Sleep Medicine:X 6 (2023) 100085

Contents lists available at ScienceDirect

Sleep Medicine: X

journal homepage: www.sciencedirect.com/journal/sleep-medicine-x

Effects of smoking on sleep architecture and ventilatory parameters including apneas: Results of the Tab-OSA study

Sibylle Mauries [a,*], Léa Bertrand [a], Justine Frija-Masson [c,d], Hélène Benzaquen [d], Sophie Kalamarides [f], Karine Sauvage [a], Michel Lejoyeux [a,b], Marie-Pia d'Ortho [c,d], Pierre A. Geoffroy [a,b,c,e,f,**]

[a] Département de Psychiatrie et d'addictologie, AP-HP, GHU Paris Nord, DMU Neurosciences, Hôpital Bichat - Claude Bernard, 46 rue Henri Huchard, 75018, Paris, France
[b] GHU Paris - Psychiatry & Neurosciences, 1 rue Cabanis, 75014, Paris, France
[c] Université de Paris, NeuroDiderot, Inserm, U1141, 48 boulevard Sérurier, 75019, Paris, France
[d] Explorations Fonctionnelles et Centre du Sommeil- Département de Physiologie Clinique, Assistance Publique des Hôpitaux de Paris, GHU Paris Nord, DMU DREAM, Hôpital Bichat, 46 rue Henri Huchard, 75018, Paris, France
[e] CNRS UPR 3212, Institute for Cellular and Integrative Neurosciences, 5 rue Blaise Pascal, 67000, Strasbourg, France
[f] Département de Psychiatrie et d'addictologie, AP-HP, GHU Paris Nord, DMU Neurosciences, Hôpital Beaujon, 100 boulevard Général Leclerc, 92110, Clichy, France

ARTICLE INFO

Keywords:
Sleep parameters
Obstructive sleep apnea syndrome
Tobacco
Smoking
Polysomnography
Sleep architecture

ABSTRACT

Background: The interaction between smoking and sleep seems appears to be bidirectional, but few studies evaluated the impact of smoking and its cessation on objective sleep parameters. In this context, this new study aimed to assess the impact of smoking and its cessation on sleep architecture and on ventilatory sleep parameters, particularly the presence of sleep apnea syndrome (apnea-hypopnea index (AHI)≥15). Methods: Patients hospitalized for polysomnographic sleep exploration were compared according to their smoking status: active smokers (AS), former smokers (FS), non-smokers (NoNi). Psychiatric and non-psychiatric co-morbidities and treatment or substance use were taken into account in the analyses.
Results: A total of 170 participants were included (N = 37 FS, 39 AS, 86 NoNi). A significant decrease in the mean nocturnal O_2 saturation was observed for FS and AS compared to NoNi. No differences were found regarding AHI. Regarding sleep architecture, we observed a significant decrease in the slow wave sleep duration for AS compared to NoNi, and interestingly not between FS and NoNi.
Conclusion: This study suggests that current smokers suffer from alterations in both sleep architecture and ventilatory parameters, the later appears to persist even after smoking cessation.

1. Introduction

With more than 8 million deaths attributable to tobacco [1], smoking remains the leading cause of preventable death worldwide [2]. Nicotine, the main active component of cigarettes, is highly addictive [3]. Nicotine is an alkaloid that acts on synapses of the parasympathetic and sympathetic nodes [4], binding to muscarinic and nicotinic receptors in the central nervous system, increasing the availability of dopamine and other neurotransmitters such as adrenaline, noradrenaline, and serotonin [4], activating the reward system [5]. On a cognitive and behavioral level, the nicotine has a psychostimulant effect [6]. However, nicotine also has several adverse effects, such as a negative impact on sleep quality and architecture. It increases sleep onset latency, decreases sleep efficiency and duration [7], and increases the production of abnormal or intense dreams [8].

Sleep disorders are a common problem, affecting 6%–15% of the general population [9]. Alterations in sleep quality or duration can have consequences for mental health [10]. The prevalence of tobacco use among individuals with reduced (<5 h) or increased (>9 h) sleep is high, affecting 27% and 21% of the population respectively [10]. The

* Corresponding author. University Hospital Bichat-Claude Bernard Department of Psychiatry and Addictive Medicine 46 rue Henri Huchard, 75018, Paris, France.
** Corresponding author. Département de Psychiatrie et d'addictologie, AP-HP, GHU Paris Nord, DMU Neurosciences, Hôpital Bichat - Claude Bernard, 46 rue Henri Huchard, 75018, Paris, France.
E-mail address: sib.mauries@gmail.com (S. Mauries).

https://doi.org/10.1016/j.sleepx.2023.100085
Received 13 June 2023; Received in revised form 6 September 2023; Accepted 6 September 2023
Available online 7 September 2023

relationships between addiction and sleep disturbances appears to be bidirectional, with both maintaining and worsening each disorder [11, 12].

Smoking cessation appears to acutely alter sleep quality and sleep architecture, resulting in frequent complaints of insomnia [13], estimated to occur in 19.7%–40.3% of cases [14]. In long-term smoking cessation, studies have shown a reduction in sleep latency and slow-wave sleep, while the percentage of REM sleep is increased [15, 16]. However, most longitudinal studies of smoking cessation, are pharmacological efficacy studies of abstinence maintenance [17], where sleep disturbances are self-reported or assessed with questionnaires. Very few studies used objective biomarkers such as polysomnography (PSG). While some studies have found a decrease in deep slow-wave sleep (N3) compared to light slow-wave sleep (N1, N2) in smokers compared to non-smokers [18]. While other authors have found no difference between former, current and non-smokers [19].

In addition, associations between sleep-disordered breathing and tobacco use have been suggested. Obstructive sleep apnea syndrome (OSA), is a chronic and common disorder characterized by a limitation (hypopnea) or cessation (apnea) of respiratory flow during sleep, leading to episodes of hypercapnia, hypoxia and nocturnal awakenings [20, 21]. It is estimated that up to 425 million people worldwide are affected [22] and recent figures in France show a 20% prevalence in the general population [23]. OSA is diagnosed clinically, with confirmation by PSG or ventilatory polygraphy. It is defined by an Apnea-Hypopnea index (AHI) $\geq$15/hour associated with symptoms or comorbidity [24]. OSA has multiple consequences, including an increased risk of daytime sleepiness [25], cognitive impairment [26], and worsening of psychiatric disorders such as depression [27]. Risk factors include obesity, male gender, and age [21]. Additionally, the interactions between OSA and cardiovascular diseases are bidirectional, with an increased risk of developing hypertension or coronary heart disease [21,28]. Interestingly, some studies identify a strong link between smoking and OSA. A large cross-sectional study of 811 participants showed a statistically higher risk of OSA (OR = 4.44), confirmed with PSG, in smokers compared to controls [29]. More recently, data obtained in the French general population confirmed that OSA was more frequent in current smokers [23]. The pathophysiological hypotheses explaining this link remain debated. Some authors suggest that an increase in inflammation of the upper airways, demonstrated by biopsy of uvular mucosa lamina propria [30], could be the origin of a decrease in the diameter of the airways. Others suggest that the nicotine withdrawal may lead to an increase in sleep-disordered breathing through a decrease in the tone of the upper airways [31–33]. All these hypotheses are not mutually exclusive and may combine at the individual level. It is worth noting that only two articles have focused on polysomnographic parameters of patients on nicotine replacement therapy, and none have reported results of sleep ventilatory parameters in participants [34,35]. Additionally, no studies have compared polysomnographic parameters (EEG and respiratory parameters) in individuals with different smoking status (without history of nicotine addiction, active smoker, former smoker or individuals with nicotine substitute use). Thus, further well controlled studies are required to clarify these relationships.

In this context, we hypothesize that nicotine has an impact on sleep ventilatory parameters and sleep architecture, and that nicotine cessation improves both parameters. Therefore, the primary objective of this study is to compare the OSA prevalence between a group of patients with chronic tobacco use and a group with no history of nicotine addiction. The secondary objectives are: i) to compare the sleep architecture and ventilatory parameters of 3 groups of patients: patients with active smoking (AS) or former smokers (FS) or without any history of nicotine addiction whatever its form (NoNi); ii) to compare the impact of patients' smoking status on sleep-disordered breathing and associated clinical characteristics.

2. Materials and methods

2.1. Study design

This study is monocentric cross-sectional on a naturalistic cohort of patients receiving routine care at the sleep center of the Bichat Hospital between November 2019 and May 2021. Patient data was collected as part of a prospective data collection process in usual care setting.

2.2. Population

Regarding the inclusion criteria, participants were adult who had been hospitalized for one or more nights at the sleep center for evaluation of a sleep disorder, and had undergone a PSG. Patients were referred to the sleep center to diagnose apnea-hypopnea syndrome, parasomnia or to characterize hypersomnia or insomnia complaints, regardless of whether they had a previous diagnosis of sleep disorder. They had to be fluent in French and agree to participate in the study. Additionally, they had to be over 18 years old and not have legal protection (guardianship or curatorship). Non-inclusion criteria included: current treatment of OSA (any form of positive airway pressure), low tobacco use (<1 time per day) that could be classified neither as smokers nor as non-smokers, tobacco use through means other than industrial cigarettes (which would have resulted in too much variability in the amount of nicotine ingested between participants), and missing data.

After their smoking status was collected, individuals were divided into 3 groups: AS, FS and NoNi (former smokers had to have quit smoking at least one year previously). A trained physician directly from patients collected data, alongside from computerized medical records.

2.3. Polysomnography

Individuals underwent PSG (Alice 5 software, Philips- Respironics, Suresnes, France or Micromed Système Plus Evolution, Italy) for one or more nights. The recorded parameters, according included electroencephalogram (EEG) with six channels (F3A2, F4A1, C3A2, C4A1, O1A2, O2A1), electro-oculogram (EOG) on the right and left, chin electromyogram (EMG), anterior tibial electromyogram and an electrocardiogram (ECG). Respiratory recording included nasobuccal flow recording by nasal cannula and oral thermistor, thoracic and abdominal movements by inductance plethysmography and oxygen saturation by finger pulse oximetry. Sleep stages were manually scored according to the AASM 2012 criteria [36].

The primary outcome was the presence of OSA syndrome, defined as an AHI $\geq$15/hour.

Secondary outcome criteria included polysomnographic data, clinical characteristics and results of questionnaires as described below.

2.3.1. Polysomnographic parameters

Polysomnographic parameters included an assessment of sleep architecture and the following ventilatory parameters: sleep stages (percentage, duration and latency), total sleep time (TST) and sleep efficiency (SE), obstructive, central and mixed or indeterminate apnea and hypopnea index, number of arousals, wake after sleep onset (WASO), microarousals and respiratory microarousals index, mean sleep saturation (mean SpO2), saturation below 90% (CT90), 3% desaturation index of more than 3/h, percentage of snoring, periodic leg movements (>15/Hour), spontaneous time of awakening, loss of muscular atonia in REM sleep, and final diagnosis of sleep pathology.

2.3.2. Clinical characteristics

The clinical characteristics included were age, sex, body mass index (BMI), medical history, including psychiatric, neurological and sleep disorders history together with COPD presence and severity if relevant, as diagnosed by pulmonologists (and when available PFT was also collected), disorders commonly associated with OSA (such as

cardiovascular diseases, dyslipidemia and type 2 diabetes), history of OSA treatments (otolaryngology and bariatric surgery), and pathology that could worsen OSA (such respiratory allergies, history of Covid-19 infection, and stroke). Additionally, information was collected on treatments (psychiatric and sleep) and substance use disorder (including cannabis, alcohol, opiates, and hallucinogens) that could impact sleep architecture (Table S4).

2.3.3. Questionnaires

We assessed the severity of tobacco dependence using the Fagerström Test [37], and collected data on the age of first cigarette, duration and daily quantity of consumption. To evaluate subjective sleep complaints and the severity of sleep disturbances, we used self-administered questionnaires such as the Insomnia Severity Index (ISI) [38], Pittsburgh Sleep Quality Index (PSQI) [39] and Epworth Sleepiness Scale (ESS) [40]. We identified the participants'seasonal pattern using the Seasonal Pattern Assessment Questionnaire (SPAQ) [41]. The participants' psychiatric disorders were evaluated using standardized scales such as the Center for Epidemiologic Studies-Depression (CES-D) [42] and the Montgomery-Åsberg Depression Rating Scale (MADRS) [43] for depression; the State-Trait Anxiety Inventory (STAI-Y) [44] or anxiety symptoms and the Positive and Negative Syndrome Scale (PANSS) [45] for psychotic symptoms. We also used, the Mannheim Dream Questionnaire (MADRE) [46] to determine the main characteristics of the participants' dreams over the past year (Table S4).

2.4. Statistical analyses

To achieve the main objective, the number of subjects needed to be included per group was 40 participants with an alpha risk of 0.05 and a statistical power of 90% and using a two-tailed test. A descriptive analysis was conducted for all collected parameters. Continuous variables were presented as means and standard deviations, while binary variables were described using absolute numbers and percentages. The comparison of sleep parameters, psychiatrics symptoms and clinical characteristics within and between smoking status was performed using univariate and multivariate analyses. For continuous variables, the normal distribution was tested using the Shapiro-Wilk test, and variance equality was tested using the Levene test. To compare results between subgroups, we used Chi2 test for categorical variables, and the Mann-Whitney U *t*-test for continuous variables with non-normal distribution, and the Student's t-test for normal distribution. In multivariate analyses, we used binomial logistic regression to adjust for confounding factors. For ventilatory sleep parameters, we adjusted for known confounders, such as age, BMI and sex, which have been shown to be associated with AHI [21]. For sleep architecture parameters, we adjusted for factors known to affect sleep architecture, such as age, BMI, sex [47], alcohol use [48], antidepressant use [49], depressive symptoms at the time of assessment (MADRS $\geq$ 15) [50], apnea with AHI $\geq$ 15/h [51] and PLM $\geq$ 15/h [52]).

Statistical analyses were performed using Jamovi 1.0.5 software, and a significance level of 0.05 was used for all analyses.

2.4.1. Ethical considerations

The study was conducted in according with the Jardé law, wich regulates research in France since 2017, and was approved by institutional and ethical committees (Institutional Review Board -IRB 00006477- of HUPNVS, Paris 7 University, AP-HP). As the analysis was conducted on data from routine care, no consent was required for participation, only the absence of opposition. However, participants received a briefing note describing the objectives of the study.

3. Results

Out of the 251 participants screened, 162 were included in the analyses after ensuring they met the inclusion and non-inclusion criteria (Fig. 1). The mean age of the participants was 51.2 years old (SD = 14.4), with a mean BMI of 27.7 kg/m^2(SD = 6.07), and 50% of the participants were men. The participants were divided into three groups as follows: 37 FS, 39 AS and 86 NoNi.

3.1. Population and socio-demographic characteristics

Regarding gender, a significantly higher proportion of men was observed in the FS group compared to the NoNi ($p < 0.001$) and AS ($p < 0.001$) groups. The FS group was significantly older compared the other two groups (FS vs NoNi $p = 0.008$ and FS vs AS $p = 0.002$). In terms of smoking behavior, all participants generally had low nicotine dependence based on Fagerström Test and the FS group had a significantly higher past daily cigarette consumption compared to the current daily consumption of the AS group ($p < 0.001$). Participants in the FS group had a mean abstinence period of 18 years (18.1) (Table 1 and Table S1).

3.2. Medical history and current treatments

In terms of medical history, the AS group had a significantly higher frequency of major depressive episode ($p = 0.046$) and of bipolar disorder ($p = 0.032$) compared to the NoNi group. Meanwhile, some patients had already undergone a PSG. The FS group had a significantly higher frequency of central sleep apnea (CSA) ($p = 0.032$), mixed sleep apnea (MSA) ($p = 0.034$). Not surprisingly AS and FS presented more often COPD compared to the NoNi group (respectively p 0.009 and $p < 0.001$) but there was no significant difference in COPD severity between AS and FS groups (FEV1 <80%: AS *vs* FS: $p = 0.206$).

Regarding usual treatments, the AS group were more frequently treated with antidepressants such as Serotonin and noradrenaline reuptake inhibitors (SNRI) ($p = 0.043$), benzodiazepines ($p = 0.023$), melatonin ($p = 0.028$) or 2nd generation antipsychotic drugs ($p = 0.017$) compared to the NoNi group (Table S1).

3.3. Consumption of psychoactive substances

Regarding the consumption of other substances patients of the FS and AS groups had a significantly higher consumption of alcohol (respectively $p = 0.003$ and $p = 0.002$) and cannabis ($p = 0.032$; AS *vs* NoNi: $p < 0.001$ *vs* NoNi: $p = 0.008$) compared to the NoNi group (Table S1).

3.4. Psychiatric symptoms

The AS group had a higher frequency of depressive symptoms compared to both FS and NoNi groups (AS *vs* FS: $p = 0.004$ and AS *vs* NoNi: $p = 0.001$), as well as a higher incidence of suicidal ideation in the past (AS *vs* NoNi: $p = 0.022$), and a more psychotic symptoms without a diagnosis of psychotic disorder (PANSS mostly lower than 40 in all groups) (AS *vs* FS: 0.046 and AS *vs* NoNi: $p = 0.006$). No significant differences were observed between groups regarding anxiety symptoms or history of suicidal behavior (Table S2). Additionally, we observed a higher prevalence of seasonal affective disorders (SPAQ $\geq$ 11) in the AS group compared to the NoNi group ($p = 0.047$) (Table S3).

3.5. Subjective evaluation of sleep

The AS group had shorter estimated sleep duration compared to the NoNi and the FS groups (AS *vs* FS: $p = 0.006$ and AS *vs* NoNi: $p = 0.020$), as well as more sleep disturbances (PSQI total score >5) compared to the FS group ($p = 0.020$).

3.6. Sleep ventilatory parameters

Regarding our primary endpoint, which is the OSA prevalence

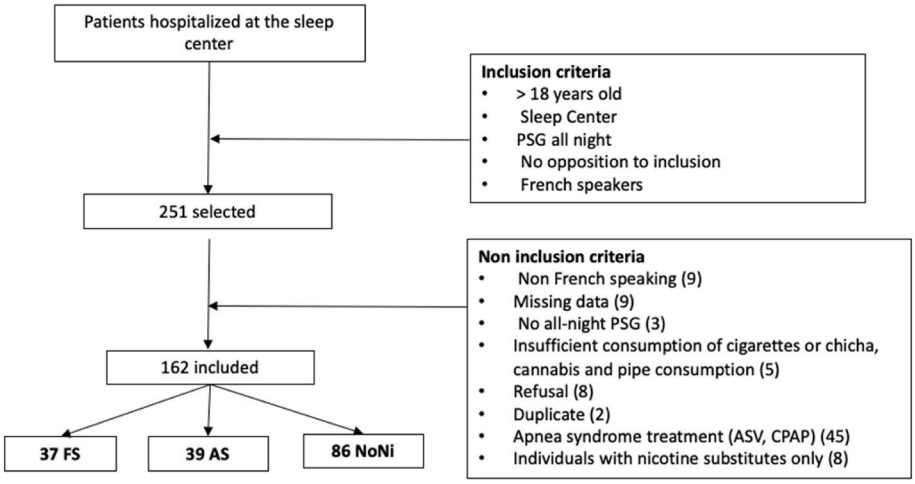

Fig. 1. Flow Chart. *AS = Active smoker; ASV = Adaptative servo-ventilation; CPAP = Continuous Positive Airway Pressure; FS = Former smoker; NoNi = Individuals* without any history of nicotine addiction*; PSG = Polysomnography; (n) = excluded individuals*.

Table 1
Socio-demographic data.

	FS (n = 37)	AS (n = 39)	NoNi (n = 86)	FS vs NoNi		AS vs Noni		FS vs AS	
	n(%)-means (SD)			Chi^2-MWU-Std	p1	Chi^2-MWU-Std	p2	Chi^2-MWU-Std	p5
Sex rowhead									
Men (n)	32 (86.5%)	20 (51.3%)	31 (36.0%)	26.3	**<0.001**	2.58	0.108	10.9	**<0.001**
Age (years)	57.7 (12.8)	48.1 (13.8)	50.2 (14.5)	2.70	**0.008**	−0.763	0.447	3.13	**0.002**
BMI (kg/m^2)	27.4 (4.86)	28.0 (7.03)	27.8 (6.33)	1525	0.980	1526	0.798	654	0.895
Smoking rowhead									
1st cigarette (age, years)	16.5 (3.69)	16.1 (3.09)	/	/	/	/	/	578	0.440
Time smoking (years)	26.8 (14.6)	32.4 (15.2)	/	/	/	/	/	−1.58	0.119
lenght of abstinence (years)	18.0 (18.1)	/	/	/	/	/	/	/	/
Cigarettes/day	22.5 (12.9)	8.21 (5.56)		/	/	/	/	215	**<0.001**
Year-pack	30.3 (24.8)	13.9 (13.2)	/	/	/	/	/	74	**<0.001**
Fagerstrom test rowhead									
No dependance	36 (97.3%)	15 (38.5%)	86 (100.0%)	/	/	/	/	29.9	**<0.001**
light	1 (2.7%)	12 (30.8%)	0 (0.0%)						
Moderate	0 (0.0%)	9 (23.1%)	0 (0.0%)						
Severe	0 (0.0%)	3 (7.7%)	0 (0.0%)						
Nicotine substitutes rowhead									
None	37 (100.0%)	31 (79.5%)	86 (100.0%)	/	/	/	/	/	/
E-cigarette	0 (0.0%)	4 (10.3%)	0 (0.0%)						
E-cigarette + Gum	0 (0.0%)	0 (0.0%)	0 (0.0%)						
Gum	0 (0.0%)	0 (0.0%)	0 (0.0%)						
Nicopass	0 (0.0%)	1 (2.6%)	0 (0.0%)						
Patch	0 (0.0%)	2 (5.1%)	0 (0.0%)						
Patch + Gum	0 (0.0%)	1 (2.6%)	0 (0.0%)						

AS =Active smoker; FS= Former smoker; MWU = Mann Withney U; NoNi=No nicotine use.
Statistically significant results in bold.
(*) Correction for the following factors: Age, gender; BMI.

defined by an AHI ≥ 15/h, there were no statically significant differences between the three groups. After adjusting for confounding factor, the FS group had lower average saturation during the night (mean SpO_2) compared to the NoNi and AS groups (FS *vs* NoNi: p = 0.016 and FS *vs* AS: p = 0.015), and saturation below 90% was more frequent in the FS group (FS *vs* NoNi: p = 0.009) (Table 2).

3.7. Sleep architecture

After adjusting for confounding factors, we observed a significant reduction in the duration of N3 sleep stage in the AS group compared to the NoNi group (p = 0.049). No differences regarding other sleep stages were found, especially REM sleep duration and structure (duration of first episode). (Table 3).

4. Discussion

In this new, which included a large population of 170 participants and compared different tobacco use statuses, we found interesting results. This study addressed effects of smoking on sleep architecture and OSA, based on polysomnography, in a large population of 170 participants. No difference in OSA prevalence was found. The mean SpO_2 was lower in former smokers than in active smokers and in non-smokers, in addition time spent with SpO_2 below 90% was longerformer smokers than in active smokers and non-smokers. Regarding the characteristics of sleep architecture, we found a decrease in N3 duration in active smokers compared to non-smokers and reported, that former smokers had comparable sleep architecture than non-smokers, suggesting a recovery.

Table 2
Sleep ventilatory parameters.

	FS (n = 37)	AS (n = 39)	NoNi (n = 86)	FS vs NoNi			AS vs Noni			FS vs AS		
	n(%)-means (SD)			Chi^2-MWU-Std	p1	p1[a]	Chi^2-MWU-Std	p2	p2[a]	Chi^2-MWU-Std	p5	p5[a]
Obstructive apnea (IAHo)	7.76 (12.2)	4.91 (13.2)	3.62 (7.52)	1352	0.184	0.289	1533	0.438	0.610	576	0.128	0.464
Central apnea (IAHc)	3.04 (7.42)	0.772 (2.11)	0.794 (2.40)	1558	0.848	0.433	1659	0.921	0.840	709	0.888	0.458
Mixed apnea (IAHm)	1.13 (3.56)	0.954 (3.75)	0.298 (1.10)	1455	0.332	0.284	1607	0.612	0.255	644	0.280	0.990
AHI total (index)	27.8 (23.5)	22.8 (28.1)	17.9 (16.0)	1269	0.076	0.498	1643	0.856	0.210	605	0.228	0.524
AHI ≥ 15 (index)	22 (59.5%)	21 (53.8%)	43 (50.0%)	0.929	0.335	0.281	0.159	0.690	0.631	0.244	0.622	0.070
mean SpO_2 (%)	92.5 (2.24)	93.4 (2.53)	94.3 (2.06)	775	**<0.001**	**0.016**	1197	**0.021**	**0.015**	513	**0.046**	0.843
CT90 (%)	16.3 (23.3)	7.31 (17.6)	3.44 (9.81)	923	**<0.001**	**0.009**	1423	0.203	0.087	512	**0.044**	0.423
Desaturation (index)	23.5 (24.7)	18.7 (28.8)	12.0 (15.8)	1165	**0.038**	0.278	1481	0.342	0.079	605	0.306	0.162
Microarousal (index)	20.0 (11.7)	20.9 (17.5)	16.2 (9.10)	1275	0.081	0.675	1489	0.318	0.087	672	0.607	0.240
Microarousal respi. (Index)	12.6 (11.3)	11.5 (16.0)	9.21 (8.09)	1373	0.230	0.925	1674	0.989	0.409	634	0.363	0.500
Snoring	3.17 (1.56)	2.94 (1.41)	2.72 (1.34)	1226	0.170	0.230	1361	0.431	0.313	581	0.569	0.763
PLM≥15 (n)	7 (18.9%)	6 (16.2%)	12 (14.0%)	0.488	0.485	0.705	0.106	0.745	0.650	0.0933	0.760	0.198

AHI = Apnea hypopnea index; AS =Active smoker; CT90 = Desaturation under 90%; FS= Former smoker; MWU = Mann Withney U; NoNi=No nicotine use; NS= Nicotine substitutes; PLM = Periodic leg movement; SPO2 = Mean saturation; Stud = Student-test.
Statistically significant results in bold.
[a] Correction for the following factors: Age, gender; BMI.

Table 3
AHI = Apnea hypopnea index; AS =Active smoker; CT = Desaturation under 90%; FS= Former smoker; MWU = Mann Withney U; N= Slow wave sleep; NoNi=No nicotine use; PLM = Periodic leg movement; REM = *Rapid eye movement; SpO_2 = Mean saturation; Stud = Student-test; TST = Total Sleep time; WASO =Wake time after sleep onset.*

	FS (n = 37)	AS (n = 39)	NoNi (n = 86)	FS vs NoNi			AS vs Noni			FS vs AS		
	n(%)-means (SD)			Chi^2-MWU-Std	p1	p1[a]	Chi^2-MWU-Std	p2	p2[a]	Chi^2-MWU-Std	p5	p5[a]
N1 (duration)	52.7 (28.6)	59.5 (39.3)	45.8 (27.2)	1333	0.155	0.860	1377	0.110	0.246	680	0.670	0.230
N1 (%)	15.2 (8.43)	16.4 (12.0)	12.6 (7.90)	1275	0.081	0.593	1405	0.147	0.219	720	0.988	0.439
N1 latency (min)	26.8 (27.5)	29.1 (34.6)	20.2 (17.0)	1475	0.522	0.539	1567	0.560	0.886	704	0.856	0.750
N2 duration (min)	157 (50.4)	160 (82.0)	163 (53.2)	−0.595	0.553	0.718	1455	0.238	0.491	672	0.611	0.829
N3 duration (min)	87.9 (40.9)	89.3 (71.1)	97.1 (43.3)	1386	0.258	0.850	1365	0.097	**0.049**	685	0.704	0.162
REM duration (min)	79.7 (39.8)	78.1 (48.9)	80.9 (43.1)	1571	0.914	0.623	1572	0.576	0.722	684	0.697	0.758
REM (%)	20.3 (7.76)	19.5 (9.76)	20.4 (6.99)	1568	0.901	0.433	1594	0.660	0.990	0.394	0.695	0.721
REM latency (min)	109 (58.3)	127 (103)	118 (92.1)	1541	0.783	0.218	1593	0.656	0.634	685	0.708	0.242
1st REM duration (min)	19.7 (14.7)	18.4 (11.2)	19.2 (12.0)	1552	0.832	0.914	1642	0.854	0.764	710	0.905	0.726
TST (min)	378 (83.4)	388 (158)	390 (72.1))	1497	0.604	0.953	1488	0.315	0.943	699	0.815	0.883
Efficiency (%)	81.3 (12.0)	80.8 (14.3)	83.8 (10.9)	1417	0.339	0.826	1537	0.457	0.763	717	0.963	0.731
WASO (min)	56.6 (49.1)	58.0 (58.7)	51.8 (51.5)	1469	0.503	0.139	1498	0.341	0.551	714	0.938	0.372

Statistically significant results in bold.
[a] Correction for the following factors: Age, gender; BMI, AHI ≥ 15, PLM ≥ 15/H; MADRS ≥ 15; alcohol consumption, antidepressant treatment.

Our study population of current and former smokers had comparable socio-demographic characteristics to those reported in previous studies. As expected, we found that AS and FS were more frequently men [53] with a mean age of approximately 50 years [54,55]. Regarding medical history and comorbidities, we found not surprisingly that AS and FS were more likely to have a diagnosis of COPD [56], and that AS were more likely to have a history of depression or bipolar disorder and depressive symptoms at the time of assessment [57]. Additionally, AS and FS were more commonly associated with cannabis or alcohol use in accordance with previous literature [58,59].

Regarding sleep ventilatory parameters, we observed a decrease in the mean saturation and an increase in time spent with SpO_2 below 90% in current and former smokers, compared to non-smokers, along with previous results reported by Conway et al. [60] and with increased prevalence of COPD in those two groups. Regarding AHI, we observed a trend towards an increase in AHI for FS compared to AS, who themselves had a higher index compared than No–Ni individuals. This non-significant observation suggests that smoking may have a small impact of smoking on AHI, which may explain the controversy and lack of replication in previous studies. Some studies have shown that AS had a significantly higher AHI compared to NoNi [60,61] and that FS had a significantly higher AHI compared to NoNi [60]. However, other authors, such as Jaehne et al., did not confirm these associations after 3 months of smoking cessation without substitutes [62]. Futhermore, some authors have reported a decrease in sleep fragmentation in participants using nicotine substitutes [33].

Our results confirmed a decrease in the duration of N3 for the AS [18], compared to the NoNi group, but not for the FS group who might have recover their N3 sleep after nicotine cessation [7,63]. With regards to REM sleep, previous studies have shown a reduction in REM sleep duration for AS and an increase for FS [63]. However, our study did not confirm these results and rather tended to observe a decrease in REM sleep duration for both AS and FS. In line with this, we also observe an increase in the sleep latency for AS and FS, which was suggested in previous works [7,15]. In addition, some previous studies observed an increase in the production of dreams and their intensity in participants with nicotine substitutes [64]. However, we did not confirm these observations. It should be noted that we assessed patients during the day and not during the night, which may have impacted the recall of dream contents [65]. Finally, our study was the first to examine the seasonal pattern, and interestingly observed a high proportion of seasonal pattern among the AS, with more than half possibly diagnosed as having a seasonal affective disorder. This particular high prevalence of seasonal pattern should be further examined and may be linked with an AS group that appears to have more psychiatric comorbidities.

Characteristics of the participants, especially their medical history demonstrateda high proportion of depressive disorders in the participants who still smoke. Several hypotheses may explain this result: either a "self-medication" by tobacco in order to reduce anxiety symptoms, or a neurotoxic effect of cigarettes increasing the susceptibility to environmental stressors [66]. We also observed that FS suffered more regularly from CSA and MSA. This result may be explained by the presence of a more frequent cardio-vascular medical history in these same participants [67].

Regarding ventilatory sleep parameters, we observed that mean saturation was lower in former smokers than in active smokers and non-smokers, instead of an increase of the AHI in current smokers. Additionally, the relatively long average period of abstinence in former smokers allows us to account for possible withdrawal symptoms. Hence, we have substantiated the hypothesis that smoking exerts a detrimental influence on nocturnal saturation, a impact that remains unaffected even after smoking cessation. It's worth mentioning that we cannot definitively determine the potential confounding impact of COPD on nocturnal SpO2; therefore, our conclusion is centered solely on establishing the association between smoking status and sleep. The lower saturation in FS compared to AS may be due to older age, higher cigarette exposure and longer smoking duration. Furthermore, our results do not support the hypothesis that smoking leads to upper airway collapse and a significant increase in AHI, but rather indicate an increase in nocturnal hypoxia due to an alteration of reflex mechanisms that are not successful in recovering nocturnal airflow [68].

Regarding the impact on sleep architecture, we observed a decrease in N3 sleep stage for AS, a difference that no longer exists in FS. This is consistent with the known effect of nicotine on acetylcholine receptors, which leads to decrease in N3 stage [69]. Another hypothesis suggests that nicotine may be used as a self-medication by depressed patients. During a major depressive episode, serotonin deficiency results in a decrease in dorsal raphe nucleus activity leading to a lack of REM sleep inhibition and a decrease in N3. Nicotine consumption increases serotonin release in the dorsal raphe nucleus [70], which could restore normal sleep architecture. However, despite assessing the depressive dimension in our participants and adjusting for it, the reduction of N3 in smokers remains, making the second hypothesis less credible and indicating that nicotine independently decreases the duration of N3.

Regarding the pathophysiological hypotheses underlying the impact of nicotine on dream production, there are still controversies. Dream production is believed to be regulated by cholinergic mechanisms [71]. In humans, the administration of cholinergic agonists or anticholinesterases increases dreams production [72]. However, the effects of nicotine on dream appear complex and contradictory. Some studies have reported an increase in in dream production in participants using nicotine substitutes, while others have found no impact on dream production [73].

While this study has a large sample size, some analyses may have suffered from a lack of power. Additionally, being a cross-sectional study, it is difficult to establish causality for the observed impact of smoking on sleep. The three groups were not stratified by key sociodemographic factors, and differences were observed regarding age, sex, and comorbidities (psychiatric diseases or COPD), substances use (like alcohol), and antidepressant treatments. However, these confounding factors were addresses by performing multivariate analyses and adjusting for these parameters. But also, sleep architecture can be altered by smoking, as we highlighted in our article. However, we did not collect information on the time between the last cigarette smoked and bedtime. The study benefited from a naturalistic design which is closer to the real-life practice and patients, but may have introduced center effect bias, given that all participants were screened at the same sleep center. Also, with regard to duration of abstinence, the former smoker group is heterogeneous. However, we opted for a minimum of one year's abstinence, so as to avoid the effects of withdrawal on sleep quality. Also, self-reported smoking status may also be subject to bias, although is usually consistent with objective measures [74]. Finally, as multiple analyses were performed without correction, all findings from this exploratory study should be interpreted with caution and validated in independent samples.

Of note, in addition to its ecologic characteristics, the other strength of our study was the examination of a large cohort assessed with objective sleep measures including PSG across different smoking statuses. Few studies have evaluated sleep in a standardized way for participants who are active smokers, or former smokers. This work highlights the importance of screening for sleep disorders in active smokers, and the motivational interest in forming of the potential improvement of their sleep architecture after nicotine cessation.

5. Conclusion

Our study sheds light on the impact of smoking on objective sleep characteristics. The reduction of slow-wave sleep only in active smokers, as well as the persistence of ventilatory sleep disorders, particularly the decrease of the mean SpO_2 after smoking cessation, provide insight into the mechanisms underlying sleep disorders in smokers and former smokers. However, as this is a cross-sectional and exploratory study, further longitudinal studies are needed to better explain these associations and to confirm the impact of smoking cessation on sleep architecture and ventilatory parameters.

Credit author statement

PAG, SM and MPO designed the study. SM wrote the first draft of the manuscript and performed the statistics. All authors participated in the results interpretation, the manuscript redaction and approved the final version of the manuscript.

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We report no financial affiliations or other relationships related to the subject of this article for any of the authors.

Declaration of competing interest

The manuscript has not been published before, is not being considered for publication elsewhere, and have been approved by each author. We report no financial affiliation or other relationship relevant to the subject matter of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleepx.2023.100085.

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