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Insomnia and Daytime Sleepiness Are Risk Factors for Depressive Symptoms in the Elderly

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Study Objectives: Previous studies have reported that insomnia and excessive daytime sleepiness (EDS) may predict depression in adults. However, these associations have not been investigated in community-dwelling elderly taking into account insomnia symptoms, EDS, and sleep medication.

Design: Four-year longitudinal study.

Setting: The French Three-City Study.

Participants: 3824 subjects aged ≥ 65 years and free of depressive symptoms at baseline.

Measurements and Results: Questionnaires were used to evaluate "insomnia symptoms," EDS, and sleep medication at baseline. Depressive symptoms (DEP-s) were assessed using the Center for Epidemiologic Studies–Depression scale at baseline, and at 2-year and 4-year follow-up. Logistic regression models controlling for potential confounders were generated to determine whether sleep disturbances were associated with incident DEP-s and to determine the effect of individual insomnia symptoms. Insomnia symptoms and EDS independently increased the risk of incident DEP-s (OR = 1.23, 95% CI = 1.01-1.49 and OR = 2.05, 95% CI = 1.30-3.23, respectively). Poor sleep quality and difficulty in initiating and in maintaining sleep—but not early morning awakening—were identified as risk factors of DEP-s, with risk increasing with the frequency of insomnia symptoms. Sleep medication was not only a risk factor for DEP-s independent of insomnia symptoms (OR = 1.62, 95% CI = 1.26-2.09), but also independent of EDS (OR = 1.71 95% = 1.33-2.20).

Conclusions: Insomnia symptoms, EDS, and the use of medication independently increase the risk of subsequent depression in the elderly. In clinical practice, disturbed sleep and prolonged use of sleep medication may be early indicators or potentially reversible risk factors for depression, suggesting the need for further clinical interventional research.

Keywords: Epidemiology, depression, insomnia, hypersomnia, elderly

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INTRODUCTION

Depressive symptoms increase with age, having a very high prevalence in the general elderly population. Depression is related not only to poor quality of life, increased comorbidity, decreased life expectancy, loss of autonomy, and risk of suicide; it is also a greater risk factor for cardiovascular disease than smoking.[1-3] The identification of potentially reversible risk factors for depression in the elderly is thus a public health priority, permitting interventions aiming to reduce the number of new cases and prevent chronicity, which in turn contributes to treatment resistance.

Cross-sectional studies have consistently observed sleep disturbance to be common in depression. Sleep disturbance forms part of the clinical algorithm used to diagnose depression and has commonly been considered to be a consequence of the disorder due to disturbances in monoamine activity. More recently there has been accumulating evidence to suggest that the sleep disorder precedes depression, as non-depressed subjects with a family history of depression commonly have disturbances of REM sleep.[4] Physiological hypotheses have implicated genes associated with both the monoamine and circadian systems,[5-7] related to stress-induced arousal responses and subsequent overactivity of the hypothalamic-pituitary-adrenal axis,[8] or alternatively mediated by an increased activation of REM sleep mechanisms.[9] The association may also be bi-directional. Prospective studies are required to clarify cause-and-effect relationships[10] and determine whether sleep disturbances are premorbid traits or independent risks factor for depression. Studies of older adults have the advantage of high rates of both incident depressive symptomatology and sleep disturbance, with genetic risk most likely to have been expressed. The very few prospective studies in older adults that have been conducted to date[11-15] have been limited by their short follow-up (one or two years) and failure to differentiate insomnia from excessive daytime sleepiness (EDS) as potential risk factors for depression,[11,13,15] although each may have distinct consequences on depressive symptoms (DEP-s). Insomnia is frequently associated with sleepiness in elderly subjects and both may have deleterious consequences on health and everyday functioning. However, little is known specifically about either EDS or insomnia, particularly the components of the insomnia phenotype, i.e.,

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sleep quality (SQ), difficulty in initiating sleep (DIS), difficulty in maintaining sleep (DMS), and early morning awakening (EMA), as independent risk factors for DEP-s.[16]

Insomnia in the elderly is associated with high rates of both over-the-counter purchase and prescription of sedative hypnotic and antidepressant medication. The effects of this have, however, rarely been taken into account in prospective studies of sleep disturbance and depression. One study in older adults suggested that depression recurrence could be predicted by sleep disturbance independently of antidepressant intake.[15] Given the potential effects of sleep medications in modifying insomnia and EDS, they may also independently contribute to the risk of developing depressive symptoms.

Thus, while there is accumulating evidence to suggest that sleep disturbance may increase the risk of late depression, this hypothesis remains to be tested within a large prospective study able to take into account multiple independent and interacting causes of depressive symptoms. The aim of the present study was to examine the relationship between sleep disturbance and the incidence of DEP-s over 4 years in community-dwelling elderly, taking into account sleep disturbance characteristics as well as sleep medication.

METHODS

Study Population

Subjects included in the present study were recruited as part of the Three City Study, an ongoing multi-site prospective study involving 3 French cities: Bordeaux, Dijon, and Montpellier. The study design is described elsewhere.[17] Briefly, 9294 subjects ≥ 65 years were recruited from the electoral rolls between March 1999 and March 2001. The study protocol was approved by the ethical committee of the Kremlin-Bicêtre University Hospital (France), and written informed consent was obtained from each participant. The participants were interviewed at baseline and followed up after 2 and 4 years.

Of the 9077 dementia-free participants initially included in the 3C study, 282 died and 712 were lost to follow-up. Of the 8083 remaining subjects, 1018 were missing either prevalent or incident data on depression (CES-D evaluation or medication use); 1374 had not fully completed the sleep questionnaire; 600 had missing data in adjustment covariables; and 1267 were excluded because they had high levels of DEP-s or were taking antidepressant medication at baseline. A further 144 participants with low levels of depressive symptoms but taking antidepressant medication at one of the 2 follows-ups were excluded. The present analyses were thus performed on 3824 subjects. Participants not included in the analyses had a lower education level, were older and more frequently female, living alone, and with chronic disease and disability ($P < 0.0001$).

Depressive Symptoms

The Center for Epidemiologic Studies Depression Scale (CES-D)[18] was completed at baseline and each consecutive follow-up, excluding the eleventh item, "my sleep was restless," which could interfere with the association between DEP-s and sleep complaints. Thus, depression symptom scores ranged from 0 to 57 instead of 0 to 60. Nevertheless, to be consistent with the CES-D cut-off point, participants with a score ≥ 16 were referred to the high depressive symptoms group in contrast to the participants with CES-D ≤ 15 included in the low depressive symptom group. Participants with CES-D scores ≥ 16 at baseline were excluded from the longitudinal analysis, as were as those taking antidepressant medication at baseline or at follow-up because antidepressants might be prescribed for reasons other than depression, such as anxiety. In longitudinal analyses, incident DEP-s was identified from the "low depressive symptom group" free of antidepressants but who subsequently had incident elevated DEP-s during at least one of the 2 follow-up examinations.

History of major depression was diagnosed according to DSM-IV criteria using the Mini-International Neuropsychiatric Interview (MINI) (French version 5.00),[19] a standardized psychiatric examination validated in the general population.

Sleep Disturbances

Sleep disturbances were assessed at baseline by a face-to-face clinical interview followed by the completion of a sleep questionnaire.[16] The participants self-rated as "never, rarely, frequently, or often" occurrence of EDS and the following insomnia symptoms; difficulty in initiating sleep (DIS), difficulty in maintaining sleep (DMS), and early morning awakening (EMA). Participants also rated sleep quality (SQ) as good, average, or poor. Insomnia symptoms were defined as reporting poor SQ or having often DIS, DMS, or EMA.

Sleep Medications

Participants reported whether they were currently using medication for sleep, anxiety, or stress. An inventory of all drugs (prescription and over-the-counter drugs) used during the preceding month was also taken and verified by the interviewer by asking to see prescriptions or the medications themselves. Sleep medication was classified as prescribed medication; benzodiazepine (BZD) and BZD-like compounds (zolpidem, zopiclone), antihistaminic compounds (doxylamine, alimemazine, hydroxyzine), miscellaneous medications (including hypnotics from different pharmacological families such as neuroleptics), and homeopathic and non-prescription treatments.

Sociodemographic and Clinical Variables

A standardized interview covered sociodemographic factors and current state of health, including gender, age, current lifestyle, education level, body mass index, and disability (assessed by the Instrumental Activities of Daily Living–IADL[20]). A lifestyle questionnaire was used to obtain information on current smoking status, alcohol intake, and coffee consumption.

Information on the history of vascular disease (angina pectoris, arrhythmia, lower limb arteritis, heart failure, myocardial infarction, coronary surgery, stroke) were established according to standardized questions with additional information given by general practitioners. Recent asthma attacks, hypertension, hypercholesterolemia, diabetes, asthma, and thyroid disease were also recorded. Participants were classified as having chronic disease if they suffered from one, two, or more of these illnesses.

Statistical Analyses

Associations between the incidence of DEP-s over the 4-year follow-up and subject characteristics, sleep complaints (in-

somnia symptoms, number of insomnia symptoms, and EDS), and sleep medication were quantified with odds ratios (OR) and their 95% confidence intervals (CI). Study center, clinical, and sociodemographic variables associated with DEP-s (at $P < 0.15$) and the CES-D score at baseline were included in logistic regression models to estimate adjusted OR for sleep complaints and sleep medication. In order to determine which insomnia symptoms were independently associated with the presence of DEP-s, the 4 insomnia symptoms were entered together in the same logistic regression model with potential confounders. Finally, to study the relationship between each of the sleep disturbances and the chronicity of DEP-s, 3 groups of subjects were compared by multinomial logistic regression; no DEP-s at any follow-up, DEP-s at 2-year follow-up only, and DEP-s at 2-year and 4-year follow-up. When appropriate, the interaction terms were tested using the Wald χ^2 test given by the logistic regression model. Significance level was set at $P < 0.05$. Analyses were performed using SAS statistical software (version 9.2; SAS Inc, Cary, NC).

Table 1—Baseline characteristics of participants (n = 3824) according to incident depressive symptoms (n = 618) over 4-year follow-up

	Depressive Symptoms						
	Low (N = 3206)		High (N = 618)				
Variable	**n**	**%**	**n**	**%**	**OR**	**95% CI**	**P***
Age (years)							
< 70	1056	32.94	169	27.35	1		< 0.0001
70-74	1132	35.30	193	31.23	1.07	0.85-1.33	
75-79	760	23.71	188	30.42	1.55	1.23-1.94	
≥ 80	258	8.05	68	11.00	1.65	1.21-2.25	
Gender							
Female vs Male	1691	52.74	442	71.52	2.25	1.86-2.72	< 0.0001
High level of education							
Yes vs No	744	23.21	104	16.83	0.67	0.53-0.84	0.0005
Living alone							
No vs Yes	2253	70.27	400	64.72	0.78	0.65-0.93	0.0062
Alcohol (g/day)							
< 12	1931	60.23	419	67.80	1		< 0.0001
12-36	936	29.20	166	26.86	0.82	0.67-0.99	
> 36	339	10.57	33	5.34	0.45	0.31-0.65	
Coffee (cups per day)							
> 2 vs ≤ 2	841	26.23	135	21.84	0.79	0.64-0.97	0.0222
Smoking status							
Never	1841	57.41	396	64.08	1		0.0014
Past	1185	36.96	198	32.04	0.78	0.65-0.94	
Current	180	5.61	24	3.88	0.62	0.40-0.96	
Past major depression							
Yes vs No	226	7.05	80	12.94	1.96	1.50-2.57	< 0.0001
Body mass index (kg/m^2)							
Normal (< 25)	1496	46.66	293	47.41	1		0.83
Overweight (25-29)	1324	41.30	242	39.16	0.93	0.78-1.12	
Obese (≥ 30)	386	12.04	83	13.43	1.10	0.84-1.44	
Number of chronic diseases[a]							
0	620	19.34	95	15.37	1		0.0016
1	1131	35.28	202	32.69	1.17	0.90-1.52	
2 and more	1455	45.38	321	51.94	1.44	1.12-1.84	
Disability							
Yes vs No	126	3.93	45	7.28	1.92	1.35-2.73	0.0003
Prescribed sleep medication intake							
Yes vs No	291	9.08	122	19.74	2.46	1.95-3.11	< 0.0001
Non-prescription treatments for sleep[b]							
Yes vs No	32	1.00	14	2.27	2.30	1.22-4.33	0.0101

[a]Includes a chronic disease (cardiovascular disease, stroke, other heart problems, high blood pressure, high cholesterol, diabetes, thyroid problems). [b]Includes homeopathic medication intake. *For variables with > 2 categories, the P-value of the test for trend is given.

RESULTS

Population Characteristics and Risk for Incident Depressive Symptoms over 4-Year Follow-Up

At baseline, 34.1% of the subjects had insomnia symptoms. EDS was reported by 16.6% of the subjects (13.1% reporting "frequent" and 3.5% "often" complaints), and 7.8% of subjects had both insomnia symptoms and EDS. Only 10.8% of the participants took prescribed sleep medication (70.2% benzodiazepine, 10.1% benzodiazepine-like compounds, 25.7% antihistaminic compounds, and 17.9% miscellaneous medication), and 1.2% took homeopathic and non-prescription treatments for sleep (of whom half took also prescribed treatment). In subjects taking sleep medication, 57.9% had persistent insomnia symptoms, and only 9.6% were free of all insomnia symptoms.

Over the 4-year follow-up, 618 (16.2%) incident cases of DEP-s were observed. Baseline characteristics of the participants according to the presence of DEP-s during the follow-up are given in Table 1. The risk of developing DEP-s increased significantly with age older than 75 years and was significantly higher in women, in subjects with a low level of education, living alone, with past major depression, having ≥ 2 chronic diseases, being more disabled, or frequent use of sleep medication. In contrast, high alcohol and coffee consumption and smoking were significantly associated with a decreased risk of DEP-s. Subsequent analyses were thus adjusted for these factors. No significant relationship was found between the presence of DEP-s and body mass index.

Table 2—Baseline sleep disturbances of participants according to incident depressive symptoms over 4-year follow-up

	Depressive Symptoms						
	Low (N = 3206)		High (N = 618)				
Variable	N	%	n	%	OR	95% CI	P*
Insomnia symptoms							
No	2186	68.18	335	54.21	1		< 0.0001
Yes	1020	31.82	283	45.79	1.81	1.52-2.16	
Sleep quality (SQ)							
Good	1790	55.83	218	35.28	1		< 0.0001
Average	1161	36.21	302	48.87	2.14	1.77-2.58	
Poor	255	7.95	98	15.86	3.16	2.40-4.14	
Difficulty initiating sleep (DIS)							
Never	695	21.68	81	13.11	1		< 0.0001
Rarely	1610	50.22	242	39.16	1.29	0.99-1.68	
Frequently	549	17.12	149	24.11	2.33	1.74-3.12	
Often	352	10.98	146	23.62	3.56	2.64-4.81	
Difficulty maintaining sleep (DMS)							
Never	213	6.64	23	3.72	1		< 0.0001
Rarely	1075	33.53	141	22.82	1.21	0.76-1.93	
Frequently	1289	40.21	273	44.17	1.96	1.25-3.07	
Often	629	19.62	181	29.29	2.66	1.68-4.22	
Early morning awakening (EMA)							
Never	852	26.58	106	17.15	1		< 0.0001
Rarely	1310	40.86	241	39.00	1.55	1.26-1.90	
Frequently	600	18.71	140	22.65	2.22	1.67-2.94	
Often	444	13.85	131	21.20	3.17	2.06-4.88	
Number of insomnia symptoms							
0	2186	68.18	335	54.21	1		< 0.0001
1	606	18.90	119	19.26	1.28	1.02-1.61	
2	233	7.27	80	12.94	2.24	1.70-2.96	
3-4	181	5.65	84	13.59	3.03	2.28-4.02	
Excessive daytime sleepiness (EDS)							
Never	1604	50.03	242	39.16	1		< 0.0001
Rarely	1108	34.56	236	38.19	1.41	1.16-1.72	
Frequently	397	12.38	104	16.83	1.74	1.35-2.24	
Often	97	3.03	36	5.83	2.46	1.64-3.69	

*For variables with > 2 categories, the P-value of the test for trend is given.

Association between Sleep Disturbances and Incident Depressive Symptoms over 4-Year Follow-Up

Table 2 shows the crude associations, and Table 3 shows the adjusted associations between insomnia symptoms, the type and number of insomnia symptoms, EDS at baseline, and the presence of DEP-s over the 4-year follow-up. A significant adjusted association was observed between insomnia symptoms and the incidence of DEP-s (OR = 1.27, 95% CI = 1.05-1.54). It should be noted that these associations persisted after subsequent adjustment for EDS (OR = 1.23, 95% CI = 1.01-1.49). The risk of developing DEP-s also increased significantly with the number of insomnia symptoms (SQ, DIS, DMS, and EMA). A significant dose-effect was observed (adjusted OR = 1.00, 95% CI = 0.78-1.27 for one symptom, OR = 1.56, 95% CI = 1.15-2.11 for 2 symptoms and OR = 1.75, 95 % CI = 1.28-2.40 for ≥ 3 symptoms; P-trend < 0.0001) (Table 3).

In order to identify insomnia symptoms best predicting DEP-s, the 4 symptoms were introduced into a multivariate model adjusted for the same potential confounders. The insomnia symptoms associated with DEP-s were often DIS (OR = 1.45, 95% CI = 1.01-2.10), and often DMS (OR = 1.40, 95% CI = 1.04-1.87) (Table 4). Conversely, SQ and EMA were not significantly associated with DEP-s.

Table 5 shows the adjusted association between sleep medication at baseline and the presence of DEP-s over the 4-year follow-up (crude associations are displayed in Table 1). The risk of developing DEP-s was associated with taking prescribed sleep medication (model 1). The increased risk of DEP-s with prescribed sleep medication persisted after adjustment for insomnia symptoms (model 2) and for EDS (model 3). There was no significant interaction between sleep medication or EDS for the risk of DEP-s.

The risk of developing DEP-s increased with the frequency of EDS (from "rarely" OR = 1.29, 95% CI = 1.04-1.60 to "often" OR = 2.15, 95% CI = 1.36-3.38, see Table 3). Further adjustment for insomnia symptoms did not modify the strength of the association (OR = 1.29, 95% CI = 1.04-1.59 and OR = 2.05, 95% CI = 1.30-3.23 for rarely and often, respectively).

There was a strong association between EDS and insomnia symptoms at baseline, regardless of insomnia frequency (P < 0.0001). However, no significant interaction was found between EDS and insomnia symptoms for incident DEP-s. The risk of incident DEP-s over 4-year follow-up after adjustment was not significantly different for the composite criterion: often EDS-no insomnia symptoms, (OR = 2.18, 95% CI = 1.08-4.40), often EDS-insomnia symptoms (OR = 2.39, 95% CI = 1.34-4.25), and rarely EDS-insomnia symptoms (OR = 1.56, 95% CI = 1.15-2.12).

To test whether the effect of insomnia symptoms on incident depressive symptoms could be due to underlying depressive symptoms, analyses were performed after excluding participants with a past history of major depression at baseline (n = 306), or those with a past history of major depression at baseline and/ or having a CES-D score between 12 and 15 (n = 778). Under both conditions, the participants without past depression and with insomnia symptoms were more likely to develop de-

Table 3—Adjusted associations between insomnia symptoms, EDS at baseline, and incident depressive symptoms over 4-year follow-up

	OR*	95% CI*	P**
Component symptoms of insomnia			
Insomnia symptoms			
No	1		0.0144
Yes	1.27	1.05-1.54	
Sleep quality (SQ)			
Good	1		< 0.0001
Average	1.62	1.32-1.98	
Poor	1.71	1.26-2.32	
Difficulty initiating sleep (DIS)			
Never	1		< 0.0001
Rarely	1.05	0.79-1.39	
Frequently	1.65	1.19-2.28	
Often	1.88	1.35-2.62	
Difficulty maintaining sleep (DMS)			
Never	1		< 0.0001
Rarely	1.09	0.67-1.78	
Frequently	1.63	1.01-2.62	
Often	1.92	1.18-3.13	
Early morning awakening (EMA)			
Never	1		0.0023
Rarely	1.31	1.01-1.70	
Frequently	1.55	1.14-2.09	
Often	1.58	1.16-2.15	
Number of insomnia symptoms			
0	1		< 0.0001
1	1.00	0.78-1.27	
2	1.56	1.15-2.11	
3-4	1.75	1.28-2.40	
Excessive daytime sleepiness (EDS)			
Never	1		< 0.0001
Rarely	1.29	1.04-1.60	
Frequently	1.74	1.30-2.34	
Often	2.15	1.36-3.38	

*Each OR was adjusted for center, CES-D baseline, gender, age, education, living alone, coffee consumption, alcohol consumption, smoking, chronic disease, past major depression, disability, prescribed sleep medication intake, and homeopathic and non-prescription treatments for sleep. **For variables with > 2 categories, the P-value of the test for trend is given.

Table 4—Common analysis[a] of the associations between the four insomnia complaints and incident depressive symptoms over 4-year follow-up

	OR*	95% CI*	P**
Sleep quality (SQ)			
Good	1		0.12
Average	1.29	1.02-1.63	
Poor	1.17	0.81-1.69	
Difficulty initiating sleep (DIS)			
Never	1		0.0171
Rarely	0.98	0.73-1.31	
Frequently	1.31	0.93-1.85	
Often	1.45	1.01-2.10	
Difficulty maintaining sleep (DMS)[b]			
Never	1.00	0.61-1.64	0.0163
Rarely	1.00		
Frequently	1.31	1.02-1.67	
Often	1.40	1.04-1.87	
Early morning awakening (EMA)			
Never	1		0.67
Rarely	1.21	0.92-1.59	
Frequently	1.20	0.86-1.66	
Often	1.10	0.78-1.56	

*All four insomnia symptoms were included in the model and were adjusted for center, CESD baseline, gender, age, education, living alone, coffee consumption, alcohol consumption, smoking, chronic disease, previous depressive episode, disability, prescribed sleep medication intake, and homeopathic and non-prescription treatments for sleep.
**For variables with > 2 categories, the P-value of the test for trend is given. [a]The four IS were entered together in the same logistic regression model with potential confounders to determine which IS were associated with the presence of depressive symptoms independently of the others.
[b]For DMS, "rarely" has been taken as the reference class instead of "never" because of a too-small sample size in the "never" class

pressive symptoms (OR = 1.28, 95% CI = 1.05-1.58; OR = 1.32, 95% CI = 1.05-1.68, respectively) as well as those with frequent/ often EDS (OR = 1.63, 95% CI = 1.22-2.19; OR = 1.70, 95% CI = 1.22-2.38, respectively).

Lastly, to examine whether insomnia and EDS could be differentially associated with acute and chronic depressive symptoms, subjects were categorized into 3 groups: group 1 without depressive symptom at any follow-up (n = 3206); group 2 with acute depressive symptoms, (i.e., depressive symptoms) at 2 years but not at 4 years (n = 196); and group 3 with chronic depressive symptoms at both follow-ups (n = 138). After adjustment for the potential confounders, the association with EDS at baseline was significant for acute (P = 0.0225 between group 1 and 2) and for chronic depressive symptoms (P = 0.0195 between groups 1 and 3). In contrast, insomnia symptoms were significantly associated with chronic (P = 0.0282) but not with acute depressive symptoms (P = 0.23).

DISCUSSION

This study has examined the relationship between insomnia symptoms, the type and number of insomnia symptoms, EDS, sleep medication, and incident DEP-s at 2-or 4-year follow-up in a large sample of participants aged 65-85 years. Insomnia symptoms and EDS appeared as significant and independent risk factors for DEP-s, increasing risk 1.3 to 2.2-fold, independent of sociodemographic, behavioral, and clinical characteristics, including history of major depression.

Few previous prospective epidemiological studies have examined the association between sleep disturbances and incident depression in the elderly. Two studies were performed within a wide age-range of adults (older than 18 years) after one-year follow-up. Ford and Kamerow found that insomnia and hypersomnia were associated with major depressive episodes,[12]

Table 5—Association between sleep medication at baseline and incident depressive symptoms over 4-year follow-up

	Model 1			Model 2			Model 3		
Variable	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Prescribed sleep medication									
Yes vs No	1.70	1.33-2.19	< 0.0001	1.62	1.26-2.09	0.0002	1.71	1.33-2.20	< 0.0001
Homeopathic and non-prescription treatments									
Yes vs No	1.48	0.75-2.91	0.25	1.38	0.70-2.72	0.35	1.52	0.77-3.00	0.23

Model 1 was adjusted for center, CES-D baseline, gender, age, education, living alone, coffee consumption, alcohol consumption, smoking, chronic disease, past major depression, and disability. Model 2 was adjusted for all the covariates in model 1 plus insomnia symptoms. Model 3 was adjusted for all the covariates in model 1 plus EDS.

whereas the other study reported a strong association between initial sleep disturbances and the subsequent development of DEP-s in women only.[11] A study of 705 subjects over 65 years reported that among several potential risk factors, sleep disturbance was the best predictor of subsequent depression over a 2-year follow-up.[13] Our findings confirm and extend these findings to elderly men and women using standardized criteria for sleep disturbance and considering type of insomnia symptoms. In addition, we showed that the risk of DEP-s increased with the frequency and number of insomnia symptoms.

A small two-year prospective cohort study of 351 adults older than 60 years demonstrated that sleep disturbance acts as an independent risk factor for depression recurrence.[15] We observed insomnia symptoms to be associated with DEP-s over four years, but not in persons whose symptoms did not persist beyond the first two years of follow-up, suggesting that insomnia symptoms may be a risk factor for chronic depression, and perhaps predisposes to treatment resistance. A previous study of subjects over 50 years reported that insomnia predicted depression after one year follow-up, but less strongly than other specific symptoms of depression such as anhedonia, feeling of worthlessness, mood disturbance, and thoughts of death.[14] However, it may be argued that these symptoms were early core symptoms of depression *per se* instead of being independent risk factors. Another study including 147 participants older than 60 years without a history of psychiatric illness reported that new episodes of major depression over one year follow-up were often preceded by periods of insomnia.[21] Whether sleep disturbances constitute precursor or prodromal states, or even core symptoms of clinical depression remains uncertain. In the present study, we were, however, able to show that the risk of developing DEP-s increased significantly with insomnia symptoms and the frequency of its four components, even in subjects without a history of major depression. A multivariate model identified DMS and DIS as predictors of depression, but not poor SQ and EMA, which were mostly reported in subjects already depressed.[22] Even if in some cases insomnia could be concomitant with a depressive state, strong evidence argues for a temporal relationship between insomnia and depression with insomnia generally preceding depression. Our data suggest that this may be driven by DIS or DMS rather than SQ and EMA. However we also hypothesize that insomnia and depression may share a common causality such as similar risk factors (ageing, gender, marital and sleep status, stress, and anxiety) and genetic predisposition especially in relation to the regulation of REM sleep and hypothalamic-pituitary-adrenal axis activity.[7,23]

In our study, unlike insomnia symptoms, EDS predicted the incidence of depression at short (2 years) and/ or long-term (4 years) follow-up, appearing as a vulnerability factor for acute and chronic depressive episodes. A previous large cross-sectional study in the general population found that EDS was strongly associated with depression,[24] but principally bipolar-II disorder and/ or atypical depression.[25] Lifetime hypomanic episodes have also been associated with EDS in the elderly.[26,27] Altogether, hypersomnia appeared as an important predictor of the development of an atypical feature subtype of major depressive disorder.[28] This hypothesis has not been addressed in the elderly general population.

The different mechanisms by which insomnia and EDS play a role in the development of DEP-s remain to be determined. One hypothesis is by the modification of sleep regulation *per se,* as REM sleep dysregulation is frequently reported in insomnia comorbid with depression[4] but not for hypersomnia associated with depression.[9,22] In addition, EDS and insomnia did not share similar temporal relationships with DEP-s: we observed in the present analyses that in contrast to insomnia symptoms, DEPs are chronic or acute in the context of preexisting EDS.

In our study the use of sleep medication was associated with the occurrence of DEP-s. Treatment was principally with benzodiazepines, which are ineffective in depression (their benefit being confined to comorbid anxiety and depression[29]) and thus cannot prevent depression *per se* in terms of underlying biological mechanisms, notably hypothalamic-pituitary-adrenal axis functioning.[30] This finding may thus be due to the prescription of benzodiazepines when a patient has been suspected of having sleep disorder in the context of subclinical depression (not reaching the level of depressive symptomatology defined at baseline). As expected, subjects with insomnia symptoms had the highest risk of sleep medication intake. However, no interaction between sleep medication and insomnia or EDS was found in the association with DEP-s. The risk of developing DEP-s was similar in subjects with insomnia taking sleep medication and in subjects without insomnia but taking medication. This result is in agreement with several studies[31,32] showing that the use of hypnotics is associated with incident depression. Our results suggest that hypnotics are not effective in preventing depression in the context of insomnia in the elderly.

Depression in the elderly is above all a clinically heterogeneous syndrome, which is likely to be the endpoint of multiple

etiological pathways. While we confirmed a strong association between sleep disorder and incident depression, in our cohort only around a quarter of subjects developing depression over the four-year observation period had sleep disturbances at baseline. This suggests a possible depression subtype for which EDS in particular may be a strong biomarker. In this case, it may be important for future work on determinants of depression to consider this subgroup separately.

Study Limitations

The present study has some limitations. Bias could have been introduced through the exclusion of demented participants (2.3%), those lost to follow-up (10.7%), and those with incomplete data on depression (11%), sleep (14.8%)m and covariates (6.4%). These subjects had a lower education level, were older and more frequently female, living alone, and with chronic diseases and disability, being therefore at high risk for the outcome of DEP-s. Although being a limitation to generalizability, the consequence is that the associations between sleep disturbances and DEP-s outcome were possibly underestimated. Except for the presence of excessive daytime sleepiness, data on impaired daytime functioning related to nighttime sleep difficulty were not available.[33] We did not have the age at onset of sleep disturbances and their causes, and we did not know if DEP-s met criteria for the atypical features subtype. We were also unable to distinguish depression which was part of an anxio-depressive state, which may have led to an underestimation of observed associations and confounded results on the effects of medication. Since we did not take into account duration,

frequency, and dose of medication, we could not definitively address the question of whether the effects are transient or whether prolonged use could precipitate DEP-s. In our study, sleep disturbance was assessed only once (at the baseline examination). We therefore could not assess the evolution of sleep disturbances in relation to DEP-s and thus determine whether sleep problems were stable, decreased, or increased in parallel with the depressive episode. The measure of EDS in this study was based on only one question, but its severity was examined using a four-point scale.

Study Strengths

The data used in the analysis comes from a large multicenter population-based prospective study of people aged 65 years and older. Sleep medication was verified by examining the prescriptions and medications themselves, thus minimizing exposure misclassification. We limited potential confounding by taking into account a wide range of risk factors for DEP-s in the elderly. However, there were only minor changes between the unadjusted and adjusted analyses, notably for other sleep disturbance characteristics, suggesting robustness of the associations. Another strength of this study was the face-to-face clinical interview. We have used a measure of DEP-s, which is a widely used indicator of clinically significant depressive disorder[18] validated in a wide range of populations including the elderly. The CES-D item on sleep symptoms was excluded to prevent the possibility of biasing the results. We also excluded subjects with absence or low levels of DEP-s (with CES-D score < 16) but taking antidepressants, as some antidepressants have stimulating or sedative effects and could favor insomnia or EDS. This may thus have reduced the proportion of depressed subjects and weakened the associations. We ensured, however, that the findings were comparable by taking them into account in a preliminary analysis (data not shown). Finally, in our study, the components of insomnia symptoms (DIS, DMS, EMA) and the characteristics of poor SQ were independently examined.

CONCLUSION

Our findings suggest that insomnia, EDS, and sleep medication were independently associated with the risk of subsequent depression in an elderly general population. There is a clear need to identify the mechanisms that trigger DEP-s to improve our understanding of risk factors and natural history of depression. This study shows the need for further clinical research into the association between sleep disturbance, prolonged sleep medication prescription, and depression onset in the elderly, to establish whether it may constitute, as our findings suggest, a possible reversible risk factor for the occurrence, relapse, and chronicity of depressive symptoms.

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DISCLOSURE STATEMENT

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