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ORIGINAL ARTICLE

# Physical and mental health status of former smokers and non-smokers patients with bipolar disorder

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## Abstract

**Objectives:** Up to 70% individuals with bipolar disorder (BD) are lifetime tobacco smokers, a major modifiable risk factor for morbidity. However, quitting smoking is rarely proposed to individuals with BD, mainly because of fear of unfavorable metabolic or psychiatric changes. Evaluating the physical and mental impact of tobacco cessation is primordial. The aim of this study was to characterize the psychiatric and nonpsychiatric correlates of tobacco smoking status (never- vs. current vs. former smokers) in individuals with BD.

**Methods:** 3860 individuals with ascertained BD recruited in the network of Fondamental expert centers for BD between 2009 and 2020 were categorized into current, former, and never tobacco smokers. We compared the sociodemographic and clinical characteristics assessed by standard instruments (e.g., BD type, current symptoms load, and non-psychiatric morbidity—including anthropometric and biological data) of the three groups using multinomial regression logistic models. Corrections for multiple testing were applied.

**Results:** Current smokers had higher depression, anxiety, and impulsivity levels than former and never-smokers, and also higher risk of comorbid substance use disorders with a gradient from never to former to current smokers—suggesting shared liability. Current smokers were at higher risk to have a metabolic syndrome than never-smokers, although this was only evidenced in cases, who were not using antipsychotics.

**Conclusions:** Tobacco smoking was associated with high morbidity level. Strikingly, as in the general population, quitting smoking seemed associated with their return to the never-smokers' levels. Our findings strongly highlight the need to spread strategies to treat tobacco addiction in the BD population.

**KEYWORDS**
addiction, bipolar disorder, former smokers, metabolic syndrome, tobacco

## 1 | INTRODUCTION

Bipolar disorder (BD) is a severe mental illness associated with 15–20 years of loss in life expectancy when compared with unaffected individuals.[42] Although BD individuals are at particularly high risk to die from unnatural causes such as suicide and accidents,[37] somatic comorbid disorders account for about 70% of premature death in this population,[42] especially because of cardiovascular and metabolic disorders (e.g., dyslipidemia, diabetes).[15,54] Tobacco smoking remains the main modifiable risk factor of cardiovascular and metabolic disorders in BD.[10,12,21,32] The lifetime prevalence of tobacco smoking is up to 70% in BD[46] - two to five times higher than in the general population[11,26] [adjusted odds = 2–5[7]]. Importantly regarding the adverse health effects of tobacco smoke, individuals with BD tend to smoke cigarettes more heavily and to extract more nicotine and chemicals than tobacco smokers without psychiatric disorders.[46]

In addition to the increased risk of developing metabolic and cardiovascular disorders, tobacco smoking may contribute to worsen the psychiatric course of BD. First, the polygenic risk for tobacco smoking has been shown to increase BD risk in two independent Mendelian randomization studies.[20,55] Second, there is a growing body of literature showing that tobacco smoking further increases the already high risk of suicidal behavior carried by individuals with BD,[17,35] especially during depressive episodes.[43] Fourthly, tobacco smoking is associated with a higher frequency of sleep disturbances, anger, impulsivity and emotional lability[6,23,27]—which can all worsen the course of BD. Moreover, tobacco smoking decreases quality of life and increases the large economic burden within patients who are likely to have already low economic income.[53] Finally, tobacco smoking interacts with medications prescribed in BD[58] by inducing the cytochrome P450 1A2, that metabolizes numerous psychotropic medications such as antidepressants[49] and antipsychotics.[3] Thus, tobacco smoking may decrease the efficiency of these treatments, as previously suggested in a randomized trial involving anti-manic medications.[5]

Overall, it appears crucial to treat tobacco smoking (which will be used as proxy term for tobacco addiction/tobacco use disorders in the current manuscript) in individuals with BD. Available evidence suggest that extant strategies are effective and safe in this population,[2,21,26] and that the motivation to quit smoking in individuals with BD is similar to that of unaffected individuals.[11] However, the remission rates (using "quit smoking" as a proxy for remission) are about 60% lower for individuals with BD[26] compared with unaffected individuals.

**Significant outcomes**

- Former and never-smokers had better clinical outcomes and less often metabolic syndrome than current smokers.
- Quitting smoking seemed to improve psychiatric and non-psychiatric outcomes.
- Clinicians should encourage BD individuals to quit smoking and provide intensive treatment for tobacco addiction in BD.

**Limitations**

- Patients referred to the expert centers may be more adherent to care than other individuals with BD.
- The transversal design did not allow to address the causality of the findings.

Clinicians may not view smoking cessation as a priority: an online survey showed that only 33% of individuals with BD reported that they had been advised to quit by a healthcare professional.[47] Overall, both patients and clinicians seem to fear that smoking cessation may increase the risk to develop metabolic disorder (induced by weight gain) and/or exacerbate anxiety and depressive symptomatology,[11,32] while available evidence suggest the opposite[20,52]—provided that proper management is applied. Overall, in BD, the subgroup of former smokers is of particular interest to develop personalized management for tobacco smoking in BD by identifying factors associated with quitting smoking and by investigating the psychiatric and non-psychiatric outcomes of quitting smoking in BD (searching for potential benefits). However, studying this subgroup requires large sample sizes and a precise assessment of tobacco smoking history. Interestingly enough, most studies to date have been studying current tobacco smoking as opposed to a mix of current + former smokers,[17,44,50] and fewer lifetime smoking as a mix of never + former smoking.[57]

To address these limitations and improve our knowledge regarding relevant tobacco smoking groups in BD and particularly address the very poorly known issue of former smoker, we analyzed data from the FACE-BD cohort, reaching more than 3000 individuals with BD. This allowed us to perform multivariable model to identify the independent risk factors for being never versus former versus current tobacco smokers in BD.

# 2 | METHODS

## 2.1 | Participant enrolment

The FACE-BD network in France consists in 12 centers from different regions in France[30] coordinated by Fondation FondaMental (www.fondation-fondamental.org). The first aim of this network is to support clinicians for the management of individuals with BD and give recommendation on personalized treatment strategies, which entirely guides the data collection in a computerized medical file to be further used for research through a web application (E-bipolar©). Anonymized data are stored in a national database FACE-BD that was approved by the French body overseeing the safety of computerized databases (Commission Nationale de l'Informatique et des Libertés, DR-2011-069). Secured access to this web-based system for research purposes is regulated by a scientific committee, who evaluates each project.

Individuals with BD are referred by a general practitioner or a psychiatrist to the expert center where they are assessed and followed annually for 3 years. Practitioners refer patients along with a referral letter that includes their main request and the related medical history. Patients are referred to the expert center for two main reasons: (1) Confirm or infirm diagnosis of BD; (2) provide personalized therapeutic guidance for BD. At inclusion and follow-up visits, the same evaluation package is used in all centers. The assessment protocol was approved by the relevant ethical review board and required only a letter of information to the patients to ascertain their non-opposition to the use of their data (CPP-IIe de France IX, 18 January 2010).

## 2.2 | Clinical assessment

### 2.2.1 | Clinical interview

Patients are first evaluated by a senior psychiatrist specialized in BD. Once the diagnosis is confirmed, a whole-day assessment is planned involving nurses, psychiatrists and psychologists from the expert center.

The type of BD [i.e., type 1, type 2 and not otherwise specified (NOS)] and the presence of current and lifetime comorbid psychiatric disorders—especially anxiety and substance use disorders (SUDs)—are ascertained using the Structured Clinical Interview for DSM-IV Axis I Disorders.[19] Then, sociodemographic characteristics (age, gender, education level, marital and employment status) are recorded. Clinical variables deemed to thoroughly reflect the lifetime and recent course of bipolar illness are collected: number of previous manic, hypomanic, and depressive episodes; presence of lifetime rapid cycling (defined by any 12-months period with ≥4 or more mood episodes), history of suicide attempt including their number and the presence of violent (e.g., hanging) and/or serious (e.g., need of intensive care) attempts. Finally, current treatment regimen and medical history were also asked to the patient and cross-checked using the referral letter (see also below).

### 2.2.2 | Assessment of current mood state

Depressive and Manic symptomatology were assessed respectively with the Montgomery and Åsberg Depression Rating Scale (MADRS)[41] and the Young Mania Rating Scale (YMRS)[59] rated by clinicians from the expert centers, respectively.

### 2.2.3 | Assessment of key dimensions of BD

A set of validated tools were further used to assess the following key dimensions of BD:

- Anxiety was assessed using the current subscale of the State Inventory Anxiety (STAI-A),[8] a 20-item self-report on current anxiety symptoms. Higher scores indicate higher current anxiety.
- The Affective Lability Scale (ALS) was used to assess emotional lability. This is a 54-item scale measuring changeability among four states: depression, elation, anger and anxiety.[24]
- The Barratt Impulsiveness Scale (BIS) was used to evaluate impulsivity. This scale is composed of 30 items assessing three dimensions of impulsivity: attentional, motor and never-planning impulsiveness. High scores indicate higher impulsivity.[4]
- The Childhood Trauma Questionnaire (CTQ) was used to assess the history of childhood trauma.[45]
- The Functioning Assessment Short Test (FAST) was used to assess global functioning.[48] The FAST is an interview developed to assess the disability level in patients with BD and includes items on autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Higher scores indicate worse functioning.

### 2.2.4 | Assessment of non-psychiatric comorbidity

Since BD is strongly associated with non-psychiatric comorbidity such as cardiovascular disease, a large panel

of medical conditions are assessed during the clinical examination done in the expert center for the clinical management of patients.

The following medical conditions were assessed or measured: history of cardiovascular disorders (high blood pressure, myocardial infarction, and cardiac arrhythmia), history of metabolic disorders (type 1 and 2 diabetes, dyslipidemia), anthropometric measurements of obesity: waist circumference in centimeters (as a marker of abdominal obesity) and body mass index (BMI, in $kg/m^2$). This clinical assessment is systematically completed with blood test including complete blood count, ionogram, lipid levels and fasting glucose.

In our study, the presence of a metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program's Adult, Treatment Panel III report (ATP III),[18] which requires that three or more of the following five criteria be met: hypertriglyceridemia (≥1.7 mmol/L or use of lipid-lowering medication), high waist circumference (>94 cm for men and >80 cm for women), high fasting glucose concentration (≥5.6 mmol/L or use of glucose-lowering medication), low HDL-C level (<1.03 mmol/L in men and <1.29 mmol/L in women) and high blood pressure (≥130/85 mm Hg or use of antihypertensive medication). We also considered dyslipidemia as a self-reported diagnosis.

Further details regarding recruitment and assessment procedure can be found elsewhere.[30–32] It is important to note that patients from the FACE-BD cohort are representative of BD outpatients attending tertiary care settings, especially regarding BD characteristics (e.g., rapid cycling, number of lifetime maniac episodes) and prevalence of comorbid anxiety disorders.[29,39] They were all referred from primary care centers, thus representing a large part of BD outpatients seen by practitioners.

Of note, given that assessments are based on DSM-IV criteria, the term "substance use disorders" will refer to lifetime abuse or dependence throughout the manuscript. To avoid working with very small subgroups, SUDs not related to alcohol nor cannabis were defined as "other SUDs" throughout the manuscript.

#### 2.2.5 | Definition of current tobacco status

We defined three groups of patients, based on their current tobacco smoking status: never-smoker, current smoker, and former smoker, as follows:

- Current smoker: "smoking at least five cigarettes per day for at least three months." This definition was chosen since it is a valid proxy to assess nicotine dependence that meets DSM-IV criteria.[32]
- Former smoker: "smoked more than 100 cigarettes over the lifespan, but none over the past year."[32]
- Never-smoker: "smoked less than 100 cigarettes over the lifespan."

Users of other forms of non-medical nicotine than cigarettes were classified as non/never-smokers and very light smokers were also most often classified as non/never-smokers.

### 2.3 | Statistical analysis

Categorical variables are presented as counts (percentages), and quantitative variables as means with standard deviation (SD) or medians with interquartile ranges (IQR). Univariate multinomial logistic regression models were used to assess the association between independent variables (sociodemographic and clinical variables) and smoking status. The never-smoker group was defined as the reference group. For comparison between current versus former smoker the current smoker group was chosen as reference except when comparing SUD and current treatment (to have the OR in the right direction). The adjusted odds ratios (OR) and 95% confidence intervals (CI) were also calculated to estimate the risk associated with smoking status and sociodemographic and clinical variables.

Finally, a multivariate multinomial logistic regression model was performed including all independent variables associated with smoking status with a $p$-value <0.1. The adjusted odds ratios (OR) and 95% confidence intervals (CI) were also estimated. Variables that were highly correlated or collinear, defined as variance inflation factor (VIF) >2.5, were excluded from the multivariate models (e.g., anxiety and depression levels were highly correlated thus we only kept depression level in the final model).

The significance level was set at $p$-value <0.05 for all global $p$-value. This was a post-hoc analysis of a cohort previously used for analysis, thus, we applied post-hoc corrections using two methods: significant $p$-values across the three smokers' groups were corrected using the Benjamini–Hochberg False Discovery Rate (FDR) and pairwise comparisons were corrected by the Bonferroni method, yielding $p < 0.05/3 = 0.016$ for significance. Analyses were performed using the SPSS software (version 26.0.0.0; IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp) and R software.

## 3 | RESULTS

Data regarding smoking status was available for 3625 (93.9% of all data extracted from the database) patients. There were 1529 (42.2%) never-smokers, 1680 (46.3%) current smokers

and 416 (11.5%) former smokers. The mean age of the sample was 40.6 (SD = 12.9) years and 61.6% were women. Regarding BD type, 45.7% were BD-1, 43.5% BD-2 and 10.8% BD-NOS, with a mean disorder duration of 16.8 (SD = 11.2) years. As previously published, participants from the FAC-BD cohort are mostly euthymic,[31] but often also show residual depressive symptoms, as shown by a mean MADRS = 10.6 (SD = 9.2) and median YMRS = 1 (IQR = 0–3).

### 3.1 | Sociodemographic characteristics according to smoking status

As compared with never-smokers, current smokers were significantly more likely to be men ($p = 0.008$). Current and former smokers were less likely to be currently employed than never-smokers group. Former smokers were older than both never- and current smokers (OR = 1.02, 95% CI = [1.01; 1.03], $p < 0.001$; OR = 1.05, 95% CI = [1.04; 1.06], $p < 0.001$, respectively), while current smokers were younger than never-smokers (OR = 0.97, 95% CI = [0.97; 0.98], $p < 0.001$). Both former and never-smokers were more often in a relationship than current smokers (both $p < 0.001$; Table 1A).

### 3.2 | Course and symptoms load of BD according to smoking status

BD-1 was preferentially associated with current smoking as compared with never-smokers ($p = 0.006$) and showed younger age at BD onset than both never- and former smokers (both $p < 0.001$), while there was no difference between the latter groups. Both current and never-smokers reported higher number of depressive episodes by duration of BD than former smokers. Current smokers had significantly higher risk of lifetime suicide attempt than both never- (OR = 1.5, 95% CI = [1.3; 1.7], $p$-value <0.001) and former smokers (OR = 1.4, 95% CI = 1.1;1.7, $p$-value = 0.04) but the difference was not significant between former and never-smokers (Table 1B).

Current smokers also had significantly higher scores of depression (MADRS), anxiety (STAI-A) and emotional lability (ALS) than never-smokers, while there were no differences with former smokers nor between former and never-smokers. Mean impulsivity showed an increasing gradient from never- to former to current smokers (all pairwise $p$ significant). Former and current smokers both reported higher CTQ total score than never-smokers ($p = 0.006$ and $p = 0.004$, respectively). Finally, current smokers reported significantly worse functioning than both never- and former smokers (OR = 1.02, 95% CI = [1.01; 1.02], $p < 0.001$; OR = 0.99, 95% CI = [0.98; 0.99], $p = 0.001$, respectively) while there were no differences between former and never-smokers.

### 3.3 | Comorbid SUDs as according to tobacco smoking status

There was a gradient toward increasing prevalence of each comorbid SUD from never- to current smokers, with odds ratios ranging from 2.5 (other SUDs, former vs. never-smokers) to 3.3 (other SUDs, current vs. never-smokers). All pairwise tests were significant (Table 1C), except regarding other SUDs between current and former smokers.

### 3.4 | Non-psychiatric disorders according to smoking status

Former smokers showed a poorer metabolic profile compared with both never and current smokers, with significantly higher BMI and waist circumference and significantly more frequent dyslipidemia and metabolic syndrome. There were different patterns of associations with high blood pressure and cardiac arrythmia, which were both significantly more frequent in never- and former smokers compared with current smokers ($p < 0.001$ and $p = 0.005$, respectively). Never smokers had significantly higher risk to report type 2 diabetes than current smokers (OR = 2, 95% CI = 1.2–3.4, $p = 0.04$) but there was no difference between former smokers and both never- and current smokers. Finally, there was no significant difference between tobacco smokers' groups regarding C-reactive protein, asthma, dysthyroidism, epilepsy and neoplasia (Table 1D).

### 3.5 | Current psychotropic medications

Neuroleptics and atypical antipsychotics were more frequently prescribed to current smokers than to the two other smokers groups (Table 1E). Those medications were pooled for further analysis. No other medication type was associated with smoking status.

### 3.6 | Multivariate analysis

When the significant variables from bivariate analyses were analyzed in a multivariate model (Table 2), the strongest factors associated with smoking status were age at interview (younger age of current smokers vs. the two other groups and older age of former vs. never-smokers, $p < 0.001$ for all) and lifetime comorbid alcohol use

**TABLE 1** Association between smoking status and sociodemographic and clinical data

**(A) Sociodemographic characteristics according to smoking status**

| Variable | Never smoker 1529 (42.2%) *N* (%) or mean (SD) | Former smoker 416 (11.5%) | Current smoker 1680 (46.3%) | Global *p*-value | Former vs. never-Smoker Odds ratio [95% CI] | *p*-Value | Current vs. former smoker Odds ratio [95% CI] | *p*-Value | Current vs. never-smoker Odds ratio [95% CI] | *p*-Value |
|---|---|---|---|---|---|---|---|---|---|---|
| Men (vs. women) | 535 (35) | 174 (41.9) | 681 (40.5) | **0.003** | 1.34 [1.07; 1.67] | 0.08 | | 0.99 | 1.27 [1.1; 1.46] | **0.008** |
| Age (years) | 42.2 (13.6) | 45.5 (12.5) | 37.9 (11.7) | **<0.001** | 1.02 [1.01; 1.03] | **<0.001** | 0.95 [0.94;0.96] | **<0.001** | 0.97 [0.97; 0.98] | **<0.001** |
| Marital status (single vs. in a relationship) | 580 (44.6) | 142 (39.8) | 588 (42) | **<0.001** | 0.82 [0.65; 1.04] | 0.46 | 0.48 [0.38; 0.61] | **<0.001** | 1.71 [1.47; 1.99] | **<0.001** |
| Educational level | | | | 0.12 | | 0.24 | | 0.02 | | 0.21 |
| Primary school | 303 (23.7) | 93 (26.5) | 328 (23.7) | | 1.18 [0.9; 1.56] | | 1.05 [0.8; 1.39] | | 1.12 [0.94; 1.35] | |
| High school | 158 (12.3) | 45 (12.8) | 265 (19.2) | | 1.1 [0.76; 1.58] | | 0.63 [0.44; 0.89] | | 1.74 [1.4; 2.17] | |
| University | 820 (64) | 213 (60.7) | 790 (57.1) | | Ref. | | Ref. | | Ref. | |
| Currently unemployed | 502 (39.2) | 170 (48.3) | 604 (43.9) | **0.005** | 1.45 [1.14; 1.84] | 0.03 | 1.19 [0.94; 1.51] | 0.44 | 1.22 [1.04; 1.42] | 0.06 |

**(B) Course and symptoms load of BD according to smoking status**

| | Never-smoker 1529 (42.2%) *N* (%) or mean (SD) | Former smoker 416 (11.5%) | Current smoker 1680 (46.3%) | Global *p*-value | Former vs. never-smoker Odds ratio [95% CI] | *p*-Value | Current vs. former smoker Odds ratio [95% CI] | *p*-Value | Current vs. never-smoker Odds ratio [95% CI] | *p*-Value |
|---|---|---|---|---|---|---|---|---|---|---|
| BD type | | | | **<0.001** | | 0.23 | | 0.94 | | **<0.001** |
| 2 | 712 (46.6) | 186 (44.7) | 678 (40.4) | | Ref. | | Ref. | | Ref. | |
| 1 | 633 (41.4) | 192 (46.2) | 832 (49.5) | | 1.16 [0.92; 1.46] | | 1.19 [0.95;1.49] | | 1.38 [1.19; 1.6] | |
| NOS | 184 (12) | 38 (9.1) | 170 (10.1) | | 0.79 [0.54; 1.16] | | 1.22 [0.84;1.82] | | 0.97 [0.77; 1.23] | |
| Rapid cycling | 227 (17.9) | 53 (15.7) | 225 (16.3) | 0.45 | | | | | | |
| Age at onset of BD (years) | 24.9 (10.4) | 25.1 (10.4) | 22.5 (8.4) | **<0.001** | 1.00 [0.99; 1.01] | 1 | 0.97 [0.96;0.98] | **<0.001** | 0.97 [0.97; 0.98] | **<0.001** |
| Disease duration (years) | 17.3 (11.9) | 20.6 (11.8) | 15.3 (10) | **<0.001** | 1.02 [1.01; 1.03] | **<0.001** | 0.96 [0.95;0.97] | **<0.001** | 0.98 [0.98; 0.99] | **<0.001** |

(Continues)

TABLE 1 (Continued)

| (B) Course and symptoms load of BD according to smoking status | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Never-smoker 1529 (42.2%) | Former smoker 416 (11.5%) | Current smoker 1680 (46.3%) | | Former vs. never-smoker | | Current vs. former smoker | | Current vs. never-smoker | |
| | *N* (%) or mean (SD) | | | Global *p*-value | Odds ratio [95% CI] | *p*-Value | Odds ratio [95% CI] | *p*-Value | Odds ratio [95% CI] | *p*-Value |
| Number of (hypo) manic episodes/ BD duration | 0.4 (0.6) | 0.3 (0.3) | 0.4 (0.4) | 0.08 | | | | | | |
| Number of depressive episodes/BD duration | 0.5 (0.8) | 0.3 (0.3) | 0.5 (0.4) | **<0.001** | 0.36 [0.23; 0.56] | **<0.001** | 3.23 [2.56; 5.26] | **<0.001** | 0.99 [0.88; 1.13] | 0.98 |
| Lifetime SA | 505 (34.7) | 143 (35.9) | 692 (43.5) | **<0.001** | 1.06 [0.84; 1.33] | 1 | 1.37 [1.09;1.73] | 0.04 | 1.45 [1.25; 1.68] | **<0.001** |
| Lifetime violent and/or serious SA | 197 (40.2) | 64 (45.7) | 294 (44.3) | 0.29 | | | | | | |
| MADRS score | 10.1 (9.1) | 10.1 (8.6) | 11.2 (9.2) | **0.003** | 1.00 [0.99; 1.01] | 1 | 1.01 [1;1.03] | 0.18 | 1.01 [1.01; 1.02] | **0.005** |
| YMRS score (median, IQR) | 2.4 (3.7) | 2.4 (4) | 2.4 (3.7) | 0.98 | | | | | | |
| STAI-A score | 41.9 (15.2) | 42.9 (14.7) | 44.2 (14.7) | **<0.001** | 1.00 [0.99; 1.01] | 0.67 | 1.01 [1;1.01] | 0.44 | 1.01 [1.01; 1.02] | **<0.001** |
| ALS score | 1.2 (0.7) | 1.3 (0.7) | 1.3 (0.7) | **<0.001** | 1.18 [0.99; 1.39] | 0.30 | 1.17 [0.99;1.38] | 0.27 | 1.38 [1.24; 1.53] | **<0.001** |
| BIS score | 65.2 (11.1) | 67.8 (11.3) | 69.3 (11.4) | **<0.001** | 1.02 [1.01; 1.03] | **0.002** | 1.01 [1;1.02] | 0.09 | 1.03 [1.03; 1.04] | **<0.001** |
| CTQ total score | 41.9 (14.4) | 44.8 (15.6) | 43.8 (14.7) | **<0.001** | 1.01 [1.01; 1.02] | **0.006** | 1 [0.99; 1.01] | 0.52 | 1.01 [1.00; 1.01] | **0.004** |
| FAST total score | 19.9 (14.5) | 20.4 (14.6) | 23 (14.8) | **<0.001** | 1 [0.99; 1.01] | 1 | 1 [1;1.02] | **0.01** | 1.02 [1.01; 1.02] | **<0.001** |

| (C) Comorbid SUDs as a function of tobacco smoking status | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Never-smoker 1529 (42.2%) | Former smoker 416 (11.5%) | Current smoker 1680 (46.3%) | | Former vs. never-smoker | | Current vs. former-smoker | | Current vs. never-smoker | |
| | *N* (%) or mean (SD) | | | Global *p*-value | OR [95% CI] | *p*-Value | OR [95% CI] | *p*-Value | OR [95% CI] | *p*-Value |
| Alcohol use disorder | 172 (12.7) | 110 (28.5) | 552 (37.4) | **<0.001** | 2.74 [2.09; 3.6] | **<0.001** | 1.5 [1.18;1.92] | **0.003** | 4.12 [3.4; 4.99] | **<0.001** |
| Cannabis use disorder | 64 (4.7) | 72 (18.7) | 507 (34.4) | **<0.001** | 4.63 [3.23; 6.63] | **<0.001** | 2.28 [1.74;3.03] | **<0.001** | 10.6 [8.05; 13.9] | **<0.001** |

TABLE 1 (Continued)

**(C) Comorbid SUDs as a function of tobacco smoking status**

| | Never-smoker 1529 (42.2%) | Former smoker 416 (11.5%) | Current smoker 1680 (46.3%) | | Former vs. never-smoker | | Current vs. former-smoker | | Current vs. never-smoker | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* (%) or mean (SD) | | | Global *p*-value | OR [95% CI] | *p*-Value | OR [95% CI] | *p*-Value | OR [95% CI] | *p*-Value |
| Sedative use disorder | 44 (3.2) | 25 (6.5) | 81 (5.5) | **0.003** | 2.07 [1.25; 3.42] | **0.005** | 1.19 [0.75; 1.89] | 0.46 | 1.73 [1.19; 2.52] | **0.004** |
| Other substance use disorder | 37 (2.7) | 33 (8.5) | 186 (12.6) | **<0.001** | 3.33 [2.05; 5.41] | **<0.001** | 1.54 [1.05; 2.28] | **0.03** | 5.14 [3.59; 7.38] | **<0.001** |

**(D) Non-psychiatric conditions according to smoking status**

| | Never-smoker 1529 (42.2%) | Former smoker 416 (11.5%) | Current smoker 1680 (46.3%) | | Former vs. never-smoker | | Current vs. former smoker | | Current vs. never-smoker | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* (%) or mean (SD) | | | Global *p*-value | OR [95% CI] | *p*-Value | OR [95% CI] | *p*-Value | OR [95% CI] | *p*-Value |
| BMI (kg/m$^2$) | 25.9 (5.5) | 26.7 (5.6) | 25.6 (5.2) | **0.001** | 1.03 [1.01; 1.05] | 0.08 | 0.96 [0.94;0.98] | **0.002** | 0.99 [0.98; 1] | 0.24 |
| Waist circumference | 91.6 (14.9) | 95.5 (16) | 91.2 (15.6) | **<0.001** | 1.02 [1.01; 1.02] | **<0.001** | 0.98 [0.98;0.99] | **<0.001** | 0.99 [0.99; 1] | 0.44 |
| Dyslipidemia | 200 (14.3) | 76 (19.7) | 232 (15.4) | **0.05** | 1.47 [1.1; 1.97] | 0.08 | 0.74 [0.56;0.99] | 0.21 | 1.09 [0.89;1.34] | 0.79 |
| Metabolic syndrome | 258 (19.8) | 100 (27) | 333 (23.8) | **0.006** | 1.5 [1.15; 1.96] | **0.04** | 0.84 [0.65;1.1] | 0.52 | 1.27 [1.05;1.52] | 0.06 |
| High blood pressure | 120 (8.6) | 56 (14.4) | 68 (4.5) | **<0.001** | 1.79 [1.28; 2.52] | **0.002** | 0.28 [0.19;0.41] | **<0.001** | 0.5 [0.37; 0.68] | **<0.001** |
| C-reactive protein (mg/L) | 3.0 (4.5) | 3.2 (5.8) | 3.8 (7.7) | **0.02** | 1.01 [0.98; 1.04] | 0.62 | 1.02 [0.99;1.05] | 0.25 | 1.03 [1.01; 1.05] | 0.01 |
| Cardiac arrythmia | 56 (4) | 20 (5.1) | 34 (2.2) | **0.005** | 1.29 [0.77; 2.18] | 0.72 | 0.42 [0.24;0.76] | **0.04** | 0.55 [0.36; 0.85] | **0.04** |
| Type 2 diabetes | 42 (3) | 12 (3.1) | 23 (1.5) | **0.03** | 1.03 [0.51;1.92] | 1 | 0.49 [0.24;0.99] | 0.28 | 0.5 [0.29;0.82] | **0.04** |
| Dysthyroidism | 172 (12.4) | 57 (14.5) | 169 (11.1) | 0.16 | | | | | | |
| Asthma | 116 (8.1) | 31 (7.8) | 141 (9.1) | 0.56 | | | | | | |
| Epilepsy | 25 (1.8) | 4 (1) | 33 (2.2) | 0.28 | | | | | | |
| Neoplasia | 47 (3.5) | 18 (4.7) | 41 (2.8) | 0.16 | | | | | | |

(Continues)

**TABLE 1** (Continued)

| (E) Psychotropic medicines according to smoking status | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Never-smoker 1529 (42.2%)** | **Former smoker 416 (11.5%)** | **Current smoker 1680 (46.3%)** | | **Former vs. never-smoker** | | **Current vs. former smoker** | | **Current vs. never-smoker** | |
| | ***N* (%) or mean (SD)** | | | **Global *p*-value** | **OR [95% CI]** | ***p*-Value** | **OR [95% CI]** | ***p*-Value** | **OR [95% CI]** | ***p*-Value** |
| Antidepressant | 679 (88) | 194 (88.2) | 721 (89.2) | 0.71 | | | | | | |
| Antipsychotic | 483 (64.3) | 139 (63.8) | 579 (72.9) | **<0.001** | 0.98 [0.71; 1.34] | 0.88 | 1.53 [1.11; 2.1] | **0.009** | 1.49 [1.2; 1.86] | **<0.001** |
| Neuroleptic | 205 (29.1) | 56 (28.9) | 258 (35.7) | **0.02** | 0.99 [0.7; 1.41] | 0.95 | 1.37 [0.97; 1.94] | 0.07 | 1.36 [1.09; 1.69] | **0.007** |
| Anxio/hypnotic | 526 (76.1) | 150 (78.1) | 553 (78.2) | 0.62 | | | | | | |
| Lithium | | | | 0.1 | | | | | | |
| No | 433 (56.5) | 105 (48.2) | 436 (54.6) | | | | | | | |
| Yes | 334 (43.5) | 113 (51.8) | 363 (45.4) | | | | | | | |
| Mood stabilizer | 568 (73) | 615 (75.8) | 152 (70) | 0.17 | | | | | | |

*Note*: Other substance use disorder: cocaine, psychostimulant, psychedelics, opiates, others.

Abbreviations: ALS, Affective Lability Scale; BD, bipolar disorder; BIS, Barratt Impulsiveness Scale; CTQ, Childhood Trauma Questionnaire; FAST, Functioning Assessment Short Test; MADRS, Montgomery and Åsberg Depression Rating Scale; NOS, not otherwise specified; SA, suicide attempt; STAI-A, State Inventory Anxiety; YMRS, Young Mania Rating Scale. Bold values represent significant results.

**TABLE 2** Multivariate analysis of factors associated with tobacco status

| | Global *p*-value | Former vs. never-smoker OR [95% CI] | Current vs. former smoker *p* | Current vs. never-smoker OR [95% CI] | *p* | OR [95% CI] | *p* |
|---|---|---|---|---|---|---|---|
| Gender | 0.61 | | | | | | |
| Age | **<0.001** | 1.03 [1.01; 1.04] | **<0.001** | 1.05 [1.03; 1.06] | **<0.001** | 0.98 [0.97; 0.99] | **<0.001** |
| Marital status | | | | | | | |
| In a relationship vs. single | **0.006** | 0.85 [0.63; 1.14] | 0.28 | 0.63 [0.47; 0.85] | **0.003** | 1.30 [1.05; 1.6] | **0.02** |
| Currently unemployed | **0.05** | 1.29 [0.95; 1.76] | 0.11 | 1.01 [0.73; 1.4] | 0.94 | 1.30 [1.04; 1.63] | **0.02** |
| BD type | **0.001** | | 0.17 | | 0.51 | | **<0.001** |
| 2 | | 1 | | 1 | | 1 | |
| 1 | | 1.23 [0.91; 1.66] | | 0.84 [0.5; 1.42] | | 1.50 [1.2; 1.86] | |
| NOS | | 0.73 [0.44; 1.20] | | 0.82 [0.6; 1.11] | | 0.88 [0.62; 1.24] | |
| Alcohol use disorder | **<0.001** | 1.83 [1.26; 2.68] | **0.002** | 1.64 [1.16; 2.31] | **0.005** | 2.96 [2.25; 3.89] | **<0.001** |
| Cannabis use disorder | **<0.001** | 4.08 [2.51; 6.62] | **<0.001** | 1.54 [1.04; 2.3] | **0.03** | 6.33 [4.42; 9.05] | **<0.001** |
| Other substance use disorder | 0.14 | | | | | | |
| MADRS | 0.87 | | | | | | |
| ALS | 0.58 | | | | | | |
| BIS | 0.16 | | | | | | |
| CTQ | 0.12 | | | | | | |
| FAST | 0.14 | | | | | | |
| Metabolic syndrome | **0.03** | 1.29 [0.92; 1.79] | 0.14 | 1.08 [0.77; 1.51] | 0.67 | 1.4 [1.09; 1.80] | **0.01** |

*Note*: Other substance use disorder: cocaine, psychostimulant, psychedelics, opiates, sedative, others. Bold values represent significant results.

disorder and cannabis use disorder (higher risk for current vs never- and former smokers and for former vs. never-smokers, with ORs ranging from 1.5 to 6.3). "Other SUDs" was no more significantly associated with smoking status. There were also strong, independent associations of smoking status with BD type showing higher rates of BD of type 1 among current versus never-smokers (OR = 1.5, 95% CI = 1.2–1.9, $p < 0.001$), and with marital status; current smokers being more often single than former smokers. Finally, the association between smoking status and metabolic syndrome was lost when adding neuroleptics and/or atypical antipsychotics use in the model (results not shown). To better understand the association between atypical antipsychotics/neuroleptics use, smoking status and metabolic syndrome, we performed additional analyses showing that: (i) both former and current smoking remained significantly associated with the presence of a metabolic syndrome in BD cases without antipsychotic/neuroleptic, compared with never smokers (18% in never-smokers vs. 27% in former- and 23% in current, $p$ corrected = 0.019 and $p$ corrected = 0.009, respectively), but not in individuals with atypical antipsychotics/neuroleptics (overall $p = 0.299$)—see Figure 1; and (ii) the association between smoking status and metabolic syndrome remained after adjustment for age, gender and antipsychotic/neuroleptic only for former- versus never smokers (OR = 1.6, 95% CI = 1.3–1.9, $p < 0.001$).

Table 3 further summarizes the patterns of associations with former or current smoking or both (i.e., "lifetime smoking").

## 4 | DISCUSSION

Previous studies on the FACE-BD cohort and SUDs focused on other SUDs (e.g., alcohol use disorders[33]) or on the presence of any SUD and specific characteristics

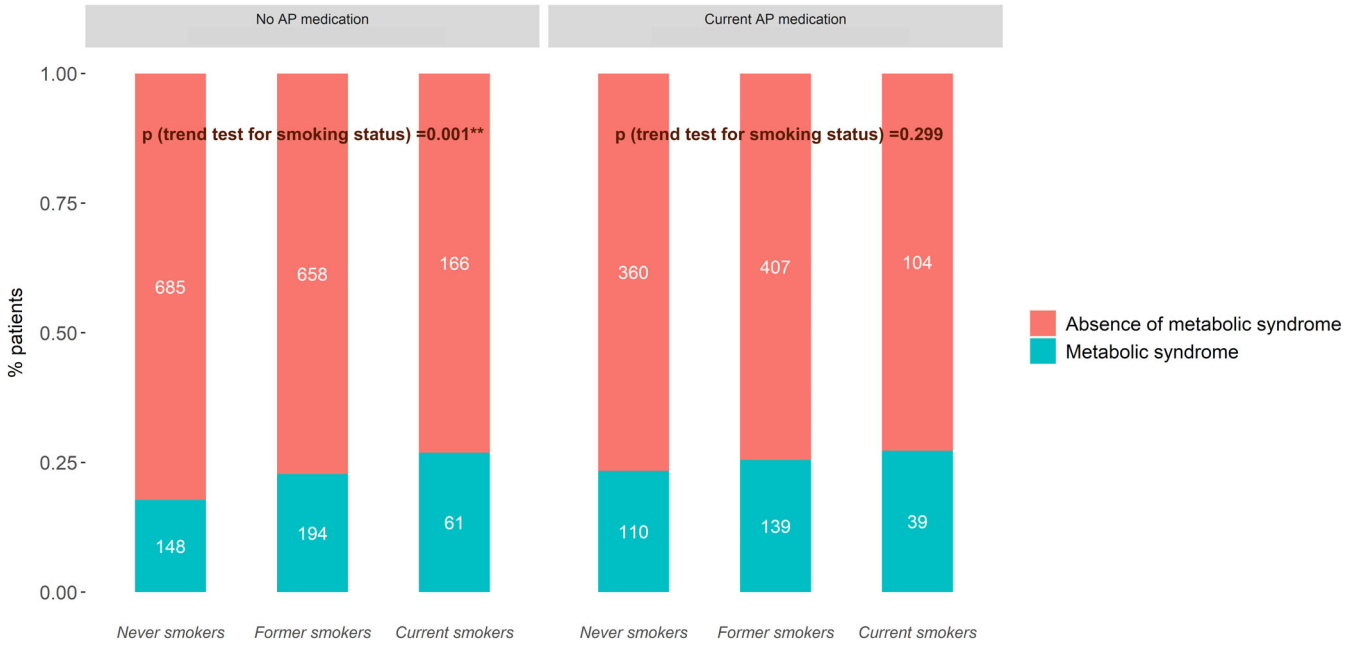


**FIGURE 1** Association between smoking status, antipsychotics intake and metabolic syndrome

**TABLE 3** Summary of findings showing associations with current, former, and/or lifetime tobacco smoking

| | Preferential associations with former tobacco smoking | Preferential associations with current tobacco smoking | Associations with any lifetime tobacco smoking |
|---|---|---|---|
| Age | Increased | Decreased | Both directions |
| Marital status | | Being single | |
| BD type | | BD type 1 more frequent | |
| Lifetime SA | | | |
| Alcohol use disorder | | | Increasing prevalence from never to current smoking |
| CTQ | Higher score vs. current smokers | | |
| Metabolic syndrome | | | Higher prevalence (may be linked to lifestyle and antipsychotic treatment) |

*Note*: Bold values represent significant results.

of BD (e.g., suicidal behavior).[34,35] In the current study, we focused specifically on lifetime tobacco smoking status, analyzing separately former smokers from the two other groups and its association with the characteristics of BD. In addition, we aimed at extending our previous findings regarding the characteristics of current versus former versus never smokers with BD, since evidence remained scarce in our previous study, where the group of former smokers was relatively small ($N = 78$) and multivariate analysis was not deemed relevant.[32] Accordingly, in this new study, we were able to investigate associations with a large range of clinical characteristics, metabolic and biological variables, and current smoking status. We first confirmed an alarming rate of about 58% lifetime smoking in BD, noticing that only 19.8% of them had quit smoking, that is, half of the rates found in the general population.[38] After adjusting for multiple confounders, we evidenced preferential associations with either current or former tobacco smoking, as follows: BD type 1, being single, and fulfilling the criteria for metabolic syndrome and current smoking; and higher scores for childhood trauma with former smoking (Table 3). Additionally, there was an increasing gradient from never- to former to current tobacco smokers regarding the risk of comorbid SUDs. Our findings initially suggested that both the use of antipsychotic and the metabolic syndrome were associated with smoking status, but that these associations were lost in the fully adjusted model, supporting the existence of complex relationships between these three variables.

Tobacco smoking has been consistently associated with other SUDs in BD[14] and in the general population.[13] This supports the hypothesis that nicotine exposure may increase the risk of associated SUDs,[16,25] but also that all SUDs may share genetic vulnerability—at least to some extent.[1] Additionally, one can also hypothesize that the likelihood of successfully quitting tobacco smoking is reduced by the presence of comorbid SUDs, whether it is because of the general profile of these patients (including impulsiveness and/or childhood trauma) or to the negative impact of SUDs on treatment-seeking and adherence.

The large sample size also allowed us to re-examine the relationships between tobacco smoking status and psychological/psychiatric outcomes, namely: suicide attempts, emotional lability, impulsivity, current mood symptoms and functioning—all being key issues in BD. Although examining trait characteristics may be considered relevant for lifetime conditions only (e.g., lifetime smoking), we kept our three smoking groups for all analyses in order to detect traits associated with the likelihood of smoking cessation. No trait characteristic remained associated with tobacco smoking status after multiple adjustment, as was previously evidenced regarding impulsivity.[27] However, although individuals were globally euthymic, current smokers had significantly higher scores for depression, anxiety, and emotional lability. They also had higher rates of suicide attempts and poorer global functioning than never- and former smokers. These findings suggest that, regarding psychiatric outcomes in BD, patients who quit tobacco smoking may show better outcomes regarding anxiety, depression and functioning than current smokers. However, these associations did not remain significant in multivariate analyses.

Regarding non-psychiatric comorbidities, former smokers had an overall less favorable metabolic profile than current smokers regarding weight, blood pressure, and dyslipidemia. Some of these findings could be explain by the appetite suppressant effect of tobacco consumption,[9,22,40] or by the fact that individuals with BD, who smoke tobacco, are not commonly using smoking cessation strategies, which are known to help reducing increase of appetite. Furthermore, impulsivity being higher for lifetime (current or former) versus never-smokers, one can hypothesize that these patients have maladaptive eating behaviors that increased their risk of metabolic syndrome. Eventually, despite bivariate analyses showing associations between lifetime smoking and increased risk of metabolic syndrome, this was no more the case when other variables—including age and antipsychotics use—were considered. This is of utmost relevance for clinicians and patients, who may fear weight gain and blood pressure changes associated with smoking cessation. Our findings regarding metabolic syndrome suggest that smoking cessation can be expected to have a very limited negative impact—if any—on the most significant components of metabolic health, despite possible increase in weight. This is all the most interesting since former smokers were older in our sample than current smokers and that metabolic syndrome is often associated with older age, reinforcing a probable "no greater negative effect" of smoking cessation on metabolic status. This is particularly similar to additional study of individuals suffering from either schizophrenia or BD in a trial of varenicline for smoking cessation, where tobacco quitters showed increases in weight and blood pressure, but decreases in cardiovascular risk.[2]

Our study has several limitations. First, the transversal design did not allow us to address the causality of our findings. We did not measure the duration and amount of exposure to tobacco, nor assessed tobacco use disorders using DSM criteria, which could have yielded different associations than those we evidenced. Further, the method used to quit smoking (e.g., with or without proper treatment) was not assessed and could increase heterogeneity of the former smoker group. Indeed, individuals who quit smoking without support may have worse clinical outcomes than the others may. In addition, both lifetime smokers groups showed higher risk of comorbid SUDs, noticing that the concurrent use of multiples substances is very likely to influence clinical characteristics, which may explain why some associations did not withhold multiple adjustments. Even if we performed a multivariate analysis adjusted on the different comorbid SUDs, the effect of multiple substance use cannot be totally ruled out. Finally, patients referred to the expert centers are followed regularly by a practitioner and volunteer to be assessed, which suggests that they have high levels of adherence to care and possibly lower clinical instability than other clinical samples with BD. With that regard, patients from the FACE-BD have been shown to present residual symptoms, including chronic perturbations, that have a major impact on levels of functioning.[29] Overall, this suggests that the FACE-BD cohort is representative of tertiary care samples with BD, somewhere between the general population and acute ward samples.

Our group and others have hypothesized that the course of bipolar illness could be improved by properly managed smoking cessation. The current findings support this view, although based on retrospective data only. BD (and probably psychiatric disorders in general) remains a risk factor for persistent smoking compared with unaffected individuals.[56] Tobacco smoking has been associated with a wide range of psychiatric/psychological and non-psychiatric difficulties in BD[25,38,44] and it decreases the plasma levels and the effectiveness of several psychotropic drugs.[5] Finally, smoking also impacts

quality of life of patients with BD.[53] For these reasons, among others, smoking cessation should be a priority. Yet, in real clinical practice smoking cessation within patients remains difficult and not often encouraged for different reasons.[36] Clinicians and patients may fear to worsen the psychiatric disorder or the metabolic status (including weight gain),[11] patients with more severe BD may be more reluctant to quit than others due to, for example, reduced feeling of self-efficacy and BD patients tend to be heavier smokers than unaffected individuals.[46] Treating tobacco addiction in BD may thus require particular and intensive strategies. Such strategies have been evidenced to be acceptable and efficient,[28] especially during teachable moments such as cancer treatment.[51]

In conclusion, prospective studies are necessary to confirm our results and to assess causality of our findings (e.g., metabolic syndrome and smoking status). Nevertheless, this study stresses the necessity to encourage smoking cessation for BD individuals, especially since recent randomized controlled trials demonstrated efficacy and security of therapies for smoking cessation in these patients.[2,21,26] Our findings suggest that quitting smoking may be more difficult for the most severe patients, but that patients with BD as a group are expected to benefit from quitting regarding their psychiatric and metabolic health. As proposed by scholarly associations such as the RANZCP, smoking cessation should be systematically proposed to people suffering from BD.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13535.

## DATA AVAILABILITY STATEMENT

Due to ethical and legal restrictions, data involving clinical participants cannot be made publicly available. All relevant data are available upon request to the Fondation FondaMental for researchers who meet the criteria for access to confidential data.

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