Effects of cannabis on lung function: a population-based cohort study

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Running Head: Cannabis and lung function
Abstract

The effects of cannabis on lung function remain unclear and may be different to tobacco. We compared the associations between use of these substances and lung function in a population-based cohort (n=1037).

Cannabis and tobacco use were reported at ages 18, 21, 26, and 32 years. Spirometry, plethysmography, and carbon monoxide transfer factor were measured at age 32. Associations between lung function and exposure to each substance were adjusted for exposure to the other substance.

Cumulative cannabis use was associated with higher forced vital capacity, total lung capacity, functional residual capacity, and residual volume. Cannabis was also associated with higher airways resistance but not with forced expiratory volume in 1 second, forced expiratory ratio, or transfer factor. These findings were similar amongst those who did not smoke tobacco. By contrast, tobacco use was associated with lower forced expiratory volume in 1 second, lower forced expiratory ratio, lower transfer factor, and higher static lung volumes, but not with airways resistance.

Cannabis appears to have different effects on lung function to those of tobacco. Cannabis use was associated with higher lung volumes suggesting hyperinflation and increased large-airways resistance, but there was little evidence for airflow obstruction or impairment of gas transfer.

Abstract word count: 200

Key words: Cannabis, Cohort Study, Marijuana, Respiratory Function, Smoking, Tobacco.
Introduction

The pulmonary effects of smoking cannabis have not been extensively researched. In common with tobacco, smoking cannabis is associated with airway inflammation and symptoms of bronchitis, although the evidence that it causes airflow obstruction is not conclusive.[1-5] Among the reasons for this continuing uncertainty are its illegal status, making it difficult to obtain reliable estimates of cannabis exposure, and the common practice of combining cannabis with tobacco which makes it difficult to separate the effects of the two substances.[6] Thus, although cannabis is widely used throughout the world there is a paucity of information on its respiratory effects.

Apart from the respective psychoactive components of cannabinoids and nicotine, cannabis and tobacco smoke contain a similar mix of toxic and irritant chemicals.[7] However, there are reasons to suspect that their effects on the respiratory system may not be the same. Cannabis smokers tend to smoke fewer cigarettes a day than tobacco smokers, but these tend to be packed more loosely and unfiltered. Differences in depth of inhalation, breath-hold time, and leaving a shorter butt may increase the deposition of tar and carbon monoxide absorption from cannabis smoke.[8-10] Several case-reports of bullous lung disease in young cannabis smokers raise the possibility that cannabis (or the techniques used to smoke it) may have a greater effect on lung parenchyma than tobacco,[11-13] although this association has been disputed.[14] A recent report comparing smokers of cannabis and tobacco found that, although both cannabis and tobacco smokers had evidence of airflow obstruction on spirometry, cannabis was associated with more lung hyperinflation on lung volume measurement but a lower risk of emphysema on CT scanning compared to tobacco.[15] Though these findings do not support the suggestion that cannabis smokers are more
susceptible to emphysema, they do indicate that cannabis and tobacco may have quite
different effects on lung function.

We investigated the impact of cannabis and tobacco smoking on lung function in a
population-based birth cohort followed to age 32.

**Methods**

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a
longitudinal study of the health and behaviour of a complete cohort of individuals born in
Dunedin, New Zealand in 1972/1973.[16] 1037 individuals (52% male; 91% of eligible
births) participated in the age-three assessment, forming the base sample for the study. Study
members represent the full range of socioeconomic status in the general population of the
South Island of New Zealand and are primarily of New Zealand/European ethnicity. The
cohort has been assessed at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, and most recently at 32
years when we assessed 972 participants (96% of the living cohort). The Otago Ethics
Committee approved the study. Written informed consent was obtained for each assessment.

Cannabis smoking history was obtained at ages 18, 21, 26, and 32.[17] At each assessment
participants were asked how many times they had used marijuana in the previous year.
Cumulative exposure to cannabis was calculated as the number of “joint-years” since age 17.
These estimates assume that the number of times marijuana had been smoked in the previous
year was representative of all years since the previous assessment. Where data were not
collected at a particular assessment, the amount smoked reported at the next assessment was
used to calculate cumulative exposure. One joint-year is defined as the equivalent of one joint
a day for one year.
Cumulative tobacco exposure was calculated from the reported number of cigarettes smoked per day up to 18 years, 18 to 21 years, 21 to 26 years, and 26 to 32 years. Where data were not collected for an assessment, the amount smoked reported at the next assessment was used to calculate cumulative exposure. One pack-year is defined as the equivalent of 20 cigarettes a day for one year. Those who had smoked less than 1 cigarette a day for a year, and less than 20 packets in their lifetime were regarded as non-smokers.[18]

Spirometry has been measured at each assessment since age 9. At age 32 a broad range of lung function tests including spirometry, total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), airway resistance (Raw), specific airway conductance adjusted for thoracic gas volume (sGaw), transfer factor for carbon monoxide (TLCO), and alveolar volume (VA) were measured using the plethysmograph and a Sensormedics Vmax 6200 module (Yorba Linda, CA).[19-21] This system uses a heated wire mass flow sensor and methane dilution for measurement of alveolar volume and calculation of TLCO. A portable spirometer (Spiropro, Sensormedics) was used to test Study members (n = 27) who declined to sit in the plethysmograph or were unable to attend the research unit. Spirometry was repeated 10-15 minutes following inhalation of 200µg salbutamol via a metered dose inhaler and Volumatic spacer device (Allen & Hanburys, Stockley Park, Middlesex, UK). Study members were asked to refrain from use of their inhalers and not to smoke on the day of the assessment. All tests were reviewed by a senior technician to ensure that only acceptable and reproducible results were entered for analysis. Equipment was calibrated daily and weekly quality control measures using biological controls were performed to ensure accuracy and precision of test equipment.
At age 32, haemoglobin was measured on a Sysmex XE2100 automated haematology analyzer (Sysmex Corporation, Japan). Exhaled carbon monoxide was measured before TLCO measurement using a Micro CO monitor, (Micromedical, UK) and the average of two tests was recorded.

Height without shoes was measured at each age. Questions were asked about current and prior asthma and asthma symptoms using previously developed questionnaires.[22] Current asthma is defined as a reported diagnosis asthma with symptoms or medication use in the previous 12 months.

**Statistical analysis**

To assess whether pre-existing differences in lung function influenced the propensity to smoke, regression analyses of cumulative pack-years and joint-years to age 32 were performed using spirometry at age 15 (FEV₁, FVC and FEV₁/FVC) as the main predictor. These analyses adjusted for sex and height at age 15.

Initial analyses of sex*cannabis and sex*tobacco smoking interaction terms found no evidence that the effect of smoking either substance was different for men and women for any of the outcomes. The independent associations between lung function measurements at age 32 years and cannabis and tobacco smoking were assessed by linear regression using the measurement of lung function as the dependent variable and estimates of both cannabis and tobacco exposure as independent variables. Analyses included terms for height and sex to adjust for differences in predicted lung function as recommended by Vollmer[23] except for FEV₁/FVC ratio which was adjusted for sex only. Analyses of TLCO also adjusted for pre-test exhaled carbon monoxide and haemoglobin. Analyses of the association of cannabis with
l lung function were repeated after excluding those with any lifetime history of cigarette smoking.

To assess changes in lung function associated with tobacco and cannabis smoking, regression analyses were repeated for FEV$_1$, FVC, and FEV$_1$/FVC ratio using the estimates of both joint-years and pack-years as predictors with adjustment for the measurements obtained at age 15. These analyses also adjusted for sex, height at age 32, change in height between ages 15 and 32, and current asthma diagnosis.

Because pregnancy may affect lung function, pregnant women were excluded (n= 31). Visual inspection of the residuals from the regression analyses identified one clear outlier who was also excluded. Lung function measurements were approximately normally distributed, except for Raw and sGaw. Repeat analyses after log-transformations of these variables to approximate normal distributions provided similar results (not shown). Analyses were performed using Stata version 10.

Results

Reported cannabis and tobacco use at each age are summarised in the online supplement. The number of Study members who reported using cannabis was higher at ages 21 and 26 years than at ages 18 or 32 (online table 1). The number of tobacco smokers was similar at all ages, although the number of heavy smokers increased with age. Cumulative pack-years of tobacco smoking by age 32 correlated with joint-years of cannabis (Spearman’s rho=0.49, p<0.0001) (table 1). None of the measures of spirometric lung function (FEV$_1$, FVC, or FEV$_1$/FVC ratio) at age 15 predicted subsequent pack-years of tobacco consumption or joint-years of cannabis use by age 32 (all p values ≥0.3).
Mean values of lung function according to the categories of cannabis and tobacco use are shown in the online supplement (online table 2). When analysed separately, cannabis and tobacco were both associated with a broad range of lung function measures (online tables 3 and 4). However, when the effects of cannabis and tobacco were considered together (i.e. with simultaneous adjustment for exposure to the other substance), different patterns of effects were observed (Table 2). After adjusting for tobacco exposure, cannabis was associated with significantly higher FVC values but there was no significant association with FEV\textsubscript{1} or FEV\textsubscript{1}/FVC ratios. By contrast, tobacco was associated with a non-significant trend to lower FEV\textsubscript{1} values and significantly lower FEV\textsubscript{1}/FVC ratios, but there was no association with FVC. The findings for post-bronchodilator spirometry were similar except that in this analysis the association between tobacco smoking and lower FEV\textsubscript{1} values was significant (online table 5). Both cannabis and tobacco were associated with higher values for TLC, FRC and RV, although the association between tobacco and TLC was of borderline statistical significance (table 2). Cannabis was significantly associated with higher Raw and lower sGaw. Tobacco was not associated with differences in Raw but was associated with lower sGaw with borderline statistical significance. Cannabis use was not significantly associated with TLCO, but because of higher values for VA, transfer factor per unit lung volume (TLCO/VA) were lower. Tobacco was associated with lower total lung TLCO and lower TLCO/VA, but not with VA.
Associations between cannabis exposure and lung function amongst non-tobacco smokers are shown in table 3. These show a similar pattern of findings to those shown in table 2. Cannabis use was associated with higher values for TLC and VA and with trends to higher values for FVC and RV. Cannabis use was not associated with FEV₁, FEV₁/FVC or TLCO amongst these Study members, but was associated with higher Raw and lower sGaw.

**Table 3 about here**

Associations between cumulative cannabis and tobacco smoking and spirometric lung function after adjustment for age 15 spirometry are shown in table 4. Cannabis use was significantly associated with higher values for FVC, but was not significantly associated with FEV₁ or FEV₁/FVC ratios. Tobacco smoking was significantly associated with lower FEV₁ values and with lower FEV₁/FVC ratios. The pattern of findings for cannabis was similar when tobacco smokers were excluded, except that the association between joint-years and FVC was of borderline statistical significance (online table 6).

**Table 4 about here**

**Discussion**

These findings indicate that cannabis is associated with changes in lung function that are independent of the effects of tobacco smoke and appear to be of a different pattern. Both substances were associated with higher values for static lung volumes indicating a tendency to hyperinflation and gas trapping, but although cannabis was associated with increased airway resistance, there was little evidence that it was associated with airflow obstruction (lower FEV₁/FVC ratios) once tobacco consumption had been taken into account. Cannabis
was also not associated with impairment of the total lung transfer factor (TLCO). By contrast, tobacco smoking was associated with both airflow obstruction and lower TLCO but not with airway resistance.

Cannabis was consistently associated with higher lung volumes whether measured as forced vital capacity by spirometry, static lung volumes (TLC, FRC, and RV) by plethysmography, or as alveolar volume by gas (methane) dilution. This consistency suggests that the findings are unlikely to be an artefact of measurement technique. Moreover, cannabis use was associated with higher values for FVC at age 32 in the analyses that adjusted for FVC at age 15. It is notable that although cannabis was not significantly associated with lower TLCO, the higher values for alveolar volume meant that the transfer factor per unit of alveolar volume (TLCO /VA) was lower in cannabis smokers. The clinical relevance of this is uncertain.

The pattern of lung function changes with cannabis is consistent with a recent report by Aldington et al who compared lung function tests and CT scan findings in a convenience sample of volunteers who were smokers of either cannabis, tobacco, both or neither.[15] They found that cannabis was associated with hyperinflation on both lung function tests and CT scans but that there was little evidence of emphysema. Aldington et al also found that cannabis smokers had evidence of airflow obstruction measured by the FEV1/FVC ratio, although this was of marginal statistical significance and less obvious than in tobacco smokers. In our analysis and in an earlier report from the Dunedin cohort (up to age 26) we also found an association between cannabis smoking and lower FEV1/FVC ratios, which was of borderline significance after adjusting for tobacco use.[24] These findings are in keeping with those of a recent meta-analysis which found no consistent association between long-term cannabis use and airflow obstruction.[5]
Our findings also confirm two previous reports of decreased specific airway conductance (sGaw) in cannabis users and indicate that cannabis impacts on large airway function despite having little effect on the FEV₁/FVC ratio.[15, 25] This finding is not explained by the increase in lung volumes (and therefore the thoracic gas volume used to calculate sGaw) amongst cannabis smokers since cannabis was also associated with increased airway resistance (Raw) without adjustment for lung volume. This observation is compatible with the high prevalence of bronchitic symptoms and evidence of bronchial epithelial injury amongst cannabis smokers.[3, 4] Although increased airway resistance may plausibly contribute to hyperinflation, the increased airway resistance amongst cannabis users did not appear to explain the higher lung volumes: adjusting for Raw made no material difference to the association between cannabis and lung volumes (data not shown).

Considered separately, cannabis and tobacco smoking were associated with a broader range of lung function findings because most smokers used both substances (online supplement: tables 3 and 4). One potential problem with the combined cannabis-tobacco analyses is whether the regression analyses adequately adjust for the confounding influence of tobacco smoking when assessing the associations with cannabis. The analyses were therefore repeated amongst those with no tobacco smoking history. Although these analyses also excluded most of the heavy users of cannabis and had smaller sample sizes, the pattern of findings was similar. Amongst non-tobacco smokers, cannabis was significantly associated with higher values for TLC, Raw, and VA, lower values for sGaw, and with non-significant trends to higher values for FVC and RV. There was no significant association with the FEV₁, FEV₁/FVC ratio or TLCO (table 4).
Why smoking cannabis might have different effects on lung function from tobacco is unclear. We found that although both substances were associated with increased lung volumes, there was little evidence of airflow obstruction or reduced gas transfer with cannabis use. It is possible that the participants had simply not smoked enough cannabis for it to have a measurable effect on lung function, but this seems unlikely in view of the evidence for increased lung volumes and airway resistance. Apart from the active ingredients of cannabinoids and nicotine, the inhaled combustion products in cannabis and tobacco smoke are qualitatively similar,[7] although cannabis smokers may inhale more tar per cigarette/joint.[8-10] One possibility is that delta-9-tetrahydrocannabinol, which is known to act as a short-term bronchodilator,[5] also has long-term biological effects. Another possibility is that differences are due to the technique of smoking cannabis. Cannabis smokers tend to inhale more deeply and hold their breath for longer than tobacco smokers.[8] It is plausible that this alters the distribution of smoke throughout the lungs and thereby alters the associated physiological effects on lung function. Alternatively, it is possible that some of the findings are due to the repeated deep inhalation and breath-holding techniques themselves.

This study has a number of limitations. Cannabis use was reported for the previous year at the four assessments, rather than for all of the intervening years. Our joint-years variable assumes that the consumption of cannabis was similar for the intervening years. We do not know how much cannabis was used on each occasion or whether the cannabis joints were smoked directly or through a device such as a bong/water pipe. By comparison, tobacco smoking histories were taken for all years of the assessment period, cigarettes tend to vary less in tobacco content,[15] and the practice of smoking tobacco through devices such as a bong is very unusual. Hence the measure of cannabis exposure may be less accurate than that of
tobacco, although this measurement error is unlikely to have biased the findings with respect to lung function. Errors in cannabis and tobacco consumption will also have occurred because if data were missing for an assessment, we used the amount reported at the next assessment for the calculation of joint- and pack-years. However, repeating the analysis after excluding those with missing data provided very similar findings. It is also possible that Study members were less honest in reporting cannabis use than tobacco use, because it is an illegal substance. However, self-reports of cannabis use correlate well with biological markers of use,[26] and our well-established record of confidentiality and non-intervention over 30 years of the lives of the Study members tends to encourage frank reports of these behaviours. We cannot rule out the possibility that some smokers mixed cannabis with tobacco in the same joint. Although this is not a common practice in New Zealand,[15] any mixing of the two substances is most likely to have obscured the differences in the pattern of lung function changes between the two and is unlikely to explain our findings.

The study also has a number of strengths. Both cannabis and tobacco smoking were assessed on a number of occasions throughout early adult life in a population-based cohort with minimal loss to follow-up. We have a comprehensive assessment of lung function at age 32, and, although plethysmography was only performed at the most recent assessment, we have measurements of spirometry pre-dating the exposure to cannabis and tobacco to investigate whether baseline lung function influenced the propensity to smoke (e.g. a “healthy smoker” effect). This analysis provided no evidence for an association between spirometry at age 15 and subsequent use of tobacco or cannabis.

In conclusion, cannabis and tobacco smoking are each associated with a distinct pattern of lung function changes in young adults. Cannabis was associated with evidence of
hyperinflation and increased large airway resistance, with little evidence of airflow obstruction or impairment of gas transfer, whereas tobacco was associated with airflow obstruction, gas-trapping and lower transfer factors. These findings suggest that smoking cannabis and tobacco have different physiological consequences for the lungs.
Acknowledgements

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References


Table 1  Cumulative cannabis and tobacco use up to age 32

\[ \chi^2 (4) = 242, \ p<0.001. \]

<table>
<thead>
<tr>
<th>Tobacco (pack-years)</th>
<th>Cannabis (joint-years)</th>
<th>Nil</th>
<th>Up to 1</th>
<th>More than 1</th>
<th>Total</th>
</tr>
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<tr>
<td>Nil</td>
<td>226</td>
<td>208</td>
<td>40</td>
<td>474 (49.0%)</td>
<td></td>
</tr>
<tr>
<td>Up to 10</td>
<td>35</td>
<td>171</td>
<td>72</td>
<td>278 (28.8%)</td>
<td></td>
</tr>
<tr>
<td>More than 10</td>
<td>23</td>
<td>82</td>
<td>110</td>
<td>215 (22.2%)</td>
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<tr>
<td>Total</td>
<td>284 (29.4%)</td>
<td>461 (47.7%)</td>
<td>222 (23.0%)</td>
<td>967</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Associations of cannabis and tobacco use with lung function at age 32

Linear regression analyses of lung function at age 32 using both cannabis and tobacco exposures as predictors. All analyses adjust for sex and, except for FEV$_1$/FVC and sGaw, for height. Analyses of TLCO also adjust for exhaled carbon monoxide and blood haemoglobin. Coefficients represent the difference in lung function associated with each joint-year of cannabis or pack-year of tobacco up to age 32, adjusted for use of the other substance.

<table>
<thead>
<tr>
<th></th>
<th>Cannabis</th>
<th></th>
<th>Tobacco</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Coeff.</td>
<td>95% CI</td>
<td>p</td>
</tr>
<tr>
<td>FEV$_1$ (mL)</td>
<td>919</td>
<td>4.0</td>
<td>-3.7 to 11.8</td>
<td>0.311</td>
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<tr>
<td>FVC (mL)</td>
<td>919</td>
<td>12.0</td>
<td>3.0 to 21.0</td>
<td>0.009</td>
</tr>
<tr>
<td>FEV$_1$/FVC (%)</td>
<td>919</td>
<td>-0.08</td>
<td>-0.18 to 0.02</td>
<td>0.127</td>
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<tr>
<td>TLC (mL)</td>
<td>883</td>
<td>25.0</td>
<td>13.9 to 36.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FRC (mL)</td>
<td>884</td>
<td>15.1</td>
<td>4.8 to 25.4</td>
<td>0.004</td>
</tr>
<tr>
<td>RV (mL)</td>
<td>883</td>
<td>12.6</td>
<td>7.0 to 18.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Raw (cmH$_2$O/L/s)</td>
<td>884</td>
<td>0.014</td>
<td>0.002 to 0.026</td>
<td>0.024</td>
</tr>
<tr>
<td>sGaw (mL/cmH$_2$O/L)</td>
<td>884</td>
<td>-3.3</td>
<td>-5.5 to -1.0</td>
<td>0.005</td>
</tr>
<tr>
<td>TLCO (mL/min/mmHg)</td>
<td>841</td>
<td>-0.019</td>
<td>-0.09 to 0.05</td>
<td>0.589</td>
</tr>
<tr>
<td>TLCO/VA (mL/min/mmHg/L)</td>
<td>841</td>
<td>-0.016</td>
<td>-0.03 to -0.01</td>
<td>0.003</td>
</tr>
<tr>
<td>VA (mL)</td>
<td>894</td>
<td>17.8</td>
<td>6.8 to 28.9</td>
<td>0.002</td>
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</table>
Table 3. Association of cannabis use with lung function at age 32 amongst non-tobacco smokers

Linear regression analyses of lung function at age 32 using cannabis exposure as the predictor. Analyses are restricted to those without a tobacco smoking history. All analyses adjust for sex and, except for FEV$_1$/FVC and sGaw, for height. Analyses of TLCO also adjust for exhaled carbon monoxide and blood haemoglobin. Coefficients represent the difference in lung function associated with each joint-year of cannabis up to age 32.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>p</th>
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<tr>
<td>FEV$_1$ (mL)</td>
<td>449</td>
<td>1.5</td>
<td>-16.0 to 19.0</td>
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<tr>
<td>FVC (mL)</td>
<td>449</td>
<td>17.5</td>
<td>-2.5 to 37.4</td>
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<td>FEV$_1$/FVC (%)</td>
<td>449</td>
<td>-0.19</td>
<td>-0.42 to 0.04</td>
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<tr>
<td>TLC (mL)</td>
<td>433</td>
<td>33.5</td>
<td>9.9 to 57.1</td>
<td>0.006</td>
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<tr>
<td>FRC (mL)</td>
<td>434</td>
<td>8.1</td>
<td>-13.1 to 29.4</td>
<td>0.452</td>
</tr>
<tr>
<td>RV (mL)</td>
<td>433</td>
<td>12.0</td>
<td>-0.3 to 24.4</td>
<td>0.057</td>
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<tr>
<td>Raw (cmH$_2$O/L/s)</td>
<td>434</td>
<td>0.029</td>
<td>0.001 to 0.057</td>
<td>0.042</td>
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<tr>
<td>sGaw (mL/s/cmH$_2$O/L)</td>
<td>434</td>
<td>-6.7</td>
<td>-11.8 to -1.7</td>
<td>0.010</td>
</tr>
<tr>
<td>TLCO (mL/min/mmHg)</td>
<td>418</td>
<td>0.032</td>
<td>-0.114 to 0.178</td>
<td>0.662</td>
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<tr>
<td>TLCO/VA (mL/min/mmHg/L)</td>
<td>418</td>
<td>-0.019</td>
<td>-0.042 to 0.004</td>
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<tr>
<td>VA (mL)</td>
<td>438</td>
<td>28.5</td>
<td>4.3 to 52.7</td>
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### Table 4. Longitudinal analyses of cannabis and tobacco exposure with spirometric lung function.

Linear regression analyses of lung function at age 32 using both cannabis and tobacco smoking as predictors, adjusted for lung function at age 15. Analyses also adjust for sex, height, change in height between age 15 and 32, and current asthma at age 32. Coefficients represent the difference in lung function at age 32 associated with each joint-year of cannabis or pack-year of tobacco up to age 32, adjusted for the use of the other substance.

<table>
<thead>
<tr>
<th></th>
<th>Cannabis</th>
<th></th>
<th>Tobacco</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Coeff.</td>
<td>95% CI</td>
<td>p</td>
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<tr>
<td>FEV₁ (mL)</td>
<td>779</td>
<td>4.4</td>
<td>-1.4 to 10.3</td>
<td>0.137</td>
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<tr>
<td>FVC (mL)</td>
<td>779</td>
<td>10.7</td>
<td>3.9 to 17.5</td>
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<td>FEV₁/FVC (%)</td>
<td>779</td>
<td>-0.07</td>
<td>-0.14 to 0.01</td>
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