



# Association between serum vitamin D levels and benign paroxysmal positional vertigo: a systematic review and meta-analysis of observational studies

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## Abstract

**Objective** Benign paroxysmal positional vertigo (BPPV) was the most common neuro-otological disorder manifests as recurrent positional vertigo, but its risk factors are elusive. Recent studies suggest that decreased Vitamin D level may be a risk factor, but the literature is inconsistent.

**Methods** The databases PubMed, Web of Science, Chinese National Knowledge Infrastructure, Wanfang, SinoMed, and Embase were systematically searched for studies on the association between BPPV and serum Vitamin D levels published up to June 2019. Data from eligible studies were meta-analyzed using Stata 12.0.

**Results** A total of 18 studies were included in the analysis. Serum Vitamin D levels were significantly lower in individuals with BPPV than in controls (WMD – 2.46, 95% CI – 3.79 to – 1.12,  $p < 0.001$ ). Subgroup analysis by geographical area showed that vitamin D level was significantly lower in BPPV than in controls in China (WMD – 3.27, 95% CI – 4.12 to – 2.43,  $p < 0.001$ ), but not outside China (WMD – 0.90, 95% CI – 4.36 to 2.56,  $p = 0.611$ ). Vitamin D levels were significantly lower in recurrent than non-recurrent BPPV across all countries in the sample (WMD 2.59, 95% CI 0.35–4.82,  $p = 0.023$ ). Vitamin D deficiency emerged as an independent risk factor of BPPV (OR 1.998, 95% CI 1.400–2.851,  $p < 0.001$ ).

**Conclusion** The available evidence suggests that BPPV is associated with decreased levels of serum Vitamin D, and vitamin D deficiency was an independent risk factor for BPPV.

**Keywords** Benign paroxysmal positional vertigo · Otolithiasis · Serum vitamin D · Meta-analysis

Baiyuan Yang, Yongxia Lu and Dongmei Xing contribute equally to the present research.

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## Introduction

Benign paroxysmal positional vertigo (BPPV), the most common neuro-otological disorder, manifests as recurrent positional vertigo. BPPV is believed to arise when the otoconia dislodges into the semicircular canals [1]. Otoconia crystals, composed of calcium carbonate and an organic core consisting predominantly of glycoproteins, form in low-calcium endolymph through a tightly controlled process; the crystals feature a predominantly organic core low in  $\text{Ca}^{2+}$  and a predominantly inorganic,  $\text{Ca}^{2+}$ -rich peripheral zone [2]. What causes otoconia to degenerate and detach from the otoconial beds is unclear. Several factors appear to contribute to these processes, including vitamin D deficiency, advanced age, high body mass index (BMI), head trauma, hypeluricemia, and osteoporosis.

Since vitamin D (25-hydroxyvitamin D3) regulates calcium metabolism, dysregulation may lead to BPPV. Indeed, several studies have shown that vitamin D levels are lower in

BPPV patients than in controls [3–9]. However, other studies failed to replicate these results [10, 11] or even reported that vitamin D levels were elevated in BPPV patients [12]. To help resolve this inconsistency, we meta-analyzed the available literature on vitamin D levels in BPPV patients and controls, as well as the association between vitamin D level and risk of BPPV recurrence. Our goal was to determine conclusively whether vitamin D deficiency is a risk factor for BPPV.

## Methods

### Search strategy

The databases PubMed, Web of Science, Chinese National Knowledge Infrastructure, Wanfang, SinoMed, and Embase were systematically searched for eligible studies published up to June 2019. The search string was as follows: [“vitamin D” or “calcifediol” or “25(OH)vitamin D” or “25-hydroxylvitamin D” or “25-hydroxyvitamin D” or “25(OH)D”] and [“benign paroxysmal positional vertigo” or “BPPV” or “BPV”]. No language or date restrictions were applied.

### Study selection criteria

To be included in the present study, the studies had to (1) be case–control studies analyzing the association between BPPV and serum vitamin D; (2) be cohort studies analyzing the association between BPPV recurrence and vitamin D; (3) be studies analyzing vitamin D deficiency as an independent factor of BPPV; (4) clearly define cases and controls (in case–control studies); (5) report mean levels of serum vitamin D for cases/controls or for recurrent/non-recurrent BPPV groups, or sufficient data to calculate these values; or (6) report the odds ratio (OR) and 95% confidence interval (CI) for risk of BPPV based on vitamin D level. If more than one study evaluated the same cohort, only the study with the most complete data was included.

Studies were excluded if they were reviews, editorials, case reports, commentaries, or critiques; or if they failed to report sufficient data for meta-analysis.

### Data extraction

Two researchers (XL Yang and BY Yang) searched the literature and collected data following predefined criteria. Inconsistencies were resolved through consultation with a third author (W Zhong). The following information was collected (Table 1): surname of the first author, country of study cohort, publication year, serum vitamin D levels, as well as ORs and 95% CIs for multiple factor analyses.

## Quality assessment of studies

Two reviewers (XL Yang and BY Yang) independently assessed the quality of studies using the Newcastle–Ottawa quality assessment scale [13]. Discrepancies were resolved through consultation with a third author (W Zhong). Scores  $\geq 6$  indicated a study of high quality (Table 2, 3).

## Statistical analysis

Heterogeneity across studies was evaluated by calculating  $I^2$ :  $I^2 < 25\%$  was recognized as homogeneity;  $25\% \leq I^2 < 50\%$ , low heterogeneity;  $50\% \leq I^2 < 75\%$ , moderate heterogeneity; and  $I^2 > 75\%$ , substantial heterogeneity [14]. Pooled results were meta-analyzed using a fixed-effects model if studies were homogeneous or of low heterogeneity; a random-effects model was used if studies showed moderate or substantial heterogeneity. Meta-analyses were performed using Stata 12.0 (StataCorp, USA). We also pooled ORs and 95% CIs for multiple-factor analysis to examine whether deficiency of vitamin D is a risk factor for BPPV. Where appropriate, pooled results were reported as weighted mean difference (WMD) and 95% CI. Significance was defined as  $p < 0.05$ . Egger’s and/or Begg’s tests were conducted to evaluate risk of publication bias [14, 15].

## Results

### Literature search and included studies

After database searches and removal of duplicates, 62 potentially eligible articles were identified, of which 41 were excluded based on titles and abstracts (Fig. 1). Of the remaining 21 studies read in full, two were excluded, because no detailed serum vitamin D level was reported, and another two were excluded, because they explored only the treatment effects of vitamin D.

The remaining 18 studies involved 1859 BPPV cases and 1495 controls [3–12, 16–23]. Eight studies were conducted in China and nine outside (Table 1). Nine studies compared the serum level of vitamin D between BPPV and controls [4–12], while eight compared the vitamin D levels between recurrent and non-recurrent BPPV (Table 1) [3, 11, 17–20, 22]. Eight studies used multiple logistic regression to investigate whether vitamin D deficiency is an independent risk factor for BPPV [4–9, 21, 23].

### Comparison of serum vitamin D levels between BPPV and controls

A random-effects model was used to meta-analyze the 9 studies because of their high heterogeneity ( $I^2 = 70.1\%$ ,

**Table 1** Main characteristics of studies on benign paroxysmal positional vertigo (BPPV) and serum Vitamin D included in this review

Study	Country	Year	Type of study	Age in case (yr)	Case	Vitamin D in case (ng/ml)	Vitamin D in control (ng/ml)	Vitamin D in non-recurrent (ng/ml) (n)	Vitamin D in recurrent (ng/ml)(n)	OR, 95% CI
Büki [3]	Austria	2013	Cohort	67 (45–85)	18	NA	NA	27 ± 15.56 (14)	14 ± 2.22 (4)	NA
Jeong [9]	Korea	2013	Case-control	61.8 ± 11.6	100	14.4 ± 8.4	19.1 ± 6.8	NA	NA	3.8, 1.51–9.38
Talaat	Egypt	2014	Case-control	Non: 47 ± 8.9 R: 48.3 ± 9.4	80	NA	19.53 ± 8.45	16.04 ± 10.26 (44)	11.93 ± 7.57 (36)	NA
Gu II Rhim	Korea	2016	Cohort	50.35 (13–88)	232	16.1 ± 7.4	NA	16.63 ± 7.4 (191)	13.64 ± 6.97 (41)	NA
Han	China	2017	Case-control	63.5 ± 9.72,	85	19.1 ± 5.2	22.5 ± 5.8	NA	NA	2.1, 1.1–3.9
Karataş	Turkey	2017	Case-control	51.4 ± 12.2	78	23.0 ± 14.4	17.0 ± 12.3	NA	NA	NA
Lee	Korea	2017	Case-control	63.0 ± 10.0	132	NA	NA	NA	NA	2.0, 0.93–1.03
Işik	Turkey	2017	Case-control	56.2 ± 13.5 (F), 55.7 ± 12 (M)	64	9.51 ± 5.49	11.02 ± 9.62	NA	NA	NA
Yang	Korea	2017	Case-control	54.9 ± 12.2	130	18.21 ± 10.3	20.0 ± 8.1	17.2 ± 9.4 (67)	19.3 ± 11.1 (63)	NA
Chen W	China	2017	Case-control	Non: 58.1 ± 13.7 R: 57.9 ± 12.6	249	NA	24.6 ± 8.8	19.0 ± 7.6 (207)	18.1 ± 6.6 (42)	NA
Maslovara	Croatia	2018	Cohort	64 ± 12	31	20.8 ± 7.87	NA	19.11 ± 6.27 (26)	22.88 ± 13.77 (5)	NA
Zhang X	China	2018	Case-control	Non: 58.81 ± 6.36 R: 60.93 ± 8.01	78	NA	NA	18.45 ± 4.28 (63)	17.15 ± 6.04 (15)	NA
Wu 2	China	2018	Case-control	Non-60.1 ± 9.43 R: 59.08 ± 10.21	67	50.56 ± 13.36	56.55 ± 16.21	NA	NA	2.054, 1.088–3.877
Wang	China	2018	Case-control	62.0 ± 9.0	176	NA	30.3 ± 17.9	NA	NA	2.0, 0.94–3.33
Wu 1	China	2018	Case-control	59.4 ± 13.2	60	20.99 ± 6.76	23.17 ± 6.49	NA	NA	3.8, 1.25–11.73
Wu 2	China	2018	Case-control	50.56 ± 13.36	67	NA	NA	NA	NA	2.054, 1.088–3.877
Ding	China	2019	Case-control	Case: 61 (54–69)	174	18.41 ± 8.67	22.6 ± 6.92	19.26 ± 7.94 (143)	13.2 ± 10.57 (31)	2.15, 1.30–4.32
Zhang W	China	2019	Case-control	48.66 ± 11.63	38	15.78 ± 6.82	19.4 ± 7.36	NA	NA	NA

Non non-recurrent BPPV, R recurrent BPPV, NA not available, OR odds ratio, CI confidence interval

**Table 2** Quality assessment for case–control study

Study	Year	Score on dimensions			Total score
		Selection	Exposure	comparability	
Jeong	2013	4	2	2	8
Talaat	2014	3	2	2	7
Han	2017	3	3	1	7
Karataş	2017	3	2	1	6
Lee	2017	3	3	1	7
Isik	2017	3	2	1	6
Yang	2017	3	2	1	6
Chen W	2017	3	2	1	6
Zhang X	2018	4	3	1	8
Wu 2	2018	3	3	1	7
Wang	2018	3	3	1	7
Wu 1	2018	3	2	1	6
Ding	2019	3	2	1	6
Zhang W	2019	3	2	1	6

Non non-recurrent BPPV, R recurrent BPPV, NA not available, OR odds ratio, CI confidence interval

$p < 0.001$ ). Serum Vitamin D levels were significantly lower in individuals with BPPV than in controls (WMD  $-2.46$ , 95% CI  $-3.79$  to  $-1.12$ ,  $p < 0.001$ ; Fig. 2). Sensitivity analysis showed that none of the 9 studies significantly affected the meta-analysis results (Supplementary Fig. 1). The funnel plot was visually symmetrical (Fig. 3) and non-significant results were indicated by Egger's test ( $p = 0.348$ ) and Begg's test ( $p = 0.410$ ), suggesting no significant publication bias.

Subgroup analysis by geographical area showed that vitamin D level was significantly lower in BPPV than in

controls in China (WMD  $-3.27$ , 95% CI  $-4.12$  to  $-2.43$ ,  $p < 0.001$ ), but not outside China (WMD  $-0.90$ , 95% CI  $-4.36$  to  $2.56$ ,  $p = 0.611$ ; Fig. 2).

### Comparison of serum vitamin D levels between recurrent and non-recurrent BPPV

There was moderate heterogeneity among the 8 studies comparing vitamin D levels between recurrent and non-recurrent BPPV, so a random-effects model was applied. Vitamin D levels were significantly lower in recurrent than non-recurrent BPPV across all countries in the sample (WMD  $2.59$ , 95% CI  $0.35$ – $4.82$ ,  $p = 0.023$ ; Fig. 4). However, in subgroup analysis by geographical region, vitamin D levels were similar between recurrent and non-recurrent BPPV within China (WMD  $2.45$ , 95% CI  $-0.37$  to  $5.27$ ,  $p = 0.089$ ; Fig. 4) and outside China (WMD  $2.83$ , 95% CI  $-1.11$  to  $6.78$ ,  $p = 0.16$ ). The funnel plot was visually symmetrical (Fig. 5), and non-significant results were obtained in Egger's test ( $p = 0.836$ ) and Begg's test ( $p = 0.711$ ), suggesting no significant publication bias. Sensitivity analysis showed that none of the eight studies significantly affected the meta-analysis when removed (Supplementary Fig. 2).

### Meta-analysis of multiple logistic regression to assess vitamin D deficiency as a risk factor for BPPV

Eight studies applied multiple logistic regression to identify whether vitamin D deficiency is a risk factor for BPPV (Table 1). The pooled data were meta-analyzed using a random-effects model because of the high heterogeneity. Vitamin D deficiency emerged as an independent

**Table 3** Quality assessment for cohort study

Study	Büki 2013	Gu Il Rhim 2016	Maslovara 2018
<i>Selection</i>			
Representativeness of the exposed cohort	1	1	1
Selection of the non-exposed cohort	0	0	0
Ascertainment of exposure	1	1	1
Demonstration that outcome of interest was not present at start of study	0	0	0
<i>Comparability</i>			
Comparability of cohorts on the basis of the design or analysis	1	1	1
<i>Exposure</i>			
Ascertainment of exposure	1	1	1
Was follow-up long enough for outcomes to occur	0	0	0
Adequacy of follow up of cohorts	1	1	1
Total	5	5	5

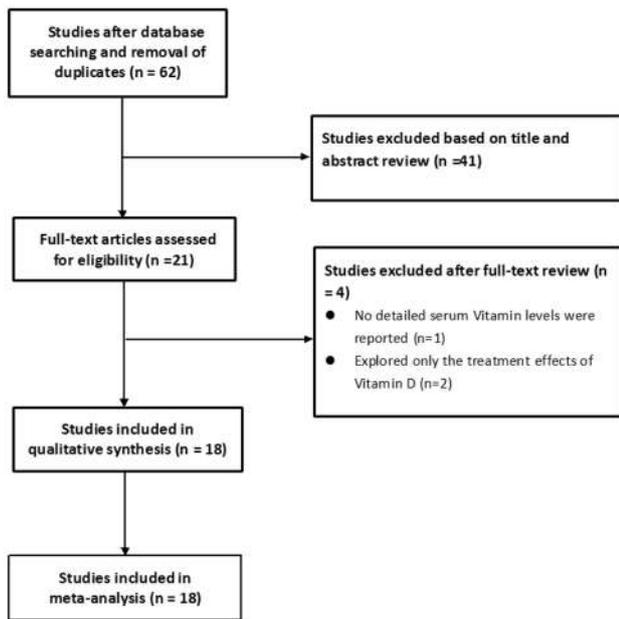
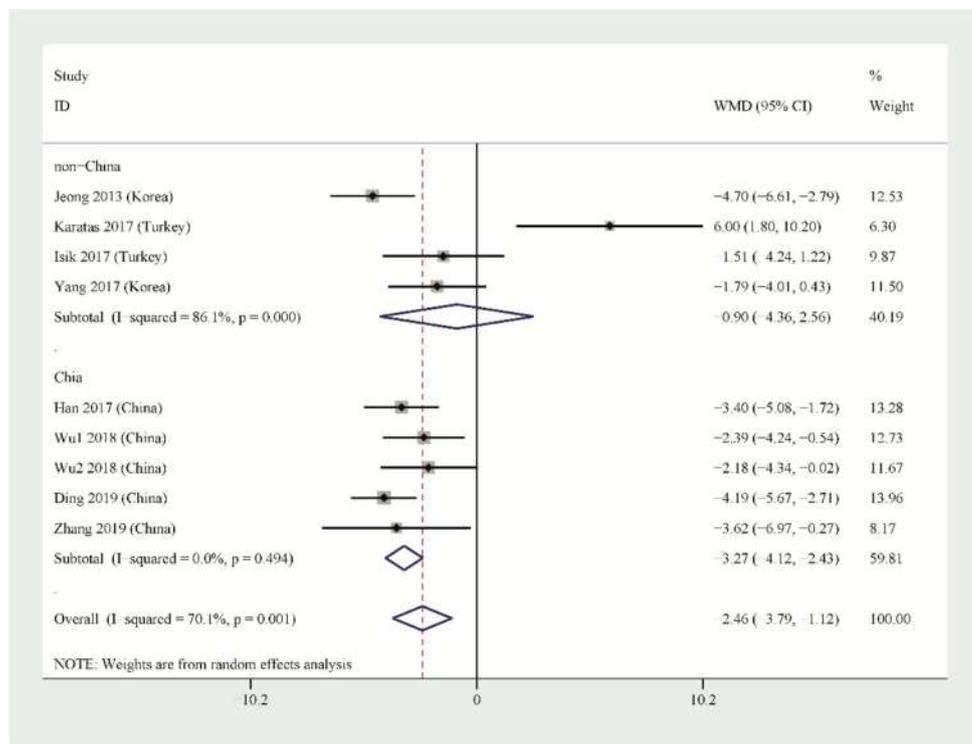


Fig. 1 Flow diagram of study selection

risk factor of BPPV (OR 1.998, 95% CI 1.400–2.851,  $p < 0.001$ ; Fig. 6). No significant risk of publication bias was observed based on the funnel plot (Fig. 7), in Egger’s test (0.887) or in Begg’s test ( $p = 0.711$ ).

Fig. 2 Forest plot of vitamin D levels in BPPV and control groups across all studies, in the subset of studies conducted within China or in the subset conducted outside China. The x-axis shows the 95% confidence interval. WMD weighted mean difference



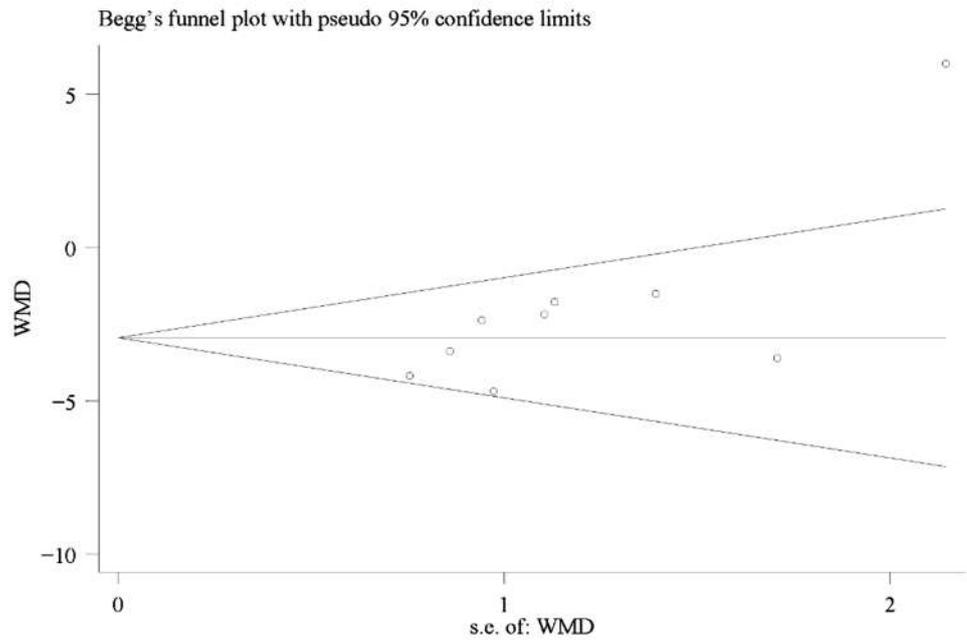
## Discussion

Our meta-analysis suggests that the serum level of vitamin D is lower in patients with BPPV, especially recurrent BPPV, than in controls. In addition, vitamin D deficiency ( $< 20 \text{ ng/dl}$ ) appears to be an independent risk factor for BPPV.

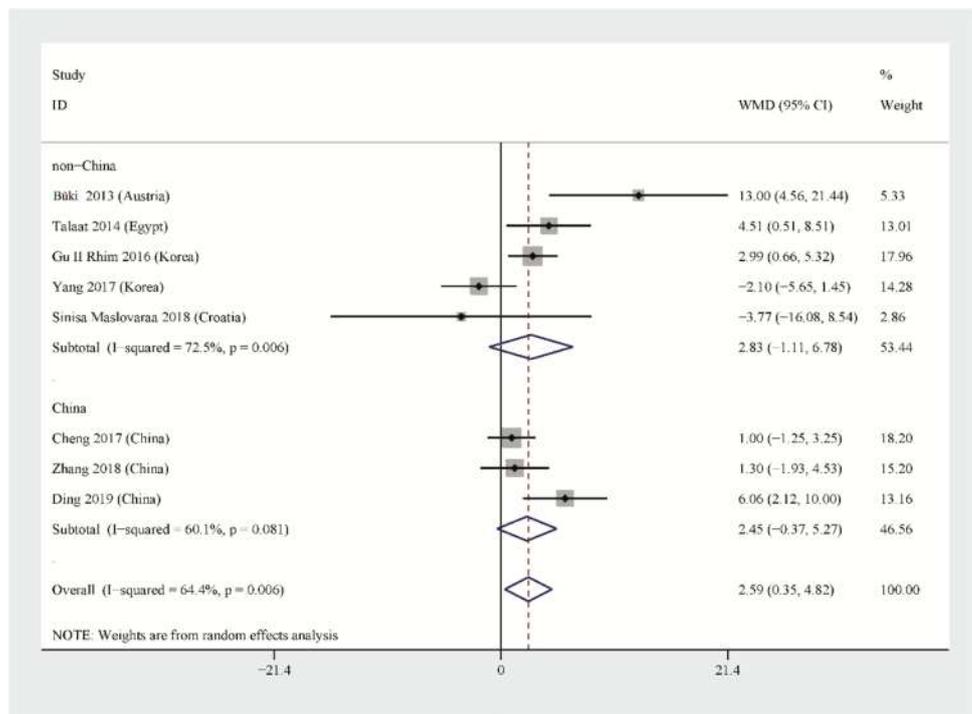
The main cause of BPPV appears to be the dissolution and dislodging of otoconia. When the free calcium concentration in internal lymphatic fluid is  $20 \mu\text{M}$ , otoconia can dissolve completely; when the concentration is  $500 \mu\text{M}$ , the crystals do not dissolve [24]. Vitamin D can help maintain a sufficiently high free calcium concentration in the inner lymphatic fluid to prevent excessive dissolution of otoconia:  $1,25\text{-}(\text{OH})_2$  vitamin D3 increases the expression of transient receptor potential vanilloid 5 to transport calcium from the epithelial cells of the utricle and saccule into cells, and  $1,25\text{-}(\text{OH})_2$  vitamin D3 also up-regulates calcium buffer proteins in the semicircular canal duct [25]. Vitamin D deficiency may disrupt calcium metabolism and lead to otoconia dissolution, as supported by studies of mice lacking the vitamin D receptor [26]. Indeed, lower vitamin D levels are associated with osteoporosis, which is a risk factor of BPPV, and raising serum levels of 25-hydroxyvitamin D3 can reduce BPPV intensity and recurrence [27, 28].

The present meta-analysis provides clear, comprehensive evidence of a close relationship between serum vitamin D levels and BPPV. At the same time, several limitations should be considered. One is that the individual studies were

**Fig. 3** Funnel plot of weighted mean difference (WMD) in vitamin D levels between BPPV and control groups



**Fig. 4** Forest plot of vitamin D levels in recurrent or non-recurrent BPPV. The x-axis shows the 95% confidence interval. WMD weighted mean difference

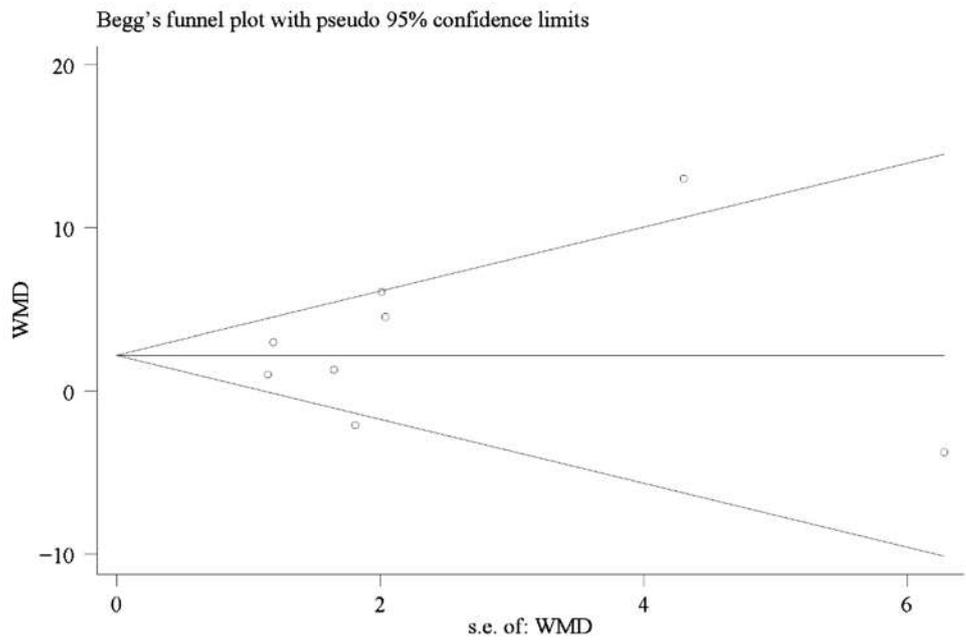


fairly small, involving from 18 to 249 BPPV patients. Nevertheless, the overall meta-analysis involved a substantial sample of 1859 BPPV cases and 1495 controls. Second, we cannot exclude the possibility of publication bias, although Egger’s and Begg’s tests suggested no significant risk. Third, future work should examine potential associations between vitamin D level and BPPV subtypes: for example, patients

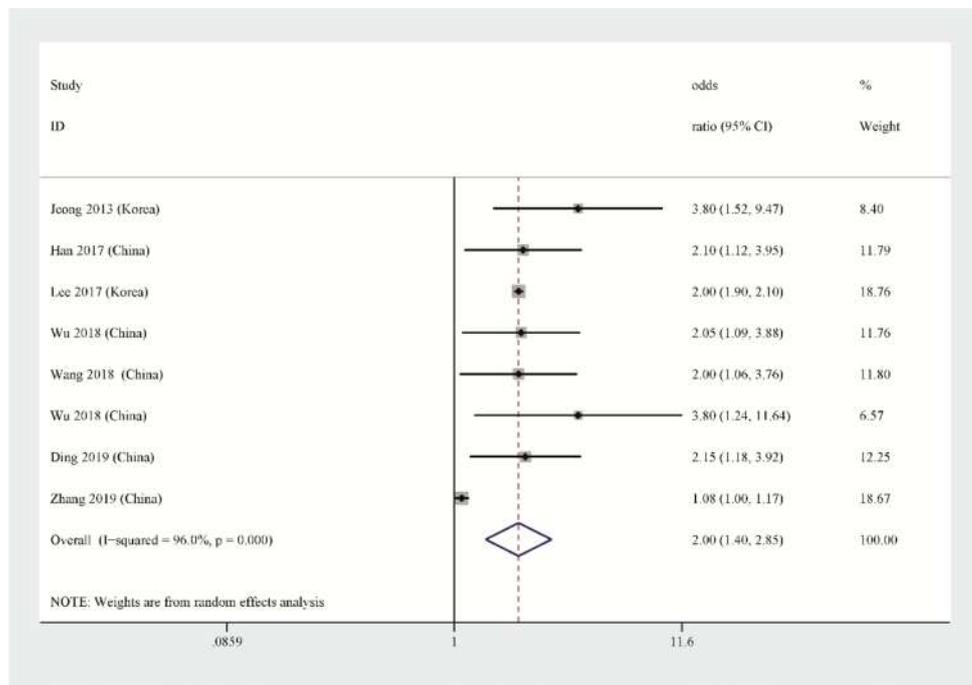
with canalolithiasis have lower vitamin D levels than those with cupulolithiasis. Future studies should also take into account factors that can affect vitamin D levels, including season, weather, skin color, lifestyle, diet and vitamin assay.

Even with these limitations, our meta-analysis provides strong evidence that decreased vitamin D levels was associated with BPPV and Vitamin D deficiency was an

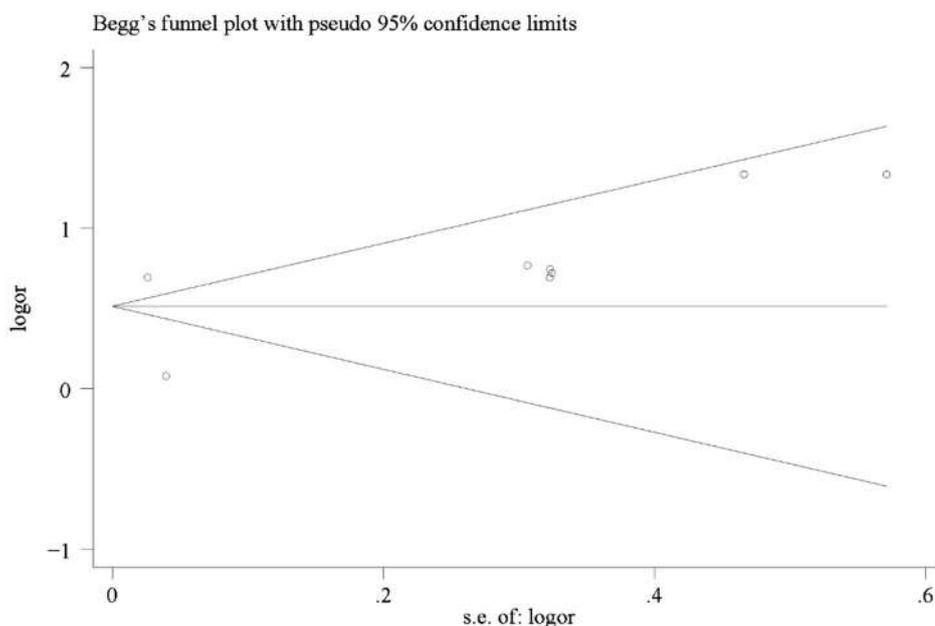
**Fig. 5** Funnel plot of weighted mean difference (WMD) in vitamin D levels between recurrent and non-recurrent BPPV



**Fig. 6** Forest plot of vitamin D deficiency as an independent risk factor for BPPV across all studies. The x-axis shows the 95% confidence interval



**Fig. 7** Funnel plot of vitamin D deficiency as an independent risk factor for BPPV



independent risk factor for BPPV. Vitamin D supplementation may reduce BPPV intensity and recurrence. Our findings should be verified and extended in large, well-designed studies involving multiple ethnic groups.

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### Compliance with ethical standards

**Conflict of interest** The authors declare no conflicts of interest.

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