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Review article

SLEEP IN THE ELDERLY: HEALTHY SLEEP FOR HEALTHY AGING

SPAVANJE KOD STARIJIH: ZDRAVO SPAVANJE ZA ZDRAVO STARENJE

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Abstract

Sleep is a vital physiological process in which humans spend almost one third of their lives. Contemporary lifestyles, shift work, social jet lag and environmental blue light pollution significantly compromise sleep quality in all age groups, especially in working adults and the elderly. Poor sleep quality has been demonstrated to be a risk factor for a number of diseases, from cardiovascular to neurological including malignancies.

Aging has been identified to be connected with poor sleep quality, making elderly people more vulnerable to the development of a number of somatic and mental disorders. Low sleep quality in the elderly accelerates aging and increases the risk of development of aging-related pathologies. There are increased societal attempts to sustain well-being and preserve health in the aged population with the concept of healthy aging being widely promoted and accepted.

Healthy sleep has been recognized as one of the pillars of healthy aging, especially in all policies related to the Decade of Healthy Aging. One of the major sleep-related issues in the elderly is the difficulty to distinguish the physiological effects of aging on sleep patterns from those sleep disruptions caused by primary sleep disorders, other diseases or medications. Poor sleep quality and impaired sleep hygiene are associated with an increased risk of various chronic cardiovascular diseases. Moreover, healthy sleep is essential for cognitive functions and prevention of cognitive decline and memory impairments in the elderly. The relationship between neurodegenerative disorders and poor sleep quality seems to be bidirectional, which is extensively studied in Parkinson's disease. Regular physical activity should be considered as a component of sleep quality management strategies in the elderly, but also as a preventive strategy to preserve healthy sleep for healthy aging.

Keywords:
sleep,
heathy aging,
elderly,
sleep quality,
cardiovascular diseases,
neurodegenerative disorders,
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Parkinson's disease,
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Sažetak

Spavanje je vitalan fiziološki proces u kojem ljudi provode gotovo jednu trećinu svog života. Savremeni stilovi života, rad u smenama, društveni *jet lag* i zagađenje plavom svetlošću iz okoline značajno kompromituju kvalitet spavanja kod svih starosnih grupa, posebno kod radno aktivnih i starijih osoba. Loš kvalitet spavanja pokazao se kao faktor rizika za niz bolesti, od kardiovaskularnih do neuroloških, uključujući malignitete.

Starenje je povezano s lošim kvalitetom spavanja, što starije ljude čini podložnijim razvoju raznih somatskih i mentalnih poremećaja. Nizak kvalitet spavanja kod starijih osoba ubrzava proces starenja i povećava rizik od razvoja različitih oboljenja. Društvo sve više nastoji da održi blagostanje i očuva zdravlje starije populacije, pri čemu se koncept zdravog starenja široko promoviše i prihvata.

Zdravo spavanje je prepoznato kao jedan od stubova zdravog starenja, posebno u svim politikama vezanim za Deceniju zdravog starenja. Jedan od glavnih problema povezanih sa spavanjem kod starijih je teškoća u razlikovanju fizioloških efekata starenja na obrasce spavanja od onih poremećaja spavanja koji su uzrokovani primarnim poremećajima spavanja, drugim bolestima ili lekovima. Loš kvalitet spavanja i narušena higijena spavanja povezani su sa povećanim rizikom od raznih hroničnih kardiovaskularnih bolesti. Pored toga, zdravo spavanje je od suštinskog značaja za kognitivne funkcije i prevenciju kognitivnog opadanja i oštećenja pamćenja kod starijih osoba. Čini se da je odnos između neurodegenerativnih poremećaja i lošeg kvaliteta spavanja bidirekcionalan, što se intenzivno proučava kod Parkinsonove bolesti. Redovna fizička aktivnost bi trebalo da bude sastavna komponenta strategija za upravljanje kvalitetom spavanja kod starijih, ali i preventivna strategija za očuvanje zdravog spavanja i zdravog starenja.

Ključne reči:
spavanje,
zdravo starenje,
starije osobe,
kvalitet spavanja,
kardiovaskularne bolesti,
neurodegenerativni poremećaji,
Alchajmerova bolest,
Parkinsonova bolest,
dugovečnost

Introduction

Sleep is a vital physiological process in which humans spend almost one-third of their lives. Despite making them vulnerable to predators, sleep has been ubiquitously preserved in mammals, birds and reptiles. However, contemporary lifestyles, shift work, social jet lag and environmental blue light pollution significantly compromise sleep quality in an increasing number of people in all age groups, especially in working adults and the elderly. Poor sleep quality has been demonstrated to be a risk factor for a number of diseases, from cardiovascular to neurological including malignancies. Therefore, there is an increasing scientific interest in research on sleep quality and sleep medicine nowadays.

Aging has been identified to be connected with poor sleep quality, making elderly people more vulnerable for the development of a number of somatic and mental disorders. Low sleep quality in the elderly accelerates aging and increases a risk of development of aging-related pathologies (1), thus making *circulus vitiosus* that should be ameliorated by proper lifestyle changes and interventions.

Human life expectancy has almost doubled in the last hundred years in developed countries. A number of factors contributed to this increase in lifespan. These factors are primarily: improvement of the health care system, better nutrition and the development of effective drugs for the treatment of hitherto incurable diseases. In the coming decades, an increase in the number of elderly people (over 65 years old) is expected, so that by 2060 they will make up about 25% of the total population. The fact of increasing life expectancy is reflected in the assumption that today's 65-year-olds are expected to live an average of 19.4 more years, which is 5.5 years longer than the 65-year-olds who lived in 1950 (2,3). Therefore, age-related disorders are topical in current scientific literature and there are increased societal attempts to sustain well-being and preserve health in the aged population. Therefore, the concept of healthy aging has been widely promoted and accepted.

"Healthy aging is more than just the absence of disease", as stated in the First World Report on Aging and Health from 2015, Acutely, the widely accepted definition of healthy aging is the one from the first WHO Global Strategy and Action Plan on Aging in 2016, by which healthy aging is defined as "the process of developing and maintaining functional ability that enables wellbeing in older age." Healthy sleep has been recognized as one of the pillars of healthy aging, especially in all policies related to the Decade of Healthy Aging.

One of the major sleep-related issues in the elderly is the difficulty to distinguish the physiological effects of aging on sleep patterns from those sleep disruptions caused by primary sleep disorders, other diseases, or medications. Namely, the incidence of a number of primary sleep disorders is higher in the elderly compared to young adults, with insomnia being the most prevalent (1,4). Therefore, we will herein briefly review the physiological changes in sleep architecture in the elderly.

Poor sleep quality and impaired sleep hygiene are associated with an increased risk of various chronic cardiovascular diseases (CVDs), including hypertension, heart failure, and coronary artery disease, as the most prevalent CVDs among the elderly (5). One of the intriguing issues in the relationship between sleep quality and CVDs is to understand the differential effects of nocturnal sleep

and daytime napping on cardiovascular outcomes, which will be the subject of review herein as well.

Brain aging is connected with different morphological and functional changes. Mild cognitive decline is frequently reported and sleep quality impairment is believed to be one of the contributing factors (6). Cognitive decline, together with progressive memory loss and behavioral changes are the major characteristics of Alzheimer's disease (AD), a neurodegenerative disorder with a bidirectional link to sleep. This relationship will be further explored herein.

Parkinson's disease (PD) is a neurodegenerative disorder of the substantia nigra characterized primarily by bradykinesia/hypokinesia, rest tremor, rigidity, and postural instability. However, it is also associated with a number of non-motor signs and symptoms, among which sleep disturbances are highly prevalent. Namely, sleep disturbances in PD are found in 71 - 88% of patients (7). Since sleep disturbances significantly impair the quality of life in patients with PD, mechanisms of the sleep-PD loop will be reviewed in this paper.

Management of poor sleep quality in the elderly is complex and requires a multidisciplinary approach. Pharmacotherapy for sleep disorders in the elderly is quite complex and should be prescribed with particular care having in mind the polypharmacy in this population due to a number of comorbidities, frequently presented in this population. Cognitive behavioral therapy for insomnia is one of the primary options for treating insomnia in the elderly. One of the beneficial add-on healthy sleep management strategies is regular physical activity (8). Namely, physical activity has been proven to be beneficial for healthy aging in general, including brain-related pathologies (9). In this paper, the effects of physical exercise on the sleep quality in the population of elderly will be reviewed.

Sleep architecture in the elderly

Sleep quality is not characterized only by total sleep duration, but also by sleep architecture (10). Some of the parameters used to quantify sleep are sleep latency, REM latency, total sleep time (TST), time in bed (TIB), Wake after sleep onset (WASO) and sleep efficiency (SE). Sleep latency is defined as the time from going to bed and lights off to sleep onset. The REM latency is the time from sleep onset to the first REM phase. Sleep efficiency is defined as a ration between TST and TIB and expressed in percentages (4, 11). Clinical sleep assessment could be done via anamnesis, self-reported sleep questionnaires and different levels of home or in-lab sleep studies, i.e. overnight polysomnographic (PSG) recordings, depending on the patient's complaint and primary sleep disorder that has been explored.

Sleep architecture denotes cyclic patterns of sleep stage alterations, i.e. basic structure of NON-REM stages (N1, N2 and N3) and REM phase transitions, each of them being characterized by specific electroencephalographic (EEG) and behavioral features. The REM sleep is characterized by sharp, rapid eye movements in electrooculogram (EOG), desynchronized EEG pattern resembling awakening (paradoxical sleep) and skeletal muscle atonia in electromyogram (EMG), while NON-REM sleep is characterized by delta waves in EEG (also referred as slow-wave sleep) (10).

Sleep architecture in healthy young adults is characterized by four to five 90-minute-long cycles of NON-REM/REM phase transitions. Sleep starts with N1 and N2 of NON-REM that further progresses to N3, especially in the first cycles with an increased percentage of slow-wave delta activity in EEG. This is frequently referred to as deep sleep. Each cycle ends with the REM phase, which duration progress with each cycle (12, 13).

Sleep quality in the elderly has been compromised by several factors including physiological changes in sleep architecture, primarily sleep disorders, a variety of other somatic and mental disorders, as well as overall behavioral changes in lifestyle, medications and polypharmacy (14, 15).

Physiological changes in sleep architecture during aging are characterized by prolonged sleep latency, sleep fragmentation, a lower percentage of N3 sleep, and an advanced phase of circadian rhythm. Namely, elderly people have problems falling asleep, thus having prolonged sleep latency.

Sleep fragmentation is manifested as frequent arousals during the night, being one of the hallmarks of sleep architecture in the elderly (16). Their total sleep time is lower consequently. Namely, linear reduction in total sleep time has been reported to occur during the lifespan, and people at age 60 have 30 minutes less of sleep that those at age of 40 (17).

The percentage of N1, N2 and N3 during overnight sleep is an important feature of sleep quality. While N1 and N2 are considered "light sleep", N3 is considered "deep sleep". In the elderly, the percentage of N1 and N2 are increased, while percentage of N3 is decreased. Thus, older people spend more time in light stages of NON-REM sleep, while acquired amount of deep sleep is not achieved often (20). This reduction in deep slow-wave sleep is of particular importance having in mind that N3 is considered as the most restorative sleep phase in which growth hormone is secreted. According to some reports, the percentage of REM sleep decreases with age, as well as we have reduction in REM latency (17).

Another hallmark feature of sleep patterns in the elderly is that they go to sleep earlier and wake up earlier in the morning compared to healthy young adults (18). This is a consequence of an advanced phase of their circadian rhythm (referred to as advanced sleep phase syndrome, or advanced sleep-wake schedule). Namely, elderly people tend to go to sleep around 20 h in the evening and wake up around 4 to 5 h in the morning (19). It has been explained by the changes in the internal circadian master clock in the suprachiasmatic nucleus of the hypothalamus. Namely, the internal master clock in the suprachiasmatic nucleus becomes less efficient and this results in interrupted sleep,

falling asleep earlier and waking up earlier in the morning, i.e. advanced sleep phase. This could be the consequence of lower melatonin secretion evident in the elderly, as well as lower light exposure (20).

Sleep changes with aging have been summarized in **table 1**.

Table 1. Aging-related changes in the sleep architecture in the elderly.

Sleep feature	Direction of change
Total sleep time	↓
Total time in bed	↓↑
Sleep efficiency	↓
Sleep latency	↑
N1 %	↑
N2 %	↑
N3 %	↓
REM phase %	↓
Wake after sleep onset	↑
Number of arousals	↑
Dim Light Melatonin Output	↓

Primary sleep disorders have been documented to have a higher incidence in the elderly. Among the most prevalent ones is insomnia. Further elaboration is out of the scope of this review. Also, neurodegenerative and cardiovascular disorders are common in this population requiring chronic drug therapy.

When sleep in the elderly is considered, it should be taken into account that polypharmacy exists in this population. Therefore, sleep issues in the elderly are multifactorial and cannot be solely explained by the process of aging (11).

In summary, physiological changes in sleep architecture in the elderly are accompanied by a higher incidence of primary sleep disorders, other physical and mental health impairments and polypharmacy. All these factors result in lower sleep quality in elderly.

Sleep and chronic diseases in elderly: focusing nighttime sleep vs daily naps in cardiovascular diseases

Cardiovascular health in the elderly could be significantly affected by reduced total sleep time, fragmented sleep, shift toward lighter sleep stages, reduced duration of slow-wave sleep, frequent awakenings, insomnia, and obstructive sleep apnea. These age-related changes in sleep architecture are more common in the elderly and may lead to the development of cardiovascular diseases including hypertension, heart failure, and coronary artery disease, as the most prevalent CVDs among the elderly (21). For optimizing care in elderly patients with CVDs, it is essential to understand the differential effects of nocturnal sleep and daytime napping on cardiovascular outcomes, and to address potent physiological mechanisms underlying the association between CVDs and impaired sleep.

Comparative effects of nocturnal sleep vs daytime naps in cardiovascular health

When comparing the effects of nocturnal sleep and daytime napping on cardiovascular health, nocturnal sleep appears to be the most critical for maintaining cardiovascular function.

Nocturnal sleep is the most restorative form of sleep, and is crucial for cardiovascular function, particularly in older adults. Its role in autonomic nervous system homeostasis and metabolic processes is vital to prevent exacerbation of age-related cardiovascular decline. Adequate sleep promotes normal heart rate variability and endothelial function, which protects against cardiovascular complications (22). Impaired nocturnal sleep is linked to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, increased cortisol levels, and heightened sympathetic nervous system activity, and impaired vascular function, all of which elevate cardiovascular risk by inducing systemic inflammation (23). Studies demonstrated that sleep deprivation characterized by short nocturnal sleep duration of less than six hours per night or disrupted sleep is linked to elevated risks of hypertension, arrhythmias, stroke, myocardial infarction, heart failure and coronary artery disease in the elderly (22). It was also demonstrated that sleep fragmentation is associated with decreased testosterone levels in experimental animals (24).

On the other hand, sleep fragmentation, marked by frequent awakenings, exacerbates sympathetic nervous system activation and promotes inflammatory pathways, both of which contribute to cardiovascular dysfunction. In the elderly population, the consequences of poor nocturnal sleep are primarily compounded by other age-related physiological changes, such as chronic low-grade inflammation, impaired endothelial function, and a decline in adaptive immune responses, underscoring the critical importance of maintaining uninterrupted, sufficient night-time sleep for elderly individuals (23).

Obstructive Sleep Apnea (OSA) characterized by repeated episodes of upper airway obstruction during sleep, is very prevalent among the elderly and it is closely intertwined with cardiovascular diseases. It is strongly associated with hypertension, heart failure, and atrial fibrillation. The intermittent hypoxia and oxidative stress caused by OSA can lead to endothelial dysfunction, increased inflammatory markers, and sympathetic activation, all of which contribute to cardiovascular damage. The management of sleep disorders, particularly OSA, has been shown to improve cardiovascular outcomes. Continuous positive airway pressure (CPAP) therapy, the standard treatment for OSA, has been demonstrated to reduce blood pressure and prevent cardiovascular events in elderly patients with CVDs (25).

Daytime naps are a common compensatory mechanism for addressing sleep deficits in older adults. Although

short naps may offer temporary cardiovascular benefits, they do not compensate for the regenerative processes associated with uninterrupted nocturnal sleep (26).

Napping may alleviate fatigue and restore energy levels, but its effects on cardiovascular health remain a topic of ongoing debate. Short naps (typically less than 30 minutes) may offer restorative benefits, including improvements in cognitive function, mood, and cardiovascular recovery. Studies also suggest that short naps are associated with transient reductions in blood pressure and stress levels, potentially counteracting the harmful effects of insufficient nocturnal sleep (27).

Conversely, excessive daytime napping, defined as napping for more than 60 minutes, has been consistently associated with adverse cardiovascular outcomes, including increased risks of hypertension, stroke, and other CVDs. The detrimental effects of prolonged napping may be attributed to the disruption of circadian rhythms and autonomic nervous system dysregulation, perpetuating the cycle of poor nocturnal sleep, and further exacerbating cardiovascular risks (26). This is particularly problematic in elderly individuals, who are already vulnerable to cardiovascular complications due to aging-related physiological decline and comorbidities.

Additionally, excessive napping may serve as a marker of underlying health conditions, such as undiagnosed CVDs or OSA, which can contribute to the exacerbation of cardiovascular dysfunction (27).

In summary (**figure 1**), we can conclude that in older adults with CVDs, both nocturnal sleep and daytime napping can influence health outcomes, but their effects differ significantly. High-quality nocturnal sleep is essential for maintaining cardiovascular health, with sleep deprivation and fragmentation posing substantial risks. While short naps may provide some temporary benefits, such as reductions in blood pressure and stress, they cannot fully compensate for the restorative effects of uninterrupted nighttime sleep.

Sleep quality and memory in elderly: implications for Alzheimer's disease

The human brain needs sleep to regulate normal body functions, restore energy, and repair and consolidate memory (1). As people age, both sleep timing and sleep quality undergo previously herein described changes (4). Among them, the decline in slow-wave sleep is one of the most significant age-related changes considered also as biomarker of cognitive decline (28). Cognitive decline, together with progressive memory loss and behavioral changes are the major characteristics of Alzheimer's disease (AD).

Numerous pathogenic mechanisms are involved in AD development and progression. Key features of AD include amyloid-β (Aβ) peptides that form insoluble extracellular plaques and neurofibrillary tangles that represent intracellular aggregates of hyper-phosphorylated tau protein important for microtubule stabilization (29). These features are followed by synaptic dysfunction, neurotransmitter imbalance, neuroinflammation, oxidative stress and mitochondrial dysfunction.

Sleep disorders and AD seem to be bidirectionally connected, since poor sleep may aggravate AD, and AD brain pathology can also affect sleep patterns (**figure 2**). The Aβ aggregation begins around 15 years before the first symptoms of cognitive impairment in AD. In the preclinical stage of AD, changes in sleep patterns can occur and serve as a predictive factor for neurodegeneration and cognitive decline. Studies have shown that sleep disturbances, low sleep quality, and increased latency to sleep strongly correlate with the Aβ accumulation contributing to AD development. Both studies in human subjects and animals showed that sleep deprivation increases Aβ levels in cerebrospinal fluid by 25 - 30% (29,30). The second pathological hallmark of AD is an intracellular accumulation of tau protein. Levels of tau protein in cerebrospinal

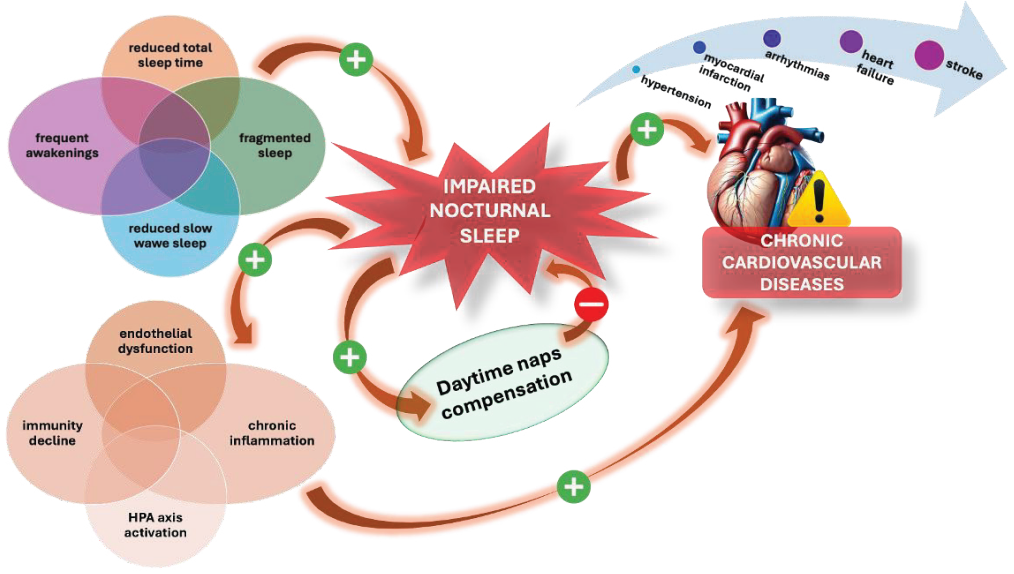

Figure 1. Sleep quality and CVD. Night sleep vs daily naps.
There is a bidirectional relationship between sleep quality and CVDs in the elderly. It should be noted that daily naps could not compensate beneficial effects of overnight sleep. For details see the text.

fluid significantly correlate with cognitive decline in AD. Studies on human subjects and animal models showed increased tau levels in cerebrospinal fluid in acute and chronic sleep disturbances (29,31,32). A recent study on 964 subjects who underwent PET scans showed that disturbed nighttime sleep was associated with greater baseline tau in the meta-temporal region and cognitive impairment (33). In addition, neuroinflammation is another pathophysiological mechanism connecting AD and sleep disorders. Amyloid-β plaques promote microglia activation and glia-derived neuropeptides undergo modulation by the sleep-wake cycle and may contribute to AD progression (34). Disrupted sleep can lead to release of proinflammatory cytokines such as interleukin (IL)-1 and IL-6 that can further affect gamma-aminobutyric acid (GABA) and serotonin neurotransmission. Sleep deprivation increases oxidative stress in the brain enhancing neuroinflammation. Free radicals further activate microglia and aggravate neuronal injury. Furthermore, chronic inflammation can impair the ability of microglia to effectively clear deposits of amyloid-β, hence contributing to plaque accumulation (35). Obstructive sleep apnea is a pathological condition characterized by intermittent hypoxia and sleep disturbances that affect middle-aged and elderly people. The OSA is a significant risk factor for dementia and cognitive decline and therefore can be considered as a risk factor for AD. Brain hypoxia triggers oxidative stress and neuroinflammation contributing to AD pathology. According to our results, sleep fragmentation which is one of the hallmarks of the OSA, is associated with increased oxidative stress in animal models (36). Additionally, hypoxic brain condition and disrupted NREM sleep impair cognitive function, and memory consolidation and exacerbate AD symptoms (37).

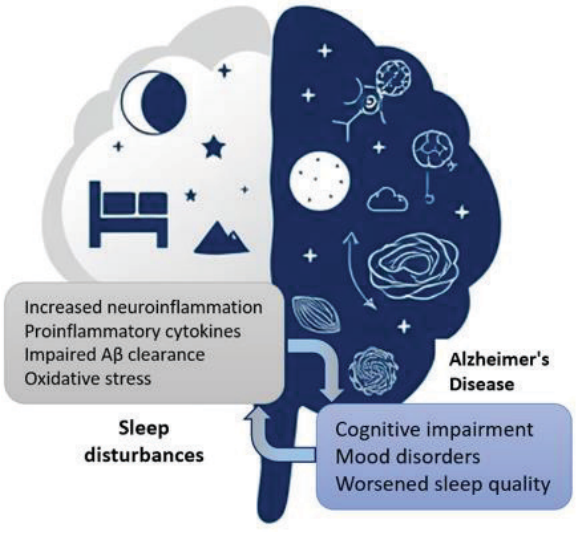

Figure 2. Interconnection between sleep disturbances and Alzheimer's disease.
The complex relationship between AD and sleep disturbances is bidirectional. For details see the text.

Having in mind all aforementioned, it could be concluded that the relationship between sleep disorders and AD is complex and multifactorial, confirming the important role of sleep in brain health.

Sleep disturbances in Parkinson's disease: pathogenetic mechanisms

Although well characterized by its motor abnormalities (bradykinesia/hypokinesia, rest tremor, rigidity, postural instability) due to degeneration of dopaminergic neurons in *pars compacta substantiae nigrae*, Parkinson's disease (PD) is also associated with non-motor signs and symptoms including hyposmia/anosmia, depression or anxiety, autonomic dysfunction, and sleep disturbances. Non-motor signs and symptoms develop due to the degeneration of neurons in other brain areas including the brainstem, hypothalamus, and olfactory bulb (38). Sleep disturbances in PD are found in 71 - 88% of patients and include insomnia, excessive daytime sleepiness, REM sleep behavior disorder, restless legs syndrome, periodic limb movements of sleep (PLMS) and sleep-disordered breathing (39-41). Along with depression and dependence, sleep disturbances significantly impair the quality of life in patients with PD. Insomnia may manifest as difficulty falling asleep, impaired sleep maintenance with sleep fragmentation, early morning awakening or non-restorative sleep (40). Excessive daytime sleepiness is caused partly by night insomnia, but also it may occur primarily due to neurodegeneration in PD (42). The REM sleep behavior disorder usually precedes the motor manifestations of PD and includes limb movements occurring during the REM sleep phase due to the absence of muscle atonia (43). Restless legs syndrome and PLMS frequently affect the quality of sleep. Restless legs syndrome refers to the discomfort in the legs during falling asleep that forces the patient to move legs (44), while PLMS includes the periodic rhythmic movements or jerking of limbs during sleep (45). Central and obstructive sleep apnea comprise sleep-disordered breathing and apnea is not related to the neurodegeneration (46). Apart from previously describes sleep disturbances PD is also associated with circadian misalignment (47).

The pathogenesis of sleep disorders in PD is multifactorial and includes the direct consequences of neurodegeneration, genetic predisposition, the impact of restless legs syndrome, PLMS, motor symptoms, autonomic dysfunction, psychiatric comorbidities including anxiety and depression, the side effects of dopaminergic drugs, and circadian disruption (48). Although most frequently studied in substantia nigra, neurodegeneration in PD is also evident in sleep-related brain regions such as locus coeruleus, raphe nuclei, pedunculopontine nucleus, posterior hypothalamus, and para-mamillary nuclei (49,50). Neurodegeneration is caused by α-synuclein aggregation due to altered proteostasis, oxidative stress, mitochondrial dysfunction, lysosomal dysfunction, alteration in intracellular calcium homeostasis, and neuroinflammation (48,51). The α-synuclein is a protein found in the soluble and membrane-bound form as monomers or tetramers mainly located in presynaptic terminals (51). Under conditions of high intracellular α-synuclein concentration and

protein misfolding α-synuclein may aggregate and form oligomers (protofibrils) which disrupt organelle function and fibrils which form Lewy bodies (52). It has been found that α-synuclein protofibrils may permeabilize vesicles with dopamine leading to the leakage of dopamine in the cytoplasm and promoting clustering of vesicles by binding to v-SNAREs thereby blocking the fusion of vesicles with the pre-synaptic membrane (53). Outside the vesicles, dopamine undergoes auto-oxidation leading to oxidative stress and the formation of dopamine quinone species, superoxide anion (O_2^-), and hydrogen peroxide (H_2O_2). Dopaminergic neurons contain a high concentration of free iron that promotes the formation of hydroxyl radicals via Fenton reaction. Additionally, dopamine metabolism by monoamine oxidase (MAO) may also increase H_2O_2 production. Oxidative stress induces further misfolding of α-synuclein and its aggregation, while dopamine quinone species form adducts with α-synuclein that promote the accumulation of protofibrils in the cytoplasm (54). This leads to a vicious cycle between oxidative stress and α-synuclein aggregation further leading to progressive neurodegeneration. Additionally, α-synuclein along with toxins in genetically predisposed individuals causes mitochondrial dysfunction further aggravating oxidative stress (55). Furthermore, it has been shown that α-synuclein may spread from one neuron to the adjacent neuron and form seeds that stimulate further aggregation of α-synuclein via prion-like mechanism (56). Aggregates of α-synuclein may also activate microglia and astrocytes which then release proinflammatory cytokines and produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) via NADPH oxidase, inducible nitric oxide synthase (iNOS) and other prooxidant enzymes (57).

Loss of dopaminergic neurons caused by previously described mechanisms contributes to the excessive daytime sleepiness in PD (42). Additionally, α-synuclein accumulation is evident in locus coeruleus, raphe nuclei, posterior hypothalamus, and suprachiasmatic nucleus suggesting that the same mechanisms found in dopaminergic neurons also promote degeneration of adrenergic, serotoninergic, cholinergic, glutamatergic neurons that physiologically regulate sleep-wake cycle (48).

Recent studies have shown that the relation between sleep disturbances and PD is bidirectional meaning that impaired sleep may increase the risk of PD (58-60). Sleep deprivation increases the risk of PD by the impairment of unfolded protein response thereby potentiating the aggregation of α-synuclein, reduced removal of α-synuclein by glymphatic system, increased oxidative stress, and dysfunction of the central clock in the suprachiasmatic nucleus (61).

The relationship between sleep and PD and the mechanisms of its relationship are summarized in **figure 3**.

Physical exercise as sleep management strategy in the elderly

Physical activity is widely regarded as one of the most effective ways to improve overall health. In recent decades, studies have shed light on its effects on brain health and the prevention of neurodegenerative and mental diseases. Furthermore, it has been shown that frequent exercise prior to reaching senility builds greater cognitive capacity, thereby delaying cognitive decline and dementia, thus contributing to healthy aging (62).

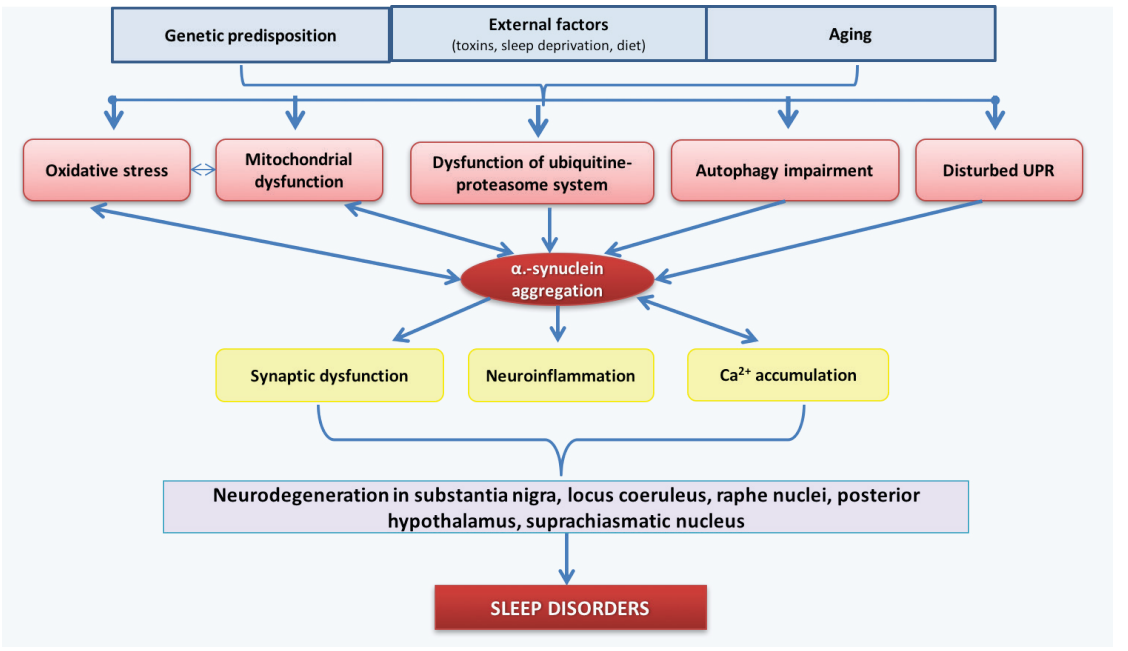

Figure 3. Pathogenetic mechanisms of sleep disturbances in sporadic Parkinson's disease.
Genetic predisposition in the combination with external factors and aging leads to oxidative stress, mitochondrial dysfunction, dysfunction of the ubiquitin-proteasome system, impaired autophagy, and alterations in UPR. These defects lead to the accumulation and aggregation of α-synuclein. Oligomers of α-synuclein are toxic to neurons leading to impaired neurotransmitter release, calcium accumulation, and aggravation of oxidative stress and mitochondrial dysfunction. This ultimately results in neurodegeneration in sleep-related brain regions leading to sleep disturbances in Parkinson's disease.

A sedentary lifestyle with low levels of physical activity in older adults poses a significant risk of developing insomnia symptoms. Keeping a high level of physical function is crucial for achieving successful aging.

The relationship between sleep quality and physical activity has been recognized for centuries; however, only in the past decade has the scientific and medical community acknowledged physical activity as an effective approach to improving sleep (63). Epidemiological data show that both acute and chronic exercise enhance sleep quality. Increased physical activity among the elderly helps prevent insomnia, reduces daytime sleepiness, and lowers the risk of sleep apnea. A meta-analysis encompassing 12 studies shows that engaging in regular physical activity enhances total sleep duration and increases slow wave sleep (SWS) (64, 65).

The relationship between sleep quality and physical activity is reciprocal - a well-rested person is more likely to participate in training sessions (66). The majority of effective physical activity interventions involve moderate or moderate-to-vigorous exercise. Several randomized controlled trials with elderly participants showed that moderate physical activity improved sleep quality by reducing sleep latency and nighttime awakenings and increasing sleep efficiency and duration.

Another meta-analysis of the elderly population reported that physical activity interventions enhanced objective measures of sleep efficiency and quality. Yoga, walking, and cycling are among the various types of exercise that have been implemented. The interventions lasted from 12 weeks to 12 months (67). According to another systematic review, exercise regimens had beneficial effects on various aspects of sleep in healthy older adults (over 60 years old). The most promising benefits in terms of improving sleep have been observed when moderate exercise is practiced three times a week for three to six months (68). Positive effects of physical exercise and sleep hygiene have been particularly observed in elderly individuals who already have a diagnosis of insomnia (69).

While most interventions focused on aerobic exercise protocols, some studies incorporated strength and flexibility exercises, which have been shown to enhance both sleep quality and quantity (70). Yoga and tai chi promote muscle strength, active range of motion, gait, balance, mobility, and physical and emotional well-being (71, 72).

Furthermore, mixed exercise techniques which combine aerobic work, strength, and balance have also been shown to increase sleep quality, reduce insomnia, and hyperinsomnia, and use of hypnotic sedatives. It can be concluded that engaging in physical activity, across all its forms, provides sustaining benefits not only for sleep quality but also for psychological and cognitive aspects, which may be closely related to mood and concentration.

On the contrary, only a limited number of studies examining moderate exercise have reported adverse effects on sleep quality (73). Regarding the implementation of vigorous, high-intensity exercise, the number of studies is limited, and the findings are mixed, however, the majority indicate that there is no improvement in sleep quality (9). The conclusions drawn from this type of research are limited due to high heterogeneity in interventions, inconsistency in training duration, types of exercise, and biological variables such as sex and age.

The science behind the potential positive effects of exercise on sleep can be attributed to several mechanisms. Consistent evidence indicates that physical activity enhances the quality of life in elderly adults. Exercise increases melatonin production, which regulates sleep cycles. Furthermore, it boosts endorphin release and promotes the release of neurotransmitters like norepinephrine and serotonin. It affects the general mood and lowers the stress levels. It shows anxiolytic and antidepressant effects. These mechanisms together allow individuals to fall asleep and stay asleep for longer bouts of time (66). Moderate aerobic exercise can reduce depressive symptoms, which is an important factor in improving sleep (69).

In summary, it can be concluded that exercise can be an effective additional intervention in sleep quality management strategies in the elderly, as it can complement pharmacological treatments and enhance overall health and healthy aging while remaining cost-effective.

Conclusion

Sleep quality in the elderly is compromised by several factors, including physiological changes in sleep patterns that undergo biological aging, primarily sleep disorders and a number of comorbidities. On the other hand, low sleep quality could be a risk factor for a number of diseases, from cardiovascular to neurodegenerative. Advanced sleep phase, sleep fragmentation, and lower amount of deep slow wave sleep are the hallmarks of age-related changes in sleep architecture in the elderly.

Addressing sleep disorders and promoting sleep hygiene are essential components of managing cardiovascular diseases in the elderly. High-quality nocturnal sleep is essential for maintaining cardiovascular health, while short daily naps cannot fully compensate for the restorative effects of uninterrupted nighttime sleep. On the other hand, long daily naps are detrimental to cardiovascular health and are recommended to avoid in the elderly. Therefore, interventions aimed at improving nocturnal sleep may help mitigate cardiovascular risks and improve overall health outcomes.

Healthy sleep is essential for cognitive functions and prevention of cognitive decline and memory impairments in the elderly. Sleep disturbances, including insomnia and obstructive sleep apnea, are associated with increased neuroinflammation, impaired clearance of Aβ and cognitive decline, which represents central pathology in AD. Disrupted sleep can exacerbate existing cognitive deficits, creating a vicious cycle that accelerates disease progression.

The relationship between neurodegenerative disorders and poor sleep quality seems to be bidirectional, which is extensively studied in PD in clinical and experimental studies (74, 75). Genetic predisposition in the combination

with external factors and aging leads to oxidative stress, mitochondrial dysfunction, dysfunction of the ubiquitin-proteasome system, impaired autophagy, and alterations in UPR. These defects lead to the accumulation and aggregation of α-synuclein and oligomers of α-synuclein are toxic to neurons. This ultimately could result in neurodegeneration in sleep-related brain regions leading to sleep disturbances in Parkinson's disease.

Sleep quality management strategies are very complex in the population of the elderly due to several factors including a high number of coexisting disorders, a number of medications used to treat them and low compliance with some of the prescribed treatments. Regular physical activity should be considered as a component of sleep quality management strategies in the elderly, but also as a mandatory lifestyle intervention in the middle-aged as a preventive strategy to preserve healthy sleep for healthy aging. Regular physical exercise in this population should be structured and supervised to ensure better compliance and outcomes.

Future research should continue to explore the complex relationship between physiological, healthy changes in sleep patterns during aging and the footprints of different diseases on sleep patterns in the elderly, including primary sleep disorders, neurodegenerative, cardiovascular and other diseases. Further exploration of the interactions between sleep and cardiovascular disease in the elderly is also needed, with the goal of developing tailored sleep interventions to optimize cardiovascular health in this vulnerable population. Also, investigating sleep disorders may offer promising therapeutic targets for intervention in AD and potentially enhancing cognitive function improving sleep quality and slowing the onset or progression of the disease. The same holds for PD, where improvements of sleep quality could significantly improve overall life quality. Physical exercise and its prescription require more thoroughly designed research regarding duration, frequency and type of the exercise itself.

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