Schizophrenia Research 236 (2021) 19–28

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Impact of previous tobacco use with or without cannabis on first psychotic experiences in patients with first-episode psychosis

Leticia González-Blanco [a], María Paz García-Portilla [a,*], Miguel Gutiérrez [b], Gisela Mezquida [c], Manuel J. Cuesta [d], Elena Urbiola [e], Silvia Amoretti [c], Fe Barcones [f], Ana González-Pinto [b], Laura Pina-Camacho [e], Iluminada Corripio [g], Eduard Vieta [h], Immaculada Baeza [i], Alba Toll [j], Pilar A. Sáiz [a], Julio Bobes [a], Miguel Bernardo [c], PEPs Group

[a] Department of Psychiatry, University of Oviedo, Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Instituto de Neurociencias del Principado de Asturias (INEUROPA), Servicio de Salud del Principado de Asturias (SESPA), Oviedo, Spain
[b] Department of Psychiatry, Araba University Hospital, Bioaraba Research Institute, Department of Neurosciences, University of the Basque Country, CIBERSAM, Alava, Spain
[c] Barcelona Clinic Schizophrenia Unit, Hospital Clinic of Barcelona, Neuroscience Institute, CIBERSAM, August Pi I Sunyer Biomedical Research Institute (IDIBAPS), University of Barcelona, Spain
[d] Department of Psychiatry, Navarre Hospital Complex, IdiSNA, Navarre Institute for Health Research, Pamplona, Spain
[e] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IiSGM, School of Medicine, Universidad Complutense, CIBERSAM, Madrid, Spain
[f] Department of Family Medicine, Hospital Universitario Miguel Servet, Department of Medicine and Psychiatry, Universidad de Zaragoza, Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza, Spain
[g] Psychiatry Department, Institut d'Investigació Biomèdica-Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona (UAB), CIBERSAM, Barcelona, Spain
[h] Bipolar Disorders Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain
[i] Child and Adolescent Psychiatry Service, Hospital Clinic of Barcelona, CIBERSAM, Barcelona, Spain
[j] Hospital del Mar Medical Research Institute (IMIM), CIBERSAM, Barcelona, Spain

ARTICLE INFO

Keywords:
Prodromal symptoms
First psychotic symptoms
Substance use

ABSTRACT

Objective: There is high prevalence of cigarette smoking in individuals with first-episode psychosis (FEP) prior to psychosis onset. The purpose of the study was to determine the impact of previous tobacco use with or without cannabis on first psychotic experiences in FEP and the impact of this use on age of onset of symptoms, including prodromes.

Methods: Retrospective analyses from the naturalistic, longitudinal, multicentre, "Phenotype-Genotype and Environmental Interaction. Application of a Predictive Model in First Psychotic Episodes (PEPs)" Study. The authors analysed sociodemographic/clinical data of 284 FEP patients and 231 matched healthy controls, and evaluated first psychotic experiences of patients using the Symptom Onset in Schizophrenia Inventory.

Results: FEP patients had significantly higher prevalence of tobacco, cannabis, and cocaine use than controls. The FEP group with tobacco use only prior to onset ($N = 56$) had more sleep disturbances (42.9% vs 18.8%, $P = 0.003$) and lower prevalence of negative symptoms, specifically social withdrawal (33.9% vs 58%, $P = 0.007$) than FEP with no substance use ($N = 70$), as well as lower prevalence of ideas of reference (80.4% vs 92.4%, $P = 0.015$), perceptual abnormalities (46.4% vs 67.4%, $P = 0.006$), hallucinations (55.4% vs 71.5%, $P = 0.029$), and disorganised thinking (41.1% vs 61.1%, $P = 0.010$) than FEP group with previous tobacco and cannabis use ($N = 144$). FEP patients with cannabis and tobacco use had lower age at first prodromal or psychotic symptom (mean = 23.73 years [SD = 5.09]) versus those with tobacco use only (mean = 26.21 [SD = 4.80]) ($P = 0.011$).

Conclusions: The use of tobacco alone was not related to earlier age of onset of a first psychotic experience, but the clinical profile of FEP patients is different depending on previous tobacco use with or without cannabis.

* Corresponding author at: Área de Psiquiatría, Universidad de Oviedo, Julián Clavería 6, 33006 Oviedo, Spain.
E-mail addresses: albert@uniovi.es (M.P. García-Portilla), MEZQUIDA@clinic.cat (G. Mezquida), elena.urbiola@iisgm.com (E. Urbiola), AMORETTI@clinic.cat (S. Amoretti), icorripio@santpau.cat (I. Corripio), vieta@clinic.cat (E. Vieta), frank@uniovi.es (P.A. Sáiz), bobes@uniovi.es (J. Bobes), BERNARDO@clinic.cat (M. Bernardo).

https://doi.org/10.1016/j.schres.2021.07.017
Received 17 May 2020; Received in revised form 14 February 2021; Accepted 12 July 2021
Available online 5 August 2021

1. Introduction

A higher prevalence of cigarette smoking has been reported in individuals with schizophrenia or first-episode psychosis (FEP) – at least twice that of the general population (Barnett et al., 2007; de Leon and Diaz, 2005; Kotov et al., 2010; Myles et al., 2012a). The association between tobacco and psychosis has been widely studied, and a causal relationship has been proposed between smoking and increased risk of psychosis (Clark et al., 2018; Gurillo et al., 2015; Hunter et al., 2020; Weiser et al., 2004), especially in individuals who start smoking at an earlier age (McGrath et al., 2016) and in individuals who are heavy smokers (Kendler et al., 2015; Wium-Andersen et al., 2015). Most studies agree that cigarette smoking generally begins before onset of psychosis (de Leon and Diaz, 2005; Smith et al., 2009); indeed, a meta-analysis by Myles et al. (2012b) reported that tobacco use precedes the onset of psychosis by about five years. The relationship between smoking and psychosis is not evidenced exclusively in the clinical population. In the general population, tobacco use (van Gastel et al., 2013) and number of cigarettes per day (Bhavsar et al., 2018) has been associated with an increase in psychotic experiences. However, a study evaluating the role of tobacco use in the development of psychosis in individuals at clinical high risk found that smoking status did not predict conversion to psychosis (Ward et al., 2019).

More controversy exists regarding whether smoking is related to age of onset of psychosis. While some studies have reported an association with an earlier onset of psychosis (Gurillo et al., 2015; McGrath et al., 2016), others did not find a relationship when controlling for confounding factors such as the use of cannabis (Hickling et al., 2017; Myles et al., 2012a). Furthermore, other studies have reported a later onset of psychosis in smokers than non-smokers (Ma et al., 2010).

Inconsistent results have also been published regarding the symptomatology of smokers with psychosis. However, while there is a good deal of data on the effects of tobacco on symptom severity and functional outcomes in patients with an established diagnosis of schizophrenia or the non-affective psychosis spectrum (Jiang et al., 2013; Krishnadas et al., 2012; Ma et al., 2010; Morisano et al., 2013; Vermeulen et al., 2019, 2018), studies on individuals with FEP are much scarcer. Some suggest that smokers with FEP presented greater severity of both positive and negative symptoms and worse cognition and quality of life (Grossman et al., 2017; Oluwoye et al., 2019), others did not find this relationship (Hickling et al., 2018, 2017; Sanchez-Gutierrez et al., 2018) or found the opposite results (Misiak et al., 2015).

Bearing in mind the above, there are many questions related to the relationship between tobacco and psychosis still open to debate. 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 etiopathogeny, clinical features, prognosis, response to conventional treatments, and/or preventive interventions, remains unknown.

To our knowledge, there are very few studies about the effects of tobacco on patients presenting with a first psychotic experience compared with those who did not use tobacco or used cannabis concomitantly. Therefore, the main objective of the present study is to describe the clinical profile of the earliest symptom of psychotic illness in individuals with FEP based on previous tobacco use with or without cannabis use. Other secondary objectives of the study are to analyse if there is a differential effect of tobacco on the age of onset of psychosis, understood as the first psychotic experience in FEP (Perkins et al., 2000), as well as to describe the pattern of tobacco and cannabis use in individuals with FEP compared with healthy controls.

2. Methods

The study was approved by the Clinical Research Ethics Committee of each participating site and was conducted according to the ethical standards of the Declaration of Helsinki and current legislation. Written informed consent was obtained from all participants or their legal guardians.

2.1. Participants

The sample consists of 335 individuals with FEP and 253 healthy controls (HC) matched by age (±10%), sex and parental socio-economic status, enrolled in a naturalistic, longitudinal, multicentre study (Phenotype-Genotype and Environmental Interaction. Application of a Predictive Model in First Psychotic Episodes: PEPs study) (Bernardo et al., 2019; Salagre et al., 2019). Methodological aspects, including inclusion and exclusion criteria, have been described elsewhere (Bernardo et al., 2013).

Individuals with missing data on age at first use of tobacco and cannabis or onset of psychosis were excluded ($N = 23$), as well as individuals who started using cannabis or tobacco after the earliest symptom ($N = 1$). Also, individuals under 16 years of age and patients who presented the earliest symptom before age 16 were excluded to minimize bias (mean age at onset of smoking in this sample was 15.45 years [SD = 2.85]) ($N = 28$). Thus, data from 283 FEP patients and 231 HC were analysed (see Fig. 1). After removing individuals from the original sample, HC were no longer matched for socioeconomic status, but no statistically significant differences in age and sex were detected [mean age: FEP 25.24 years (SD = 5.58), HC 25.22 years (SD = 5.83); sex: FEP 65.8% male, HC 63.2% male].

FEP patients were classified into 4 groups based on tobacco and/or cannabis use before onset of the earliest symptom, as follows: A. No cannabis or tobacco use ($N = 70$); B. Tobacco use only ($N = 56$); C. Both tobacco and cannabis use ($N = 144$); D. Cannabis use only ($N = 13$). It is worthy to highlight that 61 of these individuals had used cocaine at some point in their life, and all had an age at first cocaine use less than or equal (± 1 year) to the age when the earliest symptom emerged. Of those, 53 belonged to group C, 5 belonged to group B, 3 belonged to group D, and none were in group A.

2.2. Assessment

Baseline sociodemographic characteristics and clinical data were obtained from patients and controls: age, sex, marital status, living and work status, education level, and socioeconomic status based on parental sociodemographic status (Hollingshead and Redlich, 1958). Substance use data were collected retrospectively using the semi-structured interview European Adaptation of Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuropAsi) (Kokkevi and Stefanis, 1995). Lifetime and baseline use, age at first use of tobacco, cannabis, and/or cocaine, and frequency or amount of tobacco and cannabis use were determined for the present study. Clinical psychosis spectrum diagnoses were established with semi-structured diagnostic interviews using the DSM-IV criteria (Bell, 1994).

The first symptoms of the psychotic illness were systematic and retrospectively evaluated using the Symptom Onset in Schizophrenia (SOS) inventory (Mezquida et al., 2018; Perkins et al., 2000) by experienced psychiatrists or psychologists trained in the assessment tool. Using a structured clinical interview, it assesses the frequency of occurrence of 16 symptoms that may appear at the onset of the schizophrenia to dating the onset of the earliest symptom and the onset of psychosis, understood as the first psychotic experience (Perkins et al., 2000). The SOS groups the symptoms in four categories: 1) General prodromal symptoms (dysphoric mood, sleep disturbance, ideas of reference, suspiciousness, thought disorder, perceptual abnormalities, deterioration in functioning, other - including for instance magical thinking, hoarding, …-); 2) Negative symptoms (social withdrawal, avolition, decreased expression and experience of emotion); 3) Positive symptoms (hallucinations and delusions); and 4) Disorganisation symptoms (disorganised thinking and behaviour). For each symptom, there are specific frequency criteria to determine its date of onset if the

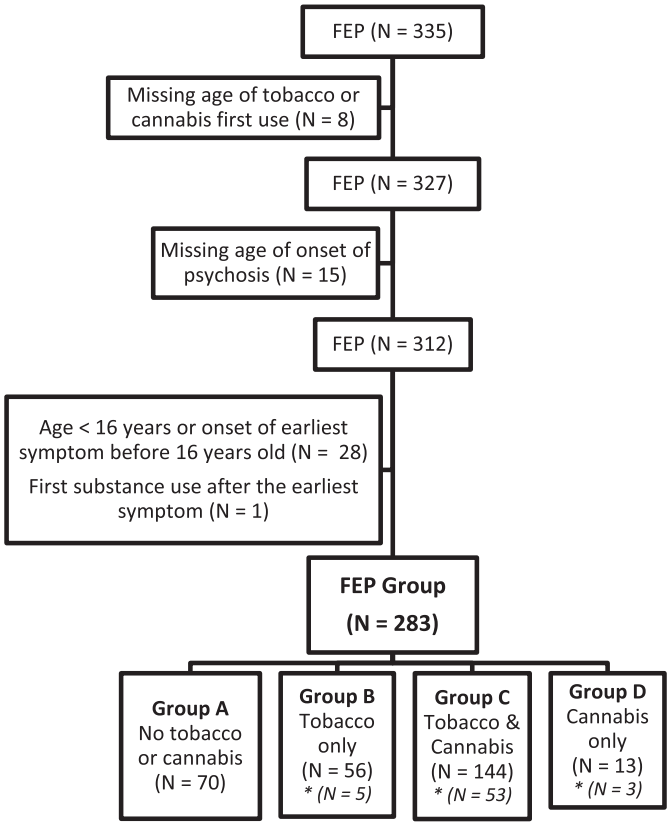


Fig. 1. Flow chart of sample selection.

symptom occurs. For instance, in the case of delusions the date of onset corresponds with the first time the individual experienced the symptom whereas, in the case of sleep disturbances or avolition, the date corresponds when the individual started to suffer these symptoms daily or almost daily. Concerning the date of onset of psychosis, the SOS provides three estimations made by the patient, the proxy, and the interviewer, respectively.

2.3. Statistical analyses

The software package IBM SPSS Statistics for Windows, Version 23.0, was used for statistical analyses. Data were expressed as percentages or mean and standard deviation (SD).

First, we calculated the age of onset for each symptom by subtracting the patient's date of birth from the symptom's onset date to determine the age of onset of the earliest symptom. Regarding the onset of psychosis, in this paper we only employed the estimation made by the interviewer.

Comparisons between FEP patients and HC characteristics and substance use patterns were made using a Chi-squared test in the case of categorical variables and Student's *t*-test for independent samples for continuous variables.

In FEP patients, differences among the four substance use groups with respect to continuous data were analysed using an analysis of variance (ANOVA) and a Bonferroni post hoc test, while differences in prevalence of each symptom among those four groups were compared using a Chi-squared test. Due to a potential confounding effect of the concomitant use of cocaine identified in some individuals (see Fig. 1), we repeated the same analyses excluding them. Finally, to minimize the effect of potential confounders (sex, age at the onset of the earliest symptom, socioeconomic status, and cocaine use), a multinomial logistic regression model (main effects model) was carried out using substance use groups as the dependent variable. All variables that were statistically significant in the bivariate analysis were included as independent variables, and "tobacco use only" was considered the category of reference. In all tests, differences were considered statistically significant when $P < 0.05$.

3. Results

3.1. Characteristics and substance use patterns of FEP patients and healthy controls

FEP patients and HC were comparable in age, sex, and marital status. However, differences were detected in education level (fewer than 50% of patients had high school or university studies versus nearly 75% of control subjects), in work status (16.8 vs 48.1% were employed, respectively), and socioeconomic status. Detailed data are presented in Table 1.

Regarding substance use (Table 2), FEP patients had significantly

Table 1
Sociodemographic characteristics of FEP patients and healthy controls.

	FEP group ($N = 283$)		Control group ($N = 231$)		Statistics	P
	Mean	*SD*	*Mean*	*SD*		
Age (years)	25.24	5.58	25.22	5.83	$t = -0.030$	0.976
	N	***%***	***N***	***%***		
Sex (male)	187	65.8	146	63.2	$X^2 = 0.389$	0.533
Married/Living as married	36	12.7	36	15.6	$X^2 = 0.896$	0.344
Education level					$X^2 = 65.386$	<0.001
University studies	47	16.5	102	44.2		
High school studies	66	23.2	66	28.6		
Others	171	60.3	63	27.3		
Work status[a]					$X^2 = 103.021$	<0.001
Employed	47	16.8	108	48.1		
Unemployed	98	35.1	18	7.8		
Student	103	36.9	100	43.3		
Others	31	11.1	2	0.9		
Socioeconomic status*[a]					$X^2 = 15.811$	<0.001
High or medium-high	82	29.4	96	42.1		
Medium	68	24.4	65	28.5		
Low or medium-low	129	46.2	67	29.4		

FEP, first-episode of psychosis; SD, standard deviation.
* Parental sociodemographic status (Hollingshead and Redlich, 1958).
[a] Missing data in FEP group ($n = 279$) and Control group ($n = 228$).

Table 2
Substance use data in FEP patients and healthy controls.

	FEP group (N = 283)		Control group (N = 231)		Statistics	*P*
Tobacco						
	N	***%***	***N***	***%***		
Lifetime users	201	70.8	106	45.9	$X^2 = 32.771$	<0.001
Baseline users	191	67.3	97	42	$X^2 = 32.981$	<0.001
Daily users	*172*	*60.6*	*71*	*30.7*		
Sporadic users	*19*	*6.7*	*26*	*11.3*		
	Mean	***SD***	***Mean***	***SD***		
Cigarettes/day	14.55	8.02	9.42	6.29	$t = -4.841$	<0.001
Age at first use	15.44	2.85	15.47	2.87	$t = 0.084$	0.933
Years of regular use [at least 1 year]	7.98 [$n = 187$]	4.89	8.69 [$n = 83$]	6.29	$t = 1.002$	0.317
Cannabis						
	N	***%***	***N***	***%***		
Lifetime users	157	55.3	68	29.4	$X^2 = 34.585$	<0.001
Baseline users	133	46.8	48	20.8	$X^2 = 37.930$	<0.001
Daily users	*84*	*29.6*	*8*	*3.5*		
Weekly users	*16*	*5.6*	*13*	*5.6*		
Monthly users	*9*	*3.2*	*18*	*7.8*		
Sporadic users	*24*	*8.5*	*9*	*3.9*		
	Mean	***SD***	***Mean***	***SD***		
Age at first use	16.19	3.00	16.51	1.86	$t = 0.823$	0.411
Years of regular use [at least 1 year]	5.68 [$n = 132$]	4.21	5.46 [n = 28]	4.21	$t = -0.248$	0.804
Cocaine						
	N	***%***	***N***	***%***		
Lifetime users	61	21.5	17	7.4	$X^2 = 21.334$	<0.001
Baseline users	39	13.7	11	4.8	$X^2 = 11.694$	0.001
	Mean	***SD***	***Mean***	***SD***		
Age at first use	19.14	4.04	19.65	3.22	$t = 0.474$	0.637

FEP, first-episode of psychosis; SD, standard deviation.

higher prevalence of tobacco, cannabis, and cocaine use than HC, both at the time of assessment and throughout their life (70.8%, 55.3%, 22.2% of FEP patients vs 44.9%, 29.4%, 7.4% of HC, respectively, all $P \leq 0.001$). These differences were especially notable in the case of cannabis and cocaine (prevalence about two and three time higher, respectively). Among tobacco and cannabis smokers, there was also a greater intensity of use in the FEP group (both $P < 0.001$). However, there was no difference between the two groups in age at first use of the three substances, nor in years of regular use of cannabis and tobacco (detailed data in Table 2).

3.2. Age at psychosis onset based on substance use patterns

FEP patients distributed into the four substance use groups were comparatively analysed. There were statistically significant differences among the four groups in age at the earliest symptom (F = 2.846, $P = 0.038$), as those with tobacco use only were older, but not in age at onset of psychosis (F = 2.637, $P = 0.050$). In post hoc analyses, these differences were detected solely between the group with tobacco use only (B) and the group with tobacco and cannabis use (C) (mean age at onset of psychosis: B = 26.31 [SD = 4.90] vs C = 23.90 [SD = 5.19], $P = 0.033$; mean age at the earliest symptom: B = 26.21 [SD = 4.80] vs C = 23.73 [SD = 5.09], $P = 0.024$) (Fig. 2).

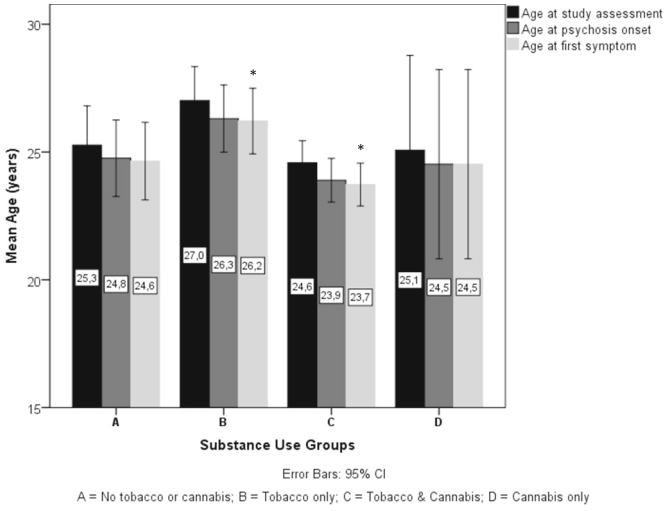


Fig. 2. Age at psychosis onset based on substance use groups.

3.3. Profile of earliest symptom based on substance use patterns

The prevalence of each SOS symptom in FEP patients is presented in the Supplementary Material. At least one general prodromal symptom meeting the frequency threshold criteria was present in nearly 98% of patients, being ideas of reference (88.7%), and suspiciousness (69.3%) the most common symptoms of this SOS group. While at least one negative symptom was present in half of the patients, at least one positive symptom was present in more than 95% of the sample. Delusions were the most common symptom (95.1%). No difference was found in the initial clinical presentation based on sex (Supplementary Table S1).

Table 3 shows the prevalence of each symptom based on substance use groups. There were no statistically significant differences between A (no cannabis or tobacco use) and C (tobacco & cannabis use). Also, no statistically significant differences were detected between D (cannabis only use) and any of the other three groups. However, differences were detected between group B (tobacco only user) vs group A on the one hand and vs group C on the other. Thus, compared to individuals with no substance use (group A), tobacco only users presented sleep disturbances much more frequently (more than 40% vs less than 20%) and negative symptoms, specifically social withdrawal, less frequently. On the other hand, patients with use of both substances (group C), more frequently presented ideas of reference, perceptual abnormalities,

Table 3
Differences in frequency of symptoms at onset in FEP patients by substance use group.

	A. Non tobacco or cannabis users (N = 70)		B. Tobacco only users (N = 56)		C. Tobacco & cannabis users (N = 144)		*D. Cannabis only users (N = 13)*		*P*[*]
	N	%	N	%	N	%	N	%	
General prodromal symptoms	68	98.6	56	100.0	139	96.5	13	100	0.407
Dysphoric mood	17	24.6	17	30.4	33	22.9	5	38.5	0.498
Sleep disturbance	13	18.8	24	42.9	42	29.2	4	30.8	0.035[a]
Ideas of reference	60	87.0	45	80.4	133	92.4	12	92.3	0.104[b]
Suspiciousness	50	72.5	38	67.9	100	69.4	8	61.5	0.862
Thought disorder	43	62.3	27	48.2	87	60.4	8	61.5	0.373
Perceptual abnormalities	39	56.5	26	46.4	97	67.4	9	69.2	0.039[c]
Deterioration in functioning	20	29.0	12	21.4	45	31.3	5	38.5	0.480
Others (obsessions, etc.)	9	13.6	12	21.4	30	20.8	4	33.3	0.368
Negative symptoms	42	60.9	21	37.5	71	51.4	6	46.2	0.075[d]
Social withdrawal	40	58.0	19	33.9	69	47.9	5	38.5	0.055[e]
Avolition	6	8.7	5	8.9	20	13.9	2	15.4	0.602
Decreased expression of emotions	9	13.0	4	7.1	14	9.7	3	23.1	0.336
Decreased experience of emotions	8	11.6	4	7.1	18	12.5	3	23.1	0.416
Positive symptoms	68	97.1	51	91.1	140	97.2	13	100	0.171
Hallucinations	41	58.6	31	55.4	103	71.5	9	69.2	0.099[f]
Delusions	65	94.2	51	91.1	139	96.5	13	100	0.344
Disorganisation symptoms	40	58.0	29	51.8	92	63.9	9	69.2	0.283
Disorganised thinking	34	49.3	23	41.1	88	61.1	9	69.2	0.037[g]
Disorganised behaviour	31	44.9	21	37.5	72	50.0	8	61.5	0.288

Post hoc analyses (chi-squared test):
[a] Sleep disturbances: A vs B, $P = 0.003$; B vs C, $P = 0.064$.
[b] Ideas of reference: B vs C, $P = 0.015$.
[c] Perceptual abnormalities: B vs C, $P = 0.006$.
[d] Negative symptoms: A vs B, $P = 0.009$.
[e] Social withdrawal: A vs B, $P = 0.007$.
[f] Hallucinations: B vs C, $P = 0.029$; A vs C, $P = 0.058$.
[g] Disorganised thinking: B vs C, $P = 0.010$; B vs D, $P = 0.067$.
[*] Differences between groups were tested for statistical significance using chi-squared test (degrees of freedom = 3).

hallucinations, and disorganised thinking, compared with those who used tobacco only.

When the 61 subjects who had used cocaine at some point in their life (but started the use prior to the onset of the earliest symptom) were excluded from these analyses, identical results were obtained for differences in the prevalence of sleep disturbances ($X^2 = 7.344$, $P = 0.025$), negative symptoms ($X^2 = 6.671$, $P = 0.036$), social withdrawal ($X^2 = 7.446$, $P = 0.024$), disorganised thinking ($X^2 = 7.588$, $P = 0.023$), and ideas of reference ($X^2 = 5.227$, $P = 0.073$; B vs C: $X^2 = 5.213$, $P = 0.022$). However, statistically significant differences disappeared for prevalence of hallucinations and perceptual abnormalities (data not shown).

Results from the multinomial regression analysis, using group B as category of reference, showed that differences previously detected between the group B ("tobacco only") and group A ("non cannabis or tobacco"), sleep disturbances (OR = 0.133–0.733) and social withdrawal (OR = 1.085–5.248), remained statistically significant in the model. On the other hand, the model exploring differences between the group B and group C ("tobacco & cannabis") retained the variables disorganised thinking (OR = 1.173–5.194) and ideas of reference (OR = 1.206–12.262), along with cocaine use (OR = 3.355–33.483), male sex (OR = 0.132–0.608) and age at first symptom (OR = 0.830–0.956). More statistical data (B, OR, and CI 95%) is presented on Table S2 of Supplementary Material.

4. Discussion

Regarding the main objective of this study, we observed a differential clinical profile of the earliest symptom of psychosis in our FEP patients who used tobacco only before the development of symptoms, compared with the no substance use group and the cannabis and tobacco use group. In comparison with patients with no tobacco or cannabis use, patients who used tobacco only presented sleep disturbances more frequently and negative symptoms, specifically social withdrawal, less frequently. On the other hand, in comparison with both tobacco and cannabis users, tobacco only users showed a lower prevalence of ideas of reference, perceptual abnormalities, hallucinations, and disorganised thinking. Furthermore, those patients who used tobacco only experienced the earliest symptom at an older age than those who used tobacco and cannabis concomitantly. This difference in age was not found between either of these two groups and the group of patients who did not use tobacco or cannabis. Also, we did not find any difference between the group of cannabis only and the other three groups, although this can be explained by the small sample size of this group ($n = 13$).

In this regard, tobacco alone does not seem to be related to an earlier age of onset of the first psychotic episode without concomitant use of cannabis, as other studies have already reported (Hickling et al., 2017; Myles et al., 2012a). Furthermore, our study suggests that tobacco use also does not influence age of onset of the earliest symptom of psychosis when compared with those who do not use.

Our results confirm what has already been published, i.e. that FEP patients use both tobacco and cannabis with greater frequency and intensity than the general population of the same age and sex (Grossman et al., 2017; Lally et al., 2019; Pauselli et al., 2018), with no difference in relation to age of onset of this use. Our results for current smoking prevalence (67.3%) and lifetime use (70.8%) in our FEP sample do not reach the rates of 78% reported by Lally et al. (2019), but are higher than the rates of 58.9% and 57%, respectively, reported by two meta-analyses (Gurillo et al., 2015; Myles et al., 2012b).

4.1. Symptom profiles in FEP patients

In the initial phase of the illness, almost all of our FEP patients have had at least one general prodromal symptom of significant persistence, and more than 95% have experienced one positive symptom. Additionally, about half have experienced at least some negative symptomatology from the early stages, which is striking considering that not all

FEP patients, including those with affective and non-affective psychosis, progress to a diagnosis of schizophrenia.

To our knowledge, this is the first study that explores differential clinical profiles of the earliest symptoms of psychosis in FEP patients based on patterns of previous substance use. One of the most important findings of this study is that patients with FEP and a history of tobacco smoking had an increased prevalence of sleep disturbances as a general prodromal symptom, reaching 43% in comparison with rates of less than 20% in non-smoking patients. Many studies have associated sleep problems with an increased risk of psychotic experience in clinical and non-clinical populations (Davies et al., 2017; Lally et al., 2019; Pauselli et al., 2018). These findings lead us to speculate whether sleep disturbances may have played an important role in the previous findings relating tobacco to an increased risk of developing psychosis (Lunsford-Avery et al., 2017; Reeve et al., 2019).

However, compared with patients who used cannabis concomitantly, FEP patients who used tobacco only showed less frequent positive symptoms, such as hallucinations, and disorganised thinking, and less frequent general prodromes, such as perceptual abnormalities or ideas of reference. Furthermore, some of the studies conducted to date have not found a significant relationship with clinical patterns of psychotic symptoms in tobacco smoking FEP patients (Hickling et al., 2018, 2017). This data contrasts with the findings of other authors who have reported that the effect of tobacco on the onset of psychosis is causally related and is independent of cannabis (Gurillo et al., 2015; Hunter et al., 2020; McGrath et al., 2016). Nevertheless, it should be mentioned that when we repeated our analyses excluding patients who had used cocaine, differences in the prevalence of perceptual abnormalities and hallucinations disappeared, but psychopathological thoughts (disorganised thinking and ideas of reference) were maintained and were more prevalent in patients using both substances. There were no changes when comparing patients with and without tobacco use, as is logical for the few that were excluded from these groups. Identical results were obtained in the regression analysis that adjusted for cocaine use, sex, age at first symptoms and socioeconomic status.

Our findings also show lower prevalence of negative symptoms, such as social withdrawal, in FEP patients with tobacco use only comparing with those with non-substance use, in keeping with prior research suggesting that smoking is related to less severity of negative symptomatology in patients with psychosis (Jiang et al., 2013; Misiak et al., 2015), but in contrast to other authors (Oluwoye et al., 2019; Vermeulen et al., 2018). Although we cannot conclude that this is a causal effect, it should be noted that every patient in our sample started smoking before onset of any general prodromal or negative symptom. Surprisingly, we found no difference in the prevalence of negative symptoms when comparing patients with no substance use with those who used tobacco plus cannabis, in contrast to Ferraro et al. (2020), who detected that lifetime cannabis use could be associated with less social withdrawal.

This study is part of a large multicentre study in patients with the first episode of psychosis; however, some limitations should be noted. One of the main limitations is that the data related to the onset of substance use and the earliest symptom of psychosis were collected retrospectively in a structured interview with patient and family, with the possibility of potential memory bias. Instead, a prospective study would allow us to draw conclusions about a causal relationship. Also, while the SOS inventory can identify a variety of early symptoms of psychosis, it does not include premorbid cognitive dysfunction that could have an effect on the results obtained. On the other hand, current and prior substance use were self-reported, and no laboratory test was used to confirm this. Another limitation would be the lack of data on the use of other drugs such as stimulants prior to the development of symptoms, which could interfere, like cocaine use, in the results obtained in this study (Bramness and Rognli, 2016). Nevertheless, it should be noted that we observed a low prevalence (less than 5%) in the use of stimulants at baseline assessment of patients with FEP.

Moreover, the current study has important strengths. As a naturalistic and multicentre study, a large number of deeply phenotyped sample of FEP patients from different regions in Spain were included in this study; this sample may be considered representative of this population and potentially generalisable. Furthermore, the group of healthy controls has been matched to our study group, achieving a comparable group in age and sex. To our knowledge, this is the first study analysing differences in prodromes of FEP patients based on previous substance use. In addition, although cannabis use has often been considered a confounding factor in previous research on tobacco and FEP, one strength of our study is the comparative analyses between a group of patients with tobacco use only and patients with concomitant cannabis and tobacco use. Another strength is the use of a structured interview to assess first psychotic experience (first psychotic and general symptoms), that collects information from both patients and relatives or caregivers.

5. Conclusions

In summary, in our study the use of tobacco alone was associated with a higher prevalence of specific general prodromal symptoms of psychosis such as sleep disturbances, while tobacco plus cannabis use was associated with psychopathological thoughts as ideas of reference and disorganised thinking. Thus, our results provide evidence against previous findings that relate tobacco alone to the onset of psychosis, as this was only found for concomitant tobacco and cannabis users. However, despite this negative result, it is still important to monitor and apply smoking prevention strategies in adolescents because cigarette use is associated with greater subsequent initiation of other drugs such as cannabis (Tullis et al., 2003), indirectly advancing the age of onset of symptoms. Of note, there was a high concurrence of tobacco and cannabis use; in fact, nearly 75% of the cigarette smokers among our FEP patients had used cannabis. In this sense, and given the high prevalence of tobacco use in our FEP patients, we propose smoking cessation, not only in patients with established mental illness (Anthenelli et al., 2016; Garcia-Portilla et al., 2016; Sarramea et al., 2019), but from the early stages.

Funding

This study received economic support from the Spanish Ministry of Economic Affairs and Competitiveness, the Carlos III Health Care Institute (Grant Number PI11/00325, PI14/00612), the European Regional Development Fund, the European Union, "*Una manera de hacer Europa/* A Way of Shaping Europe", and CIBERSAM.

CRediT authorship contribution statement

Conceptualization, LGB, MPGP, and JB; methodology and formal analysis, LGB, MPGP; writing—original draft preparation, LGB and MPGP; writing—review and editing, LGB, MPGP, MG, GM, MJC, EU, SA, FB, AGP, LPC, IC, EV, IB, AT, PAS, JB, MB and PEPs Group; project coordinator: MB. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

LGB has received honoraria for lecturing and/or travel grants for attending conferences from the Spanish Foundation of Psychiatry and Mental Health, European Psychiatric Association, Otsuka, Lundbeck, Janssen-Cilag, Servier, Angelini and Pfizer.

MPGP has been a consultant to and/or has received honoraria/grants from Angelini, Alianza Otsuka-Lundbeck, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer.

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Galenica, Janssen, Lundbeck, Novartis, Otsuka, Sage, Sanofi-Aventis, and Takeda.

AGP has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Alter, Angelini, Exeltis, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Governement, the Stanley Medical Research Institute.

PAS has been a consultant to and/or has received honoraria or grants from Adamed, CIBERSAM, European Commission, GlaxoSmithKline, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas and Servier.

JB has received research grants and served as consultant, advisor or speaker within de last 5 years for: AB-Biotics, Acadia Pharmaceuticals, Angelini, Casen Recordati, D&A Pharma, Exeltis, Gilead, GSK, Ferrer, Indivior, Janssen-Cilag, Lundbeck, Mundipharma, Otsuka, Pfizer, Reckitt-Benckiser, Roche, Sage Therapeutics, Servier, Shire, Schwabe Farma Ibérica, research funding from the Spanish Ministry of Economy and Competiveness –Centro de Investigación Biomedica en Red area de Salud Mental (CIBERSAM) and Instituto de Salud Carlos III-, Spanish Ministry of Health, Social Services and Equality - Plan Nacional sobre Drogas- and the 7th Framework Program of the European Union.

MB has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of Adamed, Angelini, Casen Recordati, Janssen-Cilag, Lundbeck, Otsuka, Menarini and Takeda.

CDC received financial support to attend scientific meetings from Janssen-Cilag, Almirall, Eli Lilly, Lundbeck, Rovi, Esteve, Novartis, and Astrazeneca.

LGA has received honoraria from the 7th Framework Program European Union.

RRJ has been a consultant for, spoken in activities of, or received grants from: Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid Regional Government (S2010/BMD-2422 AGES; S2017/BMD-3740), JanssenCilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Angelini.

Other authors report no conflict of interest.

Acknowledgements

LGB, MPGP, PAS, JB thank the support of the Ministerio de Economía y Competitividad (PI11/00325; PI14/00612), Instituto de Salud Carlos III – Fondo Europeo de Desarrollo Regional. Unión Europea. Una manera de hacer Europa, Centro de Investigación Biomédica en Red de salud Mental (CIBERSAM), The Goverment of Principality of Asturias PCTI-2018-2022 IDI/2018/235, Instituto de Investigación Biosanitaria del Principado de Asturias (ISPA) and INEUROPA.

EV thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI15/00283) integrated into the Plan Nacional de I + D + I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2017 SGR 1365) and the project SLT006/17/00357, from PERIS 2016-2020 (Departament de Salut). CERCA Programme/Generalitat de Catalunya.

MB thanks the support of the Ministerio de Economía y Competitividad (PI08/0208; PI11/00325; PI14/00612), Instituto de Salud Carlos III – Fondo Europeo de Desarrollo Regional. Unión Europea. Una manera de hacer Europa, CIBERSAM, by the CERCA Programme/Generalitat de Catalunya AND Secretaria d'Universitats i Recerca del Departament d'Economia I Coneixement (2017SGR1355). Departament de Salut de la Generalitat de Catalunya, en la convocatoria corresponent a l'any 2017 de concessió de subvencions del Pla Estratègic de Recerca i Innovació en Salut (PERIS) 2016-2020, modalitat Projectes de recerca orientats a l'atenció primària, amb el codi d'expedient SLT006/17/00345.

PEPs Group (collaborators): Miquel Bioque, Maria Sagué, Anna Alonso-Solís, Eva Grasa, Itxaso González-Ortega, Iñaki Zorrilla, Javier Santabárbara, Concepción De-la-Cámara, Eduardo Jesús Aguilar, Juan Nacher, Dani Bergé, Anna Mané, Laura Montejo, Gerard Anmella, Josefina Castro Fornieles, Elena de la Serna, Fernando Contreras, Cristina Sáiz-Masvidal, Leticia García-Álvarez, Teresa Bobes-Bascarán, Arantzazu Zabala Rabadán, Rafael Segarra Echevarría, Luis Sanchez-Pastor, Roberto Rodriguez-Jimenez, Judith Usall, Anna Butjosa, Salvador Sarró, Amalia Guerrero-Pedraza, Ángela Ibañez, María Ribeiro, Vicent Balanzá-Martínez.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.07.017.

References

Anthenelli, R.M., Benowitz, N.L., West, R., St Aubin, L., McRae, T., Lawrence, D., Ascher, J., Russ, C., Krishen, A., Evins, A.E., 2016. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 387, 2507–2520. https://doi.org/10.1016/S0140-6736(16)30272-0.

Barnett, J.H., Werners, U., Secher, S.M., Hill, K.E., Brazil, R., Masson, K., Pernet, D.E., Kirkbride, J.B., Murray, G.K., Bullmore, E.T., Jones, P.B., 2007. Substance use in a population-based clinic sample of people with first-episode psychosis. Br. J. Psychiatry 190, 515–520. https://doi.org/10.1192/bjp.bp.106.024448.

Bell, C.C., 1994. DSM-IV: diagnostic and statistical manual of mental disorders. JAMA 272, 828–829. https://doi.org/10.1001/jama.1994.03520100096046.

Bernardo, M., Bioque, M., Parellada, M., Saiz Ruiz, J., Cuesta, M.J., Llerena, A., Sanjuan, J., Castro-Fornieles, J., Arango, C., Cabrera, B., 2013. Assessing clinical and functional outcomes in a gene-environment interaction study in first episode of psychosis (PEPs). Rev. Psiquiatr. Salud Ment. 6, 4–16. https://doi.org/10.1016/j.rpsm.2012.11.001.

Bernardo, M., Cabrera, B., Arango, C., Bioque, M., Castro-Fornieles, J., Cuesta, M.J., Lafuente, A., Parellada, M., Saiz-Ruiz, J., Vieta, E., 2019. One decade of the first episodes project (PEPs): advancing towards a precision psychiatry. Rev. Psiquiatr. Salud Ment. 12, 135–140. https://doi.org/10.1016/j.rpsm.2019.03.001.

Bhavsar, V., Jauhar, S., Murray, R.M., Hotopf, M., Hatch, S.L., McNeill, A., Boydell, J., MacCabe, J.H., 2018. Tobacco smoking is associated with psychotic experiences in the general population of South London. Psychol. Med. 48, 123–131. https://doi.org/10.1017/S0033291717001556.

Bramness, J.G., Rognli, E.B., 2016. Psychosis induced by amphetamines. Curr. Opin. Psychiatry 29, 236–241. https://doi.org/10.1097/YCO.0000000000000254.

Clark, V., Conrad, A.M., Lewin, T.J., Baker, A.L., Halpin, S.A., Sly, K.A., Todd, J., 2018. Addiction vulnerability: exploring relationships among cigarette smoking, substance misuse, and early psychosis. J. Dual Diagn. 14, 78–88. https://doi.org/10.1080/15504263.2017.1416436.

Davies, G., Haddock, G., Yung, A.R., Mulligan, L.D., Kyle, S.D., 2017. A systematic review of the nature and correlates of sleep disturbance in early psychosis. Sleep Med. Rev. 31, 25–38. https://doi.org/10.1016/j.smrv.2016.01.001.

de Leon, J., Diaz, F.J., 2005. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr. Res. 76, 135–157. https://doi.org/10.1016/j.schres.2005.02.010.

Ferraro, L., Cascia, C.La., Quattrone, D., Sideli, L., Matranga, D., Capuccio, V., Tripoli, G., Gayer-anderson, C., Morgan, C., Sami, M.B., Sham, P., 2020. Premorbid adjustment and IQ in patients with first-episode psychosis : a multisite case-control study of their relationship with cannabis use. Schizophr. Bull. 46, 517–529. https://doi.org/10.1093/schbul/sbz077.

Garcia-Portilla, M.P., Garcia-Alvarez, L., Sarramea, F., Galvan, G., Diaz-Mesa, E., Bobes-Bascaran, T., Al-Halabi, S., Elizagarate, E., Iglesias, C., Saiz Martinez, P.A., Bobes, J., 2016. It is feasible and effective to help patients with severe mental disorders to quit smoking: an ecological pragmatic clinical trial with transdermal nicotine patches and varenicline. Schizophr. Res. 176, 272–280. https://doi.org/10.1016/j.schres.2016.05.011.

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 characteristics in fi rst episode psychosis. J. Psychiatr. Res. 85, 83–90. https://doi.org/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. Lancet Psychiatry 2, 718–725. https://doi.org/10.1016/S2215-0366(15)00152-2.

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, 526–532. https://doi.org/10.1111/add.13646.

Hickling, L.M., Perez-Iglesias, R., Ortiz-Garcia de la Foz, V., Balanza-Martinez, V., McGuire, P., Crespo-Facorro, B., Ayesa-Arriola, R., 2018. Tobacco smoking and its association with cognition in first episode psychosis patients. Schizophr. Res. 192, 269–273. https://doi.org/10.1016/j.schres.2017.04.018.

Hollingshead, A.B., Redlich, F.C., 1958. Social Class and Mental Illness: Community Study., Social Class and Mental Illness: Community Study. John Wiley & Sons Inc, Hoboken, NJ, US. https://doi.org/10.1037/10645-000.
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 Tob. Res. 22, 3–10. https://doi.org/10.1093/ntr/nty160.
Jiang, J., See, Y.M., Subramaniam, M., Lee, J., 2013. Investigation of cigarette smoking among male schizophrenia patients. PLoS One 8, e71343. https://doi.org/10.1371/journal.pone.0071343.
Kendler, K.S., Lonn, S.L., Sundquist, J., Sundquist, K., 2015. Smoking and schizophrenia in population cohorts of Swedish women and men: a prospective co-relative control study. Am. J. Psychiatry 172, 1092–1100. https://doi.org/10.1176/appi.ajp.2015.15010126.
Kokkevi, A., Stefanis, C., 1995. Drug abuse and psychiatric comorbidity. Compr. Psychiatry 36, 329–337. https://doi.org/10.1016/s0010-440x(95)90113-2.
Kotov, R., Guey, L.T., Bromet, E.J., Schwartz, J.E., 2010. Smoking in schizophrenia: diagnostic specificity, symptom correlates, and illness severity. Schizophr. Bull. 36, 173–181. https://doi.org/10.1093/schbul/sbn066.
Krishnadas, R., Jauhar, S., Telfer, S., Shivashankar, S., McCreadie, R.G., 2012. Nicotine dependence and illness severity in schizophrenia. Br. J. Psychiatry 201, 306–312. https://doi.org/10.1192/bjp.bp.111.107953.
Lally, J., Spaducci, G., Gardner-Sood, P., Atakan, Z., Greenwood, K., Di Forti, M., Ismail, K., Murphy, K.C., Smith, S., McNeill, A., Murray, R.M., Gaughran, F., 2019. Tobacco smoking and nicotine dependence in first episode and established psychosis. Asian J. Psychiatr. 43, 125–131. https://doi.org/10.1016/j.ajp.2019.05.002.
Lunsford-Avery, J.R., Goncalves, B.da S.B., Brietzke, E., Bressan, R.A., Gadelha, A., Auerbach, R.P., Mittal, V.A., 2017. Adolescents at clinical-high risk for psychosis: circadian rhythm disturbances predict worsened prognosis at 1-year follow-up. Schizophr. Res. 189, 37–42. https://doi.org/10.1016/j.schres.2017.01.051.
Ma, X., Li, C., Meng, H., Du, L., Wang, Q., Wang, Y., Deng, W., Liu, X., Hu, X., Murray, R. M., Collier, D.A., Li, T., 2010. Premorbid tobacco smoking is associated with later age at onset in schizophrenia. Psychiatry Res. 178, 461–466. https://doi.org/10.1016/j.psychres.2009.08.014.
McGrath, J.J., Alati, R., Clavarino, A., Williams, G.M., Bor, W., Najman, J.M., Connell, M., Scott, J.G., 2016. Age at first tobacco use and risk of subsequent psychosis-related outcomes: a birth cohort study. Aust. N. Z. J. Psychiatry 50, 577–583. https://doi.org/10.1177/0004867415587341.
Mezquida, G., Cabrera, B., Martínez-arán, A., Vieta, E., Bernardo, M., 2018. Detection of early psychotic symptoms : validation of the spanish version of the “Symptom onset in schizophrenia (SOS) inventory”. Psychiatry Res. 261, 68–72. https://doi.org/10.1016/j.psychres.2017.12.035.
Misiak, B., Kiejna, A., Frydecka, D., 2015. Assessment of cigarette smoking status with respect to symptomatic manifestation in first-episode schizophrenia patients. Compr. Psychiatry 58, 146–151. https://doi.org/10.1016/j.comppsych.2014.11.024.
Morisano, D., Wing, V.C., Sacco, K.A., Arenovich, T., George, T.P., 2013. Effects of tobacco smoking on neuropsychological function in schizophrenia in comparison to other psychiatric disorders and non-psychiatric controls. Am. J. Addict. 22, 46–53. https://doi.org/10.1111/j.1521-0391.2013.00313.x.
Myles, N., Newall, H., Compton, M.T., Curtis, J., Nielssen, O., Large, M., 2012a. The age at onset of psychosis and tobacco use: a systematic meta-analysis. Soc. Psychiatry Psychiatr. Epidemiol. 47, 1243–1250. https://doi.org/10.1007/s00127-011-0431-3.
Myles, N., Newall, H.D., Curtis, J., Nielssen, O., Shiers, D., Large, M., 2012b. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. J. Clin. Psychiatry 73, 468–475. https://doi.org/10.4088/JCP.11r07222.
Oluwoye, O., Burduli, M.M.E., Chwastiak, L., Mcpherson, S., Mcclellan, J.M., Mcdonell, M.G., 2019. In: Impact of Tobacco, Alcohol and Cannabis Use on Treatment Outcomes Among Patients Experiencing First Episode Psychosis : Data From the National RAISE-ETP Study, pp. 142–146. https://doi.org/10.1111/eip.12542.
Pauselli, L., Birnbaum, M.L., Vazquez Jaime, B.P., Paolini, E., Kelley, M.E., Broussard, B., Compton, M.T., 2018. Demographic and socioenvironmental predictors of premorbid marijuana use among patients with first-episode psychosis. Schizophr. Res. 197, 544–549. https://doi.org/10.1016/j.schres.2018.01.020.
Perkins, D.O., Leserman, J., Jarskog, L.F., Graham, K., Kazmer, J., Lieberman, A., 2000. Characterizing and dating the onset of symptoms in psychotic illness: the symptom onset in schizophrenia (SOS) inventory. Schizophr. Res. 44, 1–10.
Reeve, S., Sheaves, B., Freeman, D., 2019. Sleep disorders in early psychosis: incidence, severity, and association with clinical symptoms. Schizophr. Bull. 45, 287–295. https://doi.org/10.1093/schbul/sby129.
Salagre, E., Arango, C., Artigas, F., Ayuso-Mateos, J.L., Bernardo, M., Castro-Fornieles, J., Bobes, J., Desco, M., Fananas, L., Gonzalez-Pinto, A., Haro, J.M., Leza, J.C., Mckenna, P.J., Meana, J.J., Menchon, J.M., Mico, J.A., Palomo, T., Pazos, A., Perez, V., Saiz-Ruiz, J., Sanjuan, J., Tabares-Seisdedos, R., Crespo-Facorro, B., Casas, M., Vilella, E., Palao, D., Olivares, J.M., Rodriguez-Jimenez, R., Vieta, E., 2019. CIBERSAM: ten years of collaborative translational research in mental disorders. Rev. Psiquiatr. Salud Ment. 12, 1–8. https://doi.org/10.1016/j.rpsm.2018.10.001.
Sanchez-Gutierrez, T., Garcia-Portilla, M.P., Parellada, M., Bobes, J., Calvo, A., Moreno-Izco, L., Gonzalez-Pinto, A., Lobo, A., de la Serna, E., Cabrera, B., Torrent, C., Roldan, L., Sanjuan, J., Ibanez, A., Sanchez-Torres, A.M., Corripio, I., Bernardo, M., Cuesta, M.J., 2018. Smoking does not impact social and non-social cognition in patients with first episode psychosis. Schizophr. Res. 199, 64–74. https://doi.org/10.1016/j.schres.2018.03.025.
Sarramea, F., Jaén-Moreno, M.J., Feu, N., Redondo-Écija, J., Balanzá-Martínez, V., Gutiérrez-Rojas, L., García-Portilla, M.P., 2019. Prepare the smoking cessation in severe mental illness: early diagnosis and prevention opportunities. Rev. Psiquiatr. Salud Ment. 12, 133–134. https://doi.org/10.1016/j.rpsm.2018.08.001.
Smith, G.N., Wong, H., MacEwan, G.W., Kopala, L.C., Ehmann, T.S., Thornton, A.E., Lang, D.J., Barr, A.M., Procyshyn, R., Austin, J.C., Flynn, S.W., Honer, W.G., 2009. Predictors of starting to smoke cigarettes in patients with first episode psychosis. Schizophr. Res. 108, 258–264. https://doi.org/10.1016/j.schres.2008.12.013.
Tullis, L.M., Dupont, R., Frost-Pineda, K., Gold, M.S., 2003. Marijuana and tobacco. J. Addict. Dis. 22, 51–62. https://doi.org/10.1300/J069v22n03_05.
van Gastel, W.A., MacCabe, J.H., Schubart, C.D., Vreeker, A., Tempelaar, W., Kahn, R.S., Boks, M.P.M., 2013. Cigarette smoking and cannabis use are equally strongly associated with psychotic-like experiences: a cross-sectional study in 1929 young adults. Psychol. Med. 43, 2393–2401. https://doi.org/10.1017/S0033291713000202.
Vermeulen, J.M., Schirmbeck, F., Blankers, M., van Tricht, M., Bruggeman, R., van den Brink, W., de Haan, L., 2018. Association between smoking behavior and cognitive functioning in patients with psychosis, siblings, and healthy control subjects: results from a prospective 6-year follow-up study. Am. J. Psychiatry 175, 1121–1128. https://doi.org/10.1176/appi.ajp.2018.18010069.
Vermeulen, J., Schirmbeck, F., Blankers, M., van Tricht, M., van den Brink, W., de Haan, L., 2019. Smoking, symptoms, and quality of life in patients with psychosis, siblings, and healthy controls: a prospective, longitudinal cohort study. Lancet Psychiatry 6, 25–34. https://doi.org/10.1016/S2215-0366(18)30424-3.
Ward, H.B., Lawson, M.T., Addington, J., Bearden, C.E., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Jeffries, C.D., Mathalon, D.H., McGlashan, T.H., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., Perkins, D.O., 2019. Tobacco use and psychosis risk in persons at clinical high risk. Early Interv. Psychiatry 13, 1173–1181. https://doi.org/10.1111/eip.12751.
Weiser, M., Reichenberg, A., Grotto, I., Yasvitzky, R., Rabinowitz, J., Lubin, G., Nahon, D., Knobler, H.Y., Davidson, M., 2004. Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. Am. J. Psychiatry 161, 1219–1223. https://doi.org/10.1176/appi.ajp.161.7.1219.
Wium-Andersen, M.K., Orsted, D.D., Nordestgaard, B.G., 2015. Tobacco smoking is causally associated with antipsychotic medication use and schizophrenia, but not with antidepressant medication use or depression. Int. J. Epidemiol. 44, 566–577. https://doi.org/10.1093/ije/dyv090.

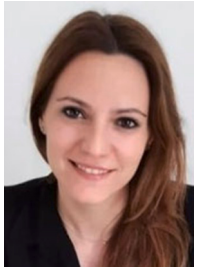
Leticia González-Blanco. Specialist in Psychiatry (2016) and PhD in Medicine (2018) from the University of Oviedo. Assistant Professor in Health Sciences (Psychiatry) at the University of Oviedo and Psychiatrist at Mental Health Center of Corredoria (Oviedo). Researcher of the *Centro de Investigación Biomédica en Red de Salud Mental -CIBERSAM*, supported by the Spanish Ministry of Economy and Competitiveness, and of the Psychiatric Research Group of the *Instituto de Investigación Sanitaria del Principado de Asturias* (*ISPA*). Collaboration in National, European, WHO Research Projects, and linked as Co-Investigator to 2 FIS Projects. Interested in clinical research, focusing on schizophrenia and psychotic spectrum disorders.

María Paz García-Portilla. Dr. García-Portilla is currently Professor of Psychiatry at the University of Oviedo (Spain) and responsible for the Mental Health Center of La Eria (Oviedo) with a catchment area of more than 80,000 people. I am co-principal investigator of the Group 05 (University of Oviedo) of the *Centro de Investigación Biomédica en Red de Salud Mental -CIBERSAM*, supported by the Spanish Ministry of Economy and Competitiveness, and of the Psychiatric Research Group of the *Instituto de Investigación Sanitaria del Principado de Asturias* (*ISPA*). My areas of interest are severe mental disorders, mainly schizophrenia and bipolar disorders, and I am co-author of more than 125 papers in peer-reviewed journals.

Miguel Gutiérrez, MD, PhD is Doctor in Medicine. Professor of Psychiatry. Royal Academy of Medicine of the Basque Country.

Gisela Mezquida, MSc, PhD. She is a research neuropsychologist, graduated in Psychology (2007–11), Master in Neuroscience (2011−12) and a Doctor in Medicine at the University of Barcelona (UB). She works at the schizophrenia group of the Hospital Clínic de Barcelona (CIBERSAM/IDIBAPS/FCRB) and is Associate professor at the medicine faculty, UB. She combines assistance, teaching and research focused on the study of the clinical, neurocognitive characteristics, biomarkers and gene-environment interactions of the first psychotic episodes and, especially, of the negative symptoms in schizophrenia. Mezquida has a h-index of 8 and 33 publications, with more than 200 citations.

Elena Urbiola, MD, is Consultant Psychiatrist at Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, and Gregorio Marañon Health Research Institute, in Madrid, Spain. She has produced posters and oral communications that have been exhibited at national and international conferences, in addition to book chapters and articles. Apart from her clinical experience with Autism, She is currently working in three Randomized Controlled Trials with different molecules for people with Autism Spectrum Disorders, she is part of AIMS2 Trials consortium. She is also developing a new Randomized Controlled Trial for parenting groups for toddlers with autism (Incredible Years programme).



Silvia Amoretti. Dr. Amoretti is psychologist at the Hospital Clinic of Barcelona, researcher of the Barcelona Clinic Schizophrenia Unit at the IDIBAPS and at Institute of Neurosciences, and Investigator of the CIBERSAM (G04). She is teacher on the Official Master Course on Initiation to Research in Mental Health and on Neuroscience of the Barcelona Univeristy. She has made outstanding contributions to the knowledge of cognitive reserve with an H index of 8. Dr. Amoretti is also involved on several projects (FIS PI08/0208; PI11/00325; PI14/00612; SLT006/17/00345), all them focused on clinical and neurocognitive characterization of a sample of first episodes of psychosis.

Laura Pina-Camacho, MD, PhD, is Consultant Psychiatrist and Postdoctoral Researcher at the Department of Child and Adolescent Psychiatry, Hospital General Universitario Gregorio Marañón, and Gregorio Marañon Health Research Insitute, in Madrid, Spain, and Visiting Lecturer of Child Psychiatry at Kings College London, in the UK. Over the past 15 years, she has moved from research with patients with neurodevelopmental disorders to subjects at high risk of developing these disorders (such as early preterm newborns). Her scientific activity has resulted in the publication of more than 20 scientific articles in journals of high impact factor and more than 10 book chapters.

Iluminada Corripio. Dr. Corripio is a senior psychiatrist and head of the Psychotic Disorders Research Group at Hospital de la Santa Creu i Sant Pau. Her line of research is focused on new therapeutic strategies in treatment resistant schizophrenia, being coordinator and principal investigator in the first and the second Deep Brain Stimulation projects in schizophrenia respectively. She also has wide experience m-Health projects and became part of the Innovation Committee of the Hospital de Sant Pau in 2018. Currently, Dr. Corripio is also coordinating an integrated intervention program for patients with schizophrenia (AMA-DABLAM program)

Eduard Vieta is Professor of Psychiatry at the University of Barcelona, head of the Department of Psychiatry and Psychology at the Hospital Clinic, and Scientific Director of the Biomedical Network Research Center on Mental Health (CIBERSAM). He has been Neuroscience advisor for the European Union Presidency, Invited professor at Harvard University, and Honorary doctor by the University of Valencia. He is the most cited scientist worldwide in the field of bipolar disorder and has been named one of the "world's most influential minds".

Alba Toll. Psychiatrist and Introduction on Mental Health Research Master graduated from Universitat Autónoma de Barcelona and Hospital del Mar (Barcelona, Spain). Member of executive board and investigation committee of Sociedad Española de Residentes de Psiquiatría from 2015 to 2016. Nowadays working as pre - doctoral researcher at Institut Hospital del Mar d'Investigacions Médiques (IMIM) and CIBERSAM. Sub - investigator and study coordinator in research studies and clinical trials and skilled in first episode psychosis, schizophrenia and neuroimaging. Author of articles in national and international journals and symposiums in national and international congresses. Peer reviews in national and international journals as International Clinical Psychopharmacology.

Pilar A. Sáiz. Clinical Biochemistry and Psychiatrist, is Professor of Psychiatry at the University of Oviedo, Spain, and also member of the Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), of the Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), and of the Instituto Universitario de Neurociencias del Principado de Asturias (INEUROPA). She has been involved in research of bio-psycho-social aspects of suicidal behaviour and major mental disorders for over 25 years and she is co-author of several publications ranging from biological aspects to psycho-social correlates of those disorders.

Julio Bobes. Professor of Psychiatry at the University of Oviedo, currently heads the Psychiatry Area of the Department of Medicine of the University and is Head of the Psychiatry Department of the Sanitary Area of Oviedo. He is the principal investigator of the Center for Biomedical Research in Mental Health Network (CIBERSAM) of Oviedo. He has published more than 100 articles and is the author and coordinator of several books, as well as a contributor to numerous chapters. His research interests include different aspects of the evaluation, management, treatment and impact of different psychiatric disorders.

Miguel Bernardo is Professor of Psychiatry, University of Barcelona. Founder and Director of the Clinic Schizophrenia Unit, (2000–2019). President of the Spanish Society of Biological Psychiatry (2012–2016), and of the Spanish Foundation of Psychiatry and Mental Health (2017–2018). Principal Investigator of CIBERSAM and Head of the Schizophrenia Group of IDIBAPS. He has directed 25 doctoral theses. Author of more than 330 articles in scientific journals with an accumulated impact factor of 1090,172 (FI JCR 2018) and an H-Index of 38 (WOS). He has been recognized International Distinguished Fellow by the American Psychiatric Association and Honorary Partner of several scientific societies.