Sleep Complaints Among Adults With Major Depressive Episode Are Associated With Increased Risk of Incident Psychiatric Disorders: Results From a Population-Based 3-Year Prospective Study

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ABSTRACT

Objective: Sleep alterations have been suggested as a cause and consequence of psychiatric disorders. In this context, we evaluated the incidence of psychiatric disorders following sleep complaints in adults with major depressive episode (MDE).

Methods: In a large, nationally representative 3-year prospective survey, the National Epidemiologic Survey on Alcohol and Related Conditions conducted in 2001–2002 (Wave 1) and 2004–2005 (Wave 2), we used structural equation modeling to examine shared and specific effects of trouble falling asleep, early morning awakening, and hypersomnia on incidence of common comorbid *DSM-IV* disorders among patients with MDE. The analyses adjusted for sociodemographic and clinical characteristics, including sedative or tranquilizer use.

Results: Among participants with MDE at Wave 1, 3-year incidence rates were dysthymia = 2.9%, general anxiety disorder = 8.2%, panic disorder = 3.4%, social anxiety disorder = 4.0%, specific phobia = 3.0%, alcohol use disorder = 8.1%, nicotine dependence = 6.2%, cannabis use disorder = 2.7%, and other drug use disorder = 4.9%. Participants with 3-year incident psychiatric disorders commonly had trouble falling asleep (67.6% for cannabis use disorder to 76.4% for panic disorder), early morning awakening (43.3% for cannabis use disorder to 55.6% for dysthymia), and hypersomnia (51.3% for nicotine use disorder to 72.1% for social anxiety disorder). The effects of the incident general psychopathology factor, representing mechanisms related to incidence of all psychiatric disorders, were exerted almost exclusively through a factor representing shared effect across all sleep complaints. Sleep complaints were associated with increased risk of incident psychiatric disorders, independent of sociodemographic and clinical characteristics.

Conclusions: These findings suggest that sleep complaints should be clinically assessed in all psychiatric disorders, as these prodromal symptoms might constitute transdiagnostic biomarkers and therapeutic targets for prevention.

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Major depressive episode (MDE) is a common and disabling psychiatric disorder, with an estimated prevalence of approximately 7% among adults.[1] Individuals with MDE are especially at risk for increased medical comorbidities including psychiatric comorbidities, with poorer medical outcomes compared to the general population.[2,3] Sleep disturbance is one of the most common symptoms associated with MDE, affecting 92% of patients.[4] Sleep alterations may be both a consequence and a cause of MDE. In addition to being a core symptom during the acute phase, sleep disturbances often precede depressive episodes and may persist into remission.[5,6] Improving sleep disturbances in patients with MDE, such as through cognitive behavioral therapy for insomnia, also tends to improve depressive symptoms and outcomes.[7,8] This bidirectional association between MDE and sleep disturbance offers a new perspective that sleep complaints might be a predictive prodromal symptom.[5] Nevertheless, the association of sleep complaints with development of other psychiatric disorders in patients with MDE remains poorly documented.

In recent years, much of the epidemiologic research on sleep in mental health has focused on sleep duration rather than quality. It is now clear that shorter sleep duration is associated with many psychiatric and addiction comorbidities.[9] Several studies have reported an association between reduced sleep and anxiety and depressive disorders; almost 1 in 2 patients with reduced sleep suffers from anxiety or depression.[10–13] Longer sleep duration also appears to be an indicator of poor mental health.[13]

Sleep complaints are associated with many psychiatric complications and adverse outcomes, including suicide attempts,[9,14] deaths by suicide,[15,16] and substance overdoses,[17,18] as well as decreased life expectancy[19,20] and lower quality of life.[21] These observations have renewed interest

Clinical Points

- A history of trouble falling asleep, early morning awakening, and hypersomnia in depressed individuals increased the risk of incident psychiatric disorders.
- The findings of this study suggest the potential value of including insomnia and hypersomnia in clinical assessments of all psychiatric disorders.
- Insomnia and hypersomnia symptoms may be prodromal transdiagnostic biomarkers and easily modifiable therapeutic targets for the prevention of psychiatric disorders.

in the relationship between sleep disturbances and psychiatric disorders.[22] Longitudinal studies may help to better understand these relationships. In previous work, we reported that sleep complaints are associated with an increased risk of attempting suicide independently of psychiatric disorders.[23] Previous research has also demonstrated that the effects of concurrent psychiatric disorders on suicidal risk are almost exclusively due to a general psychopathological factor representing the common effects of all psychiatric disorders.[24,25] Yet, there is no evidence of an association between sleep complaints and incidence of common psychiatric disorders. If sleep disturbances increase the incidence of common psychiatric disorders independent of sociodemographic and clinical characteristics, assessment of sleep symptoms could help identify individuals at high risk of developing psychiatric disorders and could be a potential therapeutic target for mental health prevention.

To assess this hypothesis, we examined the shared and specific effects of 3 different sleep complaints (trouble falling asleep, early morning awakening, and hypersomnia) on the incidence of a wide range of *DSM-IV* Axis I disorders among adults with MDE. Because antisocial personality disorder, use of sedatives or tranquilizers, and sociodemographic characteristics and other characteristics including MDE severity (number of MDE symptoms), poverty, obesity, education level, and stressful life events may confound this association,[24,26,27] we adjusted our analyses for these variables. Moreover, since dimensions underlying psychopathology are known to be correlated, we used a bifactor latent variable approach to disentangle the effects shared by all psychiatric disorders (ie, general psychopathology), those specific to dimensions of psychopathology (eg, internalizing dimension), and those specific to individual psychiatric disorders (eg, dysthymia).[24,25] To our knowledge, this is the most extensive prospective assessment of associations between sleep complaints and incident psychiatric disorders. Based on prior research, we hypothesized that sleep complaints would be associated with incidence of a broad range of incident psychiatric disorders and that these associations would be shared by all sleep complaints and primarily mediated by the independent effects of broad underlying dimensions of psychopathology. These underlying psychopathological dimensions mediate associations of the risk factors with psychiatric disorders and support a transdiagnostic orientation to etiologic research and treatment development.

METHODS

Sample

Data were drawn from Wave 1 and Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationally representative face-to-face survey of the US adult population, conducted in 2001–2002 (Wave 1) and 2004–2005 (Wave 2) by the National Institute on Alcoholism and Alcohol Abuse (NIAAA) and described in detail elsewhere.[28] Although Wave 1 of the NESARC examined a wide range of Axis I and Axis II psychiatric disorders, several disorders, including psychotic disorders and borderline personality disorder, were not evaluated. The target population included the civilian noninstitutionalized population, 18 years and older, residing in the United States. The cumulative response rate at Wave 2 was 70.2%, resulting in 34,653 Wave 2 interviews.[28] The Wave 2 NESARC data were weighted to be representative of the US civilian population based on the 2000 census. The research protocol, including written informed consent procedures, received full human subjects review and approval from the US Census Bureau and the Office of Management and Budget. The present analysis includes the 2,864 participants who met criteria for major depressive episode (MDE) in the year prior to Wave 1, with possibly other associated psychiatric diagnoses (eg, bipolar disorder), and who completed interviews at both waves.

Measures

Assessments of past-year DSM-IV Axis I disorders at Wave 1. MDE was assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule, *DSM-IV* version (AUDADIS-IV), a valid and reliable structured diagnostic instrument administered by trained lay interviewers.[28,29] MDE diagnosis was based on the past 12 months assessment prior to Wave 1.

Assessments of baseline sleep complaints at Wave 1. Three sleep complaints (trouble falling asleep, early morning awakening, and hypersomnia) were assessed on a lifetime basis among participants with MDE at Wave 1 with the 3 following questions: "Did you ever have trouble falling asleep nearly every day for at least 2 weeks?" "Did you ever wake up too early nearly every day for at least 2 weeks?" and "Did you ever sleep more than usual nearly every day for at least 2 weeks?"

Assessments of incident DSM-IV Axis I disorders between the two waves. Incident psychiatric disorders were assessed during a 3-year follow-up period at Wave 2 using the AUDADIS-IV.[28,29] Selected Axis I diagnoses included substance use disorders (alcohol use disorder, nicotine dependence, cannabis use disorder, and other drug use disorder), mood disorders (dysthymic disorder), and anxiety disorders (panic disorder, social anxiety disorder, specific

phobia, and generalized anxiety disorder). The test-retest reliability and validity of AUDADIS-IV measures of *DSM-IV* psychiatric disorders is good to excellent for substance use disorders and fair to good for other disorders.[29–31]

Covariates: sociodemographic and clinical characteristics at Wave 1. Sociodemographic and clinical characteristics included sex (men vs women), age (18–29, 30–44, 45–64, 65+ years), race-ethnicity (White vs non-White), marital status (married vs non-married), poverty (annual household income < $20,000), obesity (body mass index ≥ 30 kg/m^2), past-year use of sedatives or tranquilizers, and education level (less than high school vs high school graduate or higher). Antisocial personality disorder was assessed on a lifetime basis using the AUDADIS-IV. Number of MDE symptoms was assessed using 21 symptoms recorded based on the 12-month period prior to Wave 1. In addition, participants were asked about 12 stressful life events concerning a variety of occupational, familial, financial, and legal issues and whether they had experienced these events in the year before the Wave 1 interview. We categorized this variable into 3 classes: 0, 1, and 2+ past-year stressful life events.[24]

Statistical Analysis

Weighted percentages and their corresponding standard errors were calculated to provide descriptive information about the relationships of sleep complaints with psychiatric disorders incidence between the two waves. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated for each sleep complaint at Wave 1 with each incident psychiatric disorder at Wave 2 at the bivariate level. Because sleep complaints frequently co-occur and it is unclear whether only specific sleep complaints predict occurrence of psychiatric disorders or whether all types of sleep complaints increase this risk, we first examined the structure of sleep complaints. Based on prior work,[32] we used confirmatory factor analysis (CFA) and hypothesized that a single dimension, "general sleep complaints," representing nonspecific effects shared by all sleep complaints would provide a good fit to the latent structure underlying sleep complaints in the general population.

Because bivariate analyses do not properly model comorbidity and can lead to an inflation of type I error due to multiple comparisons (ie, each disorder times each outcome), we used CFA to identify the latent structure underlying individual incident psychiatric disorders assessed at Wave 2. Specifically, based on previous models used to examine the relationship of psychiatric disorders with suicide attempt in these data,[24,25] we performed a bifactor CFA model to determine whether a general psychopathology factor measured by all psychiatric disorders in addition to disorder-specific factors (eg, distress, fear, and externalizing dimensions) fit the underlying structure of incident psychiatric disorders assessed at Wave 2. To assess the robustness of our results and facilitate comparisons with other work, we conducted a sensitivity analysis using an alternative approach to modeling psychiatric disorder comorbidity and built upon the distress-fear-externalizing CFA model that includes antisocial personality disorder, but not other personality disorders, and performed a bifactor CFA model.[33]

We examined measures of goodness-of-fit, including the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the root mean squared error of approximation (RMSEA). CFI and TLI values > 0.95 and RMSEA values < 0.06 were used to indicate good model fit.[34]

Finally, we used a structural equation model to assess the shared and specific associations of the different sleep complaints at Wave 1 on incident psychiatric disorders at Wave 2, while adjusting for sociodemographic and clinical characteristics (sex, age, race-ethnicity, marital status, poverty, obesity, past-year use of sedatives or tranquilizers, education level, and past-year stressful life events), number of MDE symptoms, and antisocial personality disorder. Specifically, we examined 2 sets of relationships: (1) the nonspecific effect exerted by all sleep complaints, represented by the general sleep complaints factor, and (2) the specific associations of each sleep complaint beyond the effect of that factor with the incident general psychopathology factor between the two waves. The specific effect of each sleep complaint was examined using modification indices (ie, χ^2 tests with 1 degree of freedom) to test if the residuals associated with each sleep complaint were correlated with the incident general psychopathology factor between the two waves.

Because we were specifically interested in the relationship between sleep complaints and the incident general psychopathology factor, and to avoid including associations that could be significant due to multiple testing (1 factor and 3 sleep indicators times 1 outcome), we considered associations significant with 2-sided Bonferroni-corrected P value < .05/4 (P < .0125), corresponding to modification indices > 6.24, and applied the same statistical threshold to covariates, which were not the main objective of the study.

Exploratory analyses were conducted to examine two sets of relationships: (1) the associations of the general sleep complaints factor with each individual psychiatric disorder and (2) the associations of each sleep complaint with each psychiatric disorder beyond and above those prior associations.

Analyses were conducted in Mplus Version 7.3. The default estimator for the analysis was the variance-adjusted weighted least squares (WLSMV), a robust estimator appropriate for ordered categorical and dichotomous observed variables. All analyses accounted for NESARC's complex sampling design.

RESULTS

Associations of Sleep Complaints With Incident Selected Psychiatric Disorders

Among participants with MDE in the year prior to Wave 1, the incidence rates for psychiatric disorders between the two waves ranged from 2.7% (SE = 0.4) for cannabis use disorder to 8.2% (SE = 0.6) for general anxiety disorder (Table 1).

Table 1. Frequency Distribution of Sleep Complaints, Antisocial Personality Disorder, and Sociodemographic Characteristics at Wave 1 According to the Incidence of Psychiatric Disorders Between Wave 1 and Wave 2 Among Participants With a Major Depressive Episode in the Year Prior to Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (N = 2,864)[a]

	Incident Wave 2 disorders									
	Dysthymia (N = 88, 2.9%, SE = 0.4) % (SE)	General anxiety disorder (N = 244, 8.2%, SE = 0.6) % (SE)	Panic disorder (N = 110, 3.4%, SE = 0.4) % (SE)	Social anxiety disorder (N = 115, 4.0%, SE = 0.4) % (SE)	Specific phobia (N = 94, 3.0%, SE = 0.4) % (SE)	Alcohol use disorder (N = 223, 8.1%, SE = 0.6) % (SE)	Nicotine use disorder (N = 167, 6.2%, SE = 0.6) % (SE)	Cannabis use disorder (N = 76, 2.7%, SE = 0.4) % (SE)	Other drug use disorder (N = 131, 4.9%, SE = 0.6) % (SE)	No incident psychiatric disorders (N = 1,986, 69.2%, SE = 1.1) % (SE)
Sleep complaints										
Trouble falling asleep	73.5 (6.4)	68.2 (3.8)	76.4 (5.3)	70.5 (5.5)	69.5 (5.6)	71.0 (3.6)	69.3 (4.7)	67.6 (6.1)	71.3 (6.1)	70.9 (1.4)
Early morning awakening	55.6 (7.0)	50.1 (4.1)	50.4 (6.0)	45.8 (5.3)	54.4 (5.9)	44.3 (4.0)	49.7 (4.5)	43.3 (6.3)	45.6 (6.4)	57.7 (1.5)
Hypersomnia	51.3 (6.9)	52.6 (3.7)	52.8 (6.1)	72.1 (4.5)	66.8 (5.5)	53.4 (4.2)	51.3 (5.0)	71.9 (5.3)	68.3 (4.7)	46.9 (1.5)
No. of sleep complaints										
0	10.8 (5.2)	6.1 (1.9)	9.9 (4.5)	5.0 (2.1)	5.8 (2.6)	7.6 (2.3)	6.1 (2.7)	3.1 (1.9)	5.6 (2.7)	5.1 (0.7)
1	23.0 (5.7)	31.9 (3.8)	21.9 (4.5)	27.3 (5.3)	23.4 (4.8)	32.0 (3.7)	32.8 (4.5)	31.2 (6.4)	29.2 (5.3)	29.8 (1.3)
2	41.5 (6.9)	46.9 (4.1)	47.7 (6.1)	41.4 (5.9)	45.2 (6.1)	44.5 (3.8)	46.0 (4.9)	45.5 (7.8)	40.0 (5.5)	49.2 (1.4)
3	24.8 (6.0)	15.1 (2.8)	20.6 (5.1)	26.4 (5.1)	25.6 (6.0)	16.0 (2.8)	15.0 (3.2)	20.2 (5.1)	25.2 (4.8)	16.0 (1.0)
Wave 1 disorders										
Antisocial personality disorder	7.8 (3.2)	12.5 (2.6)	11.2 (4.1)	5.3 (2.3)	10.9 (3.8)	15.5 (3.2)	13.3 (3.2)	12.8 (3.5)	25.2 (5.0)	9.8 (0.9)
No. of MDE symptoms, mean (SE)	12.3 (0.6)	11.6 (0.3)	11.8 (0.4)	12.5 (0.4)	12.5 (0.4)	11.8 (0.3)	11.9 (0.3)	12.4 (0.4)	12.6 (0.4)	11.7 (0.1)
Sex										
Men	31.3 (6.9)	29.1 (3.9)	21.2 (5.0)	23.2 (4.5)	23.0 (4.9)	40.7 (4.0)	34.9 (4.4)	31.3 (5.7)	44.1 (6.1)	33.0 (1.3)
Women	68.7 (6.9)	70.9 (3.9)	78.8 (5.0)	76.8 (4.5)	77.1 (4.9)	59.3 (4.0)	65.1 (4.4)	68.7 (5.7)	55.9 (6.1)	67.1 (1.3)
Age										
18–29 y	37.5 (7. 3)	29.6 (3.8)	47.9 (5.9)	38.9 (5.8)	29.8 (6.2)	51.0 (3.9)	42.0 (4.5)	63.1 (7.0)	49.8 (5.7)	26.8 (1.3)
30–44 y	34.6 (6.5)	34.1 (3.9)	18.7 (4.3)	26.3 (4.6)	35.9 (6.5)	30.0 (3.7)	27.7 (4.0)	28.2 (5.8)	35.3 (5.6)	32.1 (1.3)
45–64 y	21.3 (5.8)	33.7 (3.8)	28.6 (5.0)	32.3 (5.4)	30.5 (5.3)	17.5 (2.7)	26.0 (4.0)	8.7 (3.1)	14.7 (3.3)	32.5 (1.4)
65+ y	6.6 (3.1)	2.7 (1.0)	4.8 (2.3)	2.4 (1.5)	3.8 (2.5)	1.6 (0.9)	4.3 (2.2)	0.0 (0.0)	0.1 (0.1)	8.6 (0.7)
Race/ethnicity										
White	85.3 (5.3)	88.0 (2.4)	84.2 (4.6)	89.3 (3.1)	92.3 (2.4)	89.5 (2.0)	77.5 (4.4)	83.5 (5.3)	89.9 (3.3)	84.9 (1.3)
Non-White	14.8 (5.3)	12.0 (2.4)	15.8 (4.6)	10.7 (3.1)	7.7 (2.4)	10.5 (2.0)	22.5 (4.4)	16.5 (5.3)	10.1 (3.3)	15.1 (1.3)
Marital status										
Married or living as if married	48.8 (6.7)	56.8 (3.9)	37.6 (5.5)	49.0 (5.7)	47.5 (6.7)	42.0 (4.3)	38.0 (5.1)	34.5 (6.2)	35.1 (5.0)	50.2 (1.5)
Not married	51.2 (6.7)	43.2 (3.9)	62.5 (5.5)	51.0 (5.7)	52.5 (6.7)	58.0 (4.3)	62.0 (5.1)	65.5 (6.2)	64.9 (5.0)	49.8 (1.5)
Poverty (household income < $20,000)	25.1 (5.2)	31.0 (3.7)	32.3 (5.3)	30.6 (5.3)	29.6 (5.1)	29.6 (3.6)	35.0 (4.4)	28.2 (6.2)	33.1 (5.1)	26.5 (1.2)
Obesity (BMI ≥ 30 kg/m^2)	25.0 (5.8)	37.7 (4.1)	27.9 (5.1)	32.5 (5.5)	30.4 (6.2)	23.0 (3.4)	27.0 (4.3)	28.1 (6.5)	27.3 (4.6)	30.0 (1.4)
Past-year use of sedatives or tranquilizers	1.8 (1.0)	5.2 (1.7)	9.6 (3.5)	9.2 (3.2)	7.4 (3.7)	9.0 (2.3)	6.2 (2.5)	20.0 (5.7)	25.4 (5.8)	4.2 (0.5)
No. of past-year stressful life events										
0	7.6 (3.2)	12.3 (3.2)	6.5 (2.8)	6.1 (2.6)	13.8 (4.2)	7.2 (2.0)	8.0 (2.3)	8.3 (3.9)	3.6 (1.9)	11.0 (0.8)
1	16.4 (5.7)	18.3 (3.1)	14.6 (4.8)	12.8 (3.4)	12.0 (3.8)	13.5 (2.5)	17.2 (4.2)	4.4 (2.9)	16.3 (4.6)	17.3 (1.0)
2+	76.1 (6.2)	69.5 (3.9)	78.9 (5.1)	81.1 (4.1)	74.2 (5.2)	79.4 (3.3)	74.8 (4.3)	87.3 (4.7)	80.1 (4.8)	71.7 (1.1)
Education level										
Less than high school	8.8 (3.8)	6.3 (2.6)	6.5 (2.5)	3.3 (1.6)	5.5 (2.6)	2.8 (1.3)	4.7 (1.8)	2.2 (1.5)	0.9 (0.6)	5.3 (0.7)
High school graduate or higher	91.2 (3.8)	93.7 (2.6)	93.5 (2.5)	96.7 (1.6)	94.5 (2.6)	97.3 (1.3)	95.4 (1.8)	97.9 (1.5)	99.1 (0.6)	94.7 (0.7)

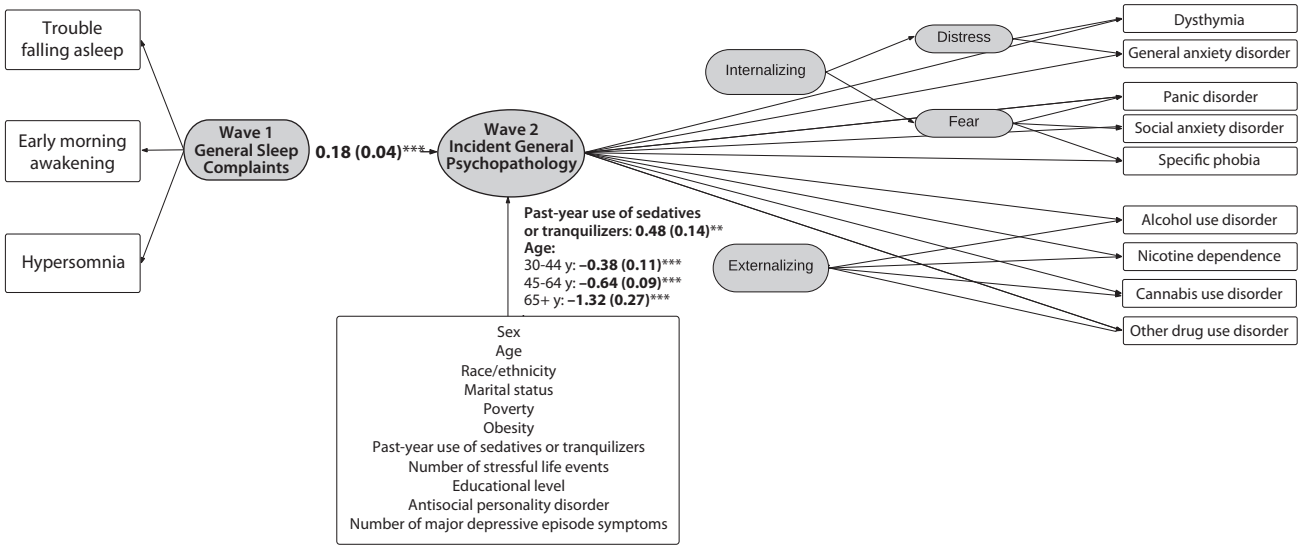
[a]Percentages are weighted.
Abbreviations: BMI = body mass index, CI = confidence interval, MDE = major depressive episode, SE = standard error.

Table 2. Associations of Sleep Complaints, Antisocial Personality Disorder, and Sociodemographic Characteristics at Wave 1 According to the Incidence of Psychiatric Disorders Between Wave 1 and Wave 2 Among Participants With a Major Depressive Episode in the Year Prior to Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (N = 2,864)[a]

	Incident Wave 2 disorders									
	Dysthymia OR [95% CI]	General anxiety disorder OR [95% CI]	Panic disorder OR [95% CI]	Social anxiety disorder OR [95% CI]	Specific phobia OR [95% CI]	Alcohol use disorder OR [95% CI]	hNicotine use disorder OR [95% CI]	Cannabis use disorder OR [95% CI]	Other drug use disorder OR [95% CI]	No incident psychiatric disorders OR [95% CI]
Sleep complaints										
Trouble falling asleep	1.2 [0.6–2.2]	0.9 [0.6–1.3]	1.4 [0.8–2.4]	1.0 [0.6–1.7]	1.0 [0.6–1.6]	1.0 [0.7–1.5]	0.9 [0.6–1.5]	0.9 [0.5–1.5]	1.0 [0.6–1.9]	1.1 [0.8–1.3]
Early morning awakening	1.0 [0.6–1.8]	0.8 [0.6–1.1]	0.8 [0.5–1.3]	0.7 [0.4–1.0]	1.0 [0.6–1.6]	0.6 [0.5–0.9]**	0.8 [0.5–1.1]	0.6 [0.4–1.0]	0.7 [0.4–1.1]	1.4 [1.1–1.7]**
Hypersomnia	1.1 [0.6–1.8]	1.1 [0.8–1.5]	1.1 [0.7–1.8]	2.7 [1.7–4.2]***	2.1 [1.3–3.4]**	1.2 [0.8–1.7]	1.1 [0.7–1.6]	2.6 [1.6–4.4]***	2.2 [1.5–3.5]***	0.7 [0.6–0.8]***
No. of sleep complaints										
0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1	0.4 [0.1–1.2]	1.0 [0.5–2.0]	0.4 [0.1–1.1]	1.0 [0.4–2.7]	0.7 [0.3–2.1]	0.8 [0.4–1.6]	1.0 [0.4–2.5]	1.9 [0.5–7.1]	1.0 [0.3–2.7]	1.2 [0.8–2.0]
2	0.4 [0.1–1.3]	0.9 [0.4–1.8]	0.5 [0.2–1.4]	0.9 [0.4–2.4]	0.9 [0.3–2.4]	0.6 [0.3–1.3]	0.8 [0.3–2.1]	1.7 [0.4–6.9]	0.8 [0.3–2.5]	1.3 [0.9–2.1]
3	0.7 [0.2–2.4]	0.8 [0.4–1.7]	0.7 [0.2–2.0]	1.8 [0.6–4.9]	1.5 [0.5–4.3]	0.7 [0.3–1.4]	0.8 [0.3–2.2]	2.1 [0.7–6.8]	1.5 [0.5–4.9]	1.0 [0.6–1.7]
Wave 1 disorders										
Antisocial personality disorder	0.7 [0.3–1.7]	1.2 [0.7–1.9]	1.0 [0.4–2.4]	0.4 [0.2–1.1]	1.0 [0.5–2.2]	1.5 [0.9–2.6]	1.3 [0.7–2.3]	1.2 [0.6–2.2]	2.9 [1.7–5.1]***	0.7 [0.5–0.9]*
No. of MDE symptoms	1.0 [1.0–1.2]	1.0 [0.9–1.0]	1.0 [0.9–1.1]	1.1 [1.0–1.1]	1.1 [1.0–1.1]	1.0 [1.0–1.1]	1.0 [1.0–1.1]	1.1 [1.0–1.1]	1.1 [1.0–1.2]*	1.0 [0.9–1.0]*
Sociodemographic characteristics										
Sex										
Men	0.9 [0.5–1.7]	0.8 [0.6–1.2]	0.5 [0.3–1.0]*	0.6 [0.36–1.0]*	0.6 [0.3–1.0]	1.4 [1.0–2.0]*	1.1 [0.7–1.6]	0.9 [0.5–1.6]	1.6 [1.0–2.7]	1.0 [0.8–1.2]
Women	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Age										
18–29 y	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
30–44 y	0.9 [0.4–1.7]	1.1 [0.7–1.7]	0.4 [0.2–0.7]**	0.6 [0.4–1.1]	1.1 [0.6–2.3]	0.5 [0.3–0.8]**	0.6 [0.4–0.9]*	0.4 [0.2–0.7]**	0.6 [0.4–1.1]	1.3 [1.0–1.7]*
45–64 y	0.5 [0.2–1.2]	1.1 [0.7–1.7]	0.6 [0.3–1.0]*	0.8 [0.5–1.4]	1.0 [0.5–1.9]	0.3 [0.2–0.5]***	0.6 [0.4–0.9]*	0.1 [0.1–0.3]***	0.3 [0.2–0.5]***	1.7 [1.3–2.1]***
65+ y	0.8 [0.3–2.2]	0.4 [0.2–0.9]*	0.4 [0.1–1.2]	0.3 [0.1–1.0]*	0.5 [0.1–2.3]	0.1 [0.0–0.4]***	0.4 [0.1–1.2]	.	0.0 [0.0–0.1]***	3.9 [2.3–6.6]***
Race/ethnicity										
White	1.0 [0.4–2.2]	1.2 [0.8–1.9]	0.9 [0.5–1.7]	1.4 [0.8–2.6]	2.0 [1.0–4.0]*	1.4 [0.9–2.2]	0.5 [0.3–0.9]*	0.8 [0.4–1.8]	1.5 [0.7–3.0]	0.8 [0.6–1.0]
Non-White	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Marital status										
Married or living as if married	1.0 [0.6–1.7]	1.4 [1.0–2.0]*	0.6 [0.4–1.0]*	1.0 [0.6–1.6]	0.9 [0.6–1.6]	0.7 [0.5–1.1]	0.6 [0.4–1.0]*	0.5 [0.3–0.9]*	0.6 [0.4–0.9]**	1.2 [1.0–1.4]
Not married	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Poverty (household income < $20,000)	0.9 [0.5–1.5]	1.2 [0.8–1.7]	1.2 [0.8–2.0]	1.2 [0.7–1.9]	1.1 [0.7–1.8]	1.1 [0.8–1.5]	1.4 [1.0–2.1]	1.0 [0.6–1.9]	1.3 [0.8–2.1]	0.8 [0.7–1.0]*
Obesity (BMI ≥ 30 kg/m^2)	0.8 [0.4–1.4]	1.5 [1.0–2.1]*	0.9 [0.5–1.5]	1.1 [0.7–1.9]	1.0 [0.6–1.9]	0.7 [0.5–1.0]	0.9 [0.5–1.3]	0.9 [0.5–1.7]	0.9 [0.6–1.4]	1.0 [0.8–1.2]
Past-year use of sedatives or tranquilizers	0.3 [0.1–0.9]*	0.8 [0.4–1.7]	1.7 [0.7–3.8]	1.6 [0.7–3.6]	1.3 [0.4–3.7]	1.6 [0.9–3.0]	1.0 [0.4–2.5]	4.2 [2.0–8.6]***	6.4 [3.3–12.3]***	0.4 [0.3–0.6]***
No. of past-year stressful life events										
0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1	1.3 [0.4–4.2]	0.9 [0.5–1.8]	1.37 [0.41–4.55]	1.26 [0.43–3.70]	0.51 [0.20–1.31]	1.1 [0.6–2.2]	1.3 [0.6–3.1]	0.3 [0.1–1.6]	2.8 [0.8–10.0]	0.8 [0.5–1.2]
2+	1.4 [0.6–3.5]	0.8 [0.4–1.4]	1.70 [0.67–4.30]	1.85 [0.74–4.62]	0.73 [0.35–1.49]	1.6 [0.9–2.9]	1.3 [0.7–2.5]	1.5 [0.5–4.0]	3.2 [1.1–9.3]*	0.7 [0.5–1.0]*
Education level										
Less than high school	1.9 [0.7–4.8]	1.3 [0.6–3.1]	1.32 [0.58–3.01]	0.64 [0.24–1.74]	1.10 [0.40–3.00]	0.5 [0.2–1.4]	0.9 [0.4–2.1]	0.4 [0.1–1.8]	0.2 [0.1–0.6]**	1.2 [0.7–2.0]
High school graduate or higher	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

[a]Crude odds ratios were obtained using logistic regression models.
*$P < .05$. **$P < .0125$. ***$P < .001$.
Abbreviations: BMI = body mass index, CI = confidence interval, MDE = major depressive episode, OR = odds ratio, SE = standard error.

Figure 1. Shared and Specific Effects of Sleep Complaints (ie, Trouble Falling Asleep, Early Morning Awakening, and Hypersomnia) on the Incidence of the General Psychopathology Factor Between the Two Waves Among Participants With a Major Depressive Episode in the Year Prior to Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (N = 2,864)[a]



[a]The ellipses denote the latent construct underlying sleep complaints at Wave 1 and the latent construct underlying the incidence of all psychiatric disorders at Wave 2. Regression coefficients are standardized. Values in parentheses indicate standard errors. Coefficients in bold indicate significant effects (Bonferroni-corrected *P* value < .05/4 [1 factor and 3 sleep indicators times 1 outcome], ie, *P* < .0125). Associations between sleep complaints and general psychopathology factor were adjusted for age, sex, race/ethnicity, marital status, poverty, obesity, number of stressful life events, education level, past-year use of sedatives or tranquilizers, antisocial personality disorder, and number of major depressive episode symptoms in Wave 1.
**$P < .005$. ***$P < .001$.

Participants who developed a psychiatric disorder between the two waves, compared to those who did not, had higher lifetime prevalence of sleep complaints (of any subtypes), ranging from 67.6% (cannabis use disorder) to 76.4% (panic disorder) for difficulty falling asleep, from 43.3% (cannabis use disorder) to 55.6% (dysthymia) for morning awakenings, and from 51.3% (nicotine use disorder) to 72.1% (social anxiety disorder) for hypersomnia (Table 1).

Among all sleep complaints, only hypersomnia significantly increased the odds of psychiatric disorders (social anxiety, specific phobia, cannabis use disorder, and other drug use disorder). Note that among participants with major depressive disorder and reporting hypersomnia, the mean number of sleep disturbances was significantly higher than in those without hypersomnia (2.08 vs 1.52, respectively) ($P < .001$). This explains why hypersomnia appears more strongly associated with the incidence of psychiatric disorders. Early morning awakening was significantly associated with lower odds of having an alcohol use disorder (Table 2). Note also that the group of participants without an incident psychiatric diagnosis at Wave 2 was significantly older and reported more sleep complaints related to early morning awakenings. Associations with other covariates are detailed in Table 2.

Effect of Sleep Disorders on the General Psychopathology Factor

A 1-factor CFA model of Wave 1 sleep complaints (left side of Figure 1) provided a good fit to the data (Supplementary Table 1), as did the bifactor models of the structure distress-fear-externalizing underlying incident psychiatric disorders (Supplementary Table 2) (CFI = 0.99, TLI = 0.99, RMSEA = 0.01).

After adjusting for sociodemographic and clinical characteristics (including the number of MDE symptoms to take into account the MDE severity) and antisocial personality disorder, the general sleep complaint factor, representing the effects shared across all sleep complaints, was significantly associated with the incident general psychopathology factor, representing mechanisms that may lead to incidence of all psychiatric disorders in the model (Figure 1). Beyond the effect of the general sleep complaint factor, there were no direct associations of any individual sleep complaint or any other factor with the incident general psychopathology factor (Figure 1). Finally, young age and use of sedative and tranquilizer were positively and significantly associated with the incident general psychopathology factor beyond the effect of the general sleep complaint factor.

DISCUSSION

In a large longitudinal US nationally representative general population sample, we found that sleep complaints among adults with MDE were independently associated with an increased risk of incident psychiatric disorders. This association was not specific to 1 type of sleep complaint, but rather was mediated by a single latent factor, representing mechanisms shared by 3 common sleep complaints: trouble falling asleep, early morning wakening, and hypersomnia. Our results suggest that sleep complaints may constitute a

prodromal psychiatric disorder biomarker and a potential preventive therapeutic target to reduce the incidence of psychiatric disorders.

Positive correlations across sleep disturbances were well explained by a single latent factor, which was significantly and independently associated with an increased incidence of psychiatric disorders. Possible underpinnings of this factor include shared cognitive and biological adverse effects of sleep disturbances that may contribute to an increased incidence of psychiatric disorders. As a recent study suggested, vulnerability to psychiatric disorders appears to be mediated by an underlying genetic predisposition interacting with environmental and epigenetic factors throughout the lifespan, which could modify the function of neuronal circuits, thus rendering an individual more likely to develop a psychiatric disorder.[35,36] Sleep alterations might contribute to the expression of this shared vulnerability through several mechanisms.

First, insomnia and hypersomnia may increase onset of psychiatric disorders in vulnerable individuals by impairing cognitive functions, such as memory, attention, concentration, processing speed, and social cognition, that are involved in major psychiatric disorders.[9,37–40] Similarly, sleep deprivation impairs decision making, problem-solving ability and emotion-processing networks, which could increase incidence of psychiatric disorders.[40–44] In addition, sleep deprivation may lead to higher levels of impulsivity, thus increasing onset of psychiatric disorders including substance use disorders.[45,46]

Second, shared biological determinants may underlie sleep disturbances and psychiatric disorders. Monoamine neurotransmitters, such as serotonin, norepinephrine, and dopamine, play a major role in depression, anxiety, and substance use disorders and in the regulation of sleep stages.[47–51] Sleep deprivation could also be responsible for hypersensitization of the dopaminergic function of the mesolimbic reward system, mainly between the ventral tegmental zone and the prefrontal cortex.[52] Because of an alteration of reward discrimination, sleep deprived individuals generally make riskier decisions and are more sensitive to rewards. In addition, sleep deprived people also show an alteration in emotionally driven pleasure responses, which leads to unhealthy decisions.[53] Sleep deprivation has been associated with down-regulation of dopamine D_2 and D_3 receptors, resulting in decreased membrane expression of the receptors in the striatum through internalization of D_2 and D_3 receptors. Therefore, the ratio between the availability of D_1 receptors and D_2/D_3 receptors is higher. Under conditions of sleep deprivation, the relative increase in striatal activation of D_1 receptors by dopamine has been linked to an increased risk of substance use disorder.[52,54,55]

Elevated immune-inflammatory signaling may also contribute to the pathophysiology of psychiatric disorders[56–58] and to sleep alterations.[59,60] Other possible mechanisms involve alterations in autonomic function and stress response during sleep deprivation, which may sensitize individuals to stress-related mood, anxiety, and substance use disorders.[61,62] Hypocretin neuropeptides are essential components in maintaining and regulating arousal stability. Several reports have shown that hypocretin-producing neurons are part of the circuits that mediate hypothalamic response to acute stress and reward system.[63,64] In particular, hypocretin is involved in drug sensitization through receptor recruitment in the ventral tegmental area, suggesting that hypocretin neuronal activation plays a critical role in developing addictions.[65,66] Moreover, hyperactivity (leading to sleep deprivation) and hypoactivity (leading to hypersomnia) of the hypocretin system are, respectively, associated with anxiety and depressive symptoms.[67,68]

Finally, at a molecular level, sleep-wake cycles are determined by a biological clock and several core clock genes. Numerous variants of these core clock genes have been associated with psychiatric disorders including bipolar disorder,[69] MDE,[70] seasonal depression,[71,72] and addictive disorders.[73–75] In this context, there may be a shared genetic vulnerability to sleep-wake rhythm and several psychiatric disorders.

Regarding the group of subjects without incident psychiatric disorders in Wave 2, our data seem to corroborate the current literature concerning an increase in complaints of early morning awakenings in the elderly. Complaints not related to psychiatric disorders could thus be related to changes in circadian rhythm with phase advancement,[76,77] to the onset or aggravation of non-psychiatric comorbidities,[76–78] to iatrogeny,[77] or to a residual symptom of depression.[77,79]

Implications

We found that sleep symptoms predict the incidence of psychiatric disorders. These results suggest the importance of systematically assessing insomnia and hypersomnia when evaluating psychiatric disorders and considering these symptoms as non-specific prodromal or at-risk symptoms, also shared with suicidal behaviors.[23] In addition, since most individuals who developed a psychiatric disorder had at least 1 sleep complaint, all psychiatric disorders should be carefully screened among individuals with sleep complaints. A subjective assessment of the 3 main sleep complaints that appeared in our study as a risk factor for developing psychiatric comorbidities in depressed patients seems of major interest because it has the advantages of being readily available to most clinicians in their daily routine, rapid, inexpensive, and practical for epidemiologic and research studies.

Objective measures of sleep may also help to better characterize the association between sleep complaints and psychiatric disorder onset. The use of objective markers may facilitate identification of more specific associations than the sleep complaints in this study that share similar or stronger psychopathological risks. Polysomnography (PSG) allows examination of sleep architecture and has been usefully applied in research on psychiatric disorders. For instance, patients with MDE have been observed to exhibit decreased sleep efficiency (ie, longer sleep latency, more

frequent awakenings, and morning awakenings), decreased slow wave sleep, decreased REM sleep latency, and increased REM sleep density.[80] Other tools such as actigraphy may be used to follow activities in ecological conditions. Actigraphy has been widely used in mood disorders and has permitted identification of trait markers in bipolar disorder that during remitted phases is associated with a decrease sleep efficiency, more wake after sleep onset, and longer sleep latency and duration.[81] Other biological markers such as melatonin or cortisol may be measured in blood, saliva, or urine of patients with psychiatric disorders to assess biological rhythms.[82]

Limitations

The analysis has several limitations. First, sleep disturbance assessments were made only among individuals with MDE, and so our results may not be applicable to the general population. Second, sleep symptoms were assessed on qualitative self-reports[83] that are not as accurate as quantitative[84–87] and objective measurements.[81,88–90] Therefore, only hypotheses about possible mechanisms linking sleep and the incidence of psychiatric disorders can be advanced, and future studies are needed that use objective measures of sleep disturbances. Third, despite its prospective design, our study cannot establish a causal relationship between sleep disturbances and the incidence of psychiatric disorders due to the potential role of unmeasured confounds,[91] although these analyses controlled for several important measured confounds. Fourth, although past-year use of sedatives or tranquilizers was assessed, specific dosages and medications were not assessed, limiting our ability to explore their possible confounding effects. Fifth, our study examined the incidence of psychiatric disorders over a 3-year period, and the pattern of associations may differ over shorter or longer time periods. Sixth, although Wave 1 of the NESARC examined a wide range of Axis I and Axis II psychiatric disorders, several disorders, including psychotic disorders and borderline personality disorder, were not assessed. Seventh, our study did not distinguish between unipolar and bipolar depression. Therefore, further longitudinal studies are needed to determine whether these sleep complaints predict psychiatric disorders in remitted or chronic depressed patients, as well as for other MDE subtypes. Finally, the NESARC was conducted more than 15 years ago, and some of the measures, such as the prevalence of sleep problems and sociodemographic and clinical characteristics, may be slightly different today. Nevertheless, it is unlikely that the pattern of associations between sleep disorders and the incidence of psychiatric disorders would have appreciably changed during the past 2 decades.

CONCLUSION

In a large longitudinal nationally representative sample, a history of trouble falling asleep, early morning awakening, and hypersomnia were associated with increased risk of incident psychiatric disorders, independent of sedative or tranquilizer use and sociodemographic and clinical characteristics. These associations were mediated by a single latent factor, representing mechanisms shared by all 3 sleep complaints. Our results suggest the potential value of including insomnia and hypersomnia in clinical assessments of all psychiatric disorders and their potential role as prodromal transdiagnostic biomarkers and as therapeutic targets for the prevention of psychiatric disorders. The assessment of sleep complaints appears to be a simple, quick, and accessible new screening tool in the early management of a current depressive episode. Moreover, these sleep alterations are a modifiable risk factor of psychiatric disorders, and the validation of objective sleep markers may help to better identify these at-risk populations.[92,93]

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Supplementary Material

Article Title: Sleep Complaints Among Adults With Major Depressive Episode Are Associated With Increased Risk of Incident Psychiatric Disorders: Results From a Population-Based 3-Year Prospective Study

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List of Supplementary Material for the article

1. Table 1 — Single Factor Confirmatory Factor Analysis (CFA) of Lifetime Sleep Complaints (ie, Trouble Falling Asleep, Early Wake-Up, Hypersomnia) Among Participants With a Major Depressive Episode in The Year Prior to Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (N=2864)

2. Table 2 — Bifactor Model of the Structure Distress-Fear-Externalizing Underlying Past-Year Axis I Disorders and Antisocial Personality Disorder Among Participants With a Major Depressive Episode in the Year Prior to Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (N=2864)

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Supplementary Table 1. Single factor confirmatory factor analysis (CFA) of lifetime sleep complaints (i.e., trouble falling asleep, early wake-up, hypersomnia) among participants with a major depressive episode in the year prior to Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (N=2864).

CFI		0.99
TLI		0.99
RMSEA		0.01
		Sleep complaints
Trouble falling asleep		0.71**
Early wake-up		0.83**
Hypersomnia		-0.52**

Abbreviations: CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, Root Mean Square Error of Approximation.
** p-value<0.01.

Supplementary Table 2. Bifactor model of the structure distress-fear-externalizing underlying past-year Axis I disorders and antisocial personality disorder among participants with a major depressive episode in the year prior to Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (N=2864).

CFI		0.99			
TLI		0.99			
RMSEA		0.01			
Psychiatric disorders		**General Psychopathology factor**	**Distress**	**Fear**	**Externalizing**
Dysthymia		0.50**	0.71**		
General anxiety disorder		0.34**	0.26*		
Panic disorder		0.49**		0.68**	
Social anxiety disorder		0.86**		-0.20	
Specific phobia		0.47**		-0.04	
Alcohol use disorder		0.20*			0.69**
Nicotine dependence		0.14			0.37**
Cannabis use disorder		0.48**			0.58**
Drug use disorder		0.43**			0.47**
Factor loading of the factor Internalizing			0.71**	0.60*	
Factor correlation					
General Psychopathology factor		1.00			
Distress		0.00	1.00		
Fear		0.00	0.00	1.00	
Externalizing		0.00	0.00	0.00	1.00

Abbreviations: CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, Root Mean Square Error of Approximation.
* p-value<0.05; ** p-value<0.01.