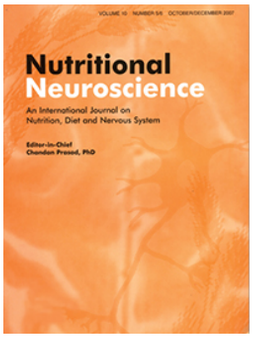

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Vitamin D status and risk of dementia and Alzheimer's disease: A meta-analysis of dose-response†

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Objective: We aimed to test the dose-response association of serum 25(OH)D and risk of dementia and Alzheimer's disease (AD).

Methods: We performed a systematic search of PubMed and Scopus from database inception up to September 2017. Longitudinal cohort studies reporting risk estimates of incident dementia or AD in the general population, and for three or more quantitative categories of serum 25(OH)D were included. Pooled hazard ratios (HRs) were calculated using fixed-effects/random-effects models.

Results: Seven prospective cohort studies and one retrospective cohort study (total $n = 28{,}354$) involving 1953 cases of dementia and 1607 cases of AD were included. The pooled HRs of dementia and AD were 1.09 (95%CI: 0.95, 1.24) and 1.19 (95%CI: 0.96, 1.41) for vitamin D insufficiency (10–20 ng/ml), and 1.33 (95%CI: 1.08, 1.58) and 1.31 (95%CI: 0.98, 1.65) for deficiency (<10 ng/ml), respectively. The lower risk of dementia was observed at serum 25(OH)D of ~25 ng/ml, whereas the risk of AD decreased continuously along with the increase of serum 25(OH)D up to ~35 ng/ml.

Conclusion: Higher levels of serum 25(OH)D was associated with a lower risk of dementia and AD, but we have no conclusive evidence regarding serum 25(OH)D levels of >35 ng/ml.

Keywords: Alzheimer disease, Dementia, Meta-analysis, Vitamin D deficiency

Introduction

The number of people with dementia is estimated to increase from 35.6 million in 2010 up to 65.7 million by the year 2030 and 115.4 million by the year 2050.[1] Alzheimer's disease (AD) is the most common cause of dementia, and up to 75% of all cases of dementia are attributable to AD.[2] The average life span is expected to increase another 10 years by 2050,[3] and no definitive cure for dementia has been found yet.[4]

Besides the potentially modifiable risk factors of dementia such as obesity, diabetes, hypertension, and smoking,[5] a potentially prognostic role for vitamin D deficiency has been proposed. Owing to the proposed roles of vitamin D in the brain development, brain function and cognition,[6,7] it has been suggested that vitamin D deficiency might have a contributing role in the development of dementia and its subtypes including AD.[8] Several longitudinal studies have revealed that vitamin D deficiency might increase the risk of cognitive impairment and memory decline.[9–11] In accordance with these findings, two large population-based studies indicated that lower dietary intake of vitamin D and less sunlight exposure were associated with a greater risk of cognitive impairment.[12,13]

So far, several meta-analyses addressed the relationship between vitamin D deficiency and cognitive decline, which suggested a possible positive relationship.[14–16] However, due to the inclusion of case-control and cross-sectional studies, the interpretation of their results may have been limited by reverse causation bias. Older populations with declined cognitive function are more likely to have poorer dietary intakes and have less sunlight exposure[17,18]; thus, it is possible that they have lower concentration of serum 25-hydroxyvitamin D (25(OH)D), and as a result the findings of the previous reviews may have

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been biased toward a greater effect size. Another meta-analysis of five cohort studies suggested that severe vitamin D deficiency (<10 ng/ml) was associated with a 54% greater risk of dementia.[19] However, the degree of the association for milder degrees of vitamin D deficiency (10–20 ng/ml) has not been determined, and the shape of the dose-response relationship has not also been established. Considering the fact that some investigations have suggested a possible U-shaped association between serum 25(OH)D and health outcomes,[20,21] determining the shape of the dose-response relationship between serum 25(OH)D and risk of dementia and AD may provide valuable information to establish whether higher levels of serum 25(OH)D are associated with a higher risk of cognitive decline.

Vitamin D deficiency is highly prevalent all over the world and among all age subgroups.[22] A cross-sectional analysis of 254 adults in Middle East indicated that vitamin D deficiency not only among older adults, but also in younger ones (aged 30–60 years) was associated with a significant decline in cognitive performance.[23] Thus, owing to the correctable nature of vitamin D deficiency, clarifying the association of different levels of serum 25 (OH)D and risk of dementia and AD, and determining the shape of the dose-response relationships may confer valuable information to promote simple and applicable advices in order to reduce the growing prevalence of dementia in the world. Therefore, the aim of this study was to examine the association of different levels of serum 25 (OH)D and risk of dementia and AD, and also to test the linear and potential nonlinear dose-response relationships using prospective and retrospective cohort studies.

Methods

We followed the Meta-analysis of Observational Studies in Epidemiology checklist to write this systematic review and report the results.[24]

Search strategy

A systematic literature search was conducted using PubMed and Scopus, with studies published from 1966 up to 1 September 2017. The search included combinations of keywords relevant to vitamin D, cognition, and study design (Supplemental Table 1). The reference lists of all related articles and reviews were also manually searched. The search was restricted to only articles published in English.

Eligibility and study selection

Two independent authors (AJ, SS-b) reviewed the titles and abstracts of all studies identified. Prospective and retrospective cohort studies were obtained and included in this review if they: (1) were conducted in the general population aged 18 years or older; (2) measured and reported baseline serum 25(OH)D as exposure and in at least three quantitative categories; (3) reported the outcome of interest as dementia or AD incidence at follow-up; (4) reported risk estimates (relative risk or hazard ratio (HR)) and the corresponding 95% confidence intervals (CIs) of dementia or AD for each category of serum 25(OH)D; and (5) reported number of cases and participants/person-years in each category of serum 25(OH)D. Studies that reported results per unit increment or decrement in serum 25(OH)D were also included. We excluded: (1) cross-sectional and case-control studies to avoid reverse causation bias; (2) studies with only two categories of serum 25(OH)D; and (3) studies conducted among patients with specific diseases such as hospitalized patients.

Data extraction and assessment for study quality

Two independent authors (AJ, SS-b) reviewed the full text of selected eligible studies, and extracted the following information: first author's name, publication year, study design, study name, location, follow-up duration, mean age and/or age range, gender, assessment method of serum 25(OH)D, covariates adjusted in the multivariate analysis, exposure levels, number of participants/cases, and reported risk estimates and the 95%CIs of dementia and AD across different categories of serum 25 (OH)D. The models with the most covariate adjustments were selected and included in the meta-analysis. The Newcastle-Ottawa scale was used to assess the quality of the included studies.[25] We contacted with the authors of the Cardiovascular Health Study to obtain the number of cases in each category of serum 25(OH)D. Any discrepancy was resolved through discussion to reach consensus between the two authors.

Data synthesis and statistical analysis

The hazard ratios (HRs) and 95% CIs were considered the effect size for all studies. Two different types of analyses were conducted for this meta-analysis. First, to examine the association of serum vitamin D status and risk of dementia and AD, we standardized and categorized serum vitamin 25(OH)D into three categories according to the recommendations of the Institute of Medicine,[26] which was used in almost all primary studies in the present review: <10 ng/ml (deficiency), 10–20 ng/ml (insufficiency), and ≥20 ng/ml (non-deficient or sufficient, as reference category). Then, we assigned each HR from the original studies to its corresponding category. If more than one category of serum 25(OH)D from an original study fell into the same group in our

meta-analysis, we combined the study-specific estimates using a fixed-effects model and used the pooled estimate for that group. Conversely, if one category of serum 25(OH)D from an original study covered more than one category in our meta-analysis, we assigned risk estimate of that category by its median. For studies in which the reference category was not the highest one, we recalculated risk estimates assuming the highest category as reference.[27] Compared with the highest category, the pooled HRs and 95% CIs of dementia and AD for all other categories of serum 25(OH)D were estimated using fixed-effects models.

Second, we conducted a random-effects dose-response meta-analysis. The linear dose-response relation was estimated using generalized least squares trend estimation, according to the methods developed by Greenland and Longnecker.[28,29] This method needs distribution of cases and non-cases/person-years across different categories of serum 25(OH)D, median value and adjusted HR with its 95% CI for each category of serum 25(OH)D. If in a given study the reference category was not the lowest one, we recalculated risk estimates assuming the lowest category as reference.[27] We also tested the nonlinear dose-response association. In the first stage, a restricted cubic spline model with four knots at the 5th, 35th, 65th and 95th percentiles of the serum 25(OH)D levels was estimated using generalized least squares regression considering the correlation within each set of published HRs.[29] Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis.[30] A *P*-value for nonlinearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. If studies reported results separately for men and women or other subgroups we combined the subgroup-specific estimates using a fixed-effects model and used the combined effect size for meta-analysis. To test the potential effect of each study on pooled effect size, influence analysis was done with one study removed at a time. Subgroup analyses were conducted on the basis of some of the study and participants characteristics. In addition, we conducted a sensitivity analysis by restricting only to studies that considered seasonal variation of serum 25(OH)D levels or used seasonally adjusted serum 25(OH)D in their analyses. Between-study heterogeneity was explored using Cochrane's Q test of heterogeneity and I^2 statistic ($P < 0.05$).[31] Publication bias tests were not conducted because of the low number of studies ($n < 10$). All analyses were conducted with Stata software, version 13 (Stata Corp, College Station, TX, USA). A *P*-value <0.05 was considered statistically significant.

Results

As shown in Supplemental Figure 1, systematic search identified 931 studies, of which 228 studies were duplicates and another 612 studies were not relevant which were excluded at initial screening of the title and abstract. Ninety-one full-text articles were assessed to examine their eligibility for inclusion in the present meta-analysis, and of these, 83 studies were excluded. Detailed reasons for study exclusion are presented in Supplemental Figure 1. Finally, 8 studies with a total of 28,354 participants and 1953 cases of dementia and 1607 cases of AD were included in the final analysis.[32–39] Three studies were from the US,[34,37,39] and five studies were from Europe.[32,33,35,36,38] One study included only men,[38] and the rest included both sexes. One study was a retrospective cohort study,[35] and the remainder were prospective cohort studies. Median follow-up duration ranged from 5.6 to 21 years. All studies were at high quality (≥7 scores) and all have been published after 2014. Four studies adjusted results for month or season of blood collection,[35–38] two studies did not account for seasonal variation in the multivariate analyses, but instead used seasonally adjusted 25(OH)D,[32,33] and two studies did not take seasonal variation of serum 25 (OH)D into account.[34,39] The general characteristics of the primary studies are presented in Table 1, and reported risk estimates of dementia and AD across different categories of serum 25(OH)D in each study are provided in Supplemental Table 2.

Vitamin D status and risk of dementia

Seven studies involving 18,168 participants and 1953 cases were included in the analysis of vitamin D and dementia.[33–39] The meta-analysis indicated that vitamin D insufficiency (10–20 ng/ml) was not associated with the risk of dementia (pooled HR: 1.09, 95%CI: 0.95, 1.24), with no evidence of heterogeneity, $I^2 = 29.3\%$, $P_{\text{heterogeneity}} = 0.21$ ($n = 6$ studies, Supplemental Figure 2). In sensitivity analysis removing each study at a time, none of the excluded studies changed the pooled HR materially. A non-significant association persisted across all subgroups apart from studies conducted in the US (pooled HR: 1.45, 95%CI: 1.03, 1.87; $n = 2$ studies).[37,39] Vitamin D deficiency (<10 ng/ml) was positively and significantly associated with the risk of dementia (pooled HR: 1.33, 95%CI: 1.08, 1.58), with no evidence of heterogeneity, $I^2 = 3.5\%$, $P_{\text{heterogeneity}} = 0.38$ ($n = 5$ studies, Fig. 1).

All studies were eligible for the linear trend estimation, and meta-analysis suggested that the risk of dementia decreased by 17% for a 10-ng/ml increment in serum 25(OH)D (pooled HR: 0.83, 95%CI: 0.70, 0.96), with extreme heterogeneity, $I^2 = 80.8\%$, $P_{\text{heterogeneity}} < 0.001$ (Fig. 2). In sensitivity analysis

Table 1 Characteristics of included studies in the meta-analysis of vitamin D status and risk of dementia and Alzheimer disease.

Author, year, study name, country	Study design	Follow-up duration, y	Participants	Sex	Mean/median age, y	Dementia (*n*)	Alzheimer disease (*n*)	Quality score (max. 9 point)	Vitamin D assessment method	Adjustments
Afzal[32], 2014 The Copenhagen City Heart Study, Denmark	Prospective cohort	21	10,186 Danish general population	W/M	58.0	Not reported	418	9	Chemiluminescent immunoassay (CLIA)	Age, sex, smoking status, BMI, physical activity, alcohol consumption, income level, education, baseline DM, HTN, TC, HDL, and Cr.
Feart[33], 2017 The Bordeaux Three-City study, France	Prospective cohort	11.4	916 community dwellers	W/M	73.3	177	124	8	One-step immunoassay	Gender, education, income, depressive symptomatology, number of drugs per day, apolipoprotein E ϵ4 allele, BMI, practice of physical exercise, DM, history of CVD and stroke, HTN, hypercholesterolemia, hypertriglyceridemia, smoking status, and Mediterranean diet score
Karakis[34], 2016 Framingham Heart Study, US	Prospective cohort	9	1663 participants from the original and Offspring's Framingham Heart Studies	W/M	72.4	267	208	8	Competitive protein-binding assay and radioimmunoassay	Age, gender, smoking, HTN, DM, prevalent CVD, homocysteine, BMI, and vitamin D supplement use.
Knekt[35], 2014 Mini–Finland Health Survey, Finland	Retrospective cohort	17	5010 men and women aged 40–79 years	W/M	56.4	151	Not reported	8	Radioimmunoassay	Age, month of blood drawn, education, marital status, physical activity, smoking status, alcohol consumption, BMI,BP, FPG, serum TG, and serum TC.
Licher[36], 2017 The Rotterdam Study, Netherland	Prospective cohort	13.3	6087 general population in Netherland	W/M	69.2	795	641	9	Electrochemiluminescence binding assay	Age, sex, season of blood collection, BMI, SBP, DBP, educational level, smoking, alcohol use, calcium serum levels, ethnicity, eGFR, TC, HDL, history of DM, HF, stroke, MI, depressive symptoms, outdoor activity, and *APOE* _4 carrier status.
Littlejohns[37], 2014 Cardiovascular Health Study, US	Prospective cohort	5.6	1658 ambulatory adults	W/M	73.6	168	100	8	Liquid chromatography-tandem mass spectrometry (LC-MS)	Age, season of vitamin D collection, education, sex, BMI, smoking, alcohol consumption, depressive symptoms, DM, and HTN.

Olsson[38], 2017 the Uppsala Longitudinal Study, Sweden	Prospective cohort	12	1182 Swedish adult men	M		71.0	250	8	HPLC atmospheric pressure chemical ionization-mass spectrometry	Age, season of blood collection, BMI, education, physical activity, smoking, DM, HTN, hypercholesterolemia, use of vitamin D supplements, and alcohol intake.
Schneider[39], 2014 the ARIC Brain MRI Study, US	Prospective cohort	16.6	1652 black and white adults	W/M		62.0	145	Not reported	8	Liquid chromatography-tandem mass spectrometry	Age, sex, education, income, physical activity, smoking, alcohol use, BMI, WC, and vitamin D supplementation.

Abbreviations: ARIC, atherosclerosis risk in communities; BMI, body mass index; BP, blood pressure; Cr, creatinine; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high density lipoprotein; HPLC, high performance liquid chromatography; HTN, hypertension; MRI, magnetic resonance imaging; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

removing each study at a time, the association ranged from 0.79 (95%CI: 0.66, 0.93) with the exclusion of the Uppsala Longitudinal Study,[38] to 0.88 (95%CI: 0.76, 1.00) with the exclusion of the Bordeaux Three-City study[33] (Supplemental Table 3). None of the excluded studies explained the between-study heterogeneity. In the subgroup analyses, significant inverse associations were found only in the subgroup of studies that considered the seasonal variation of serum 25(OH)D compared to studies without considering the seasonal variation (pooled HRs: 0.77, 95%CI: 0.59, 0.95; n = 5 studies vs. 0.97, 95%CI: 0.88, 1.07; $n = 2$ studies, respectively), in the subgroup with participants >5000 compared to <5000 (pooled HRs: 0.77, 95% CI: 0.58, 0.96; $n = 3$ studies vs. 0.88, 95%CI: 0.71, 1.06; $n = 4$ studies, respectively), and in the subgroup with follow-up duration ≥13 years compared to <13 years (pooled HRs: 0.83, 95%CI: 0.72, 0.94; $n = 3$ studies vs. 0.83, 95%CI: 0.59, 1.06; $n = 4$ studies, respectively). Subgroup analyses yielded follow-up duration and adjustment for main confounders as the potential sources of the heterogeneity (Supplemental Table 4). A nonlinear dose-response meta-analysis suggested a relatively U-shaped association between serum 25(OH)D and risk of dementia,[33,35–39] with a nadir at serum 25(OH)D of 25 ng/ml ($P_{\text{nonlinearity}} = 0.05$, $n = 6$ studies; Fig. 3). However, only one study reported risk estimates of dementia for serum 25(OH)D levels >35 ng/ml,[38] so we repeated the analysis after exclusion of this study, and sensitivity analysis showed that the risk of dementia decreased continuously with increasing serum levels of 25(OH)D from a baseline of 5 ng/ml up to ~30 ng/ml ($P_{\text{nonlinearity}} = 0.22$, Fig. 4).

Vitamin D status and risk of AD

Six studies comprising a total of 25,520 participants and 1607 cases were included in the analysis of vitamin D and AD.[32–34, 36–38] The meta-analysis indicated that neither vitamin D insufficiency nor deficiency were associated with the risk of AD (pooled HRs: 1.19, 95%CI: 0.96, 1.41; $I^2 = 17.4\%$, $P_{\text{heterogeneity}} = 0.30$; $n = 4$ studies; Supplemental Figure 2 and 1.31, 95%CI: 0.98, 1.65; $I^2 = 25.3\%$, $P_{\text{heterogeneity}} = 0.26$; $n = 3$ studies; Fig. 1, respectively).

All six studies were eligible for the linear trend estimation, and summary result showed that a 10-ng/ml increment in serum 25(OH)D was associated with a significant decrement in the risk of AD (pooled HR: 0.83, 95%CI: 0.68, 0.98), with extreme heterogeneity, $I^2 = 82.1\%$, $P_{\text{heterogeneity}} < 0.001$ (Fig. 2). In sensitivity analysis removing each study, in turn, the association ranged from 0.77 (95%CI: 0.63, 0.92) with the exclusion of the Framingham Heart Study,[34] to 0.88 (95% CI: 0.74, 1.01) with the exclusion of the Bordeaux Three-City study[33] (Supplemental Table 5). None of

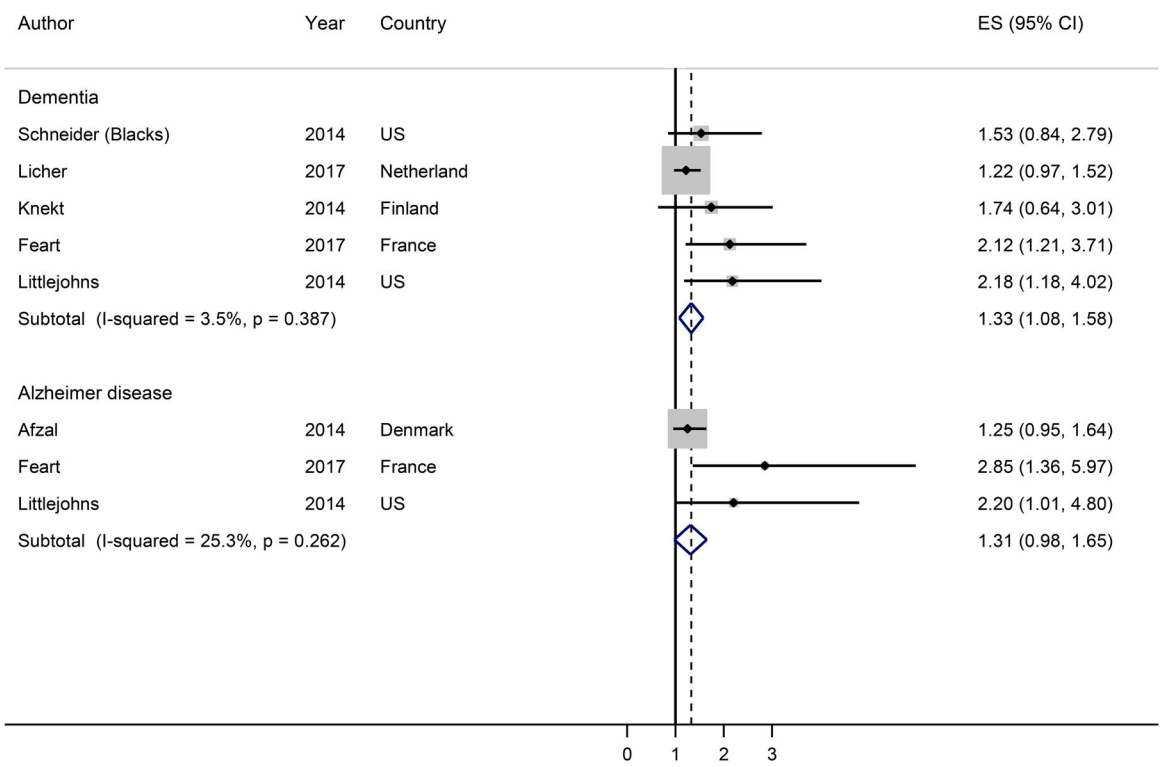

Figure 1 HRs of dementia and AD associated with vitamin D Deficiency (serum 25(OH)D <10 ng/ml).

the excluded studies explained the large degree of the heterogeneity in the data. The pooled HR changed to 0.77 (95%CI: 0.63, 0.92; $I^2 = 76.6\%$, $n = 5$ studies) when the analysis was restricted only to studies that considered the seasonal variation of serum 25 (OH)D. Subgroup analyses suggested that follow-up duration, number of participants and adjustment for history of cardiovascular disease were potential

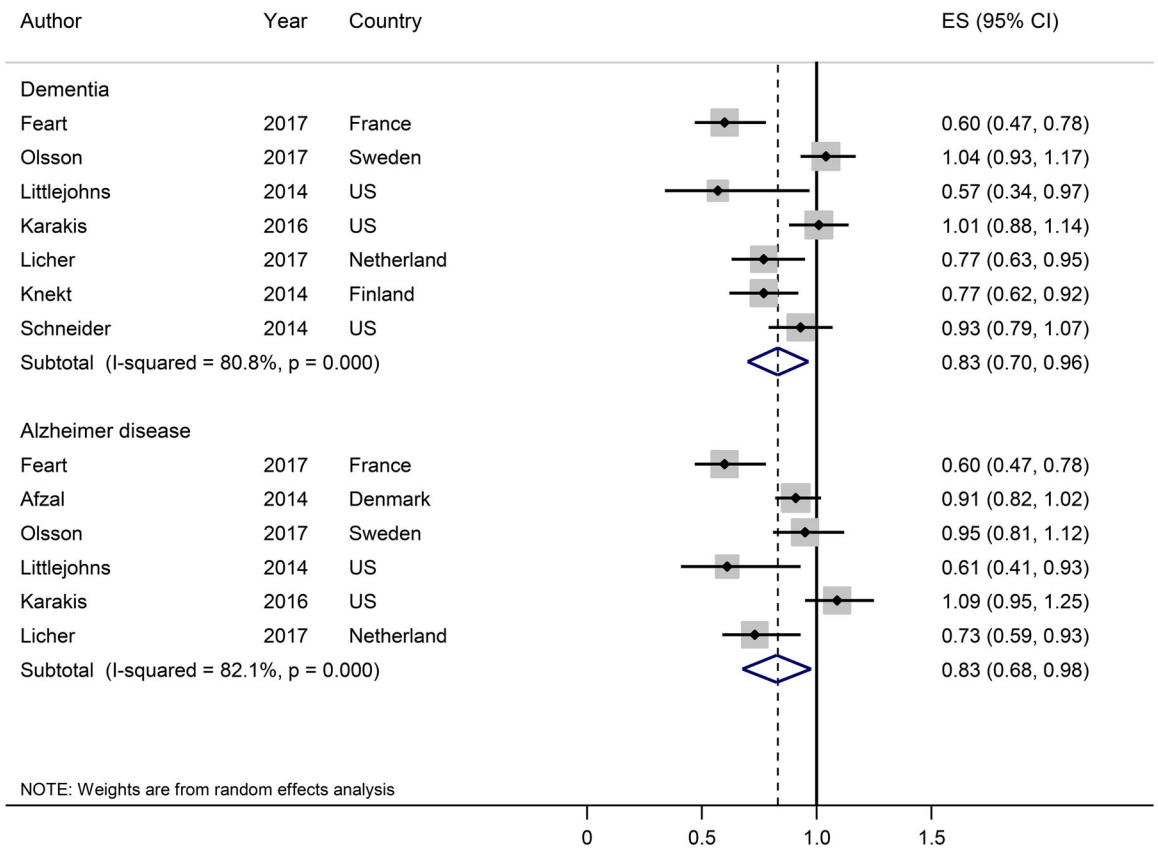

Figure 2 HRs of dementia and AD for a 10-ng/ml increment in serum 25(OH)D.

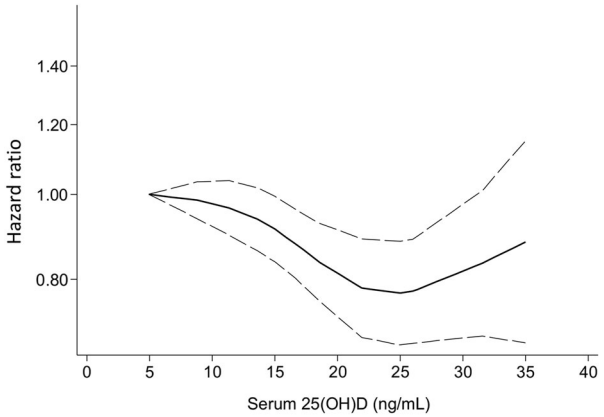

Figure 3 Dose-response association of serum 25(OH)D and risk of dementia (from all included studies). *P* for nonlinearity was 0.05. Solid line represents HRs and long-dash lines represent 95%CI.

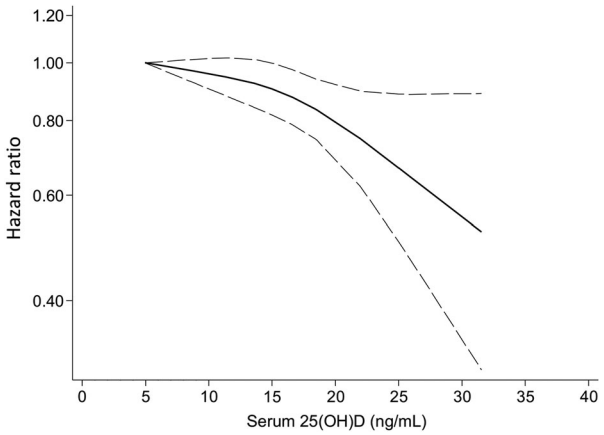

Figure 4 Dose-response association of serum 25(OH)D and risk of dementia (with the exclusion of the Uppsala Longitudinal Study). *P* for nonlinearity was 0.22. Solid line represents HRs and long-dash lines represent 95%CI.

sources of the heterogeneity (Supplemental Table 6). A nonlinear dose-response meta-analysis showed a continuous decrement in the risk with increasing serum 25(OH)D levels from a baseline of 5 up to 35 ng/ml,[32,33,37,38] ($P_{\text{nonlinearity}} = 0.08$, $n = 4$ studies; Fig. 5).

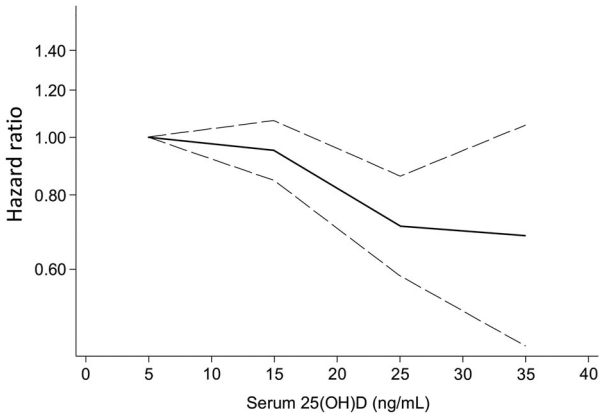

Figure 5 Dose-response association of serum 25(OH)D and risk of AD. *P* for nonlinearity was 0.08. Solid line represents HRs and long-dash lines represent 95%CI.

Discussion

The present meta-analysis provided additional evidence about the association of vitamin D status and risk of dementia and AD. The current analysis indicated that vitamin D deficiency (<10 ng/ml) was significantly and positively associated with the risk of dementia (by 33%), and marginally and positively associated with the risk of AD (by 31%). A 10-ng/ml increment in serum 25(OH)D concentration was associated with a 17% lower risk of dementia and AD. A nonlinear dose-response meta-analysis suggested a U-shaped association in the analysis of dementia, whereas the association appeared to be linear in the analysis of AD.

To our knowledge, no such review has examined the dose-response association of serum 25(OH)D and risk of dementia and AD. Two previous meta-analyses of cross-sectional and case-control studies indicated that serum 25(OH)D concentrations among patients with AD were lower than cognitively healthy control groups.[14,15] Another meta-analysis of five cohort and cross-sectional studies indicated that those with vitamin D deficiency (defined as serum 25(OH)D < 20 ng/ml) had a 21% higher risk of dementia, and a 49% higher risk of AD as compared to those with serum 25(OH)D ≥ 20 ng/ml.[16] However, as above mentioned, due to the inclusion of cross-sectional and case-control studies, their results may have been affected by reverse causation bias. In comparison with previous reviews, the current meta-analysis included only cohort studies, and a larger number of studies, which conferred stronger evidence and enabled us to appropriately test the associations across several subgroups.

In the analysis of dementia, a subgroup analysis yielded a significant positive association only in those studies with follow-up duration ≥13 years compared to <13 years. Generally, in the prospective cohort studies, the strength of the association between serum 25(OH)D and risk of health outcomes such as all-cause mortality tend to decrease along with the increase in follow-up duration, such that prospective studies with shorter duration of follow-up showed stronger inverse association.[40,41] However, in the present meta-analysis, the number of participants was substantially higher in those studies with longer follow-up duration (22,935 vs. 5419), making it possible to get stronger effect size. Furthermore, neurodegenerative disorders are age-related diseases, and their prevalence increases with increasing age. Thus, it is reasonable for studies with longer follow-up duration to show stronger associations.

In the analyses of dementia and AD, summary results for a 10-ng/ml increment in serum 25(OH)D

were more protective in the subgroup of studies which used seasonally adjusted serum 25(OH)D in their analyses, compared with studies without considering seasonal variation of serum vitamin D. Generally, circulating 25(OH)D concentrations vary substantially within individuals over the year, and single measurements of serum 25(OH)D may not accurately reflect the long-term 25(OH)D exposure.[42] Thus, by restricting the analyses only to studies with considering the seasonal variation we may have a more precise estimation from the association between vitamin D and risk of dementia and AD.

A nonlinear dose-response meta-analysis suggested a relatively U-shaped association between serum 25(OH)D and risk of dementia in the main analysis. Of six included studies, only one study (Uppsala Longitudinal Study) reported risk estimates of dementia for serum 25(OH)D levels >35 ng/ml, and a sensitivity analysis with the exclusion of this study did not show such an increased risk. Generally, most of the investigations regarding the association between serum vitamin D status and cognitive decline have reported an inverse linear relationship, and only few studies did report a U-shaped association.[43–45] Furthermore, in the analysis of dementia, the risk of dementia increased at serum 25(OH)D level of >25 ng/ml, which is lower than the cutoff level of 30 ng/ml, as the normal serum 25(OH)D threshold. It has been proposed that the U-shaped association between serum 25(OH)D and risk of chronic diseases found in some observational studies may possibly be due to the chance, or due to the self-supplementation with vitamin D before baseline assessment among participants with prolonged vitamin D deficiency and early stages of chronic diseases, which misleadingly put these participants into the upper categories of serum 25(OH)D, and as a result, might result in misclassification.[46] In accordance with this hypothesis, the proportion of participants with vitamin D supplementation in the Uppsala Longitudinal study was higher in the third compared with the first tertile of serum 25(OH)D (4 vs. 1%, respectively). Thus, it is possible that participants in the third tertile were more likely to suffer from long-term vitamin D deficiency, but because of supplementation with vitamin D due to the appearance of early signs of chronic illnesses before baseline assessment, were placed into the upper categories of serum 25(OH)D. However, regarding the cognitive outcomes of serum 25(OH)D levels >35 ng/ml in this review we had not data to include, and the interpretation of the results should be made with caution.

A recent randomized controlled trial on vitamin D_3 supplementation indicated that even modestly high doses of vitamin D_3 supplementation (a single monthly dose of 60,000 IU vitamin D_3), over the 12-month follow-up, were associated with increased risk of falls among 200 community-dwelling men and women aged 70 years and older with a prior fall compared with control group (a single monthly dose of 24,000 IU).[47] Although the authors concluded that the possible physiological mechanisms behind this detrimental effect remain unclear and need further investigations; however, the possible risks of high-dose supplementation with vitamin D_3 should be well considered before potential suggestions promoting vitamin D_3 supplementation for dementia prevention.

Several reasonable explanations were proposed to justify the observed positive association between vitamin D deficiency and risk of cognitive decline. Vitamin D deficiency exerts its effects indirectly, by increasing the levels of cardiovascular risk factors and the risk of endothelial dysfunction, the two risk factors for development of dementia and AD,[48,49] and directly, by promoting neurodegenerative changes. It seems that, possibly due to the widespread distribution of 1,25-dihydroxivitamin D_3 receptors in the brain, vitamin D acts as a neurosteroid hormone in the brain.[50] Therefore, it is possible that its deficiency through exertion of neurodegenerative changes might be associated with cognitive decline.[51] Vitamin D has some anti-inflammatory and antioxidant properties,[18] and inflammatory processes and oxidative stress-induced mitochondrial damages are involved in the development of neurodegenerative disorders.[51] Furthermore, vitamin D deficiency increases deposition of amyloid plaques in the brain,[52] the underlying cause of dementia and AD.[53]

The present meta-analysis was accompanied by some advantages. First, we included only cohort studies, with acceptable follow-up duration, and high-quality scores which enabled us to appropriately show the longitudinal association between serum 25 (OH)D status and risk of dementia and AD across different subgroups. As above mentioned, cross-sectional and case-control studies are subjected to be affected by reverse causation bias. Thus, by restricting only to cohort studies, we may have a more reliable estimation from the associations. Additionally, we could show the shape of the dose-response relations, which may provide valuable information to provide simple and applicable advices in order to reduce the growing prevalence of neurodegenerative disorders.

We also were faced with some important limitations which should be considered. Our main limitation was the observational design of included studies; thus, we were unable to conclude a causal relationship from the results. Existing evidence from interventional studies is scarce, and two previous clinical trials have failed to show that vitamin D supplementation can decrease the risk of cognitive decline in patients with

AD and in the general population.[54,55] Second, some investigations have suggested a possible association between vitamin D-associated genetic factors and the risk of cognitive decline.[56,57] In the present review, only one study took genetic factors into account in the multivariate analysis.[36] Third, primary studies only assessed baseline serum 25(OH)D, and did not perform repeated measurements over the follow-up period. Thus, without cindering these factors we may have a biased conclusion. Fourth, none of the included studies measured available vitamin D, whereas some evidence indicated that available vitamin D may be a more reliable marker of vitamin D status than total 25(OH)D.[58] Fifth, the data displayed extreme heterogeneity in the linear dose-response meta-analyses of dementia and AD. The subgroup analyses suggested that follow-up duration, seasonal variation of serum 25(OH)D, and adjustment for some of the confounders were potential sources of the heterogeneity. Additionally, only two studies in the analysis of dementia, and one study in the analysis of AD reported risk estimates greater than 1. Thus, the observed heterogeneity may be mainly attributable to the differences in effect sizes of studies examined, rather than inconsistencies in the direction of the association. Finally, all of the studies included in this analysis were published after 2014, and publication bias tests were not performed because of the low number of studies (<10), possibly leading to overestimation of the dementia an AD risks.

Conclusions

The present meta-analysis provided additional evidence regarding the cognitive outcomes of vitamin D deficiency in relatively older age populations, and indicated that vitamin D deficiency (<10 ng/ml) was significantly and positively associated with the risk of dementia, and marginally associated with the risk of AD. We did not find any significant association for vitamin D insufficiency (10–20 ng/ml). The lower risk of dementia was observed at serum 25(OH)D of ~25 ng/ml, but concerning cognitive outcomes of serum 25(OH)D levels >35 ng/ml we had no clear evidence, and future longitudinal investigations may be needed to assess the cognitive outcomes of higher 25 (OH)D levels.

Disclaimer statements

Contributors SS-b and AJ conceived and designed the study, conducted systematic search, screened articles, selected eligible articles, and extracted the information from eligible studies. AJ, SS-b, and ARP performed the analyses and interpreted the results. All authors contributed to writing, reviewing or revising the paper. SS-b is the guarantor.

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