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EDITORIAL

Does cannabis use predispose to chronic airflow obstruction?

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Cannabis (derived from the ubiquitous plant, *Cannabis sativa*, and also known as marijuana) is the most widely used illicit drug worldwide, as well as the second most commonly smoked substance after tobacco, with an estimated 166 million users (3.9% of 15–64 yr olds) [1]. Its wide popularity is due to the euphoric effects of its major psychoactive ingredient, Δ^9-tetrahydrocannabinol (THC). Since the gas and particulate phase constituents of the smoke of marijuana are at least qualitatively similar to those of tobacco, the major exception being the nicotine in tobacco and the ~60 cannabinoid (THC-like) components in marijuana [2, 3], there has long been concern that regular smoking of marijuana might increase the risk of developing chronic airflow obstruction and chronic obstructive pulmonary disease (COPD), by analogy with the well-known detrimental effects of tobacco. Several studies have documented that smokers of marijuana, even in the absence of tobacco smoking, show a higher prevalence of symptoms of chronic bronchitis than nonsmokers [4–7]. However, the association between marijuana smoking and airflow obstruction is less clear. Several groups of investigators have addressed the latter question by measuring lung function in convenience samples or stratified random population samples of users and nonusers of marijuana and/or tobacco both cross-sectionally [4–6, 8–10] and longitudinally [11–13]. The most recent study of the possible association of marijuana use with lung function abnormality appears in this issue of the *European Respiratory Journal* [14].

Previously published studies have yielded conflicting results relating to marijuana use and lung function. An early cross-sectional study of 74 young (mean age 24 yrs) habitual marijuana smokers showed no differences in either spirometric indices or sensitive measures of small airways function (closing volume or percentage change in nitrogen concentration between 750 and 1,250 mL of expired volume ($\Delta N_{2750–1250}$)) among marijuana users compared with non-marijuana smoking controls matched on age and tobacco smoking [8]. Interestingly, however, the 50 non-tobacco-smoking marijuana smokers (MSs) exhibited airway resistances (R_{aw}) that were modestly (28%) but significantly ($p<0.001$) higher than R_{aw} among both nonsmoker (NS) and tobacco smoker (TS) controls; similar differences were noted for specific airway conductance (sG_{aw}). These findings suggested that marijuana smoking may cause mild, but significant, narrowing of larger airways not detectable in similarly aged tobacco smokers, but no demonstrable abnormality involving the smaller airways. A later cross-sectional study by the same authors in a Los Angeles convenience sample of young (mean age 34 yrs) heavy MSs (n=144), smokers of both marijuana and tobacco (MTSs; n=135), TSs (n=79) and NSs (n=97) showed similar results [4], *i.e.* no abnormalities in spirometric or small airways indices (closing volume, $\Delta N_{2750–1250}$ or measures derived from flow–volume curves obtained with air and a helium–oxygen mixture) among the MSs in contrast to modest-but-significant abnormalities in the TSs and MTSs. In addition, in accord with the previous findings was a modest-but-significant increase in R_{aw} and decrease in sG_{aw} in the MSs but not the TSs compared to the NSs. A decrement in diffusing capacity was noted in the TSs but not the MSs.

Reports from other investigators, however, have revealed somewhat contradictory results. Data from the Tucson epidemiological study showed a small-but-significant decrement in expiratory flow rates at low lung volumes and in forced expiratory volume in 1 s (FEV_1)/vital capacity (VC) in young (age 27 yrs) male MSs that was even greater than the decrement noted in the same measures in the TSs, despite the fact that these MSs smoked marijuana less heavily than those in the Los Angeles cohort [5]. A later study from Dunedin, New Zealand, in a birth cohort of 943 young adults (age 21 yrs) showed that a significantly higher proportion (36%) of cannabis-dependent subjects (n=28) who did not use tobacco had an FEV_1/forced vital capacity (FVC) ratio of <80% compared to the proportion (20%) of NSs (n=577) ($p<0.04$) [6]. Moreover, the proportion of cannabis-dependent individuals with a ratio of <80% was numerically higher than that of the TSs. Conversely, in a convenience sample (mean age 43 yrs) from Wellington, New Zealand, of 75 MSs, 91 MTsS, 92 TSs and 81 NSs, tobacco but not marijuana was associated with decrements in FEV_1 and forced expiratory flow between 25 and 75% of VC, whereas both marijuana and tobacco smoking were associated with a reduction in FEV_1/FVC ratio, although the effect of marijuana was of only marginal significance [9]. Interestingly, the latter authors also found that marijuana increased total lung capacity to a marginally significant extent, whereas tobacco did not. Moreover, as in the Los Angeles study, tobacco, but not marijuana, reduced the diffusing capacity. In addition, high-resolution computed tomography, also performed in the Wellington study, demonstrated evidence of macroscopic emphysema in the tobacco smokers but not marijuana smokers, although a higher proportion of low-attenuation lung tissue was noted in the apical slices from the marijuana smokers [9].

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Findings different from those cited above have been reported by other authors. Using data from a nationally representative sample of the US population who participated in the Third National Health and Nutrition Examination Survey (NHANES III) between 1988 and 1994, of whom 4,789 were nonsmokers (mean age 35 yrs), 414 reported smoking marijuana (mean age 31 yrs) and 1,525 tobacco (mean age 41 yrs), MOORE *et al.* [7] reported that the odds ratio (95% confidence interval (CI)) for having an FEV1/FVC ratio of <70% was 1.01 (0.51–1.94) for the marijuana users (p=0.99) in contrast to 4.17 (3.03–5.88) for the tobacco smokers (p<0.001), after adjustment for sex, age and smoking other substances. In a separate random Canadian sample of 878 people aged ⩾40 yrs residing in Vancouver who participated in a survey to assess the prevalence of COPD defined by spirometric criteria [10], 124 participants reported having smoked >50 marijuana cigarettes in their lifetime and 89 were smoking marijuana currently. The post-bronchodilator FEV1 exceeded 100% of the predicted value in the marijuana smokers and was significantly higher in these subjects than among the nonusers (p<0.001). FVC was also significantly higher in the marijuana users (p<0.001).

Taken together, therefore, the available data on the association between marijuana use and lung function abnormality derived from cross-sectional studies reveal disparities that could conceivably be due to differences in potentially confounding variables in the different populations sampled, although adjustment for the major potential confounder, namely tobacco use, was made in all of the studies. In view of these conflicting results from cross-sectional studies, it is worthwhile considering findings from longitudinal studies. SHERRILL *et al.* [11] conducted a longitudinal analysis of lung function based on data from 856 subjects from the Tucson cohort who were tested in at least two of four surveys conducted from 1981–1983 to 1985–1988. The authors found that FEV1/FVC, FEV1 and maximal expiratory flow after exhalation of 50% of FVC ($\dot{V}'_{E,max,50}$) were significantly reduced in subjects reporting marijuana smoking in at least one previous survey. The estimated decrement in FEV1 due to marijuana smoking reported in a previous survey was 142 mL, which was twice as large as the estimated decrement due to current tobacco smoking. What is confusing about this study is that a longitudinal analysis based on data from 1,239 subjects tested in at least one of the four surveys indicated that FEV1/FVC and $\dot{V}'_{E,max,50}$ were not significantly reduced in the marijuana smokers and that FEV1 was even 58 mL higher in the current marijuana smokers than in the other subjects. In a Los Angeles longitudinal study in which lung function was measured on up to seven occasions at intervals of ⩾1 yr over a period of 8 yrs in 255 subjects who were NSs, MSs, TSs or MTSs, mean rates of decline in FEV1 were estimated using random-effects models [12]. The results revealed an annual rate of decline in FEV1 in the MSs (30.8 mL·yr^{-1}) that was similar to that of the NSs (25.3 mL·yr^{-1}) and significantly lower (p<0.05) than that of the TSs (56.5 mL·yr^{-1}). Moreover, when the amount of marijuana use was entered into the model, no difference in the slope of decline in FEV1 was noted in smokers of 3 joints·day^{-1} (33.4 mL·yr^{-1}) compared to no marijuana (33.6 mL·yr^{-1}), whereas a clear dose–response effect was noted for tobacco (46.3 mL·yr^{-1} for 27 cigarettes·day^{-1} *versus* 40.4 mL·yr^{-1} for 18 cigarettes·day^{-1} and 28.5 mL·yr^{-1} for no tobacco). A third study also made longitudinal observations over a period of 8 yrs (age 18–26 yrs) in a birth cohort of young users and nonusers of marijuana and/or tobacco [13]. This study used a fixed-effects regression model and stratified the sample for cumulative use of marijuana, adjusting for confounding factors, such as tobacco. In the adjusted model, only a marginally significant dose-dependent relationship was observed between cumulative marijuana use and decline in FEV1/VC, although results for other independent lung function variables, such as FEV1 and VC, were not reported. Thus the available longitudinal studies replicate the inconsistencies observed in the cross-sectional studies.

The article by HANCOX *et al.* [14] in this issue of the *European Respiratory Journal* is the latest study to address the question of whether marijuana use leads to chronic airflow obstruction. This study is an extension of a previously reported study [13] in the same cohort that examined the associations between smoking marijuana or tobacco and various pulmonary function tests in a large birth cohort followed from age 15 to 32 yrs. The current report includes plethysmographically measured lung volumes that had not been measured during the earlier surveys in the same birth cohort. These new measurements reveal modest-but-significant elevations in lung volumes (FVC, functional residual capacity, total lung capacity and residual volume) in association with marijuana. Although the mechanism of the marijuana-associated hyperinflation is unclear, it is unlikely to be related to early emphysema in view of the absence of any observed abnormality in diffusing capacity of the lung for carbon monoxide, in contrast to the findings associated with tobacco use. It might be speculated that the hyperinflation could be related to the deep inspiratory capacity manoeuvres that marijuana users customarily perform in smoking marijuana, compared to the much lower inhaled volumes that routinely accompany tobacco smoking [15]. Such repeated deep inhalations could conceivably stretch the lung and lead to enlarged lung volumes, with a reduced lung elastic recoil.

Furthermore, in contrast to the previously reported finding of a reduced FEV1/FVC ratio in the same cohort in association with increasing marijuana use [13], the current analysis at an older age of the cohort fails to show a significant association of FEV1/FVC ratio with marijuana use when adjusted for concomitant tobacco use, nor is there any suggestion of a reduction in FEV1 itself in association with marijuana (indeed, the reverse seems to be suggested). In addition, previous findings from other studies of a reduced FEV1/FVC are probably attributable to an elevated FVC, rather than a reduced FEV1, thus possibly resolving some of the inconsistencies regarding the FEV1/FVC ratio in earlier reports.

Finally, sGaw was reduced in association with cannabis, as has been reported previously [4, 8, 9], but here the explanation is not entirely due to the elevated alveolar volume since *R*aw was modestly but significantly elevated. The reduced sGaw and increased *R*aw are consistent with previous observations of mucosal oedema, congestion and increased secretions in the central airways of habitual smokers of marijuana during bronchoscopy [16], and presumably related to large airway injury and inflammation induced by the smoke of marijuana. Why similar changes do not appear to occur in the smaller airways leading to chronic airflow obstruction in habitual marijuana smokers is unclear, but might possibly be related to

the anti-inflammatory and immunosuppressive effects of THC, including its inhibition of alveolar macrophage function [17].

In summary, the weight of evidence does not suggest an independent effect of marijuana smoking on airway dynamics, nor is there evidence of an interaction between marijuana and tobacco, suggesting that smoking marijuana of itself does not lead to COPD. Conversely, marijuana use appears to lead to a modest degree of hyperinflation neither the mechanism nor the clinical significance of which is clear. It is possible, however, that the hyperinflation may have played a role in some of the instances of spontaneous pneumothorax and/or pneumomediastinum and of the peripheral apical lung bullae that have been reported in isolated cases of marijuana smokers (reviewed in [18]).

Since lung cancer, like COPD, is largely attributable to tobacco smoking and marijuana tar contains more of some carcinogens, including the highly carcinogenic aromatic polycyclic hydrocarbon, benzo[a]pyrene, than does the tar from tobacco [2, 3], a related question with important public health implications is whether marijuana, like tobacco, is a risk factor for lung cancer. A review of the evidence relating to this question in 2005 concluded that insufficient data were available from which to come to definitive conclusions [18]. Subsequently, two carefully designed prospective case–control studies have been published specifically addressing this issue [19, 20]. The first of these, a large-scale study that included 611 lung cancer cases and 1,040 matched controls, of whom 183 cases and 112 controls reported a heavy history of marijuana smoking, failed to show any association between marijuana use and lung cancer with odds ratios after adjustment for potential confounders ranging 0.60–0.94 for various levels of marijuana use [19]. In contrast, the second study, which included only 79 cases and 324 controls, of whom only 14 cases and four controls had a history of heavy cannabis use, reported an adjusted risk ratio of 5.7 (95% CI 1.5–21.6) for the heaviest tertile of cannabis users [20]. In the same study, however, the lower two tertiles of cannabis use were associated with risk ratios of only 0.3 (0.5–2.6) and 0.9 (0.3–2.9). Although the latter authors concluded that marijuana smoking was associated with an increased risk of lung cancer (8% increased risk for each joint-yr of marijuana smoking, equivalent to only 365 lifetime joints, compared to 7% increased risk for each pack-yr of tobacco smoking, equivalent to 7,300 lifetime tobacco cigarettes), the possibility should be considered, when assessed in conjunction with the clearly negative results of the earlier and larger-scale study, that the small sample size led to inflated risk estimates. Thus the possible relationship between marijuana use and lung cancer remains unclear.

STATEMENT OF INTEREST

None declared.

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