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Smoking may increase the risk of influenza hospitalization and reduce influenza vaccine effectiveness in the elderly

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Background: Through its effects on the immune system, smoking may facilitate influenza virus infection, its severity and its most frequent complications. The objective was to investigate the smoking history as a risk factor for influenza hospitalization and influenza vaccine effectiveness in elderly smokers/ex-smokers and non-smokers. **Methods**: We carried out a multicenter case–control study in the 2013–2014 and 2014–2015 influenza seasons. Cases aged ≥65 years and age-, sex-matched controls were selected from 20 Spanish hospitals. We collected epidemiological variables, comorbidities, vaccination history and the smoking history. The risk of hospitalization due to smoking (current smokers and ex-smokers) was determined using the adjusted odds ratio (aOR) with conditional logistic regression models. Vaccine effectiveness (VE) was calculated using the formula: VE = (1 – aOR) × 100. **Results**: We studied 728 cases and 1826 controls. Cases had a higher frequency of smoking (47.4% vs 42.1%). Smoking was associated with an increased risk of influenza hospitalization (aOR = 1.32, 95% CI: 1.04–1.68). Influenza vaccine effectiveness in preventing hospitalization was 21% (95% CI: -2 to 39) in current/ex-smokers and 39% in non-smokers (95% CI: 22–52). **Conclusions**: A history of smoking may increase the risk of hospitalization in smokers and ex-smokers. Preventing smoking could reduce hospitalizations due to influenza. Smokers and ex-smokers should be informed of the risk of hospitalization due to influenza infection, and encouraged to stop smoking. Smokers should be considered an at-risk group to be aggressively targeted for routine influenza vaccination.

Introduction

Influenza affects a large percentage of the population each year, with estimates as high as 15%.[1] The smoking prevalence of 30.5% in men and 20.5% in woman found in the Spanish population according to the latest National Health Survey remains very high,[2] but is lower in the elderly (16.2% in men and 4.6% in woman aged 65–74 years).

Smoking favors the frequency and severity of several respiratory diseases.[3] Tobacco smoke causes the deposition of particles in the airways that damage the protection mechanisms of the respiratory system at different levels, alters the function of the ciliary mucus and the clearance of inhaled substances, enables the adherence of bacteria to airway epithelial cells, increases alveolar permeability and decreases cellular and humoral immunity.[4,5]

Through these effects on the immune system, smoking may facilitate influenza virus infection, its severity, and its most frequent complications, such as bacterial pneumonia.[6,7] Studies have estimated that smokers have more than twice the risk of clinical disease[8,9] compared with non-smokers and also present more severe forms.[10] Some authors suggest that these effects are dependent on the chronicity of smoking and may persist, although to a lesser extent, after stopping smoking.[11–13]

The presence of concomitant diseases strongly associated with smoking, such as chronic obstructive pulmonary disease (COPD) and congestive heart disease, make it difficult to assess the role of smoking in increasing the severity of influenza.[14,15] The role of smoking in influenza in the elderly may be more difficult to assess due to the lower prevalence of smokers and the higher prevalence of ex-smokers and because some smokers die before the age of 65 years due to tobacco-related causes.[16] Thus, there is a need to determine the effect of smoking as a risk factor for influenza hospitalization in the elderly.

The aim of this study was to estimate the smoking history as a risk factor for influenza hospitalization and influenza vaccine effectiveness in smokers/ex-smokers and non-smokers in the 2013–2014 and 2014–2015 influenza seasons in Spain in people aged ≥65 years.

Methods

Study design

We designed a multicenter, case–control study in 20 Spanish hospitals from seven Spanish regions (Andalusia, the Basque Country, Castile and Leon, Catalonia, Madrid, Navarre and Valencia Community). All were public reference hospitals located in the main cities of each community and all provided free-at-the-point-of-delivery healthcare under the auspices of the Spanish National Health Service. Cases hospitalized due to influenza in the participating hospitals in the 2013–2014 and 2014–2015 influenza seasons and corresponding inpatient controls were recruited.

Selection of cases and controls

Patients aged ≥65 years hospitalized for at least 24 h with laboratory-confirmed influenza virus infection [reverse-transcription polymerase chain reaction (RT-PCR), culture or immunofluorescence] were selected. Patients with nosocomial infection, defined as influenza virus infection appearing ≥ 48 h after admission for other reasons, were excluded.

Three matched controls were selected for each case from patients aged ≥65 years with unplanned hospital admission due to causes other than influenza or acute respiratory disease. Controls were matched with each case according to age (±3 years), sex and date of hospitalization (±10 days). Controls were selected from patients admitted to the general surgery, internal medicine service, ophthalmology, otorhinolaryngology, dermatology, or traumatology services. Patients referred from nursing homes and those who did not provide written informed consent were excluded.

Data collection

Hospitalized cases and controls were interviewed by specifically-trained health professionals using the same structured questionnaire at a similar time after hospitalization and their medical records were reviewed.

The following demographic variables and pre-existing medical conditions were recorded: age, sex, marital status, educational level, smoking and alcohol intake, the Barthel index as a measurement of limitations in activity (ranging from 0—complete dependence to 100—complete independence), COPD, chronic respiratory failure, history of pneumonia during the last two years, other lung diseases, neoplasia, transplantation, diabetes, renal failure, congestive heart disease, disabling neurological disease, obesity [body mass index (BMI) ≥ 30] and chronic liver disease.

Definition

We defined the variable 'Any risk medical condition' as: Yes (≥1: COPD, congestive heart disease, renal failure, diabetes, chronic liver disease) or No (no risk medical conditions). High alcohol consumption as: Yes (>40 g/day for men and >24 g/day for women) or No. Smoking was defined as habitual smoker (any smoking in the last 6 months), ex-smoker (former smoker who gave up and had not smoked in the last 6 months) and never smoker. As the prevalence of smokers was very low, we combined smoker and ex-smoker in the same category for the analysis.

Information on the seasonal influenza vaccine status and pneumococcal vaccination status was obtained from medical records or vaccination cards. Cases and controls were considered vaccinated with the seasonal influenza vaccine if they had received a dose of the trivalent inactivated vaccine at least 14 days before the onset of symptoms of the case.

Statistical analysis

A bivariate comparison was made between cases and controls for demographic variables, smoking, alcohol intake, Barthel index, influenza vaccine and any medical conditions using the McNemar test for categorical variables. Unadjusted matched odds ratios (OR) were estimated using the McNemar test.

Multivariate analysis using conditional logistic regression was made to estimate the adjusted OR (aOR) for smoking status (smokers and ex-smokers). Covariates were introduced into the model using a backward stepwise procedure, with a cut-off point of $P < 0.2$.

In the different regression models, the aOR for smoking for all cases and controls considered together and by sex and age-group (65–74; 75–84; and ≥85 years) were calculated to evaluate possible differences and rule out selection bias. The analysis according to sex or age group was adjusted using conditional logistic regression.

The effect of the vaccine was evaluated according to the smoking categories (smokers/ex-smokers and nonsmokers) using unconditional logistic regression with backward selection of variables, with a cut-off point of $P < 0.2$. Vaccine effectiveness (VE) was calculated using the formula: $VE = (1 - aOR) \times 100$.

The fraction of influenza hospitalization attributable to smoking in the exposed population was calculated by estimating the attributable risk in the exposed population: $(ARe) = [(aOR–1)/(aOR–1) + 1] \times 100$.

The analysis was performed using the SPSS v.23 statistical package and the R v3.3.0 statistical software (http://cran.r-project.org).

Ethical considerations

All data collected were treated as confidential, in strict observance of legislation on observational studies. The study was approved by the Ethics Committees of the participating hospitals. Written informed consent was obtained from all patients included in the study.

Results

We studied 728 cases with RT-PCR-confirmed influenza (443 cases from season 2013–2014 and 295 from season 2014–2015) and 1826 controls.

Cases and controls had a similar frequency of females (47.1% vs 48.4%), and patients in each age group ($P = 0.29$) (Table 1). However, compared with controls, cases had a different distribution of the marital status ($P = 0.02$) and the Barthel index ($P = 0.08$), a lower prevalence of influenza vaccination (49.3% vs 57.7%; $P < 0.001$) and a higher frequency of smoking (47.4% vs 42.1%; $P = 0.01$) (Table 1). The proportion of ex-smokers and current smokers was 39.6% and 7.8% in cases vs 35.0% and 7.1% in controls.

The prevalence of smoking among cases was 58.9% in the 65–74 years age group, 45.6% in the 75–84 years age group and 31.4% in the ≥85 years age group; 75.3% in males vs 16.0% in females ($P < 0.001$); 66.7% in separated/divorced people, 59.0% in single people, 54.0% in married/cohabiting subjects and 29.5% in widowed persons; 51.2% in patients with a higher Barthel index vs 28.5% in those without ($P < 0.001$); 81.3% in patients with high alcohol consumption vs 46.6% in those without ($P < 0.001$); and 52.7% in persons with any risk medical condition vs 35.3% in those without ($P < 0.001$) (Table 2). Controls had a lower prevalence of smoking than cases although the patterns and differences within groups were similar (Table 2). In addition, the prevalence of smoking in non-vaccinated controls was 45.1% compared with 39.9% in vaccinated controls ($P = 0.02$) (Table 2).

In the multivariate analysis, smoking (aOR = 1.32, 95% CI: 1.04–1.68) was significantly associated with the risk of influenza hospitalization ($P = 0.02$) (Table 3). In the logistic regression models according to age groups, the aOR between smoking and influenza hospitalization was > 1 in all age groups, but was only statistically significant in the ≥85 years age group (aOR = 2.27, 95% CI: 1.16–4.44) due to the low power of the estimates. Analysis by sex showed that the aOR for influenza hospitalization were all > 1, but were higher in females (aOR = 1.95, 95% CI: 1.28–2.97) than in males

Table 1 Distribution of cases and controls according to demographic variables, medical conditions and vaccination history

Characteristics	Cases (*N* = 728)	Controls (*N* = 1826)	*P*-value
Smoking status			
Smoker	57 (7.8%)	130 (7.1%)	
Ex-smoker	288 (39.6%)	639 (35.0%)	
Smoker/ex-smoker	345 (47.4%)	769 (42.1%)	
Non smoker	383 (52.6%)	1057 (57.9%)	0.01
Age group			
65–74 years	248 (34.1%)	614 (33.6%)	
75–84 years	340 (46.7%)	883 (48.4%)	
≥85 years	140 (19.2%)	329 (18.0%)	0.29
Sex			
Female	343 (47.1%)	884 (48.4)	
Male	385 (52.9%)	942 (51.6%)	1.00
Marital status			
Married/cohabiting	450 (61.9%)	1020 (56.0%)	
Single	39 (5.4%)	145 (8.0%)	
Widowed	217 (29.8%)	615 (33.8%)	
Separated/divorced	21 (2.9%)	42 (2.3%)	0.02
Barthel index			
0–60	123 (16.9%)	336 (20.1%)	0.08
>60	605 (83.1%)	1458 (70.9%)	
High alcohol consumption			
Yes	16 (2.2%)	53 (2.9%)	
No	712 (97.8%)	1772 (97.1%)	0.38
Risk medical conditions			
Yes	507 (69.6%)	1217 (66.6%)	
No	221 (30.4%)	609 (33.4%)	0.04
Influenza vaccine			
Yes	359 (49.3%)	1053 (57.7%)	<0.001
No	369 (50.7%)	773 (42.3%)	
Pneumococcal vaccine			
Yes	372 (51.1%)	836 (45.8%)	0.06
No	356 (48.9%)	990 (54.2%)	

Table 2 Distribution of smoking status in cases and controls according to demographic variables, medical conditions and vaccination history

Characteristics	Smoking/total, *n*/*N* (%) Cases	*P*-value	Controls	*P*-value
Total	345/728 (47%)		769/1826 (42%)	
Age group				
65–74 years	146 (58.9%)		329 (53.6%)	
75–84 years	155 (45.6%)		367 (41.6%)	
≥85 years	44 (31.4%)	<0.001	73 (22.2%)	<0.001
Sex				
Female	55 (16.0%)		82 (9.3)	
Male	290 (75.3%)	<0.001	687 (72.9%)	<0.001
Marital status				
Married/cohabiting	243 (54.0%)		521 (51.0%)	
Single	23 (59.0%)		66 (45.5%)	
Widowed	64 (29.5%)		151 (24.6%)	
Separated/divorced	14 (66.7%)	<0.001	31 (73.8%)	<0.001
Barthel index				
0–60	35 (28.5%)		128 (35.0%)	
>60	310 (51.2%)	<0.001	641 (43.9%)	<0.001
High alcohol consumption				
No	332 (46.6%)		721 (40.7%)	
Yes	13 (81.3%)	<0.001	48 (90.6%)	<0.001
Risk medical conditions				
Yes	267 (52.7%)		579 (47.6%)	
No	78 (35.3%)	<0.001	190 (31.2%)	<0.001
Influenza vaccine				
Yes	175 (48.7%)		420 (39.9%)	
No	170 (46.1%)	0.47	349 (45.1%)	0.02
Pneumococcal vaccine				
Yes	180 (48.4%)		328 (39.2%)	
No	165 (46.3%)	0.58	441 (44.5%)	0.02

(aOR = 1.14, 95% CI: 0.85–1.52) (Supplementary Table). The fraction of the risk of influenza hospitalization attributable to smoking was 24.2% (95% CI: 3.84% to -410.5%) in current smokers/ex-smokers.

The influenza vaccine was effective in preventing hospitalization both in current smokers/ex-smokers and non-smokers but was slightly lower in smokers/ex-smokers in whom it was not statistically significant due to the lower statistical power. Influenza vaccine effectiveness in current smokers/ex-smokers was 21% (95% CI: -2 to 39) and 39% in non-smokers (95% CI: 22–52) (Table 4).

Discussion

The results of this study of cases aged ≥ 65 years hospitalized due to influenza and their corresponding controls show that the risk of influenza hospitalization was 30% higher in patients with a history of smoking (smokers and ex-smokers). After controlling for potential confounders and influenza vaccination, smoking was responsible for 24.2% of hospitalizations due to influenza in patients with a history of smoking. The results hold true for different age groups, with variations attributable to the low power of the analysis, and in females, who had a much higher risk than men, probably due to different patterns of susceptibility to tobacco. In addition, the influenza vaccine was effective in preventing hospitalization but was slightly less effective in smokers/ex-smokers than in non-smokers.

The estimated risk of influenza hospitalization in patients with a history of smoking (aOR = 1.31) may be attributed to the effects of tobacco in ex-smokers aged ≥ 65 years. Similarly, we estimated in another study[11] that the risk of hospitalization was slightly higher (aOR = 1.73) in ex-smokers aged ≥18 years although lower than in smokers (aOR = 2.18). Likewise, Ward et al.[17] found that the risk of hospitalization remains very high in ex-smokers aged ≥16 years (aOR = 2.18). All these studies reported that the risk of hospitalization was greater, although less so, in ex-smokers, suggesting that the lesions caused by smoking remain over time, although their effects lessen.

The risk of the history of smoking on influenza hospitalization remained in different age groups, with variations due to the low power of the analysis in some cases. There was an increased risk in patients with a history of smoking aged ≥ 85 years. Likewise, other studies suggest the increased risk in ex-smokers may be due to the cumulative effect of smoking over time.[11,18]

The risk of influenza hospitalization in patients aged ≥65 years with a history of smoking was greater in females than in males. The study by Kark et al.[19] showed a higher risk ratio in female soldiers who smoked (RR = 1.44) than in those who did not, while Ward et al.[17] reported a higher risk of influenza hospitalization in female former smokers of childbearing age (OR = 2.8). In contrast, other studies found a higher risk in male smokers than in female smokers and ex-smokers.[11,17] As we only studied the history of smoking in patients aged ≥ 65 years, a possible survival effect in males and smokers cannot be ruled out, as women and never-smokers tend to live longer.[16]

Influenza vaccine effectiveness was moderate (21% in smokers and 39% in non-smokers), and was similar to that found in other observational studies in patients aged ≥ 65 years.[20] Furthermore, influenza vaccination is strong recommended by the main public health agencies.[21,22] The prevalence of smoking in controls was higher in non-influenza vaccinated patients than in vaccinated ones and suggests, similar to other studies, that a history of smoking may be negatively associated with influenza vaccination.[23] Vander et al. found that, in the Behavioral Risk Factor Surveillance System of US adults, daily smokers were less likely to receive influenza vaccination despite their increased risk for respiratory disease.[24]

Our results are consistent with studies in animal models which found that smoking damages the immune system of the airways, causing a reduction in interferon gamma (IFN γ) and CD4

Table 3 Smoking status (smoker and ex-smoker) as a risk factor for hospitalization in patients aged ≥ 65 years with laboratory-confirmed influenza in the regression model

Characteristics	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Smoking status				
Smoker/ex-smoker	1.39 (1.09–1.77)	0.01	1.32 (1.04–1.68)	0.02
Non smoker	1		1	
Age group				
65–74 years	1		1	
75–84	0.85 (0.57–1.27)	0.42	0.87 (0.57–1.32)	0.76
≥85 years	1.13 (0.63–2.00)	0.69	1.28 (0.71–2.32)	0.42
Marital status				
Married/cohabiting	1		1	
Single	0.57 (0.39–0.83)	0.004	0.54 (0.36–0.79)	0.001
Widowed	0.76 (0.61–0.95)	0.02	0.73 (0.58–0.92)	0.007
Separated/divorced	1.17 (0.68–2.00)	0.57	1.13 (0.66–1.95)	0.66
Barthel index				
>60	1.25 (0.97–1.60)	0.08	1.31 (1.02–1.70)	0.03
0–60	1		1	
Any medical conditions				
High risk	1.23 (1.01–1.50)	0.04	1.27 (1.04–1.56)	0.02
Non high risk	1		1	
Influenza vaccination				
Yes	0.73 (0.61–0.87)	<0.001	0.70 (0.58–0.83)	<0.001
No	1		1	

Table 4 Effectiveness of influenza vaccine in avoiding influenza hospitalization in patients aged ≥ 65 years with laboratory-confirmed influenza in regression models according to smoking status

	Cases vaccinated/*N* (%)	Controls vaccinated/*N* (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Smoking status						
Smoker/ex-smoker[a]	175/345 (50.7%)	420/769 (54.6%)	0.85 (0.66–1.10)	0.11	0.79 (0.61–1.02)	0.08
Non-smoker [a]	184/383 (48.0%)	633/1057 (59.9%)	0.62 (0.49–0.78)	<0.001	0.61 (0.48–0.78)	<0.001

OR, odds ratio; CI, confidence interval.
a: Adjusted OR for: age group, marital status, high alcohol consumption, Barthel index, risk medical conditions.

lymphocytes, thus enabling not only infection but also the severity of influenza.[4,13,25] A cohort study[26] in volunteer smokers, ex-smokers, second-hand smokers and non-smokers who were inoculated with an attenuated influenza virus in the nasal mucosa found not only suppression of the response to the virus but also a higher viral load in people exposed to smoking. It also found greater disease severity and persistence of the effect of smoking in ex-smokers.

This study has some limitations. Smoking consumption was collected through interviews and the history of smoking was self-reported by patients. However, as all patients, cases and controls were hospitalized and as a structured questionnaire was used, potential observer bias was minimized. We also matched cases and controls for the date of hospitalization ± 10 days, to avoid recall bias or other errors associated with the moment patients contacted the health system. Some risk factors were related to age. We matched cases and control by age ± 3 years to control for the effect of age and to obtain a sufficient number of controls for logistic reasons. In cases and controls, the prevalence of smoking decreased with age and was much higher in males than in females. Therefore, the risk in some subgroups (males and younger adults) may have been diluted by the possible confounding effect of sex and age.[16] For this reason, we also estimated the risks using separate regression models according to gender and age group. The outcome measure used in this study was hospitalization due to influenza, and smoking is also associated with an increased risk of other factors that influence hospitalization, including the marital status, high alcohol consumption, the Barthel index and chronic diseases including COPD, diabetes, congestive heart disease and renal failure.[15,27] However, all these variables were entered in the final regression models and their effects controlled for, but residual confounding cannot be ruled out.

The results of this study have implications for public health. The fraction of the risk of influenza hospitalization attributable to smoking was 24.2% in smokers and ex-smokers aged ≥65 years, slightly lower than the 40.6% found by Kark et al.,[9] and suggests that patients with a history of smoking should be informed about their risk of hospitalization due to influenza. Likewise, studies have shown lower rates of influenza vaccination in smokers[23,28] which could add to the negative effect of smoking.

The effectiveness of influenza vaccination in our study was slightly lower in smokers than in non-smokers. Horvath et al. found that cytotoxic NK cell activity and IFNγ levels were suppressed in smokers following live attenuated influenza vaccination.[29] However, Woolpert et al. studied 28 929 vaccination events during two influenza seasons, including 22 734 (79%) live attenuated vaccinations and 6195 (21%) trivalent inactivated influenza vaccinations, and found that, in the final adjusted model, the relative effectiveness of the two vaccine types did not differ by smoking status ($P = 0.10$).[30] Other studies have shown a high effectiveness of influenza vaccination in vaccinated smokers compared with non-vaccinated smokers.[23] Therefore, smoking should be an indication for vaccination for current smokers and ex-smokers, as suggested by the Centers for Disease Control and Prevention for the 23-valent pneumococcal polysaccharide vaccine.[31]

In conclusion, a history of smoking may increase the risk of hospitalization in smokers and ex-smokers. Preventing smoking could reduce hospitalizations due to influenza. Smokers and ex-smokers should be informed of the risk of hospitalization due to influenza infection, and encouraged to stop smoking. Smokers should be considered an at-risk group to be aggressively targeted for routine influenza vaccination.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Key points

- Smoking was associated with an increased risk of influenza hospitalization due to influenza in the elderly.
- Smoking reduces influenza vaccine effectiveness in the elderly.
- Smoking prevention could reduce hospitalizations due to influenza.

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Interactive effects of sleep duration and morning/evening preference on cardiovascular risk factors

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Background: Sleep duration and morningness/eveningness (circadian preference) have separately been associated with cardiovascular risk factors (i.e. tobacco use, physical inactivity). Interactive effects are plausible, resulting from combinations of sleep homeostatic and circadian influences. These have not been examined in a population sample. **Methods**: Multivariable regression models were used to test the associations between combinations of sleep duration (short [≤6 h], adequate [7–8 h], long [≥9 h]) and morning/evening preference (morning, somewhat morning, somewhat evening, evening) with the cardiovascular risk factors of tobacco use, physical inactivity, high sedentary behaviour, obesity/overweight and eating fewer than 5 daily servings of fruit and vegetables, in a cross-sectional sample of 439 933 adults enrolled in the United Kingdom Biobank project. **Results**: Participants were 56% female, 95% white and mean age was 56.5 (SD = 8.1) years. Compared with adequate sleep with morning preference (referent group), long sleep with evening preference had a relative odds of 3.23 for tobacco use, a 2.02-fold relative odds of not meeting physical activity recommendations, a 2.19-fold relative odds of high screen-based sedentary behaviour, a 1.47-fold relative odds of being obese/overweight and a 1.62-fold relative odds of <5 fruit and vegetable daily servings. Adequate sleep with either morning or somewhat morning preference was associated with a lower prevalence and odds for all cardiovascular risk behaviours except fruit and vegetable intake. **Conclusions**: Long sleepers with evening preference may be a sleep phenotype at high cardiovascular risk. Further work is needed to examine these relationships longitudinally and to assess the effects of chronotherapeutic interventions on cardiovascular risk behaviours.

Introduction

Cardiovascular disease is the largest contributor to global mortality[1] with the triad of behavioural risk factors for cardiovascular diseases—tobacco use, physical inactivity and poor dietary intake, accounting for much of the incidence of poor cardiovascular health outcomes such as stroke, angina and hypertension.[2] Sleep is an independent risk factor for cardiovascular risk behaviours and outcomes. As a complex set of physiological functions, sleep patterns are regulated by two independent but related biological systems—sleep–wake homeostasis and circadian rhythms. The homeostatic process mediates the rise of sleep propensity across the day and its dissipation during sleep; this homeostatic process is directly implicated in sleep duration.[3] Circadian rhythms are a clocklike mechanism that function independently of prior sleep and waking and determine the alternation and timing of periods with high and low sleep propensity.[4] Sleep "chronotype" (degree to which an individual prefers morning or evening) is directed by circadian processes.[4] Circadian phase, circadian period, and wake time are highly correlated with morningness and eveningness, or self-reported preference for morning or evening time.[5]