Cannabis use and risk of type 2 diabetes mellitus: a two-sample Mendelian randomization study

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Supplement

Supplementary Table 1 SNPs used as instruments for lifetime cannabis use and cannabis use disorder

SNP	CHR	Position (hg19/b37)	EA	OA	EAF	BETA	SE	P value	R^2	F
Lifetime cannabis use from Pasman et al. (1)										
rs2875907	3	85518580	A	G	0.648	0.071	0.009	9.381e-17	7.631163e-05	68.5
rs9919557	11	112877408	T	C	0.386	-0.055	0.009	9.935e-11	4.644591e-05	41.7
rs10499	16	28915527	A	G	0.349	0.053	0.009	1.134e-09	4.163202e-05	37.4
rs9773390	8	81565692	T	C	0.067	-0.171	0.029	5.659e-09	3.784176e-05	34.0
rs10085617	7	3634711	A	T	0.584	0.046	0.008	2.934e-08	3.419837e-05	30.7
rs17761723	17	2107090	T	C	0.654	0.047	0.009	3.236e-08	3.447706e-05	31.0
rs466765	6	111668494	A	T	0.791	0.056	0.010	5.884e-08	3.286069e-05	29.5
rs11191511	10	104769709	T	C	0.080	-0.087	0.016	6.058e-08	3.266088e-05	29.3
rs1154693	3	117804154	A	G	0.854	-0.063	0.012	6.921e-08	3.228168e-05	29.0
rs714008	22	40406272	T	C	0.883	0.067	0.013	1.888e-07	3.023287e-05	27.2
rs1957725	4	37028512	T	C	0.178	0.055	0.011	2.526e-07	2.984694e-05	26.8
rs12211611	6	57065443	C	G	0.808	-0.054	0.010	2.552e-07	2.979516e-05	26.8
rs1066339	6	87403659	A	G	0.832	0.147	0.029	2.719e-07	2.949386e-05	26.5
rs9972422	15	96303368	A	G	0.291	-0.046	0.009	2.754e-07	2.933911e-05	26.4
rs437021	1	61738270	T	C	0.541	-0.042	0.008	2.770e-07	2.948799e-05	26.5
rs10008926	4	31133967	A	G	0.713	-0.047	0.009	2.891e-07	2.919693e-05	26.2
rs421983	3	84892866	T	C	0.485	0.042	0.008	3.118e-07	2.879338e-05	25.9
rs7586062	2	77305160	C	G	0.525	0.043	0.009	3.691e-07	2.875928e-05	25.8
rs576076	11	64360623	A	G	0.747	0.048	0.009	4.431e-07	2.867011e-05	25.8
Cannabis use disorder from Demontis et al. (2)										
rs56372821	8	27436500	A	G	0.092	-0.318	0.0467	9.305e-12	5.167074e-05	46.4
rs138164450	6	18196215	T	C	0.014	0.389	0.0750	2.158e-07	2.996187e-05	26.9
rs28575033	21	38549749	T	C	0.027	0.312	0.0619	4.605e-07	2.830560e-05	25.4
rs9416630	10	59575742	T	C	0.424	0.158	0.0318	6.941e-07	2.746616e-05	24.7

rs61983980	14	63990587	A	G	0.033	0.322	0.0670	1.495e-06	2.575299e-05	23.1
rs78671224	5	179607467	A	G	0.091	-0.272	0.0566	1.594e-06	2.567696e-05	23.1
rs803090	7	101950500	A	G	0.240	0.159	0.0333	1.858e-06	2.529177e-05	22.7
rs200077684	9	97765447	T	C	0.117	-0.263	0.0553	1.943e-06	2.521857e-05	22.7
rs9877179	3	185426493	T	G	0.094	-0.275	0.0583	2.420e-06	2.471897e-05	22.2
rs6840518	4	122532992	A	G	0.144	0.243	0.0518	2.766e-06	2.445962e-05	22.0
rs7008181	8	1111158	T	C	0.090	-0.310	0.0672	3.872e-06	2.374534e-05	21.3
rs76846069	8	71982559	A	G	0.069	0.309	0.0669	3.932e-06	2.370065e-05	21.3
rs77364030	7	16832242	T	C	0.019	-0.338	0.0733	4.051e-06	2.365367e-05	21.2
rs75877538	2	198865820	T	G	0.013	0.320	0.0699	4.582e-06	2.338441e-05	21.0

EA, effect allele. OA, other allele. EAF, effect allele frequency. SE, standard error.

Supplementary Table 2 Associations of SNPs used as instruments with type 2 diabetes (from the GWAS by Mahajan et al. (3))

SNP	CHR	Position (hg19/b37)	EA	OA	EAF	BETA	SE	P value
Lifetime cannabis use from Pasman et al. (1)								
rs10008926	4	31133967	A	G	0.290	-0.005	0.007	0.510
rs10085617	7	3634711	A	T	0.580	-0.003	0.006	0.690
rs10499	16	28915527	A	G	0.000	0.029	0.450	0.950
rs1066339	6	87403659	A	G	0.911	0.000	0.011	0.960
rs11191511	10	104769709	T	C	0.920	0.004	0.011	0.700
rs1154693	3	117804154	A	G	0.160	-0.022	0.009	0.011
rs12211611	6	57065443	C	G	0.800	-0.013	0.008	0.099
rs17761723	17	2107090	T	C	0.029	-0.022	0.021	0.300
rs1957725	4	37028512	T	C	0.820	-0.004	0.008	0.620
rs2875907	3	85518580	A	G	0.350	0.002	0.007	0.820
rs421983	3	84892866	T	C	0.510	-0.011	0.006	0.092
rs437021	1	61738270	T	C	0.460	0.003	0.006	0.670
rs466765	6	111668494	A	T	0.790	-0.022	0.008	0.005
rs576076	11	64360623	A	G	0.250	-0.003	0.007	0.650
rs714008	22	40406272	T	C	0.880	0.025	0.010	0.017
rs7586062	2	77305160	C	G	0.520	-0.005	0.006	0.420
rs9773390	8	81565692	T	C	0.068	-0.006	0.013	0.630
rs9919557	11	112877408	T	C	0.600	0.010	0.006	0.120
rs9972422	15	96303368	A	G	0.700	-0.007	0.007	0.310
Cannabis use disorder from Demontis et al. (2)								
rs138164450	6	18196215	T	C	0.041	-0.001	0.017	0.940
rs28575033	21	38549749	T	C	0.070	0.013	0.013	0.290

rs56372821	8	27436500	A	G	0.160	0.008	0.009	0.360
rs61983980	14	63990587	A	G	0.063	-0.004	0.015	0.760
rs6840518	4	122532992	A	G	0.089	-0.004	0.011	0.690
rs7008181	8	1111158	T	C	0.950	-0.043	0.015	0.004
rs75877538	2	198865820	T	G	0.034	0.005	0.019	0.800
rs76846069	8	71982559	A	G	0.057	0.002	0.014	0.890
rs77364030	7	16832242	T	C	0.000	0.033	0.280	0.900
rs78671224	5	179607467	A	G	0.920	-0.002	0.012	0.860
rs803090	7	101950500	A	G	0.300	0.001	0.007	0.910
rs9416630	10	59575742	T	C	0.410	0.004	0.006	0.510
rs9877179	3	185426493	T	G	0.930	-0.075	0.012	0.001

EA, effect allele. OA, other allele. EAF, effect allele frequency. SE, standard error.

Supplementary Table 3 Association ($P<5x10^{-8}$) of the SNPs used as instruments with confounders in PhenoScanner (accessed on 2020/09/18)

SNP	CHR	Position (hg19/b37)	Confounders/ risk factors
Lifetime cannabis use from Pasman et al. (1)			
rs2875907	3	85518580	-
rs9919557	11	112877408	-
rs10499	16	28915527	-
rs9773390	8	81565692	-
rs10085617	7	3634711	-
rs17761723	17	2107090	-
rs466765	6	111668494	-
rs11191511	10	104769709	-
rs1154693	3	117804154	-
rs714008	22	40406272	-
rs1957725	4	37028512	-
rs12211611	6	57065443	-
rs1066339	6	87403659	-
rs9972422	15	96303368	-
rs437021	1	61738270	-
rs10008926	4	31133967	-
rs421983	3	84892866	-
rs7586062	2	77305160	-
rs576076	11	64360623	-
Cannabis use disorder from Demontis et al. (2)			
rs56372821	8	27436500	-
rs138164450	6	18196215	-

rs28575033	21	38549749	-
rs9416630	10	59575742	-
rs61983980	14	63990587	-
rs78671224	5	179607467	-
rs803090	7	101950500	-
rs200077684	9	97765447	-
rs9877179	3	185426493	-
rs6840518	4	122532992	-
rs7008181	8	1111158	-
rs76846069	8	71982559	-
rs77364030	7	16832242	-
rs75877538	2	198865820	-

Tobacco smoking, alcohol, physical activity and diet were considered as relevant confounders or risk factors for type 2 diabetes.

Supplementary Table 4 Heterogeneity of Wald ratios and MR-Egger test for directional pleiotropy in the primary outcome GWAS (Mahajan 2018)

Exposure	Outcome dataset	Heterogeneity			
		Q	Degrees of Freedom	P value	I^2
Lifetime cannabis use	Mahajan el al. 2018 (3)	32.1	17	0.0148	0.32
	Xue el al. 2018 (4)	30.6	17	0.0221	0.26
Cannabis use disorder	Mahajan el al. 2018 (3)	43.6	12	1.813e-05	0.35
	Xue el al. 2018 (4)	28.7	5	2.690e-05	0.63
		MR-Egger test for directional pleiotropy			
		Intercept	Standard error	P value	
Lifetime cannabis use	Mahajan el al. 2018 (3)	-0.005	0.007	0.486	
	Xue el al. 2018 (4)	-0.006	0.008	0.469	
Cannabis use disorder	Mahajan el al. 2018 (3)	1.282e-04	0.021	0.995	
	Xue el al. 2018 (4)	-0.026	0.044	0.587	

Supplementary Table 5 Inverse variance weighted estimates for cannabis use and type 2 diabetes mellitus in leave-one-out analysis in primary analysis (Mahajan et al. 2018 GWAS (3))

SNP excluded	OR[a]	(95% CI)[a]	P value
Lifetime cannabis use			
rs10008926	1.00	(0.92;1.09)	0.987
rs10085617	1.01	(0.92;1.1)	0.885
rs10499	1.00	(0.92;1.09)	0.937
rs1066339	1.00	(0.92;1.1)	0.942
rs11191511	1.01	(0.92;1.1)	0.880
rs1154693	0.99	(0.91;1.06)	0.731
rs12211611	0.99	(0.92;1.08)	0.876
rs17761723	1.01	(0.93;1.09)	0.895
rs1957725	1.01	(0.92;1.1)	0.880
rs2875907	1.00	(0.92;1.09)	0.976
rs421983	1.01	(0.94;1.1)	0.727
rs437021	1.01	(0.92;1.1)	0.886
rs466765	1.02	(0.95;1.1)	0.551
rs576076	1.01	(0.92;1.1)	0.885
rs714008	0.99	(0.92;1.07)	0.755
rs9773390	1.00	(0.91;1.09)	0.955
rs9919557	1.02	(0.94;1.1)	0.702
rs9972422	1.00	(0.92;1.08)	0.947
Cannabis use disorder			
rs138164450	1.03	(0.98;1.09)	0.179
rs28575033	1.03	(0.98;1.08)	0.240
rs56372821	1.05	(0.99;1.1)	0.081
rs61983980	1.03	(0.99;1.09)	0.170
rs6840518	1.04	(0.99;1.09)	0.163
rs7008181	1.02	(0.98;1.07)	0.319
rs75877538	1.03	(0.98;1.08)	0.203
rs76846069	1.03	(0.98;1.09)	0.193
rs77364030	1.03	(0.98;1.08)	0.204
rs78671224	1.03	(0.98;1.09)	0.194
rs803090	1.03	(0.98;1.09)	0.192
rs9416630	1.03	(0.98;1.08)	0.220
rs9877179	1.01	(0.99;1.03)	0.404

OR, odds ratio. CI, confidence interval.

Supplementary Table 6 Mendelian randomization estimates for the relationship between cannabis use and type 2 diabetes mellitus in replication analysis using the type 2 diabetes GWAS by Xue 2018 (4)

Exposure	No. SNPs	Method	OR[a]	(95% CI)	P value
Lifetime cannabis use (Pasman et al. 2018)	19	Inverse variance weighted	0.94	(0.86;1.04)	0.217
	19	Weighted median	0.99	(0.89;1.1)	0.843
	19	Robust adjusted profile score	0.96	(0.89;1.04)	0.328
	19	IVW radial	0.94	(0.86;1.04)	0.216
	19	MR PRESSO	0.96	(0.89;1.05)	0.398
	76	IVW (correlated variants)	1.00	(0.93;1.07)	0.947
	76	Maximum likelihood (correlated variants)	1.00	(0.92;1.08)	0.944
Cannabis use disorder (Demontis et al. 2019)	14	Inverse variance weighted	1.04	(0.95;1.14)	0.416
	14	Weighted median	0.97	(0.92;1.03)	0.332
	14	Robust adjusted profile score	1.06	(0.97;1.16)	0.210
	14	IVW radial	1.04	(0.95;1.14)	0.415
	13	MR PRESSO	1.00	(0.94;1.07)	0.935
	104	IVW (correlated variants)	1.01	(0.99;1.03)	0.219
	104	Maximum likelihood (correlated variants)	1.01	(0.99;1.03)	0.216

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