The effects of marijuana smoking on lung function in older people

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Prolonged heavy marijuana smoking increases the risk of COPD and accelerates FEV_1 decline in concomitant tobacco cigarette smokers beyond the effects of tobacco alone http://bit.ly/2lI2lEu

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ABSTRACT

Background: Previous studies have associated marijuana exposure with increased respiratory symptoms and chronic bronchitis among long-term cannabis smokers. The long-term effects of smoked marijuana on lung function remain unclear.

Methods: We determined the association of marijuana smoking with the risk of spirometrically defined chronic obstructive pulmonary disease (COPD) (post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio <0.7) in 5291 population-based individuals and the rate of decline in FEV_1 in a subset of 1285 males and females, aged ⩾40 years, who self-reported use (or non-use) of marijuana and tobacco cigarettes and performed spirometry before and after inhaled bronchodilator on multiple occasions. Analysis for the decline in FEV_1 was performed using random mixed effects regression models adjusted for age, sex and body mass index. Heavy tobacco smoking and marijunana smoking was defined as >20 pack-years and >20 joint-years, respectively.

Results: ∼20% of participants had been or were current marijuana smokers with most having smoked tobacco cigarettes in addition (83%). Among heavy marijuana users, the risk of COPD was significantly increased (adjusted OR 2.45, 95% CI 1.55–3.88). Compared to never-smokers of marijuana and tobacco, heavy marijuana smokers and heavy tobacco smokers experienced a faster decline in FEV_1 by 29.5 mL·year^{-1} (p=0.0007) and 21.1 mL·year^{-1} (p<0.0001), respectively. Those who smoked both substances experienced a decline of 32.31 mL·year^{-1} (p<0.0001).

Interpretation: Heavy marijuana smoking increases the risk of COPD and accelerates FEV_1 decline in concomitant tobacco smokers beyond that observed with tobacco alone.

Introduction

Marijuana is the second most common substance smoked in the world after tobacco [1], and the most common illicit drug used by the older population in the United States [2]. Concerns regarding the respiratory effects of marijuana smoking are based on the fact that marijuana and tobacco are qualitatively similar, with the exception of the active ingredients, δ-9-tetrahydro-cannabinol and other cannabinoids in marijuana and nicotine in tobacco.

The harmful respiratory effects of tobacco are well characterised [3], but comparable data for marijuana are not available [4]. Most epidemiological studies support an increased association between marijuana smoking and chronic respiratory symptoms [5], but the effects on lung function remain unclear. Some cross-sectional studies [6–9] have demonstrated that marijuana smoking was associated with a decrease in forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio and isolated impaired large airway function as indicated by specific airway conductance, while other studies have failed to find such an association [10, 11], with three reporting an increase in FVC [9, 12, 13]. To date, longitudinal studies [12, 14–17] have also shown conflicting results: no accelerated decline in FEV_1 in a convenience sample of heavy smokers [16]; a suggestion of gas trapping in a population cohort [12]; a possible reduction in FEV_1 or FEV_1/FVC ratio associated with high levels of marijuana smoking [14, 15]; and a paradoxical increase in FEV_1 in current marijuana smokers in a study of four consecutive surveys of non-tobacco smokers assumed to be marijuana smokers [17].

In this study, we analysed cross-sectional [18] and longitudinal data from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study consisting of males and females, aged 40–85 years [19] to investigate the association of marijuana smoking with the risk of chronic obstructive pulmonary disease (COPD) and the decline in lung function over time.

Methods

Study design and participants

Written informed consent was obtained from all participants in this multicentre study (nine sites in six Canadian provinces), which was approved by the institutional review boards of each site. Briefly, the study comprised two phases: an initial cross-sectional component called the Canadian Obstructive Lung Disease (COLD) study, which was a population-based prevalence study that recruited a random sample of 5291 participants aged ⩾40 years from nine Canadian urban sites [18, 20]; and a subsequent longitudinal phase (CanCOLD study), which comprised a subset of 1285 participants who were assessed every 18 months [19]. These participants were derived from the COLD cross-sectional cohort and consisted of individuals with COPD (defined as post-bronchodilator FEV_1/FVC ratio <0.7) and approximately equal number of age- and sex-matched never-smokers and ever-smokers who demonstrated normal lung function. Full details of the longitudinal phase of the study have been published elsewhere [19, 21, 22]. Data from both the cross-sectional and longitudinal phases of the study were collected between August 2005 and January 2017, with 80% retention rate of the longitudinal cohort at the end of January 2017. The study was registered with ClinicalTrials.gov identifier NCT00920348.

Procedures and definitions

At each visit, participants answered structured questionnaires on respiratory symptoms, self-reported doctor diagnosis of respiratory diseases, and smoking of tobacco and marijuana (the marijuana smoking questionnaire can be found in the supplementary material). Study definitions were as follows. Tobacco smokers if participants had smoked ⩾365 cigarettes in a lifetime [23] and marijuana smokers if they had smoked ⩾50 joints in a lifetime [10]. Cumulative marijuana exposure was quantified as "joint-years" (number of joints smoked per day multiplied by years) [7, 14]. Cumulative tobacco exposure was quantified as "pack-years" (number of packs of cigarettes (20 per pack) smoked per day multiplied by years) [14]. Chronic cough, chronic phlegm, wheeze and dyspnoea were defined as in previous publications [10, 18, 23, 24].

Smoking patterns were defined as marijuana-only, tobacco-only, both marijuana and tobacco (MT) and never-smokers of both marijuana and tobacco. Current smokers were defined as those smoking at the time of the interview and former smokers as those who had quit smoking at the time of the interview. Based on the findings from a previous longitudinal study [14], the associations between smoking exposures and lung

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function were stratified based on levels of exposure (mild 1–5, moderate >5–20, heavy >20) in joint-years or pack-years marijuana or tobacco use, respectively.

All participants performed spirometry testing using an EasyOne spirometer (ndd Medical Technologies, Andover, MA, USA) before and 15 min after inhalation of 200 μg albuterol [25] according to the American Thoracic Society guidelines [26].

Statistical analyses

The cross-sectional data from 5291 participants were utilised to evaluate the relationship of marijuana smoking or tobacco smoking with the risk of COPD (post-bronchodilator FEV_1/FVC <0.7) [27] using multivariable logistic regression analyses. A separate model was constructed for each of the subgroups of marijuana smokers and tobacco smokers, controlling for pack-years or joint-years, respectively, and for age, sex and body mass index (BMI). The adjusted odds ratios (aORs) and 95% confidence intervals were computed for each level of marijuana or tobacco exposure. The reference category for all analyses was never-smokers. Linear relationships across the smoking categories were assessed using a Cochran–Armitage test of trend.

A linear random mixed effects model was used [16, 28] on the longitudinal data to estimate the declines in FEV_1 over time (details in supplementary material). Separate models were constructed for marijuana smoking (controlling for pack-years) and tobacco smoking (controlling for joint-years). The predictor variable was marijuana or tobacco exposure defined at baseline by joint-year or pack-year cut-offs; the outcome variable was decline in FEV_1 over time ($mL \cdot year^{-1}$), controlling for potential confounding variables which included BMI, follow-up time, sex, baseline FEV_1 and baseline age (more details in supplementary material). Current and former smoking status was similarly examined in heavy marijuana smokers (>20 joint-years) and heavy tobacco smokers (>20 pack-years). In a sensitivity analysis, we directly compared the change over time across the different strata of tobacco smoking exposure, segregating the data on whether or not there was concurrent marijuana smoking.

The assumptions of the linear mixed effect models were checked to ensure the validity of the model (details in supplementary material). The Akaike information criterion [29] was used for testing the goodness of fit and model selection for the regression methods. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The cross-sectional data (COLD) included 5291 participants with information on marijuana and tobacco smoking and the longitudinal data (CanCOLD) included 1285 participants (details for each visit are shown in the flow diagram in supplementary figure E1 and table E1). The baseline characteristics of the participants in COLD and CanCOLD stratified by smoking habits are summarised as univariate descriptive statistics in tables 1 and 2, respectively. Compared with the COLD cohort, the CanCOLD cohort contained older individuals (median age 65 years *versus* 59 years), more males and more tobacco smokers (supplementary table E1). The median duration of follow-up in the CanCOLD cohort was 5.9 (interquartile range (IQR) 4.9–6.7) years and range 2.5–10.5 years.

The frequencies of tobacco and marijuana smoking were similar in the COLD and CanCOLD cohorts: 36% were tobacco smokers, 3% were marijuana smokers and 17% were smokers of both marijuana and tobacco in COLD, *versus* 44% tobacco smokers, 3% marijuana smokers and 16% smokers of both marijuana and tobacco in CanCOLD. Tobacco-only smokers comprised the majority (69% COLD, 73% CanCOLD) of all tobacco smokers, while marijuana-only smokers comprised a minority of all marijuana smokers (17% COLD, 14% CanCOLD) and 83% and 86% of all marijuana smokers also smoked tobacco in the two cohorts, respectively.

In both cohorts, marijuana smokers were younger, included more males, and were better educated than tobacco smokers. The ages of onset of smoking for marijuana and tobacco smokers were 17–19 years and 15–18 years, respectively. The median durations of marijuana exposure at baseline were the same in the two cohorts (~11 years) while that for tobacco exposure was 26 years in COLD and 33 years in CanCOLD. The cumulative marijuana exposure at baseline in smokers of both marijuana and tobacco was more than twice that in marijuana smokers: mean 17.02 joint-years *versus* 7.23 joint-years in COLD and 16.68 joint-years *versus* 5.45 joint-years in CanCOLD. Current marijuana smokers in CanCOLD smoked more than twice as much as former smokers: mean 25.72 joint-years *versus* 10.40 joint-years.

Cumulative marijuana smoking and FEV_1/FVC ratio

Cumulative marijuana exposure of >20 joint-years controlled for tobacco pack-year exposure was associated with the presence of COPD (post-bronchodilator FEV_1/FVC <0.7) (figure 1a, supplementary

TABLE 1 Baseline demographics and general characteristics of the participants in the initial cross-sectional (Canadian Obstructive Lung Disease (COLD)) cohort stratified into four smoking subgroups

	All participants	NS	T	M	MT
Subjects	5291 (100)	2299 (43)	1926 (36)	181 (3)	885 (17)
Age years	59.0 (50.0–68.0)	59.0 (50.0–68.0)	65.0 (56.0–72.0)*	51.0 (46.0–58.0)*	53.0 (47.0–59.0)*
Male	2443 (46.2)	889 (38.7)	897 (46.6)*	114 (63.0)*	543 (61.4)*
BMI kg·m^{-2}	26.8 (24.0–30.5)	26.5 (23.7–30.1)	27.3 (24.4–31.2)*	25.8 (23.3–29.4)	26.9 (24.0–30.8)*
Education years of school	15.0 (13.0–18.0)	16.0 (14.0–18.0)	14.0 (12.0–17.0)*	17.0 (15.0–19.0)*	15.0 (13.0–17.0)*
Marijuana smoking status					
Current	346 (6.5)			45 (24.9)	301 (34.0)
Former	720 (13.6)			136 (75.1)	584 (66.0)
Joint-years of marijuana				1.6 (0.6–4.7)	4.3 (1.3–12.9)
Years of smoking marijuana				10.0 (4.0–20.0)	12.0 (5.0–36.0)
Age of onset of marijuana smoking	17.0 (15.0–20.0)			18.0 (16.0–20.0)	17.0 (15.0–19.0)
Tobacco smoking status					
Current	726 (13.7)		406 (21.1)		320 (36.2)
Former	2085 (39.4)		1520 (78.9)		565 (63.8)
Pack-years of tobacco			18.8 (6.0–36.0)		22.0 (10.0–36.3)
Years of smoking tobacco			26.0 (14.0–39.0)		27.0 (17.0–36.0)
Age of onset of tobacco smoking			17.0 (15.0–20.0)		16.0 (14.0–18.0)
Post-bronchodilator FEV_1/FVC	76.2 (70.8–80.7)	77.4 (72.6–81.6)	74.7 (67.8–79.6)*	77.4 (73.9–81.5)	75.9 (70.6–80.2)*
>20 joint-years[#]				77.1 (72.9–80.7)	74.0 (67.4–78.6)****
⩽20 joint-years[¶]				77.5 (73.9–81.6)	76.3 (71.3–80.6)****
Post-bronchodilator FEV_1 % pred	95.4 (84.3–105.5)	96.9 (86.8–106.2)	93.2 (80.6–104.7)*	99.0 (90.8–108.4)*	95.0 (84.7–104.4)*
Post-bronchodilator FVC % pred	96.5 (86.9–106.9)	96.4 (87.2–106.0)	95.6 (85.1–107.4)	100.8 (92.1–110.9)*	97.8 (89.5–107.1)*
COPD[+]	1204 (22.8)	361 (15.7)	612 (31.8))*	19 (10.5)	212 (24.0))*
Respiratory symptoms					
Chronic cough	676 (12.8)	215 (9.4)	300 (15.6)*	15 (8.3)	146 (16.5)*
Chronic phlegm	505 (9.5)	145 (6.3)	232 (12.1)*	13 (7.2)	115 (13.0)*
Wheezing	1503 (28.4)	494 (21.5)	590 (30.6)*	50 (27.6)	369 (41.7)*
Dyspnoea mMRC score	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	1.0 (0.0–1.0)	1.0 (1.0–2.0)

Data are presented as n (%) or median (interquartile range). NS: never-smokers of either tobacco or marijuana; T: tobacco smoking only; M: marijuana smoking only; MT: smokers of both marijuana and tobacco; BMI: body mass index; joint-years: number of joints per day×total duration of smoking in years; pack-years: number of packs (20 cigarettes per pack) per day×total duration of smoking in years; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; mMRC: modified Medical Research Council. [#]: n=17 (M), n=168 (MT); [¶]: n=164 (M), n=717 (MT); [+]: the proportion of COPD in any marijuana smoker is 21.7%, and the proportion of COPD in any tobacco smoker is 29.3%. *: significantly different to NS as reference (p<0.05); ****: significantly different to each other (p<0.0001).

table E2). Lower cut-offs of joint-years were not significantly associated, but a trend was found with increasing cumulative marijuana exposure: aOR (95% CI) 1.39 (0.96–2.02) for 1–5 joint-years, 1.28 (0.84–1.95) for >5–20 joint-years and 2.45 (1.55–3.90) for >20 joint-years, with a significant Cochran–Armitage test of trend for increasing marijuana smoked (p<0.0001). The results for cumulative tobacco exposure showed that cumulative tobacco exposure of >5 pack-years was associated with COPD (figure 1b, supplementary table E3). There was a significant interaction between marijuana and tobacco smoking on FEV_1/FVC ratio (p=0.042).

Cumulative marijuana smoking and the longitudinal decline in FEV_1

The results of four separate random mixed-effect models comparing the decline of FEV_1 in marijuana smokers (controlled for tobacco exposure) and tobacco smokers (controlled for marijuana exposure) *versus* never-smokers are summarised as β-coefficients (95% CI and absolute change) in table 3.

For all marijuana smokers with >20 joint-years exposure, the rate of decline in FEV_1 (controlled for tobacco exposure and independent of the presence of COPD) was significantly greater than in never-smokers by, on average 29.6 mL·year^{-1} (absolute decline 40.5 mL·year^{-1}). For all tobacco smokers with >20 pack-years of exposure, the decline in FEV_1 (controlled for marijuana exposure) was significantly greater than that in never-smokers by 21.1 mL·year^{-1} (absolute decline 32.5 mL·year^{-1}) (table 3, figure 2a,b). The declines in FEV_1 for smokers with lower exposures of marijuana or tobacco were not signficant compared with never-smokers. There was a significant interaction between marijuana and tobacco smoking (p<0.0001). FVC declined with a pattern similar to FEV_1 (supplementary table E4).

TABLE 2 Baseline characteristics of the participants in the longitudinal Canadian Cohort Obstructive Lung Disease (CanCOLD) cohort stratified into four smoking subgroups

	All participants	NS	T	M	MT
Subjects	1285	482 (37)	561 (44)	33 (3)	209 (16)
Age years	65.0 (59.0–72.0)	66.0 (59.0–72.0)	68.0 (63.0–74.0)*	53.0 (51.0–60.0)*	58.0 (52.0–63.0)*
Male	712 (55.4)	249 (52.0)	297 (52.9)	23 (69.7)*	143 (68.4)*
BMI kg·m^{-2}	26.8 (24.0–30.4)	26.6 (23.9–29.7)	27.1 (24.4–30.9)*	24.7 (22.4–28.1)	26.5 (23.5–29.9)
Education years of school	16.0 (13.0–18.0)	16.0 (14.0–18.0)	15.0 (12.0–17.0)*	17.0 (15.0–18.0)	16.0 (14.0–18.0)
Follow-up time years	5.9 (4.9–6.7)	6.1 (5.4–7.0)	5.7 (4.1–6.3)*	6.6 (6.0–8.1)	5.4 (3.2–7.3)*
Marijuana smoking status					
Current	91 (7.1)			7 (21.2)	84 (40.2)
Former	151 (11.8)			26 (78.8)	125 (59.8)
Joint-years of marijuana				1.7 (0.7–5.4)	5.3 (1.4–17.1)
Years of smoking marijuana				10.0 (4.0–20.0)	12.0 (5.0–34.0)
Age of onset of marijuana	18.5 (16.0–21.0)			18.0 (16.0–20.0)	19.0 (16.0–21.0)
Tobacco smoking status					
Current	222 (17.3)		134 (23.9)		88 (42.11)
Former	548 (42.7)		427 (76.1)		121 (57.9)
Pack-years of tobacco			23.4 (9.4–41.0)		27.3 (14.1–44.0)
Years of smoking tobacco			33.0 (19.0–43.0)		33.0 (21.0–42.0)
Age of onset of tobacco			18.0 (15.0–20.0)		15.0 (14.0–18.0)
Post-bronchodilator FEV_1/FVC	69.4 (64.3–76.7)	72.4 (66.5–78.3)	68.4 (62.5–75.4)*	74.7 (67.3–79.7)	68.6 (63.1–75.5)*
>20 joint-years[#]				74.7 (65.8–83.6)	63.8 (60.1–70.0)***
⩽20 joint-years[¶]				74.8 (67.3–79.7)	69.6 (64.8–76.5)***
Post-bronchodilator FEV_1 % pred	91.4 (77.6–103.5)	96.0 (83.0–106.6)	87.0 (73.6–100.0)*	97.5 (90.1–105.5)	88.5 (75.7–101.8)*
Post-bronchodilator FVC % pred	97.5 (86.9–109.5)	100.0 (90.0–110.3)	94.7 (83.7–108.1)*	105.6 (92.2–114.0)	97.9 (88.6–109.4)
COPD[+]	659 (54.1)	214 (44.4)	349 (62.2)*	11 (33.3)	121 (57.9)*
Respiratory symptoms					
Chronic cough	199 (15.5)	53 (11.0)	102 (18.2)*	3 (9.1)	41 (19.6)*
Chronic phlegm	160 (12.5)	31 (6.4)	83 (14.8)*	4 (12.1)	42 (20.1)*
Wheezing	415 (32.3)	110 (22.8)	196 (34.9)*	9 (27.3)	100 (47.9)*
Dyspnoea mMRC score	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.0 (1.0–2.0)

Data are presented as n, median (interquartile range) or n (%). NS: never-smokers of either tobacco or marijuana; T: tobacco smoking only; M: marijuana smoking only; MT: smokers of both marijuana and tobacco; BMI: body mass index; follow-up time: baseline to last visit for each individual; joint-years: number of joints per day×total duration of smoking in years; pack-years: number of packs (20 cigarettes per pack) per day×total duration of smoking in years; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; mMRC: modified Medical Research Council. [#]: n=3 (M), n=48 (MT); [¶]: n=30 (M), n=161 (MT); [+]: the proportion of COPD in any marijuana smoker is 54.5%, and the proportion of COPD in any tobacco smoker is 61.0%. *: significantly different to NT as reference (p<0.05); ***: significantly different to each other (p=0.001).

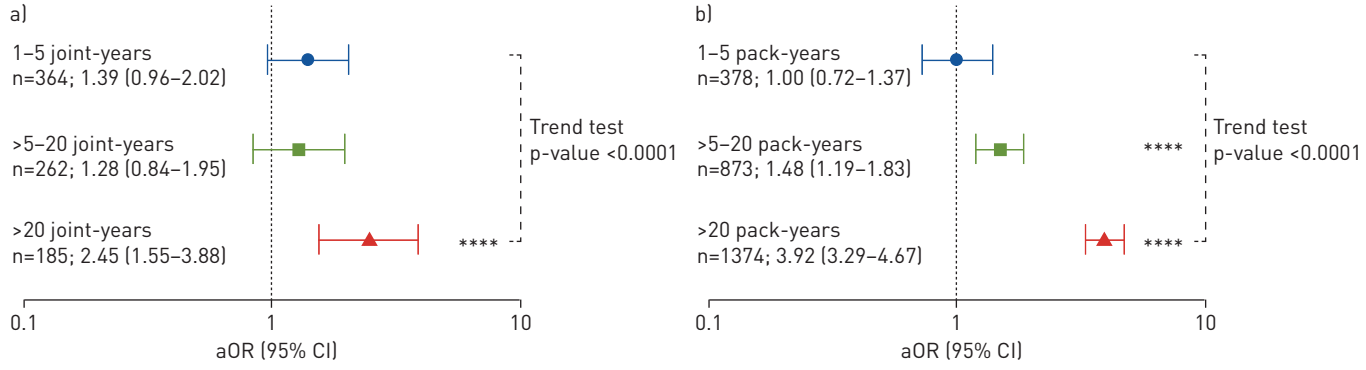

FIGURE 1 Adjusted odds ratios (aORs) with 95% confidence interval for association of a) cumulative marijuana exposures by three joint-years cut-offs (1–5, >5–20, >20), b) cumulative tobacco exposures by three pack-years cut-offs (1–5, >5–20, >20), with presence of chronic obstructive pulmonary disease (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity ratio <0.7). The aORs and 95% confidence intervals for the lowest exposure subgroup for marijuana >0 and <1 (n=253) and for tobacco >0 and <1 (n=124) are not significant and not shown in the figures, but values are in supplementary tables E2 and E3. The aORs were adjusted for a) age, sex, body mass index and pack-years or b) joint-years. A potential trend was evaluated using a Cochran–Armitage test of trend. ****: p<0.0001.

TABLE 3 Results from mixed-effects regression models for marijuana smokers and tobacco smokers showing the longitudinal lung function decline (adjusted for pack-years or joint-years and other covariates) shown as rate of change in forced expiratory volume in 1 s (FEV_1)

Predictor variables	Subjects n	Rate of change in FEV_1 mL·year^{-1}	
		β-coefficient (95% CI)	Absolute change
Model 1			
Never-smokers (reference)	482	−10.75	−10.75
Marijuana smoking joint-years groups			
>0–1	56	−7.28 (−17.95–3.40)	−18.03
>1–5	72	−16.51 (−33.18–0.17)	−27.26
>5–20	63	2.12 (−9.55–13.78)	−8.63
>20	51	−29.45 (−46.58– −12.32)*	−40.20
Model 2			
Never-smokers (reference)	482	−11.20	−11.20
Tobacco smoking pack-years groups			
>0–1	59	2.22 (−15.67–20.10)	−8.98
>1–5	65	1.22 (−9.88–12.32)	−9.98
>5–20	207	−6.78 (−15.37–1.80)	−17.98
>20	439	−21.13 (−27.46– −14.81)*	−32.33
Model 3			
Never-smokers (reference)	482	−11.46	−11.46
Heavy marijuana smoking (>20 joint-years)			
Current	34	−30.91 (−53.56– −8.27)*	−42.37
Former	17	−27.10 (−51.78– −2.42)*	−38.56
Model 4			
Never-smokers (reference)	482	−9.74	−9.74
Heavy tobacco smoking (>20 pack-years)			
Current	272	−40.32 (−51.54– −29.11)*	−50.06
Former	167	−8.42 (−14.33– −2.51)*	−18.16

The β-coefficient for each smoking subgroup/category is the mean rate of change of FEV_1 relative to (compared with) the reference (never-smokers of either tobacco or marijuana). The absolute rate of decline for the smoking subgroup is therefore β-coefficient of the subgroup added to the rate of decline of the reference (never-smoker); for example, in model 1, the absolute change for marijuana smokers of >20 joint-years is the sum of −29.45 and −10.75, that is −40.20 mL·year^{-1}. In model 2, the absolute change for tobacco smokers of >20 pack-years is −32.33 mL·year^{-1}, and so on for models 3 and 4. *: significantly different compared with that of never-smokers of either marijuana or tobacco, p<0.05.

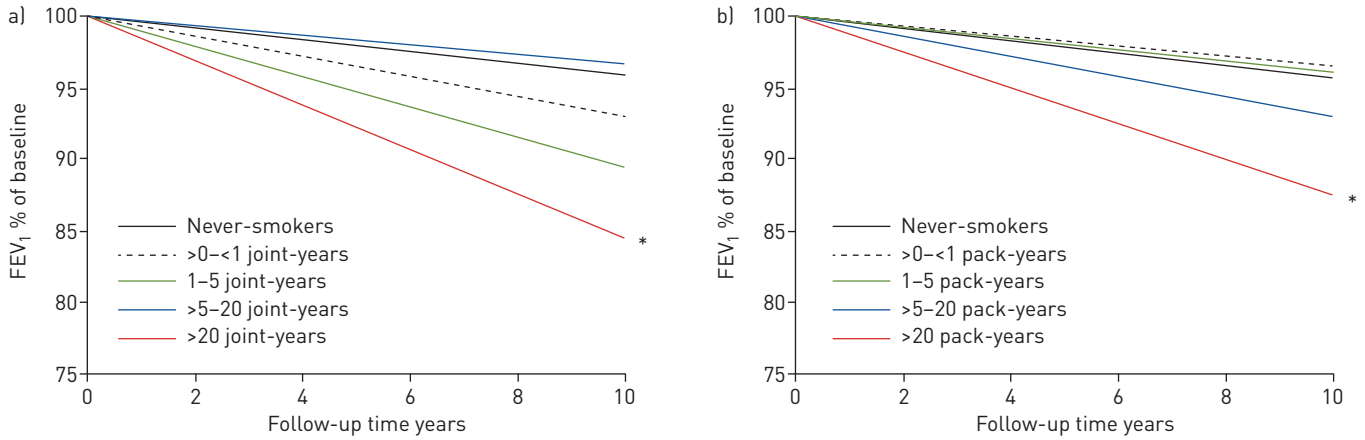

FIGURE 2 Decline in forced expiratory volume in 1 s (FEV_1) over time for a) cumulative exposure to marijuana smoke controlled for pack-years; b) cumulative exposure to tobacco smoke, controlled for joint-years. Other covariates controlled for: sex, body mass index, baseline age, baseline FEV_1, follow-up time and presence or absence of chronic obstructive pulmonary disease (FEV_1/forced vital capacity <0.7). The decline in FEV_1 is expressed as percentage of baseline FEV_1 over time, projected using the β-coefficients from the mixed-effect models (data in table 3) and right-truncated at 10 years of follow-up. *: significantly different from never-smokers.

TABLE 4 Results from mixed-effects regression models showing the change in forced expiratory volume in 1 s (FEV_1) over time between the different strata of tobacco smoking exposures, segregated by whether or not there was concurrent marijuana smoking

Tobacco-smoking groups by pack-years	Rate of change in FEV_1 mL·year^{-1}	
	β-coefficient (95% CI)	p-value
0–1 (T)	Reference	
>1–5 (T)	12.59 (−2.22–27.40)	0.0955
>1–5 (MT)	−4.74 (−16.08–6.60)	0.412
>5–20 (T)	7.05 (−4.52–18.61)	0.232
>5–20 (MT)	−2.392 (−12.51–7.72)	0.6428
>20 (T)	−23.66$^{\#}$ (−34.52– −12.79)	<0.0001
>20 (MT)	−32.31$^{\#}$ (−42.02– −22.6)	<0.0001

T: tobacco smoking only; MT: smokers of both marijuana and tobacco. $^{\#}$: significantly different from each other; p=0.019 (F-test).

In a sensitivity analysis, the trajectories of the subgroups of different strata of tobacco smoking exposure segregated by whether or not there was concurrent marijuana smoking showed that the presence of marijuana significantly increased the magnitude of change for tobacco exposure >20 joint-years (table 4), further supporting the findings in table 3.

Current and former marijuana and tobacco smoking was further explored in those with >20 joint-years and >20 pack-years exposures, respectively. In marijuana smokers, current and former smoking status was significantly associated with declines in FEV_1 compared to never-smokers; by 30.9 mL·year^{-1} (absolute decline 42.4 mL·year^{-1}) for current smokers and 27.1 mL·year^{-1} (absolute decline 38.6 mL·year^{-1}) for former smokers (table 3; figure 3a). Similarly, in tobacco smokers, the current and former tobacco status was significantly associated with declines in FEV_1 compared to never-smokers; by 40.3 mL·year^{-1} (absolute decline 50.1 mL·year^{-1}) for current tobacco smokers and 8.4 mL·year^{-1} (absolute decline 18.2 mL·year^{-1}) for former tobacco smokers (table 3; figure 3b).

Discussion

To our knowledge, this is the first longitudinal study of marijuana smoking in older individuals in a general population whose median age was 65 years. The results from previous longitudinal studies [11, 12, 14, 15, 17] in younger people have shown that marijuana smoking produced marginal or no effects on lung function. The results of the present study address a major gap in marijuana research [30] by

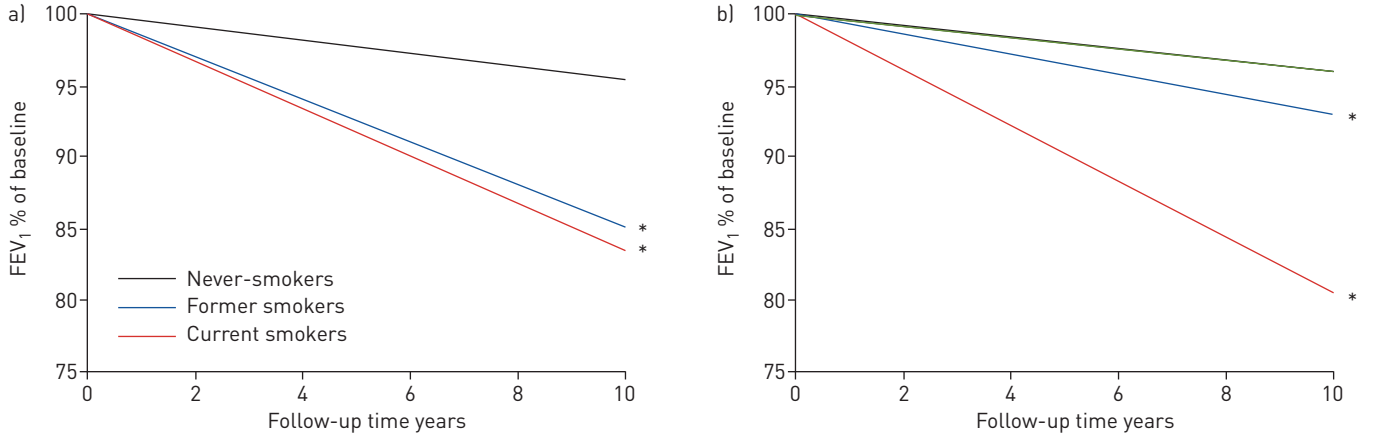

FIGURE 3 Decline in forced expiratory volume in 1 s (FEV_1) over time for current and former smokers in a) marijuana smokers with cumulative exposure to >20 joint-years, controlled for pack-years; b) tobacco smokers with cumulative exposure to >20 pack-years, controlled for joint-years. Other covariates controlled for: sex, body mass index, baseline age, baseline FEV_1, follow-up time and presence or absence of chronic obstructive pulmonary disease (FEV_1/forced vital capacity <0.7). The decline in FEV_1 is expressed as percentage of baseline FEV_1 over time, projected using the β-coefficients from the mixed-effect models (data in table 3) and right-truncated at 10 years of follow-up. *: significantly different from never-smokers.

demonstrating that marijuana smoking amplifies the harmful effects of tobacco smoking on risk of COPD and FEV_1 decline over time.

Meta-analyses and systematic reviews [5, 31, 32] generally agree that marijuana smoking causes respiratory symptoms and increases the risk of chronic bronchitis among long-term cannabis smokers. Yet, several cross-sectional studies and five longitudinal studies [12, 14–17] that have previously evaluated the effects of marijuana smoking on lung function have yielded mixed results. Three [7–9] out of the 11 studies [6–13, 17, 33, 34] found an association with low FEV_1/FVC ratio; three studies [9, 12, 13] reported an increase in FVC, casting doubt on airflow limitation as defined by FEV_1/FVC ratio; and four studies [6, 11, 12, 35] demonstrated a significant decrease in specific airway conductance, indicating large-airway obstruction. Explanations for these conflicting results are unclear, but could be attributed to 1) heterogeneity of study designs such as convenience sampling of volunteers [6, 11, 13, 35] *versus* community-based sampling [10, 12, 17, 33] *versus* birth cohorts [7, 12]; 2) small sample sizes and short follow-up times [10, 35]; 3) wide age ranges with many predominantly recruiting adults aged <40 years [7, 8, 34]; and 4) uncertainty in the accuracy of self-reports of marijuana use.

Two previous longitudinal studies, one a birth-cohort study [15] and a more recent population-based study [14] involving younger adults (<40 years) found that the association between cumulative marijuana exposure and FEV_1 was non-linear, with a positive relationship among those who had minor exposures to marijuana and a negative relationship among those who had higher joint-years of exposure. In the present study, we did not find a clear trend between marijuana exposure and lung function, which may be due to the small number of subjects who smoked marijuana exclusively and the challenges in accurately quantifying their exposure history; however, we did find a significant association between cumulative joint-years and presence of COPD (FEV_1/FVC <0.7), suggesting that marijuana on its own or in conjunction with tobacco smoking contributes to increased risk of COPD.

In addition, we observed an accelerated FEV_1 decline in heavy marijuana smokers who had a cumulative exposure >20 joint-years. However, these data should be interpreted cautiously, as the absolute numbers of "pure" marijuana smokers were small (representing just 3% of the entire cohort) and we could not validate their self-report with objective measurements of exposure. Moreover, there were significant differences in the age distribution of marijuana smokers *versus* all other groups. Although we used well-accepted statistical methods to adjust for these differences, residual confounding effects of age and other factors could have distorted the overall findings.

The importance of the age effect on rate of FEV_1 decline deserves some emphasis. In clinical practice, the risk of COPD increases exponentially with increasing age, especially among those aged ⩾40 years [27]. Thus, the effects of marijuana smoke with or without concomitant tobacco exposure on the rate of lung function decline are likely best evaluated in middle-aged or older adults. Most of the previous studies on this topic have studied largely younger adults in contrast to our cohort of older individuals which had a median age of 65 years. This may in part explain some of the discrepancies in results between the present study and those previously reported [11, 12, 14, 15, 17].

The observations for former and current smokers in this study are consistent with previous data showing that smoking cessation of tobacco reduces the rate of FEV_1 decline to normal or near-normal levels [36, 37]. Our findings extend these observations by raising the possibility that elimination of exposure to marijuana cigarettes may also have a modifying effect on FEV_1 decline, but perhaps not to the same extent as tobacco smoking cessation. However, as noted previously, measurement of marijuana exposure is not standardised; thus, some active marijuana smokers may have been misclassified as ex-smokers. Future studies will be required to elucidate the exact mechanisms behind this observation.

Strength and limitations

The strengths of this study included a large sample size of >1200 individuals, who were chosen from a larger cross-sectional study of >5200 individuals, who had been randomly selected from a general population; a large number of individuals who were in their fifth and sixth decades of life, and thus were at a peak susceptibility for the development of COPD; and a detailed exposure history of marijuana and tobacco smoke use and careful ascertainment of post-bronchodilator lung function measurements over time.

There were some limitations to the study. For example, not all participants from the cross-sectional cohort were included in the subsequent longitudinal component of the study, which may limit the generalisability of the longitudinal findings to the general population. It was reassuring that the baseline characteristics of the cross-sectional cohort and the derived longitudinal cohort were similar and the results from both cross-sectional and longitudinal analyses were concordant, suggesting that the CanCOLD sampling was unbiased. Another limitation was that the CanCOLD cohort was not specifically designed for the current analysis and the enrichment of the longitudinal cohort with COPD subjects could have caused a potential

bias towards a more rapid decline in FEV_1 in the smokers. However, because COPD subjects were present in all smoking subgroups as well as the reference group, it is unlikely that this feature of the study design would have significantly impacted the overall findings. Other limitations included 1) residual confounding by tobacco smoke: although we adjusted statistically for the history of tobacco smoking, this may not have fully captured the effects of life-time exposure of tobacco given that most "hard-core" marijuana smokers have also smoked tobacco cigarettes in the past [9, 13, 14]; 2) challenges in accurately measuring exposure to marijuana smoke; and 3) the small numbers of heavy marijuana-only smokers, and a much larger group of individuals who smoked both marijuana and tobacco, which is a common smoking behaviour in North American and European communities [38, 39].

In summary, the present study indicates that individuals who smoke or smoked both marijuana and tobacco experienced a faster decline in lung function compared with tobacco-only smokers. The harmful effects of marijuana smoke on the rate of FEV_1 decline appear to occur with exposures that are >20 joint-years. Although our study did not have sufficient power to evaluate the effects of marijuana smoke alone on lung function decline, these data raise concerns that marijuana exposure (especially in ex- and current tobacco smokers) may increase the risk of COPD and accelerate its progression for those who already have the disease. In view of marijuana smoking becoming more mainstream with increasing prevalence, following the legalisation of recreational marijuana in many countries and jurisdictions, there is a pressing need for larger longitudinal cohort studies that are specifically powered to evaluate the effects of marijuana alone on the risk of COPD and on lung function decline in those with established disease.

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