

Vitamin D concentration and risk of Alzheimer disease

A meta-analysis of prospective cohort studies

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Abstract

Background: Considerable controversy exists on the association between serum vitamin D concentrations and Alzheimer disease (AD) risk. This study aimed to synthesize the association of serum vitamin D concentrations with AD in adults.

Methods: PubMed, Embase, and Cochrane library databases were searched for prospective cohort studies with data on serum vitamin D concentrations and AD risk.

Result: The studies that reported the adjusted relative risks (RRs) with 95% confidence intervals (CIs) of AD associated with serum vitamin D concentrations were included and subjected to subgroup analyses. Six prospective cohort studies with 1607 AD cases and 21,692 individuals were included in the meta-analysis. In 4 cohort studies with information about serum vitamin D concentrations <25 and 25 to 50 nmol/L, the random effects summary estimate did not show an increased risk of AD after adjustment for the established risk factors, while 3 cohort studies reported the RRs for incident AD per standard deviation (SD) decrease in serum vitamin D concentration and the random effects summary estimate did not show an increased risk of AD after adjustment for the established risk factors.

Conclusions: The current meta-analysis indicated that serum vitamin D deficiency (<25 nmol/L) or insufficiency (25–50 nmol/L) was not statistically significant and associated with the risk of AD.

Abbreviations: A β = amyloid beta, AD = Alzheimer's disease, CIs = confidence intervals, CVD = cardiovascular disease, HR = hazard ratio, RRs = relative risks, SD = standard deviation.

Keywords: Alzheimer's disease, meta-analysis, risk factor, vitamin D

1. Introduction

Alzheimer disease (AD) is the most common cause of dementia, and up to 75% of all the cases of dementia are attributable to AD.^[1] The average lifespan is expected to increase by an additional 10 years by 2050, and no definitive cure for AD has yet been found.^[2] The accumulation of dysfunctional proteins, such as amyloid beta (A β) and tau protein derivatives in the brain,

followed by oxidative damage and inflammation, leading to deranged energy metabolism, localized synaptic failure, and neuronal loss are speculated as the pathogenic hallmarks of AD.^[3]

As the population continues to age rapidly, identifying the modifiable risk factors for AD with respect to lifestyle and diet is essential. In addition to the potentially modifiable risk factors of AD such as obesity, diabetes, hypertension, and smoking, a potential prognostic role for vitamin D deficiency has been proposed.^[4]

Vitamin D has been implicated to be crucial in maintaining the cognitive function in old age.^[5] Vitamin D receptors are present in the brain regions responsible for memory development and cognitive functions and may also be involved in plaque clearance.^[6,7] Furthermore, the cutoffs for vitamin D deficiency and the optimum value for physical and mental health have not yet reached a global consensus.^[8–10]

A meta-analysis of studies comparing the patients with and without dementia has indicated that those with AD have low levels of vitamin D.^[11] Similarly, a meta-analysis of cross-sectional studies has identified that low serum vitamin D concentrations are associated with prevalent AD.^[12,13]

The serum vitamin D concentrations independently increase the incidence of AD or whether this correlation is confounded by the population's prevalent modifiable risk factors in the primary prevention of AD is demonstrated in the recently published meta-analysis of 8 cohort studies. These studies showed that high levels of serum vitamin D status were associated with a low risk of AD.^[14] However, the meta-analysis found insufficient evidence in

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the subgroup meta-analysis by adjusting for baseline cardiovascular disease (CVD) and cancer (yes vs no), adjusting for physical activity (yes vs no), adjusting for serum cholesterol (yes vs no), and adjusting for alcohol (yes vs no).

To fill in these gaps, we systematically evaluated the association between serum vitamin D concentrations and incidence of AD by conducting an updated meta-analysis of prospective cohort studies.

2. Material and methods

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist^[15] for reporting the results in this systematic review.

2.1. Literature search

A systematic search of PubMed, Embase, and the Cochrane library databases was conducted to retrieve the potential prospective cohort studies published before March 2018. The terms used for the PubMed search are provided in online-only Supplemental Data 1, <http://links.lww.com/MD/D190>, and similar searches were conducted in the Embase and Cochrane library. The current search was restricted to studies conducted in humans, and no restriction was imposed with respect to the language of publications. We also screened the reference lists of eligible reviews and included the relevant articles in these lists. When the same or a similar patient cohort was included in these publications, only the most recent or complete report was selected for analysis.

2.2. Study selection

Studies that satisfied the following criteria were included in the current meta-analysis:

- (1) the study of adult patients had a prospective cohort design;
- (2) the exposure of interest was serum vitamin D at the baseline;
- (3) the outcome of interest was AD;
- (4) the reported risk estimates [relative risk (RR) or hazard ratio (HR)] and the corresponding 95% confidence intervals (CIs) of dementia or AD; and
- (5) a follow-up period >1 year.

Also, studies that reported results as per the unit increment or decrement in serum vitamin D were included. The studies were excluded if:

- (1) it had a cross-sectional or case-control design or clinical trial;
- (2) unadjusted or only age- or gender-adjusted RR was reported;
- (3) studies conducted among patients with specific diseases, such as hospitalized patients;
- (4) the study was duplicated;
- (5) the follow-up period of the study was <1 year.

2.3. Data abstraction

Two reviewers independently reviewed the full text of selected eligible studies and extracted the following information: the first author's name, publication year, study design, country of origin, number of participants, participants' age, follow-up years, gender, assessment method of serum vitamin D and AD, number of AD cases, and adjusted covariates. Any discrepancy was

resolved by discussion to reach a consensus between the 2 authors; the original authors were contacted in case supplementary information was required. According to the World Health Organization (WHO)^[16] and the US Institute of Medicine,^[8] a sufficient vitamin D status was defined as a deseasonalized serum vitamin D concentration >50 nmol/L, while vitamin D insufficiency was defined as a deseasonalized serum vitamin D concentration between 25 and 50 nmol/L, and deseasonalized vitamin D deficiency at <25 nmol/L (to convert to ng/mL, divide by 2.496).

2.4. Assessment of study quality

The quality was assessed in accordance with the Newcastle-Ottawa scale (NOS) for non-randomized studies.^[17] A score of up to 9 stars was assigned to each study: participant selection (up to 4 stars), comparability of study groups (up to 2 stars), and assessment of outcome or exposure of the cohorts (up to 3 stars). A high score represented a superior methodological quality. The scores of 0 to 3, 4 to 6, and 7 to 9 indicated low, moderate, and high quality, respectively.

2.5. Statistical analysis

Multivariate-adjusted outcome data were used for analysis, and HRs and incidence rate ratio were considered as approximate RRs. These values in every study were converted using their natural logarithms and standard errors calculated based on the corresponding 95% CIs. The results were expressed as RRs with 95% CIs (a fixed-effect approach was used unless a significant heterogeneity was noted, in which case, a random-effects statistical model was applied).^[18] The heterogeneity of the study was explored using τ^2 , and the amount of variance in the summary effect due to between-study heterogeneity was defined by I^2 . This was considered as statistically significant at the $P < .10$ level, as determined by the Cochran Q statistical test.^[19] If heterogeneity was evident, subgroup synthesis and sensitivity analysis were employed to explicate the contribution to the heterogeneity. Subgroup analyses of serum vitamin D were conducted by adjusting for the baseline CVD and cancer (yes vs no), adjusting for physical activity (yes vs no), adjusting for serum cholesterol (yes vs no), and adjusting for the presence of alcohol (yes vs no). Publication bias was assessed by Egger test and the symmetry of the funnel plot.^[20–22] In the case of publication bias, the “nonparametric trim-and-fill” method was used for computing the risk estimates corrected for this bias.^[23] All statistical analyses were performed using the Review Manager version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) and Stata version 11 (Stata Corporation, College Station, TX). Except otherwise noted, differences with a P value <.05 were considered as statistically significant.

3. Results

3.1. Literature search and characteristics

Figure 1 illustrates the study selection process and the results of our literature search, which retrieved a total of 706 studies. After excluding the duplicate records and the reports with findings of studies that did not meet the inclusion criteria, 19 potentially eligible studies were assessed by reviewing the full text. Consequently, 13 articles were further excluded due to the

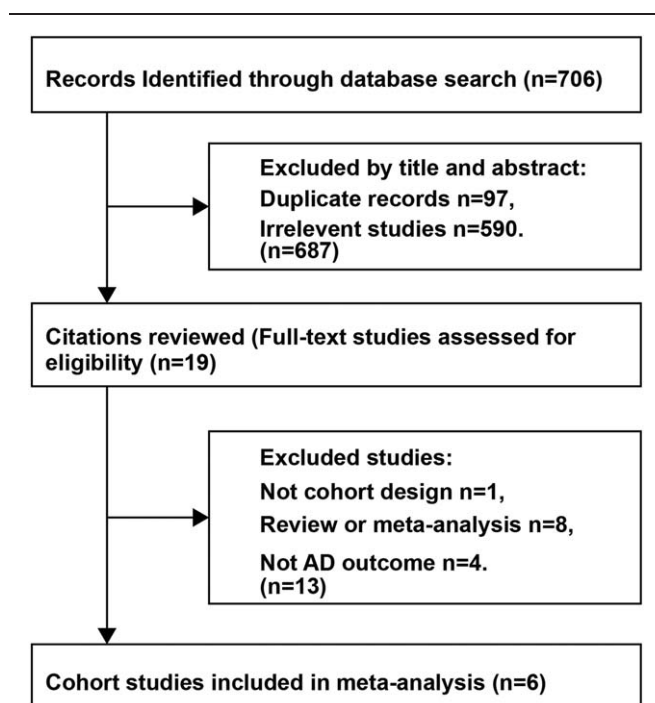


Figure 1. Process of literature search and study selection.

following reasons: the outcome was the absence of AD ($n=4$), review or meta-analysis ($n=8$), or lack of a cohort design ($n=1$). Finally, the present meta-analysis included results from 6 independent prospective cohort studies.^[24–29] Six studies on the relationship between serum vitamin D concentration and AD risk (1607 AD cases among 21,692 individuals) were published between 2014 and 2017 (Table 1).^[24–29] The number of participants ranged from 916 (in the study conducted by Feart et al^[27]) to 10,186 (in the study conducted by Afzal et al^[24]). Furthermore, the follow-up duration ranged from 5.6 to 30 years,^[24,25] with a median of 10.2 years. All articles were graded as high-quality according to the NOS (online-only Supplemental Table 1, <http://links.lww.com/MD/D190>).

3.2. Vitamin D concentrations and risk of AD

In 4 cohort studies with information about the serum vitamin D concentrations <25 nmol/L, the random effects summary estimate did not show an increased risk of AD after adjustment for the established risk factors (RR 1.55, 95% CI: 0.97–2.49; $P=.07$) (Fig. 2) with significant heterogeneity across studies ($I^2=57%$).^[24–27] No significant publication bias was observed according to the funnel plot (online-only Supplemental Fig. 1, <http://links.lww.com/MD/D190>) and Egger's test ($P=.535$).

In 4 cohort studies with information about serum vitamin D concentrations 25 to 50 nmol/L, the random effects summary estimate did not show an increased risk of AD after adjustment for the established risk factors (RR 1.29, 95% CI: 0.83–2.02; $P=.26$) (Fig. 2) with extreme heterogeneity across studies ($I^2=79%$).^[24–27] No significant publication bias was observed according to the funnel plot (online-only Supplemental Fig. 1, <http://links.lww.com/MD/D190>) and Egger test ($P=.507$).

Furthermore, 3 cohort studies reported the RRs for the incidence of AD per SD decrease in serum vitamin D

concentration. The random effects summary estimate did not show an increased risk of AD after adjustment for the established risk factors (RR 1.06, 95% CI: 0.96–1.18; $P=.27$) (online-only Supplemental Fig. 2, <http://links.lww.com/MD/D190>) with significant heterogeneity across studies ($I^2=62%$).^[26,28,29] No significant publication bias was observed according to the funnel plot (online-only Supplemental Fig. 3, <http://links.lww.com/MD/D190>) and Egger test ($P=.918$).

3.3. Subgroup analysis

The serum vitamin D concentrations <25 nmol/L subgroup did not demonstrate an association of serum vitamin D concentration with increased risk of AD (Table 2). Additionally, in the serum vitamin D concentrations 25 to 50 nmol/L subgroup, similar associations were evident in several strata of the study characteristics (data not shown).

3.4. Sensitivity analysis

The robustness of our results was evaluated by sensitivity analysis. When studies included in the meta-analysis were excluded sequentially, the results of the meta-analysis remained largely unchanged. This indicated that the results of the present meta-analysis were stable (data not shown).

4. Discussion

4.1. Principal findings

The present meta-analysis provided additional evidence on the association of vitamin D concentration and the risk of AD. The current analysis indicated that serum vitamin D deficiency (<25 nmol/L) was not statistically significant and associated with the risk of AD (by 55%), and only marginally associated with the risk of AD in participants with serum vitamin D insufficiency (25–50 nmol/L) (by 29%). A 1 nmol/L decrement in serum vitamin D concentration was associated with a 6% high risk of AD, albeit not significantly.

4.2. Strengths and limitations of the study

A major strength of our meta-analysis was the prospective design of the included cohort studies with adjusted RRs from general populations, which might have greatly reduced the potential of selection bias. In addition, we used NOS score and found that all studies had a high-quality. As the sample size of the single primary study was relatively small, our meta-analysis increased the statistical power to detect the possible association between serum vitamin D concentration and AD risk in order to determine the accurate risk estimation. Nevertheless, the potential limitations of the study should be considered. First, we could not exclude the potential bias due to the different methods used for assessing the vitamin D concentration. Second, primary studies only assessed the baseline serum vitamin D and did not perform repeated measurements over the follow-up period. Thus, without considering these factors, we might obtain a biased conclusion. Third, despite the major confounders seemed unlikely to alter the role of vitamin D concentration on the increment of AD risk based on the subgroup analyses of adjustments, other factors (such as unknown confounders and imprecise adjustment) potentially accounted for the observed association, which could

Table 1
Study characteristics.

References, y	Country	Study type	Participants	Sex	Mean age, y	Follow-up duration, y	Vitamin D assessment	AD assessment	AD cases	Adjustments covariates	Quality score
Afzal et al ^[25] 2014	Denmark	PC	10,186 general population	W/M	58	30	CLIA	ICD-8, 10	418	Age, sex, month of blood sample, smoking status, BMI, leisure time and work-related PA, alcohol, income level, education, baseline DM, hypertension, cholesterol, HDL, and creatinine	9
Littlejohns et al ^[26] 2014	UK	PC	1658 ambulatory adults	W/M	73.6	5.6	LC-MS	NINCDS-ADRDA	100	Age, season of vitamin D collection, education, sex, BMI, smoking, alcohol, and depressive symptoms	8
Karakis et al ^[27] 2016	USA	PC	1663 participants from the original and Offspring's Framingham Heart Studies	W/M	72.4	9	Competitive protein-binding assay and radioimmunoassay	NINCDS-ADRDA	208	Age, sex, smoking, hypertension, DM, prevalent CVD, homocysteine, BMI	8
Feart et al ^[28] 2017	France	PC	916 community dwellers	W/M	73.3	11.4	One-step immunoassay	NINCDS-ADRDA	124	Sex, education, income, depressive symptomatology, number of drugs per day, APOE 4 allele, BMI, practice of physical exercise, DM, history of CVD, stroke, hypertension, hypercholesterolemia, hypertriglyceridemia, smoking status, and mediterranean diet score	8
Olsson et al ^[29] 2017	Sweden	PC	1182 adult men	M	71	12	HPLC atmospheric pressure chemical ionization-mass spectrometry	NINCDS-ADRDA	116	Age, season of blood collection, BMI, education, PA, smoking, DM, hypertension, hypercholesterolemia, use of vitamin D supplements, alcohol intake	8
Licher et al ^[30] 2017	Netherland	PC	6087 general population	W/M	69.2	13.3	Electrochemiluminescence binding assay	DSM-III-R, NINCDS-ADRDA	641	Age, sex, season of blood collection, BMI, SBP, DBP, educational level, smoking, alcohol, calcium serum levels, ethnicity, eGFR, TC, HDL, history of DM, HF, stroke, MI, depressive symptoms, outdoor activity, and APOE_4 carrier status	9

AD = Alzheimer disease; PC = prospective cohort; W = woman; M = man; BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; TC = total cholesterol; DM = diabetes mellitus; HF = heart failure; MI = myocardial infarction; APOE = apolipoprotein E; HDL = high-density lipoprotein; eGFR = estimated glomerular filtration rate; PA = physical activity; DSM-III-R = Diagnostic and Statistical Manual-III-R, NINCDS-ADRDA = National Institute of Neurological and Communication Disorders and Stroke and Alzheimer disease and Related Disorders Association; CLIA = chemiluminescent immunoassay; ICD = International Classification of Diseases; LC-MS = liquid chromatography-tandem mass spectrometry; HPLC = high performance liquid chromatography.

not be ruled out. For example, information with respect to genetic factors was not available in most studies. Fourth, men and women have different overall AD incidence, while sufficient data was not available to perform gender subgroup analysis for exploring the effect of gender on the association between vitamin D deficiency and risk of developing AD.^[30,31] Finally, only published cohort data was included in the current meta-analysis, which increased the risk of publication bias via the exclusion of unpublished studies. However, after carefully examining all the relevant articles, including several meta-analyses^[12,13,32,33] and reviews,^[34,35] any relevant unpublished studies were not retrieved.

4.3. Comparison with other studies

Several previous meta-analyses have returned consistent results on vitamin D concentration and dementia.^[12,13,32,33] Similarly, another published meta-analysis that included 8 cohort studies including 28,354 participants reported that high levels of serum vitamin D were associated with a low risk of dementia and

AD.^[14] However, the meta-analysis did not find sufficient evidence in the subgroup meta-analysis by adjusting for baseline CVD, cancer, physical activity, serum cholesterol, and alcohol.

In recent decades, evidence indicated that vitamin D deficiency or insufficiency exerts its effects indirectly by increasing the levels of CVD risk factors and the risk of endothelial dysfunction—the 2 risk factors for the development of AD.^[36,37] Shen et al included 5 study populations from 3 prospective cohort studies and found that vitamin D deficiency was associated with an increased risk of AD occurrence as compared to the subjects with serum vitamin D level >50 nmol/L.^[33] Similarly, the large sample size in our meta-analysis allowed further analysis of the risk of different subgroups. Additionally, in a large prospective population-based cohort, Licher et al found that low serum vitamin D concentrations were associated with a high incidence of dementia.^[29] Conversely,^[29] Olsson et al did not find any no evidence supporting that baseline vitamin D concentration was an independent risk factor for dementia or cognitive impairment in adult males.^[28] Furthermore, Olsson et al did not analyze the risk of serum vitamin D deficiency (<25 nmol/L) according to the

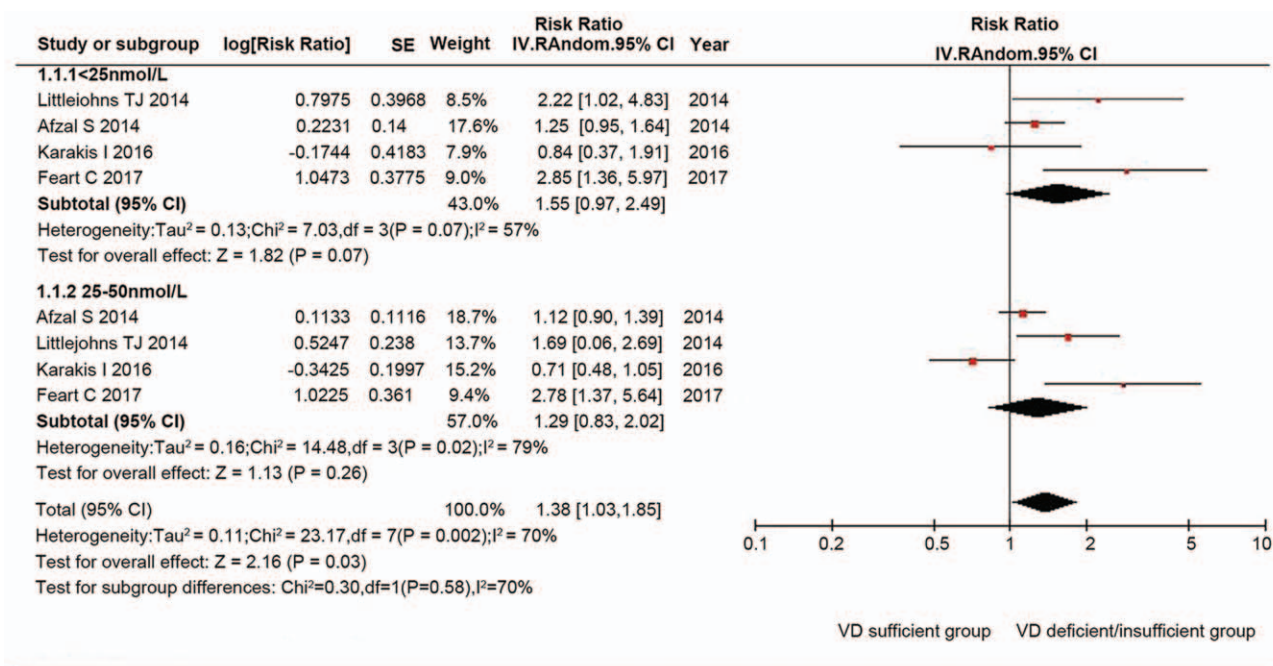


Figure 2. Random effects analysis of fully adjusted studies for the association between serum vitamin D concentrations and Alzheimer disease risk. The square box in the graph portrays the weight that each study contributed to the analysis. CI=confidence interval, IV=inverse variance, SE=standard error, VD=vitamin D.

guidelines of the National Academy of Medicine (NAM) in the USA.^[28]

4.4. Potential mechanisms

Although the pathophysiological etiology of AD is not fully understood, different mechanisms of neurodegeneration have emerged, including deposition of amyloid plaques, inflammatory processes, neurofibrillary degeneration, glutamatergic excitotoxicity, excessive intraneuronal calcium influx, and oxidative stress.^[3] Vitamin D is hypothesized to exert its effects via different neural pathways.^[38,39] Although the exact mechanisms are unclear, evidence suggests that vitamin D might protect against cognitive dysfunction via its effect on neuroprotection, neurotransmission, synaptic plasticity, immune modulation, neuronal calcium regulation, and enhanced nerve conduction,^[40,41] with

secondary protective effects on vascular systems and modulation of vascular risk factors.^[42] Additionally, the in vitro analysis showed that vitamin D treatment inhibits the production TNF- α and IL 6, suggesting an anti-inflammatory role.^[43] In vitamin D-deficient mice, specific calcium channels are also shown to be unregulated leading to an increase in Ca²⁺ level and in vitro evidence has shown that vitamin D can downregulate these calcium channels.^[44] Finally, vitamin D might partially prevent the AD-related defects in acetylcholine since vitamin D supplementation in rats caused an increase in choline acetyltransferase activity in several brain areas.^[45] This experimentally proved the involvement of vitamin D in brain pathways together with the present finding that serum vitamin D concentrations are overall lower in AD as compared to controls provides new insight on the putative involvement of vitamin D in the course of AD.

Table 2
Stratified analyses of serum vitamin D concentrations <25nmol/L and Alzheimer disease risk.

Group	No. of studies	Test of association		Heterogeneity test			P* for interaction
		RR (95% CI)	P value	χ^2	P value	I ² , %	
Adjust for baseline CVD and cancer							.07
yes	2	1.57 (0.47–5.19)	.46	4.7	.03	79	
no	2	1.48 (0.89–2.46)	.13	1.86	.17	46	
Adjust for physical activity							.07
yes	2	1.75 (0.79–3.88)	.17	4.19	.04	76	
no	2	1.38 (0.53–3.57)	.51	2.84	.09	65	
Adjust for serum cholesterol							.07
yes	2	1.75 (0.79–3.88)	.17	4.19	.04	76	
no	2	1.38 (0.53–3.57)	.51	2.84	.09	65	
Adjust for alcohol							.07
yes	2	1.48 (0.89–2.46)	.13	1.86	.17	46	
no	2	1.57 (0.47–5.19)	.46	4.70	.03	79	

P* for interaction was utilized to assess the stratified differences.
CI=confidence interval, CVD=cardiovascular disease, RR=relative risk.

In conclusion, the current meta-analysis indicated that serum vitamin D deficiency (<25 nmol/L) was neither statistically significant nor associated with the risk of AD; however, it was marginally associated with the risk of AD in participants with serum vitamin D insufficiency (25–50 nmol/L). Nowadays, lifestyle modification is the primary management of individuals with vitamin D deficiency or insufficiency. Thus, randomized clinical trials will be essential to address the issue of causality and determine whether vitamin D supplementation is effective for the prevention or treatment of AD.

Author contributions

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