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Associations of nonrestorative sleep and insomnia symptoms with incident depressive symptoms over 1–2 years: longitudinal results from the Hispanic Community Health Study/Study of Latinos and Sueño Ancillary Study

Short running title: Incident depressive symptoms and nonrestorative sleep

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Abstract

***Background*:** Nonrestorative sleep (NRS), defined as insufficiently rested or refreshed sleep, is considered to play an important role in the development of depression. The aim of this study is to investigate the predictive ability of insomnia-related symptoms, including NRS, for incident depressive symptoms (DEPs) in a longitudinal manner.

***Methods*:** We used data of 1196 samples aged 18–64 years who participated in both the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) conducted in 2008–2010 and the follow-up study (Sueño Ancillary Study) conducted in 2010–2013. DEPs and insomnia-related symptoms (difficulty initiating sleep [DIS], difficulty maintaining sleep [DMS], early morning awakening [EMA], difficulty returning to sleep [DRS], and NRS) were evaluated by the 10-item Center for Epidemiologic Studies Depression Scale and the Women's Health Initiative Insomnia Rating Scale, respectively. A logistic regression analysis was used to evaluate the predictive ability of each insomnia-related symptom at baseline for incident DEPs in couple-years.

***Results*:** In the univariate logistic regression analysis, all insomnia-related symptoms had significant associations with incident DEPs (DIS, odds ratio [OR]=1.6; DMS, OR=1.6; EMA, OR=1.5; DRS, OR=1.9; NRS, OR=2.5). After adjusting for sociodemographic factors and the

confounding effects of other insomnia-related symptoms, only NRS (OR=2.2, 95% confidence interval=1.4–3.5, p=0.001) was significantly associated with incident DEPs.

***Conclusions*:** NRS was a risk factor for incident DEPs, which includes a predictive ability for other insomnia-related symptoms. Our results suggest that focusing on NRS is an effective strategy for preventing depression in public health promotions.

(242/250 words)

Keywords:

depressive symptoms, insomnia, nonrestorative, sleep, longitudinal, Hispanic, public health

1 Introduction

Depression is one of the greatest social problems (Wong & Licinio, 2001). It is estimated that almost 300 million people around the world are suffering from depression (James et al., 2018; Organization, 2020). This disorder impairs multiple aspects of patient well-being (Kessler et al., 2003) and is a leading cause of suicide, with more than half of suicide cases suffering from depression at the time of death (Hawton & van Heeringen, 2009). Consequently, effective prevention approaches for depression are urgently needed.

Insomnia is a widely accepted as one of the risk factors for depression (Baglioni et al., 2011; Li et al., 2016). A recent meta-analysis of 34 cohort studies revealed that people having insomnia were at double the risk of incident depression compared with people without insomnia (Li et al., 2016). A few studies have further tried to identify which basic insomnia symptoms are risk factors for developing depression (Hartz et al., 2007; Yokoyama et al., 2010). Yokoyama et al. (2010) examined the associations between three basic insomnia subtypes (difficulty initiating sleep [DIS], difficulty maintaining sleep [DMS], and early morning awakening [EMA]) and the development of depression 3 years later in the general population aged 65 years and over, and found that DIS was a risk factor for depression.

Nonrestorative sleep (NRS) refers to insufficiently rested or refreshed sleep (Stone et al., 2008). Recently, a growing body of evidence has shown that NRS is associated with various

health problems, including chronic fatigue syndrome, fibromyalgia, heart disease, diabetes, and gastroesophageal reflux disease (Leineweber et al., 2003; Moldofsky, 1989; Okamoto et al., 2017; Zhang et al., 2012). Therefore, NRS has recently been attracting attention as a prospective risk factor of various diseases, although it is not listed as a basic insomnia symptom in the International Classification of Sleep Disorders, 3rd Edition (American Academy of Sleep Medicine, 2014).

NRS is considered to play an important role in the development of depression (Stone et al., 2008). Several studies have shown that NRS is cross-sectionally associated with depression (Matsumoto et al., 2017; Ohayon, 2005; Roth et al., 2006). Furthermore, NRS was reported to predict suicide in a longitudinal study in the elderly (Bernert et al., 2014). Given these findings, NRS could be a possible predictor for incident depression. However, the predictive ability of NRS for incident depression or depressive symptoms (DEPs) remains unclear.

In this study, we investigated the longitudinal association between insomnia-related symptoms including NRS for incident DEPs using existing cohort studies among Hispanics or Latinos living in the USA (Redline et al., 2014; Zhang et al., 2018).

2 Methods

2.1 Description of the data set

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (Visit 1: V1) was a community-based cohort study of Hispanic or Latinos living in the USA conducted from 2008 to 2010 at four sites (Bronx, Chicago, Miami, San Diego). The aim of the HCHS/SOL was to specify protective and harmful factors regarding the health of Hispanics/Latinos. The total number of participants was 16,415 individuals aged 18–74 years. The details of the HCHS/SOL sample and design are described elsewhere (LaVange et al., 2010; Sorlie et al., 2010). In that baseline study, the participants were asked about their physical and mental status with questionnaires, and underwent several physical tests including a sleep examination (Sorlie et al., 2010). Most (80%) of the participants were screened for sleep apnea using a home sleep apnea monitoring system (ARES Unicorder 5.2; B-Alert, Carlsbad, CA, USA).

All participants in V1 who expressed willingness to be contacted for future ancillary studies, who had no other ancillary tests within the last year, were within 30 months of V1, were aged 18–64 years, and were able to converse in either English or Spanish were eligible for recruitment into the Sueño Ancillary Study (Visit 2: V2) (Patel et al., 2015). The exclusion criteria were having a diagnosis of narcolepsy or sleep apnea by a physician, having been treated with continuous positive airway pressure or bi-level positive airway pressure, having an apnea–hypopnea index (AHI) ≥ 50 events per hour at V1, or being a woman who was pregnant. A total of 4,185 candidates were notified about the V2 study, and their eligibility and willingness to

participate were confirmed. Consequently, 2,252 participants were included in V2; these participants underwent a reexamination including questionnaires and actigraphy. Among these participants, 1,912 consented to share their data with external researchers. The average follow-up period between V1 and V2 was 775±148 days.

Both study protocols were approved by the institutional review boards at each of the participating sites. Written informed consent was obtained from all participants. The present study was approved by the ethics committee of National Center of Neurology and Psychiatry (A2020-012). All analyzed data are publicly available (sleepdata.org).

2.2 Additional criteria for the present study

We added the following inclusion criteria for the present study: 1) follow-up period between V1 and V2 ≥365 days, 2) having successfully answered the question items regarding sociodemographic variables, the Women's Health Initiative Insomnia Rating Scale (WHIIRS), sleep duration, and sleeping pill use at V1 and the follow-up period, 3) having undergone home sleep apnea monitoring to compute AHI at V1, 4) having answered all items on the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10) at both V1 and V2, and 5) having no DEPs according to the 9-item Center for Epidemiologic Studies Depression Scale (CES-D-9) at V1. Finally, 1196 subjects were included in the present study (Figure 1).

2.3 Measures

2.3.1 Incident DEPs

The CES-D-10 was used to assess DEPs (Andresen et al., 1994). This shortened form of the original 20-item version (Radloff, 1977) is composed of 10 items to evaluate DEPs in the past week. Andresen et al. (1994) reported that the cutoff score for DEPs of 16 points on the original version of the CES-D was equivalent to 10 points on the CES-D-10. The validity and reliability of the CES-D-10 have also confirmed among the HCHS/SOL samples (González et al., 2017).

Since the aim of this study was to investigate the relationship between insomnia-related symptoms at baseline and development of DEPs during the study period, the item related sleep (item 7: "My sleep was restless") was excluded considering a possible bias. Accordingly, we used nine items (CES-D-9) and calculated total scores using the following formula (items 5 and 8 were reverse-coded): total CES-D-9 scores = SUM (items 1–6, items 8–10) × 10/9. The cutoff point for DEPs on the CES-D-9 was set at 10 points, the same as the CES-D-10. The participants without DEPs according to the CES-D-9 at both V1 and V2 were defined as non-incident DEPs cases, and those with DEPs at only V2 were defined as incident DEPs cases.

2.3.2 Insomnia-related symptoms

The WHIIRS was used for the assessment of the following five insomnia-related symptoms for the past 4 weeks (Levine et al., 2003):

1) DIS: “Did you have trouble falling asleep?”

2) DMS: “Did you wake up several times at night?”

3) EMA: “Did you wake up earlier than planned?”

4) DRS: “Did you have trouble getting back to sleep after you woke up too early?”

5) NRS: “Overall, how was your typical night’s sleep during the past 4 weeks?”

There were five response categories for questions 1) through 4): 1, “No, not in the past 4 weeks”; 2, “Yes, less than once a week”; 3, Yes, “1 or 2 times a week”; 4, “Yes, 3 or 4 times a week”; and 5, “Yes, 5 or more times a week”. Those who answered 1 and 2 to the questions were regarded as not having each sleep problem, and those who answered 3 to 5 were regarded as having each sleep problem (Carroll et al., 2017). There were five different answers for question 5): 1, “Very sound or restful”; 2, “Sound or restful”; 3, “Average quality”; 4, “Restless”; and 5, “Very restless”. Those who answered 1–3 to the questions were regarded as having restorative sleep, and those who answered 4 and 5 were regarded as having NRS. The response score on the original version ranged from 0 to 4, whereas the version used in the HCHS/SOL and the Sueño Ancillary Study ranged from 1 to 5. Therefore, WHIIRS total scores were calculated using the

following formula: WHIIRS total scores = DIS + DMS+ EMA + DRS + NRS – 4. Levine et al. (2003) reported that the internal consistency of the WHIIRS was acceptable ($\alpha = 0.78$) and that clinically significant insomnia had a cutoff value of 9.

2.3.3 Covariates

2.3.3.1 Sociodemographic variables

The sociodemographic data were evaluated at V1. We treated all sociodemographic data as categorical variables, including age (≤29, 30–39, 40–49, 50–59, ≥60 years), gender (male, female), BMI (<18.5, ≥18.5–25, ≥25 kg/m^2), site (Bronx, Chicago, Miami, San Diego), household income (<30,000 USD; ≥30,000 USD; not reported), educational history (less than high school; high school and more than high school), marital status (single; married or living with a partner; separated, divorced, or widower), alcohol use (never, former, current), and cigarette use (never, former, current).

2.3.3.2 Obstructive sleep apnea (OSA)

The presence of OSA at V1 was examined with a home sleep apnea monitoring device (B-Alert). We defined those who had an AHI ≥15 as having OSA.

2.3.3.3 Sleeping pill use

The following question was used to assess sleeping pill use at V1: “Do you take sleeping pills to help you sleep?” (1, “No, not in the past 4 weeks”; 2, “Yes, less than once a week”; 3, Yes, “1 or 2 times a week”; 4, Yes, “3 or 4 times a week”; 5, Yes, “5 or more times a week”). Those who answered 1 were defined as non-users of sleeping pills, while those who answered 2 to 5 were defined as users of sleeping pills.

2.3.3.4 Sleep duration

Sleep duration was assessed separately for weekdays and weekends using the following questions: “What time do you usually go to bed?” and “What time do you usually wake up?”. After estimating the sleep duration for weekdays and weekends, the average sleep duration for the week was calculated using the following formula: average sleep duration = ([weekend sleep duration] × 2 + [weekday sleep duration] × 5) / 7. We divided sleep duration into five groups (<6; ≥6 to 7; ≥7 to 8; ≥8 to 9; ≥9 hours). Kaneita et al. (2006) reported that sleep duration showed a U-shaped association with depression, with the bottom at 7 hours. Thus, the reference sleep duration was the sleep duration ≥7 to 8 hours group.

2.3.3.5 Follow-up period

The follow-up period was classified into two groups (follow-up 1 year: ≥365 to 729, follow-up 2 years: ≥730 days).

2.4 Statistical analysis

The differences in demographic categories between subjects with and without incident DEPs were examined using the χ^2 test.

The relationship between insomnia-related symptoms and incident DEPs was analyzed on the basis of univariate and multivariate logistic regression analyses with incident DEPs as a dependent variable and each insomnia-related symptom at V1 as an independent variable. After conducting univariate analysis, each insomnia-related symptom at V1 was regressed on incident DEPs while adjusting for the covariates (age, sex, BMI, center, marital status, alcohol use, cigarette use, household income, educational history, sleeping pill use, sleep duration, OSA and follow-up period) (Adjusted 1). We then performed a further multivariate logistic regression analysis in addition to covariates to assess the confounding effects of other insomnia-related symptoms (Adjusted 2). The multicollinearity of the insomnia-related symptoms was tested using the variance inflation factor (VIF). The statistical level of significance was set at $p<0.05$. All statistical analyses were conducted using SPSS Statistics ver. 26.0 (IBM, Armonk, NY, USA).

3 Results

3.1 Demographic characteristics and incident DEPs

The demographic characteristics of the entire sample at V1 are shown in Table 1. Females were predominant (60%) and the mean age was 44.4±12.0 years. The average sleep duration was 7.8±1.4 hours. The average follow-up period between V1 and V2 was 785±129 days, and almost 70% of the participants had more than 2 years of follow-up. The average CES-D-9 scores at V1 and V2 were 3.6±2.8 and 5.6±4.9, respectively. Of the 1196 subjects, 235 (19.6%) had DEPs at V2.

The demographic characteristics of the participants with and without incident DEPs are also shown in Table 1. The prevalence of the incident DEPs was 28% in those who had insomnia at V1, and 16% in those who had no insomnia at V1 (χ^2=19.4, df=1, p<0.001). In addition to insomnia, incident DEPs was significantly higher in those who were female, were examined in Chicago, had lower education, were current smokers, and used sleeping medication.

3.2 Insomnia-related symptoms

At V1, the mean WHIIRS score was 6.2±5.0 and the prevalence of insomnia was 29.5%. Table 2 shows the prevalence of the five insomnia-related symptoms by gender and age group at V1. DIS was more prevalent in females than in males (χ^2=7.9, df=1, p=0.005). No gender

differences were found for the other insomnia-related symptoms. The prevalence of DIS (χ^2=12.2, df=4, p=0.016), DMS (χ^2=21.5, df=4, p<0.0001), EMA (χ^2=14.0, df=4, p=0.007), and DRS (χ^2=21.6, df=4, p<0.0001) significantly differed among the age groups, showing a tendency to be higher with advanced age. No significant difference was found for NRS by age.

3.3 Association between insomnia-related symptoms and incident DEPs

The longitudinal associations between insomnia-related symptoms and incident DEPs are shown in Table 3. In the univariate logistic regression analysis, all insomnia-related symptoms had significant associations with incident DEPs (DIS, OR=1.6; DMS, OR=1.6; EMA, OR=1.5; DRS, OR=1.9; NRS, OR=2.5). After adjusting for covariates (Adjusted 1), the same results were obtained. In the multivariate logistic regression analyses adjusted for covariates and the confounding effects of other insomnia-related symptoms (Adjusted 2), only NRS (OR=2.2, 95% confidence interval=1.4–3.5, p=0.001) was significantly associated with incident DEPs. No multicollinearity problems were detected for the insomnia-related symptoms (VIF=1.2–1.7).

4 Discussion

The present study examined the longitudinal associations between insomnia-related symptoms (DIS, DMS, EMA, DRS, and NRS) and incident DEPs among Hispanic/Latino adults

in the USA. In the univariate logistic regression analysis, all insomnia-related symptoms showed significant associations with incident DEPs, even after adjusting for covariates. However, after adjusting for the confounding effects of other insomnia-related symptoms, only NRS showed a significant association with incident DEPs. These results suggest that NRS is a risk factor for incident DEPs, which includes a predictive ability for other insomnia-related symptoms.

4.1 Prevalence of insomnia-related symptoms

In the present study, the prevalence of insomnia as defined by the WHIIRS was 30%, which was comparable with that reported in a previous study (Hartz et al., 2007). As for basic insomnia symptoms, Hartz et al. (2007) summarized the literature on basic insomnia symptoms and reported that the prevalence range for each insomnia symptom in the general population (>18 years of age) was as follows: DIS, 8.3%–23.4%; DMS, 15%–66.7%; and EMA, 9%–18.8%. While the prevalence of DMS was comparable to that in previous studies, those of DIS and EMA were higher than those in previous studies (Hartz et al., 2007). The different age and gender compositions in the present study might be a cause of the higher prevalence of each basic insomnia symptom.

The prevalence of NRS in this study was 11%, which was comparable with studies in the European general population (8.9%–10.8%) (Ohayon, 2005; Ohayon & Roth, 2001).

Although we did not find gender and age differences in the prevalence of NRS, some studies have reported conflicting findings. In the former European survey, more young adults and women complained of NRS compared with older adults and men, respectively (Ohayon, 2005). In another general population survey conducted in South Korea, the prevalence of NRS peaked in the age group of 25–34 years and was the lowest in the age group of 55–64 years, but no gender difference was observed (Ohayon & Hong, 2002). Consequently, gender and age differences in NRS remain controversial. These contradictions might be due to methodological differences between studies such as sampling and the evaluation of NRS.

4.2 Association between basic insomnia symptoms and incident DEPs

The prevalence of incident DEPs in our sample was comparable to a previous report that investigated the prevalence of DEPs in the U.S. also using a self-reported questionnaire (Wittayanukorn et al., 2014).

Our study revealed that all insomnia-related symptoms (DIS, DMS, EMA, DRS, and NRS) were associated with incident DEPs even after adjusting for covariates. As for basic insomnia symptoms (DIS, DMS, and EMA), the ORs were all 1.4. In the previous study, DIS was a predictor for DEPs, but not DMS and EMA (Yokoyama et al., 2010). This distinction may be due to differences in the participants' ages. While their study was intended for older people, our

study included participants with a wide age range (18–64 years). Furthermore, we excluded those who already had DEPs at baseline, while the previous study did not. This might be another explanation for the discrepant results.

4.3 NRS as a predictor for incident DEPs

Although NRS is considered to play an important role in the development of depression (Matsumoto et al., 2017; Ohayon, 2005; Roth et al., 2006), whether NRS is a cause of depression remained unclear. The present study demonstrated that NRS is a risk factor for incident DEPs, which includes a predictive ability for other insomnia-related symptoms. Given that NRS is reportedly closely associated with daytime dysfunction (Ohayon, 2005; Roth et al., 2006), it may reflect daytime dysfunction resulting from insomnia symptoms.

The finding that NRS was a risk factor for incident DEPs might also be explained by the characteristics of sleep architecture in NRS. A previous study on the sleep macrostructure reported that subjects with NRS had mean latency to persistent sleep and mean wake after sleep onset equivalent to those of healthy volunteers; however, rapid eye movement (REM) sleep and stage 3/4 sleep were decreased in subjects with compared with those without NRS (Roth et al., 2010). Furthermore, especially in the subjects with NRS who also had symptoms of DIS, DMS or both, REM sleep and slow wave sleep decreased remarkably (Roth et al., 2010). REM sleep

has been reported to play an important role in regulating emotions such as anxiety and fear by attenuating the emotional function of the amygdala (van der Helm et al., 2011), and slow wave sleep has been shown to implicate plasticity in the central nervous system (Tononi & Cirelli, 2006, 2014). These findings suggest that subjects with NRS get less sleep that plays an important role in regulating rest, emotion, and neural plasticity in the central nervous system, and this might be associated with the strong predictive ability of NRS for incident DEPs.

In addition, a study on the sleep microstructure reported an association between NRS and the cyclic alternating pattern (CAP). The CAP is considered to indicate arousal of the central nervous system, and is considered to be a solid marker of sleep instability (Parrino et al., 2012; Terzano et al., 2001). Terzano et al. (2003) examined the CAP rate in patients with insomnia who complained of one of the basic insomnia symptoms together with NRS, and found that the CAP rate increased in such patients. Therefore, sleep instability might be associated with both NRS and the risk of DEPs.

4.4 Limitations

Our results should be viewed in light of some methodological limitations. First, our sample was relatively small, including only Hispanics/Latinos in the USA, and we enrolled subjects up to the age of 64 years. Since the prevalence of depression was high among the elderly,

future research with a larger sample size and wider age range among other races will be required to increase the generalizability. Second, this study used subjective sleep assessments. The observations about NRS should be confirmed with an objective instrument such as actigraphy or polysomnography. Our findings should be also confirmed in future research using these objective instruments. Third, we did not consider other possible confounding factors for the association between sleep-related problems and incident depression, such as caffeine intake and shift work. Fourth, other diseases related to NRS, such as chronic fatigue syndrome and fibromyalgia, were not evaluated. Fifth, we used the CES-D for the assessment of depression, and did not actually treat patients with clinical depression. However, this evaluation of DEPs has been widely used in many epidemiology studies, and the validity of the CES-D has been sufficiently established. Sixth, we did not adjust for the increased probability of a Type I error, because this was an exploratory study.

5 Conclusion

NRS was a risk factor for incident DEPs, which includes a predictive ability for other insomnia-related symptoms. Our results suggest the importance of focusing on NRS to develop more effective public health strategies for preventing depression.

(3438/3500 words)

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Table 1. Prevalence of incident depression by participant demographics.

		All (N=1196)		With incident depression (N=235)		Without incident depression (N=961)		Prevalence of depression (%)		
		N	(%)	N	(%)	N	(%)		p	
Insomnia	WHIIRS <9	843	70	138	59	705	73	16%	<0.001	***
	WHIIRS ≥9	353	30	97	41	256	27	28%		
Gender	Men	480	40	79	34	401	42	17%	0.023	*
	Female	716	60	156	66	560	58	22%		
Age (years)	18–29	182	15	34	15	148	15	19%	0.215	
	30–39	172	14	27	12	145	15	16%		
	40–49	375	31	67	29	308	32	18%		
	50–59	371	31	84	36	287	30	23%		
	60–64	96	8	23	10	73	8	24%		
BMI (kg/m^2)	<18.5	9	1	4	2	5	1	44%	0.11	
	≥18.5–25	221	19	48	20	173	18	22%		
	≥25	966	81	183	78	783	82	19%		
Site	Bronx	300	25	62	26	238	25	21%	0.025	*
	Chicago	306	26	76	32	230	24	25%		
	Miami	392	33	63	27	329	34	16%		

	San Diego	198	17	34	15	164	17	17%		
Income (USD)	<30,000	760	64	159	68	601	63	21%	0.073	
	≥30,000	383	32	62	26	321	33	16%		
	Not reported	53	4	14	6	39	4	26%		
Education	Less than HS	347	29	90	38	257	27	26%	<0.001	***
	HS and more than HS	849	71	145	62	704	73	17%		
Marital status	Single	325	27	65	28	260	27	20%	0.407	
	Married or living with a partner	669	56	124	53	545	57	19%		
	Separated, divorced, or widower	202	17	46	19	156	16	23%		
Alcohol use	Never	249	21	55	23	194	20	22%	0.205	
	Former	392	33	83	35	309	32	21%		
	Current	555	46	97	41	458	48	18%		
Cigarette use	Never	748	63	136	58	612	64	18%	0.002	**
	Former	246	21	41	17	205	21	17%		
	Current	202	17	58	25	144	15	29%		
Sleeping medication use	Not, in the past 4 weeks	1063	89	200	85	863	90	19%	0.04	*
	Yes, in the past 4 weeks	133	11	35	15	98	10	26%		
Obstructive sleep apnea (AHI ≥15)	OSA–	1091	91	216	92	875	91	20%	0.675	
	OSA+	105	9	19	8	86	9	18%		
Sleep duration (h)	<6	78	7	18	8	60	6	23%	0.547	
	≥6 to 7	189	16	39	17	150	16	21%		

	≥7 to 8	374	31	63	27	311	32	17%	
	≥8 to 9	326	27	69	29	257	27	21%	
	≥9	229	19	46	20	183	19	20%	
Follow-up years	1	386	32	85	36	301	31	22%	0.154
	2	810	68	150	64	660	69	19%	

*p<0.05, **p<0.01, ***p<0.001.

Abbreviations: WHIIRS, Women's Health Initiative Insomnia Rating Scale; BMI, body mass index; HS, high school; USD, United States dollar; AHI, apnea–hypopnea index.

Table 2. Prevalence of insomnia-related symptoms by age and gender.

		Difficulty initiating sleep[a,b]	Difficulty maintaining sleep[a]	Early morning awakening[a]	Difficulty returning to sleep[a]	Nonrestorative sleep
All	18–29	30%	41%	30%	24%	9%
	30–39	31%	49%	34%	27%	11%
	40–49	32%	49%	38%	26%	12%
	50–59	41%	60%	45%	37%	12%
	60–64	40%	59%	43%	42%	12%
	Total	35%	52%	39%	31%	11%
Male (N=480)	18–29	37%	39%	33%	25%	13%
	30–39	32%	54%	37%	31%	6%
	40–49	29%	47%	43%	28%	10%
	50–59	30%	61%	39%	29%	10%
	60–64	16%	49%	27%	24%	5%
	Total	30%	51%	38%	28%	10%
Female (N=716)	18–29	25%	43%	28%	22%	6%
	30–39	30%	46%	33%	24%	13%
	40–49	33%	51%	35%	26%	13%
	50–59	49%	60%	49%	43%	13%
	60–64	54%	66%	53%	53%	15%
	Total	38%	53%	39%	33%	12%

[a]significantly different among age groups, [b]significantly different between genders.

Table 3. Incident depression and insomnia-related symptoms in the logistic regression analysis.

N=1196	Crude OR (95% CI)	p		Adjusted 1 OR (95% CI)	p		Adjusted 2 OR (95% CI)	p	
Difficulty initiating sleep	1.6 (1.2–2.1)	<0.01	**	1.4 (1.0–1.9)	0.042	*	0.9 (0.6–1.4)	0.699	
Difficulty maintaining sleep	1.6 (1.2–2.1)	<0.01	**	1.4 (1.0–1.9)	0.024	*	1.1 (0.8–1.6)	0.501	
Early morning awakening	1.5 (1.1–2.0)	<0.01	**	1.4 (1.0–1.9)	0.031	*	1.0 (0.7–1.4)	0.943	
Difficulty returning to sleep	1.9 (1.4–2.5)	<0.001	***	1.8 (1.3–2.4)	<0.001	***	1.5 (1.0–2.2)	0.071	
Nonrestorative sleep	2.5 (1.7–3.7)	<0.001	***	2.6 (1.7–3.9)	<0.001	***	2.2 (1.4–3.5)	0.001	**

*p<0.05, **p<0.01, ***p<0.001

Abbreviations: OR, odds ratio; CI, confidence interval.

Adjusted 1: age, gender, BMI (body mass index), field center, annual household income, years of education, marital status, alcohol use, cigarette use, sleep medication use, OSA (obstructive sleep apnea), sleep duration, follow-up years.

Adjusted 2: Adjusted 1 + difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, difficulty returning to sleep, nonrestorative sleep.

Figure Legends

Figure 1. Flowchart of the present study.

Associations of nonrestorative sleep and insomnia symptoms with incident depressive symptoms over 1–2 years: longitudinal results from the Hispanic Community Health Study/Study of Latinos and Sueño Ancillary Study

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Abstract

***Background*:** Nonrestorative sleep (NRS), defined as insufficiently rested or refreshed sleep, is considered to play an important role in the development of depression. The aim of this study is to investigate the predictive ability of insomnia-related symptoms, including NRS, for incident depressive symptoms (DEPs) in a longitudinal manner.

***Methods*:** We used data of 1196 samples aged 18–64 years who participated in both the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) conducted in 2008–2010 and the follow-up study (Sueño Ancillary Study) conducted in 2010–2013. DEPs and insomnia-related symptoms (difficulty initiating sleep [DIS], difficulty maintaining sleep [DMS], early morning awakening [EMA], difficulty returning to sleep [DRS], and NRS) were evaluated by the 10-item Center for Epidemiologic Studies Depression Scale and the Women's Health Initiative Insomnia Rating Scale, respectively. A logistic regression analysis was used to evaluate the predictive ability of each insomnia-related symptom at baseline for incident DEPs in couple-years.

***Results*:** In the univariate logistic regression analysis, all insomnia-related symptoms had significant associations with incident DEPs (DIS, odds ratio [OR]=1.6; DMS, OR=1.6; EMA, OR=1.5; DRS, OR=1.9; NRS, OR=2.5). After adjusting for sociodemographic factors and the

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confounding effects of other insomnia-related symptoms, only NRS (OR=2.2, 95% confidence interval=1.4–3.5, p=0.001) was significantly associated with incident DEPs.

***Conclusions*:** NRS was a risk factor for incident DEPs, which includes a predictive ability for other insomnia-related symptoms. Our results suggest that focusing on NRS is an effective strategy for preventing depression in public health promotions.

(242/250 words)

Keywords:

depressive symptoms, insomnia, nonrestorative, sleep, longitudinal, Hispanic, public health

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1 Introduction

Depression is one of the greatest social problems (Wong & Licinio, 2001). It is estimated that almost 300 million people around the world are suffering from depression (James et al., 2018; Organization, 2020). This disorder impairs multiple aspects of patient well-being (Kessler et al., 2003) and is a leading cause of suicide, with more than half of suicide cases suffering from depression at the time of death (Hawton & van Heeringen, 2009). Consequently, effective prevention approaches for depression are urgently needed.

Insomnia is a widely accepted as one of the risk factors for depression (Baglioni et al., 2011; Li et al., 2016). A recent meta-analysis of 34 cohort studies revealed that people having insomnia were at double the risk of incident depression compared with people without insomnia (Li et al., 2016). A few studies have further tried to identify which basic insomnia symptoms are risk factors for developing depression (Hartz et al., 2007; Yokoyama et al., 2010). Yokoyama et al. (2010) examined the associations between three basic insomnia subtypes (difficulty initiating sleep [DIS], difficulty maintaining sleep [DMS], and early morning awakening [EMA]) and the development of depression 3 years later in the general population aged 65 years and over, and found that DIS was a risk factor for depression.

Nonrestorative sleep (NRS) refers to insufficiently rested or refreshed sleep (Stone et al., 2008). Recently, a growing body of evidence has shown that NRS is associated with various

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health problems, including chronic fatigue syndrome, fibromyalgia, heart disease, diabetes, and gastroesophageal reflux disease (Leineweber et al., 2003; Moldofsky, 1989; Okamoto et al., 2017; Zhang et al., 2012). Therefore, NRS has recently been attracting attention as a prospective risk factor of various diseases, although it is not listed as a basic insomnia symptom in the International Classification of Sleep Disorders, 3rd Edition (American Academy of Sleep Medicine, 2014).

NRS is considered to play an important role in the development of depression (Stone et al., 2008). Several studies have shown that NRS is cross-sectionally associated with depression (Matsumoto et al., 2017; Ohayon, 2005; Roth et al., 2006). Furthermore, NRS was reported to predict suicide in a longitudinal study in the elderly (Bernert et al., 2014). Given these findings, NRS could be a possible predictor for incident depression. However, the predictive ability of NRS for incident depression or depressive symptoms (DEPs) remains unclear.

In this study, we investigated the longitudinal association between insomnia-related symptoms including NRS for incident DEPs using existing cohort studies among Hispanics or Latinos living in the USA (Redline et al., 2014; Zhang et al., 2018).

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削除：Given these findings, NRS could be a possible predictor for incident depression. However, no studies have been conducted to examine longitudinally the association between NRS and incident depression.

削除：In this study, we investigated the predictive ability of insomnia-related symptoms (DIS, DMS, EMS, difficulty returning to sleep [DRS], and NRS) for incident depression using existing cohort studies among Hispanics or Latinos living in the USA. Our hypothesis was that NRS would be a stronger predictor than basic insomnia symptoms for the development of depression because NRS is a feeling that could reflect daytime dysfunction resulting from sleep problems, including insomnia.

2 Methods

2.1 Description of the data set

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (Visit 1: V1) was a community-based cohort study of Hispanic or Latinos living in the USA conducted from 2008 to 2010 at four sites (Bronx, Chicago, Miami, San Diego). The aim of the HCHS/SOL was to specify protective and harmful factors regarding the health of Hispanics/Latinos. The total number of participants was 16,415 individuals aged 18–74 years. The details of the HCHS/SOL sample and design are described elsewhere (LaVange et al., 2010; Sorlie et al., 2010). In that baseline study, the participants were asked about their physical and mental status with questionnaires, and underwent several physical tests including a sleep examination (Sorlie et al., 2010). Most (80%) of the participants were screened for sleep apnea using a home sleep apnea monitoring system (ARES Unicorder 5.2; B-Alert, Carlsbad, CA, USA).

All participants in V1 who expressed willingness to be contacted for future ancillary studies, who had no other ancillary tests within the last year, were within 30 months of V1, were aged 18–64 years, and were able to converse in either English or Spanish were eligible for recruitment into the Sueño Ancillary Study (Visit 2: V2) (Patel et al., 2015). The exclusion criteria were having a diagnosis of narcolepsy or sleep apnea by a physician, having been treated with continuous positive airway pressure or bi-level positive airway pressure, having an apnea–hypopnea index (AHI) ≥ 50 events per hour at V1, or being a woman who was pregnant. A total of 4,185 candidates were notified about the V2 study, and their eligibility and willingness to

削除： The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (Visit 1: V1) was conducted from 2008 to 2010. The participants in this multicenter cohort study were Hispanics or Latinos living in the USA. It was conducted at four sites (Bronx, Chicago, Miami, San Diego) that have large Hispanic/Latino communities.

削除： Population-based sampling was used to identify and recruit participants for the HCHS/SOL.

participate were confirmed. Consequently, 2,252 participants were included in V2; these participants underwent a reexamination including questionnaires and actigraphy. Among these participants, 1,912 consented to share their data with external researchers. The average follow-up period between V1 and V2 was 775±148 days.

Both study protocols were approved by the institutional review boards at each of the participating sites. Written informed consent was obtained from all participants. The present study was approved by the ethics committee of National Center of Neurology and Psychiatry (A2020-012). All analyzed data are publicly available (sleepdata.org).

2.2 Additional criteria for the present study

We added the following inclusion criteria for the present study: 1) follow-up period between V1 and V2 ≥365 days, 2) having successfully answered the question items regarding sociodemographic variables, the Women's Health Initiative Insomnia Rating Scale (WHIIRS), sleep duration, and sleeping pill use at V1 and the follow-up period, 3) having undergone home sleep apnea monitoring to compute AHI at V1, 4) having answered all items on the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10) at both V1 and V2, and 5) having no DEPs according to the 9-item Center for Epidemiologic Studies Depression Scale (CES-D-9) at V1. Finally, 1196 subjects were included in the present study (Figure 1).

削除: The total number of participants was 16,415 individuals aged 18–74 years. The details of the HCHS/SOL sample and design are described elsewhere (LaVange et al., 2010; Sorlie et al., 2010).
The Sueño Ancillary Study (Visit 2: V2) was a follow-up study to the HCHS/SOL conducted from 2010 to 2013. The inclusion criteria for participating in this study were as follows: those who were aged 18–64 years at V2, those who had never been treated for obstructive sleep apnea (OSA), and those who were without an apnea–hypopnea index (AHI) > 50 events per hour at V1 or a narcolepsy diagnosis. Consequently, 2252 individuals were selected to participate in the Sueño Ancillary Study . Participants came to each field center to undergo a reexamination including questionnaires and actigraphy. Finally, data were obtained ... [1]

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2.3 Measures

2.3.1 Incident DEPs

The CES-D-10 was used to assess DEPs (Andresen et al., 1994). This shortened form of the original 20-item version (Radloff, 1977) is composed of 10 items to evaluate DEPs in the past week. Andresen et al. (1994) reported that the cutoff score for DEPs of 16 points on the original version of the CES-D was equivalent to 10 points on the CES-D-10. The validity and reliability of the CES-D-10 have also confirmed among the HCHS/SOL samples (González et al., 2017).

Since the aim of this study was to investigate the relationship between insomnia-related symptoms at baseline and development of DEPs during the study period, the item related sleep (item 7: "My sleep was restless") was excluded considering a possible bias. Accordingly, we used nine items (CES-D-9) and calculated total scores using the following formula (items 5 and 8 were reverse-coded): total CES-D-9 scores = SUM (items 1–6, items 8–10) × 10/9. The cutoff point for DEPs on the CES-D-9 was set at 10 points, the same as the CES-D-10. The participants without DEPs according to the CES-D-9 at both V1 and V2 were defined as non-incident DEPs cases, and those with DEPs at only V2 were defined as incident DEPs cases.

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2.3.2 Insomnia-related symptoms

The WHIIRS was used for the assessment of the following five insomnia-related symptoms for the past 4 weeks (Levine et al., 2003):

1) DIS; "Did you have trouble falling asleep?"

2) DMS; "Did you wake up several times at night?"

3) EMA; "Did you wake up earlier than planned?"

4) DRS; "Did you have trouble getting back to sleep after you woke up too early?"

5) NRS; "Overall, how was your typical night's sleep during the past 4 weeks?"

There were five response categories for questions 1) through 4): 1, "No, not in the past 4 weeks"; 2, "Yes, less than once a week"; 3, Yes, "1 or 2 times a week"; 4, "Yes, 3 or 4 times a week"; and 5, "Yes, 5 or more times a week". Those who answered 1 and 2 to the questions were regarded as not having each sleep problem, and those who answered 3 to 5 were regarded as having each sleep problem (Carroll et al., 2017). There were five different answers for question 5): 1, "Very sound or restful"; 2, "Sound or restful"; 3, "Average quality"; 4, "Restless"; and 5, "Very restless". Those who answered 1–3 to the questions were regarded as having restorative sleep, and those who answered 4 and 5 were regarded as having NRS. The response score on the original version ranged from 0 to 4, whereas the version used in the HCHS/SOL and the Sueño Ancillary Study ranged from 1 to 5. Therefore, WHIIRS total scores were calculated using the

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following formula: WHIIRS total scores = DIS + DMS+ EMA + DRS + NRS – 4. Levine et al. (2003) reported that the internal consistency of the WHIIRS was acceptable ($\alpha = 0.78$) and that clinically significant insomnia had a cutoff value of 9.

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2.3.3 Covariates

2.3.3.1 Sociodemographic variables

The sociodemographic data were evaluated at V1. We treated all sociodemographic data as categorical variables, including age (≤29, 30–39, 40–49, 50–59, ≥60 years), gender (male, female), BMI (<18.5, ≥18.5–25, ≥25 kg/m^2), site (Bronx, Chicago, Miami, San Diego), household income (<30,000 USD; ≥30,000 USD; not reported), educational history (less than high school; high school and more than high school), marital status (single; married or living with a partner; separated, divorced, or widower), alcohol use (never, former, current), and cigarette use (never, former, current).

2.3.3.2 Obstructive sleep apnea (OSA)

The presence of OSA at V1 was examined with a home sleep apnea monitoring device (B-Alert). We defined those who had an AHI ≥15 as having OSA.

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2.3.3.3 Sleeping pill use

The following question was used to assess sleeping pill use at V1: “Do you take sleeping pills to help you sleep?” (1, “No, not in the past 4 weeks”; 2, “Yes, less than once a week”; 3, Yes, “1 or 2 times a week”; 4, Yes, “3 or 4 times a week”; 5, Yes, “5 or more times a week”). Those who answered 1 were defined as non-users of sleeping pills, while those who answered 2 to 5 were defined as users of sleeping pills.

2.3.3.4 Sleep duration

Sleep duration was assessed separately for weekdays and weekends using the following questions: “What time do you usually go to bed?” and “What time do you usually wake up?”. After estimating the sleep duration for weekdays and weekends, the average sleep duration for the week was calculated using the following formula: average sleep duration = ([weekend sleep duration] × 2 + [weekday sleep duration] × 5) / 7. We divided sleep duration into five groups (<6; ≥6 to 7; ≥7 to 8; ≥8 to 9; ≥9 hours). Kaneita et al. (2006) reported that sleep duration showed a U-shaped association with depression, with the bottom at 7 hours. Thus, the reference sleep duration was the sleep duration ≥7 to 8 hours group.

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2.3.3.5 Follow-up period

The follow-up period was classified into two groups (follow-up 1 year: ≥365 to 729, follow-up 2 years: ≥730 days).

2.4 Statistical analysis

The differences in demographic categories between subjects with and without incident DEPs were examined using the χ^2 test.

The relationship between insomnia-related symptoms and incident DEPs was analyzed on the basis of univariate and multivariate logistic regression analyses with incident DEPs as a dependent variable and each insomnia-related symptom at V1 as an independent variable. After conducting univariate analysis, each insomnia-related symptom at V1 was regressed on incident DEPs while adjusting for the covariates (age, sex, BMI, center, marital status, alcohol use, cigarette use, household income, educational history, sleeping pill use, sleep duration, OSA and follow-up period) (Adjusted 1). We then performed a further multivariate logistic regression analysis in addition to covariates to assess the confounding effects of other insomnia-related symptoms (Adjusted 2). The multicollinearity of the insomnia-related symptoms was tested using the variance inflation factor (VIF). The statistical level of significance was set at $p<0.05$. All statistical analyses were conducted using SPSS Statistics ver. 26.0 (IBM, Armonk, NY, USA).

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3 Results

3.1 Demographic characteristics and incident DEPs

The demographic characteristics of the entire sample at V1 are shown in Table 1. Females were predominant (60%) and the mean age was 44.4±12.0 years. The average sleep duration was 7.8±1.4 hours. The average follow-up period between V1 and V2 was 785±129 days, and almost 70% of the participants had more than 2 years of follow-up. The average CES-D-9 scores at V1 and V2 were 3.6±2.8 and 5.6±4.9, respectively. Of the 1196 subjects, 235 (19.6%) had DEPs at V2.

The demographic characteristics of the participants with and without incident DEPs are also shown in Table 1. The prevalence of the incident DEPs was 28% in those who had insomnia at V1, and 16% in those who had no insomnia at V1 (χ^2=19.4, df=1, p<0.001). In addition to insomnia, incident DEPs was significantly higher in those who were female, were examined in Chicago, had lower education, were current smokers, and used sleeping medication.

3.2 Insomnia-related symptoms

At V1, the mean WHIIRS score was 6.2±5.0 and the prevalence of insomnia was 29.5%. Table 2 shows the prevalence of the five insomnia-related symptoms by gender and age group at V1. DIS was more prevalent in females than in males (χ^2=7.9, df=1, p=0.005). No gender

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differences were found for the other insomnia-related symptoms. The prevalence of DIS (χ^2=12.2, df=4, p=0.016), DMS (χ^2=21.5, df=4, p<0.0001), EMA (χ^2=14.0, df=4, p=0.007), and DRS (χ^2=21.6, df=4, p<0.0001) significantly differed among the age groups, showing a tendency to be higher with advanced age. No significant difference was found for NRS by age.

3.3 Association between insomnia-related symptoms and incident DEPs

The longitudinal associations between insomnia-related symptoms and incident DEPs are shown in Table 3. In the univariate logistic regression analysis, all insomnia-related symptoms had significant associations with incident DEPs (DIS, OR=1.6; DMS, OR=1.6; EMA, OR=1.5; DRS, OR=1.9; NRS, OR=2.5). After adjusting for covariates (Adjusted 1), the same results were obtained. In the multivariate logistic regression analyses adjusted for covariates and the confounding effects of other insomnia-related symptoms (Adjusted 2), only NRS (OR=2.2, 95% confidence interval=1.4–3.5, p=0.001) was significantly associated with incident DEPs. No multicollinearity problems were detected for the insomnia-related symptoms (VIF=1.2–1.7).

4 Discussion

The present study examined the longitudinal associations between insomnia-related symptoms (DIS, DMS, EMA, DRS, and NRS) and incident DEPs among Hispanic/Latino adults

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The correlations among insomnia-related symptoms are shown in Table 3. In all cases, Spearman's coefficients were <0.7; therefore, the relationships among insomnia subtypes were not considered to be very strong.

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in the USA. In the univariate logistic regression analysis, all insomnia-related symptoms showed significant associations with incident DEPs, even after adjusting for covariates. However, after adjusting for the confounding effects of other insomnia-related symptoms, only NRS showed a significant association with incident DEPs. These results suggest that NRS is a risk factor for incident DEPs, which includes a predictive ability for other insomnia-related symptoms.

削除: The present study aimed to examine the longitudinal associations between insomnia-related symptoms and incident depression in a sample of Hispanic/Latino adults in the USA, and found that not only basic insomnia symptoms, but also NRS, were predictors for the development of depression. Furthermore, in the multivariate analysis adjusted for the confounding effects of other sleep-related symptoms, only NRS showed a significant association with incident depression, suggesting that NRS is a risk factor for depression, which includes a predictive ability for other insomnia-related symptoms.

4.1 Prevalence of insomnia-related symptoms

In the present study, the prevalence of insomnia as defined by the WHIIRS was 30%, which was comparable with that reported in a previous study (Hartz et al., 2007). As for basic insomnia symptoms, Hartz et al. (2007) summarized the literature on basic insomnia symptoms and reported that the prevalence range for each insomnia symptom in the general population (>18 years of age) was as follows: DIS, 8.3%–23.4%; DMS, 15%–66.7%; and EMA, 9%–18.8%. While the prevalence of DMS was comparable to that in previous studies, those of DIS and EMA were higher than those in previous studies (Hartz et al., 2007). The different age and gender compositions in the present study might be a cause of the higher prevalence of each basic insomnia symptom.

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The prevalence of NRS in this study was 11%, which was comparable with studies in the European general population (8.9%–10.8%) (Ohayon, 2005; Ohayon & Roth, 2001).

Although we did not find gender and age differences in the prevalence of NRS, some studies have reported conflicting findings. In the former European survey, more young adults and women complained of NRS compared with older adults and men, respectively (Ohayon, 2005). In another general population survey conducted in South Korea, the prevalence of NRS peaked in the age group of 25–34 years and was the lowest in the age group of 55–64 years, but no gender difference was observed (Ohayon & Hong, 2002). Consequently, gender and age differences in NRS remain controversial. These contradictions might be due to methodological differences between studies such as sampling and the evaluation of NRS.

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4.2 Association between basic insomnia symptoms and incident DEPs

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The prevalence of incident DEPs in our sample was comparable to a previous report that investigated the prevalence of DEPs in the U.S. also using a self-reported questionnaire (Wittayanukorn et al., 2014).

Our study revealed that all insomnia-related symptoms (DIS, DMS, EMA, DRS, and NRS) were associated with incident DEPs even after adjusting for covariates. As for basic insomnia symptoms (DIS, DMS, and EMA), the ORs were all 1.4. In the previous study, DIS was a predictor for DEPs, but not DMS and EMA (Yokoyama et al., 2010). This distinction may be due to differences in the participants' ages. While their study was intended for older people, our

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study included participants with a wide age range (18–64 years). Furthermore, we excluded those who already had DEPs at baseline, while the previous study did not. This might be another explanation for the discrepant results.

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4.3 NRS as a predictor for incident DEPs

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Although NRS is considered to play an important role in the development of depression (Matsumoto et al., 2017; Ohayon, 2005; Roth et al., 2006), whether NRS is a cause of depression remained unclear. The present study demonstrated that NRS is a risk factor for incident DEPs, which includes a predictive ability for other insomnia-related symptoms. Given that NRS is reportedly closely associated with daytime dysfunction (Ohayon, 2005; Roth et al., 2006), it may reflect daytime dysfunction resulting from insomnia symptoms.

The finding that NRS was a risk factor for incident DEPs might also be explained by the characteristics of sleep architecture in NRS. A previous study on the sleep macrostructure reported that subjects with NRS had mean latency to persistent sleep and mean wake after sleep onset equivalent to those of healthy volunteers; however, rapid eye movement (REM) sleep and stage 3/4 sleep were decreased in subjects with compared with those without NRS (Roth et al., 2010). Furthermore, especially in the subjects with NRS who also had symptoms of DIS, DMS or both, REM sleep and slow wave sleep decreased remarkably (Roth et al., 2010). REM sleep

削除: Although NRS is considered to play an important role in the development of depression (Matsumoto et al., 2017; Ohayon, 2005; Roth et al., 2006), it remains unknown whether NRS is a cause of depression. Moreover, the strength of the association remains unclear, especially in comparison with that between insomnia symptoms and depression. The present study highlighted that having NRS can predict incident depression, and that the predictive ability of NRS for incident depression is stronger than that of basic insomnia symptoms. These findings, together with previous studies showing close associations between NRS and daytime dysfunction (Ohayon, 2005; Roth et al., 2006), suggest that NRS may reflect daytime dysfunction accompanied by insomnia symptoms. A decrease in NRS may contribute to psychosomatic recovery and the prevention of depression.

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has been reported to play an important role in regulating emotions such as anxiety and fear by attenuating the emotional function of the amygdala (van der Helm et al., 2011), and slow wave sleep has been shown to implicate plasticity in the central nervous system (Tononi & Cirelli, 2006, 2014). These findings suggest that subjects with NRS get less sleep that plays an important role in regulating rest, emotion, and neural plasticity in the central nervous system, and this might be associated with the strong predictive ability of NRS for incident DEPs.

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In addition, a study on the sleep microstructure reported an association between NRS and the cyclic alternating pattern (CAP). The CAP is considered to indicate arousal of the central nervous system, and is considered to be a solid marker of sleep instability (Parrino et al., 2012; Terzano et al., 2001). Terzano et al. (2003) examined the CAP rate in patients with insomnia who complained of one of the basic insomnia symptoms together with NRS, and found that the CAP rate increased in such patients. Therefore, sleep instability might be associated with both NRS and the risk of DEPs.

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4.4 Limitations

Our results should be viewed in light of some methodological limitations. First, our sample was relatively small, including only Hispanics/Latinos in the USA, and we enrolled subjects up to the age of 64 years. Since the prevalence of depression was high among the elderly,

future research with a larger sample size and wider age range among other races will be required to increase the generalizability. Second, this study used subjective sleep assessments. The observations about NRS should be confirmed with an objective instrument such as actigraphy or polysomnography. Our findings should be also confirmed in future research using these objective instruments. Third, we did not consider other possible confounding factors for the association between sleep-related problems and incident depression, such as caffeine intake and shift work. Fourth, other diseases related to NRS, such as chronic fatigue syndrome and fibromyalgia, were not evaluated. Fifth, we used the CES-D for the assessment of depression, and did not actually treat patients with clinical depression. However, this evaluation of DEPs has been widely used in many epidemiology studies, and the validity of the CES-D has been sufficiently established. Sixth, we did not adjust for the increased probability of a Type I error, because this was an exploratory study.

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5 Conclusion

NRS was a risk factor for incident DEPs, which includes a predictive ability for other insomnia-related symptoms. Our results suggest the importance of focusing on NRS to develop more effective public health strategies for preventing depression.

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Table 1. Prevalence of incident depression by participant demographics.

		All (N=1196)		With incident depression (N=235)		Without incident depression (N=961)		Prevalence of depression (%)		
		N	(%)	N	(%)	N	(%)		p	
Insomnia	WHIIRS <9	843	70	138	59	705	73	16%	<0.001	***
	WHIIRS ≥9	353	30	97	41	256	27	28%		
Gender	Men	480	40	79	34	401	42	17%	0.023	*
	Female	716	60	156	66	560	58	22%		
Age (years)	18–29	182	15	34	15	148	15	19%	0.215	
	30–39	172	14	27	12	145	15	16%		
	40–49	375	31	67	29	308	32	18%		
	50–59	371	31	84	36	287	30	23%		
	60–64	96	8	23	10	73	8	24%		
BMI (kg/m^2)	<18.5	9	1	4	2	5	1	44%	0.11	
	≥18.5–25	221	19	48	20	173	18	22%		
	≥25	966	81	183	78	783	82	19%		
Site	Bronx	300	25	62	26	238	25	21%	0.025	*
	Chicago	306	26	76	32	230	24	25%		
	Miami	392	33	63	27	329	34	16%		

	San Diego	198	17	34	15	164	17	17%		
Income (USD)	<30,000	760	64	159	68	601	63	21%	0.073	
	≥30,000	383	32	62	26	321	33	16%		
	Not reported	53	4	14	6	39	4	26%		
Education	Less than HS	347	29	90	38	257	27	26%	<0.001	***
	HS and more than HS	849	71	145	62	704	73	17%		
Marital status	Single	325	27	65	28	260	27	20%	0.407	
	Married or living with a partner	669	56	124	53	545	57	19%		
	Separated, divorced, or widower	202	17	46	19	156	16	23%		
Alcohol use	Never	249	21	55	23	194	20	22%	0.205	
	Former	392	33	83	35	309	32	21%		
	Current	555	46	97	41	458	48	18%		
Cigarette use	Never	748	63	136	58	612	64	18%	0.002	**
	Former	246	21	41	17	205	21	17%		
	Current	202	17	58	25	144	15	29%		
Sleeping medication use	Not, in the past 4 weeks	1063	89	200	85	863	90	19%	0.04	*
	Yes, in the past 4 weeks	133	11	35	15	98	10	26%		
Obstructive sleep apnea	OSA–	1091	91	216	92	875	91	20%	0.675	
(AHI ≥15)	OSA+	105	9	19	8	86	9	18%		
Sleep duration (h)	<6	78	7	18	8	60	6	23%	0.547	
	≥6 to 7	189	16	39	17	150	16	21%		

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	≥7 to 8	374	31	63	27	311	32	17%	
	≥8 to 9	326	27	69	29	257	27	21%	
	≥9	229	19	46	20	183	19	20%	
Follow-up years	1	386	32	85	36	301	31	22%	0.154
	2	810	68	150	64	660	69	19%	

*p<0.05, **p<0.01, ***p<0.001.

Abbreviations: WHIIRS, Women's Health Initiative Insomnia Rating Scale; BMI, body mass index; HS, high school; USD, United States dollar; AHI, apnea–hypopnea index.

Table 2. Prevalence of insomnia-related symptoms by age and gender.

		Difficulty initiating sleep[a,b]	Difficulty maintaining sleep[a]	Early morning awakening[a]	Difficulty returning to sleep[a]	Nonrestorative sleep
All	18–29	30%	41%	30%	24%	9%
	30–39	31%	49%	34%	27%	11%
	40–49	32%	49%	38%	26%	12%
	50–59	41%	60%	45%	37%	12%
	60–64	40%	59%	43%	42%	12%
	Total	35%	52%	39%	31%	11%
Male (N=480)	18–29	37%	39%	33%	25%	13%
	30–39	32%	54%	37%	31%	6%
	40–49	29%	47%	43%	28%	10%
	50–59	30%	61%	39%	29%	10%
	60–64	16%	49%	27%	24%	5%
	Total	30%	51%	38%	28%	10%
Female (N=716)	18–29	25%	43%	28%	22%	6%
	30–39	30%	46%	33%	24%	13%
	40–49	33%	51%	35%	26%	13%
	50–59	49%	60%	49%	43%	13%
	60–64	54%	66%	53%	53%	15%
	Total	38%	53%	39%	33%	12%

[a]significantly different among age groups, [b]significantly different between genders.

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削除: Table 3. Spearman correlation coefficients among insomnia-related symptoms.

Table 3 Incident depression and insomnia-related symptoms in the logistic regression analysis.

N=1196	Crude OR (95% CI)	p		Adjusted 1 OR (95% CI)	p		Adjusted 2 OR (95% CI)	p	
Difficulty initiating sleep	1.6 (1.2–2.1)	<0.01	**	1.4 (1.0–1.9)	0.042	*	0.9 (0.6–1.4)	0.699	
Difficulty maintaining sleep	1.6 (1.2–2.1)	<0.01	**	1.4 (1.0–1.9)	0.024	*	1.1 (0.8–1.6)	0.501	
Early morning awakening	1.5 (1.1–2.0)	<0.01	**	1.4 (1.0–1.9)	0.031	*	1.0 (0.7–1.4)	0.943	
Difficulty returning to sleep	1.9 (1.4–2.5)	<0.001	***	1.8 (1.3–2.4)	<0.001	***	1.5 (1.0–2.2)	0.071	
Nonrestorative sleep	2.5 (1.7–3.7)	<0.001	***	2.6 (1.7–3.9)	<0.001	***	2.2 (1.4–3.5)	0.001	**

*p<0.05, **p<0.01, ***p<0.001

Abbreviations: OR, odds ratio; CI, confidence interval.

Adjusted 1: age, gender, BMI (body mass index), field center, annual household income, years of education, marital status, alcohol use, cigarette use, sleep medication use, OSA (obstructive sleep apnea), sleep duration, follow-up years.

Adjusted 2: Adjusted 1 + difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, difficulty returning to sleep, nonrestorative sleep.

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Figure Legends

Figure 1. Flowchart of the present study.

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ページ 10: [1] 削除　　作成者

ページ 45: [2] 削除　　作成者