ORIGINAL ARTICLE

Cannabis Use, Pulmonary Function, and Lung Cancer Susceptibility: A Mendelian Randomization Study

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ABSTRACT

Introduction: Because of widespread use, understanding the pulmonary effects of cannabis use is important; but its role independent from tobacco smoking is yet to be elucidated. We used Mendelian randomization (MR) to assess the effect of genetic liability to lifetime cannabis use and cannabis use disorder on pulmonary function and lung cancer.

Methods: We used four single nucleotide polymorphisms associated with lifetime cannabis use (p value $<5 \times 10^{-8}$) from a genome-wide association study (GWAS) of 184,765 individuals of European descent from the International Cannabis Consortium, 23andme, and U.K. Biobank as instrumental variables. Seven single nucleotide polymorphisms (p value $<5 \times 10^{-8}$) were selected as instruments for cannabis use disorder from a GWAS meta-analysis of 17,068 European ancestry cases and 357,219 controls of European descent from Psychiatric Genomics Consortium Substance Use Disorders working group, Lundbeck Foundation Initiative for Integrative PsychiatricResearch, and deCode. To assess lung function, GWAS included 79,055 study participants of the SpiroMeta Consortium, and for lung cancer GWAS from the International Lung Cancer Consortium contained 29,266 cases and 56,450 controls.

Results: MR revealed that genetic liability to lifetime cannabis use was associated with increased risk of squamous cell carcinoma (OR = 1.22, 95%, confidence interval = 1.07–1.39, p value = 0.003, q value = 0.025). Pleiotropy-robust methods and positive and negative control analyses did not indicate bias in the primary analysis.

Conclusions: The findings of this MR analysis suggest evidence for a potential causal association between genetic liability for cannabis use and the risk of squamous cell

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carcinoma. Triangulating MR and observational studies and addressing orthogonal sources of bias are necessary to confirm this finding.

Keywords: Cannabis; Pulmonary function; Lung cancer; Mendelian randomization; Genetic susceptibility

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease with a growing global burden.[1] It is characterized by persistent symptoms and progressive airflow limitations diagnosed by lung function testing.[2] COPD is a well-recognized risk factor for lung cancer.[2,3] Cannabis is the most widely smoked substance after tobacco and its prevalence is increasing as more legal markets emerge.[4] Tobacco smoke includes 43 known carcinogens and other toxins that induce harm in the airways.[5] Cannabis smoke is qualitatively similar to tobacco except for cannabinoids.[6] It contains higher quantities of ammonia, hydrogen cyanide, nitric oxide, and nitrogen oxides, and elicits greater oxidative stress, apoptosis, and inflammatory response in lung cells than tobacco smoke.[6-8] Many of these compounds are carcinogens and damage the respiratory epithelium and raise concern that cannabis smoke not only has inflammatory effects on the central airway mucosa but that it exerts premalignant changes at the cellular and molecular levels.[6,8] Cellular histologic structure studies focused on epithelial changes revealed functional impairments in alveolar macrophages collected from cannabis users suggesting unique biologic effects from inhaled cannabinoids.[9] Although clear evidence exists for the progression of COPD and lung cancer risk in tobacco smokers,[2,10-12] the pulmonary effects of habitual cannabis use are unresolved.[7,13-15] Cannabis smoking has been linked to a variety of pulmonary symptoms such as coughing and wheezing, sputum production, bronchodilation, and acute or chronic bronchitis.[6,7,13] However, limited and conflicting evidence from epidemiologic studies exists for COPD and lung cancer because studies included few cannabis-only users and were subject to suboptimal exposure assessment.[7,13,14,16]

All previous studies were observational and did not allow for a direct assessment of whether the observed differences in cannabis use act as a causal factor for respiratory conditions, a consequence of worsening of symptoms, or are confounded by tobacco smoking. As much as 70% to 90% of cannabis users smoke cigarettes.[17] Because of the co-occurrence of cannabis and tobacco smoke exposure, it is difficult to isolate the influence of cannabis on pulmonary health when relying on observational study designs.[18] One approach to strengthening causal inference is the method of Mendelian randomization (MR), a form of instrumental variable analysis.[19] In MR, the instrument is comprised one or more genetic variants that are robustly associated with the exposure of interest. As individuals inherit alleles at random, these individuals are assigned to experience different dosages of the exposure. The most widely adopted approach is to rely on inferences from single nucleotide polymorphisms (SNPs) identified through genome-wide association studies (GWAS).[19] In the present study, we used the MR approach to investigate any potential causal relationship among cannabis use, pulmonary function, and lung cancer susceptibility.

Materials and Methods

We performed a two-sample, summary-based MR analysis in which the instrument-exposure and instrument-outcome associations were estimated in different samples. We retrieved associations of SNPs from GWAS of lifetime cannabis use[20] and cannabis use disorder.[21] SNP-outcome associations were derived from meta-analyses of GWAS of pulmonary function[22] and lung cancer.[23] In addition, we adopted positive and negative control outcome analyses for assessing the potential biasing influences from horizontal pleiotropy and selection bias.[19,24,25] A positive control outcome is an outcome for which it is already well established that the exposure is causal. A negative control is an outcome lacking a causal link with the exposure.

Instrumental Variables for Lifetime Cannabis Use and Cannabis Use Disorder

GWAS summary statistics of 184,765 individuals of European descent for lifetime cannabis use (defined as any use during lifetime) were used.[20] The data consisted of three sources and included the International Cannabis Consortium, 23andMe, and U.K. Biobank. Genotyping was performed on various genotyping platforms and standard quality control checks were performed before imputation. Genotype data were imputed using the 1000 Genomes phase 1 release reference set for International Cannabis Consortium and 23andMe, and the Haplotype Reference Consortium reference set for the U.K. Biobank sample. The GWAS model for lifetime use had been adjusted for age, sex, ancestry, and genotype batch. Details regarding ethical approval and informed consent can be found in the original article.[20] Summary statistics for cannabis use disorder were derived from a GWAS meta-analysis of 17,068 European ancestry cases and 357,219 controls using 18 samples from the Psychiatric Genomics Consortium Substance Use Disorders working

group, Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), and deCODE.[21] Psychiatric Genomics Consortium cases met the criteria for a lifetime diagnosis of Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV (or DSM-III-R) cannabis abuse or dependence, derived from clinician ratings or semistructured interviews. Cases from iPSYCH had International Classification of Diseases–10 codes of F12.1 (cannabis abuse) or F12.2 (cannabis dependence). Cases in deCODE were defined as lifetime DSM-III-R or DSM-IV cannabis abuse or dependence or DSM-5 cannabis use disorder. For the Psychiatric Genomics Consortium and iPSYCH, quality control, and imputation were applied using the Ricopili pipeline.[21] For deCODE samples, the IMPUTE HMM imputation model was used. Association analyses were conducted for each sample using logistic models and further included sex and principal components as covariates.

We performed the primary analysis using a conservative instrument selection strategy[19] using genome-wide significant SNPs associated with the exposures (p value $<5 \times 10^{-8}$) and applying a PLINK linkage disequilibrium clumping algorithm (r^2 threshold $= 0.1$ and window size $= 10$ mB). We removed SNPs with effect sizes greater in the outcome than in the exposure (using Steiger filtering[26]). Four SNPs associated with lifetime cannabis and seven SNPs associated with cannabis use disorder at p value $<5 \times 10^{-8}$ were selected as instrumental variables (Supplementary Table 1). In addition, we adopted a liberal instrument selection approach (p value $<5 \times 10^{-4}$, $r^2 = 0.1$, window size $= 10$ mB[19,27] to strengthen the genetic instrument and achieve statistical power to detect previously reported effect sizes from observational studies.[28]

GWAS Summary Statistics for Pulmonary Function and Lung Cancer

We assessed the consistency of effects on several spirometric indices (forced expiratory volume in one second (FEV_1), lower forced vital capacity (FVC), FEV_1-to-FVC ratio) using summary data from a meta-analysis of the SpiroMeta consortium[22] in up to 79,055 individuals of European ancestry from 22 studies. The GWAS model was adjusted for age, sex, and height. Some studies were imputed to the 1000 Genomes Project Phase 1 panel and others to the Haplotype Reference Consortium panel, as per the work of Shrine et al.[22] for details on the phenotyping, genotyping, and analysis. Genetic variants associated with lung cancer were obtained from a meta-analysis of GWAS,[23] comprising the International Lung Cancer Consortium (ILCCO) lung cancer GWAS (29,266 lung cancer cases and 56,450 controls). The individual studies were genotyped on different arrays, imputed based on 1000 Genomes (phase 3).[23] The GWAS model was adjusted for principal components and was further stratified by histologic subtype, including 11,273 adenocarcinomas, 7426 squamous cell carcinomas, and 2664 SCLC. In addition, analyses were stratified by tobacco smoking status defined as ever smoker (current and former smokers; 23,223 cases and 16,964 controls) and never-smokers (2355 cases and 7504 controls).

Positive and Negative Controls

Tobacco smoking was chosen as a positive control outcome because it often co-occurs with cannabis use and shares confounders with cannabis use. Summary statistics for tobacco smoking (ever-lifetime use) came from the Sequencing Consortium of Alcohol and Nicotine Use conducted in over 1.2 million individuals of European ancestry.[29] Height at age 10 years served as a negative control outcome. As cannabis is typically initiated after puberty, if our instruments affect lung function and lung cancer solely through cannabis phenotypes, we expect to find no effect on prepuberty height.[30] SNP-outcome associations for height at age 10 years were taken from the Neale 2017 U.K. Biobank phenomewide GWAS included in mrbase.org (access date September 9, 2020)[31]

Statistical Analyses

A priori statistical power was calculated according to Brion et al.[32] After data harmonization, we calculated Wald ratios by dividing the per-allele SD increments in FEV_1, FVC, FEV_1-to-FVC ratio, and the log OR for lung cancer by the corresponding log OR of the same SNP in the GWAS for lifetime cannabis use and cannabis use disorder; and obtained SE by the delta method. Wald ratios were pooled using the multiplicative random effects inverse variance weighted (IVW) method.[27] Estimates for FEV_1, FVC, and FEV_1-to-FVC ratio obtained from IVW models are on the scale of one SD outcome difference per doubling of the prevalence of lifetime cannabis or cannabis use disorder. Estimates were scaled to the increase in (the odds of the) outcome per doubling of the prevalence of binary cannabis exposure variables by multiplying the causal estimate by 0.693 ($=\log_e 2$),[33] and interpreted as a genetic liability to lifetime cannabis use or cannabis use disorder.[34,35] We applied the Benjamini-Hochberg procedure (by exposure variable and method across outcome) to adjust for multiple testing and presented q values.[36] One issue threatening the validity of MR that is of particular concern is that the instrument influences the outcome only through exposure.[25] Violations of this assumption through horizontal pleiotropy, whereby the instruments

exert an effect on the outcome independent of the exposure, can introduce bias. To evaluate correlated horizontal pleiotropy, we checked instrument SNPs and their proxies ($r^2 > 0.8$) in the largest available GWAS,[29] the GWAS catalog, and PhenoScanner[37] for associations (p value $<5 \times 10^{-8}$) with tobacco smoking and environmental tobacco smoke exposure. If there was a reported association with tobacco smoking or environmental tobacco smoke exposure, we used multivariable MR[38] to adjust for indirect effects. The presence of pleiotropy was further investigated using the Cochran Q heterogeneity test, the I^2 statistic, and the MR-Egger intercept test.[25,39] If the pleiotropy is 'balanced' (i.e., pleiotropic effects are independent in the magnitude of the SNP-exposure associations; and if the mean pleiotropic effect is zero), the effect can be reliably estimated by the multiplicative random effects IVW method.[19,25] We performed the weighted median estimator as a pleiotropy-robust method,[40] leave-one-out analysis, to assess whether the IVW estimate was driven by a single SNP, and positive and negative control analyses.[19,24,25] After applying the liberal instrument selection strategy (p value $<5 \times 10^{-4}$), we did the multiplicative random effects IVW and pleiotropy-robust methods (weighted median, Robust Adjusted Profile Score, Radial regression, MR-Pleiotropy Residual Sum and Outlier)[40] on sets of weak instruments. Analyses were performed using the meta (version 4.11.0), MendelianRandomization (version 0.4.3), MRPRESSO (version 1.0), phenoscanner (version 1.0), and TwoSampleMR (version 0.5.5) packages in R, version 4.0.3 (R Core Team, Vienna, Austria).

Results

In the primary analysis, the 4 SNPs selected for lifetime cannabis use explained 0.3% and the seven SNPs for cannabis use disorder explained 0.09% of the phenotypic variance. For overall lung cancer, given alpha equals 5%, we had greater than or equal to 80% power when the expected ORs were greater than or equal to 1.28 and greater than or equal to 1.31 for lifetime cannabis use and cannabis use disorder, respectively. In the secondary analysis using a liberal threshold, we selected 545 SNPs for lifetime cannabis use and 854 SNPs for cannabis use disorder and achieved greater than or equal to 80% power at alpha equals 5% to detect ORs of 1.05 (lifetime cannabis use) and 1.11 (cannabis use disorder).

The MR analysis exhibited genetic liability to cannabis use disorder having an effect estimate consistent with decreased levels of FEV, which did not persist multiplicity correction (IVW Beta = −0,015, 95% CI: −0.028–0.003, p value = 0.019, q value = 0.168) (Fig. 1). Genetic liability to lifetime cannabis use illustrated having an effect estimate consistent with increased risk of squamous cell lung cancer (OR = 1.22, 95% confidence interval [CI] = 1.07-1.39, p value = 0.003, q value = 0.025) (Fig. 2). None of our selected instruments or their proxies exhibited previously reported associations with prespecified confounders or outcome risk factors (Supplementary Table 2). The IVW estimates were broadly consistent with estimates from weighted median sensitivity analyses, although the weighted median estimates were less precise (Supplementary Table 3).

There was moderate heterogeneity (in terms of I_{GX}^2) among Wald ratios for lifetime cannabis use and cannabis use disorder with FEV_1, FVC, FEV_1-to-FVC ratio, and adenocarcinoma, and low heterogeneity for the remaining Wald ratios (Supplementary Table 4). The MR-Egger intercept analysis did not indicate directional pleiotropy (Supplementary Table 4). The leave-one-out analysis identified one SNP that influenced the IVW estimate for lifetime cannabis use and FEV_1, and one SNP

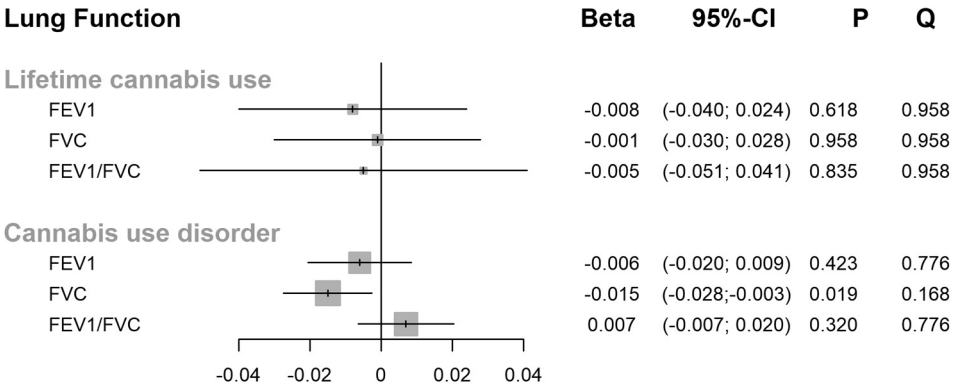

Figure 1. Per one SD increment (beta) in FEV1, FVC, and FEV1-to-FVC ratio associated with genetic liability to lifetime cannabis use and cannabis use disorder using the inverse variance weighted method. CI, confidence interval; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; P, p value; Q, q value.

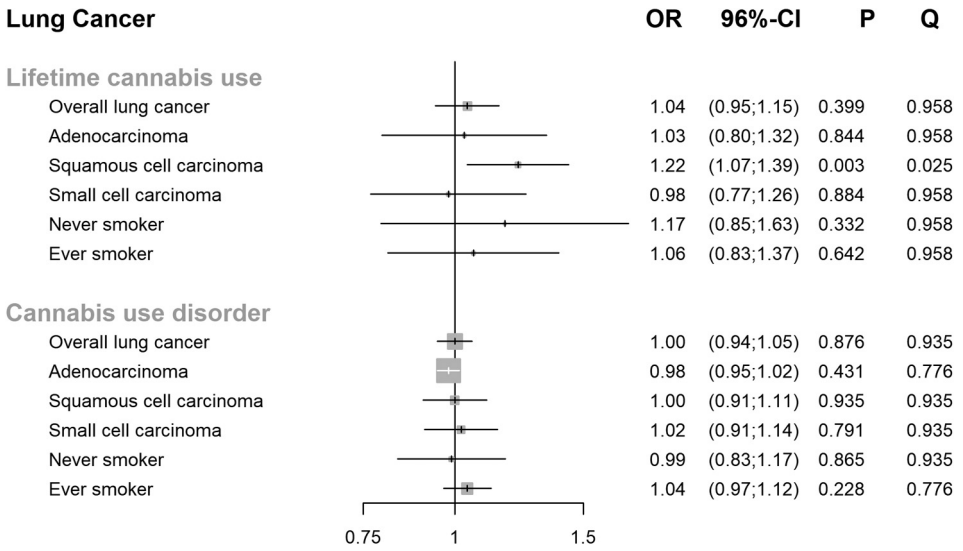

Figure 2. OR for the associations of genetic liability to lifetime cannabis use and lung cancer and histologic subtypes using the inverse variance weighted method. CI, confidence interval; P, *p* value; Q, *q* value.

that influenced the IVW estimate for cannabis use disorder and FVC (Supplementary Table 5). However, further inspection did not reveal the SNPs rs2875907 and rs17514242 has previously exhibited associations apart from cannabis use. MR analyses adopting a liberal threshold for SNP selection found that estimates were attenuated toward the null (Supplementary Tables 6 and 7). In the liberal analysis, genetic liability to lifetime cannabis use did not retain a relationship with squamous cell carcinoma (IVW OR = 1.00, 95% CI = 0.97–1.02, p value = 0.701, q value = 0.811). In contrast, there was a weak association of genetically predicted cannabis use disorder with slightly increased risk for squamous cell carcinoma (IVW OR = 1.03, 95% CI = 1.02–1.04, p value < 0.001, q value < 0.001). In positive control analyses, cannabis use traits were positively associated with ever tobacco smoking (Supplementary Table 8). The negative control analyses indicated a lack of association between lifetime cannabis use and cannabis use disorder with height at age 10 years (Supplementary Table 8).

Discussion

In this study, we used genetic instruments for lifetime cannabis use from more than 180,000 individuals and related these to pulmonary function traits from 79,000 individuals and 29,000 lung cancer cases. Cannabis use disorder was used as a secondary exposure reflecting heavy lifetime use. The MR analyses provided some evidence for an association between cannabis use with squamous cell lung cancer. The primary analysis supported a relationship between lifetime cannabis use and squamous cell carcinoma. The liberal analysis with more SNPs used as instruments suggested an effect of cannabis use disorder on squamous cell carcinoma.

Several lines of evidence have been put forward to suggest that the damage from cannabis to the lungs can potentially be as devastating as tobacco smoke.[6-8,41] First, although the daily consumption of cannabis is lower than the consumption of tobacco cigarettes, the lack of filters, looser packing density of cannabis cigarettes, the larger puff volume, and longer breathholding can intensify to the particulates within cannabis smoke.[6,42,43] Second, cannabis-only and combined cannabis and tobacco smokers exhibit more histopathologic alterations in their bronchial mucosa (e.g., squamous metaplasia), which are cancer precursors.[44] Third, cannabis and tobacco smoke contain similar concentrations of polycyclic aromatic hydrocarbons, benzo[a]pyrene, and benz[a]anthracene.[45] Fourth, delta-9 tetrahydrocannabinol (THC) present in cannabis tar activates the aryl hydrocarbon receptor and induces the CYP1A1 gene in a dose-dependent manner.[46] Although THC levels are low in dried cannabis buds, it is concentrated up to 5-fold in the tar fraction and therefore can exert potent effects on the induction of CYP1A1. Fifth, THC has exhibited immunosuppressive effects in animal studies, suggesting that THC could suppress antitumor response.[47] Six, histologic structure studies of lung biopsies from cannabis-only smokers found higher expression of KI-67 and EGRF.[41] In addition, there are cytomorphologic changes, alveolar macrophage tumoricidal dysfunction, enhanced oxidative stress, and histopathologic alterations specific to cannabis smoking. Ex vivo analyses revealed distinct functional impairments in alveolar macrophages from cannabis-only smokers pointing to a unique biological impact of

inhaled burned cannabinoids. The findings of animal studies, histologic studies, and cell line studies offer biological evidence that cannabis smoking could impair pulmonary function and enhance lung cancer risk.

Previous observational studies have produced unclear conclusions for the association of long-term heavy use and respiratory symptoms and COPD.[6,7,13,15] In most of these studies, cannabis smokers have been more likely to have reported cough, sputum, and wheezing but no more likely to report shortness of breath. Several cross-sectional studies have found cannabis used to be associated with lower values of FEV_1-to-FVC ratio, suggesting that cannabis use may cause airflow obstruction.[7,13,16] A systematic review of six prospective and seven cross-sectional studies published before 2018 found insufficient evidence for impairments in FEV1, FVC, or FEV_1-to-FVC ratio.[13] The findings for airflow obstruction vary, with some exhibiting lower FEV_1/FVC among cannabis smokers, other studies have not found changes in FEV_1-to-FVC ratio, despite symptoms of bronchitis.[13] Several authors have speculated that this was a result of an increase in FVC rather than a decline in FEV_1, as is typical with obstructive airway disease.[12,16,41] In a more recent study in elderly patients, the rate of decline in FEV_1 in cannabis users over three years was increased after detailed adjustment for tobacco smoking history.[42] However, there were only a few cannabis-only users in this study and the decline in cannabis-only users was not different from never-smokers of either tobacco or cannabis. As reported in many previous observational studies, most cannabis smokers were also tobacco smokers, which hampers confounding adjustment.

Several case-control and prospective studies have evaluated the association between cannabis use and lung cancer. A study with a cohort of 49,321 Swedish men with 189 incident cases assessed cannabis use at military conscription from 1969 to 1970, followed them for up to 40 years, and found that heavy use was associated with an increased lung cancer risk.[48] A weakness of the study is that it did not adjust for postconscription tobacco smoking history. A pooled analysis of six case-control studies with 2169 cases and 2965 controls from the United States, Canada, United Kingdom, and New Zealand within ILCCO found little evidence for an increased risk of lung cancer among habitual or long-term cannabis smokers[28] after conditioning for tobacco smoking, pack-years, and other confounders. Similar to our MR estimate for overall lung cancer, the OR for habitual versus nonhabitual or never–cannabis use was 0.96 (95% CI: 0.66–1.38).[28] A limitation of the pooled case-control study is the small number of heavy and chronic users of cannabis. A systematic review of eight case-control and cohort studies judged the available evidence to be insufficient because of the small number of cannabis-only users and low levels of exposure to cannabis.[14] A National Academy of Science Expert Panel concluded that there is moderate evidence of a lack of association between cannabis smoking and the incidence of lung cancer.[49] Collectively, using cannabis has not been found to be a risk factor for the development of lung cancer, but the available observational studies have been limited by small study size, possible misclassification owing to self-reporting of use, a small number of heavy cannabis smokers, and confounding with other known causative agents for lung cancer (such as parallel tobacco use).[7,12,16]

An important point to consider when performing two-sample MR is how to interpret a causal effect estimate of a binary exposure (i.e., presence of lifetime cannabis exposure or cannabis use disorder). Because cannabis exposure is uncommon because of its legal status, the effect of the exposure can often not be attributed to the exposure itself. Participants in the pulmonary function and lung cancer GWAS may carry the risk allele but may have never been exposed to cannabis. In such situations, the causal effect estimate should be interpreted as the effect of genetic liability to cannabis.[35] Two-sample MR enabled the use of the largest GWAS of pulmonary function and lung cancer to date. The minimum F statistic was 28, consistent with the absence of weak instrument bias. None of our instruments or their proxies were associated with tobacco smoking or environmental tobacco smoke exposure. Moreover, pleiotropy-robust methods produced similar point estimates. It is possible that our observation related to squamous cell carcinoma might be because of tobacco smoking exposures that are not adequately captured by the genetic variants alone, and, therefore, not completely accounted for in the pleiotropy assessment. However, the findings from our positive and negative control analyses provided additional reassurance against biasing pleiotropic pathways. A limitation is that a more detailed dose assessment of self-reported lifetime cannabis exposure or a biomarker for direct cannabis exposure was unavailable. Future MR studies will be able to exploit results from GWAS of biomarkers of cannabis exposure, such as 11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid or DNA methylation markers.[50] The present study did not allow us to investigate the route of administration, the composition of plant components, or the age at exposure to cannabis.

In summary, the present study found some evidence for an effect of genetic liability to cannabis use on squamous cell carcinoma. Triangulating MR and observational studies addressing orthogonal sources of bias are necessary to confirm this finding.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.03.025

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