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Review Article

The association between obstructive sleep apnea and shortened telomere length: a systematic review and meta-analysis

Pan Huang [a, b, 1], Jianghua Zhou [c, 1], Shanping Chen [c], Chuan Zou [c], Xiufang Zhao [a, b, **], Jiping Li [d, *]

[a] Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China
[b] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, People's Republic of China
[c] Geriatrics Department, Chengdu Fifth People's Hospital, Chengdu, Sichuan, People's Republic of China
[d] West China Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China

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ABSTRACT

Objective: We aimed to provide a more precise estimate of the relationship between telomere length and obstructive sleep apnea (OSA) by systematically reviewing evidence.
Method: We conducted a systematic electronic search in the databases of the PUBMED, PsycINFO, OVID (Medline), EMBASE and other resources (such as Google Scholar). The methodological quality of the articles was assessed according to the Newcastle Ottawa Scale. Heterogeneity was assessed using the chi-square test for Cochrane's Q statistic and I-squared. When heterogeneity was found to be reasonably high between studies, the random-effects model with the mean difference (95% confidence interval [CI]) was conducted using RevMan 5 software by using the inverse variance method ($P < 0.05$; chi-square test). By contrast, the fixed-effects model was carried out.
Results: Eight eligible studies involving 2639 participants were included in our meta-analysis. Shortened telomere length was significantly associated with OSA with mean difference of −0.03 (95% CI: −0.06, −0.00; $P = 0.003$ with I-square of 85%) . The results of subgroup analysis preformed by age and sample number suggested that shorter telomere length was significantly associated with OSA, with mean difference of −0.07 (95% CI: −0.07, −0.01; $P = 0.005$) for adult group and −0.04 (95% CI: −0.02, −0.06; $P = 0.005$) for large-sample studies.
Conclusion: Compared to healthy people, individuals with OSA have shorter telomere lengths which implicates early intervention and timely treatment for preventing future adverse outcomes.

1. Introduction

Human telomeres consist of a series of TTAGGG tandem repeats at the end of chromosomes, which maintains chromosomal stability and integrity and allows effective replication of deoxyribonucleic acid (DNA) [1,2]. Telomerase is responsible for maintaining telomere length by synthesizing TTAGGG repeats at the end, whereas it is repressed in most mammalian somatic cells [3]. Consequently, 25–200 base pairs will be lost from the terminal region of chromosomes during each cell division [4]. Therefore, telomere lengths have been proposed to act as a common biomarker of aging. In animal models, shortened or lengthened telomeres mean decreased or increased lifespan of mice, respectively [5,6]. Similarly, a meta-analyses conducted in a human study have found that the shortened telomeres increase mortality risk [7]. In addition, telomerase deficiency is closely related to many premature diseases such as dyskeratosis congenita and aplastic anemia [8]. Shortened telomeres may lead to the cessation of cell division, thus promoting cellular senescence and apoptosis [4]. Meanwhile, shortened telomeres are more sensitive to systematic inflammation and oxidative stress, which can further promote aging [9–11].

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repeated events of respiratory pauses or partial upper airway obstruction [12]. It is often associated with

* Corresponding author. No. 37 Guoxuexiang, Wuhou District, Chengdu, 610041, China.
** Corresponding author. Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China
E-mail address: jp-li@163.com (J. Li).
[1] co-first authors.

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reduced blood oxygen saturation, sleep disruption, snoring, and daytime sleepiness [12]. The pathogenesis of OSA is related to oxidative stress and systemic inflammation [13], which may cause further intercellular communication and mitochondrial dysfunction in individuals with OSA [14–16], thereby leading to cellular damage and aging acceleration [3]. Some studies have found that OSA was significantly related to shortened telomere length [17], whereas Kim et al. and Polonis et al. demonstrated telomere length may be prolonged in moderate-to-severe OSA [18,19].

Given the observed contradictory relationship between shortened telomere length and OSA in some studies, further studies are needed to warrant this. Therefore, our present study aims to give more precise estimate of the relationship between telomere length and OSA by using meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Materials and methods

2.1. Search strategy and selection criteria

Our systematic review was registered at http://www.crd.york.ac.uk/PROSPERO/, with the registration number CRD42017071920.

We conducted this systematic review in adherence to the guidelines of the PRISMA [20]. The databases of the PUBMED, PsycINFO, OVID (Medline), EMBASE, and other resources (such as Google Scholar) were used for the systematic electronic search from inception to August 2017. We used MeSH terms, truncation symbols, and keywords in the search strategy. Because of the varying search surfaces between the databases, we used different combinations of keywords as well as subject terms such as [("Sleep Apnea, Obstructive") or ("Sleep") or ("Sleep Apnea Syndromes")] and [("telomere")]. Our search strategy can be found in the online supplementary material. Furthermore, we actively searched the references of original studies and reviews on this topic for studies that were thought to be suitable for inclusion criteria.

2.2. Eligibility and exclusion criteria

Studies that met the following inclusion criteria were included into the meta-analysis: (1) studies investigating the association between telomere length and OSA; (2) the types of studies that were case–control and cohort studies; and (3) Studies that had a sample size of 50 were excluded if they (1) had insufficient data; (2) were review articles or conference abstracts; and (3) in a language other than English.

2.3. Study selection

All articles identified by our search strategy were examined (title and abstract) independently by two review authors (Huang Pan and Zhou JH). We obtained and identified a full text of the article if abstract was unavailable. The potentially eligible articles were reassessed by retrieving and evaluating full text. In case of disagreement on the inclusion or the exclusion of studies, the differences between reviewers were resolved through discussion and re-examination of the article.

2.4. Data extraction and management

We designed a form to extract data for each included article. Data were extracted by two independent reviewers (Huang Pan and Zhou JH). The following data were collected from the included studies: country, study design, gender, sample number, year of publication, measure methods of telomere length and OSA, tissue for telomere length measurement, and study quality. In this study, if articles were suitable for the meta-analysis without crucial data, the authors of original studies were also contacted directly. Authors were then asked to provide means and standard deviation (SD) for telomere length.

2.5. Assessment of risk of bias

The methodological quality of included articles was performed by two independent reviewers and was assessed according to the Newcastle Ottawa Scale (NOS) [21] (1): the representativeness of the exposed cohort (2); Comparability of groups (3); blinding of investigators who measured outcomes (4); the time and completeness of follow-up (5); contamination bias; and (6) other potential sources of bias. Articles were scored as follows: >7 as high quality (NOS).

2.6. Statistical analysis

We performed a meta-analysis to assess a summary outcome. Heterogeneity was assessed by using the chi-square test for Cochrane's Q statistic and I-squared, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. When heterogeneity was found to be reasonably high between studies, the random-effects model with the mean difference (95% confidence interval [CI]) was conducted using RevMan 5 software (The Cochrane Collaboration) by the inverse variance method ($P < 0.05$; chi-square test). By contrast, the fixed-effects model was carried out. Subgroup analyses were planned by country, gender, study design, sample size, study quality, and the measure method of OSA, if there was more than one study in the subgroup.

3. Results

3.1. Search results

The search yielded 655 relevant articles. A flowchart of screening literature was outlined in Fig. 1. After removing duplicated articles, 523 studies were potentially eligible, but the number decreased to 30 after screening titles and abstracts. These studies were all screened in according with the predefined inclusion and exclusion criteria for inclusion into the study. Finally, eight studies were eligible for analysis [18,19,22–27].

3.2. Included studies

Table 1 showed details of the characteristics of included papers with 2639 participants. Seven case–control studies and one cohort study were included in our meta-analysis. OSA was diagnosed according to the Berlin questionnaire and polysomnography. Telomere length was determined by using the quantitative polymerase chain reaction (q-PCR) with the tissue from leukocytes.

3.3. Quality assessment

The methodological quality evaluation is summarized in Table 1. The scores ranged from six to nine points. Six studies were more than six points, and one study achieved a maximum score of nine points [24].

3.4. Results of meta-analysis

In the present study, we pooled all eligible articles into the meta-analysis. Shortened telomere length was significantly