Association Between Marijuana Exposure and Pulmonary Function Over 20 Years

Mark J. Pletcher, MD, MPH
Eric Vittinghoff, PhD
Ravi Kalhan, MD, MS
Joshua Richman, MD, PhD
Monika Safford, MD
Stephen Sidney, MD, MPH
Feng Lin, MS
Stefan Kertesz, MD

Exposure to tobacco smoke causes lung damage with clinical consequences that include respiratory symptoms, chronic obstructive pulmonary disease, and lung cancer.1,2 Chronic obstructive pulmonary disease and lung cancer are leading causes of death,3,4 and smoking tobacco cigarettes is the most important preventable cause of death in the United States.5,6

Marijuana smoke contains many of the same constituents as tobacco smoke,6 but it is unclear whether smoking marijuana causes pulmonary damage similar to that caused by tobacco. Prior studies of marijuana smokers have demonstrated consistent evidence of airway mucosal injury and inflammation7,8 as well as increased respiratory symptoms such as cough, phlegm production, and wheeze, similar to that seen in tobacco smokers.10-12 However, analyses of pulmonary function and lung disease have failed to detect clear adverse effects of marijuana use on pulmonary function.10-13 It is possible that cumulative damage to the lungs from years of marijuana use could be masked by short-term effects; prior analyses have not attempted to disentangle these factors. Smoking marijuana is increasingly common in the United States,14 and understanding whether it causes lasting damage to lung function has important implications for public health messaging and medical use of marijuana.15,16

The Coronary Artery Risk Development in Young Adults (CARDIA) study collected repeated measures of tobacco and marijuana smoking as well as pulmonary function over the course

Context  Marijuana smoke contains many of the same constituents as tobacco smoke, but whether it has similar adverse effects on pulmonary function is unclear.

Objective  To analyze associations between marijuana (both current and lifetime exposure) and pulmonary function.

Design, Setting, and Participants  The Coronary Artery Risk Development in Young Adults (CARDIA) study, a longitudinal study collecting repeated measurements of pulmonary function and smoking over 20 years (March 26, 1985-August 19, 2006) in a cohort of 5115 men and women in 4 US cities. Mixed linear modeling was used to account for individual age-based trajectories of pulmonary function and other covariates including tobacco use, which was analyzed in parallel as a positive control. Lifetime exposure to marijuana joints was expressed in joint-years, with 1 joint-year of exposure equivalent to smoking 365 joints or filled pipe bowls.

Main Outcome Measures  Forced expiratory volume in the first second of expiration (FEV1) and forced vital capacity (FVC).

Results  Marijuana exposure was nearly as common as tobacco exposure but was mostly light (median, 2-3 episodes per month). Tobacco exposure, both current and lifetime, was linearly associated with lower FEV1 and FVC. In contrast, the association between marijuana exposure and pulmonary function was nonlinear (P <.001): at low levels of exposure, FEV1 increased by 13 mL/joint-year (95% CI, 6.4 to 20; P <.001) and FVC by 20 mL/joint-year (95% CI, 12 to 27; P <.001), but at higher levels of exposure, these associations leveled or even reversed. The slope for FEV1 was −2.2 mL/joint-year (95% CI, −4.6 to 0.3; P = .08) at more than 10 joint-years and −3.2 mL per marijuana smoking episode/mo (95% CI, −5.8 to −0.6; P = .02) at more than 20 episodes/mo. With very heavy marijuana use, the net association with FEV1 was not significantly different from baseline, and the net association with FVC remained significantly greater than baseline (eg, at 20 joint-years, 76 mL [95% CI, 34 to 117]; P <.001).

Conclusion  Occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function.

Author Affiliations: Department of Epidemiology and Biostatistics (Drs Pletcher and Vittinghoff and Mr Lin) and Division of General Internal Medicine, Department of Medicine (Dr Pletcher), University of California, San Francisco; Asthma-COPD Program, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Dr Kalhan); Department of Surgery (Dr Richman) and Division of Preventive Medicine (Drs Safford and Kertesz), University of Alabama at Birmingham; Center for Surgical, Medical and Acute Care Research and Transitions, Veterans Affairs Medical Center, Birmingham (Drs Richman and Kertesz); and Division of Research, Kaiser Permanente of Northern California, Oakland (Dr Sidney).

Corresponding Author: Mark J. Pletcher, MD, MPH, Department of Epidemiology and Biostatistics, University of California, San Francisco, 185 Berry St, Ste 5700, San Francisco, CA 94107 (mplechter@epi.ucsf.edu).

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of 20 years (March 26, 1985-August 19, 2006) in more than 5000 study participants. We estimated both current intensity and lifetime cumulative exposure to tobacco and marijuana smoking and analyzed their associations with spirometric measures of pulmonary function over the 20 years of follow-up.

METHODS

Study Design and Sample

CARDIA is a longitudinal study designed to measure risk factors for coronary artery disease in a cohort of black and white women and men (n = 5115) aged 18 through 30 years and healthy at enrollment in 1985. Participants were sampled from 4 US communities without selection for smoking behaviors and comprise a broad cross-section of typical tobacco and marijuana use patterns.

With the written informed consent of participants and the approval of institutional review boards at each study center (Oakland, Chicago, Minneapolis, and Birmingham), participants underwent a baseline examination and 6 follow-up examinations, with 69% retention at year 20. Pulmonary function testing was performed at years 0, 2, 5, 10, and 20. For this investigation, we included all visits for which pulmonary function, smoking behavior, secondhand smoke exposure, height, and waist circumference were available.

Tobacco and Marijuana Exposure

Current intensity of tobacco use (cigarettes smoked per day) was assessed at each examination. These data, along with baseline examination data on past years of smoking, were used to estimate cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 365 cigarettes (1 year × 365 days/y × 1 pack/d × 20 cigarettes/pack). Misclassification of smoking exposure by self-report, measured by comparisons with serum cotinine levels, is uncommon.

Current intensity of marijuana use (episodes in the last 30 days) was also assessed at each examination. Using baseline examination data on past lifetime exposure to marijuana, current intensity of marijuana use, and another question designed to assess number of joints or filled pipe bowls smoked per episode (eMethods, available at http://www.jama.com), we calculated total lifetime exposure to marijuana joints in joint-years, with 1 joint-year of exposure equivalent to 365 joints or filled pipe bowls smoked (1 year × 365 days/y × 1 joint/d), as described previously.

Outcome Measures

Study outcomes were forced expiratory volume in the first second of expiration (FEV1) and forced vital capacity (FVC) measured by forced spirometry. These were collected using a Collins Survey 8-L water-sealed spirometer and an Eagle II microprocessor (years 0, 2, 5, and 10) and then an OMI rolling seal spirometer (year 20). A comparability study performed among 25 participants demonstrated an average difference of less than 1% for both measurements. Standard quality control and testing procedures were maintained according to established guidelines.

Other Covariates

CARDIA was designed to recruit approximately equal numbers of self-identified “black, not Hispanic” and “white, not Hispanic” men and women to ensure an adequate sample of the largest minority group in the United States at that time. Height and waist circumference were measured at each examination. As a proxy for socioeconomic status, we used the maximum educational grade attained for each participant. Secondhand smoke exposure in hours per week (sum of exposure in the home, small enclosed spaces, and large spaces) was assessed at each examination, with linear interpolation for missing data. Asthma was self-reported at each examination; we used the baseline assessment. We obtained average annual city-specific levels of airborne particulate matter less than 10 microns and less than 2.5 microns in size around the 4 CARDIA study centers from the Environmental Protection Agency (eMethods).

Statistical Analysis

Participants were categorized by whether they ever reported current use of tobacco, marijuana, or both at a CARDIA examination and compared across these categories using descriptive statistics. We then categorized participants according to degree of current and lifetime tobacco and marijuana exposure at each examination and described pulmonary function (FEV1 and FVC) across categories before and after adjustment. Tests of trend and interaction were performed in fully adjusted models.

The categorized exposure models described above represent a standard approach to multivariable-adjusted association testing. Categorization models, however, use necessarily arbitrary category thresholds and do not take full advantage of the continuous exposure measurements for estimation or adjustment purposes. To fully explore and test potential nonlinear associations, we modeled tobacco and marijuana exposure variables as flexible cubic splines (eMethods) in adjusted models to allow associations with pulmonary function to take different shapes at lower vs higher levels of exposure.

For each adjusted analysis described above, we used mixed models accounting for repeated measures of pulmonary function within participants, with a random intercept and a random 3-knot age spline within each individual and an unstructured variance-covariance structure. Fully adjusted models included fixed effects for year, center, and center-year (their interaction), race-sex category, education, and asthma; cubic splines for age, height, waist circumference, secondhand smoke exposure, and exposure to airborne particulate matter less than 10 microns and less than 2.5 microns in size; and interactions between the age-spline variables and race-sex, asthma,
MARIJUANA EXPOSURE AND PULMONARY FUNCTION

RESULTS

The 5115 CARDIA participants recruited in 1985-1986 contributed 20 777 total visits that included pulmonary function testing. Of these, 959 visits were excluded for lack of complete information on smoking behavior, 114 for lack of height or waist measurements, and 1 for an unknown visit date, leaving 19 703 visits (95%) with complete data from 5016 participants (98%). Participants contributed 3.9 visits/participant on average; attrition was near (98%). Participants contributed 3.9 visits/participant on average; attrition was near (98%).

Figure 1. Pulmonary Function Measurements by Age

Smoothed averageObservation

Participants (n=5017) contributed an average of 3.9 measurements per person (n=19 705 total) over the course of 20 years. A lowess smoother was used to calculate the smoothed average. FEV1 indicates forced expiratory volume in first second of expiration; FVC, forced vital capacity.

waist-spline variables, and height-spline variables to allow for differing flexible age-based trajectories of pulmonary function for participants with differing characteristics. Models were queried to produce adjusted estimates of slope (reflecting the incremental difference in pulmonary function observed with additional tobacco or marijuana smoking) and net association (reflecting the net observed difference between persons with a particular level of consumption and persons with none) at various points along the association curve. All analyses were performed using Stata version 11 and used 2-sided tests for significance at the .05 level, with 95% CIs.

The median intensity of tobacco use in tobacco smokers was substantially higher (8-9 cigarettes/d) than the median intensity of marijuana use in marijuana smokers (2-3 episodes in the last 30 days). Although marijuana smokers (2-3 episodes in the past 30 days and 101 mL lower (95% CI, −136 to −65; P < .001 for trend) with lifetime tobacco exposure of up to 10 joints-years and then declined to 36 mL (95% CI, −6.5 to 79) greater than the zero exposure level (P = .049 for trend). FVC increased with smoking intensity up to 20 marijuana smoking episodes in the past 30 days and then declined to 20 mL greater than the zero exposure level (P = .03 for trend). We found no statistically significant interactions between tobacco and marijuana exposure for either FEV1 or FVC.

In fully adjusted models that considered 4-level categorizations of current and lifetime exposure to tobacco and marijuana, tobacco smoking (both current and lifetime) was associated with a lower FEV1 and current smoking with a lower FVC (Table 2). For example, compared with zero exposure, FEV1 was 63 mL lower (95% CI, −89 to −36; P < .001 for trend) and FVC was 69 mL lower (95% CI, −97 to −41; P < .001 for trend) with current tobacco exposure of more than 20 cigarettes per day and 101 mL lower (95% CI, −136 to −65; P < .001 for trend) with lifetime tobacco exposure of more than 20 pack-years.

In contrast, exposure to marijuana (both current and lifetime) was associated with higher FVC and lifetime exposure with higher FEV1. For example, compared with zero exposure, FVC increased with greater lifetime exposure in joint-years (P = .01 for trend) and FEV1 increased with greater lifetime exposure of up to 10 joint-years and then declined to 36 mL (95% CI, −6.5 to 79) greater than the zero exposure level (P = .049 for trend). FVC increased with smoking intensity up to 20 marijuana smoking episodes in the past 30 days and then declined to 20 mL greater than the zero exposure level (P = .03 for trend). We found no statistically significant interactions between tobacco and marijuana exposure for either FEV1 or FVC.

When we modeled current and lifetime tobacco and marijuana exposure

TABLE 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Current</th>
<th>Lifetime</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>None</td>
<td>−89</td>
<td>−36</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>FVC</td>
<td>None</td>
<td>−97</td>
<td>−41</td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>

TABLE 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Current</th>
<th>Lifetime</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>None</td>
<td>63</td>
<td>36</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>FVC</td>
<td>None</td>
<td>69</td>
<td>101</td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>
as continuous exposures and permitted flexible nonlinear associations (via splines), we again found strong, dose-related associations (P < .001) between increasing exposure to tobacco and lower FEV₁ and FVC (Figure 2), with no evidence of nonlinearity (Table 3). Declining slopes ranged as steep as −2.8 mL (95% CI, −4.8 to −0.7; P = .007) per additional cigarette smoked per day and −7.0 mL (95% CI, −10 to −3.7; P < .001) per additional pack-year for FEV₁, and were of similar magnitude for FVC (Table 3). At 50 pack-years of exposure, FEV₁ was on average 332 mL lower (95% CI, −401 to −263; P < .001) and FVC was 229 mL lower (95% CI, −310 to −147; P < .001), compared with no exposure.

For marijuana, we found strong statistical evidence that associations between marijuana use and pulmonary function were nonlinear (Figure 2, Table 3). At low lifetime exposure levels, increasing marijuana use was associated with a steep increase in both FEV₁ (13 mL/joint-year higher [95% CI, 6.4 to 20], P < .001) and FVC (20 mL/joint-year higher [95% CI, 12 to 27], P < .001), but at higher levels of exposure (>7 joint-years), the slope leveled or even turned downward. At more than 10 joint-years of lifetime exposure, we found a nonsignificant decline in FEV₁ (−2.2 mL/joint-year [95% CI, −4.8 to 0.3], P = .08) but a significant decline in FEV₁ at more than 20 episodes of marijuana use per month (−3.2 mL/episode [95% CI, −5.8 to −0.6], P = .02). Although net associations with FEV₁ became negative at very high exposure levels (>40 joint-years or >25 episodes/mo), these negative deflections were not statistically significant (Table 3). FVC remained significantly elevated in even heavy users (eg, 76 mL [95% CI, 34 to 117; P < .001] at 20 joint-years).

Table 1. Characteristics of CARDIA Participants With Pulmonary Function Test Results, by Smoking Behavior

<table>
<thead>
<tr>
<th>Baseline Characteristicsb</th>
<th>Neither (n = 2305)</th>
<th>Tobacco Only (n = 851)</th>
<th>Marijuana Only (n = 795)</th>
<th>Both (n = 1065)</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>25 (4)</td>
<td>25 (4)</td>
<td>25 (4)</td>
<td>25 (4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race-sex, No. (%)d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White men</td>
<td>525 (23)</td>
<td>133 (16)</td>
<td>251 (32)</td>
<td>249 (23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White women</td>
<td>672 (29)</td>
<td>266 (31)</td>
<td>186 (23)</td>
<td>172 (16)</td>
<td></td>
</tr>
<tr>
<td>Black men</td>
<td>399 (17)</td>
<td>167 (20)</td>
<td>185 (23)</td>
<td>167 (20)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>709 (31)</td>
<td>285 (33)</td>
<td>173 (22)</td>
<td>277 (26)</td>
<td></td>
</tr>
<tr>
<td>College educated at any examination, No. (%)b</td>
<td>1291 (56)</td>
<td>245 (29)</td>
<td>381 (48)</td>
<td>240 (22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Income &gt;$50,000/y at any examination, No. (%)</td>
<td>1414 (68)</td>
<td>324 (46)</td>
<td>429 (60)</td>
<td>344 (35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>25 (5)</td>
<td>25 (5)</td>
<td>24 (4)</td>
<td>25 (5)</td>
<td>.22</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>170 (10)</td>
<td>169 (9)</td>
<td>172 (9)</td>
<td>171 (9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist circumference, mean (SD), cm</td>
<td>77.4 (11.9)</td>
<td>77.6 (11.5)</td>
<td>78.0 (10.6)</td>
<td>78.8 (11.2)</td>
<td>.009</td>
</tr>
<tr>
<td>History of asthma at the baseline visit, No. (%)</td>
<td>89 (4)</td>
<td>45 (5)</td>
<td>39 (5)</td>
<td>43 (4)</td>
<td>.001</td>
</tr>
<tr>
<td>Secondhand smoke exposure, median (IQR), h/wk</td>
<td>7 (3-25)</td>
<td>28 (10-56)</td>
<td>12 (4-38)</td>
<td>33 (12-62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Airborne particulate matter exposure, mean (SD), μg/m³</td>
<td>86 (19)</td>
<td>85 (20)</td>
<td>87 (21)</td>
<td>84 (19)</td>
<td>.006</td>
</tr>
<tr>
<td>PM10</td>
<td>33 (8)</td>
<td>35 (8)</td>
<td>33 (8)</td>
<td>33 (8)</td>
<td>.002</td>
</tr>
<tr>
<td>PM2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average intensity of tobacco use, median (IQR), cigarettes/db</td>
<td>8 (3-15)</td>
<td>9 (4-15)</td>
<td>9 (4-15)</td>
<td>9 (4-15)</td>
<td>.37</td>
</tr>
<tr>
<td>Average intensity of marijuana use, median (IQR), episodes in last 30 db</td>
<td>2 (1-6)</td>
<td>3 (1-9)</td>
<td>3 (1-9)</td>
<td>3 (1-9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lifetime tobacco use, median (IQR), pack-yearsb</td>
<td>7 (3-15)</td>
<td>9 (3-16)</td>
<td>9 (3-16)</td>
<td>9 (3-16)</td>
<td>.07</td>
</tr>
<tr>
<td>Lifetime marijuana use, median (IQR), joint-yearsb</td>
<td>0.9 (0.2-2.8)</td>
<td>1.5 (0.6-4.3)</td>
<td>1.5 (0.6-4.3)</td>
<td>1.5 (0.6-4.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CARDIA examinations with PFT results recorded, No. (SD)</td>
<td>4.0 (1.1)</td>
<td>3.6 (1.2)</td>
<td>4.0 (1.2)</td>
<td>3.9 (1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Attended year 20 examination, No. (%)</td>
<td>1442 (63)</td>
<td>357 (42)</td>
<td>492 (62)</td>
<td>516 (48)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults study; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PFT, pulmonary function test; PM10, airborne particulate matter less than 10 microns in size; PM2.5, airborne particulate matter less than 2.5 microns in size.

a Unless otherwise noted, values at the first available examination at which pulmonary function was measured. For average smoking intensity, an average across all examinations was calculated, and the median (IQR) of these averages is presented. For lifetime smoking exposure, the maximum (last) value was used, and the median (IQR) of these maximums is presented.

b P values are from a 1-way analysis of variance test for age, body mass index, race-sex, height, waist circumference, and FVC. For FEV₁ and were of similar magnitude (95% CI, −3.2 mL/episode [95% CI, −5.8 to −0.6], P = .02). Although net associations with FEV₁ became negative at very high exposure levels (>40 joint-years or >25 episodes/mo), these negative deflections were not statistically significant (Table 3). FVC remained significantly elevated in even heavy users (eg, 76 mL [95% CI, 34 to 117; P < .001] at 20 joint-years).

c By design, the CARDIA study sampled white men, white women, black men, and black women in roughly equal numbers as weight in kilograms divided by height in meters squared.

d Measured at the level of the city or metropolitan area.
COMMENT
In this 20-year study of marijuana and pulmonary function, we confirmed the expected reductions in FEV₁ and FVC from tobacco use. In contrast, marijuana use was associated with higher FEV₁ and FVC at the low levels of exposure typical for most marijuana users. With up to 7 joint-years of lifetime exposure (eg, 1 joint/d for 7 years or 1 joint/wk for 49 years), we found no evidence that increasing exposure to marijuana adversely affects pulmonary function. This association, however, was nonlinear: at higher exposure levels, we found a leveling off or even a reversal in this association, especially for FEV₁. Although our sample contained insufficient numbers of heavy users to confirm a detrimental effect of very heavy marijuana use on pulmonary function, our findings suggest this possibility.

The associations we found between tobacco and pulmonary function are consistent with a large body of prior research on the adverse pulmonary consequences of tobacco smoking. The high prevalence of tobacco smoking, the wide range of exposure intensity among smokers, and the legality of tobacco have made tobacco smoking an easy target for observational epidemiology. Exposure predicts reduced expiratory flow and air trapping, gas-exchange abnormalities, and emphysema, and smoking cessation interventions reduce the rate of FEV₁ decline in smokers (ie, these associations are likely causal). Our findings of a linear dose-response relationship showing lower FEV₁ and FVC with increasing tobacco expo-

### Table 2. Associations Between Categorized Exposure to Tobacco and Marijuana Smoke and Pulmonary Function

<table>
<thead>
<tr>
<th>Smoking Exposure Category</th>
<th>FEV₁</th>
<th>FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>19,704</td>
<td>3420 (810)</td>
</tr>
<tr>
<td>Current tobacco/marijuana smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>12,288</td>
<td>3.41 (0.80)</td>
</tr>
<tr>
<td>Tobacco only</td>
<td>3,483</td>
<td>3.27 (0.77)</td>
</tr>
<tr>
<td>Marijuana only</td>
<td>2,021</td>
<td>3.73 (0.81)</td>
</tr>
<tr>
<td>Both</td>
<td>1,912</td>
<td>3.52 (0.79)</td>
</tr>
<tr>
<td>Current tobacco smoking intensity, cigarettes/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14,313</td>
<td>3.45 (0.81)</td>
</tr>
<tr>
<td>1-10</td>
<td>2,972</td>
<td>3.29 (0.76)</td>
</tr>
<tr>
<td>11-20</td>
<td>1,852</td>
<td>3.41 (0.79)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>567</td>
<td>3.63 (0.82)</td>
</tr>
<tr>
<td>Current marijuana smoking intensity, episodes in the last 30 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15,771</td>
<td>3.38 (0.80)</td>
</tr>
<tr>
<td>1-10</td>
<td>2,784</td>
<td>3.59 (0.81)</td>
</tr>
<tr>
<td>11-20</td>
<td>665</td>
<td>3.68 (0.80)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>484</td>
<td>3.75 (0.77)</td>
</tr>
<tr>
<td>Lifetime exposure to tobacco, pack-years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11,183</td>
<td>3.44 (0.82)</td>
</tr>
<tr>
<td>1-10</td>
<td>6,458</td>
<td>3.44 (0.77)</td>
</tr>
<tr>
<td>11-20</td>
<td>1,447</td>
<td>3.35 (0.83)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>616</td>
<td>3.29 (0.85)</td>
</tr>
<tr>
<td>Lifetime exposure to marijuana, joint-years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5,619</td>
<td>3.28 (0.79)</td>
</tr>
<tr>
<td>1-5</td>
<td>13,493</td>
<td>3.49 (0.80)</td>
</tr>
<tr>
<td>6-10</td>
<td>371</td>
<td>3.57 (0.78)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>221</td>
<td>3.45 (0.86)</td>
</tr>
</tbody>
</table>

Abbreviations: FEV₁, forced expiratory volume in first second of expiration; FVC, forced vital capacity.

*For trend, except for current tobacco/marijuana smoking status,* for which a nominal test is used.

**Adjusted differences represent comparisons of average pulmonary function (FEV₁ and FVC), in mL, between persons in the given smoking exposure category and the reference category. Mixed models with a random intercept and a random 3-knot age spline were used to adjust for repeated measures, and fixed effects were included for year, center and center-year (their interaction), race-sex category, education, and asthma; cubic splines for age, height, waist circumference, secondhand smoke exposure, and exposure to airborne particulate matter less than 10 microns and less than 2.5 microns in size; and interactions between the age spline variables and race-sex, asthma, waist spline variables, and height spline variables. Except for in the first subsection (current tobacco/marijuana smoking status), all 4 smoking variables (4 categories each) were included in the same model, including current and lifetime smoking intensity for both tobacco and marijuana.

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sure, consistent with prior findings, represent a positive control for our study of the association between marijuana smoking and pulmonary function.

Prior studies of marijuana smoking and pulmonary function have yielded apparently conflicting results.\textsuperscript{10-13} Many studies have focused on FEV\textsubscript{1}:FVC ratio, lower values of which suggest the presence of airway obstruction, and have found either no association\textsuperscript{10,20,27} or lower FEV\textsubscript{1}:FVC ratios with marijuana use.\textsuperscript{28-32} Lower FEV\textsubscript{1}:FVC ratios in marijuana smokers, however, can be explained at least partly by a tendency toward higher FVC or total lung capacity.\textsuperscript{28,29,32} A recent longitudinal study, which demonstrated significantly higher FVC and total lung capacity with marijuana exposure, strongly supports this notion,\textsuperscript{13,20} as does our study.

The potential association of marijuana smoking with FEV\textsubscript{1} has been even less clear. Tobacco smoking reduces FEV\textsubscript{1}, but despite the similarities in the constituents of marijuana smoke and tobacco smoke and our a priori expectations that marijuana smoking might have similar effects, prior research has not demonstrated this. In studies that report FEV\textsubscript{1} in association with marijuana use, findings have mostly been null,\textsuperscript{20,28,32-35} although one study reported the apparently paradoxical finding of a lower FEV\textsubscript{1} with past marijuana use but a nonsignificantly higher FEV\textsubscript{1} with current use.\textsuperscript{29}

Our study suggests a way to reconcile these findings. Because of the many thousands of measurements obtained over 20 years among more than 5000 participants with a wide range of smoking habits, we could simultaneously account for levels of current and past lifetime use of both marijuana and tobacco and test for nonlinearity in their associations with pulmonary function to disentangle short-term and long-term effects. We found highly significant nonlinearity, with a positive association for both FEV\textsubscript{1} and FVC at low

![Figure 2. Associations Between Continuous Smoothed Exposure to Current and Lifetime Tobacco and Marijuana and Pulmonary Function](image-url)
Table 3. Estimated Slopes and Net Associations Between Continuous Smoothed Exposure to Current and Lifetime Tobacco and Marijuana and Pulmonary Function

<table>
<thead>
<tr>
<th>Smoking Exposure Type</th>
<th>FEV₁</th>
<th>FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Estimate (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Current marijuana exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of overall association</td>
<td>.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Test of nonlinearity</td>
<td>.02</td>
<td>.04</td>
</tr>
<tr>
<td>Slope, mL per episode per mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 episodes/mo</td>
<td>0.8 (-1.4 to 3.1)</td>
<td>.47</td>
</tr>
<tr>
<td>At 10 episodes/mo</td>
<td>2.6 (-0.3 to 5.4)</td>
<td>.07</td>
</tr>
<tr>
<td>At 20 episodes/mo</td>
<td>-3.2 (-5.8 to -0.6)</td>
<td>.02</td>
</tr>
<tr>
<td>At 40 episodes/mo</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Net association, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 episodes/mo</td>
<td>4.1 (-7.1 to 15)</td>
<td>.47</td>
</tr>
<tr>
<td>At 10 episodes/mo</td>
<td>11 (-6.2 to 29)</td>
<td>.21</td>
</tr>
<tr>
<td>At 20 episodes/mo</td>
<td>14 (-4.7 to 32)</td>
<td>.14</td>
</tr>
<tr>
<td>At 40 episodes/mo</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lifetime marijuana exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of overall association</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Test of nonlinearity</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Slope, mL per joint-year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 joint-years</td>
<td>13 (6.4 to 20)</td>
<td>.001</td>
</tr>
<tr>
<td>At 7 joint-years</td>
<td>-0.4 (-2.6 to 1.8)</td>
<td>.74</td>
</tr>
<tr>
<td>At 20 joint-years</td>
<td>-2.2 (-4.6 to 0.3)</td>
<td>.08</td>
</tr>
<tr>
<td>At 50 joint-years</td>
<td>-2.2 (-4.6 to 0.3)</td>
<td>.08</td>
</tr>
<tr>
<td>Net association, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 joint-years</td>
<td>30 (8.4 to 59)</td>
<td>.007</td>
</tr>
<tr>
<td>At 7 joint-years</td>
<td>53 (28 to 79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 20 joint-years</td>
<td>27 (-10 to 64)</td>
<td>.16</td>
</tr>
<tr>
<td>At 50 joint-years</td>
<td>-39 (-141 to 64)</td>
<td>.46</td>
</tr>
<tr>
<td>Current tobacco exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of overall association</td>
<td>&lt;.001</td>
<td>.003</td>
</tr>
<tr>
<td>Test of nonlinearity</td>
<td>.29</td>
<td>.73</td>
</tr>
<tr>
<td>Slope, mL per cigarettes/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 cigarettes/d</td>
<td>-0.2 (-2.3 to 1.9)</td>
<td>.85</td>
</tr>
<tr>
<td>At 10 cigarettes/d</td>
<td>-2.8 (-4.8 to -0.7)</td>
<td>.007</td>
</tr>
<tr>
<td>At 20 cigarettes/d</td>
<td>-1.1 (-2.7 to 0.5)</td>
<td>.16</td>
</tr>
<tr>
<td>At 40 cigarettes/d</td>
<td>-1.1 (-2.7 to 0.5)</td>
<td>.16</td>
</tr>
<tr>
<td>Net association, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 cigarettes/d</td>
<td>-1.0 (-11 to 9.4)</td>
<td>.85</td>
</tr>
<tr>
<td>At 10 cigarettes/d</td>
<td>-6.3 (-23 to 11)</td>
<td>.47</td>
</tr>
<tr>
<td>At 20 cigarettes/d</td>
<td>-34 (-53 to -16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 40 cigarettes/d</td>
<td>-57 (-92 to -22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lifetime tobacco exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of overall association</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Test of nonlinearity</td>
<td>.98</td>
<td>.85</td>
</tr>
<tr>
<td>Slope, mL per pack-year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 pack-years</td>
<td>-6.5 (-12 to -1.2)</td>
<td>.02</td>
</tr>
<tr>
<td>At 7 pack-years</td>
<td>-7.0 (-10 to -3.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 20 pack-years</td>
<td>-6.6 (-8.4 to -4.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 50 pack-years</td>
<td>-6.6 (-8.4 to -4.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Net association, mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 pack-years</td>
<td>-13 (-23 to -2.4)</td>
<td>.02</td>
</tr>
<tr>
<td>At 7 pack-years</td>
<td>-46 (-72 to -21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 20 pack-years</td>
<td>-135 (-166 to -104)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 50 pack-years</td>
<td>-332 (-401 to -263)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: FEV₁, forced expiratory volume in 1 second of expiration; FVC, forced vital capacity; NA, not available.

aAssociations between continuous current and lifetime exposure measurements and pulmonary function were modeled via cubic splines (see “Methods”), and the estimates presented here describe the same analyses illustrated in Figure 2. The estimates presented are for slope (reflecting the incremental difference in pulmonary function observed with 1 unit of additional tobacco or marijuana smoking exposure) and net association (reflecting the net observed difference between persons with a particular level of consumption and persons with none). As illustrated in Figure 2, slopes vary at different exposure levels (ie, associations are not constrained to be linear).

bEstimates are from the 2 models (1 each for FEV₁ and FVC) illustrated in Figure 2 and include all 4 smoking exposure types (current and lifetime tobacco and marijuana). Mixed models with a random intercept and a random 3-knot age spline were used to adjust for repeated measures, and fixed effects were included for year, center and center-year (their interaction), race-sex category, education, and asthma; cubic splines for age, height, waist circumference, secondhand smoke exposure, and exposure to airborne particulate matter less than 10 microns and less than 2.5 microns in size; and interactions between the age spline variables and race-sex, asthma, waist spline variables, and height spline variables.

cData not available at this exposure level.

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levels of exposure that reversed in di-
rection toward a possibly negative as-
sociation for FEV1 at higher levels of ex-
posure (Figure 2 and slopes in Table 3).
These findings could explain the para-
dox previously noted regarding past and
current use26 and are also consistent
with the average null association re-
ported in studies20,28,32-35 that either
dichotomized marijuana exposure
(user/nonuser)28-31,33,36 or constrained
the association to be linear across all lev-
eels of exposure.20,27,32,36 When we looked
at “marijuana only” smokers (Table 2),
we also found a null association with
FEV1 and FVC. Only after parsing the
association at different levels of expo-
sure, with careful control for confound-
ing, did the suggestion emerge of a
negative association for FEV1 at high
levels of exposure.

These findings suggest that mari-
juana smoking could influence pulmo-
nary function via multiple mecha-
nisms. To explain the higher FVC
previously observed in marijuana smok-
ers,20,32 some investigators have pro-
posed that the deep inspiratory maneu-
vers practiced by marijuana smokers
could stretch the lungs,11,20 resulting in
larger lung volumes.20,32 Another specu-
lative possibility is strengthening of
chest wall musculature or another
“training” effect that allows marijuana
users to inspire more fully (closer to
total lung capacity) on spirometry test-
ing. A nondestructive stretch or train-
ing effect is consistent with previously
reported findings in marijuana smok-
ers of lower lung density32 and a lack
of emphysematous change32 or dimin-
ished diffusion capacity.20,27,32,36 This
mechanism would explain our FVC re-
sults and could explain the positive de-
flection of FEV1. The functional ef-
ects of this association on lung health
or respiratory function in daily life are
unclear.13 An alternate explanation is
the acute bronchodilatory effect of mari-
juana use that has been directly ob-
served in some studies.11 This effect,
however, is transient (lasting approxi-
mately 60 minutes11) and seems un-
likely to explain higher lung volumes
measured during the CARDIA exami-
nation unless many marijuana users
smoked immediately before the exami-
nation.

The suggestion of a negative asso-
ciation with FEV1 at higher exposure
levels could reflect mixing of this pu-
tative stretch/training effect with a sec-
ond mechanism operating on a differ-
ent time-exposure scale. A negative
association with heavy exposure to
marijuana smoke aligns with our a
priori hypothesis that marijuana smok-
ing should produce damage to the air-
ways and accelerated loss of lung func-
tion similar to that caused by tobacco
smoking. Hypothetically speaking, a
positive effect from marijuana in the
short term (the stretch/training effect)
and a negative effect in the long term
(damage from smoke exposure) should
result in a nonlinear association such
as the one we observed. According to
this explanation, the predominant ef-
fect for FEV1 at very high exposure
(more than 40 joint-years) reflects cu-
mulative damage; the predominant ef-
fect for FVC at all levels of exposure is
from the stretch/training mechanism.

Our study has limitations. Al-
though CARDIA offers longitudinal spi-
rometry measurements, it lacked body
plethysmographic measurements of
static lung volumes (total lung capac-
ity and residual volume) and mea-
sures of diffusing capacity and radi-
ographic emphysema. A minority of
our participants reported very high levels
of marijuana exposure (and a smaller
minority of these were nonsmokers of
tobacco), so our estimates at high mari-
juana exposure levels are imprecise.
The self-reported measures of marijuana
and tobacco smoking are certain to in-
clude recall error, both random and sys-
tematic, and do not include any indi-
cation of smoking method (joint, pipe,
“bong”, etc). It is unlikely, however,
that such error would differentially oc-
cur in association with pulmonary func-
tion, and nondifferential error would
most likely bias results toward the null.
Our mixed modeling approach is ideal
for filtering out random error and tak-
ing advantage of individual-level cor-
relations in the data.

As with any observational analysis,
unmeasured or inadequately modeled
confounding effects could be mixed
with our estimates, but the extensive co-
variate measurements and large sample
in our study permitted more extensive
efforts to control confounding than
were possible in previous studies. This
study addressed respiratory exposure
to marijuana and not exposure by in-
gestion. Recent increases in the po-
tency of marijuana are unlikely to have
influenced our estimates, because we
did not detect an interaction of mari-
juana and pulmonary function by cal-
endar time.

Marijuana may have beneficial ef-
effects on pain control, appetite, mood,
and management of other chronic
symptoms.15,16 Our findings suggest that
occasional use of marijuana for these
or other purposes may not be associ-
ated with adverse consequences on pul-
monary function. It is more difficult to
estimate the potential effects of regu-
lar heavy use, because this pattern of
use is relatively rare in our study
sample; however, our findings do sug-
gest an accelerated decline in pulmo-
nary function with heavy use and a re-
sulting need for caution and moderation
when marijuana use is considered.

Author Contributions: Dr Pletcher had full access
to all of the data in the study and takes responsibility for the
integrity of the data and the accuracy of the data
analysis.
Study concept and design: Pletcher, Richman, Safford.
Acquisition of data: Sidney.
Analysis and interpretation of data: Pletcher, Vittinghoff, Kalhan, Richman, Safford, Lin, Kertesz.
Drafting of the manuscript: Pletcher, Safford.
Critical revision of the manuscript for important in-
tellectual content: Pletcher, Vittinghoff, Kalhan, Richman, Safford, Sidney, Lin, Kertesz.
Statistical analysis: Pletcher, Vittinghoff, Richman, Lin.
Obtained funding: Pletcher, Sidney, Kertesz.
Administrative, technical, or material support: Kertesz.
Study supervision: Kertesz.
Conflict of Interest Disclosures: The authors have
completed and submitted the ICME Form for Disclo-
sure of Potential Conflicts of Interest. Dr Kalhan
reported serving as a consultant for Boehringer-
Ingelheim, Forest Laboratories, and AstraZeneca;
receiving honoraria for lectures from GlaxoSmithKline
and AstraZeneca; receiving honoraria for develop-
ment of educational materials from Quantu Commu-
nications and Medscape Education; and receiving
industry-sponsored grants from GlaxoSmithKline
and Boehringer-Ingelheim. Dr Kertesz reported chairing
a committee that advised the Drug Treatment Task
Force for the Chief Justice of the State of Alabama
and that he is an employee of the Department of
Veterans Affairs. No other authors reported disclo-
sures.

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MARIJUANA EXPOSURE AND PULMONARY FUNCTION

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Disclaimer: The views expressed in this article do not reflect positions of the Department of Veterans Affairs or of any other entity of the federal government.

Online-Only Material: The eMethods, eTable, eFigures 1 and 2, and Author Video Interview are available at http://www.jama.com.

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