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## CHRONIC INSOMNIA AND DEMENTIA RISK

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## ХРОНИЧЕСКАЯ ИНСОМНИЯ И РИСК РАЗВИТИЯ ДЕМЕНЦИИ

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According to recent studies, the standard duration of nocturnal sleep may be critical for cognitive processing and normal metabolism and elimination of amyloid precursor protein in Alzheimer's disease. So, insufficient sleep could constitute a significant risk factor for Alzheimer's disease or cognitive decline in the elderly. The objective of this review was to assess the link between chronic insomnia and the risk of dementia. We performed a search using the keywords «insomnia AND dementia» for all available articles written in English from January 2010 to January 2020. We identified more than 471 potentially eligible articles from keyword searches; 9 of them met inclusion-exclusion criteria and were included in our non-systematic review. Chronic insomnia was significantly associated with the all-cause dementia manifestation in 5 studies (three retrospective and two prospective) and with cognitive decline in 1 prospective study. However, in 4 other studies, insomnia was not significantly linked with dementia. Thus, there is currently insufficient evidence to state that chronic insomnia is a risk factor for dementia or cognitive decline in the elderly. Further research is needed to evaluate the place of insomnia and its significance in reducing the risk or slowing the progression of cognitive impairment.

*Keywords: dementia, insomnia, cognitive decline, sleep disorder*

Структура и продолжительность ночного сна могут иметь определенное значение для когнитивных процессов, поэтому недостаточность сна может быть одним из факторов риска болезни Альцгеймера или иного ухудшения когнитивных функций. Целью данного обзора было оценить связь между хронической инсомнией и риском деменции. Мы провели поиск по ключевым словам «инсомния» и «деменция» всех доступных статей, опубликованных с 2010 по 2020 год. Из первоначальных 471 статьи 9 были включены в данный обзор. Хроническая инсомния была достоверным фактором риска деменции в 5 исследованиях (3 ретроспективных и 2 проспективных) и когнитивного снижения в 1 проспективном исследовании. Однако в 4 других работах не было получено статистически значимой связи между инсомнией и деменцией. Таким образом, в настоящее время недостаточно данных для того, чтобы утверждать, что хроническая инсомния является фактором риска деменции или ухудшения когнитивных функций в пожилом возрасте. Необходимы дальнейшие исследования по оценке места инсомнии и ее значения в снижении риска или замедлении прогрессирования когнитивных расстройств.

*Ключевые слова: деменция, инсомния, когнитивное снижение, расстройства сна*

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AD	– Alzheimer's disease	GDS	– Global Deterioration Scale
Aβ	– amyloid-beta	HR	– Hazard ratio
CNS	– central nervous system	ICD-9	– International Classification of Diseases, 9th Revision
DSM-III-R	– Diagnostic and Statistical Manual of Mental Disorders, third edition, revised	ICSD-3	– International Classification of Sleep Disorders
DSM-IV	– Diagnostic and Statistical Manual of Mental Disorders, fourth edition	MMSE	– mini-mental status examination

**D**ementia is one of the most critical medical problems with a rapidly growing prevalence in modern society. Nowadays, over 50 million people have

dementia. Up to 10 million diagnoses are made annually. It is estimated that the number of patients with dementia will reach 82 million in 2030 and 152 million

by 2050 [1]. Dementia is a polyetiological syndrome caused by various diseases of the brain, primarily of a neurodegenerative and vascular nature. Yet, there is no disease-modifying evidence-based therapy for the most common causes of dementia. In this regard, the search for modifiable risk factors is of great interest today, the identification and control of which can constitute a perspective approach to delaying the onset or slowing down cognitive decline.

Strong epidemiological data shows that the risk of dementia in later life is determined by many factors: age, gender, ApoE genotype, hypertension, hyperlipidemia, obesity, low physical activity, and low educational level [2].

Insomnia is significant for particular difficulties in falling asleep, maintaining sleep, and/or struggling with frequent night awakenings which negatively affect the subsequent quality of wakefulness [3]. The International Classification of Sleep Disorders (ICSD-3) [4] defines insomnia as a disturbance of nocturnal sleep and related impairment of daily functioning. The criterion for the diagnosis of «chronic insomnia» is sleep disturbances that recur at least three nights a week for three or more months. According to epidemiological studies, chronic is very common among patients with cognitive impairment or dementia [5–8]. Recently, it has been thought that chronic insomnia can be an independent factor and a reliable risk factor [9].

Chronic insomnia may affect cognition because of a memory consolidation deficit that is thought to be tightly linked with the rapid eye movements (REM) phase of sleep [10]. However, particular interest in studying the possible role of sleep disorders in the development of cognitive impairment appeared after the description of the so-called cerebral glymphatic system. Experimental studies on animals indicate that the elimination of neuronal metabolic products, including peptide precursors of the Alzheimer's amyloid protein, occurs during nocturnal sleep. In the phase of slow sleep, special glial channels stay open, through which pulsating arterioles squeeze out the intercellular fluid of the periaxonal spaces into the perivenular space, where it is absorbed into the blood. Theoretically, insufficient duration of non-REM sleep may impede the elimination of amyloid protein from the brain and, therefore, accelerate the progression of Alzheimer's disease in genetically predisposed individuals [11]. In addition, insomnia may exacerbate other risk factors for AD, including diabetes mellitus, hypertension, depression and obesity [12].

This review aims to analyze the studies on the association between chronic insomnia and dementia or cognitive decline in the elderly.

**Material and Methods.** We reviewed all available articles published in English from 2010 to 2020. The keywords used for searching were «insomnia AND dementia». After obtaining the initial search results, titles and abstracts of articles were evaluated for suitability against the selection criteria. Full-text articles were then retrieved and assessed for inclusion. The following inclusion criteria for the studies were: 1) retrospective, longitudinal or cross-sectional studies, 2) the number of patients is at least 100; 3) the presence of a control group; 4) the use of generally accepted diagnostic criteria for insomnia, dementia, or cognitive decline; 5) the results and the course of the study are precise.

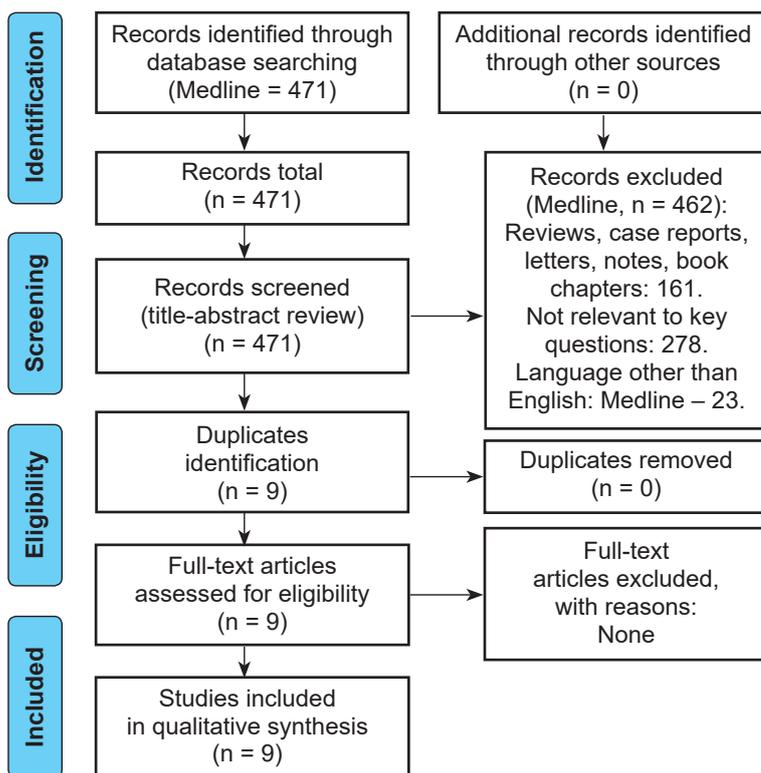


Fig. Articles search and exclusion according to PRISMA statement

The systematic review was performed according to PRISMA guidelines (Figure). During the keyword search, 471 potentially relevant articles were selected; of these, nine articles met the inclusion/exclusion criteria and were included in this review (Table) [3, 13–20].

**Results and Discussion. Cross-sectional studies.**

G. Merlino et al. evaluated sleep and cognitive disturbances in 750 subjects aged 65 years or older. Cognitive functions were assessed with a mini-mental status examination (MMSE) and Global Deterioration Scale (GDS). Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. The presence of at least one of three symptoms: difficulty falling asleep, frequent awakenings which bring problems to falling asleep again, or early morning awakenings at least three times a week is a criterion for the diagnosis of insomnia. Insomnia was diagnosed in 85.4 % of older adults with normal cognitive functions and 78.8 % of patients with dementia. Differences in the prevalence of insomnia among patients with and without cognitive impairment were insignificant [13].

**Retrospective studies («case-control»).** P.-L. Chen et al. studied the risk of dementia in patients with chronic insomnia taking sleeping pills. Data from the Taiwan Health Insurance Database were retrospectively analyzed. Insomnia was defined using the criteria for the International Classification of Diseases, Ninth Revision (ICD-9). The main group included patients over 50 years of age who had insomnia in their medical records at least twice a year and ones who have prescribed at least 30 standard daily doses of sleeping pills for one year. The comparison group consisted of individuals without insomnia matched by age and gender. The patient's medical history was followed up for at least three years after diagnosis of chronic insomnia. Dementia was diagnosed according to ICD-9 criteria. Over three years, dementia was diagnosed in 220 of 5693 patients with insomnia (3.86 %) and 424 of

28041 non-insomniacs (1.49 %). Thus, the relative risk of developing dementia in chronic insomnia was significantly higher ( $p=0.001$ ; HR, 2.34; 95 % CI, 1.92–2.85).

The incidence of dementia was not affected by the type of hypnotic therapy administered (benzodiazepine or non-benzodiazepine drugs, dosage) [14].

Table

**Insomnia and the risk of development dementia**

Study	Sample	Period of study	Definition of insomnia	Definition of dementia	Results
Cross-sectional study					
G. Merlino [13]	750 adults aged $\geq 65$ years		Clinical interview	DSM-IV	No connection
Retrospective case-control study					
P.-L. Chen et al. [14]	34 158 adults aged $\geq 50$ years	3 years	ICD-9	ICD-9	Patients with primary insomnia aged 50 to 65 years had a higher risk of dementia
C.-M. Hung et al. [3]	310 458 adults aged $\geq 20$ years 51 743 – test group	3 years	ICD-9	ICD-9	Primary insomnia was associated with a 2.14-fold increase in dementia risk
R. Hoile et al. [15]	25 758 adults aged $\geq 65$ years 15 209 – test group	10 years	Clinical interview	Clinical diagnosis	Insomnia symptoms were associated with a higher risk of dementia
Prospective studies					
M. Cricco et al. [16]	6 444 adults aged $\geq 65$ years	3 years	Original questionnaire	Neuro-psychological tests	Chronic insomnia was associated with a higher risk of cognitive decline in men without depression
D. Foley et al. [17]	2 346 men aged $\geq 71$ years	3 years	Original questionnaire	DSM-III-R Neuro-psychological tests	No connection
R. Osorio et al. [18]	346 adults aged 24–96	7.7 years	Items 4, 5, and 6 from the Hamilton Depression Rating Scale (HAM-D)	Mini-Mental State Examination	Insomnia was associated with greater risk of Alzheimer’s disease
I. Jausse et al. [25]	4 894 adults aged $\geq 65$ years	8 years	Clinical interview and original questionnaire	DSM-IV Neuro-psychological tests	Insomnia was associated with greater risk of cognitive decline, but not dementia
K. Yaffe et al. [26]	179 738 men aged $\geq 55$ years	8 years	ICD-9	ICD-9	Insomnia was associated with greater risk of Alzheimer’s disease

C.-M. Hung et al. also assessed the relationship between chronic insomnia and dementia in a retrospective study [3]. Data from the Taiwan Medical Database were analyzed. Outpatients who visited the polyclinic at least twice during 2002–2004 for primary insomnia were included. Insomnia and dementia were diagnosed according to the ICD-9 classification. Each patient’s medical history was followed for at least three years from the date of diagnosis of primary insomnia. To assess the risk of developing dementia between the main group and the comparison group, the Kaplan-Meier method and the logarithmic rank test were used as well as the model of proportional risks by age groups. A total of 51,743 people aged 20 years and over were included in the core cohort of patients with primary insomnia. The control group included 258715 individuals without insomnia. During the three-year follow-up period, dementia developed in 1316 patients with primary insomnia and 3472 patients without it. Patients with primary insomnia had a significantly higher risk of developing dementia (HR=2.17; 95 % CI 2.04–2.32;  $p<0.05$ ). After adjusting for the area of residence and some comorbidities, primary insomnia remained a statistically significant risk factor for dementia. It was associated with a 2.14-fold increase in the incidence of this disorder (95 % CI 2.01–2.29). The effect of insomnia on the risk of developing dementia was significant in all age groups, but a stronger effect was observed in younger patients.

As a result, in patients aged 20–39 years, HR was 4.77 (95 % CI 2.92–7.84;  $P<0.05$ ); at the age of 40–

59 years – 3.24 (95 % CI 2.91–4.36;  $P<0.05$ ); at the age of 60–74 years – 2.12 (95 % CI 1.92–2.34;  $P<0.05$ ); over the age of 75 years, the adjusted HR was 1.95 (95 % CI 1.77–2.14;  $P<0.05$ ). Thus, primary insomnia was associated with a higher risk of dementia, especially in relatively young age groups [3].

R. Hoile et al. hypothesized dementia to be more common in people who visited their general practitioner for insomnia within the previous 5–10 years. Data from the UK’s Clinical Practice Research Datalink was analyzed [23]. All included patients had to be at least 65 years old during the period of dementia diagnosis. The conclusion about the presence of insomnia was based on one of two criteria: 1) difficulties in falling asleep or maintaining sleep, leading to night wakefulness or insufficient sleep; 2) the presence of hypnotic medication in the prescribing history. Multivariable logistic regression was used to investigate the relationship between dementia and insomnia. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated. Twelve thousand eight hundred seventy-nine cases of dementia were identified and compared with 12 879 age- and sex-matched controls without dementia. As a result, it was shown that the risk of developing dementia was significantly higher in individuals with insomnia (OR 1.34, 95 % CI 1.20–1.50) [15].

*Longitudinal prospective studies.* M. Cricco et al. evaluated the risk of cognitive decline in elderly patients with insomnia in a prospective study design [18]. In 14 457 individuals aged 65 and over, cognitive function was assessed using the nine-point version of the Pfeiffer short

mental state questionnaire [16]. Among them, 6 444 patients (2 429 men and 4 015 women) had no cognitive impairment at the start of the study; they were asked to complete a sleep quality questionnaire. Cognitive decline was defined as impairment on the Pfeiffer scale by at least 2 points during follow-up [22]. Sex-stratified multiple logistic regression models were computed. The study showed that the risk of cognitive decline was significantly higher in men with chronic insomnia (OR 1.49; 95 % CI 1.03–2.14) without depression. At the same time, no significant association was found in men with depression or in women.

Longitudinal associations between sleep disturbances (insomnia or daytime sleepiness) and incidence of dementia or cognitive decline were assessed in the study of D. Foley et al. [17] within the framework of the Honolulu-Asia Aging Study [23]. Only men aged 71 and more were included in the study (n=2346). At the beginning of the observation, they underwent insomnia screening using a special questionnaire, as well as a study of cognitive functions. Re-assessment was carried out after three years. There was a significant association between daytime sleepiness and dementia or cognitive decline. However, no significant association between dementia or cognitive decline with insomnia was found [17].

The relationship between insomnia and dementia was also studied by R. Osorio et al. Cognitively normal adults aged 24–96 years (n=346) were followed up for 7.7 years. Insomnia was diagnosed according to the corresponding points of the Hamilton scale, dementia – using the mini-mental state examination (MMSE). The presence of insomnia was found to be a significant risk factor for dementia (odds ratio (OR)=2.39, 95 % confidence interval (CI)=1.03–5.55). At the same time, patients with insomnia showed a shorter time to dementia diagnosis than those without insomnia ( $\chi^2=3.94$ ,  $p=0.047$ ) [18].

In a prospective study of I. Jaussent et al. the association of sleep complaints (insomnia or excessive daytime sleepiness) with cognitive decline and dementia were assessed in an 8-year follow-up in the elderly. There were 4894 patients without dementia at the age of 65 years or more from 3 cities in France. Cognitive function was assessed at the start of the study and each follow-up visit (2, 4, and 8 years later) using the Mini Mental State Examination (MMSE) and other neuropsychological tests. Cognitive decline was defined as a stable decrease in MMSE of at least 4 points or a stable deterioration in the results of other tests. DSM-IV diagnosed dementia. Sleep complaints were assessed using an appropriate questionnaire [24]. The severity of insomnia was determined by the number of complaints (e.g. poor sleep quality, frequent/often difficulties initiating sleep or awakenings during the night or early morning awakening). Excessive daytime sleepiness was significantly associated with cognitive impairment, while signs of insomnia did not affect cognitive decline or dementia risk. Paradoxically, less cognitive decline was observed in patients with a more significant number of insomnia complaints [25].

K. Yaffe et al. also tried to determine whether a diagnosis of sleep disturbance (including insomnia) is associated with the risk of dementia. The study population included 179 738 male veterans aged 55 years or older, each of them were followed up for seven years. Insomnia was diagnosed according to ICD-9 criteria. In addition to all-cause dementia, several dementia subtypes were analyzed: Alzheimer's disease, vascular dementia and Lewy body dementia. Authors estimated hazard ratios with extended Cox regression models. After adjustment for potential confounders, relative risk of dementia was approximately 30 % higher in veterans with insomnia (HR:

1.29, 95 % CI: 1.20, 1.39,  $\chi^2=44.0$ ,  $df=1$ ,  $p<0.0001$ ). Insomnia was mainly associated with Alzheimer's type of dementia (hazard ratios from 1.19–1.26) [26].

There are few large studies on the association between insomnia and cognitive impairment. Over the past ten years, we have managed to find only three retrospective analyses in international search engines, five prospective clinical trials, and one profile work. The analyzed studies are characterized by significant heterogeneity in the number of patients (from 349 to 179 738) and the time of observation of patients (from 3 to 10 years).

Most studies analyze the relationship between chronic insomnia and the incidence of dementia. We have found only a limited number of papers investigating the relationship between chronic insomnia and non-dementia cognitive impairment. Meanwhile, given the high prevalence of non-dementia cognitive impairments in the population, such studies are of considerable interest. It should be noted that the study of the association between insomnia and dementia requires a significantly longer observational period compared to non-dementia cognitive impairment because dementia develops only as a result of a very long period of disease progression.

It is important to note that there is a significant difference in the approaches to the diagnosis of dementia in different studies. The authors used other clinical diagnostic criteria (ICD-9, DSM-III-R, DSM-IV), which may affect the results. Approaches to the diagnosis of insomnia are no less different: the authors used their original questionnaires in most studies. In addition to the incidence of dementia, some prospective studies have analyzed the effect of insomnia on cognitive decline. However, various neuropsychological techniques have also been used to measure cognitive decline.

Thus, studies of the relationship between insomnia and the risk of cognitive impairment performed to date are characterized by a significant heterogeneity of methods and diagnostic approaches, which explains the considerable variability of the results obtained. If in retrospective observations there is a significant relationship between the presence of chronic insomnia and the risk of dementia, then in prospective studies, this relationship is not confirmed. At the same time, some prospective studies have shown an association between insomnia and cognitive decline or between insomnia and certain types of dementia, primarily Alzheimer's disease.

The pathophysiological mechanisms of interactions between sleep disturbances and cognitive decline are likely to be linked with the dysfunction of the brain's glymphatic system in patients. Some studies show that changes in sleep and wakefulness patterns increase the level of amyloid-beta ( $A\beta$ ) in the interstitial fluid, and chronic sleep restriction accelerates the deposition of amyloid plaques, which can lead to the development of Alzheimer's disease (AD) [27]. Examination of cerebrospinal fluid in patients with insomnia showed an increased level of  $A\beta$ , possibly reflecting an impaired metabolism of  $A\beta$  in the central nervous system, which can lead to the development of AD [28].

Soluble beta-amyloid and tau-oligomers, metabolic waste products associated with AD, are normally excreted from the interstitial fluid of the central nervous system through the glymphatic system. Sleep enhances the clearance of waste products, including  $A\beta$ , via the glymphatic pathway [29]. It has been shown that in rodents, glymphatic influx was increased by 95 %, and  $A\beta$  was cleared 2-fold faster in the cortex during slow wave sleep [30]. It also has been found that a deficiency of melatonin in the cerebrospinal fluid is critical for developing AD because of the lack of its scavenger action [31]. Thus,

insomnia could provoke the progression of dementia due to compromising the «washing» sleep function or possibly suppressing endogenous melatonin production.

Older age can exacerbate the harmful effects of insomnia. Under the influence of stress on the cell, for example, during sleep deprivation, aggregation and improper folding of proteins are prevented by special protective mechanisms implemented in the endoplasmic reticulum. It has been shown that these defensive biochemical reactions are impaired during aging and can activate pro-apoptotic signaling [32].

Sleep disturbance can also activate stress response pathways, such as increased noradrenergic activity. Activation of the sympathetic system could increase systemic inflammation by stimulating the expression of genes of pro-inflammatory factors [33]. It is hypothesized that systemic inflammation drives the alterations in microglia, spreading the inflammation into the central nervous system (CNS). This may increase the risk of cognitive de-

cline and AD development [34, 35]. The inflammation might also be a pathogenic link between sleep disturbances and AD [36].

**Conclusions.** Currently, there is insufficient evidence that chronic insomnia significantly increases the risk of dementia. The results of the studies carried out are controversial, which is explained by the heterogeneity of approaches to the diagnosis of both insomnia and dementia. However, several prospective studies performed at a high methodological level have shown a connection between chronic insomnia and the main nosological form of dementia, Alzheimer's disease, and chronic insomnia and subsequent decline in cognitive functions. Perhaps this connection is due to dysfunction of the glymphatic cerebral system associated with the decreased sleep duration, which leads to an acceleration of the deposition of amyloid protein in the brain. Further research is needed to explain whether normalized sleep could reduce the risk of dementia or slow its' progression.

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