Association Between Marijuana Exposure and Pulmonary Function Over 20 Years

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

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 inflammation\(^7\)-\(^9\) 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 of 20 years.\(^1\),\(^2\) 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 FEV\(_1\) and FVC. In contrast, the association between marijuana exposure and pulmonary function was nonlinear (\(P<.001\)): at low levels of exposure, FEV\(_1\) 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 FEV\(_1\) was −2.2 mL/joint-year (95% CI, −4.6 to 0.3; \(P=0.08\)) at more than 10 joint-years and −3.2 mL per marijuana smoking episode/mo (95% CI, −5.8 to −0.6; \(P=0.02\)) at more than 20 episodes/mo. With very heavy marijuana use, the net association with FEV\(_1\) 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.


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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 1985.17,18 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 7300 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.19

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.20

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.21,22

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 size23 around the 4 CARDIA study centers from the Environmental Protection Agency24 (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.25

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

Figure 1. Pulmonary Function Measurements by Age

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.

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 more common in tobacco smokers but not associated with marijuana use. FEV1 and FVC varied across participants, increased slightly with age through the late 20s, and declined slowly thereafter (Figure 1).

More than half of participants (54%; mean age at baseline, 25 years) reported current marijuana smoking, tobacco smoking, or both at 1 or more examinations (Table 1). Smoking patterns differed by race and sex, with black women most likely to smoke tobacco only, white men most likely to smoke marijuana only, and black men most likely to smoke both. Tobacco smokers tended to have lower education and income and to be slightly shorter and less active, whereas marijuana smokers tended to be taller and more active. 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 and tobacco exposures were strongly correlated, our sample included 91 participants with no tobacco exposure and more than 10 joint-years of marijuana exposure (contributing 153 observations of pulmonary function), 40 (56 observations) of whom had more than 20 joint-years of exposure.

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...
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, −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 (−2.0 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/episodic [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>Marijuana/Tobacco Use</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 Value</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. (%)</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>155 (23)</td>
<td>367 (34)</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. (%)</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>38 (8)</td>
<td>33 (8)</td>
<td>33 (8)</td>
<td>.002</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-years</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-years</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.

Values are from a 1-way analysis of variance test for age, body mass index, height, waist circumference, PM10 and PM2.5 exposure, and number of CARDIA examinations; from a Kruskal-Wallis nonparametric test for smoking variables, limiting comparisons to smokers of the relevant substance for each test.

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**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 expos-

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

<table>
<thead>
<tr>
<th>Smoking Exposure Category</th>
<th>No.</th>
<th>FEV₁ (Mean, SD, L)</th>
<th>Adjusted Difference (95% CI), mL</th>
<th>P Value</th>
<th>FVC (Mean, SD, L)</th>
<th>Adjusted Difference (95% CI), mL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>19,704</td>
<td>3.420 (810)</td>
<td></td>
<td></td>
<td></td>
<td>4.23 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Current tobacco/marijuana smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither</td>
<td>12,288</td>
<td>3.41 (0.80)</td>
<td>-24 (-38 to -11)</td>
<td>.003</td>
<td>4.19 (1.03)</td>
<td>-19 (-33 to -4.6)</td>
<td>.004</td>
</tr>
<tr>
<td>Tobacco only</td>
<td>3,493</td>
<td>3.27 (0.77)</td>
<td>-23 (-38 to -11)</td>
<td></td>
<td>4.07 (0.97)</td>
<td>-19 (-33 to -4.6)</td>
<td></td>
</tr>
<tr>
<td>Marijuana only</td>
<td>2,021</td>
<td>3.73 (0.81)</td>
<td>0.7 (-12 to 13)</td>
<td></td>
<td>4.60 (1.04)</td>
<td>8.2 (-5 to 22)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1,912</td>
<td>3.52 (0.79)</td>
<td>-13 (-29 to 3)</td>
<td></td>
<td>4.39 (1.02)</td>
<td>2.7 (-14 to 20)</td>
<td></td>
</tr>
<tr>
<td>Current tobacco smoking intensity, cigarettes/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14,313</td>
<td>3.45 (0.81)</td>
<td>1 (Reference)</td>
<td></td>
<td>4.24 (1.04)</td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>2,972</td>
<td>3.29 (0.76)</td>
<td>-13 (-27 to 1.0)</td>
<td></td>
<td>4.05 (0.96)</td>
<td>-15 (-30 to -0.4)</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>1,852</td>
<td>3.41 (0.79)</td>
<td>-36 (-53 to -19)</td>
<td></td>
<td>4.27 (1.00)</td>
<td>-30 (-49 to -12)</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>567</td>
<td>3.63 (0.82)</td>
<td>-63 (-89 to -36)</td>
<td></td>
<td>4.60 (1.05)</td>
<td>-69 (-97 to -41)</td>
<td></td>
</tr>
<tr>
<td>Current marijuana smoking intensity, episodes in the last 30 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15,771</td>
<td>3.38 (0.80)</td>
<td>1 (Reference)</td>
<td></td>
<td>4.16 (1.02)</td>
<td>5.8 (-5.4 to 17)</td>
<td>.03</td>
</tr>
<tr>
<td>1-10</td>
<td>2,784</td>
<td>3.59 (0.81)</td>
<td>0.8 (-10 to 11)</td>
<td></td>
<td>4.44 (1.03)</td>
<td>35 (15 to 55)</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>665</td>
<td>3.68 (0.80)</td>
<td>16 (-3.5 to 35)</td>
<td></td>
<td>4.57 (1.03)</td>
<td>35 (15 to 55)</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>484</td>
<td>3.75 (0.77)</td>
<td>-18 (-42 to 6.1)</td>
<td></td>
<td>4.75 (1.01)</td>
<td>20 (-5.2 to 49)</td>
<td></td>
</tr>
<tr>
<td>Lifetime exposure to tobacco, pack-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11,183</td>
<td>3.44 (0.82)</td>
<td>1 (Reference)</td>
<td></td>
<td>4.22 (1.05)</td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>1-10</td>
<td>6,458</td>
<td>3.44 (0.77)</td>
<td>3.2 (-18 to 25)</td>
<td></td>
<td>4.24 (0.99)</td>
<td>37 (12 to 61)</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>1,447</td>
<td>3.35 (0.83)</td>
<td>-41 (-38 to -14)</td>
<td></td>
<td>4.24 (1.07)</td>
<td>11 (-20 to 41)</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>616</td>
<td>3.29 (0.85)</td>
<td>-101 (-136 to -65)</td>
<td></td>
<td>4.27 (1.09)</td>
<td>-35 (-76 to 5.0)</td>
<td></td>
</tr>
<tr>
<td>Lifetime exposure to marijuana, joint-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5,619</td>
<td>3.28 (0.79)</td>
<td>1 (Reference)</td>
<td></td>
<td>4.00 (1.00)</td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>13,493</td>
<td>3.49 (0.80)</td>
<td>38 (15 to 62)</td>
<td></td>
<td>4.31 (1.03)</td>
<td>41 (14 to 67)</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>371</td>
<td>3.57 (0.78)</td>
<td>66 (32 to 100)</td>
<td></td>
<td>4.50 (1.02)</td>
<td>54 (16 to 91)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>221</td>
<td>3.45 (0.86)</td>
<td>36 (-6.5 to 79)</td>
<td></td>
<td>4.44 (1.08)</td>
<td>59 (12 to 107)</td>
<td></td>
</tr>
</tbody>
</table>

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

*Refers to the number of observations; the 5016 participants contributed an average of 3.9 observations per participant.

*For trend, except for “current tobacco/marijuana smoking status,” for which a nonordered 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.

*One pack-year of exposure to tobacco smoke equals 7300 cigarettes (1 pack/d × 20 cigarettes/pack × 365 d/y); 1 joint-year of exposure to marijuana smoke equals 365 joints of marijuana (1 joint/d × 365 d/y).
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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Associations Between Continuous Smoothed Exposure to Current and Lifetime Tobacco and Marijuana and Pulmonary Function}
\end{figure}

Associations between continuous current and lifetime exposure measurements and pulmonary function were modeled via cubic splines (see “Methods”). All 4 exposure measurements were included in each model (one model each for forced expiratory volume in the first second of expiration [FEV\textsubscript{1}] and forced vital capacity [FVC]). 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. Point estimates and confidence intervals for slopes and net associations at different exposure levels are provided in Table 3.
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>P Value</th>
<th>FVC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted Estimate (95% CI)</td>
<td></td>
<td>Adjusted Estimate (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Current marijuana exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of overall association</td>
<td>.06</td>
<td>&lt;.001</td>
<td>.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Test of nonlinearity</td>
<td>.02</td>
<td>.04</td>
<td>.02</td>
<td>.04</td>
</tr>
<tr>
<td>Slope, mL per episode per mo</td>
<td></td>
<td></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>
<td>2.8 (0.4 to 5.1)</td>
<td>.02</td>
</tr>
<tr>
<td>At 10 episodes/mo</td>
<td>2.6 (0.3 to 5.4)</td>
<td>.07</td>
<td>3.7 (0.7 to 6.6)</td>
<td>.02</td>
</tr>
<tr>
<td>At 20 episodes/mo</td>
<td>−3.2 (−5.8 to −0.6)</td>
<td>.02</td>
<td>−1.5 (−4.2 to 1.3)</td>
<td>.30</td>
</tr>
<tr>
<td>At 40 episodes/mo</td>
<td>NA²</td>
<td>NA²</td>
<td>NA²</td>
<td>NA²</td>
</tr>
<tr>
<td>Net association, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 episodes/mo</td>
<td>4.1 (−7.1 to 15)</td>
<td>.47</td>
<td>14 (1.9 to 26)</td>
<td>.02</td>
</tr>
<tr>
<td>At 10 episodes/mo</td>
<td>11 (−6.2 to 29)</td>
<td>.21</td>
<td>29 (11 to 48)</td>
<td>.002</td>
</tr>
<tr>
<td>At 20 episodes/mo</td>
<td>14 (−4.7 to 32)</td>
<td>.14</td>
<td>43 (23 to 63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 40 episodes/mo</td>
<td>NA²</td>
<td>NA²</td>
<td>NA²</td>
<td>NA²</td>
</tr>
<tr>
<td>Lifetime marijuana exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of overall association</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Test of nonlinearity</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Slope, mL per joint-year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 joint-years</td>
<td>13 (6.4 to 20)</td>
<td>&lt;.001</td>
<td>20 (12 to 27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 7 joint-years</td>
<td>−0.4 (−2.6 to 1.8)</td>
<td>.74</td>
<td>0.0 (−2.4 to 2.5)</td>
<td>.97</td>
</tr>
<tr>
<td>At 20 joint-years</td>
<td>−2.2 (−4.6 to 0.3)</td>
<td>.08</td>
<td>1.0 (−1.8 to 3.7)</td>
<td>.49</td>
</tr>
<tr>
<td>At 50 joint-years</td>
<td>−2.2 (−4.6 to 0.3)</td>
<td>.08</td>
<td>1.0 (−1.8 to 3.7)</td>
<td>.49</td>
</tr>
<tr>
<td>Net association, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 joint-years</td>
<td>30 (8.4 to 59)</td>
<td>.007</td>
<td>59 (35 to 83)</td>
<td>.001</td>
</tr>
<tr>
<td>At 7 joint-years</td>
<td>53 (28 to 79)</td>
<td>&lt;.001</td>
<td>64 (36 to 92)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 20 joint-years</td>
<td>27 (10 to 64)</td>
<td>.16</td>
<td>76 (34 to 117)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 50 joint-years</td>
<td>−39 (−141 to 64)</td>
<td>.46</td>
<td>104 (−12 to 220)</td>
<td>.08</td>
</tr>
<tr>
<td>Current tobacco exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of overall association</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Test of nonlinearity</td>
<td>.29</td>
<td>.73</td>
<td>.29</td>
<td>.73</td>
</tr>
<tr>
<td>Slope, mL per cigarettes/d</td>
<td></td>
<td></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>
<td>−0.8 (−3.1 to 1.4)</td>
<td>.46</td>
</tr>
<tr>
<td>At 10 cigarettes/d</td>
<td>−2.8 (−4.8 to −0.7)</td>
<td>.007</td>
<td>−1.3 (−3.4 to 0.9)</td>
<td>.25</td>
</tr>
<tr>
<td>At 20 cigarettes/d</td>
<td>−1.1 (−2.7 to 0.5)</td>
<td>.16</td>
<td>−1.9 (−3.6 to −0.2)</td>
<td>.02</td>
</tr>
<tr>
<td>At 40 cigarettes/d</td>
<td>−1.1 (−2.7 to 0.5)</td>
<td>.16</td>
<td>−1.9 (−3.6 to −0.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Net association, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 5 cigarettes/d</td>
<td>−1.0 (−11 to 9.4)</td>
<td>.85</td>
<td>−4.2 (−15 to 6.9)</td>
<td>.46</td>
</tr>
<tr>
<td>At 10 cigarettes/d</td>
<td>−6.3 (−23 to 11)</td>
<td>.47</td>
<td>−9.1 (−27 to 8.9)</td>
<td>.32</td>
</tr>
<tr>
<td>At 20 cigarettes/d</td>
<td>−34 (−53 to −16)</td>
<td>&lt;.001</td>
<td>−26 (−46 to −7.0)</td>
<td>.008</td>
</tr>
<tr>
<td>At 40 cigarettes/d</td>
<td>−57 (−92 to −22)</td>
<td>&lt;.001</td>
<td>−65 (−102 to −28)</td>
<td>.001</td>
</tr>
<tr>
<td>Lifetime tobacco exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test of overall association</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Test of nonlinearity</td>
<td>.96</td>
<td>.85</td>
<td>.96</td>
<td>.85</td>
</tr>
<tr>
<td>Slope, mL per pack-year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 pack-years</td>
<td>−6.5 (−12 to −1.2)</td>
<td>.02</td>
<td>−3.5 (−9.3 to 2.4)</td>
<td>.25</td>
</tr>
<tr>
<td>At 7 pack-years</td>
<td>−7.0 (−10 to −3.7)</td>
<td>&lt;.001</td>
<td>−5.5 (−9.3 to −1.8)</td>
<td>.004</td>
</tr>
<tr>
<td>At 20 pack-years</td>
<td>−6.6 (−8.4 to −4.7)</td>
<td>&lt;.001</td>
<td>−4.5 (−6.8 to −2.3)</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>
<td>−4.5 (−6.8 to −2.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Net association, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 2 pack-years</td>
<td>−13 (−23 to −2.4)</td>
<td>.02</td>
<td>−6.9 (−19 to 4.8)</td>
<td>.25</td>
</tr>
<tr>
<td>At 7 pack-years</td>
<td>−46 (−72 to −21)</td>
<td>&lt;.001</td>
<td>−28 (−57 to 0.1)</td>
<td>.05</td>
</tr>
<tr>
<td>At 20 pack-years</td>
<td>−135 (−166 to −104)</td>
<td>&lt;.001</td>
<td>−95 (−130 to −59)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At 50 pack-years</td>
<td>−332 (−401 to −263)</td>
<td>&lt;.001</td>
<td>−229 (−310 to −147)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: FEV₁, forced expiratory volume in first 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.
levels of exposure that reversed in direction toward a possibly negative association for FEV1 at higher levels of exposure (Figure 2 and slopes in Table 3). These findings could explain the paradox previously noted regarding past and current use20 and are also consistent with the average null association reported in studies.20,28,32–35 That either dichotomized marijuana exposure (user/nonuser)20,21,31,32 or constrained the association to be linear across all levels of exposure.20,28,32–35 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 exposure, with careful control for confounding, did the suggestion emerge of a negative association for FEV1 at high levels of exposure.

These findings suggest that marijuana smoking could influence pulmonary function via multiple mechanisms. To explain the higher FVC previously observed in marijuana smokers,20,32 some investigators have proposed that the deep inspiratory maneuvers practiced by marijuana smokers could stretch the lungs,13,20 resulting in larger lung volumes.20,32 Another speculative 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 testing. A nondestructive stretch or training effect is consistent with previously reported findings in marijuana smokers of lower lung density32 and a lack of emphysematous change32 or diminished diffusion capacity.20,27,32,36 This mechanism would explain our FVC results and could explain the positive deflection of FEV1. The functional effects of this association on lung health or respiratory function in daily life are unclear.13 An alternate explanation is the acute bronchodilatory effect of marijuana use that has been directly observed in some studies.11 This effect, however, is transient (lasting approximately 60 minutes)11 and seems unlikely to explain higher lung volumes measured during the CARDIA examination unless many marijuana users smoked immediately before the examination.

The suggestion of a negative association with FEV1 at higher exposure levels could reflect mixing of this putative stretch/training effect with a second mechanism operating on a different time-exposure scale. A negative association with heavy exposure to marijuana smoke aligns with our a priori hypothesis that marijuana smoking should produce damage to the airways and accelerated loss of lung function 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 effect for FEV1 at very high exposure (more than 40 joint-years) reflects cumulative damage; the predominant effect for FVC at all levels of exposure is from the stretch/training mechanism.

Our study has limitations. Although CARDIA offers longitudinal spirometry measurements, it lacked body plethysmographic measurements of static lung volumes (total lung capacity and residual volume) and measures of diffusing capacity and radiographic 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 marijuana exposure levels are imprecise. The self-reported measures of marijuana and tobacco smoking are certain to include recall error, both random and systematic, and do not include any indication of smoking method (joint, pipe, “bong”, etc.). It is unlikely, however, that such error would differentially occur in association with pulmonary function, and nondifferential error would most likely bias results toward the null. Our mixed modeling approach is ideal for filtering out random error and taking advantage of individual-level correlations in the data.

As with any observational analysis, unmeasured or inadequately modeled confounding effects could be mixed with our estimates, but the extensive covariate 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 ingestion. Recent increases in the potency of marijuana are unlikely to have influenced our estimates, because we did not detect an interaction of marijuana and pulmonary function by calendar time.

Marijuana may have beneficial effects on pain control, appetite, mood, and management of other chronic symptoms.11,16 Our findings suggest that occasional use of marijuana for these or other purposes may not be associated with adverse consequences on pulmonary function. It is more difficult to estimate the potential effects of regular heavy use, because this pattern of use is relatively rare in our study sample; however, our findings do suggest an accelerated decline in pulmonary function with heavy use and a resulting 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 intellectual 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 ICMJE Form for Disclosure 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 development of educational materials from Quantia Communications 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 disclosures.
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