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The effects of marijuana smoking on lung function in older people.

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Supplementary : 1 efigure and 4 etables.

CONTRIBUTORS

WCT, JB, DDS contributed to the design and implementation of the study, the collection of data, the analysis and interpretation of the data and the writing of the manuscript. SDA, KRC, BLW,

JMF, PH, FM, DDM, DOD, JCH and JR contributed to the collection and interpretation of data, and the revision of the manuscript. TY, GZ, LZ, TT, AB contributed to the analysis and interpretation of the data and revision of manuscript. WCT, JB had full access to all the data in this study, and had final responsibility for the decision to submit this manuscript for publication. All authors approved the final version of the manuscript.

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SHORT RUNNING HEAD: Marijuana smoking and lung function decline [44 words]

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 COPD [post-bronchodilator FEV_1/FVC <0·7] in 5291 population-based individuals and the rate of decline in FEV_1 in a subset of 1285 men and women, aged 40 years and older, who self-reported use (or nonuse) 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, gender, and body mass index. Heavy tobacco smoking and marijunana smoking was defined as >20 pack-years and >20 joint-years, respectively.

RESULTS

Approximately 20% of participants had been or were current marijuana smokers with most also having smoked tobacco cigarettes (83%). Among heavy marijuana users, the risk of COPD was significantly increased (adjusted odds ratio, aOR, 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 (p=0·0007) and 21·1 ml/year (p<0.0001), respectively.Those who smoked both experienced a decline of 32.31 ml/year (p<.0001).

INTERPRETATION

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

[word count=240]

Key words: Smoking; Marijuana or cannabis; decline in FEV1; chronic airway obstruction.

For Twitter feed (@ERSpublications)

“Prolonged heavy marijuana smoking increases the risk of COPD and accelerates FEV1 decline in concomitant tobacco cigarette smokers beyond the effects of tobacco alone ”.

INTRODUCTION

Marijuana is the second most common substance smoked in the world after tobacco[1], and the most common illicit drug used in 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, delta-9-tetrahydro-cannabinol (THC) and other cannabinoids in marijuana and nicotine in tobacco.

The harmful respiratory effects of tobacco are well characterized[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 1second (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 3 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 associated with high levels of marijuana smoking [14, 15]; and a paradoxical increase in FEV_1 in current marijuana smokers in a study of 4 consecutive surveys of non-tobacco smokers assumed to be marijuana smokers.[17]

In this study, we analyzed cross-sectional[18] and longitudinal data from the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study consisting of men and women, 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 multi-centred (9 sites in 6 Canadian provinces) study, 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 and older from nine Canadian urban sites[18, 20]; and a subsequent longitudinal phase called the Canadian Cohort of Obstructive Lung Disease (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 $FEV_1/FVC<0.7$) and approximately equal number of aged- 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-January 2017, with 80% retention rate of the longitudinal cohort at the end of January 2017. **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 [Marijuana smoking questionnaire: see online data supplement]. Study definitions were: tobacco smokers if participants had smoked at least 365 cigarettes in a lifetime [23] and marijuana

smokers if they had smoked at least 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 dyspnea were defined as in previous publications.[10, 18, 23, 24]

Smoking patterns were defined as: marijuana-only (M); tobacco-only (T); both marijuana and tobacco (MT); and never-smokers of both marijuana and tobacco (NS). 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 function were stratified based on levels of exposure (mild, 1-5; moderate, >5-20; heavy, >20) in joint years or pack-years, respectively.

All participants performed spirometry testing using an EasyOne spirometer (ndd Medical Technologies Inc., Andover, MA, USA) before and 15 minutes following inhalation of 200 mcg 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, gender, body mass index (BMI). The adjusted odds ratios and confidence intervals (aOR, 95% CI) were computed for each level of marijuana or tobacco exposure. The reference category for all analyses was NS. 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 online supplement). 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/year), controlling for potential confounding variables which included BMI, follow-up time, sex, baseline FEV_1, and baseline age(more details in online supplement). 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 online supplement). The Akaike Information Criterion (AIC)[29] was used for testing the goodness of fit and model selection for the regression methods. All statistical analyses were performed with SAS 9.4 software (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 flow diagram eFig1 and etable1 in online supplement]. The baseline characteristics of the participants in COLD and CANCOLD stratified by smoking habits are summarized as univariate descriptive statistics in **Table 1** and **Table 2,** respectively. Compared with the COLD cohort, the CanCOLD cohort contained older individuals (median age 65 years versus 59 years), more men and more tobacco smokers (e-table 1, online supplement). The median duration of follow-up in the CanCOLD cohort was 5·9 years [IQR 4·9-6·7] and range: 2·5 to 10·5 years.

The frequencies of tobacco and marijuana smoking were similar in the COLD and CANCOLD cohorts: 36% were Tobacco-only (T), 3% were Marijuana-only (M), and 17% were concomittent smokers of marijuana and tobacco (MT) in COLD, versus 44% were T, 3% were M and 16% were MT in CanCOLD. T smokers comprised the majority (69% COLD; 73% CANCOLD) of all tobacco smokers, while M 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 men, 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 (about 11 years) while that for tobacco exposure was 26 years in COLD and 33 years in CanCOLD. The cumulative marijuana exposure (joint-years) at baseline in MT smokers was more than twice that in M smokers: mean,17.02 versus 7.23 in COLD and 16.68 versus 5.45 in CANCOLD. Current marijuana smokers in CanCOLD smoked more than twice as much as former smokers: mean, 25.72 versus 10.40 joint years.

Cumulative marijuana smoking and FEV_1/FVC

Cumulative marijuana exposure of >20 joint-years controlled for tobacco pack-year exposure, was associated with the presence of COPD (postbronchodilator $FEV_1/FVC<0·7$). **[Figure1a] [etable2** in online supplement**]**. Lower cut-offs of joint-years were not significantly associated but a trend was found with increasing cumulative marijuana exposures : 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 ($p<·0001$). The results for cumulative tobacco exposure showed that cumulative tobacco exposure of greater than 5 pack-years was associated with COPD **[Fig 1b]; [etable3 in the online supplement).** There was a significant interaction between marijuana and tobacco smoking on FEV_1/FVC ($p=0.042$).

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 summarized as beta 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, of 29·6 ml/year (absolute decline 40·5 ml/year). 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 (NS) by 21·1 ml/year (absolute

decline 32·5 ml/year). **(Table 3; Figure 2a; Figure 2b).** 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 also declined with a pattern similar to FEV_1 (etab4, online supplement).

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 (NS): by 30·9 ml/year (absolute decline 42·4ml/year) for current smokers and 27·1 ml/year (absolute decline 38·6 ml/year) 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 (absolute decline 50·1 ml/year) for current tobacco smokers and 8·4ml/year (absolute decline 18·2 ml/year) 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 addresse a major gap in marijuana research [30] by 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] of the 11 studies[6-13, 17, 33, 34] found an association with low FEV_1/FVC; 3 studies[9, 12, 13] reported an increase in FVC casting doubt on airflow limitation as defined by FEV_1/FVC; and 4 studies[6, 11, 12, 35] demonsrated a significant decrease in specific airway conductance (SGaw) indicating large airway obstruction. Explanations for these conflicting results are unclear but could be attributed to: i) 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]; ii) small sample sizes and short follow-up times [10, 35], iii) wide age ranges with many predominantly recruiting adults younger than 40 years of age[7, 8, 34]; and iv) 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 old) 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 small number of subjects who exclusively smoked marijuana and the challenges in accurately quantifying their exposure history; however we did find a significant association between cumulative joint-years and presence of COPD ($FEV_1/FVC<0{\cdot}7$), suggesting that marijuana on its own or in conjunction with tobacco smoking contributes to increased risk of COPD.

We also 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 40 years of age and older [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 discrepanices 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 standardized; 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) a large sample size of over 1200 individuals, who were chosen from a larger cross-sectional study of over 5200 individuals, who had been randomly selected from a general population; b) a large number of individuals who were in their 5th and 6th decades of life, and thus were at a peak susceptibility for the development of COPD; and c) 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 assuring that the baseline characteritics 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: a) residual confounding by tobacco smoke. Although we statistically adjusted 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 in the past also smoked tobacco cigarettes [9, 13, 14]; b) challenges in accurately measuring exposure to marijuana smoke; and c) 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 behavior in North American and European communities.[38, 39]

In summary, the present study indicates that individuals who smoke or smoked both marijuna 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 main-stream with increasing prevalence, following the legalization 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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LEGENDS:

Figure 1a and 1b.

Adjusted odds ratios(aORs) with 95% confidence interval (CI) for association of :a) cumulative marijuana exposures by three joint-years cut-offs (1-5, >5-20,>20) (Fig 1a), b) cumulative tobacco exposures by three pack-years cut-offs(1-5, >5-20,>20) (Fig 1b), with presence of COPD (post-bronchodilator FEV_1/FVC<0·7). The adjusted odds ratio, 95% CI for lowest exposure subgroup for marijuana >0<1 (n=253) and for Tobacco >0<1 (n=124) are not significant and not shown in the figures but values are in e tables 2 and 3 in the online supplement. The aORs were adjusted for age, sex, BMI and pack- years (figure 1a), or joint-years (fig 1b). A potential trend was evaluated using a Cochran-Armitage test of trend.

Figure 2a and 2b

Decline in FEV1 over time for: a) cumulative exposure to marijuana smoke controlled for pack-years (Figure 2a); b) cumulative exposure to tobacco smoke, controlled for joint-years (Figure 2b).Also controlled for other covariates: sex, BMI, baseline age, baseline FEV_1; follow-up time and presence or absence of COPD (FEV1/FVC<0.7). The decline in FEV_1 is expressed as percentage of baseline FEV_1 over time, projected using the beta coefficients from the mixed effect models (data in table 3) and right truncated at 10 years of follow-up.The lines in different colours represent: black= never-smokers of both marijuana and tobacco [both fig 2a and fig2b]; dash black=smokers of >0<1 joint-years[fig 2a], >0<1 pack-years[fig 2b]; green=smokers of 1-5 joint-years[fig 2a], 1-5 pack-years [fig 2b]; blue=smokers of 5-20 joint-years[fig 2a], 5-20 pack-years [fig 2b]; red=smokers of >20 joint-years[fig 2a], >20 pack-years [fig 2b]. * significantly different from never-smokers.

Figure 3a and 3b.

Decline in FEV1 over time for current and former smokers in : a) marijuana smokers with cumulative exposure to >20 joint-years, controlled for pack-years (Figure 3a); b) tobacco smokers with cumulative exposure to >20 pack-years, controlled for joint-years (Figure 3b). Also controlled for other covariates: sex, BMI, baseline age, baseline FEV_1; follow-up time and presence or absence of COPD (FEV1/FVC<0.7). The decline in FEV_1 is expressed as percentage of baseline FEV_1 over time, projected using the beta coefficients from the mixed effect models (data in table 3) and right truncated at 10 years of follow-up.The lines in different colours represent: black= never-smokers of both marijuana and tobacco; blue=former smokers ; red=current smokers. * significantly different from never-smokers.

Table 1. Baseline demographics and general characteristics of the participants in the initial cross-sectional [COLD] cohort stratified into four smoking subgroups (N=5291)

Characteristics	Smoking Status				
	All Participants	Never smokers of either [NN]	Tobacco smoking only [T]	Marijuana smoking only [M]	Marijuana and Tobacco smoking.[MT]
	N=5291	N=2299(43%)	N=1926(36%)	N=181(3%)	N=885(17%)
Age, years, median(IQR)	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)*
Sex, male, n (%)	2443(46·2)	889(38·7)	897(46·6)*	114(63·0)*	543(61·4)*
BMI, kg/m^2, median(IQR)	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, median(IQR)	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, n(%)					
Current	346(6·5)	-----	-----	45(24·9)	301(34·0)
Former	720(13·6)	-----	-----	136(75·1)	584(66·0)
Joint years of marijuana, median(IQR)	-----	-----	-----	1·6(0·6-4·7)	4·3(1·3-12·9)
Years of smoking marijuana, Median(IQR)	-----	-----	-----	10·0(4·0-20·0)	12·0(5·0-36·0)
Age of onset of marijuana, Median(IQR)	17·0(15·0-20·0)	-----	-----	18·0(16·0-20·0)	17·0(15·0-19·0)
Tobacco smoking status, n(%)					
Current	726(13·7)	-----	406(21·1)	-----	320(36·2)
Former	2085(39·4)	-----	1520(78·9)	-----	565(63·8)
Pack years of tobacco, median(IQR)	-----	-----	18·8(6·0-36·0)	-----	22·0(10·0-36·3)
Years of smoking tobacco, Median (IQR)	-----	-----	26·0(14·0-39·0)	-----	27·0(17·0-36·0)
Age of onset of tobacco, Median(IQR)	-----	-----	17·0(15·0-20·0)	-----	16·0(14·0-18·0)
Pulmonary function and Spirometry test, median(IQR)					
Post-BD FEV1/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)*
Jt_yrs > 20 (17M; 168MT)	-----	-----	-----	77·1(72·9-80·7)	74·0(67·4-78·6)#
Jt_yrs ≤20 (164M; 717MT)	-----	-----	-----	77·5(73·9-81·6)	76·3(71·3-80·6)#
Post-BD FEV1, % predicted	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-BD FVC, % predicted	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, yes, n(%)	1204(22·8)	361(15·7)	612(31·8))*	19(10·5)	212(24·0))*
Respiratory symptoms, n(%)					
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)*
Dyspnea(mMRC score), median(IQR)	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)

*Significantly different to "Neither Marijuana nor Tobacco smoking" as reference (p<0·05). # Significantly different to each other (P<0.0001). BMI= body mass index. Follow-up time = baseline to last visit for each individual. Joint-years= number of joints/day x total duration of smoking in years. Pack-years= number of packs (20 cigarettes per pack) x total duration of smoking in years.

The proportion of COPD in any marijuana smoker is 21.7%, and the proportion of COPD in any tobacco smoker is 29.3%

Table 2. Baseline characteristics of the participants in the longitudinal [CANCOLD] cohort stratified into four smoking subgroups (N=1285)

Characteristics	Smoking Status				
	All Participants	Never smokers of either [NN]	Tobacco smoking only [T]	Marijuana smoking only [M]	Marijuana and Tobacco smoking [MT]
	N=1285	N=482(37%)	N=561(44%)	N=33(3%)	N=209(16%)
Age, years, median(IQR)	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)*
Sex, male, n (%)	712(55·4)	249(52·0)	297(52·9)	23(69·7)*	143(68.4)*
BMI, kg/m^2, median(IQR)	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, median(IQR)	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, median(IQR)	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, n(%)					
Current	91(7·1)	-----	-----	7(21·2)	84(40·2)
Former	151(11·8)	-----	-----	26(78·8)	125(59·8)
Joint years of marijuana, median(IQR)	-----	-----	-----	1·7(0·7-5·4)	5·3(1·4-17·1)
Years of smoking marijuana, Median (IQR)	-----	-----	-----	10·0(4·0-20·0)	12·0(5·0-34·0)
Age of onset of marijuana, Median(IQR)	18·5(16·0-21·0)	-----	-----	18·0(16·0-20·0)	19·0(16·0-21·0)
Tobacco smoking status, n(%)					
Current	222(17·3)	-----	134(23·9)	-----	88(42·11)
Former	548(42·7)	-----	427(76·1)	-----	121(57·9)
Pack years of tobacco, median(IQR)	-----	-----	23·4(9·4-41·0)	-----	27·3(14·1-44·0)
Years of smoking tobacco, Median (IQR)	-----	-----	33·0(19·0-43·0)	-----	33·0(21·0-42·0)
Age of onset of tobacco, Median(IQR)	-----	-----	18·0(15·0-20·0)	-----	15·0(14·0-18·0)
Spirometry test, median(IQR)					
Post-BD FEV1/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)*
Jt_yrs >20 (N=3M; 48MT)	-----	-----	-----	74·7(65·8-83·6)	63·8(60·1-70·0)#
Jt_yrs ≤20 (N=30M; 161MT)	-----	-----	-----	74·8(67·3-79·7)	69·6(64·8-76·5)#
Post-BD FEV1, % predicted	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-BD FVC, % predicted	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, yes, n(%)	659(54·1)	214(44·4)	349(62·2)*	11(33·3)	121(57·9)*
Respiratory symptoms, n(%)					
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)*
Dyspnea(mMRC score), median(IQR)	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)

*Significantly different to "Neither Marijuana nor Tobacco smoking" as reference (p<0·05). # Significantly different to each other (P=0.001). BMI= body mass index. Follow-up time = baseline to last visit for each individual. Joint-years= number of joints/day x total duration of smoking in years. Pack-years= number of packs (20 cigarettes per pack) x total duration of smoking in years.The proportion of COPD in any marijuana smoker is 54.5%, and the proportion of COPD in any tobacco smoker is 61.0%

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 FEV_1,

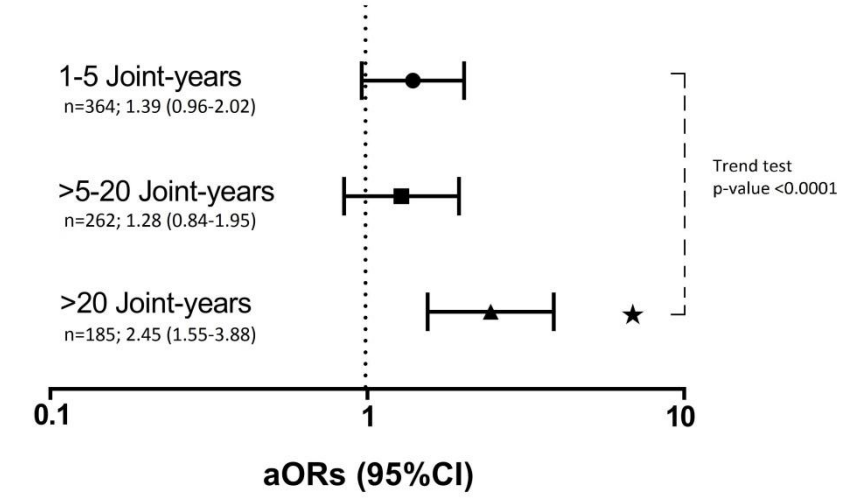
	Predictor Variables	N	Rate of change in FEV_1 (ml/yrs)		
			β Coefficient	95% CI	Absolute change#
Model 1	**Never smokers [reference]**	482	-10·75		-10·75
	Marijuana smoking joint-years groups:				
	>0-1	56	-7·28	-17·95,3·40	-18·03
	>1-5	72	-16·51	-33·18,0·17	-27·26
	>5-20	63	2·12	-9·55,13·78	-8·63
	>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

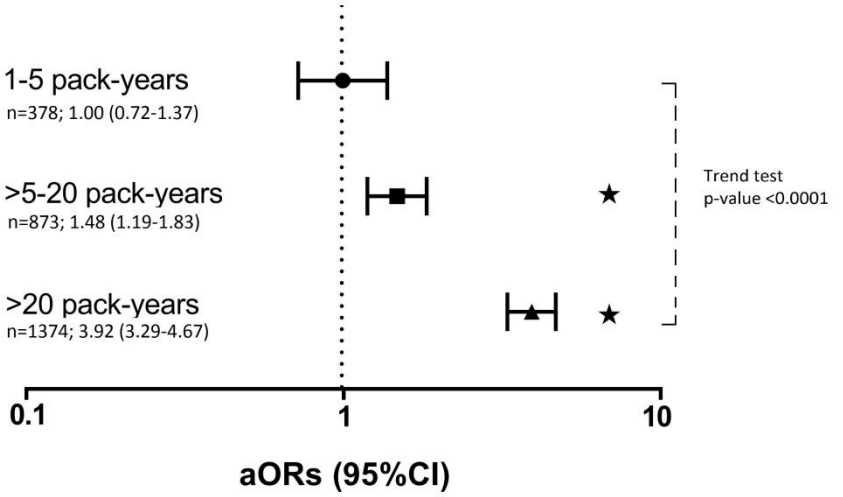
*significantly different compared with that of never-smokers of both marijuana and tobacco. Significance at P< 0.05. The β coefficient for each smoking subgroup/ category is the mean rate of change of FEV1 relative to /(compared with) the reference (never smokers of both tobacco or marijuana). # The absolute rate of decline for the smoking subgroup is therefore beta coefficient of the subgroup added to the rate of decline of the reference (never-never-smoker): for example in model 1 above, 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. In model 2, the absolute change for tobacco smokers of >20 pack-years is -32.33 ml/year; and so on for model 3 and model 4.

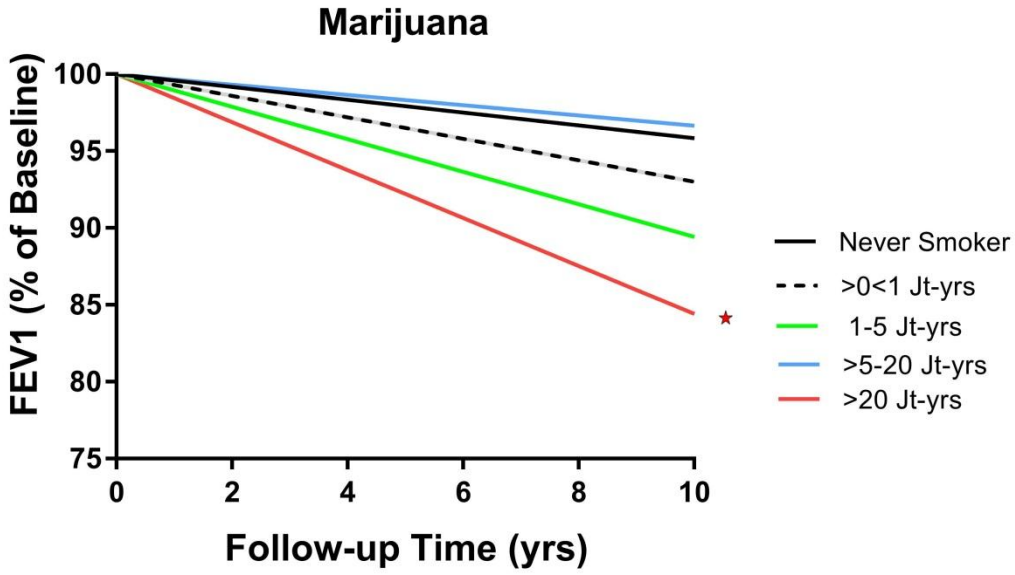
Table 4. Results from mixed effects regression models showing the change in FEV1 over time between the different strata of tobacco smoking exposures, segregated by whether or not there was concurrent marijuana smoking.

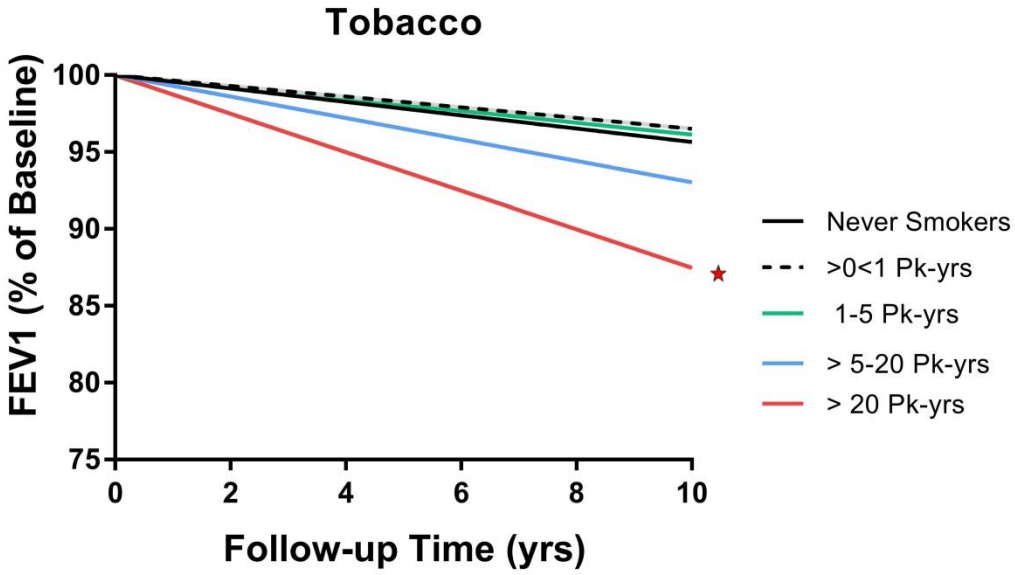
		Rate of Change in FEV_1 (ml/yrs)	
Tobacco Smoking Groups by Pack_years	**β Coefficients**	**95% CI**	**P-value**
0-1 (T-only)	**Reference**		
>1-5 (T-only)	12.59	-2.22,27.40	0.0955
>1-5 (T+M)	-4.74	-16.08,6.60	0.412
>5-20 (T-only)	7.05	-4.52,18.61	0.232
>5-20 (T+M)	-2.392	-12.51,7.72	0.6428
> 20 (T-only)	-23.66*	-34.52,-12.79	<.0001
>20 (T+M)	-32.31*	-42.02,-22.6	<.0001

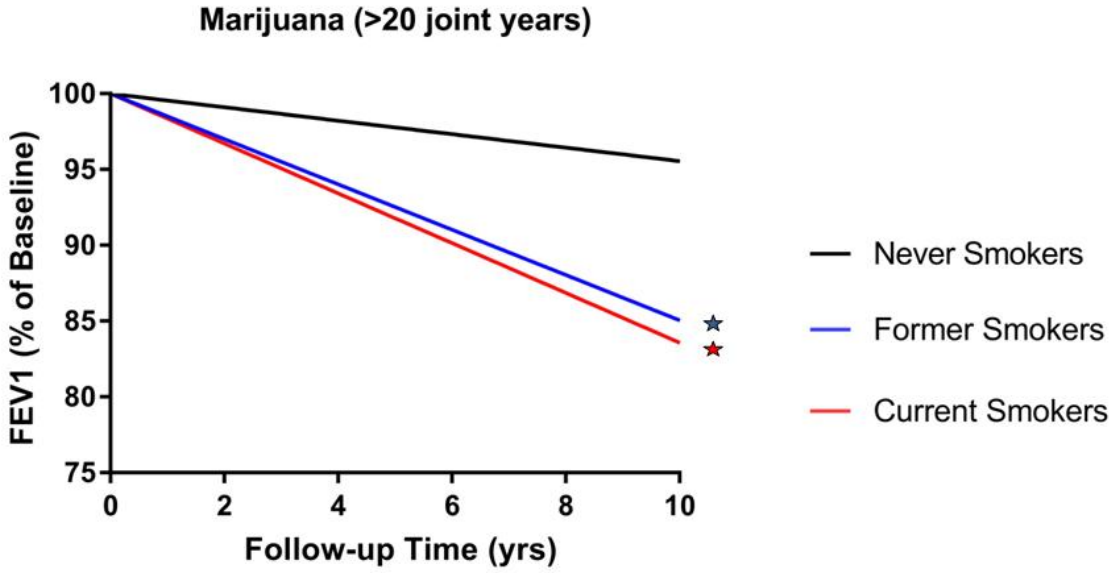
*Significantly different from each other; p=0.019. [F test]

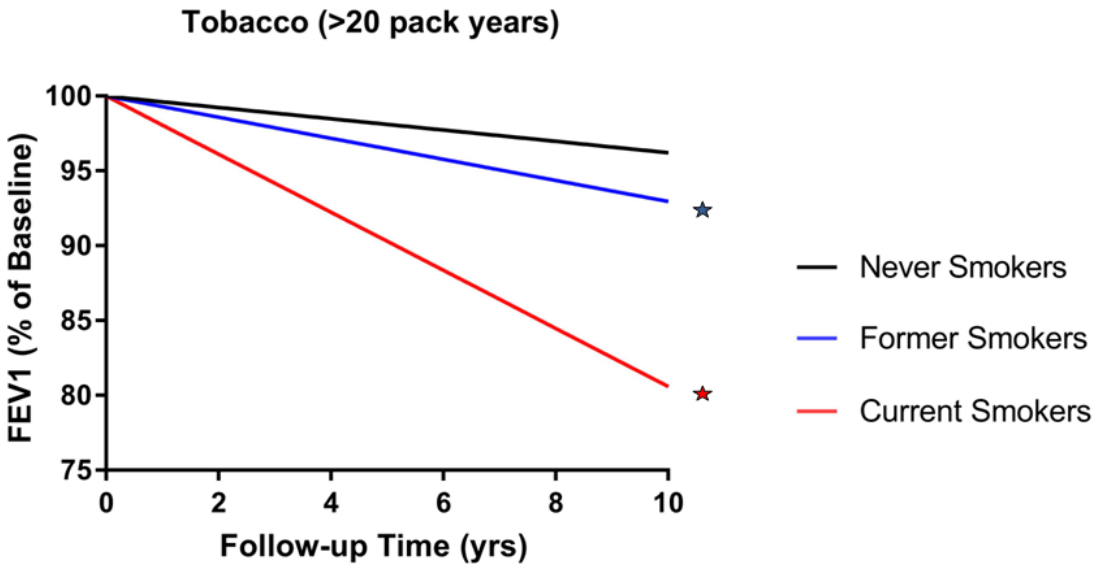

1-5 Joint-years
n=364; 1.39 (0.96-2.02)
>5-20 Joint-years
n=262; 1.28 (0.84-1.95)
>20 Joint-years
n=185; 2.45 (1.55-3.88)
Trend test
p-value <0.0001
0.1
1
10
aORs (95%CI)


1-5 pack-years
n=378; 1.00 (0.72-1.37)
>5-20 pack-years
n=873; 1.48 (1.19-1.83)
>20 pack-years
n=1374; 3.92 (3.29-4.67)
Trend test
p-value <0.0001
0.1
1
10
aORs (95%CI)


Marijuana
FEV1 (% of Baseline)
100
95
90
85
80
75
0
2
4
6
8
10
Follow-up Time (yrs)
Never Smoker
>0<1 Jt-yrs
1-5 Jt-yrs
>5-20 Jt-yrs
>20 Jt-yrs


Tobacco
FEV1 (% of Baseline)
100
95
90
85
80
75
0
2
4
6
8
10
Follow-up Time (yrs)
Never Smokers
>0<1 Pk-yrs
1-5 Pk-yrs
> 5-20 Pk-yrs
> 20 Pk-yrs


Marijuana (>20 joint years)
100
95
90
85
80
75
FEV1 (% of Baseline)
0
2
4
6
8
10
Follow-up Time (yrs)
Never Smokers
Former Smokers
Current Smokers


Tobacco (>20 pack years)
100
95
90
85
80
75
FEV1 (% of Baseline)
0
2
4
6
8
10
Follow-up Time (yrs)
Never Smokers
Former Smokers
Current Smokers

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to:

The effects of Marijuana smoking on lung function in older people.

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Supplementary Appenidx

Supplement to:
Wan C Tan, M.D, Jean Bourbeau, M.D., Shawn Aaron et al. on behalf of the CanCOLD Collaborative Research Group.*

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13. References:

2. List of collaborators

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3. Canadian Obstructive Lung Disease (COLD) (baseline cross-sectional phase of study):

METHODS

The Canadian Obstructive Lung Disease [COLD] initiative was a cross-sectional multisite, nation-wide, population-based, epidemiological study on lung health, that was initiated in Vancouver in August 2005 and completed in 9 sites in Canada by September 2009.

The design and rationale of the 'COLD' study were identical to that conducted for the Vancouver site of the international Burden of Obstructive Lung Disease [BOLD] initiative, the full details of which has been published elsewhere[1]. The details of the COLD study was also previously published.

Briefly, random samples were drawn from census data from Statistics Canada (Survey and Analysis Section; Victoria, Canada) and comprised of non-institutionalized adults, aged 40 years and older in nine urban cities across Canada (Vancouver, Montreal,

Toronto, Halifax, Calgary, Quebec City, Kingston, Saskatoon and Ottawa). Recruitment was conducted by Nordic Research Group (NRG) Research group (Vancouver, Canada) by random telephone digit dialling to identify eligible who were invited to attend a clinic visit to complete interviewer administered respiratory questionnaires and to perform pre- and post-bronchodilator spirometry. The mean clinic visit participation rate was 74% (range 63–87% across 9 sites)[2]. A random sample of 6,592 persons were recruited into the cross-sectional phase of the initiative.

4. Canadian Cohort of Obstructive Lung Disease (CANCOLD) (longitudinal phase)[3]:

Methods

We enrolled subjects from a random sample of 6,592 persons recruited from 9 sites across Canada in the cross-section phase of the COLD study [see page 4 in this supplementary appendix] to form the CANCOLD prospective cohort which included spirometrically-defined (FEV1/FVC<0.7) COPD (GOLD 1 , GOLD 2-4) and two aged- and sex-matched balanced subsets of non-COPD (never-smoking and ever-smoking/' at risk' individuals). Participants were 40 years and older who were: i) healthy persons who never smoked (never-smokers) more than 1/20 pack year or total of more than 365 tobacco cigarettes in a lifetime, and post-bronchodilator FEV1/FVC greater than 0.7; ii): smokers (ever-smokers) with post-bronchodilator FEV1/FVC greater than 0.7; iii) mild COPD[GOLD grade 1] (post-bronchodilator FEV1/FVC< 0.7 &FEV1pred. greater than 80%); iv) moderate COPD [GOLD grade 2] (FEV1/FVC< 0.7 and FEV1pred<80%>50%); and severe to very severe COPD [GOLD grade 3 and 4 (FEV1/FVC< 0.7 & FEV1pred<50%)[3] Full subject assessments of spirometry, full lung function tests, cardiopulmonary exercise tests, computed tomography scans of the lungs were performed every 18 months , the full details, were previously described [3] . For this analysis 1285 subjects had marijuana and tobacco smoking data and longitudinal follow-up assessments. Details of the selection of participants are shown in Figure S1.

5. Marijuana Questionnaire

Pot/marijuana Smoking

Now I am going to ask you about recreational smoking other than cigarettes.

1. Have you ever smoked pot/marijuana? Yes ☐ 1 A1
No ☐ 2

If the answer is Yes, ask the following questions:

1A. How old were you when you first started smoking pot/marijuana? _____ _____ years old A2

1B. Have you smoked pot/marijuana in the past year? Yes ☐ 1 A3
No ☐ 2

1C. If you have stopped pot/marijuana, how old were you when you last stopped? (If the participant has not stopped smoking, record as code '99'.) _____ _____ years old A4

! Choose to respond to the most appropriate answes below; choose one answer for "joints" [1D, 1D.2, 1D.3 or 1D.6] and one answer for "Grams" [1D.4 or 1D.5]:

1D. On average over the entire time that you smoke(d), about how many joints per week do (did) you smoke? ____ ____ ___ joints/week A5

1D.2. On average over the entire time that you smoke(d), about how many joints per month do (did) you smoke? ____ ____ ___ joints/month A5.1

1D.3. On average over the entire time that you smoke(d), about how many joints per year do (did) you smoke? ____ ____ ___ joints/year A5.2

ID.4 On average over the entire time that you smoke(d), about how many grams per week do (did) you smoke? ____ ____ gram/week A5.3

1D.5 On average over the entire time that you smoke(d), about how grams per month do (did) you smoke? ____ ____ grams/month A5.4

1D.6 On average over the entire time that you smoke(d), about how many joints have you ever smoked? ____ __ joints ever smoked A5.5

! Choose most appropriate response below:

1E. In an average week how many days do (did) you smoke pot/marijuana? _____ no. of days per week A6

1E.2 In an average month how many days do (did) you smoke pot/marijuana? _____ no. of days per month A6.1

1E.3 On average how many days have you smoked pot/marijuana in total? A6.2

1F *How many years have you smoked pot/marijuana? ____ _____ no. of years A7

2. Would you be willing to be contacted again for future studies on lung health?

Yes □1

A8

No □2

Completed by: ___ ___ ____ ___ A9

** the minimum number of years for any "ever marijuana" smoker is 1*

6. Definitions *of Chronic Respiratory symptoms*

Chronic cough or chronic phlegm was defined as cough or phlegm not occurring during a 'cold' and on most days for as much as three months each year for 2 years (ref). Wheezing was the presence of "episodes of wheezing or whistling in the chest associated with feeling of shortness of breath, in the past 1 year not occurring during a cold".[4] Breathlessness was defined as "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level" (mMRC dyspnoea scale 2 [0-4] or greater).[5]

7. Statistical analyses

a) Sample size calculation for CanCOLD cohort:

Details of the sample size calculation to ensure an adequate sample size to assess the questions that relate to the progression of COPD(annual decline in FEV_1) has been previously published [3] Briefly we used the tables in Hedeker et al[6], for the longitudinal data, with 4 measurement occasions and assuming that the data was auto-correlated (autocorrelation of 0.5 between observations on the same subject), we have adequate sample size to detect a medium effect size of 0.5SD for linear between group trend with about 133 subjects per group. This estimate allowed a 10% attrition and alpha=0.05, with 80% power. Assuming SD of annual decline in FEV_1 of 30-44mls, this would allow change of 15 to 22 mls/year over the follow-up period.[3,7]

b) missing and irregularly spaced measured data handling:

In the cross-sectional analyses, for logistic regression. listwise deletion was used to handle data; predictors missing in the model were excluded from the computation of the estimates.

In the longitudinal analysis, not all subjects remain in the study for the entire period of the study[8]. In this prospective, non interventional, naturalistic cohort, individuals varied in the number of repeated measurements they contributed and at the time at which these were obtained, due to dropouts or scheduling availabilities.

Because mixed-effects regression models are quite robust to missing data and irregularly spaced measurement occasions[9], we used the statistical approach of linear mixed effect modeling [Using the 'proc mixed' procedure in SAS] which used all of the available data from each subject, regardless of when it was specifically obtained.[9]

c) sensitivity analyses on COPD as covariate

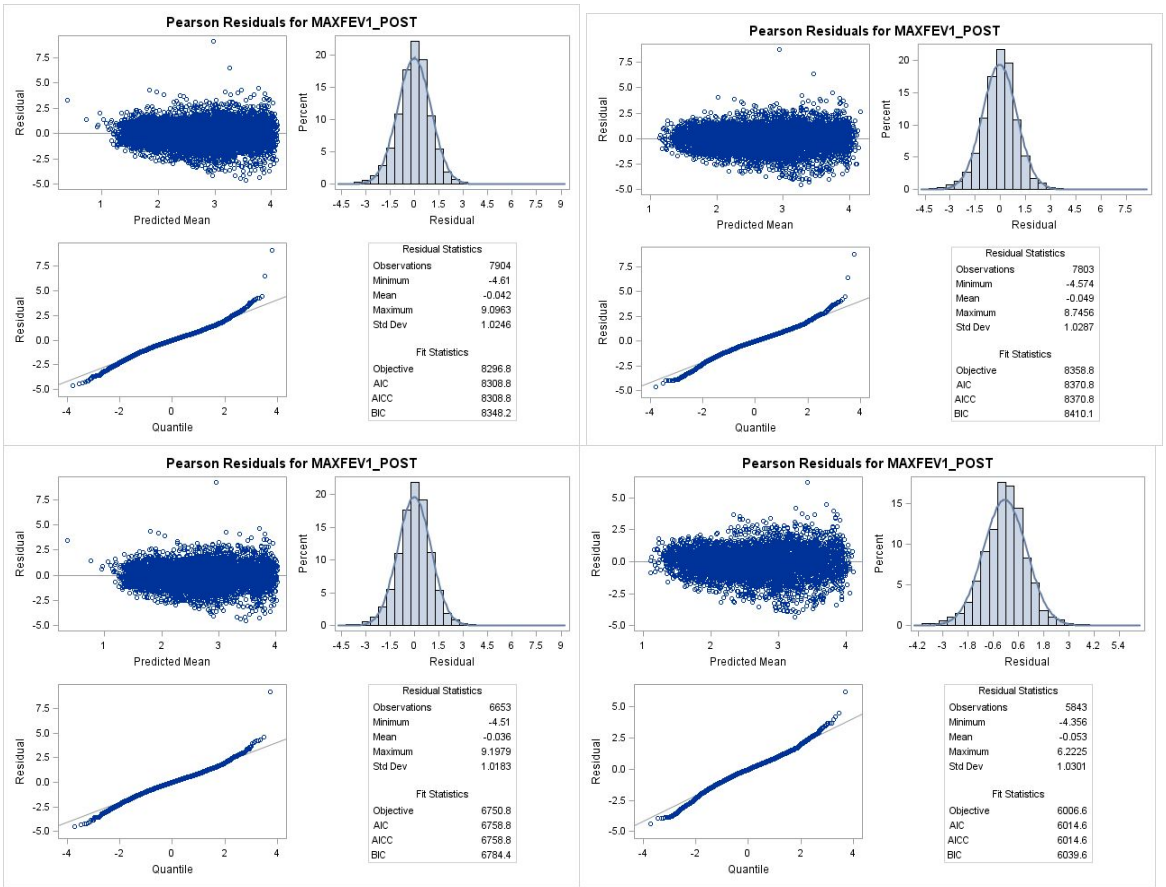
Sensitivity analyses were performed in the assessment of the effect of marijuana smoking on decline in FEV, a) by including and excluding COPD as covariate to address the possibility that

presence of COPD may increase the decline in FEV1; b) by excluding baseline FEV1 as covariate to address the possibility of regression to the mean.

d) Checking assumptions of linear mixed effect models

Linear mixed effect model has been widely used in previous literature for outcomes such as FEV1 decline in general (1–7) and in longitudinal marijuana studies [Tashkin DP et al. Am J Respir Crit Care Med 1997: 155(1): 141-148.; Sherrill DL, et al. Int J Epidemiol 1991: 20(1): 132-137.; Hancox RJ, et al.. Eur Respir J 2010: 35(1): 42-47.]

Within our linear mixed effect model, we have included a time interaction term for each time-varying variable to account for the nature of time-varying variables.
We have also check the linear mixed effect model assumptions to ensure the validity of the model. The diagnostic plots for the four models [clockwise 1-4 in main table 3] are shown below. Based on the Pearson residuals plots (the top left panel), the homoscedasticity of variance assumption was satisfied. The linearity assumption was also satisfied as the plots did not show an obvious non-linear pattern. Based on the histogram and QQ-plot of the Pearson residuals (top right and bottom left), there is no obvious departure from a normal distribution. We have also check for the presence of auto-correlation to ensure the independency of the residuals.



Reference

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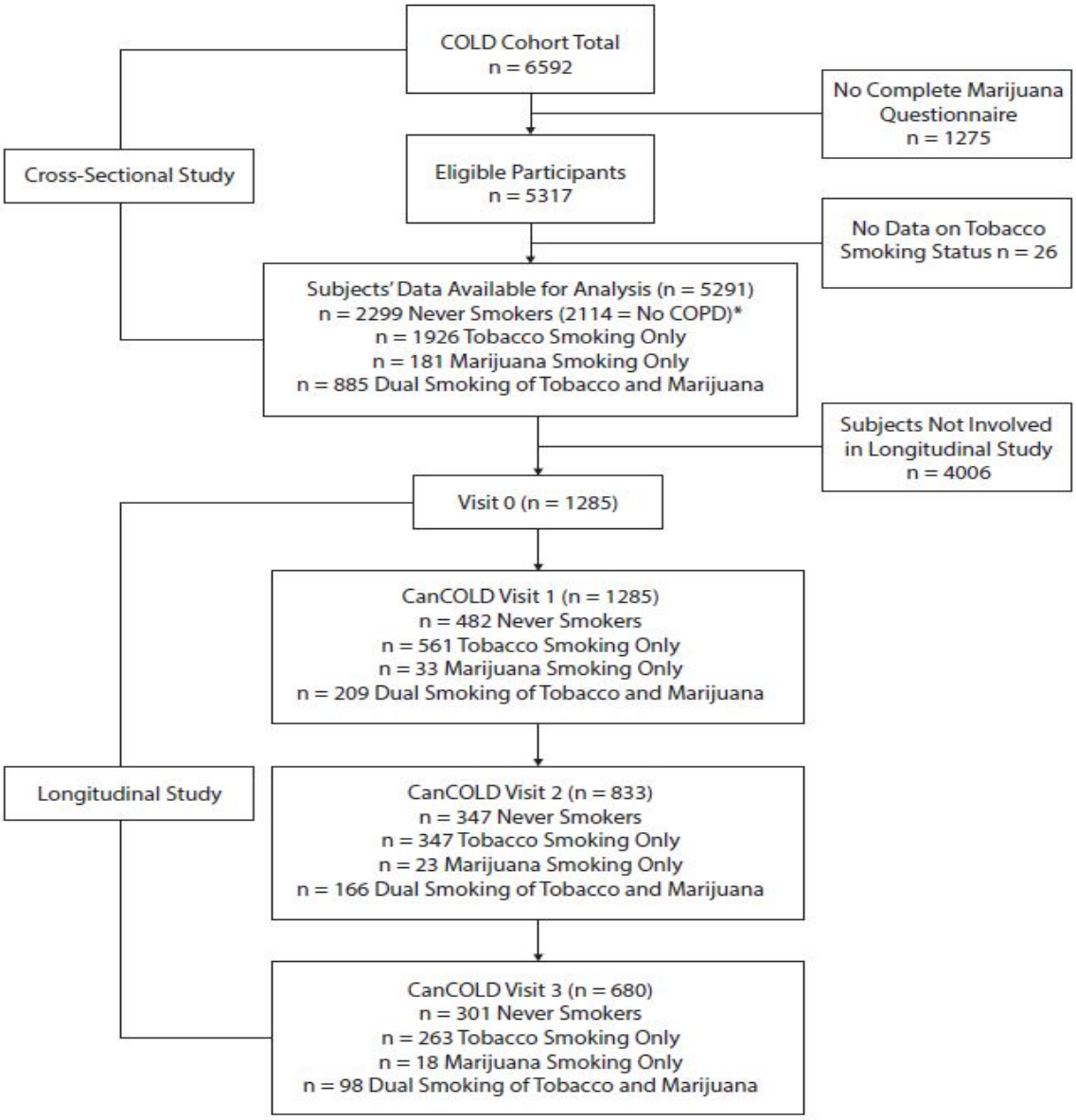
e) Statistical Model building

Our full list of confounders include: asthma status, COPD status, medication use, pack years of tobacco use, joint years of marijuana use, sex, baseline age, baseline BMI, baseline FEV1 as well as their interaction with time. We used the backward procedure for model selection. Sex, baseline age, baseline BMI and baseline FEV1 and their interaction with time were forced to be included into the model because of their biological importance on FEV1. Asthma status, COPD status and medication use were removed from the final model based on the lowest AIC.

8. eFigure1.

The selection of participants for analysis of lung function: in Cross-sectional analysis, n=5291 participants. In longitudinal analysis , n=1285 participants. Never smokers= never smokers of either marijuana or tobacco; smokers of were either smokers of marijuana only or tobacco only or were dual smokers of both.


COLD Cohort Total
n = 6592
No Complete Marijuana Questionnaire
n = 1275
Cross-Sectional Study
Eligible Participants
n = 5317
No Data on Tobacco Smoking Status n = 26
Subjects' Data Available for Analysis (n = 5291)
n = 2299 Never Smokers (2114 = No COPD)*
n = 1926 Tobacco Smoking Only
n = 181 Marijuana Smoking Only
n = 885 Dual Smoking of Tobacco and Marijuana
Subjects Not Involved in Longitudinal Study
n = 4006
Visit 0 (n = 1285)
CanCOLD Visit 1 (n = 1285)
n = 482 Never Smokers
n = 561 Tobacco Smoking Only
n = 33 Marijuana Smoking Only
n = 209 Dual Smoking of Tobacco and Marijuana
Longitudinal Study
CanCOLD Visit 2 (n = 833)
n = 347 Never Smokers
n = 347 Tobacco Smoking Only
n = 23 Marijuana Smoking Only
n = 166 Dual Smoking of Tobacco and Marijuana
CanCOLD Visit 3 (n = 680)
n = 301 Never Smokers
n = 263 Tobacco Smoking Only
n = 18 Marijuana Smoking Only
n = 98 Dual Smoking of Tobacco and Marijuana

9. e table 1. Comparison of Demographic characteristics, tobacco and marijuana smoking status, for cross-sectional cohort COLD, and longitudinal cohort CanCOLD at 4 Visits [V0, V1, V2, V3]

	Cross-Sectional Phase	Longitudinal Phase				
Variable	**COLD (n = 5291)**	**CanCOLD Visit 0 (n=1285)**	**CanCOLD Visit 1 (n=1285)**	**CanCOLD Visit 2** (n=832)**	**CanCOLD Visit 3** (n=680)**	**P-value**
Demographics						
Age, mean (sd)	59.76 (11.59)	65.10 (9.93)*	67.5 (9.80) *	68.94 (9.65) * #	70.44 (9.41) * # §	<.0001
BMI, mean (sd)	27.93 (7.13)	27.83 (9.92)	27.73 (5.46)	27.74 (5.57)	27.45 (5.62)	0.6537
YSchool, mean (sd)	15.41 (3.72)	15.53 (3.76)	15.54 (3.77)	15.43 (3.58)	15.54 (3.58)	0.8699
Sex, n(%)						<.0001
male	2443 (46.17)	712 (55.41) *	712 (55.41) *	425 (53.01) *	354 (52.10) *	
female	2848 (53.83)	573 (44.59)	573 (44.59)	375 (46.99)	326 (47.90)	
Race, n(%)						<.0001
Caucasian	4789 (90.51)	1213 (94.4)	1213 (94.4)	787 (94.59)	643 (94.5)	
Asian	287 (5.42)	38 (2.96)	38 (2.96)	21 (2.52)*	16 (2.36)*	
Other	108 (2.04)	22 (1.71)	22 (1.71)	17 (2.04)	16 (2.36)	
African	66 (1.25)	8 (0.62)	8 (0.62)	5 (0.6)	4 (0.63)	
Hispanic	41 (0.77)	4 (0.31)	4 (0.31)	2(0.24)	1 (0.16)	
Tobacco Smoking n(%)						<.0001
Never	2480 (46.87)	515 (40.08)	468 (36.42)	322 (40.35)	288 (42.42)	
Former	2085 (39.41)	548 (42.65) *	623 (48.48) *	381 (47.74) ł #	316 (46.45) ł #	
Current	726 (13.72)	222 (17.28) *	194 (15.1) * ł	95 (11.9) *	76 (11.13) *	
Pack_years, mean (sd)	13.24 (21.40)	17.33 (24.15)	17.33 (24.15) *	16.31 (23.38) *	15.75 (22.18)	
						<.0001
Marijuana Smoking n(%)						0.0784
Never	4225 (79.85)	1043 (81.17)	1043 (81.17)	693 (94.29)	569 (83.65)	
Former	346 (6.54)	151 (11.75)	151 (11.75)	89 (10.70)	75 (11.01)	
Current	720 (13.61)	91 (7.08)	91 (7.08)	50 (6.01)	36 (5.35)	
Joint_years, mean (sd)	2.73 (8.05)	3.16 (9.20)	3.16 (9.20)	2.49 (8.04)	2.48 (8.07)	0.5047

Race, pack_years, pot_status, and pot_years are retrieved from COLD;

NOTE2: * = different from COLD; ł = different from V0; # = different from V1;§= different from V2

** the unequal numbers were due to different scheduling availabilities in an ongoing longitudinal study.

10. eTable 2. Multivariable Logistic Regression Models and test for trend for the association between any marijuana smoking subgroups by Joint-years cut-offs (controlled for pack-years) and Post-bronchodilator $FEV_1/FVC < 0{\cdot}7$.: cross sectional data COLD

Marijuana Subgroups	N	Adjusted Odds Ratio (95%C.I.)	Cochran-Armitage Trend Test P-value
Never Smokers (Reference)	2299	1	
Marijuana subgroups:			<.0001#
>0-1 joint years	253	0·631(0·106,1·407)	
>1-5 joint-years	364	1·334(0·924,1·928)	
>5-20 joint-years	262	1·210(0·802,1·826)	
>20 joint-years	185	2·302(1·468,3·609)*	

Model is adjusted for age, sex, BMI, post-bronchodilator FVC and pack-years. Test for interaction for marijuana smoking and tobacco smoking was not significant.*significant association between marijuana smoking burden and post-bronchodilator $FEV_1/FVC < 0{\cdot}7$. #Significant test of trend for association between increasing joint-years with post-bronchodilator $FEV_1/FVC < 0{\cdot}7$.

11. eTable 3: Multivariable Logistic Regression Models and test for trend for the association between tobacco smoking subgroups burden of Pack-years cut-offs (controlled for joint-years) and Post-bronchodilator $FEV_1/FVC < 0{\cdot}7$.: Cross-sectional data COLD

Tobacco Subgroups	N	Adjusted Odds Ratio (95%C.I.)	Cochran-Armitage Trend Test P-value
Never Smokers (Reference)	2299	1	
Tobacco subgroups:			<.0001#
>0-1 pack-years	124	0·883(0·508,1·536)	
>1-5 pack-years	378	0·994(0·719,1·374)	
>5-20 pack-years	873	1·475(1·190,1·829)*	
>20 pack-years	1374	3·930(3·297,4·685)*	

Model is adjusted for age, sex, BMI, and joint-years. Test for interaction for marijuana smoking and tobacco smoking was not significant.*Significant association between tobacco smoking burden and post-bronchodilator $FEV_1/FVC < 0{\cdot}7$. #Significant test of trend for association between increasing pack-years with post-bronchodilator $FEV_1/FVC < 0{\cdot}7$.

12. eTable 4. 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) shown as rate of change in FVC,

	Predictor Variables	N	Rate of change in FVC (ml/yrs)			
			β Coefficient	95% CI	Std Error	P value
Model 1	**Never smokers [reference]**	482	-7·36			
	Marijuana smoking joint-years groups:					
	>0-1	56	-4·96	-20·07,10·15	7·71	0·5197
	>1-5	72	-23·32	-42·08,-4·55	9·57	0·0149*
	>5-20	63	4·51	-11·60,20·62	8·22	0·5833
	>20	51	-38·25	-62·55,-13·95	12·39	0·0020*
Model 2	**Never smokers [reference]**	482	-5·84			
	Tobacco smoking pack-years groups:					
	>0-1	59	5·85	-16·34,28·03	11·32	0·6055
	>1-5	65	-8·86	-24·70,6·99	8·08	0·2733
	>5-20	207	-6·23	-17·16,4·71	5·58	0·2642
	>20	439	-6·07	-14·99,2·86	4·55	0·1828
Model 3	**Never smokers [reference]**	482	-7·96			
	Heavy marijuana smoking (>20 Joint-years):					
	Current	34	-32·26	-63·68,-0·83	16·02	0·0442*
	Former	17	-47·68	-85·17,-10·18	19·12	0·0127*
Model 4	**Never smokers [reference]**	482	-3·93			
	Heavy tobacco smoking (>20 Pack-years):					
	Current	272	-17·41	-32·07,-2·74	7·48	0·0200*
	Former	167	-0·51	-9·26,8·23	4·46	0·9082

Never smokers are never smokers of both marijuana and tobacco. Smoking groups are stratified by baseline pack-years or joint-years. Current and former smoking are defined by baseline smoking status. In each model the predictor variables are: a) time-varying variables (assessed at each visit) of marijuana or tobacco smoking exposure (pack-years or joint-years); BMI, follow-up time and FVC; b) other variables :sex, baseline FVC, baseline age. *significantly different compared with that of never-smokers of both marijuana and tobacco.The β coefficient is the difference in the mean rate of change of FVC compared with the reference (never smokers of both) and corrected for exposure (either joint-years or pack-years accordingly). The β coefficient for never smokers of tobacco and marijuana is computed as the sum of the β coefficient for age, BMI, follow-up time and baseline FVC.

13.

eTable 5. Sensitivity analysis :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) shown as rate of change in FEV_1 (baseline FEV1 excluded as covariate)

			Rate of change in FEV_1 (ml/yrs)			
	Predictor Variables	**N**	**β Coefficient**	**95% CI**	**Std Error**	**P value**
Model 1	**Never smokers [reference]**	482	-0.693			
	Marijuana smoking joint-years groups:					
	>0-1	56	-6·69	-17·49,4·11	5·50	0·2248
	>1-5	72	-18·78	-35·93,-1·62	8·75	0·0320*
	>5-20	63	-0·96	-12·44,10·52	5·85	0·8694
	>20	51	-32·41	-49·36,-15·46	8·64	0·0002*

In each model the predictor variables are: a) time-varying variables (assessed at each visit) of marijuana or tobacco smoking exposure (pack-years or joint-years); BMI, follow-up time; b) other variables :sex, baseline age.
*significantly different compared with that of never-smokers of both marijuana and tobacco.

14.

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