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Regular cannabis use, with and without tobacco co-use, is associated with respiratory disease

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ABSTRACT

Background: Cannabis use is a potential risk factor for respiratory disease but its role apart from tobacco use is unclear. We evaluated the association between regular cannabis use, with and without tobacco co-use, and onset of asthma, chronic obstructive pulmonary disease (COPD), and pneumonia.

Methods: Analysis of a limited data set obtained through IBM Watson Health Explorys, an electronic-health-record-integration platform. Matched controls using Mahalanobis distance within propensity score calipers were defined for: 1) cannabis-using patients (n = 8932); and subgroups of cannabis-using patients: 2) with an encounter diagnosis for tobacco use disorder (TUD; n = 4678); and 3) without a TUD diagnosis (non-TUD; n = 4254). Patients had at least: one recorded blood pressure measurement and one blood chemistry lab result in the MetroHealth System (Cleveland, Ohio). Cannabis-using patients had an encounter diagnosis of cannabis abuse/dependence and/or ≥2 cannabis-positive urine drug screens (UDSs). Control patients, not having cannabis-related diagnoses or cannabis-positive UDSs, were matched to the cannabis-using patients on demographics, residential zip code median income, body mass index, and, for the total sample, TUD-status.

Results: Regular cannabis use was significantly associated with greater risk for asthma (odds ratio (OR) = 1.44; adjusted odds ratio (aOR) = 1.50; OR = 1.32), COPD (OR = 1.56; aOR = 1.44; OR = 2.17), and pneumonia (OR = 1.80; OR = 1.84; OR = 2.13) in the total sample and TUD and non-TUD subgroups, respectively. TUD-patients had the greatest prevalence of respiratory disease, regardless of cannabis-use indication.

Conclusions: Regular cannabis use is associated with significantly greater risk of respiratory disease regardless of TUD status. Future research to understand the impact of cannabis use on respiratory health is warranted.

1. Introduction

Respiratory diseases, including asthma (Centers for Disease Control and Prevention, 2018), chronic obstructive pulmonary disease (COPD) (Heron, 2018; World Health Organization, 2018), and pneumonia (Heron, 2018; World Health Organization, 2018) account for significant morbidity and mortality worldwide. In US adults, the prevalence of asthma has been estimated at 8% (Centers for Disease Control and Prevention, 2018), the prevalence of COPD has been estimated to be 6.2% (Wheaton et al., 2019), and 1.7 million adults were hospitalized for pneumonia in 2017 (Ramirez et al., 2017). In 2017, it was estimated that 14% of US adults were current tobacco cigarette smokers (Wang et al., 2018). Tobacco smoking is a well-established risk factor for developing asthma (Coogan et al., 2015; Gilliland et al., 2006; Jaakkola et al., 2003; Polosa et al., 2008; Strachan et al., 1996) and COPD (Pauwels et al., 2001; U.S. Department of Health and Human Services, 2014) and for contracting pneumonia (Almirall et al., 1999; Nuorti et al., 2000).

Cannabis use has been increasing in the US and it is estimated that 1.5% of US adults has cannabis use disorder (Compton et al., 2016). Research suggests that smoking a cannabis joint exposes the user to 3–5 times more carbon monoxide and tar deposition relative to smoking a tobacco cigarette (Wu et al., 1988). Additionally, the airflow obstruction produced by smoking a cannabis joint is equivalent to that produced by smoking 2.5–5 tobacco cigarettes (Aldington et al., 2007). Thus, it has been predicted that smoking cannabis on a regular basis

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will significantly increase the risk for respiratory disease but recent literature reviews have concluded that existing research is insufficient for evaluating the association between use and respiratory disease (Ghasemiesfe et al., 2018; National Academies of Sciences Engineering and Medicine, 2017). Limitations of past research include reliance on cross-sectional studies and self-report measures, small sample sizes, and difficulty with differentiating between the effects of tobacco and cannabis use (Ghasemiesfe et al., 2018; National Academies of Sciences Engineering and Medicine, 2017); the latter is important given the high prevalence of tobacco smoking among people with cannabis use disorder (CUD), which has been estimated to be 47% (Moore and Budney, 2001). The increasing use of cannabis in the US, with smoking being the most prevalent form of use (National Institutes of Health, 2015; Steigerwald et al., 2018), increases the urgency of research to elucidate the potential impact of cannabis use on respiratory health. The present study evaluated the association between regular cannabis use, with and without tobacco co-use, and respiratory disease using a method (Winhusen et al., 2019) that addresses many of the limitations of past research. This approach included using EHR data, rather than self-report measures, of cannabis use and respiratory diseases, use of a multi-year data set, which allows detection of effects that may take several years to develop, large sample sizes, and the use of rigorous matching and analytic procedures to control for potential confounding factors. We hypothesized that an association between regular cannabis use and respiratory disease would be found.

2. Methods

2.1. Setting

The study data were derived from the Explorys (IBM Watson Health; Cleveland, OH) technology platform, which utilizes a health data gateway server behind the firewall of each participating healthcare organization. The server collects data from a variety of health information systems (e.g., EHR, billing systems, lab/tests systems, etc.). The data are then de-identified and passed into the Explorys data grid, which is a private cloud-based data store, and are standardized and normalized (Kaelber et al., 2012). The Explorys dataset has been validated in past research (Kaelber et al., 2012; Pfefferle et al., 2014). Our analytic approach, in which substance-using patients are “matched” to patients without evidence of substance use to decrease the possibility of study confounds (Winhusen et al., 2019), requires a limited dataset available to us only from the MetroHealth System Explorys dataset. MetroHealth is an integrated healthcare system in Northeast Ohio that consists of 1 tertiary care academic medical center, 4 emergency departments, and over 2 dozen ambulatory clinics, seeing approximately 25,000 inpatients per year, with over 1.2 million outpatient visits annually. A data use agreement between the MetroHealth System and the University of Cincinnati was established to allow the use of limited datasets, which include detailed patient record data but no individually identifiable information. This study was deemed not to be human subjects research by the institutional review board of the University of Cincinnati. This study was funded by the National Institute on Drug Abuse Clinical Trials Network (CTN) for the Ohio Valley Node Network (Grant UG1DA013732). The CTN Publications committee reviewed and approved an earlier draft of this manuscript.

2.2. Study population

The Explorys Cohort Discovery tool was used to identify adult patients (age ≥18) in the MetroHealth System who received a medical evaluation as evidenced by having at least one recorded blood pressure measurement and at least one blood chemistry lab result. Patients needed to have data that spanned at least one year in order to be included in the analysis. At the time of Explorys query, the MetroHealth System data included 405,778 patients meeting these criteria and covered the years of 1999–2018.

2.2.1. Cannabis-using group

The a priori definition of the cannabis-using group, which was designed to identify regular cannabis users, was patients having: 1) at least one encounter diagnosis code for cannabis abuse or dependence (see Supplement Table S1 for ICD-9/10 codes), indicating CUD; and/or 2) at least two urine drug screens (UDSs) results positive for cannabinoids. The rationale for this definition is that having at least one CUD diagnosis is evidence that a patient is very likely a regular cannabis user. On the other hand, a single positive UDS could occur for an infrequent cannabis user. Our consensus was that two or more such positive results are indicative of regular use (i.e., on multiple separate occasions, a clinician ordered this testing to be done, and it was positive at least twice). The cannabis-using group included 8932 patients. To further elucidate the potential impact of regular cannabis use, with and without tobacco use, the cannabis-using group was divided into patients who had at least one encounter diagnosis code for tobacco abuse or dependence (see Supplement Table S1 for ICD-9/10 codes), referred to as the tobacco use disorder (TUD) subgroup (n = 4678) and patients who did not have a TUD diagnosis, referred to as the non-TUD subgroup (n = 4254).

2.2.2. Control groups

For each of the three groups (total sample, TUD subgroup, non-TUD subgroup), a control group was identified. To be included as a potential control participant for each of the three groups, a patient could not have any encounter diagnoses with a cannabis-related ICD-9/10 code and could not have any cannabinoid-positive UDS results. A total of 388,906 patients met these criteria. Because cannabis-using patients may differ from patients without evidence of cannabis use on a variety of factors that could impact respiratory health, we created control groups that were matched to each cannabis-using group. Matching variables included: age, sex, race, ethnicity, median income of zip code of residence, and body mass index (BMI), and, for the total sample, TUD status (yes/no).

The Ohio Valley Node (OVN) matching programs (Winhusen et al., 2019), which are SAS macros (version 9.4; Cary, NC) were used for this study. The OVN programs and associated documentation are available at the National Drug Abuse Clinical Trials Network dissemination website (http://ctndisseminationlibrary.org/display/1287.htm); the programs are open-source and can be used free of charge. The OVN matching program uses Mahalanobis Distance within Propensity Score Calipers as the distance measure (Hintze, 2007) and allows for two matching methods: “optimal” and “greedy”. For this study, we utilized optimal matching, which matches patients from the cohort of interest (e.g., cannabis-using group) to respective control patients so as to minimize the sum of the distances over all pairs (Stuart, 2010).

2.3. Respiratory diseases

The respiratory diseases evaluated, asthma, COPD, and pneumonia, were selected based on their substantial morbidity and mortality and, hence, clinical importance. COPD has been described as airflow obstruction resulting from emphysema, chronic bronchitis, or a combination of both (Kim and Criner, 2013; U.S. Department of Health and Human Services, 2014); we thus defined COPD using codes for these diagnoses as well as broader codes describing such obstruction (e.g., “ICD-9 496: chronic airway obstruction not elsewhere classified”). The ICD-9/10 codes used for each disease, along with the number of patients having each code, are provided in the Supplement (Table S2). While the data are correlational in nature (i.e., patients are not randomized to cannabis-using and control groups), our approach helped to ensure that the respiratory encounter diagnosis occurred after the patient’s first indication of cannabis use (i.e., either CUD diagnosis or positive UDS) and, thus, that cannabis use could have played a role in developing the condition. To this end, patients were scored as: 1) positive for the condition if the initial respiratory encounter diagnosis date was later than the initial cannabis-use indication date (controls were assessed using the initial cannabis-use indication date of their respective matched cannabis-using patient, corrected for differences in respective dates of birth); 2) negative for the condition if they did not have the respiratory encounter diagnosis; or 3) missing if the initial respiratory encounter diagnosis date was not later than the initial cannabis-use indication date. The rationale for using the missing code is based on the potential for patients to have a condition prior to it being entered into the EHR. For example, a patient could be using cannabis for years before a UDS is completed. Hence, there is no way to ascertain whether a respiratory encounter diagnosis preceding the initial cannabis-use indication date reflects the respiratory disease actually preceding the patient using cannabis or simply reflects the respiratory disease diagnosis preceding the cannabis-use indication being added to the EHR. The missing code reflects the unknown temporal relationship.

2.4. Data analysis

All analyses were completed using SAS, Version 9.4. Statistical tests were defined a priori and were conducted at an α level of 0.05 (two-tail) for all measures. Logistic generalized mixed-model regressions (with a random effect to account for matched patient pairs) were used to evaluate whether cannabis-using status was significantly associated with each of the respiratory diseases. For each planned regression, all possible models (i.e., all combinations of covariates) were estimated. The covariates considered for inclusion were other substance use disorders (opioid, cocaine, and alcohol; see Supplement Table S3 for ICD 9/10 codes) and the matching covariates; the variable indicating cannabis-use group vs. control group was included in all models. The model with the covariates resulting in the best corrected Akaike Information Criterion (AIC-C) was selected; Tables S4-S6 list the covariates included in each regression. The proportion of data coded as missing (i.e., when initial respiratory encounter diagnosis date was not later than the initial cannabis-use indication date) was 12.4% for asthma, 5.1% for COPD, and 4.6% for pneumonia for the total study sample.

3. Results

As can be seen in Table 1, the matching procedure created very comparable matched groups, with no significant difference on demographics. Table 2 displays the results of the comparisons between each cannabis-using group and its matched control for each of the respiratory diseases. The crude odds ratio (OR) results were yielded by the comparison of the cannabis-using group with its matched control without controlling for additional variables (i.e., other substance use disorders including opioid, cocaine and alcohol; time since the earliest observation/diagnosis in the EHR; and demographics including age, sex, race, ethnicity, median income of zip code of residence, and BMI). The adjusted odds ratio (aOR) reflects the results from a logistic regression comparing the cannabis-using group with its matched control using AIC-C to determine inclusion of additional variables. Discrepancies between the OR and aOR results may reflect the more precise control provided by the logistic regression analysis and/or may reflect complicating factors such as the relatively low prevalence of a respiratory disease and the number of variables selected by AIC-C in the statistical model. The most conservative interpretation of the findings is to consider a cannabis-using-control group comparison to be significant based on the results of the logistic regression (i.e., as indicated by the aOR column in Table 2) and to judge the degree to which the difference is clinically meaningful based on the aOR or crude OR value, whichever is closer to 1.0; the summary of findings in this section reflects this conservative approach.

3.1. Sample

The total sample was approximately 57% male and 46% African American, and participants were a mean age of 42 years. The average number of years of EHR data available for all patients was 15.4 years (SD = 8.0). The prevalence of CUD within the cannabis-using group was 76.9%; the remainder of the cannabis-using group met the cannabinoid-positive UDS criterion described in Methods. For the cannabis-using group, the average number of years since first cannabis-use indication was 7.5 (SD = 5.0). Among all TUD-diagnosed patients in the total sample, the average number of years since first TUD diagnosis was 7.1 (SD = 4.6). The TUD subgroup was approximately 55% male and 45% African American, and participants were a mean age of 45 years. The average number of years of EHR data available for TUD patients was 16.4 years (SD = 8.4). The prevalence of CUD within the cannabis using TUD subgroup was 79.8%. For the cannabis-using group, the average number of years since first cannabis-use indication was 7.6 (SD = 4.9). The average number of years since first TUD diagnosis was 7.1 (SD = 4.6). The non-TUD subgroup was approximately 59% male and 47% African American, and participants were a mean age of 39 years. The average number of years of EHR data available for non-TUD patients was 14.4 years (SD = 7.4). The prevalence of CUD within the cannabis using non-TUD subgroup was 73.7%. For the cannabis-using group, the average number of years since first cannabis-use indication was 7.5 (SD = 5.2).

3.2. Asthma

As can be seen in Table 2, the prevalence of asthma was highest in the TUD subgroup relative to either the total sample or non-TUD subgroup. The logistic regression results revealed significantly higher prevalence of asthma in the cannabis-using, compared to control, group for the total sample (10.2% vs. 7.3%, OR = 1.44 (1.29–1.61)), the TUD subgroup (14.3% vs. 9.6%, aOR = 1.50 (1.28–1.76)) and the non-TUD subgroup (5.9% vs. 4.6%, OR = 1.32 (1.08–1.62)).

3.3. COPD

As can be seen in Table 2, the prevalence of COPD was highest in the TUD subgroup relative to either the total sample or non-TUD subgroup. The logistic regression results revealed significantly higher prevalence of COPD in the cannabis-using, compared to control, group for the total sample (8.1% vs. 5.4%, OR = 1.56 (1.38–1.76)), the TUD subgroup (14.1% vs. 9.0%, aOR = 1.44 (1.20–1.73)) and the non-TUD subgroup (2.1% vs. 1.0%, OR = 2.17 (1.50–3.13)).

3.4. Pneumonia

As can be seen in Table 2, the prevalence of pneumonia was highest in the TUD subgroup relative to either the total sample or non-TUD subgroup. The logistic regression results revealed significantly higher prevalence of pneumonia in the cannabis-using, compared to control, group for the total sample (6.4% vs. 3.7%, OR = 1.80 (1.56–2.08)), the TUD subgroup (9.7% vs. 5.5%, OR = 1.84 (1.56–2.16)) and the non-TUD subgroup (3.0% vs. 1.4%, OR = 2.13 (1.56–2.91)).

4. Discussion

The present study utilized multi-year EHR data to evaluate the associations between documented cannabis use and the onset of respiratory diseases, including asthma, COPD, and pneumonia, using a rigorous procedure to define matched controls for a sample of cannabis-using patients and subgroups of cannabis-using patients with and without tobacco use disorder (TUD). The results of the present study suggest that regular cannabis use is associated with a significantly greater risk of respiratory disease regardless of TUD status.

Table 1
Demographics for cannabis use and matched control cohorts for the total, TUD, and non-TUD samples.

Total Sample	Control (n = 8932)	Cannabis Use (n = 8932)	Test statistic (p-value)*
Age, m (sd)	42.3 (13.5)	42.3 (13.6)	W = 0.2 (p = 0.85)
Female n (%)	3862 (43.2%)	3862 (43.2%)	$\chi^2(1)$ = 0.0 (p = 1.00)
Race n (%)			$\chi^2(2)$ = 0.0 (p = 1.00)
Black/African American	4121 (46.1%)	4124 (46.2%)	
White	4048 (45.3%)	4044 (45.3%)	
Other †	763 (8.5%)	764 (8.6%)	
Hispanic n (%)	238 (2.7%)	238 (2.7%)	$\chi^2(1)$ = 0.0 (p = 1.00)
Median income for the zip code of residence m (sd)	$36,320.6 (13,965.9)	$36,354.7 (14,081.5)	W = 0.1 (p = 0.96)
Tobacco Use Disorder n (%)	4678 (52.4%)	4678 (52.4%)	$\chi^2(1)$ = 0.0 (p = 1.00)
Average BMI m (sd)	28.1 (7.3)	28.1 (7.4)	W = 0.0 (p = 0.99)
TUD Subgroup	**Control (n = 4678)**	**Cannabis Use (n = 4678)**	**Test statistic (p-value)***
Age, m (sd)	45.0 (13.1)	45.0 (13.2)	W = 0.2 (p = 0.84)
Female n (%)	2117 (45.3%)	2118 (45.3%)	$\chi^2(1)$ = 0.0 (p = 0.98)
Race n (%)			$\chi^2(2)$ = 0.0 (p = 0.99)
Black/African American	2100 (44.9%)	2106 (45.0%)	
White	2239 (47.9%)	2232 (47.7%)	
Other †	339 (7.2%)	340 (7.3%)	
Hispanic n (%)	117 (2.5%)	117 (2.5%)	$\chi^2(1)$ = 0.0 (p = 1.00)
Median income for the zip code of residence m (sd)	$35,620.5 (12,940.1)	$35,704.3 (13,231.4)	W = 0.1 (p = 0.89)
Average BMI m (sd)	28.3 (7.2)	28.3 (7.4)	W = -0.1 (p = 0.93)
Non-TUD Subgroup	**Control (n = 4254)**	**Cannabis Use (n = 4254)**	**Test statistic (p-value)***
Age, m (sd)	39.4 (13.3)	39.3 (13.3)	W = 0.1 (p = 0.93)
Female n (%)	1744 (41.0%)	1744 (41.0%)	$\chi^2(1)$ = 0.0 (p = 1.00)
Race n (%)			$\chi^2(2)$ = 0.0 (p = 1.00)
Black/African American	2018 (47.4%)	2018 (47.4%)	
White	1812 (42.6%)	1812 (42.6%)	
Other †	424 (10.0%)	424 (10.0%)	
Hispanic n (%)	121 (2.8%)	121 (2.8%)	$\chi^2(1)$ = 0.0 (p = 1.00)
Median income for the zip code of residence m (sd)	$37,055.7 (14,876.5)	$37,070.0 (14,929.6)	W = 0.0 (p = 0.98)
Average BMI m (sd)	27.9 (7.4)	27.9 (7.4)	W = 0.1 (p = 0.94)

*Quantitative measures were tested with the Wilcoxon rank-sum test (W); Categorical measures were tested with Pearson's chi-square test of independence (χ^2 (degrees of freedom)). †: "Other" race includes: American Indian / Alaska Native, Asian, Multiracial, Native Hawaiian / Pacific Islander, and "missing" (i.e., no race data available).

Table 2
Respiratory diagnosis prevalence in cannabis-using vs. matched control cohort and cannabis-use ORs for total, TUD, and non-TUD samples for Asthma (a), COPD (b) and Pneumonia (c).

a. Asthma

Sample	Prevalence* (Cannabis vs. Control)	Odds Ratio (95% CI), p-value	aOR (95% CI), p-value
Total Sample (N = 17,864)	10.2% vs. 7.3%	**1.44 (1.29 - 1.61), p < 0.0001**	**2.13 (1.75 - 2.59), p < 0.0001**
TUD Subgroup (N = 9356)	14.3% vs. 9.6%	**1.57 (1.37 - 1.80), p < 0.0001**	**1.50 (1.28 - 1.76), p < 0.0001**
Non-TUD Subgroup (N = 8508)	5.9% vs. 4.6%	**1.32 (1.08 - 1.62), p = 0.0066**	**1.86 (1.30 - 2.66), p < 0.0001**

b. COPD

Sample	Prevalence* (Cannabis vs. Control)	Odds Ratio (95% CI), p-value	aOR (95% CI), p-value
Total Sample (N = 17,864)	8.1% vs. 5.4%	**1.56 (1.38 - 1.76), p < 0.0001**	**2.88 (2.20 - 3.76), p < 0.0001**
TUD Subgroup (N = 9356)	14.1% vs. 9.0%	**1.66 (1.45 - 1.90), p < 0.0001**	**1.44 (1.20 - 1.73), p < 0.0001**
Non-TUD Subgroup (N = 8508)	2.1% vs. 1.0%	**2.17 (1.50 - 3.13), p < 0.0001**	**6.95 (3.02 - 16.01), p < 0.0001**

c. Pneumonia

Sample	Prevalence* (Cannabis vs. Control)	Odds Ratio (95% CI), p-value	aOR (95% CI), p-value
Total Sample (N = 17,864)	6.4% vs. 3.7%	**1.80 (1.56 - 2.08), p < 0.0001**	**3.44 (2.62 - 4.51), p < 0.0001**
TUD Subgroup (N = 9356)	9.7% vs. 5.5%	**1.84 (1.56 - 2.16), p < 0.0001**	**2.60 (1.92 - 3.53), p < 0.0001**
Non-TUD Subgroup (N = 8508)	3.0% vs. 1.4%	**2.13 (1.56 - 2.91), p < 0.0001**	**8.35 (4.23 - 16.47), p < 0.0001**

*Prevalence is the prevalence of the diagnosis in the cannabis-using versus matched control cohorts. aOR = adjusted Odds Ratio; bold = statistically significant ($p < 0.05$) effect.

A recent review by the National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that there is insufficient evidence to determine whether there is a link between cannabis use and asthma due to both the small number of studies and the limitations of the studies conducted (National Academies of Sciences Engineering and Medicine, 2017). The present results revealed that asthma in adult patients was significantly more prevalent in cannabis-using, relative to control, patients in the total sample, which controlled for TUD status, and in the TUD and non-TUD subgroups. The crude cannabis-use OR was larger for the TUD subgroup (OR = 1.57) relative to the total sample (OR = 1.44) and non-TUD subgroup (OR = 1.32), which might suggest that the risk of asthma from regular cannabis use is greater for patients who are tobacco users. A review of the literature revealed only one study in adults evaluating the potential impact of cannabis and tobacco use on asthma, which found that cannabis, but not tobacco, use was associated with having an asthma diagnosis after the age of 16 (Aldington et al., 2007). Two studies evaluating the association between cannabis use and asthma have been conducted with adolescents, both of which relied on self-report assessments, with one finding a significant association (Jones et al., 2006) and one finding no association (Bechtold et al., 2015).

The present results revealed that the onset of COPD, as indicated by encounter diagnoses of emphysema, chronic bronchitis, and/or chronic airway obstruction, in adult patients was significantly more prevalent in cannabis-using, relative to control, patients in the total sample, which controlled for TUD status, and in the TUD and non-TUD subgroups. The crude cannabis-use OR was larger for the non-TUD subgroup (OR = 2.17) relative to the total sample (OR = 1.56) and TUD subgroup (OR = 1.66), which might suggest that the risk of COPD onset from regular cannabis use is greater for patients who are not tobacco users. The present findings are consistent with the NASEM conclusion that there is a significant association between long-term cannabis smoking and worse respiratory functioning, including chronic bronchitis (National Academies of Sciences Engineering and Medicine, 2017). A recent review by Ghasemiesfe and colleagues noted that existing research is insufficient for evaluating the association between regular cannabis use and obstructive lung disease and suggested that research with larger cohorts of middle-aged to older populations of heavier cannabis users might be necessary for evaluating the potential impact of cannabis use on obstructive lung disease (Ghasemiesfe et al., 2018). The present study, which included 8932 regular cannabis users, 77% of whom had a diagnosis of cannabis abuse or dependence, with an average age of 42, does, indeed suggest that there is a significant association between regular cannabis use and obstructive lung disease.

Finally, the present results revealed that the onset of infectious pneumonia in adult patients was significantly more prevalent in cannabis-using, relative to control, patients in the total sample, which controlled for TUD status, and in the TUD and non-TUD subgroups. The cannabis-use OR was larger for the non-TUD subgroup (OR = 2.13), relative to the total sample (OR = 1.80) and TUD subgroup (OR = 1.84), which might suggest that the risk of pneumonia onset from regular cannabis use is greater for patients who are not tobacco users. While there is some evidence to suggest that regular cannabis use may decrease the lung's ability to fight infection (Tashkin et al., 2018), past research has not found a significant association between cannabis use and pneumonia (Macleod et al., 2015; Moore et al., 2005). The discrepant results may be due to differences in study samples, with the present sample including older and heavier cannabis users than in prior research (Macleod et al., 2015; Moore et al., 2005). In addition, past research has relied on self-reported cannabis use and self-reported pneumonia experienced within the prior 12 months (Moore, 2005; Macleod, 2015) whereas the present study utilized EHR cannabis-use indicators and encounter diagnoses of pneumonia occurring after the EHR cannabis-use indicator was recorded.

The present study contributes needed evidence for understanding the potential associations between regular cannabis use and respiratory disease with and without tobacco co-use. Although our study was not intended to directly evaluate the effect of TUD on respiratory disease, it should be noted that control patients *with* TUD, compared to cannabis-using patients *without* TUD, had higher rates of asthma (9.6% vs. 5.9%), COPD (9.0% vs. 2.1%), and pneumonia (5.5% vs. 3.0%). This suggests that, although regular cannabis use was associated with respiratory disease, TUD is a more dominant factor in respiratory disease. Of note, the present study avoided many of the limitations of past research in this area (Ghasemiesfe et al., 2018; National Academies of Sciences Engineering and Medicine, 2017). First, the definition of the cannabis-using group was based on documentation in the EHR and, thus, was not open to recall bias. Second, a longitudinal design was utilized, which allows the detection of effects that may take years to develop. Moreover, the sample of cannabis-users included heavier users, in whom potential health effects are more likely to be seen, with 77% of the sample having a diagnosis of cannabis abuse or dependence. Additional strengths include a large sample size (N = 17,864) and the use of rigorous matching and analytic approaches.

This study also has important limitations. First, cause and effect determinations cannot be made because the study utilized observational data (i.e., patients were not randomly assigned to be either regular cannabis users or controls). Second, while the sample size was large, the sample was limited to patients being treated in the MetroHealth System, located in Northeast Ohio. Although its Hispanic population is small relative to the rest of the US, the demographics of Northeast Ohio are broadly representative of the nation as a whole (US Census Bureau, 2019); still, the extent to which the results are generalizable to the rest of the U.S. and other countries is unknown. Third, while the Explorys dataset has been validated in past research (Kaelber et al., 2012; Pfefferle et al., 2014) there is still the potential for data quality issues. For example, as is the case with medical conditions generally, the under-diagnosis, misclassification, or under-coding of substance use disorder by clinicians is possible (Wu et al., 2015). The CUD prevalence in our full, unmatched, sample of potential patients (N = 397,838) was 1.7%, which is similar to the national estimate of 1.5% for CUD (Compton et al., 2016). Similarly, the prevalence of TUD in the cannabis-use patients was 52%, which is consistent with the 47% prevalence found in past research with individuals with cannabis use disorder (Moore and Budney, 2001). Still, some "control" participants may have been cannabis users despite not having had a positive UDS or cannabis diagnosis in the EHR; this would serve to weaken the associations observed in this study and, thus, the reported associations may be overly conservative. In addition, some cigarette smokers may not have been given a TUD diagnosis and, thus, classified as non-smokers; such misclassification could reduce the accuracy of the subgroup-specific effect estimates.

Another limitation of EHR analyses is the inability to evaluate factors not included in the EHR such as cannabis route of administration, severity and duration of use. Another potential weakness is the definition of COPD, which included encounter diagnoses of emphysema, chronic bronchitis, and/or chronic airway obstruction and, thus, did not necessarily include spirometry data. However, the definition of COPD is consistent with what has been utilized in past research (Kim and Criner, 2013; U.S. Department of Health and Human Services, 2014) and the COPD prevalence in our full, unmatched sample of potential patients (N = 397,838), was 7.5% (data not shown), which is consistent with the CDC estimated COPD prevalence of 7.6% (6.9%–8.2%) for Ohio (Wheaton et al., 2019). Finally, there may have been other potential confounding factors that were not accounted for in the statistical models. With these limitations in mind, the present results suggest that regular cannabis use is associated with a significantly greater risk of respiratory disease. Future research to understand the potential impact of cannabis use on respiratory health seems warranted.

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Contributors

TW, JT, DCK, and DL contributed to the conception or design of the work. TW, JT, DCK, and DL contributed to the acquisition, analysis, or interpretation of data for the work. TW drafted the manuscript. TW, JT, DCK, and DL critically revised the manuscript. All authors contributed to and have approved the final manuscript.

TW, JT, and DL declare no conflicts of interest. DCK is the Chief Medical Informatics Officer of the MetroHealth System. In exchange for contributing de-identified data to the Explorys network, the MetroHealth System receives access to the Explorys Cohort Discovery tool, which was used to conduct this study. Neither DCK nor the MetroHealth System have any direct financial ties to Explorys (IBM Watson Health).

Declaration of Competing Interest

TW, JT, and DL declare no conflicts of interest. DCK is the Chief Medical Informatics Officer of the MetroHealth System. In exchange for contributing de-identified data to the Explorys network, the MetroHealth System receives access to the Explorys Cohort Discovery tool, which was used to conduct this study. Neither DCK nor the MetroHealth System have any direct financial ties to Explorys (IBM Watson Health).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107557.

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