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COMMENTARY

Short Telomere Length and Endophenotypes in Sleep Medicine

Commentary on Tempaku et al. Long sleep duration, insomnia, and insomnia with short objective sleep duration are independently associated with short telomere length. *J Clin Sleep Med*. 2018;14(12):2037–2045.

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The sleep field in its beginnings was perceived as the interest of curious minds, particularly psychiatrists, physiologists and neuroscientists that focused on the association of sleep with brain-related phenomena such as dreams and their meaning or the effect of sleep loss on human minds. Soon, in the 1960s and 1970s sleep researchers with a clinical background switched their interest on the association of sleep with health and disease and established the first sleep medicine clinics primarily on the West Coast (University of California Los Angeles and Stanford University). One of the first discoveries was the association of insomnia with mental disorders such as depression and anxiety.[1] This was followed by the discovery of obstructive sleep apnea (OSA) and the first reports of its association with physical illnesses such as hypertension, diabetes, cardiovascular problems and death.[2] These early findings that were replicated in large population-based studies[3–5] established the field of sleep medicine as a "true medical field" of significant importance for public health as a whole. Consequently, the sleep field expanded from a few academic research centers to hundreds and thousands of sleep clinics and laboratories established in almost every academic or community hospital or as free standing facilities. In the last 20 years, there has been a systematic effort in exploring biological markers such as the end products of the stress system (eg, cortisol and catecholamines), of the immune system (eg, pro-inflammatory cytokines and oxidative stress) and their usefulness in understanding the pathophysiology, helping with the prognosis, and improving the diagnosis of highly-prevalent and rare sleep disorders. Even more recent are the studies focusing on the association of molecular and genetic findings with sleep and health.

In this issue of the *Journal of Clinical Sleep Medicine*, Tempaku et al. examine the association of the telomeric DNA with sleep variables and sleep disorders using self-reported and objective measures of sleep in a large population-based sample.[6] Telomere length has been shown to diminish with aging and, thus, shorter telomere length is strongly correlated with mortality risk. In this study, insomnia, insomnia with objective short sleep duration, self-reported sleep duration, and OSA were examined for their association with a short telomere length. The authors found the strongest association of a short telomere length with the insomnia phenotype with objective short sleep duration (< 6 hours).

Insomnia, the most prevalent sleep disorder, is associated with important health consequences including fatigue, depression, increased suicide risk, impaired social/vocational functioning and reduced quality of life. However, it is only within the last 10 years that insomnia has also been identified as a novel risk factor for cardiometabolic morbidity and mortality conferring a threefold to fivefold increased odds of hypertension, diabetes, cardiovascular disease, or all-cause mortality.[7] In 2009, the sleep researchers at Penn State University (PSU) demonstrated that insomnia with short sleep duration, defined as < 6 hours of total sleep time by polysomnography (PSG), is a distinct insomnia phenotype associated with a higher risk for hypertension.[8] Subsequently, it was demonstrated that this insomnia phenotype, in contrast to the phenotype of insomnia with normal sleep duration, is associated with increased risk of diabetes, cognitive impairment, incident depression, incident hypertension, chronic unremitting course, higher familial aggregation and prevalent cardiovascular/cerebrovascular disease.[9–11] These findings, initially from the PSU group are now supported by an increasing number of studies from other investigators and cohorts that show differences between the two insomnia phenotypes in cardiometabolic and neurocognitive morbidity and mortality risk.[12–14] Importantly, these findings may be explained by preceding studies investigating the pathophysiology of insomnia that reported activation of the stress and immune systems associated with the short sleep duration insomnia phenotype.[15,16] These findings are expanded and significantly strengthened by the results of the study by Tempaku et al. that demonstrated, using molecular techniques, for the first time the association of the insomnia with objective short sleep duration phenotype with short telomere length, a biomarker of accelerated aging and mortality risk as mentioned above. Of note is the finding that self-reported insomnia symptoms (ie, poor sleepers without insomnia disorder) were not associated with short telomere length, consistent with previous findings that such poor sleepers are not associated with significant cardiometabolic morbidity and mortality.

Another interesting finding from this study was the association between self-reported sleep duration and telomere length. The authors found that self-reported long sleep duration, but not self-reported short sleep duration, was significantly

associated with short telomere length. This finding may reflect the fact that self-reported long sleep duration is a marker of declining physical and neurocognitive health in older adults and a surrogate of excessive time in bed.[17,18] Alternatively, this finding may indicate that self-reported long sleepers may also suffer from accelerated aging given its previous association with cardiometabolic health, mental health and inflammation. Paradoxically, however, self-reported excessive daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS) score, was not significantly associated with short telomere length. Future studies should examine whether objective measures of daytime sleepiness and sleep propensity, such as the Multiple Sleep Latency Test,[19] Maintenance of Wakefulness Test or Psychomotor Vigilance Test, are associated with short telomere length regardless of nocturnal self-reported long sleep duration or ESS scores.

There is another important finding in this study that deserves to be discussed and that may require future studies. The authors did not find a significant association between OSA, defined solely by apnea-hypopnea index (AHI), and short telomere length in multivariable-adjusted analyses. This finding, at a first glance, is surprising given the vast literature supporting the association of OSA with cardiometabolic morbidity and mortality. A univariate analysis showed a higher frequency of individuals with mild (AHI 5–14 events/h) or moderate-to-severe (AHI ≥ 15 events/h) OSA in the short telomere group when compared to those without OSA (AHI < 5 events/h). However, the results did not remain significant after adjustment of age, sex and body mass index. It is well-established that obesity, particularly central/visceral adiposity, is the strongest risk factor for OSA and tightly associated with cardiometabolic morbidity.[20] Furthermore, age appears to modify significantly the association of OSA with morbidity and mortality. Although the prevalence of OSA, defined solely by AHI criteria, increases linearly with age, its severity tends to diminish with age.[21] This was reported in the Penn State Adult Cohort and several cross- sectional and prospective studies have shown that the associations between AHI and cardiovascular morbidity and mortality are not as strong, or even nonsignificant, in older adults compared to young and middle-aged adults. Based on these data it has been proposed that OSA in the young and middle-aged is a different phenotype than in older adults.[20] It is possible that the loss of the association after controlling for age between OSA and short telomere length in the study by Tempaku et al. is likely due to the high prevalence of OSA in the older group given that this was a study in a general population sample. Another potential factor may be central obesity, particularly in the association of moderate-to-severe OSA with short telomere length in young and middle-aged adults. Future studies should explore the association of OSA and short telomere length in young and middle aged individuals who have this sleep disorder.

In conclusion, the results of the study by Tempaku et al. offer strong molecular support to the emerging endophenotypes in insomnia and OSA that have been proposed based on clinical characteristics, underlying pathophysiology and their association with clinically meaningful outcomes.

CITATION

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REFERENCES

1. Kales A, Kales JD. *Evaluation and Treatment of Insomnia*. New York, NY: Oxford University Press; 1984.
2. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. *Annu Rev Med*. 1976;27:465–484.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328(17):1230–1235.
4. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men: I. prevalence and severity. *Am J Respir Crit Care Med*. 1998;157(1):144–148.
5. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):608–613.
6. Tempaku P, Hirotsu C, Mazzotti D, et al. Long sleep duration, insomnia, and insomnia with short objective sleep duration are independently associated with short telomere length. *J Clin Sleep Med*. 2018;14(12):2037–2045.
7. Vgontzas AN, Fernandez-Mendoza J, Liao D, Bixler EO. Insomnia with objective short sleep duration: the most biologically severe phenotype of the disorder. *Sleep Med Rev*. 2013;17(4):241–254.
8. Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep*. 2009;32(4):491–497.
9. Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diabetes Care*. 2009;32(11):1980–1985.
10. Fernandez-Mendoza J, Calhoun S, Bixler EO, et al. Insomnia with objective short sleep duration is associated with deficits in neuropsychological performance: a general population study. *Sleep*. 2010;33(4):459–465.
11. Fernandez-Mendoza J, Vgontzas AN, et al. Insomnia with objective short sleep duration and incident hypertension: the Penn State Cohort. *Hypertension*. 2012;60(4):929–935.
12. Bertisch SM, Pollock BD, Mittleman MA, et al. Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. *Sleep*. 2018;41(6).
13. Bathgate CJ, Edinger JD, Wyatt JK, Krystal AD. Objective but not subjective short sleep duration associated with increased risk for hypertension in individuals with insomnia. *Sleep*. 2016;39(5):1037–1045.
14. Parthasarathy S, Vasquez MM, Halonen M, et al. Persistent insomnia is associated with mortality risk. *Am J Med*. 2015;128(3):268–275.
15. Vgontzas AN, Bixler EO, Lin HM, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab*. 2001;86(8):3787–3794.
16. Vgontzas AN, Zoumakis M, Papanicolaou DA, et al. Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. *Metabolism*. 2002;51(7):887–892.
17. Kurina LM, McClintock MK, Chen JH, Waite LJ, Thisted RA, Lauderdale DS. Sleep duration and all-cause mortality: a critical review of measurement and associations. *Ann Epidemiol*. 2013;23(6):361–370.
18. Bliwise DL, Young TB. The parable of parabola: what the U-shaped curve can and cannot tell us about sleep. *Sleep*. 2007;30(12):1614–1615
19. Li Y, Vgontzas AN, Fernandez-Mendoza J, et al. Objective, but not subjective, sleepiness is associated with inflammation in sleep apnea. *Sleep*. 2017;40(2).
20. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Bixler EO. Obstructive sleep apnea and the metabolic syndrome: the road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. *Sleep Med Rev*. 2018;42:211–219.

21. Bixler EO, Vgontzas AN, Lin HM, et al. Association of hypertension and sleep-disordered breathing. *Arch Intern Med.* 2000;160(15):2289–2295.

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DISCLOSURE STATEMENT

The authors report no conflicts of interest.