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Systematic Review

Association of Vitamin D Levels with Risk of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of Prospective Studies

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Abstract.
Background: Emerging evidence suggests the potential relationship between vitamin D deficiency and risk of cognitive impairment or dementia. To what extent the excess risk of dementia conferred by vitamin D deficiency is less clear.
Objective: We summarized the current evidence from several aspects and further quantified these associations.
Methods: We collected relevant prospective cohort studies by searching PubMed, Embase and Cochrane up to July 2023. The pooled relative risks (RR) were evaluated by random-effects models. Dose-response analyses were conducted by the method of two-stage generalized least squares regression.
Results: Of 9,267 identified literatures, 23 were eligible for inclusion in the meta-analyses, among which 9 and 4 literatures were included in the dose-response analyses for the risk of dementia and Alzheimer's disease (AD). Vitamin D deficiency exhibited a 1.42 times risk for dementia (95% confidence interval (CI) = 1.21–1.65) and a 1.57-fold excess risk for AD (95% CI = 1.15–2.14). And vitamin D deficiency was associated with 34% elevated risk with cognitive impairment (95% CI = 1.19–1.52). Additionally, vitamin D was non-linearly related to the risk of dementia ($p_{nonlinearity} = 0.0000$) and AD ($p_{nonlinearity} = 0.0042$). The approximate 77.5–100 nmol/L 25-hydroxyvitamin D [25(OH)D] was optimal for reducing dementia risk. And the AD risk seemed to be decreased when the 25(OH)D level >40.1 nmol/L.
Conclusions: Vitamin D deficiency was a risk factor for dementia, AD, and cognitive impairment. The nonlinear relationships may further provide the optimum dose of 25(OH)D for dementia prevention.

Keywords: Alzheimer's disease, cognitive impairment, dementia, dose-response, meta-analysis, vitamin D

INTRODUCTION

Due to the global population aging, the number of individuals with dementia is increasing, which has become a major health challenge with rapidly growing burden in modern societies [1]. The underlying etiology of dementia was complicated with genetic

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and environmental factors [2]. In fact, about one-third of Alzheimer's disease (AD) cases could be explained by potential modifiable risk factors [3]. Given that there exist no available effective strategies for dementia especially AD, during the long prodromal period, appropriate emphasis should be focused on the prevention of dementia via addressing the modifiable risk factors.

Dietary nutritional deficiencies are commonly considered as risk factors for dementia, particularly, approximately 1 billion individuals suffer from vitamin D insufficiency globally and vitamin D deficiency is more common in the elderly [4, 5]. Notably, vitamin D is fat-soluble and its receptors are expressed in the central nervous system especially the hippocampal pyramidal regions, which may exert a crucial role in memory function [6]. The indicators of serum or plasma 25-hydroxyvitamin D [25(OH)D] could reflect the vitamin D level in the body [7]. However, controversies still persisted among a number of prospective studies exploring the relationships between the 25(OH)D level and cognitive disorders. Several meta-analyses explored the effects of vitamin D deficiency or sufficient vitamin D on the risk of dementia, AD and cognitive impairment, whereas a global consensus was restricted by the small number and the types of included studies [8–16]. The quantification of the above relationships was assessed only in few findings [10, 12], the cutoffs and the optimum value of vitamin D for cognitive health need to be further validated. Thus, we aimed to conduct inclusive and comprehensive meta-analyses and dose-response analyses of prospective studies to determine the relationship between the vitamin D level and the risk of dementia, AD, and cognitive impairment.

METHODS

Search strategy

We systematically searched PubMed, EMBASE, and the Cochrane Database from inception to July 28, 2023, according to the recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [17] (Supplementary Material). The registration information is available on the PROSPERO and the registration number is CRD42023448539. We restricted our searching in English papers, using the following full search strategy: ("Vitamin D" OR "25 hydroxyvitamin D" OR "calciferol*" OR "ergocalciferol*" OR "eldecalcitol*" OR "cholecalciferol*" OR "alphacalcidol*" OR "calcitriol*" OR "calcidiol*" OR "calcifediol*" OR "calciferol*" OR "dihydroxycholecalciferol" OR "alfacalcidol" OR "paricalcitol" OR "doxercalciferol" OR "1,25 dihydroxyvitamin d3") AND ("dementia" OR "Alzheimer" OR "mild cognitive impairment" OR "cognit*" OR "memory"). Bibliographies of relevant publications were also hand-searched for complement.

Selection criteria

Studies were included if they: 1) were prospective cohort studies; 2) assessed the relationship between vitamin D level and cognitive disorders (cognitive impairment and dementia); 3) reported multivariate adjusted relative risk (RR), hazard ratio (HR) or odds ratio (OR); 4) proposed explicit definitions of 25(OH)D categories; 5) had at least a 2-year follow-up. Literatures were excluded for the following reasons: 1) case-control studies, cross-sectional studies or clinical trials; 2) using continuous variables of vitamin D measurement; 3) individuals with dementia or cognitive impairment at baseline; 4) individuals with dementia death as the outcome. The criteria were conducted by two independent researchers, and any disagreement would be reassessed detailly by consensus with a third reviewer.

Data extraction

Two independent investigators systematically extracted the following data, including name of the first author, publication year, cohort name, study design, the region of population, age, gender, follow-up duration, sample size, method of assessing 25(OH)D levels, measurement of outcome, case number for analysis, statistical models, measures of effect size, and adjustment variables. If there was gender/race stratification, we would regard the results separately following different genders/races. When the same population was reported by at least two literatures, we incorporated the literature with larger sample size into the same analysis; however, all these literatures would be included in different analyses. If the RR/HR was not available, we would convert OR to RR by particular formulae and calculate the effect estimates of RR/HR using the raw data [18]. Any controversies were resolved by discussion.

Quality assessment of studies

The quality of the included studies was evaluated by the Newcastle-Ottawa Scale (NOS), including three sections of selection (4 points), comparability (2 points), and outcome (3 points) [19]. Based on this scale, a study can get between 0 and 9 points, with higher scores representing the higher quality.

Risk of bias in 25(OH)D categories

Considering the differences among 25(OH)D categories, we generally classified all these literatures into two subgroups.

The first subgroup analysis was based on the clinical guidelines of The Endocrine Society, the mean level of 25(OH)D was classified into four categories: adequate (>75 nmol/L), insufficient (50–75 nmol/L), deficient (25–50 nmol/L), and severely deficient (<25 nmol/L) [20]. With the adequate 25(OH)D level (>75 nmol/L) as the reference, we included approximately 7 articles for the risk of dementia and 5 articles for cognitive impairment. In some literatures, the lowest 25(OH)D level was defined <50 nmol/L, we also incorporated this group into the category of 25–50 nmol/L for a greater sample size analysis [21–26].

In the second subgroup analysis, the sufficient 25(OH)D concentration (≥50 nmol/L) was considered as the reference category, according to the 25(OH)D levels using clinically relevant cut-points: <25 nmol/L (severely deficient), 25–50 nmol/L (deficient), and ≥50 nmol/L (sufficient) [27]. There were about 10 articles for the risk of dementia, 6 articles for AD, and 5 articles for cognitive impairment using this guideline. We expanded the classification criteria to enlarge the number of individuals included. Specifically, in three literatures, the boundary of the category was similar to the above classification criteria, we also incorporated these articles into this second subgroup analysis [28–30]. Additionally, in another literature, the 25(OH)D categorization followed cut-off values of <50 nmol/L as insufficiency, we classified the insufficient (<50 nmol/L) 25(OH)D into the category of 25–50 nmol/L for further analysis [31].

Statistical analysis

A random-effects model was used to calculate the summary effect of 25(OH)D categories on the risk of cognitive disorders. In addition, we conducted subgroup analyses based on different categories of 25(OH)D level.

The heterogeneity among studies was assessed by I^2 statistic and Cochrane Q test, with $I^2 < 40\%$ being considered as possibly low heterogeneity. Sensitivity analyses were carried out by deleting each study sequentially to inspect the source of heterogeneity and the stability of the results. Regarding those studies with moderate or high heterogeneity, we also utilized univariate meta regression analyses to explore whether the potential variables [the source of participants (population or community), the region of participants, sample size, follow-up years, the source of 25(OH)D (serum or plasm), NOS scores, and significant adjust factors like vitamin D supplement intake and *Apolipoprotein E* (*APOE*)] would be a confounder in the model or not. If the significant mediators were found, we would further perform subgroup analyses. Additionally, publication bias was examined using the Egger and Begg test and the trim-and-fill method was used to adjust the possible statistically significant bias [32, 33].

Afterwards, the method of two-stage generalized least squares trend estimation was adopted to depict dose-response analyses for 25(OH)D level by per nmol/L [34, 35]. First, we evaluated the potential curve association between 25(OH)D level and dementia or AD in the restricted cubic spline models with three knots at 25, 50, and 75% of the 25(OH)D level distribution. Second, we pooled study-specific trends and judged the non-linearity by testing the null hypothesis that the regression coefficient of the second spline equals zero. More specifically, as the reference category should be the least exposure in dose-response analyses, the effect size would be recalculated using the method by Orsini et al. when necessary [36]. Furthermore, if the median or mean 25(OH)D level of each category was unavailable, we regarded the midpoint of the lower and upper bound as the mean level. For studies with an open-ended upper/lower boundary, the boundary of 25(OH)D level was estimated to have the same range as the adjoining category.

All statistical analyses and figure preparation were conducted via R software (version 4.3.1), with the two-tailed $p < 0.05$ for statistical significance.

RESULTS

After literature searching and selection, a total of 7,779 papers were found after deduplication. 7,383

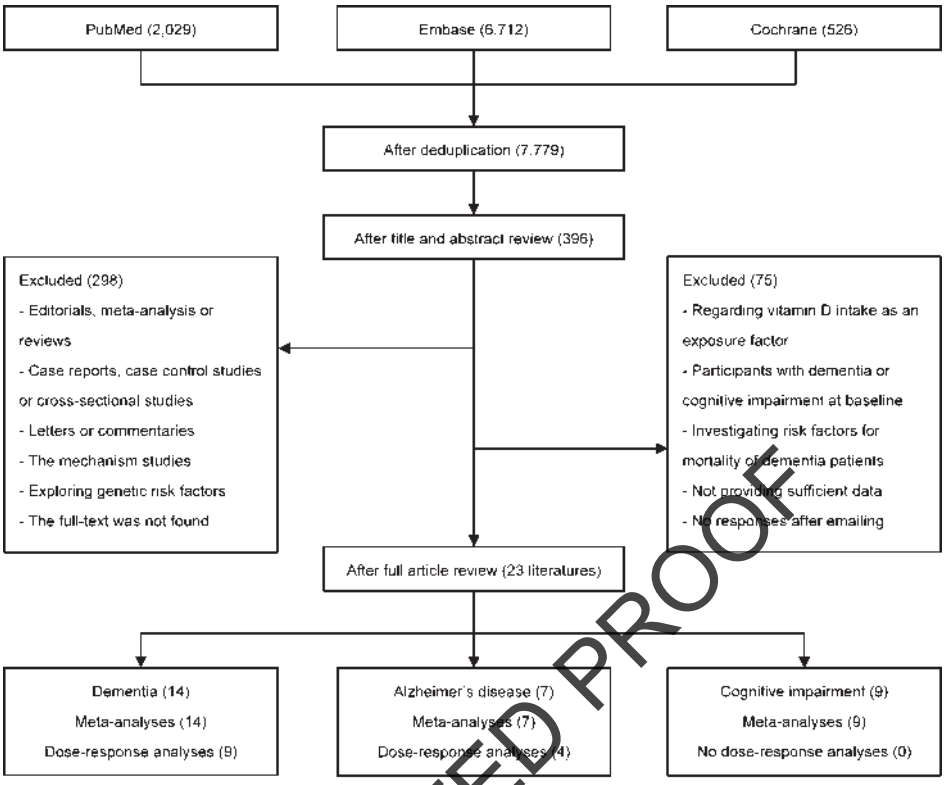

Fig. 1. Flowchart of literature screening.

were excluded after reviewing the titles and abstracts, leaving 396 papers with full-text available. Finally, 23 literatures were included for meta-analysis and 10 literatures for dose-response analysis (Fig. 1). The characteristics of included studies are listed in Supplementary Table 1.

Description of studies included in the meta-analyses

In the meta-analyses, thirty studies with a total of 525,714 individuals were included (dementia, 17 studies with 486,921 individuals; AD, 7 studies with 30,425 individuals; cognitive impairment, 10 studies with 14,261 individuals). The mean duration of follow-up ranged from 2 to 21 years. During follow-up, all 7,632 and 1,278 individuals without dementia at baseline were finally diagnosed as dementia (2–21 years) and AD (5.6–21 years), and 2,456 individuals developed cognitive impairment (4.4–10.0 years) (Supplementary Table 1). The mean NOS quality score of the included studies was 7.96 ± 0.98 (Supplementary Table 2).

Vitamin D deficiency and risk of cognitive disorders

With the highest 25(OH)D level as the reference, we assessed the potential associations of the lowest 25(OH)D level with the risk of dementia, AD, and cognitive impairment. As for dementia, all 17 studies with 486,921 individuals were included in the meta-analysis. We observed that the pooled RR of the lowest 25(OH)D level with dementia increased by 42% (RR = 1.42, 95% confidence interval (CI) = 1.21–1.65) in comparison with the highest 25(OH)D level, with moderate heterogeneity ($p < 0.01$, $I^2 = 64\%$, Fig. 2). Similarly, meta-analysis of the 7 studies for AD showed that compared with the highest 25(OH)D level, the risk of developing AD was 1.57 (95% CI = 1.15–2.14) among those individuals with the lowest level (Fig. 3a). And the heterogeneity of this meta-analysis was moderate ($p = 0.03$, $I^2 = 58\%$) (Fig. 3a). In addition, ten studies were identified on severe vitamin D deficiency and risk of cognitive impairment, the lowest 25(OH)D level was associated with 34% increased risk of cognitive impairment (RR = 1.34, 95% CI = 1.19–

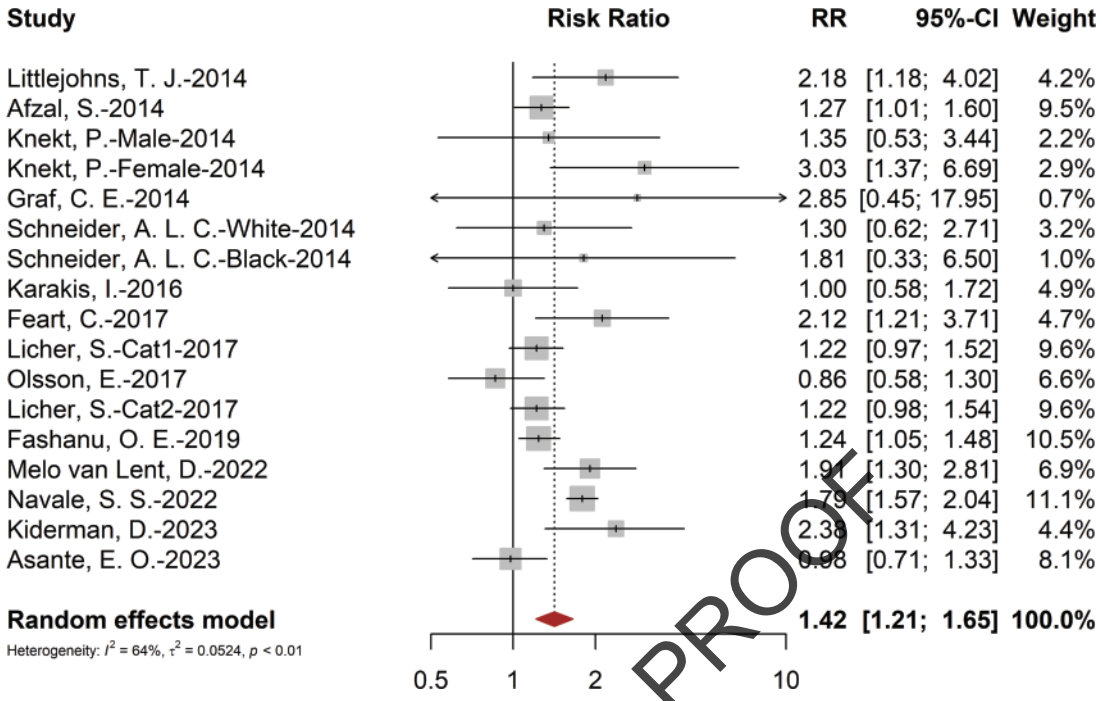

Fig. 2. Forest plot for the risk of dementia in subjects with vitamin D deficiency. The estimated pooled RR was 1.42 (95% CI = 1.21–1.65) with high heterogeneity (I^2 = 64%). RR, risk ratio; CI, confidence interval.

1.52) with no heterogeneity (p = 0.20, I^2 = 27%) (Fig. 3b).

There was no significant publication bias among the above meta-analyses (Egger's test, p for dementia = 0.8259, p for AD = 1.0000, p for cognitive impairment = 0.4743; Begg's test, p for dementia = 0.1740, p for AD = 0.5284, p for cognitive impairment = 0.6024). And the funnel plots were showed in the supplementary material (Supplementary Figures 1–3). Additionally, the above results of the meta-analyses were still stable after sensitivity analysis that no single study influenced the pooled RRs (range for dementia, 1.21–1.65; range for AD, 1.15–2.14; range for cognitive impairment, 1.19–1.52) (Supplementary Figures 4–6).

Notably, concerning the relationship between vitamin D deficiency and risk of AD, the meta-regression analyses showed that whether controlling *APOE4* as a confounder in the model was a significant moderator (p = 0.0042). The pooled RR of studies adjusting *APOE4* in the model was significantly higher (RR = 2.15, 95% CI = 1.58–2.92, I^2 = 0%) than that in studies not controlling *APOE4* (RR = 1.25, 95% CI = 1.02–1.54, I^2 = 36%) (Supplementary Figure 7).

Subgroup analyses stratified by the reference category of 25(OH)D level

The reference category of 25(OH)D level >75 nmol/L

With the 25(OH)D level >75 nmol/L as the reference, we included 7 studies with 26,484 participants for dementia and 5 studies with 9,684 participants for cognitive impairment (Fig. 4). Concerning dementia, we observed that the relationship between 50–75 nmol/L 25(OH)D and risk of dementia was insignificant (RR = 1.10, 95% CI = 0.99–1.23, I^2 = 0), while the pooled RR of dementia increased by 24% (RR = 1.24, 95% CI = 1.10–1.40, I^2 = 44) among participants with 25–50 nmol/L 25(OH)D (Fig. 4, Supplementary Figures 8–10). As for cognitive impairment, the meta-analyses revealed that among participants with 50–75 nmol/L, 25–50 nmol/L, and <25 nmol/L 25(OH)D, the risk of developing cognitive impairment increased by 14% (RR = 1.14, 95% CI = 1.02–1.27, I^2 = 0), 24% (RR = 1.24, 95% CI = 1.10–1.41, I^2 = 0), and 54% (RR = 1.54, 95% CI = 1.28–1.86, I^2 = 0), respectively (Fig. 4, Supplementary Figure 11). The overall pooled RR of dementia or cognitive impairment was 1.16

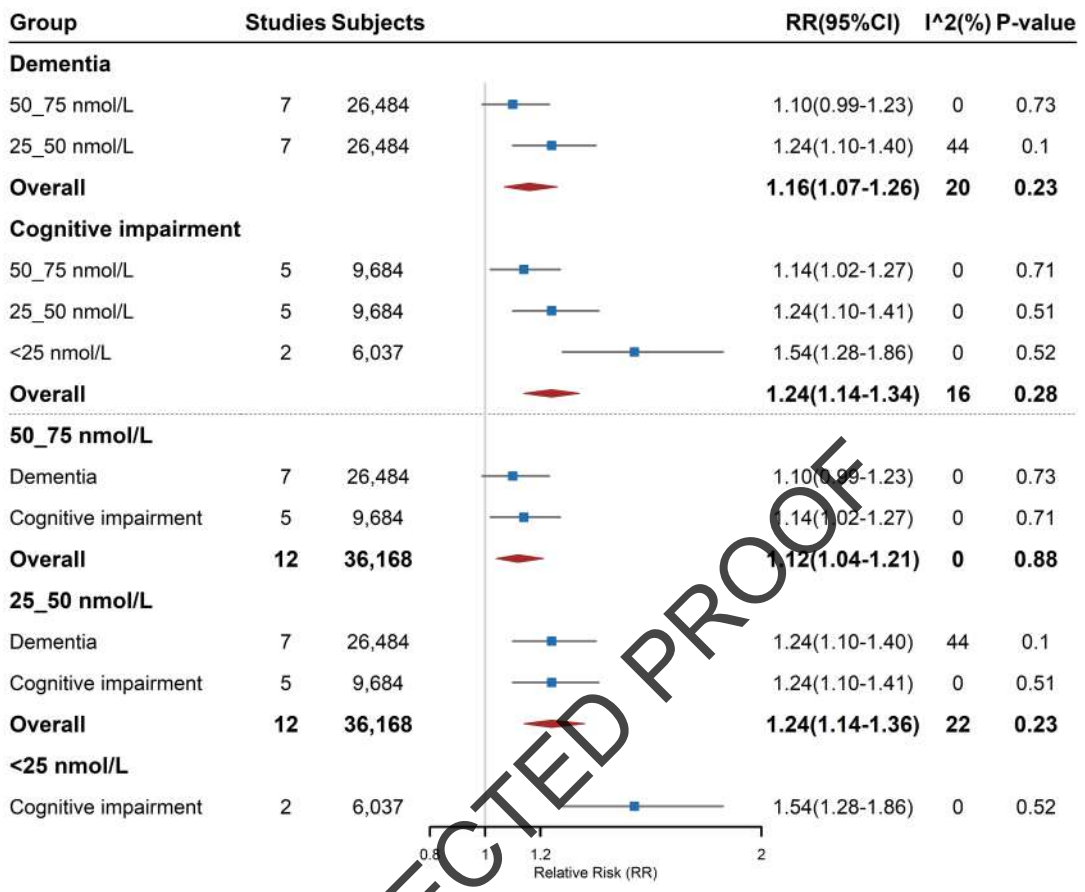

Fig. 3. Forest plot for the risk of AD and cognitive impairment in subjects with vitamin D deficiency. (a) Vitamin D deficiency was associated with 57% increased AD risk (RR = 1.57, 95% CI = 1.15–2.14) with moderate heterogeneity (I^2 = 58%). (b) Vitamin D deficiency conferred 1.34-fold excess risk (95% CI = 1.19–1.52) for cognitive impairment without heterogeneity (I^2 = 27%). AD, Alzheimer's disease; RR, risk ratio; CI, confidence interval.

(95% CI = 1.07–1.26, I^2 = 20) and 1.24 (95% CI = 1.14–1.34, I^2 = 16), respectively (Fig. 4, Supplementary Figures 8 and 11).

Regarding the 25(OH)D category of 50–75 nmol/L and 25–50 nmol/L, the lower level of 25(OH)D was associated with elevated risk of developing cognitive disorders (cognitive impairment and dementia) than the higher level (The overall effect of cognitive disorders: 25–50 nmol/L, RR = 1.24, 95% CI = 1.14–1.36; 50–75 nmol/L, RR = 1.12, 95% CI = 1.04–1.21. Fig. 4). More detailed meta-analyses are shown in Supplementary Figures 12 and 13.

The reference category of 25(OH)D level >50 nmol/L

With the 25(OH)D level >50 nmol/L as the reference, 10 studies with 455,621 participants for dementia, 6 studies with 29,243 participants for AD and 5 studies with 4,577 participants for cognitive impairment were incorporated into the meta-analyses (Fig. 5). With respect to dementia, 25–50 nmol/L (RR = 1.18, 95% CI = 1.08–1.30, I^2 = 41) and <25 nmol/L 25(OH)D (RR = 1.58, 95% CI = 1.30–1.91, I^2 = 61) were showed to elevate the dementia risk (Fig. 5, Supplementary Fig. 14). The AD risk was insignificant when participants had 25–50 nmol/L 25(OH)D (RR = 1.30, 95% CI = 0.94–1.81, I^2 = 66), while the <25 nmol/L 25(OH)D was a risk factor for AD (RR = 1.65, 95% CI = 1.15–2.35, I^2 = 63) (Fig. 5, Supplementary Fig. 15). Similarly, no obvious association was found between 25–50 nmol/L 25(OH)D and the cognitive impairment risk (RR = 1.10, 95% CI = 0.92–1.32, I^2 = 38), whereas the <25 nmol/L 25(OH)D was shown to increase cognitive impairment risk (RR = 1.40, 95% CI = 1.03–1.90, I^2 = 33)

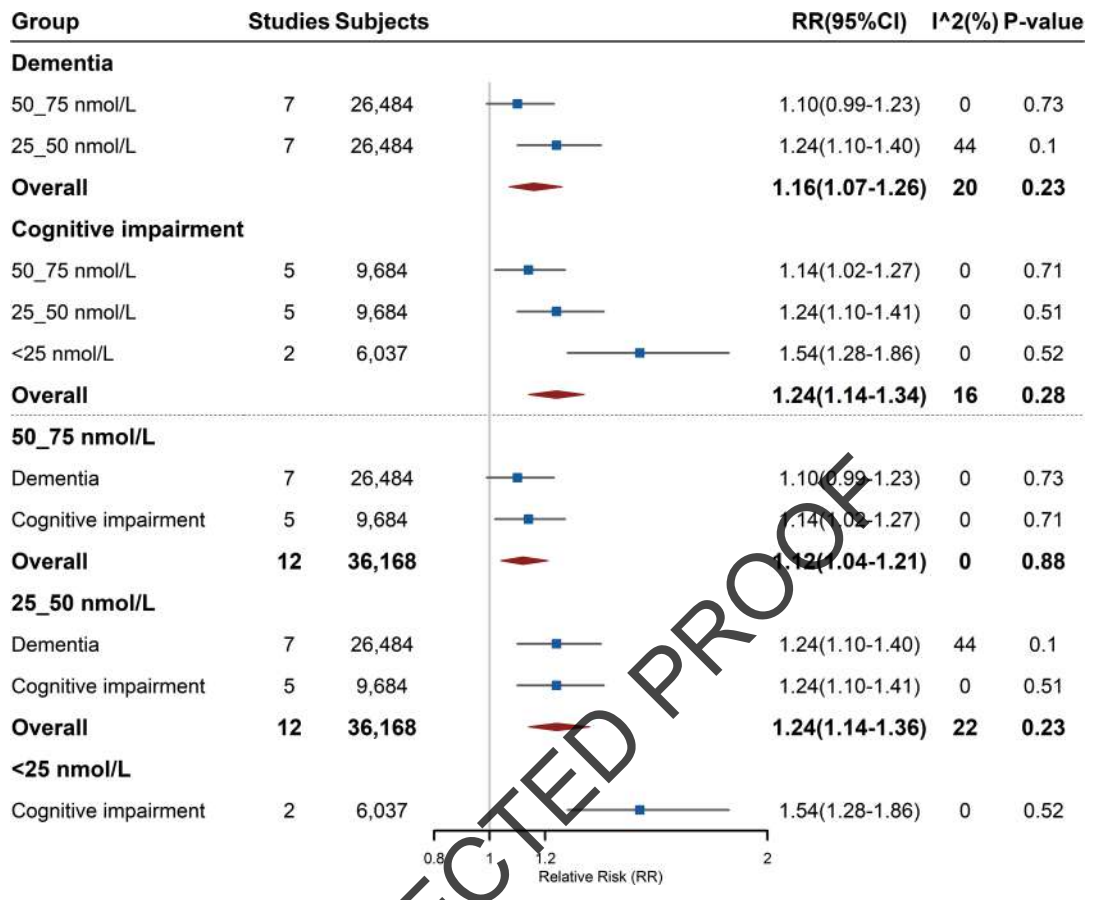

Fig. 4. The relationship between vitamin D status and cognitive disorders with the 25(OH)D level >75 nmol/L as the reference. The upper half part: the risk of dementia or cognitive impairment in subjects with different categories of vitamin D status; the lower half part: the risk of whole cognitive disorders stratified by the levels of vitamin D. 25(OH)D, 25-hydroxyvitamin D.

(Fig. 5, Supplementary Fig. 16). The overall pooled RR of dementia, AD or cognitive impairment was 1.35 (95% CI = 1.19–1.54, $I^2 = 69$),1.46 (95% CI = 1.14–1.85, $I^2 = 64$) and 1.22 (95% CI = 1.02–1.45, $I^2 = 44$), respectively (Fig. 5, Supplementary Figs. 14–16).

Concerning the 25(OH)D category of 25–50 nmol/L and <25 nmol/L, it seemed that the harmful effects from vitamin D deficiency on cognition would be greater in the lowest category of 25 (OH)D. [The overall effect of cognitive disorders (dementia, AD, and cognitive impairment): <25 nmol/L, RR = 1.55, 95% CI = 1.35–1.79, $I^2 = 58$; 25–50 nmol/L, RR = 1.18, 95% CI = 1.08–1.30, $I^2 = 48$. Fig. 5]. We also displayed more detailed analyses are in Supplementary Figures 17–19.

Additionally, the meta-regression results indicated the *APOE4* status significantly influenced the association of the vitamin D and risk of AD ($p = 0.0088$). We found a roughly 115% increase of AD risk (RR = 2.15, 95% CI = 1.58–2.92, $I^2 = 0\%$) among those severely vitamin D deficient participants after controlling the status of *APOE4*, while this relationship not adjusting the *APOE4* was non-significant (RR = 1.25, 95% CI = 0.75–2.06, $I^2 = 57\%$) that should be cautious due to the higher heterogeneity (Supplementary Figure 19).

Dose-response analyses

All 12 studies were included for dementia and 4 studies for AD in dose-response analyses. A total of 6,863 and 758 individuals without dementia at baseline were finally diagnosed as dementia and AD during follow-up (Supplementary Tables 3 and 4). The mean NOS quality score of the included studies was 8.08 ± 0.10 and 8.50 ± 0.58 (Supplementary Tables 3 and 4).

Downtrend non-linear association were detected in dementia ($p_{model} = 0.0000$, $p_{heterogeneity} =$

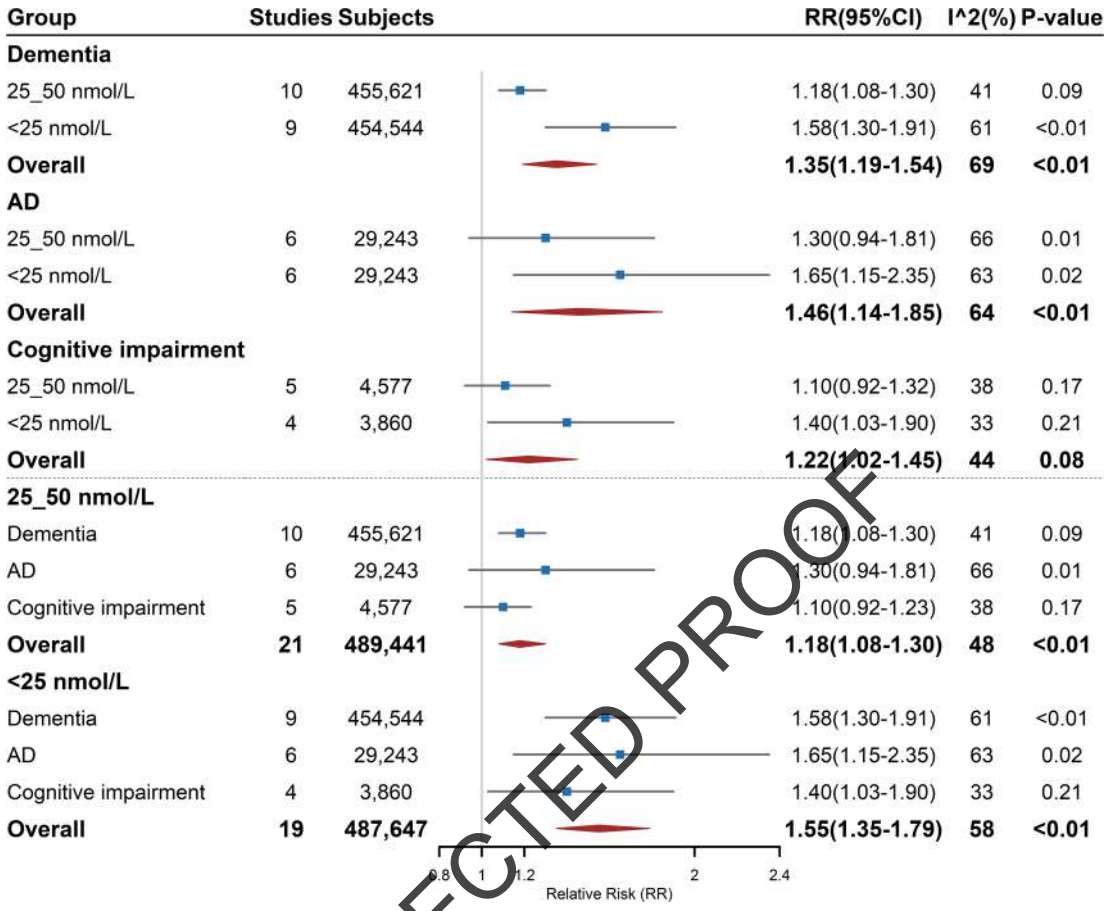

Fig. 5. The association of vitamin D level and cognitive disorders regarding the 25(OH)D level >50 nmol/L as the reference. The upper half part: the risk of dementia, AD, or cognitive impairment in subjects with different categories of vitamin D level; the lower half part: the risk of whole cognitive disorders based on the levels of vitamin D. 25(OH)D, 25-hydroxyvitamin D; AD, Alzheimer's disease.

0.0596, $p_{nonlinearity} = 0.0000$; Fig. 6a) and in AD ($p_{model} = 0.0042$, $p_{heterogeneity} = 0.2527$, $p_{nonlinearity} = 0.0042$; Fig. 6b). Specifically, the risk of dementia was completely decreased when 25(OH)D level increased from 12.5 nmol/L to 77.5 nmol/L, suggesting that the optimal 25(OH)D level was about 77.5 to 100 nmol/L for lower risk of dementia. Moreover, when the 25(OH)D level surpassed the cut-off of 40.1 nmol/L, the risk of AD may significantly descend.

DISCUSSION

In our meta-analyses, vitamin D deficiency was a risk factor of cognitive disorders (dementia, AD, and cognitive impairment). And the lower 25(OH)D level may exert greater harmful effects on cognition in subgroup analyses. Notably, *APOE4* as a significant mediator could influence the association of vitamin D level with the AD risk. Additionally, the dose-response analyses indicated the nonlinear relationship between 25(OH)D level and the risk of dementia or AD suggesting that there may exist an optimal window of vitamin D benefiting the cognition the most.

The meta-analyses results of this study discovered that severely deficient 25(OH)D level was associated with the risk of dementia and cognitive impairment, whereas insufficient vitamin D status seemed to exert slightly adverse effects on these cognitive disorders. Specifically, we found that in the first subgroup analyses with the adequate 25(OH)D level (>75 nmol/L) as the reference, it is less likely for participants with insufficient (50–75 nmol/L) 25(OH)D to develop dementia, while there existed the possibility of suffering cognitive impairment; the deficient (25–50 nmol/L) vitamin D level was regarded as the

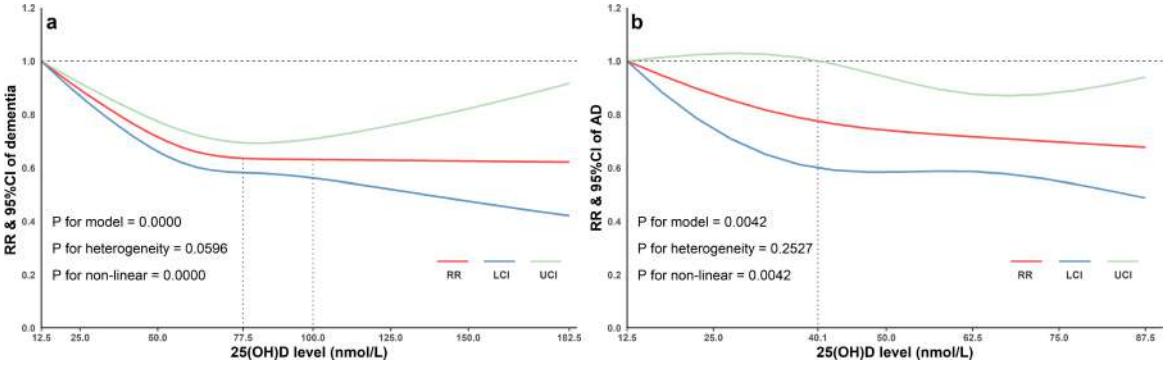

Fig. 6. Dose-response analyses between 25(OH)D level and risk of cognitive disorders. (a) The relationship between 25(OH)D level and the risk of dementia was negative and nonlinear indicating that 77.5 to 100 nmol/L 25(OH)D might be superior for individuals' cognition. (b) A nonlinear association of 25(OH)D level with AD was also observed, when the 25(OH)D level is >40.1 nmol/L, the risk of AD may decrease by >20%. 25(OH)D, 25-hydroxyvitamin D; AD, Alzheimer's disease.

risk factor for dementia and cognitive impairment; and the severely deficient (<25 nmol/L) 25(OH)D level was more prominently associated with the risk of cognitive impairment. Our meta-analyses seemed to be the first exploring the associations of 25(OH)D level with the risk of dementia or cognitive impairment using the category of 25(OH)D >75 nmol/L as the reference. However, there existed no relevant prospective studies exploring the AD risk via this reference.

Bedsides, in the second subgroup analyses, we observed that both the 25–50 nmol/L and the <25 nmol/L 25(OH)D were linked to elevated risk of dementia compared with the level >50 nmol/L, which was consistent with a recent meta-analysis [8]. This analysis also offered that the insufficient 25(OH)D level was a risk factor for dementia. The <25 nmol/L 25(OH)D conferred a 1.15- to 2.35-fold excess risk for AD and linked to a higher risk of cognitive impairment, while the non-significant relationship was observed between the 25–50 nmol/L 25(OH)D and the risk of AD or cognitive impairment in our analyses, which was a little different from the previous meta-analyses [8, 9]. Kalra et al. revealed the significant association of 25–50 nmol/L 25(OH)D with AD risk, whereas Yang et al. observed that neither the <25 nmol/L nor 25–50 nmol/L 25(OH)D level was related to the AD risk. Additionally, these findings did not offer the results involving the risk of cognitive impairment. Relatively speaking, the credibility in our analyses could be higher due to the larger sample size than others. Furthermore, we found that the overall pooled RR of AD was higher than dementia and cognitive impairment suggesting that vitamin D deficiency may strongly influence the AD risk.

The meta-regression results revealed the important role of *APOE4* in the relationship between vitamin D deficiency and the AD risk. After adjusting the *APOE4* status, the pooled RR of AD risk was significantly higher than that not controlling it. Notably, a previous study put forward that vitamin D deficiency showing a higher risk for *APOE4* non-carriers AD patients versus carriers [37]. Similarly, a prospective cohort study revealed the effects of vitamin D supplementation on reducing dementia incidence were significantly greater in *APOE4* non-carriers than carriers [38]. Inconsistently, a recent study found that higher vitamin D level combined with grip strength may alleviate the harmful effects of *APOE4* on dementia by half [39]. It is important to clarify the role of vitamin D level interacting *APOE4* for AD and needs more studies with high level of evidence to explore the potential relationship.

More importantly, the dose-response analyses in our study revealed downtrend non-linear association between vitamin D level and dementia or AD risk. Detailly, the 77.5–100 nmol/L 25(OH)D may be an optimal dose range to reduce the dementia risk, which corresponded to the clinical guidelines of The Endocrine Society [adequate 25(OH)D >75 nmol/L] [20]. This finding could help highlight the crucial 25(OH)D dose range for dementia prevention and suggest that regarding the adequate 25(OH)D level (>75 nmol/L) as the reference would be reasonable to assess the relationship between vitamin D deficiency and the risk of dementia. In addition, the AD risk would be decreased by >20% when the 25(OH)D level surpass the 40.1 nmol/L, indicating that the 40.1–87.5 nmol/L vitamin D level may exert no adverse effects on AD risk. Consistently, the results

of our meta-analyses revealed that 25–50 nmol/L 25(OH)D was slightly linked to elevated AD risk. However, a previous study discovered the linearly negative dose-response relationship with dementia or AD risk [12]. Our results may be more convincing than others due to the more prospective studies included, whereas inadequate data constrained the dose-response analysis of the 25(OH)D level and the risk of cognitive impairment. The potential dose-response association of 25(OH)D level with cognition requires further work.

Interestingly, according to the dose-response analyses, we could find that the effects of 25(OH)D level were more pronounced on the reducing the risk of dementia than AD. On the one hand, the number of included individuals was smaller in AD group than dementia group, the sample size may influence the results of dose-response analyses about AD. On the other hand, in demented cases vitamin D deficiency was more prominent in the vascular dementia [40], and the vitamin D receptor (VDR) gene polymorphism also exerted different effects on cerebral small vessel disease resulting in vascular dementia [41, 42].

The cognitive benefits of vitamin D could be attributed to different neural pathways, including the promotion of neurotrophins expression, the role of anti-inflammatory effect, the improvement of insulin resistance, the regulation of calcium balance and the improvement of amyloid-β (Aβ) clearance. More concretely, vitamin D could upregulate the expression of neurotrophins, such as nerve growth factor, brain-derived and glial cell-derived neurotrophic factor [43]; the anti-inflammatory role of vitamin D was reflected by the decreased production of TNF-α and IL-6 [44]; insulin resistance, as a risk factor for AD, could be alleviated by vitamin D supplementation, which could promote the metabolism of glucose and lipid [45–47]; the neuronal calcium is partly under control of vitamin D via downregulating the calcium channels [48]; vitamin-D-binding protein and vitamin D could alleviate the aggregation of Aβ and improve the removal of Aβ, and there exists a cross-talk between Aβ and VDR, the VDR expression could be regulated by Aβ [49–51]. Interestingly, the haplotypes of VDR exert different effects on neurodegenerative disorders [52]. More importantly, in neurons VDR plays an essential role in mitochondrial function [53]. All of these potential neuroprotective effects of vitamin D may further support the association of higher vitamin D level with lower risk of cognitive disorders. Additionally, the vitamin D metabolism and transport could be controlled by APOE, consequently, the influences of the coexistence of vitamin D and *APOE4* should be considered [37, 54], which could provide the underlying biological explanations for the interaction effects of *APOE4* with vitamin D level on AD risk.

There existed several strengths and limitations in this study. Strengths: 1) we conducted the pre-planned subgroup analysis based on the reference of 25(OH)D level; 2) the quantification relationship between 25(OH)D level and risk of dementia or AD was performed via the dose-response design; 3) we revealed the potential role of *APOE4* combined with vitamin D level in the risk of AD. Limitations: 1) part of the included studies did not adjust for important confounders; 2) we failed to perform the meta-analyses for the risk of vascular dementia and the dose-response analysis for cognitive impairment because of the limited of data; 3) the dose-response modeling was dependent on the restricted, collective observational data and thus needs further validation; 4) it is noteworthy that the role of vitamin D level interacting *APOE4* for AD requires further analyses with more high-quality prospective studies; 5) the generalizability of the findings should be interpreted with great caution due to the included studies only with English language.

Conclusion

In summary, vitamin D deficiency was related to the risk of dementia, AD, and cognitive impairment. And the nonlinear association of 25(OH)D level with the risk of dementia or AD suggested that the superior window of 25(OH)D level may be 77.5–100 nmol/L for lower dementia risk, and the risk of AD may significantly decrease when the 25(OH)D level >40.1 nmol/L. Notably, *APOE4* as a significant mediator could affect the relationship between vitamin D level and the AD risk.

CREDIT AUTHOR STATEMENT

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-231381.

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