A meta-analysis: Does vitamin D play a promising role in sleep disorders?

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Abstract

Background: Sleep disorders, one of the most common problems in the general population, have been related to a series of harmful health consequences. Vitamin D appears to be associated with sleep disorders. However, the difference in vitamin D levels between sleep disorder subjects and people without a sleep disorder is unclear. Simultaneously, the influence of vitamin D replenishment on sleep disorders remains controversial.

Methods: PubMed, MEDLINE, Web of Science, and Cochrane Library were searched for literatures published until October 2019. Using a random effects model, a meta-analysis was conducted to calculate the standard mean difference to evaluate the difference in vitamin D concentrations between sleep disorder subjects and normal people and the efficacy of vitamin D supplementation on sleep disorders.

Results: Our study found that the serum vitamin D levels in the sleep disorder subjects were lower than that in the normal people (SMD = −0.75 ng/ml, 95% CI = −0.93, −0.57 ng/ml). Moreover, the Pittsburgh Sleep Quality Index (PSQI) in the subjects with vitamin D supplementation was lower than that in the controls (SMD = −0.45, 95% CI = −0.76, −0.13).

Conclusions: Vitamin D could play a promising role in sleep disorders. More data are required to confirm the efficacy of vitamin D supplementation for improving sleep disorders.

KEYWORDS

meta-analysis, PSQI, sleep disorders, sleep quality, vitamin D

1 | INTRODUCTION

Sleep is a complex physiological state that involves a period of intense metabolic activity (de Oliveira, Hirotsu, Tufik, & Andersen, 2017). Shortening or interrupting sleep may cause some nonspecific symptoms, including general weakness, physical discomfort, cognitive, and emotional impairment (McCarty, Chesson, Jain, & Marino, 2014). Most sleep disorders, such as sleep apnea, periodic

Abbreviations: CI, chemiluminescence immunoassay; CIs, confidence intervals; EI, electrochemiluminescence immunoassay; NOS, Newcastle–Ottawa Scale; OSAS, obstructive sleep apnea syndrome; PSQI, Pittsburgh Sleep Quality Index; RCTs, randomized control trials; SMD, standard mean difference.

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leg dyskinesia, and restless legs syndrome, cause sleep deprivation (Tufik, Andersen, Bittencourt, & Mello, 2009). Sleep disorders have been related to a series of adverse health consequences, involving an elevated risk of hypertension, diabetes, and other chronic diseases (Institute of Medicine Committee on Sleep & Research, 2006; Riemann, 2009). Studies have shown that the prevalence of sleep disorders tends to rise with age. Almost 41% of elderly people have sleep disorders with insomnia (Tsou, 2013). Young people today also experience a number of sleep disorders, which may impact academic performance, health, and mood (Gaultney, 2010). Similarly, sleep problems are currently common in children, with approximately 25% have experienced sleep problems (McDonagh, Holmes, & Hsu, 2019).

As a fat-soluble vitamin, vitamin D not only plays a role in regulating bone homeostasis but also is involved in the presentation and severity of sleep disorders (Archontogeorgis, Nena, Papanas, & Steiropoulos, 2018; Kulie, Groff, Redmer, Hounshell, & Schrager, 2010). Vitamin D target neurons are supposed to be participated in sleep regulation, and its receptors have been found in the hypothalamus and other brain regions, which are related to the regulation of sleep–wake cycle (Gominak & Stumpf, 2012; Saper, Scammell, & Lu, 2005). Previous studies have shown that abnormally low concentrations of vitamin D are general in patients seeking sleep medication and may be the causes or contributors to sleep disorder (McCarty et al., 2014). Furthermore, Majid’s study has shown that the vitamin D supplementation improves sleep quality and raises sleep duration in subjects with sleep disorders (Majid, Ahmad, Bizhan, Hosein, & Mohammad, 2018). However, the results of other studies are not consistent with it (Gunduz et al., 2016; Shiue, 2013). The dispute remains existed between vitamin D and sleep disorders. Therefore, a meta-analysis was performed evaluating the difference in vitamin D between sleep disorder people and normal people. Additionally, the meta-analysis also evaluated all related randomized control trials (RCTs) with a focus on the influence of vitamin D supplementation on sleep disorders.

### TABLE 1  Search strategy

| Criteria | Descriptions and search terms used for each criteria |
|----------|---------------------------------------------------|
| Patient/population | sleep duration OR sleep quality OR sleep disorders OR short sleep OR hypersomnia OR sleep OR sleep time OR short-term sleep restriction OR daytime sleepiness OR long sleepers OR short sleepers OR sleep initiation and maintenance disorders OR habitual short sleepers OR sleep deprivation OR nap OR napping OR sleep disturbance OR siesta OR sleep time OR drowse OR insomnia OR drowsiness OR 24-hr sleep duration OR night time sleep duration OR short sleep duration OR long sleep duration OR dysomnia OR hypersomnia OR excessive sleepiness OR parasomnias |
| Exposure/Intervention | vitamin D analogues OR doxercalciferol OR alfalcidol OR vitamin D3 OR vitamin D2 OR activated vitamin D OR 1alpha-vitamin D OR calcitriol OR calcidiol OR 1,25-dihydroxycholecalfierol OR 25-hydroxyvitamin D2 OR calcifediol OR 1,25OH2D OR dihydrotachysterol OR ergocalciferol OR 25OHD OR Vit D OR 25-hydroxy vitamin D2 OR VitD OR vitamin D 3 OR 25-hydroxycholecalciferol OR 25OHD OR 25-hydroxy-vitamin D OR ergocalciferol OR 1,25-dihydroxyvitamin D3 OR 25-OH vitamin D OR cholecalciferol OR 25-hydroxyvitamin D OR vitamin D |
response to supplementation with vitamin D must be RCTs, and the results must include specific values of the PSQI. Two researchers independently evaluated all studies, resolved divergence by discussion, and extracted final eligible literatures (Figure 1).

2.3 | Data abstraction

All included literatures were assessed, and the following data were extracted: first author, nationality, publication year, numbers, mean age, and gender of case/supplementation groups and controls. We also extracted data on the assay method of vitamin D, sleep disorder types, and vitamin D levels in the subjects with sleep disorders and controls. Moreover, the intervention time and dose and the PSQI score in the vitamin D supplementation groups and controls were also extracted.

2.4 | Risk of bias within individual studies

Cochrane Collaboration (RevMan version 5.3) software was used to estimate the risk of bias for RCTs. Simultaneously, the Newcastle–Ottawa scale (NOS) was used to estimate the risk of bias (including selection, comparability, and exposure) for the case-control study and cross-sectional study.

2.5 | Statistical analysis

Statistical analysis was performed using the statistical software RevMan version 5.3 and Stata version 12.0. The data from all the individual studies were used to calculate the standard mean difference (SMD) and 95% confidence intervals (CIs) using the random
| Author                  | Region     | Year | Assay Method | Score | Sleep Disorder Types | n  | Age | Gender (M/F) | Vitamin D (ng/ml) | Gender (M/F) |
|-------------------------|------------|------|--------------|-------|----------------------|----|-----|--------------|------------------|---------------|
| Kerley et al.           | Ireland    | 2015 | CI           | 8     | OSAS (mild)          | 22 | 54.00±19.00 | 17/5         | 16.03±8.81       | 16/15          |
| Kerley et al.           | Ireland    | 2015 | CI           | 8     | OSAS (moderate)      | 18 | 57.00±17.00 | 12/6         | 14.94±12.02      | 16/15          |
| Kerley et al.           | Ireland    | 2015 | CI           | 8     | OSAS (severe)        | 35 | 55.50±17.00 | 28/7         | 14.82±10.42      | 16/15          |
| Hatice et al.           | Turkey     | 2012 | EI           | 8     | restless leg         | 8  | 41.50±6.27  | 8/0          | 11.40±6.23       | 10/11          |
| Hatice et al.           | Turkey     | 2012 | EI           | 8     | restless leg         | 28 | 39.64±7.65  | 0/24         | 3.71±4.63        | 0/27           |
| Cikrikoğlu et al.       | Turkey     | 2016 | EI           | 7     | restless leg         | 78 | 46.45±11.26 | 0/78         | 14.18±17.51      | 18/21          |
| Huzmeli et al.          | Turkey     | 2018 | -            | 9     | restless leg         | 33 | 59.60±12.90 | 9/24         | 10.76±4.56       | 26/16          |
| Neves et al.            | Brazil     | 2017 | CI           | 8     | restless leg         | 29 | 47.00±18.00 | 11/18        | 28.80±10.20      | 43/29          |
| Celik et al.            | Turkey     | 2015 | EI           | 8     | restless leg         | 31 | 43.61±10.51 | 0/31         | 15.10±14.17      | 24/28          |
| Wali et al.             | Saudi Arabia | 2018 | -            | 8     | restless leg         | 78 | 43.79±6.04  | 38/40        | 12.63±7.03       | 59/64          |
| Claudio et al.          | Italy      | 2015 | -            | 7     | OSAS (severe)        | 90 | 61.10±12.68 | 60/24        | 19.34±9.54       | 22/10          |
| Mete et al.             | Turkey     | 2013 | EI           | 7     | OSAS (mild)          | 50 | 46.58±9.37  | 25/25        | 20.65±9.65       | 16/16          |
| Mete et al.             | Turkey     | 2013 | EI           | 7     | OSAS (moderate)      | 50 | 47.64±7.22  | 25/25        | 18.40±9.02       | 16/16          |
| Mete et al.             | Turkey     | 2013 | EI           | 7     | OSAS (severe)        | 50 | 47.40±9.48  | 25/25        | 14.66±8.19       | 16/16          |
| Mete et al.             | Turkey     | 2013 | EI           | 7     | OSAS (moderate)      | 50 | 47.64±7.22  | 25/25        | 18.40±9.02       | 16/16          |
| Zicari et al.           | Italy      | 2016 | CI           | 7     | other                | 45 | 9.00±1.75   | 29/16        | 26.21±10.70      | 40/30          |
| Zicari et al.           | Italy      | 2016 | CI           | 7     | OSAS (unclassified)  | 22 | 7.62±3.09   | 15/7         | 20.80±7.57       | 40/30          |
| Terzi et al.            | Turkey     | 2015 | other        | 8     | other                | 30 | 52.37±8.58  | 30/0         | 14.06±4.23       | 20/0           |
| Toujani et al.          | Tunisia    | 2017 | other        | 9     | OSAS (severe)        | 92 | 52.30±12.70 | 48/44        | 16.80±3.10       | 17/13          |
| Pazarli et al.          | Turkey     | 2018 | CI           | 8     | OSAS (mild)          | 28 | 46.50±11.50 | 17/11        | 19.95±15.87      | 10/11          |
| Pazarli et al.          | Turkey     | 2018 | CI           | 8     | OSAS (moderate)      | 13 | 51.00±13.80 | 5/8          | 19.95±15.87      | 10/11          |
| Pazarli et al.          | Turkey     | 2018 | CI           | 8     | OSAS (severe)        | 27 | 50.40±11.90 | 24/3         | 13.14±10.58      | 10/11          |
| Gong et al.             | China      | 2018 | EI           | 8     | other                | 262 | 12.22±1.75 | 128/134      | 24.30±5.80       | 205/148        |
| Uygur et al.            | Turkey     | 2016 | CI           | 6     | OSAS (mild)          | 35 | 26.90±8.40  | -            | 31.00±7.90       | -              |
| Uygur et al.            | Turkey     | 2016 | CI           | 6     | OSAS (moderate)      | 35 | 22.30±6.00  | -            | 31.00±7.90       | -              |
| Author          | Region    | Year  | Assay Method | Score | Sleep Disorder Types       | n       | Age Case / Control | Vitamin D (ng/ml) Case / Control | Gender (M/F) Case / Control |
|-----------------|-----------|-------|--------------|-------|-----------------------------|---------|--------------------|----------------------------------|-------------------------------|
| Uygur et al (3) | Turkey    | 2016  | CI           | 6     | OSAS (severe)               | 33/58   | 46.70 ± 9.20 / 44.60 ± 9.70 | 17.60 ± 4.60 / 31.00 ± 7.90   | - / -                          |
| Uygur et al (4) | Turkey    | 2016  | CI           | 6     | OSAS (unclassified)         | 103/58  | 42.00 ± 9.00 / 45.00 ± 14.00 | 22.05 ± 7.19 / 29.54 ± 9.09    | 54/49 / 23/35                   |
| Erden et al (1) | Turkey    | 2014  | CI           | 9     | OSAS (moderate)             | 23/43   | 40.10 ± 10.00 / 45.00 ± 14.00 | 23.53 ± 7.73 / 29.54 ± 9.09    | 53/9 / 21/22                    |
| Erden et al (2) | Turkey    | 2014  | CI           | 9     | OSAS (severe)               | 62/43   | 48.56 ± 9.74 / 50.00 ± 14.00 | 23.13 ± 7.57 / 29.54 ± 9.09    | 70/15 / 21/22                   |
| Zhao et al.     | China     | 2017  | EI           | 8     | other                       | 181/100 | 43.16 ± 10.78 / 44.31 ± 10.33 | 23.01 ± 9.18 / 26.41 ± 9.05    | 52/129 / 32/68                  |
| Gunduz et al.   | Turkey    | 2016  | other        | 8     | other                       | 58/34   | 29.70 ± 4.80 / 30.50 ± 4.20 | 22.10 ± 16.40 / 24.30 ± 16.19  | 0/58 / 0/34                     |
| Han et al.      | China     | 2017  | -            | 7     | other                       | 88/53   | 59.70 ± 15.30 / 62.80 ± 12.50 | 15.64 ± 11.64 / 31.24 ± 14.96  | 52/36 / 34/19                   |
| Bozkurt et al (1)| Turkey    | 2012  | other        | 8     | OSAS (severe)               | 50/47   | 49.66 ± 10.38 / 42.79 ± 9.55 | 16.31 ± 6.98 / 19.93 ± 7.81    | 29/21 / 28/19                   |
| Bozkurt et al (2)| Turkey    | 2012  | other        | 8     | OSAS (moderate)             | 47/47   | 49.79 ± 10.62 / 42.79 ± 9.55 | 17.55 ± 7.42 / 19.93 ± 7.81    | 28/19 / 28/19                   |
| Bozkurt et al (3)| Turkey    | 2012  | other        | 8     | OSAS (mild)                 | 46/47   | 47.78 ± 10.35 / 42.79 ± 9.55 | 18.29 ± 6.48 / 19.93 ± 7.81    | 28/18 / 28/19                   |
| Bozkurt et al (4)| Turkey    | 2012  | other        | 8     | OSAS (unclassified)         | 143/47  | 42.79 ± 9.55 / 42.79 ± 9.55 | 17.40 ± 6.90 / 19.93 ± 7.81    | 85/58 / 28/19                   |
| Qiao et al (1)  | China     | 2018  | EI           | 8     | OSAS (unclassified)         | 32/32   | 51.80 ± 8.10 / 50.10 ± 7.30 | 17.62 ± 5.88 / 27.23 ± 7.59    | 32/0 / 32/0                     |
| Qiao et al (2)  | China     | 2018  | EI           | 8     | OSAS (moderate)             | 55/32   | 48.20 ± 9.90 / 50.10 ± 7.30 | 10.83 ± 6.80 / 27.23 ± 7.59    | 55/0 / 32/0                     |

a) Chemiluminescence immunoassay.
b) Electrochemiluminescence immunoassay.
c) Obstructive sleep apnea syndrome.
effects model. Cochran’s Q statistic and the $I^2$ statistic were used to evaluate the statistical heterogeneity (Kochran, 1954). $p < .05$ was defined significant for heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Heterogeneity was analyzed via sensitivity analysis and subgroup analyses. Egger’s test was used to calculate the publication bias. Subgroup analyses were conducted based on the region (Eurasia (owing to Turkey’s special geographical location), Europe and Asia), assay method of vitamin D (chemiluminescence immunoassay (CI), electrochemiluminescence immunoassay (EI), and other), sleep disorder type (obstructive sleep apnea syndrome (OSAS) (mild), OSAS (moderate), OSAS (severe), OSAS (unclassified), restless leg, and other), and study type (case-control study and cross-sectional study) for the studies including subjects with sleep disorders and controls. Additionally, we used subgroup analyses based on the region (Asia and America), intervention time (≤2 months and >2 months), and serum vitamin D concentration after intervention (sufficiency (≥30 ng/ml) and insufficiency (<30 ng/ml)) to evaluate the source of heterogeneity for studies including the vitamin D supplementation groups and the controls.

### RESULTS

Our study evaluated 1563 relevant literatures, but only 25 studies met the inclusion criteria, which contained a total of 3,603 subjects (Balaban et al., 2012; Bozkurt et al., 2012; Celik et al., 2015; Cikrikcioglu et al., 2016; Erden et al., 2014; Ghaderi et al., 2017; Gong et al., 2018; Gunduz et al., 2016; Han, Zhu, Shi, Wu, & Gu, 2017; Huang, Shah, Crankshaw, & Tangpricha, 2013; Huzmeli, 2018; Kerley et al., 2016; Liguori et al., 2015; Majid et al., 2018; Mason et al., 2016; Mete et al., 2013; Neves et al., 2017; Pazarli et al., 2014; Qiao et al., 2018; Terzi & Yilmaz, 2016; Toujani et al., 2017; Uygur, Baki, Tanriverdi, Ornek, & Atalay, 2016; Wall et al., 2018; Zhao et al., 2017; Zicari et al., 2016). These 25 articles included 21 papers analyzing differences in vitamin D concentrations between sleep disorders and controls (Balaban et al., 2012; Bozkurt et al., 2012; Celik et al., 2015; Cikrikcioglu et al., 2016; Erden et al., 2014; Gong et al., 2018; Gunduz et al., 2016; Han, Zhu, Shi, Wu, & Gu, 2017; Huang, Shah, Crankshaw, & Tangpricha, 2013; Huzmeli, 2018; Kerley et al., 2016; Liguori et al., 2015; Majid et al., 2018; Mason et al., 2016; Mete et al., 2013; Neves et al., 2017; Pazarli et al., 2014; Qiao et al., 2018; Terzi & Yilmaz, 2016; Toujani et al., 2017; Uygur, Baki, Tanriverdi, Ornek, & Atalay, 2016; Wall et al., 2018; Zhao et al., 2017; Zicari et al., 2016) and 4 papers (RCTs) evaluating the change in the PSQI score in response to supplementation with vitamin D (Ghaderi et al., 2017; Huang et al., 2013; Majid et al., 2018; Mason et al., 2016). The detailed outcomes are presented in Table 2, Table 3, Table S1, and Table S2.

#### 3.1 Differences in vitamin D concentrations between sleep disorders and controls

For the 21 papers analyzing differences in vitamin D levels, 11 studies were conducted in Eurasia (Balaban et al., 2012; Bozkurt et al., 2012; Cikrikcioglu et al., 2016; Erden et al., 2014; Ghaderi et al., 2017; Gong et al., 2018; Gunduz et al., 2016; Han, Zhu, Shi, Wu, & Gu, 2017; Huang, Shah, Crankshaw, & Tangpricha, 2013; Huzmeli, 2018; Kerley et al., 2016; Liguori et al., 2015; Majid et al., 2018; Mason et al., 2016; Mete et al., 2013; Neves et al., 2017; Pazarli et al., 2014; Qiao et al., 2018; Terzi & Yilmaz, 2016; Toujani et al., 2017; Uygur, Baki, Tanriverdi, Ornek, & Atalay, 2016; Wall et al., 2018; Zhao et al., 2017; Zicari et al., 2016) and 4 papers (RCTs) evaluating the change in the PSQI score in response to supplementation with vitamin D (Ghaderi et al., 2017; Huang et al., 2013; Majid et al., 2018; Mason et al., 2016).
Celik et al., 2015; Cikrikcioglu et al., 2016; Erden et al., 2014; Gunduz et al., 2016; Huzmeli, 2018; Mete et al., 2013; Pazarli et al., 2019; Terzi & Yilmaz, 2016; Uygur et al., 2016), 3 studies were performed in Europe (Kerley et al., 2016; Liguori et al., 2015; Zicari et al., 2016), and 5 studies were performed in Asia (Gong et al., 2018; Han et al., 2017; Qiao et al., 2018; Wali et al., 2018; Zhao et al., 2017) (the America group and Africa group were not analyzed because only 1 paper was included, respectively (Neves et al., 2017; Toujani et al., 2017)). Seven studies used EI to analyze the vitamin D levels (Balaban et al., 2012; Celik et al., 2015; Cikrikcioglu et al., 2016; Gong et al., 2018; Mete et al., 2013; Pazarli et al., 2019; Uygur et al., 2016), and 6 studies used CI (Erden et al., 2014; Kerley et al., 2016; Neves et al., 2017; Pazarli et al., 2019; Uygur et al., 2016; Zicari et al., 2016), while the remaining studies (Bozkurt et al., 2012; Gunduz et al., 2016; Terzi & Yilmaz, 2016; Toujani et al., 2017) (n = 4) used other methods (4 studies (Han et al., 2017; Huzmeli, 2018; Liguori et al., 2015; Wali et al., 2018) did not provide an assay method). The type of sleep disorder was OSAS (mild) in 5 studies (Bozkurt et al., 2012; Kerley et al., 2016; Mete et al., 2013; Pazarli et al., 2019; Uygur et al., 2016), OSAS (moderate) in 7 studies (Bozkurt et al., 2012; Erden et al., 2014; Kerley et al., 2016; Mete et al., 2013; Pazarli et al., 2019; Qiao et al., 2018; Uygur et al., 2016), OSAS (severe) in 9 studies (Bozkurt et al., 2012; Erden et al., 2014; Kerley et al., 2016; Liguori et al., 2015; Mete et al., 2013; Pazarli et al., 2019; Qiao et al., 2018; Toujani et al., 2017; Uygur et al., 2016), OSAS (unclassified) in 5 studies (Bozkurt et al., 2012; Erden et al., 2014; Mete et al., 2013; Uygur et al., 2016; Zicari et al., 2016), restless legs syndrome in 6 studies (Balaban et al., 2012; Celik et al., 2015; Cikrikcioglu et al., 2016; Huzmeli, 2018; Neves et al., 2017; Wali et al., 2018), and other in 6 studies (Gong et al., 2018; Gunduz et al., 2016; Han et al., 2017; Terzi & Yilmaz, 2016; Zhao et al., 2017; Zicari et al., 2016). Seventeen studies were case–control studies (Balaban et al., 2012; Bozkurt et al., 2012; Celik et al., 2015; Cikrikcioglu et al., 2016; Erden et al., 2014; Han et al., 2017; Huzmeli, 2018; Liguori et al., 2015; Mete et al., 2013; Neves et al., 2017; Qiao et al., 2018; Terzi & Yilmaz, 2016; Toujani et al., 2017; Uygur et al., 2016; Wali et al., 2018; Zhao et al., 2017; Zicari et al., 2016), and 4 studies were cross-sectional studies (Gong et al., 2018; Gunduz et al., 2016; Kerley et al., 2016; Pazarli et al., 2019). The risk of bias within individual studies for analyzing differences in vitamin D levels via NOS is presented in Table 2 and Table S1. In addition, the GRADE system was conducted to determine the quality of evidence (Table 4).

We performed a meta-analysis of the serum vitamin D concentration in 1864 sleep disorder subjects and 1,340 control peoples. The average serum vitamin D concentration in the sleep disorder subjects was 0.75ng/ml lower than that in the control group (SMD = −0.75 ng/ml, 95% CI = −0.93−0.57 ng/ml, I² = 86.2%, p < .001; Figure 2). Simultaneously, publication bias was not found in the serum vitamin D concentration (Egger’s test: coefficient = −0.255, t = −0.98, p = .334). Additionally, the subgroup analysis was conducted based on the region, assay method of vitamin D, sleep disorder types, and study types. The details are shown in Table 5. Studies were separated into three groups: Eurasia, Asia, and Europe based on the geographical study area. For the three groups,

### Good sleep quality compared with poor sleep quality in vitamin D levels

| Population: Subjects with sleep disorders vs. normal subjects |
|---|
| Settings: Eleven studies were conducted in Eurasia; three studies were conducted in Europe; five studies were conducted in Asia; one study was conducted in America; one study was conducted in Africa. |
| Cases: Subjects with sleep disorders |
| Controls: Normal subjects |

| Outcomes | SMD (95% CI) | No of participants (studies) | Quality of the evidence |
|---|---|---|---|
| Vitamin D levels | −0.75 (−0.93, −0.57) | 3204 (21 case-control/cross-sectional studies) | @@@HIGHb,c |

**GRADE working group grades of evidence.**

**High quality**: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate quality**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low quality**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Very low quality**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

**Abbreviations**: CI, confidence interval; SMD, standard mean deviation.

bUpgraded by one level due to all the results of the included studies were almost identical (subjects with sleep disorders had lower vitamin D levels).

cUpgraded by one level due to the America group and Africa group were not analyzed because only 1 paper was included, respectively (Neves et al., 2017; Toujani et al., 2017).

| TABLE 4 | The Summary of Findings (SoF) with GRADE system (vitamin D levels) |
|---|---|
| GRADE working group grades of evidence. |
| High quality: We are very confident that the true effect lies close to that of the estimate of the effect. |
| Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. |
| Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect. |
| Abbreviations: CI, confidence interval; SMD, standard mean deviation. |

aResults for vitamin D levels of subjects with sleep disorders compared with controls.

bUpgraded by one level due to all the results of the included studies were almost identical (subjects with sleep disorders had lower vitamin D levels).

cUpgraded by one level due to sleep disorders were associated with vitamin D levels (The more serious the sleep disorder, the lower the vitamin D levels).
the average serum vitamin D concentrations were lower than those of the controls (Figure S1). Simultaneously, a subgroup analysis was conducted based on the assay method, and the studies were separated into three methods: CI, EI, and other. The average serum vitamin D concentrations were lower than those of the controls in all three groups (Figure S2). The main types of sleep disorders in the included studies were OSAS (mild), OSAS (moderate), OSAS (severe), OSAS (unclassified), restless legs syndrome, and other. The average serum vitamin D concentrations were lower in all of the groups compared to those of the controls except for the OSAS (mild) group (Figure S3). Moreover, we separated the studies into two groups (case-control study and cross-sectional study) based on the included study types. For the two groups, statistically significant differences with the controls were observed (Figure S4).

3.2 Effect of vitamin D supplementation on sleep disorders

For the 4 papers evaluating the change in the PSQI score, 2 studies were performed in Asia (Ghaderi et al., 2017; Majid et al., 2018), and the remaining studies (Huang et al., 2013; Mason et al., 2016) (n = 2)
were conducted in America. The intervention time was ≤2 months in 1 paper (Majid et al., 2018) and >2 months in 3 studies (Ghaderi et al., 2017; Huang et al., 2013; Mason et al., 2016). The serum vitamin D concentrations after intervention were sufficient (Majid et al., 2018; Mason et al., 2016) in 2 papers and insufficient in the others (Ghaderi et al., 2017; Huang et al., 2013). The basic situation of the subjects is shown in Table 3 and Table S2.

The risk of bias within individual studies for evaluating the change in the PSQI score is shown in Figure 3 and Table S2. All 4 studies were randomized and had complete outcome data (Ghaderi et al., 2017; Huang et al., 2013; Majid et al., 2018; Mason et al., 2016). Additionally, 3 trials might have controlled the reporting bias via registering in a clinical trial registry (Ghaderi et al., 2017; Majid et al., 2018; Mason et al., 2016). The methods of allocation concealment and blinding of participants and study personnel were properly described in 3 studies (Ghaderi et al., 2017; Majid et al., 2018; Mason et al., 2016). Two studies conducted the methods of blinding of the outcome (Majid et al., 2018; Mason et al., 2016). Moreover, no commercial company was involved and no conflict of interest existed in all the studies, so the studies were considered free of potential bias (Ghaderi et al., 2017; Huang et al., 2013; Majid et al., 2018; Mason et al., 2016). Similarly, the GRADE system was conducted to determine the quality of evidence (Table 6).

We performed a meta-analysis of the PSQI in 189 subjects with vitamin D supplementation and 210 control subjects. The PSQI in the vitamin D supplementation group was 0.45 lower than that in the control group (SMD = −0.45, 95% CI = −0.76, −0.13, I² = 76.8%, p < .001; Figure 4). Similarly, publication bias was not found in the PSQI (Egger’s test: coefficient = −3.29, t = −1.56, p = .164). Moreover, the subgroup analysis was conducted based on the region, intervention time, and serum vitamin D concentration after intervention. Details are shown in Table 7. Studies were separated into two regions based on the geographical study area. For the Asia group, the PSQI was lower than that of the controls. However, the researches in America did not indicate differences in the PSQI between the supplementation subjects and control subjects (Figure S5). Simultaneously, the studies were separated into two groups based on the intervention time: ≤2 months and >2 months. The PSQI was lower than that of the controls in the ≤2 months’ group, while the studies in the >2 months’ group did not indicate differences between the supplementation and control subjects (Figure S6). Additionally, all subjects were separated into two groups based on their serum vitamin D levels after intervention (Figure S7).

4 DISCUSSION

Sleep disorders bring a heavy burden on the healthcare system. The personal average annual medical expense may increase by $2000 due to chronic sleep disorders (Xie et al., 2017). It has been reported that vitamin D deficiency is related to a higher risk of sleep disorders.

| Subgrouped by          | No. of studies | SMD    | 95% CI       | I² (%) | P for heterogeneity |
|------------------------|----------------|--------|--------------|--------|---------------------|
| **Region**             |                |        |              |        |                     |
| Eurasia                | 11             | −0.54  | −0.72, −0.37 | 73.1   | <.001               |
| Europe                 | 3              | −0.89  | −1.09, −0.69 | 3.8    | .392                |
| Asia                   | 5              | −1.23  | −1.77, −0.69 | 94.4   | <.001               |
| **Assay method**       |                |        |              |        |                     |
| EI                     | 7              | −0.58  | −0.86, −0.29 | 85.2   | <.001               |
| CI                     | 6              | −0.79  | −1.00, −0.58 | 68.1   | <.001               |
| Other methods          | 4              | −0.75  | −1.36, −0.14 | 92.8   | <.001               |
| **Sleep disorder types**|               |        |              |        |                     |
| OSAS (mild)            | 5              | −0.27  | −0.56, 0.01  | 46.4   | .113                |
| OSAS (moderate)        | 7              | −0.68  | −1.08, −0.29 | 75.8   | <.001               |
| OSAS (severe)          | 9              | −1.26  | −1.82, −0.71 | 91.7   | <.001               |
| OSAS (unclassified)    | 5              | −0.72  | −1.14, −0.30 | 83.1   | <.001               |
| Restless leg           | 6              | −0.63  | −1.08, −0.17 | 85.7   | <.001               |
| Other types            | 6              | −0.66  | −0.97, −0.34 | 82.7   | <.001               |
| **Study types**        |                |        |              |        |                     |
| Case–control study     | 17             | −0.83  | −1.05, −0.61 | 88.0   | <.001               |
| Cross-sectional study  | 4              | −0.43  | −0.56, −0.30 | 0.0    | .473                |

**TABLE 5** Subgroup analyses for the serum vitamin D concentrations in patients with sleep disorder and controls.
However, it is controversial whether supplementation with vitamin D is truly beneficial to improving sleep quality. This meta-analysis found that vitamin D concentrations in sleep disorders were significantly lower than those in normal controls. In addition, vitamin D supplementation can effectively improve sleep quality. Although the specific mechanism of the role of vitamin D on sleep disorders has not yet been illustrated, some potential mechanisms have been considered. Low concentrations of vitamin D can disrupt sleep by creating and developing myopathic pain (Lee, Greenfield, & Campbell, 2009). Meanwhile, as central sleep regulators, inflammatory mediators (including TNF-α and IL-1) and prostaglandin D2 indicated negative correlation with vitamin D levels. Inflammatory mediators and prostaglandin D2 were increased in cases of vitamin D deficiency, thus leading to sleep disorders, including OSAS. Therefore, vitamin D supplementation could effectively improve sleep quality (Barcelo et al., 2007; Bellia et al., 2013; Khoo et al., 2011).

When we analyzed the outcomes of the vitamin D concentrations and the PSQI score in the included papers, a high level of heterogeneity was found in both outcomes, so we conducted a subgroup analysis to determine the source of heterogeneity. The subgroup analysis of the region indicated that the heterogeneity was decreased in both results. Therefore, we concluded that different regions could be the source of heterogeneity in the included studies. In addition, the PSQI was significantly lower in the vitamin D supplementation subjects than in the control subjects for the Asia group, while there was no significant difference for the America group. Several decades ago, as one of the industrialized countries, America had undertaken fortification of milk and other food products with vitamin D (Marwaha & Dabas, 2019). Therefore, there may be other factors or diseases that cause sleep disorders in Americans. In contrast, in Asian countries, urbanization is likely to be related to lifestyle changes, lower physical activity, an increase in indoor living, and lack of sun exposure, thus leading to an increase in vitamin D deficiency (Mithal, Bansal, Kyer, & Ebeling, 2014). Additionally, in different areas of Asia, nutritional status and sunlight exposure are diversity; hence, the vitamin D supplementation may be more necessary for Asian people (Lau et al., 2006). Furthermore, due to Turkey’s special geographical location (across Eurasia), we took it as a subgroup when we analyzed the differences in vitamin D concentrations between the sleep disorders and control subjects by subgroup analysis based on region. We considered the combination of east and
Vitamin D supplementation compared with no vitamin D intervention for improving sleep quality

**Population:** Subjects with sleep disorders  
**Settings:** Two studies were conducted in Asia, and two studies were conducted in America  
**Intervention:** Vitamin D supplementation  
**Comparison:** No vitamin D intervention

| Outcomes\(^a\) | SMD (95% CI)\(^b\) | No of participants (studies) | Quality of the evidence Comments (GRADE) |
|----------------|--------------------|-----------------------------|------------------------------------------|
| PSQI score     | –0.45 (–0.76, –0.13) | 399 (4RCTs)                | ⊙⊙⊙⊙HIGH                                |

**GRADE Working group grades of evidence.**  
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.  
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.  

**Abbreviations:** CI, confidence interval; RCT, randomized controlled trial; SMD, standard mean deviation.

\(^a\)All subjects were followed up range 8 weeks to 12 months.  
\(^b\)Results for PSQI score of treatments compared with controls (including PSQI score of postsupplementation compared with presupplementation in the treatments).

**Figure 4 Forest plot of the PSQI in the vitamin D supplementation vs. control groups.**

**Table 6 The Summary of Findings (SoF) with GRADE system (PSQI score)**
west in various fields, and the complexity of race may be the reason for the high heterogeneity in the Eurasia group.

Comparing the subjects with sleep disorders with the control group at the vitamin D level, the results indicated that OSAS severity may correlate with vitamin D levels. As one of the major sleep disorders, the more serious the disease is, the lower the level of vitamin D. The result is similar to the K’s study (Archontogeorgis, Nena, Papanas, Zissimopoulos, et al., 2018). Although the mechanism of vitamin D insufficiency or deficiency in OSAS is inadequately understood, several possible pathogeneses indicated that they may affect each other. OSAS subjects are probably to have excessive daytime sleepiness or obesity, thus reducing the outdoor activities and sunlight exposure, leading to the decrease in vitamin D synthesis (Igelstrom, Emtner, Lindberg, & Asenlof, 2013). Meanwhile, vitamin D has immunomodulatory properties. Multiple immune cells, such as antigen-presenting cells, T cells, B cells, and monocytes, have vitamin D metabolizing enzymes and vitamin D receptors (Archontogeorgis, Nena, Papanas, & Steiropoulos, 2018; Prietl, Treiber, Pieber, & Amrein, 2013). Recurrent infections and immune system imbalance caused by vitamin D deficiency could lead to tonsillar hypertrophy and chronic rhinitis, both of which elevate the risk of OSAS or aggravate it (Reid, Morton, Salkeld, & Bartley, 2011). Therefore, OSAS patients are more likely to fall into the vicious circle of vitamin D deficiency-OSAS aggravation.

According to the results of the vitamin D supplementation, the studies in >2 months did not demonstrate differences between the supplementation and control subjects. The reason may be that the guidelines for vitamin D supplementation in people with sleep disorders were lacking. We could only refer to the existing supplemental guidelines, which suggested 50,000 IU once a week for 8 weeks for clinical management of vitamin D deficiency in adults (Cesareo et al., 2018) (since only one group in the included studies was 50,000 IU/week, we were unable to perform the subgroup analysis according to intervention dose). Therefore, considering the small sample size, more RCTs are required to assess the relationship between vitamin D supplementation and sleep disorders. In the meantime, a guideline of vitamin D supplementation for sleep disorders patients is urgently needed.

This meta-analysis also has some limitations. Some papers did not provide the detection method of vitamin D, so we could not include it when the subgroup analysis was conducted based on the detection method. Meanwhile, few studies met the existing guidelines for vitamin D supplementation, so we could not conduct a subgroup analysis based on the intervention dose. Most importantly, there are fewer RCTs about vitamin D supplementation for sleep disorders. Although RCTs are supposed to valid evidence compared to other studies, true vitamin D supplementation roles could be biased by the quality of the data from the original papers and the limited sample size and included studies.

5 | CONCLUSIONS

Vitamin D could play a promising role in sleep disorders. Considering several limitations found in this meta-analysis, more data from RCTs are required to confirm the efficacy of vitamin D supplementation for improving sleep disorders.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

BL, WC, and SY made the study design; SY, ZT, HZ, and YP conducted the study; SY, ZT, CW, and NY analyzed the data and wrote the manuscript; SY, ZT, YG, and HW participated amending the manuscript. SY and ZT contributed equally to this work. All authors agreed with the final version of the manuscript.

STUDIES INVOLVING HUMAN SUBJECTS

Although the study involves human subjects, it is a meta-analysis based on evaluating published research data. Therefore, no ethical issues are involved.

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Additional supporting information may be found online in the Supporting Information section.