

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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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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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 elsewhere¹. 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 E1.

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 _____ years old A2
pot/marijuana?

- 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 _____ years old A4
you when you last stopped? (If the participant has
not stopped smoking, record as code '99'.)

! Choose to respond to the most appropriate answers 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 _____ joints/week A5
smoke(d), about how many joints per week
do (did) you smoke?

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

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

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

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

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

! Choose most appropriate response below:

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

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

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 FEV₁) has been previously published³ Briefly we used the tables in Hedeker et al⁶, 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 FEV₁ 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 study⁸. 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 occasions⁹, 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

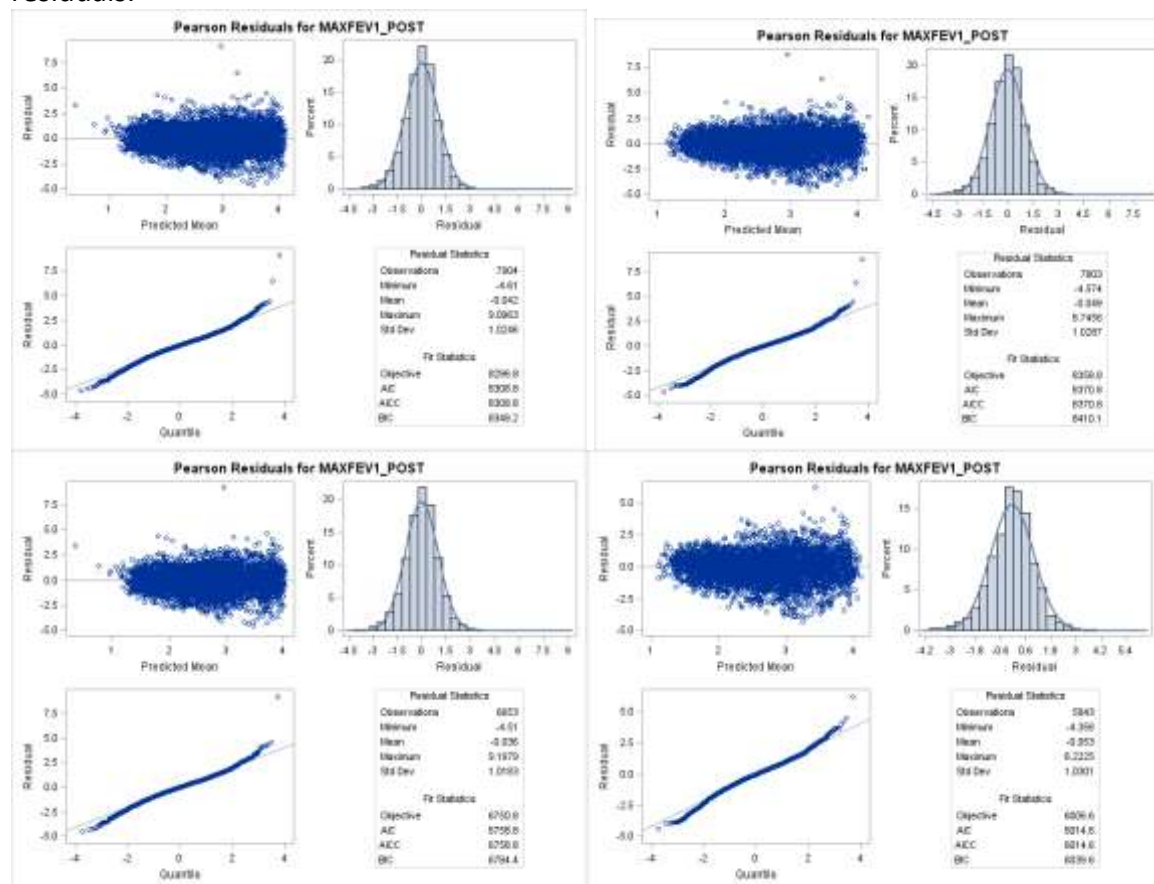
presence of COPD may increase the decline in FEV1; b) by excluding baseline FEV1 as covariate to address the possibility of regression to the mean.

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

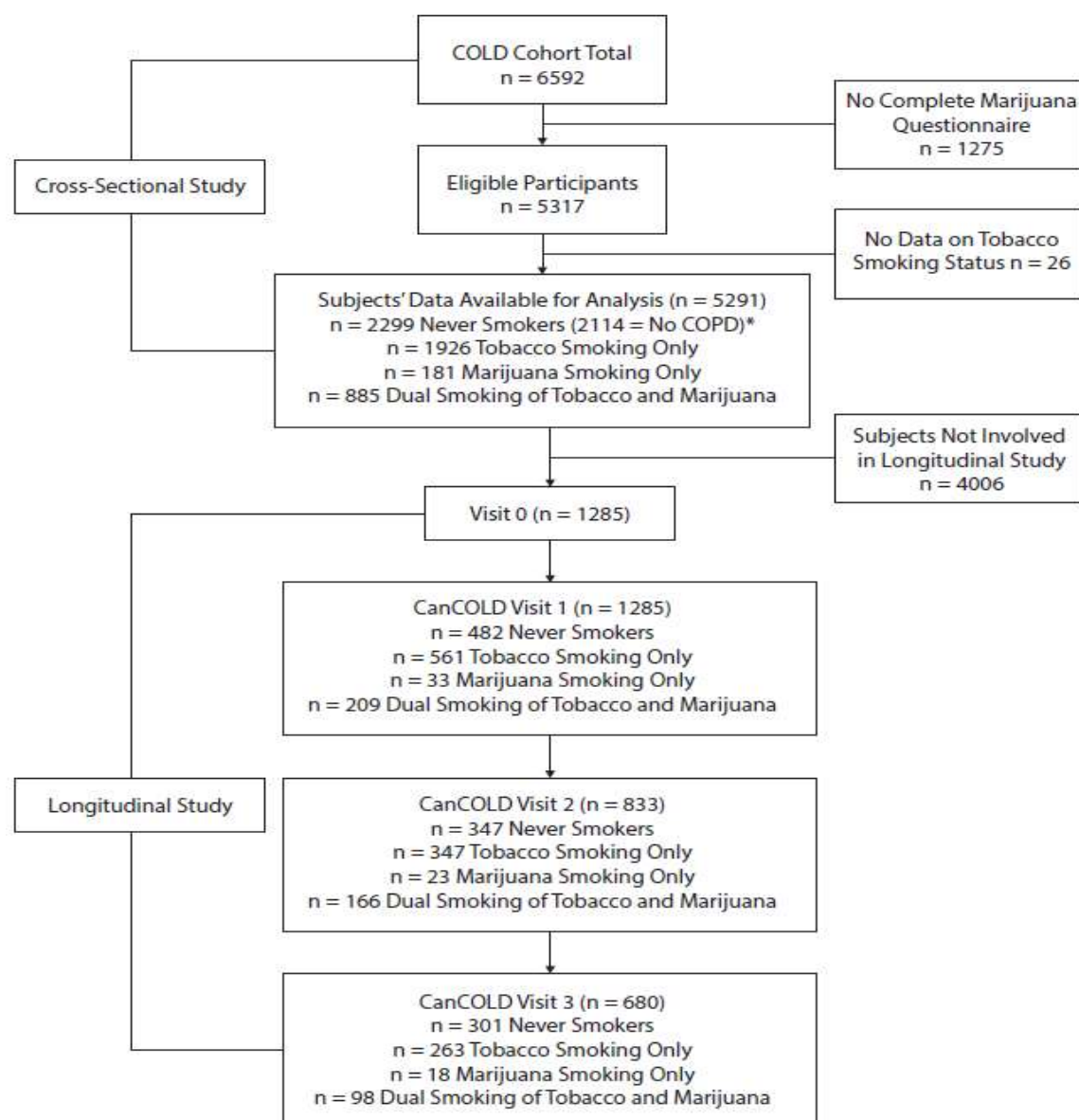
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e) Statistical Model building

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. Figure E1.

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.



9. Table E1. 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
<u>Demographics</u>						
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)	
<u>Race</u> , 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)	
<u>Tobacco Smoking</u>						<.0001
n(%)						
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) † #	316 (46.45) † #	
Current	726 (13.72)	222 (17.28) *	194 (15.1) * †	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
<u>Marijuana Smoking</u>						0.0784
n(%)						
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; † = different from V0; # = different from V1;§= different from V2

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

10. Table E2. 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 FEV₁/FVC < 0.7.: 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:			
>0-1 joint years	253	0.631(0.106,1.407)	<.0001#
>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 FEV₁/FVC < 0.7. #Significant test of trend for association between increasing joint-years with post-bronchodilator FEV₁/FVC < 0.7.

11. Table E3: 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 FEV₁/FVC < 0.7.: 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:			
>0-1 pack-years	124	0.883(0.508,1.536)	<.0001#
>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 FEV₁/FVC < 0.7. #Significant test of trend for association between increasing pack-years with post-bronchodilator FEV₁/FVC < 0.7.

12. Table E4. 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*
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
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.

Table E5. 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 FEV₁ (baseline FEV1 excluded as covariate)

Predictor Variables	N	Rate of change in FEV ₁ (ml/yrs)			
		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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