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Tobacco use in first-episode psychosis, a multinational EU-GEI study

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Original Article

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Abstract

Background. Tobacco is a highly prevalent substance of abuse in patients with psychosis. Previous studies have reported an association between tobacco use and schizophrenia. The aim of this study was to analyze the relationship between tobacco use and first-episode psychosis (FEP), age at onset of psychosis, and specific diagnosis of psychosis.

Methods. The sample consisted of 1105 FEP patients and 1355 controls from the European Network of National Schizophrenia Networks Studying Gene–Environment Interactions (EU-GEI) study. We assessed substance use with the Tobacco and Alcohol Questionnaire and performed a series of regression analyses using case-control status, age of onset of psychosis, and diagnosis as outcomes and tobacco use and frequency of tobacco use as predictors. Analyses were adjusted for sociodemographic characteristics, alcohol, and cannabis use.

Results. After controlling for cannabis use, FEP patients were 2.6 times more likely to use tobacco [$p \leqslant 0.001$; adjusted odds ratio (AOR) 2.6; 95% confidence interval (CI) [2.1–3.2]] and 1.7 times more likely to smoke 20 or more cigarettes a day ($p = 0.003$; AOR 1.7; 95% CI [1.2–2.4]) than controls. Tobacco use was associated with an earlier age at psychosis onset ($\beta = -2.3$; $p \leqslant 0.001$; 95% CI [−3.7 to −0.9]) and was 1.3 times more frequent in FEP patients with a diagnosis of schizophrenia than in other diagnoses of psychosis (AOR 1.3; 95% CI [1.0–1.8]); however, these results were no longer significant after controlling for cannabis use.

Conclusions. Tobacco and heavy-tobacco use are associated with increased odds of FEP. These findings further support the relevance of tobacco prevention in young populations.

Introduction

Psychotic disorders (e.g. schizophrenia, schizoaffective, schizophreniform, delusional or brief psychotic disorder) are a group of heterogeneous syndromes with indeterminate neurobiological mechanisms (Kahn et al., 2015). The onset of a first-episode psychosis (FEP) is usually preceded for many years by several underlying biological processes at both the peripheral level and the central nervous system (Kahn & Sommer, 2015). Both FEP and patients with established psychosis are at markedly increased risk for substance use disorders, particularly nicotine dependence (Hartz et al., 2014; Volkow, 2009).

Tobacco use is common in the general population, with a worldwide prevalence estimated at 17.5% (WHO, 2021) and remains specially high in patients with psychosis (de Leon & Diaz, 2005; de Leon, Becona, Gurpegui, Gonzalez-Pinto, & Diaz, 2002; Lally et al., 2019; Mallet et al., 2017, 2019). Eleven percent of smokers in the general population are heavy smokers (i.e. smoking 25 or more cigarettes per day), as compared with 60–80% rates of heavy smokers among patients with psychosis who smoke (Kelly & McCreadie, 1999; Lally et al., 2019; Zhang et al., 2013). In the case of FEP, approximately 50–70% of patients report using tobacco (Coletti et al., 2015; Grossman et al., 2017; Wade et al., 2005).

The relationship between tobacco use and earlier age at onset of psychosis is controversial. Several studies have found no evidence of an association between tobacco use and earlier age of onset in FEP patients (Hickling et al., 2017; Myles et al., 2012). However, a meta-analysis showed that daily tobacco smoking was associated with earlier age at onset of psychosis (Gurillo, Jauhar, Murray, & MacCabe, 2015).

Moreover, previous studies report that patients with schizophrenia show a 5-fold greater likelihood of having a comorbid substance use disorder (SUD) compared with the general population (Regier et al., 1990), with two-thirds of patients with schizophrenia and comorbid SUD reporting tobacco use (Depp et al., 2015; McCreadie, 2002). Furthermore, tobacco smokers with schizophrenia extract 1.3 times more nicotine from each cigarette than smokers in

the general population (Lally et al., 2019; Olincy, Young, & Freedman, 1997; Williams, Farmer, Ackenheil, Kaufmann, & McGuffin, 1996).

Some studies have found a positive association between tobacco smoking and a diagnosis of schizophrenia in the general population (Hunter, Murray, Asher, & Leonardi-Bee, 2020), with regular tobacco use preceding the onset of psychosis (Beratis, Katrivanou, & Gourzis, 2001; Kelly & McCreadie, 1999; Kotov, Guey, Bromet, & Schwartz, 2010; Ma et al., 2010) and with a dose–response relationship (Saha et al., 2011). Moreover, among patients with psychosis, there is some evidence linking tobacco smoking with higher odds of a diagnosis of schizophrenia than of other non-affective psychoses (King, Jones, Petersen, Hamilton, & Nazareth, 2021).

There is evidence that nicotine alters signaling in the dopaminergic, cholinergic, and glutamatergic neurotransmitter systems, which results in a negative impact on brain development, based on early exposure to this substance (Ferreira & Coentre, 2020; Smith, McDonald, Bergstrom, Ehlinger, & Brielmaier, 2015). Like cannabis, tobacco is implicated in the pathophysiology of schizophrenia (de Leon et al., 2002; Kelly & McCreadie, 1999; Moore et al., 2007; Zammit et al., 2009) and the shared genetic, environmental, and socioeconomic factors of cannabis and tobacco use make it difficult to address the separate influence of each substance on the onset of FEP and its clinical course (Agrawal, Budney, & Lynskey, 2012; Gage et al., 2014; Grossman et al., 2017).

Based on previous data, we hypothesized that (1) tobacco use would be more frequent in FEP than in controls even after controlling for cannabis use, (2) FEP tobacco users would show an earlier age at onset of psychosis, and (3) would receive a diagnosis of schizophrenia more frequently than non-users after controlling for cannabis use.

Methods

Study design

The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) project is a large, international, multisite, observational study. The network recruited participants between May 2010 and April 2015 from 17 catchment areas across six countries (Brazil, France, Italy, the Netherlands, Spain, and the UK). A subset of these incident cases was recruited for a concurrent case-control study, with controls selected from the same catchment areas as the incident cases. The aim of the project was to examine the interactive genetic, clinical, and environmental determinants involved in the development, severity, and outcome of schizophrenia. Further information about the study procedures can be found elsewhere (Gayer-Anderson et al., 2020; van Os et al., 2014).

Participants

A total of 2774 participants with FEP comprised of the EU-GEI study sample (Gayer-Anderson et al., 2020; Jongsma et al., 2018). Of those, 1130 FEP patients and 1497 healthy controls (HC) consented to participate in the case-control study. We excluded 167 subjects due to lack of data on tobacco consumption, so we analyzed data from 1105 FEP patients and 1355 HC. Within the group of tobacco-user FEP patients ($n = 613$), from 35 patients data on frequency of use were missing; therefore, we analyzed data from 224 heavy users and 354 non-heavy users. A recruitment flow chart is shown in the online Supplementary material.

The inclusion criteria for FEP patients were: (1) a diagnosis of psychotic disorder based on the International Classification of Diseases, 10th Edition (ICD-10), codes F20–F33 (WHO, 1992), (2) age between 18 and 64 years, and (3) to be users of the mental health services in the catchment areas. We excluded participants whose psychotic symptoms were due to acute intoxication (ICD-10: F1X.5) or organic psychosis (ICD-10: F09) or if they had previously received antipsychotic medication. Volunteers from the same catchment areas were selected for the control sample, using a mixture of random ad quota sampling, resulting in controls representative of local populations with regard to age, gender, and ethnicity. They had to meet the following inclusion criteria: (1) age between 18 and 64 years, (2) to be a resident of the same catchment area as the group of patients at the time of consent, (3) fluency in the site primary language, and (4) absence of current or past psychotic disorder. Further details about the sample recruitment can be found elsewhere (Gayer-Anderson et al., 2020).

Participants gave written informed consent before inclusion in the study. The research ethics committees of each site approved the study.

Measures

The modified version of the Medical Research Council (MRC) Sociodemographic Schedule (Mallet, 1997) was used to collect sociodemographic data. Diagnoses were obtained using clinical interviews and the 90-item computerized Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT) system (McGuffin, Farmer, & Harvey, 1991; Quattrone et al., 2019; Williams et al., 1996) and assigned to one of two categories: (1) schizophrenia and (2) other psychotic diagnoses. Age of onset of psychosis was calculated by subtracting duration of untreated psychosis from age at the time of assessment. The EU-GEI Tobacco and Alcohol Questionnaire was used to collect information about the use of tobacco in the year prior to the assessment and other legal and illegal substances by trained personnel at each site, whose reliability was assessed throughout the study ($\kappa = 0.7$) (Quattrone et al., 2019). For purposes of categorizing the severity of tobacco use in this manuscript we assigned ⩾20 cigarettes per day, equivalent to one pack of cigarettes per day, to the heavy use group and anything less to the non-heavy use group, a cutoff value supported in the tobacco literature (Chin, Hong, Gillen, Bates, & Okechukwu, 2013; Kay-Lambkin et al., 2013; Shelef, Diamond, Diamond, & Myers, 2009). We used a modified version of the Cannabis Experience Questionnaire from the EU-GEI project ($CEQ_{EU\text{-}GEI}$), and categorized lifetime frequency of use into three groups: (1) never or occasional use (less than once a week), (2) more than weekly use (but less than daily), and (3) daily use (Di Forti et al., 2019). Impairment of functionality was measured with the Global Assessment of Functionality (GAF) (Jones, Thornicroft, Coffey, & Dunn, 1995).

Statistical analysis

Normality distribution of quantitative outcomes in a large sample was tested following Satorra–Bentler's procedure (Russell, 2016; West, Sandler, Pillow, Baca, & Gersten, 1991) in which a variables' distribution was considered normal if skewness was <2 and

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kurtosis was <7. Little's missing completely at random (MCAR) test showed data were missing at random ($\chi^2 = 13.9$; $p = 0.179$) and comparisons between included and excluded participants showed no significant differences in sociodemographic and clinical variables (sex, age, years of education, tobacco use, alcohol use, other drug use, age of psychosis onset, and diagnosis). We used means and standard deviations for continuous variables and frequency and percentages for categorical variables. For comparisons between two groups, we used χ^2 tests for categorical variables. For continuous variables, we used t tests. For comparisons of more than two groups [those between: (1) tobacco-user FEP, (2) tobacco non-user FEP, (3) tobacco-user controls, and (4) tobacco non-user controls), we used analysis of variance and analysis of covariance (ANCOVA) followed by Bonferroni post-hoc correction. We used η^2 and Cohen's d tests to calculate the effect sizes, as appropriate. Binary logistic regression model analyses were performed to examine the association of tobacco use and frequency of tobacco use with the case and control groups and with the dichotomous variable for diagnosis (schizophrenia *v.* other psychotic disorders). Linear regression model analyses were used to analyze the association of tobacco use and frequency of tobacco use with age at onset of psychosis.

Two models were conducted for each regression analysis: model 1 was adjusted for: age, sex, country, years of education, and alcohol use (except for the age-of-onset analysis, in which the confounding variable 'age' was not included to avoid collinearity). Model 2 additionally included cannabis use frequency [categorized as never or occasional use, used more than once a week or daily use (Di Forti et al., 2019)]. All categorical confounders were included as fixed factors. For logistic regression models we report adjusted odds ratios (AORs) and for linear regression models, we report beta values.

Supplementary ANCOVA (for age at psychosis onset) and binary logistic regression analyses (for case-control status and diagnosis) were used to assess the main and interaction effects of tobacco (yes/no) and cannabis use (yes/no) on the different outcomes. In addition, we conducted ANCOVAs with a Bonferroni correction of the post-hoc comparisons and binary logistic regression analyses including categorical variables reflecting the possible combinations of (i) tobacco and cannabis use [i.e. (1) tobacco only (TO), (2) tobacco and cannabis (T&C), (3) cannabis-only (CO), and (4) nonuse (NU)] and (ii) frequency of tobacco use and cannabis use [(1) heavy-tobacco only (HTO), (2) non-heavy-tobacco only (NHTO), (3) heavy tobacco and cannabis (HT&C), (4) non-heavy tobacco and cannabis (NHT&C), (5) cannabis-only (CO), (6). nonuse (NU)] to assess the effect of the different combined patterns of use on the same outcomes.

Finally, we performed supplementary analyses substituting the covariable 'country' for 'site' to check if there were any effects related to specific locations and we repeated the main analyses after including the covariable 'other substance use'. A cut-off value of $p < 0.05$ was chosen for statistical significance. All statistical analyses were conducted using SPSS 25.

Results

Sociodemographic and clinical description

FEP v. controls

The sample comprised of a total of 1105 (44.9%) patients [613 (55.5%) tobacco users and 492 (44.5%) non-users] and 1355 (55.1%) controls [329 (24.3%) tobacco users and 1026 (75.7%) non-users]. Compared to controls, FEP patients were younger ($t = -10.5$; $p \leqslant 0.001$; $d = 0.4$), more often men [$\chi^2 = 54.6$; $p \leqslant 0.001$, OR 1.8; 95% confidence interval (CI) [1.5–2.1]], and had a lower education level ($t = -10.8$; $p \leqslant 0.001$; $d = 0.4$). Controls were more likely to have been employed ($\chi^2 = 22.6$; $p \leqslant 0.001$, OR 1.9; 95% CI [1.5–2.6]) and more often presented a higher socioeconomic status ($\chi^2 = 205.7$; $p \leqslant 0.001$).

More patients than controls reported having used tobacco ($\chi^2 = 250.6$; $p \leqslant 0.001$; OR 3.9; 95% CI [3.3–4.6]) and in a heavy use frequency ($\chi^2 = 7.6$; $p = 0.006$; OR 1.5; 95% CI [1.1–2.0]). Patients were more frequently TO users ($\chi^2 = 157.6$; $p \leqslant 0.001$; OR 3.4; 95% CI [2.8–4.1]) and T&C users ($\chi^2 = 165.2$; $p \leqslant 0.001$; OR 5.6; 95% CI [4.2–7.4]) than controls. Patients also reported smoking more tobacco cigarettes ($t = 3.3$; $p \leqslant 0.001$; $d = 0.24$) than controls users. We found no difference in type of tobacco used (cigarettes, cigars, pipes, snuff, or chewing tobacco) between FEP and control tobacco users (see Table 1). Further information about the sociodemographic distribution of the site and the use of other drugs is shown in the online Supplementary material.

FEP users v. FEP non-users

Bivariate analyses showed that FEP patients with a history of tobacco use were more frequently male ($\chi^2 = 34.5$; $p \leqslant 0.001$; OR 2.1; 95% CI [1.6–2.7]), on average 3.3 years younger ($t = 5.1$; $p \leqslant 0.001$; $d = 0.3$), and received half a year of education less ($t = -2.1$; $p = 0.037$; $d = 0.02$) than FEP non-users. A diagnosis of schizophrenia was more common in FEP tobacco users than in non-users ($\chi^2 = 19.057$; $p = 0.002$) than in people with another diagnosis of psychosis. FEP tobacco users had an earlier onset of psychosis compared with FEP non-users ($t = -4.76$; $p \leqslant 0.001$; $d = 0.3$) (see Table 2).

FEP heavy users v. FEP non-heavy users

FEP patients with heavy-tobacco use were on average 1.6 years younger ($t = -1.8$; $p = 0.075$; $d = 0.2$) and had received almost 2 more years of education less ($t = 4.6$; $p \leqslant 0.001$; $d = -0.4$) than non-heavy-tobacco users. There were no differences in diagnosis or age at onset of psychosis between groups based on frequency of tobacco use (see Table 3).

Rates of tobacco use

FEP v. controls

Logistic regression models showed that tobacco use was 3.3 times higher in the FEP group than in the control group (AOR 3.3, 95% CI [2.7–4.0]). After including the frequency of cannabis use as a covariate in the model there was a slight reduction in the effect size of tobacco use (AOR 2.6, 95% CI [2.1–3.3]). In this model, daily cannabis use was associated with increased odds of FEP (AOR = 3.1, 95% CI [2.3–4.1]) compared with never or occasional use (see Table 4).

Participants who were TO users (AOR 3.0, 95% CI [2.4–3.7]) and those who were T&C users (AOR 3.9, 95% CI [2.9–5.4]) had higher odds of FEP that NU, with a non-significant trend for differences between the CO and the NU groups ($p = 0.051$; AOR 0.6, 95% CI [0.3–1.0]) (see the online Supplementary material).

Heavy users v. non-heavy users

Logistic regression models showed that heavy-tobacco users had higher odds of FEP than non-heavy users, even after covarying by the cannabis use [model 1 (AOR 1.7, 95% CI [1.2–2.4]), model 2 (AOR 1.7, 95% CI [1.2–2.4])]. Both HTO (AOR 1.6,

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Table 1. Sociodemographic and substance use comparisons between the four groups

Variables	FEP users ($N = 613$)	FEP non-users ($N = 492$)	HC users ($N = 329$)	HC non-users ($N = 1026$)	Statistics (F; p; η^2); (χ^2; p); (t; d)	Post-hoc analyses*
Age (mean ± s.d.)	29.8 ± 10.0	33.1 ± 11.1	35.1 ± 12.3	36.6 ± 13.2	**($F = 42.8$; $p \leqslant 0.001$; $\eta^2 = 0.05$)**	FEPU < FEPNU[a], HCU[b], HCNU[c] FEPNU < HCNU[d]
Sex, *N* (%)					**($\chi^2 = 89.3$; $p \leqslant 0.001$)**	
Males	425 (69.3)	256 (52.0)	173 (52.6)	466 (45.4)		FEPU males > FEPU females[e], HCNU females > HCNU males[f]
Females	188 (30.7)	236 (48)	156 (47.4)	560 (54.6)		
Country, *N* (%)					**($\chi^2 = 98.3$; $p \leqslant 0.001$)**	
UK	139 (24.5)	101 (17.8)	55 (9.7)	272 (48.0)		Netherlands: FEPU > FEPNU[g], HCU[h]; Brazil: FEPNU > FEPU[i]; HCNU > HCU[j], FEPU[k] UK: FEPU > HCU[l]; HCNU > HCU[m], FEPNU[n]
Netherlands	125 (31.2)	68 (17)	42 (10.5)	166 (41.4)		
Spain	113 (27.3)	84 (20.3)	71 (17.1)	146 (35.3)		
France	60 (24.1)	44 (17.7)	35 (14.1)	110 (44.2)		
Italy	100 (29.3)	82 (24)	69 (20.2)	90 (26.4)		
Brazil	76 (15.6)	113 (23.2)	57 (11.7)	242 (49.6)		
Ethnicity, *N* (%)					**($\chi^2 = 86.7$; $p \leqslant 0.001$)**	
White	394 (64.3)	307 (62.4)	267 (81.4)	780 (76)		White: FEPU > HCU[o]; HCNU > FEPU[p], FEPNU[q], HCU[r] Black: HCU < FEPU[s], FEPNU[t], HCNU > HCU[u]
Black	97 (15.8)	82 (16.7)	17 (5.2)	100 (9.7)		
Mixed	54 (8.8)	54 (11)	27 (8.2)	87 (8.5)		
Asian	19 (3.1)	14 (2.8)	5 (1.5)	25 (2.4)		
North African	35 (5.7)	16 (3.3)	6 (1.8)	16 (1.6)		
Other	14 (2.3)	19 (3.9)	6 (1.8)	18 (1.8)		
Migrant (yes), *N* (%)	158 (27.4)	144 (25)	41 (7.1)	233 (40.5)	**($\chi^2 = 33.6$; $p \leqslant 0.001$)**	HCU < FEPU[v], FEPNU[w], HCNU[x], HCNU > FEPNU[y]
History of employment (yes), *N* (%)	555 (24.7)	422 (18.8)	308 (13.7)	961 (42.8)	**($\chi^2 = 29.0$; $p \leqslant 0.001$)**	FEPU > FEPNU[z] HCNU > FEPU[aa], FEPNU[ab]
Years of education (mean ± s.d.)	12.7 ± 4.0	13.2 ± 4.4	14.0 ± 4.1	15.0 ± 4.2	**($F = 43.8$; $p \leqslant 0.001$; $\eta^2 = 0.05$)**	FEPU < HCU[ac], HCNU[ad]; FEPNU < HCNU[ae] HCU < HCNU[af]
Main socioeconomic status, *N* (%)					**($\chi^2 = 230.0$; $p \leqslant 0.001$)**	
Professional or management	47 (9.4)	62 (15.6)	73 (26.4)	312 (36.9)		Professional or management: HCU > FEPU[ag], HCNU > FEPU[ah], FEPNU[ai], HCU[aj] Technical middle class: HCNU > FEPU[ak], FEPNU[al] Working class or service sector: FEPU > FEPNU[am]; HCU < FEPU[an]; FEPNU[ao], HCNU[ap]
Technical middle class	94 (18.8)	79 (19.8)	68 (24.5)	219 (25.9)		
Working class or service sector	336 (67.1)	232 (58.3)	134 (48.4)	308 (36.4)		
Long-term unemployed	24 (4.8)	25 (6.3)	2 (0.7)	6 (0.7)		
GAF (mean ± s.d.)	50.3 ± 16.2	51.3 ± 17.2	83.5 ± 12.4	83.9 ± 11.2	**($F = 1063$; $p \leqslant 0.001$; $\eta^2 = 0.6$)**	FEPU < HCU[aq], HCNU[ar] FEPNU < HCU[as], HCNU[at]
Alcohol use, lifetime (yes), *N* (%)	410 (27.2)	197 (13)	257 (17)	646 (42.8)	**($\chi^2 = 129.1$; $p \leqslant 0.001$)**	FEPU > FEPNU[au], HCU[av] HCNU > FEPU[aw], FEPNU[ax], HCU[ay]
Ever used cannabis (yes), *N* (%)	526 (39.1)	172 (12.8)	237 (17.6)	409 (30.4)	**($\chi^2 = 444.3$; $p \leqslant 0.001$)**	FEPU > FEPNU[az], HCU[ba]

Currently use cannabis (yes), *N* (%)	210 (53.8)	29 (7.4)	80 (20.5)	71 (18.2)	**(χ^2 = 270.5; $p \leqslant 0.001$)**	FEPU > FEPNU[bb], HCU[bc], HCNU[bd]
Currently use other drugs (yes), *N* (%)	117 (58.8)	33 (16.6)	17 (8.5)	32 (16.1)	**(χ^2 = 24.2; $p \leqslant 0.001$)**	FEPU > HCU[be], HCNU[bf] FEPNU > HCU[bg]
Type of tobacco use (yes) *N* (%)						
Cigarettes or rolled tobacco	601 (98.0)	–	321 (97.6)	–	(χ^2 = 0.2; p = 0.630)	
Cigars	27 (4.4)	–	11 (3.3)	–	(χ^2 = 0.6; p = 0.430)	
Pipe	2 (0.3)	–	1 (0.3)	–	(χ^2 = 0.003; p = 0.954)	
Snuff or chewing tobacco	2 (0.3)	–	4 (1.2)	–	(χ^2 = 2.7; p = 0.102)	
Total frequency of tobacco use	15.5 ± 11.2	–	13.0 ± 9.9	–	**(t = 3.3; $p \leqslant 0.001$; d = 0.24)**	
Dichotomized frequency of tobacco use (heavy use), *N* (%)	224 (70.7)	–	93 (29.3)	–	**(χ^2 = 7.6; p = 0.006)**	

FEP, first-episode psychosis; HC, healthy controls; GAF, General Assessment of Functioning. Significant results are highlighted in bold.
*Bonferroni test values: [a] ($p \leqslant 0.001$); [b] ($p \leqslant 0.001$); [c] ($p \leqslant 0.001$); [d] ($p \leqslant 0.001$); [e] ($p \leqslant 0.001$); [f] ($p = 023$); [g] ($p = 0.004$); [h] ($p \leqslant 0.001$); [i] ($p = 003$); [j] ($p \leqslant 0.001$); [k] ($p \leqslant 0.017$); [l] ($p = 0.031$); [m] ($p \leqslant 0.001$); [n] ($p = 0.011$); [o] ($p \leqslant 0.001$); [p] ($p \leqslant 0.001$); [q] ($p \leqslant 0.001$); [r] ($p = 0.043$); [s] ($p \leqslant 0.001$); [t] ($p \leqslant 0.001$); [u] ($p = 0.010$); [v] ($p \leqslant 0.001$); [w] ($p \leqslant 0.001$); [x] ($p \leqslant 0.001$); [y] ($p = 0.006$); [z] ($p = 0.014$); [aa] ($p = 0.022$); [ab] ($p \leqslant 0.001$); [ac] ($p \leqslant 0.001$); [ad] ($p \leqslant 0.001$); [ae] ($p \leqslant 0.001$); [af] ($p = 001$); [ag] ($p \leqslant 0.001$); [ah] ($p \leqslant 0.001$); [ai] ($p \leqslant 0.001$); [aj] ($p \leqslant 0.001$); [ak] ($p = 0.003$); [al] ($p = 0.019$); [am] ($p = 0.007$); [an] ($p \leqslant 0.001$); [ao] ($p = 0.011$); [ap] ($p \leqslant 0.001$); [aq] ($p \leqslant 0.001$); [ar] ($p \leqslant 0.001$); [as] ($p \leqslant 0.001$); [at] ($p \leqslant 0.001$); [au] ($p \leqslant 0.001$); [av] ($p = 0.011$); [aw] ($p = 0.004$); [ax] ($p \leqslant 0.001$); [ay] ($p \leqslant 0.001$); [az] ($p \leqslant 0.001$); [ba] ($p \leqslant 0.001$); [bb] ($p \leqslant 0.001$); [bc] ($p \leqslant 0.001$); [bd] ($p \leqslant 0.001$); [be] ($p \leqslant 0.001$); [bf] ($p = 0.007$).

95% CI [1.1–2.4]) and HT&C users (AOR 2.8, 95% CI [1.4–5.9]) showed significantly higher odds of FEP than NHTO users. No significant differences were found between the HTO and the HT&C groups. Heavy users also showed significantly higher odds of FEP than tobacco non-users even after controlling by cannabis use [model 1 (AOR 4.0, 95% CI [3.0–5.4]), model 2 (AOR 3.4, 95% CI [2.5–4.7])] (for more information, see the online Supplementary material). Figure 1 presents the OR of patients and controls for the combined measure of use and frequency of tobacco and cannabis.

Age of onset

Tobacco use was associated with an earlier age at psychosis onset ($\beta = -2.3$; $p \leqslant 0.001$; 95% CI [−3.7 to −0.9]), but this result became non-significant when cannabis use frequency was included as a covariate ($\beta = -0.4$; $p = 0.610$; 95% CI [−1.1 to 1.9]). Heavy-tobacco use (*v.* non-heavy use) was not significantly associated with an earlier age of psychosis onset [model 1 ($\beta = -0.5$; $p = 0.590$; 95% CI [−1.3 to −2.3]); model 2 ($\beta = -0.1$; $p = 0.876$; 95% CI [−1.6 to 1.9])]. Supplementary ANCOVA analyses revealed a significant interaction effect of tobacco and cannabis use ($F = 18.6$; $p \leqslant 0.001$). Concretely, the group of T&C users had an earlier age at onset than the NU and TO groups, and the CO group presented an earlier age of psychosis onset than the NU and TO groups (see the online Supplementary material). Concerning frequency of use, the NHTO group presented an earlier age of psychosis onset than the NU group; the HT&C group had an earlier age at onset than the HTO, NHTO, and NU groups; the NHT&C group presented an earlier age at onset than the HTO and NU groups; and the CO group showed an earlier age of psychosis onset than the HTO and the NU groups (see the online Supplementary material).

Diagnosis

FEP patients who used tobacco had 1.3 times higher odds of being diagnosed with schizophrenia than other psychotic disorders. When we included frequency of cannabis use in the model, tobacco use was no longer significantly associated with diagnosis [model 1 (AOR 1.3; 95% CI [1.0–1.8]); model 2 (AOR 1.1; 95% CI [0.8–1.5])].

Supplementary logistic regression analyses did not detect a significant interaction effect of cannabis and tobacco use on diagnosis ($p = 0.125$; AOR −1.6; 95% CI [0.9–3.1]). The group of T&C use presented higher odds of schizophrenia diagnosis than both the TO (AOR 1.5; 95% CI [1.0–2.3]) and NU groups (AOR 1.9; 95% CI [1.3–2.9]) (see the online Supplementary material). Regarding frequency of tobacco use, the HT&C (AOR 2.0; 95% CI [1.1–3.7]) and NHT&C (AOR 1.7; 95% CI [1.1–2.7]) groups presented higher odds of receiving a schizophrenia diagnosis than NU, with no significant differences between the remaining patterns of use; see the online Supplementary material for further details.

Analyses controlled by site found comparable results in terms of the direction and magnitude of the effects (see the online Supplementary material). Analyses controlled by use of other substances showed that tobacco use was 5.7 times higher in the FEP group than in the control group (model 1: AOR 5.7, 95% CI [3.5–9.1]). This effect remained significant after the inclusion of frequency of cannabis use as a covariate in model 2 (AOR 5.4, 95% CI [3.3–8.9]). However, we observed no significant effects

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Table 2. Comparisons between tobacco user and non-user patients in sociodemographic and clinical variables

Variables	FEP users ($N = 613$)	FEP non-users ($N = 492$)	Statistics (χ^2; p; OR[a]; 95% CI); (t; p; d)
Age (mean ± S.D.)	29.8 ± 10.0	33.1 ± 11.1	**($t = 5.1$; $p \leqslant 0.001$; $d = 0.3$)**
Sex: males *N* (%)	425(62.4)	256 (37.6)	**($\chi^2 = 34.5$; $p \leqslant 0.001$; OR 2.1; 95% CI 1.6–2.7)**
Ethnicity: white *N* (%)	394 (64.3)	307 (62.4)	($\chi^2 = 7.5$; $p = 0.187$)
Migrant: Yes *N* (%)	158 (52.3)	144 (47.7)	($\chi^2 = 1.6$; $p = .201$; OR = 0.8; 95% CI 0.6–1.1)
Years of education (mean ± S.D.)	12.7 ± 4.0	13.2 ± 4.4	**($t = -2.1$; $p = 0.037$; $d = 0.1$)**
Ever used cannabis (Yes) *N* (%)	526 (75.4)	172 (24.6)	**($\chi^2 = 295.5$; $p \leqslant 0.001$; OR 11.3; 95% CI 8.4–15.3)**
Currently use cannabis (Yes) *N* (%)	210 (87.9)	29 (12.1)	**($\chi^2 = 126.3$; $p \leqslant 0.001$; OR 8.2; 95% CI 5.4–12.3)**
Alcohol use, lifetime (Yes) *N* (%)	410 (67.5)	197 (32.5)	**($\chi^2 = 81.9$; $p \leqslant 0.001$; OR 3.2; 95% CI 2.5–4.2)**
Currently use other drugs (Yes) *N* (%)	117 (78.0)	33 (22.0)	($\chi^2 = 0.001$; $p = 0.976$; OR = 1.0; 95% CI 0.6–1.7)
GAF (mean ± S.D.)	50.3 ± 16.2	51.3 ± 17.2	($t = -0.4$; $p = 0.719$; $d = 0.02$)
Diagnosis *N* (%)			**($\chi^2 = 19.1$; $p = .002$)**
Schizophrenia	337 (56.2)	225 (46.7)	
Schizoaffective disorder	32 (5.3)	26 (5.4)	
Depression	61 (10.2)	88 (18.3)	
Bipolar type I	85 (14.2)	67 (13.9)	
Delusional disorder	34 (5.7)	24 (5.0)	
Psychosis NOS	51 (8.5)	52 (10.8)	
DUP (mean ± S.D.)	63.1 ± 183.3	60 ± 164.2	($t = 0.3$; $p = 0.776$; $d = 0.3$)
Age at onset of psychosis (mean ± S.D.)	27.9 ± 10.0	31.1 ± 11.1	**($t = -4.7$; $p \leqslant 0.001$; $d = .3$)**

FEP, first-episode psychosis; GAF, General Assessment of Functioning; DUP, duration of untreated psychosis. Significant results are highlighted in bold.
[a]OR and 95% CI were calculated for dichotomous variables.

Table 3. Comparisons between heavy and non-heavy-tobacco user FEP patients in sociodemographic and clinical variables

Variables	Non-heavy users FEP ($N = 354$)	Heavy users FEP ($N = 224$)	Statistics (χ^2; p; OR[a]; 95% CI); (t; p; d)
Age (mean ± S.D.)	29.1 ± 9.3	30.7 ± 10.8	**($t = -1.8$; $p = 0.075$; $d = 0.2$)**
Sex: males *N* (%)	244 (68.9)	152 (38.4)	($\chi^2 = 0.1$; $p = 0.787$; OR 1.0; 95% CI 0.7–1.5)
Ethnicity: white *N* (%)	207 (58.5)	168 (75.0)	**($\chi^2 = 21.1$; $p = 0.001$)**
Migrant (Yes) *N* (%)	94 (67.1)	46 (32.9)	($\chi^2 = 2.6$; $p = 0.106$; OR 0.7; 95% CI 0.5–1.1)
Years of education (mean ± S.D.)	13.3 ± 3.9	11.7 ± 4.0	**($t = 4.6$; $p \leqslant 0.001$; $d = -0.4$)**
Alcohol use, lifetime (Yes) *N* (%)	239 (60.2)	158 (39.8)	($\chi^2 = 0.1$; $p = 0.737$; OR 1.1; 95% CI 0.7–1.5)
Ever used cannabis (Yes) *N* (%)	309 (62.3)	187 (37.7)	($\chi^2 = 2.0$; $p = 0.155$; OR 0.7; 95% CI 0.4–1.1)
Currently use cannabis (Yes) *N* (%)	127 (65.1)	68 (34.9)	($\chi^2 = 1.8$; $p = 0.176$; OR 0.8; 95% CI 0.5–1.1)
Currently use other drugs (Yes) *N* (%)	63 (57.3)	47 (42.7)	($\chi^2 = 1.3$; $p = 0.262$; OR 1.4; 95% CI 0.8–2.3)
GAF (mean ± S.D.)	50.7 ± 15.7	50.0 ± 16.8	($t = 0.3$; $p = 0.760$; $d = -0.03$)
Diagnosis, *N* (%)			($\chi^2 = 1.1$; $p = 0.953$)
Schizophrenia	192 (55.2)	121 (55.8)	
Schizoaffective disorder	20 (5.7)	9 (4.1)	
Depression	37 (10.6)	24 (11.1)	
Bipolar type I	51 (14.7)	31 (14.3)	
Delusional disorder	21 (6.0)	12 (5.5)	
Psychosis NOS	27 (7.8)	20 (9.2)	
Age at onset of psychosis (mean ± S.D.)	27.3 (9.6)	28.6 (10.4)	($t = -1.5$; $p = 0.135$; $d = 0.1$)

FEP, first-episode psychosis; GAF, General Assessment of Functioning. Significant results are highlighted in bold.
[a]OR and 95% CI were calculated for dichotomous variables.

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Table 4. Logistic regression including patients and controls with and without cannabis use covariate

	No cannabis control (predictive value of the model: 70.2%)								Frequency of cannabis (predictive value of the model: 71.3%)							
							95% CI for AOR								95% CI for AOR	
Variables	*B*	S.E.	Wald χ^2	df	Sig.	AOR	Lower	Upper	*B*	S.E.	Wald χ^2	df	Sig.	AOR	Lower	Upper
Age	−0.03	0.004	70.3	1	**⩽0.001**	0.97	0.96	0.97	−0.03	0.004	50.0	1	**⩽0.001**	0.97	0.96	0.98
Sex	−0.5	0.1	26.7	1	**⩽0.001**	0.6	0.5	0.7	−0.4	0.1	13.8	1	**⩽0.001**[a]	0.7	0.6	0.8
Country																
UK	0.6	0.2	13.6	1	**⩽0.001**	1.8	1.3	2.4	0.5	0.2	11.0		**0.001**	1.7	1.2	2.3
Netherlands	1.2	0.2	48.0	1	**⩽0.001**	3.3	2.4	4.6	1.1	0.2	40.0	1	**⩽0.001**	3.1	2.2	4.3
Spain	0.7	0.2	19.4	1	**⩽0.001**	2.0	1.5	2.7	0.6	0.2	15.5	1	**⩽0.001**	1.9	1.4	2.6
France	0.5	0.2	6.7	1	**0.010**	1.6	1.1	2.3	0.5	0.2	6.0	1	**0.014**	1.6	1.1	2.3
Italy	0.9	0.2	30.0	1	**⩽0.001**	2.5	1.8	3.5	0.9	0.2	27.8	1	**⩽0.001**	2.5	1.8	3.4
Brazil			55.8	5	**⩽0.001**[a]						48.2	5	**⩽0.001**[a]			
Years of education	−0.1	0.01	84.1	1	**⩽0.001**	0.9	0.9	0.9	−0.1	0.01	74.3	1	**⩽0.001**	0.9	0.9	0.9
Alcohol use	−0.8	0.1	56.3	1	**⩽0.001**	0.4	0.4	0.6	−0.8	0.1	56.6	1	**⩽0.001**	0.4	0.4	0.5
Tobacco use	1.2	0.1	143.4	1	**⩽0.001**	3.3	2.7	4.0	1.0	0.1	80.3	1	**⩽0.001**	2.6	2.1	3.2
Cannabis frequency																
Never/ occasional use	–	–	–	–	–	–	–	–			56.6	2	**⩽0.001**[a]			
More than once weekly	–	–	–	–	–	–	–	–	0.2	0.2	1.5	1	0.217	1.2	0.9	1
Daily use	–	–	–	–	–	–	–	–	1.126	0.1	56.3	1	**⩽0.001**	3.1	2.3	4.1

AOR, adjusted odds ratio. Significant results are highlighted in bold.
[b]The reference group for 'sex' was male; for 'country' was Brazil. For 'Cannabis frequency', the reference group was 'Never/Occasional use'.

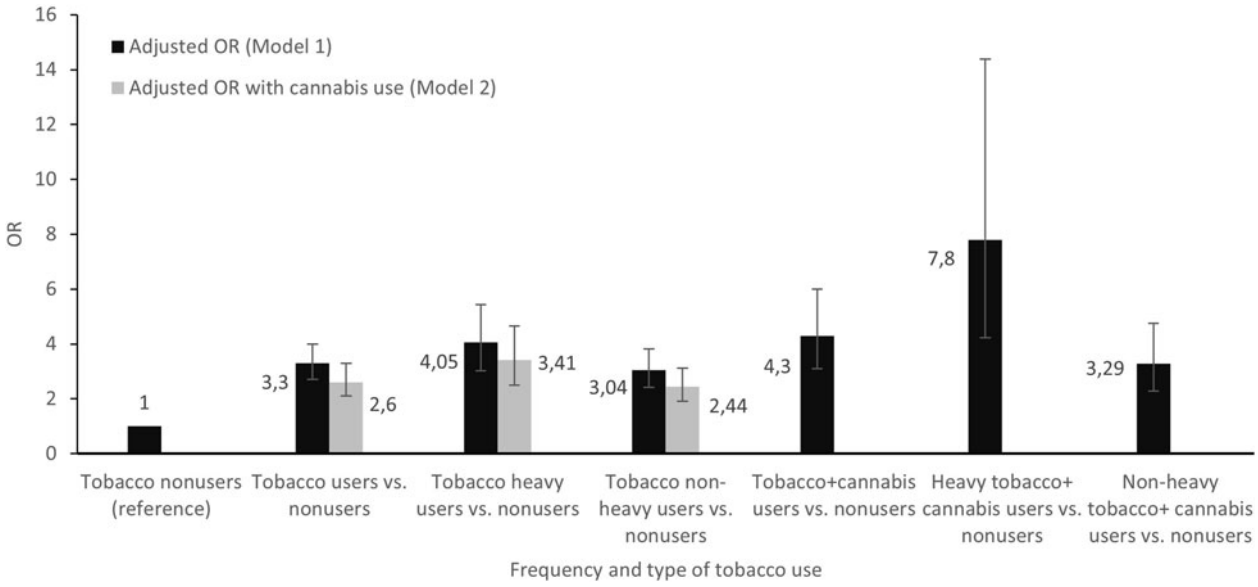

Fig. 1. ORs of patients and controls for the combined measure of use and frequency of tobacco and cannabis. ORs in model 1 were adjusted for age, sex, country, years of education, and alcohol use and ORs in model 2 were additionally adjusted for cannabis use frequency (categorized as never or occasional use, used more than once a week, or daily use). Error bars represent 95% CIs. OR, odds ratio.

of tobacco use on age of psychosis onset and diagnosis (schizophrenia *v.* other psychosis) regardless of the patterns of tobacco and cannabis use or the frequency of tobacco use (see the online Supplementary material for further information).

Discussion

Tobacco users had more than thrice the odds of experiencing FEP than did non-tobacco users and heavy-tobacco users had almost twice the odds of experiencing FEP than did non-heavy-tobacco users. These results remained significant after controlling for cannabis use. Tobacco use was associated with an earlier age at psychosis onset and higher odds of receiving a diagnosis of schizophrenia. However, the latter two associations were no longer significant after controlling for cannabis use.

As expected, FEP patients smoked tobacco more frequently and more heavily than controls, which is consistent with previous literature (Coletti et al., 2015; Depp et al., 2015; Grossman et al., 2017; Kelly & McCreadie, 1999; Lally et al., 2019; McCreadie, 2002; Wade et al., 2005; Zhang et al., 2013). This result was also observed in patients with established psychosis, concretely schizophrenia [with a 60% prevalence of tobacco regular use (Jamal et al., 2015)]. However, the increase in the exposure to tobacco, particularly in adolescence (Smith et al., 2015) is crucial to examine the evidence regarding the early stages of psychosis and increased risk for nicotine dependence (Hartz et al., 2014; Scott et al., 2018; Volkow, 2009). In that regard, we observed in our study that heavy-tobacco-only use and the combination of heavy-tobacco and current cannabis use were more frequently observed in FEP patients than in non-users. This result is consistent with previous findings showing that daily tobacco smoking is associated with a greater risk of onset of psychosis (Gurillo et al., 2015), this could possibly be explained by signaling alterations produced by nicotine on the dopaminergic, cholinergic, and glutamatergic neurotransmitter systems (Smith et al., 2015) that may involve interactions between the cholinergic-nicotinic system and the dopaminergic system (Gurillo et al., 2015; Mallet et al., 2019). However, the cross-sectional methodology of this study and the use of self-reported and 1 year retrospective measures to assess the use of tobacco precludes an inference about causality. Moreover, heavy substance use during critical periods for brain development, such as pregnancy, adolescence, and young adulthood, could be specifically associated with later onset of psychosis in genetically vulnerable individuals (Gage et al., 2014; McGrath et al., 2016; Mustonen et al., 2018; van Os, Kenis, & Rutten, 2010; Zammit et al., 2009). Besides the hypothesis of considering tobacco *per se* as a risk factor for psychosis, its impact on the phenotypic expression of the disorder and, consequently, the possibility of inducing a differentiated entity in terms of etiopathogenesis, clinical features, prognosis, response to conventional treatments, and/or preventive interventions, is still inconclusive (Gonzalez-Blanco et al., 2021). Shared genetic risk for schizophrenia and smoking behaviors in a European population have been observed, suggesting the presence of common mechanisms underlying these associations (Peterson et al., 2021). In our sample, tobacco, cannabis, and other drugs were more frequently used in the group of FEP patients, suggesting a potential vulnerability that could make patients more prone to use other substances because of their reinforcing effects on the dopaminergic system, often referred to as 'the gateway effect' (Kandel, 2002). An alternative explanation would concern the self-medication hypothesis in FEP, as substance intake may reduce psychotic symptoms (Fang et al., 2019).

We found a significant difference between the FEP tobacco user and non-user groups in age at onset, but including cannabis covariation diluted the effect. Contrary to our hypothesis, this finding is consistent with previous literature that observed an absence of association between tobacco use and age at onset of psychosis (Gonzalez-Blanco et al., 2021; Hickling et al., 2017; Myles et al., 2012), and it is also consistent with previous studies in which cannabis use was related to earlier age at onset of psychosis (Di Forti et al., 2014; Large, Sharma, Compton, Slade, & Nielssen, 2011; Murray et al., 2017). One explanation of the attenuation of the tobacco effects after including cannabis as a

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covariate may be the differences in the duration assessed with the self-reported measures for each substance. In the case of cannabis, we asked participants to report their lifetime use but in the case of tobacco, we only asked about the last year. This could have influenced the weight of the effect of each of the two substances. Similarly, when we analyzed the association between tobacco users and diagnosis, we primarily observed that FEP patients had 1.3 times higher odds of a diagnosis of schizophrenia, but this association disappeared after controlling for cannabis use. This is consistent with earlier findings that both the earlier onset of psychosis and the more frequent diagnosis of schizophrenia may be explained by the cannabis use itself (Belbasis et al., 2018; Di Forti et al., 2014; Lowe, Sasiadek, Coles, & George, 2019). Nevertheless, schizophrenia was more frequently diagnosed in FEP patients who used the combination of tobacco and cannabis than in the group of only-tobacco or non-users. Also, the combination of tobacco (both heavy and non-heavy use) and cannabis use was associated with an earlier age of psychosis onset than heavy-tobacco-only use and non-use. Cannabis-only users showed an earlier age of psychosis onset than non-users or heavy-tobacco users. The fact that only 2.7% of the FEP sample used cannabis-only limits the interpretation of these results. In the present study, we could identify co-use of tobacco and cannabis in FEP patients, but we could not quantify the proportion of tobacco and cannabis in each joint. Most people who use cannabis in Europe include tobacco in a variable proportion (Dekker et al., 2012; Gage et al., 2014; Jones et al., 2018; Rabin & George, 2015), either concurrently with cigarettes (co-use) or as a component of cannabis joints (simultaneous use), so cannabis-only use is very rare (Quigley & MacCabe, 2019). Disentangling the independent contributions of each substance is challenging, as most of the information regarding substance use was retrospectively self-reported by participants (Gonzalez-Blanco et al., 2021) and also most studies about cannabis use and its relation with psychosis have not taken into consideration the potential effects of the mixture of cannabis and tobacco in a simultaneous use. We know that smoking cannabis and tobacco together increases the amount of tetrahydrocannabinol inhaled per g (Van der Kooy, Pomahacova, & Verpoorte, 2008), thus enhancing the effects of cannabis, which could lead to a higher risk of psychosis. In this regard, the results of a recent study suggest that there is a synergistic effect of tobacco and cannabis on psychosis risk (Jones et al., 2018; Quigley & MacCabe, 2019). In our study we found a significant interaction effect between tobacco and cannabis use on age of onset, but we did not find differences between tobacco-only and tobacco and cannabis use in FEP odds or diagnosis. Prospective studies may help to clarify whether these associations are due to cannabis or due to the combination of tobacco and cannabis.

To our knowledge, this is the first study to examine the association between tobacco use and its frequency of use, with FEP diagnosis, controlling for the use of other substances such as cannabis, alcohol, and other substance of abuse and examining the differences between use of tobacco-only and the combination of tobacco and cannabis in a large, international study dataset consisting of patients with FEP and HC. Some limitations of the study include: first, cross-sectional studies limit assessment of causality. Therefore, prospective measurements are needed to confirm if tobacco use increases the risk of psychotic disorders. Second, the presence and absence, as well as the frequency of tobacco use and other substances of abuse, was self-reported, and this information was not validated by biological samples, like urine analysis or expired carbon monoxide measures, in the case of tobacco smoking severity. However, research has shown that reporting of drug abuse by adults with psychosis is generally accurate (Van Dorn, Desmarais, Scott Young, Sellers, & Swartz, 2012). Third, although we analyzed the independent effect of tobacco-only, tobacco and cannabis co-use, cannabis-only and non-use on the outcomes, this study did not quantify the proportion of tobacco which could have been included in cannabis preparations in cannabis-only users. Fourth, reports about tobacco use in patients and controls were limited to the 12 months prior to enrolment in the study, so we lack information about lifetime tobacco use. Therefore, we are not able to explore the cumulative effect of chronic tobacco use on the odds and age at onset of psychosis. Finally, another limitation of this study is the use of an arbitrary cut-off value to categorize the continuous variable of tobacco use frequency.

In conclusion, tobacco use and heavy-tobacco use are associated with higher odds of FEP. An earlier age at onset and greater odds of receiving a diagnosis of schizophrenia is found in patients who have used both tobacco and cannabis than in non-users. Given these results, tobacco consumption should be thoroughly assessed and treated in clinical practice, especially in concurrent cannabis users and in populations vulnerable to psychosis.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723000806

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References

Agrawal, A., Budney, A. J., & Lynskey, M. T. (2012). The co-occurring use and misuse of cannabis and tobacco: A review. *Addiction*, *107*(7), 1221–1233. doi: 10.1111/j.1360-0443.2012.03837.x

Belbasis, L., Kohler, C. A., Stefanis, N., Stubbs, B., van Os, J., Vieta, E., … Evangelou, E. (2018). Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: An umbrella review of meta-analyses. *Acta Psychiatrica Scandinavica*, *137*(2), 88–97. doi: 10.1111/acps.12847

Beratis, S., Katrivanou, A., & Gourzis, P. (2001). Factors affecting smoking in schizophrenia. *Comprehensive Psychiatry*, *42*(5), 393–402. doi: 10.1053/comp.2001.26273

Chin, D. L., Hong, O., Gillen, M., Bates, M. N., & Okechukwu, C. A. (2013). Heavy and light/moderate smoking among building trades construction workers. *Public Health Nursery*, *30*(2), 128–139. doi: 10.1111/j.1525-1446.2012.01041.x

Coletti, D. J., Brunette, M., John, M., Kane, J. M., Malhotra, A. K., & Robinson, D. G. (2015). Responses to tobacco smoking-related health messages in young people with recent-onset schizophrenia. *Schizophrenia Bulletin*, *41*(6), 1256–1265. doi: 10.1093/schbul/sbv122

Dekker, N., Meijer, J., Koeter, M., van den Brink, W., van Beveren, N., Kahn, R. S., … Investigators, G. (2012). Age at onset of non-affective psychosis in relation to cannabis use, other drug use and gender. *Psychological Medicine*, *42*(9), 1903–1911. doi: 10.1017/S0033291712000062

de Leon, J., Becona, E., Gurpegui, M., Gonzalez-Pinto, A., & Diaz, F. J. (2002). The association between high nicotine dependence and severe mental illness may be consistent across countries. *Journal of Clinical Psychiatry*, *63*(9), 812–816. doi: 10.4088/jcp.v63n0911

de Leon, J., & Diaz, F. J. (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Research*, *76*(2-3), 135–157. doi: 10.1016/j.schres.2005.02.010

Depp, C. A., Bowie, C. R., Mausbach, B. T., Wolyniec, P., Thornquist, M. H., Luke, J. R., … Harvey, P. D. (2015). Current smoking is associated with worse cognitive and adaptive functioning in serious mental illness. *Acta Psychiatrica Scandinavica*, *131*(5), 333–341. doi: 10.1111/acps.12380

Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., … Group, E.-G. W. (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study. *The Lancet. Psychiatry*, *6*(5), 427–436. doi: 10.1016/S2215-0366(19)30048-3

Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. A., … Murray, R. M. (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin*, *40*(6), 1509–1517. doi: 10.1093/schbul/sbt181

Fang, Y., Wang, W., Zhu, C., Lin, G. N., Cheng, Y., Zou, J., & Cui, D. (2019). Use of tobacco in schizophrenia: A double-edged sword. *Brain and Behavior*, *9*(11), e01433. doi: 10.1002/brb3.1433

Ferreira, A., & Coentre, R. (2020). A systematic review of tobacco use in first-episode psychosis. *The European Journal of Psychiatry*, *34*(3), 132–142. https://doi.org/10.1016/j.ejpsy.2020.03.005.

Gage, S. H., Hickman, M., Heron, J., Munafo, M. R., Lewis, G., Macleod, J., & Zammit, S. (2014). Associations of cannabis and cigarette use with psychotic experiences at age 18: Findings from the Avon longitudinal study of parents and children. *Psychological Medicine*, *44*(16), 3435–3444. doi: 10.1017/S0033291714000531

Gayer-Anderson, C., Jongsma, H. E., Di Forti, M., Quattrone, D., Velthorst, E., de Haan, L., … Morgan, C. (2020). The European network of national schizophrenia networks studying gene–environment interactions (EU-GEI): Incidence and first-episode case-control programme. *Social Psychiatry and Psychiatric Epidemiology*, *55*(5), 645–657. doi: 10.1007/s00127-020-01831-x

Gonzalez-Blanco, L., Garcia-Portilla, M. P., Gutierrez, M., Mezquida, G., Cuesta, M. J., Urbiola, E., … Group, P. E. (2021). Impact of previous tobacco use with or without cannabis on first psychotic experiences in patients with first-episode psychosis. *Schizophrenia Research*, *236*, 19–28. doi: 10.1016/j.schres.2021.07.017

Grossman, M., Bowie, C. R., Lepage, M., Malla, A. K., Joober, R., & Iyer, S. N. (2017). Smoking status and its relationship to demographic and clinical

https://doi.org/10.1017/S0033291723000806 Published online by Cambridge University Press

characteristics in first episode psychosis. *Journal of Psychiatry Research*, *85*, 83–90. doi: 10.1016/j.jpsychires.2016.10.022

Gurillo, P., Jauhar, S., Murray, R. M., & MacCabe, J. H. (2015). Does tobacco use cause psychosis? Systematic review and meta-analysis. *The Lancet. Psychiatry*, *2*(8), 718–725. doi: 10.1016/S2215-0366(15)00152-2

Hartz, S. M., Pato, C. N., Medeiros, H., Cavazos-Rehg, P., Sobell, J. L., Knowles, J. A., … Genomic Psychiatry Cohort, C. (2014). Comorbidity of severe psychotic disorders with measures of substance use. *JAMA Psychiatry*, *71* (3), 248–254. doi:10.1001/jamapsychiatry.2013.3726

Hickling, L. M., Ortiz-Garcia de la Foz, V., Ayesa-Arriola, R., Crespo-Facorro, B., McGuire, P., & Perez-Iglesias, R. (2017). The effects of tobacco smoking on age of onset of psychosis and psychotic symptoms in a first-episode psychosis population. *Addiction*, *112*(3), 526–532. doi: 10.1111/add.13646

Hunter, A., Murray, R., Asher, L., & Leonardi-Bee, J. (2020). The effects of tobacco smoking, and prenatal tobacco smoke exposure, on risk of schizophrenia: A systematic review and meta-analysis. *Nicotine & Tobacco Research*, *22*(1), 3–10. doi: 10.1093/ntr/nty160

Jamal, A., Homa, D. M., O'Connor, E., Babb, S. D., Caraballo, R. S., Singh, T., … King, B. A. (2015). Current cigarette smoking among adults – United States, 2005–2014. *MMWR Morbidity and Mortal Weekly Report*, *64*(44), 1233–1240. doi: 10.15585/mmwr.mm6444a2

Jones, H. J., Gage, S. H., Heron, J., Hickman, M., Lewis, G., Munafo, M. R., & Zammit, S. (2018). Association of combined patterns of tobacco and Cannabis use in adolescence with psychotic experiences. *JAMA Psychiatry*, *75*(3), 240–246. doi: 10.1001/jamapsychiatry.2017.4271

Jones, S. H., Thornicroft, G., Coffey, M., & Dunn, G. (1995). A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). *The British Journal of Psychiatry*, *166*(5), 654–659. doi: 10.1192/bjp.166.5.654

Jongsma, H. E., Gayer-Anderson, C., Lasalvia, A., Quattrone, D., Mule, A., Szoke, A., … European Network of National Schizophrenia Networks Studying Gene–Environment Interactions Work Package, G. (2018). Treated incidence of psychotic disorders in the multinational EU-GEI study. *JAMA Psychiatry*, *75*(1), 36–46. doi: 10.1001/jamapsychiatry.2017.3554

Kahn, R. S., & Sommer, I. E. (2015). The neurobiology and treatment of first-episode schizophrenia. *Molecular Psychiatry*, *20*(1), 84–97. doi: 10.1038/mp.2014.66

Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., … Insel, T. R. (2015). Schizophrenia. *Nature Reviews Disease Primers*, *1*, 15067. doi: 10.1038/nrdp.2015.67

Kandel, D. B. (2002). *Stages and pathways of drug involvement: Examining the gateway hypothesis*. London: Cambridge University Press.

Kay-Lambkin, F., Edwards, S., Baker, A., Kavanagh, D., Kelly, B., Bowman, J., & Lewin, T. (2013). The impact of tobacco smoking on treatment for comorbid depression and alcohol misuse. *International Journal of Mental Health and Addiction*, *11*, 619–633. doi: 10.1007/s11469-013-9437-2

Kelly, C., & McCreadie, R. G. (1999). Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. *American Journal of Psychiatry*, *156*(11), 1751–1757. doi: 10.1176/ajp.156.11.1751

King, M., Jones, R., Petersen, I., Hamilton, F., & Nazareth, I. (2021). Cigarette smoking as a risk factor for schizophrenia or all non-affective psychoses. *Psychological Medicine*, *51*(8), 1373–1381. doi: 10.1017/S0033291720000136

Kotov, R., Guey, L. T., Bromet, E. J., & Schwartz, J. E. (2010). Smoking in schizophrenia: Diagnostic specificity, symptom correlates, and illness severity. *Schizophrenia Bulletin*, *36*(1), 173–181. doi: 10.1093/schbul/sbn066

Lally, J., Spaducci, G., Gardner-Sood, P., Atakan, Z., Greenwood, K., Di Forti, M., … Gaughran, F. (2019). Tobacco smoking and nicotine dependence in first episode and established psychosis. *Asian Journal of Psychiatry*, *43*, 125–131. doi: 10.1016/j.ajp.2019.05.002

Large, M., Sharma, S., Compton, M. T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry*, *68*(6), 555–561. doi: 10.1001/archgenpsychiatry.2011.5

Lowe, D. J. E., Sasiadek, J. D., Coles, A. S., & George, T. P. (2019). Cannabis and mental illness: A review. *European Archives of Psychiatry and Clinical Neurosciences*, *269*(1), 107–120. doi: 10.1007/s00406-018-0970-7

Ma, X., Li, C., Meng, H., Du, L., Wang, Q., Wang, Y., … Li, T. (2010). Premorbid tobacco smoking is associated with later age at onset in schizophrenia. *Psychiatry Research*, *178*(3), 461–466. doi: 10.1016/j.psychres.2009.08.014

Mallet, J., Le Strat, Y., Schurhoff, F., Mazer, N., Portalier, C., Andrianarisoa, M., … Group, F.-S. (2017). Cigarette smoking and schizophrenia: A specific clinical and therapeutic profile? Results from the FACE-Schizophrenia cohort. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *79*(Pt B), 332–339. doi: 10.1016/j.pnpbp.2017.06.026

Mallet, J., Le Strat, Y., Schurhoff, F., Mazer, N., Portalier, C., Andrianarisoa, M., … Group, F.-S. (2019). Tobacco smoking is associated with anti-psychotic medication, physical aggressiveness, and alcohol use disorder in schizophrenia: Results from the FACE-SZ national cohort. *European Archives of Psychiatry and Clinical Neurosciences*, *269*(4), 449–457. doi: 10.1007/s00406-018-0873-7

Mallet, R. (1997). *Sociodemographic schedule*. London: Section of Social Psychiatry, Institute of Psychiatry.

McCreadie, R. G. (2002). Use of drugs, alcohol and tobacco by people with schizophrenia: Case-control study. *The British Journal of Psychiatry*, *181*, 321–325. doi: 10.1192/bjp.181.4.321

McGrath, J. J., Alati, R., Clavarino, A., Williams, G. M., Bor, W., Najman, J. M., … Scott, J. G. (2016). Age at first tobacco use and risk of subsequent psychosis-related outcomes: A birth cohort study. *Australia & New Zealand Journal of Psychiatry*, *50*(6), 577–583. doi: 10.1177/0004867415587341

McGuffin, P., Farmer, A., & Harvey, I. (1991). A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Archives of General Psychiatry*, *48*(8), 764–770. doi: 10.1001/archpsyc.1991.01810320088015

Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet (London, England)*, *370*(9584), 319–328. doi: 10.1016/S0140-6736(07)61162-3

Murray, R. M., Englund, A., Abi-Dargham, A., Lewis, D. A., Di Forti, M., Davies, C., … D'Souza, D. C. (2017). Cannabis-associated psychosis: Neural substrate and clinical impact. *Neuropharmacology*, *124*, 89–104. doi: 10.1016/j.neuropharm.2017.06.018

Mustonen, A., Ahokas, T., Nordstrom, T., Murray, G. K., Maki, P., Jaaskelainen, E., … Niemela, S. (2018). Smokin' hot: Adolescent smoking and the risk of psychosis. *Acta Psychiatrica Scandinavica*, *138*(1), 5–14. doi: 10.1111/acps.12863

Myles, N., Newall, H. D., Curtis, J., Nielssen, O., Shiers, D., & Large, M. (2012). Tobacco use before, at, and after first-episode psychosis: A systematic meta-analysis. *Journal of Clinical Psychiatry*, *73*(4), 468–475. doi: 10.4088/JCP.11r07222

Olincy, A., Young, D. A., & Freedman, R. (1997). Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. *Biological Psychiatry*, *42*(1), 1–5. doi: 10.1016/S0006-3223(96)00302-2

Peterson, R. E., Bigdeli, T. B., Ripke, S., Bacanu, S. A., Gejman, P. V., Levinson, D. F., … Fanous, A. H. (2021). Genome-wide analyses of smoking behaviors in schizophrenia: Findings from the psychiatric genomics consortium. *Journal of Psychiatry Research*, *137*, 215–224. doi: 10.1016/j.jpsychires.2021.02.027

Quattrone, D., Di Forti, M., Gayer-Anderson, C., Ferraro, L., Jongsma, H. E., Tripoli, G., … Reininghaus, U. (2019). Transdiagnostic dimensions of psychopathology at first episode psychosis: Findings from the multinational EU-GEI study. *Psychological Medicine*, *49*(8), 1378–1391. doi: 10.1017/S0033291718002131

Quigley, H., & MacCabe, J. H. (2019). The relationship between nicotine and psychosis. *Therapeutic Advances in Psychopharmacology*, *9*, 1–12. 10.1177/2045125319859969.

Rabin, R. A., & George, T. P. (2015). A review of co-morbid tobacco and cannabis use disorders: Possible mechanisms to explain high rates of co-use. *The American Journal of Addictions*, *24*(2), 105–116. doi: 10.1111/ajad.12186

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. *JAMA*, *264*(19), 2511–2518. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2232018.

https://doi.org/10.1017/S0033291723000806 Published online by Cambridge University Press

Russell, D. W. (2016). In search of underlying dimensions: The use (and abuse) of factor analysis in personality and social psychology bulletin. *Personality and Social Psychology Bulletin*, *28*(12), 1629–1646. doi: 10.1177/014616702237645

Saha, S., Scott, J. G., Varghese, D., Degenhardt, L., Slade, T., & McGrath, J. J. (2011). The association between delusional-like experiences, and tobacco, alcohol or cannabis use: A nationwide population-based survey. *BMC Psychiatry*, *11*, 202. doi: 10.1186/1471-244X-11-202

Scott, J. G., Matuschka, L., Niemela, S., Miettunen, J., Emmerson, B., & Mustonen, A. (2018). Evidence of a causal relationship between smoking tobacco and schizophrenia spectrum disorders. *Frontiers in Psychiatry*, *9*, 607. doi: 10.3389/fpsyt.2018.00607

Shelef, K., Diamond, G. S., Diamond, G. M., & Myers, M. G. (2009). Changes in tobacco use among adolescent smokers in substance abuse treatment. *Psychology of Addictive Behaviors*, *23*(2), 355–361. doi: 10.1037/a0014517

Smith, R. F., McDonald, C. G., Bergstrom, H. C., Ehlinger, D. G., & Brielmaier, J. M. (2015). Adolescent nicotine induces persisting changes in development of neural connectivity. *Neurosciences and Biobehavioral Reviews*, *55*, 432–443. doi: 10.1016/j.neubiorev.2015.05.019

Van der Kooy, F., Pomahacova, B., & Verpoorte, R. (2008). Cannabis smoke condensate I: The effect of different preparation methods on tetrahydrocannabinol levels. *Inhalation Toxicology*, *20*(9), 801–804. doi: 10.1080/08958370802013559

Van Dorn, R. A., Desmarais, S. L., Scott Young, M., Sellers, B. G., & Swartz, M. S. (2012). Assessing illicit drug use among adults with schizophrenia. *Psychiatry Research*, *200*(2-3), 228–236. doi: 10.1016/j.psychres.2012.05.028

van Os, J., Kenis, G., & Rutten, B. P. (2010). The environment and schizophrenia. *Nature*, *468*(7321), 203–212. doi: 10.1038/nature09563

van Os, J., Rutten, B. P., Myin-Germeys, I., Delespaul, P., Viechtbauer, W., van Zelst, C., … Mirjanic, T. (2014). Identifying gene–environment interactions in schizophrenia: Contemporary challenges for integrated, large-scale investigations. *Schizophrenia Bulletin*, *40*(4), 729–736. doi: 10.1093/schbul/sbu069

Volkow, N. D. (2009). Substance use disorders in schizophrenia – Clinical implications of comorbidity. *Schizophrenia Bulletin*, *35*(3), 469–472. doi: 10.1093/schbul/sbp016

Wade, D., Harrigan, S., Edwards, J., Burgess, P. M., Whelan, G., & McGorry, P. D. (2005). Patterns and predictors of substance use disorders and daily tobacco use in first-episode psychosis. *Australia & New Zealand Journal of Psychiatry*, *39*(10), 892–898. doi: 10.1080/j.1440-1614.2005.01699.x

West, S. G., Sandler, I., Pillow, D. R., Baca, L., & Gersten, J. C. (1991). The use of structural equation modeling in generative research: Toward the design of a preventive intervention for bereaved children. *American Journal of Community Psychology*, *19*(4), 459–480. doi: 10.1007/BF00937987

WHO (1992). The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guideline. Retrieved from https://www.who.int/publications-detail-redirect/9241544228.

WHO (2021). WHO report on the global tobacco epidemic 2021: addressing new and emerging products. Retrieved from https://www.who.int/publications/i/item/9789240032095.

Williams, J., Farmer, A. E., Ackenheil, M., Kaufmann, C. A., & McGuffin, P. (1996). A multicentre inter-rater reliability study using the OPCRIT computerized diagnostic system. *Psychological Medicine*, *26*(4), 775–783. doi: 10.1017/s003329170003779x

Zammit, S., Thomas, K., Thompson, A., Horwood, J., Menezes, P., Gunnell, D., … Harrison, G. (2009). Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. *The British Journal of Psychiatry*, *195*(4), 294–300. doi: 10.1192/bjp.bp.108.062471

Zhang, X. Y., Chen, D. C., Xiu, M. H., Haile, C. N., He, S. C., Luo, X., … Kosten, T. R. (2013). Cigarette smoking, psychopathology and cognitive function in first-episode drug-naive patients with schizophrenia: A case-control study. *Psychological Medicine*, *43*(8), 1651–1660. doi: 10.1017/S0033291712002590