Prevalence of Obstructive Sleep Apnea

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Keywords: aging ; sleep ; obstructive sleep apnea ; cognitive decline ; mild cognitive impairment ; Alzheimer's disease

1. Introduction

More and more people are living with dementia worldwide, with no curative treatment in sight. Alzheimer's disease (AD) is by far the most common form of dementia, representing 60–70% of all dementia cases [1], and is generally preceded by a predementia stage of mild cognitive impairment (MCI). Around 40% of worldwide dementia cases are thought to be attributable to potentially modifiable risk factors, including diabetes, hypertension, obesity, physical inactivity, depression, smoking, low educational attainment, hearing impairment, low social contact, excessive alcohol consumption, and air pollution [2]. In addition, there is a growing body of evidence supporting the role of sleep disorders in the development of MCI and dementia [3][4][5], among which obstructive sleep apnea (OSA) could represent a modifiable risk factor of particular interest [6][7][8][9]. Therapeutic interventions targeting these modifiable risk factors may have the potential to delay dementia onset and slow its progression. Therefore, it is essential to properly identify these modifiable risk factors, and to fully understand the mechanisms by which they may increase the risk of dementia. Moreover, it is also essential to better understand how modifiable risk and protective factors interact to increase or reduce a person's vulnerability to dementia. Better identifying individuals who could benefit from potential preventive therapies and those who should be included in clinical trials is a worldwide objective [10][11].

2. Definition and Prevalence of OSA

OSA is a respiratory disorder characterized by repeated episodes of partial (hypopnea) and complete (apnea) obstructions of the upper airway during sleep [12][13]. These recurrent respiratory events lead to cortical arousal and sleep fragmentation, intermittent hypoxemia, and increased sympathetic activity, affecting sleep quality and daytime functioning [14]. OSA severity is typically assessed with the apnea–hypopnea index (AHI), which is the average number of apneas and hypopneas per hour of sleep. The severity of OSA is determined according to the following thresholds: mild (AHI ≥ 5 and <15), moderate (AHI ≥ 15 and <30) or severe (AHI ≥ 30) [15]. According to a systematic review in the adult population, 9–38% of individuals present with mild OSA and 6–17% present with moderate to severe OSA [16]. In the elderly, these estimations reach up to 84% for mild OSA and 36% for moderate to severe OSA [16]. Even more worrying, one study observed that 56% of adults aged 65 and older were at high risk of OSA, while only 8% of them had been tested for OSA and diagnosed [17]. Thus, many older adults remain undiagnosed, and therefore not treated. Furthermore, when people do get diagnosed, only about 41% remain adherent to their continuous positive airway pressure (CPAP) treatment after one year [18]. This low CPAP adherence is alarming, especially considering that this treatment could delay cognitive decline in individuals with OSA [9].

3. Potential Mechanisms Linking OSA and Cognitive Decline in Older Adults

It is well established that OSA causes sleep fragmentation and intermittent hypoxemia. More specifically, repeated micro-arousals alter both sleep macroarchitecture (time spent in stage N3 and rapid-eye movement (REM) sleep) [19] and microstructure (slow-wave and spindle characteristics) [20][21][22][23]. Considering the critical roles of sleep continuity, slow-wave sleep, REM sleep, and sleep spindles in neurogenesis, brain plasticity, alertness, and memory formation and consolidation [24][25], chronic sleep changes caused by OSA could negatively affect cognitive health [6][26][27]. REM-dependent OSA could be particularly harmful to the brain, with respiratory events occurring during this sleep stage being associated with reduced daytime regional cerebral blood flow, even in mild OSA [28]. Indeed, muscle atonia during REM

sleep can increase the occurrence and the hypoxic levels of respiratory obstructive events, and thus, some individuals present respiratory events mostly in this sleep stage. Further, REM-dependent OSA is more strongly associated with excessive daytime sleepiness than NREM-OSA [29], which is in turn related to cognitive impairment [30].

Moreover, both sleep fragmentation and intermittent hypoxia interfere with brain structure and function, increasing their vulnerability to neurodegenerative diseases. Indeed, it has been suggested that a biphasic pattern of neuroimaging findings could be in play in OSA [31], with acute transitory or compensatory responses (i.e., gray matter hypertrophy, restricted white matter diffusivities) followed by evidence of cellular damage (i.e., gray matter atrophy, higher white matter hyperintensity burden, lower white matter fractional anisotropy, higher water diffusivities). In addition, OSA has been recently associated with increased amyloid and tau burden [21][32][33][34][35][36][37][38][39][40][41][42][43], two proteins involved in AD pathophysiology. Several mechanisms likely underlie these neuroimaging or pathological findings and include inflammation, oxidative stress, metabolic disturbances, cerebral edema and endothelial dysfunction [27]. Indeed, inflammation is involved in neurodegenerative processes, notably by triggering a positive feedback loop that increases amyloid beta production and oxidative stress, facilitating amyloid and tau pathology [26][44].

4. Cohort Studies Investigating the Association between OSA and Cognitive Decline in Older Adults

4.1. Cross-Sectional Studies

The majority of large cross-sectional cohort studies investigating the association between OSA and cognitive impairment in middle-aged and older adults have used objective sleep measures, i.e., polysomnography or portable devices, to evaluate OSA [45][46][47][48][49][50][51][52], and one study used a questionnaire to screen for OSA [53]. While some studies have investigated cognitive performance using comprehensive neuropsychological batteries [51][53][54], others used a limited number of neuropsychological tests targeting specific cognitive functions or global functioning [45][46][49][52]. In studies showing that OSA is associated with poorer cognitive functioning, associations were found for long-term verbal memory [47], working memory [47] and global cognition [52]. The OSA severity markers or OSA-related symptoms associated with cognition were highly heterogeneous across studies, including snoring [53], self-reported apneas [53], hypoxemia [45][54] and AHI [50][51]. Other studies have not found a significant association between any OSA severity marker and cognition [46][48][49].

Despite the heterogenous results emerging from cross-sectional studies, associations between OSA and cognitive functioning seem better established in the domains of attention, memory, and processing speed, while less evidence supports an association between OSA and working memory, executive functions, language and visual abilities in middle-aged and older adults. Interestingly, in younger adults, the most affected cognitive domains in OSA are attention, episodic memory, working memory, and executive functions [14]. This suggests that while some cognitive domains appear to be affected by OSA regardless of the age (namely, memory and attention), other cognitive domains seem less impacted by OSA with increasing age, such as executive function and working memory.

4.2. Longitudinal Studies

Longitudinal cohort studies have the advantage of quantifying cognitive decline over time. They used self-reported diagnoses (e.g., [9][55]) or in-home polysomnography or portable devices (e.g., [7][56][57][58][59]) to identify OSA cases. Furthermore, the majority of these studies used global cognitive measures or screening tools, such as the Mini-Mental State examination (MMSE; e.g., [7][59]), while a comprehensive neuropsychological battery was used in one study [58].

Among the main longitudinal cohort studies, the Study of Osteoporotic Fractures included 298 82-year-old women and found that 45% of women with OSA developed MCI or dementia at five-year follow-up, compared to 31% of women without OSA [59]. However, neither of the two neuropsychological tests used to assess global cognition and executive functions could identify impairment of specific cognitive functions related to OSA. This result was also obtained in the Atherosclerosis Risk in Communities Study that included men and women aged 45–64 years and failed to show an association between OSA and specific cognitive tests at 15-year follow-up [56], while highlighting an increased risk of dementia in individuals with severe OSA [57]. In the Osteoporotic Fractures in Men Sleep Study, including men aged 65 and older, another team showed a negative relationship between baseline nocturnal hypoxemia and global cognitive functioning after three years, while executive functions were not associated with OSA [7]. On the other hand, the Proof-SYNAPSE study used a wide selection of neuropsychological tests in men and women aged 65 years and showed only a slight decline in attention related to OSA after eight years, without any change in executive functions and memory [58].

In summary, studies using measures of global cognition and clinical diagnosis of cognitive impairment or dementia were more susceptible to highlight cognitive decline associated with OSA over time than those using comprehensive neuropsychological batteries [56][57][58]. This suggests that longitudinal studies are more susceptible to identify major OSA-related cognitive decline over time, but not milder cognitive decline in specific domains.

4.3. Meta-Analyses, Meta-Reviews and Systematic Reviews

Most meta-analyses and systematic reviews concluded that a significant association between OSA and cognition exists [8][60][61][62] and that OSA increases the risk of AD [63][64][65]. Interestingly, these meta-analyses and systematic reviews highlighted the fact that small cohorts and controlled case studies from sleep clinics have shown effects of OSA on cognition [66][67], while most studies of large community-based cohort studies failed to show significant associations [45][56]. Another systematic review concluded that the link between OSA and cognition is weak [68], possibly due to the age range used (50 years and over, while others included studies of participants aged 30 years and over [8][60][62]). Similarly, another systematic review showed a significant association between OSA and cognition only in adults younger than 60 years [60]. In addition to age, the variability in the strength of the association could also be due to the study types and designs, the recruitment methods and/or that only more severe OSA cases are associated with cognitive dysfunction.

References

1. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. Alzheimer Dement. 2016, 12, 459–509.
2. Livingston, G.; Huntley, J.; Sommerlad, A.; Ames, D.; Ballard, C.; Banerjee, S.; Brayne, C.; Burns, A.; Cohen-Mansfield, J.; Cooper, C.; et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020, 396, 413–446.
3. Bubu, O.M.; Brannick, M.; Mortimer, J.; Umasabor-Bubu, O.; Sebastião, Y.V.; Wen, Y.; Schwartz, S.; Borenstein, A.R.; Wu, Y.; Morgan, D.; et al. Sleep, Cognitive impairment, and Alzheimer's disease: A Systematic Review and Meta-Analysis. Sleep 2017, 40, 1–18.
4. Yaffe, K.; Falvey, C.M.; Hoang, T. Connections between sleep and cognition in older adults. Lancet Neurol. 2014, 13, 1017–1028.
5. Diem, S.J.; Blackwell, T.L.; Stone, K.L.; Yaffe, K.; Tranah, G.; Cauley, J.A.; Ancoli-Israel, S.; Redline, S.; Spira, A.P.; Hillier, T.A.; et al. Measures of Sleep-Wake Patterns and Risk of Mild Cognitive Impairment or Dementia in Older Women. Am. J. Geriatr. Psychiatry 2016, 24, 248–258.
6. Gosselin, N.; Baril, A.-A.; Osorio, R.S.; Kaminska, M.; Carrier, J. Obstructive Sleep Apnea and the Risk of Cognitive Decline in Older Adults. Am. J. Respir. Crit. Care Med. 2019, 199, 142–148.
7. Blackwell, T.; Yaffe, K.; Laffan, A.; Redline, S.; Ancoli-Israel, S.; Ensrud, K.E.; Song, Y.; Stone, K.L. Associations Between Sleep-Disordered Breathing, Nocturnal Hypoxemia, and Subsequent Cognitive Decline in Older Community-Dwelling Men: The Osteoporotic Fractures in Men Sleep Study. J. Am. Geriatr. Soc. 2015, 63, 453–461.
8. Leng, Y.; McEvoy, C.T.; Allen, I.E.; Yaffe, K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: A systematic review and meta-analysis. J. Am. Med. Assoc. Neurol. 2017, 74, 1237–1245.
9. Osorio, R.S.; Gumb, T.; Pirraglia, E.; Varga, A.W.; Lu, S.E.; Lim, J.; Wohlleber, M.E.; Ducca, E.L.; Koushyk, V.; Glodzik, L.; et al. Sleep-Disordered Breathing Advances Cognitive Decline in the Elderly. Neurology 2015, 84, 1964–1971.
10. Hing Tang, E.Y.; Robinson, L.; Maree Stephan, B.C. Dementia risk assessment tools: An update. Neurodegener. Dis. Manag. 2017, 7, 345–347.
11. Lindley, R.I.; Waite, L.; Cullen, J. Dementia treatment: The need for a paradigm shift. Australas. J. Ageing 2019, 38, 149–150.
12. Kryger, M.H.; Roth, T.; Dement, W.C. Principles and Practice of Sleep Medicine, 5th ed.; Elsevier Saunders: Philadelphia, PA, USA, 2011.
13. Young, T.; Peppard, P.E.; Gottlieb, D.J. Epidemiology of Obstructive Sleep Apnea: A Population Health Perspective. Am. J. Respir. Crit. Care Med. 2002, 165, 1217–1239.
14. Gagnon, K.; Baril, A.A.; Gagnon, J.F.; Fortin, M.; Décary, A.; Lafond, C.; Desautels, A.; Montplaisir, J.; Gosselin, N. Cognitive impairment in obstructive sleep apnea. Pathol. Biol. 2014, 62, 233–240.
15. Berry, R.B.; Budhiraja, R.; Gottlieb, D.J.; Gozal, D.; Iber, C.; Kapur, V.K.; Marcus, C.L.; Mehra, R.; Parthasarathy, S.; Quan, S.F.; et al. Rules for Scoring Respiratory Events in Sleep: Update of the 2007 AASM Manual for the Scoring of Sle

ep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J. Clin. Sleep Med. 2012, 8, 597–619.

16. Senaratna, C.V.; Perret, J.L.; Lodge, C.J.; Lowe, A.J.; Campbell, B.E.; Matheson, M.C.; Hamilton, G.S.; Dharmage, S. C. Prevalence of Obstructive Sleep Apnea in the General Population: A Systematic Review. Sleep Med. Rev. 2017, 34, 70–81.
17. Braley, T.J.; Dunietz, G.L.; Chervin, R.D.; Lisabeth, L.D.; Skolarus, L.E.; Burke, J.F. Recognition and diagnosis of obstr uctive sleep apnea in older Americans. J. Am. Geriatr. Soc. 2018, 66, 1296–1302.
18. Lee, C.H.K.; Leow, L.C.; Song, P.R.; Li, H.H.; Ong, T.H. Acceptance and Adherence to Continuous Positive Airway Pres sure Therapy in Patients with Obstructive Sleep Apnea (OSA) in a Southeast Asian Privately Funded Healthcare Syste m. Sleep Sci. 2017, 10, 57–63.
19. Heinzer, R.; Gaudreau, H.; Décary, A.; Sforza, E.; Petit, D.; Morisson, F.; Montplaisir, J. Slow-Wave Activity in Sleep Ap nea Patients Before and After Continuous Positive Airway Pressure Treatment: Contribution to Daytime Sleepiness. Ch est 2001, 119, 1807–1813.
20. Carvalho, D.Z.; Gerhardt, G.J.L.; Dellagustin, G.; de Santa-Helena, E.L.; Lemke, N.; Segal, A.Z.; Schönwald, S.V. Loss of sleep spindle frequency deceleration in Obstructive Sleep Apnea. Clin. Neurophysiol. 2014, 125, 306–312.
21. Ju, Y.E.S.; Zangrilli, M.A.; Finn, M.B.; Fagan, A.M.; Holtzman, D.M. Obstructive sleep apnea treatment, slow wave activ ity, and amyloid-β. Annals of neurology. Physiol. Behav. 2019, 85, 291–295.
22. Peregrim, I.; Grešová, S.; Štimmelová, J.; Bačová, I.; Fulton, B.L.; Tokárová, D.; Gáborová, M.; Brandeburová, A.; Doni čová, V.; Rusnáková, S.; et al. Strong coincidence between slow wave sleep and low AHI is explainable by the high inst ability of slow wave sleep to obstructive apnea exposure. Physiol. Res. 2019, 68, 857–865.
23. Ren, R.; Covassin, N.; Zhang, Y.; Lei, F.; Yang, L.; Zhou, J.; Tan, L.; Li, T.; Li, Y.; Shi, J.; et al. Interaction between Slow Wave Sleep and Obstructive Sleep Apnea in Prevalent Hypertension. Hypertension 2020, 516–523.
24. Born, J.; Wilhelm, I. System Consolidation of Memory During Sleep. Psychol. Res. 2012, 76, 192–203.
25. Cirelli, C. Sleep and Synaptic Changes. Curr. Opin. Neurobiol. 2013, 23, 841–846.
26. Polsek, D.; Gildeh, N.; Cash, D.; Winsky-Sommerer, R.; Williams, S.C.R.; Turkheimer, F.; Leschziner, G.D.; Morrell, M. J.; Rosenzweig, I. Obstructive Sleep Apnoea and Alzheimer's Disease: In Search of Shared Pathomechanisms. Neuros ci. Biobehav. Rev. 2018, 86, 142–149.
27. Rosenzweig, I.; Glasser, M.; Polsek, D.; Leschziner, G.D.; Williams, S.C.R.; Morrell, M.J. Sleep Apnoea and the Brain: A Complex Relationship. Lancet Respir. Med. 2015, 3, 404–414.
28. Baril, A.-A.; Gagnon, K.; Brayet, P.; Montplaisir, J.; Carrier, J.; Soucy, J.-P.; Lafond, C.; Blais, H.; D'Aragon, C.; Gagnon, J.-F.; et al. Obstructive sleep apnea during REM sleep and daytime cerebral functioning: A regional cerebral blood flow study using high-resolution SPECT. J. Cereb. Blood Flow Metab. 2020, 40, 1230–1241.
29. Gabryelska, A.; Białasiewicz, P. Association between excessive daytime sleepiness, REM phenotype and severity of ob structive sleep apnea. Sci. Rep. 2020, 10, 1–6.
30. Gagnon, K.; Baril, A.-A.; Montplaisir, J.; Carrier, J.; De Beaumont, L.; D'Aragon, C.; Chami, S.; Pelleieux, S.; Poirier, J.; Gauthier, S.; et al. Disconnection Between Self-Reported and Objective Cognitive Impairment in Obstructive Sleep Apn ea. J. Clin. Sleep Med. 2019, 15, 409–415.
31. Baril, A.A.; Martineau-Dussault, M.È.; Sanchez, E.; André, C.; Thompson, C.; Legault, J.; Gosselin, N. Obstructive Slee p Apnea and the Brain: A Focus on Gray and White Matter Structure. Curr. Neurol. Neurosci. Rep. 2021, 21, 1–11.
32. Ju, Y.-E.S.; Finn, M.B.; Sutphen, C.L.; Herries, E.M.; Jerome, G.M.; Ladenson, J.H.; Crimmins, D.L.; Fagan, A.M.; Holtz man, D.M. Obstructive sleep apnea decreases central nervous system- derived proteins in the cerebrospinal fluid. Ann. Neurol. 2016, 80, 154–159.
33. Yun, C.H.; Lee, H.Y.; Lee, S.K.; Kim, H.; Seo, H.S.; Bang, S.A.; Kim, S.E.; Greve, D.N.; Au, R.; Shin, C.; et al. Amyloid Burden in Obstructive Sleep Apnea. J. Alzheimer Dis. 2017, 59, 21–29.
34. André, C.; Rehel, S.; Kuhn, E.; Landeau, B.; Moulinet, I.; Touron, E.; Ourry, V.; Le Du, G.; Mézenge, F.; Tomadesso, C.; et al. Association of Sleep-Disordered Breathing with Alzheimer Disease Biomarkers in Community-Dwelling Older Adul ts: A Secondary Analysis of a Randomized Clinical Trial. JAMA Neurol. 2020, 77, 716–724.
35. Jackson, M.L.; Cavuoto, M.; Schembri, R.; Doré, V.; Villemagne, V.L.; Barnes, M.; O'Donoghue, F.J.; Rowe, C.C.; Robi nson, S.R. Severe Obstructive Sleep Apnea Is Associated with Higher Brain Amyloid Burden: A Preliminary PET Imagin g Study. J. Alzheimer Dis. 2020, 78, 611–617.
36. Liguori, C.; Mercuri, N.B.; Izzi, F.; Romigi, A.; Cordella, A.; Sancesario, G.; Placidi, F. Obstructive sleep apnea is associ ated with early but possibly modifiable Alzheimer's disease biomarkers changes. Sleep 2017, 40.

37. Liguori, C.; Maestri, M.; Spanetta, M.; Placidi, F.; Bonanni, E.; Mercuri, N.B.; Guarnieri, B. Sleep-disordered breathing a nd the risk of Alzheimer's disease. Sleep Med. Rev. 2021, 55, 101375.

38. Bubu, O.M.; Pirraglia, E.; Andrade, A.G.; Sharma, R.A.; Gimenez-Badia, S.; Umasabor-Bubu, O.Q.; Hogan, M.M.; Shi m, A.M.; Mukhtar, F.; Sharma, N.; et al. Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker chang es. Sleep 2019, 42, 1–13.

39. Elias, A.; Cummins, T.; Tyrrell, R.; Lamb, F.; Dore, V.; Williams, R.; Rosenfeld, J.V.; Hopwood, M.; Villemagne, V.L.; Ro we, C.C. Risk of Alzheimer's Disease in Obstructive Sleep Apnea Syndrome: Amyloid-β and Tau Imaging. J. Alzheimer Dis. 2018, 66, 733–741.

40. Sharma, R.A.; Varga, A.W.; Bubu, O.M.; Pirraglia, E.; Kam, K.; Parekh, A.; Wohlleber, M.; Miller, M.D.; Andrade, A.; Lew is, C.; et al. Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly. Am. J. Respir. Crit. Care Med. 2018, 197, 933–943.

41. Spira, A.P.; Yager, C.; Brandt, J.; Smith, G.S.; Zhou, Y.; Mathur, A.; Kumar, A.; Brašić, J.R.; Wong, D.F.; Wu, M.N. Objec tively measured sleep and β-amyloid burden in older adults: A pilot study. SAGE Open Med. 2014, 2, 20503121145465 2.

42. Osorio, R.S.; Ayappa, I.; Mantua, J.; Gumb, T.; Varga, A.; Mooney, A.M.; Burschtin, O.E.; Taxin, Z.; During, E.; Spector, N.; et al. The interaction between sleep-disordered breathing and apolipoprotein E genotype on cerebrospinal fluid bio markers for Alzheimer's disease in cognitively normal elderly individuals. Neurobiol. Aging 2014, 35, 1318–1324.

43. Motamedi, V.; Kanefsky, R.; Matsangas, P.; Mithani, S.; Jeromin, A.; Brock, M.S.; Mysliwiec, V.; Gill, J. Elevated tau and interleukin-6 concentrations in adults with obstructive sleep apnea. Sleep Med. 2018, 43, 71–76.

44. Kinney, J.W.; Bemiller, S.M.; Murtishaw, A.S.; Leisgang, A.M.; Salazar, A.M.; Lamb, B.T. Inflammation as a Central Mec hanism in Alzheimer's Disease. Alzheimer Dement. Transl. Res. Clin. Interv. 2018, 4, 575–590.

45. Blackwell, T.; Yaffe, K.; Ancoli-Israel, S.; Redline, S.; Ensrud, K.E.; Stefanick, M.L.; Laffan, A.; Stone, K.L. Associations Between Sleep Architecture and Sleep-Disordered Breathing and Cognition in Older Community-Dwelling Men: The Os teoporotic Fractures in Men Sleep Study. J. Am. Geriatr. Soc. 2011, 59, 2217–2225.

46. Boland, L.L.; Shahar, E.; Iber, C.; Knopman, D.S.; Kuo, T.F.; Javier Nieto, F. Measures of Cognitive Function in Persons with Varying Degrees of Sleep-Disordered Breathing: The Sleep Heart Health Study. J. Sleep Res. 2002, 11, 265–272.

47. Cosentino, F.I.I.; Bosco, P.; Drago, V.; Prestianni, G.; Lanuzza, B.; Iero, I.; Tripodi, M.; Spada, R.S.; Toscano, G.; Carac i, F.; et al. The APOE ε4 Allele Increases the Risk of Impaired Spatial Working Memory in Obstructive Sleep Apnea. Sle ep Med. 2008, 9, 831–839.

48. Dlugaj, M.; Weinreich, G.; Weimar, C.; Stang, A.; Dragano, N.; Wessendorf, T.E.; Teschler, H.; Winkler, A.; Wege, N.; M oebus, S.; et al. Sleep-Disordered Breathing, Sleep Quality, and Mild Cognitive Impairment in the General Population. J. Alzheimer Dis. 2014, 41, 479–497.

49. Foley, D.J.; Masaki, K.; White, L.; Larkin, E.K.; Monjan, A.; Redline, S. Sleep-Disordered Breathing and Cognitive Impai rment in Elderly Japanese-American Men. Sleep 2003, 26, 596–599.

50. Haba-Rubio, J.; Marti-Soler, H.; Tobback, N.; Andries, D.; Marques-Vidal, P.; Waeber, G.; Vollenweider, P.; Von Gunten, A.; Preisig, M.; Castelao, E.; et al. Sleep Characteristics and Cognitive Impairment in the General Population: The Hyp noLaus study. Neurology 2017, 88, 463–469.

51. Sforza, E.; Roche, F.; Thomas-Anterion, C.; Kerleroux, J.; Beauchet, O.; Celle, S.; Maudoux, D.; Pichot, V.; Laurent, B.; Barthélémy, J.C. Cognitive Function and Sleep Related Breathing Disorders in a Healthy Elderly Population: The Syna pse Study. Sleep 2010, 33, 515–521.

52. Spira, A.P.; Blackwell, T.; Stone, K.L.; Redline, S.; Cauley, J.A.; Ancoli-Israel, S.; Yaffe, K. Sleep-Disordered Breathing a nd Cognition in Older Women. J. Am. Geriatr. Soc. 2008, 56, 45–50.

53. Dealberto, M.-J.; Pajot, N.; Courbon, D.; Alpérovitch, A. Breathing Disorders During Sleep and Cognitive Performance i n an Older Community Sample: The EVA Study. J. Am. Geriatr. Soc. 1996, 44, 1287–1294.

54. Quan, S.F.; Wright, R.; Baldwin, C.M.; Kaemingk, K.L.; Goodwin, J.L.; Kuo, T.F.; Kaszniak, A.; Boland, L.L.; Caccappol o, E.; Bootzin, R.R. Obstructive Sleep Apnea-Hypopnea and Neurocognitive Functioning in the Sleep Heart Health Stu dy. Sleep Med. 2006, 7, 498–507.

55. Ding, X.; Kryscio, R.J.; Turner, J.; Jicha, G.A.; Cooper, G.; Caban-Holt, A.; Schmitt, F.A.; Abner, E.L. Self-Reported Slee p Apnea and Dementia Risk: Findings from the Prevention of Alzheimer's Disease with Vitamin E and Selenium Trial. J. Am. Geriatr. Soc. 2016, 64, 2472–2478.

56. Lutsey, P.L.; Bengtson, L.G.S.; Punjabi, N.M.; Shahar, E.; Mosley, T.H.; Gottesman, R.F.; Wruck, L.M.; MacLehose, R. F.; Alonso, A. Obstructive Sleep Apnea and 15-Year Cognitive Decline: The Atherosclerosis Risk in Communities (ARI C) Study. Sleep 2016, 39, 309–316.

57. Lutsey, P.L.; Misialek, J.R.; Mosley, T.H.; Gottesman, R.F.; Punjabi, N.M.; Shahar, E.; MacLehose, R.; Ogilvie, R.P.; Knopman, D.; Alonso, A. Sleep Characteristics and Risk of Dementia and Alzheimer's Disease: The Atherosclerosis Risk in Communities Study. Alzheimer Dement. 2018, 14, 157–166.
58. Saint Martin, M.; Sforza, E.; Roche, F.; Barthélémy, J.C.; Thomas-Anterion, C. Sleep Breathing Disorders and Cognitive Function in the Elderly: An 8-Year Follow-up Study. The Proof-Synapse Cohort. Sleep 2015, 38, 179–187.
59. Yaffe, K.; Laffan, A.M.; Harrison, S.L.; Redline, S.; Spira, A.P.; Ensrud, K.E.; Ancoli-Israel, S.; Stone, K.L. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. J. Am. Med. Assoc. 2011, 306, 613–619.
60. Bubu, O.M.; Andrade, A.G.; Umasabor-Bubu, O.Q.; Hogan, M.M.; Turner, A.D.; de Leon, M.J.; Ogedegbe, G.; Ayappa, I.; Jean-Louis, G.; Jackson, M.L.; et al. Obstructive Sleep Apnea, Cognition and Alzheimer's Disease: A Systematic Review Integrating Three Decades of Multidisciplinary Research. Sleep Med. Rev. 2020, 50, 101250.
61. Bucks, R.S.; Olaithe, M.; Eastwood, P. Neurocognitive Function in Obstructive Sleep Apnoea: A Meta-Review. Respirology 2013, 18, 61–70.
62. Olaithe, M.; Bucks, R.S.; Hillman, D.R.; Eastwood, P.R. Cognitive Deficits in Obstructive Sleep Apnea: Insights from a Meta-Review and Comparison with Deficits Observed in COPD, Insomnia, and Sleep Deprivation. Sleep Med. Rev. 2018, 38, 39–49.
63. Emamian, F.; Khazaie, H.; Tahmasian, M.; Leschziner, G.D.; Morrell, M.J.; Hsiung, G.Y.R.; Rosenzweig, I.; Sepehry, A.A. The Association Between Obstructive Sleep Apnea and Alzheimer's Disease: A Meta-Analysis Perspective. Front. Aging Neurosci. 2016, 8, 1–8.
64. Zhu, X.; Zhao, Y. Sleep-disordered breathing and the risk of cognitive decline: A meta-analysis of 19,940 participants. Sleep Breath. 2018, 22, 165–173.
65. Shi, L.; Chen, S.J.; Ma, M.Y.; Bao, Y.P.; Han, Y.; Wang, Y.M.; Shi, J.; Vitiello, M.V.; Lu, L. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep Med. Rev. 2018, 40, 4–16.
66. Kim, S.J.; Lee, J.H.; Lee, D.Y.; Jhoo, J.H.; Woo, J.I. Neurocognitive dysfunction associated with sleep quality and sleep apnea in patients with mild cognitive impairment. Am. J. Geriatr. Psychiatry 2011, 19, 374–381.
67. Terpening, Z.; Lewis, S.J.; Yee, B.; Grunstein, R.; Hickie, I.B.; Naismith, S.L. Association between sleep-disordered breathing and neuropsychological performance in older Adults with mild cognitive impairment. J. Alzheimer Dis. 2015, 46, 157–165.
68. Cross, N.; Lampit, A.; Pye, J.; Grunstein, R.R.; Marshall, N.; Naismith, S.L. Is Obstructive Sleep Apnoea Related to Neuropsychological Function in Healthy Older Adults? A Systematic Review and Meta-Analysis. Neuropsychol. Rev. 2017, 27, 389–402.