Impact of Smoking on Sleep Macro– and Microstructure

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Abstract

OBJECTIVES Existing data suggest that smoking may be associated with sleep disturbances. This study aimed to determine the association between smoking and both subjective and objective sleep quality.

METHODS Cross-sectional analysis of sleep characteristics in 3233 participants from the population-based CoLaus-HypnoLaus cohort (52.2% women, mean age 56.6±10.2 years) who completed questionnaires on sleep quality, of whom 1489 (46%) had a full polysomnography. Smoking data were self-reported; participants were classified by smoking status as current, former or never smokers. Primary outcomes were subjective sleep quality assessed by sleep questionnaires, and objective sleep quality based on polysomnography (sleep macrostructure), including power spectral analysis of the electroencephalogram on C4 electrode (sleep microstructure), quantifying the relative amount of delta power (1-4 Hz), a marker of sleep depth, and arousal-associated alpha power (8-12 Hz).

RESULTS Current smokers had a shift toward faster sleep electroencephalogram activity with lower delta power in non-REM sleep compared with former and never smokers (–2.8±0.4% and –2.4±0.4%, respectively; both $p<0.001$) and higher alpha power (+0.8±0.2%; $p<0.001$) compared with never smokers. There was a dose-dependent negative association between electroencephalogram delta power and smoking intensity (r^2=–1.2 [–1.9, –0.5]; $p=0.001$). Additionally, mean nocturnal oxygen saturation was lower in current smokers.

CONCLUSIONS Current smokers had decreased objective sleep quality, with a dose-dependent association between smoking intensity and decrease in electroencephalogram delta power during non-REM sleep, in addition to an increase

in alpha power. Considering the importance of sleep quality for wellbeing and health, these results provide further data to support smoking cessation.

Abstract word count: 250

Keywords: sleep quality; sleep structure; polysomnography; power spectral analysis; delta power; smoking

Introduction

Tobacco smoking is the leading preventable cause of death in Western countries. Smoking is associated with increased health risks, mainly cardiovascular disease, respiratory disease and cancer.[1] Existing data suggest smoking could also be associated with both subjective and objective sleep disturbances.[2] In particular, a longitudinal study showed that smoking is associated with difficulty initiating sleep and waking up in both sexes, excessive daytime sleepiness (EDS) in female smokers, and increased nightmares and disturbing dreams in male smokers.[3] One cross-sectional study also found higher rates of EDS, minor accidents relating to EDS, depression and caffeine intake among smokers,[4] while another study showed shorter self-reported total sleep time, longer sleep onset latency, and earlier waking time in smokers compared with non-smokers.[5]

Objective sleep quality is usually assessed according to its macrostructure based on visual scoring of polysomnography (PSG) recordings including electroencephalogram (EEG), electromyogram and electrooculogram. This allows determination of sleep duration, sleep cycles and the different sleep stages. Sleep macrostructure is altered in smokers, as shown by a cross-sectional study which found that smokers have lower total sleep time and sleep efficiency, longer sleep onset latency, and a larger proportion of time spent in light stages of sleep (N1 and N2) than non-smokers.[6] Conversely, no difference in sleep structure was observed between former and non-smokers.[6] Another cross-sectional study showed a higher arousal index in smokers.[7]

Sleep can also be assessed according to its microstructure using EEG spectral power analysis, which is a computer-based quantification of the different types of EEG brain waves typically seen during sleep. Upon falling asleep, the waking EEG, characterized by a low-amplitude and high-frequency signal, is progressively replaced by high-

amplitude and low-frequency oscillations called slow waves. Slow waves are reflected in the delta power range (1-4 Hz). Usually, delta power is high early in the night, when sleep is considered “deepest”, and declines progressively over the course of the night, as a function of homeostatic sleep pressure.[8-10] An increase in alpha waves and other higher frequency waves is seen when the brain transiently reactivates (during awakenings or arousals). The results of a small study including 40 pairs of smokers and non-smokers suggest that sleep microstructure is also altered in smokers, as demonstrated by lower delta spectral power compared with non-smokers, with the greatest difference occurring during the early part of the sleep period.[11] However, the inclusion criteria of this study were restrictive and it is unclear if such findings can be extrapolated to the general population. Furthermore, the dose-response relationship between smoking intensity and sleep alterations was not investigated.

The aim of our study was to determine the association between smoking and both subjective and objective sleep quality, with a focus on EEG power spectral analysis. We hypothesized that current smoking would be associated with a dose-dependent decrease in sleep quality compared with former and never smokers.

Methods

Population sampling

HypnoLaus is a sleep cohort study that was conducted in Lausanne, Switzerland, between 2009 and 2013.[12] Participants were recruited from CoLaus, a population-based cohort study conducted between 2003 and 2006, which aims to investigate the epidemiology and genetic determinants of cardiovascular risk factors. The initial CoLaus cohort included 6734 participants (of whom 52.5% were women) from a random sample of adults aged 35–75 years living in Lausanne, Switzerland.[13] In the

first follow-up of the CoLaus study, the first consecutive 3043 participants were invited to undergo a full-night PSG at home. Of these, 2168 (71%) accepted the invitation, and 54 (2%) agreed to undergo a second PSG due to technical issues. Overall, 2162 complete PSG recordings were obtained for the HypnoLaus cohort.[12] All participants from the CoLaus-HypnoLaus studies who had PSG and questionnaire data on sleep quality or questionnaire data alone were included in the current cross-sectional analysis, but those using sedative or hypnotic medication or nicotine substitutes (nicotine patches, varenicline or bupropion), or who had missing data for subjective/objective sleep variables or covariates were excluded.

Polysomnography

PSG procedure and sleep parameters are described in **Supplemental methods** in the online supplement. Sleep stages and arousals were scored according to the 2007 American Academy of Sleep Medicine (AASM) manual.[14] Apneas and hypopneas were scored according to the 2012 AASM manual.[15] The following sleep parameters were analyzed: total recording time (TRT), total sleep time (TST), sleep efficiency, sleep onset latency, time spent in the sleep stages N1, N2, N3 and rapid eye movement (REM), arousal index (ArI), periodic limb movements in sleep index (PLMSI), apnea-hypopnea index (AHI), stage shifts, oxygen desaturation index (ODI 3%), time spent with an oxygen saturation (SpO_2) below 90% (T90), and mean SpO_2. After an automatic artifact rejection procedure,[16] EEG recordings (n=1447) were re-referenced to the average of the two mastoid channels and band-pass filtered between 0.5 and 35 Hz with a finite impulse response. Power spectral densities were calculated on the C4 electrode using the pwelch method on artifact-free consecutive, non-overlapping 6-second epochs (Hamming windows, 8 segments, 50% overlap) and

used to compute signal power in typical frequency bands, including delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), and beta (18–30 Hz). The resulting power values were averaged across epochs within each sleep stage and normalized to the total signal power (1–30 Hz) allowing for between-groups comparisons. Power spectral densities were analyzed for the following sleep stages: N1, N2 and N3 separately; N2 and N3 together (N2N3), which constitute deep sleep; and N1, N2 and N3 together, which constitute non-REM (NREM) sleep.

Subjective sleep characteristics

Subjective sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI). PSQI scores range from 0 to 21, and a score of ≥6 points is considered to reflect significant sleep disturbance.[17] Subjective daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS). ESS scores range from 0 to 24, and a score of ≥11 is considered to indicate EDS.[18] The Restless Legs Syndrome (RLS) screening questionnaire was self-administered and based on the four diagnostic criteria of RLS developed by the National Institutes of Health and approved by the International Restless Legs Syndrome Study Group. Diagnosis of RLS is considered definite if all four criteria are met.[19]

Smoking

Smoking data were self-reported, and included information on type of tobacco smoked, age of first consumption, and age of quitting (for quitters). Participants were defined as current smokers if they currently smoked ≥1 cigarette/day, as former smokers if they had quit smoking at the time of the study interview, and as never smokers if they had never smoked. Tobacco smoked using a pipe or as cigars was converted to cigarette

equivalents.[20] Smoking intensity was defined as the number of cigarette equivalents smoked daily.

Covariates

Participants reported their age, sex, socioeconomic status, lifestyle and health status. Marital status was categorized into living in a couple or alone. Educational level was categorized into mandatory, apprenticeship, high school and university. Physical activity was assessed using the self-reported Physical Activity Frequency Questionnaire[21] and participants were considered to have sedentary behavior, if they spent >90% of daily energy in activities below moderate and high intensity.[22] Alcohol consumption was expressed in number of units/week and caffeine consumption by categories defined by units/day. Depression was assessed by the Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire,[23] and anxiety was assessed by interview using the Diagnostic Interview for Genetic Studies (DIGS).[24] According to the Anatomical Therapeutic Chemical (ATC) Classification System, psychoactive medication was assessed as intake of psycholeptics [N05], which include antipsychotics and anxiolytics, and psychoanaleptics [N06], including antidepressants and psychostimulants. High blood pressure (HBP) was defined as blood pressure measured ≥140/90 mmHg or intake of HBP medications. Anthropometric measurements were performed by trained observers with standard techniques. Participants were classified as overweight if their body mass index (BMI) was ≥25 and <30 kg/m^2, and as obese if BMI was ≥30 kg/m^2.

Statistical analysis

Statistical analyses were conducted with Stata version 16.1 (StataCorp, College Station, TX, USA). Between-group comparisons were performed using chi-square for categorical variables and analysis of variance (ANOVA) or nonparametric Kruskal-Wallis test for continuous variables. Multivariable analyses were performed using logistic regression for categorical variables and ANOVA for continuous variables. Multivariable models were adjusted for age and sex, which could potentially affect sleep quality,[25] and additionally for a large set of covariates that differed between groups, as well as for the use of psychoactive medication, which could impact sleep patterns. Post-hoc comparisons were performed using Scheffe's method. The dose-response association between specific EEG power expressed as relative values (dependent variable) and smoking intensity was assessed using linear and robust regression adjusting for age and sex. Results were expressed as slope (95% CI) per 10 cigarette equivalents increase.

Two additional analyses were conducted to check the dose dependency. The first analyzed the dose-response association between EEG power in absolute values (i.e. uV^2/Hz) and smoking intensity. The second compared relative EEG power within two smoking intensity groups ($\leq$ and >10 cigarettes equivalents).

To account for multiple testing, we opted to define the statistical significance level at a lower p-value of <0.005, according to several recent recommendations concerning scientific publications, notably from Benjamin *et al.*,[26] and Ioannidis.[27]

Ethical statement

The institutional Ethics Committee of the University of Lausanne, which subsequently became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the

baseline CoLaus and HypnoLaus studies: reference 16/03. The approval was renewed for the first (reference 33/09), the second (reference 26/14) and the third (reference PB 2018-00040). The studies were performed in agreement with the Helsinki declaration and its former amendments. All participants gave their written informed consent before entering the studies.

Results

Selection criteria and characteristics of the participants

Of the 5064 subjects initially selected from the CoLaus cohort, subjective sleep was analyzed in 3233 (63.8%) subjects and objective sleep characteristics (PSG in the HypnoLaus cohort) were determined in 1489 (29.4%) subjects, including 1447 (28.6%) power spectral analyses. A flowchart of the study population and exclusion procedure is shown in **Figure 1**. The characteristics of included and excluded subjects are summarized in **Table S1**. Excluded subjects were older, had higher BMI and waist-to-hip ratio, lower education level, lived alone more frequently, and were more often sedentary and depressed. They also had a higher total number of medications, including psychoactive medications, and had higher prevalence of HBP. **Table S2** shows the characteristics of participants with subjective sleep variables only and of participants with both subjective and objective sleep variables. No difference was found between these two groups, in terms of demographic and health parameters.

Compared with former and never smokers, current smokers were younger, had a lower BMI, a lower educational level, lived alone more frequently, were more depressed, and consumed alcohol and caffeine more frequently (**Table 1**). Former smokers were more frequently men and older, had a higher BMI and a higher total number of medications, and were more frequently diagnosed with obesity and HBP.

Association between sleep characteristics and smoking status

Table 2 (multivariable) and **Table S3** (bivariate) show the associations between subjective sleep characteristics, sleep macrostructure and smoking status. Bivariate analysis revealed significant between-group differences regarding ESS, TRT, sleep efficiency and mean SpO_2 (**Table S3**). After multivariable adjustment, current smokers had a higher T90 and a lower mean SpO_2 than former and never smokers. No significant difference was observed in subjective sleep characteristics between groups (**Table 2**).

Association between EEG spectral power and smoking status

Table 3 shows the association between relative EEG power in NREM sleep (N1+N2+N3 stages) and smoking status. Current smokers had lower delta power than former and never smokers, and this difference remained significant after multivariable adjustment. Additionally, current smokers displayed higher alpha power than never smokers after adjustment. There was no between-group difference (**Table 3** and **Figure 2**) in EEG power for other frequency bands (theta, sigma and beta).

Complementary analysis confirmed that current smokers had lower delta power in N1 and N2 stages, as well as N2N3, compared to the other groups (**Table S4** and **Table S5**). Current smokers also had higher alpha power in N2 and N3 stages considered separately, in addition to N2N3, than never smokers. It should be noted that our spectral analysis focused on NREM sleep, in which delta power is most prominent and has been shown to reflect homeostatic sleep pressure.[28]

The dose-dependent association between relative delta power and smoking intensity is shown in **Table 4**. Negative associations were found for all sleep stages. An example

of the association between delta power in NREM sleep and smoking intensity is provided in **Figure 3**. When absolute values of delta power were used, negative associations with smoking intensity for N2 and N3 stages, and a borderline ($p<0.007$) negative association for NREM (N1+N2+N3 stages) remained (**Table S6**). In additional post-hoc analyses, no dose-response relationship was found between smoking intensity and relative EEG power in frequency bands other than delta. Also, there was no dose-response relationship between smoking intensity and either subjective sleep scores or parameters of sleep macrostructure (data not shown).

Discussion

To our knowledge, this is the first study analyzing both sleep macro- and micro-structure in a large and unselected population-based sample. Our results showed that current smoking was dose-dependently associated with lower delta and higher alpha power in NREM sleep. Current smokers also had lower nocturnal oxygen saturation than former and never smokers.

Although we found no association between sleep macrostructure and smoking status, unlike some previous studies,[6, 7] our results showed a significant alteration of sleep microstructure in current smokers compared with former and never smokers, with a shift toward faster sleep EEG activity. Current smokers had lower relative delta power in all NREM sleep stages than former and never smokers. These results confirm those of Zhang *et al*., which showed that current smokers had lower delta power than never smokers.[11] In our study, current smokers had higher relative alpha power in NREM sleep than never smokers, which is also consistent with previous findings.[11, 29]

The effect of nicotine on sleep regulation is the most likely explanation for the effect of smoking on delta power in sleep. In animal models, sleep-promoting GABAergic

neurons in the ventrolateral preoptic nucleus are indirectly inhibited by nicotine through presynaptic enhancement of noradrenaline release, while neurons in arousal systems are directly excited by nicotine.[30] Indeed, a previous study showed that transdermal nicotine administered to non-smoking individuals decreased delta power and increased alpha power in sleep.[31]

Delta power is a marker of sleep depth and is considered to be the most restorative component of sleep.[28] An increase in alpha power and other high-frequency bands (beta, gamma) is typically related to arousal. Lower relative delta power and higher relative alpha power in smokers could therefore reflect decreased activity of sleep-promoting systems and increased activity of arousal systems, respectively, which may impair the restorative aspects of sleep.

Although a higher ESS score was found in current smokers compared with never smokers in bivariate analysis, suggesting greater sleepiness, this difference was not significant in multivariable analysis. This discrepancy in our results between subjective sleep reports and objective sleep assessment was also found in previous work.[32] Further studies are needed to understand the interrelations between subjective sleep quality and sleep macro– and microstructure.[33-35]

Changes in sleep microstructure have been associated with clinical outcomes. Decreased delta power was associated with increased incident cardiovascular risk in follow-up of the CoLaus-HypnoLaus study, which could suggest another possible connection between smoking and cardiovascular risk.[36] A study showed an association between lower total delta power and increased diastolic blood pressure, as well as higher risk for incident HBP in a multi-ethnic cohort of women.[37] Also, results from another study showed positive correlations between delta power and

performance in declarative memory and procedural learning, indicating a potential connection between smoking and cognitive performance.[38]

In addition to sleep microstructure modification, our study showed that current smokers had a higher T90 and lower nocturnal mean oxygen saturation than former and never smokers. These results are consistent with one previous study in which current smokers (≥15 pack-years) were more likely to spend over 5% of TST with SpO_2 of <90% than never smokers,[7] and with another study that showed current smokers had a higher nocturnal hypoxia index than never smokers,[39] but should be interpreted cautiously in the absence of pulmonary function tests. Adding mean nocturnal SpO_2 among the adjustment variables did not change the results on sleep macro– and microstructure. This suggests that nocturnal hypoxemia does not have a major impact on sleep architecture.

Although previous studies reported conflicting results regarding the association between smoking and PLMS or RLS,[40, 41] we did not find any association between smoking status and PLMS or RLS. Finally, we also did not find any association between smoking and obstructive sleep apnea, which is in line with results from other studies and one recent meta-analysis.[7, 39, 42]

Overall, we believe that the deleterious effects of tobacco consumption on sleep microstructure and nocturnal oxygen saturation documented in our study provide a novel argument for strategies to promote smoking cessation. Indeed, because there was no difference in EEG power spectral density between former and never smokers, it could be suggested that changes in sleep microstructure are reversible upon smoking cessation.

Limitations and Strengths

The key strengths of our study were the number of participants and the unselected population nature of our sample. Compared with earlier studies, these allowed for a more in-depth analysis of the association between smoking and sleep microstructure. Indeed, the dose-response relationship we found strengthen this association. Considering that our population sample was almost exclusively of Caucasian ancestry, the generalizability of our results to non-Caucasian populations is limited. Studies of smoking effect on sleep architecture should thus be replicated in the population of other ethnicities. We also acknowledge several other limitations. First, smoking data included neither exact time of quitting nor quantity smoked during lifetime (pack-years), which prevented us from studying the association between nicotine withdrawal or dependence and sleep quality. Further studies should include this specific aspect. In a sensitivity analysis, we excluded quitters for < 1 year, who could be subject to some degree of withdrawal syndrome influencing sleep macro– and microstructure, and found no difference in our results. The number of quitters for < 1 year was however low (N=25) and represented only 4% of former smokers with analysis of sleep structure in our sample. Second, the cross-sectional analysis design means that the direction of the association between smoking and impaired sleep quality cannot be assessed. However, the dose-response association between smoking intensity and lower delta power suggests that nicotine has a negative effect on sleep quality. Moreover, the study by Jaehne *et al.* showed that higher cotinine levels are associated with lower amount of slow-wave sleep,[29] which also indicates an impact of nicotine on sleep rather than vice versa. Third, inherent limitations to PSG measurements may be present, such as the “first-night effect”, and results based on a single night study do not capture the night-to-night variability of sleep. However, in the HypnoLaus study, a

subsample had sleep studies on two nights and no significant differences were found between the two nights, suggesting that the “first-night effect” for PSG at home is probably negligible.[12] Finally, confounding factors such as cardiovascular (except HBP) and pulmonary diseases were not accounted for. In particular, pulmonary function testing could have participated in a better assessment of nocturnal oxygen saturation alterations. However, because these conditions are commonly related to smoking, excluding participants with cardiovascular or pulmonary diseases would have significantly reduced the number of smokers in the study population.

Conclusions

This study showed decreased objective sleep quality in current smokers compared with former and never smokers, with altered nocturnal oxygen saturation parameters and faster sleep EEG activity. There was a dose-dependent association between smoking intensity and decrease in EEG delta power, a marker of sleep depth, during non-REM stage, in addition to an increase in arousal-associated alpha power. Considering the importance of sleep quality for wellbeing and overall health, we believe that these negative effects of tobacco smoking on sleep should further stimulate smoking cessation strategies.

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Author contributions: MT, PMV and RH designed the study. JHR contributed to data collection. FS supervised the electroencephalogram power spectral analysis. PMV made the statistical analysis and wrote part of the manuscript. PMV had full access to the data and is the guarantor of the study. MT drafted the manuscript. All authors interpreted the data and critically reviewed the manuscript.

Data access

Due to the sensitivity of the data and the lack of consent for online posting, individual data cannot be made accessible. Only metadata will be made available in digital repositories. Metadata requests can also be made via the study website: www.colaus-psycolaus.ch.

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Figures

Figure 1. Flowchart of the study population and exclusion procedure (dashed arrows). Nicotine replacement therapy includes nicotine patches, varenicline or bupropion. Missing data refer to sleep variables or covariates.

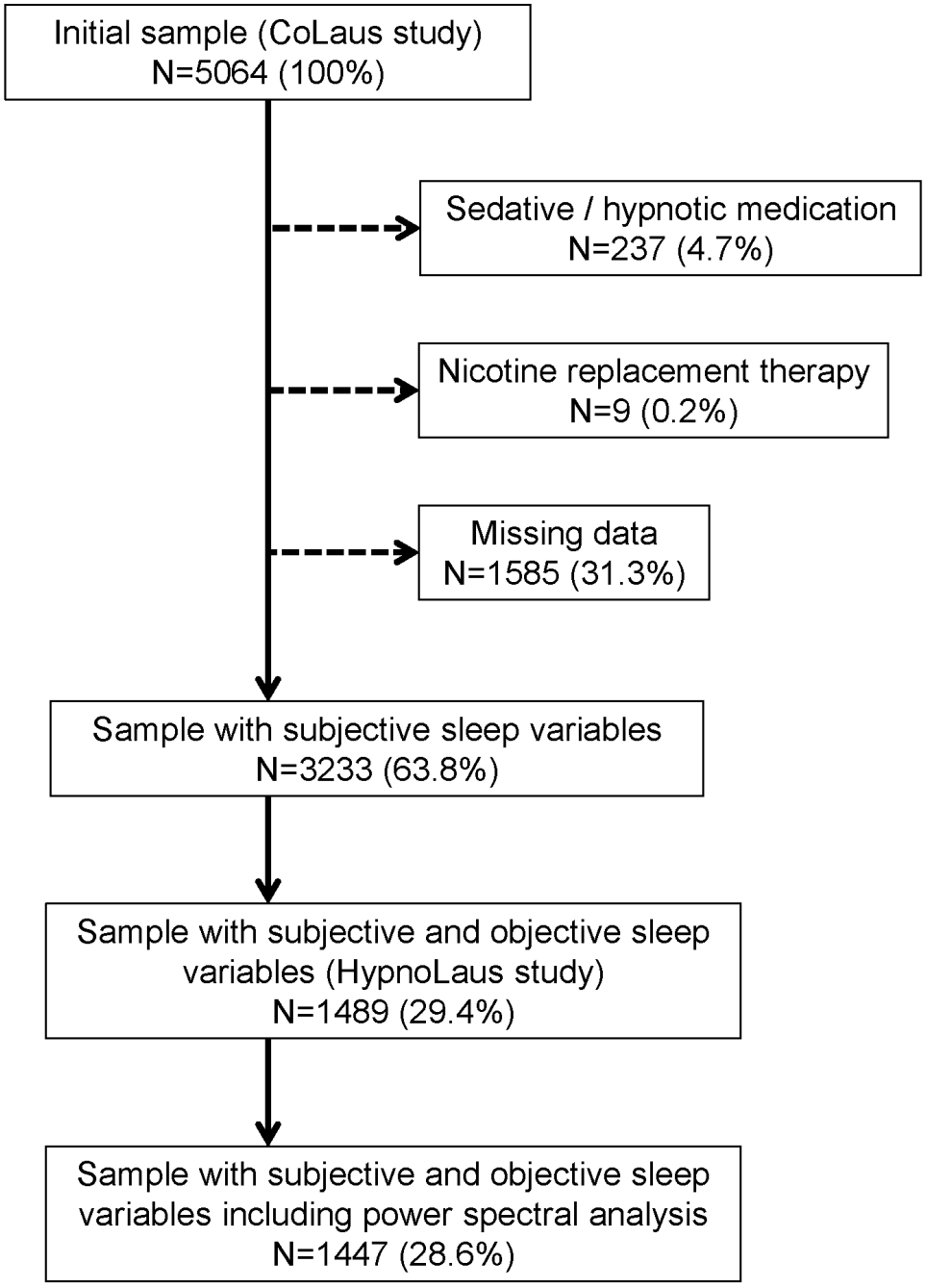

Figure 2. Multivariable-adjusted differences in relative EEG spectral power by frequency band between current and former smokers, and between current and never smokers, in non-REM sleep (N1+N2+N3 stages). Error bars indicate standard errors. *p<0.001.

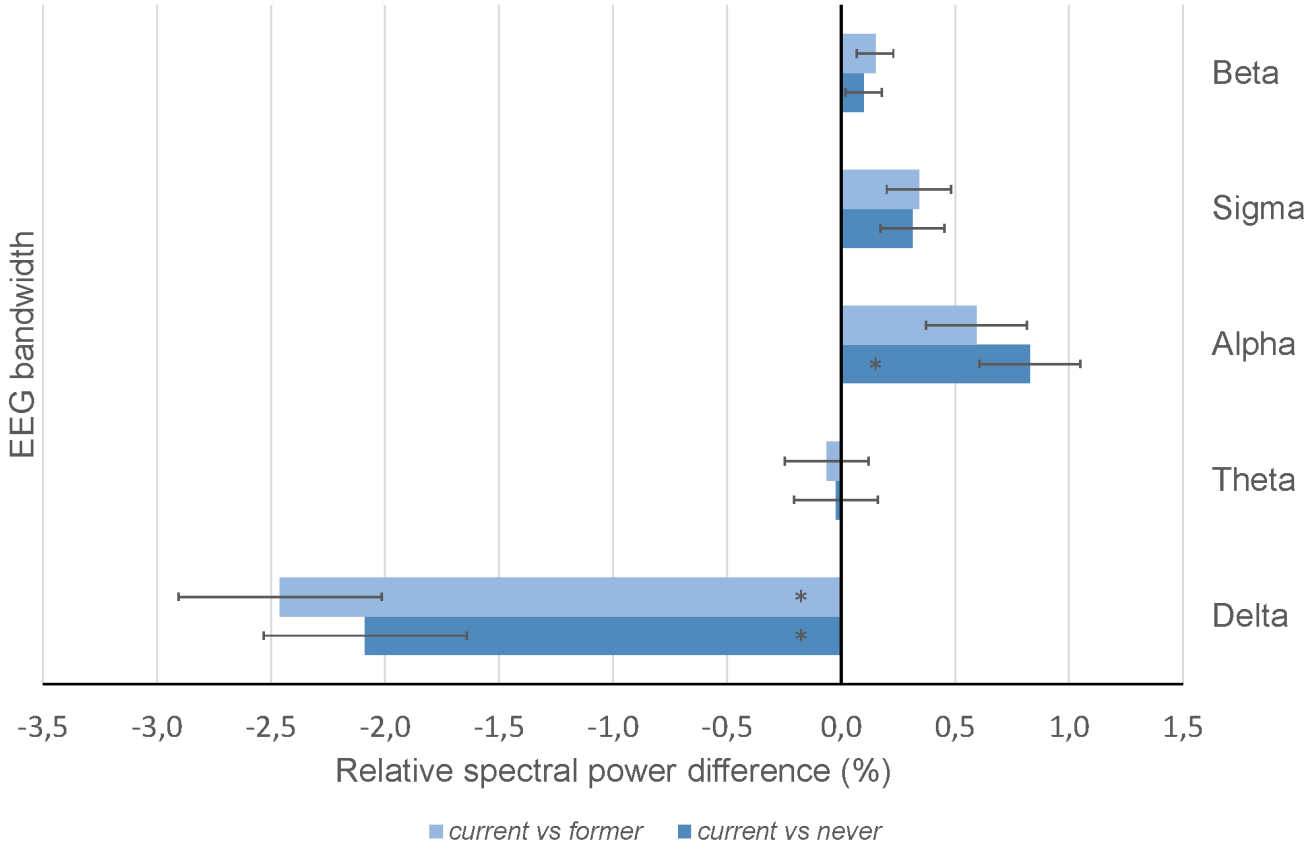

Figure 3. Linear regression between relative EEG delta power in non-REM sleep (N1+N2+N3 stages) and cigarette equivalents smoked daily.

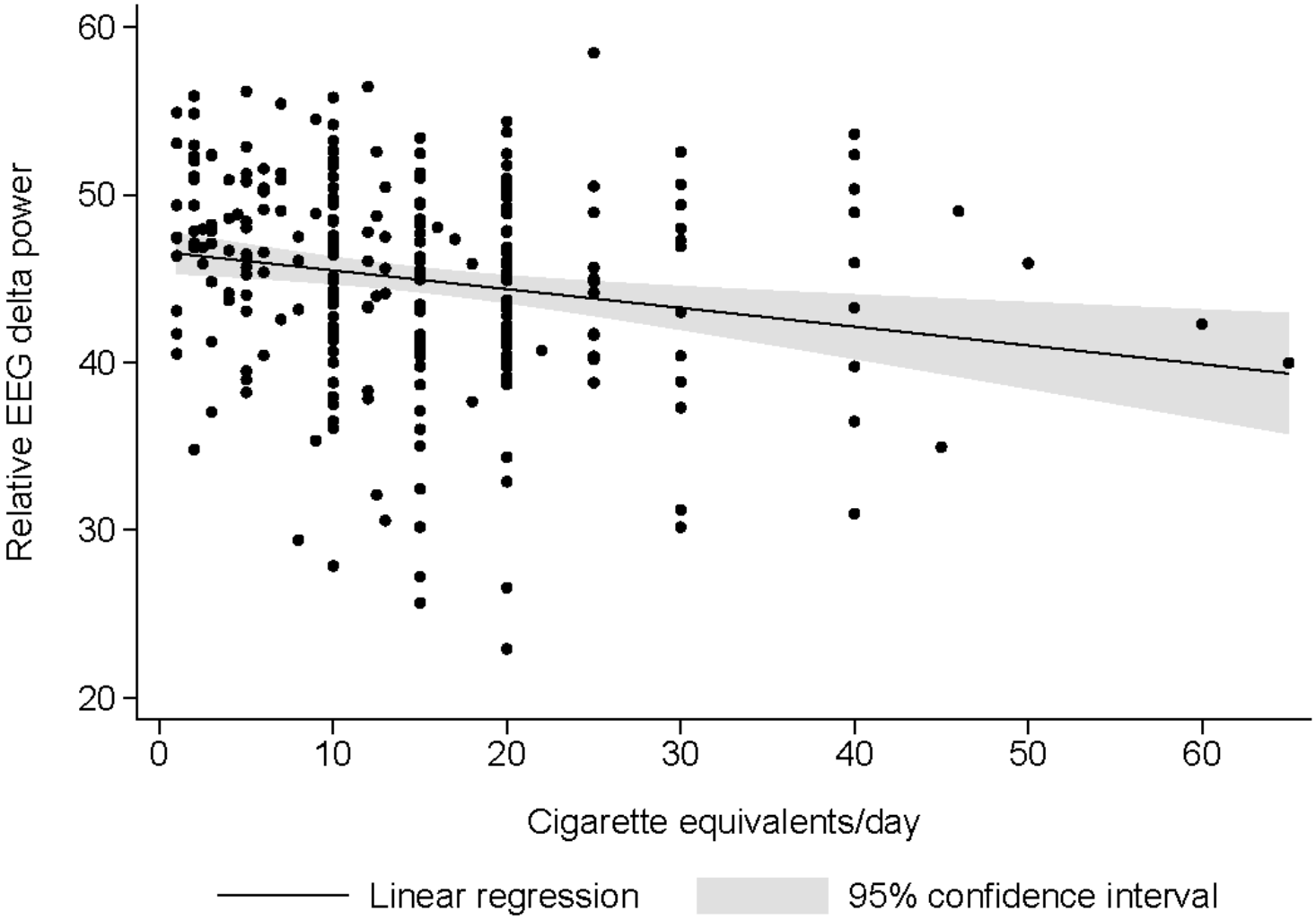

Table 1. Characteristics of the participants by smoking category.

	Never (n=1353)	Former (n=1209)	Current (n=671)	P-value
Age (years)	56.7 ± 10.5	57.9 ± 10.4	54.1 ± 8.7	<0.001
Male, No. (%)	583 (43.1)	636 (52.6)	326 (48.6)	<0.001
BMI (kg/m^2)	25.7 ± 4.3	26.3 ± 4.4	25.4 ± 4.2	<0.001
BMI categories, No. (%)				<0.001
Normal	650 (48.0)	497 (41.1)	342 (51.0)	
Overweight	525 (38.8)	498 (41.2)	251 (37.4)	
Obese	178 (13.2)	214 (17.7)	78 (11.6)	
Waist-to-hip ratio	0.90 ± 0.07	0.92 ± 0.07	0.92 ± 0.07	<0.001
Living alone, No. (%)	531 (39.3)	450 (37.2)	329 (49.0)	<0.001
Education level, No. (%)				<0.001
University	353 (26.1)	289 (23.9)	130 (19.4)	
High school	359 (26.5)	326 (27.0)	198 (29.5)	
Apprenticeship	445 (32.9)	465 (38.5)	245 (36.5)	
Mandatory education	196 (14.5)	129 (10.7)	98 (14.6)	
Sedentary behavior, No. (%)	729 (53.9)	670 (55.4)	404 (60.2)	0.025
Alcohol intake (units/week)	3 [0–7]	5 [2–10]	6 [2–14]	<0.001*
Caffeine intake, No. (%)				<0.001
None	114 (8.4)	62 (5.1)	33 (4.9)	
1 to 3 units/day	956 (70.7)	790 (65.3)	369 (55.0)	
4 to 6 units/day	261 (19.3)	307 (25.4)	227 (33.8)	
>6 units/day	22 (1.6)	50 (4.1)	42 (6.3)	
Depression, No. (%)	147 (10.9)	130 (10.8)	105 (15.7)	0.003
Anxiety, No. (%)	36 (3.3)	36 (3.7)	21 (3.9)	0.800
Psychoactive medication, No. (%)	69 (5.1)	51 (4.2)	43 (6.4)	0.114
Total number of medications	1.4 ± 1.9	1.6 ± 2.1	1.4 ± 2.0	<0.001
High blood pressure, No. (%)	522 (38.6)	543 (44.9)	204 (30.4)	<0.001

Abbreviations: BMI, body mass index.

Results expressed as number of participants (%) for categorical variables and mean ± standard deviation or median [interquartile range] for continuous variables. Between-groups comparisons performed using chi-square for categorical variables and analysis of variance or Kruskal-Wallis test* for continuous variables.

Table 2. Multivariable associations between subjective sleep characteristics (n=3233), sleep macrostructure (n=1489) and smoking status.

	Never	Former	Current	P-value
Subjective sleep (n)	1353	1209	671	
PSQI	4.9 ± 0.1	4.9 ± 0.1	4.4 ± 0.2	0.044
ESS	6.1 ± 0.2	6.7 ± 0.2	6.5 ± 0.2	0.022
RLS	1	1.17 (0.82–1.67)	1.57 (1.03–2.42)	0.038*
Sleep macrostructure (n)	627	582	280	
TST (min)	404 ± 3	399 ± 3	395 ± 4	0.194
TRT (min)	493 ± 3	489 ± 3	480 ± 4	0.045
Sleep efficiency (%)	85.0 ± 0.4	84.5 ± 0.4	85.7 ± 0.6	0.267
Sleep onset latency (min)	17 ± 1	14 ± 1	18 ± 1	0.040
N1 stage (% of TST)	11.8 ± 0.3	11.8 ± 0.3	12.4 ± 0.4	0.465
N2 stage (% of TST)	46.3 ± 0.4	45.0 ± 0.4	45.8 ± 0.6	0.052
N3 stage (% of TST)	19.9 ± 0.3	20.9 ± 0.3	19.6 ± 0.5	0.035
REM sleep (% of TST)	22.0 ± 0.2	22.3 ± 0.2	22.2 ± 0.4	0.053
ArI (N/h)	21.3 ± 0.4	20.4 ± 0.4	20.6 ± 0.6	0.232
PLMSI (N/h)	14.4 ± 0.9	12.1 ± 0.9	14.7 ± 1.4	0.140
AHI (N/h)	15.5 ± 0.5	14.4 ± 0.6	14.0 ± 0.8	0.232
Stage shifts (N/night)	142 ± 2	138 ± 2	139 ± 3	0.277
ODI 3% (N/h)	14.4 ± 0.5	13.6 ± 0.5	13.1 ± 0.8	0.303†
T90 (min)	2.6 ± 0.4	3.6 ± 0.5	5.6 ± 0.7[a,b]	0.002†
Mean SpO_2 (%)	94.3 ± 0.1	94.3 ± 0.1	93.5 ± 0.2[a,b]	<0.001†

Abbreviations: AHI, apnea-hypopnea index (according to 2012 AASM criteria); ArI, arousal index; ESS, Epworth Sleepiness Scale; ODI 3%, oxygen desaturation index; PLMSI, periodic limb movements in sleep index; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; T90, time spent with oxygen saturation below 90%; TRT, total recording time; TST, total sleep time.

Results expressed as multivariable-adjusted odds ratio (95% confidence interval) for categorical variables or as multivariable-adjusted mean ± standard error for continuous variables. Between-groups comparisons performed using logistic regression for categorical variables and analysis of variance for continuous variables, adjusting for sex, age (continuous), body mass index categories (normal/overweight/obese), alcohol intake (continuous), marital status (alone/in couple), educational level (university/high school/apprenticeship/mandatory), sedentary status (yes/no), caffeine intake

(none/1-3/4-6/>6), depression (yes/no), psychoactive medication (yes/no), total number of medications (continuous), high blood pressure (yes/no), and mean nocturnal SpO_2 (continuous; except when indicated by †). Post-hoc comparisons performed using Scheffe's method for continuous variables. *p-value for trend. Results differing at $p<0.005$: [a] significantly different vs. never smokers, [b] significantly different vs. former smokers.

Table 3. Bivariate and multivariable associations between relative EEG spectral power in non-REM sleep (N1+N2+N3 stages) and smoking status.

	Never (n=612)	Former (n=561)	Current (n=274)	P-value
Bivariate				
Delta	47.2 ± 5.8	47.6 ± 5.8	45.0 ± 6.2	<0.001
Theta	7.1 ± 2.4	7.2 ± 2.5	6.8 ± 2.5	0.159
Alpha	5.9 ± 2.8	6.2 ± 2.9	6.6 ± 3.1	0.014
Sigma	3.2 ± 1.9	3.1 ± 1.8	3.4 ± 1.9	0.069
Beta	1.3 ± 1.1	1.2 ± 0.9	1.3 ± 1.3	0.467
Multivariable*				
Delta	47.3 ± 0.2	47.6 ± 0.2	44.9 ± 0.4[a,b]	<0.001
Theta	7.1 ± 0.1	7.1 ± 0.1	7.0 ± 0.1	0.762
Alpha	5.9 ± 0.1	6.1 ± 0.1	6.7 ± 0.2[a]	0.003
Sigma	3.2 ± 0.1	3.1 ± 0.1	3.4 ± 0.1	0.057
Beta	1.3 ± 0.1	1.2 ± 0.1	1.4 ± 0.1	0.094
Multivariable†				
Delta	47.2 ± 0.2	47.6 ± 0.2	45.1 ± 0.4[a,b]	<0.001
Theta	7.0 ± 0.1	7.1 ± 0.1	7.0 ± 0.2	0.930
Alpha	5.9 ± 0.1	6.1 ± 0.1	6.7 ± 0.2[a]	<0.001
Sigma	3.1 ± 0.1	3.1 ± 0.1	3.5 ± 0.1	0.041
Beta	1.3 ± 0.1	1.2 ± 0.1	1.4 ± 0.1	0.174

EEG power reported as relative values (with respect to total power). Frequency bands: Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Sigma (12-16 Hz), Beta (18-30 Hz).

For bivariate analyses: results expressed as mean ± standard deviation and between-groups comparisons performed using analysis of variance. For multivariable analyses: results expressed as multivariable-adjusted mean ± standard error and between-groups comparisons performed using analysis of variance. Post-hoc comparisons conducted using Scheffe's method in multivariable models. Results differing at p<0.005: [a] significantly different vs. never smokers, [b] significantly different vs. former smokers.

*Adjusted for sex and age (continuous). †Adjusted for sex, age (continuous), body mass index categories (normal/overweight/obese), alcohol intake (continuous), marital status (alone/in couple), educational level (university/high school/apprenticeship/mandatory), sedentary status (yes/no), caffeine intake (none/1-3/4-6/>6), depression (yes/no), psychoactive medication (yes/no), total number of medications (continuous), high blood pressure (yes/no), and mean nocturnal SpO_2 (continuous).

Table 4. Regression slopes between relative EEG delta power in sleep and cigarette equivalents.

	Unadjusted	P-value	Sex and age- adjusted	P-value
N1				
Linear	–1.0 (–1.7; –0.3)	0.008	–1.2 (–1.9; –0.5)	0.001
Robust	–1.0 (–1.7; –0.2)	0.010	–1.2 (–1.9; –0.4)	0.002
N2				
Linear	–1.1 (–1.8; –0.4)	0.003	–1.2 (–1.9; –0.5)	0.001
Robust	–1.1 (–1.8; –0.4)	0.002	–1.2 (–1.9; –0.5)	0.001
N3				
Linear	–1.1 (–1.8; –0.3)	0.007	–1.1 (–1.9; –0.3)	0.007
Robust	–0.9 (–1.7; –0.2)	0.012	–1.0 (–1.7; –0.2)	0.010
N2N3				
Linear	–1.1 (–1.9; –0.4)	0.002	–1.2 (–1.9; –0.5)	0.001
Robust	–1.1 (–1.8; –0.5)	0.001	–1.2 (–1.9; –0.5)	0.001
Non-REM				
Linear	–1.1 (–1.8; –0.4)	0.002	–1.2 (–1.9; –0.5)	0.001
Robust	–1.1 (–1.8; –0.4)	0.001	–1.2 (–1.9; –0.5)	0.001

Results expressed as slope (95% confidence interval) per 10 cigarette equivalent increase.