REVIEW ARTICLE

Association between bone mineral density and benign paroxysmal positional vertigo: a meta-analysis

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Abstract

Background The association between bone mineral density (BMD) and benign paroxysmal positional vertigo (BPPV) has been investigated by multiple studies, but the conclusions are controversial. This meta-analysis was conducted to evaluate whether the bone mineral density is associated with BPPV.

Methods The relevant studies were identified by searching PubMed, EMBASE, Cochrane Library, ScienceDirect, Web of Science database up to June 2018. Statas14.0 software was used for meta-analysis. We used the pooled odds ratio (OR) and 95% confidence interval (CI) to assess the incidence of osteoporosis and osteopenia in patients with BPPV and controls (free of BPPV disease). The standardized mean difference (SMD) and 95% confidence interval (CI) were used to assess the T score in BPPV patients and controls. This meta-analysis has been registered at International Prospective Register of Systematic Reviews (PROSPERO) (number CRD42018082271).

Results A total of 11 studies were eligible for meta-analysis, including 1982 subjects. When compared with the controls, the total incidence of osteoporosis and osteopenia was significantly higher in BPPV patients (OR 3.27, 95% CI 2.66–4.03, $p < 0.0001$). Further analysis was conducted by separate discussion about the incidence of osteoporosis and osteopenia in BPPV patients, the result of which shows that both the incidence of osteoporosis (OR 3.48, 95% CI 1.86–6.51, $p < 0.0001$) and the incidence of osteopenia (OR 1.75, 95% CI 1.01–3.04, $p < 0.0001$) were higher in BPPV patients than that in controls. There was an significant reduction in T scores of BPPV patients (SMD −0.82, 95% CI −1.18 to −0.46, $p < 0.0001$). Publication bias for each analysis was evaluated by Egger's test and Begg's indicating that no publication bias existed. Sensitivity analysis was conducted for each analysis demonstrating that the results were robust.

Conclusions Our meta-analysis provided stronger evidence that patients with BPPV were associated with a lower T score and a higher risk of osteoporosis and osteopenia. The results demonstrated that lower bone mineral density may be a risk factor for BPPV. However, large-scare, multicenter clinical studies need to be carried out to explore the precise risk of osteoporosis and osteopenia in patients with BPPV in future.

Keywords Benign paroxysmal positional vertigo · BPPV · Osteoporosis · Osteopenia · Bone mineral density · Meta-analysis

Abbreviations

BMD	Bone mineral density
BPPV	Benign paroxysmal positional vertigo
PROSPERO	Prospective register of systematic reviews
NOS	Newcastle-Ottawa Scale
RCTs	Randomized controlled trial

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Introduction

Benign paroxysmal vertigo (BPPV) is the most common peripheral vertigo, which is characterized by brief episodes of vertigo and nystagmus induced by changes of

head position [1]. The 1-year and lifetime prevalence rate of BPPV is 1.6% and 2.4%, respectively [2]. The incidence of BPPV increases along with the age especially in females [3]. At present, the potential etiology and pathophysiology of BPPV have not been fully elucidated. About 50–97% of BPPV cases are isolated and the etiology cannot be found (called idiopathic BPPV) [4]. BPPV can also be secondary to head trauma, viral nerve loss, meniere disease, migraine, ear or dental surgery and bed rest [5]. Previous studies have shown that the potential risk factors of BPPV included age [6], women [7], bed rest [6], migraine [8], cerebrovascular diseases [9] and anxiety [10]. BPPV is thought to be caused by dislodged otoconia floating into semicircular canals and inducing endolymph flow by head motion. Otoconia is comprised by calcium carbonate crystals and an organic core [11], which is similar to bone tissue in the human body, containing 99% calcium ions. According to classical theories, calcium metabolism disorder and vitamin D deficiency may be related to the movement of otolith in BPPV [12, 13]. Some studies have been noted that the disorder of calcium balance in patients with osteoporosis may lead to the occurrence of BPPV [14].

Previous studies have focused on the association between bone mineral density and BPPV [15, 16]. However, no consensus has been reached among those studies, the results still have been controversial. Some studies have demonstrated that patients with BPPV may be associated with lower bone mineral density and higher prevalence of osteoporosis and osteopenia [17, 18]. While the other studies have reported that there is no association between bone mineral density and BPPV, the coexistence of BPPV with osteoporosis is coincidental [19]. Therefore, this meta-analysis was performed to provide sufficient evidence to evaluate the association between BPPV and bone mineral density.

Methods

This meta-analysis was drafted according to the guideline of PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [20]. In addition, this meta-analysis has been registered at International Prospective Register of Systematic Reviews (PROSPERO) (number CRD42018082271).

Fig. 1 Study selection process
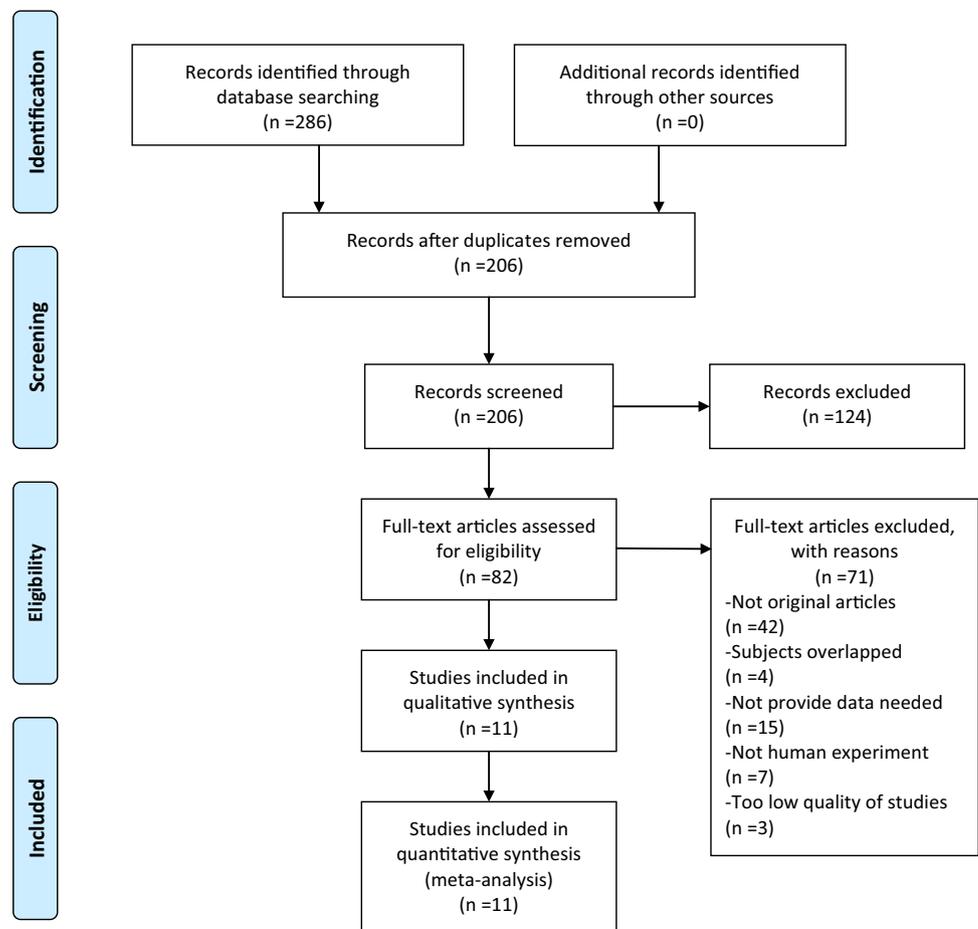
Search strategy

The Pubmed, EMBASE, the Cochrane library, ScienceDirect and Web of Science databases were searched by two researchers independently to identify the original papers on the relationship between bone mineral density and BPPV that have been published in English from databases establishment to October, 2018. The MeSH terms "Bone Density", "Osteoporosis", "Benign Paroxysmal Positional Vertigo", "Osteopenia" and related free words were combined to search relevant papers. Furthermore, we did a manual retrieval to identify potentially relevant papers.

Table 1 Characteristics and quality of included studies

First author, year	Country	Mean age		Female (%)	Case number	T score		NOS
		BPPV	Control		BPPV/control	BPPV	Control	
Wu, 2017 [18]	China	58.4 ± 11.4	58.5 ± 10.3	204 (100%)	51/61	− 1.26 ± 1.52	− 0.47 ± 1.45	7
Vibert, 2003 [23]	Switzerland	69 ± 9.2	Age matched	112 (100%)	20/19	− 1.354 ± 0.87	− 0.299 ± 0.67	5
Jeong, 2009 [24]	Korea	59. 8 ± 12.15	56.3 ± 8.6	238 (58%)	138/76	− 1.5 ± 1.2	− 0.84 ± 1.2	7
Zhai, 2016 [3]	China	48.98 ± 12.89	48.66 ± 13.51	109 (66%)	61/19	− 2.01 ± 1.658	0.361 ± 0.875	7
Talaat, 2015 [25]	Egypt	47.59 ± 9.09	44.4 ± 11.2	119 (66%)	48/26	− 0.90 ± 1.2	0.06 ± 1.16	6
Yang, 2017 [26]	Korea	54.9 ± 12.2	Age matched	200 (77%)	68/41	− 1.44 ± 1.29	− 1.0 ± 0.93	7
Jeong, 2013 [27]	Korea	61. 8 ± 11.6	60.3 ± 11.3	163 (56%)	76/101	NA	NA	8
Ko, 2013 [28]	Korea	48.0 ± 11.3	Age matched	67 (100%)	7/4	NA	NA	6
Karatas, 2017 [19]	Turkey	51.4 ± 12.2	48.9 ± 12.5	94 (60%)	NA	−1.5 ± 1.3	−1.7 ± 1.0	6
Jang, 2009 [29]	Korea	48	50	225 (100%)	NA	− 1.4 ± 0.94	− 0.01 ± 0.91	8
Kim, 2016 [30]	Korea	62.3 ± 12.06	Age matched	NA	NA	− 1.5 ± 1.19	− 0.68 ± 1.28	4

BPPV benign paroxysmal positional vertigo, *NA* not available, *NOS* Newcastle-Ottawa Scale
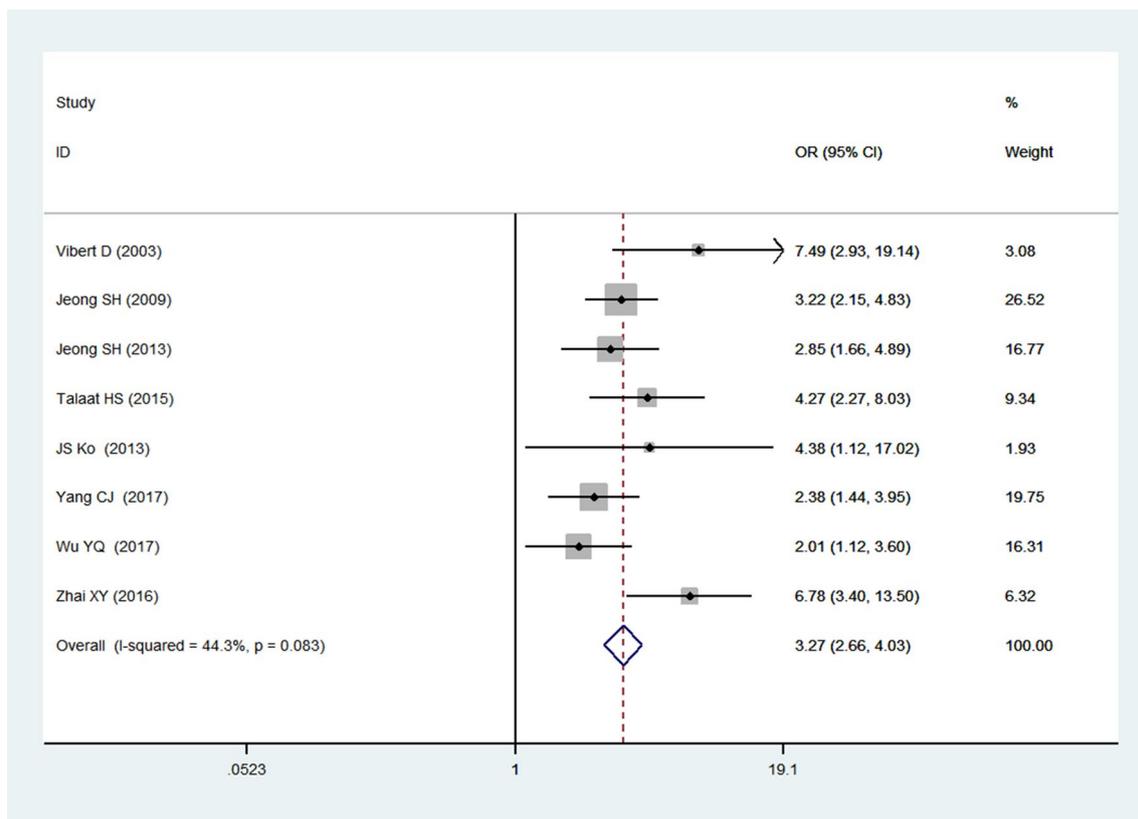

Fig. 2 Forest plot of the incidence of osteoporosis and osteopenia in BPPV patients

Selection criteria

Inclusion criteria: (1) original studies (not reviews); (2) case control or cohort studies; (3) using standardized diagnostic criteria for the diagnosis of BPPV; (4) the outcome was the incidence of osteoporosis and osteopenia or T score in patients with BPPV and controls; (5) BDM was measured in the lumbar spine or femur using dual X-ray absorptiometry or omnisense, the T score was defined as the standard deviation of BDM ,and classified in accordance with the World Health Organization (WHO) classification of BMD: normal ($T > -1$), osteopenia ($-2.5 < T < -1$), osteoporosis ($T < -2.5$) [21].

Exclusion criteria:(1) non-original studies (case report, editorial, summary and basic research); (2) studies with no comparison group; (3) data incomplete and cannot be obtained by contacting authors of the original studies; (4) too low quality of literatures (less than three points); (5) multiple publication or overlapping subjects (if more than one paper report the same or overlapping studies, only the most complete and high quality study was included).

Data extraction and quality assessment

Two researchers (LL H, XQ L) independently extracted data abiding by the pre-defined eligibility criteria, then compared every data point for consistency interactively. The discrepancy was resolved by consulting and discussing with the third researcher (XI L). The following data are extracted from included studies: last name of first author, publication year, country, gender of subjects, prevalence of osteoporosis and osteopenia or T score in patients with BPPV and controls, sample size and average age.

The Newcastle-Ottawa Scale (NOS) [22] was used to assess the quality of each enrolled studies by two researchers (LL H, XQ L) independently. A total of 9 points can be assigned on this scale including case selection (four projects, 4 points), comparability category (one projects, 2 points), exposure assessment (three project, 3 points). High quality (7–9 points), medium quality (4–6 points) and low quality (1–3 points) were set in this meta-analysis. The Newcastle-Ottawa Scale (NOS) [22] was used to assess the quality of each enrolled studies by two researchers independently. A total of 9 points can be assigned on this scale including case selection (four projects, 4 points), comparability category (one projects, 2 points), exposure assessment (three
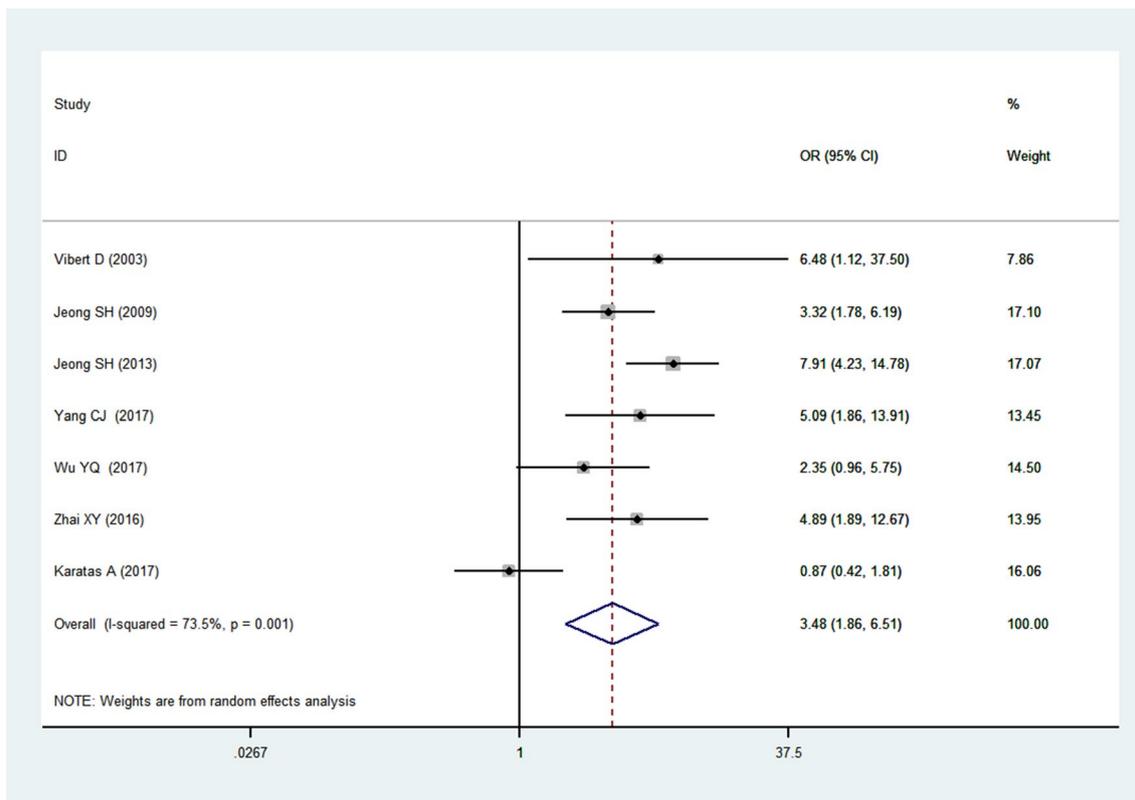

Study ID	OR (95% CI)	% Weight
Vibert D (2003)	6.48 (1.12, 37.50)	7.86
Jeong SH (2009)	3.32 (1.78, 6.19)	17.10
Jeong SH (2013)	7.91 (4.23, 14.78)	17.07
Yang CJ (2017)	5.09 (1.86, 13.91)	13.45
Wu YQ (2017)	2.35 (0.96, 5.75)	14.50
Zhai XY (2016)	4.89 (1.89, 12.67)	13.95
Karatas A (2017)	0.87 (0.42, 1.81)	16.06
Overall (I-squared = 73.5%, p = 0.001)	3.48 (1.86, 6.51)	100.00

NOTE: Weights are from random effects analysis

.0267   1   37.5

Fig. 3 Forest plot of the incidence of osteoporosis in BPPV patients

project, 3 points). High quality (7–9 points), medium quality (4–6 points) and low quality (1–3 points) were set in this meta-analysis.

Statistical analysis

The data were all analyzed using Stata (version 14.0). OR and 95% CI were used to assess the incidence of osteoporosis and osteopenia, SMD and 95% CI were used to assess the T score in patients with BPPV and controls. If the mean and standard deviation of T score were reported separately for subgroups, we combined the results of each category and calculated a pooled T score for the meta-analysis.

The Q test and I^2 statistic were used to evaluate statistical heterogeneity across individual studies. The p value ≥ 0.1 was considered not statistically significant heterogeneity. I^2 value of above 25, 50 and 75% was considered of low, medium and high heterogeneity, respectively. When the combined effects were homogeneous ($p < 0.1$ or $I^2 \geq 50\%$), the fixed-effects model was applied, otherwise, the random-effects model was used. Subgroup analysis was conducted to explore the potential source of heterogeneity. Egger's linear regression test and Begg's rank correlation test were used

to evaluate potential publication bias, p value < 0.1 was considered as a measure of high publication bias. Sensitivity analysis was performed to evaluate the robustness of the meta-analysis by omitting a single study each time and then estimating the combined effects of the remaining studies.

Results

Study selection

Our systematic search finally identified 206 studies. We strictly omitted the duplicates and reviewed the abstracts and titles. Full-texts of 82 potentially eligible records were obtained for further assessment. Eventually, a total of 11 studies were enrolled in our final meta-analysis. The flow-chart in Fig. 1 shows the study search progress.

Study characteristics and study quality

The characteristics of included studies were detailed in Table 1. All our included studies were case–control or cohort studies. Eight studies reported the total incidence of
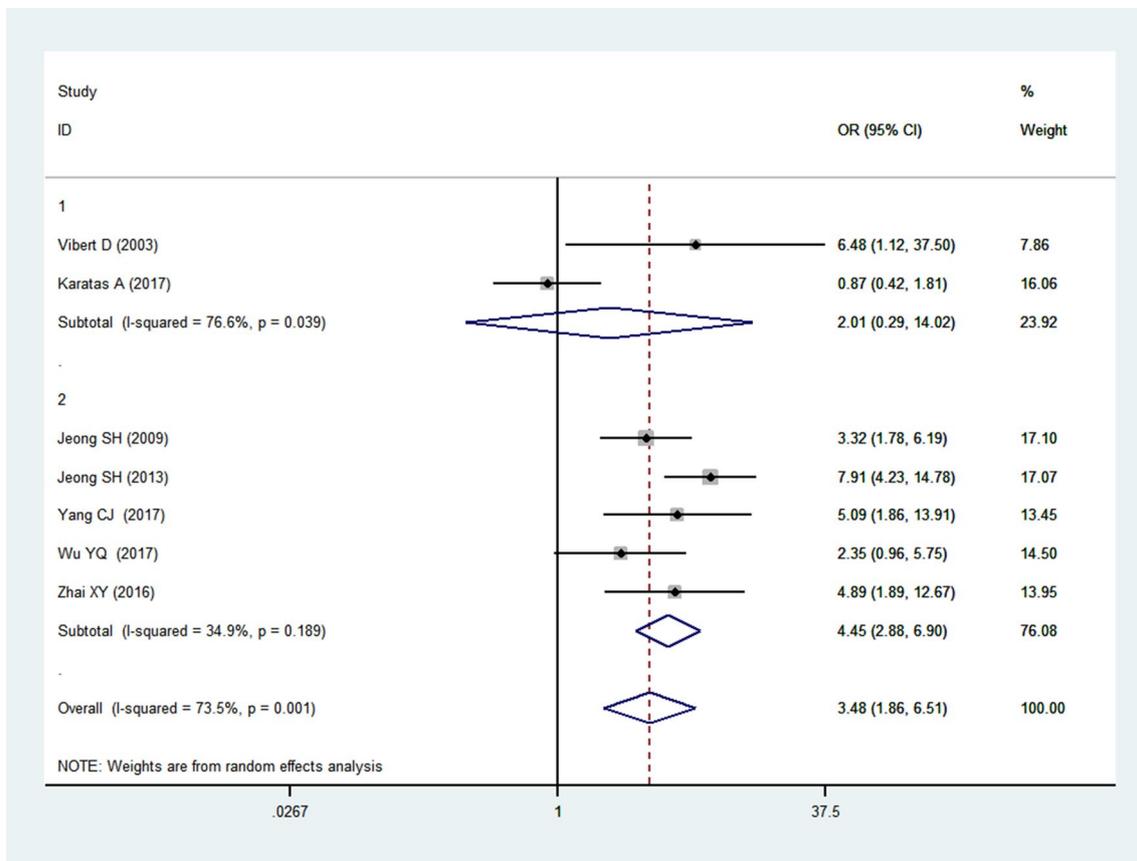

Fig. 4 Forest plot of the incidence of osteoporosis split by race

osteoporosis and osteopenia in BPPV and control groups, furthermore, seven studies reported the incidence of osteoporosis, and six studies reported the incidence of osteopenia, respectively. Nine studies reported the T score of BPPV and control groups. Four studies only analyzed the female. The subjects of eight studies were xanthoderm, two studies were Caucasian and one study was melanoderm. The quality assessment of the included studies was displayed in Table 1. Six of the included studies were considered high quality, another six studies were considered medium quality.

The incidence of osteoporosis and osteopenia in BPPV patients

A total of eight included studies analyzed the incidence of osteoporosis and osteopenia in BPPV patients compared with control groups. The heterogeneity test among individual studies was low ($I^2 = 44.3\%$). consequently, the fixed-effects model was applied. The incidence of osteoporosis and osteopenia in BPPV patients compared with controls was significantly higher (OR 3.27, 95% CI 2.66–4.03, $p < 0.0001$) (Fig. 2).

Publication bias was respectively detected by Egger's test ($p = 0.15$) and Begg's test ($p = 0.27$) indicating that there was no significant publication bias. Sensitivity analysis by

sequential omitting of a single study did not alter the combined effects of the remaining studies, indicating that the results were robust.

The incidence of osteoporosis in BPPV patients

A total of seven included studies analyzed the incidence of osteoporosis in BPPV patients compared with control groups. The heterogeneity among the studies included was medium ($I^2 = 73.5\%$), and the random-effects model was applied. The incidence of osteoporosis in BPPV patients was significantly higher, when compared with controls (OR 3.48, 95% CI 1.86–6.51, $p < 0.0001$) (Fig. 3). Furthermore, to identify the source that may contribute to the heterogeneity, we had conducted a subgroup analysis split by race. The incidence of osteoporosis was higher in xanthoderm BPPV patients compared with controls (OR 4.45, 95% CI 2.88–6.90, $p < 0.0001$) (Fig. 4), and the heterogeneity decreased significantly ($I^2 = 34.9\%$), indicating that race could be main source of heterogeneity.

Moreover, the result of Egger's ($p = 0.99$) and Begg's test ($p = 0.37$) indicated that there was no publication bias. Sensitivity analysis by sequential omission of individual studies did not alter the overall combined OR, suggesting that the results were valid and credible.
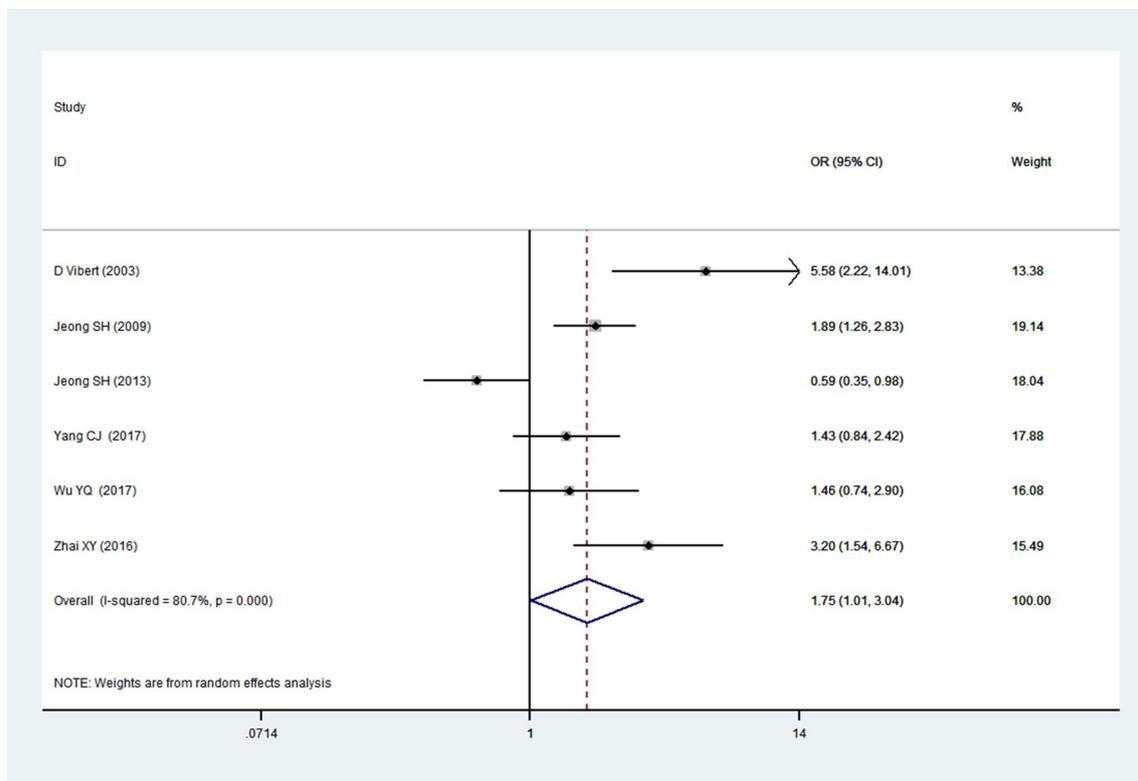

Fig. 5 Forest plot of the incidence of osteopenia in BPPV patients

The incidence of osteopenia in BPPV patients

A total of six included studies analyzed the incidence of osteopenia in BPPV patients compared with control groups. The heterogeneity among individual studies was significantly high ($I^2 = 80.7\%$), thus the random-effects model was applied. The incidence of osteopenia in BPPV patients compared with controls was significantly higher (OR 1.75, 95% CI 1.01–3.04, $p < 0.0001$) (Fig. 5). Subgroup analysis was performed by race, and the incidence of osteopenia in BPPV patients was higher than controls in xanthoderm patients (OR 1.46, 95% CI 0.87–2.47, $p < 0.0001$) (Fig. 6), and the heterogeneity deceased slightly ($I^2 = 77.7\%$), indicating that race may be partly responsible for heterogeneity.

The result of Egger's test ($p = 0.15$) and Begg's test ($p = 0.13$) revealed that there was no significant publication bias. Sensitivity analysis showed that sequential omission of individual studies did not alter the results.

The T score in BPPV patients

A total of nine included studies analyzed T score in BPPV patients compared with controls. The T score in BPPV patients was significantly lower than controls (SMD -0.82, 95% CI -1.18 to -0.46, $p < 0.0001$) (Fig. 7). However, there was significantly statistical heterogeneity among studies ($I^2 = 92.7\%$), consequently, the random-effects model was applied. A subgroup analysis split by mean age was performed, the results showed that the T score in BPPV patients was significantly lower than controls in subgroup (age ≥ 50 years) (SMD -0.54, 95% CI -0.85 to -0.23, $p = 0.001$) (Fig. 8). The significant heterogeneity among mean age deceased but not radically eliminated ($I^2 = 86\%$), indicating that mean age could partly explain source of heterogeneity. We hypothesized that the cause of significant heterogeneity may be the differences in measuring method and location of BMD, gender and the severity of BPPV.

Publication bias was detected by Egger's test ($p = 0.21$) and Begg's test ($p = 0.25$), respectively, which indicated that there was no risk of publication bias. Sensitivity analysis showed that omitting individual studies did not alter the combined effects suggesting that the results were robust.
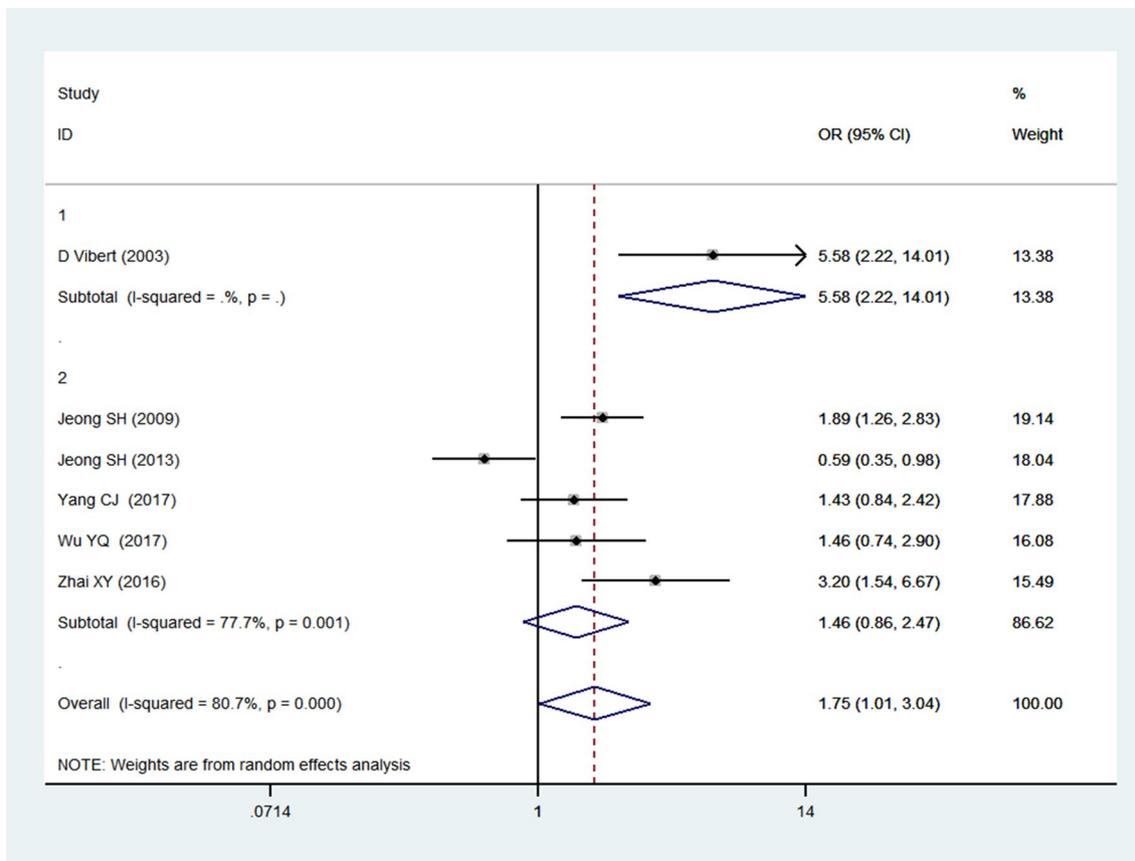

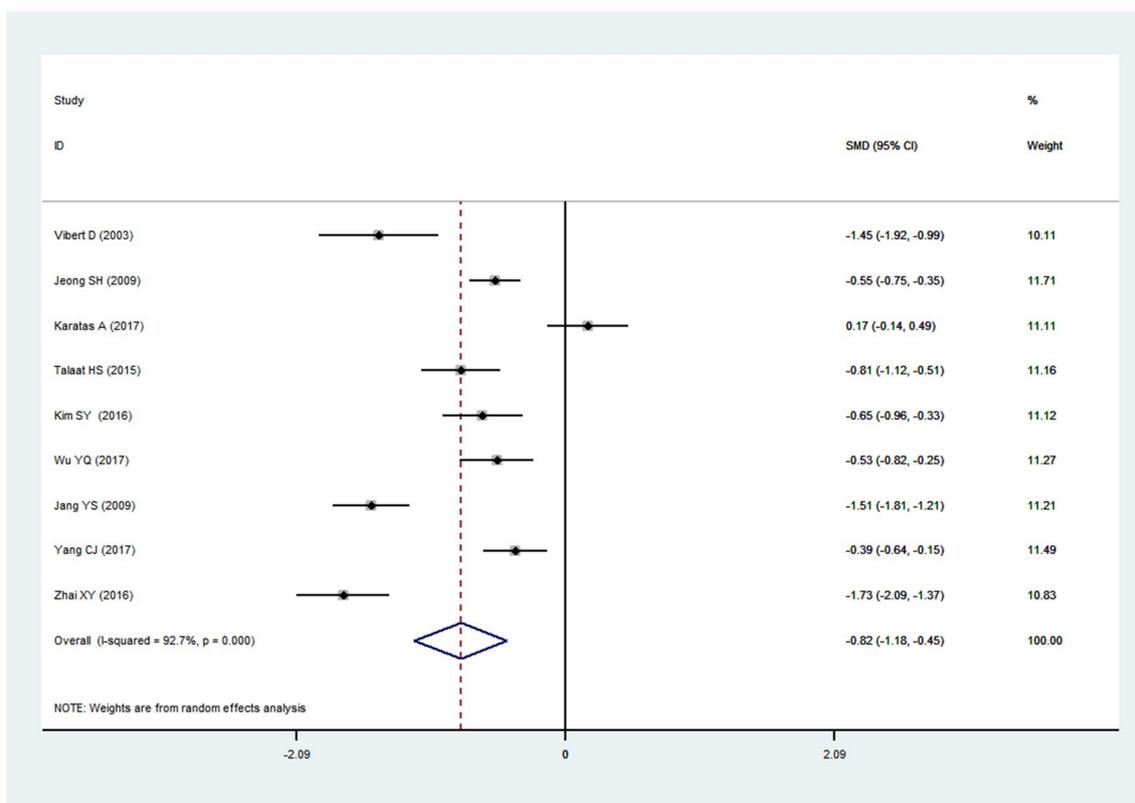**Fig. 6** Forest plot of the incidence of osteopenia split by race

Fig. 7 Forest plot of *T* score in BPPV patients

Discussion

In our systematic review and meta-analysis, we found that patients with BPPV are associated with higher prevalence of osteoporosis and osteopenia especially in xanthoderm and lower *T* score, especially in patients whose age is over 50 years. All of those provided adequate evidence of an association between BPPV and BMD. Previously, a systematic review conducted by Shu-dong et al. [31] trying to clarify the association between osteoporosis and benign paroxysmal positional vertigo, but the evidence was not sufficient, therefore, we carried our meta-analysis and further illustrated the relationship between BPPV and BMD.

Currently, more attention has been focused on the bone turnover and osteoporosis in the etiology of BPPV [32]. Otoconia are composed of a number of proteins, of which otolin-1 is the main protein of otoconia, otolin-1 was considered as a useful biomarker of BPPV [33]. The *T* score was used to define BMD. Sacks et al. [34] found a strong correlation between *T* scores and serum otolin-1 levels further supporting the association between BPPV and osteoporosis. A large retrospective cohort study based on the Taiwanese population reported that patients with osteoporosis had a 1.82-fold increase in the risk of BPPV than those without osteoporosis [35]. Some studies reported that medication (such as calcium

preparations) used to treat osteoporosis may contribute to prevent the occurrence and recurrence of BPPV [36, 37].

At present, there is no consensus on the etiology and pathogenesis of BPPV. It is generally believed that the fragmented otoconcial particles entering canal or adhesion to the ampulla, resulting in vertigo and nystagmus of BPPV [1]. In a study involving elderly rats, the density of otoconia decreased in the rats with osteoporosis/osteopenia compared with controls, the bodies of otoconia were fissured, pitted, penetrated and eventually broken into numerous fragments [38]. Decreased ionized Ca^{2+} level and vitamin D deficiency may account for the association of BPPV and osteoporosis [13, 14]. Calcium metabolism plays a vital role in the synthesis/absorption of otoconia made of calcium carbonate. Calcium is used to mineralize otoconia and to maintain turnover in the otolith disturbances of calcium metabolism cause the anomalous composition of otoconia, otoconia degeneration and eventually BPPV [15]. In addition, a number of investigations straightly showed that low levels of 25(OH)-D associated with occurence and recurrence of BPPV [39, 40]. A study conducted by Parham et al. [41] demonstrated a relationship between vitamin D and otolin-1 in subjects over 70 years. Vitamin D deficiency may indirectly act on calcium homeostasis and induce calcium loss. Vitamin D deficiency decreases calcium absorption and disturbs local
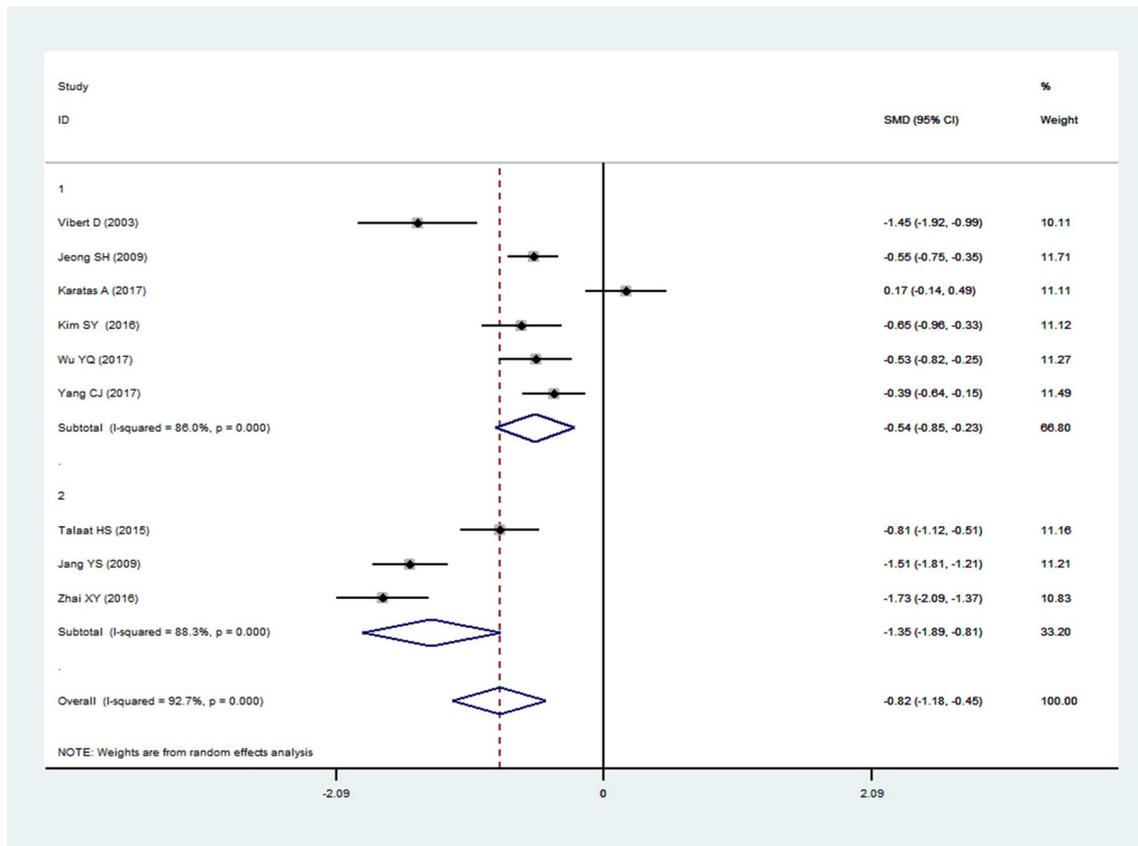
Fig. 8 Forest plot of *T* score split by mean age

calcium homeostasis in the inner ear, eventually leading to destruction of otolith structure or their interconnection. Correction of serum vitamin D deficiency such as received an additional supplement of vitamin D may substantially reduce attacks and recurrence of BPPV [42, 43].

Inevitably, our meta-analysis also has several limitations. First, all studies included were case–control or cohort studies, which were not as reliable as randomized controlled trial (RCTs), therefore, more RCTs studies are expected to be conducted to strongly confirm the relationship between BPPV and bone mineral density. Second, there was a language bias. The included literatures were limited to English, which may lead to the relevant studies published in other language be missed. So we need to expand the range of languages in future study. Finally, significantly statistical heterogeneity was existed among studies of *T* score in BPPV patients and controls. Gender, severity of BPPV and the difference in measuring method and location of BMD may greatly contribute to the heterogeneity, more subgroup analysis are to be conducted to eliminate heterogeneity.

Conclusion

In conclusion, this study confirmed that BMD closely related to BPPV especially in xanthoderm, which has important practical implications for understanding the pathophysiology and proactive management of BPPV. Further studies with a larger population need to be conducted to clarify the pathophysiology and for prevention of BPPV from the perspective of bone metabolism.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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