ORIGINAL ARTICLE

Older Adults with High-risk of Obstructive Sleep Apnea Associated with Frailty among Outpatients in a Tertiary Care in Northeast Thailand

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Background: Several pieces of evidence demonstrated poor sleep quality is associated with frailty. However, the present study demonstrates the association between obstructive sleep apnea (OSA) and frailty is still limited.

Objective: To determine the association between the older adults who had a high-risk of OSA and adverse events including frailty, cognitive frailty, quality of life, history of admission within previous year and history falling within previous 6 months.

Materials and Methods: A cross-sectional study was conducted between October 1, 2019 to January 31, 2022, at Srinagarind Hospital, Thailand. Participants aged ≥60 years who visited outpatient of internal medicine department were included. The Thai Frailty Index (TFI) was used to evaluate frailty status. STOP-BANG questionnaire was used to evaluate the risk of OSA and a score ≥3 was defined as a high-risk of OSA. The demographic data, TFI, the Thai version of the World Health Organization Quality of Life Brief–Old and Montreal Cognitive Assessment (MoCA) were obtained. The association between the older adults who had a high-risk of OSA and adverse events was analyzed by multiple logistic regression and presented as adjusted odds ratio (aOR) with 95% confidence interval (CI).

Results: A total of 198 participants were included. The older adults who had a high-risk of OSA was 124 (62.6%). The older adults who had a high-risk of OSA were associated with frailty (aOR of 3.37, 95% CI 1.56 to 7.71, p-value=0.003). The older adults who had a high-risk of OSA were not associated with cognitive frailty, fair quality of life, history of admission within previous year and falling within previous 6 months.

Conclusion: The older adults who had a high-risk of OSA were associated with frailty. The screening and diagnosis of OSA are recommended for the older adults who attend the outpatient clinic.

Keywords: Frailty; High-risk of OSA; Older adults

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The number of older adults increased worldwide. The global population aged 60 years or over was 962 million in 2017 and is expected to be nearly 2.1 billion in 2050[1]. Obstructive sleep apnea (OSA) is a recurrent upper airway obstruction during sleep and its prevalence increases in older adults[2]. Between 13 to 32% of people over 65 years old reported OSA[3]. This syndrome causes sleep fragmentation, sleep deprivation, increased sympathetic activity and systemic inflammation[4]. OSA is an important comorbidity of older adults. It has many potential consequences such as increased risk of hypertension, cardiovascular events, cerebrovascular accidents and mortality[3,5,6]. OSA are also increased risk of excessive daytime sleepiness, cognitive deterioration and motor vehicle accidents[3,5]. Furthermore, a recent report demonstrated OSA was associated with impaired gait and balance[7]. This might increase falling in older adults, however, the present study demonstrated an association between OSA and falling is still limited[7].

Frailty is a state of increased vulnerability and poor resolution of homeostasis after a stressor event according to multiple physiological systems declined[8]. This is a common and problematic syndrome in older adults. From a systematic review by Collard et al., the prevalence of frailty varied from 4.0 to 59.1% and had a weighted prevalence of 9.9%[9]. Another systematic review

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that included studies from low-income and middle-income countries revealed the prevalence of frailty varied from 3.9 to 51.4% and pooled prevalence of 17.4%[10]. Frailty is associated with worse outcomes including falling[11,12], fractures[13], disability[12,14,15], cognitive impairment[16-18] and poor quality of life[19,20]. Moreover, this condition increased hospitalization[20,21], health care utilization[22], healthcare cost[23] and mortality[24-26]. There were several risk factors associated with frailty from previous reports for example age[27,28], female[27,29], cardiovascular disease[30], depressive symptoms[31,32], lower education[27] and lower socioeconomic status[27].

A growing body of evidence demonstrated the association between sleep disturbance and frailty in older adults[33]. The previous studies revealed poor sleep quality was associated with frailty[34-36] and some studies showed OSA was associated with frailty[37-39]. However, the present study evaluating the association between older adults who had a high-risk OSA and frailty is still limited particularly in Thailand. Therefore, the study was conducted for evaluating the association between older adults who had a high-risk OSA and adverse events including frailty, cognitive frailty, quality of life, history of admission within previous year, and history falling within previous 6 months.

Materials and Methods

Participants and setting

This is a cross-sectional study that was a part of a research project "Prevalence of frailty and associated adverse events in older patients of internal medicine outpatient clinic: a cross-sectional study"[20]. Data were collected at the ambulatory medicine outpatient clinic, Srinagarind Hospital, Khon Kaen Thailand, from October 1, 2019 to January 31, 2022. The inclusion criteria consisted of 1) age ≥60 years, 2) having attended Srinagarind Hospital's ambulatory medicine outpatient clinic. The present study excluded older adults who met any of the following criteria 1) inability to speak Thai language, 2) dementia or acute psychosis, 3) inability to communicate with others, 4) inability to stand upright or acute arthritis, 5) acute infection, 6) severe visual impairment.

Operational definitions

Risk of OSA

The Thai version of the STOP-BANG questionnaire was used to determine the risk of OSA[40]. This questionnaire consists of 8 items with a total score of 8. The STOP-BANG score of ≥3 indicated as a high-risk of OSA[41].

Adverse events

For this study, adverse events included frailty, cognitive frailty, quality of life, history of admission within previous year, and falling within previous 6 months.

Quality of life

The Thai version of the World Health Organization Quality of Life Brief–Old (WHOQOL-Old) was used to examine participants' quality of life status. This is a self-reported questionnaire containing 24 items. All items are divided into 6 domains which are 1) perceptive ability, 2) autonomy, 3) social activity, 4) intimacy, 5) activities of daily living, 6) fear of death. The score ranges from 24 to 120. A score of 24 to 55 means poor quality of life, 56 to 88 means fair quality of life and 89 to 120 means good quality of life[42].

Frailty

The Thai Frailty Index (TFI) was used to clarify participants' frailty status. This tool contains 30 variables to evaluate current medical problems, mental status, and functional ability. The total score is derived from the total number of items divided by 30, therefore the possible total score is 1. Participants with TFI of more than 0.25 are estimated to have frailty[43].

Cognitive frailty

This is a coexisting condition of frailty and cognitive impairment. The frailty status was defined by having TFI greater than 0.25, while cognitive status was evaluated by the Thai version of the Montreal Cognitive Assessment test (MoCA-T)[44]. According to the previous study which was conducted at the ambulatory medicine Srinagarind Hospital, a MoCA-T score <20 was a suitable cut-off point to define mild cognitive impairment with 76% of sensitivity and 71% of specificity[45]. Therefore, the participants who have TFI >0.25 and MoCA-T <20 meet the criteria of cognitive frailty.

Procedure

The present study was approved by Ethics Committee for Human Research of the Khon Kaen University (HE631065) in accordance with the Helsinki Declaration. The written informed consent was provided to all participants before data collection. Participants' demographic data including age, gender, body weight, height, body mass index (BMI), years of education, marital status, family incomes, history of falling, history of admission, numbers of medication and underlying diseases were collected using convenience sampling. Afterward, a trained clinical researcher administered the Thai version of MoCA, TFI and Thai version of STOP-BANG score to participants.

Sample size calculation

The sample size calculation was based on the previous study by Manchumad et al which revealed the prevalence of frailty was 0.28[20]. The estimate infinite population proportion formula was calculated with a proportion of 0.28, alpha (α) of 0.05, Z(0.975) of 1.96 and error of 0.1. The sample size required at least 78 subjects. A total of 198 cases were included in the present study.

Statistical analysis

The participants' demographic data were presented as percentages, mean and standard deviation (SD) based on descriptive statistics. If the data distribution was not normal, median and interquartile range(IQR) were used instead. Univariate analysis was used to evaluate the association between the older adults who had a high-risk of OSA and adverse outcomes in terms of quality of life, frailty, cognitive frailty, falling within previous 6 months and history of admission within previous year. The results were presented as crude odds ratio (cOR) with 95% confidence interval (CI). Afterward, multivariate analysis was used and the results were adjusted to history of alcohol consumption, educational level, history of admission within previous year, income and number of medications. To determine the effect size, the results were presented as adjusted odds ratio (aOR) with 95% CI. R version 4.1.2 was performed for data analysis.

Results

A total of 198 participants were included in the study. The median age of participants was 68 (IQR 64, 72) years. The older adults who had a high-risk of OSA was 124 subjects, thus the prevalence was 62.6%. The median STOP-BANG score was 3 (IQR 2,4). Participants' demographic data was shown in Table 1. The older adults who had a high-risk of OSA were more likely to have comorbidities such as hypertension, diabetes mellitus and chronic kidney disease (CKD). There were no participant in the present study has a poor quality of life, however, The older adults who had a high-risk of OSA had a higher percentage of fair quality of life than the older adults who had a low-risk of OSA group. Moreover, The older adults who had a high-risk of OSA had a higher percentage of adverse events in terms of frailty, cognitive frailty, falling within previous 6 months and history of admission within previous year.

The association between the older adults who had a high-risk of OSA and adverse events was evaluated by univariate and multivariate analysis. The analysis was shown in Table 2. On these analysis, the older adults who had a high-risk of OSA were significantly associated with frailty (aOR of 3.37, 95% CI 1.56 to 7.71, p-value=0.003). The older adults who had a high-risk of OSA were not significantly associated with cognitive frailty, falling within previous 6 months, history of admission within previous year and fair quality of life.

Discussion

Several reports suggested that poor sleep quality was associated with frailty in older adults[33-36]. The authors hypothesized that the poor sleep quality from primary sleep disorders particularly OSA may be associated with frailty. The present study demonstrated that the older adults who had a high-risk of OSA was associated with frailty. The result of this study was similar to the previous studies[37,39,46]. The possible explanation link between OSA and frailty were as followings: 1) several studies demonstrated frailty was associated with low insulin-like growth factor-1 (IGF-1) levels[47]. IGF-1 is an anabolic hormone synthesized mainly by the liver and stimulated by growth hormone (GH)[48,49]. IGF-1 is related to poor muscle strength, sarcopenia, physical performance and chronic inflammation[50]. Likewise, IGF-1 is associated with alteration of nutritional status particularly micronutrients such as selenium, magnesium and zinc[50]. GH/IGF-1 axis plays an important role in the pathogenesis of frailty[50]. GH prefer secretes during slow wave sleep[51]. Reduction of GH and IGF-1 levels are observed in sleep deprivation[49,52-55] and obstructive sleep apnea[56,57]. Treatment of OSA with continuous positive airway pressure (CPAP) increased GH and IGF-1 levels[58-60], 2) a low testosterone level is observed in frailty[61-63]. Poor sleep quality affects testosterone levels[64,65]. OSA is associated with lower testosterone levels[66-68]. Low testosterone level leads to cognitive impairment[69,70], reduced muscle mass[71], muscle strength[72], sarcopenia[73], physical function and performance[74-76]. These might contribute to frailty in older adults, 3) systemic inflammation including interleukin-6, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) levels increased in those who had OSA[77-80] as well as frailty[47,81-90]. Chronic inflammation is related to physical decline[87], physical disability[91], sarcopenia[92] and frailty development[90]. Otherwise, chronic inflammation is associated with several comorbidities such as cardiovascular disease, congestive heart failure, type 2 diabetes, cancer, osteoporosis, cognitive decline and mortality[91]. The prevalence of frailty was higher in some of these comorbidities including cardiovascular disease[93,94], congestive heart failure[95], cancer[96] and cognitive impairment[97], 4) exhaustion and depression are important clinical characteristics of OSA[98-100] as well as frailty[31,101]. 5) OSA is a well-known risk factor for cardiovascular disease[102,103], cerebrovascular disease[102,103] and cognitive impairment[104,105]. These conditions are the risk of frailty in older adults[93,94,106-108].

Moreover, sleep is essential to the process of memory formation and consolidation particularly sleep continuity, K-complex, sleep spindles, slow-wave sleep and rapid eye movement (REM) sleep[104,109-111]. Sleep fragmentation, sleep architectural changes and intermittent hypoxia occurring in OSA lead to neurogenesis reduction, synaptic plasticity reduction, small vessel disease, microinfarcts, brain structure changes, cerebral networks alteration, amyloid plaques and hyperphosphorylated tau protein in the brain[104]. These might contribute to cognitive impairment in OSA. However, the current study did not show the significant

Table 1. Demographic data of participants

Baseline characteristics	Low-risk OSA, n=74	High-risk OSA, n=124	p-value
Female, n (%)	67 (54.0)	57 (46.0)	<0.001
Age (year), median (IQR)	68 (64, 72)	68 (64, 73)	0.83
BMI, median (IQR)	22.9 (20.3, 24.8)	25 (22.6, 28.7)	<0.001
Educational level, n (%)			0.03
<6 years	50 (67.6)	63 (50.8)	
≥6 years	24 (32.4)	61 (49.2)	
Family incomes/month, n (%)			0.08
≤20,000 baht	62 (83.8)	89 (71.8)	
>20,000 baht	12 (16.2)	35 (28.2)	
Underlying disease, n (%)			
Hypertension	33 (44.6)	95 (76.6)	<0.001
Diabetes mellitus	16 (21.6)	57 (46.0)	0.001
Cerebrovascular disease	8 (10.8)	8 (6.5)	0.41
COPD/asthma	4 (5.4)	8 (6.5)	1.00
CKD	4 (5.4)	30 (24.2)	<0.001
Falling within 6 months, n (%)	7 (9.5)	21 (16.9)	0.21
Medication ≥5, n (%)	33 (44.6)	60 (48.4)	0.71
History of admission within previous year, n (%)	20 (27.0)	49 (39.5)	0.10
Current alcohol drinking, n (%)	2 (2.7)	24 (19.4)	<0.001
Current smoking, n (%)	7 (9.5)	49 (39.5)	<0.001
MoCA <20, n (%)	57 (46.0)	44 (59.5)	0.09
Quality of life, n (%)			0.77
Good quality of life	60 (81.1)	97 (78.2)	
Fair quality of life	14 (18.9)	27 (21.8)	
Frailty, n (%)	12 (16.2)	45 (36.3)	0.004
Cognitive frailty, n (%)	12 (16.2)	29 (23.4)	0.31

OSA=obstructive sleep apnea; IQR=interquartile range; BMI=body mass index; COPD=chronic obstructive pulmonary disease; CKD=chronic kidney disease; MoCA=Montreal Cognitive Assessment

Table 2. Adverse events in participants who had a high-risk of OSA comparing with the participants who had a low-risk of OSA

Adverse events	cOR	95% CI	p-value	aOR	95% CI	p-value
Frailty[1]	2.94	1.47 to 6.25	0.003	3.37	1.56 to 7.71	0.003
Cognitive frailty[1]	1.58	0.76 to 3.43	0.23	2.08	0.94 to 4.79	0.07
History of admission within previous year[2]	1.76	0.95 to 3.35	0.07	1.77	0.88 to 3.53	0.11
Falling within previous 6 months[3]	1.95	0.82 to 5.18	0.15	2.07	0.83 to 5.74	0.13
Fair quality of life[4]	1.19	0.59 to 2.51	0.63	1.06	0.48 to 2.41	0.87

cOR=crude odds ratio; aOR=adjusted odd ratio; CI=confidence interval

[1] Adjusted by history of alcohol consumption, educational level, history of admission within previous year, income, number of medications and quality of life

[2] Adjusted by history of alcohol consumption, educational level, income, number of medications, frailty, falling within previous 6 months and quality of life

[3] Adjusted by history of alcohol consumption, educational level, history of admission within previous year, income, number of medications, frailty and quality of life

[4] Adjusted by history of alcohol consumption, educational level, history of admission within previous year, income, number of medications, frailty and falling within previous 6 months

association between the older adults who had a high-risk OSA and cognitive frailty (aOR 2.08, 95% CI 0.94 to 4.79, p-value=0.07). This might be explained by the number of the older adults with cognitive frailty in the current study was relatively low. Therefore, the association should be evaluated in the further study.

The study emphasized that the older adults who had a high-risk of OSA were associated with frailty. STOP-BANG questionnaire is the simple and practical tool for screening of OSA at ambulatory outpatient clinic. The sleep study should be performed in the older adults who had a high-risk of OSA. Treatment of OSA might modify the natural history of frailty.

The study had some limitations. First, the sleep study

was not performed, misclassification might occur. Second, some factors were found significantly associated with OSA in previous studies but could not identify in the present study, this might be from this study was relatively small sample size. Third, the temporal relationship was unable to determine according to the study design.

Conclusion

The older adults who had a high-risk of OSA was associated with frailty. The screening and diagnosis of OSA were recommended in the older adults who attended at an outpatient clinic.

What is already known on the topic?

OSA is highly prevalent and cause poor sleep quality in the older adults. It is an important comorbidity and increased risk of worse outcome. Frailty is a common geriatric syndrome that is a vulnerable state and can lead to many adverse outcomes. Poor sleep quality is associated with frailty.

What this study adds?

The older adults who had a high-risk of OSA was associated with frailty. Diagnosis and treatment of OSA might modify the natural history of this condition.

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Conflicts of interest

The authors declare no conflict of interests.

References

1. United Nations, Department of Economic and Social Affairs, Population Division. World population ageing 2017 - Highlights (ST/ESA/SER.A/397) [Internet]. 2017 [cited 2022 Aug 11]. Available from: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Highlights.pdf.
2. Durán J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001;163:685-9.
3. Glasser M, Bailey N, McMillan A, Goff E, Morrell MJ. Sleep apnoea in older people. Breathe 2011;7:248-56.
4. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev 2010;90:47-112.
5. Harding SM. Complications and consequences of obstructive sleep apnea. Curr Opin Pulm Med 2000;6:485-9.
6. Ou Q, Chen YC, Zhuo SQ, Tian XT, He CH, Lu XL, et al. Continuous positive airway pressure treatment reduces mortality in elderly patients with moderate to severe obstructive severe sleep apnea: A cohort study. PLoS One 2015;10:e0127775.
7. Stevens D, Jackson B, Carberry J, McLoughlin J, Barr C, Mukherjee S, et al. The impact of obstructive sleep apnea on balance, gait, and falls risk: A narrative review of the literature. J Gerontol A Biol Sci Med Sci 2020;75:2450-60.
8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752-62.
9. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 2012;60:1487-92.
10. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. BMJ Open 2018;8:e018195.
11. Kojima G. Frailty as a predictor of future falls among community-dwelling older people: A systematic review and meta-analysis. J Am Med Dir Assoc 2015;16:1027-33.
12. Zhang Q, Zhao X, Liu H, Ding H. Frailty as a predictor of future falls and disability: a four-year follow-up study of Chinese older adults. BMC Geriatr 2020;20:388.
13. Kojima G. Frailty as a predictor of fractures among community-dwelling older people: A systematic review and meta-analysis. Bone 2016;90:116-22.
14. Kojima G. Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. Disabil Rehabil 2017;39:1897-908.
15. Choi YS, Kim MJ, Lee GY, Seo YM, Seo AR, Kim B, et al. The association between frailty and disability among the elderly in rural areas of Korea. Int J Environ Res Public Health 2019;16.
16. Kojima G, Taniguchi Y, Iliffe S, Walters K. Frailty as a predictor of Alzheimer disease, vascular dementia, and all dementia among community-dwelling older people: A systematic review and meta-analysis. J Am Med Dir Assoc 2016;17:881-8.
17. Borges MK, Canevelli M, Cesari M, Aprahamian I. Frailty as a predictor of cognitive disorders: A systematic review and meta-analysis. Front Med (Lausanne) 2019;6:26.
18. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment--a review of the evidence and causal mechanisms. Ageing Res Rev 2013;12:840-51.
19. Kojima G, Iliffe S, Jivraj S, Walters K. Association between frailty and quality of life among community-

dwelling older people: a systematic review and meta-analysis. J Epidemiol Community Health 2016;70:716-21.
20. Limpawattana P, Khammak C, Manjavong M, So-Ngern A. Frailty as a predictor of hospitalization and low quality of life in geriatric patients at an internal medicine outpatient clinic: A cross-sectional study. Geriatrics (Basel) 2022;7:89.
21. Kojima G. Frailty as a predictor of hospitalisation among community-dwelling older people: a systematic review and meta-analysis. J Epidemiol Community Health 2016;70:722-9.
22. Roe L, Normand C, Wren MA, Browne J, O'Halloran AM. The impact of frailty on healthcare utilisation in Ireland: evidence from the Irish longitudinal study on ageing. BMC Geriatr 2017;17:203.
23. García-Nogueras I, Aranda-Reneo I, Peña-Longobardo LM, Oliva-Moreno J, Abizanda P. Use of health resources and healthcare costs associated with frailty: The FRADEA study. J Nutr Health Aging 2017;21:207-14.
24. Kojima G. Frailty defined by FRAIL scale as a predictor of mortality: A systematic review and meta-analysis. J Am Med Dir Assoc 2018;19:480-3.
25. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age Ageing 2018;47:193-200.
26. Salminen M, Viljanen A, Eloranta S, Viikari P, Wuorela M, Vahlberg T, et al. Frailty and mortality: an 18-year follow-up study among Finnish community-dwelling older people. Aging Clin Exp Res 2020;32:2013-9.
27. Kendhapedi KK, Devasenapathy N. Prevalence and factors associated with frailty among community-dwelling older people in rural Thanjavur district of South India: a cross-sectional study. BMJ Open 2019;9:e032904.
28. Fhon JRS, Rodrigues RAP, Santos JLF, Diniz MA, Santos EBD, Almeida VC, et al. Factors associated with frailty in older adults: a longitudinal study. Rev Saude Publica 2018;52:74.
29. Ottenbacher KJ, Ostir GV, Peek MK, Snih SA, Raji MA, Markides KS. Frailty in older Mexican Americans. J Am Geriatr Soc 2005;53:1524-31.
30. Newman AB, Gottdiener JS, McBurnie MA, Hirsch CH, Kop WJ, Tracy R, et al. Associations of subclinical cardiovascular disease with frailty. J Gerontol A Biol Sci Med Sci 2001;56:M158-66.
31. Soysal P, Veronese N, Thompson T, Kahl KG, Fernandes BS, Prina AM, et al. Relationship between depression and frailty in older adults: A systematic review and meta-analysis. Ageing Res Rev 2017;36:78-87.
32. Vaughan L, Corbin AL, Goveas JS. Depression and frailty in later life: a systematic review. Clin Interv Aging 2015;10:1947-58.
33. Piovezan R, Poyares D, Tufik S. Frailty and sleep disturbances in the elderly: Possible connections and clinical implications. Sleep Sci 2014;6:175-9.
34. Alqahtani BA. Association between physical frailty and sleep quality among Saudi older adults: A community-based, cross-sectional study. Int J Environ Res Public Health 2021;18:12741.
35. Çavuşoğlu Ç, Deniz O, Tuna Doğrul R, Çöteli S, Öncül A, Kızılarslanoğlu MC, et al. Frailty is associated with poor sleep quality in the oldest old. Turk J Med Sci 2021;51:540-6.
36. Sun XH, Ma T, Yao S, Chen ZK, Xu WD, Jiang XY, et al. Associations of sleep quality and sleep duration with frailty and pre-frailty in an elderly population Rugao longevity and ageing study. BMC Geriatr 2020;20:9.
37. 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;170:193-202.
38. Ensrud KE, Blackwell TL, Redline S, Ancoli-Israel S, Paudel ML, Cawthon PM, et al. Sleep disturbances and frailty status in older community-dwelling men. J Am Geriatr Soc 2009;57:2085-93.
39. Mehawej J, Saczynski JS, Kiefe CI, Abu HO, Tisminetzky M, Wang W, et al. Association between risk of obstructive sleep apnea and cognitive performance, frailty, and quality of life among older adults with atrial fibrillation. J Clin Sleep Med 2022;18:469-75.
40. Banhiran W, Durongphan A, Saleesing C, Chongkolwatana C. Diagnostic properties of the STOP-Bang and its modified version in screening for obstructive sleep apnea in Thai patients. J Med Assoc Thai 2014;97:644-54.
41. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108:812-21.
42. Somrongthong R, Wongchalee S, Yodmai K, Kuhirunyaratn P, Sihapark S, Mureed S. Quality of life and health status among thai elderly after economic crisis, Khon Kaen province, Thailand. Eur J Sci Res 2013;112:314-24.
43. Srinonprasert V, Chalermsri C, Aekplakorn W. Frailty index to predict all-cause mortality in Thai community-dwelling older population: A result from a National Health Examination Survey cohort. Arch Gerontol Geriatr 2018;77:124-8.
44. Tangwongchai S, Phanasathit M, Charernboon T, Akkayagorn L, Hemrungrojn S, Phanthumchinda K, et al. The validity of Thai version of The Montreal Cognitive Assessment (MoCA-T). Dement Neuropsychol 2009;3:136-78.
45. Manjavong M, Limpawattana P, Sawanyawisuth K. Can RUDAS be an alternate test for detecting mild cognitive impairment in older adults, Thailand? Geriatrics (Basel) 2021;6:117.
46. 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;13:1217-25.
47. Semmarath W, Seesen M, Yodkeeree S, Sapbamrer R,

Ayood P, Malasao R, et al. The association between frailty indicators and blood-based biomarkers in early-old community dwellers of Thailand. Int J Environ Res Public Health 2019;16:3457.
48. Ohlsson C, Mohan S, Sjögren K, Tivesten A, Isgaard J, Isaksson O, et al. The role of liver-derived insulin-like growth factor-I. Endocr Rev 2009;30:494-535.
49. Chennaoui M, Léger D, Gomez-Merino D. Sleep and the GH/IGF-1 axis: Consequences and countermeasures of sleep loss/disorders. Sleep Med Rev 2020;49:101223.
50. Maggio M, De Vita F, Lauretani F, Buttò V, Bondi G, Cattabiani C, et al. IGF-1, the cross road of the nutritional, inflammatory and hormonal pathways to frailty. Nutrients 2013;5:4184-205.
51. Sassin JF, Parker DC, Mace JW, Gotlin RW, Johnson LC, Rossman LG. Human growth hormone release: relation to slow-wave sleep and sleep-walking cycles. Science 1969;165:513-5.
52. Brandenberger G, Gronfier C, Chapotot F, Simon C, Piquard F. Effect of sleep deprivation on overall 24 h growth-hormone secretion. Lancet 2000;356:1408.
53. Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP. Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. Clin Endocrinol (Oxf) 1999;51:205-15.
54. Everson CA, Crowley WR. Reductions in circulating anabolic hormones induced by sustained sleep deprivation in rats. Am J Physiol Endocrinol Metab 2004;286:E1060-70.
55. Rusch HL, Guardado P, Baxter T, Mysliwiec V, Gill JM. Improved sleep quality is associated with reductions in depression and PTSD arousal symptoms and increases in IGF-1 concentrations. J Clin Sleep Med 2015;11:615-23.
56. Lanfranco F, Motta G, Minetto MA, Ghigo E, Maccario M. Growth hormone/insulin-like growth factor-I axis in obstructive sleep apnea syndrome: an update. J Endocrinol Invest 2010;33:192-6.
57. Izumi S, Ribeiro-Filho FF, Carneiro G, Togeiro SM, Tufik S, Zanella MT. IGF-1 levels are inversely associated with metabolic syndrome in obstructive sleep apnea. J Clin Sleep Med 2016;12:487-93.
58. Cooper BG, White JE, Ashworth LA, Alberti KG, Gibson GJ. Hormonal and metabolic profiles in subjects with obstructive sleep apnea syndrome and the acute effects of nasal continuous positive airway pressure (CPAP) treatment. Sleep 1995;18:172-9.
59. Saini J, Krieger J, Brandenberger G, Wittersheim G, Simon C, Follenius M. Continuous positive airway pressure treatment. Effects on growth hormone, insulin and glucose profiles in obstructive sleep apnea patients. Horm Metab Res 1993;25:375-81.
60. Hoyos CM, Killick R, Keenan DM, Baxter RC, Veldhuis JD, Liu PY. Continuous positive airway pressure increases pulsatile growth hormone secretion and circulating insulin-like growth factor-1 in a time-dependent manner in men with obstructive sleep apnea: a randomized sham-controlled study. Sleep 2014;37:733-41.
61. Leng SX, Cappola AR, Andersen RE, Blackman MR, Koenig K, Blair M, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. Aging Clin Exp Res 2004;16:153-7.
62. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SA, et al. Low free testosterone predicts frailty in older men: the health in men study. J Clin Endocrinol Metab 2010;95:3165-72.
63. Peng X, Hou L, Zhao Y, Lin T, Wang H, Gao L, et al. Frailty and testosterone level in older adults: a systematic review and meta-analysis. Eur Geriatr Med 2022;13:663-73.
64. Barrett-Connor E, Dam TT, Stone K, Harrison SL, Redline S, Orwoll E. The association of testosterone levels with overall sleep quality, sleep architecture, and sleep-disordered breathing. J Clin Endocrinol Metab 2008;93:2602-9.
65. Kim SD, Cho KS. Obstructive sleep apnea and testosterone deficiency. World J Mens Health 2019;37:12-8.
66. Bercea RM, Mihaescu T, Cojocaru C, Bjorvatn B. Fatigue and serum testosterone in obstructive sleep apnea patients. Clin Respir J 2015;9:342-9.
67. Viana A Jr, Daflon AC, Couto A, Neves D, de Araujo-Melo MH, Capasso R. Nocturnal hypoxemia is associated with low testosterone levels in overweight males and older men with normal weight. J Clin Sleep Med 2017;13:1395-401.
68. Li Z, Tang T, Wu W, Gu L, Du J, Zhao T, et al. Efficacy of nasal continuous positive airway pressure on patients with OSA with erectile dysfunction and low sex hormone levels. Respir Med 2016;119:130-4.
69. Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab 1999;84:3681-5.
70. Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab 2002;87:5001-7.
71. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. Mech Ageing Dev 1999;107:123-36.
72. Roy TA, Blackman MR, Harman SM, Tobin JD, Schrager M, Metter EJ. Interrelationships of serum testosterone and free testosterone index with FFM and strength in aging men. Am J Physiol Endocrinol Metab 2002;283:E284-94.
73. Shin MJ, Jeon YK, Kim IJ. Testosterone and sarcopenia. World J Mens Health 2018;36:192-8.
74. O'Connell MD, Tajar A, Roberts SA, Wu FC. Do androgens play any role in the physical frailty of ageing men? Int J Androl 2011;34:195-211.
75. Saad F. The relationship between testosterone

deficiency and frailty in elderly men. Horm Mol Biol Clin Investig 2010;4:529-38.
76. Krasnoff JB, Basaria S, Pencina MJ, Jasuja GK, Vasan RS, Ulloor J, et al. Free testosterone levels are associated with mobility limitation and physical performance in community-dwelling men: the Framingham Offspring Study. J Clin Endocrinol Metab 2010;95:2790-9.
77. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 2003;107:1129-34.
78. 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;105:2462-4.
79. Kheirandish-Gozal L, Gozal D. Obstructive sleep apnea and inflammation: Proof of concept based on two illustrative cytokines. Int J Mol Sci 2019;20:459.
80. Cao Y, Song Y, Ning P, Zhang L, Wu S, Quan J, et al. Association between tumor necrosis factor alpha and obstructive sleep apnea in adults: a meta-analysis update. BMC Pulm Med 2020;20:215.
81. Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, 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;162:2333-41.
82. Leng SX, Yang H, Walston JD. Decreased cell proliferation and altered cytokine production in frail older adults. Aging Clin Exp Res 2004;16:249-52.
83. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med 2000;51:245-70.
84. Van Epps P, Oswald D, Higgins PA, Hornick TR, Aung H, Banks RE, et al. Frailty has a stronger association with inflammation than age in older veterans. Immun Ageing 2016;13:27.
85. Tembo MC, Holloway-Kew KL, Bortolasci CC, Brennan-Olsen SL, Williams LJ, Kotowicz MA, et al. Association between serum interleukin-6 and frailty in older men: cross-sectional data. Eur Geriatr Med 2021;12:887-92.
86. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. Ageing Res Rev 2016;31:1-8.
87. Pothier K, Gana W, Bailly N, Fougère B. Associations between frailty and inflammation, physical, and psycho-social health in older adults: A systematic review. Front Psychol 2022;13:805501.
88. Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. J Am Geriatr Soc 2007;55:864-71.
89. Xu Y, Wang M, Chen D, Jiang X, Xiong Z. Inflammatory biomarkers in older adults with frailty: a systematic review and meta-analysis of cross-sectional studies. Aging Clin Exp Res 2022;34:971-87.
90. Vatic M, von Haehling S, Ebner N. Inflammatory biomarkers of frailty. Exp Gerontol 2020;133:110858.
91. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev 2011;10:319-29.
92. Dalle S, Rossmeislova L, Koppo K. The role of inflammation in age-related sarcopenia. Front Physiol 2017;8:1045.
93. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. Am J Cardiol 2009;103:1616-21.
94. Afilalo J. Frailty in patients with cardiovascular disease: Why, When, and How to measure. Curr Cardiovasc Risk Rep 2011;5:467-72.
95. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Kurdi S, Lee CS. The prevalence of frailty in heart failure: A systematic review and meta-analysis. Int J Cardiol 2017;236:283-9.
96. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2015;26:1091-101.
97. Kojima G, Liljas A, Iliffe S, Walters K. Prevalence of frailty in mild to moderate Alzheimer's disease: a systematic review and meta-analysis. Curr Alzheimer Res 2017;14:1256-63.
98. Ejaz SM, Khawaja IS, Bhatia S, Hurwitz TD. Obstructive sleep apnea and depression: a review. Innov Clin Neurosci 2011;8:17-25.
99. Jehan S, Auguste E, Pandi-Perumal SR, Kalinowski J, Myers AK, Zizi F, et al. Depression, obstructive sleep apnea and psychosocial health. Sleep Med Disord 2017;1:00012.
100. Chotinaiwattarakul W, O'Brien LM, Fan L, Chervin RD. Fatigue, tiredness, and lack of energy improve with treatment for OSA. J Clin Sleep Med 2009;5:222-7.
101. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
102. Jean-Louis G, Zizi F, Clark LT, Brown CD, McFarlane SI. Obstructive sleep apnea and cardiovascular disease: role of the metabolic syndrome and its components. J Clin Sleep Med 2008;4:261-72.
103. Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, et al. Obstructive sleep apnea in cardiovascular disease: A review of the literature and proposed multidisciplinary clinical management strategy. J Am Heart Assoc 2019;8:e010440.
104. Gosselin N, Baril AA, Osorio RS, Kaminska M, Carrier J. Obstructive sleep apnea and the risk of cognitive decline in older adults. Am J Respir Crit Care Med 2019;199:142-8.
105. Buratti L, Luzzi S, Petrelli C, Baldinelli S, Viticchi G,

Provinciali L, et al. Obstructive sleep apnea syndrome: An emerging risk factor for dementia. CNS Neurol Disord Drug Targets 2016;15:678-82.
106. Frisoli A Jr, Ingham SJ, Paes Â T, Tinoco E, Greco A, Zanata N, et al. Frailty predictors and outcomes among older patients with cardiovascular disease: Data from Fragicor. Arch Gerontol Geriatr 2015;61:1-7.
107. Kleipool EE, Hoogendijk EO, Trappenburg MC, Handoko ML, Huisman M, Peters MJ, et al. Frailty in older adults with cardiovascular disease: Cause, effect or both? Aging Dis 2018;9:489-97.
108. Brigola AG, Rossetti ES, Dos Santos BR, Neri AL, Zazzetta MS, Inouye K, et al. Relationship between cognition and frailty in elderly: A systematic review. Dement Neuropsychol 2015;9:110-9.
109. Rasch B, Born J. About sleep's role in memory. Physiol Rev 2013;93:681-766.
110. Born J, Wilhelm I. System consolidation of memory during sleep. Psychol Res 2012;76:192-203.
111. De Gennaro L, Gorgoni M, Reda F, Lauri G, Truglia I, Cordone S, et al. The fall of sleep K-complex in Alzheimer disease. Sci Rep 2017;7:39688.