Sleep apnea plays a more important role on sleep N3 stage than chronic tinnitus in adults

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Abstract
Sleep apnea is negatively associated with N3 sleep in children. However, the association between tinnitus and sleep N3 stage was still inconclusive. We aimed to clarify the relationship between sleep apnea, chronic tinnitus, and sleep N3 stage in adults. Clinical and overnight polysomnography data of 2847 adults were collected retrospectively. Univariate and multivariate linear regression was used to test the impacts of sleep apnea indices and chronic tinnitus on the percentage of sleep N3 stage in all adults. Univariate linear regression analysis showed that sleep apnea indices, chronic tinnitus, age, sex, hypertension, diabetes mellitus, dyslipidemia, subjective insomnia, sleep efficiency, and rapid eye movement sleep were significantly associated with sleep N3 stage. However, multivariate linear regression showed that apnea–hypopnea index, but not chronic tinnitus, has a significant negative association with the percentage of sleep N3 stage. Sleep apnea plays a more important role on sleep N3 stage than chronic tinnitus in adults.

Keywords: chronic tinnitus, polysomnography, sleep apnea, sleep N3 stage

1. Introduction
Poor sleep is a common and serious problem in the world. Although the precise function of sleep is unknown, slow-wave sleep or sleep N3 stage was known to be involved in central nervous system energy recuperation and cognitive function, and rapid eye movement (REM) sleep was involved in memory, dementia, mood regulation, and possible emotional adaptation. Also, sleep problems are related to many human diseases. For example, anxiety, depression, sleep apnea, chronic tinnitus, Parkinson disease, and Alzheimer disease were commonly presented with sleep disorders.

The pattern of sleep stages and/or sleep architecture are influenced by biological, behavioral, and clinical variables. Delayed sleep, morning or mid-sleep awakenings, and fewer sleep hours were reported in tinnitus subjects. A mild positive correlation was found between the increase of light sleep and the tinnitus handicap inventory (THI) score in tinnitus subjects. However, the sleep problems of tinnitus subjects were almost reported basing on limited case numbers, imperfect matching, and/or imperfect statistical strategy and/or adjustment.

Till now, only few studies had reported the sleep characteristics of tinnitus subjects using polysomnography (PSG). Attanasio et al. and Teixeira et al. found that tinnitus subjects had roughly higher percentages of sleep N1 and N2 stages, but lower percentage of sleep N3 stage and REM stage than nontinnitus subjects had. However, only the percentage of sleep REM stage was significantly different between tinnitus and nontinnitus subjects after adjusting for some variables. Compared to matched controls, tinnitus subjects had lower subjective sleep quality, but no significant difference in objective sleep parameters on PSG. Even so, the negative results about the relationship between tinnitus and sleep N3 stage were still not convincing due to small case numbers, imperfect matching, low statistical power, and/or imperfect statistical strategy.

Besides, the relationship between chronic tinnitus and sleep N3 stage might be confounded by sleep apnea, hypertension, Alzheimer disease, Parkinson diseases, etc. If they were not considered, the results about chronic tinnitus and sleep N3 stage would be not convincing at all. The statistical strategy of previous studies had often regarded chronic tinnitus, but not the sleep N3 stage, as the dependent variable. In such cases, the logic for the relationship between chronic tinnitus and sleep N3 stage would be misleading. Therefore, we aimed to study the actual relationship between sleep apnea, chronic tinnitus, and sleep N3 stage in adults using a larger case number and proper statistical strategy.

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2. Methods

From November 2011 to June 2017, clinical data of 2847 adult patients who had received overnight PSG at the Dalin Tzu Chi Hospital were retrospectively collected. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10604018). Informed written consent was waived by the Research Ethics Committee of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, because the study was a retrospective de-identified data analysis.

Clinical data including age, sex, several common diseases, subjective insomnia, and various sleep parameters and apnea indices from PSG were recorded. Among those data, several common diseases were graded as “no” and “yes.” Chronic tinnitus was defined as having persistent tinnitus at least for 3 months before enrollment in this study, was graded as “no” and “yes.” Subjective insomnia was graded into 5 grades as “no,” “rare,” “sometimes,” “often,” and “usually.” Age, sleep onset, sleep efficiency, apnea–hypopnea index (AHI), oxygen desaturation index (ODI), mean O₂%, minimal O₂%, percentages of sleep N3 and REM stages, and percentages of oxygen saturation <90% and <85% were continuous data.

2.1. Statistical analysis

Percentage of sleep N3 stage was regarded as a dependent variable in this study. Univariate and multivariate linear regression was used to test the effects of sleep apnea indices and chronic tinnitus on the percentage of sleep N3 stage with adjustment of other variables in all adults. All analyses were performed using STATA 10.0 software (Stata Corp, College Station, TX). A P value of <.05 was considered to be significant.

3. Results

Table 1 shows the basic characteristics of all adults. The mean age for sleep N3 stage by univariate linear regression analysis. Tinnitus, AHI, ODI, mean O₂%, minimal O₂%, O₂% <90, O₂% <85, age, sex, hypertension, diabetes mellitus, dyslipidemia, subjective insomnia, sleep efficiency, and REM sleep were significantly associated with sleep N3 stage for all adults.

Table 3 shows the results of sleep apnea indices, chronic tinnitus, and subjective insomnia on the percentage for sleep N3 stage by multivariate linear regression analysis. AHI, age, sex, subjective insomnia, and sleep efficiency, but not chronic tinnitus, have a significant negative association with the percentage of sleep N3 stage for all adults. Furthermore, subgroup analysis by chronic tinnitus showed that AHI, age, sex, and subjective insomnia have a significant negative association with the percentage of sleep N3 stage in adults without tinnitus, whereas AHI, O₂% <90, age, and sex have a significant negative association with the percentage of sleep N3 stage in adults without tinnitus.

4. Discussion

This large-scale clinical study has revised our knowledge about the relationship between sleep apnea, chronic tinnitus, and sleep N3 stage in adults. In previous studies, no significant association between tinnitus and sleep N3 stage was claimed under imperfect study design, without adjustment of other sleep indices, small case number, and statistical power. Instead, we found that AHI, but not chronic tinnitus, was significantly associated with the percentage of sleep N3 stage under proper statistical logic and well adjustment of other variables in this study.

Diverse relationship between sleep quality and chronic tinnitus existed mainly due to different study methodology. In the studies without PSG, most results were concluded based on various sleep questionnaires. The relationship between chronic tinnitus and sleep N3 stage could not be analyzed objectively. As for studies with PSG, Hebert et al[12] reported that, compared to matched controls, tinnitus subjects had lower subjective sleep quality but no significant difference in objective sleep quality. However, in our study, we found that AHI, but not chronic tinnitus, was significantly associated with the percentage of sleep N3 stage in all adults. Furthermore, subgroup analysis by chronic tinnitus showed that AHI, age, sex, and subjective insomnia have a significant negative association with the percentage of sleep N3 stage in adults without tinnitus, whereas AHI, O₂% <90, age, and sex have a significant negative association with the percentage of sleep N3 stage in adults without tinnitus.

Table 1 Basic characteristics for 2847 adults.

| Variable                  | All adults (18–91 years old) |
|---------------------------|------------------------------|
| Mean age, yr (SD)         | 50.6 (13.3)                  |
| Females/males            | 989/1858                     |
| HTN                       | 913                          |
| DM                        | 310                          |
| Dyslipidemia              | 454                          |
| CKD                       | 87                           |
| Parkinson disease         | 25                           |
| Dementia                  | 8                            |
| Chronic tinnitus          | 962                          |
| Subjective insomnia       | 614                          |
| Sleep onset, min (SD)     | 24.1 (31.8)                  |
| Sleep efficiency, % (SD)  | 75.6 (15.9)                  |
| REM, % (SD)               | 20.1 (1.7)                   |
| Sleep N3 stage, % (SD)    | 1.7 (4.0)                    |
| AHI, /hr (SD)             | 28.0 (23.9)                  |
| ODI, /hr (SD)             | 20.2 (23.7)                  |
| Mean O₂%, % (SD)          | 94.8 (2.8)                   |
| Minimal O₂%, % (SD)       | 82.9 (9.3)                   |
| O₂% <90, % (SD)           | 6.0 (13.8)                   |
| O₂% <85, % (SD)           | 2.6 (9.1)                    |

AHI = apnea–hypopnea index, CKD = chronic kidney disease, DM = diabetes mellitus, HTN = hypertension, ODI = oxygen desaturation index, REM = rapid eye movement, SD = standard deviation.

Table 2 Results of each variables on the percentage for sleep N3 stage by univariate linear regression analysis.

| Variables                  | Coefficient ± standard error (P value) |
|----------------------------|----------------------------------------|
| Age                       | -0.079 ± 0.005 (<.001)                 |
| Sex                       | -0.028 ± 0.158 (<.001)                 |
| HTN                       | -1.062 ± 0.161 (<.001)                 |
| DM                        | -0.690 ± 0.243 (0.05)                  |
| Dyslipidemia              | -0.610 ± 0.207 (0.003)                 |
| CKD                       | -0.834 ± 0.436 (0.056)                 |
| Parkinson disease         | -0.955 ± 0.812 (0.223)                 |
| Dementia                  | -1.698 ± 1.432 (0.238)                 |
| Chronic tinnitus          | -0.503 ± 0.160 (0.002)                 |
| Subjective insomnia       | -0.275 ± 0.059 (<.001)                 |
| Sleep onset               | 0.033 ± 0.002 (0.02)                   |
| Sleep efficiency          | 0.011 ± 0.005 (0.021)                  |
| REM                       | 0.033 ± 0.010 (<.001)                  |
| AHI                       | -0.029 ± 0.003 (<.001)                 |
| ODI                       | -0.025 ± 0.003 (<.001)                 |
| Mean O₂%                  | 0.207 ± 0.027 (<.001)                  |
| Minimal O₂%               | 0.032 ± 0.008 (<.001)                  |
| O₂% <90                   | 0.028 ± 0.005 (<.001)                  |
| O₂% <85                   | 0.033 ± 0.008 (<.001)                  |

AHI = apnea–hypopnea index, CKD = chronic kidney disease, DM = diabetes mellitus, HTN = hypertension, ODI = oxygen desaturation index, REM = rapid eye movement.
parameters on PSG. Teixeira et al.\textsuperscript{(10)} also claimed that only the percentage of REM sleep, but not sleep N3 stage, could show a significantly negative association with tinnitus. However, these negative results about chronic tinnitus and sleep N3 stage were not convincing enough due to the imperfect matching process of limited items, small case numbers, and lower statistical power.

Most importantly, most studies had set tinnitus as the dependent variable during analysis. By doing so, we could only see roughly which items in the sleep questionnaires or PSG were different in the tinnitus and non-tinnitus groups. Those conclusions were directed to say that some kinds of sleep disturbances might contribute to tinnitus roughly. However, the logic might be questionable during statistical analysis because our aim was not to see whether age, sex, common diseases, or any sleep characteristics had any association with tinnitus. On the contrary, due to sleep characteristics being affected by many clinical variables and sleep indexes,\textsuperscript{(1,3,4,9,14-16)} we should treat sleep N3 stage as the dependent variable to test whether tinnitus had any significant association with sleep N3 stage under well adjustment for age, sex, sleep indexes, and other important confounding variables. By doing so, we found that sleep apnea, but not chronic tinnitus, had a specific association with sleep N3 stage.

One study reported that a longer sleep latency and lower percentage of stage N3 sleep were found in children with OSA compared with healthy controls.\textsuperscript{(11)} However, Wächter et al.\textsuperscript{(17)} reported that the effects of OSA severity and potential confounders on sleep architecture are small, but sleep-stage transitions are influenced by OSA severity, age, and gender.\textsuperscript{(17)} Further, higher frequencies of alternating (symmetric) patterns (e.g., N2 \rightarrow N1 \rightarrow N2, N2 \rightarrow wake \rightarrow N2) in sleepy patients.\textsuperscript{(17)}

In this study, we found that the N3 sleep was most affected by sex and subjective insomnia in order in the view of categorical variables, and by age, AHI, and sleep efficiency in order in the view of continuous variables. As for tinnitus, a higher prevalence (33.8\%) of chronic tinnitus was presented in this study due to the higher mean age (50.6 years old). The effect size was estimated initially at 1\% of sleep N3 stage between tinnitus and non-tinnitus group. By doing 2 group Student \(t\) test, we found that only 0.5\% was found with significance (\(P = .0017\)) between 2 groups finally. However, tinnitus lost its significance on N3 sleep during multivariate linear regression analysis, in which many more important variables were considered simultaneously.

The strength of this study was that our conclusions were based on a larger case number, PSG data, and a proper statistical strategy with well adjustment of many confounding factors. Even so, our study had some limitations. First, only adult patients who had sleep problems and received overnight PSG were collected. Second, multicollinearity was present more or less in the multivariate analysis, such as between AHI and common diseases, oxygen saturation indexes, sleep efficiency, or chronic tinnitus. It will certainly make the issue of interpreting \(p\) values unstable.

### 5. Conclusion

As we know, N3 sleep stage is an important indicator of sleep quality. This large-scale PSG study renewed our knowledge about the relationship between sleep apnea, chronic tinnitus, and sleep N3. We found that AHI, but not chronic tinnitus, was related to the percentage of sleep N3 stage in adults.

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### Author contributions

H.-H.T.: wrote the initial manuscript; S.-W.H., S.-R.H.: data acquisition; J.-H.H.: conception and design, analysis and interpretation of data, final approval of the version to be published.

### References

\[1\] Kyung LE, Douglass AB. Sleep in psychiatric disorders: where are we now? Can J Psychiatry. 2010;55:403–12.

### Table 3

| Variables                | All dBa | Without tinnitus dBa | With tinnitus dBa |
|-------------------------|---------|----------------------|-------------------|
| AHI                     | -0.040 ± 0.009 (0.001) | -0.045 ± 0.012 (0.001) | -0.034 ± 0.015 (0.020) |
| ODI                     | 0.017 ± 0.011 (0.124) | 0.021 ± 0.014 (0.134) | 0.013 ± 0.017 (0.467) |
| Mean O2%                | 0.028 ± 0.062 (0.647) | -0.034 ± 0.079 (0.661) | 0.148 ± 0.099 (1.34) |
| Minimal O2%             | -0.009 ± 0.014 (0.527) | -0.012 ± 0.017 (0.493) | -0.007 ± 0.023 (1.762) |
| O2% <90                 | 0.013 ± 0.016 (0.410) | -0.013 ± 0.021 (0.546) | 0.056 ± 0.024 (0.019) |
| O2% <85                 | -0.027 ± 0.020 (0.181) | -0.013 ± 0.026 (0.624) | -0.044 ± 0.033 (1.178) |
| Chronic tinnitus        | -0.143 ± 0.163 (0.381) | -0.083 ± 0.008 (0.001) | -0.074 ± 0.011 (0.001) |
| Age                     | -1.047 ± 0.167 (0.001) | -1.237 ± 0.218 (0.001) | -1.743 ± 0.254 (0.004) |
| Sex                     | 0.088 ± 0.233 (0.707) | 0.077 ± 0.231 (0.978) | 0.004 ± 0.271 (0.467) |
| HTN                     | 0.135 ± 0.328 (0.822) | 0.298 ± 0.382 (0.436) | -0.086 ± 0.233 (0.832) |
| Dystolicemia             | -0.025 ± 0.283 (0.931) | -0.066 ± 0.310 (0.832) | -0.025 ± 0.559 (0.965) |
| CKD                     | 0.006 ± 0.643 (0.900) | 0.150 ± 0.677 (0.965) | 0.004 ± 0.643 (0.993) |
| Parkinson disease        | 0.498 ± 0.818 (0.559) | 0.135 ± 0.328 (0.822) | 0.150 ± 0.677 (0.965) |
| Dementia                 | -0.356 ± 1.404 (0.800) | -0.849 ± 1.838 (0.644) | 0.552 ± 2.151 (0.797) |
| Subjective insomnia      | -0.324 ± 0.062 (0.001) | -0.414 ± 0.080 (0.001) | -0.156 ± 0.094 (0.098) |
| Sleep onset              | 0.001 ± 0.003 (0.632) | 0.003 ± 0.004 (0.260) | -0.004 ± 0.005 (0.373) |
| Sleep efficiency         | -0.015 ± 0.006 (0.016) | -0.015 ± 0.008 (0.061) | -0.016 ± 0.010 (0.128) |
| REM                      | 0.015 ± 0.010 (0.143) | 0.008 ± 0.013 (0.563) | 0.029 ± 0.016 (0.066) |

The data in all cells were shown as coefficient ± standard error (\(P\) value).

\(AHI = \) apnea–hypopnea index, \(CKD = \) chronic kidney disease, \(DM = \) diabetes mellitus, \(HTN = \) hypertension, \(ODI = \) oxygen desaturation index, \(REM= \) rapid eye movement.
[2] Pase MP, Himali JJ, Grima NA, et al. Sleep architecture and the risk of incident dementia in the community. Neurology. 2017;89:1244–50.

[3] Durdik P, Sujanska A, Suroviakova S, et al. Sleep architecture in children with common phenotype of obstructive sleep apnea. J Clin Sleep Med. 2018;14:9–14.

[4] Thompson JA, Tekriwal A, Felsen G, et al. Sleep patterns in Parkinson’s disease: direct recordings from the subthalamic nucleus. J Neurol Neurosurg Psychiatry. 2018;89:95–104.

[5] Liu S, Pan J, Tang K, et al. Sleep spindles, K-complexes, limb movements and sleep stage proportions may be biomarkers for amnestic mild cognitive impairment and Alzheimer’s disease. Sleep Breath. 2020;24:637–51.

[6] Alster J, Shemesh Z, Ornan M, et al. Sleep disturbance associated with chronic tinnitus. Biol Psychiatry. 1993;34:84–90.

[7] Izuhara K, Wada K, Nakamura K, et al. Association between tinnitus and sleep disorders in the general Japanese population. Ann Otol Rhinol Laryngol. 2013;122:701–6.

[8] Bhatt JM, Bhattacharyya N, Lin HW. Relationships between tinnitus and the prevalence of anxiety and depression. Laryngoscope. 2017;127:466–9.

[9] Yetton BD, McDevitt EA, Cellini N, et al. Quantifying sleep architecture dynamics and individual differences using big data and Bayesian networks. PLoS One. 2018;13:e0194604.

[10] Attanasio G, Russo FY, Roukos R, et al. Sleep architecture variation in chronic tinnitus patients. Ear Hear. 2013;34:503–7.

[11] Teixeira LS, Oliveira CAC, Granjeiro RC, et al. Polysomnographic findings in patients with chronic tinnitus. Ann Otol Rhinol Laryngol. 2018;127:953–61.

[12] Hébert S, Fullum S, Carrier J. Polysomnographic and quantitative electroencephalographic correlates of subjective sleep complaints in chronic tinnitus. J Sleep Res. 2011;20:38–44.

[13] Koo M, Hwang JH. Risk of tinnitus in patients with sleep apnea: a nationwide, population-based, case-control study. Laryngoscope. 2017;127:2171–5.

[14] Javaheri S, Zhao YY, Punjabi NM, et al. Slow-wave sleep is associated with incident hypertension: the sleep heart health study. Sleep. 2018;41:zsy179.

[15] Fung MM, Peters K, Redline S, et al; Osteoporotic Fractures in Men Research Group. Decreased slow wave sleep increases risk of developing hypertension in elderly men. Hypertension. 2011;58:596–603.

[16] Haba-Rubio J, Marti-Soler H, Tobback N, et al. Sleep characteristics and cognitive impairment in the general population: the HypnoLaus study. Neurology. 2017;88:463–9.

[17] Wächter M, Kantelhardt JW, Bonsignore MR, et al. Unique sleep-stage transitions determined by obstructive sleep apnea severity, age and gender. J Sleep Res. 2020;29:e12895.