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Risk of excessive daytime sleepiness in Parkinson's disease: A meta-analysis

Yu Gao, Fengju Jia, Liang Shen, Dongfeng Zhang, Xiaoli Shen

[1]Department of Epidemiology and Health Statistics, Qingdao University, Qingdao, China

[2]Department of Physiology, Shandong Provincial Key Laboratory of Pathogenesis and Prevention of Neurological Disorders and State Key Disciplines: Physiology, Qingdao University, Qingdao, China

[3]Department of Business School, Qingdao University of Technology, Qingdao, China

Abstract: **The present meta-analysis was conducted to estimate the pooled prevalence of EDS in PD and explore the association of PD with the risk of EDS. PubMed, EMBASE, and Web of Science database were systematically searched up to Apr 2020, aim to find observational studies on investigating excessive daytime sleepiness in Parkinson disease. Random effects models were selected to evaluate the pooled prevalence of EDS in PD and the Odds Ratio (OR) of EDS in PD comparing with healthy control. Subgroup analysis and meta-regression were conducted to explore sources of heterogeneity. The funnel plot and Egger test were used to assess publication bias. Thirteen articles with 3912 participants were included to pool the prevalence of EDS in PD. The pooled prevalence of EDS in all PD patients was 30% (95% CI: 24%-36%). Ten articles with a total number of 1375 PD patients and 1161 age-matched health controls were enrolled to evaluate the association between PD and the risk of EDS. The pooled OR for the risk of EDS in PD was 2.86 (95% CI: 1.89-4.33), indicating that PD was significantly associated with an increased risk of EDS. EDS may cause diminished life quality and hazardous accidents in PD patients, early prevention and interventions of EDS were essential in the treatment of PD.**

Keywords: Excessive daytime sleepiness; Meta-analysis; Parkinson's disease; Sleep disorders

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*Corresponding Author: Xiaoli Shen, shenxiaoli@qdu.edu.cn

1. Post-traumatic stress disorder

Sleep disturbance are dramatic non-motor symptoms of Parkinson's disease (PD). Excessive daytime sleepiness (EDS), one of sleep disorders, was defined by the American Academy of Sleep Medicine as the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months[1]. Due to the sudden and irresistible sleep attacks, EDS may diminish the quality of life and cause automobile accidents in PD patients [2]. Moreover, long time of sleep was thought to increase all-cause mortality[3].

EDS was evaluated by a subjective screening tool called the Epworth Sleepiness Scale (ESS) which ranged from 0-24 in the clinic [4]. Patients were diagnosed as EDS when ESS score is greater than or equal to 10[5, 6]. The frequency and persistency of EDS appeared incrementally with development of disease duration [7], but the underlying mechanism of EDS in PD patients has yet been fully understood. EDS may be the result of a disorder of the sleep-wake system[8], or an adverse event of dopaminergic medications commonly used in the treatment of the disease[9]. Patients with PD have difficulties in initiation and maintenance of sleep, and then EDS might also be the consequence of poor sleep [10].

Although the research on sleep disorders in PD patients, even on EDS in PD patients independently, has growingly increased, inconsistent results was reported on the prevalence of EDS. Here, we conducted a meta-analysis to estimate both the pooled prevalence of EDS in PD patients, and the risk of EDS in PD.

2. Methods

2.1 Search Strategy

We conducted a systematic search in the databases of PubMed, EMBASE, and Web of Science up to Apr 2020, with aim to find observational studies published in English on investigate excessive daytime sleepiness in Parkinson disease. The search terms included "Parkinson's disease" OR "Parkinson's syndrome" AND "daytime sleepiness" OR "daytime somnolence" OR "Excessive daytime sleepiness" OR "EDS".

2.2 Study Selection

To estimate the pooled prevalence of EDS in PD patients, the inclusion criteria were as follows: 1) observational studies only included cross-sectional studies, and cohort studies that provided baseline data; 2) primarily aimed to evaluate the prevalence or frequency of EDS in PD patients; 3) the prevalence of EDS in PD patients or raw data to calculate the

prevalence were provided.

To explore the association between PD and the risk of EDS, the inclusion criteria were as follows: 1) observational studies published as original articles including case-control, cross-sectional, prospective studies; 2) the exposure of interest was PD; 3) the outcome of interest was EDS; 4) Odds radios (ORs), Relative risks (RRs), Hazard ratios (HRs) with 95% confidence intervals (CIs) or raw data to calculate these were provided.

Studies would be excluded if they were: drug trials, reviews, case reports, meeting abstract, or did not involve patients with PD or EDS, did not report necessary data for our study. Any doubt or disagreement was resolved by two reviewers through discussion.

2.3 Data Extraction

Two reviewers evaluated all eligible studies independently according to inclusion criteria and exclusion criteria. The following information were extracted from studies: surname of the first author, year of publication, the country of study conducted, study design, the primary aim of the study, EDS symptom evaluation method, diagnosis criteria, PD duration, sample size, the number or prevalence of EDS in PD patients for cross-sectional and cohort study. For the study selected to explore the association between PD and the risk of EDS, besides above information, odds ratio (OR) and its 95% confidence intervals (CIs), or raw data to calculate OR was also extracted.

2.4 Statistical Analysis

All statistical analysis was performed using the STATA version15.0 (Stata Corporation, College Station, TX, USA). Initially, we evaluated the pooled prevalence of EDS in PD patients based on the point prevalence of each article. Baseline of cohort study was considered be equivalent to a cross-sectional study, and pooled as cross-sectional study. To estimate the association of PD with the risk of EDS, we calculated ORs with corresponding 95% CIs of each articles and weighted the study-specific log OR by the inverse of within-study and between-study variation to evaluate a pooled estimate and its 95% CIs based on the Dersimonian and Laird random effects model[11].

Heterogeneity among studies was calculated by I^2-statistics. I^2 values of 0%, 25%, 50%, 75% mean no, low, moderate, high heterogeneity respectively[11]. Pooled effect size of data with no or low heterogeneity was analyzed with a fixed effect model, pooled effect size of data with moderate or high heterogeneity was analyzed with a random effect model. Meta-regression with restricted maximum likelihood estimation and subgroup analysis was conducted to explore the potential source of heterogeneity. Influence analysis was performed by excluding one study at a time to evaluate whether the pooled result was influenced by a single study. Leave-one-out sensitivity analysis was conducted to evaluate the key studies on the substantial effect of heterogeneity between studies[12]. Publication bias was accessed by funnel plot and Egger test, the trim and fill method was applied when there was evidence of publication bias.

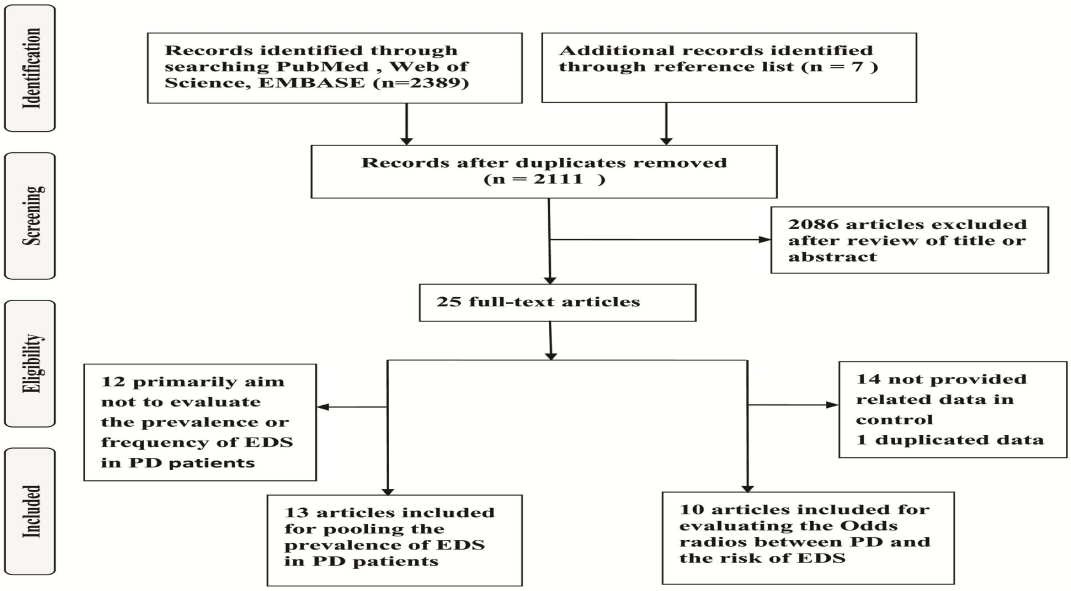

Figure 1. Flow chart of study selection. EDS, Excessive daytime sleepiness.

3. Results

3.1 Literature Selection and Study Characteristics

A total of 2111 articles were included in our study after eliminating duplication. 2086 articles were excluded based on the title and abstract, and we obtained 25 observational articles for further full-text review. Finally, 13 articles[6, 13-24] were included to pool the prevalence of EDS in PD patients and 10 articles[13, 14, 16-19, 22, 25-27] were included to evaluate the association between PD and the risk of EDS. The process of searching and article selection was shown in Figure 1.

3.2 The Pooled Prevalence of EDS in Patients with PD

The characteristics of the selected study for pooling the prevalence EDS in PD patients were shown in Table 1. Overall, 13 eligible articles including 3912 participants published from 1992 to 2018 were selected in our meta-analysis, including 12 cross-sectional studies and 1 case-control study. Among all articles, 4 were conducted in Asia, 2 were conducted in America, 6 were conducted in Europe, and 1 was conducted both in Europe and America. Mean age of included studies ranged from 58.4 to 73.8 years, PD duration ranged from 5.7 to 10.0 years (2 studies not reported).

As shown in Figure 2, the estimated pooled prevalence of EDS in PD patients was 30% (95% CI: 24%-36%) by random-effect model. High heterogeneity was found among the studies (I^2=94%, P=0.000). The result of subgroup analysis was shown in Table 2. Meta-regression was performed with the same covariate included in subgroup analysis, in which the covariate of continent was reclassified into Asia and non-Asia. In meta-regression, the p value was 0.066(continent), 0.368(diagnostic criteria), 0.073(mean age), 0.174(PD duration), respectively, as well as we failed to detect the source of heterogeneity.

Influence analysis and leave-one-out sensitivity analysis showed no individual article had excessive influence on the pooled prevalence. Publication bias was not significant, inspected from the visually symmetrical funnel plot and the result of Egger test (P=0.344, 95% CI: 3.03-7.98).

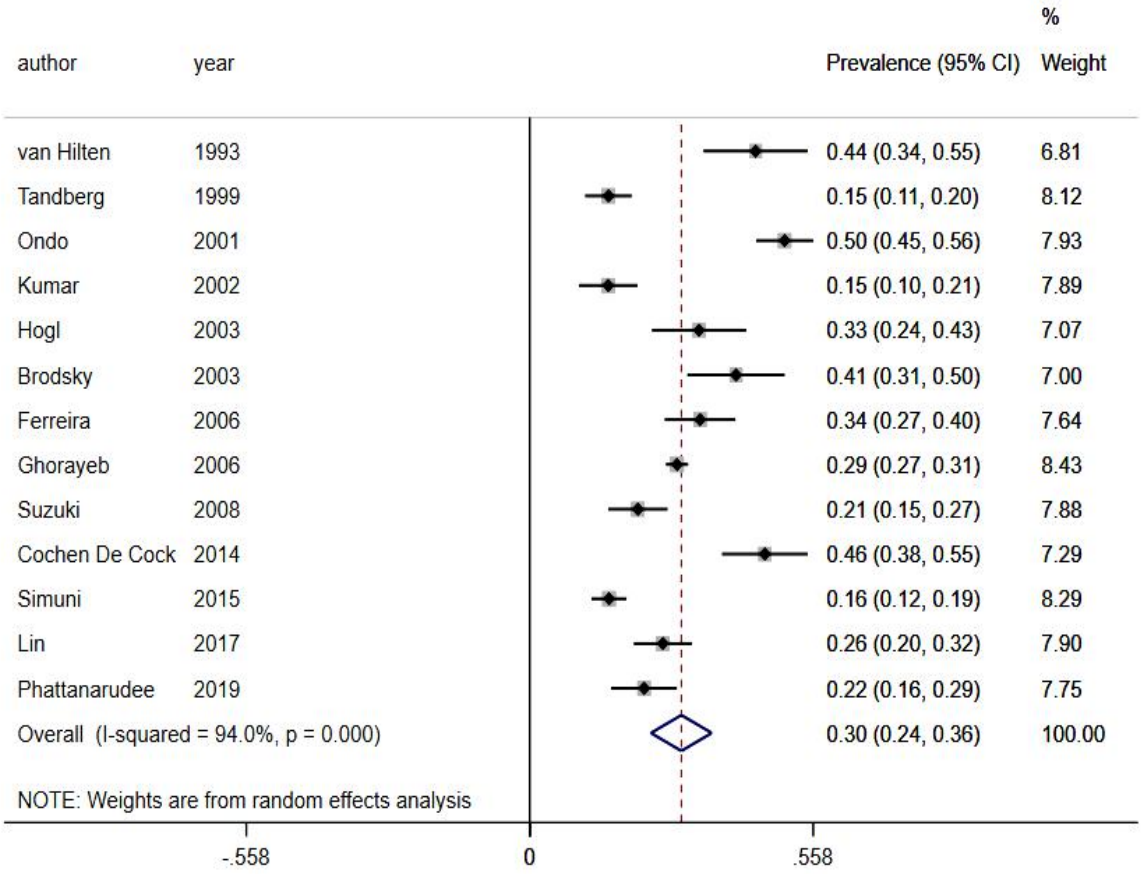

Figure 2. Forest plot of the pooled prevalence of excessive daytime sleepiness in PD. CI, confidence interval.

Table 1. Characteristics of studies on the prevalence of EDS in PD patients

Author	Year	Continent	Study design	Diagnosis criteria	Mean age	PD duration	n	EDS in PD
van Hilten et al.[13]	1993	Europe	Cross-section	A similar 5 point questionnaire >3	67.5±10.8	11±6.4	90	40
Tandberg et al.[14]	1999	Europe	Cross-section	Fell asleep>3 times a day or total sleeping time>2 hours during the day	73.8±8.4	9.1±5.8	239	37
Ondo et al.[15]	2001	America	Cross-section	ESS>10	67.1±10.7	9.1±5.7	303	152
Hogl et al.[17]	2002	Europe	Case-control	ESS≥10	67.7±10.3	7.4±6.7	99	33
Kumar et al.[16]	2002	Asia	Cross-section	ESS>8	58.4±10.4	5.7±3.8	149	23
Brodsky et al.[18]	2003	America	Case-control	ESS≥10	65.4±11.0	NR	101	41
Ferreira et al.[19]	2005	Europe	Cross-section	ESS≥10	65±10	10.0±5.9	176	59
Ghorayeb et al.[20]	2007	Europe	Cross-section	ESS>10	69.5±9.3	6.1±4.6	1625	471
Suzuki et al.[32]	2008	Asia	Cross-section	ESS≥10	66.4±8.7	6.9±5.3	188	40
Cochen De Cock et al.[21]	2014	Europe	Cross-section	ESS>10	65.9	8.1±5.8	134	62
Simuni et al.[22]	2015	America and Europe	Case-control	ESS≥10	NR	NR	423	66
Lin et al.[23]	2017	Asia	Cross-section	ESS≥10	65.7±8.9	8.18±5.2	225	59
Phattanarudee[24]	2019	Thailand	Cross-section	ESS > 10	64.0±11.0	9.2±5.2	160	36

PD, Parkinson's disease; EDS, Excessive daytime sleepiness; n, number of Parkinson's patients. ESS, Epworth Sleepiness Scale; NR, not reported.

Table 2. Analysis for prevalence of EDS in PD in subgroup

Study characteristics	Number of study	Pooled Prevalence(95%CI)	I^2-value (%)	*P* value
All studies	13	30% (24%-36%)	94.0	0.000
Continent				
Asia	4	21% (17%-26%)	56.4	0.076
Europe	6	33% (25%-41%)	91.7	0.000
America	2	46% (37%-55%)	64.9	0.091
Diagnosis criteria(ESS scale threshold value of 10)				
yes	10	32% (25%-38%)	93.8	0.000
not	3	24% (11%-38%)	92.7	0.000
Mean age				
<65	4	21% (14%-29%)	86.9	0.000
≥65	9	34% (26%-41%)	93.6	0.000
PD duration				
<8 year	5	23% (15%-30%)	92.8	0.000
≥8 year	6	32% (21%-44%)	95.4	0.000

CI, confidence interval. ESS, Epworth Sleepiness Scale.

Table 3. Characteristics of studies on the risk of the EDS in PD patients and controls

Author	Year	Continent	Study design	Diagnosis criteria	EDS in PD	EDS in HC	OR(95% CI)	Adjustment for covariates
van Hilten et al.[13]	1993	Europe	Cross-section	A similar 5 point questionnaire >3	40/90	22/71	1.78(0.93,3.42)	-
Tandberg et al. [14]	1999	Europe	Cross-section	Fell asleep>3 times a day or total sleeping time>2 hours during the day	37/239	1/100	18.13(2.45,134.09)	Age, sex
Kumar et al. [16]	2002	Asia	Cross-section	ESS>8	23/149	7/115	2.82(1.16,6.82)	Age
Fabbrini et al. [25]	2002	Europe	Case-control	ESS≥10	37/50	1/25	68.31(8.38,556.60)	Age, sex
Hogl et al. [17]	2003	Europe	Cross-section	ESS≥10	33/99	5/44	3.90(1.41,10.82)	-
Brodsky et al. [18]	2003	America	Cross-section	ESS≥10	41/101	19/100	2.91(1.54,5.51)	Age
Ferreira et al. [19]	2006	Europe	Cross-section	ESS≥10	59/176	28/174	2.63(1.58,4.38)	Age
Wegelin et al. [26]	2005	America	Cross-section	ESS>10	13/22	5/16	3.18(0.82,12.34)	Age
Tholfsen et al. [27]	2015	Europe	Cohort study	ESS≥11	18/153	8/169	2.63(1.11,6.22)	Age, sex
Simuni et al. [22]	2015	America and Europe	Case-control	ESS≥10	66/423	24/195	1.32(0.80,2.17)	Age, sex, and education

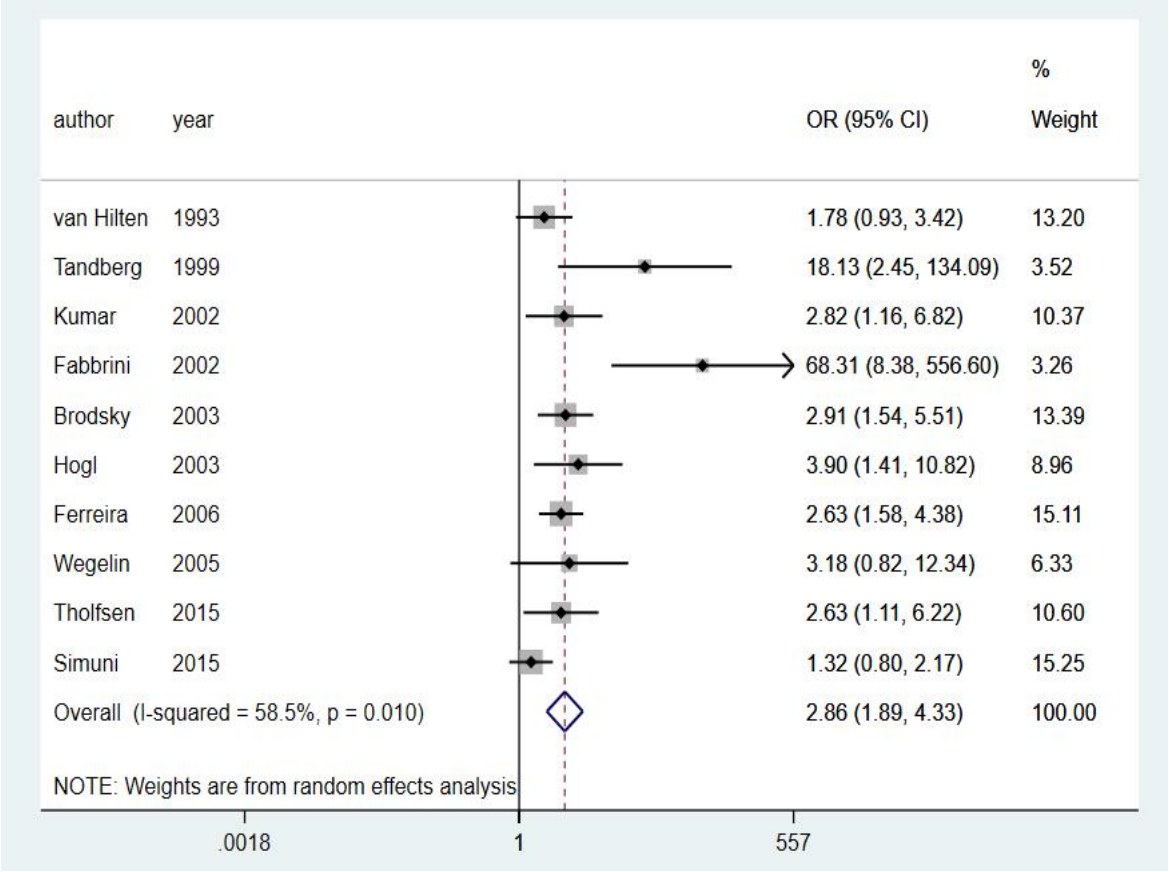

Figure 3. Forest plot for the pooled OR for the risk of excessive daytime sleepiness in PD. OR, Odds Risk; CI, confidence interval.

3.3 The Association between PD and the Risk of EDS

The characteristics of the selected study for assessing the association of PD and the risk of EDS were shown in Table 3. Ten articles were included with a total number of 1375 PD patients and 1161 age-matched health controls . Articles included in the meta-analysis contained 6 cross-sectional studies, 2 case-control studies, and 1 cohort study. As showing in Figure 3, after pooling the ORs of 10 articles with a random effect model, the OR for the risk of EDS in PD was 2.86 (95% CI: 1.89-4.33) with moderate heterogeneity (I^2=58.5%, P=0.01). By leave-one-out sensitivity analysis, 2 articles were found that have an important influence on heterogeneity. After excluding these 2 articles, no heterogeneity was found (I^2=0%) and the pooled OR was 2.91 (95% CI: 2.22-3.83). Egger test (P=0.004, 95% CI: 1.27-4.76) and asymmetrical funnel plot found publication bias existed among included articles. After trim and fill analysis, the recalculated OR was 2.18 (95% CI: 1.40-3.41) based on the filled funnel plot.

4. Discussion

This meta-analysis evaluated the prevalence of EDS in PD patients, and also explored the association of PD with the risk of EDS. The pooled result indicated the prevalence of EDS in PD patients was 30% (95% CI: 28%-38%), and PD patients carried a 2.86-fold (95% CI: 1.89-4.33) likelihood of EDS compared with control.

In studies for pooling prevalence of EDS in PD, the pooled results showed EDS was commonly prevalent in PD patients. Subgroup analysis and meta-regression analysis failed to find the source of high heterogeneity. In influence analysis and leave-one-out sensitivity, no article had excessive influence when we pooling prevalence. In studies for assessing the association of PD and the risk of EDS, the pool OR indicated that PD may increase the risk of EDS. Despite of the presence of publication bias, the adjusted result didn't change substantially after the trim and fill method, indicating the result was stable.

Etiology of EDS in PD was multifactorial. Numerous studies reported daytime sleepiness syndrome appeared after antiparkinsonian treatment, even some indicating the syndrome may be a side-

effect of therapeutic drugs, especially dopaminergic drugs[28-30]. EDS increased significantly at the initial stage of PD, and was related to dopaminergic therapy with dose increased [31]. Several studies suggested that severe EDS can be explained by the primary pathology of PD. EDS was associated with dopaminergic nigrostriatal degeneration and circadian dysfunction which were influenced by a decrease in melatonin production in PD[32]. Using imaging technology of Single Photon Emission Computed Tomography, Matsui found that the cortical hypofunction which was relative to hyperfunction of the brain stem may relate to EDS in Parkinson disease[33]. Furthermore, it was still in debated that whether EDS was related to other sleep disorders[34] [35].

There were some limitations in this study. Firstly, diagnostic criteria between included articles weren't consistent, which may lead to underestimation of prevalence. We conducted a subgroup analysis on diagnostic criteria , the pooled results was 32% (95% CI: 25%-38%) in groups using ESS as the diagnostic criteria, and 24% (95%: CI 11%-38%) in groups selecting other diagnostic criteria. Secondly, high heterogeneity was found among articles that pooling the prevalence of EDS in PD patients. Subgroup analysis and meta-regression analysis failed to find the source of heterogeneity. Moreover, influence analysis and leave-one-out sensitivity analysis showed the result was stable. Publication bias was found in articles for estimating the association between EDS and PD , but the adjusted result was still positive with the trim and fill method. Last, if the patient has more than two sleep disorders, we cannot tell whether excessive daytime sleepiness was caused or consequence of by another sleep disorder.

5. Conclusions

In summary, EDS was commonly prevalent in PD patients and the pooled prevalence is 30% (95% CI: 28%-38%), as well as PD was significantly associated with a 2.86-fold (95% CI: 1.89-4.33) increased risk of EDS. Since EDS may cause diminished life quality and hazardous accidents in PD patients, early prevention and interventions of EDS were essential in the treatment of PD.

Disclosure statement

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