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NATURAL HISTORY OF EXCESSIVE DAYTIME SLEEPINESS

Natural History of Excessive Daytime Sleepiness: Role of Obesity, Weight Loss, Depression, and Sleep Propensity

Julio Fernandez-Mendoza, PhD[1]; Alexandros N. Vgontzas, MD[1]; Ilia Kritikou, MD[1]; Susan L. Calhoun, PhD[1]; Duanping Liao, MD, PhD[2]; Edward O. Bixler, PhD[1]

[1]Sleep Research and Treatment Center, Department of Psychiatry, Pennsylvania State University College of Medicine, Hershey, PA; [2]Department of Public Health Sciences, Pennsylvania State University College of Medicine, Hershey, PA

Study Objectives: Excessive daytime sleepiness (EDS) is highly prevalent in the general population and is associated with occupational and public safety hazards. However, no study has examined the clinical and polysomnographic (PSG) predictors of the natural history of EDS.

Design: Representative longitudinal study.

Setting: Sleep laboratory.

Participants: From a random, general population sample of 1,741 individuals of the Penn State Adult Cohort, 1,395 were followed up after 7.5 years.

Measurements and Results: Full medical evaluation and 1-night PSG at baseline and standardized telephone interview at follow-up. The incidence of EDS was 8.2%, while its persistence and remission were 38% and 62%, respectively. Obesity and weight gain were associated with the incidence and persistence of EDS, while weight loss was associated with its remission. Significant interactions between depression and PSG parameters on incident EDS showed that, in depressed individuals, incident EDS was associated with sleep disturbances, while in non-depressed individuals, incident EDS was associated with increased physiologic sleep propensity. Diabetes, allergy/asthma, anemia, and sleep complaints also predicted the natural history of EDS.

Conclusions: Obesity, a disorder of epidemic proportions, is a major risk factor for the incidence and chronicity of excessive daytime sleepiness (EDS), while weight loss is associated with its remission. Interestingly, objective sleep disturbances predict incident EDS in depressed individuals, whereas physiologic sleep propensity predicts incident EDS in those without depression. Weight management and treatment of depression and sleep disorders should be part of public health policies.

Keywords: daytime sleepiness, depression, incidence, obesity, persistence, polysomnography

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INTRODUCTION

Excessive daytime sleepiness (EDS) is a pervasive problem that clinicians encounter very frequently in their practice. Population-wise, EDS is highly prevalent, affecting up to 30% of the general public, and is associated with significant personal and occupational sequelae and public safety hazards.[1–7] However, its etiology and pathophysiology is still poorly understood and little is known about how to treat EDS in specific patient populations.

Cross-sectional studies have shown that EDS is associated with psychiatric, cardiometabolic, and sleep disorders, particularly depression, obesity, and sleep apnea.[8–18] Despite its high prevalence and significant medical correlates, the natural history of EDS in the general population remains to be documented, and consequently, very little is known about the determinants of the incidence, persistence, and remission of EDS.[1,19,20] In fact, no study to date has explored the role of sleep, psychiatric, and medical disorders in the natural history of EDS using physiologic sleep data, i.e., polysomnography (PSG).

The aim of this study was to longitudinally examine the predictors of the natural history of EDS in a large, random, general population sample using both subjective and PSG data. We hypothesized that psychiatric, cardiometabolic, and sleep disorders are the main predictors of the incidence and persistence of EDS, and that different mechanisms account for such associations. Specifically, we hypothesized that (1) obesity and weight gain are strong predictors of the incidence and persistence of EDS, whereas weight loss is associated with its remission; and (2) depression and increased physiologic sleep propensity are independent risk factors for EDS, suggesting the presence of two distinct pathophysiologic pathways leading to EDS.

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Address correspondence to: Julio Fernandez-Mendoza, PhD, Sleep Research & Treatment Center, Department of Psychiatry, College of Medicine, Pennsylvania State University, 500 University Drive H073, Hershey, PA 17033; Tel: (717) 531-6385; Fax: (717) 531-6491; Email: jfernandez-mendoza@hmc.psu.edu

METHODS

Population

The data presented here were collected as part of the Penn State Adult Cohort, a population-based study of sleep disorders that used a 2-phase protocol to randomly select adult (age ≥ 20 years) men and women using standard sampling methods.[21–23] A comprehensive presentation of the design and sampling methodology has been presented elsewhere.[10,24–36] In brief, phase I included 16,583 men and women (response rates of 73.5% and 74.1%, respectively) and phase II included 1,741 randomly selected men and women studied in the sleep laboratory (response rates of 67.8% and 65.8%, respectively). Of those, 1,395 were followed up after an average of 7.5 years with a standardized telephone interview (response rates of 79.7% for the 1,741 and 90.9% for the 1,526 alive).[26–30] After giving a complete description of the study to the subjects, written and verbal informed consents were obtained at baseline and follow-up, respectively. The whole study procedure was approved by

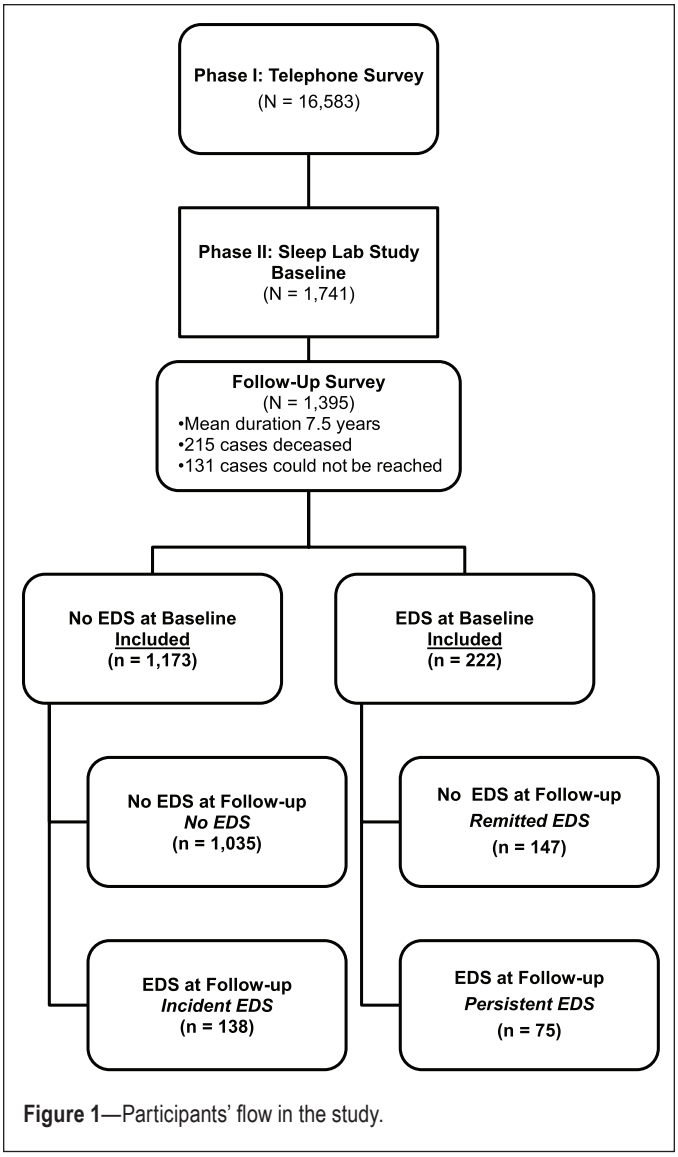

Figure 1—Participants' flow in the study.

the university's institutional review board. Figure 1 shows the participant flow in the study.

Definition of Incident, Persistent, and Remitted EDS

Commensurate with our previous cross-sectional study,[10] the presence of EDS was established based on a moderate-to-severe self-report of daytime drowsiness or sleepiness occurring most of the day *("Do you feel drowsy or sleepy most of the day but manage to stay awake?"*) and/or irresistible sleep attacks (*"Do you have any irresistible sleep attacks during the day?"*). Each question was answered on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe), and the presence of EDS was defined as a moderate or severe report to either of the 2 questions. Of the 1,395 subjects who were followed-up, 222 reported EDS at baseline and 1,173 did not. Subjects were classified according to their baseline and follow-up status into: *no EDS* (i.e., individuals without EDS at baseline and at follow-up; n = 1,035), *incident EDS* (i.e., individuals without EDS at baseline and with EDS at follow-up; n = 138), *remitted EDS* (i.e., individuals with EDS at baseline and without EDS at follow-up; n = 147), and *persistent EDS* (i.e., individuals with EDS at baseline and at follow-up; n = 75).

Key Measurements

All subjects completed a comprehensive sleep history and physical examination and were evaluated for one night in the sleep laboratory (8 h fixed-time period) in sound-attenuated, light- and temperature-controlled rooms using 16-channel PSG. Sleep recordings were scored according to standard criteria and evaluated for parameters of sleep continuity (sleep onset latency, total sleep time, etc.) as well as sleep architecture (e.g., percentage of sleep stages such as REM).[37] Increased physiologic sleep propensity was defined as a sleep onset latency ≤ 8 minutes.[38] Respiration was monitored throughout the night by use of thermocouples at the nose and mouth and thoracic strain gauges, and all-night recordings of hemoglobin oxygen saturation (SpO_2) were obtained with an oximeter attached to the finger. Sleep apnea was defined as an apnea-hypopnea index (AHI) ≥ 15.[24,25] Body mass index was based on measured height (cm) and weight (kg) during the subjects' sleep laboratory visit. Obesity was defined as a BMI ≥ 30 kg/m^2. We also ascertained the presence of sleep, physical and mental health problems, and substance use using a standardized questionnaire. The presence of sleep difficulty was established on 3 levels of severity: *insomnia*, *poor sleep*, and *normal sleep,* as defined elsewhere.[26–36] We ascertained whether the respondent was currently being treated for physical (ulcer, anemia, allergy/asthma, etc.) and mental (e.g., depression, alcohol abuse, drug abuse) health problems.[26,28] Hypertension and diabetes were also defined based on blood pressure measured in the evening and fasting blood glucose measured in the morning during the sleep laboratory visit, respectively.[32,33] Finally, we ascertained participants' daily consumption of caffeine, tobacco, and alcohol.[26–28]

Follow-up measures taken through telephone interview included the standardized questionnaire that subjects completed at baseline during their sleep laboratory visit,[26–29] which included self-reported height and weight data.[30] Sleep-related questions were used to establish the presence of EDS at follow-up as mentioned above.

Statistical Analyses

The design of this study included oversampling of those at higher risk for sleep apnea and women with markedly higher levels of BMI to increase the precision of the risk estimates. A sampling weight was developed so that the estimates could be inferred to the general population, including the use of the NHANES III laboratory data as the standard to be representative of the national population, as reported elsewhere.[10,21,24,55] Thus, all analyses were adjusted for the sampling weight, including the incidence rate (proportion of cases developing EDS at follow-up among those without EDS at baseline) and persistence or remission rates (proportion of cases with or without EDS at follow-up among those with EDS at baseline, respectively). Descriptive data (means, standard deviations, and proportions) of all variables were calculated for the entire population, as well as stratified by EDS status. Bivariate logistic regression was used to assess the odds ratios (OR) associated with each baseline risk factor with the incidence or persistence of EDS. Multivariable logistic regression models were used to assess the independent association and relative significance of each baseline risk factor with the incidence or persistence of

Table 1—Sociodemographic and behavioral characteristics at baseline.

	All (n = 1,395)	No EDS (n = 1,035)	Incident EDS (n = 138)	Remitted EDS (n = 147)	Persistent EDS (n = 75)
Gender					
Female, %	49.4	49.7	33.3	55.4	71.4†
Male, %	50.6	50.3	66.7**	45.6	28.6
Race					
Caucasian, %	93.2	94.5	86.7	88.2	81.0
Non-Caucasian, %	6.8	5.5	13.3**	11.8	19.0
Age, years	49.2 (13.1)	49.5 (12.9)	49.5 (15.6)	46.2 (13.0)	44.7 (9.7)
≤ 30, %	7.8	6.7	16.3*	13.2	7.1
31–49, %	47.0	47.2	36.5	47.1	66.7
50–64, %	31.4	32.3	24.0	32.4	23.8
≥ 65, %	13.9	13.8	23.1*	7.4	2.4
Caffeine, cups/day	2.3 (2.9)	2.3 (2.7)	2.1 (2.5)	2.7 (3.8)	2.7 (4.6)
None, %	33.6	33.2	38.1	30.4	38.1
1–2 cups/day, %	31.2	31.1	29.5	33.3	33.3
≥ 3 cups/day, %	35.2	35.6	32.4	36.2	28.6
Tobacco, cigarettes/day	4.0 (10.4)	3.8 (10.4)	4.0 (9.3)	5.5 (11.6)	6.2 (10.3)
None, %	78.8	79.7	76.9	73.5	66.7
1–20 cigarettes/day, %	9.8	10.0	9.6	7.4	9.5
≥ 20 cigarettes/day, %	11.4	10.3	13.5	19.1	23.8
Alcohol, drinks/day	1.2 (5.9)	1.3 (6.3)	1.3 (3.3)	0.7 (2.2)	0.5 (1.2)
None, %	73.2	72.1	76.9	80.9	81.0
1 drink/day, %	10.7	11.3	6.7	7.4	7.1
≥ 2 drinks/day, %	16.2	16.6	16.3	11.8	11.9

Data are mean (standard deviation), unless otherwise stated. All data are adjusted for sampling weight, except absolute number of cases across groups.
†P < 0.10, *P < 0.05, **P < 0.01.

EDS. We calculated the adjusted odds ratios (AOR) and their 95% confidence intervals (95% CI) from the multivariable regression models to estimate the odds associated with each risk factor. Given the known clustering of clinical risk factors, particularly obesity, sleep apnea, diabetes, and hypertension, a stepwise procedure examined which of these were the strongest predictors of incident EDS, using a backward conditional model followed by forced entry of sociodemographic factors (see supplemental material). Furthermore, based on previous clinical studies,[8,9] we further tested the interaction between depression and PSG parameters on incident EDS in multivariable logistic regression models adjusting for potential confounding factors associated with depression, PSG parameters, or incident EDS (i.e., gender, race, age, obesity, hypertension, diabetes, allergy/asthma, sleep difficulties, and sleep apnea). The no EDS group served as the reference for incident EDS, while the remitted EDS group served as the reference for persistent EDS. Finally, given the association of obesity with EDS,[12–15] we examined the role of weight gain and weight loss with the natural history of EDS. All analyses were conducted with SPSS version 21.0 for Windows.

RESULTS

The demographic and behavioral characteristics of the overall study sample and stratified by the natural history of EDS are presented in Table 1.

Incident EDS

The incidence of EDS was 8.2%. Male gender (OR = 2.0, 95% CI = 1.3–3.0, P < 0.01), non-Caucasian race (OR = 2.6, 95% CI = 1.4–4.8, P < 0.01), and young and older age were associated with incident EDS (see Table 1). Figure 2 depicts the U-shaped relationship between age and the incidence of EDS. Consistently, age was modeled using fine-grained, clinically meaningful categories in multivariable analyses, i.e., young adults (≤ 30 y), middle-age (31–64 y, which served as the reference group), and older adults (≥ 65 y).

As shown in Table 2, depression (OR = 2.8, 95% CI = 1.8–4.5, P = 0.00002), sleep apnea (OR = 2.2, 95% CI = 1.1–4.4, P = 0.031), obesity (OR = 2.1, 95% CI = 1.4–3.1, P = 0.001), and diabetes (OR = 2.0, 95% CI = 1.2–3.3, P = 0.008) were significantly associated with incident EDS, whereas hypertension (OR = 1.5, 95% CI = 1.0–2.2, P = 0.063), allergy/asthma (OR = 1.5, 95% CI = 1.0–2.3, P = 0.085), and migraine (OR = 1.7, 95% CI = 1.0–2.9, P = 0.073) were marginally associated. Other medical conditions (e.g., stroke, cancer, colitis, epilepsy, kidney/bladder, thyroidism, arthritis, and alcohol or drug abuse) were not associated with incident EDS. A multivariable backward regression model showed that depression (AOR = 2.6, 95% CI = 1.6–4.2, P = 0.0002), obesity (AOR = 1.8, 95% CI = 1.2–2.8, P = 0.011), diabetes (AOR = 1.7, 95% CI = 1.0–3.0, P = 0.046), and allergy/asthma (AOR = 1.5, 95% CI = 1.0–2.4, P = 0.057) were the strongest

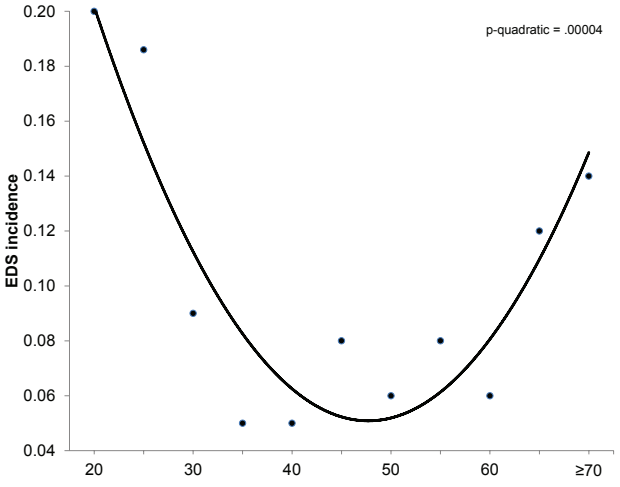

Figure 2—Age-specific incidence of EDS.

clinical predictors of incident EDS (see Table S1, supplemental material).

Table 3 shows that several subjective and objective sleep parameters were associated with the incidence of EDS. Reporting short (≤ 5 h) or long (> 8 h) sleep duration were significantly associated with incident EDS (OR = 2.7, 95% CI = 1.4–5.0, P = 0.002 and OR = 2.2, 95% CI = 1.0–4.8, P = 0.044, respectively), while reporting sleep difficulties was not significantly associated with incident EDS (OR = 1.3, 95% CI = 0.8–2.1 for poor sleep and OR = 1.5, 95% CI = 0.7–3.2 for insomnia, P-linear = 0.166). Snoring was significantly associated with incident EDS, particularly in those with milder levels of sleep apnea (OR = 1.9, 95% CI = 1.2–2.9, P = 0.004). Furthermore, PSG markers of sleep fragmentation, such as increased wake (P = 0.008) and stage 1 (P = 0.005) and decreased stage 2 (P = 0.037) and slow wave sleep (P = 0.083), as well as PSG markers of increased physiologic sleep propensity (i.e., sleep onset latency ≤ 8 min, OR = 2.7, 95% CI = 1.6–4.7, P = 0.0002) were associated with incident EDS.

Importantly, we found significant interactions between depression and PSG parameters of sleep onset latency (P = 0.001), total sleep time (P = 0.004), sleep efficiency (P = 0.005), total wake time (P = 0.007), percent of stage 1 (P = 0.010), and percent of REM sleep (P = 0.002) on incident EDS, even after adjusting for gender, race, age, obesity, hypertension, diabetes, allergy/asthma, sleep difficulties, and sleep apnea. As shown in Figure 3, the association of PSG parameters with incident EDS differed in depressed and non-depressed individuals. Longer sleep latency, higher wake time and percent of stage 1, and lower sleep efficiency and percent of REM sleep were associated with incident EDS in depressed individuals. In contrast, longer sleep duration, higher sleep efficiency, shorter sleep latency, and lower wake time, were associated with incident EDS in non-depressed individuals. In fact, increased physiologic sleep propensity (sleep onset latency ≤ 8 min) was significantly associated with incident EDS in those without depression (AOR = 3.1, 95% CI = 1.8–5.6, P = 0.0001) but not in those with depression (AOR = 0.9, 95% CI = 0.1–8.1, P = 0.993). Please see also Figure S1 (supplemental material).

Persistent EDS

The persistence and remission rates of EDS were 38% and 62%, respectively. Ulcer (OR = 3.6, 95% CI = 1.1–11.1, P = 0.030), anemia (OR = 2.9, 95% CI = 1.1–7.8, P = 0.040), and sleep difficulties (OR = 2.0, 95% CI = 1.1–3.6, P = 0.020) were significantly associated with persistent EDS, whereas depression (OR = 2.1, 95% CI = 1.0–4.6, P = 0.063), hypertension (OR = 2.1, 95% CI = 1.0–4.6, P = 0.064), allergy/asthma (OR = 2.0, 95% CI = 0.9–4.5, P = 0.096), female gender (OR = 2.0, 95% CI = 0.9–4.6, P = 0.095), and BMI (2 kg/m^2 increase OR = 1.1, 95% CI = 1.0–1.2, P = 0.125) were only marginally associated with persistent EDS. PSG parameters did not differ between remitted and persistent EDS, while reporting short or long sleep duration were associated with persistent EDS (see Table 3). A multivariable backward regression model showed that anemia (AOR = 3.4, 95% CI = 1.1–10.0, P = 0.031), sleep difficulties (AOR = 3.0, 95% CI = 1.1–8.1, P = 0.029), and BMI (2 kg/m^2 AOR = 1.1, 95% CI = 1.0–1.3, P = 0.088) were the strongest predictors of persistent EDS, whereas ulcer, depression, allergy/asthma, and hypertension did not enter the model when sleep difficulties were included (see Table S2, supplemental material).

Weight Gain and Weight Loss

Given the association of baseline obesity with EDS, we further explored whether weight gain and weight loss, as measured by ΔBMI, were associated with the natural history of EDS. As shown in Table 4, individuals with incident or persistent EDS gained significantly more weight as compared to those without EDS (ΔBMI 2.5 ± 3.5 and 2.8 ± 2.8 vs. 1.3 ± 3.2 kg/m^2, respectively), even after adjusting for baseline obesity (ΔBMI 2.4 ± 3.6, P = 0.001 and 2.7 ± 4.1, P = 0.006 vs. 1.4 ± 2.9 kg/m^2, respectively). Interestingly, individuals with remitted EDS gained significantly less weight as compared to individuals without EDS (ΔBMI 0.4 ± 2.7 vs. 1.3 ± 3.2 kg/m^2, P = 0.027), which indicated that an important proportion of remitted EDS cases lost weight over time (see Table 4). In fact, weight loss (i.e., ΔBMI ≤ −2.0 kg/m^2) was associated with remitted EDS (OR = 2.5, 95% CI = 1.2–5.1, P = 0.013), whereas weight gain (i.e., ΔBMI ≥ + 2.0 kg/m^2) was associated with incident (OR = 2.8, 95% CI = 1.8–4.3, P = 0.00006) and persistent EDS (OR = 2.7, 95% CI = 1.4–5.2, P = 0.003). These findings were similar when other indices of weight gain/loss (i.e., absolute or percent change in body weight) were examined (see Table 4) and when analyses were further adjusted for baseline sleep duration (ΔBMI = 1.4, 2.4, 2.9, and 0.5 kg/m^2 for none, incident, persistent, and remitted EDS, respectively).

DISCUSSION

The main findings of this population-based, longitudinal study are that (1) obesity, weight gain, and weight loss are associated with the incidence, persistence, and remission of EDS, respectively; and (2) objective sleep disturbance predicts the incidence of EDS in individuals with depression, while physiologic sleep propensity predicts the incidence of EDS in individuals without depression. These findings underscore that

Table 2—Clinical characteristics at baseline.

	All (n = 1,395)	No EDS (n = 1,035)	Incident EDS (n = 138)	Remitted EDS (n = 147)	Persistent EDS (n = 75)
Physical Health Problems					
No, %	35.9	38.5	27.9	22.1	7.1
Yes, %	64.1	61.5	72.1*	77.9	92.9*
Allergy/asthma					
No, %	72.9	74.4	66.7	70.3	53.7
Yes, %	27.1	25.6	33.3†	29.7	46.3†
Anemia					
No, %	91.5	92.3	92.4	88.2	72.1
Yes, %	8.5	7.7	7.6	11.8	27.9*
Diabetes					
No, %	86.2	88.1	79.0	72.1	73.8
Yes, %	13.8	11.9	21.0**	27.9	26.2
Hypertension					
No, %	64.4	66.2	57.1	58.8	40.5
Yes, %	35.6	33.8	42.9*	41.2	59.5†
Migraine					
No, %	87.2	89.2	83.7	73.5	61.9
Yes, %	12.8	10.8	16.3†	26.5	38.1
Obesity					
No, %	74.7	77.8	62.9	54.4	50.0
Yes, %	25.3	22.2	37.1**	45.6	50.0
Sleep apnea					
No, %	94.8	95.3	90.4	94.2	92.9
Yes, %	5.2	4.7	9.6*	5.8	7.1
Ulcer					
No, %	95.0	96.0	93.3	92.6	76.2
Yes, %	5.0	4.0	6.7	7.4	23.8*
Mental Health Problems					
No, %	80.6	84.6	70.5	54.4	38.1
Yes, %	19.4	15.4	29.5**	45.6	61.9†
Depression					
No, %	84.6	88.7	73.3	58.8	40.5
Yes, %	15.4	11.3	26.7**	41.2	59.5†

All data are adjusted for sampling weight, except absolute number of cases across groups. Diabetes = fasting blood sugar ≥ 126 mg/dL or being treated for diabetes. Hypertension = systolic ≥ 140 mm Hg and/or diastolic ≥ 90 mm Hg blood pressure or use of antihypertensive medication. Obesity = body mass index ≥ 30 kg/m^2. Sleep apnea = apnea-hypopnea index ≥ 15 events/hour of sleep. Depression = lifetime history of treatment for depression, including a history of suicidal thoughts or attempts. †P < 0.10, *P < 0.05, **P < 0.01.

obesity, depression, and sleep disorders should be our priority in terms of public health policies and early clinical interventions for EDS.

Incidence, Persistence, and Remission of EDS

As stated above, up to 30% of the general population complains of EDS, depending on the definition used.[1,2] For example, 8% to 10% of the general population has moderate-to-severe complaints of EDS.[1,10] Using this latter definition, we found that the incidence of EDS is about 8% and that it is very likely to remit (62%), with only about 38% persisting with the complaint after a long follow-up. This scenario is similar to that of "poor sleep," which is more likely to remit, while "insomnia" is a highly persistent disorder.[27,28] Thus, this study further suggests that EDS is a symptom rather than a disorder *per se* (i.e., hypersomnia).[2,10,11]

Role of Obesity, Weight Gain, and Weight Loss

In line with previous cross-sectional studies,[10,12–15] obesity and diabetes were independent risk factors for EDS. An important and novel finding in our study was that weight gain was a strong predictor of the incidence and persistence of EDS even in non-obese individuals. A recent longitudinal study showed that EDS was not a significant predictor of the incidence of obesity.[30] Together, these studies indicate that EDS is likely to be a consequence of metabolic aberrations associated with obesity rather than a premorbid characteristic of obese subjects. From a mechanistic standpoint, these data further suggest that metabolic aberrations and chronic low-grade inflammation, conditions common in obesity and diabetes, may play a role in the pathogenesis of EDS and fatigue[13–15,39] in a large proportion of individuals from the general population.

Table 3—Subjective and objective sleep characteristics at baseline.

	All (n = 1,395)	No EDS (n = 1,035)	Incident EDS (n = 138)	Remitted EDS (n = 147)	Persistent EDS (n = 75)
Subjective Sleep Difficulty					
Normal sleep, %	72.0	76.2	70.5	35.3	16.7
Poor sleep, %	20.7	17.8	21.0	50.0	54.8
Insomnia, %	7.3	6.0	8.6	14.7	28.6*
Subjective Sleep Duration, h	6.8 (1.3)	6.8 (1.2)	6.6 (1.7)	6.5 (1.5)	6.6 (1.8)
> 8 hours, %	6.1	5.5	10.1*	4.8	19.4*
7–8 hours, %	53.0	55.1	44.9	44.4	22.6
5–7 hours, %	30.9	31.1	27.0	34.9	29.0
≤ 5 hours, %	9.9	8.3	18.0*	15.9	29.0*
Sleep Onset Latency, min	33.1 (32.6)	32.7 (30.8)	32.5 (33.0)	32.0 (36.2)	39.3 (48.2)
≥ 30 minutes, %	41.1	41.8	39.0	33.3	38.1
8–30 minutes, %	45.1	45.6	35.2	49.3	50.0
≤ 8 minutes, %	13.8	12.6	25.7**	17.4	11.9
WASO, min	91.7 (56.7)	92.5 (56.5)	83.3 (55.9)	87.4 (53.3)	97.0 (58.6)
Awakenings, #	11.3 (7.0)	11.3 (6.9)	13.2 (8.1)**	10.4 (7.2)	8.7 (4.8)
Total Wake Time, min	124.9 (71.6)	125.2 (70.8)	116.2 (72.8)	119.4 (69.7)	136.2 (72.4)
Total Sleep Time, h	5.9 (1.2)	5.8 (1.2)	6.1 (1.2)†	5.9 (1.3)	5.6 (1.4)
7–8 hours, %	16.5	15.7	23.1	22.1	11.9
6–7 hours, %	36.9	37.1	40.4	26.5	38.1
5–6 hours, %	23.4	24.2	11.5	27.9	21.4
≤ 5 hours, %	23.3	23.0	25.0	23.5	28.6
Sleep Efficiency, %	73.8 (14.9)	73.7 (14.8)	75.8 (15.0)	74.8 (14.6)	70.9 (16.3)
Stage 1, %	11.3 (9.6)	11.1 (9.3)	13.8 (12.3)**	10.1 (8.6)	12.7 (10.8)
Stage 2, %	69.1 (9.3)	69.4 (9.3)	67.4 (9.1)*	68.4 (9.1)	67.3 (11.9)
SWS , %	3.0 (5.2)	2.9 (5.1)	2.0 (3.9)†	4.7 (7.7)	3.6 (4.7)
REM, %	16.6 (7.0)	16.6 (6.9)	16.7 (7.7)	16.9 (5.3)	16.4 (9.6)
Apnea-Hypopnea Index	2.5 (7.5)	2.3 (7.1)	3.6 (9.2)	1.5 (6.2)	4.7 (12.2)
Minimum SpO_2	92.6 (6.2)	92.7 (6.2)	92.4 (5.7)	93.1 (5.1)	92.2 (7.8)
Snoring					
No, %	70.7	74.4	61.5	35.3	47.6
Yes, %	29.3	25.6	38.5**	64.7	52.4

Data are mean (standard deviation), except otherwise stated. All data are adjusted for sampling weight, except absolute number of cases across groups. REM, rapid eye movement sleep; SWS, slow wave sleep; WASO, wake time after sleep onset. †P < 0.10, *P < 0.05, **P < 0.01.

Moreover, weight loss was a significant predictor of the remission of EDS in the present study. These data not only reinforce the etiological link between obesity/weight gain and the development and chronicity of EDS but also suggest that focusing on modifiable behavioral and metabolic factors associated with weight gain and weight loss will lead to higher success in reducing the prevalence and severity of EDS. It is important to keep in mind that weight gain or loss is likely to be associated with other factors (e.g., changes in diet and physical activity) that may be the actual cause of incident or remitted EDS. For example, increased physical activity may lead to both weight loss and reduced EDS or weight change may (partially or fully) mediate the association of physical activity with EDS. Future experimental and clinical studies should examine the underlying mechanisms in energy balance leading to weight loss and EDS remission.

Role of Depression and Objective Sleep Disturbances

We found a strong association between depression and EDS, which is consistent with previous cross-sectional studies.[8–12,18–20] A novel and important finding of this longitudinal study was that PSG characteristics were differentially associated with the incidence of EDS in individuals with and without depression. Specifically, we found that in individuals with depression, incident EDS was associated with PSG sleep disturbances, such as increased sleep onset latency. These longitudinal, population-based findings are consistent with previous clinical studies showing that the complaint of EDS in psychiatric disorders is more likely associated with a state of physiologic hyperarousal rather than with physiologic sleep propensity (i.e., hypoarousal of central origin).[8,9,11]

Role of Physiologic Sleep Propensity

In contrast, the incidence of EDS in individuals without depression was associated with increased physiologic sleep propensity. Previous studies have shown that increased daytime sleep propensity is associated with shorter nighttime sleep onset latency and longer sleep duration[5,40] as well as with significant genetic influences.[41–45] Our data suggest the existence of a phenotype of individuals without psychiatric disorders who

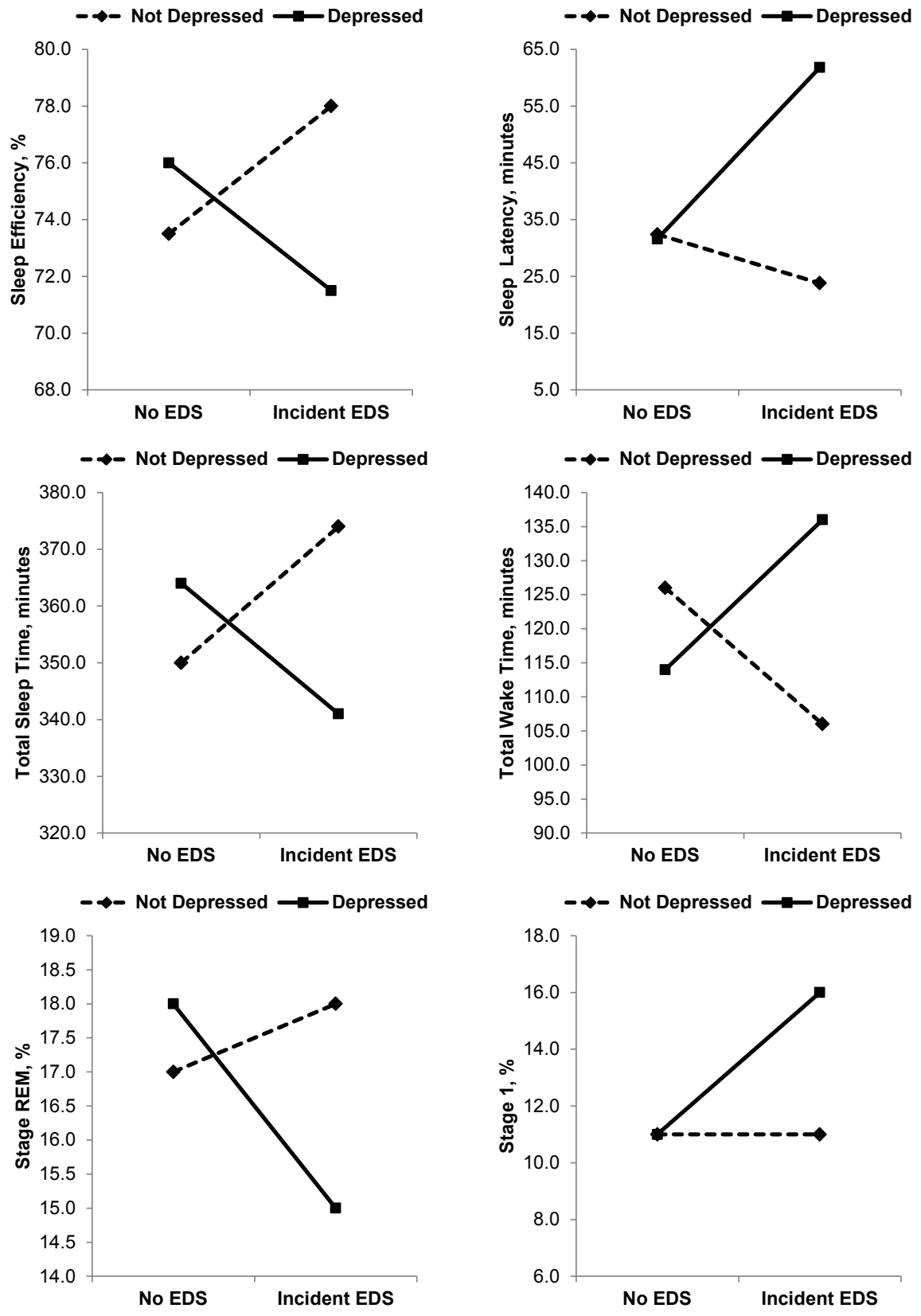

Figure 3—Graphic representation of the interaction between depression and polysomnographic characteristics on incident EDS. Depressed individuals with incident EDS showed sleep disturbances at baseline (longer sleep onset latency, shorter sleep duration, lower sleep efficiency, more time awake and in stage 1, and less time in REM sleep), while non-depressed individuals with incident EDS showed increased physiologic sleep propensity (shorter sleep latency, longer sleep duration, higher sleep efficiency, and less time awake). Data adjusted for gender, race, age, obesity, diabetes, hypertension, allergy/asthma, sleep difficulty, and sleep apnea.

Table 4—Association of weight gain and weight loss with the natural history of EDS.

	No EDS (n = 1,035)	Incident EDS (n = 138)	Remitted EDS (n = 147)	Persistent EDS (n = 75)
Weight at baseline, kg	76.6 (17.1)	81.3 (15.9)**	82.4 (12.3)	85.1 (15.8)
Weight at follow-up, kg	80.0 (19.3)	87.6 (18.1)**	83.2 (12.7)	92.0 (16.6)*
Δweight, kg	3.4 (9.1)	6.3 (10.8)**	0.8 (7.1)	6.9 (8.0)**
≤ −5 kg weight loss, %	8.7	10.7	17.9	7.1
No change, %	60.6	37.9	58.2	52.4
≥ +5 kg weight gain, %	30.7	51.5	23.9	40.5
Δweight, %	4.7 (11.3)	8.6 (13.5)**	1.6 (7.6)	9.1 (10.3)**
≤ −1% weight loss, %	26.4	25.0	29.4	11.9
No change, %	49.1	26.0	51.5	54.8
≥ +10% weight gain, %	24.4	49.0	19.1	33.3
BMI at baseline, kg/m^2	26.0 (4.8)	27.4 (4.3)**	28.5 (3.8)	30.3 (5.6)
BMI at follow-up, kg/m^2	27.3 (5.5)	29.9 (5.2)**	28.9 (4.1)	33.1 (6.1)**
ΔBMI, kg/m^2	1.3 (3.2)	2.5 (3.5)**	0.4 (2.7)	2.8 (2.8)**
≤ −2 kg/m^2 weight loss, %	6.7	11.5	16.7	7.1
No change, %	58.6	33.7	57.6	35.7
≥ +2 kg/m^2 weight gain, %	34.8	54.8	25.8	57.1

Data are mean (standard deviation), except otherwise stated. All data are adjusted for sampling weight, except absolute number of cases across groups. BMI, body mass index. * P < 0.05, ** P < 0.01.

have increased physiologic sleep propensity and significant risk of developing a disorder of EDS (e.g., hypersomnia of central origin). It is not clear, however, why these individuals with physiologic sleep propensity develop the complaint of EDS later on in life. Several putative mechanisms include (1) impaired homeostatic sleep/arousal mechanisms with increasing age, (2) fatigue-mediating factors (e.g., inflammatory) that increase with age, and/or (3) increased personal, occupational, and social demands that do not allow extended nighttime sleep or brief daytime naps to alleviate physiologic sleep pressure.

It is important to note that many patients with hypersomnia of central origin present with depressive symptoms or even clinical diagnosis of depression.[11] In this instance, the differential diagnosis of hypersomnia of central origin vs. hypersomnia related to depression becomes a challenge in the clinic if it is only based on clinical history and subjective reports. Our longitudinal data confirm and expand our previous findings[9] that objective measures of EDS may be necessary to confirm or rule-out the presence of increased physiologic sleep propensity, particularly in depressed individuals.

Role of Aging, Sleep, and Other Medical Conditions

The incidence of EDS was higher in the young and in the old; the former most likely as a result of increased unmet sleep needs and the latter associated with increased health problems and medical illness,[1,2,10] which was evidenced by the association of reported insufficient and long sleep with incident EDS. Snoring, particularly in those with milder levels of sleep apnea, was significantly associated with incident EDS, which indicates that these individuals are likely to progress into more severe forms of sleep apnea, most likely through further weight gain, and develop clinical symptoms of the disorder, i.e., EDS. Interestingly, moderate-to-severe sleep apnea at baseline was significantly associated with EDS; however, it did not enter the multivariable model after adjusting for obesity. These data reinforce the hypothesis that metabolic and inflammatory aberrations may play a major role in the pathogenesis of EDS, even in individuals with sleep apnea.[39] Furthermore, allergy/asthma, anemia, ulcer, and hypertension were associated with the incidence or persistence of EDS. The association of allergy/asthma with incident EDS was weaker than that of metabolic and mood disorders, while the link between ulcer, allergy/asthma, depression, and hypertension with the persistence of EDS was the presence of complaints of sleep difficulties, which may be the final common path for the persistence of the complaint of EDS in individuals with those conditions. It remains to be tested whether treatment of underlying sleep difficulties improves both the medical disorder and associated EDS or whether treatment of the underlying medical disorder improves sleep and associated EDS. These data reinforce the inclusion of blood, respiratory, pain, and sleep disorders, including unmet sleep needs, as part of the thorough assessment of patients with EDS.

Limitations

Some limitations should be taken into account when interpreting our results. The objective sleep in this study was based on one night of PSG, which may not be representative of the subjects' typical or optimal sleep and may be affected by the "first night effect." Nevertheless, large epidemiological studies show high consistency in sleep parameters (e.g., average sleep duration of about 6 h) independent of whether sleep is recorded at home with PSG,[46] for three consecutive nights with actigraphy,[47] or in the sleep laboratory with PSG.[32–36] The consistency among these three large epidemiological studies supports the validity of our findings. In the present study, we did not ascertain EDS using standardized questionnaires or physiologic measures of daytime sleep propensity, i.e., multiple sleep latency test. Despite the limitations of using two

items to ascertain the complaint of EDS, these items specifically referred to two core symptoms used in the diagnosis of hypersomnia (sleepiness or drowsiness and irresistible sleep attacks) and capture the complaints typically expressed by patients.[38] Importantly, the prevalence estimate in the Penn State Cohort using this definition of EDS[10] is consistent with that of other population-based studies, where the complaint of EDS is defined based on severity criteria.[1,2] Nevertheless, the potential effect of measurement characteristics, measurement error, and regression to the mean in our natural history estimates cannot be entirely ruled out. The study had one long follow-up time point, which precludes an assessment of a potential waxing and waning pattern and short-term, stronger associations with baseline predictors. Similarly, the lack of measures of habitual sleep duration at follow-up precludes examining the trajectory of sleep duration as it relates to the natural history of EDS, particularly its incidence and persistence. Another potential limitation is that we had to rely on self-reported data for our weight gain/loss analyses. However, we have previously shown that objectively measured and self-reported weight data highly correlated in our cohort,[30] which provides further validity to the present findings.

Implications for Clinical Practice and Public Health Policy

In summary, our data indicate that obesity and weight gain play a key role in the development and chronicity of EDS, whereas weight loss is associated with its remission. Furthermore, EDS in individuals with depression is associated with objective sleep disturbances, while increased physiologic sleep propensity is an independent predictor of EDS. These data suggest potentially different etiologic mechanisms for the complaint of EDS in the presence of psychiatric disorders, i.e., physiologic hyperarousal vs. central nervous system hypoarousal. Future clinical studies should test whether (1) the complaint of EDS in depression may respond better to treatments targeting mood and nighttime sleep disturbances rather than pharmacological agents increasing physiologic alertness, and (2) whether extending sleep (e.g., regular sleep schedules, brief daytime naps) and/or enhancing alertness through pharmacological agents (stimulants) prevent EDS in individuals with physiologic sleep propensity. From a public health policy perspective, this study suggests that obesity, depression, and sleep disorders should be a priority in the prevention and reduction of EDS in the general population.

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Table S1—Multivariable regression models of clinical factors predicting incident excessive daytime sleepiness.

	Incident EDS	
	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**
R^2	0.06	0.13
Male	–	2.0 (1.2–3.3) **
Non-Caucasian	–	2.8 (1.4–5.4) **
Age ≤ 30 years	–	4.2 (2.3–7.8) **
Age ≥ 65 years	–	2.2 (1.3–3.8) **
Allergy/asthma	1.5 (1.0–2.4) †	1.6 (1.0–2.6) *
Diabetes	1.7 (1.0–3.0) *	1.4 (0.8–2.5)
Hypertension	1.1 (0.7–1.8)	–
Migraine	1.2 (0.7–2.2)	–
Obesity	1.8 (1.2–2.8) **	2.0 (1.2–3.2) **
Sleep apnea	1.7 (0.8–3.7)	–
Depression	2.6 (1.6–4.2) **	3.1 (1.8–5.2) **

Model 1 = multivariable backward conditional model of clinical risk factors. Model 2 = model 1 plus forced entry of sociodemographic factors. OR, odds ratio; 95% CI, 95% confidence interval. † P < 0.10, * P < 0.05, ** P < 0.01.

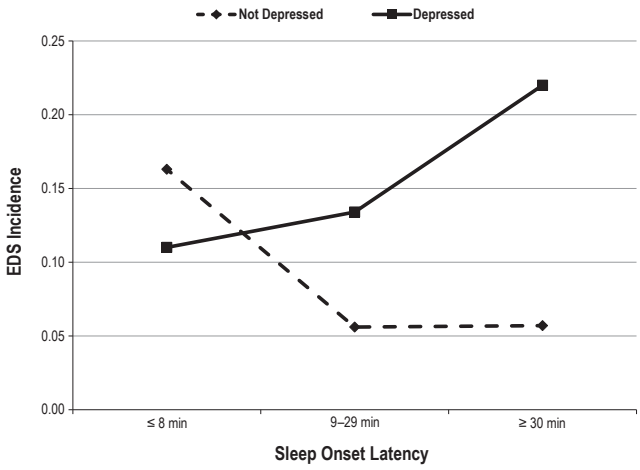

Figure S1—Interaction between depression and polysomnographic sleep onset latency on incident excessive daytime sleepiness. Depressed individuals had a higher incidence of EDS (17%) than non-depressed individuals (7%). Individuals with physiologic sleep propensity (≤ 8 min) had a higher incidence of EDS (15%) than those with normal (9–29 min) or increased (≥ 30 min) sleep latency (7% and 8%, respectively). A significant interaction between these two factors showed that depressed individuals with increased sleep latency had a higher incidence of EDS (22%) than depressed individuals with normal sleep latency or physiologic sleep propensity (13.4% and 11.0%, respectively), whereas in contrast non-depressed individuals with physiologic sleep propensity had a higher incidence of EDS (16.3%) than non-depressed individuals with normal or increased sleep latency at baseline (5.6% and 5.7%, respectively). Data adjusted for gender, race, age, obesity, hypertension, diabetes, allergy/asthma, sleep difficulties, and sleep apnea.

Table S2—Multivariable regression models of clinical factors predicting persistent excessive daytime sleepiness.

	Persistent EDS	
	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**
R^2	0.15	0.19
Female	–	1.4 (0.6–3.5)
Race	–	2.4 (0.6–9.3)
Age ≤ 30 years	–	0.5 (0.1–2.7)
Age ≥ 65 years	–	0.3 (0.1–4.3)
Allergy/asthma	1.7 (0.7–4.2)	–
Anemia	3.4 (1.1–10.0) *	3.2 (1.0–10.3) *
Hypertension	1.6 (0.7–3.9)	–
BMI (per 2 kg/m^2 increase)	1.1 (0.9–1.2) †	1.1 (1.0–1.2)
Ulcer	2.6 (0.8–9.0)	–
Depression	1.4 (0.6–3.6)	–
Sleep difficulties	3.0 (1.1–8.1) *	2.9 (1.0–8.3) *

Model 1 = multivariable backward conditional model of clinical risk factors. Model 2 = model plus forced entry of sociodemographic factors. OR, odds ratio; 95% CI, 95% confidence interval. † P < 0.10, * P < 0.05.