# Lifetime cannabis exposure and small airway function in a population-based cohort study

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**Lifetime cannabis exposure is associated with measures of small airway dysfunction indicating higher small airway resistance and greater reactance** https://bit.ly/3pWnZTu

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## Abstract

***Background and objective*** The long-term effects of cannabis on small airway function remain unclear. We investigated associations between cannabis use and small airway function in a general population sample.

***Methods*** Cannabis use was ascertained at multiple ages from age 18 to 45 years and quantified as joint-years among 895 participants in the Dunedin Multidisciplinary Health and Development Study. Small airway function at ages 38 and 45 years was measured using impulse oscillometry (IOS) before and after inhalation of salbutamol. Analyses used multiple linear regression adjusting for tobacco use, body mass index and height. Longitudinal analyses of cannabis use between 38 and 45 years also adjusted for IOS at age 38 years.

***Results*** Associations between lifetime cannabis joint-years and IOS differed between men and women: in women, cannabis use was associated with pre-bronchodilator resistance at 5 Hz ($R_5$) and 20 Hz ($R_{20}$), reactance at 5 Hz, area of reactance and resonant frequency, and marginally associated with the difference between $R_5$ and $R_{20}$. Cannabis use was only statistically significantly associated with pre-bronchodilator resonant frequency in men. Cannabis use between the ages of 38 and 45 years was associated with a similar pattern of changes in IOS measures. After salbutamol, cannabis use was only statistically significantly associated with $R_5$ and $R_{20}$ among women and none of the IOS measures among men.

***Conclusions*** Cannabis use is associated with small airway dysfunction at age 45 years, indicating an increase in peripheral airway resistance and reactance. These associations were greater and mostly only statistically significant among women. Associations were weaker and mostly nonsignificant after bronchodilator use, suggesting that cannabis-induced changes in small airways may be at least partially reversible.

## Introduction

Cannabis is the second most smoked substance and one of the most widely used recreational drugs in the world [1]. In New Zealand, 80% of New Zealanders have tried cannabis at least once by the age of 21 years and 12% of the adult population report using cannabis in the past 12 months [2]. Despite the high prevalence of cannabis use, we do not understand the impact that it has on respiratory health. This is partly due to the illegal status of cannabis in many countries, making it difficult to study, and also because most cannabis users also smoke tobacco, making it difficult to distinguish the effects of cannabis from those of tobacco [3]. However, there is accumulating evidence that smoking cannabis has effects on lung function and respiratory symptoms [4–7].

Long-term cannabis smoking has been associated with higher lung volumes measured as forced vital capacity by spirometry, with little change in forced expiratory volume in 1 s in several studies, a pattern distinct from that of tobacco smoking [6–11]. The reasons for this difference between tobacco and

cannabis are unknown and it raises the question of what other effects cannabis has on lung health. Little is known about the effect of cannabis on small airways (defined as airways with a diameter <2 mm) [12]. Cannabis use has been associated with hyperinflation on both lung function tests and computed tomography scans, which could reflect small airways dysfunction, suggesting that further investigation of the effect of cannabis on small airways is needed [13].

One way of investigating peripheral airway function is to use impulse oscillometry (IOS) to measure respiratory impedance using sound waves, typically at frequencies of 4–30 Hz, superimposed upon tidal breathing [14, 15]. Impedance comprises resistance and reactance. Resistance provides information regarding the forward pressure of the conducting airways from the mouth to the respiratory bronchi [16]. Sound waves of lower frequency travel deeper into the lung than those of higher frequency, hence resistance at 5 Hz ($R_5$) and 20 Hz ($R_{20}$) reflect total and central airway obstruction, respectively, while the difference between $R_5$ and $R_{20}$ ($R_5$–$R_{20}$) reflects peripheral airway obstruction, and is a measure of small airways narrowing [17]. Reactance captures both the elastic properties of the small airways, known as capacitance, and the forces of the moving air through the airways, known as inertance [16]. At lower frequencies, capacitance is the more dominant component of reactance, hence reactance at 5 Hz ($X_5$) provides information regarding the capacitive or elastic energy of the small airways. The frequency at which the magnitude of the capacitive and inertance are the same is known as resonant frequency ($f_{res}$). The area of reactance (A$X$) represents the sum of reactance at all frequencies between 5 Hz and $f_{res}$ [18]. These IOS measures are believed to be altered by small airway disease, and correlate with other measures of small airway dysfunction in patients with asthma [19, 20], exacerbations [21] and response to inhaled corticosteroids [22].

In an exploratory investigation into the determinants of peripheral airway function in 38-year-olds in the Dunedin Multidisciplinary Health and Development Study (a birth cohort of 1037 individuals born in 1972/1973), lifetime history of cannabis consumption was associated with multiple IOS parameters ($R_5$, $R_{20}$, $R_5$–$R_{20}$, $X_5$, A$X$ and $f_{res}$) in women and $R_5$–$R_{20}$ and $X_5$ in men [23]; however, age 38 years is still early for the development of smoking-related lung diseases and we are not aware of any other investigations of IOS and cannabis use. Therefore, we investigated whether the relationship between cannabis use and peripheral airways function measured by IOS persists up to the age of 45 years; whether cannabis use between 38 and 45 years was associated with changes in IOS; and whether these associations differed by sex.

## Methods

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal study of the health and behaviour of a complete cohort of individuals born in Dunedin, New Zealand in 1972/1973 [23, 24]. At age 3 years, 1037 individuals (52% male; 91% of eligible births) participated in the assessment, 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 ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32 and 38 years, and most recently at age 45 years, when we assessed 938 (94%) out of 997 surviving participants. Respiratory information, including asthma diagnoses, has been obtained at each assessment from 9 years onwards. Childhood socioeconomic status was based on the income and education associated with the occupation of parents, assessed repeatedly from birth to age 15 years on a six-point scale (1=high), as reported previously [25]. Adult socioeconomic status was assessed on a similar scale based on the participants' occupation at age 45 years. The Dunedin Study was approved by the Health and Disability Ethics Committee, Ministry of Health, New Zealand. Study members gave informed consent before participating.

Cannabis smoking history was obtained at ages 18, 21, 26, 32, 38 and 45 years [26]. 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 years, whereby using cannabis once a day for a year is equivalent to one joint-year. These estimates assume that the number of times marijuana had been used in the previous year was representative of all years since the previous assessment. At ages 38 and 45 years, the maximum recorded use in the previous year was capped at 365 (*i.e.* once a day). Therefore, maximum use was truncated to 1 joint-year each year (*i.e.* the maximum possible between age 17 and 45 year was recorded at 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. Where data were not collected for an assessment, the amount of cannabis or tobacco smoked reported at the next assessment was used to calculate cumulative exposure. 1 pack-year

is defined as the equivalent of 20 cigarettes per day for 1 year. Those who had smoked <1 cigarette per day for a year, and <20 packets in their lifetime, were regarded as nonsmokers [27].

At age 45 years, IOS was measured using the Jaeger MasterScreen Impulse Oscillometry system (Jaeger, Wurzburg, Germany), with a recording based on five impedance spectra (five impulses) per second. Subjects wore nose clips, with their face supported to decrease the shunt compliance of the cheeks. A single technically acceptable recording (free of artefacts caused by coughing, breath-holding, swallowing or vocalisation) was performed during stable tidal breathing for a 30-s interval through a mouthpiece and bacterial filter. IOS parameters included $R_5$, $R_{20}$, $R_5$–$R_{20}$, $X_5$, AX and $f_{res}$. Pre-bronchodilator IOS was measured before spirometry or any forced exhalation measures, but after measurements of exhaled breath, which involved deep inhalations. IOS was repeated 15–20 min after 200 µg salbutamol, administered using a large volume spacer. The post-bronchodilator measurements took place after spirometry and body plethysmograph measurements. All equipment was calibrated daily. Height and weight were measured in light clothing without shoes to calculate body mass index (BMI) in $kg \cdot m^{-2}$.

### Statistical analysis

$R_5$, $R_{20}$, $R_5$–$R_{20}$, $X_5$, A$X$ and $f_{res}$ were transformed using natural logarithms to achieve a parametric distribution. By convention $X_5$ values are negative, so were first converted to positive values to permit log-transformation. Differences between pre- and post-salbutamol values were evaluated using paired t-tests. Multivariable linear regression was used to assess the independent associations of joint-years of cannabis and pack-years smoking with each measure of IOS adjusting for height, BMI and sex. Because analyses at 38 years had found that cannabis was more strongly associated with IOS parameters in women than men, sex interaction terms were fitted [23]. A small number of other individuals had extreme IOS values that influenced the initial analyses: those with IOS values more than 5 SDS from the mean (after log-transformation) were excluded from the analyses of pre- (n=1) and post-salbutamol (n=2) IOS values. Otherwise, all available data were included in each analysis and missing data were assumed to be missing at random. The final regression models were checked by inspection of scatterplots of residuals against continuous predictors and fitted values.

To assess whether change in cannabis use was associated with change in IOS measures, the joint-years estimated between age 38 and 45 years (based on the amount reported at 45 years) were used as the main predictor in analyses of IOS measures at age 45 years with adjustments for the IOS measure at 38 years, tobacco use between 38 and 45years and height and BMI at 45 years.

Analyses used Stata 15.1 (Stata Corporation, College Station, TX, USA). p-values $\leqslant 0.05$ were considered statistically significant. No adjustments were made for multiple testing.

## Results

Sufficient exposure and outcome data for analysis were available for 895 participants. More men had used cannabis than women (79% and 65%, respectively; p<0.001). Women were slightly more likely to have smoked tobacco than men (52% and 50%, respectively), although this difference was not statistically significant. Median cannabis and tobacco use and BMI are shown in table 1. Childhood-onset asthma (a diagnosis reported by age 15 years) was not associated with subsequent cannabis or tobacco use, indicating that participants with asthma were not more likely to avoid smoking these substances. At age 45 years, 141

**TABLE 1** Descriptive values

| | Whole sample | Women | Men |
|---|---|---|---|
| **Cannabis use (joint-years)** | 0.08 (0–28) | 0.03 (0–26.45) | 0.17 (0–28) |
| **Cannabis use (non-tobacco users only)** | 0.01 (0–28) | 0 (0–19.32) | 0.03 (0–28) |
| **Cannabis use (tobacco and cannabis users only)** | 0.62 (0.003–27.97) | 0.23 (0.003–26.45) | 2.12 (0.003–27.97) |
| **Tobacco use (pack-years)** | 0.11 (0–51.03) | 0.25 (0–41.41) | 0 (0–51.03) |
| **BMI ($kg \cdot m^{-2}$)** | 27.6 (16.2–62.2) | 27.1 (16.2–62.2) | 27.8 (19.0–47.5) |
| **Childhood SES** | 3.3 (1–6) | 3.3 (1–6) | 3.3 (1–6) |
| **Adult SES** | 4 (1–6) | 4 (1–6) | 4 (1–6) |

Data are presented as median (range). Socioeconomic status (SES) is on a 1–6 scale with 1 representing the highest SES. Childhood SES is based on parental occupations between birth and age 15 years. Adult SES is based on occupation at age 45 years.

**TABLE 2** Pre-bronchodilator impulse oscillometry (IOS) values at age 45 years

| | Women | | Men | |
|---|---|---|---|---|
| | Participants (n) | Mean (95% CI) | Participants (n) | Mean (95% CI) |
| $R_5$ ($cmH_2O{\cdot}L{\cdot}s^{-1}$) | 441 | 5.17 (5.00–5.35) | 454 | 4.49 (4.34–4.64) |
| $R_{20}$ ($cmH_2O{\cdot}L{\cdot}s^{-1}$) | 441 | 4.15 (4.01–4.28) | 454 | 3.65 (3.54–3.77) |
| $R_5$–$R_{20}$ ($cmH_2O{\cdot}L{\cdot}s^{-1}$) | 441 | 1.03 (0.94–1.13) | 454 | 0.84 (0.76–0.84) |
| $X_5$ ($cmH_2O{\cdot}L{\cdot}s^{-1}$) | 440 | −1.60 (−1.69– −1.50) | 454 | −1.19 (−1.26– −1.12) |
| *AX* ($cmH_2O{\cdot}L{\cdot}s^{-1}$) | 437 | 6.99 (6.32–7.67) | 449 | 4.86 (4.35–5.37) |
| $f_{res}$ (Hz) | 440 | 14.29 (13.81–14.77) | 452 | 13.06 (12.61–13.51) |

Means are geometric means of raw IOS values. The n values differ slightly because of missing data. $R_5$: resistance at 5 Hz; $R_{20}$: resistance at 20 Hz; $R_5$–$R_{20}$: difference between $R_5$ and $R_{20}$; $X_5$: reactance at 5 Hz; *AX*: area under the reactance curve between 5 Hz and resonant frequency ($f_{res}$).

(31%) women and 135 (30%) men reported having had asthma at some time in their lives, while 93 (21%) women and 79 (17%) men had current asthma with symptoms or treatment in the past year.

The geometric means for all IOS values by sex are shown in table 2. There were statistically significant differences in the mean log-transformed values between before and after bronchodilator (all p-values <0.001 by paired t-tests; supplementary table S1). IOS measures according to categories of smoking history (never, cannabis only, tobacco only or both cannabis and tobacco) are shown in supplementary table S2. Most IOS measures were moderately or strongly correlated with each other (supplementary tables S3 and S4).

After adjustment for pack-years, BMI and height, cannabis joint-years were associated with pre-salbutamol $R_5$, $R_5$-$R_{20}$, $X_5$, AX and $f_{res}$, but were not significantly associated with $R_{20}$ (table 3).

The interaction term for sex by cannabis joint-years was tested for each of the IOS parameters. Several of the interaction terms were statistically significant for the pre-salbutamol measures (table 3), so the results are also presented separately by sex (table 4). In women, cannabis was statistically significantly associated with pre-salbutamol $R_5$, $R_{20}$, $X_5$, *AX* and $f_{res}$. The association with $R_5$–$R_{20}$ did not reach formal statistical significance (p=0.061). In men, cannabis was only statistically significantly associated with $f_{res}$ (table 4). After salbutamol use, cannabis use was only statistically significantly associated with $R_5$ and $R_{20}$ among women and not statistically associated with IOS measures among men (supplementary tables S5 and S6).

The pattern of associations between pack-years tobacco use and IOS measures was quite different to that for joint-years of cannabis. Whereas cannabis joint-years were associated with a wide range of pre-bronchodilator, but not post-salbutamol, IOS measures in women, tobacco pack-years were only

**TABLE 3** Adjusted associations of cannabis and tobacco with pre-bronchodilator impulse oscillometry (IOS) measures for the whole sample

| | $R_5$ | $R_{20}$ | $R_5$–$R_{20}$ | $X_5$ | *AX* | $f_{res}$ |
|---|---|---|---|---|---|---|
| **Participants (n)** | 877 | 877 | 877 | 876 | 868 | 870 |
| **Joint-years** | | | | | | |
| β (95% CI) | **0.104** (0.033–0.175) | 0.073 (−0.001–0.148) | **0.086** (0.013–0.158) | **0.110** (0.039–0.174) | **0.130** (0.060–0.200) | **0.133** (0.062–0.204) |
| p-value | 0.004 | 0.054 | 0.020 | 0.002 | <0.001 | <0.001 |
| **Pack-years** | | | | | | |
| β (95% CI) | 0.042 (−0.029–0.113) | 0.003 (−0.072–0.077) | **0.076** (0.004–0.149) | 0.041 (−0.027–0.108) | 0.052 (−0.018–0.123) | 0.047 (−0.025–0.119) |
| p-value | 0.248 | 0.946 | 0.039 | 0.237 | 0.147 | 0.197 |
| **Interaction term[#] (p-value)** | **0.031** | 0.131 | **0.034** | 0.062 | **0.034** | 0.054 |

All IOS measures are log-transformed and analyses are adjusted for use of both substances and also adjusted for sex, body mass index and height. Bolded values are statistically significant. β-values are standardised regression coefficients, which represent the standard deviation difference in IOS measure associated with each standard deviation change in joint- or pack-years. $R_5$: resistance at 5 Hz; $R_{20}$: resistance at 20 Hz; $R_5$–$R_{20}$: difference between $R_5$ and $R_{20}$; $X_5$: reactance at 5 Hz; *AX*: area under the reactance curve between 5 Hz and resonant frequency ($f_{res}$). [#]: interaction term p-values are for joint-years by sex in the adjusted model for each IOS measure tested for after the adjusted model was run.

**TABLE 4** Adjusted associations of cannabis and tobacco with pre-bronchodilator impulse oscillometry (IOS) measures stratified by sex

| | $R_5$ | $R_{20}$ | $R_5$–$R_{20}$ | $X_5$ | A$X$ | $f_{res}$ |
|---|---|---|---|---|---|---|
| **Women** | | | | | | |
| Participants (n) | 434 | 434 | 434 | 433 | 430 | 432 |
| Joint-years | | | | | | |
| β (95% CI) | **0.187** (0.058–0.315) | **0.150** (0.014–0.286) | 0.137 (−0.007–0.281) | **0.234** (0.109–0.358) | **0.240** (0.116–0.364) | **0.222** (0.095–0.350) |
| p-value | 0.004 | 0.030 | 0.061 | <0.001 | <0.001 | 0.001 |
| Pack-years | | | | | | |
| β (95% CI) | 0.058 (−0.058–0.175) | −0.005 (−0.128–0.119) | **0.139** (0.009–0.270) | −0.038 (−0.151–0.075) | 0.015 (−0.098–0.128) | 0.030 (−0.086–0.146) |
| p-value | 0.327 | 0.940 | 0.037 | 0.510 | 0.796 | 0.612 |
| **Men** | | | | | | |
| Participants (n) | 443 | 443 | 443 | 443 | 438 | 438 |
| Joint-years | | | | | | |
| β (95% CI) | 0.070 (−0.015–0.156) | 0.042 (−0.047–0.132) | 0.066 (−0.011–0.143) | 0.053 (−0.026–0.113) | 0.083 (−0.003–0.168) | **0.094** (0.009–0.179) |
| p-value | 0.107 | 0.351 | 0.095 | 0.186 | 0.058 | 0.030 |
| Pack-years | | | | | | |
| β (95% CI) | 0.024 (−0.066–0.114) | <0.001 (−0.095–0.094) | 0.032 (−0.049–0114) | 0.079 (−0.005–0.163) | 0.067 (−0.024–0.158) | 0.051 (−0.040–0.142) |
| p-value | 0.599 | 0.996 | 0.437 | 0.064 | 0.150 | 0.272 |

All IOS measures are transformed and analyses are adjusted for use of both substances and also adjusted for body mass index and height; significant associations are shown in bold. β-values are standardised regression coefficients, which represent the standard deviation difference in IOS measure associated with each standard deviation change in joint- or pack-years. $R_5$: resistance at 5 Hz; $R_{20}$: resistance at 20 Hz; $R_5$–$R_{20}$: difference between $R_5$ and $R_{20}$; $X_5$: reactance at 5 Hz; A$X$: area under the reactance curve between 5 Hz and resonant frequency ($f_{res}$).

associated with pre-salbutamol $R_5$–$R_{20}$ in women, but were associated with several IOS measures in both sexes after salbutamol (supplementary tables S5 and S6).

In the longitudinal analyses adjusting for IOS measures at 38 years, the amount of cannabis use reported at age 45 years was associated with $R_5$, $X_5$, A$X$ and $f_{res}$ among women at 45 years (tables 5 and 6), whereas the amount of tobacco reported at age 45 years was not associated with any IOS measure. For men, the amount of cannabis use was not associated with IOS measures in these analyses, whereas tobacco use was associated with higher values for $X_5$, but no other measures.

In analyses restricted to participants who had never smoked tobacco, there were no statistically significant associations between cannabis use and IOS measures in the whole sample (supplementary table S7) or

**TABLE 5** Longitudinal analyses of cannabis and tobacco use between ages 38 and 45 years with pre-bronchodilator impulse oscillometry (IOS) measures for the whole sample

| | $R_5$ | $R_{20}$ | $R_5$–$R_{20}$ | $X_5$ | A$X$ | $f_{res}$ |
|---|---|---|---|---|---|---|
| **Participants (n)** | 864 | 864 | 864 | 862 | 856 | 857 |
| **Joint-years 38–45 years** | | | | | | |
| β (95% CI) | **0.078** (0.023–0.132) | 0.060 (−0.002–0.121) | 0.043 (−0.014–0.100) | **0.059** (0.003–0.114) | **0.076** (0.023–0.129) | **0.091** (0.037–0.145) |
| p-value | 0.005 | 0.056 | 0.140 | 0.038 | 0.005 | 0.001 |
| **Pack-years 38–45 years** | | | | | | |
| β (95% CI) | 0.017 (−0.038–0.072) | −0.004 (−0.066–0.058) | 0.044 (−0.014–0.101) | 0.048 (−0.009–0.104) | 0.037 (−0.016–0.091) | 0.015 (−0.040–0.069) |
| p-value | 0.553 | 0.903 | 0.134 | 0.099 | 0.173 | 0.601 |

All IOS measures are log-transformed. Analyses are adjusted for use of both substances and also adjusted for sex, body mass index, height and the relevant IOS measure at age 38 years (*e.g.* resistance at 5 Hz ($R_5$) at 38 years is the adjustment for age 45 years $R_5$); bolded values are statistically significant. β-values are standardised regression coefficients, which represent the standard deviation difference in IOS measure associated with each standard deviation change in joint- or pack-years. $R_{20}$: resistance at 20 Hz; $R_5$–$R_{20}$: difference between $R_5$ and $R_{20}$; $X_5$: reactance at 5 Hz; A$X$: area under the reactance curve between 5 Hz and resonant frequency ($f_{res}$).

**TABLE 6** Longitudinal analyses of cannabis and tobacco use between ages 38 and 45 years with pre-bronchodilator impulse oscillometry (IOS) measures stratified by sex

| | $R_5$ | $R_{20}$ | $R_5$–$R_{20}$ | $X_5$ | AX | $f_{res}$ |
|---|---|---|---|---|---|---|
| **Women** | | | | | | |
| Participants (n) | 426 | 426 | 426 | 425 | 422 | 423 |
| Joint-years 38–45 years | | | | | | |
| β (95% CI) | **0.125** (0.035–0.214) | 0.075 (−0.025–0.176) | 0.085 (−0.019–0.189) | **0.125** (0.035–0.218) | **0.140** (0.054–0.226) | **0.129** (0.042–0.217) |
| p-value | 0.006 | 0.142 | 0.109 | 0.008 | 0.001 | 0.004 |
| Pack-years 38–45 years | | | | | | |
| β (95% CI) | 0.002 (−0.107–0.111) | −0.007 (−0.129–0.115) | 0.077 (−0.049–0.203) | −0.064 (−0.176–0.047) | −0.017 (−0.121–0.087) | 0.013 (−0.093–0.120) |
| p-value | 0.972 | 0.906 | 0.232 | 0.258 | 0.749 | 0.804 |
| **Men** | | | | | | |
| Participants (n) | 438 | 438 | 438 | 437 | 434 | 434 |
| Joint-years 38–45 years | | | | | | |
| β (95% CI) | 0.049 (−0.019–0.117) | 0.049 (−0.029–0.127) | 0.015 (−0.047–0.077) | 0.023 (−0.045–0.091) | 0.039 (−0.028–0.107) | 0.066 (−0.003–0.135) |
| p-value | 0.158 | 0.214 | 0.644 | 0.510 | 0.255 | 0.062 |
| Pack-years 38–45 years | | | | | | |
| β (95% CI) | 0.025 (−0.038–0.088) | <0.001 (−0.073–0.073) | 0.034 (−0.023–0.091) | **0.093** (0.029–0.157) | 0.060 (−0.003–0.122) | 0.017 (−0.047–0.081) |
| p-value | 0.432 | 0.999 | 0.242 | 0.005 | 0.063 | 0.601 |

All IOS measures are log-transformed and analyses are adjusted for use of both substances and also adjusted for body mass index, height and the relevant IOS measure at age 38 years (*e.g.* resistance at 5 Hz ($R_5$) at 38 years is the adjustment for age 45 years $R_5$); statistically significant associations are bolded. β-values are standardised regression coefficients, which represent the standard deviation difference in IOS measure associated with each standard deviation change in joint- or pack-years. $R_{20}$: resistance at 20 Hz; $R_5$–$R_{20}$: difference between $R_5$ and $R_{20}$; $X_5$: reactance at 5 Hz; AX: area under the reactance curve between 5 Hz and resonant frequency ($f_{res}$).

when stratified by sex (not shown). Adjusting for childhood and adult socioeconomic status or excluding those who had ever reported asthma also provided similar results (supplementary tables S8 and S9).

## Discussion

We have found that lifetime cannabis use is associated with multiple IOS measures of small airway dysfunction at age 45 years, suggesting that cannabis smoking leads to increases in peripheral airway resistance and reactance. The associations of cannabis use with IOS measures were stronger and only statistically significant among women, and were weaker and mostly nonsignificant after bronchodilator use. Longitudinal analyses of cannabis use since age 38 years, which adjusted for the same IOS measure at 38 years, confirmed that cannabis use was associated with multiple IOS measures of pre-bronchodilator airway dysfunction among women, but not among men.

Consistent with findings from an analysis of IOS measures at age 38 years and several studies of other lung function measures [11], cannabis had a different pattern of associations to tobacco. Among the pre-salbutamol IOS measures, lifetime history of tobacco smoking was only statistically associated with $R_5$-$R_{20}$ (table 3), but tobacco smoking was associated with all post-salbutamol IOS measures when men and women were analysed together and several of the measures in each sex when they were analysed separately (supplementary tables S5 and S6). By contrast, the associations between cannabis use and IOS measures were weaker and mostly nonsignificant after salbutamol use, suggesting that cannabis-induced changes in the small airways may be at least partially reversible. These reasons for these differences are not clear, but confirm that cannabis and tobacco appear to have distinct effects on small airways as well as different effects on measures of large airway function. However, we did not find associations between cannabis use and IOS measures in tobacco never-smokers (supplementary table S7), but this may have been because the amount of cannabis used by tobacco never-smokers tended to be very low (median 0.008 joint-years compared to 0.41 joint-years for ever tobacco smokers).

The finding that cannabis was associated with pre-bronchodilator, but not post-bronchodilator IOS measures raises the question of whether asthma could influence the observed associations. In fact, childhood-onset asthma (by age 15 years) was not associated with adult cannabis or tobacco use, indicating that these participants did not avoid smoking either substance and, therefore, asthma is not a

confounder of the analyses. Since cannabis use has been shown to cause respiratory symptoms, cannabis could lead to a diagnosis of late-onset "asthma" or cause an asthma-like syndrome. There was a weak association between joint-years and asthma at age 45 years (OR 1.035), which was statistically significant in men, but not women. A *post hoc* analysis adjusting for asthma diagnoses at age 45 years made no material difference to the findings (data not shown).

Cannabis was associated with a broader range of IOS associations in women than men. Most of the sex-interaction terms were significant for pre-bronchodilator IOS measures, indicating that these sex differences in the associations were statistically significant. These findings are similar to an exploratory analysis of multiple determinants of IOS at age 38 years in this cohort, when we found a broader association between cannabis use and IOS parameters in women than men. They extend the findings of the earlier study by adding a longitudinal analysis, which supports the findings of the cross-sectional analyses. Why these sex differences occur is not clear, particularly as women tend to use less cannabis than men. It is possible that baseline differences in lung size, and therefore the small airways, could explain a difference in susceptibility. There may also be more generalised differences in the susceptibility of men and women to the effects of cannabis: a human laboratory study of the acute effects of smoked cannabis on young adults found that women require lower cannabis doses to experience the same subjective and physiological effects as men [28]. In addition, there is some evidence that the hormone oestradiol could increase the susceptibility of women to COPD [29], and it is possible that this hormone also influences the effect of cannabis smoke on small airways.

The clinical implications of our findings are not yet clear, but the published literature and current findings (supplementary tables S3 and S4) show that these IOS measures correlate with one another and are all associated with small airways function [30]. Our findings are consistent with several animal models on the long-term effects of inhaled cannabis on small airways. In rhesus monkeys, for example, a direct relationship was found between the amount of cannabis smoke inhaled and the severity and frequency of inflammatory damage visible in the small airways on histopathological examination [31]. However, due to the difficulty of examining small airway pathology in humans and the confounding effects of tobacco use in many human studies, the exact mechanisms of cannabis effects on human small airways are unknown. Given that studies have consistently found that cannabis use is associated with large airway conductance (including among these participants) [11], it is surprising that $R_{20}$ (an IOS measure of central airway function) was not associated with cannabis in men. The reasons for this apparent discrepancy are unknown.

The study has a number of strengths as a longitudinal study with prospective collection of cannabis and tobacco exposure at several ages from age 18 to 45 years with a high rate of follow-up. A limitation of the study is that because of time constraints, only single measures of IOS before and after bronchodilator were taken rather than the recommended three measurements [32]. Although this may have led to measurement errors, the effect of these errors would be likely to bias any association towards the null. Another source of error will be from the self-report of cannabis and tobacco use and the assumption that past-year cannabis use was representative of all of the years between assessments. These measurement errors would also be likely to bias the estimates of associations towards the null; however, there could be residual confounding of the association between cannabis or tobacco and IOS if exposure to the other substance was not accurately measured. *Post hoc* adjustment for childhood and adult socioeconomic status or excluding those with a history of asthma did not change the pattern of findings (supplementary tables S8 and S9). We have not assessed other potential confounders such as environmental smoke or pollution exposure. As an exploratory analysis of patterns of IOS association with cannabis, we analysed a large number of associations, but have not adjusted the analyses for multiple comparisons. Therefore, the findings for individual analyses should be interpreted cautiously.

Although the effects of cannabis on the lungs remain poorly understood, this analysis adds to the evidence that smoking cannabis does have an impact on lung function and respiratory health [11], and indicates that these effects are different to those of tobacco. While the clinical consequences of prolonged exposure of the lungs to cannabis are still uncertain, the accumulating evidence of harm should be considered in policies concerned with cannabis use and harm reduction. We need more epidemiological and pathophysiological research on the effects of cannabis on small airways and lung function. In particular, we need to understand why there appear to be sex differences in effects of cannabis smoking on small airways.

In conclusion, lifetime cannabis exposure is associated with measures of small airways dysfunction indicating higher small airway resistance and greater reactance. These associations appear to be stronger in

women than men. The findings indicate that that the peripheral airways may be a site where cannabis-associated damage differs from the effects of tobacco.

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