7E-01
31	GSCAN tobacco	Cigarettes smoked per day		UKB	tobacco	Cigarettes smoked per day	0.941	0.117	8.036	9.3E-16
32	GSCAN tobacco	Cigarettes smoked per day		UKB	caffeine	Caffeine consumed per day	0.411	0.087	4.748	2.1E-06
33	GSCAN tobacco	Cigarettes smoked per day		ICC	cannabis	Cannabis initiation	0.005	0.048	0.100	9.2E-01
34	GSCAN tobacco	Cigarettes smoked per day		GSCAN	tobacco	Regular smoking initiation	0.425	0.054	7.909	2.6E-15
35	GSCAN tobacco	Cigarettes smoked per day		GSCAN	tobacco	Smoking cessation	0.335	0.058	5.739	9.5E-09
36	GSCAN tobacco	Cigarettes smoked per day		GSCAN	alcohol	Drinks consumed per week	0.121	0.056	2.185	2.9E-02
37	GSCAN tobacco	Age of initiation of regular smoking		UKB	tobacco	Pack years of smoking	-.821	0.061	-13.5	1.0E-41
38	GSCAN tobacco	Age of initiation of regular smoking		UKB	alcohol	Estimated standard drinks per week	-.130	0.052	-2.50	1.3E-02
39	GSCAN tobacco	Age of initiation of regular smoking		UKB	tobacco	Cigarettes smoked per day	-.245	0.112	-2.18	2.9E-02
40	GSCAN tobacco	Age of initiation of regular smoking		UKB	caffeine	Caffeine consumed per day	-.196	0.061	-3.20	1.4E-03
41	GSCAN tobacco	Age of initiation of regular smoking		ICC	cannabis	Cannabis initiation	-.196	0.057	-3.46	5.0E-04
42	GSCAN tobacco	Age of initiation of regular smoking		GSCAN	tobacco	Regular smoking initiation	-.785	0.056	-14.1	4.5E-45
43	GSCAN tobacco	Age of initiation of regular smoking		GSCAN	tobacco	Smoking cessation	-.321	0.078	-4.10	4.2E-05
44	GSCAN tobacco	Age of initiation of regular smoking		GSCAN	alcohol	Drinks consumed per week	-.214	0.070	-3.06	2.2E-03
45	GSCAN tobacco	Age of initiation of regular smoking		GSCAN	tobacco	Cigarettes smoked per day	-.443	0.062	-7.10	1.3E-12

Table S3 Proportion of variance of exposure traits that were explained by individual genetic instruments (R^2). SNP: genome-wide significant SNPs selected as genetic instruments for exposure traits in MR analyses. PVALUE: association p values of the instruments. A1FREQ: effect allele frequency. BETA: effect size. R_square_SNP: R^2 by individual SNPs. R^2 by all SNPs is shown as the last row for each exposure (SNP= Total). See supporting information for the equation for calculating R^2 .

No.	Exposure	SNP	β	p value	A1FREQ	R^2
1	Regular smoking initiation	rs2155646		1.03E-10	0.61252	
2	Regular smoking initiation	rs7613360	-0.0183941	1.88E-9	0.602016	0.0006745746
3	Regular smoking initiation	rs62025923		2.6E-9	0.795548	
4	Regular smoking initiation	rs2162965	-0.0363663	2.79E-9	0.751556	0.0020548843
5	Regular smoking initiation	rs6756212	0.00740253	4.73E-9	0.461532	0.0001133239
6	Regular smoking initiation	rs184584210		1.06E-8		
7	Regular smoking initiation	rs325535	-Inf	2.02E-8	0.837055	
8	Regular smoking initiation	rs951740	-0.0285353	4.58E-8	0.377472	0.0015922373
9	Regular smoking initiation	Total				0.0044350201
10	Cannabis initiation	rs1368740	-0.067282549	1.338E-13	0.749198	0.0099061078
			2080111			
11	Cannabis initiation	rs9919557		6.534E-11	0.612214	
12	Cannabis initiation	rs4099556	-0.071523929	5.908E-9	0.180395	0.0088085088
			0552926			
13	Cannabis initiation	rs17761723	-0.036106048	2.153E-8	0.653659	0.0034370484
			7603084			
14	Cannabis initiation	Total				0.022151665
15	Caffeine consumed per day	rs2472297	-15.3909	7.8E-126	0.727035	0.0032870353
16	Caffeine consumed per day	rs4410790	-9.93959	2.6E-61	0.359539	0.0015907052
17	Caffeine consumed per day	rs17685	-6.21188	2.1E-22	0.720091	0.0005438316
18	Caffeine consumed per day	rs6947616	7.45343	1.2E-16	0.878457	0.0004147409
19	Caffeine consumed per day	rs9624470	-4.57915	5.9E-15	0.420057	0.0003571719
20	Caffeine consumed per day	rs199980439	-6.12289	2.8E-12	0.874447	0.0002877979
21	Caffeine consumed per day	rs6062679	-3.92816	1E-11	0.532389	0.0002686001
22	Caffeine consumed per day	rs182565048	-19.404	3.1E-11	0.974287	0.0006595326
23	Caffeine consumed per day	rs565223578	-11.5033	1.7E-10	0.947765	0.0004580588
24	Caffeine consumed per day	rs6145633	9.40229	1.8E-10	0.931778	0.0003929328
25	Caffeine consumed per day	rs8614	-4.77086	1.8E-10	0.81981	0.0002350993
26	Caffeine consumed per day	rs11383974	3.6289	1.2E-9	0.356802	0.0002113178
27	Caffeine consumed per day	rs780093	-3.57811	1.3E-9	0.379809	0.0002108687
28	Caffeine consumed per day	rs199736118	8.25393	3.5E-9	0.919365	0.0003531402
29	Caffeine consumed per day	rs117968677	11.195	9.1E-9	0.976221	0.0002034248

Table S3 Proportion of variance of exposure traits that were explained by individual genetic instruments (R^2). SNP: genome-wide significant SNPs selected as genetic instruments for exposure traits in MR analyses. PVALUE: association p values of the instruments. A1FREQ: effect allele frequency. BETA: effect size. R_square_SNP: R^2 by individual SNPs. R^2 by all SNPs is shown as the last row for each exposure (SNP= Total). See supporting information for the equation for calculating R^2 .

No.	Exposure	SNP	β	p value	A1FREQ	R^2
30	Caffeine consumed per day	rs9611522	3.70119	1.1E-8	0.741721	0.000183496
31	Caffeine consumed per day	rs1481012	5.21775	1.3E-8	0.888339	0.0001888256
32	Caffeine consumed per day	rs587714234	-3.26114	1.3E-8	0.529127	0.0001852749
33	Caffeine consumed per day	rs539726870	-5.31437	1.5E-8	0.881063	0.0002069386
34	Caffeine consumed per day	rs571868206	-16.4571	2.7E-8	0.980835	0.0003559799
35	Caffeine consumed per day	rs6415788	-3.25726	4E-8	0.396426	0.0001775054
36	Caffeine consumed per day	rs199879971	3.94336	4.3E-8	0.809886	0.0001674113
37	Caffeine consumed per day	Total				0.0109396895
38	Estimated standard drinks per week	rs1229984	-3.65259	8E-155	0.0217686	0.0020994901
39	Estimated standard drinks per week	rs1260326	-0.577313	1.6E-44	0.393415	0.0005877669
40	Estimated standard drinks per week	rs11940694	-0.514113	3.2E-35	0.391387	0.0004652696
41	Estimated standard drinks per week	rs1302808	-0.532449	2.6E-25	0.800307	0.0003348231
42	Estimated standard drinks per week	rs13107325	0.696931	9.7E-20	0.924731	0.0002498337
43	Estimated standard drinks per week	rs572771346	0.442567	3.2E-16	0.809947	0.0002228072
44	Estimated standard drinks per week	rs1004787	-0.314259	7.2E-15	0.469081	0.0001817571
45	Estimated standard drinks per week	rs61873510	0.332841	2.7E-14	0.672933	0.0001801864
46	Estimated standard drinks per week	rs56094641	0.313235	2.8E-14	0.596995	0.0001744462
47	Estimated standard drinks per week	rs9822731	-0.345202	4.1E-13	0.776068	0.0001530391
48	Estimated standard drinks per week	rs13413953	0.295064	1.5E-12	0.641508	0.0001479633
49	Estimated standard drinks per week	rs11604680	0.285453	3.1E-11	0.678383	0.0001313781
50	Estimated standard drinks per week	rs528834309	-0.293752	3.6E-11	0.635621	0.0001476907
51	Estimated standard drinks per week	rs2925635	-0.281023	4.3E-11	0.400473	0.0001401218
52	Estimated standard drinks per week	rs7132908	0.257574	2.4E-10	0.615544	0.0001160245
53	Estimated standard drinks per week	rs113441031	0.333488	4.2E-10	0.827707	0.0001172046
54	Estimated standard drinks per week	rs34305371	0.404585	7.1E-10	0.898949	0.0001098842
55	Estimated standard drinks per week	rs7786376	-0.283968	7.4E-10	0.720681	0.0001199561
56	Estimated standard drinks per week	rs141769737	-0.385074	1.1E-9	0.884177	0.0001122179
57	Estimated standard drinks per week	rs11078696	-0.316889	1.3E-9	0.196746	0.000117277
58	Estimated standard drinks per week	rs11860773	0.309727	1.5E-9	0.804905	0.000111324
59	Estimated standard drinks per week	rs72726477	0.372624	1.9E-9	0.877918	0.0001099733
60	Estimated standard drinks per week	rs28929474	0.853481	2E-9	0.980066	0.0001051665
61	Estimated standard drinks per week	rs758239226	0.312353	2.3E-9	0.805912	0.0001127762

Table S3 Proportion of variance of exposure traits that were explained by individual genetic instruments (R^2). SNP: genome-wide significant SNPs selected as genetic instruments for exposure traits in MR analyses. PVALUE: association p values of the instruments. A1FREQ: effect allele frequency. BETA: effect size. R_square_SNP: R^2 by individual SNPs. R^2 by all SNPs is shown as the last row for each exposure (SNP= Total). See supporting information for the equation for calculating R^2 .

No.	Exposure	SNP	β	p value	A1FREQ	R^2
62	Estimated standard drinks per week	rs113443718	0.262322	3.1E-9	0.689752	0.0001088206
63	Estimated standard drinks per week	rs4480324	0.26101	3.4E-9	0.295394	0.0001047857
64	Estimated standard drinks per week	rs60180050	-0.249526	4.2E-9	0.563907	0.0001131509
65	Estimated standard drinks per week	rs322764	-0.232074	6E-9	0.440461	0.0000980913
66	Estimated standard drinks per week	rs10267593	-0.316961	7.9E-9	0.832641	0.0001034566
67	Estimated standard drinks per week	rs11696120	-0.240623	9.3E-9	0.359358	0.0000985047
68	Estimated standard drinks per week	rs34869453	-0.239079	1E-8	0.571896	0.0001034163
69	Estimated standard drinks per week	rs429150	0.236987	1.1E-8	0.558503	0.0001023392
70	Estimated standard drinks per week	rs838145	0.232882	1.1E-8	0.459182	0.0000995286
71	Estimated standard drinks per week	rs33705	0.237729	1.7E-8	0.354743	0.0000955984
72	Estimated standard drinks per week	rs6999407	-0.286874	1.9E-8	0.187039	0.000092475
73	Estimated standard drinks per week	rs67404678	-0.347545	2.8E-8	0.878894	0.0000950089
74	Estimated standard drinks per week	rs11692435	-0.418218	3.1E-8	0.916227	0.0000992093
75	Estimated standard drinks per week	rs2955256	0.234174	3.7E-8	0.674818	0.0000889263
76	Estimated standard drinks per week	rs11428617	-0.228214	3.9E-8	0.362456	0.0000889385
77	Estimated standard drinks per week	Total				0.007840628

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS			Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait		n SNPs	Method	Q p value	Effect size [95%CI]	p value
GSCAN	Regular smoking initiation	1.0E-05	ICC	Cannabis initiation		76	IVW	6.4E-06	1.185 [1.035 , 1.355]	1.36E-02
GSCAN	Regular smoking initiation	1.0E-05	ICC	Cannabis initiation		76	Egger	7.6E-06	0.993 [0.694 , 1.422]	9.70E-01
GSCAN	Regular smoking initiation	1.0E-05	ICC	Cannabis initiation		76	W Median		1.147 [0.985 , 1.335]	7.67E-02
GSCAN	Regular smoking initiation	1.0E-05	ICC	Cannabis initiation		76	W Mode		1.173 [0.865 , 1.591]	3.08E-01
GSCAN	Regular smoking initiation	5.0E-08	ICC	Cannabis initiation		7	IVW	8.6E-05	1.223 [0.697 , 2.145]	4.82E-01
GSCAN	Regular smoking initiation	5.0E-08	ICC	Cannabis initiation		7	Egger	5.2E-05	4.696 [0.010 , 2288]	6.45E-01
GSCAN	Regular smoking initiation	5.0E-08	ICC	Cannabis initiation		7	W Median		1.090 [0.752 , 1.581]	6.49E-01
GSCAN	Regular smoking initiation	5.0E-08	ICC	Cannabis initiation		7	W Mode		1.099 [0.706 , 1.709]	6.91E-01
GSCAN	Regular smoking initiation	1.0E-05	UKB	Caffeine consumed per day	67	IVW	1.1E-01		15.28 [8.389 , 22.16]	1.38E-05
GSCAN	Regular smoking initiation	1.0E-05	UKB	Caffeine consumed per day	67	Egger	9.5E-02		9.686 [-18.4 , 37.74]	5.01E-01
GSCAN	Regular smoking initiation	1.0E-05	UKB	Caffeine consumed per day	67	W Median			14.12 [5.076 , 23.16]	2.21E-03
GSCAN	Regular smoking initiation	1.0E-05	UKB	Caffeine consumed per day	67	W Mode			12.33 [-9.36 , 34.02]	2.69E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Caffeine consumed per day	7	IVW	8.9E-01		40.17 [24.01 , 56.33]	1.10E-06
GSCAN	Regular smoking initiation	5.0E-08	UKB	Caffeine consumed per day	7	Egger	8.1E-01		57.69 [-111 , 226.2]	5.32E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Caffeine consumed per day	7	W Median			38.67 [18.27 , 59.07]	2.03E-04

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS			Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait		n SNPs	Method	Q p value	Effect size [95%CI]	p value
GSCAN	Regular smoking initiation	5.0E-08	UKB	Caffeine consumed per day		7	W Mode		37.92 [7.917 , 67.92]	4.80E-02
GSCAN	Regular smoking initiation	1.0E-05	UKB	Cigarettes smoked per day		67	IVW	1.5E-01	1.024 [0.143 , 1.905]	2.27E-02
GSCAN	Regular smoking initiation	1.0E-05	UKB	Cigarettes smoked per day		67	Egger	1.4E-01	-.309 [-3.89 , 3.277]	8.66E-01
GSCAN	Regular smoking initiation	1.0E-05	UKB	Cigarettes smoked per day		67	W Median		0.562 [-.628 , 1.753]	3.55E-01
GSCAN	Regular smoking initiation	1.0E-05	UKB	Cigarettes smoked per day		67	W Mode		0.195 [-2.53 , 2.921]	8.89E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Cigarettes smoked per day		7	IVW	6.2E-01	0.918 [-1.18 , 3.012]	3.90E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Cigarettes smoked per day		7	Egger	5.0E-01	4.144 [-17.8 , 26.06]	7.26E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Cigarettes smoked per day		7	W Median		0.633 [-2.12 , 3.387]	6.52E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Cigarettes smoked per day		7	W Mode		1.274 [-2.76 , 5.312]	5.59E-01
GSCAN	Regular smoking initiation	1.0E-05	UKB	Estimated standard drinks per week		67	IVW	7.7E-21	1.111 [0.286 , 1.936]	8.32E-03
GSCAN	Regular smoking initiation	1.0E-05	UKB	Estimated standard drinks per week		67	Egger	2.6E-16	-3.75 [-6.88 , -.612]	2.22E-02
GSCAN	Regular smoking initiation	1.0E-05	UKB	Estimated standard drinks per week		67	W Median		0.514 [-.191 , 1.218]	1.53E-01
GSCAN	Regular smoking initiation	1.0E-05	UKB	Estimated standard drinks per week		67	W Mode		0.389 [-.966 , 1.743]	5.76E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Estimated standard drinks per week		7	IVW	4.9E-01	0.988 [-.144 , 2.121]	8.72E-02
GSCAN	Regular smoking initiation	5.0E-08	UKB	Estimated standard drinks per week		7	Egger	3.7E-01	1.763 [-10.5 , 14.05]	7.90E-01

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
GSCAN	Regular smoking initiation	5.0E-08	UKB	Estimated standard drinks per week	7	W Median		0.495 [-1.03, 2.023]	5.25E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Estimated standard drinks per week	7	W Mode		0.563 [-1.40, 2.528]	5.95E-01
GSCAN	Regular smoking initiation	1.0E-05	UKB	Pack years of smoking	67	IVW	3.6E-11	4.309 [3.390, 5.227]	3.82E-20
GSCAN	Regular smoking initiation	1.0E-05	UKB	Pack years of smoking	67	Egger	7.7E-10	0.447 [-3.17, 4.062]	8.09E-01
GSCAN	Regular smoking initiation	1.0E-05	UKB	Pack years of smoking	67	W Median		4.153 [3.230 , 5.075]	1.12E-18
GSCAN	Regular smoking initiation	1.0E-05	UKB	Pack years of smoking	67	W Mode		4.195 [2.232 , 6.157]	8.47E-05
GSCAN	Regular smoking initiation	5.0E-08	UKB	Pack years of smoking	7	IVW	1.6E-03	6.279 [3.483, 9.074]	1.07E-05
GSCAN	Regular smoking initiation	5.0E-08	UKB	Pack years of smoking	7	Egger	3.8E-02	-18.0 [-41.7, 5.754]	1.98E-01
GSCAN	Regular smoking initiation	5.0E-08	UKB	Pack years of smoking	7	W Median		4.766 [2.571 , 6.961]	2.08E-05
GSCAN	Regular smoking initiation	5.0E-08	UKB	Pack years of smoking	7	W Mode		4.845 [2.017, 7.672]	1.53E-02
ICC	Cannabis initiation	1.0E-05	GSCAN	Age of initiation of regular smoking	83	IVW	7.4E-02	-.000 [-.011, .011]	9.63E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Age of initiation of regular smoking	83	Egger	8.8E-02	0.010 [-.008, .028]	2.79E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Age of initiation of regular smoking	83	W Median		0.010 [-.006, .027]	2.20E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Age of initiation of regular smoking	83	W Mode		0.011 [-.006, .027]	2.19E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Age of initiation of regular smoking	4	IVW	6.9E-01	0.006 [-.042, .054]	8.09E-01

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
ICC	Cannabis initiation	5.0E-08	GSCAN	Age of initiation of regular smoking	4	Egger	4.8E-01	-0.006 [-.349 , 0.337]	9.76E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Age of initiation of regular smoking	4	W Median		0.012 [-.046 , 0.070]	6.85E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Age of initiation of regular smoking	4	W Mode		0.024 [-.051 , 0.099]	5.80E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Cigarettes smoked per day	83	IVW	2.2E-01	0.005 [-.005 , 0.016]	3.38E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Cigarettes smoked per day	83	Egger	2.0E-01	0.001 [-.016 , 0.019]	8.65E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Cigarettes smoked per day	83	W Median		0.008 [-.010 , 0.025]	4.02E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Cigarettes smoked per day	83	W Mode		0.008 [-.011 , 0.026]	4.16E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Cigarettes smoked per day	4	IVW	6.1E-01	-.015 [-.063 , 0.033]	5.33E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Cigarettes smoked per day	4	Egger	5.5E-01	-.155 [-.498 , 0.189]	4.71E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Cigarettes smoked per day	4	W Median		-.023 [-.076 , 0.029]	3.83E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Cigarettes smoked per day	4	W Mode		-.028 [-.101 , 0.046]	5.12E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Drinks consumed per week	83	IVW	1.9E-02	0.014 [0.005 , 0.023]	3.08E-03
ICC	Cannabis initiation	1.0E-05	GSCAN	Drinks consumed per week	83	Egger	8.6E-02	-.003 [-.017 , 0.010]	6.45E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Drinks consumed per week	83	W Median		0.009 [-.004 , 0.023]	1.85E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Drinks consumed per week	83	W Mode		0.008 [-.005 , 0.022]	2.11E-01

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
ICC	Cannabis initiation	5.0E-08	GSCAN	Drinks consumed per week	4	IVW	2.9E-02	0.059 [-0.008, 0.126]	8.25E-02
ICC	Cannabis initiation	5.0E-08	GSCAN	Drinks consumed per week	4	Egger	5.2E-01	0.443 [0.169, 0.717]	8.68E-02
ICC	Cannabis initiation	5.0E-08	GSCAN	Drinks consumed per week	4	W Median		0.042 [-0.009, 0.092]	1.04E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Drinks consumed per week	4	W Mode		0.006 [-0.094, 0.106]	9.09E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Smoking cessation	80	IVW	3.1E-02	1.000 [0.996, 1.003]	8.62E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Smoking cessation	80	Egger	2.7E-02	1.000 [0.996, 1.004]	9.08E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Smoking cessation	80	W Median		1.001 [0.997, 1.005]	5.94E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Smoking cessation	80	W Mode		1.000 [0.997, 1.003]	8.55E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Smoking cessation	4	IVW	4.0E-02	0.992 [0.925, 1.064]	8.32E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Smoking cessation	4	Egger	1.8E-02	0.914 [0.497, 1.680]	8.00E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Smoking cessation	4	W Median		0.966 [0.915, 1.020]	2.09E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Smoking cessation	4	W Mode		0.963 [0.906, 1.024]	3.13E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Regular smoking initiation	83	IVW	8.0E-11	1.012 [1.000, 1.024]	4.40E-02
ICC	Cannabis initiation	1.0E-05	GSCAN	Regular smoking initiation	83	Egger	2.7E-07	0.985 [0.969, 1.002]	9.47E-02
ICC	Cannabis initiation	1.0E-05	GSCAN	Regular smoking initiation	83	W Median		0.991 [0.978, 1.004]	1.90E-01
ICC	Cannabis initiation	1.0E-05	GSCAN	Regular smoking initiation	83	W Mode		0.990 [0.975, 1.005]	1.84E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Regular smoking initiation	4	IVW	9.6E-06	1.111 [0.997, 1.238]	5.58E-02
ICC	Cannabis initiation	5.0E-08	GSCAN	Regular smoking initiation	4	Egger	7.5E-06	0.907 [0.371, 2.216]	8.50E-01
ICC	Cannabis initiation	5.0E-08	GSCAN	Regular smoking initiation	4	W Median		1.106 [1.044, 1.172]	6.73E-04

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
ICC	Cannabis initiation	5.0E-08	GSCAN	Regular smoking initiation	4	W Mode		1.110 [1.032 , 1.193]	6.74E-02
ICC	Cannabis initiation	1.0E-05	UKB	Caffeine consumed per day	73	IVW	1.5E-02	0.244 [-1.42 , 1.905]	7.73E-01
ICC	Cannabis initiation	1.0E-05	UKB	Caffeine consumed per day	73	Egger	1.3E-02	0.672 [-2.28 , 3.624]	6.57E-01
ICC	Cannabis initiation	1.0E-05	UKB	Caffeine consumed per day	73	W Median		0.483 [-2.03 , 2.997]	7.06E-01
ICC	Cannabis initiation	1.0E-05	UKB	Caffeine consumed per day	73	W Mode		0.396 [-1.90 , 2.696]	7.37E-01
ICC	Cannabis initiation	5.0E-08	UKB	Caffeine consumed per day	4	IVW	2.2E-01	5.904 [-2.35 , 14.16]	1.61E-01
ICC	Cannabis initiation	5.0E-08	UKB	Caffeine consumed per day	4	Egger	1.6E-01	26.65 [-38.8 , 92.13]	5.09E-01
ICC	Cannabis initiation	5.0E-08	UKB	Caffeine consumed per day	4	W Median		6.881 [-1.60 , 15.36]	1.12E-01
ICC	Cannabis initiation	5.0E-08	UKB	Caffeine consumed per day	4	W Mode		7.966 [-3.67 , 19.60]	2.72E-01
ICC	Cannabis initiation	1.0E-05	UKB	Cigarettes smoked per day	73	IVW	6.1E-01	-.144 [-.327 , 0.038]	1.21E-01
ICC	Cannabis initiation	1.0E-05	UKB	Cigarettes smoked per day	73	Egger	5.8E-01	-.086 [-.409 , 0.237]	6.03E-01
ICC	Cannabis initiation	1.0E-05	UKB	Cigarettes smoked per day	73	W Median		-.101 [-.406 , 0.205]	5.17E-01
ICC	Cannabis initiation	1.0E-05	UKB	Cigarettes smoked per day	73	W Mode		-.109 [-.362 , 0.145]	4.03E-01
ICC	Cannabis initiation	5.0E-08	UKB	Cigarettes smoked per day	4	IVW	3.3E-01	-.815 [-1.75 , 0.124]	8.88E-02
ICC	Cannabis initiation	5.0E-08	UKB	Cigarettes smoked per day	4	Egger	1.9E-01	-2.00 [-10.0 , 6.001]	6.73E-01

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
ICC	Cannabis initiation	5.0E-08	UKB	Cigarettes smoked per day	4	W Median		-.679 [-1.76, 0.398]	2.17E-01
ICC	Cannabis initiation	5.0E-08	UKB	Cigarettes smoked per day	4	W Mode		-.546 [-1.96, 0.871]	5.05E-01
ICC	Cannabis initiation	1.0E-05	UKB	Estimated standard drinks per week	73	IVW	4.2E-23	0.170 [-0.018, 0.357]	7.58E-02
ICC	Cannabis initiation	1.0E-05	UKB	Estimated standard drinks per week	73	Egger	7.4E-20	-.177 [-.496, 0.142]	2.80E-01
ICC	Cannabis initiation	1.0E-05	UKB	Estimated standard drinks per week	73	W Median		-.065 [-.231, 0.100]	4.38E-01
ICC	Cannabis initiation	1.0E-05	UKB	Estimated standard drinks per week	73	W Mode		-.001 [-.149, 0.148]	9.94E-01
ICC	Cannabis initiation	5.0E-08	UKB	Estimated standard drinks per week	4	IVW	1.1E-05	1.287 [-.103, 2.677]	6.96E-02
ICC	Cannabis initiation	5.0E-08	UKB	Estimated standard drinks per week	4	Egger	5.0E-02	8.840 [3.015, 14.66]	9.69E-02
ICC	Cannabis initiation	5.0E-08	UKB	Estimated standard drinks per week	4	W Median		1.041 [0.313, 1.768]	5.06E-03
ICC	Cannabis initiation	5.0E-08	UKB	Estimated standard drinks per week	4	W Mode		1.046 [-.210, 2.302]	2.01E-01
ICC	Cannabis initiation	1.0E-05	UKB	Pack years of smoking	73	IVW	1.4E-09	0.219 [0.022, 0.415]	2.96E-02
ICC	Cannabis initiation	1.0E-05	UKB	Pack years of smoking	73	Egger	7.0E-09	-.034 [-.377, 0.308]	8.44E-01
ICC	Cannabis initiation	1.0E-05	UKB	Pack years of smoking	73	W Median		-.020 [-.245, 0.206]	8.65E-01
ICC	Cannabis initiation	1.0E-05	UKB	Pack years of smoking	73	W Mode		-.007 [-.187, 0.173]	9.36E-01
ICC	Cannabis initiation	5.0E-08	UKB	Pack years of smoking	4	IVW	1.1E-03	1.267 [-.172, 2.705]	8.44E-02
ICC	Cannabis initiation	5.0E-08	UKB	Pack years of smoking	4	Egger	3.4E-04	0.613 [-11.8, 13.07]	9.32E-01
ICC	Cannabis initiation	5.0E-08	UKB	Pack years of smoking	4	W Median		1.689 [0.843, 2.536]	9.17E-05
ICC	Cannabis initiation	5.0E-08	UKB	Pack years of smoking	4	W Mode		2.002 [1.041, 2.963]	2.66E-02
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Age of initiation of regular smoking	77	IVW	2.8E-03	-.024 [-.042, -.005]	1.21E-02

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Age of initiation of regular smoking	77	Egger	1.5E-02	0.018 [-0.17, 0.053]	3.09E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Age of initiation of regular smoking	77	W Median		-.012 [-.037, 0.014]	3.84E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Age of initiation of regular smoking	77	W Mode		-.013 [-.041, 0.015]	3.66E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Age of initiation of regular smoking	14	IVW	2.9E-01	-.006 [-.030, 0.017]	5.90E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Age of initiation of regular smoking	14	Egger	2.6E-01	0.008 [-.039, 0.055]	7.50E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Age of initiation of regular smoking	14	W Median		-.013 [-.043, 0.017]	3.93E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Age of initiation of regular smoking	14	W Mode		-.015 [-.044, 0.014]	3.17E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Cigarettes smoked per day	77	IVW	1.4E-17	0.026 [-.001, 0.052]	5.51E-02
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Cigarettes smoked per day	77	Egger	6.7E-15	-.033 [-.083, 0.017]	2.03E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Cigarettes smoked per day	77	W Median		-.005 [-.029, 0.020]	7.19E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Cigarettes smoked per day	77	W Mode		-.013 [-.041, 0.015]	3.74E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Cigarettes smoked per day	14	IVW	6.7E-04	-.001 [-.037, 0.035]	9.58E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Cigarettes smoked per day	14	Egger	8.8E-04	-.030 [-.102, 0.041]	4.20E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Cigarettes smoked per day	14	W Median		-.014 [-.044, 0.015]	3.39E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Cigarettes smoked per day	14	W Mode		-.016 [-.045, 0.014]	3.18E-01

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Drinks consumed per week	79	IVW	4.4E-06	0.011 [-.005, .027]	1.69E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Drinks consumed per week	79	Egger	4.2E-06	0.001 [-.027, .030]	9.21E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Drinks consumed per week	79	W Median		0.028 [0.007, 0.049]	8.57E-03
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Drinks consumed per week	79	W Mode		0.020 [-.000, .041]	5.69E-02
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Drinks consumed per week	14	IVW	7.8E-06	0.026 [-.007, .059]	1.25E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Drinks consumed per week	14	Egger	7.6E-06	0.005 [-.062, .073]	8.76E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Drinks consumed per week	14	W Median		0.030 [0.006, 0.053]	1.22E-02
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Drinks consumed per week	14	W Mode		0.029 [0.005, 0.052]	3.28E-02
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Smoking cessation	77	IVW	1.9E-04	1.008 [0.996, 1.019]	1.79E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Smoking cessation	77	Egger	1.8E-04	1.000 [0.979, 1.022]	9.76E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Smoking cessation	77	W Median		1.007 [0.994, 1.020]	2.99E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Smoking cessation	77	W Mode		1.007 [0.993, 1.021]	3.36E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Smoking cessation	14	IVW	5.1E-01	1.018 [1.001, 1.035]	4.00E-02
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Smoking cessation	14	Egger	5.6E-01	0.998 [0.963, 1.034]	8.96E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Smoking cessation	14	W Median		1.012 [0.989, 1.035]	3.25E-01

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Exposure GWAS			Outcome GWAS			Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait		n SNPs	Method	Q p value	Effect size [95%CI]	p value
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Smoking cessation		14	W Mode		1.008 [0.985 , 1.032]	5.04E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Regular smoking initiation		78	IVW	5.9E-06	1.020 [1.004 , 1.036]	1.17E-02
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Regular smoking initiation		78	Egger	4.1E-05	0.990 [0.961 , 1.020]	5.14E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Regular smoking initiation		78	W Median		1.014 [0.993 , 1.035]	1.95E-01
UKB	Caffeine consumed per day	1.0E-05	GSCAN	Regular smoking initiation		78	W Mode		1.010 [0.990 , 1.030]	3.39E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Regular smoking initiation		15	IVW	1.4E-03	1.008 [0.983 , 1.034]	5.39E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Regular smoking initiation		15	Egger	8.4E-04	1.003 [0.952 , 1.057]	9.06E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Regular smoking initiation		15	W Median		1.013 [0.992 , 1.036]	2.33E-01
UKB	Caffeine consumed per day	5.0E-08	GSCAN	Regular smoking initiation		15	W Mode		1.010 [0.990 , 1.030]	3.53E-01
UKB	Caffeine consumed per day	1.0E-05	ICC	Cannabis initiation		74	IVW	4.0E-02	0.957 [0.918 , 0.998]	4.12E-02
UKB	Caffeine consumed per day	1.0E-05	ICC	Cannabis initiation		74	Egger	4.0E-02	0.925 [0.851 , 1.004]	6.68E-02
UKB	Caffeine consumed per day	1.0E-05	ICC	Cannabis initiation		74	W Median		0.916 [0.856 , 0.980]	1.05E-02
UKB	Caffeine consumed per day	1.0E-05	ICC	Cannabis initiation		74	W Mode		0.917 [0.858 , 0.980]	1.22E-02
UKB	Caffeine consumed per day	5.0E-08	ICC	Cannabis initiation		12	IVW	7.1E-02	0.926 [0.866 , 0.989]	2.30E-02
UKB	Caffeine consumed per day	5.0E-08	ICC	Cannabis initiation		12	Egger	1.8E-01	0.836 [0.738 , 0.947]	1.81E-02

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
UKB	Caffeine consumed per day	5.0E-08	ICC	Cannabis initiation	12	W Median		0.913 [0.850 , 0.980]	1.19E-02
UKB	Caffeine consumed per day	5.0E-08	ICC	Cannabis initiation	12	W Mode		0.905 [0.844 , 0.971]	1.80E-02
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Age of initiation of regular smoking	174	IVW	3.1E-04	-0.001 [-0.004 , 0.002]	4.10E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Age of initiation of regular smoking	174	Egger	3.3E-04	0.001 [-0.005 , 0.008]	6.38E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Age of initiation of regular smoking	174	W Median		0.000 [-0.005 , 0.006]	9.23E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Age of initiation of regular smoking	174	W Mode		0.001 [-0.005 , 0.006]	8.10E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Age of initiation of regular smoking	32	IVW	1.0E-01	-0.001 [-0.005 , 0.004]	7.68E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Age of initiation of regular smoking	32	Egger	8.1E-02	-0.001 [-0.009 , 0.007]	7.98E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Age of initiation of regular smoking	32	W Median		0.000 [-0.005 , 0.006]	9.29E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Age of initiation of regular smoking	32	W Mode		0.000 [-0.006 , 0.006]	9.82E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Cigarettes smoked per day	174	IVW	1.5E-05	-0.002 [-0.005 , 0.001]	2.72E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Cigarettes smoked per day	174	Egger	1.2E-05	-0.002 [-0.009 , 0.004]	5.24E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Cigarettes smoked per day	174	W Median		-0.001 [-0.006 , 0.005]	7.58E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Cigarettes smoked per day	174	W Mode		-0.003 [-0.009 , 0.002]	2.65E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Cigarettes smoked per day	32	IVW	3.0E-02	-0.005 [-0.009 , 0.000]	7.05E-02	

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Cigarettes smoked per day	32	Egger	3.0E-02	-0.001 [-0.009, 0.007]	7.26E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Cigarettes smoked per day	32	W Median		-0.001 [-0.007, 0.005]	7.05E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Cigarettes smoked per day	32	W Mode		-0.002 [-0.007, 0.003]	4.56E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Smoking cessation	173	IVW	3.5E-02	1.001 [1.000, 1.003]	1.71E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Smoking cessation	173	Egger	3.6E-02	1.000 [0.998, 1.002]	9.16E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Smoking cessation	173	W Median		1.000 [0.998, 1.003]	7.82E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Smoking cessation	173	W Mode		1.001 [0.998, 1.003]	6.00E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Smoking cessation	31	IVW	8.7E-02	1.000 [0.998, 1.003]	8.67E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Smoking cessation	31	Egger	6.9E-02	1.000 [0.997, 1.003]	9.49E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Smoking cessation	31	W Median		1.000 [0.998, 1.003]	7.98E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Smoking cessation	31	W Mode		1.000 [0.998, 1.003]	7.32E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Regular smoking initiation	174	IVW	2.7E-17	1.005 [1.002, 1.008]	1.15E-03	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Regular smoking initiation	174	Egger	2.2E-15	0.998 [0.992, 1.003]	4.04E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Regular smoking initiation	174	W Median		0.998 [0.995, 1.002]	2.98E-01	
UKB	Estimated standard drinks 1.0E-05 per week	GSCAN	Regular smoking initiation	174	W Mode		0.997 [0.992, 1.001]	1.21E-01	

Table S5-4. Two-sample Mendelian randomisation results on the causal associations between the initiation and use of different substances. Independent SNPs associated with exposure trait were clumped with LD window 10000 kb, R-squared 0.01. n SNPs: Number of independent SNPs used in each exposure-outcome pair. p1: Significance threshold for index SNPs. Heterogeneity tests were available from MR-Egger and inverse variance weighted MR (IVW). Raw estimates (β , SE) are the estimates from the MR estimators. These estimates were converted to interpretable scales as described in the method (Effect size [95%CI]). Abbreviated consortia: (1) GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use, (2) ICC: international cannabis consortium, (3) UKB: UK Biobank. The significance threshold was 0.002173913 (0.05/23). MR analyses that survived heterogeneity tests (i.e. Q p value ≥ 0.05) and multiple testing are shown in blue and boldface.

Exposure GWAS			Outcome GWAS		Two-sample MR analysis			Converted Estimates	
Sample	Trait	p1	Sample	Trait	n SNPs	Method	Q p value	Effect size [95%CI]	p value
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Regular smoking initiation	32	IVW	6.6E-08	1.000 [0.995 , 1.005]	8.96E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Regular smoking initiation	32	Egger	6.3E-08	0.998 [0.990 , 1.006]	6.35E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Regular smoking initiation	32	W Median		0.997 [0.993 , 1.001]	1.60E-01	
UKB	Estimated standard drinks 5.0E-08 per week	GSCAN	Regular smoking initiation	32	W Mode		0.997 [0.992 , 1.001]	1.39E-01	
UKB	Estimated standard drinks 1.0E-05 per week	ICC	Cannabis initiation	176	IVW	2.7E-22	1.016 [1.007 , 1.026]	9.20E-04	
UKB	Estimated standard drinks 1.0E-05 per week	ICC	Cannabis initiation	176	Egger	3.0E-15	0.973 [0.956 , 0.991]	3.77E-03	
UKB	Estimated standard drinks 1.0E-05 per week	ICC	Cannabis initiation	176	W Median		0.998 [0.985 , 1.011]	7.52E-01	
UKB	Estimated standard drinks 1.0E-05 per week	ICC	Cannabis initiation	176	W Mode		0.982 [0.968 , 0.996]	1.40E-02	
UKB	Estimated standard drinks 5.0E-08 per week	ICC	Cannabis initiation	30	IVW	1.0E-18	0.999 [0.978 , 1.020]	9.13E-01	
UKB	Estimated standard drinks 5.0E-08 per week	ICC	Cannabis initiation	30	Egger	1.9E-14	0.968 [0.937 , 1.000]	5.74E-02	
UKB	Estimated standard drinks 5.0E-08 per week	ICC	Cannabis initiation	30	W Median		0.984 [0.970 , 0.998]	2.86E-02	
UKB	Estimated standard drinks per week	5.0E-08	ICC	Cannabis initiation	30	W Mode		0.977 [0.964 , 0.990]	1.38E-03

Table S5-5. Global test results of Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO). Raw estimates were obtained from the MR-PRESSO estimators. These estimates were converted to interpretable effect sizes and confidence intervals (Effect size [95%CI]). The significance threshold, corrected by Bonferroni procedure, was 0.0125 (0.05/4). Analyses that survived multiple testing are shown in blue and boldface. The global test with outliers removed is shown as blank if no outliers were detected.

Exposure GWAS			Outcome GWAS			Raw Estimates			Converted Estimates
Sample	Trait	p1	Sample	Trait	Method	β	SD	p value	Effect size[95%CI]
GSCAN	Regular smoking initiation	1.0E-05	UKB	Caffeine consumed per day	MR-PRESSO global test	22.039	5.070	4.9E-05	15.28 [8.389 , 22.16]
GSCAN	Regular smoking initiation	1.0E-05	UKB	Caffeine consumed per day	MR-PRESSO global test with outliers removed				
GSCAN	Regular smoking initiation	5.0E-08	UKB	Caffeine consumed per day	MR-PRESSO global test	57.956	7.394	2.3E-04	40.17 [30.13 , 50.22]
GSCAN	Regular smoking initiation	5.0E-08	UKB	Caffeine consumed per day	MR-PRESSO global test with outliers removed				
ICC	Cannabis initiation	5.0E-08	GSCAN	Regular smoking initiation	MR-PRESSO global test	0.152	0.079	1.5E-01	1.111 [0.997 , 1.238]
ICC	Cannabis initiation	5.0E-08	GSCAN	Regular smoking initiation	MR-PRESSO global test with outliers removed	0.147	0.006	2.4E-02	1.107 [1.099 , 1.116]
ICC	Cannabis initiation	5.0E-08	UKB	Pack years of smoking	MR-PRESSO global test	1.827	1.059	1.8E-01	1.267 [-.172 , 2.705]
ICC	Cannabis initiation	5.0E-08	UKB	Pack years of smoking	MR-PRESSO global test with outliers removed	2.744	0.415	2.2E-02	1.902 [1.338 , 2.466]

Table S5-6. Results of Mendelian randomization leave-one-out analysis on the causal association between regular smoking initiation on caffeine consumed per day. SNPs that were associated with smoking initiation were clumped at p value < 1e-5 and < 5e-8. Raw estimates were obtained from the MR estimators. These estimates were converted to interpretable effect sizes and confidence intervals (Effect size [95%CI]). The significance thresholds, corrected by Bonferroni procedure, were 0.0007352941 (0.05/68) and 0.00625 (0.05/8), respectively for the clumping p value < 1e-5 and < 5e-8. Analysis that survived multiple testing was put in blue boldface.

No.	SNP removed	Exposure SNPs clumped at p value < 1e-5				Exposure SNPs clumped at p value < 5e-8				
		Raw Estimates		Converted Estimates		Raw Estimates		Converted Estimates		
		β	SE	p value	Effect size [95%CI]			SE	p value	Effect size [95%CI]
1	rs10095986	23.41	4.949	2.2E-06	16.23 [9.506 , 22.95]					
2	rs10186133	22.41	5.122	1.2E-05	15.54 [8.577 , 22.49]					
3	rs1036591	22.19	5.132	1.5E-05	15.38 [8.408 , 22.35]					
4	rs10745822	21.80	5.167	2.5E-05	15.11 [8.091 , 22.13]					
5	rs10790448	22.18	5.137	1.6E-05	15.37 [8.395 , 22.35]					
6	rs10796907	21.33	5.085	2.7E-05	14.78 [7.873 , 21.69]					
7	rs11016103	23.37	4.998	2.9E-06	16.20 [9.406 , 22.99]					
8	rs11078716	21.89	5.149	2.1E-05	15.17 [8.175 , 22.16]					
9	rs111747805	21.99	5.138	1.9E-05	15.24 [8.264 , 22.22]					
10	rs112417011	22.05	5.139	1.8E-05	15.28 [8.300 , 22.26]					
11	rs117503378	22.41	5.119	1.2E-05	15.53 [8.577 , 22.49]					
12	rs11759026	23.15	5.008	3.8E-06	16.05 [9.244 , 22.85]					
13	rs117695734	21.49	5.094	2.5E-05	14.89 [7.972 , 21.81]					
14	rs118038478	22.76	5.080	7.4E-06	15.78 [8.875 , 22.68]					
15	rs12575370	22.38	5.134	1.3E-05	15.51 [8.539 , 22.49]					
16	rs12727441	22.27	5.140	1.5E-05	15.43 [8.451 , 22.42]					
17	rs12729364	22.68	5.100	8.7E-06	15.72 [8.792 , 22.65]					
18	rs12731986	22.65	5.104	9.1E-06	15.70 [8.767 , 22.64]					
19	rs1291851	21.74	5.133	2.3E-05	15.07 [8.099 , 22.05]					
20	rs13109980	22.19	5.153	1.7E-05	15.38 [8.381 , 22.38]					
21	rs13239186	21.91	5.146	2.1E-05	15.19 [8.197 , 22.18]					
22	rs1369588	22.91	5.079	6.5E-06	15.88 [8.980 , 22.78]					
23	rs145553056	22.11	5.131	1.6E-05	15.33 [8.355 , 22.30]					
24	rs1474368	21.56	5.113	2.5E-05	14.94 [7.995 , 21.89]					
25	rs1475642	22.33	5.133	1.4E-05	15.48 [8.502 , 22.45]					
26	rs1552313	20.95	5.019	3.0E-05	14.52 [7.700 , 21.34]					
27	rs1656366	21.86	5.146	2.2E-05	15.15 [8.162 , 22.14]					
28	rs17207212	21.74	5.133	2.3E-05	15.07 [8.097 , 22.04]					
29	rs1774240	22.71	5.088	8.1E-06	15.74 [8.831 , 22.66]					

Table S5-6. Results of Mendelian randomization leave-one-out analysis on the causal association between regular smoking initiation on caffeine consumed per day. SNPs that were associated with smoking initiation were clumped at p value < 1e-5 and < 5e-8. Raw estimates were obtained from the MR estimators. These estimates were converted to interpretable effect sizes and confidence intervals (Effect size [95%CI]). The significance thresholds, corrected by Bonferroni procedure, were 0.0007352941 (0.05/68) and 0.00625 (0.05/8), respectively for the clumping p value < 1e-5 and < 5e-8. Analysis that survived multiple testing was put in blue boldface.

No.	SNP removed	Exposure SNPs clumped at p value < 1e-5				Exposure SNPs clumped at p value < 5e-8			
		Raw Estimates		Converted Estimates		Raw Estimates		Converted Estimates	
		β	SE	p value	Effect size [95%CI]	β	SE	p value	Effect size [95%CI]
30	rs186535126	22.10	5.159	1.8E-05	15.32 [8.309 , 22.33]				
31	rs2155646	21.02	5.113	3.9E-05	14.57 [7.622 , 21.51]	57.27	13.06	1.2E-05	39.70 [21.96 , 57.44]
32	rs2158359	22.33	5.132	1.4E-05	15.48 [8.506 , 22.45]				
33	rs2162965	20.98	5.089	3.7E-05	14.54 [7.631 , 21.46]	56.00	12.87	1.4E-05	38.82 [21.33 , 56.31]
34	rs2256012	22.31	5.129	1.4E-05	15.47 [8.499 , 22.44]				
35	rs2326213	20.99	5.016	2.9E-05	14.55 [7.734 , 21.36]				
36	rs281287	22.48	5.127	1.2E-05	15.58 [8.614 , 22.55]				
37	rs28717373	21.81	5.142	2.2E-05	15.12 [8.133 , 22.10]				
38	rs310333	22.13	5.139	1.7E-05	15.34 [8.356 , 22.32]				
39	rs325535	21.40	5.124	2.9E-05	14.84 [7.875 , 21.80]	58.27	12.71	4.5E-06	40.39 [23.12 , 57.65]
40	rs34253747	22.64	5.117	9.7E-06	15.69 [8.740 , 22.64]				
41	rs376345767	21.77	5.159	2.4E-05	15.09 [8.084 , 22.10]				
42	rs3781295	21.34	5.097	2.8E-05	14.79 [7.868 , 21.72]				
43	rs4352629	22.18	5.148	1.6E-05	15.37 [8.380 , 22.37]				
44	rs559928	21.40	5.105	2.8E-05	14.83 [7.899 , 21.77]				
45	rs6110373	21.90	5.142	2.1E-05	15.18 [8.194 , 22.17]				
46	rs62025923	21.35	5.131	3.2E-05	14.80 [7.831 , 21.77]	58.71	12.85	4.9E-06	40.70 [23.24 , 58.16]
47	rs62170823	22.78	5.110	8.3E-06	15.79 [8.848 , 22.73]				
48	rs6417681	21.80	5.137	2.2E-05	15.11 [8.134 , 22.09]				
49	rs6756212	20.61	5.016	4.0E-05	14.29 [7.471 , 21.10]	52.90	12.83	3.7E-05	36.67 [19.24 , 54.10]
50	rs72782486	22.57	5.105	9.8E-06	15.64 [8.708 , 22.58]				
51	rs72906609	22.42	5.154	1.4E-05	15.54 [8.539 , 22.54]				
52	rs75082010	22.00	5.129	1.8E-05	15.25 [8.279 , 22.21]				
53	rs75177132	22.63	5.106	9.4E-06	15.68 [8.746 , 22.62]				
54	rs7613360	21.40	5.140	3.1E-05	14.83 [7.848 , 21.81]	59.37	12.91	4.2E-06	41.15 [23.61 , 58.69]
55	rs76172101	23.04	5.019	4.4E-06	15.97 [9.149 , 22.79]				
56	rs77311064	21.19	5.102	3.3E-05	14.69 [7.760 , 21.62]				
57	rs7737703	21.65	5.120	2.4E-05	15.00 [8.049 , 21.96]				
58	rs7872818	22.36	5.129	1.3E-05	15.50 [8.528 , 22.46]				

Table S5-6. Results of Mendelian randomization leave-one-out analysis on the causal association between regular smoking initiation on caffeine consumed per day. SNPs that were associated with smoking initiation were clumped at p value < 1e-5 and < 5e-8. Raw estimates were obtained from the MR estimators. These estimates were converted to interpretable effect sizes and confidence intervals (Effect size [95%CI]). The significance thresholds, corrected by Bonferroni procedure, were 0.0007352941 (0.05/68) and 0.00625 (0.05/8), respectively for the clumping p value < 1e-5 and < 5e-8. Analysis that survived multiple testing was put in blue boldface.

No.	SNP removed	Exposure SNPs clumped at p value < 1e-5				Exposure SNPs clumped at p value < 5e-8			
		Raw Estimates		Converted Estimates		Raw Estimates		Converted Estimates	
		β	SE	p value	Effect size [95%CI]	β	SE	p value	Effect size [95%CI]
59	rs7894565	22.65	5.131	1.0E-05	15.70 [8.732 , 22.67]				
60	rs793103	23.01	5.049	5.2E-06	15.95 [9.090 , 22.81]				
61	rs7984262	22.21	5.141	1.6E-05	15.40 [8.412 , 22.38]				
62	rs883323	21.74	5.131	2.3E-05	15.07 [8.098 , 22.04]				
63	rs895632	21.38	5.099	2.7E-05	14.82 [7.895 , 21.75]				
64	rs9411438	22.23	5.138	1.5E-05	15.41 [8.431 , 22.39]				
65	rs951740	22.04	5.156	1.9E-05	15.28 [8.272 , 22.28]	63.04	12.71	7.0E-07	43.69 [26.43 , 60.96]
66	rs9645884	21.97	5.135	1.9E-05	15.23 [8.250 , 22.20]				
67	rs9651873	20.36	4.834	2.5E-05	14.12 [7.548 , 20.68]				
68	All	22.04	5.070	1.4E-05	15.28 [8.389 , 22.16]	57.96	11.89	1.1E-06	40.17 [24.01 , 56.33]

Table S5-7. Phenotypic associations between use or initiation of different substances in the UK Biobank cohort. The dependent variables and independent variables (in blue) in the 21 logistic or linear regression models matched the outcome traits and exposure traits used in the MR analyses. Each model contained covariates : Age, sex, overall health rating, educational attainment, Townsend Deprivation Index, and the first 10 genetic principle components (PC1- PC10). Raw estimates from the modelling were converted to interpretable scales as described in the method. Results were in bold phase when the association p values of the predictor lower than a significance threshold, 0.002380952 (0.05/21), obtained from Bonferroni correction.

Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
1	linear regression	Age at starting smoking in current smokers	Caffeine consumed per day	-0.00 [-0.00 , -0.00]	1.2E-07
		Age at starting smoking in current smokers	Age	0.051 [0.036 , 0.066]	1.8E-11
		Age at starting smoking in current smokers	Sex	0.429 [0.264 , 0.594]	3.6E-07
		Age at starting smoking in current smokers	Overall health rating	-0.42 [-0.58 , -0.25]	5.3E-07
		Age at starting smoking in current smokers	Educational attainment	0.778 [0.662 , 0.895]	8.3E-39
		Age at starting smoking in current smokers	Townsend deprivation index	-0.00 [-0.04 , 0.027]	6.3E-01
		Age at starting smoking in current smokers	PC1	-0.07 [-0.14 , 0.003]	6.1E-02
		Age at starting smoking in current smokers	PC2	0.082 [0.002 , 0.162]	4.3E-02
		Age at starting smoking in current smokers	PC3	0.005 [-0.07 , 0.081]	9.0E-01
		Age at starting smoking in current smokers	PC4	-0.02 [-0.07 , 0.027]	3.7E-01
		Age at starting smoking in current smokers	PC5	-0.01 [-0.03 , 0.011]	3.5E-01
		Age at starting smoking in current smokers	PC6	-0.03 [-0.10 , 0.037]	3.7E-01
		Age at starting smoking in current smokers	PC7	0.004 [-0.04 , 0.059]	8.6E-01
		Age at starting smoking in current smokers	PC8	0.046 [-0.00 , 0.100]	9.0E-02
		Age at starting smoking in current smokers	PC9	0.004 [-0.02 , 0.031]	7.6E-01

Table S5-7. Phenotypic associations between use or initiation of different substances in the UK Biobank cohort. The dependent variables and independent variables (in blue) in the 21 logistic or linear regression models matched the outcome traits and exposure traits used in the MR analyses. Each model contained covariates : Age, sex, overall health rating, educational attainment, Townsend Deprivation Index, and the first 10 genetic principle components (PC1- PC10). Raw estimates from the modelling were converted to interpretable scales as described in the method. Results were in bold phase when the association p values of the predictor lower than a significance threshold, 0.002380952 (0.05/21), obtained from Bonferroni correction.

Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
2	linear regression	Age at starting smoking in current smokers	PC10	0.084 [0.027 , 0.142]	3.9E-03
		Age at starting smoking in current smokers	Cannabis initiation	0.152 [-0.09 , 0.401]	2.3E-01
		Age at starting smoking in current smokers	Age	0.049 [0.026 , 0.072]	2.9E-05
		Age at starting smoking in current smokers	Sex	0.564 [0.331 , 0.797]	2.1E-06
		Age at starting smoking in current smokers	Overall health rating	-0.45 [-0.69 , -0.22]	1.1E-04
		Age at starting smoking in current smokers	Educational attainment	0.894 [0.719 , 1.069]	2.2E-23
		Age at starting smoking in current smokers	Townsend deprivation index	-0.00 [-0.05 , 0.048]	9.0E-01
		Age at starting smoking in current smokers	PC1	-0.09 [-0.19 , 0.015]	9.2E-02
		Age at starting smoking in current smokers	PC2	0.019 [-0.09 , 0.131]	7.3E-01
		Age at starting smoking in current smokers	PC3	-0.00 [-0.11 , 0.097]	8.9E-01
		Age at starting smoking in current smokers	PC4	-0.06 [-0.13 , 0.007]	8.1E-02
		Age at starting smoking in current smokers	PC5	-0.00 [-0.03 , 0.029]	9.7E-01
		Age at starting smoking in current smokers	PC6	0.038 [-0.06 , 0.137]	4.4E-01
		Age at starting smoking in current smokers	PC7	0.001 [-0.07 , 0.079]	9.7E-01
		Age at starting smoking in current smokers	PC8	0.012 [-0.06 , 0.089]	7.5E-01

Table S5-7. Phenotypic associations between use or initiation of different substances in the UK Biobank cohort. The dependent variables and independent variables (in blue) in the 21 logistic or linear regression models matched the outcome traits and exposure traits used in the MR analyses. Each model contained covariates : Age, sex, overall health rating, educational attainment, Townsend Deprivation Index, and the first 10 genetic principle components (PC1- PC10). Raw estimates from the modelling were converted to interpretable scales as described in the method. Results were in bold phase when the association p values of the predictor lower than a significance threshold, 0.002380952 (0.05/21), obtained from Bonferroni correction.

Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
3	linear regression	Age at starting smoking in current smokers	PC9	-0.01 [-0.05 , 0.024]	4.9E-01
		Age at starting smoking in current smokers	PC10	0.062 [-0.01 , 0.142]	1.3E-01
		Age at starting smoking in current smokers	Estimated standard drinks per week	-0.00 [-0.00 , 0.001]	2.4E-01
		Age at starting smoking in current smokers	Age	0.052 [0.041 , 0.062]	2.2E-22
		Age at starting smoking in current smokers	Sex	0.396 [0.275 , 0.517]	1.4E-10
		Age at starting smoking in current smokers	Overall health rating	-0.47 [-0.58 , -0.36]	5.2E-17
		Age at starting smoking in current smokers	Educational attainment	0.750 [0.668 , 0.831]	3.5E-72
		Age at starting smoking in current smokers	Townsend deprivation index	-0.02 [-0.04 , 0.002]	8.4E-02
		Age at starting smoking in current smokers	PC1	-0.07 [-0.13 , -0.02]	3.5E-03
		Age at starting smoking in current smokers	PC2	0.034 [-0.02 , 0.089]	2.3E-01
		Age at starting smoking in current smokers	PC3	0.000 [-0.05 , 0.052]	9.9E-01
		Age at starting smoking in current smokers	PC4	-0.02 [-0.06 , 0.008]	1.4E-01
		Age at starting smoking in current smokers	PC5	-0.00 [-0.02 , 0.008]	3.7E-01
		Age at starting smoking in current smokers	PC6	0.013 [-0.03 , 0.061]	6.0E-01
		Age at starting smoking in current smokers	PC7	0.026 [-0.01 , 0.065]	1.7E-01

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
4	linear regression	Age at starting smoking in current smokers	PC8	0.033 [-0.00 , 0.071]	8.4E-02
		Age at starting smoking in current smokers	PC9	0.007 [-0.01 , 0.026]	4.2E-01
		Age at starting smoking in current smokers	PC10	0.068 [0.028 , 0.108]	8.5E-04
		Caffeine consumed per day	Cannabis initiation	5.788 [3.827 , 7.749]	7.2E-09
		Caffeine consumed per day	Age	-0.60 [-0.75 , -0.44]	1.8E-14
		Caffeine consumed per day	Sex	-21.6 [-23.2 , -20.0]	2.E-158
		Caffeine consumed per day	Overall health rating	4.479 [2.771 , 6.187]	2.8E-07
		Caffeine consumed per day	Educational attainment	-3.03 [-4.29 , -1.76]	2.7E-06
		Caffeine consumed per day	Townsend deprivation index	0.849 [0.421 , 1.277]	1.0E-04
		Caffeine consumed per day	PC1	-0.62 [-1.36 , 0.102]	9.2E-02
5	linear regression	Caffeine consumed per day	PC2	-1.15 [-1.91 , -0.39]	2.9E-03
		Caffeine consumed per day	PC3	-0.80 [-1.52 , -0.07]	3.1E-02
		Caffeine consumed per day	PC4	0.299 [-0.18 , 0.784]	2.3E-01
		Caffeine consumed per day	PC5	0.248 [0.031 , 0.464]	2.5E-02
		Caffeine consumed per day	PC6	0.394 [-0.28 , 1.072]	2.5E-01
		Caffeine consumed per day	PC7	-0.32 [-0.85 , 0.215]	2.4E-01
		Caffeine consumed per day	PC8	-0.73 [-1.27 , -0.19]	7.6E-03
		Caffeine consumed per day	PC9	-0.09 [-0.34 , 0.158]	4.6E-01
		Caffeine consumed per day	PC10	0.342 [-0.20 , 0.889]	2.2E-01
		Caffeine consumed per day	Smoking initiation	11.41 [10.35 , 12.48]	5.8E-98

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
6	logistic regression	Caffeine consumed per day	PC3	-0.34 [-0.81 , 0.139]	1.6E-01
		Caffeine consumed per day	PC4	0.498 [0.174 , 0.822]	2.5E-03
		Caffeine consumed per day	PC5	0.108 [-0.03 , 0.250]	1.3E-01
		Caffeine consumed per day	PC6	0.297 [-0.14 , 0.742]	1.9E-01
		Caffeine consumed per day	PC7	-0.38 [-0.74 , -0.03]	3.1E-02
		Caffeine consumed per day	PC8	-0.52 [-0.87 , -0.16]	3.8E-03
		Caffeine consumed per day	PC9	-0.05 [-0.22 , 0.106]	4.9E-01
		Caffeine consumed per day	PC10	0.252 [-0.10 , 0.611]	1.7E-01
		Cannabis initiation	Caffeine consumed per day	1.000 [1.000 , 1.000]	1.9E-09
		Cannabis initiation	Age	0.928 [0.926 , 0.931]	0.0E+00
		Cannabis initiation	Sex	0.716 [0.696 , 0.736]	1.E-121
		Cannabis initiation	Overall health rating	1.046 [1.016 , 1.077]	2.6E-03
		Cannabis initiation	Educational attainment	1.552 [1.513 , 1.591]	5.E-259
7	logistic regression	Cannabis initiation	Townsend deprivation index	1.156 [1.148 , 1.164]	0.0E+00
		Cannabis initiation	PC1	1.014 [1.001 , 1.027]	3.0E-02
		Cannabis initiation	PC2	1.005 [0.992 , 1.019]	4.2E-01
		Cannabis initiation	PC3	1.021 [1.008 , 1.034]	1.2E-03
		Cannabis initiation	PC4	0.989 [0.981 , 0.997]	1.2E-02
		Cannabis initiation	PC5	1.005 [1.002 , 1.009]	2.0E-03
		Cannabis initiation	PC6	1.007 [0.995 , 1.019]	2.1E-01
		Cannabis initiation	PC7	1.000 [0.991 , 1.009]	9.6E-01
		Cannabis initiation	PC8	1.002 [0.992 , 1.011]	6.4E-01
		Cannabis initiation	PC9	0.992 [0.988 , 0.997]	1.5E-03
		Cannabis initiation	PC10	0.985 [0.975 , 0.994]	2.8E-03
		Cannabis initiation	Estimated standard drinks per week	1.021 [1.020 , 1.022]	0.0E+00
		Cannabis initiation	Age	0.932 [0.930 , 0.934]	0.0E+00
		Cannabis initiation	Sex	0.830 [0.812 , 0.849]	3.9E-58
		Cannabis initiation	Overall health rating	1.062 [1.039 , 1.087]	1.1E-07
		Cannabis initiation	Educational attainment	1.515 [1.487 , 1.545]	0.0E+00

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
8	logistic regression	Cannabis initiation	Townsend deprivation index	1.147 [1.141 , 1.154]	0.0E+00
		Cannabis initiation	PC1	1.012 [1.002 , 1.022]	1.5E-02
		Cannabis initiation	PC2	1.001 [0.990 , 1.011]	8.0E-01
		Cannabis initiation	PC3	1.009 [0.999 , 1.019]	5.1E-02
		Cannabis initiation	PC4	0.982 [0.975 , 0.988]	4.5E-08
		Cannabis initiation	PC5	1.006 [1.003 , 1.009]	4.5E-06
		Cannabis initiation	PC6	1.004 [0.995 , 1.013]	3.6E-01
		Cannabis initiation	PC7	1.002 [0.994 , 1.009]	5.7E-01
		Cannabis initiation	PC8	1.004 [0.997 , 1.011]	2.0E-01
		Cannabis initiation	PC9	0.990 [0.987 , 0.994]	1.5E-07
		Cannabis initiation	PC10	0.982 [0.975 , 0.989]	3.8E-06
		Cannabis initiation	Smoking initiation	3.938 [3.827 , 4.053]	0.0E+00
		Cannabis initiation	Age	0.919 [0.917 , 0.921]	0.0E+00
		Cannabis initiation	Sex	0.737 [0.720 , 0.754]	1.E-150
		Cannabis initiation	Overall health rating	0.993 [0.969 , 1.017]	5.9E-01
		Cannabis initiation	Educational attainment	1.623 [1.591 , 1.656]	0.0E+00
		Cannabis initiation	Townsend deprivation index	1.140 [1.133 , 1.146]	0.0E+00
		Cannabis initiation	PC1	1.009 [0.999 , 1.020]	7.3E-02
		Cannabis initiation	PC2	1.002 [0.991 , 1.013]	6.6E-01
		Cannabis initiation	PC3	1.010 [0.999 , 1.020]	6.1E-02
9	linear regression	Cannabis initiation	PC4	0.986 [0.979 , 0.993]	9.5E-05
		Cannabis initiation	PC5	1.007 [1.004 , 1.010]	9.9E-07
		Cannabis initiation	PC6	1.004 [0.994 , 1.014]	4.0E-01
		Cannabis initiation	PC7	1.001 [0.993 , 1.009]	7.0E-01
		Cannabis initiation	PC8	1.001 [0.993 , 1.009]	7.2E-01
		Cannabis initiation	PC9	0.992 [0.988 , 0.996]	5.7E-05
		Cannabis initiation	PC10	0.985 [0.977 , 0.992]	2.1E-04
		Cigarettes per day	Caffeine consumed per day	0.006 [0.006 , 0.007]	1.9E-68
		Cigarettes per day	Age	0.043 [0.022 , 0.063]	5.5E-05
		Cigarettes per day	Sex	-1.46 [-1.68 , -1.23]	5.0E-36

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
10	linear regression	Cigarettes per day	Overall health rating	1.840 [1.613 , 2.066]	3.0E-56
		Cigarettes per day	Educational attainment	-0.61 [-0.77 , -0.45]	1.2E-13
		Cigarettes per day	Townsend deprivation index	0.188 [0.138 , 0.238]	1.6E-13
		Cigarettes per day	PC1	-0.07 [-0.17 , 0.034]	1.9E-01
		Cigarettes per day	PC2	0.020 [-0.08 , 0.131]	7.1E-01
		Cigarettes per day	PC3	-0.02 [-0.13 , 0.077]	6.0E-01
		Cigarettes per day	PC4	0.106 [0.035 , 0.177]	3.3E-03
		Cigarettes per day	PC5	0.034 [0.004 , 0.063]	2.5E-02
		Cigarettes per day	PC6	0.059 [-0.03 , 0.156]	2.3E-01
		Cigarettes per day	PC7	0.048 [-0.02 , 0.123]	2.1E-01
		Cigarettes per day	PC8	0.044 [-0.03 , 0.119]	2.5E-01
		Cigarettes per day	PC9	0.039 [0.001 , 0.077]	4.2E-02
		Cigarettes per day	PC10	0.009 [-0.06 , 0.089]	8.1E-01
		Cigarettes per day	Cannabis initiation	-0.78 [-1.12 , -0.44]	7.3E-06
		Cigarettes per day	Age	0.029 [-0.00 , 0.061]	6.8E-02
		Cigarettes per day	Sex	-1.50 [-1.82 , -1.17]	1.5E-19
		Cigarettes per day	Overall health rating	1.814 [1.495 , 2.133]	1.7E-28
		Cigarettes per day	Educational attainment	-0.59 [-0.83 , -0.34]	1.7E-06
		Cigarettes per day	Townsend deprivation index	0.143 [0.072 , 0.214]	7.3E-05
		Cigarettes per day	PC1	0.021 [-0.12 , 0.170]	7.7E-01
		Cigarettes per day	PC2	-0.03 [-0.19 , 0.115]	6.2E-01
		Cigarettes per day	PC3	-0.13 [-0.28 , 0.007]	6.3E-02
		Cigarettes per day	PC4	-0.00 [-0.10 , 0.091]	9.3E-01
		Cigarettes per day	PC5	0.055 [0.014 , 0.097]	8.6E-03
		Cigarettes per day	PC6	0.073 [-0.06 , 0.210]	2.9E-01
		Cigarettes per day	PC7	0.105 [-0.00 , 0.213]	5.4E-02
		Cigarettes per day	PC8	0.005 [-0.10 , 0.111]	9.2E-01
		Cigarettes per day	PC9	0.066 [0.013 , 0.120]	1.4E-02
		Cigarettes per day	PC10	0.129 [0.018 , 0.240]	2.2E-02

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
11	linear regression	Cigarettes per day	Estimated standard drinks per week	0.022 [0.016 , 0.028]	9.7E-15
		Cigarettes per day	Age	0.044 [0.028 , 0.059]	2.0E-08
		Cigarettes per day	Sex	-1.44 [-1.61 , -1.26]	1.0E-56
		Cigarettes per day	Overall health rating	1.736 [1.574 , 1.898]	1.5E-96
		Cigarettes per day	Educational attainment	-0.68 [-0.80 , -0.56]	3.4E-29
		Cigarettes per day	Townsend deprivation index	0.201 [0.164 , 0.237]	2.1E-27
		Cigarettes per day	PC1	-0.06 [-0.14 , 0.014]	1.1E-01
		Cigarettes per day	PC2	0.008 [-0.07 , 0.089]	8.4E-01
		Cigarettes per day	PC3	-0.02 [-0.10 , 0.052]	5.3E-01
		Cigarettes per day	PC4	0.060 [0.008 , 0.112]	2.3E-02
		Cigarettes per day	PC5	0.035 [0.014 , 0.057]	1.2E-03
		Cigarettes per day	PC6	0.015 [-0.05 , 0.087]	6.6E-01
		Cigarettes per day	PC7	0.002 [-0.05 , 0.058]	9.3E-01
		Cigarettes per day	PC8	0.011 [-0.04 , 0.067]	6.9E-01
12	linear regression	Estimated standard drinks per week	Cannabis initiation	3.390 [3.240 , 3.540]	0.0E+00
		Estimated standard drinks per week	Age	0.082 [0.071 , 0.094]	4.8E-44
		Estimated standard drinks per week	Sex	-6.39 [-6.51 , -6.27]	0.0E+00
		Estimated standard drinks per week	Overall health rating	-0.72 [-0.84 , -0.59]	4.1E-28
		Estimated standard drinks per week	Educational attainment	0.093 [-0.00 , 0.189]	5.8E-02
		Estimated standard drinks per week	Townsend deprivation index	-0.00 [-0.03 , 0.029]	8.7E-01
		Estimated standard drinks per week	PC1	-0.01 [-0.07 , 0.036]	5.0E-01
		Estimated standard drinks per week	PC2	0.028 [-0.03 , 0.086]	3.5E-01
		Estimated standard drinks per week	PC3	-0.06 [-0.11 , -0.00]	3.1E-02

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
13	linear regression	Estimated standard drinks per week	PC4	0.044 [0.007 , 0.081]	2.0E-02
		Estimated standard drinks per week	PC5	0.080 [0.064 , 0.097]	5.1E-22
		Estimated standard drinks per week	PC6	0.025 [-0.02 , 0.077]	3.4E-01
		Estimated standard drinks per week	PC7	-0.00 [-0.04 , 0.036]	8.1E-01
		Estimated standard drinks per week	PC8	0.000 [-0.04 , 0.041]	9.8E-01
		Estimated standard drinks per week	PC9	0.058 [0.038 , 0.077]	3.7E-09
		Estimated standard drinks per week	PC10	0.124 [0.082 , 0.166]	7.2E-09
		Estimated standard drinks per week	Smoking initiation	3.586 [3.506 , 3.665]	0.0E+00
		Estimated standard drinks per week	Age	-0.03 [-0.04 , -0.02]	4.1E-20
		Estimated standard drinks per week	Sex	-6.99 [-7.07 , -6.91]	0.0E+00
		Estimated standard drinks per week	Overall health rating	-0.82 [-0.90 , -0.74]	2.4E-89
		Estimated standard drinks per week	Educational attainment	0.343 [0.286 , 0.400]	5.0E-32
		Estimated standard drinks per week	Townsend deprivation index	-0.01 [-0.03 , 0.009]	3.1E-01
		Estimated standard drinks per week	PC1	-0.00 [-0.04 , 0.028]	6.9E-01
		Estimated standard drinks per week	PC2	0.021 [-0.01 , 0.059]	2.6E-01
		Estimated standard drinks per week	PC3	-0.06 [-0.09 , -0.02]	8.6E-04
		Estimated standard drinks per week	PC4	0.050 [0.025 , 0.074]	5.1E-05
		Estimated standard drinks per week	PC5	0.093 [0.082 , 0.103]	2.5E-67
		Estimated standard drinks per week	PC6	-0.02 [-0.05 , 0.008]	1.4E-01
		Estimated standard drinks per week	PC7	-0.02 [-0.05 , -0.00]	3.8E-02

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
14	linear regression	Estimated standard drinks per week	PC8	0.002 [-0.02 , 0.028]	8.7E-01
		Estimated standard drinks per week	PC9	0.062 [0.050 , 0.074]	4.1E-23
		Estimated standard drinks per week	PC10	0.132 [0.105 , 0.160]	7.9E-22
		Pack years of smoking	Cannabis initiation	6.332 [6.164 , 6.500]	0.0E+00
		Pack years of smoking	Age	0.345 [0.333 , 0.358]	0.0E+00
		Pack years of smoking	Sex	-1.72 [-1.85 , -1.59]	8.E-150
		Pack years of smoking	Overall health rating	2.146 [2.011 , 2.282]	7.E-210
		Pack years of smoking	Educational attainment	-1.87 [-1.97 , -1.76]	6.E-285
		Pack years of smoking	Townsend deprivation index	0.342 [0.307 , 0.376]	3.0E-83
		Pack years of smoking	PC1	-0.01 [-0.07 , 0.044]	6.1E-01
15	linear regression	Pack years of smoking	PC2	0.003 [-0.05 , 0.065]	9.1E-01
		Pack years of smoking	PC3	-0.02 [-0.08 , 0.031]	3.6E-01
		Pack years of smoking	PC4	0.000 [-0.03 , 0.040]	9.9E-01
		Pack years of smoking	PC5	0.055 [0.037 , 0.072]	6.5E-10
		Pack years of smoking	PC6	-0.00 [-0.06 , 0.047]	7.8E-01
		Pack years of smoking	PC7	-0.04 [-0.08 , -0.00]	4.4E-02
		Pack years of smoking	PC8	0.030 [-0.01 , 0.074]	1.8E-01
		Pack years of smoking	PC9	0.016 [-0.00 , 0.037]	1.2E-01
		Pack years of smoking	PC10	0.032 [-0.01 , 0.077]	1.5E-01
		Pack years of smoking	Smoking initiation	NC	
		Pack years of smoking	Age	0.155 [0.149 , 0.161]	0.0E+00
		Pack years of smoking	Sex	-1.30 [-1.36 , -1.23]	0.0E+00
		Pack years of smoking	Overall health rating	1.505 [1.438 , 1.572]	0.0E+00
		Pack years of smoking	Educational attainment	-0.68 [-0.73 , -0.63]	3.E-175
		Pack years of smoking	Townsend deprivation index	0.266 [0.249 , 0.283]	1.E-204
		Pack years of smoking	PC1	-0.02 [-0.05 , 0.007]	1.4E-01
		Pack years of smoking	PC2	0.018 [-0.01 , 0.050]	2.4E-01
		Pack years of smoking	PC3	0.001 [-0.02 , 0.031]	9.4E-01

Table S5-7. Phenotypic associations between use or initiation of different substances in the UK Biobank cohort. The dependent variables and independent variables (in blue) in the 21 logistic or linear regression models matched the outcome traits and exposure traits used in the MR analyses. Each model contained covariates : Age, sex, overall health rating, educational attainment, Townsend Deprivation Index, and the first 10 genetic principle components (PC1- PC10). Raw estimates from the modelling were converted to interpretable scales as described in the method. Results were in bold phase when the association p values of the predictor lower than a significance threshold, 0.002380952 (0.05/21), obtained from Bonferroni correction.

Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
16	linear regression	Pack years of smoking	PC4	0.023 [0.002 , 0.043]	2.6E-02
		Pack years of smoking	PC5	0.029 [0.020 , 0.038]	3.9E-11
		Pack years of smoking	PC6	-0.02 [-0.05 , 0.005]	1.1E-01
		Pack years of smoking	PC7	-0.01 [-0.03 , 0.004]	1.3E-01
		Pack years of smoking	PC8	0.026 [0.003 , 0.048]	2.1E-02
		Pack years of smoking	PC9	0.008 [-0.00 , 0.019]	9.1E-02
		Pack years of smoking	PC10	0.024 [0.001 , 0.046]	3.6E-02
		Smoking cessation	Caffeine consumed per day	0.000 [0.000 , 0.000]	0.0E+00
		Smoking cessation	Age	-0.00 [-0.00 , -0.00]	0.0E+00
		Smoking cessation	Sex	-0.01 [-0.01 , -0.00]	8.3E-12
		Smoking cessation	Overall health rating	0.048 [0.044 , 0.052]	2.E-119
		Smoking cessation	Educational attainment	-0.01 [-0.02 , -0.01]	1.3E-42
		Smoking cessation	Townsend deprivation index	0.015 [0.014 , 0.016]	7.E-218
		Smoking cessation	PC1	0.000 [-0.00 , 0.002]	5.7E-01
		Smoking cessation	PC2	0.001 [3.085 , 0.003]	4.6E-02
17	linear regression	Smoking cessation	PC3	-0.00 [-0.00 , 9.636]	6.4E-02
		Smoking cessation	PC4	0.000 [-0.00 , 0.001]	6.7E-01
		Smoking cessation	PC5	0.001 [0.000 , 0.001]	8.2E-08
		Smoking cessation	PC6	0.000 [-0.00 , 0.002]	2.5E-01
		Smoking cessation	PC7	-0.00 [-0.00 , 0.001]	8.6E-01
		Smoking cessation	PC8	0.000 [-0.00 , 0.002]	1.6E-01
		Smoking cessation	PC9	0.000 [-9.70 , 0.001]	9.8E-02
		Smoking cessation	PC10	0.000 [-0.00 , 0.001]	3.6E-01
		Smoking cessation	Cannabis initiation	0.028 [0.022 , 0.033]	1.7E-24
		Smoking cessation	Age	-0.00 [-0.00 , -0.00]	9.E-162
		Smoking cessation	Sex	-0.02 [-0.02 , -0.01]	2.0E-21
		Smoking cessation	Overall health rating	0.039 [0.034 , 0.044]	1.2E-55
		Smoking cessation	Educational attainment	-0.01 [-0.01 , -0.01]	6.6E-16
		Smoking cessation	Townsend deprivation index	0.010 [0.009 , 0.011]	2.0E-66
		Smoking cessation	PC1	-0.00 [-0.00 , 0.001]	4.5E-01

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
18	linear regression	Smoking cessation	PC2	-0.00 [-0.00 , 0.001]	5.9E-01
			PC3	-0.00 [-0.00 , 0.000]	2.6E-01
			PC4	0.000 [-0.00 , 0.001]	4.8E-01
			PC5	0.000 [1.772 , 0.001]	4.4E-02
			PC6	0.000 [-0.00 , 0.002]	4.3E-01
			PC7	0.001 [-7.57 , 0.003]	6.2E-02
			PC8	0.001 [-0.00 , 0.002]	9.6E-02
			PC9	0.000 [-0.00 , 0.000]	6.8E-01
			PC10	-0.00 [-0.00 , 0.001]	5.8E-01
			Estimated standard drinks per week	0.001 [0.001 , 0.001]	2.9E-88
			Age	-0.00 [-0.00 , -0.00]	0.0E+00
			Sex	-0.01 [-0.01 , -0.00]	1.5E-11
			Overall health rating	0.056 [0.053 , 0.059]	4.E-270
			Educational attainment	-0.02 [-0.02 , -0.02]	8.E-113
19	logistic regression	Smoking cessation	Townsend deprivation index	0.017 [0.016 , 0.017]	0.0E+00
			PC1	-0.00 [-0.00 , 0.001]	5.7E-01
			PC2	1.231 [-0.00 , 0.001]	9.9E-01
			PC3	-0.00 [-0.00 , 2.379]	5.4E-02
			PC4	0.000 [-0.00 , 0.001]	3.6E-01
			PC5	0.001 [0.000 , 0.001]	8.8E-07
			PC6	0.000 [-0.00 , 0.002]	2.1E-01
			PC7	0.000 [-0.00 , 0.001]	7.7E-01
			PC8	0.001 [-1.83 , 0.002]	5.0E-02
			PC9	0.000 [-0.00 , 0.000]	4.2E-01
			PC10	4.573 [-0.00 , 0.001]	9.3E-01
			Caffeine consumed per day	1.000 [1.000 , 1.000]	1.3E-98
			Age	1.014 [1.013 , 1.015]	4.E-105
			Sex	0.795 [0.784 , 0.806]	5.E-223
			Overall health rating	1.186 [1.168 , 1.203]	3.E-110

Table S5-7. Phenotypic associations between use or initiation of different substances in the UK Biobank cohort. The dependent variables and independent variables (in blue) in the 21 logistic or linear regression models matched the outcome traits and exposure traits used in the MR analyses. Each model contained covariates : Age, sex, overall health rating, educational attainment, Townsend Deprivation Index, and the first 10 genetic principle components (PC1- PC10). Raw estimates from the modelling were converted to interpretable scales as described in the method. Results were in bold phase when the association p values of the predictor lower than a significance threshold, 0.002380952 (0.05/21), obtained from Bonferroni correction.

Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
20	logistic regression	Smoking initiation	Educational attainment	0.973 [0.963 , 0.984]	6.7E-07
		Smoking initiation	Townsend deprivation index	1.057 [1.053 , 1.061]	3.E-183
		Smoking initiation	PC1	1.004 [0.998 , 1.011]	1.7E-01
		Smoking initiation	PC2	1.000 [0.994 , 1.007]	7.7E-01
		Smoking initiation	PC3	1.005 [0.999 , 1.012]	8.6E-02
		Smoking initiation	PC4	0.991 [0.987 , 0.996]	2.8E-04
		Smoking initiation	PC5	1.002 [1.000 , 1.004]	4.4E-03
		Smoking initiation	PC6	1.004 [0.998 , 1.010]	1.2E-01
		Smoking initiation	PC7	0.999 [0.994 , 1.004]	7.6E-01
		Smoking initiation	PC8	1.007 [1.002 , 1.012]	2.2E-03
		Smoking initiation	PC9	0.996 [0.994 , 0.999]	7.1E-03
		Smoking initiation	PC10	0.997 [0.992 , 1.002]	3.0E-01
		Smoking initiation	Cannabis initiation	3.874 [3.766 , 3.986]	0.0E+00
		Smoking initiation	Age	1.041 [1.039 , 1.043]	0.0E+00
		Smoking initiation	Sex	0.884 [0.868 , 0.901]	5.3E-38
		Smoking initiation	Overall health rating	1.163 [1.140 , 1.186]	1.9E-50
		Smoking initiation	Educational attainment	0.846 [0.833 , 0.858]	2.E-108
		Smoking initiation	Townsend deprivation index	1.021 [1.016 , 1.026]	3.4E-16
21	logistic regression	Smoking initiation	PC1	1.004 [0.995 , 1.012]	3.3E-01
		Smoking initiation	PC2	1.001 [0.992 , 1.010]	8.0E-01
		Smoking initiation	PC3	0.998 [0.990 , 1.007]	7.6E-01
		Smoking initiation	PC4	0.991 [0.985 , 0.996]	2.4E-03
		Smoking initiation	PC5	1.003 [1.000 , 1.005]	1.5E-02
		Smoking initiation	PC6	1.002 [0.994 , 1.010]	5.6E-01
		Smoking initiation	PC7	0.998 [0.992 , 1.005]	7.3E-01
		Smoking initiation	PC8	1.008 [1.001 , 1.014]	1.1E-02
		Smoking initiation	PC9	0.998 [0.995 , 1.001]	3.2E-01
		Smoking initiation	PC10	1.003 [0.997 , 1.010]	2.6E-01
		Smoking initiation	Estimated standard drinks per week	1.026 [1.026 , 1.027]	0.0E+00

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Model no.	Method	Outcome	Predictor	Converted Estimates	
				Effect size (95% CI)	P value
		Smoking initiation	Age	1.017 [1.016 , 1.018]	5.E-266
		Smoking initiation	Sex	0.946 [0.935 , 0.957]	2.2E-21
		Smoking initiation	Overall health rating	1.213 [1.199 , 1.227]	6.E-246
		Smoking initiation	Educational attainment	0.957 [0.949 , 0.964]	6.3E-27
		Smoking initiation	Townsend deprivation index	1.059 [1.056 , 1.062]	0.0E+00
		Smoking initiation	PC1	1.003 [0.998 , 1.008]	1.5E-01
		Smoking initiation	PC2	0.999 [0.994 , 1.004]	9.0E-01
		Smoking initiation	PC3	1.004 [0.999 , 1.009]	9.2E-02
		Smoking initiation	PC4	0.988 [0.985 , 0.992]	4.3E-11
		Smoking initiation	PC5	1.001 [0.999 , 1.002]	1.0E-01
		Smoking initiation	PC6	1.005 [1.000 , 1.010]	2.3E-02
		Smoking initiation	PC7	0.999 [0.995 , 1.002]	6.4E-01
		Smoking initiation	PC8	1.006 [1.003 , 1.010]	3.5E-04
		Smoking initiation	PC9	0.996 [0.994 , 0.997]	5.1E-06
		Smoking initiation	PC10	0.995 [0.991 , 0.999]	1.3E-02