**Cannabis use, pulmonary function, and lung cancer susceptibility: A Mendelian randomization study**

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Supplementary tables

Supplementary Table 1 Associations of single nucleotide polymorphisms for lifetime cannabis use and cannabis use disorder

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | Estimates for exposure | Estimates for FEV1 | Estimates for overall lung cancer |
| SNP | EA | OA | EAF | BETA | SE | P | F | BETA | SE | P | BETA | SE | P |
| Lifetime cannabis use 1 |
| rs10085617 | A | T | 0.584 | 0.046 | 0.008 | 2.934e-08 | 30.7 | -0.003 | 0.002 | 0.217 | 0.008 | 0.018 | 0.682 |
| rs2875907 | A | G | 0.648 | 0.071 | 0.009 | 9.381e-17 | 68.5 | 0.004 | 0.002 | 0.134 | -0.012 | 0.016 | 0.459 |
| rs9773390 | T | C | 0.067 | -0.171 | 0.029 | 5.659e-09 | 34.0 | 0.004 | 0.005 | 0.386 | -0.030 | 0.026 | 0.250 |
| rs9919557 | T | C | 0.386 | -0.055 | 0.009 | 9.935e-11 | 41.7 | 0.002 | 0.002 | 0.318 | -0.004 | 0.012 | 0.745 |
| Cannabis use disorder 2 |
| rs11715758 | A | G | 0.277 | -0.094 | 0.018 | 8.911e-08 | 28.5 | -0.001 | 0.002 | 0.707 | 0.003 | 0.012 | 0.829 |
| rs1392816 | T | C | 0.293 | -0.100 | 0.018 | 6.140e-08 | 29.4 | 0.001 | 0.002 | 0.646 | -0.008 | 0.014 | 0.542 |
| rs1509513 | A | G | 0.483 | 0.086 | 0.017 | 3.179e-07 | 26.0 | -0.001 | 0.002 | 0.664 | 0.007 | 0.012 | 0.541 |
| rs17271123 | T | G | 0.258 | 0.128 | 0.025 | 3.543e-07 | 26.0 | -0.004 | 0.002 | 0.086 | -0.010 | 0.016 | 0.517 |
| rs17514242 | C | G | 0.284 | -0.088 | 0.017 | 2.561e-07 | 26.5 | -0.004 | 0.002 | 0.063 | 0.018 | 0.012 | 0.137 |
| rs553920 | T | C | 0.491 | 0.104 | 0.020 | 1.597e-07 | 27.6 | -0.003 | 0.003 | 0.296 | 0.009 | 0.019 | 0.638 |
| rs72818514 | T | C | 0.020 | -0.183 | 0.034 | 9.331e-08 | 28.6 | 0.003 | 0.005 | 0.622 | -0.023 | 0.034 | 0.485 |

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

Supplementary Table 2 Association (P<5x10-8) of the SNPs used as instruments with confounders or outcome risk factors in PhenoScanner (accessed on 2021/01/07)

|  |  |
| --- | --- |
| SNP | Confounders/ risk factors |
| Lifetime cannabis use 1 |
| rs10085617 | - |
| rs2875907 | - |
| rs9773390 | - |
| rs9919557 | - |
| Cannabis use disorder 2 |
| rs11715758 | - |
| rs1392816 | - |
| rs1509513 | - |
| rs17271123 | - |
| rs17514242 | - |
| rs553920 | - |
| rs72818514 | - |

Tobacco smoking and environmental tobacco smoke exposure were considered as relevant confounders or risk factors for pulmonary function or lung cancer.

Supplementary Table 3 Estimates from weighted median method for the relationship between cannabis use, pulmonary function and lung cancer

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Exposure | Outcome | Beta/OR | 95% CI | P | Q |
| Lifetime cannabis use | FEV1 | -0.018 | (-0.051;0.016) | 0.309 | 0.825 |
|  | FVC | -0.001 | (-0.031;0.028) | 0.930 | 0.972 |
|  | FEV1/FVC | -0.012 | (-0.049;0.025) | 0.540 | 0.825 |
|  | Overall lung cancer | 1.11 | (0.93;1.32) | 0.253 | 0.825 |
|  | Adenocarcinoma | 0.97 | (0.76;1.23) | 0.796 | 0.972 |
|  | Squamous cell carcinoma | 1.21 | (0.93;1.57) | 0.161 | 0.825 |
|  | Small cell carcinoma | 0.99 | (0.67;1.46) | 0.972 | 0.972 |
|  | Never smoker | 1.19 | (0.75;1.88) | 0.468 | 0.825 |
|  | Ever smoker | 1.07 | (0.86;1.32) | 0.550 | 0.825 |
| Cannabis use disorder  | FEV1 | -0.008 | (-0.026;0.009) | 0.338 | 0.789 |
|  | FVC | -0.022 | (-0.038;-0.005) | 0.009 | 0.080 |
|  | FEV1/FVC | 0.009 | (-0.007;0.025) | 0.264 | 0.789 |
|  | Overall lung cancer | 1.04 | (0.96;1.12) | 0.351 | 0.789 |
|  | Adenocarcinoma | 0.99 | (0.90;1.08) | 0.763 | 0.859 |
|  | Squamous cell carcinoma | 0.97 | (0.86;1.11) | 0.688 | 0.859 |
|  | Small cell carcinoma | 1.00 | (0.81;1.22) | 0.963 | 0.963 |
|  | Never smoker | 0.92 | (0.73;1.17) | 0.502 | 0.859 |
|  | Ever smoker | 1.02 | (0.92;1.12) | 0.764 | 0.859 |

FEV1, forced expiratory volume in one second. FVC, lower forced vital capacity. Beta, linear regression coefficient per standard deviation increment in spirometry indices

Supplementary Table 4 Heterogeneity of Wald ratios and MR-Egger test for directional pleiotropy

|  |  |  |  |
| --- | --- | --- | --- |
| Exposure | Outcome | Heterogeneity |  |
|  |  | Q | Degrees of Freedom | P | I² |
| Lifetime cannabis use | FEV1 | 5.0 | 3 | 0.172 | 0.20 |
|  | FVC | 4.1 | 3 | 0.246 | 0.04 |
|  | FEV1/FVC | 4.6 | 2 | 0.100 | 0.36 |
|  | Overall lung cancer | 2.0 | 4 | 0.742 | 0.00 |
|  | Adenocarcinoma | 5.8 | 3 | 0.120 | 0.40 |
|  | Squamous cell carcinoma | 0.9 | 3 | 0.827 | 0.00 |
|  | Small cell carcinoma | 3.1 | 5 | 0.691 | 0.00 |
|  | Never smoker | 4.6 | 5 | 0.472 | 0.00 |
|  | Ever smoker | 6.7 | 3 | 0.083 | 0.60 |
| Cannabis use disorder | FEV1 | 1038.7 | 677 | 0.000 | 0.35 |
|  | FVC | 920.0 | 677 | 0.000 | 0.26 |
|  | FEV1/FVC | 13.6 | 9 | 0.138 | 0.57 |
|  | Overall lung cancer | 9.1 | 10 | 0.518 | 0.00 |
|  | Adenocarcinoma | 2.7 | 10 | 0.988 | 0.00 |
|  | Squamous cell carcinoma | 12.3 | 10 | 0.263 | 0.16 |
|  | Small cell carcinoma | 5.5 | 10 | 0.853 | 0.00 |
|  | Never smoker | 9.6 | 10 | 0.476 | 0.20 |
|  | Ever smoker | 7.5 | 9 | 0.585 | 0.00 |
|  |  | MR-Egger test for directional pleiotropy |  |
|  |  | Intercept | Standard error | P |  |
| Lifetime cannabis use | FEV1 | -7.630e-04 | 0.005 | 0.888 |  |
|  | FVC | 4.689e-04 | 0.004 | 0.926 |  |
|  | FEV1/FVC | 1.906e-03 | 0.007 | 0.822 |  |
|  | Overall lung cancer | -1.228e-02 | 0.017 | 0.514 |  |
|  | Adenocarcinoma | -3.764e-02 | 0.035 | 0.393 |  |
|  | Squamous cell carcinoma | 1.287e-02 | 0.032 | 0.725 |  |
|  | Small cell carcinoma | 9.097e-04 | 0.041 | 0.983 |  |
|  | Never smoker | 1.619e-02 | 0.042 | 0.722 |  |
|  | Ever smoker | -5.228e-02 | 0.024 | 0.156 |  |
| Cannabis use disorder | FEV1 | -7.881e-04 | 0.000 | 0.054 |  |
|  | FVC | -5.395e-04 | 0.000 | 0.164 |  |
|  | FEV1/FVC | 1.465e-02 | 0.005 | 0.012 |  |
|  | Overall lung cancer | -2.277e-02 | 0.028 | 0.442 |  |
|  | Adenocarcinoma | -3.645e-02 | 0.035 | 0.330 |  |
|  | Squamous cell carcinoma | -5.222e-02 | 0.057 | 0.387 |  |
|  | Small cell carcinoma | -6.627e-02 | 0.067 | 0.350 |  |
|  | Never smoker | -1.517e-01 | 0.071 | 0.063 |  |
|  | Ever smoker | -2.746e-02 | 0.036 | 0.470 |  |

FEV1, forced expiratory volume in one second. FVC, lower forced vital capacity

Supplementary Table 5 Inverse variance weighted estimates in leave-one-out analysis in primary analysis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| SNP excluded |  | SNP | Beta/OR | (95% CI) | P value |
| Lifetime cannabis use | FEV1 | rs10085617 | -0.003 | (-0.057;0.05) | 0.8668 |
|  |  | rs2875907 | -0.025 | (-0.045;-0.004) | 0.0006 |
|  |  | rs9773390 | -0.002 | (-0.074;0.071) | 0.9507 |
|  |  | rs9919557 | -0.003 | (-0.062;0.055) | 0.8669 |
|  | FVC | rs17761723 | 0.007 | (-0.019;0.033) | 0.6230 |
|  |  | rs2875907 | -0.004 | (-0.045;0.038) | 0.8640 |
|  |  | rs9773390 | 0.005 | (-0.041;0.05) | 0.8426 |
|  |  | rs9919557 | -0.010 | (-0.035;0.016) | 0.4566 |
|  | FEV1/FVC | rs10499 | -0.022 | (-0.045;0.002) | 0.0761 |
|  |  | rs17761723 | 0.004 | (-0.056;0.063) | 0.9080 |
|  |  | rs9773390 | 0.010 | (-0.084;0.105) | 0.8293 |
|  | Overall lung cancer | rs10085617 | 1.04 | (0.93;1.16) | 0.5260 |
|  |  | rs17761723 | 1.05 | (0.95;1.17) | 0.3320 |
|  |  | rs2875907 | 1.09 | (1.01;1.17) | 0.0290 |
|  |  | rs9773390 | 0.98 | (0.88;1.08) | 0.6590 |
|  |  | rs9919557 | 1.04 | (0.92;1.18) | 0.5380 |
|  | Adenocarcinoma | rs10499 | 1.05 | (0.78;1.42) | 0.7439 |
|  |  | rs2875907 | 1.16 | (0.94;1.43) | 0.1757 |
|  |  | rs9773390 | 0.86 | (0.64;1.16) | 0.3243 |
|  |  | rs9919557 | 1.00 | (0.75;1.33) | 0.9974 |
|  | Squamous cell carcinoma | rs17761723 | 1.24 | (1.07;1.44) | 0.0046 |
|  |  | rs2875907 | 1.20 | (1.02;1.4) | 0.0248 |
|  |  | rs9773390 | 1.34 | (1.07;1.68) | 0.0115 |
|  |  | rs9919557 | 1.18 | (1.06;1.31) | 0.0018 |
|  | Small cell carcinoma | rs10085617 | 0.97 | (0.72;1.3) | 0.8295 |
|  |  | rs10499 | 1.04 | (0.84;1.28) | 0.7302 |
|  |  | rs17761723 | 0.91 | (0.74;1.12) | 0.3694 |
|  |  | rs2875907 | 1.02 | (0.74;1.4) | 0.9211 |
|  |  | rs9773390 | 0.95 | (0.7;1.29) | 0.7559 |
|  |  | rs9919557 | 1.01 | (0.76;1.36) | 0.9301 |
|  | Never smoker | rs10085617 | 1.14 | (0.8;1.63) | 0.4675 |
|  |  | rs10499 | 1.09 | (0.78;1.51) | 0.6075 |
|  |  | rs17761723 | 1.12 | (0.79;1.61) | 0.5222 |
|  |  | rs2875907 | 1.31 | (0.93;1.86) | 0.1221 |
|  |  | rs9773390 | 1.15 | (0.72;1.83) | 0.5665 |
|  |  | rs9919557 | 1.25 | (0.92;1.71) | 0.1504 |
|  | Ever smoker | rs17761723 | 1.10 | (0.89;1.36) | 0.3838 |
|  |  | rs2875907 | 1.14 | (0.83;1.57) | 0.4194 |
|  |  | rs9773390 | 0.87 | (0.67;1.13) | 0.3099 |
|  |  | rs9919557 | 1.07 | (0.77;1.48) | 0.6912 |
| Cannabis use disorder | FEV1 | rs11715758 | -0.008 | (-0.024;0.008) | 0.3439 |
|  |  | rs1392816 | -0.006 | (-0.023;0.012) | 0.5249 |
|  |  | rs1509513 | -0.006 | (-0.022;0.011) | 0.5122 |
|  |  | rs17271123 | 0.000 | (-0.016;0.015) | 0.9499 |
|  |  | rs17514242 | -0.012 | (-0.02;-0.003) | 0.0101 |
|  |  | rs553920 | -0.004 | (-0.02;0.012) | 0.6297 |
|  |  | rs72818514 | -0.005 | (-0.022;0.011) | 0.5241 |
|  | FVC | rs11715758 | -0.015 | (-0.03;-0.001) | 0.0403 |
|  |  | rs1392816 | -0.014 | (-0.029;0) | 0.0545 |
|  |  | rs1509513 | -0.014 | (-0.029;0) | 0.0512 |
|  |  | rs17271123 | -0.014 | (-0.029;0.002) | 0.0773 |
|  |  | rs17514242 | -0.021 | (-0.026;-0.015) | 0.0000 |
|  |  | rs553920 | -0.014 | (-0.029;0) | 0.0531 |
|  |  | rs719504 | -0.013 | (-0.027;0.001) | 0.0664 |
|  |  | rs72818514 | -0.017 | (-0.031;-0.003) | 0.0207 |
|  | FEV1/FVC | rs11783093 | 0.012 | (0.001;0.024) | 0.0362 |
|  |  | rs1392816 | 0.004 | (-0.01;0.018) | 0.5473 |
|  |  | rs1509513 | 0.004 | (-0.009;0.018) | 0.5312 |
|  |  | rs17271123 | 0.010 | (-0.004;0.025) | 0.1628 |
|  |  | rs17514242 | 0.005 | (-0.009;0.019) | 0.4810 |
|  |  | rs553920 | 0.007 | (-0.008;0.021) | 0.3932 |
|  |  | rs719012 | 0.005 | (-0.009;0.02) | 0.4657 |
|  |  | rs72818514 | 0.008 | (-0.007;0.022) | 0.2939 |
|  |  | rs7783012 | 0.005 | (-0.01;0.02) | 0.5091 |
|  |  | rs9787909 | 0.008 | (-0.007;0.023) | 0.3029 |
|  | Overall lung cancer | rs11715758 | 1.00 | (0.94;1.06) | 0.9328 |
|  |  | rs1392816 | 0.99 | (0.93;1.05) | 0.7237 |
|  |  | rs1509513 | 0.99 | (0.93;1.05) | 0.7224 |
|  |  | rs17271123 | 1.00 | (0.94;1.06) | 0.9454 |
|  |  | rs17514242 | 1.01 | (0.96;1.06) | 0.7241 |
|  |  | rs553920 | 0.99 | (0.94;1.05) | 0.7889 |
|  |  | rs719012 | 1.01 | (0.95;1.06) | 0.8108 |
|  |  | rs719504 | 1.01 | (0.95;1.07) | 0.7887 |
|  |  | rs72818514 | 0.99 | (0.94;1.05) | 0.7474 |
|  |  | rs7783012 | 0.98 | (0.93;1.04) | 0.5790 |
|  |  | rs9787909 | 0.98 | (0.93;1.04) | 0.5676 |
|  | Adenocarcinoma | rs11715758 | 0.99 | (0.96;1.03) | 0.7068 |
|  |  | rs1392816 | 0.99 | (0.94;1.03) | 0.5003 |
|  |  | rs1509513 | 0.99 | (0.95;1.03) | 0.6308 |
|  |  | rs17271123 | 0.98 | (0.94;1.02) | 0.2612 |
|  |  | rs17514242 | 0.99 | (0.95;1.03) | 0.6210 |
|  |  | rs553920 | 0.97 | (0.94;1.01) | 0.1501 |
|  |  | rs719012 | 0.99 | (0.95;1.03) | 0.5411 |
|  |  | rs719504 | 0.99 | (0.95;1.03) | 0.5737 |
|  |  | rs72818514 | 0.98 | (0.94;1.02) | 0.3492 |
|  |  | rs7783012 | 0.98 | (0.94;1.03) | 0.4398 |
|  |  | rs9787909 | 0.98 | (0.94;1.02) | 0.3958 |
|  | Squamous cell carcinoma | rs11715758 | 1.02 | (0.91;1.13) | 0.7533 |
|  |  | rs1392816 | 0.98 | (0.89;1.09) | 0.7541 |
|  |  | rs1509513 | 0.99 | (0.89;1.1) | 0.8787 |
|  |  | rs17271123 | 1.01 | (0.91;1.13) | 0.8228 |
|  |  | rs17514242 | 1.02 | (0.91;1.13) | 0.7814 |
|  |  | rs553920 | 1.01 | (0.9;1.12) | 0.9162 |
|  |  | rs719012 | 1.03 | (0.93;1.13) | 0.6134 |
|  |  | rs719504 | 1.03 | (0.93;1.14) | 0.5591 |
|  |  | rs72818514 | 0.99 | (0.9;1.09) | 0.8658 |
|  |  | rs7783012 | 0.98 | (0.88;1.09) | 0.7577 |
|  |  | rs9787909 | 0.99 | (0.89;1.1) | 0.8431 |
|  | Small cell carcinoma | rs11715758 | 1.04 | (0.93;1.18) | 0.4756 |
|  |  | rs11783093 | 0.99 | (0.89;1.1) | 0.8564 |
|  |  | rs1509513 | 1.01 | (0.9;1.15) | 0.8229 |
|  |  | rs17271123 | 1.02 | (0.9;1.15) | 0.7894 |
|  |  | rs17514242 | 1.02 | (0.9;1.16) | 0.7527 |
|  |  | rs553920 | 1.01 | (0.89;1.14) | 0.8912 |
|  |  | rs719012 | 1.03 | (0.91;1.17) | 0.6006 |
|  |  | rs719504 | 1.05 | (0.93;1.18) | 0.4326 |
|  |  | rs72818514 | 1.02 | (0.9;1.15) | 0.7984 |
|  |  | rs7783012 | 1.01 | (0.88;1.15) | 0.9172 |
|  |  | rs9787909 | 0.98 | (0.88;1.08) | 0.6626 |
|  | Never smoker | rs11715758 | 0.99 | (0.83;1.19) | 0.9454 |
|  |  | rs11783093 | 0.94 | (0.79;1.13) | 0.5394 |
|  |  | rs1392816 | 1.01 | (0.83;1.22) | 0.9324 |
|  |  | rs1509513 | 1.01 | (0.85;1.21) | 0.8735 |
|  |  | rs17514242 | 1.00 | (0.82;1.2) | 0.9594 |
|  |  | rs553920 | 0.96 | (0.81;1.14) | 0.6540 |
|  |  | rs719012 | 0.97 | (0.81;1.18) | 0.7883 |
|  |  | rs719504 | 1.00 | (0.84;1.19) | 0.9906 |
|  |  | rs72818514 | 0.94 | (0.81;1.09) | 0.4013 |
|  |  | rs7783012 | 0.99 | (0.82;1.2) | 0.9162 |
|  |  | rs9787909 | 1.02 | (0.85;1.22) | 0.8288 |
|  | Ever smoker | rs11715758 | 1.05 | (0.97;1.13) | 0.2136 |
|  |  | rs1392816 | 1.04 | (0.96;1.12) | 0.3521 |
|  |  | rs1509513 | 1.03 | (0.96;1.1) | 0.4316 |
|  |  | rs17271123 | 1.05 | (0.98;1.14) | 0.1861 |
|  |  | rs17514242 | 1.06 | (1;1.13) | 0.0576 |
|  |  | rs553920 | 1.05 | (0.98;1.13) | 0.1827 |
|  |  | rs719504 | 1.05 | (0.97;1.13) | 0.2231 |
|  |  | rs72818514 | 1.03 | (0.97;1.1) | 0.3588 |
|  |  | rs7783012 | 1.04 | (0.96;1.12) | 0.3438 |
|  |  | rs9787909 | 1.03 | (0.97;1.1) | 0.3635 |

Supplementary Table 6 Inverse variance weighted and robust method estimates for pulmonary function when using SNPs associated with lifetime cannabis and cannabis use disorder at *P* < 5 x 10-4

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Exposure | No. SNPs | Outcome | Method | Beta | 95% CI | P | Q |
| Lifetime cannabis use | 545 | FEV1 | Inverse variance weighted | 0.004 | (0.001;0.007) | 0.0222 | 0.1000 |
|  |  |  | Weighted median | 0.002 | (-0.003;0.008) | 0.3750 | 0.6515 |
|  |  |  | Robust adjusted profile score | 0.004 | (0.001;0.008) | 0.0170 | 0.0766 |
|  |  |  | IVW radial | 0.004 | (0.001;0.007) | 0.0222 | 0.0997 |
|  |  |  | MR PRESSO | 0.004 | (0.001;0.007) | 0.0226 | 0.1018 |
|  |  | FVC | Inverse variance weighted | 0.004 | (0.001;0.007) | 0.0063 | 0.0564 |
|  |  |  | Weighted median | 0.007 | (0.002;0.012) | 0.0103 | 0.0923 |
|  |  |  | Robust adjusted profile score | 0.006 | (0.002;0.009) | 0.0028 | 0.0249 |
|  |  |  | IVW radial | 0.004 | (0.001;0.007) | 0.0062 | 0.0556 |
|  |  |  | MR PRESSO | 0.004 | (0.001;0.007) | 0.0065 | 0.0582 |
|  |  | FEV1/FVC | Inverse variance weighted | -0.001 | (-0.004;0.002) | 0.6282 | 0.8114 |
|  |  |  | Weighted median | -0.001 | (-0.007;0.005) | 0.7167 | 0.8063 |
|  |  |  | Robust adjusted profile score | -0.001 | (-0.005;0.002) | 0.4364 | 0.7856 |
|  |  |  | IVW radial | -0.001 | (-0.004;0.002) | 0.6282 | 0.8113 |
|  |  |  | MR PRESSO | -0.001 | (-0.004;0.002) | 0.6284 | 0.8116 |
| Cannabis use disorder  | 854 | FEV1 | Inverse variance weighted | -0.001 | (-0.002;0.001) | 0.3153 | 0.4054 |
|  |  |  | Weighted median | 0.000 | (-0.002;0.002) | 1.0000 | 1.0000 |
|  |  |  | Robust adjusted profile score | -0.001 | (-0.002;0.001) | 0.3846 | 0.4327 |
|  |  |  | IVW radial | -0.001 | (-0.002;0.001) | 0.3153 | 0.4054 |
|  |  |  | MR PRESSO | -0.001 | (-0.002;0.001) | 0.3156 | 0.4057 |
|  |  | FVC | Inverse variance weighted | -0.001 | (-0.002;0.001) | 0.2992 | 0.4054 |
|  |  |  | Weighted median | -0.001 | (-0.004;0.001) | 0.2488 | 0.4493 |
|  |  |  | Robust adjusted profile score | -0.001 | (-0.003;0.001) | 0.3137 | 0.4327 |
|  |  |  | IVW radial | -0.001 | (-0.002;0.001) | 0.2992 | 0.4054 |
|  |  |  | MR PRESSO | -0.001 | (-0.002;0.001) | 0.2995 | 0.4057 |
|  |  | FEV1/FVC | Inverse variance weighted | -0.001 | (-0.002;0.001) | 0.4069 | 0.4578 |
|  |  |  | Weighted median | -0.001 | (-0.003;0.001) | 0.4304 | 0.5534 |
|  |  |  | Robust adjusted profile score | -0.001 | (-0.003;0.001) | 0.3527 | 0.4327 |
|  |  |  | IVW radial | -0.001 | (-0.002;0.001) | 0.4069 | 0.4578 |
|  |  |  | MR PRESSO | -0.001 | (-0.002;0.001) | 0.4071 | 0.4580 |

MR PRESSO, MR Pleiotropy RESidual Sum and Outlier. a OR (odds ratio) comparing cannabis use and non-use.

Supplementary Table 7 Inverse variance weighted and robust method estimates for lung cancer when using SNPs associated with lifetime cannabis and cannabis use disorder at *P* < 5 x 10-4

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Exposure | No. SNPs | Outcome | Method | OR | 95% CI | P | Q |
| Lifetime cannabis use | 586 | Overall lung cancer | Inverse variance weighted | 1.00 | (0.98;1.01) | 0.6416 | 0.8114 |
|  |  |  | Weighted median | 1.00 | (0.97;1.03) | 0.9714 | 0.9714 |
|  |  |  | Robust adjusted profile score | 1.00 | (0.98;1.02) | 0.8119 | 0.9134 |
|  |  |  | IVW radial | 1.00 | (0.98;1.01) | 0.6417 | 0.8113 |
|  |  |  | MR PRESSO | 1.00 | (0.98;1.01) | 0.6418 | 0.8116 |
|  |  | Adenocarcinoma | Inverse variance weighted | 1.00 | (0.98;1.02) | 0.7213 | 0.8114 |
|  |  |  | Weighted median | 0.98 | (0.94;1.02) | 0.3909 | 0.6515 |
|  |  |  | Robust adjusted profile score | 0.99 | (0.97;1.02) | 0.6841 | 0.9134 |
|  |  |  | IVW radial | 1.00 | (0.98;1.02) | 0.7212 | 0.8113 |
|  |  |  | MR PRESSO | 1.00 | (0.98;1.02) | 0.7214 | 0.8116 |
|  |  | Squamous cell carcinoma | Inverse variance weighted | 1.00 | (0.97;1.02) | 0.7006 | 0.8114 |
|  |  |  | Weighted median | 1.02 | (0.97;1.07) | 0.5067 | 0.6515 |
|  |  |  | Robust adjusted profile score | 0.99 | (0.97;1.02) | 0.7119 | 0.9134 |
|  |  |  | IVW radial | 1.00 | (0.97;1.02) | 0.7004 | 0.8113 |
|  |  |  | MR PRESSO | 1.00 | (0.97;1.02) | 0.7007 | 0.8116 |
|  |  | Small cell carcinoma | Inverse variance weighted | 1.00 | (0.97;1.04) | 0.9873 | 0.9873 |
|  |  |  | Weighted median | 1.03 | (0.95;1.11) | 0.5016 | 0.6515 |
|  |  |  | Robust adjusted profile score | 1.00 | (0.95;1.05) | 0.9620 | 0.9620 |
|  |  |  | IVW radial | 1.00 | (0.97;1.04) | 0.9873 | 0.9873 |
|  |  |  | MR PRESSO | 1.00 | (0.97;1.04) | 0.9873 | 0.9873 |
|  |  | Never smoker | Inverse variance weighted | 0.97 | (0.93;1.02) | 0.2085 | 0.6256 |
|  |  |  | Weighted median | 0.92 | (0.84;1.01) | 0.0766 | 0.3446 |
|  |  |  | Robust adjusted profile score | 0.97 | (0.92;1.03) | 0.2847 | 0.7856 |
|  |  |  | IVW radial | 0.97 | (0.93;1.02) | 0.2088 | 0.6264 |
|  |  |  | MR PRESSO | 0.97 | (0.93;1.02) | 0.2090 | 0.6271 |
|  |  | Ever smoker | Inverse variance weighted | 1.01 | (0.99;1.03) | 0.3754 | 0.8114 |
|  |  |  | Weighted median | 1.02 | (0.99;1.06) | 0.2164 | 0.6491 |
|  |  |  | Robust adjusted profile score | 1.01 | (0.99;1.04) | 0.4154 | 0.7856 |
|  |  |  | IVW radial | 1.01 | (0.99;1.03) | 0.3752 | 0.8113 |
|  |  |  | MR PRESSO | 1.01 | (0.99;1.03) | 0.3757 | 0.8116 |
| Cannabis use disorder  | 913 | Overall lung cancer | Inverse variance weighted | 1.01 | (1;1.02) | 0.0191 | 0.0860 |
|  |  |  | Weighted median | 1.01 | (1;1.02) | 0.0693 | 0.3121 |
|  |  |  | Robust adjusted profile score | 1.01 | (1;1.02) | 0.0261 | 0.1177 |
|  |  |  | IVW radial | 1.01 | (1;1.02) | 0.0191 | 0.0860 |
|  |  |  | MR PRESSO | 1.01 | (1;1.02) | 0.0193 | 0.0870 |
|  |  | Adenocarcinoma | Inverse variance weighted | 1.01 | (1;1.02) | 0.1359 | 0.3058 |
|  |  |  | Weighted median | 1.01 | (0.99;1.03) | 0.3359 | 0.5038 |
|  |  |  | Robust adjusted profile score | 1.01 | (1;1.02) | 0.1486 | 0.3344 |
|  |  |  | IVW radial | 1.01 | (1;1.02) | 0.1359 | 0.3058 |
|  |  |  | MR PRESSO | 1.01 | (1;1.02) | 0.1362 | 0.3065 |
|  |  | Squamous cell carcinoma | Inverse variance weighted | 1.03 | (1.02;1.04) | 0.0000 | 0.0000 |
|  |  |  | Weighted median | 1.03 | (1.01;1.05) | 0.0127 | 0.1142 |
|  |  |  | Robust adjusted profile score | 1.03 | (1.02;1.05) | 0.0000 | 0.0001 |
|  |  |  | IVW radial | 1.03 | (1.02;1.04) | 0.0000 | 0.0000 |
|  |  |  | MR PRESSO | 1.03 | (1.02;1.04) | 0.0000 | 0.0000 |
|  |  | Small cell carcinoma | Inverse variance weighted | 1.01 | (0.99;1.03) | 0.2431 | 0.4054 |
|  |  |  | Weighted median | 1.02 | (0.99;1.05) | 0.2496 | 0.4493 |
|  |  |  | Robust adjusted profile score | 1.01 | (0.99;1.04) | 0.2911 | 0.4327 |
|  |  |  | IVW radial | 1.01 | (0.99;1.03) | 0.2431 | 0.4054 |
|  |  |  | MR PRESSO | 1.01 | (0.99;1.03) | 0.2434 | 0.4057 |
|  |  | Never smoker | Inverse variance weighted | 1.00 | (0.98;1.03) | 0.6785 | 0.6785 |
|  |  |  | Weighted median | 1.00 | (0.96;1.04) | 0.8689 | 0.9775 |
|  |  |  | Robust adjusted profile score | 1.00 | (0.97;1.03) | 0.8611 | 0.8611 |
|  |  |  | IVW radial | 1.00 | (0.98;1.03) | 0.6785 | 0.6785 |
|  |  |  | MR PRESSO | 1.00 | (0.98;1.03) | 0.6786 | 0.6786 |
|  |  | Ever smoker | Inverse variance weighted | 1.01 | (1;1.02) | 0.0810 | 0.2430 |
|  |  |  | Weighted median | 1.01 | (1;1.03) | 0.1158 | 0.3473 |
|  |  |  | Robust adjusted profile score | 1.01 | (1;1.02) | 0.1179 | 0.3344 |
|  |  |  | IVW radial | 1.01 | (1;1.02) | 0.0810 | 0.2430 |
|  |  |  | MR PRESSO | 1.01 | (1;1.02) | 0.0813 | 0.2440 |

MR PRESSO, MR Pleiotropy RESidual Sum and Outlier. a OR (odds ratio) comparing cannabis use and non-use.

Supplementary Table 8 Positive and negative control analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Exposure | Outcome | OR | (95% CI) | P-value |
| Lifetime cannabis use | Ever cigarette smoking | 1.24 | (0.91;1.7) | 0.0503 |
| Cannabis use disorder | Ever cigarette smoking | 1.07 | (1.02;1.14) | 0.0044 |
|  |  | Beta |  |  |
| Lifetime cannabis use | Height at age 10 years | -0.0168 | (-0.09;0.057) | 0.5170 |
| Cannabis use disorder | Height at age 10 years | 0.0010 | (-0.021;0.023) | 0.9269 |

Estimates from the multiplicative random effects inverse variance weighted method.

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