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Cannabis increased the risk of primary spontaneous pneumothorax in tobacco smokers: a case-control study

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Abstract

OBJECTIVES: Previous smaller case series suggested that cannabis smoking may cause spontaneous pneumothorax, but this finding remains controversial. We investigated the possible association between smoking tobacco and cannabis and the risk of having a primary spontaneous pneumothorax in a large, homogeneous cohort of young, healthy individuals.

METHODS: In a case-control study, we prospectively investigated young (≤ 40 years) patients admitted in Western Denmark from 2009 to 2016 with their first episode of primary spontaneous pneumothorax. Baseline characteristics and smoking habits including both tobacco and cannabis were obtained from questionnaires presented on admittance. We compared our findings with those of a population-based control group matched by age, sex and geographical area. Calculated odds ratios were compared using the Fisher's exact test for small frequencies and the χ^2 test or the Mann-Whitney test for larger frequencies.

RESULTS: A total of 416 patients participated (male/female ratio = 3.9). We observed a significantly increased risk of primary spontaneous pneumothorax in daily smokers compared with female never smokers (odds ratio = 8.10, 95% confidence interval: 4.61–14.14, $P < 0.001$) and male never smokers (odds ratio = 4.85, 95% confidence interval: 3.23–7.19, $P < 0.001$). The combination of smoking both cannabis and tobacco in men increased the risk of spontaneous pneumothorax significantly (odds ratio = 8.74, 95% confidence interval: 4.30–19.51, $P < 0.001$). In contrast, the cannabis habits of female patients did not differ from those of the Danish population in general.

CONCLUSIONS: Combined smoking of tobacco and cannabis significantly aggravates the risk of having a primary spontaneous pneumothorax in young men compared to both never smokers and daily smokers.

Keywords: Pneumothorax • Smoking • Cannabis • Risk factors

INTRODUCTION

Several studies reported that tobacco smoking leads to an increased risk of developing primary spontaneous pneumothorax (PSP) [1, 2], but only limited information is available on the effects of cannabis smoking. Cannabis consumption in the general population has increased over the last decades, and it has become the most widespread illegal drug in the Western world [3, 4]. Young adults, in particular, often consider cannabis a relatively safe drug with minimal side effects, and up to 40–45% have tried cannabis during their lifetime [5, 6].

It has been suggested that cannabis smoking may have a causative link to spontaneous pneumothorax [7–9], but this association is still unclear [10]. Most of the previous studies on cannabis smoking and PSP were case reports or small case series, none of which considered the combined risk of simultaneous smoking of tobacco and cannabis [11–13].

The aim of the present study was to investigate tobacco and cannabis habits in a homogeneous cohort of young, otherwise healthy individuals who were admitted to the hospital with their first episode of primary spontaneous pneumothorax and to compare these results with those from the general population.

MATERIALS AND METHODS

The present study was approved by the Regional Ethics Committee of Southern Denmark (Project-ID S-20090052) and the Danish Data Protection Agency. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients.

We performed a case-control study comparing the self-reported smoking habits related to tobacco and cannabis in individuals admitted with their first episode of primary spontaneous pneumothorax with the habits of a Danish control group matched by sex, age and geographical area to determine the odds ratio. First, we investigated the effects of tobacco and cannabis smoking separately. Then, we looked for possible effect modification between the 2 substances to evaluate the isolated effect of each substance.

Case population

Inclusion criteria were consecutive patients admitted over a 7-year period (1 April 2009 until 31 March 2016) with their first episode of primary spontaneous pneumothorax, verified by chest radiography on admittance. Patients were enrolled from 3 of the 4 national cardiothoracic surgical departments in Denmark. We included otherwise healthy patients with limited previous contact with the health care system, no medication for lung diseases and no acknowledged somatic comorbidity. Exclusion criteria included recurrent pneumothorax and secondary spontaneous pneumothorax. Likewise, patients older than 40 years of age were excluded to diminish bias from unacknowledged underlying comorbidities, because previous studies showed that primary spontaneous pneumothorax rarely occurs in patients older than 40 years [14, 15].

All eligible patients were prospectively presented on admittance with a specific questionnaire. From this questionnaire, we obtained baseline characteristics including age, sex, height, weight and history of tobacco smoking. Patients were considered ex-smokers if they had stopped smoking more than 6 months ago [16]. Furthermore, patients were asked to disclose any history of abuse of illegal substances in general and smoking of cannabis in particular.

Control group

We used data from The Danish Health and Morbidity Survey 2010 as our control [17]. The Danish Health and Morbidity Survey is a nationwide survey where a representative sample ($n=25\,000$) of the Danish population aged 16 to 64 years is invited to participate. In total, 15 165 individuals completed the self-administered questionnaire (participation rate: 61%). In the survey, the use of selected drugs, including cannabis, was assessed based on the recommendations by the European Monitoring Centre for Drugs and Drug Addiction [18]. Hence, all respondents were asked the following questions: 'Have you ever tried one or more of the following drugs?', with the 4 possible answer categories: 'no', 'yes, during the past month', 'yes, during the past year (but not during the past month)' and 'yes, previously (but not during the past year)'.

Because it was possible to link both participants and non-participants individually to national administrative registers by use of their unique personal registration numbers, the national

survey was able to adjust for non-response as suggested by Särndal and Lundström [19]. The weights were computed by Statistics Denmark based on register information on sex, age, municipality of residence, educational level and so forth. To optimize the comparisons, we used these weighted results and furthermore extracted specific information about the exact geographical region and matching age groups from The Danish Health and Morbidity Survey 2010 [17], including only individuals ≤ 40 years of age.

Statistical analysis

The smoking habits related to both tobacco and cannabis of the case population with primary spontaneous pneumothorax were compared with those of the population-based control group. Analyses were stratified by sex and age. In cases of expected small frequencies (fewer than 5), the calculated odds ratios were compared using the Fisher's exact test [20]. Comparisons between larger frequencies were performed using the χ^2 test for categorical data and the Mann-Whitney test in case of numerical data. All data were analysed using STATA (Release 13; StataCorp, College Station, TX, USA) [21].

RESULTS

Case population

During the 7-year study period, 438 young patients were admitted with their first episode of primary spontaneous pneumothorax. Twenty-two patients (5%) refused to disclose information about abuse and were excluded from the analysis. This subgroup of patients did not differ significantly from the included patients regarding sex, age, affected lung or smoking habits. In total, 416 questionnaires from 331 men and 85 women (male/female ratio = 3.9) were available for analyses.

With a median age at first admittance of 28 years (range, 13–40) and 23 years (range, 12–40) in women and men, respectively, women were significantly older at pneumothorax debut ($P<0.001$). We observed no significant difference between the 2 sexes regarding median body mass index (20.4, range, 12.7–33.0, $P=0.98$). Both lungs were equally affected at first admittance: The right lung was affected in 219 patients (53%), the left lung in 192 (46%) and bilateral pneumothorax in 5 (1%). No difference was observed between the 2 sexes ($P=0.18$).

Tobacco smoking

Smoking habits regarding both tobacco and cannabis in cases and controls are shown for comparison in Table 1. By matching our control group by age and geography, we limited our controls to 5743 responders (38%) of the overall control group, and only 5723 controls disclosed information about cannabis habits (Table 1). We observed an increased risk for having a PSP in daily smokers [odds ratio (OR)=5.24, 95% confidence interval (CI): 3.31–8.32 in women and OR=5.96, 95% CI: 4.66–7.63 in men] (Table 2). Individuals between the ages of 25 and ≤ 35 years demonstrated a particularly high occurrence of daily smoking with an OR of 11.35 (95% CI: 4.83–28.68) and 9.31 (95% CI: 5.98–14.74) in women and men, respectively.

Table 1: Cannabis and tobacco use by cases and control group members, respectively, stratified by sex

	Cases <i>n</i> (%)			Control group <i>n</i> (%)		
	Female	Male	Overall	Female	Male	Overall
Tobacco smoking	<i>n</i> = 85	<i>n</i> = 331	<i>n</i> = 416	<i>n</i> = 2831	<i>n</i> = 2912	<i>n</i> = 5743
Never smokers	34 (40.0%)	98 (29.7%)	132 (31.7%)	1624 (57.4%)	1562 (53.6%)	3186 (55.5%)
Daily smokers	44 (51.8%)*	206 (62.2%)*	250 (60.1%)*	481 (17.0%)	631 (21.7%)	1112 (19.4%)
Less than daily smoking	3 (3.5%)	16 (4.8%)	19 (4.6%)	208 (7.3%)	279 (9.6%)	487 (8.5%)
Ex-smokers	4 (4.7%)	11 (3.3%)	15 (3.6%)	518 (18.3%)	440 (15.1%)	958 (16.7%)
Cannabis smoking	<i>n</i> = 85	<i>n</i> = 331	<i>n</i> = 416	<i>n</i> = 2822	<i>n</i> = 2901	<i>n</i> = 5723
Never users	61 (71.8%)	126 (38.1%)	187 (45.0%)	1790 (63.4%)	1342 (46.3%)	3132 (54.7%)
Within last month	5 (5.9%)	114 (34.4%)*	119 (28.6%)*	71 (2.5%)	195 (6.7%)	266 (4.6%)
Within last year	6 (7.1%)	139 (42.0%)*	145 (34.9%)*	229 (8.1%)	428 (14.7%)	657 (11.5%)
Ever users	24 (28.2%)	205 (61.9%)	229 (55.0%)	1032 (36.6%)	1559 (53.7%)	2163 (37.8%)

n: number of cases.

**P* < 0.001: we tested cases versus control group.

Cannabis smoking

In total, 229 patients (55%) reported smoking cannabis sometime during their lifetime. In 210 patients (92%), cannabis was the only illegal substance ever used. The remaining 19 patients (8%) reported the usage of various illegal substances in addition to cannabis—including heroin, ecstasy and cocaine. As displayed in Table 1, female patients did not differ from the women in the control group regarding cannabis abuse, regardless of whether we considered ever users (*P* = 0.153) or usage within the last month (*P* = 0.149) or last year (*P* = 1.00). Male patients, however, had a significantly higher prevalence of cannabis use compared with men in the control group, both regarding use within the last month (*P* < 0.001) and the last year (*P* < 0.001). But we observed no significant difference in men when we studied 'ever users' of cannabis (*P* = 0.289, Table 1).

We detected a significantly higher occurrence of cannabis smoking within the last month in individuals with primary spontaneous pneumothorax: OR = 8.22 (95% CI: 6.37–10.57, Table 3). However, the observed increased occurrence was only significant in men (*P* < 0.001), and we observed no isolated effect of cannabis: OR = 0.85 (95% CI: 0.17–2.61, *P* = 0.789).

Concomitant smoking of tobacco/cannabis

Daily tobacco smokers were more likely to also smoke cannabis on a frequent basis compared with never smokers (Table 4), suggesting a possible confounding effect. Table 4 also shows a much higher occurrence in the patient population of individuals who smoked daily and also smoked cannabis within the last month: OR = 5.01 (95% CI: 3.64–6.88, *P* < 0.001). There was no significant isolated effect of cannabis smoking in never smokers (OR = 0.85, 95% CI: 0.17–2.61, *P* = 0.789).

The isolated effect of tobacco smoking is shown in Table 5. There was a significantly higher occurrence of daily smokers (OR 4.85, 95% CI: 3.23–7.19, *P* < 0.001 and OR 8.10, 95% CI: 4.61–14.14, *P* < 0.001) in women and men, respectively (Table 5). We observed an even higher occurrence of men with concomitant usage of both substances (OR 8.74, 95% CI: 4.30–19.51, *P* < 0.001). This result suggests either an effect modification or an additive effect (Table 5).

We observed a significantly higher age at smoking debut (*P* = 0.011, Table 6) in male patients with PSP who smoked daily

but never used cannabis. We found no other significant differences between male daily smokers who never used cannabis versus those who smoked cannabis within the last month (Table 6).

DISCUSSION

In a population of 416 patients admitted with their first episode of PSP, we observed that patients with PSP smoked significantly more than the general population. This result is in concordance with the results from previous studies examining the association between spontaneous pneumothorax and tobacco smoking [1, 2]. Bense *et al.* [1] found a strong association between spontaneous pneumothorax and tobacco smoking. They observed an increased relative risk in heavy smokers: 9-fold in women and 22-fold in men. They also demonstrated a dose-response relationship, with heavy smokers being at significantly higher risk. In the present study, we detected a 5- to 6-fold increased risk in women and men, respectively (Table 2). The higher risk observed by Bense *et al.* may be caused by the differences in ages of the included patients and, in particular, the inclusion of patients diagnosed with secondary spontaneous pneumothorax in their study. A case-control study from the Netherlands published in 1975 [2] reported a frequency of daily smoking in patients with PSP as high as 90%. Although we observed a higher prevalence of daily tobacco smoking in our cases compared with the general population, the prevalence in our study was lower (60%). This difference may simply reflect changes in smoking habits over time.

The principal difference between the present and previous publications is the large number of homogeneous young patients included and the fact that none of the previous studies included information about concomitant smoking of cannabis. We found a higher proportion of recent cannabis smoking in male smokers than in the general population (Table 1). In fact, the risk was more than 7-fold higher in male patients with PSP (Table 3). The observed differences between the 2 sexes may be due to women having a different smoking pattern than men, because women smoked both tobacco and cannabis less frequently than men, but biological differences may also play a role.

Because many male patients smoked tobacco and cannabis regularly, both substances were possible confounders to each other. Surprisingly, we observed no isolated effect of cannabis smoking in male never smokers; instead, cannabis smoking

Table 2: Odds ratio [OR (95% CI)] of smoking habits by sex and age in patients with primary spontaneous pneumothorax

Tobacco smoking	Female age (years)			Male age (years)			Total
	<25 n = 31	25 to ≤35 n = 29	≥35 n = 25	<25 n = 186	25 to ≤35 n = 121	≥35 n = 24	Total n = 331
Never smokers	1 ^a n = 18	1 ^a n = 6	1 ^a n = 10	1 ^a n = 66	1 ^a n = 24	1 ^a n = 0	1 ^a n = 98
Daily smokers	2.74** (1.16–6.14) n = 11	11.35* (4.83–28.68) n = 20	4.85* (1.99–11.87) n = 13	4.66* (3.31–6.54) n = 101	9.31* (5.98–14.74) n = 89	7.29* (2.88–19.96) n = 16	5.96* (4.66–7.63) n = 206
Less than daily smoking	0.53 (0.06–2.15) n = 2	0.49 (0.01–3.08) n = 1	n = 0	0.70 (0.37–1.23) n = 15	0.08* (0.02–0.45) n = 1	n = 0	0.50*** (0.27–0.81) n = 16
Ex-smokers	n = 0	0.28 (0.03–1.12) n = 2	0.25 (0.03–1.02) n = 2	0.25*** (0.07–0.68) n = 4	0.27* (0.11–0.59) n = 7	n = 0	0.19* (0.09–0.35) n = 11

OR: odds ratio; CI: confidence interval; n: number of cases.
^aReference.
*P < 0.001.
**P < 0.05.
***P < 0.01.

Table 3: Odds ratio [OR (95% CI)] of cannabis habits by sex in patients with primary spontaneous pneumothorax

Cannabis smoking	Odds ratio (CI)		
	Female n = 85	Male n = 331	Overall n = 416
Never users	1 ^a n = 61	1 ^a n = 126	1 ^a n = 187
Within last month	2.42 (0.74–6.15) n = 5	7.29* (5.51–9.61) n = 114	8.22* (6.37–10.57) n = 119
Within last year	0.86 (0.30–1.99) n = 6	4.18* (3.26–5.36) n = 139	4.13* (3.29–5.15) n = 145
Ever users	0.68 (0.40–1.12) n = 24	1.40 (1.10–1.78) n = 205	2.02* (1.64–2.48) n = 229

OR: odds ratio; CI: confidence interval; n: number of cases.
^aReference.
*P < 0.001.

within the last year led to a decreased risk of pneumothorax (Table 4). However, only 3 of the never smoking men reported frequent consumption of cannabis smoking within the last month, and only 4 reported cannabis smoking within the last year. The rest only tried cannabis a few times during their life-time. Therefore, these conclusions are based on a very limited population. In contrast, 96% of the patients who reported cannabis smoking within the last month actually smoked cannabis on a daily or weekly basis, and the vast majority also smoked tobacco daily. These differences in cannabis consumption can likely explain why we did not observe an isolated effect of cannabis. More exact information about cannabis habits was not available in the control group; therefore, it was not possible to examine this point further.

Although we could not detect an isolated effect of cannabis, we observed that smoking cannabis in combination with daily tobacco smoking led to an increased risk of male patients having a PSP compared with male patients who only smoked tobacco (Table 4). Actually, the isolated effect of tobacco smoking in male patients only corresponded to a 5-fold higher OR compared with men who never smoked either tobacco or cannabis (Table 5). In contrast, the combined effect of smoking both substances resulted in a 9-fold higher risk compared to men who never smoked, indicating that concomitant use of both substances resulted in a modified effect. In fact, the effect of cannabis was added to the tobacco effect and seemed to intensify the effect of daily tobacco smoking (Table 5). Male patients with PSP who never smoked cannabis had a significantly higher age at smoking debut, but no other differences were observed regarding smoking habits between daily smokers with recent cannabis consumption versus daily smokers who never used cannabis (Table 6). Hence, we concluded that the observed higher risk associated with simultaneous smoking of tobacco and cannabis described in the present study could not be explained by differences in smoking habits.

The preponderance of men with PSP who smoked both tobacco and cannabis in our study suggests that both substances could be involved in the causal pathway for PSP. Unfortunately,

Table 4: Odds ratio [OR (95% CI)] of cannabis habits stratified by sex and smoking habits

Cannabis smoking	Female tobacco smoking		Male tobacco smoking		Overall tobacco smoking	
	<i>n</i> = 78		<i>n</i> = 304		<i>n</i> = 382	
	Daily smoker	Never smoker	Daily smoker	Never smoker	Daily smoker	Never smoker
	<i>n</i> = 27	<i>n</i> = 30	<i>n</i> = 206	<i>n</i> = 98	<i>n</i> = 250	<i>n</i> = 132
Never users	1 ^a <i>n</i> = 27	1 ^a <i>n</i> = 30	1 ^a <i>n</i> = 46	1 ^a <i>n</i> = 74	1 ^a <i>n</i> = 73	1 ^a <i>n</i> = 104
Within last month	1.35 (0.33–4.10) <i>n</i> = 4	<i>n</i> = 0	4.68* (3.27–6.67) <i>n</i> = 104	0.83 (0.16–2.58) <i>n</i> = 3	5.01* (3.64–6.88) <i>n</i> = 108	0.85 (0.17–2.61) <i>n</i> = 3
Within last year	0.65 (0.20–1.74) <i>n</i> = 5	<i>n</i> = 0	4.04* (2.86–5.70) <i>n</i> = 126	0.34** (0.09–0.91) <i>n</i> = 4	3.68* (2.73–4.94) <i>n</i> = 131	0.32** (0.09–0.86) <i>n</i> = 4
Ever users	0.43** (0.21–0.84) <i>n</i> = 17	0.28** (0.07–0.81) <i>n</i> = 4	1.01 (0.69–1.52) <i>n</i> = 160	0.36* (0.22–0.58) <i>n</i> = 24	1.05 (0.77–1.44) <i>n</i> = 177	0.41* (0.26–0.63) <i>n</i> = 28

OR: odds ratio; CI: confidence interval; *n*: number of cases.^aReference.**P* < 0.001.***P* < 0.05.**Table 5:** Odds ratio [OR (95% CI)] of smoking habits stratified by sex and cannabis habits in patients with primary spontaneous pneumothorax

Tobacco smoking	Female cannabis smoking		Male cannabis smoking		Overall cannabis smoking	
	<i>n</i> = 66		<i>n</i> = 240		<i>n</i> = 306	
	Within last month	Never users	Within last month	Never users	Within last month	Never users
	<i>n</i> = 5	<i>n</i> = 61	<i>n</i> = 114	<i>n</i> = 126	<i>n</i> = 250	<i>n</i> = 132
Never smokers	1 ^a <i>n</i> = 0	1 ^a <i>n</i> = 27	1 ^a <i>n</i> = 3	1 ^a <i>n</i> = 74	1 ^a <i>n</i> = 3	1 ^a <i>n</i> = 101
Daily smokers	<i>n</i> = 4	8.10* (4.61–14.14) <i>n</i> = 30	8.74* (4.30–19.51) <i>n</i> = 104	4.85* (3.23–7.19) <i>n</i> = 46	8.93* (4.56–19.02) <i>n</i> = 108	5.76* (4.18–7.89) <i>n</i> = 76
Less than daily smoking	<i>n</i> = 1	0.37 (0.01–2.24) <i>n</i> = 1	0.17* (0.06–0.43) <i>n</i> = 5	0.19 (0.05–1.08) <i>n</i> = 1	0.19* (0.07–0.46) <i>n</i> = 6	0.25** (0.03–0.92) <i>n</i> = 2
Ex-smokers	<i>n</i> = 0	0.35 (0.07–1.09) <i>n</i> = 3	0.17*** (0.02–0.71) <i>n</i> = 2	0.32** (0.10–0.77) <i>n</i> = 5	0.15*** (0.02–0.59) <i>n</i> = 2	0.33* (0.14–0.66) <i>n</i> = 8

OR: odds ratio; CI: confidence interval; *n*: number of cases.^aReference.**P* < 0.001.***P* < 0.05.****P* < 0.01.

our data do not allow us to elaborate further on this. Furthermore, we could not elaborate on the specific adverse respiratory effect caused by cannabis smoking, because the present study was limited by lack of information on the presence or absence of bullous lung disease because these observations were obtained from a computed tomography scan, which is rarely used in our country in relation to the first episode of PSP. However, previous studies suggested that cannabis smoking may result in a greater respiratory burden of carbon monoxide and tar than smoking a similar quantity of tobacco, hence leading to an accelerated state of pulmonary emphysema [22–29]. This finding may be a result of the method of smoking cannabis with a

different inhalation pattern compared with tobacco smoking [22]. Although purely speculative, the problem may be the combination of direct pulmonary toxicity together with pleural pressure changes and airway barotrauma associated with the high inspiratory pressures deployed in cannabis smoking [11].

By definition, the designation 'primary' in PSP is made by exclusion [30]. If cannabis and tobacco smoking are strongly associated with spontaneous pneumothorax, one might argue that these patients should be shifted into the 'secondary' group. However, the patients presented here are all otherwise healthy young individuals who fit the general clinical features of a patient with PSP; therefore, we believe that the diagnostic frame is appropriate.

Table 6: Smoking habits in the male population with primary spontaneous pneumothorax

Tobacco smoking	Patient type			P-value
	All male daily tobacco smokers <i>n</i> = 206	Daily tobacco smokers and cannabis within last month <i>n</i> = 104	Daily tobacco smokers never users of cannabis <i>n</i> = 46	
Age at smoking debut				
Median, years (range)	15 (7–23)	14 (7–21)	15 (8–20)	0.011
Mean (95% CI)	14.4 (14.0–14.8)	13.7 (13.2–14.2)	14.7 (14.1–15.4)	
Years of daily smoking				
Median, years (range)	10 (1–28)	11 (3–28)	11 (1–28)	0.684
Mean (95% CI)	11.1 (10.3–11.9)	11.4 (10.2–12.6)	11.8 (9.7–13.8)	
Pack years ^a				
Median, years (range)	8.3 (0.5–54)	8.0 (0.5–54)	10.0 (0.5–49)	0.424
Mean (95% CI)	10.2 (9.0–11.4)	10.4 (8.6–12.2)	10.9 (8.2–13.6)	
Number of heavy smokers ≥20 cigarettes a day	<i>n</i> = 103 (50%)	<i>n</i> = 50 (48%)	<i>n</i> = 26 (57%)	0.203

n: number of cases.

^aTwenty cigarettes a day for 1 year = 1 pack-year.

Our study is limited by the use of a population-based control group. Also, this study suffers from the inherited possibility for recall bias and selection bias in the case-control design. For example, our data were based upon self-reported smoking habits retrospectively, and having a PSP may potentially cause the patients to over-report smoking. Furthermore, in order to make comparison possible in the present study, we had to accept and preserve the categorization of groups concerning age, tobacco and cannabis smoking originally chosen by the National Institute of Public Health in the existing control group [17]. To comply with these limitations and limit bias, we used non-response-weighted estimates and extracted specific information on the exact geographical region and matching sex and age groups.

In conclusion, we observed that smoking is associated with a higher risk of having a PSP and that combined smoking of cannabis and tobacco intensifies this risk significantly, probably by accentuating the known side effects and damage caused by conventional tobacco smoking.

We recommend that an elaborate history of all smoked substances should be obtained on admittance in future patients diagnosed with PSP and that patients need to be informed about the increased risk associated with smoking.

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