

# Marijuana and Lung Disease



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As marijuana smoking prevalence increases in the United States, concern regarding its potential risks to lung health has also risen, given the general similarity in the smoke contents between marijuana and tobacco. Most studies have found a significant association between marijuana smoking and chronic bronchitis symptoms after adjustment for tobacco. Although reports are mixed regarding associations between marijuana smoking and lung function, none have shown a relationship to decrements in FEV<sub>1</sub> and few have found a relationship to a decreased ratio of FEV<sub>1</sub>/FVC, possibly related to an association between marijuana and an increased FVC. A few studies have found a modest reduction in specific airway conductance in relation to marijuana, probably reflecting endoscopic evidence of bronchial mucosal edema among habitual marijuana smokers. Diffusing capacity in marijuana smokers has been normal, and two studies of thoracic high-resolution CT scan have not shown any association of marijuana smoking with emphysema. Although bronchial biopsies from habitual marijuana smokers have shown precancerous histopathologic changes, a large cohort study and a pooled analysis of six well-designed case-control studies have not found evidence of a link between marijuana smoking and lung cancer. The immunosuppressive effects of delta-9 tetrahydrocannabinol raise the possibility of an increased risk of pneumonia, but further studies are needed to evaluate this potential risk. Several cases series have demonstrated pneumothoraces/pneumomediastinum and bullous lung disease in marijuana smokers, but these associations require epidemiologic studies for firmer evidence of possible causality. CHEST 2018; 154(3):653-663

**KEY WORDS:** chronic bronchitis; lung cancer; lung function; marijuana; smoking; tobacco

Marijuana is the second most commonly smoked substance in our society after tobacco. According to US national surveys, after an initial decline in marijuana use from 1990 through 2005 among adults  $\geq 18$  years of age, its use prevalence increased markedly over the following 10 years.<sup>1</sup> This surge in use was most notable among those 40 to 59 years of age, and by 2014 to 2015, 12.9% of all adults reported using marijuana within the last year. More potentially concerning has been the increase in daily or near-daily

use from 5.1% to 7.6% over roughly the same time interval among individuals  $\geq 12$  years of age.<sup>2</sup> This rise in use prevalence has been accompanied by changing perceptions regarding the risks and benefits of marijuana use that are likely related to the legalization of marijuana for medicinal use by 29 states in the United States and for recreational use in seven states as of 2017.

The smoke of marijuana contains many of the same volatile and particulate

**ABBREVIATIONS:** AM = alveolar macrophage; ROS = reactive oxygen species; THC = delta-9 tetrahydrocannabinol

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components found in tobacco smoke, including a variety of chemicals (phenols, aldehydes, acrolein, etc) that are injurious to lung tissue, and carcinogens, including benzpyrene and benzanthracene.<sup>3,4</sup> The major exceptions are nicotine, found only in tobacco, and delta-9 tetrahydrocannabinol (THC), the major psychoactive ingredient, and a number of THC-like compounds, namely cannabinoids, in marijuana. In view of the similarity in the smoke contents of marijuana and tobacco, the increasing use of marijuana in our society, particularly on a daily or near-daily basis, raises concern regarding a potential link between marijuana smoking and the well-known deleterious effects of regular tobacco smoking on the lung, particularly regarding increased risks for developing COPD and lung cancer. Complicating this public health issue is the observation that most marijuana smokers also smoke tobacco, requiring methods of analysis that control for concomitant tobacco use and examine possible interactive effects and/or restricting the analysis to a comparison of marijuana smokers alone vs nonsmokers of any substance. The aim of this article is to review the evidence mainly from the limited number of publications largely based on observational cohort studies that have systematically addressed these concerns. In addition, findings from case series and other observational studies pertaining to a possible link between marijuana and other forms of lung disease, including pneumothorax/pneumomediastinum, bullous lung disease, and pneumonia risk, will also be reviewed. Although increasing numbers of users of marijuana are adopting other modes of use than smoking (eg, vaping, ingestion of edibles), little information concerning the impact of these alternative modes of use on lung health is available. Therefore, the focus of this review will be confined to smoked marijuana.

## Marijuana and Symptoms of Chronic Bronchitis

Ten cross-sectional or prospective cohort studies have examined the association between marijuana use and chronic respiratory symptoms (mainly cough, sputum, wheeze, and/or dyspnea) after adjusting for tobacco or comparing the marijuana-only users with nonsmokers.<sup>5-14</sup> The findings are shown in [Table 1](#). Despite the heterogeneity of the populations studied regarding age, amount of marijuana smoked, the presence of concomitant tobacco smoking (controlled

for in the analysis), and geographic location, the results reveal general, albeit incomplete, agreement regarding a significant association of marijuana use with symptoms of chronic bronchitis (cough, sputum, and wheeze). The notable exceptions were the studies of Tan et al<sup>11</sup> and Morris et al,<sup>14</sup> which included older subjects who may not have smoked as much marijuana as their younger counterparts. In addition, Tan et al<sup>11</sup> appeared to find an interaction between marijuana and tobacco such that the smokers of both substances were more likely to have chronic respiratory symptoms than the smokers of either substance alone. On the other hand, a similar interaction was not reported by other investigators. In addition, one study showed an increased incidence of acute bronchitic episodes over the previous 3 years in habitual marijuana smokers compared with nonsmokers.<sup>6</sup> Somewhat consistent with the latter findings, a large prospective cohort study in Northern California found that a subgroup of 452 frequent marijuana smokers who reported never smoking tobacco had a significantly increased risk of outpatient visits for respiratory illnesses than 450 nonsmoking control subjects.<sup>15</sup> As part of another cohort study in upstate New York, investigators interviewed 749 participants at 14, 16, 22, and 27 years of age and found a significant association of marijuana use with self-reported respiratory problems (not specifically defined) occurring by their late twenties. However, the analysis was not adjusted for concomitant tobacco use.<sup>16</sup> Two longitudinal studies have shown at least partial resolution of chronic respiratory symptoms in marijuana smokers who quit smoking marijuana.<sup>13,17</sup> In one of these studies, resolution of symptoms occurred only in those former marijuana smokers who did not also smoke tobacco.<sup>17</sup>

Bronchoscopic studies performed in habitual smokers of marijuana alone (n = 40), tobacco alone (n = 31), marijuana plus tobacco (n = 44), and never smokers (n = 53) provide a clue as to the possible underlying mechanism for the association of marijuana use with chronic bronchitic symptoms.<sup>18</sup> Bronchial mucosal biopsies revealed widespread histopathologic changes in the bronchial mucosa in marijuana smokers alone that were comparable with those in the tobacco-only smokers, consisting of destruction of the ciliated columnar bronchial epithelial cells and their replacement by mucus-secreting surface epithelial (goblet) cells or reserve cells ([Fig 1](#)).<sup>18</sup> An increase in mucus secretion in the face of an impairment in the mucociliary escalator could contribute to cough as an alternative mechanism to cleanse the

**TABLE 1 ]** Associations of Regular Marijuana Use With Chronic Respiratory Symptoms Compared With Nonsmokers of Any Substance or Controlling for Concomitant Tobacco

Study/Year	Total No.	Age, y	MJ Use Amount	Cough	Sputum	Wheeze	Shortness of Breath
Bloom et al <sup>5</sup> / 1987	990	15-40	Mean 58.2 joints-years	Numeric increase	Significant increase	Significant increase	NS
Tashkin et al <sup>6</sup> / 1987	446	25-49	Mean 54.4 joint-years	Significant increase	Significant increase	Significant increase	NS
Sherrill et al <sup>7</sup> / 1991	1,239	20-60	Not reported	Significant increase <sup>a</sup>	Significant increase <sup>a</sup>	Significant increase <sup>a</sup>	NS
Taylor et al <sup>8</sup> / 2000	943	Birth-21	Mean 230 uses past year	Significant increase	Significant increase	Significant increase	Significant increase
Moore et al <sup>9</sup> / 2004	6,728	20-59	Use on mean of 10.2 d in last month (always with T)	Significant increase	Significant increase	Significant increase	NS
Aldington et al <sup>10</sup> / 2007	339	25-75	Mean 54.2 joint-years	Significant increase	Significant increase	Significant increase	Not reported
Tan et al <sup>11</sup> / 2009	878	Mean 54.3 (no COPD) to 65.4 (COPD)	Lifetime median No. of joints: no COPD (n = 708): 80.5; COPD (n = 148): 208	No significant increase in symptoms consistent with COPD			
MacLeod et al <sup>12</sup> / 2015	500	Mean 36.5-38 (MJ/T) to 43-47 (T only)	Mean 53.2 (women) to 104.5 (men) joint-years	Significant increase	Significant increase	Significant increase	NS
Hancox et al <sup>13</sup> / 2015	933-943	36 (birth cohort)	99 frequent users <sup>b</sup> ; 146 occasional users <sup>c</sup>	Significant increase	Significant increase	Significant increase	Significant increase
Morris et al <sup>14</sup> / 2018	2641	Mean 58.5-65.9	Mean 10.6 joint-years (former MJ), mean 49 joint-years (current MJ)	NS	NS (for chronic bronchitis)	Significant increase (former MJ) NS (current MJ)	NS

joint-years = average number of joints per day used times the number of years smoked; MJ = marijuana; NS = no significant association; T = tobacco.

<sup>a</sup>Significant increase in cough and sputum was observed in each of the three follow-up surveys of this longitudinal study.

<sup>b</sup>Frequent is  $\geq 52$  times in previous year (weekly).

<sup>c</sup>Occasional is one to 51 occasions in previous year.

airway of excess mucus. A follow-up bronchoscopic study in 10 habitual smokers of marijuana alone, 10 smokers of tobacco alone, 10 smokers of both marijuana and tobacco, and 10 nonsmoking control subjects derived from the same cohort showed visual endoscopic evidence of bronchial mucosal inflammation and injury, along with increased secretions, in the marijuana smokers that was comparable with that noted in the tobacco-only smokers (Fig 2).<sup>19</sup>

## Marijuana and Lung Function

### Cross-Sectional Studies

Associations between marijuana smoking with or without concomitant tobacco smoking and lung function abnormality have been systematically examined in 10 cross-sectional observational studies.<sup>5,6,8-11,14,20-22</sup> This included two studies of a birth cohort in Dunedin, New Zealand,<sup>8,21</sup> in which analyses

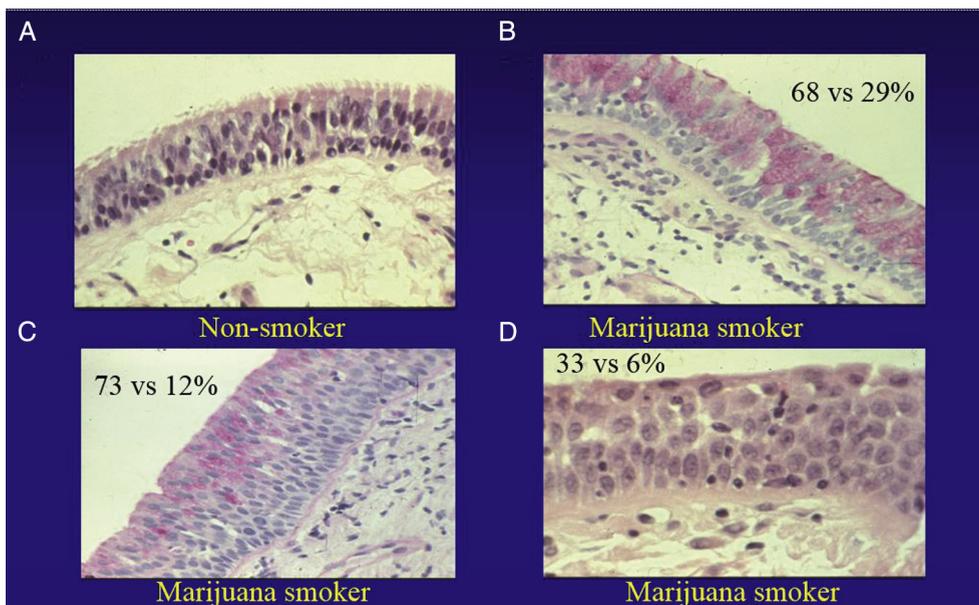


Figure 1 – A-D, Bronchial mucosal histopathology in selected habitual smokers of marijuana only ( $n = 40$ ) in comparison with nonsmokers ( $n = 53$ ). A, Normal ciliated epithelium from a representative nonsmoker. B, Goblet cell hyperplasia (defined by goblet cells representing  $> 25\%$  of all epithelial cells) from a selected marijuana smoker (68% of the marijuana smokers exhibited goblet cell hyperplasia compared with 29% of nonsmokers). C, Reserve cell hyperplasia (defined as more than three rows of reserve cells) in a selected marijuana smoker (73% of marijuana smokers exhibited reserve cell hyperplasia compared with 12% of nonsmokers). D, Squamous metaplasia (defined by stratification involving all of the mucosa with a total loss of cilia) in a selected marijuana smoker (33% of marijuana smokers had squamous metaplasia compared with 6% of nonsmokers). Based on data reported by Fligel et al.<sup>18</sup> (Hematoxylin-eosin stain, magnification  $\times 400$ ).

were performed cross-sectionally at a specified age of the cohort. Results are summarized in Table 2. The studies included both convenience samples of volunteers to advertising and community-based samples in a variety of geographic locations in the United States, Canada, and New Zealand and covered a relatively

broad age range. However, several of the studies included predominantly younger subjects. The average amount of marijuana smoked by the self-reported marijuana smokers among the study participants varied widely, but relatively heavy smokers (ie,  $> 10$  joint-years) were also represented. A joint-year is defined by a

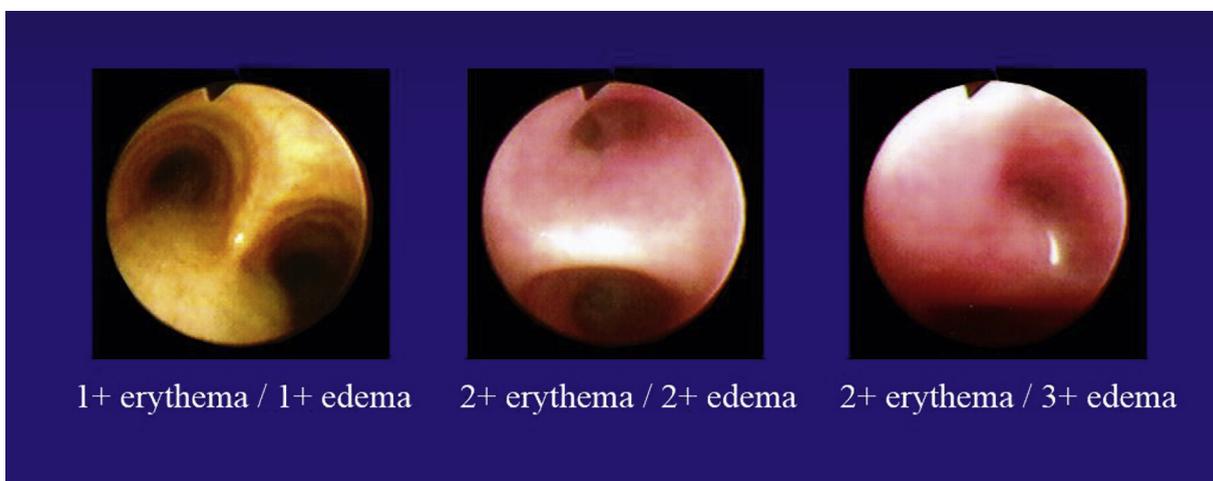


Figure 2 – Videobronchoscopic appearance of the mucosa of the large visible airways in habitual marijuana smokers. The degree of erythema and edema was scored on a scale of 0, 1+, 2+, and 3+ from a blinded review of the bronchoscopic videos, as follows: erythema none, light red, red, and beefy red, respectively; and edema none, loss of definition, blunting of bifurcation, and airway narrowing, respectively. Scores represented the worst abnormality observed within each of the three tracheobronchial zones (upper: distal trachea, proximal mainstem bronchi, and right upper lobe bronchus; middle: bronchus intermedius, distal left mainstem, and left upper lobe/lingua; lower: right and left lower lobe bronchi). Based on data reported by Roth et al.<sup>19</sup>

**TABLE 2 ] Association of Regular Marijuana Smoking With Lung Function Abnormality Compared With Nonsmoking With Adjustment for Tobacco Use in Dual Smokers of Marijuana and Tobacco (Cross-Sectional Studies)**

Study/Year	Total No.	Age, y	MJ Use Amount	FEV <sub>1</sub>	FVC	FEV <sub>1</sub> /FVC	TLC	FRC	RV	SGaw	Dlco
Tashkin et al <sup>20</sup> /1980	74 MS, 74 matched control subjects	Mean 24.1	3 d/wk, several times per day over > 2-5 y	NS	NS	...	NS	NS	...	Signif. decrease	NS
Bloom et al <sup>5</sup> /1987	990	15-40	Mean 58.2 joint-years	NS	...	Signif. decrease	...	...	...	...	...
Tashkin et al <sup>6</sup> /1987	446	25-59	Mean 54.4 joint-years	NS	NS	NS	NS	NS	NS	Signif. decrease	NS
Taylor et al <sup>8</sup> /2000	943	21 (birth cohort)	Mean 230 uses last year	...	...	Signif. decrease	...	...	...	...	...
Moore et al <sup>9</sup> /2004	6,728	20-59	Mean 10.2 d in last month	...	...	NS	...	...	...	...	...
Aldington et al <sup>10</sup> /2007	339	25-75	Mean 54.2 joint-years	NS	...	NS	NS	NS	NS	Signif. decrease	NS
Hancox et al <sup>21</sup> /2010	967	32 (birth cohort)	≤ 1 joint-year (461/967) > 1 joint-year (222/967)	NS	Trend to increase	NS	Signif. increase	Signif. increase	Signif. increase	Signif. decrease	NS
Tan et al <sup>11</sup> /2009	878	See Table 1	See Table 1	Signif. increase	Signif. increase	NS	...	...	...	...	...
Kempker et al <sup>22</sup> /2015 (NHANES 2007-2010)	7,716	18-59	Mean 15.8 joint-years	NS	Signif. increase	Signif. decrease <sup>a</sup>	...	...	...	...	...
Morris et al <sup>14</sup> /2018	2,641	See Table 1	See Table 1	Trend to ↑ <i>P</i> < .06	Signif. increase (former)	NS	...	...	...	...	...

... = not reported; FRC = functional residual capacity; NHANES = National Health and Nutrition Examination Survey; RV = residual volume; SGaw = specific airway conductance; Signif. = significant (*P* < .05); TLC = total lung capacity. See Table 1 legend for expansion of other abbreviations.

<sup>a</sup>Significantly decreased (*P* = .02) in the subgroup with > 20 joint-years of marijuana use (NHANES 2009).

history of smoking one joint (marijuana cigarette) per day times the number of years smoked. In none of these studies was marijuana smoking associated with significant decrements in FEV<sub>1</sub> compared with nonsmoking control subjects or after adjustment for concomitant tobacco smoking. In contrast, marijuana smoking was associated with a significant increase in FVC in three of the studies,<sup>11,14,22</sup> with a trend toward an increase in an additional study.<sup>21</sup> Marijuana was also associated with a significant decrement in the FEV<sub>1</sub>/FVC ratio in three of the studies.<sup>5,8,22</sup> However, in one of the latter three studies, the decrease was noted only in the very small subpopulation of heavy marijuana smokers with a cumulative lifetime use of > 20 joint-years.<sup>22</sup> Hancox et al<sup>21</sup> have observed an association between marijuana smoking and increases in several subdivisions of lung volume, including total lung capacity, functional residual capacity, and residual volume. Although the mechanism for the association with increased lung volume is not clear, it has been speculated that it might involve stretching of the lung by the repeated deep inhalations and long breath-holding times that are uniquely characteristic of the smoking topography for marijuana,<sup>23,24</sup> by analogy with the increased lung volumes that have been observed in swimmers who also take frequent large breaths with long periods of breath-holding during swimming.<sup>25</sup> Furthermore, it has been suggested that the reduced FEV<sub>1</sub>/FVC ratio observed in some studies could be attributable to an increase in FVC, as opposed to being an indicator of airflow obstruction.<sup>21,22</sup>

In four of the studies in which whole body plethysmography was performed, specific airway conductance was found to be significantly, albeit modestly, decreased among the marijuana smokers.<sup>6,10,20,21</sup> These findings are consistent with the visual evidence of bronchial mucosal edema and increased secretions endoscopically observed by Roth et al<sup>19</sup> among habitual marijuana smokers in large central airways (Fig 2). These bronchial abnormalities likely significantly compromised the airway lumen in a portion of the tracheobronchial tree that represents the major site of resistance in individuals without widespread airflow obstruction.

In all four studies in which DLCO was measured, it was not found to be decreased in association with marijuana smoking.<sup>6,10,20,21</sup> Because DLCO is a sensitive but nonspecific indicator of emphysema, these findings argue against an association of marijuana with clinically significant emphysema.

### Longitudinal Studies

In four longitudinal studies, associations between marijuana smoking and changes in lung function over time have been examined. Tashkin et al<sup>26</sup> measured FEV<sub>1</sub> serially in 255 habitual male and female smokers of marijuana and/or tobacco and nonsmokers of either substance on up to seven occasions at intervals of ≥ 1 year over a total period of up to 8 years. Random effects models were used in men and women separately to estimate mean rates of decline in FEV<sub>1</sub> and to compare these rates between smokers of marijuana or tobacco alone, smokers of both substances, and nonsmokers of either substance. Smoking marijuana was not found to be associated with greater declines in FEV<sub>1</sub> than nonsmoking nor was a relationship seen between the daily number of marijuana joints smoked and rate of decline in FEV<sub>1</sub>. In contrast, smoking tobacco had a significant effect on FEV<sub>1</sub> decline in men ( $P < .05$ ) in a dose-responsive manner (number of tobacco cigarettes smoked per day). Findings are illustrated in Figure 3.

Hancox et al<sup>13</sup> performed serial lung function measurements in 779 members of a birth cohort in Dunedin, New Zealand, at 18, 21, 26, and 32 years of age. They assessed changes in FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC associated with tobacco and marijuana smoking using regression analyses and estimates of both joint-years and pack-years as predictors, adjusting for sex and height at 32 years of age, changes in height between 15 and 32 years of age, and concomitant tobacco or marijuana use. The results are shown in Table 3. Among marijuana smokers, FVC increased significantly over time, whereas

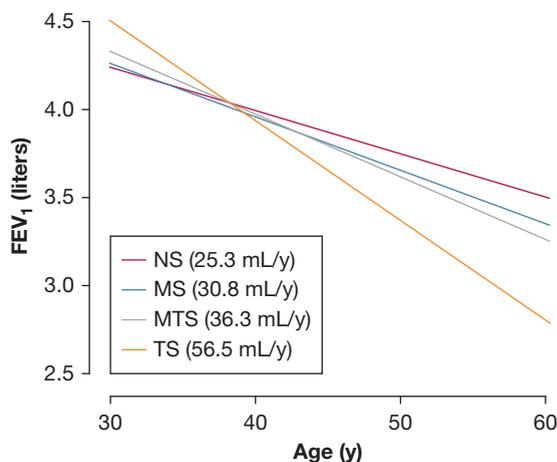


Figure 3 – Decline in FEV<sub>1</sub> with age in 131 heavy, habitual MS, 112 MTS, 65 regular TS, and 86 NS followed for up to 8 y. MS = smokers of marijuana alone; MTS = smokers of both marijuana and tobacco; NS = nonsmokers; TS = smokers of tobacco alone. Based on data reported by Tashkin et al.<sup>26</sup>

**TABLE 3 ]** Longitudinal Analyses of Marijuana and Tobacco Exposure With Lung Function

Lung Function Measure	Total No.	Cannabis			Tobacco		
		Coefficient	95% CI	P Value	Coefficient	95% CI	P Value
FEV <sub>1</sub> , mL	779	4.4	−1.4 to 10.3	.137	−4.3	−8.2 to −0.4	.031
FVC, mL	779	10.7	3.9 to 17.5	.002	0.2	−4.4 to 4.8	.928
FEV <sub>1</sub> /FVC, %	779	0.07	−0.14 to 0.01	.069	−0.09	−0.14 to −0.04	.001

Linear regression analyses of lung function at age 32 y using both cannabis and tobacco smoking as predictors, adjusted for lung function at 15 y of age, sex, height, change in height between 15 and 32 y of age, and current smoking at 32 y of age. Coefficients represent the difference in lung function at 32 y of age associated with each joint-year of cannabis or pack-year of tobacco up to 32 y of age, adjusted for the use of the other substance. Adapted with permission from Hancox et al.<sup>13</sup>

FEV<sub>1</sub> showed a nonsignificant increase and FEV<sub>1</sub>/FVC exhibited a nonsignificant decline. In contrast, among tobacco smokers, FEV<sub>1</sub> and FEV<sub>1</sub>/FVC both showed significant declines, whereas FVC showed no change.

Pletcher et al<sup>27</sup> performed repeated measurements of lung function and assessments of smoking status over 20 years in 5,115 men and women in 4 US cities as part of the Coronary Artery Risk Development in Young Adults (CARDIA) study. The association between marijuana exposure (median 2-3 uses per month) was nonlinear, such that at low levels of exposure FEV<sub>1</sub> increased by 13 mL per joint-year ( $P < .001$ ), at moderate levels ( $< 10$  joint-years) no association was noted, at higher levels ( $> 10$  joint-years) a nearly significant negative association of  $-2.2$  mL/joint-year was observed ( $P = .08$ ), and with particularly heavy use a slightly more negative association was found among those with  $> 20$  uses per month ( $-3.2$  mL per marijuana use per month;  $P = .02$ ). In contrast, with heavy use, the association with FVC was significantly positive (70 mL at 20 joint-years;  $P < .001$ ).

Sherrill et al<sup>7</sup> used data from four consecutive surveys of the Tucson longitudinal study of obstructive airways disease conducted in subjects 15 to 60 years of age over a 6-year period to examine the relation between pulmonary function and nontobacco cigarette smoking (thought to represent marijuana smoking), adjusting for age and concomitant tobacco smoking. Mean consumption of nontobacco cigarettes was  $< 1$  per day. Longitudinal analysis of lung function performed in 856 subjects who were tested in at least two of the four surveys revealed significant reductions in FEV<sub>1</sub> ( $-142 \pm 44$  mL), maximal expiratory flow at 50% of the forced vital capacity ( $-294 \pm 124$  mL/s), and FEV<sub>1</sub>/FVC ( $-1.9\% \pm 0.7\%$ ) after adjustment for tobacco, age, sex, and with the exception of FEV<sub>1</sub>/FVC, height, among those reporting nontobacco smoking in at least one previous survey. Paradoxically, however, among 1,209

subjects participating in at least one of the surveys, no significant reductions in these measures were noted in current nontobacco smokers, among whom FEV<sub>1</sub> was actually increased ( $58 \pm 27$  mL;  $P < .05$ ).

### Thoracic High-Resolution CT Scan Studies

High-resolution CT scans were obtained in two studies.<sup>10-14</sup> In one of these, which included 75 smokers of marijuana only, 91 smokers of both marijuana and tobacco, 92 smokers of tobacco only, and 81 nonsmokers from a community-based sample, no evidence of macroscopic emphysema was noted in the marijuana-only smokers. However, a small but significant increase in the proportion of marijuana smokers was found to have very low levels of lung attenuation in the lung apices compared with both nonsmokers and tobacco-only smokers.<sup>10</sup> In the SubPopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS), both current and former cannabis users ( $n = 196$  and  $n = 1,008$ , respectively) were found to have significantly less emphysema on high-resolution CT scan (as determined by computer-aided quantitative scoring based on lung attenuation) than never users, even after adjusting for age, race, sex, FEV<sub>1</sub> % predicted, current tobacco smoking status, and pack-years of tobacco.<sup>14</sup>

### Marijuana and Alveolar Macrophage Number and Function

Alveolar macrophages (AMs) harvested from bronchoalveolar lavage performed in 14 smokers of marijuana only, 16 smokers of both marijuana and tobacco, 13 smokers of tobacco only, and 19 nonsmokers revealed a threefold increase in the numbers of AMs obtained from marijuana-only smokers and smokers of tobacco only and a sixfold increase in the number of AMs from smokers of both marijuana and tobacco compared with nonsmokers, and increases in neutrophils from all smoking groups.<sup>28</sup> On the other hand, functional studies performed ex vivo

demonstrated an impairment in the phagocytic and microbicidal activity of the AMs obtained from marijuana-only smokers but not from smokers of tobacco only.<sup>29</sup> This marijuana-linked impairment in AM function might be related to an immunosuppressive effect of THC mediated by cannabinoid-type 2 receptors expressed on immune cells,<sup>30</sup> as reflected by impairment in stimulated production by AMs from marijuana-only smokers of reactive oxygen species (ROS)<sup>31</sup> and of proinflammatory cytokines.<sup>32</sup> The latter is required during infection for upregulation of inducible nitric oxide synthase<sup>33</sup> needed for production of nitric oxide, which along with ROS, serves as an effector molecule in microbial killing. It is tempting to speculate that the THC-related impairment in AM function, while possibly increasing the risk of lung infection, may, on the other hand, also have a protective role against the development of inflammation-related structural damage leading to COPD.

## Marijuana and Lung Cancer

Several lines of evidence exist both for and against a link between marijuana smoking and lung cancer.

### *Evidence for a Link*

The smoke contents of marijuana cigarettes contain the same procarcinogenic components, including the very potent human carcinogen, benzpyrene, found in tobacco smoke.<sup>3,4</sup> Bronchial biopsies obtained from heavy, habitual marijuana smokers have shown the same widespread histopathologic epithelial abnormalities noted in tobacco smokers, including squamous metaplasia and cellular disorganization,<sup>18</sup> that are widely thought to be precancerous.<sup>34</sup> Immunohistologic examination of bronchial biopsies from marijuana smokers has shown higher levels of the protein products of oncogenes, including Ki67 and EGFR,<sup>35</sup> whereas laryngeal cancer specimens from marijuana smokers have been shown to exhibit increased expression of oncoproteins (EGFR, Akt, P50, and Cox-2) compared both with tobacco smokers and nonsmokers.<sup>36</sup> A few older epidemiologic studies from North Africa have shown a positive association with lung cancer<sup>37-39</sup>; however, the common practice of admixing marijuana and tobacco within the same cigarette (kiff) in these societies precludes disentangling the effects of marijuana from those of tobacco.

A population-based cohort study of men (N = 49,321) 18 to 20 years of age conscripted into the Swedish military in 1969 to 1970 tracked these men until 2009 for incident lung cancer cases using linked nationwide medical

registries.<sup>40</sup> Cox regression was used to assess the relationship between lifetime use of marijuana self-reported at the time of conscription (ie, up until only 18-20 years of age) and risk of subsequent lung cancer diagnosis over the ensuing 40 years, adjusting for tobacco use also up to only 18 to 20 years of age.<sup>40</sup> The hazard ratio for lung cancer was significantly positive (2.12; 95% CI, 1.08-4.14) in relation to lifetime marijuana use of > 50 times. However, because neither marijuana nor tobacco use was determined after the baseline assessment, the authors were unable to adjust for true lifetime use of tobacco, a crucially important residual confounder.

### *Evidence Against a Link*

Several investigators have demonstrated a tumor suppressive effect of THC and other cannabinoids on a variety of malignancies, including lung, in both cell culture systems and animal models, as previously reviewed by Bifulco et al<sup>41</sup> and Velasco et al.<sup>42</sup> These findings appear to reflect antiproliferative, proapoptotic, and antiangiogenic properties of THC that might counteract the tumor-initiating or tumor-promoting effects of the carcinogens contained with the smoke of marijuana. A large cohort study of health plan participants in Northern California (N = 64,855) failed to show an increased risk of tobacco-related cancers in association with self-reported marijuana use (relative risk, 0.8; 95% CI, 0.5-1.2).<sup>43</sup> A pooled analysis of six well-designed case-control studies of the association between habitual marijuana smoking and lung cancer that totaled 2,159 cases and 2,985 control subjects did not find any increased risk of lung cancer in association with marijuana use (odds ratio, 0.95; 95% CI, 0.66-1.38; *P* = .807) (Fig 4).<sup>44</sup> Only one of the six studies included in the pooled analysis showed a significantly positive association between lung cancer and marijuana use, mainly in the heaviest marijuana use tertile, but the latter tertile included only four matched control subjects, making the estimates of risk imprecise.<sup>45</sup>

## Marijuana and Pneumonia

Marijuana smoking might predispose to lower respiratory tract infection in at least three ways. First, the destruction of ciliated epithelium in the large central airways and the associated hyperplasia of mucus-secreting surface epithelial cells demonstrated in bronchial biopsies of habitual marijuana smokers<sup>18</sup> may lead to increased production of mucus in the face of a diminished capacity to cleanse the lung of the excess mucus because of ciliary loss, thereby providing a substrate for potentially pathogenic microbial organisms colonizing the lower respiratory tract.

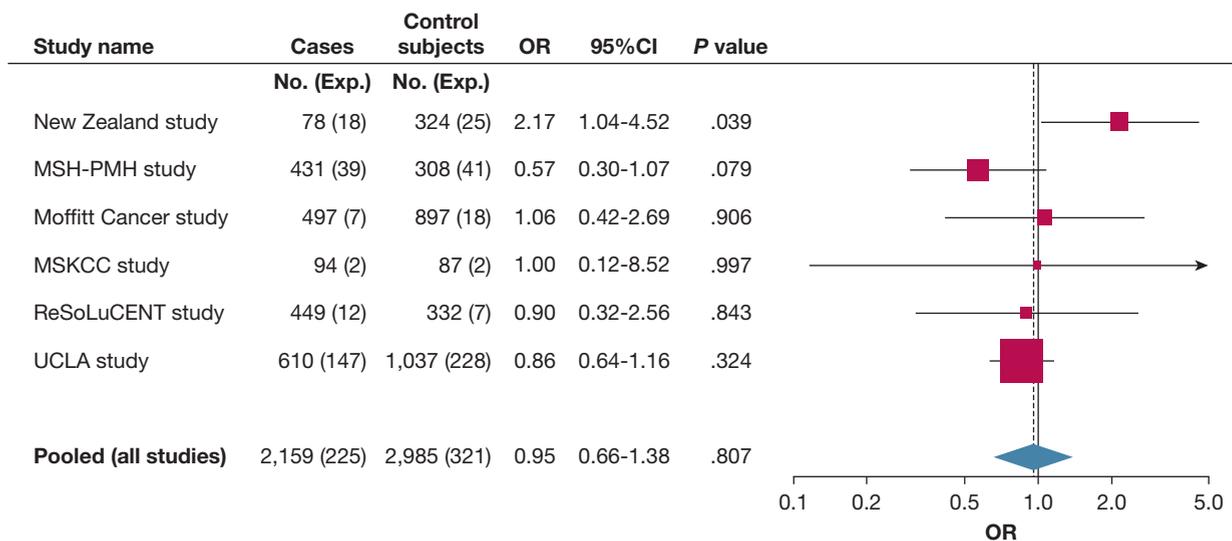


Figure 4 – Pooled analysis of case-control studies of the association between habitual marijuana smoking and lung cancer. Exp. = number exposed; MSH-MPH = The Mount Sinai Hospital-Princess Margaret Hospital Study; MSKCC = Memorial Sloan-Kettering Cancer Center Study; ReSoLuCENT = Resource for the Study of Lung Cancer Epidemiology in North Trent; UCLA = University of California at Los Angeles Study. Reproduced with permission from Zhang et al.<sup>44</sup>

Second, the immunosuppressive effect of THC leading to impairment of the bactericidal and fungicidal activity of AMs<sup>29,33</sup> further compromises the lung’s defense against microbial infection. Finally, marijuana has been shown to be frequently contaminated with *Aspergillus fumigatus*<sup>46</sup> and potentially pathogenic gram-negative bacteria.<sup>47</sup> Therefore, introduction of these microorganisms into the lung in the face of marijuana-related impairment in the lung’s host defense provides another possible mechanism for increasing the risk of pneumonia.

The possible association of marijuana with an increased risk of pneumonia is supported by older case reports of *Aspergillus* pneumonia in smokers of marijuana immunocompromised by AIDS,<sup>48</sup> chronic granulomatous disease,<sup>49</sup> bone marrow transplantation,<sup>50</sup> renal transplantation,<sup>51</sup> or lung cancer treated with chemotherapy.<sup>52</sup> In addition, a cluster of five patients with cavitary TB who used a marijuana water pipe (bong) was reported in Australia in 2003,<sup>53</sup> followed by another report from Australia 10 years later of three additional cases of open cavitary TB in marijuana bong users.<sup>54</sup> In these cases, it is not clear whether the spread of TB infection was because of close contact with patients with cavitary TB who might have shared a water pipe to smoke marijuana and/or to marijuana-related impairment in the lung’s defense against infection.

Although a few older epidemiologic studies have suggested that marijuana use might be a significant independent risk factor for opportunistic infection in individuals who are HIV positive,<sup>55-57</sup> an early analysis

of data from the Multicenter AIDS Cohort Study (MACS) failed to find evidence that marijuana was a risk factor for progression of individuals who are HIV positive to full-blown AIDS.<sup>58</sup> Further preliminary analysis of the possible association of marijuana use with pneumonia risk using the Multicenter AIDS Cohort Study (MACS) data set updated to 2013 has not shown a significant association of marijuana use with increased risk of either community-acquired or opportunistic pneumonia in either the HIV-negative or HIV-positive members of the cohort, after adjustment for tobacco, age, and among the individuals who are HIV positive, cluster of differentiation 4 cell counts and viral load.<sup>59</sup>

### Marijuana and Pneumothorax/ Pneumomediastinum and Bullous Lung Disease

A number of cases of pneumothorax and/or pneumomediastinum have been reported in association with marijuana smoking.<sup>60-67</sup> It has been suggested that the mechanism for this apparent association might involve the deep inhalation maneuver followed by a prolonged breath-holding time that is characteristic of the smoking topography for marijuana. Furthermore, if the smoker performed a Valsalva or Muller maneuver during the breath-hold, this could potentially lead to alveolar rupture and leakage of air through the visceral pleural surface, as suggested by Birrer and Calderon<sup>61</sup> and Hazouard et al,<sup>65</sup> respectively. Several cases of large lung bullae have been reported in smokers of mainly large amounts of marijuana, all of whom also smoked

tobacco in varying quantities.<sup>68-70</sup> However, one cannot necessarily assume a causal relationship between marijuana use and lung bullae based on case series alone, which represent uncontrolled observations, particularly because the prevalence of bullous lung disease in the general population is not known.<sup>71</sup>

## Summary and Conclusions

Although regular smoking of marijuana is associated with an increased risk of symptoms of chronic bronchitis and evidence of inflammation and injury involving the larger airways, lung function findings, although mixed, do not provide compelling evidence that habitual marijuana smoking in the manner and amount that it is generally smoked increases the risk of COPD, at least at the population level. Despite the presence of carcinogens in marijuana smoke in concentrations comparable with those that are found in tobacco smoke, the weight of evidence from well-designed epidemiologic studies does not support the concept that habitual marijuana use in the manner and quantity in which it is customarily smoked, when adjusted for tobacco, is a significant risk factor for the development of lung cancer. The immunosuppressive effect of THC and injurious structural changes in the larger airways of habitual marijuana smokers raise the possibility of an increased predisposition to pneumonia. Although a few older epidemiologic studies support this possibility, further studies are required. Several case series have reported evidence of lung barotrauma (pneumothorax/pneumomediastinum) and bullous lung disease in marijuana smokers; however, epidemiologic studies are needed to bolster these uncontrolled observations.

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