Tobacco Smoking and Psychotic-Like Experiences in a General Population Sample

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ABSTRACT

Objective: Recent findings suggest an association between tobacco and psychosis, but whether this association is mediated by confounding factors is unknown. Psychosis-like experiences (PLEs) are a subclinical expression of psychosis. To disentangle the association of tobacco with PLEs, we examined data from a large US population–based, nationally representative sample.

Methods: Analysis was conducted on Wave 2 of the National Epidemiologic Survey of Alcohol and Related Conditions (N = 34,653 adults, conducted from 2004 to 2005). Participants were assessed with the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV. Twenty-two PLEs previously described as observed indicators of psychosis were used. Participants were stratified according to their smoking status (never/former/current) for 5 different types of tobacco.

Results: There was a significant association (ie, with 95% CIs for which the lower value was ≥ 1) between smoking status and 14 of the 22 assessed PLEs. These associations remained significant after adjustment for sociodemographic variables (including urbanicity or ethnicity), lifetime drug use disorder, and past-year cannabis use. While 26.33% of nonsmokers reported at least 1 PLE, this prevalence was slightly higher in former smokers (27.48%) and rose as high as 39.09% in current smokers (for current smokers vs lifetime abstainers, adjusted OR = 1.33; 95% CI, 1.23–1.45). All 22 PLEs had higher prevalence in smokers than in former smokers or lifetime abstainers. A total of 8.56% of smokers reported at least 5 PLEs, compared to 3.42% in lifetime abstainers (aOR = 1.56; 95% CI, 1.32–1.84).

Conclusions: In a large population-based, nationally representative sample, smoking status was associated with various PLEs. This association was not explained only by other known risk factors of PLEs or schizophrenia. There is a need to identify the potential neurobiological mechanisms by which smoking and PLEs are associated, for patients and from a public health perspective.

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Tobacco smoking is one of the main causes of premature mortality and is the primary cause of preventable disease and death.[1] People with psychosis are more likely to smoke than the general population.[2] It was initially hypothesized that people with psychosis, including schizophrenia, smoke to alleviate their symptoms, but recent findings challenge this self-medication hypothesis. Several prospective population-based studies[3,4] have found that cannabis use is associated with an increased risk of developing psychotic experiences and psychotic disorders later in life. The recent interest surrounding tobacco consumption in the assertion of psychotic experiences emerged from recent findings disentangling the links between schizophrenia and cannabis. The link between cannabis use and schizophrenia in longitudinal studies could indeed be partly explained by concurrent cigarette use.[5] Growing evidence suggests that cigarette smoking itself might be a risk factor for schizophrenia that is independent of the risk associated with cannabis use. The first case of psychosis induced by nicotine was reported in the 1990s (following the administration of transdermal nicotine patches).[6] More recently, in a prospective registry-based cohort study,[7] tobacco smoking predicted schizophrenia; this association was not explained by tobacco smoking onset during the prodromal period, and it showed a dose-response relationship. Daily tobacco use was prospectively associated with increased risk of psychosis and an earlier age at onset of psychotic illness in a meta-analysis.[8] Whether a causal link between tobacco use and psychosis exists and what is the direction of this link, if any, warrant further examination.

Psychotic-like experiences (PLEs) represent a subclinical expression of psychosis and would lie on a continuum with psychotic illness.[9] They are reported in nonclinical settings, including in the general population, with a median lifetime prevalence of 7.2%[10] (range, 1%[11] to 17.5%[12]). These findings indicate that a large part of the population may exhibit psychotic symptoms without meeting criteria for psychotic disorder. Nevertheless, PLEs are associated with an increased risk of later psychotic mental disorder,[13–15] even in non–help-seeking population-based samples.[16]

While numerous studies have examined the cross-sectional association of cannabis use with psychotic symptoms, some studies[5,7] have recently suggested that this association could be driven by tobacco consumption associated with cannabis use. To disentangle the association of substance use (including tobacco and cannabis) with PLEs, we examined the association between tobacco smoking and PLEs in

Clinical Points

- Recent studies suggest an association between tobacco and psychosis, but whether this association is mediated by usual confounding factors is unclear.
- The findings of the present study converge toward an association between tobacco use and psychotic-like experiences in the general population after adjustment for usual confounding variables. Longitudinal studies and preclinical studies are needed to confirm the causal role of this association.
- Smoking cessation should be encouraged in all patients, particularly those affected by the broad spectrum of psychosis, to improve both somatic and mental health.

a large US population–based, nationally representative sample, taking into account numerous confounding factors, including cannabis use.

METHODS

Sample

We analyzed cross-sectional data from the second wave of a population-based nationally representative sample, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).[17] NESARC Wave 2 is a face-to-face survey of 34,653 adults (response rate, 86.7%), aged 18 years and older from the civilian non-institutionalized population residing in the United States, conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) from 2004 to 2005. It was designed to be representative of the civilian, non-institutionalized adult population of the United States, including residents of the District of Columbia, Alaska, and Hawaii. Recruitment and informed consent procedures received full ethical review and approval from the US Census Bureau and the Office of Management and Budget. The NESARC oversampled black and Hispanic individuals and young adults. Data were adjusted for oversampling and household- and person-level nonresponse. The weighted data were then further adjusted to represent the civilian population in the United States based on the 2000 Decennial Census.[17] Characteristics of interviewers, training, and field quality control has been described elsewhere.[17,18]

Diagnostic Interview

Participants were assessed with the NIAAA's Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV).[19,20] The AUDADIS-IV is a fully structured, self-report diagnostic interview designed to be administered by clinicians or trained laypersons. It assesses various psychiatric disorders, including substance use disorders, with high reliability in general population samples.[19,20]

Measures

PLEs. The AUDADIS-IV includes 22 items assessing psychotic symptoms,[9] selected on the basis of their conceptual similarity with Positive and Negative Syndrome Scale (PANSS) items ().[21] These 22 items encompass the large groupings of positive, negative, mania, disorganization, and depression factors.[9] For example, "blunted affect" was assessed with the following question: "Have you had trouble expressing your emotions and feelings?"[9] The symptoms were assessed by trained laypersons, using direct questions in a fully structured interview.

Smoking status. The AUDADIS-IV asks questions separately about the following 5 different types of tobacco: cigarettes, cigars, pipe, snuff, and chewing tobacco. In the present study, participants were considered as current smokers if they used at least 1 type of tobacco in the 12 months prior to the Wave 2 interview. Participants were considered as former smokers if they did not use any type of tobacco in the 12 months prior to the Wave 2 interview, but did use 1 or more types of tobacco before. Participants were considered as lifetime abstainers if they did not use any type of tobacco in their lifetime.

Cannabis and drug/alcohol use disorders. The AUDADIS-IV included an extensive list of symptom questions that separately operationalized *DSM-IV* criteria for substance use disorders, including lifetime cannabis use disorder and lifetime drug use disorder involving alcohol, sedatives, tranquilizers, opiates (other than heroin or methadone), stimulants, hallucinogens, cocaine (including crack cocaine), and inhalants/solvents. The test-retest reliabilities of AUDADIS-IV alcohol and drug disorder measures were excellent, exceeding $\kappa = 0.74$ for alcohol diagnoses and $\kappa = 0.79$ for drug diagnoses.

Cannabis use characteristics. Respondents were grouped into 4 categories of cannabis use[22]: no use in the last 12 months, at least once a year but less than once a month, from once a month or more to twice per week, and from 3 days per week to every day.

Demographic and medical characteristics. We considered sociodemographic characteristics including sex, race/ethnicity, nativity, age, educational level, individual income, marital status, urbanicity, and region of residence. Race/ethnicity categories were white, black, Asian/Native Hawaiian/Pacific Islander, Hispanic/Latino, and American Indian/Alaska Native.

Nativity categories were US born and foreign born. Age at interview categories were 18–29, 30–44, 45–64, and ≥ 65 years. Educational levels were less than high school, high school, and some college or higher. Individual income was classified as $0–$19,999, $20,000–$34,999, $35,000–$69,999, or $70,000 or greater. Marital status groups were married or common-law; widowed, divorced, or separated; and never married. Urbanicity was classified as rural or urban. Region of residence was classified as Northeast, Midwest, South, or West.

Statistical analyses. Weighted prevalence estimates and standard errors (SEs) were computed using SUDAAN, version 11.0.1 (Research Triangle Park, NC). This software implements a Taylor linearization to adjust SEs of estimates for complex survey sampling design effects including

Table 1. Sociodemographic Characteristics in NESARC 2004–2005 According to Smoking Status[a]

Characteristic	Lifetime Abstainers (n = 18,356) %	SE	Former Smokers (n = 8,364) %	SE	Current Smokers (n = 7,933) %	SE	Current Smokers vs Former Smokers, OR (95% CI)	Current Smokers vs Lifetime Abstainers, OR (95% CI)
Sex								
Male	39.08	0.48	56.46	0.71	57.96	0.68	[reference]	[reference]
Female	60.92	0.48	43.54	0.71	42.04	0.68	0.94 (0.87–1.02)	**0.47 (0.44–0.50)**
Race/ethnicity								
White	64.66	1.99	79.35	1.3	75.58	1.10	[reference]	[reference]
Black	12.76	0.81	7.82	0.52	10.71	0.73	**1.44 (1.30–1.60)**	**0.72 (0.64–0.81)**
American Indian/Alaska Native	1.68	0.19	1.86	0.19	3.61	0.38	**2.04 (1.56–2.67)**	**1.83 (1.42–2.37)**
Asian/Native Hawaiian/Pacific Islander	6.09	0.68	2.47	0.44	2.25	0.38	0.96 (0.69–1.34)	**0.32 (0.25–0.40)**
Hispanic/Latino	14.81	1.61	8.51	0.87	7.85	0.69	0.97 (0.84–1.11)	**0.45 (0.38–0.53)**
Nativity								
US born	81.08	1.85	90.16	0.92	92.73	0.75	**1.39 (1.22–1.59)**	**2.97 (2.68–3.30)**
Foreign born	18.92	1.85	9.84	0.92	7.27	0.75	[reference]	[reference]
Age, y								
18–29	18.39	0.45	7.20	0.39	21.32	0.60	[reference]	[reference]
30–44	32.77	0.51	20.60	0.58	32.64	0.64	**0.54 (0.46–0.62)**	**0.86 (0.78–0.95)**
45–64	31.41	0.42	39.58	0.66	36.33	0.66	**0.31 (0.27–0.35)**	1.00 (0.91–1.10)
65+	17.43	0.46	32.61	0.68	9.72	0.36	**0.10 (0.09–0.12)**	**0.48 (0.42–0.55)**
Education								
Less than high school	5.87	0.39	5.89	0.40	4.57	0.30	[reference]	[reference]
High school	30.46	0.61	36.41	0.81	47.16	0.87	**1.67 (1.41–1.98)**	**1.99 (1.68–2.37)**
Some college or higher	63.69	0.78	57.69	0.86	48.28	0.89	1.08 (0.90–1.29)	0.97 (0.81–1.17)
Individual income, $								
0–19,999	39.66	0.71	35.52	0.74	42.81	0.79	[reference]	[reference]
20,000–34,999	23.21	0.45	24.68	0.62	25.89	0.60	**0.87 (0.79–0.96)**	1.03 (0.96–1.12)
35,000–69,999	25.34	0.54	27.34	0.66	23.81	0.65	**0.72 (0.65–0.80)**	**0.87 (0.80–0.95)**
≥ 70,000	11.80	0.57	12.46	0.66	7.49	0.46	**0.50 (0.43–0.58)**	**0.59 (0.51–0.68)**
Marital status								
Married/common-law married	64.33	0.67	69.84	0.62	56.46	0.72	[reference]	[reference]
Widowed/divorced/separated	16.40	0.35	20.72	0.47	22.20	0.52	**1.33 (1.21–1.45)**	**1.54 (1.42–1.67)**
Never married	19.27	0.57	9.44	0.44	21.35	0.70	**2.80 (2.49–3.14)**	**1.23 (1.16–1.38)**
Urbanicity								
Urban	83.66	0.58	83.41	0.73	84.06	0.69	[reference]	[reference]
Rural	16.34	0.58	16.59	0.73	15.94	0.69	0.95 (0.86–1.05)	0.97 (0.89–1.06)
Region of residence								
Northeast	17.59	1.32	17.74	1.16	18.20	1.15	[reference]	[reference]
Midwest	18.67	1.20	18.83	1.15	17.72	1.08	0.92 (0.81–1.04)	0.92 (0.80–1.05)
South	38.64	1.59	37.61	1.65	38.87	1.67	1.01 (0.90–1.12)	0.97 (0.87–1.09)
West	25.09	1.01	25.82	1.09	25.21	1.07	0.95 (0.84–1.08)	0.97 (0.85–1.11)

[a]Numbers are unweighted; percentages are weighted values. Significant differences are in bold.
Abbreviations: NESARC = National Epidemiologic Survey on Alcohol and Related Conditions, OR = odds ratio.

clustering data. Multivariate logistic regressions were conducted with simultaneous entry of sociodemographics and medical covariates. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are presented to reflect association strength and significance.

RESULTS

Sociodemographic Characteristics According to Smoking Status

Sociodemographic characteristics according to smoking status are presented in Table 1. Current smoking was more common in men than in women compared to lifetime abstaining. Odds of smoking were greater in participants born in the United States than in participants born outside the United States. Odds of smoking decreased with increasing income. The odds of smoking were greater in never married or widowed participants than in those currently married or living with a partner. The association of smoking status with race/ethnicity or educational level was inconsistent (Table 1).

Relationship Between PLEs and Smoking Status

There was an association between smoking status and 14 of the 22 assessed PLEs (Table 2). These associations remained significant after adjustment for age, sex, race/ethnicity, marital status, educational level, nativity, income, urbanicity, region of residence, lifetime drug use disorder, and cannabis use within the past 12 months (Model 1). As tobacco smoking in the United States is strongly associated with depression and alcohol use, we controlled for these variables in a second, more stringent model (Model 2).

While 26.33% of nonsmokers reported at least 1 PLE, this prevalence was slightly higher in former smokers (27.48%) and rose as high as 39.09% in current smokers. The severity, as reflected by the number of psychotic symptoms, was also different according to smoking status. For example, the frequency of reporting at least 5 psychotic symptoms

Table 2. Lifetime Prevalence of Psychotic Symptoms According to Tobacco Status[a]

Symptom	Lifetime Abstainers (n = 18,356) % (SE)	Former Smokers (n = 8.364) % (SE)	Current Smokers (n = 7,933) % (SE)	Current Smokers vs Lifetime Abstainers (Model 1[b]) AOR (95% CI)	Current Smokers vs Former Smokers (Model 1[b]) AOR (95% CI)	Current Smokers vs Lifetime Abstainers (Model 2[c]) AOR (95% CI)	Current Smokers vs Former Smokers (Model 2[c]) AOR (95% CI)
Delusions	0.29 (0.04)	0.36 (0.07)	0.72 (0.11)	1.60 (0.88–2.89)	1.55 (0.86–2.77)	1.34 (0.75–2.37)	1.50 (0.83–2.70)
Hallucinations	0.25 (0.05)	0.20 (0.06)	0.61 (0.11)	1.21 (0.64–2.26)	**1.95 (1.01–3.76)**	1.18 (0.65–2.15)	1.89 (0.98–3.64)
Grandiosity	2.19 (0.14)	3.00 (0.21)	3.85 (0.25)	**1.44 (1.14–1.81)**	1.09 (0.85–1.39)	**1.29 (1.03–1.61)**	1.06 (0.83–1.36)
Suspiciousness	2.02 (0.12)	1.99 (0.19)	4.44 (0.29)	**1.49 (1.21–1.84)**	**1.47 (1.14–1.91)**	**1.29 (1.04–1.59)**	**1.43 (1.10–1.86)**
Unusual thought	0.75 (0.08)	0.74 (0.11)	1.55 (0.15)	1.27 (0.92–1.76)	1.22 (0.82–1.82)	1.19 (0.85–1.65)	1.19 (0.80–1.79)
Blunted affect	4.38 (0.20)	4.37 (0.27)	7.41 (0.34)	1.12 (0.95–1.31)	**1.35 (1.14–1.61)**	0.98 (0.84–1.16)	**1.32 (1.11–1.57)**
Emotional withdrawal	2.86 (0.16)	2.72 (0.20)	6.58 (0.33)	**1.48 (1.24–1.75)**	**1.57 (1.29–1.91)**	**1.29 (1.08–1.53)**	**1.52 (1.24–1.86)**
Poor rapport	4.10 (0.21)	4.54 (0.25)	6.57 (0.34)	0.99 (0.82–1.18)	1.12 (0.94–1.34)	0.88 (0.73–1.05)	1.10 (0.92–1.31)
Passive social withdrawal	1.28 (0.11)	1.48 (0.15)	2.37 (0.23)	1.23 (0.88–1.70)	1.20 (0.84–1.70)	1.14 (0.82–1.59)	1.18 (0.83–1.67)
Motor retardation	4.95 (0.17)	4.57 (0.24)	7.33 (0.35)	**1.24 (1.05–1.46)**	**1.30 (1.09–1.55)**	1.12 (0.94–1.33)	**1.27 (1.05–1.54)**
Disturbance of volition	1.46 (0.11)	1.23 (0.26)	3.58 (0.12)	**1.75 (1.35–2.27)**	**2.08 (1.58–2.72)**	**1.60 (1.23–2.08)**	**2.03 (1.53–2.68)**
Active social withdrawal	4.06 (0.20)	3.59 (0.24)	5.97 (0.32)	1.13 (0.95–1.34)	1.13 (0.92–1.39)	1.03 (0.86–1.24)	1.10 (0.89–1.36)
Tension/anxiety	5.06 (0.22)	4.78 (0.27)	8.81 (0.39)	**1.51 (1.28–1.78)**	**1.48 (1.26–1.74)**	**1.37 (1.15–1.64)**	**1.46 (1.23–1.72)**
Guilt	6.41 (0.22)	5.49 (0.29)	11.55 (0.45)	**1.41 (1.23–1.61)**	**1.59 (1.37–1.86)**	**1.25 (1.08–1.44)**	**1.61 (1.36–1.91)**
Depression	5.81 (0.23)	5.37 (0.28)	10.90 (0.46)	**1.42 (1.24–1.63)**	**1.54 (1.32–1.79)**	**1.25 (1.07–1.45)**	**1.53 (1.30–1.81)**
Excitement	4.37 (0.21)	3.47 (0.22)	8.24 (0.35)	**1.48 (1.28–1.72)**	**1.60 (1.35–1.89)**	**1.39 (1.19–1.61)**	**1.57 (1.32–1.86)**
Hostility	5.04 (0.20)	6.08 (0.31)	11.77 (0.45)	**1.69 (1.46–1.96)**	**1.37 (1.18–1.60)**	**1.50 (1.29–1.75)**	**1.34 (1.15–1.57)**
Uncooperativeness	2.10 (0.13)	2.86 (0.23)	4.70 (0.30)	**1.34 (1.08–1.67)**	1.20 (0.94–1.52)	1.21 (0.97–1.50)	1.18 (0.92–1.50)
Impulsivity	3.34 (0.16)	4.95 (0.29)	7.73 (0.37)	**1.41 (1.20–1.65)**	**1.20 (1.02–1.42)**	**1.21 (1.03–1.42)**	1.17 (0.99–1.39)
Conceptual disorganization (1)[d]	1.15 (0.10)	1.06 (0.12)	2.00 (0.19)	1.04 (0.75–1.44)	1.27 (0.89–1.82)	0.91 (0.66–1.25)	1.24 (0.87–1.77)
Mannerisms and posturing	0.87 (0.08)	0.96 (0.12)	1.88 (0.18)	1.05 (0.76–1.45)	1.17 (0.81–1.70)	0.97 (0.70–1.34)	1.13 (0.78–1.65)
Conceptual disorganization (2)[d]	0.93 (0.09)	1.09 (0.14)	1.64 (0.16)	0.83 (0.59–1.18)	0.98 (0.68–1.41)	0.77 (0.55–1.06)	0.95 (0.66–1.37)
Exactly 1 of the aforementioned	12.75 (0.30)	13.31 (0.44)	15.43 (0.51)	**1.14 (1.03–1.27)**	1.12 (0.99–1.27)	1.07 (0.96–1.18)	1.11 (0.98–1.26)
Exactly 2 of the aforementioned	5.34 (0.20)	5.99 (0.30)	6.81 (0.29)	1.13 (0.99–1.30)	1.01 (0.86–1.20)	1.01 (0.87–1.16)	0.99 (0.83–1.17)
Exactly 3 of the aforementioned	4.91 (0.28)	3.06 (0.23)	3.12 (0.17)	1.18 (0.98–1.42)	**1.23 (1.00–1.51)**	1.06 (0.87–1.29)	1.20 (0.97–1.48)
Exactly 4 of the aforementioned	1.71 (0.12)	1.88 (0.15	3.28 (0.25)	**1.54 (1.17–2.01)**	**1.41 (1.09–1.82)**	**1.39 (1.06–1.81)**	**1.37 (1.07–1.77)**
Exactly 5 of the aforementioned	1.19 (0.09)	0.99 (0.13)	2.78 (0.24)	**1.81 (1.33–2.46)**	**1.86 (1.34–2.57)**	**1.64 (1.19–2.25)**	**1.79 (1.29–2.51)**
At least 1 of the aforementioned	26.33 (0.47)	27.48 (0.63)	39.09 (0.72)	**1.33 (1.23–1.45)**	**1.30 (1.19–1.42)**	**1.19 (1.09–1.30)**	**1.29 (1.18–1.42)**
At least 2 of the aforementioned	13.58 (0.34)	14.18 (0.45)	23.66 (0.60)	**1.37 (1.24–1.52)**	**1.34 (1.20–1.48)**	**1.22 (1.09–1.36)**	**1.33 (1.18–1.49)**
At least 3 of the aforementioned	8.24 (0.26)	8.18 (0.33)	16.85 (0.53)	**1.46 (1.30–1.65)**	**1.51 (1.33–1.70)**	**1.31 (1.16–1.49)**	**1.51 (1.32–1.72)**
At least 4 of the aforementioned	5.12 (0.19)	5.13 (0.27)	11.94 (0.49)	**1.58 (1.36–1.83)**	**1.61 (1.37–1.88)**	**1.41 (1.21–1.65)**	**1.60 (1.35–1.89)**
At least 5 of the aforementioned	3.42 (0.16)	3.24 (0.39)	8.56 (0.39)	**1.56 (1.32–1.84)**	**1.33 (1.38–2.00)**	**1.36 (1.14–1.61)**	**1.63 (1.34–1.98)**

[a]Numbers are unweighted, percentages are weighted values. Significant differences are in bold.
[b]Model 1: Adjusted for sex, race/ethnicity, nativity, age, educational level, income, marital status, urbanicity, region of residence, lifetime drug use disorder, and cannabis use frequency within the past 12 months.
[c]Model 2: Adjusted for sex, race/ethnicity, nativity, age, educational level, income, marital status, urbanicity, region of residence, lifetime drug use disorder, cannabis use frequency within the past 12 months, lifetime alcohol dependence, and lifetime depression.
[d]Conceptual disorganization was evaluated by 2 questions concerning ideas and appearance. Conceptual disorganization (1) was evaluated by the question, "Have people thought you have strange ideas?" while conceptual disorganization (2) was evaluated by the question, "Have people thought you are odd, eccentric, or strange?"
Abbreviation: AOR = adjusted odds ratio.

was similar in nonsmokers (3.42%) and in former smokers (3.24%), while the prevalence rose to 8.56% in current smokers.

All 22 PLEs had higher prevalence in smokers than in former smokers or lifetime abstainers. In Model 1, when current smokers were compared to lifetime abstainers, this association was significant in 12 of 22 tests. When current smokers were compared to former smokers, this association was also significant in 12 of 22 tests.

While smokers and former smokers reported higher odds of PLEs than nonsmokers, this difference was not straightforward when considering each symptom separately. The odds of hallucinations in current smokers were 1.95 times higher than in former smokers (95% CI, 1.01–3.76), but there was no significant difference between current smokers and lifetime abstainers (OR = 1.21; 95% CI, 0.64–2.26). Similarly, the odds of blunted affect were 1.35 times higher in current smokers than in former smokers (95% CI, 1.14–1.61), but again there was no significant difference between current smokers and lifetime abstainers (OR = 1.12; 95% CI, 0.95–1.31). When Model 1 was compared with Model 2 (which is more stringent), all associations observed in the Model 1 remained significant except for the items "uncooperativeness" and "hallucinations."

No relationship was found between smoking status and delusions, unusual thought, poor rapport, passive social withdrawal, active social withdrawal, conceptual disorganization, or mannerisms and posturing. Associations listed in Table 2 remained significant after correction for multiple testing.

DISCUSSION

We found evidence of a cross-sectional association between daily nicotine consumption and various psychotic symptoms in a large population-based nationally representative sample.

This association was not explained by usual confounding factors, including cannabis consumption, drug use disorder, urbanicity, or ethnicity. We showed a higher proportion of psychotic symptoms in current smokers in comparison to lifetime abstainers as well as former smokers. Current smoking was associated with higher odds of psychotic symptoms, but also with higher number of PLEs. This association remained significant after control for lifetime depression and alcohol use disorder, both of which are frequently associated with tobacco use in the United States.

Family status other than being married was associated with higher likelihood of current smoking. Higher likelihood of current smoking among divorced/widowed/never-married people was already reported in the older US population, probably underpinned by a lack of social support or a lack of incentives to stop smoking.[23]

The major finding of the present study is the association between daily nicotine consumption and various psychotic symptoms. Few studies have focused on the links between tobacco consumption and psychotic symptoms. Moreover, other studies have not allowed for distinguishing of different risk factors (use of self-report instrument rather than gold-standard face-to-face interview, absence of measure of cannabis use). In an 18-month longitudinal study assessing self-reported psychotic symptoms in the general population (1,795 participants for the two assessments), tobacco smoking was associated with a higher incidence of psychotic symptoms.[24] This association was not replicated in another, independent cohort,[25] although cannabis was still involved in a temporal association. The links between psychotic symptoms and smoking have been studied in the World Health Survey,[26] showing a strong association. However, symptoms were self-reported, with only 4 items covering the psychotic spectrum. More importantly, the lack of data did not allow taking into account major confounders, including cannabis use. Another study found an association between tobacco and delusional-like experiences (without dose-response effect).[27] One study[28] has examined the relationship between smoking status and psychotic experiences in the United States, using data from 3 large surveys of the US general population. The assessment of psychotic symptoms consisted of 6 questions. The current smokers had greater odds of reporting a lifetime psychotic experience when compared to never smokers, but this effect disappeared after control for co-occurring disorders (except in Asian Americans), indicating possible biological and non-biological factors subtending this heterogeneity in different ethnic groups.

Overall, our findings are broadly consistent with recent findings suggesting a possible link between nicotine and psychotic symptoms. The design of the study allows adjusting the findings for usual confounding factors (such as cannabis use, ethnicity, and urbanicity).

From a physiopathologic point of view, nicotine may have prodopaminergic effects by fixating on cholinergic/nicotinic receptors of dopaminergic neurons, both inducing "positive" symptoms in the mesolimbic system and decreasing "negative" symptoms in the mesocortical system.[29] Martin et al[30] have suggested that the high level of smoking associated with schizophrenia may be linked to abnormalities in the nicotinic-cholinergic system. These include abnormalities of regulation and expression of receptors, in numbers and functions, as well as alteration of regulation of nicotinic receptors in response to nicotine. The hypothesis of self-medication with tobacco assumes that patients with more psychotic symptoms would smoke to alleviate their symptoms. Actually, smoking often precedes the onset of the disease (from 49% to 90% of the time according to different studies),[31,32] and quitting smoking is not followed by a symptomatic exacerbation.[33–35]

Tobacco may be involved in the etiopathogeny of psychosis. Since experiencing PLEs is associated with an increased risk of later psychotic mental disorder, we could speculate a link between our findings and the subsequent risk of developing psychotic disorders, including schizophrenia. We also found a higher proportion of psychotic symptoms in current smokers compared to former smokers, suggesting that smoking cessation decreases the odds of reporting PLEs. In line with a recent study based on the general population of South London,[36] this finding may suggest the reversibility of the observed association between smoking and PLEs, at least in some participants and for some (but not all) PLEs. A recent PET study[37] found that tobacco smokers have impaired inflammatory functioning compared to nonsmokers and that constituents of tobacco smoke other than nicotine also affect inflammatory process. As many findings converge toward a key role of neuro-inflammation in mental diseases, especially psychosis,[38] we could speculate that PLEs are increased in smokers through the action of tobacco on microglia homeostasis at different stages of brain neurodevelopment. Finally, perturbations of nicotinic acetylcholine receptors that regulate critical facets of the brain maturation might be irreversible only during adolescence.[39] Overall, different biological explanations could account for part of our findings, and further clinical and preclinical research is needed.

Several limitations should be considered. First, similar to many previous general population-based surveys, homeless, incarcerated, or institutionalized persons were not included. However, data were adjusted to represent the civilian population in the United States based on the 2000 Decennial Census.[17] Moreover, since tobacco smoking and psychosis are more prevalent in these populations,[40–42] our results are likely to underestimate the strength of the association between tobacco smoking and PLEs. Second, due to the cross-sectional nature of the study, it is impossible to draw any conclusions on factors involved in tobacco consumption and/or PLEs or to impute any causal link. The design precludes any temporal association between smoking and experiencing PLEs, and while smoking usually precedes PLEs, it is at least possible that some participants with PLEs use tobacco to diminish anxiety. We cannot exclude that subthreshold psychosis precedes smoking. Prospective studies are needed to confirm a potential causal link between

tobacco and PLEs. Preclinical study may also be contributive. Third, information on smoking habits was self-reported and was not validated by testing biomarkers, including cotinine blood or urine levels. Thus, possible differential misclassification by sex, ethnicity, and other characteristics cannot be excluded. However, the study sample was large and representative, and the high consent rate provided high precision and external validity to our study results. The large set of social characteristics on which data were collected allowed us to study characteristics that are significantly and independently associated with smoking, after controlling for other closely related variables. Finally, interviews were conducted by lay interviewers. It is therefore possible that clinician-based interviews could have led to different results. However, the reliability (κ) for psychiatric diagnoses ranges from moderate to high and is similar to that of clinician-administered interviews.

CONCLUSION

In conclusion, in a large population-based, nationally representative sample, daily nicotine consumption was associated with various psychotic symptoms. Further longitudinal study is required to confirm our findings. Tobacco smoking is a potent and modifiable cause of morbidity, but its prevalence is still elevated in people with mental health problems compared with those without them. There is a need to identify the potential neurobiological mechanisms by which smoking and PLEs are associated, for patients and from a public health perspective.

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