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Association of Vitamin D Levels with Incident All-Cause Dementia in Longitudinal Observational Studies: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: The role of vitamin D is not only limited to bone health and pathogenesis of chronic diseases. Evidence now suggests that it is also involved in the development of various dementias and Alzheimer's disease (AD).

OBJECTIVE: To carry out a systematic review and meta-analysis to evaluate the association between vitamin D levels and increased risk of incident all-cause dementia in longitudinal studies.

DESIGN: We conducted a systematic review and meta-analysis using the electronic bibliographic databases PubMed and Scopus.

SETTING: Prospective cohort studies.

PARTICIPANTS: Community-dwelling older adults.

MEASUREMENTS: Vitamin D serum concentrations were categorized in three groups: normal levels (>50 nmol/L), insufficient levels (25 - 49.9 nmol/L), and deficient levels (<25 nmol/L). We performed a meta-analysis using the general inverse variance method to calculate the pooled risk of AD and all-cause dementia according to vitamin D levels. Random-effects or fixed-effect model were used to calculate the pooled risk based on the heterogeneity analysis.

RESULTS: Five studies were included in the meta-analysis. The pooled risk of all-cause dementia and AD was significantly higher in those with deficient serum vitamin D level compared to those with normal level (1.33, CI95% [1.15, 1.54], and 1.87, CI95% [1.03, 3.41], respectively). Those with insufficient level also had a higher pooled risk of all-cause dementia and AD, but the strength of association was less robust (1.14 CI95% [1.02, 1.27] and 1.25, CI95% [1.04 - 1.51], respectively).

CONCLUSION: We found a gradient effect for the risk of all-cause dementia and AD according to the vitamin D level, with higher risk in those in the deficient levels group and intermediate risk in those with insufficient levels. Our findings were limited by the relatively small number of studies included in the meta-analysis and their geographic restriction.

Key words: Vitamin D, all-cause dementia, Alzheimer's disease, risk factor.

Introduction

Vitamin D is a fat-soluble vitamin and the hydroxylated form (1,25 dihydroxy vitamin D [1,25(OH)2D] or calcitriol) is its biologically active form in humans. It exerts its biological effects by activating the vitamin D nuclear receptors (VDR) and triggering downstream gene transcription (1). Vitamin D most commonly has been known for its role in the maintenance of bone health and in the prevention and treatment of osteoporosis (2, 3). More recently, a growing body of evidence has suggested that it is also involved in the pathogenesis of chronic conditions, including the development of Alzheimer's disease (AD) and other dementias in geriatric population (4).

Several longitudinal studies have shown mixed results regarding the association between low vitamin D levels and cognitive decline. Goodwill et al. (2018) and Bartali et al. (2014) showed that low vitamin D concentrations are associated with poor cognitive functioning in women, but not in men (5) (6). Knekt et al. (2014) also reported that women with low vitamin D concentration (i.e., below 28 nmol/L) had an increased risk of developing dementia in comparison to those with higher concentrations (i.e., greater than 54 nmol/L) (7). Slinin et al. (2010) found a small, but significant association between low vitamin D and cognitive decline in men (8). Conversely, Karakis et al. (2016) found no association between vitamin D levels and incident dementia & AD (9). Similarly, Schneider et al. (2014) reported that low levels of vitamin D measured during middle-age were not associated with the risk of developing dementia (10).

Given the absence of preventive or curative interventions for AD and other degenerative dementias, the search for potentially modifiable risk factors for these conditions is of paramount importance. The present systematic review and meta-analysis by Annweiler et al. (2013) and Balion et al. (2012) found that serum 25(OH)D concentrations were lower in individuals with AD (11) (12). Due to the inherent nature of cross-sectional studies no causality can be concluded. However, the

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most recent, Jayedi et al. (2018) examined the association between deficient & insufficient vitamin D levels, including both retrospective and prospective longitudinal studies (13).

There are no systematic reviews and meta-analysis that have focused on the association between both deficient & insufficient vitamin D levels and the prospective risk of AD & all-cause dementia. The past systematic reviews did not use standardized definition of vitamin D deficient, insufficient and sufficient levels and used different methodological approaches. Therefore, the primary objective of this study was to carry out a systemic review and meta-analysis of the literature to evaluate whether serum levels of vitamin D are associated with increased risk of AD and all-cause dementia in longitudinal studies.

Methods

This meta-analysis followed the PRISMA guidelines for conducting and reporting systematic reviews.

Search strategy

We carried out a systematic literature search for potentially relevant studies on vitamin D and dementia & AD in the electronic bibliographic databases PubMed and Scopus which provide a comprehensive range of journals published worldwide. The literature search was conducted in January 2018. There was no time or publication language limits. Search included the following terms: "(Vitamin D) AND (Alzheimer's disease OR Dementia OR Vascular dementia)." The search retrieved a total of 801 references. In addition, we also did a manual search for potentially relevant references in the reference sections of previous original studies, narrative or systematic reviews of the literature on the association between vitamin D, cognitive decline and dementia in the elderly (Figure 1). The search was conducted by both AK and BSD.

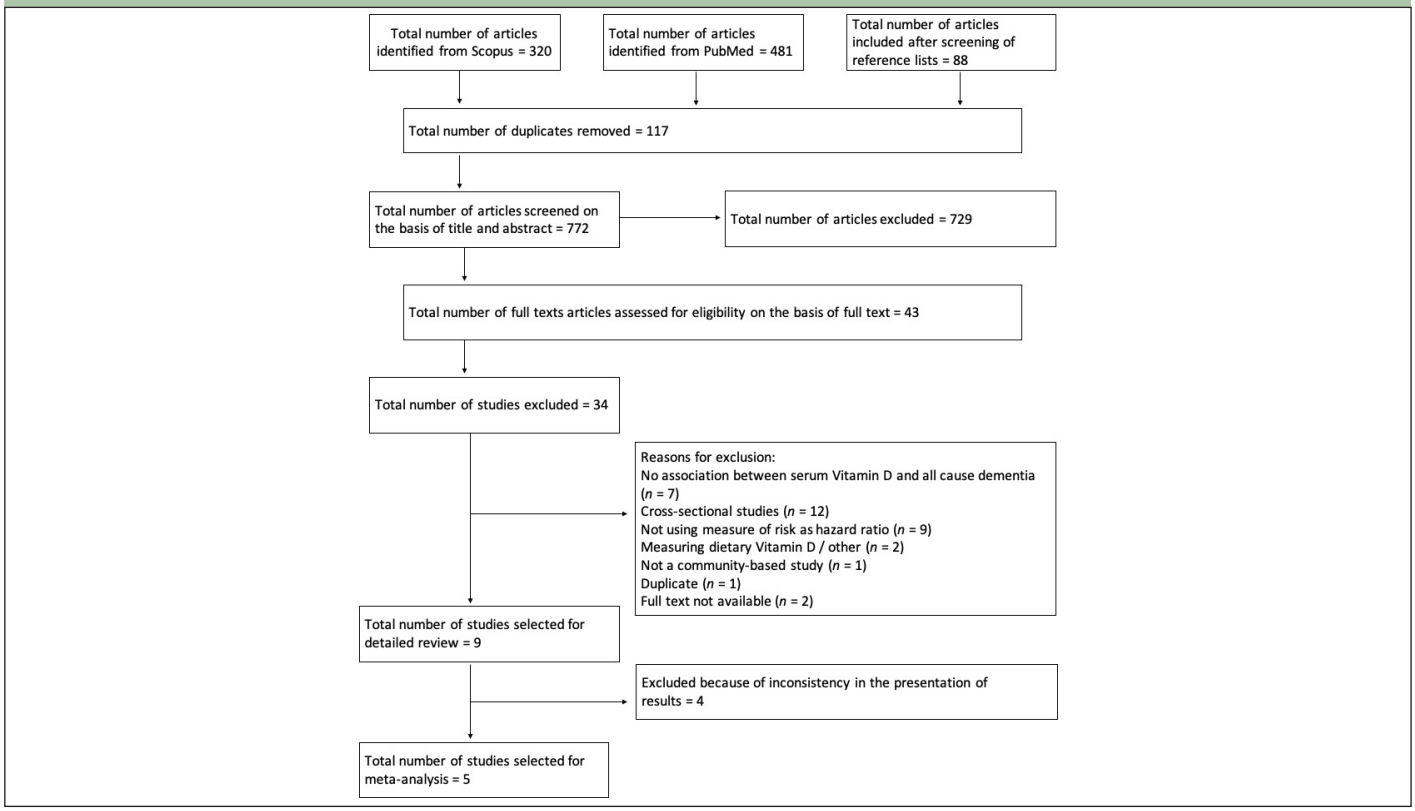
Study selection

We selected studies for data extraction and analysis based on the following criteria: (a) Community-based prospective cohort studies (b) free of dementia or AD or vascular dementia at baseline (c) measured serum vitamin D as an exposure variable (d) information on incident dementia (all-cause) and/or AD /or Vascular dementia as an outcome measure (e) risk measure information and its 95% CI for the risk of dementia (all-cause) and/or AD and/or Vascular dementia and (f) age over 50 years at baseline assessment of participants.

Risk of bias assessment

We used the Newcastle Ottawa Scale (NOS) to assess the method quality (risk of bias) of each study included in

Figure 1. Flow chart of the study search and selection for inclusion in the meta-analysis



the meta-analysis. This measure assesses methodological aspects of observational studies such as selection of participants, comparability of cohorts by design, adjustment for confounders and outcome assessment. The overall result of each study was marked as good, fair or poor quality. The risk-of-bias rating for each study was marked as low, unclear and high risk of bias. All the included studies were assessed as of good quality (14).

Exposure Variable

The exposure variable for this review was vitamin D levels. By using standardized definition, vitamin D serum concentrations were categorized in three groups: normal levels (>50 nmol/L), insufficient levels (25 - 49.9 nmol/L), and deficient levels (<25 nmol/L) (15, 16).

Outcome Variable

Alzheimer's disease and all-cause dementia.

Data extraction

To calculate the pooled risk of incident dementia, we extracted the reported risk measure, the 95% confidence interval for AD and all-cause dementia. When possible, we also extracted the total sample and total number of events in each vitamin D groups (vitamin D < 25 nmol/L (deficiency); 25 - 49.9 nmol/L (insufficiency); and > 50 nmol/L (normal). The values were extracted for all the models as presented in each study generally representing model 1 as adjusted for age, gender, education & season of blood collection. Model 2 and model 3 were fully adjusted models including all the confounders identified by individual studies. For this review, we used the fully adjusted models.

Statistical analysis

We performed the meta-analysis using the generic inverse variance method to calculate the pooled risk of AD or all-cause dementia according to the vitamin D levels. Random-effects or fixed-effect model were used to calculate the pooled risk based on the heterogeneity analysis. If the heterogeneity was not statistically significant, we used a fixed-effect model; otherwise, we used a random-effect model. Heterogeneity was assessed by the Q-test and I2 index. The pooled analysis was considered significantly heterogeneous if the p-value was below 0.05 in the Q-test and/or the I2 index was more than 50%.

Sensitivity analysis was performed by excluding one study at a time and recalculating the risk effect to assess whether the summary risk effect was biased by the effect of any individual study ("leave one out" technique). Publication bias was assessed by visual inspection of a funnel plot. All analyses were carried with the Statistical Software RevMan 5.1 (https://community.cochrane.org/help/tools-and-software/revman-5/revman-5-download). AK and BSD were independently involved in the study selection, data extraction, quality appraisal and statistical analysis process. Regular meetings were held between the authors to minimize the risk of errors for each of the review stages. Inconsistencies were resolved by the senior author.

Results

Five studies met the criteria for inclusion in the meta-analysis (17-21). Table 1 provides the characteristics of each study included in the meta-analysis. All studies reported incident all-cause dementia and 4 studies included data for AD, with follow-up ranging from 5 years to 30 years. Four studies were conducted in Europe (Denmark, France, Netherlands & Sweden), one study was conducted in United States and one was conducted in Korea. The mean age of the particpants was 63 years. The most common diagnostic criteria used for AD and dementia was National Institute of Neurological and Communicative Disorders & Stroke & the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and Diagnostic and Statistical Manual of Mental Disorders (DSM).

The total sample included in the pooled analysis for all-cause dementia for normal levels was composed of 5,147 participants, for insufficient levels by 7,505 participants, and deficient levels by 3,548 participants. Analysis for AD was based on data from 5,035 participants for normal levels, 4,634 participants for insufficient levels and 2,672 participants for deficient levels respectively.

We first meta-analyzed the hazard ratio for incident all-cause dementia and AD between the groups with vitamin D concentration above 50nmol/L (normal vitamin D levels) and between 25 and 49.9 nmol/L (insufficient vitamin D levels). There was no evidence of significant heterogeneity in the analyses for all-cause dementia (Q statistics = 6.44, df = 4 P = 0.17) and AD (Q statistics = 5.81, df = 2, P = 0.05). The pooled HR (fixed-effect model) for all-cause dementia was 1.14 CI95% [1.02, 1.27], Z = 2.28, df = 4, P = 0.02. The pooled HR (fixed-effect model) for AD was 1.25, CI95% [1.04, 1.51], Z = 2.36, df = 2, P = 0.02. Figures 2a and 2b show, the forest plots for the meta-analyses.

We then meta-analyzed the hazard ratio for all-cause dementia and AD between the group with vitamin D concentrations above 50 nmol/L (normal vitamin D levels) and between <25 nmol/L (deficient vitamin D levels). There was no evidence of significant heterogeneity in the analysis for all-cause dementia (Q statistics = 8.63, df = 4, P = 0.07). However, there was evidence of significant heterogeneity in the analysis for AD (Q statistics = 6.61, df = 2, P = 0.04). The pooled HR

Table 1. Study characteristics

Authors	Duration of follow-up (Median, years)	Geography / Ethnicity	Age of participants (years)	Gender (%)	Total sample analyzed	Vitamin D test	Diagnostic criteria for Alzheimer's Disease (AD)	Diagnostic criteria for Dementia	Events (During follow up)
Afzal S, Bojesen SE and Nordestgaard BG (2014)	21	Denmark / Whites	50 - 65	Men: <25nmo/L - 45 25 - 49.9 nmol/L- 44 >50 nmol/L - 43	10,186	DiaSorin Liaison 25(OH)D TOTAL assay (Diasorin, Stillwater, MN)	ICD, 8th edition, codes 290.0 - 290.1 and ICD, 10th edition, codes F00 and G30	ICD, 8th edition, codes 293.09 - 293.1 and ICD, 10th edition, codes F01	AD = 418 VD = 92
Fear C. et al (2017)	11.4	France / Whites	≥ 65	Women: <25 nmol/L - 75.7 25 - 50 nmol/L - 60.3 >50 nmol/L - 50.3	916	Immunoassay, Architect 25-OH Vitamin D Assay; Abbott Diagnostics, Germany	NINCDS - ADRDA criteria	DSM-IV-TR	AD = 124 ACD = 177
Lisher S. et al (2017)	13.3	Rotterdam, Netherlands/ Whites	≥ 55	Women: 66.1	6087	COBAS Roche Diagnostics GmbH, Germany	NINCDS - ADRDA criteria	DSM-III-R	AD = 641 ACD = 795
Littlejohns TJ. et al (2014)	6.1	United States / Whites	≥ 65	Women: <25 nmol/L - 88.6 ≥25 - ≤50 nmol/L - 78.8 >50 nmol/L - 64.7	1,658	Waters Quattro micro mass spectrometer (Waters, Milford, MA)	NINCDS - ADRDA criteria	NINCDS - ADRDA criteria	AD = 102 ACD = 171
Moon JH. et al (2015)	5	Korea / Asians	≥ 65	Men/Women: <25 nmol /L - 33.3/ 66.7 25 - 49.9 nmol/L - 53 / 47 ≥50 nmol/L - 51.8/ 48.2	412	Diels–Alder derivatization and ultrahigh performance liquid chromatography–tandem mass spectrometry (Waters, Milford, MA, USA)	NA	DSM-IV-TR	AD = NA ACD = 23

Figure 2a. Forest plot for the risk of incident all-cause dementia in patients with insufficiency

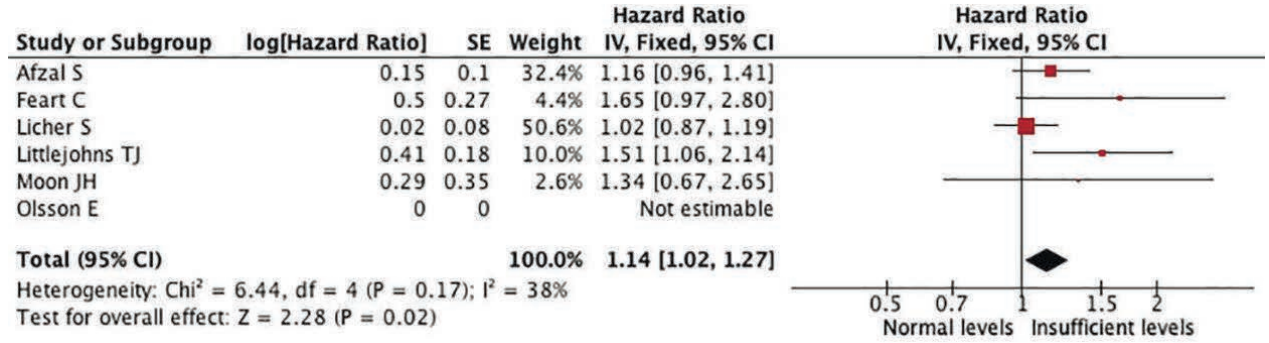


Figure 2b. Forest plot for the risk of incident Alzheimer's disease in patients with insufficiency

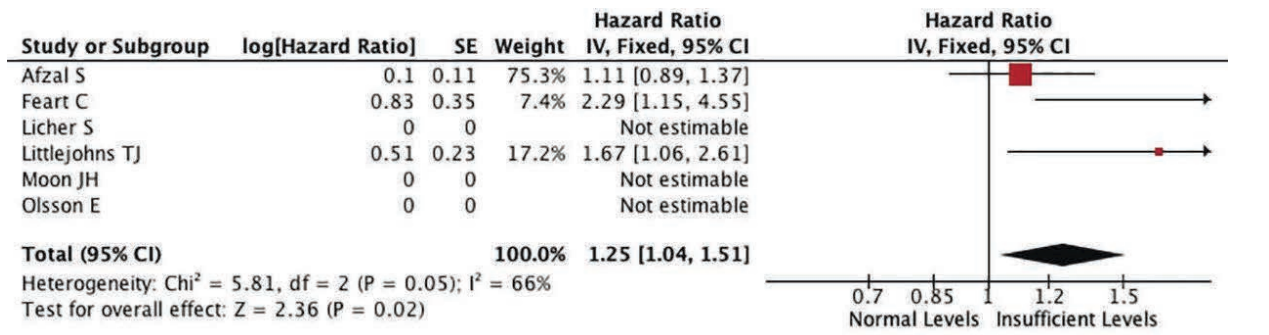


Figure 3a. Forest plot for the risk of incident all-cause dementia in patients with deficiency

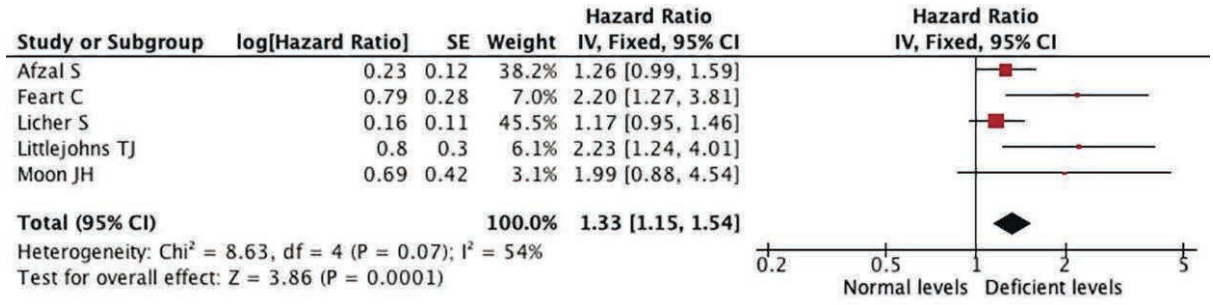
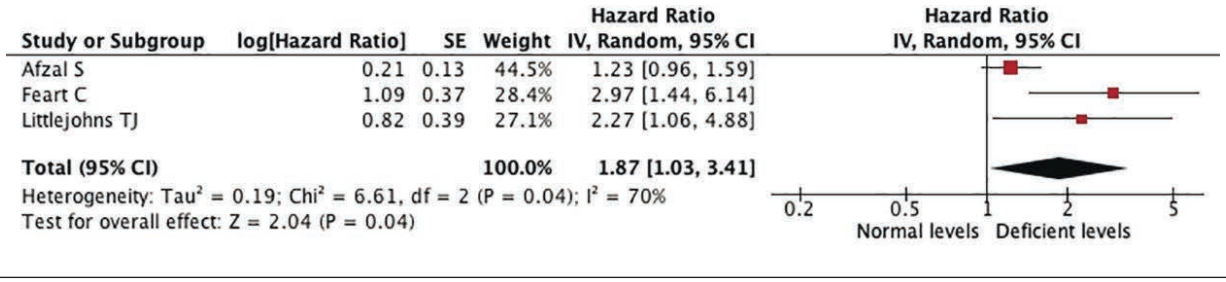


Figure 3b. Forest plot for the risk of Alzheimer's disease in patients with deficiency



(fixed-effect model) for all-cause dementia was 1.33, CI95% [1.15, 1.54], Z = 3.86, df = 4, P = 0.0001. The pooled HR (random-effect model) for AD was 1.87, CI95% [1.03, 3.41], Z = 2.04, df = 2, P = 0.04. Figures 3a and 3b show the forest plots for the meta-analyses.

We carried out additional subgroup analysis to evaluate if the risk of developing all-cause dementia or AD differed between the groups with deficient and insufficient vitamin D levels. We found no statistically significant differences in the pooled risk of all-cause dementia (deficient group, pooled risk 1.33 [1.15, 1.54]; insufficient group, pooled risk 1.14 [1.02, 1.27]; Chi2 = 2.83, df = 1, p = 0.09) or AD (deficient group, pooled risk 1.42 [1.13, 1.79]; insufficient group, pooled risk 1.25 [1.04, 1.51]; Chi2 = 0.72, df = 1, p = 0.4). Figures 4a and 4b show the forest plots for the meta-analyses.

We did additional sensitivity analysis with leave one out technique to evaluate the impact of individual studies in the pooled HR. In the normal vs insufficient vitamin D level, we found a significant impact on the pooled HR for all-cause dementia when we removed Littlejohns' study (HR 1.10 CI95% [0.98, 1.24) and for AD when we removed the studies Littlejohns (HR = 1.18, CI95% [0.96, 1.45]) and Feart (HR = 1.19 CI95% [0.98, 1.45]). Sensitivity analysis did not show a significant influence of any individual studies in the pooled HR for all-cause dementia and AD between the groups with normal vs deficiency vitamin D levels. We found no publication bias by visually assessing the funnel plots (supplementary figure 1).

Discussion

In this meta-analysis we evaluated the association between deficient & insufficient vitamin D concentration and all-cause dementia & AD focusing on community-based longitudinal prospective cohort studies. We found that both insufficient levels (25 - 49.9nmol/L) and deficient levels (<25 nmol/L) were associated with higher risk of incident all-cause dementia and AD when compared with normal levels (>50 nmol/L). Moreover, the risk of dementia and AD were higher in the deficient level group.

Our results are in line with a recent meta-analysis that included different profile of studies (randomized and non-randomized clinical trials, prospective cohort studies, nested case-control studies), showing that individuals with deficient vitamin D levels (<25 nmol/L) had a higher odds (i.e., OR = 1.54) of developing dementia than individuals with normal serum 25(OH)D levels (>50 nmol/L). Since the study could not identify any direct evidence on exposure to sunlight and risk of developing dementia, it focused on indirect evidence from studies using vitamin D status as a surrogate parameter (22). Likewise, another meta-analysis including different study designs reported that individuals with deficient vitamin D levels were at a higher risk of developing AD and dementia in comparison to individuals with sufficient vitamin D levels (23). Another, previous meta-analysis including studies with both retrospective and prospective designs

Figure 4a. Forest plot for the risk of incident all-cause dementia in patients between deficient and insufficient levels

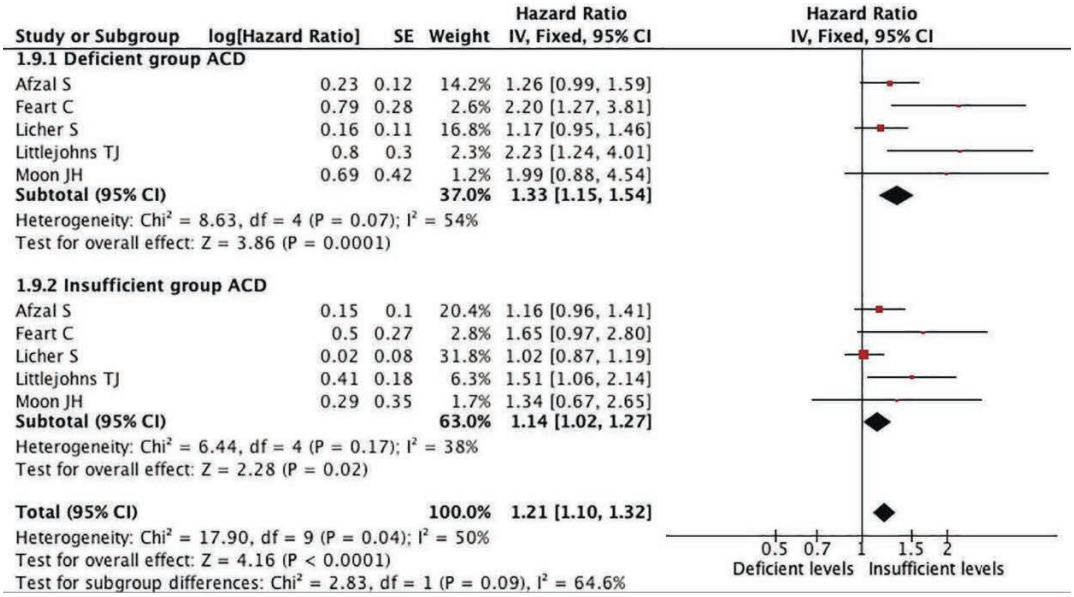
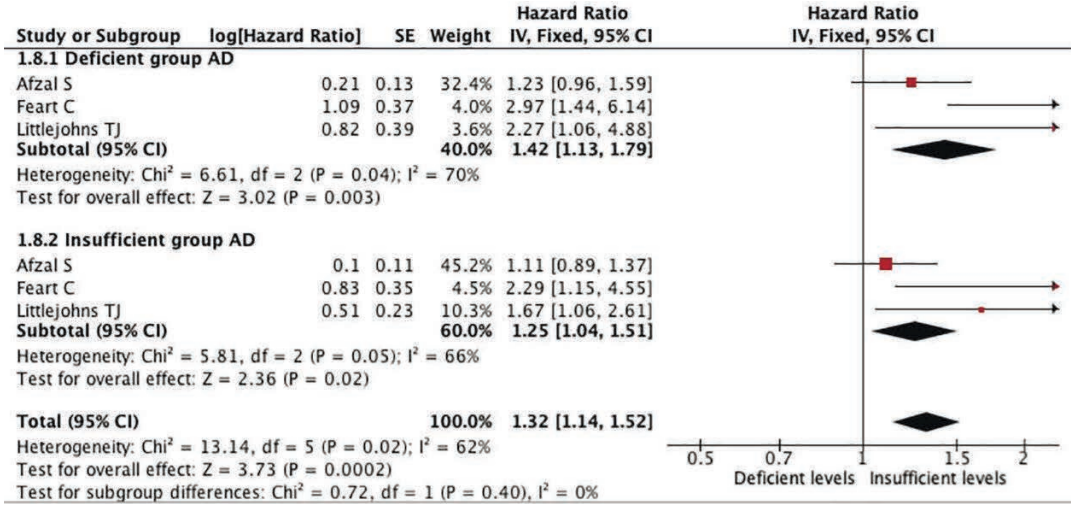


Figure 4b. Forest plot for the risk of Alzheimer's disease in patients between deficient and insufficient levels



showed that those with serum vitamin D concentrations below 10ng/ml was positively associated with higher risk of developing dementia (HR = 1.33, CI95% [1.08, 1.58]) and marginally positively associated with risk of AD. It further reported that vitamin D insufficiency was not associated with the risk of dementia (13). Our study moved a step forward by using standardized definition for vitamin D levels and addressed the prospective risk of dementia and AD in those with insufficient vitamin D levels (between 25 nmol/L and 49.9nmol/L) as well. We also conducted a subgroup analysis to evaluate the degree of risk between deficient and insufficient vitamin D levels. Altogether, the results of our meta-analysis and the current literature suggest that there is probably a gradient effect of the association between vitamin D levels and the risk of dementia. There was a minimal overlap of studies included in our review with Sommer et al. (2017) and Shen and Ji. (2015) (22, 23). But, there was a overlap of three studies for prospective longitudinal studies with Jayedi et al. (2018) (13).

The current meta-analysis has some limitations. First, the observational design of the included studies prevents definite causal assumptions. Second, the number of studies in the meta-analysis is small and comes mostly from developed countries with predominantly white population. Thus, these finding may not be generalized to other countries and/or ethnic groups. Third, the studies had very different follow-up periods. This wide range of follow-up can influence the estimate of progression to dementia and, as consequence, the strength of the potential association between vitamin D and risk of dementia. Fourth, the studies measured vitamin D only

at the baseline; therefore, we cannot determine if there is an association between the trajectory of changes in the vitamin D levels and cognitive decline. Finally, we were not able to evaluate the risk of vascular dementia or other demetia types.

On the other hand, our analysis has major strengths. First, unlike previously published meta-analyses we included only prospective studies that can identify and relate events to exposure, to establish the order of events, following changes over time within the cohort, and to eliminate recall bias (24). We also included studies that used the same criteria for classifying the serum vitamin D measurements in deficient, insufficient and sufficient levels.

The current meta-analysis adds to the pool of existing evidence regarding the association between vitamin D concentrations and the risk of developing dementia and AD. Once more robust evidence is available, this might ultimately lead to preventive strategies to fight dementia at the public health level. Future prospective studies must assess vitamin D not only at the baseline but also perform repeated measurements over the follow-up periods in order to strengthen the results and to evaluate potential associations between the trajectories of vitamin D changes and cognitive decline. Further, the current evidence does not provide enough data to carry out gender-based analysis, and this must be accounted for in the future studies. Also, there is negligible data available for low-middle income countries and more focus should be geared towards them as they would have the highest burden of the ageing population.

Ethical standards: No informed conscent was required due to the observational design of our study. No Humans and animals were involved in the present study.

Conflict of interest: The authors declared no potential conflicts of this article.

References

1. Keeney JT, Butterfield DA. Vitamin D deficiency and Alzheimer disease: Common links. Neurobiol Dis [Internet]. 2015;84:84–98. Available from: http://dx.doi.org/10.1016/j.nbd.2015.06.020
2. Lips P, Van Schoor NM. The effect of vitamin D on bone and osteoporosis. Best Pract Res Clin Endocrinol Metab [Internet]. 2011;25(4):585–91. Available from: http://dx.doi.org/10.1016/j.beem.2011.05.002
3. Laird E, Ward M, McSorley E, Strain JJ, Wallace J. Vitamin D and bone health; Potential mechanisms. Nutrients. 2010;2(7):693–724.
4. Meehan M, Penckofer S. The Role of Vitamin D in the Aging Adult Meghan. J Aging Gerontol [Internet]. 2015;2(2):60–71. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4399494/pdf/nihms662547.pdf
5. Goodwill AM, Campbell S, Simpson S, Bisignano M, Chiang C, Dennerstein L, et al. Vitamin D status is associated with executive function a decade later: Data from the Women's Healthy Ageing Project. Maturitas [Internet]. 2018;107(July 2017):56–62. Available from: https://doi.org/10.1016/j.maturitas.2017.10.005
6. Bartali B, Devore E, Grodstein F, Kang JH. Plasma vitamin D levels and cognitive function in aging women: The nurses' health study. J Nutr Heal Aging. 2014;18(4):400–6.
7. Knekt P, Sääksjärvi. K, Järvinen R, Marniemi J, Männistö S, Kanerva N, et al. Serum 25-hydroxyvitamin D concentration and risk of dementia. Epidemiology. 2014;25(6):799–804.
8. Slinin Y, Paudel ML, Taylor BC, Fink HA, Ishani A, Canales MT, et al. 25-Hydroxyvitamin D levels and cognitive performance and decline in elderly men. Neurology. 2010;74(1):33–41.
9. Karakis I, Pase MP, Beiser A, Booth SL, Jacques PF, Rogers G, et al. Association of serum Vitamin D with the risk of incident dementia and subclinical indices of brain aging: The framingham heart study. J Alzheimer's Dis. 2016;51(2):451–61.
10. Schneider AL., Lutsey PL, Alonso A, Gottesmann RF, Sharrett RA, Carson KA, et al. Vitamin D and Cognitive Function and Dementia Risk in a Biracial Cohort: the ARIC Brain MRI Study Andrea. Eur J Neurol [Internet]. 2014;21(9):1211-1e70. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4114998/
11. Annweiler C, Llewellyn DJ, Beauchet O. Low serum vitamin D concentrations in Alzheimer's disease: A systematic review and meta-analysis. J Alzheimer's Dis. 2013;33(3):659–74.
12. Balion C, Griffith LE, Strffler L, Henderson M, Patterson C, Heckman G, et al. Vitamin D, cognition, and dementia A systematic review and meta-analysis. Neurology. 2012;25(79):1397–405.
13. Jayedi A, Rashidy-Pour A, Shab-Bidar S. Vitamin D status and risk of dementia and Alzheimer's disease: A meta-analysis of dose-response. Nutr Neurosci [Internet]. 2018;8305:1–10. Available from: https://sci-hub.tw/10.1080/1028415X.2018.1436639
14. Wells GA, Shea B. Newcastle-Ottawa Quality Assessment Form for Cohort Studies. 2013;17–8. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
15. WHO Scientific G. Prevention and management of osteoporosis Report of a WHO Scientific Group. WHO Tech Rep Ser [Internet]. 2003;1–206. Available from: https://apps.who.int/iris/bitstream/handle/10665/42841/WHO_TRS_921.pdf?sequence=1&isAllowed=y
16. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine : What Clinicians Need to Know. J Clin Endocrinol Metab [Internet]. 2011;96(1):53–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3046611/
17. Afzal S, Bojesen SE, Nordestgaard BG. Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia. Alzheimer's Dement [Internet]. 2014;10(3):296–302. Available from: http://dx.doi.org/10.1016/j.jalz.2013.05.1765
18. Feart C, Helmer C, Merle B, Herrmann FR, Annweiler C, Dartigues JF, et al. Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. Alzheimer's Dement. 2017;13(11):1207–16.
19. Licher S, De Bruijn RFAG, Wolters FJ, Zillikens MC, Ikram MA, Ikram MK. Vitamin D and the Risk of Dementia: The Rotterdam Study. J Alzheimer's Dis. 2017;60(3):989–97.
20. Littlejohns TJ, Henley WE, Lang IA, Annweiler C, Beauchet O, Chaves PHM, et al. Vitamin D and the risk of dementia and Alzheimer disease. Neurology. 2014;83(10):920–8.
21. Moon JH, Lim S, Han JW, Kim KM, Choi SH, Kim KW, et al. Serum 25-hydroxyvitamin D level and the risk of mild cognitive impairment and dementia: The Korean Longitudinal Study on Health and Aging (KLoSHA). Clin Endocrinol (Oxf). 2015;83(1):36–42.
22. Sommer I, Griebler U, Kien C, Auer S, Klerings I, Hammer R, et al. Vitamin D deficiency as a risk factor for dementia: a systematic review and meta-analysis. BMC Geriatr. 2017;17(1):1–13.
23. Shen L, Ji HF. Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: Evidence from meta-analysis. Nutr J [Internet]. 2015;14(76):1–5. Available from: http://dx.doi.org/10.1186/s12937-015-0063-7
24. Caruana EJ, Roman M, Sánchez JH, Solli1 SP. Longitudinal studies. J Thorac Dis. 2015;7(11):537–40.