Sleep Science

REVIEW ARTICLE

Frailty and sleep disturbances in the elderly: possible connections and clinical implications

Fragilidade e distúrbios do sono em idosos: possíveis conexões e implicações clínicas

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ABSTRACT

Frailty results from decreased physiological and functional reserves during pathologic aging processes and leads to vulnerability to minor stress, increasing morbidity and mortality. The majority of older persons more than 85 years are frail or pre-frail. Sleep disturbances are also more prevalent in the elderly and possible associations between frailty and sleep problems have been studied. This article aims to summarize clinical and biological data favoring this hypothesis and discuss future research implications. Keywords related to frailty and sleep were searched by means of a non-systematic search in the National Library of Medicine's MedLine database's PubMed system. Observational studies found associations between frailty parameters and subjective and objective measurements indicating poor sleep, circadian rhythm disruption and sleep disorders in aged persons. Unbalances between catabolic and anabolic hormones, enhanced inflammatory response and reduced energy expenditure are shared pathways that can explain a bidirectional correlation between frailty states and poor sleep in advanced ages. Interventions over circadian rhythm or sleep disorders have potential clinical implications in the frail elderly. As a complex entity with sparse and still emergent therapeutic options, frailty can benefit from sleep quality improvement along advanced ages.

Keywords: aging, frail elderly, sleep disorders.

RESUMO

A síndrome de fragilidade resulta da diminuição das reservas fisiológicas e funcionais durante o processos de envelhecimento patológico e leva à vulnerabilidade a leves estímulos estressores, aumentando a morbidade e mortalidade. A maioria das pessoas idosas com mais de 85 anos são frágeis ou pré-frágeis. Os distúrbios do sono também são mais prevalentes em idosos e possíveis associações entre a síndrome de fragilidade e alterações de sono tem sido estudadas. Este artigo visa resumir os dados clínicos e biológicos que favorecem esta hipótese e discutir as implicações futuras de sua investigação. As palavras-chave relacionadas com a síndrome de fragilidade e o sono foram pesquisadas por meio de uma revisão não-sistemática nas bases de dados National Library of Medicine's MedLine database's PubMed system. Estudos observacionais encontraram associações entre parâmetros de fragilidade e as medidas subjetivas e objetivas que indicam qualidade ruim de sono, alteração dos ritmos circadianos e distúrbios do sono em pessoas idosas. Desequilíbrios entre hormônios catabólicos e anabólicos, resposta inflamatória potencializada e redução do gasto energético são as vias comuns que podem explicar a correlação bidirecional entre os estados de fragilidade e as alterações de sono em idades avançadas. As intervenções sobre o ritmo circadiano ou distúrbios do sono têm potenciais implicações clínicas no idoso frágil. Como uma entidade complexa, com opções terapêuticas esparsas e ainda emergentes, a fragilidade pode se beneficiar com a melhoria da qualidade do sono em idades avançadas

Descritores: distúrbios do sono, envelhecimento, fragilidade, idosos, ritmo circadiano.

INTRODUCTION

Population aging happens for the first time in human history worldwide. In 2012, people older than 60 years achieved 810 million and global estimates expect 2 billion or approximately 20% of total population arriving at this age group in 2050[1].

Aging impacts in health care systems primarily because of frailty, which is a clinical condition related to decline in physiological and functional reserves during the life course[2]. Table 1 depicts one of the proposed clinical criteria for frailty phenotype. Vulnerability results from this condition and minor stress can lead to worsening of chronic conditions, new acute events or even death. Among people older than 85 years, until 50% are frail[3].

Table 1. Frailty criteria based on phenotypes[2].

1.	Weight loss: unintentional weight loss in the last year (> 4.5 kg or 5% of body weight)
2.	Exhaustion: fatigue symptoms (assessed by items 7 and 20 from the Center for Epidemiologic Studies Depression Scale - CES-D)
3.	Strength: decreased grip strength (lowest 20%, by gender and BMI), assessed by hand dynamometer
4.	Slowness: decreased gait speed in seconds (lowest 20%, by gender and height), asssed by walking 4.6 meters at usual pace
5.	Decreased physical activity (in the previous 2 weeks): Kcals/week: lowest 20% males: < 383 Kcals/week; females: < 270 Kcals/week, assessed by physical activity questionnaire

Frailty diagnosis: >3 criteria; Intermediate state or prefrail: 1 or 2 criteria.

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Similarly, aging deteriorates sleep physiology[4-6]. Sleep complaints increase as age advances and circadian rhythm changes disturb aged persons[7]. Frequent and long nocturnal awakenings, increased number of naps and poor sleep quality may result of degenerative conditions, which affect regions of the circadian rhythm control, such as the suprachiasmatic nucleus[8,9]. Visual deterioration, depression, dementia, chronic pain, nocturia and environmental or social factors favor poor sleep quality and daytime sleepiness in advanced ages[10,11].

Sleep disturbances are more frequent in older populations. About 50% of them have some difficulty sleeping[12-16]. The opposite is also prevalent and comorbidities contribute to sleep problems[17]. The relationship between chronic diseases and sleep disorders, either directly or indirectly, can progress in the form of a vicious cycle.

The perception of parallel long-term development for two conditions, such as frailty and sleep disorders, raises hypotheses about possible associations between them and intrinsic shared causal pathways that can lead to new therapeutic proposals for both problems. The current article aims to summarize published findings on sleep and frailty in older adults with focus on recent discoveries. Topics in geriatric sleep medicine, epidemiological findings and potential mechanisms underlying the connections between sleep disorders and frailty and possible future research considerations will be also discussed.

METHODS

A non-systematic scientific literature search in the National Library of Medicine's MedLine database's PubMed system was performed and limited to studies written in the English language. Keywords searched were: frailty AND sleep (sleep OR circadian rhythms) or frailty AND sleep disorders (insomnia OR sleep-disordered breathing OR obstructive sleep apnea OR restless legs syndrome OR periodic limb movement during sleep). After the qualitative review of the articles found from these key word parameters, we include the reference sections as sources for additional articles. Inclusion criteria to include studies designs for the final review were limited to randomized controlled trials, clinical trials, prospective cohort studies, case-control studies, cross-sectional studies and meta-analyses in human subjects. We exclude case reports, case series, general review articles and guideline publications of the selection criteria for formal rigorous review.

Sleep in the elderly

Sleep parameters change over the lifetime. Older age groups suffer more from circadian rhythm disruptions, sleep complaints and sleep disturbances. The amplitude of the sleep-wake cycle reduces through the aging process[18]. Older adults expose less to daytime light and secret lower nocturnal pineal melatonin levels, which influence the circadian function and result in decreased sleep quality and daytime sleepiness[19].

Significant changes in sleep structure occur with aging. The total sleep time, the sleep efficiency and the amount and intensity of slow-wave sleep (SWS) reduce while the wake time after sleep onset increases in this population. Although aged persons have more difficulty to obtain adequate sleep, even at very advanced ages, good sleep quality benefits the health status[20,21].

Timing for sleep also changes across lifespan. Circadian rhythmicity tends to phase advancement in the older population, which has more difficulties to adapt to rapid phase shifts work and jet lag[22]. Moreover, napping behavior is increasingly observed across advanced aged subjects[23]. The benefits of such habit for the promotion of daytime wakefulness and nighttime sleep quality are uncertain[7]. Therefore, aging favors sleep-wake maladaptation because of circadian rhythm changes. It remains elusive whether regular napping contributes to compensate this problem or results from excessive daytime sleepiness (EDS) in this population[24].

Some primary sleep disorders, such as SDB, are more common in older age groups. Community-dwelling elderly individuals have a progressively higher SDB prevalence. A population-based study found an apnea/hypopnea index (AHI) $\geq$ 10 in 62% of elderly participants; an AHI $\geq$ 20, in 44%; and an AHI $\geq$ 40, in 24%[17]. A longitudinal study demonstrated that body mass index (BMI) has a positive correlation with AHI in older persons. Hormonal consequences of SDB may also develop in this age group[16].

Severe obstructive sleep apnea (OSA) not treated with continuous positive airway pressure treatment (CPAP) possibly increases cardiovascular death risk in the elderly. The adequate long-term CPAP treatment can reduce this risk, but randomized controlled trials are needed to clarify this assumption[25]. However, the relevance of mild obstructive sleep apnea as a risk factor for comorbidities and death in the elderly is still controversial[26-31]. Recent studies, which demonstrate correlations between AHI and frailty clinical criteria, add data to elucidate the importance of SDB for the general health maintenance of this age group.

Insomnia is increasingly prevalent in older population, with prevalence that ranges from 30 to 60%. Frequent awakenings during the night, daytime sleepiness, frequent napping and fatigue are symptoms associated with insomnia that could increase the risk of falls. Some studies have suggested that insomnia is a possible independent risk factor for falls in the aged group. Otherwise, psychotropic drugs used for insomnia and other psychiatric comorbidities are also related to fall accidents and fractures[32]. Insomnia possibly correlates directly and indirectly with frailty by means of daytime somnolence, fatigue, decreased general activity and reduced functional capacity. Effective strategies to reduce the burden of disease associate with insomnia at this population group need more studies about efficacy[33,34].

What correlates sleep to frailty in aging: evidence from observational studies

Increasing evidence favors possible associations between sleep problems and frailty in older persons. Some studies found associations between components of frailty and sleep-disordered breathing (SDB), insomnia, sleep fragmentation, decreased sleep efficiency, hypoxia during sleep and greater daytime sleep[35-39]. Others found high prevalence of frailty syndrome in the elderly

with low sleep quality, excessive daytime sleepiness, decreased sleep efficiency, prolonged sleep latency and SDB[40,41].

A prospective large cohort study has concluded that poor subjective sleep quality, greater nighttime wake time, and nocturnal hypoxemia are risk factors for development of frailty and death among older men[42].

Recently, a cross-sectional study evaluated the prevalence of some sleep problems in institutionalized elderly people with frailty. Institutionalization relates to degradation in parameters of sleep quality and poor sleep is referred by 70% of aged institutionalized residents[43]. Frailty phenotype was associated with worse sleep quality according to Pittsburgh Sleep Quality Index results. Frail older persons had higher sleep latency, daytime sleepiness and fatigue symptoms. Sleep fragmentation, assessed by actimetry, was also correlated with frailty status.

Pathophysiologic connections between frailty and sleep disorders

Sleep patterns influence diverse physiological functions. Beyond the role on central nervous system, sleep mediates a large range of metabolic activities through neuroendocrine interactions[44]. Mechanisms involved in the risk of frailty among older adults with sleep disturbances may be similar to those hypothesized to explain how sleep parameters might influence metabolism and body composition in advanced ages. Biochemical explanations related to reductions in testosterone levels, chronic inflammation, oxidative stress and unbalance in GH secretion are possible shared pathways between frailty and sleep disorders on their relationship with increased morbidity and mortality in the elderly[45-47].

Sleep disturbances affects hypothalamus-pituitary-adrenal axis and hypothalamic-pituitary-gonadal axis functions[48]. Higher cortisol levels result from sleep curtailment and testosterone secretion impairs with sleep-wake cycle instability. Furthermore, anabolic hormone secretions decrease in SDB[49-55].

Decreased levels of IGF-1 are present in frailty as well as in sleep deprivation[56]. Besides sleep loss is associated with muscle proteolysis, one of explanations for weight loss in frail individuals. The majority of GH secretion occurs during slow wave sleep, which is reduced in the elderly[57].

On one hand, sleep relates directly to overall health perception and to chronic conditions in older adults. On the other hand, clinical and neuropsychiatric conditions further increase the risk of sleep disturbances. Obstructive sleep apnea, advanced sleep phase disorder, insomnia and daytime sleepiness are possible mediators of immunological pathways, which raises levels of inflammatory molecules related to frailty risk, such as interleukin6 and C-reactive protein[58-61].

Sedentary lifestyle is also a shared risk factor for frailty and changes in sleep pattern. As clinical criteria for frailty, fatigue associates with impaired physical and mental states and possibly links non-restorative sleep to the frail phenotype[62,63].

Rest-activity rhythm instability generates from less exposure to light and social activities[64]. Visual deterioration also compromises the circadian cycle in this population[65]. As these factors further reduce physical activity and total energy expenditure, sleep-wake cycle alterations are also possible risk factors for frailty in advancing age.

Sleep disturbances as risk factors for frailty in the elderly: clinical implications

Patients and their families will increasingly suffer with the burden of disease associated with the aging population. Among the most prevalent conditions in this age range, frailty and sleep disorders have major impact in the quality of life, functional capacity and mortality risk.

Clinical trials regarding interventions in sleep disorders and with frailty variables as a target are missing. Approaches proven effectiveness in frail elderly people include comprehensive geriatric assessment and focus on exercises. Nutritional interventions are promising strategies, but data is still inconclusive[66-68].

However, no pharmacological therapy has been effective and hormonal replacement lacks long-term gains in functional capacity and carries-out safety concerns[69,70].

Hence, interventions over sleep disturbances and circadian rhythm disruptions in the elderly possibly influence frailty parameters over time. Future studies testing therapeutic approaches such as continuous positive airway pressure for OSA, bright light therapy or validated strategies for insomnia could be performed with regards to evaluate frailty parameter as primary outcomes.

CONCLUSION

Recently, a few number of observational studies emerged favoring clinical associations between sleep disturbances and frailty in the elderly. Although pathophysiological explanations suggest a bidirectional correlation for these 2 entities, sleep alterations as risk factors for frailty has clear practical appealing. Chronic partial sleep deprivation is an increasing concern in our society and the reduced total sleep time and progressively growing prevalence of sleep disorders through adult age can potentially explain future health deterioration in older populations[71].

Preventive measures are the best strategies to deal with health questions in aging. Frailty is a complex syndrome, with complicated multi-systemic pathologic pathways and scarce therapeutic proposals. Therefore, clinical trials addressing the assumption of sleep disturbances management or prevention may predict the course of frailty parameters and offer a novel approach to handle with clinical deterioration in aging.

REFERENCES

1. United Nations. Population Ageing and Development 2012 [assessed in October 12, 2013]. Available at: http://social.un.org/ageingworking-group/documents/2012popageing.pdf
2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56. PMID: 11253156 DOI: http://dx.doi.org/10.1093/gerona/56.3.M146
3. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc. 2010;58(4):681-7. PMID: 20345864 DOI: http://dx.doi.org/10.1111/j.1532-5415.2010.02764.x
4. Hofman MA, Swaab DF. Living by the clock: the circadian pacemaker in older people. Ageing Res Rev. 2006;5(1):33-51. DOI: http://dx.doi.org/10.1016/j.arr.2005.07.001

5. Dijk DJ, Duffy JF, Riel E, Shanahan TL, Czeisler CA. Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. J Physiol. 1999;516 (Pt 2):611-27. PMID: 10087357 DOI: http://dx.doi.org/10.1111/j.1469-7793.1999.0611v.x
6. Dijk DJ, Duffy JF, Czeisler CA. Age-related increase in awakenings: impaired consolidation of nonREM sleep at all circadian phases. Sleep. 2001;24(5):565-77.
7. Vitiello MV. Sleep in normal aging. Sleep Med Clin. 2006;1(2):171-16. DOI: http://dx.doi.org/10.1016/j.jsmc.2006.04.007
8. Satinoff E, Li H, Tcheng TK, Liu C, McArthur AJ, Medanic M, et al. Do the suprachiasmatic nuclei oscillate in old rats as they do in young ones? Am J Physiol. 1993;265(5 Pt 2):R1216-22.
9. Farajnia S, Deboer T, Rohling JH, Meijer JH, Michel S. Aging of the Suprachiasmatic Clock. Neuroscientist. 2013; 7. DOI: http://dx.doi.org/10.1177/1073858413498936
10. Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging: 2. Management of sleep disorders in older people. CMAJ. 2007;176(10):1449-54. PMID: 17485699 DOI: http://dx.doi.org/10.1503/cmaj.070335
11. Zepelin H, McDonald CS, Zammit GK. Effects of age on auditory awakening thresholds. J Gerontol. 1984;39(3):294-300. PMID: 6715806 DOI: http://dx.doi.org/10.1093/geronj/39.3.294
12. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep. 1995;18(6):425-32. PMID: 7481413
13. Foley DJ, Monjan A, Simonsick EM, Wallace RB, Blazer DG. Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6,800 persons over three years. Sleep. 1999;22Suppl 2:S366-72. PMID: 10394609
14. Vitiello MV, Foley D, Stratton KL, White E. Prevalence of sleep complaints and insomnia in the Vitamins And Lifestyle (VITAL) Study cohort of 77,000 older men and women [abstract]. Sleep 2004;27:A120.
15. van Someren EJ, Hagebeuk EE, Lijzenga C, Scheltens P, de Rooij SE, Jonker C, et al. Circadian rest-activity rhythm disturbances in Alzheimer's disease. Biol Psychiatry. 1996;40(4):259-70. PMID: 8871772 DOI: http://dx.doi.org/10.1016/0006-3223(95)00370-3
16. Ancoli-Israel S, Gehrman P, Kripke DF, Stepnowsky C, Mason W, Cohen-Zion M, et al. Long-term follow-up of sleep disordered breathing in older adults. Sleep Med. 2001;2(6):511-6. DOI: http://dx.doi.org/10.1016/S1389-9457(00)00096-4
17. Neikrug AB, Ancoli-Israel S. Sleep disorders in the older adult - a mini-review. Gerontology. 2010;56(2):181-9. DOI: http://dx.doi.org/10.1159/000236900
18. Hofman MA, Swaab DF. Living by the clock: the circadian pacemaker in older people. Ageing Res Rev. 2006;5(1):33-51. DOI: http://dx.doi.org/10.1016/j.arr.2005.07.001
19. Van Someren EJ. Circadian and sleep disturbances in the elderly. Exp Gerontol. 2000;35(9-10):1229-37. DOI: http://dx.doi.org/10.1016/S0531-5565(00)00191-1
20. Tafaro L, Cicconetti P, Baratta A, Brukner N, Ettorre E, Marigliano V, et al. Sleep quality of centenarians: cognitive and survival implications. Arch Gerontol Geriatr. 2007;44 Suppl 1:385-9. DOI: http://dx.doi.org/10.1016/j.archger.2007.01.054
21. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. Sleep. 1991;14(6):486-95. PMID: 1798880
22. Monk TH. Aging human circadian rhythms: conventional wisdom may not always be right. J Biol Rhythms. 2005;20(4):366-74. PMID: 16077155 DOI: http://dx.doi.org/10.1177/0748730405277378
23. Metz ME, Bunnell DE. Napping and sleep disturbances in the elderly. Fam Pract Res J. 1990;10(1):47-56.
24. Ancoli-Israel S, Martin JL. Insomnia and daytime napping in older adults. J Clin Sleep Med. 2006;2(3):333-42.
25. Martínez-García MA, Campos-Rodríguez F, Catalán-Serra P, Soler-Cataluña JJ, Almeida-Gonzalez C, De la Cruz Morón I, et al. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study. Am J Respir Crit Care Med. 2012;186(9):909-16. DOI: http://dx.doi.org/10.1164/rccm.201203-0448OC
26. Launois SH, Pépin JL, Lévy P. Sleep apnea in the elderly: a specific entity? Sleep Med Rev. 2007;11(2):87-97. DOI: http://dx.doi.org/10.1016/j.smrv.2006.08.005
27. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163(1):19-25. PMID: 11208620 DOI: http://dx.doi.org/10.1164/ajrccm.163.1.2001008
28. Degache F, Sforza E, Dauphinot V, Celle S, Garcin A, Collet P, et al.; PROOF Study Group. Relation of central fat mass to obstructive sleep apnea in the elderly. Sleep. 2013;36(4):501-7. DOI: http://dx.doi.org/10.5665/sleep.2532
29. Bing MH, Jennum P, Moller LA, Mortensen S, Lose G. Obstructive sleep apnea in a Danish population of men and women aged 60-80 years with nocturia. J Clin Sleep Med. 2012;8(5):515-20.
30. Parthasarathy S, Fitzgerald M, Goodwin JL, Unruh M, Guerra S, Quan SF. Nocturia, sleep-disordered breathing, and cardiovascular morbidity in a community-based cohort. PLoS One. 2012;7(2):e30969. DOI: http://dx.doi.org/10.1371/journal.pone.0030969
31. Assoumou HG, Gaspoz JM, Sforza E, Pichot V, Celle S, Maudoux D, et al. Obstructive sleep apnea and the metabolic syndrome in an elderly healthy population: the SYNAPSE cohort. Sleep Breath. 2012;16(3):895-902. DOI: http://dx.doi.org/10.1007/s11325-011-0593-y
32. Modén B, Merlo J, Ohlsson H, Rosvall M. Psychotropic drugs and falling accidents among the elderly: a nested case control study in the whole population of Scania, Sweden. J Epidemiol Community Health. 2010;64(5):440-6. PMID: 20445213 DOI: http://dx.doi.org/10.1136/jech.2009.098947
33. Sivertsen B, Omvik S, Pallesen S, Bjorvatn B, Havik OE, Kvale G, et al. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial. JAMA. 2006;295(24):2851-8. PMID: 16804151 DOI: http://dx.doi.org/10.1001/jama.295.24.2851
34. El Kady HM, Ibrahim HK, Mohamed SG. Cognitive behavioral therapy for institutionalized elders complaining of sleep disturbance in Alexandria, Egypt. Sleep Breath. 2012;16(4):1173-80. DOI: http://dx.doi.org/10.1007/s11325-011-0629-3
35. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, et al.; Sleep Heart Health Study Research Group. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. Arch Intern Med. 2002;162(8):893-900. PMID: 11966340 DOI: http://dx.doi.org/10.1001/archinte.162.8.893
36. Goldman SE, Ancoli-Israel S, Boudreau R, Cauley JA, Hall M, Stone KL, et al.; Health, Aging and Body Composition Study. Sleep problems and associated daytime fatigue in community-dwelling older individuals. J Gerontol A Biol Sci Med Sci. 2008;63(10):1069-75. PMID: 18948557 DOI: http://dx.doi.org/10.1093/gerona/63.10.1069
37. Dam TT, Ewing S, Ancoli-Israel S, Ensrud K, Redline S, Stone K.; Osteoporotic Fractures in Men Research Group. Association between sleep and physical function in older men: the osteoporotic fractures in men sleep study. J Am Geriatr Soc. 2008;56(9):1665-73. PMID: 18759758 DOI: http://dx.doi.org/10.1111/j.1532-5415.2008.01846.x
38. Endeshaw YW, Unruh ML, Kutner M, Newman AB, Bliwise DL. Sleep-disordered breathing and frailty in the Cardiovascular Health Study Cohort. Am J Epidemiol. 2009;170(2):193-202. PMID: 19465743 DOI: http://dx.doi.org/10.1093/aje/kwp108
39. Goldman SE, Stone KL, Ancoli-Israel S, Blackwell T, Ewing SK, Boudreau R, et al. Poor sleep is associated with poorer physical performance and greater functional limitations in older women. Sleep. 2007;30(10):1317-24.
40. Ensrud KE, Blackwell TL, Redline S, Ancoli-Israel S, Paudel ML, Cawthon PM, et al.; Osteoporotic Fractures in Men Study Group. Sleep disturbances and frailty status in older community-dwelling men. J Am Geriatr Soc. 2009;57(11):2085-93. DOI: http://dx.doi.org/10.1111/j.1532-5415.2009.02490.x
41. Vaz Fragoso CA, Gahbauer EA, Van Ness PH, Gill TM. Sleep-wake disturbances and frailty in community-living older persons. J Am Geriatr Soc. 2009;57(11):2094-100. DOI: http://dx.doi.org/10.1111/j.1532-5415.2009.02522.x
42. Ensrud KE, Blackwell TL, Ancoli-Israel S, Redline S, Cawthon PM, Paudel ML, et al. Sleep disturbances and risk of frailty and mortality in older men. Sleep Med. 2012;13(10):1217-25. DOI: http://dx.doi.org/10.1016/j.sleep.2012.04.010
43. Alessi CA, Schnelle JF. Approach to sleep disorders in the nursing home setting. REVIEW ARTICLE. Sleep Med Rev. 2000;4(1):45-56. DOI: http://dx.doi.org/10.1053/smrv.1999.0066
44. Rial RV, Nicolau MC, Gamundí A, Akaârir M, Aparicio S, Garau C, et al. The trivial function of sleep. Sleep Med Rev. 2007;11(4):311-25. DOI: http://dx.doi.org/10.1016/j.smrv.2007.03.001
45. Barrett-Connor E, Dam TT, Stone K, Harrison SL, Redline S, Orwoll E.; Osteoporotic Fractures in Men Study Group. The association of testosterone levels with overall sleep quality, sleep architecture, and sleep-disordered breathing. J Clin Endocrinol Metab. 2008;93(7):2602-9. DOI: http://dx.doi.org/10.1210/jc.2007-2622

46. Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, et al. Sleep duration and biomarkers of inflammation. Sleep. 2009;32(2):200-4.
47. Ferrie JE, Kivimäki M, Akbaraly TN, Singh-Manoux A, Miller MA, Gimeno D, et al. Associations between change in sleep duration and inflammation: findings on C-reactive protein and interleukin 6 in the Whitehall II Study. Am J Epidemiol. 2013;178(6):956-61. DOI: http://dx.doi.org/10.1093/aje/kwt072
48. Balbo M, Leproult R, Van Cauter E. Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity. Int J Endocrinol. 2010;2010:759234. PMID: 20628523 DOI: http://dx.doi.org/10.1155/2010/759234
49. Andersen ML, Martins PJ, D'Almeida V, Bignotto M, Tufik S. Endocrinological and catecholaminergic alterations during sleep deprivation and recovery in male rats. J Sleep Res. 2005;14(1):83-90. DOI: http://dx.doi.org/10.1111/j.1365-2869.2004.00428.x
50. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999;354(9188):1435-9. DOI: http://dx.doi.org/10.1016/S0140-6736(99)01376-8
51. von Treuer K, Norman TR, Armstrong SM. Overnight human plasma melatonin, cortisol, prolactin, TSH, under conditions of normal sleep, sleep deprivation, and sleep recovery. J Pineal Res. 1996;20(1):7-14. DOI: http://dx.doi.org/10.1111/j.1600-079X.1996.tb00232.x
52. Weibel L, Follenius M, Spiegel K, Ehrhart J, Brandenberger G. Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. Sleep. 1995;18(7):549-56. PMID: 8552925
53. Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J. Cortisol secretion is inhibited during sleep in normal man. J Clin Endocrinol Metab. 1983;56(2):352-8.
54. Luboshitzky R, Zabari Z, Shen-Orr Z, Herer P, Lavie P. Disruption of the nocturnal testosterone rhythm by sleep fragmentation in normal men. J Clin Endocrinol Metab. 2001;86(3):1134-9.
55. Gambineri A, Pelusi C, Pasquali R. Testosterone levels in obese male patients with obstructive sleep apnea syndrome: relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. J Endocrinol Invest. 2003;26(6):493-8.
56. Everson CA, Crowley WR. Reductions in circulating anabolic hormones induced by sustained sleep deprivation in rats. Am J Physiol Endocrinol Metab. 2004;286(6):E1060-70. PMID: 14871886 DOI: http://dx.doi.org/10.1152/ajpendo.00553.2003
57. Van Cauter E, Plat L, Copinschi G. Interrelations between sleep and the somatotropic axis. Sleep. 1998;21(6):553-66.
58. Arnardottir ES, Maislin G, Schwab RJ, Staley B, Benediktsdottir B, Olafsson I, et al. The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort. Sleep. 2012;35(7):921-32.
59. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation. 2002;105(21):2462-4. PMID: 12034649 DOI: http://dx.doi.org/10.1161/01.CIR.0000018948.95175.03
60. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med. 2002;162(20):2333-41. PMID: 12418947 DOI: http://dx.doi.org/10.1001/archinte.162.20.2333
61. Bollinger T, Bollinger A, Oster H, Solbach W. Sleep, immunity, and circadian clocks: a mechanistic model. Gerontology. 2010;56(6):574-80. DOI: http://dx.doi.org/10.1159/000281827
62. de Castro Toledo Guimaraes LH, de Carvalho LB, Yanaguibashi G, do Prado GF. Physically active elderly women sleep more and better than sedentary women. Sleep Med. 2008;9(5):488-93. DOI: http://dx.doi.org/10.1016/j.sleep.2007.06.009
63. Nóbrega PV, Maciel AC, de Almeida Holanda CM, Oliveira Guerra R, Araújo JF. Sleep and frailty syndrome in elderly residents of long-stay institutions: A cross-sectional study. Geriatr Gerontol Int. 2013 Sep 11 [Epub ahead of print].
64. Murphy PJ, Campbell SS. Enhanced performance in elderly subjects following bright light treatment of sleep maintenance insomnia. J Sleep Res. 1996;5(3):165-72. DOI: http://dx.doi.org/10.1046/j.1365-2869.1996.t01-1-00001.x
65. Zizi F, Jean-Louis G, Magai C, Greenidge KC, Wolintz AH, Heath-Phillip O. Sleep complaints and visual impairment among older Americans: a community-based study. J Gerontol A Biol Sci Med Sci. 2002;57(10):M691-4. DOI: http://dx.doi.org/10.1093/gerona/57.10.M691
66. Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. BMJ. 2011;343:d6553. PMID: 22034146 DOI: http://dx.doi.org/10.1136/bmj.d6553
67. de Vries NM, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Staal JB, Nijhuis-van der Sanden MW. Effects of physical exercise therapy on mobility, physical functioning, physical activity and quality of life in community-dwelling older adults with impaired mobility, physical disability and/or multi-morbidity: a meta-analysis. Ageing Res Rev. 2012;11(1):136-49. PMID: 22101330 DOI: http://dx.doi.org/10.1016/j.arr.2011.11.002
68. Lammes E, Rydwik E, Akner G. Effects of nutritional intervention and physical training on energy intake, resting metabolic rate and body composition in frail elderly. a randomised, controlled pilot study. J Nutr Health Aging. 2012;16(2):162-7. DOI: http://dx.doi.org/10.1007/s12603-011-0157-7
69. Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging. 2008;12(7):433-50. DOI: http://dx.doi.org/10.1007/BF02982704
70. Iqbal J, Denvir M, Gunn J. Frailty assessment in elderly people. Lancet. 2013;381(9882):1985-6. DOI: http://dx.doi.org/10.1016/S0140-6736(13)61203-9
71. Santos-Silva R, Castro LS, Taddei JA, Tufik S, Bittencourt LR. Sleep disorders and demand for medical services: evidence from a population-based longitudinal study. PLoS One. 2012;7(2):e30085. DOI: http://dx.doi.org/10.1371/journal.pone.0030085