Differential Effects of Cannabis and Tobacco on Lung Function in Mid-Adult Life

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At A Glance

What is the current scientific knowledge on this subject?

The effects of long-term cannabis use of pulmonary function are uncertain and appear to be different to smoking tobacco.

What does this study add to the field?

Cumulative cannabis and tobacco use was studied up to age 45 in a large population-based cohort. Cannabis was associated with range of pulmonary function measures indicating

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hyperinflation, large airway resistance, and impaired gas transfer. The pattern of these associations was different to that observed for tobacco smoking

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Abstract

Rationale. Evidence suggests that the effects of smoking cannabis on lung function are different to tobacco. However, long-term follow-up data are scarce, and mostly based on young adults.

Objective. To assess the effects of cannabis and tobacco on lung function in mid-adult life.

Methods. Cannabis and tobacco use were reported at ages 18, 21, 26, 32, 38, and 45 years in a population-based cohort study of 1037 participants. Spirometry, plethysmography, and carbon monoxide transfer factor were measured at age 45. Associations between lung function and cannabis use were adjusted for tobacco use.

Measurements and Main Results. Data were available from 881 (88%) of 997 surviving participants. Cumulative cannabis use was associated with lower Forced Expiratory Volume in one second to Forced Vital Capacity ratios, due to a tendency towards higher Forced Vital Capacities. Cannabis use was also associated with higher total lung capacity, functional residual capacity, residual volume, and alveolar volume along with lower mid-expiratory flows, airway conductance, and transfer factor. Quitting regular cannabis use between assessments was not associated with changes in spirometry.

Conclusions. Cannabis use is associated with higher lung volumes suggesting hyperinflation. There is evidence of increased large-airways resistance and lower mid-expiratory airflow, but impairment of Forced Expiratory Volume in one second to Forced Vital Capacity ratio is due to higher Vital Capacities. This pattern of effects is different to those of tobacco. We provide the first evidence that lifetime cannabis use may be associated with impairment of gas transfer.

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Introduction

The effects of smoking cannabis on lung function are controversial.[1] Several studies indicate that smoking cannabis leads to changes in lung function, but the pattern of these changes appears to be different from those of tobacco, and their clinical significance is uncertain. Thus, while smoking cannabis is associated with airway inflammation and symptoms of bronchitis, the evidence that persistent cannabis use causes airflow obstruction and chronic obstructive pulmonary disease is unconvincing.

Although cannabis has been associated with lower Forced Expiratory Volume in one second to Forced Vital Capacity (FEV_1/FVC) ratios in some studies, this mostly appears to be due to an increase in the FVC rather than a reduction in FEV_1.[1-4] Cannabis use has also been associated with greater static lung volumes suggesting hyperinflation and gas-trapping, but there is no evidence that it impairs gas transfer.[2,5-7] A consistent finding is that cannabis users have higher large airway resistance and lower conductance, which is compatible with the evidence that cannabis causes bronchitis.[1,2,5-7] However, there is considerable uncertainly about the effects of long-term cannabis use on lung function.

Cannabis is still illegal in most countries, making it difficult to study. Few studies have long-term data on cannabis use and lung function. Most cannabis users also smoke tobacco and it is difficult to separate the effects of the two substances in observational, particularly cross-sectional, studies.[1] Furthermore, much of the existing research has been on young adult populations, whereas any effects on lung function may not become evident until mid-to-late adult life. There are also questions about what happens after quitting cannabis use. Symptoms of bronchitis tend to improve after stopping cannabis, but whether the effects of cannabis on lung function are reversible is unknown.[8,9] One study suggested that the FEV_1 of ex-users of cannabis continued to decline after quitting, but this was based on a very small number of

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heavy cannabis users, most of whom also smoked tobacco.[10,11]

We have previously reported associations between cannabis use and lung function in the Dunedin Multidisciplinary Health and Development Study (Dunedin study): a population-based cohort followed to age 32 years.[2] We now have follow-up data at age 45 years, thereby adding a further 13 years of follow-up into mid-adult life. We report on the associations between long-term cannabis use and a comprehensive range of lung function tests at age 45.

Methods (500 words)

Full methods are in the online supplement. Briefly, the Dunedin study comprises a population-based cohort of 1037 individuals born in 1972/1973 and followed to age 45 years, when 938 of 997 surviving participants (94%) were assessed.[12] The appropriate ethics committee approved each assessment.

At ages 18, 21, 26, 32, 38, and 45 years, participants were asked how many times they had used marijuana (cannabis) in the previous year.[2,13] Cumulative exposure to cannabis was calculated as the number of "joint-years" since age 17 (using cannabis once a day for a year equals one joint-year), assuming that cannabis use in the previous year was representative of the years between assessments. The maximum use was censored at one joint-year each year. Cumulative tobacco exposure was calculated from the reported number of pack-years (20 cigarettes a day for one year equals one pack-year) up to 18 years, and between each assessment.

At age 45, FEV_1, FVC, forced expiratory flow between 25 and 75% of the vital capacity (FEF_{25-75}), total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), specific airway conductance adjusted for thoracic gas volume (sGaw), transfer factor for carbon monoxide (T_{LCO}), and alveolar volume by methane dilution (V_A) were measured

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using a body plethysmograph (Care Fusion, CA).[14-16] Spirometry was repeated 10-15 minutes following inhalation of 200μg salbutamol. Exhaled carbon monoxide was measured just before TLCO. Haemoglobin, height, and weight were measured.

Statistical analysis

Associations between lifetime cannabis and tobacco exposure and lung function were assessed by linear regression using estimates of both joint-years and pack-years as independent variables. Analyses adjusted for height, sex, and weight. Analyses of TLCO also adjusted for exhaled carbon monoxide, haemoglobin, and whether the participant had smoked on the day of assessment. We tested whether sex or any tobacco smoking modified the association of lung function with cannabis use by fitting interaction terms and conducting separate analyses for men and women and for never and current/former tobacco smokers. Models were checked by diagnostic plots of the residuals.

Sex-specific spirometry prediction equations for each age were derived from never-tobacco smoking, non-asthmatic participants. We compared percent-predicted spirometry before and after the first occasion of quitting regular cannabis use. Because residuals were not normally distributed, we used quantile regression of median joint-years to assess whether spirometry at age 15 or childhood asthma predicted subsequent cannabis use.

We further analysed repeated measures of percent-predicted spirometry at ages 18, 21, 26, 32, 38, and 45 using mixed models with recent cannabis and tobacco use as the main predictors. These adjusted for spirometry at age 15, sex, weight, and age.

To visually compare trajectories between cannabis users and non-users for tobacco smokers and non-smokers, linear mixed models with a random participant effect, estimated using restricted maximum likelihood, were constructed including assessment age as a factor along

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with linear and quadratic joint-years and linear and quadratic pack-years at age 45, and the four interactions between these variables and assessment age.

Analyses used Stata version 17 (College Station, TX). Two-sided $p<0.05$ was considered statistically significant.

Results

Descriptive statistics of the cohort according to cannabis use by age 45 are summarised in Table 1. Women were less likely to have ever used cannabis than men and tended to use less of it (median (25^{th}–75^{th} percentile) joint-years 0.03 (0 to 0.27) and 0.22 (0.01 to 3.30) respectively, $p<0.001$ by quantile regression). There was no significant association between asthma at age 45 and joint-years cannabis or pack-years tobacco (Tables 1 and E1). Childhood asthma (by age 15) did not predict subsequent cannabis or tobacco use (data not shown). Cannabis smokers were more likely to smoke tobacco and cumulative pack-years of tobacco smoking by age 45 correlated with joint-years of cannabis (Spearman's rho=0.51, $p<0.001$). The mean percent-predicted FEV_1, FVC, and FEV_1/FVC measures at age 15 were not associated with subsequent cannabis use (Online Table E2) and were not associated with median joint-years by age 45 (p values>0.76 in sex-adjusted quantile regression analyses).

Of the 143 participants who reported using cannabis at least 6 times in the previous year at age 45, 137 reported on how they usually used it, with multiple responses permitted. Most reported smoking joints or cones (61%), a pipe or bong (42%), "spots" (a method of heating cannabis to inhale the smoke (9%), or a combination of these methods. Only three did not report inhaling cannabis smoke at age 45 (two oral, one vaping).

Overall, cannabis use was associated with higher lung volumes as measured by TLC, FRC, RV and V_A, with a non-significant association with higher FVC values (Table 2). Cannabis

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was also associated with lower FEV_1/FVC ratios, lower FEF_{25-75}, and lower sGaw, but there was no significant association with FEV_1. There was also an association with lower gas transfer, both with and without adjustment for lung volume (T_{LCO} and T_{LCO}/V_A) (Table 2). By contrast, tobacco smoking was associated with lower FEV_1 as well as higher static lung volumes (but not FVC or V_A) and lower gas transfer. Adjusting the analyses for childhood-onset asthma made no material difference to the findings. Excluding the three cannabis users at age 45 who did not report smoking it also made no material difference to the results.

Joint-years cannabis exposure was also associated with a similar pattern of differences in post-bronchodilator spirometry, except that in this instance the association with higher FVC values was statistically significant (Table 3).

The interaction tests between sex and joint-years were mostly not statistically significant, providing little evidence that the associations between cannabis use and lung function differed by sex (Online Table E3). The only statistically significant sex-interaction with cannabis exposure was for RV, for which there was a stronger association with cannabis in women, although the association was in the same direction and also statistically significant in men. However, when analysed separately, the associations between cannabis and higher FVC and V_A and lower FEV_1/FVC, FEF_{27-75} were only significant in men, whereas the associations with higher FRC and lower T_{LCO} were only significant in women. Cannabis was associated with higher TLC and lower sGaw and T_{LCO}/V_A in both sexes.

There was also little statistical evidence that tobacco smoking modified the association between cannabis and spirometry (most interaction p values>0.05). Both subgroups of ever and never tobacco smokers had statistically significant associations with lower FEV_1/FVC ratios and higher TLC values, but the association between cannabis use and FVC was only significant in those who had never smoked tobacco (Table 4). However, the other static lung

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volumes, FRC and RV, were only significantly associated with cannabis among tobacco smokers, with a statistically significant interaction between cannabis and tobacco for FRC. Associations between cannabis and lower sGaw, T_{LCO}/V_A, and higher V_A were also only statistically significant among tobacco smokers, although the associations were of similar magnitude and direction among never tobacco smokers.

158 participants cut down or quit using cannabis from weekly or more to less than weekly during follow up. This change in cannabis use was not associated with clinically or statistically significant changes in spirometry: FEV_1 improved by 0.1 percent predicted (95% CI: -1.0 to 1.3; p=0.803), FVC decreased by 0.3 percent predicted (95% CI: -1.4 to 0.8; p=0.561), and the FEV_1/FVC ratio increased by 0.5% predicted (95% CI: -0.3 to 1.3; p=0.181).

Longitudinal analyses of the lifecourse spirometry data from ages 18 to 45 with adjustment for baseline measurements at age 15 are shown in supplemental Table E4. These found statistically significant associations between recent cannabis use with higher percent-predicted FVC, and lower FEV_1/FVC ratios. Tobacco was associated with lower FEV_1 and FEV_1/FVC ratios.

Estimated trajectories of FEV_1, FVC and the FEV_1/FVC ratio from the mixed models are shown in the Figure for participants who were non-tobacco smokers or had accumulated 15 pack-years by age 45 according to whether that had not used cannabis or had accumulated 5 joint-years.

Discussion

Findings from this longitudinal investigation of cannabis and tobacco use up to mid-adult life indicate that cannabis is associated with changes in lung function that are independent of the

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effects of tobacco smoke and appear to be of a different pattern. Both cannabis and tobacco were associated with lower values for the FEV_1/FVC ratio. However, this was mostly due to higher values for FVC among cannabis users with little difference in FEV_1, whereas tobacco smokers had lower FEV_1 values.

Both tobacco and cannabis use were also associated with higher values for static lung volumes (TLC, FRC, and RV) by plethysmography, indicating a tendency towards hyperinflation and gas trapping, but only cannabis was associated with increased alveolar volume by gas dilution. Both cannabis and tobacco were also associated with lower airway conductance (sGaw) and lower mid-expiratory airflow (FEF_{25-75}).

Unlike our earlier assessment of this cohort at age 32,[2] we found that by age 45 cannabis was now associated with lower values for gas transfer (T_{LCO}). The transfer factor per unit of alveolar volume (T_{LCO} /V_A) was even more strongly associated with cannabis use, but this is partly explained by higher volumes of gas distribution (V_A). As far as we are aware, this is the first time that a reduction in gas transfer has been reported in association with cannabis use, with previous cross-sectional studies finding no association.[5-7] It is likely that our earlier report and other studies did not follow cannabis users for long enough to demonstrate an impairment of gas transfer. This finding could indicate that long-term cannabis use may lead to emphysematous changes. Although emphysema does not appear to be common among cannabis users unless they also smoke tobacco,[7] there are numerous reports of giant bullous emphysema among heavy cannabis users suggesting that long term cannabis may lead to alveolar destruction.[1] Our finding of an association between cannabis use and gas transfer should be interpreted with some caution however, given the p value of 0.045. We only found an association between cannabis use and lower gas transfer factor among those who also smoked tobacco, although the lack of association among non-tobacco users could also be

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explained by their much lower exposure to cannabis.

Except for the new finding of a lower gas transfer, the pattern of lung function associations with cannabis use is consistent with the findings from the same cohort 13 years earlier (age 32). At that age, cannabis use was associated with greater dynamic and static lung volumes, and lower airway conductance, but an association with lower FEV_1/FVC ratio was due to higher FVC values with no evidence of a reduction in FEV_1. These findings are also consistent with other reports that cannabis is associated with greater vital capacity but little difference in FEV_1.[1-4] The finding of a pattern of the associations with higher values for TLC, FRC, RV, and V_A as well as FVC support the inference that cannabis use leads to greater lung volumes. An association between cannabis and lower airway conductance (sGaw) has been a consistent finding, suggesting that cannabis impacts on large airway function despite having little effect on FEV_1.[2,5-7] This observation is compatible with the high prevalence of bronchitis symptoms and evidence of bronchial epithelial injury amongst cannabis smokers.[19-22] In support of this, we also found an association between cannabis use and lower mid-expiratory flow (FEF_{25-75}).

Women were less likely to use cannabis than men in this cohort, and if they did, they tended to use less. However, for some of the lung function measures, the associations with cannabis use were equally strong or stronger among women (Online Table E3). Although mostly not supported by statistically significant tests for sex-interactions, there were several apparent differences between men and women when analysed separately. The associations of cannabis with spirometry (FVC, FEV_1/FVC, and FEF_{25-75}) and alveolar volume (V_A) were stronger in men, but the associations with higher FRC and RV and lower gas transfer (T_{LCO}) were stronger in women. Whether there are biological mechanisms underlying these apparent differences in susceptibility, whether they reflect differences in cannabis use, or whether

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these are chance findings is not clear and these observations require confirmation in other cohorts.

The main difficulty in assessing the effects of cannabis on lung function is distinguishing these from tobacco. Most cannabis users also smoked tobacco and there was a strong correlation between reported joint-years and pack-years (rho = 0.51). We adjusted for pack-years tobacco use in all analyses, but any errors in reported tobacco use may mean that the regression analyses do not adequately adjust for the confounding influence of tobacco smoking. We therefore analysed the associations between cannabis use and lung function in those who had never used tobacco (Table 4). It is important to note that most heavy cannabis users were also tobacco smokers, reducing the power to detect associations among never tobacco-users. Nevertheless, the pattern of associations was similar to those among tobacco smokers: both ever- and never-tobacco users had associations between cannabis and the FEV_1/FVC ratio and TLC, while there were also tendencies to lower values for FEF_{25-75}, sGaw, and DL_{CO}/V_A and higher values V_A among never tobacco users. There was only one statistically significant interaction between ever tobacco smoking and cannabis use, and that was for FRC, which was only associated with cannabis among tobacco users.

Although our primary aim was to assess the impact of cumulative cannabis and tobacco exposure on lung function in mid-adult life, we also undertook supplementary longitudinal analyses of the repeated spirometry measures throughout adult life. These adjusted for percent-predicted spirometry at age 15 and used recent use of cannabis and tobacco as the main predictors. These analyses provided consistent findings: cannabis use was associated with higher percent predicted FVC values, but not with FEV_1, whereas tobacco was associated with lower FEV_1 values, but not with FVC (Supplementary Table E4). Hence both were associated with lower FEV_1/FVC ratios, but due to different mechanisms.

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The modelled trajectories of spirometry from age 9 to 45 years are consistent with our other analyses (Figure). These show no material difference in early lung function among those who would subsequently smoke tobacco or cannabis (using cumulative use at age 45). Over adulthood, tobacco smoking was associated with a progressive decline in percent-predicted FEV_1, little change in FVC, and hence a decline in the FEV_1/FVC ratio. By contrast, cannabis use was not associated with a decline in FEV_1, but a tendency to higher FVC values, also resulting in lower FEV_1/FVC ratios.

It is unclear why cannabis has different associations with lung function from tobacco. Cannabis users tend to smoke far fewer times a day than tobacco smokers and it is possible that the participants have not smoked enough cannabis for it to have a measurable effect on some aspects of lung function. However, this seems unlikely in view of the strong associations with higher lung volumes and lower airway conductance. Apart from the active ingredients of cannabinoids and nicotine, the inhaled combustion products in cannabis and tobacco smoke are qualitatively similar.[23] The consistency of our findings with other studies indicates that there are likely to be real biological differences between the effects of cannabis and tobacco smoke, but we can only speculate about the reasons for this. Delta-9-tetrahydrocannibiol is a short-term bronchodilator and it is possible that it has long-term effects.[24] The commonly-used technique of smoking cannabis, with deeper inhalations and breath-holding, may be another reason.[25]

This study has a number of limitations. Cannabis use was reported for the previous year at each assessment and our estimate of use assumes that the consumption of cannabis was similar for the intervening years. At some assessments, the maximum amount of cannabis recorded was censored at once a day (365 days a year) and we will have underestimated consumption for those who used cannabis more often than this. We also do not know how

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much cannabis was used on each occasion. Hence, our measure of cannabis exposure will be less accurate than that of tobacco. Study members may have under-reported cannabis use because it is an illegal substance, although our well-established record of confidentiality and non-intervention over 45 years of the lives of the Study members tends to encourage honest reports. For most assessment ages, we do not know how the cannabis was used, although, when asked at age 45, nearly all users (98%) said that they usually smoked it using one or more of several techniques. By necessity we have assumed that our measure of joint-years represents smoked cannabis. Excluding the three participants who took cannabis by other means at age 45 made no material difference to the findings. We have not collected data on vaping, either cannabis or tobacco, through the lifecourse, although vaping has only recently become available and is unlikely to substantially influence the lifetime exposures in this cohort. We have undertaken a large number of statistical analyses and have not adjusted the p values for multiple testing. Hence our interpretation is based on the overall pattern for findings and individual statistically significant findings should be interpreted cautiously.

The study also has a number of strengths. Both cannabis and tobacco smoking were assessed on a number of occasions throughout early to mid-adult life in a population-based cohort with a high rate of follow-up. We have measurements of spirometry since childhood, which enabled us to test whether early lung function influenced the likelihood of smoking. We found no evidence that spirometric lung function at age 15 was associated with subsequent use of tobacco or cannabis providing no evidence of a “healthy smoker” effect for cannabis.

The findings of this and other studies should inform the current debates around the world about the legalisation and/or decriminalisation of cannabis. In some countries, there has been little discussion about the potential respiratory health consequences of increased cannabis consumption. Interpreting the evidence in the context of forming policies presents difficulties

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however: it is increasingly clear that cannabis has different effects on lung function to tobacco and the effects of widespread cannabis use will not necessarily mirror the harms caused by tobacco smoking. The long-term consequences of the hyperinflation, gas-trapping, and lower airway conductance observed in several studies are not yet known. Despite this, bronchitis with symptoms of cough and sputum production has been documented.[1,8] We have added the observation of impaired gas transfer to this list of concerns. There are also many reports of severe bullous lung disease in heavy cannabis users, but epidemiological data on this association are lacking. We also need research into the mechanisms of the effects of cannabis on lung function.

In conclusion, cannabis is associated with evidence of hyperinflation, increased large airway resistance, and impairment of gas transfer in mid adulthood. The pattern of lung function changes is distinct from those of tobacco, suggesting that smoking cannabis and tobacco have different physiological consequences for the lungs.

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Declaration of interests

None of the authors has a conflict of interest with this manuscript.

Data sharing statement

We do not have ethical approval to share individual level data. Summary data may be available on reasonable request.

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Figure legend

Estimated mean percent-predicted (95% CI) spirometry function at each assessment for non-tobacco smokers (top row) and tobacco smokers of 15 pack-years by age 45 (bottom row). The open circles and dotted lines are the estimated values for non-cannabis users. The squares and solid lines show the estimates for a person who has accumulated 5 joint-years by age 45. Estimates are from linear mixed models of lung function using joint-years cannabis (linear and quadratic terms), pack-years tobacco (linear and quadratic terms), age, and the four interactions between age and the continuous variables as the independent variables alongside a random participant effect.

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Table 1. Age 45 descriptive variables.

		Cumulative cannabis use by age 45			
		None (n=242)	**≤5 joint-years (n=510)**	**>5 joint-years (n=129)**	**P**
Sex	**Women (%)**	150 (34%)	250 (57%)	40 (9%)	<0.001* a, b, c
	Men (%)	92 (21%)	260 (59%)	89 (20%)	
Cumulative tobacco use	**None (%)**	193 (45%)	218 (51%)	14 (3%)	<0.001* a, b, c
	≤5 pack-years (%)	17 (13%)	96 (78%)	10 (8%)	
	>5 pack-years (%)	32 (10%)	196 (59%)	105 (32%)	
Current asthma	**No (%)**	194 (27%)	421 (59%)	96 (14%)	0.109*
	Yes (%)	48 (28%)	89 (52%)	33 (19%)	
BMI (kg/m^2)	**Mean (SD)**	29.1 (6.1)	28.3 (5.6)	27.2 (5.3)	0.008† b

Only participants with spirometry data from age 45 are included. P values are from χ^2-tests* and Wald test from one-way ANOVA†. [a] p<0.0 5 for no cannabis group compared to ≤5 joint-year group, [b] p<0.0 5 for no cannabis group compared to >5 joint-year group, [c] p<0.0 5 for ≤5 joint-year cannabis group compared to >5 joint-year group

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Table 2. Association of cannabis and tobacco use with lung function at age 45

Linear regression analyses of lung function at age 45 using cumulative cannabis and tobacco as the exposures of interest. Analyses are adjusted for sex, height, weight, and use of the other substance. Analyses of TLCO also adjust for exhaled carbon monoxide, blood haemoglobin, and reported smoking on the day of assessment. Coefficients represent the difference in lung function associated with each joint-year of cannabis or pack-year of tobacco up to age 45.

		Cannabis				**Tobacco**		
	n	**Coefficient**	**95% CI**	**p**		**Coefficient**	**95% CI**	**p**
FEV_1 (mL)	881	-2.7	-9.0 to 3.6	0.404		-7.8	-11.1 to -4.4	**<0.001**
FVC (mL)	881	6.6	-0.1 to 13.9	0.079		-2.8	-6.6 to 1.1	0.160
FEV_1/FVC (%)	881	-0.13	-0.22 to -0.04	**0.004**		-0.13	-0.18 to -0.08	**<0.001**
FEF_{25-75} (mL/s)	881	-14.4	-26.2 to -2.5	**0.018**		-17.5	-23.7 to -11.2	**<0.001**
TLC (mL)	866	18.1	8.5 to 27.8	**<0.001**		6.8	1.7 to 12.0	**0.009**
FRC (mL)	869	11.3	3.7 to 18.9	**0.004**		10.8	6.8 to 14.8	**<0.001**
RV (mL)	866	10.7	5.6 to 15.8	**<0.001**		9.4	6.7 to 12.1	**<0.001**
sGaw (mL/s/cmH_2O/L)	865	-1.15	-1.75 to -0.54	**<0.001**		-0.65	-0.97 to -0.34	**<0.001**
TLCO (mL/min/mmHg)	839	-0.051	-0.100 to -0.001	**0.045**		-0.073	-0.105 to -0.042	**<0.001**
TLCO/VA (mL/min/mmHg/L)	839	-0.016	-0.024 to -0.008	**<0.001**		-0.012	-0.017 to -0.007	**<0.001**
VA (mL)	839	11.2	1.7 to 20.7	**0.021**		0.0	-6.1 to 6.1	0.999

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Table 3. Association of cannabis and tobacco use with post-bronchodilator spirometry at age 45

Linear regression analyses of post-bronchodilator spirometry lung function at age 45 using cumulative cannabis and tobacco as the exposures of interest. Analyses are adjusted for sex, height, weight, and use of the other substance. Coefficients represent the difference in lung function associated with each joint-year of cannabis or pack-year of tobacco up to age 45.

		Cannabis				**Tobacco**		
	n	**Coefficient**	**95% CI**	**p**		**Coefficient**	**95% CI**	**p**
FEV_1 (mL)	871	-0.8	-7.2 to 5.6	0.810		-7.9	-11.2 to -4.6	**<0.001**
FVC (mL)	871	10.1	2.6 to 17.6	**0.008**		-1.9	-5.7 to 2.0	0.340
FEV_1/FVC (%)	871	-0.16	-0.25 to -0.08	**<0.001**		-0.15	-0.19 to -0.10	**<0.001**
FEF_{25-75} (mL/s)	871	-17.4	-30.5 to -4.3	**0.009**		-21.2	-28.0 to -14.5	**<0.001**

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Table 4. Associations of cannabis use with lung function at age 45 in tobacco smokers and non-smokers

Linear regression analyses of lung function at age 45 using joint-years cannabis exposure as the exposure of interest. All analyses adjust for sex, weight, and height. Analyses among ever smokers also adjust for pack-years tobacco exposure and analyses of TLCO also adjust for exhaled carbon monoxide and blood haemoglobin and reported smoking on the day of the test. Coefficients represent the difference in lung function associated with each joint-year of cannabis up to age 45. *p int values are the p values for the interaction between ever smoking and joint-years.

	Never tobacco smokers					**Current or ex-tobacco smokers**				***p int**
	n	**Coeff**	**95% CI**	**p**		**n**	**Coeff.**	**95% CI**	**p**	
FEV_1 (mL)	425	0.8	-14.8 to 16.3	0.924		456	-3.1	-10.3 to 4.0	0.391	0.220
FVC (mL)	425	19.8	1.3 to 38.2	**0.035**		456	4.0	-4.0 to 12.1	0.326	0.054
FEV_1/FVC (%)	425	-0.25	-0.46 to -0.05	**0.015**		456	-0.11	-0.22 to -0.00	**0.042**	0.611
FEF_{25-75} (mL/s)	425	-25.2	-55.3 to 4.9	0.101		456	-12.4	-25.5 to 0.6	0.062	0.989
TLC (mL)	419	25.0	1.6 to 48.3	**0.036**		447	17.4	6.3 to 28.4	**0.002**	0.709
FRC (mL)	421	-1.3	-19.0 to 16.4	0.888		448	13.7	4.9 to 22.6	**0.002**	**0.034**
RV (mL)	419	5.7	-5.2 to 16.7	0.302		447	11.9	5.6 to 18.2	**<0.001**	0.066
sGaw (mL/s/cmH_2O/L)	417	-1.23	-2.88 to 0.42	0.145		448	-1.13	-1.76 to -0.49	**0.001**	0.679
TLCO (mL/min/mmHg)	410	-0.011	-0.135 to 0.114	0.868		429	-0.053	-0.108 to -0.002	0.057	0.261
TLCO/VA (mL/min/mmHg/L)	410	-0.012	-0.032 to 0.008	0.238		429	-0.016	-0.025 to -0.008	**<0.001**	0.575

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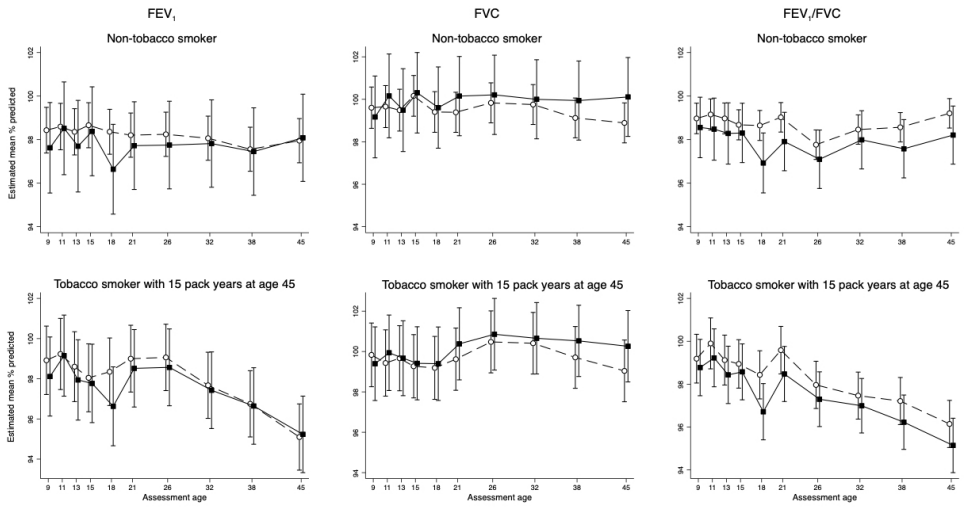

Estimated mean percent-predicted (95% CI) spirometry function at each assessment for non-tobacco smokers (top row) and tobacco smokers of 15 pack-years by age 45 (bottom row). The open circles and dotted lines are the estimated values for non-cannabis users. The squares and solid lines show the estimates for a person who has accumulated 5 joint-years by age 45. Estimates are from linear mixed models of lung function using joint-years cannabis (linear and quadratic terms), pack-years tobacco (linear and quadratic terms), age, and the four interactions between age and the continuous variables as the independent variables alongside a random participant effect.

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Differential Effects of Cannabis and Tobacco on Lung Function in Mid-Adult Life

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Online data supplement

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Methods

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal study of health and behaviour in a population-based birth cohort of individuals born in Dunedin, New Zealand in 1972/1973.(E1) 1037 individuals (52% male; 91% of eligible births) participated in an assessment at age 3 years, forming the base sample for the study. Study members represent the full range of socioeconomic status in the general population of the South Island of New Zealand and are primarily of New Zealand/European ethnicity. The cohort has been assessed at multiple ages through childhood and adulthood and most recently at 45 years when we assessed 938 of 997 surviving participants (94%). Each assessment for the study was approved by the appropriate ethics committee (most recently the Health and Disability Ethics Committee: 17/STH/25/AM05).

Cannabis (marijuana) smoking history was obtained at ages 18, 21, 26, 32, 38, and 45 years.(E2, E3) At each assessment, participants were asked how many times they had used marijuana in the previous year. Cumulative exposure to cannabis was calculated as the number of "joint-years" since age 17, whereby using cannabis once a day for a year is equivalent to one joint-year. These estimates assume that the number of times cannabis had been used in the previous year was representative of the years since the previous assessment. At ages 38 and 45, the maximum recorded use in the previous year was capped at 365 (i.e. the equivalent of once a day). Therefore maximum use was censored at one joint-year each year (hence the maximum possible recorded use between age 17 and 45 years was 28 joint-years). Cumulative tobacco exposure was calculated from the reported number of cigarettes smoked per day up to 18 years, and between each of the assessments up to age 45 years. One pack-year is defined as the equivalent of 20 cigarettes a day for one year. Where cannabis or tobacco data were missing for an assessment, the amount reported at the next assessment was

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used to calculate cumulative exposure.

Spirometry has been measured at each assessment since age 9. At age 45, a broad range of lung function tests including spirometry (FEV_1, FVC, and forced expiratory flow between 25 and 75% of the vital capacity (FEF_{25-75})), total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), specific airway conductance adjusted for thoracic gas volume (sGaw), transfer factor for carbon monoxide (T_{LCO}), and alveolar volume by methane dilution (V_A) were measured using a body plethysmograph (Care Fusion, CA).(E4-6) Spirometry was repeated 10-15 minutes following inhalation of 200µg salbutamol via a metered dose inhaler and large volume spacer device. Study members were requested to refrain from using any inhalers and to avoid smoking on the day of the assessment, but were asked to report if they had. Equipment was calibrated daily and regular biological controls were performed to ensure accuracy and precision of test equipment.

Participants were asked about asthma diagnoses, symptoms and treatment at each assessment.(E7, E8) Current asthma is defined as a reported diagnosis of asthma with symptoms or medication use in the previous 12 months. Childhood-onset asthma is defined as current asthma at any of the assessments at ages 9, 11, 13, or 15. Haemoglobin was measured using an automated haematology analyser. Exhaled carbon monoxide was measured just before T_{LCO} measurement using a MicroCO monitor (Micromedical, UK) and the mean of two tests was recorded. Height and weight in light clothing without shoes were measured at each age using calibrated stadiometers and scales.

Statistical analysis

Demographic and other descriptive variables were compared between those who had never reported cannabis use, and those who had accumulated up to 5 and more than 5 joint-years using χ^2-tests and one-way ANOVA for categorical and continuous outcomes respectively.

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The association between cannabis and tobacco use by age 45 was assessed using Spearman's correlation coefficient.

Associations between lung function measurements at age 45 years and cumulative cannabis and tobacco exposure were assessed by linear regression using lung function as the dependent variable in each model, with estimates of both cumulative cannabis and cumulative tobacco exposure as independent variables. All analyses included linear terms for height, sex, and weight to adjust for differences in predicted lung function. Analyses of TLCO also adjusted for pre-test exhaled carbon monoxide, haemoglobin, and whether the participant reported smoking on the day of assessment. Analyses were repeated using post-bronchodilator spirometry values. We further tested whether sex or any tobacco smoking modified the association of lung function with cannabis use by fitting interaction terms involving these variables and cumulative cannabis exposure. Analyses of the associations of cannabis with lung function were repeated separately for men and women and for those with and without any lifetime history of cigarette smoking. Models were checked by visual inspection of the residuals using histograms to ensure that the residuals were approximately normally distributed and with further inspection of residual vs. fitted, residual vs. predictor, and leverage vs. residual plots. Sensitivity analyses further adjusted for childhood-onset asthma and excluded participants who reported using cannabis by non-inhalation methods at age 45.

For each age, we developed sex-specific spirometry prediction equations derived using separate multiple linear regression models from never-tobacco smoking, non-asthmatic women and men using height and height squared as predictors. To assess whether quitting cannabis affected lung function, we identified the first occasion that participants had stopped regular (weekly or more) cannabis use between assessment ages and compared percent-predicted spirometry before and after quitting using paired t-tests (as differences were

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approximately normally distributed). To assess whether people with better lung function were more or less likely to use cannabis, we assessed whether percent-predicted spirometry at age 15 was associated with subsequent cannabis lifetime use by age 45. This analysis used quantile regression of the median joint-years adjusted for sex because the residuals from models of joint-years were not normally distributed. Similar models were investigated for childhood-onset asthma and to investigate differences in cannabis use by men and women.

Further models assessed the associations between recent cannabis and tobacco use reported at each assessment with the spirometric lung function at each assessment age. These models adjusted for percent-predicted lung function at age 15 years (the last measurement before the quantification of cannabis use started at age 18) and further adjusted for use of the other substance, sex, weight, age at assessment, and accounted for repeated measures in each person by including a random participant effect. Estimation was performed using maximum likelihood.

To visually compare trajectories between cannabis users and non-users for tobacco smokers and non-smokers, linear mixed models with a random participant effect, estimated using restricted maximum likelihood, were constructed including assessment age as a factor along with linear and quadratic joint-years at age 45, linear and quadratic pack-years at age 45, and the four interactions between these variables and assessment age.

Analyses were performed using Stata version 15 (College Station, TX). Two-sided $p<0.05$ was considered statistically significant. No adjustments were made for multiple testing.

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Table E1. Age 45 descriptive variables according to tobacco smoking history.
Only participants with spirometry data from age 45 are included. P values are from χ^2-tests* and Wald test from one-way ANOVA†. Post-hoc comparisons were not performed.

		Cumulative tobacco use by age 45			
		None (n=435)	**≤5 pack-years (n=125)**	**>5 pack-years (n=336)**	**P**
Sex	**Women (%)**	210 (47%)	74 (17%)	161 (36)	0.071*
	Men (%)	225 (50%)	51 (11%)	175 (39%)	
Current asthma	**No (%)**	360 (50%)	100 (14%)	265 (37%)	0.380*
	Yes (%)	75 (44%)	25 (15%)	71 (42%)	
BMI (kg/m^2)	**Mean (SD)**	28.5 (5.7)	28.6 (6.0)	28.2 (5.7)	0.686†

Table E2. Age 15 spirometry according to subsequent cannabis exposure by age 45
Values are % predicted (95% CI). P-values are for Wald tests from one-way ANOVAs. Post-hoc comparisons were not performed.

	Cumulative cannabis use by age 45			
	None (n=204)	**≤5 joint-years (n=433)**	**>5 joint-years (n=107)**	**P**
FEV_1	99.0 (97.3 to 100.7)	98.7 (97.6 to 99.7)	99.5 (97.2 to 101.9)	0.706
FVC	100.6 (99.1 to 102.2)	100.1 (99.1 to 101.1)	101.4 (99.3 to 103.5)	0.503
FEV_1/FVC	98.6 (97.5 to 99.6)	98.7 (98.0 to 99.4)	98.3 (96.8 to 99.7)	0.919

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Table E3. Associations of cannabis use with lung function in men and women at age 45
Linear regression analyses of lung function at age 45 using joint-years cannabis exposure as the exposure of interest. All analyses adjust for pack-years tobacco exposure, weight, and height. Analyses of TLCO also adjust for exhaled carbon monoxide and blood haemoglobin and reported smoking on the day of the test. Coefficients represent the difference in lung function associated with each joint-year of cannabis up to age 45. *p int values are the p values for the interaction between sex and joint-years.

		Women				**Men**				***p int**
	n	**Coeff**	**95% CI**	**p**		**n**	**Coeff.**	**95% CI**	**p**	
FEV_1 (mL)	440	-1.9	-11.1 to 7.4	0.690		441	-2.7	-11.6 to 6.1	0.545	0.710
FVC (mL)	440	0.5	-10.8 to 11.7	0.993		441	10.0	0.0 to 19.9	**0.049**	0.317
FEV_1/FVC (%)	440	-0.04	-0.19 to 0.12	0.641		441	-0.18	-0.29 to -0.07	**0.001**	0.314
FEF_{25-75} (mL/s)	440	-2.6	-20.4 to 15.6	0.802		441	-19.7	-36.0 to -3.5	**0.017**	0.238
TLC (mL)	431	18.9	4.0 to 33.4	**0.013**		435	19.6	5.4 to 31.8	**0.006**	0.759
FRC (mL)	431	19.3	7.2 to 31.4	**0.002**		438	8.1	-1.9 to 18.1	0.113	0.107
RV (mL)	431	18.3	10.2 to 26.4	**<0.001**		435	7.5	0.7 to 14.3	**0.030**	**0.034**
sGaw (mL/s/cmH_2O/L)	428	-1.6	-2.7 to -0.5	**0.006**		437	-0.9	-1.7 to -0.2	**0.011**	0.432
TLCO (mL/min/mmHg)	414	-0.096	-0.167 to -0.026	**0.008**		425	-0.032	-0.102 to 0.037	0.358	0.505
TLCO/VA (mL/min/mmHg/L)	414	-0.023	-0.038 to -0.009	**0.002**		425	-0.013	-0.023 to -0.004	**0.007**	0.085
VA (mL)	414	6.6	-8.2 to 21.3	0.382		425	13.7	0.8 to 26.6	**0.038**	0.532

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Table E4. Longitudinal associations of cannabis use with spirometry

Mixed effects regression analyses of percent-predicted spirometry values at ages 18, 21, 26, 32, 38, and 45 years using cannabis and tobacco use since the previous assessment as the exposures of interest. Analyses are adjusted for sex, height, weight, use of the other substance, and percent predicted lung function at age 15 and include a random participant effect. Estimation was performed using maximum likelihood. Analyses are based on 4610 observations from 838 participants. Coefficients represent the difference in percent-predicted spirometry associated with each joint-year of cannabis or pack-year of tobacco used since the previous assessment.

	Cannabis				**Tobacco**		
	Coefficient (per joint-year)	**95% CI**	**p**		**Coefficient (per pack-year)**	**95% CI**	**p**
FEV_1	0.05	-0.12 to 0.23	0.550		-0.34	-0.47 to -0.22	**<0.001**
FVC	0.33	0.17 to 0.49	**<0.001**		-0.05	-0.16 to 0.06	0.372
FEV_1/FVC	-0.29	-0.42 to -0.17	**<0.001**		-0.29	-0.38 to -0.20	**<0.001**

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