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### Authors

Ghasemiesfe, Mehrnaz  
Ravi, Divya  
Vali, Marzieh  
[et al.](#)

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## Marijuana Use, Respiratory Symptoms, and Pulmonary Function:

### A Systematic Review and Meta-analysis

**Mehrnaz Ghasemiesfe, MD,**

University of California, San Francisco, and San Francisco Veterans Affairs Medical Center, San Francisco, California

**Divya Ravi, MD, MPH,**

The Wright Center for Graduate Medical Education, Scranton, Pennsylvania

**Marzieh Vali, MSc,**

Northern California Institute for Research and Education, San Francisco Veterans Affairs Medical Center, San Francisco, California

**Deborah Korenstein, MD,**

Memorial Sloan Kettering Cancer Center, New York, New York

**Mehrdad Arjomandi, MD,**

University of California, San Francisco, and San Francisco Veterans Affairs Medical Center, San Francisco, California

**James Frank, MD,**

University of California, San Francisco, and San Francisco Veterans Affairs Medical Center, San Francisco, California

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**Corresponding Author:** Mehrnaz Ghasemiesfe, MD, San Francisco VA Medical Center, 4150 Clement Street, San Francisco, CA 94121; mehrnaz.ghasemiesfe@va.gov.

**Current Author Addresses:** Drs. Ghasemiesfe, Arjomandi, Frank, and Keyhani and Ms. Vali: San Francisco VA Medical Center, 4150 Clement Street, San Francisco, CA 94121.

Dr. Ravi: The Wright Center for Graduate Medical Education, 111 North Washington Avenue, Scranton, PA 18503.

Dr. Korenstein: Memorial Sloan Kettering Cancer Center, 485 Lexington Avenue, 2nd Floor, New York, NY 10017.

Dr. Austin: University of Toronto Institute of Health Policy, Management and Evaluation, G1 06, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada.

**Author Contributions:** Conception and design: M.Ghasemiesfe, D. Ravi, J. Frank, S. Keyhani.

Analysis and interpretation of the data: M. Ghasemiesfe, M. Vali, D. Korenstein, M. Arjomandi, J. Frank, S. Keyhani.

Drafting of the article: M. Ghasemiesfe, D. Ravi, M. Arjomandi, S. Keyhani.

Critical revision of the article for important intellectual content: M. Ghasemiesfe, D. Korenstein, M. Arjomandi, J. Frank, P.C. Austin, S. Keyhani.

Final approval of the article: M. Ghasemiesfe, D. Ravi, M. Vali, D. Korenstein, M. Arjomandi, J. Frank, P.C. Austin, S. Keyhani.

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Statistical expertise: M. Vali, P.C. Austin.

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[Annals.org](http://Annals.org)). Additional data are available from Dr. Ghasemiesfe ([mehrnaz.ghasemiesfe@va.gov](mailto:mehrnaz.ghasemiesfe@va.gov)).

**Peter C. Austin, PhD,** and  
University of Toronto, Toronto, Ontario, Canada

**Salomeh Keyhani, MD, MPH**  
University of California, San Francisco, and San Francisco Veterans Affairs Medical Center, San Francisco, California

## Abstract

**Background:** The health effects of smoking marijuana are not well-understood.

**Purpose:** To examine the association between marijuana use and respiratory symptoms, pulmonary function, and obstructive lung disease among adolescents and adults.

**Data Sources:** PubMed, Embase, PsycINFO, MEDLINE, and the Cochrane Library from 1 January 1973 to 30 April 2018.

**Study Selection:** Observational and interventional studies published in English that reported pulmonary outcomes of adolescents and adults who used marijuana.

**Data Extraction:** Four reviewers independently extracted study characteristics and assessed risk of bias. Three reviewers assessed strength of evidence. Studies of similar design with low or moderate risk of bias and sufficient data were pooled.

**Data Synthesis:** Twenty-two studies were included. A pooled analysis of 2 prospective studies showed that marijuana use was associated with an increased risk for cough (risk ratio [RR], 2.04 [95% CI, 1.02 to 4.06]) and sputum production (RR, 3.84 [CI, 1.62 to 9.07]). Pooled analysis of cross-sectional studies (1 low and 3 moderate risk of bias) showed that marijuana use was associated with cough (RR, 4.37 [CI, 1.71 to 11.19]), sputum production (RR, 3.40 [CI, 1.99 to 5.79]), wheezing (RR, 2.83 [CI, 1.89 to 4.23]), and dyspnea (RR, 1.56 [CI, 1.33 to 1.83]). Data on pulmonary function and obstructive lung disease were insufficient.

**Limitation:** Few studies were at low risk of bias, marijuana exposure was limited in the population studied, cohorts were young overall, assessment of marijuana exposure was not uniform, and study designs varied.

**Conclusion:** Low-strength evidence suggests that smoking marijuana is associated with cough, sputum production, and wheezing. Evidence on the association between marijuana use and obstructive lung disease and pulmonary function is insufficient.

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Approximately 13.3% of U.S. adults use marijuana (1), and rates are rising. Use by young adults (aged 18 to 29 years) doubled from 10.5% in 2002 to 21.2% in 2014 (2), and an estimated 7000 persons start using marijuana each day. Smoking remains the main method of consumption (3). The increasing prevalence of marijuana use, especially by smoking and vaping (4), raises concerns about effects on pulmonary health.

Similarities between marijuana and tobacco smoke are concerning from a public health perspective. Marijuana cigarettes are believed to contain particulate matter, toxic gases, reactive oxygen species, and polycyclic aromatic hydrocarbons (5) at a concentration

possibly 20 times that of tobacco smoke. Studies have shown that marijuana is associated with histopathologic changes in bronchial inflammation that are similar to changes seen with smoking tobacco (6). In addition, tetrahydrocannabinol may have adverse immunomodulatory effects (6, 7) that could lead to infections and cancer.

Marijuana's high particulate content and toxins suggest that long-term use may lead to chronic respiratory symptoms and adverse health effects, such as obstructive lung disease. Widespread use and increasing social acceptance mean that a better understanding of its health effects is needed. We did a systematic review and meta-analysis to examine whether marijuana use is associated with respiratory symptoms, obstructive lung disease, and changes in pulmonary function.

## Methods

Our review was consistent with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (8). The protocol was registered with PROSPERO (CRD42017059224). This review focuses on the association between marijuana use and pulmonary symptoms and function; our protocol also included review of the association between marijuana and respiratory tract neoplasms, which is not reported here.

### Data Sources and Searches

We did a systematic literature review using several online databases (PubMed, Embase, PsycINFO, MEDLINE, and the Cochrane Library) from 1 January 1973 to 30 April 2018. We chose 1973 as the start date because Oregon decriminalized possession of marijuana in that year (9) (Part 1 of the Supplement, available at [Annals.org](http://Annals.org)).

### Study Selection

Two reviewers (M.G. and D.R.) independently screened all titles and abstracts. We included observational studies (cohort, case-control, and cross-sectional) and interventional studies (randomized controlled and experimental) that were published in English and involved participants older than 12 years who had at least 30 days of lifetime marijuana use. This cutoff was chosen to ensure meaningful marijuana exposure. We excluded studies reporting only outcomes after short-term exposure in a laboratory setting and those including fewer than 10 marijuana users. Our search was augmented by author and reference tracking to identify additional articles. The same 2 investigators independently reviewed the full text of all titles and abstracts that passed the initial screen, and disagreements were resolved by discussion or by a third reviewer (S.K.). Interrater reliability on 80 randomly selected abstracts for the 2 primary reviewers was excellent (Cohen  $\kappa$ , 0.81) (Part 2 of the Supplement).

### Data Extraction and Quality Assessment

For each included study, 4 reviewers independently extracted data on all outcomes, which were categorized as symptoms, obstructive lung disease, pulmonary function, or other respiratory outcomes. They also extracted data on design (observational or experimental), study population, participant age, exposure route, average marijuana use, percentage of

marijuana-only users, confounders (such as tobacco use, occupational exposure, or respiratory disease), exposure duration, funding source, and baseline variables.

Risk of bias (ROB) in individual studies was assessed independently by 4 reviewers (M.G., D.R., S.K., and D.K.) at both study and outcome levels using either the Cochrane Risk of Bias Tool for outcomes in trial studies (10) or the Newcastle-Ottawa Scale for outcomes in observational studies (11) (Part 3 of the Supplement). We rated studies as having low ROB if they had robust assessment and adjustment for tobacco use, had sufficient follow-up for outcomes to occur, provided detail on exposure assignment (for example, marijuana-only smokers vs. marijuana and tobacco smokers), and quantified marijuana use.

## Data Synthesis and Analysis

Meta-analyses were done separately for prospective cohort and cross-sectional studies if each design had 2 or more studies with low or moderate ROB. In the symptoms category, we collected data on marijuana users and nonusers (nonmarijuana and nontobacco users) for the following 4 specific symptoms: cough, sputum production, wheezing, and dyspnea. For binary outcomes (such as cough), we extracted risk ratios (RRs) or calculated them (with 95% CIs) when adequate data were provided. For continuous outcomes (such as pulmonary function test indices), we extracted means and SDs for marijuana smokers and nonsmokers and calculated mean differences with 95% CIs. When several studies examined the same cohort (that is, similar participants over a similar period) we included only data from the study with the longest follow-up for each outcome. We present a narrative synthesis of data for which pooled analysis was not possible.

We pooled data using a random-effects model. We used the Paule–Mandel method (12) to estimate  $\tau^2$  and the Knapp–Hartung method (13) to adjust for small sample sizes. Statistical analysis was done using R software (package “meta”), version 3.3.3. Heterogeneity was evaluated using forest plots and the  $I^2$  statistic;  $I^2$  values of 25%, 50%, and 75% were considered evidence of low, moderate, and high heterogeneity, respectively (14).

Three reviewers (M.G., S.K., and D.K.) discussed the overall strength of evidence for each outcome and graded it as insufficient, low, moderate, or high on the basis of methods outlined by the Agency for Healthcare Research and Quality (15).

## Role of the Funding Source

This study was not funded.

## Results

### Literature Search

Initial searches across databases identified 1265 abstracts; we selected 927 for further evaluation and 70 of those for full-text review. We identified 3 additional articles by reference tracking, yielding 73 potentially relevant articles, of which 22 met inclusion criteria. Of these, 3 were rated as having high ROB (Figure 1). Supplement Tables 2 to 4 (available at [Annals.org](https://annals.org)) list all articles meeting inclusion criteria; studies with sufficient data for metaanalysis are referenced in Figures 2 and 3.

## Study Characteristics

We included 22 studies (10 prospective cohort and 12 cross-sectional). Methods of quantifying marijuana use varied (for example, monthly vs. weekly vs. daily use and joint-years vs. cigarette-years). Across all outcomes and studies, 1255 participants had more than 10 joint-years of exposure (equal of 1 joint a day for more than 10 years) and 756 marijuana-only smokers had more than 20 joint-years of exposure. We identified 13 distinct outcomes (Supplement Figure 1, available at [Annals.org](https://www.annals.org)), of which 5 had sufficient supporting data in 2 or more studies and could be pooled in a meta-analysis.

## Respiratory Symptoms

Four prospective observational studies (16, 17, 23, 24) and 7 cross-sectional studies (18–21, 25–27) examined the association between marijuana use and cough, sputum production, wheezing, or dyspnea. One prospective study with moderate ROB (24) followed a random sample of the population of Tucson, Arizona ( $n = 1802$ ), in 4 sequential surveys from 1981 through 1988. Current marijuana smoking was associated with chronic cough (odds ratio [OR], 1.73 [95% CI, 1.21 to 2.47]), chronic sputum production (OR, 1.53 [CI, 1.08 to 2.18]), and wheezing (OR, 2.01 [CI, 1.50 to 2.70]). Although the study had strengths (robust exposure assessment and moderate length of follow-up), it presented limited data and could not be included in the pooled analysis. The other prospective study with moderate ROB (17) included participants from Los Angeles, California ( $n = 299$ ), who had smoked a mean ( $\pm$  SE) of  $3.0 \pm 0.4$  joints per day for 9.8 years. Baseline exposure assessment was adequate, but loss to follow-up was substantial (49%). Two prospective studies (low ROB) (16, 23) used the Dunedin Multidisciplinary Health and Development Study cohort of 1037 children born in Dunedin, New Zealand, in 1972 and 1973. Marijuana exposure and outcome data (self-reported respiratory symptoms and pulmonary function test results) were collected several times during a mean follow-up of 15 years. Participants smoked an average of once a week for a year. Data were included only from the study with longer follow-up (16), leaving 2 prospective studies for meta-analysis (16, 17). Compared with nonsmokers, marijuana users had increased risks for cough (RR, 2.04 [CI, 1.02 to 4.06]; risk difference [RD], 0.07 [CI, 0.02 to 0.13]) and sputum production (RR, 3.84 [CI, 1.62 to 9.07]; RD, 0.12 [CI, -0.02 to 0.25]). Heterogeneity between the pooled studies was low (Figure 2). Both found that quitting smoking marijuana led to a significant reduction in respiratory symptoms. The Dunedin Study (16) also examined wheezing and dyspnea. Marijuana use was associated with wheezing (OR, 1.55 [CI, 1.23 to 1.94];  $P < 0.001$ ), with a trend toward association with dyspnea (OR, 1.23 [CI, 0.97 to 1.56];  $P = 0.086$ ) (Supplement Table 2).

Seven cross-sectional studies (3 low ROB [21, 26, 27], 3 moderate [18–20], and 1 high [25]) examined the association between marijuana use and cough and wheezing; 5 of these also assessed sputum production (19–21, 25, 26) or dyspnea (18–21, 25). All studies included moderate to heavy marijuana users. Pooled analysis of cross-sectional studies with low or moderate ROB showed that marijuana use was associated with cough (RR, 4.37 [CI, 1.71 to 11.19]; RD, 0.18 [CI, 0.15 to 0.21]), sputum production (RR, 3.40 [CI, 1.99 to 5.79]; RD, 0.14 [CI, 0.1 to 0.17]), wheezing (RR, 2.83 [CI, 1.89 to 4.23]; RD, 0.22 [CI, 0.14 to 0.29]), and dyspnea (RR, 1.56 [CI, 1.33 to 1.83]; RD, 0.06 [CI, -0.01 to 0.13]) (Figure 3).

## Obstructive Lung Disease

Six studies (1 prospective observational cohort [17] and 5 cross-sectional [18, 19, 22, 25, 27]) examined the association between marijuana exposure and chronic bronchitis. The prospective cohort study (moderate ROB) (17) recruited participants in 1983 to 1985. It included comprehensive baseline and outcome data collected in person (self-reported respiratory symptoms and pulmonary function test results) and several exposure assessments over a mean of 9.8 years but was limited by substantial loss to follow-up (49%). The study found that marijuana use (mean  $\pm$  SE),  $3.0 \pm 0.4$  joints per day) in healthy participants increased risk for bronchitis episodes (OR, 2.3 [CI, 1.2 to 4.4];  $P=0.011$ ) compared with nonuse (Supplement Table 3).

In pooled data from the 3 cross-sectional studies (1 low ROB [22] and 2 moderate [18, 19]), the association between marijuana use and chronic bronchitis did not reach statistical significance (RR, 2.28 [CI, 0.68 to 7.72]; RD, 0.06 [CI, -0.04 to 0.16]) (Figure 3). One of the remaining studies (low ROB) (27) analyzed 1174 participants in SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) and found no association between current or former use of marijuana and chronic bronchitis (OR, 0.87 [CI, 0.59 to 1.31] or OR, 1.0 [CI, 0.79 to 1.26], respectively). However, the sample included only current and former tobacco smokers, limiting generalizability. The final study (high ROB) (25) examined chronic obstructive pulmonary disease and found that each additional joint-year of marijuana use increased its prevalence (absolute increase per additional joint-year, 0.3% [CI, 0.0% to 0.5%]). However, reported outcomes were for cannabis and tobacco users combined rather than cannabis users alone (Supplement Table 3).

## Change in Pulmonary Function

Thirteen studies (6 prospective observational [23, 24, 28–31] and 7 cross-sectional [18–21, 27, 32, 33]) investigated the effect of marijuana exposure on pulmonary function. Seven were rated as having low ROB. Most analyzed 1 or 2 variables of pulmonary function and did not report all metrics, precluding meta-analysis (Supplement Table 4).

**FEV<sub>1</sub>**—Ten studies (4 prospective observational cohort [24, 28, 29, 31] and 6 cross-sectional [18, 20, 21, 27, 32, 33]) evaluated marijuana exposure and changes in FEV<sub>1</sub>. One prospective study (low ROB) (28) used data from the CARDIA (Coronary Artery Risk Development in Young Adults) Study cohort, which began in 1985 with 5115 men and women aged 18 to 30 years. Participants had repeated exposure assessments over 20 years, and baseline adjustment for confounding was adequate. Current marijuana use was not associated with FEV<sub>1</sub> (adjusted mean difference, -18 mL [CI, -42 to 6.1 mL];  $P=0.32$ ), which did not show a significant decrease compared with that of nonsmokers. However, exposure was minimal (2 to 3 episodes per month). The other prospective study (low ROB) (31) was a longitudinal study based in Los Angeles that included a young cohort (mean age, 33 years) with average use of more than 3.5 joints per day at cohort inception. Exposure was assessed several times over 8 years, and adjustment for confounders was adequate. Neither continuing nor intermittent marijuana smokers had significant decreases in FEV<sub>1</sub> compared with non-marijuana smokers. The Tucson study (moderate ROB) (24) was done over 6 years in 4 sequential surveys. Among current marijuana smokers (4 to 5 marijuana cigarettes per

week), researchers found significant reductions in FEV<sub>1</sub> ( $P < 0.01$ ) after 1 year of follow-up. The remaining low-ROB prospective study (Dunedin) (29) did not report median cumulative exposure but followed smokers (aged 18 to 32 years) over 10 years and found no change in FEV<sub>1</sub>.

Six cross-sectional studies (3 low ROB [21, 27, 32], 2 moderate [18, 20], and 1 high [33]) compared FEV<sub>1</sub> in marijuana smokers versus nonsmokers. NHANES (National Health and Nutrition Examination Survey) (2007 to 2008 and 2009 to 2010) and SPIROMICS (both low ROB) (27, 32) had large sample sizes, lifetime exposure assessments, and adequate adjustment for key confounders; however, they reported FEV<sub>1</sub> outcomes only for smokers of marijuana and tobacco together, limiting interpretation. The remaining 4 studies (1 low ROB [21], 2 moderate [18, 20], and 1 high [33]) found no effect on FEV<sub>1</sub> but were limited by small sample sizes, young populations, and inadequate assessment of baseline characteristics (Supplement Table 4).

**FVC**—Six studies (21, 27–29, 32, 33) assessed the effect of marijuana on FVC; 2 were prospective observational cohorts (CARDIA and Dunedin) (28, 29), and 4 were cross-sectional (21, 27, 32, 33). In CARDIA (low ROB) (28), current marijuana use (>20 episodes in the past 30 days) was associated with higher FVC (adjusted mean difference, 20 mL [CI, –5.2 to 49 mL];  $P = 0.03$ ), as was lifetime marijuana use (>10 joint-years) (adjusted mean difference, 59 mL [CI, 12 to 107 mL];  $P = 0.01$ ). In the Dunedin Study (low ROB) (29), 1037 participants completed questionnaires about health, sociodemographics, and cannabis smoking history at ages 18, 21, 26, and 32 years. Cannabis dependence was nonsignificantly associated with higher FVC (adjusted mean difference, 17.5 mL [CI, –2.5 to 37.4 mL];  $P = 0.087$ ).

Four cross-sectional studies (3 low ROB [21, 27, 32] and 1 high [33]) examined the association between marijuana use and FVC. The large SPIROMICS study (low ROB) (27) reported higher FVC among current and former marijuana users ( $P < 0.001$  for each). One study (32) based on NHANES (low ROB) with an average cumulative exposure of 15.8 joint-years reported an increase in FVC (mean, 0.07% [SD, 0.02%];  $P = 0.004$ ) for each additional joint-year smoked. The other 2 cross-sectional studies (1 low ROB [21] and 1 high [33]) found no effect on FVC. The low-ROB study (21) had an average exposure of 50.4 joint-years (SD, 4.6), whereas the high-ROB study (33) was limited by inadequate exposure and a small sample of marijuana-only smokers ( $n = 50$ ) (Supplement Table 4).

**FEV<sub>1</sub>–FVC Ratio**—Three prospective observational cohorts (2 low ROB [23, 29] and 1 moderate [30]) were based on 3 follow-up periods of the Dunedin Study. These studies measured exposure at ages 21, 26, and 32 years and had robust assessment of baseline characteristics and outcomes. The study (29) with the longest follow-up (10 years) showed no change in FEV<sub>1</sub>–FVC ratio (adjusted mean difference, –0.19 [CI, –0.42% to 0.04%];  $P = 0.100$ ). However, median cumulative marijuana exposure in the cohort was not reported, limiting interpretability. In the Tucson study (moderate ROB) (24), marijuana use (4 to 5 marijuana cigarettes per week) was associated with a significant reduction in FEV<sub>1</sub>–FVC ratio after 1 year of follow-up.



Six studies were cross-sectional (18–21, 27, 32). Two (19, 32) were based on 3 waves of NHANES (1988 to 1994, 2007 to 2008, and 2009 to 2010). One of these (2007 to 2008 and 2009 to 2010) (low ROB) (32) showed that more than 20 joint-years of marijuana exposure was associated with an FEV<sub>1</sub>–FVC ratio less than 70% (OR, 2.1 [CI, 1.1 to 3.9]; *P* = 0.02) compared with nonsmokers after adjustment for tobacco and other variables. The other NHANES study (moderate ROB) (19) found no definite relationship between marijuana use and an FEV<sub>1</sub>–FVC ratio less than 70%. However, average ( $\pm$  SE) cumulative exposure was 10.2  $\pm$  0.84 days in the past month, and relatively few marijuana-only smokers were included, limiting interpretation of the findings. SPIROMICS (low ROB) (27) had a large sample (*n* = 1174) with a mean cumulative exposure of 30.1 joint-years (SD, 68.5). Current marijuana smoking was positively associated with FEV<sub>1</sub>–FVC ratio (*P* < 0.001) after adequate adjustment for key confounders. However, this study was limited by reporting results on marijuana and tobacco smokers together. Another study (moderate ROB) (18) recruited 339 participants through 2 populations (the Wellington Respiratory Survey and the greater Wellington area in New Zealand). Sample recruitment was not representative because marijuana smokers and nonsmokers came from different populations. Marijuana use (mean, 54.2 joint-years [SD, 75.3]) was associated with a marginally lower FEV<sub>1</sub>–FVC ratio (estimate of difference, –1.1% [CI, –2.6% to 0.1%]). The 2 remaining studies (20, 21) showed no association with reduced FEV<sub>1</sub>–FVC ratio, but both had limited generalizability. One was cross-sectional (low ROB) (21) and recruited users aged 25 to 49 years who had smoked at least 10 joints per week for at least 5 years. The other (moderate ROB) (20) included few marijuana-only smokers (*n* = 38 [3.8%]). It analyzed data on male current marijuana smokers, who had significantly lower FEV<sub>1</sub>–FVC ratios (*P* < 0.05) than nonsmokers.

**Airway Resistance and Specific Conductance of Airways**—Airway resistance and specific conductance of airways were examined in 1 prospective cohort (low ROB) (29) and 3 cross-sectional studies (1 low ROB [21], 1 moderate [18], and 1 high [33]). All studies reported a significantly higher airway resistance and decreased specific conductance of airways in marijuana smokers (Supplement Table 4).

### Other Respiratory Outcomes

Two prospective observational studies (1 low ROB [34] and 1 high [35]) and 2 cross-sectional studies (low ROB) (36, 37) described other respiratory outcomes (such as upper respiratory tract infection, hospitalization, or airway reactivity). The 2 prospective studies (34, 35) followed participants over 8 years. Current marijuana use was associated with more outpatient visits for respiratory illnesses (such as cold, flu, or sore throat) (34) and respiratory problems (35), with no increased risk for hospital admission (34). The high-ROB study (35) was limited by inadequate adjustment for key confounders and lack of reporting on the nature of respiratory problems. The 2 cross-sectional studies (36, 37) examined the effect of methacholine challenge on airway reactivity among marijuana users compared with nonusers and found no difference (Supplement Table 5, available at [Annals.org](https://annals.org)).

## Strength of Evidence

Low-strength evidence suggests that smoking marijuana is associated with cough, sputum production, and wheezing. Evidence is insufficient on the association between daily marijuana use and changes in pulmonary function or development of obstructive lung disease (Table).

## Discussion

Because of increasing social acceptance and widespread use, understanding the health effects of smoking marijuana is important. Our review suggests that use (more than once per week for at least 1 year) is associated with cough, sputum production, and wheezing. Evidence on the association between daily use and obstructive lung disease and impaired pulmonary function testing is insufficient.

An English-language MEDLINE search returned 3 other reviews (38–40) that examined short- and long-term effects of smoking marijuana. A 2007 systematic review (38) noted an association between marijuana use and respiratory symptoms and outlined the need for more data on marijuana's association with pulmonary function. Two more recent studies (39, 40) also noted an association with increased respiratory symptoms, including cough, sputum production, and wheezing, but reported conflicting data on the association between long-term marijuana smoking and changes in pulmonary function. Our study confirmed these findings and built on the existing literature by assessing risk of bias, pooling data where feasible, and providing a clear picture of the gaps in evidence by rating the strength of the overall evidence.

Marijuana may be expected to cause respiratory symptoms. Its smoke contains particulate matter and compounds that induce oxidative stress and inflammation in the lung (41). Data comparing endobronchial biopsies from marijuana users versus nonusers support the clinical relevance of this type of effect from marijuana smoke exposure. Findings among marijuana users (26, 42, 43) are consistent with chronic airway inflammation and epithelial injury, including basal cell hyperplasia, goblet cell hyperplasia, and subepithelial inflammation, suggesting a mechanistic link between long-term marijuana use and respiratory symptoms.

Although our review found no relationship between marijuana use and impairment in spirometric indices, these data should be interpreted with caution because low-strength evidence suggests increased airway resistance with marijuana use, which can precede changes in lung function. Further, exposure in the included studies may have been insufficient to alter pulmonary function test results. Studies of long-term tobacco use suggest that changes to FEV<sub>1</sub> become measurable only after 5 to 10 pack-years of smoking (36 500 to 73 000 cigarettes) (44–46). Our review included 243 marijuana users (131 marijuana-only users) with exposure greater than 20 joint-years (1 joint a day for 20 years = 7300 joints) across all prospective evaluations of lung function. These low exposure levels limit our ability to draw conclusions about the effect of daily marijuana use. Because obstructive lung disease develops in only about a third of long-term tobacco smokers (47), is usually not identified until after age 35 or 40 years, and increases in prevalence with age, large cohorts with middle-aged to older populations of heavier marijuana users may be necessary to

identify effects on lung function and obstructive lung disease. On the other hand, given the psychoactive effects of tetrahydrocannabinol and its effect on overall function (48), few users may have heavy enough exposure to cause significant changes in pulmonary function testing. In other words, marijuana's effect on lung function may not be among its most important health outcomes in the long term.

Our review has important limitations. We excluded articles not published in English; thus, we may have overlooked relevant studies. Study populations were young, and marijuana exposure was limited in most prospective studies. Most studies inadequately assessed exposure, and some did not report effect size or details on exposure; this prevented meta-analysis for several outcomes. Although we report complete data for all analyses, meta-analyses of cross-sectional studies examining cough, sputum production, and wheezing were limited by heterogeneity. Heterogeneity was likely related to the lack of uniform assessment of marijuana use (for example, joint-year, times per week, or times in lifetime) and outcome ascertainment (for example, cough definition of most days for 3 consecutive months vs. >6 times a day). Our current understanding of the long-term health effects of marijuana could be improved by standardized assessment tools for marijuana use and studies with larger samples of marijuana-only users and longer follow-up times.

Low-strength evidence indicates that smoking marijuana is associated with cough, sputum production, and wheezing. Current understanding of marijuana's effect on pulmonary function tests and development of obstructive lung disease is insufficient and is limited by low exposure and young study populations. Given rapidly expanding use, we need large-scale longitudinal studies examining the long-term pulmonary effects of daily marijuana use.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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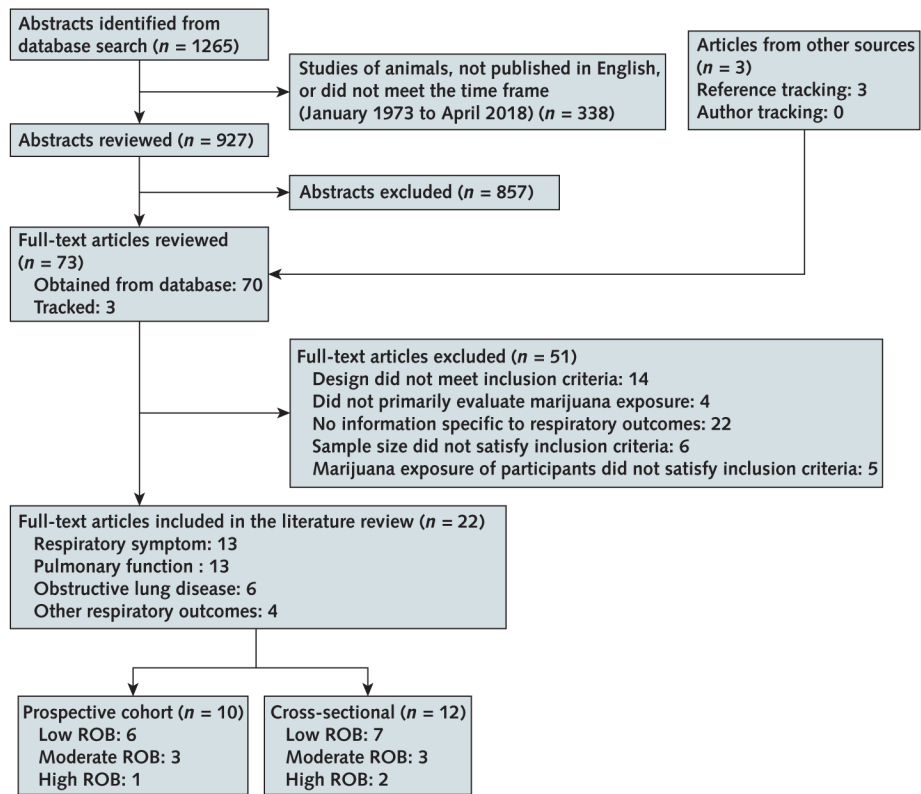
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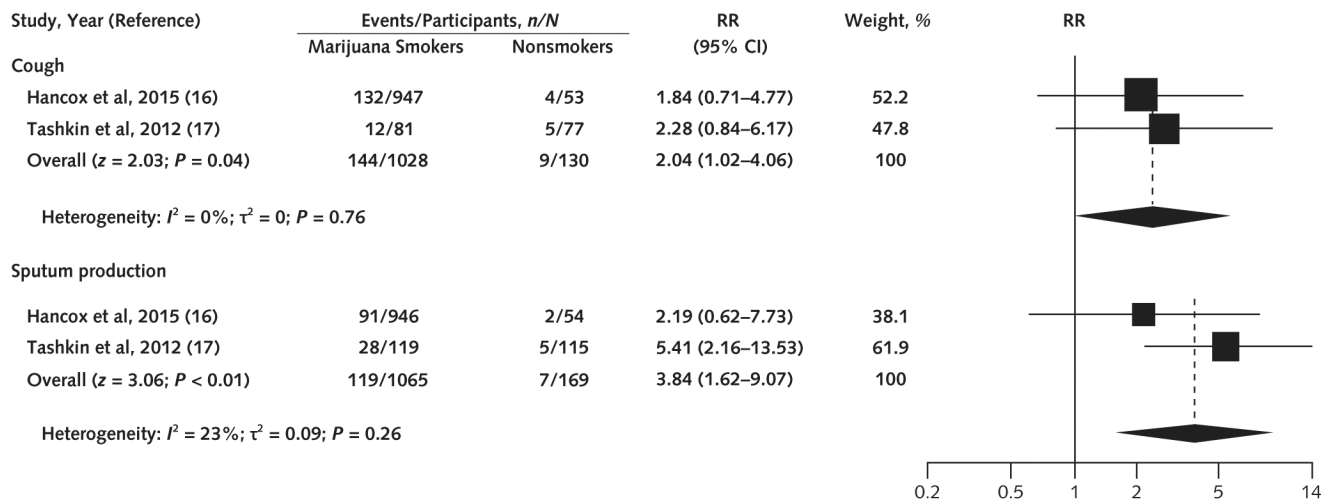
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**Figure 1. Evidence search and selection.**

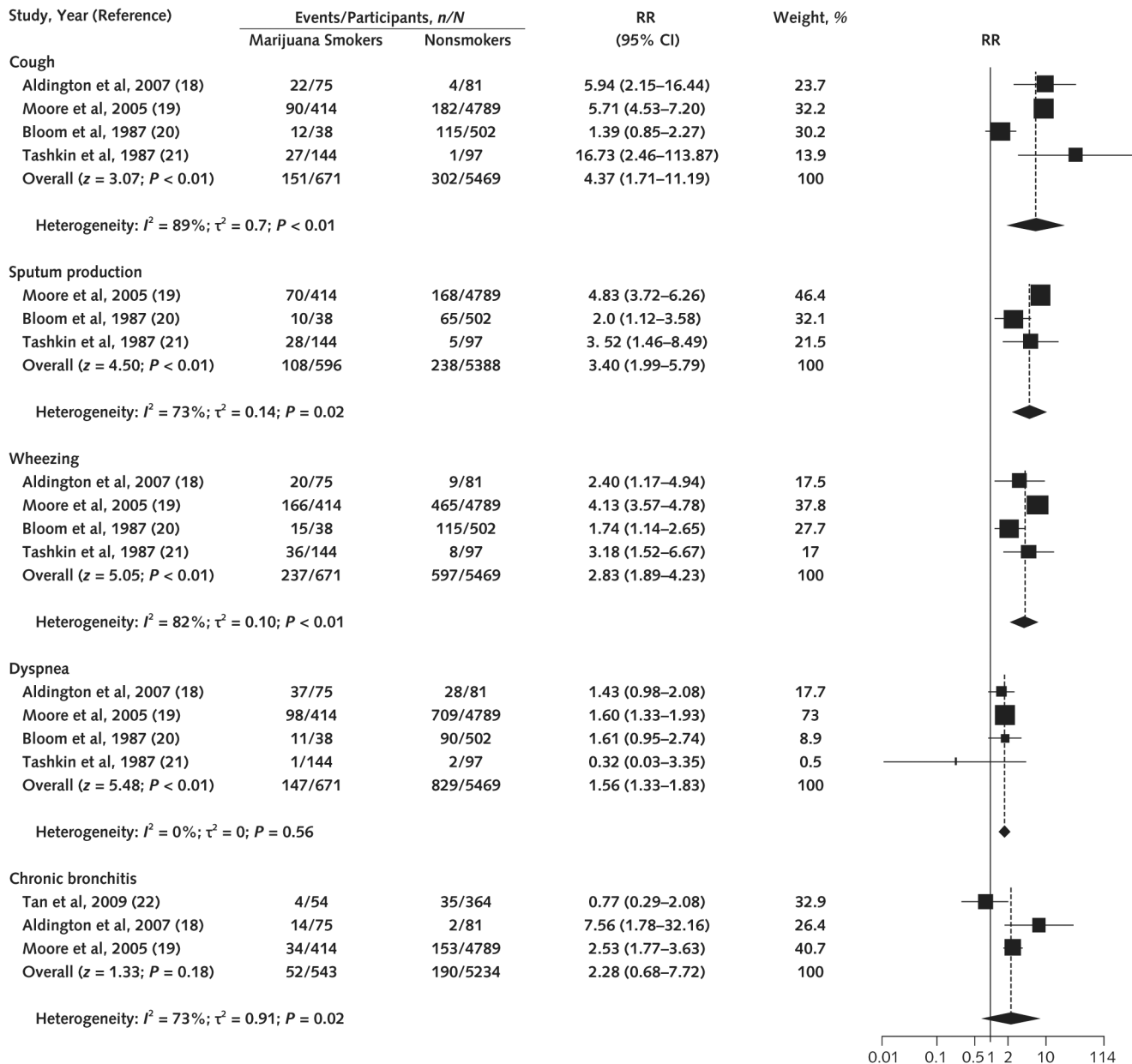
Some studies were assigned >1 outcome label and are counted twice. ROB = risk of bias.





**Figure 2. Association between marijuana use and cough and sputum production in prospective cohort studies.**

We used the Paule–Mandel method for estimating  $\tau^2$ . The squares indicate RRs from primary studies, and size reflects the statistical weight of the studies. The horizontal lines indicate 95% CIs. The diamonds represent the subtotal and overall RR and 95% CI. The vertical solid line shows the line of no effect (RR = 1). The pooled RR was not significant after the Knapp–Hartung small-sample adjustment for cough ( $P = 0.10$ ) and sputum production ( $P = 0.20$ ). RR = risk ratio.



**Figure 3. Association between marijuana use and cough, sputum production, wheezing, dyspnea, and chronic bronchitis in cross-sectional studies.**

We used the Paule–Mandel method for estimating  $\tau^2$ . The squares indicate RRs from primary studies, and size reflects the statistical weight of the studies. The horizontal lines indicate 95% CIs. The diamonds represent the subtotal and overall RR and 95% CI. The vertical solid line shows the line of no effect (RR = 1). After the Knapp–Hartung small-sample adjustment, pooled RRs were significant for cough ( $P = 0.05$ ), sputum production ( $P = 0.05$ ), wheezing ( $P = 0.01$ ), and dyspnea ( $P < 0.01$ ) but not for chronic bronchitis ( $P = 0.31$ ). RR = risk ratio.

**Table.** Strength of Evidence for Each Respiratory Symptom, Obstructive Lung Disease, Pulmonary Function, and Other Respiratory Outcomes

Outcome	Study Type	Strength of Evidence	Comments
Respiratory symptoms			
Cough	4 prospective observational studies (2 low,* and 2 moderate ROB) and 7 cross-sectional studies (3 low, 3 moderate, and 1 high ROB)	Low	All prospective studies rated as low or moderate ROB and the pooled cross-sectional studies found an association between marijuana use and cough.
Sputum production	4 prospective observational studies (2 low,* and 2 moderate ROB) and 5 cross-sectional studies (2 low, 2 moderate, and 1 high ROB)	Low	Low- and moderate-ROB studies showed a consistent trend toward increased risk for sputum production with marijuana use. Pooled data showed that marijuana use was associated with an increased risk for sputum production.
Wheezing	4 prospective observational studies (2 low,* and 2 moderate ROB) and 7 cross-sectional studies (3 low, 3 moderate, and 1 high ROB)	Low	Three prospective studies (1 low and 2 moderate ROB) showed that marijuana use was associated with increased risk for wheezing. Pooled analysis of 4 cross-sectional studies (1 low and 3 moderate ROB) showed that marijuana use was associated with wheezing, but heterogeneity was high. Low- and moderate-ROB studies showed a consistent trend toward an association between marijuana use and wheezing.
Dyspnea	2 prospective observational studies* (low ROB) and 5 cross-sectional studies (2 low, 2 moderate, and 1 high ROB)	Insufficient	The prospective studies were based on the same cohort, and the study with the longest follow-up found no effect on increased risk for dyspnea. This study was limited because the median marijuana exposure was not reported; however, the pooled analysis from cross-sectional studies showed that marijuana use was associated with increased risk for dyspnea.
Obstructive lung disease	1 prospective observational cohort study (moderate ROB) and 5 cross-sectional studies (2 low, 2 moderate, and 1 high ROB)	Insufficient	One prospective study found an increased risk for chronic bronchitis during a long follow-up. Pooled analysis of 3 cross-sectional studies (1 low and 2 moderate ROB) did not show that marijuana use was associated with increased risk for chronic bronchitis. All studies showed a trend toward increased risk for chronic bronchitis from marijuana use; however, the body of available evidence was limited.
Pulmonary function			
FEV <sub>1</sub>	4 prospective observational cohort studies (3 low and 1 moderate ROB) and 6 cross-sectional studies (3 low, 2 moderate, and 1 high ROB)	Insufficient	The low-ROB prospective studies found no effect on decrease of FEV <sub>1</sub> ; however, the studies were limited by minimal exposure to marijuana and the young age of participants. The cross-sectional studies were limited by small sample size, a young population, and variable rigor in analysis; the experimental study was limited by lack of adjustment for key confounders.
FVC	2 prospective observational cohort studies (low ROB) and 4 cross-sectional studies (3 low and 1 high ROB)	Insufficient	The prospective studies showed mixed results with marijuana use and an increase in FVC, and the 2 cross-sectional studies showed no effect of marijuana on FVC, but study quality and rigor in analysis varied.
FEV <sub>1</sub> -FVC ratio	4 prospective observational cohort studies (2 low* and 2 moderate ROB) and 6 cross-sectional studies (3 low and 3 moderate ROB)	Insufficient	All low-ROB prospective studies were based on the same cohort study. The studies with the longest follow-up did not report average marijuana exposure in the cohort. The cross-sectional studies were limited by few marijuana-only smokers, variable rigor in analysis, and mixed findings.
Airway resistance and specific conductance of airways	1 prospective cohort study (low ROB) and 3 cross-sectional studies (1 low, 1 moderate, and 1 high ROB)	Low	All relevant studies found that marijuana use was associated with increased airway resistance and decreased specific conductance of airways.
Other respiratory outcomes	2 prospective observational studies (1 low and 1 high ROB) and 2 cross-sectional studies (low ROB)	Insufficient	The prospective studies were limited by inadequate marijuana exposure, inadequate adjustment for confounders, and many other methodological flaws with mixed findings.

ROB = risk of bias.

\* Both studies were based on the same cohort.

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