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A systematic review and meta-analysis of the effect of low vitamin D on cognition

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Abstract

Background/objective: With an aging population and no cure for dementia on the horizon, risk factor modification prior to disease onset is an urgent health priority. Therefore, this review examined the effect of low vitamin D status or vitamin D supplementation on cognition in midlife and older adults without a diagnosis of dementia.

Design: Systematic review and random effect meta-analysis.

Setting: Observational (cross-sectional and longitudinal cohort) studies comparing low and high vitamin D status and interventions comparing vitamin D supplementation with a control group were included in the review and meta-analysis.

Participants: Studies including adults and older adults without a dementia diagnosis were included.

Measurements: Medline (PubMed), AMED, Psych INFO, and Cochrane Central databases were searched for articles until August 2016. The Newcastle-Ottawa Scale and Physiotherapy Evidence Database assessed methodological quality of all studies.

Results: Twenty-six observational and three intervention studies (n=19 to 9,556) were included in the meta-analysis. Low vitamin D was associated with worse cognitive performance (OR=1.24, CI=1.14-1.35) and cognitive decline (OR=1.26, CI=1.09-1.23); with cross-sectional yielding a stronger effect compared to longitudinal studies. Vitamin D supplementation showed no significant benefit on cognition compared with control (SMD=0.21, CI=-0.05-0.46).

Conclusion: Observational evidence demonstrates low vitamin D is related to poorer cognition; however interventional studies are yet to show a clear benefit from vitamin D supplementation. From the evidence to date, there is likely a therapeutic age window relevant to the development of disease and therefore vitamin D therapy. Longitudinal lifespan studies are necessary to depict the optimal timing and duration in which

repletion of vitamin D may protect against cognitive decline and dementia in aging, to better inform trials and practice towards a successful therapy.

Keywords: Dementia: cognitive aging: cognitive decline: neuropsychology: prevention: Vitamin D.

INTRODUCTION

Cognitive decline and dementia are among leading chronic conditions undermining the quality of life in our aging population. With over 150 unsuccessful compounds tested[1] and a cure for dementia yet to be discovered[1], identifying modifiable risk factors towards disease prevention is a high priority. Previously identified lifestyle risk factors have been attributed to half the cases of dementia,[2] and should inform clinical intervention towards preventing or delaying cognitive decline in aging.

Emerging evidence suggests vitamin D deficiency is an important marker of cognitive decline.[3, 4] While the involvement of vitamin D in musculoskeletal health is well-established, associations with cognitive health have been identified.[5-10] However, longitudinal evidence remains inconsistent, with some studies reporting cognitive decline related to vitamin D deficiency,[11-14] whilst others failed to observe associations.[15-18]

Previous reviews and meta-analyses[3, 4, 19, 20] support the association between low vitamin D, poor cognition and risk of cognitive impairment or dementia,[21] however conclusions have been drawn from a small pool of studies ($n \leq 12$). These reviews have also included both cognitively healthy and impaired participants; therefore, the relationship between vitamin D and cognition prior to the manifestation of clinical symptoms remains unclear. Given the long prodromal stage of cognitive impairment and dementia,[22, 23] vitamin D repletion may be particularly important in midlife, prior to symptom onset in later-life. Therefore, this review aims to address this question through synthesizing all available data quantifying the effect of low vitamin D on cognition in cognitively intact adults and older adults, a key population for a preventive intervention.

METHODS

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-2009) and Meta-Analysis for Observational Studies in Epidemiology (MOOSE) guidelines.

Search strategy

Medline (PubMed), AMED, Psych INFO, and Cochrane Central Database were searched with the end-date restricted to August 31st 2016 and English language. Eight search terms pertaining to vitamin D ("Vitamin D" or "vitamin D2" or "vitamin D3" or "25OHD" or "25(OH)D" or "25-hydroxyvitamin D" or "Hydroxycholecalciferols" or "hypovitaminosis D") and 10 for cognition ("cognition" or "cognitive" or "memory" or "attention" or "executive functions" or "dementia" or "mild cognitive impairment" or "mini mental state examination" or "MMSE" or "neuropsychological") were used. References from previous published literature were additionally searched.

Study selection

Selection criteria; 1) human, 2) >18 years 3) observational (cross-sectional, case-control, longitudinal) or interventional design with control group, 4) blood measurement of 25OHD, 5) valid neuropsychological test, 6) vitamin D reported categorically or as a continuous variable were included for the review. Studies with a diagnosis of dementia or cognitive impairment at baseline were excluded. Studies reporting results separately for cognitively impaired and intact participants were included, and data for intact participants was extracted. Studies where dementia or mild cognitive impairment was the primary outcome or where vitamin D was compared between dementia and healthy controls were excluded. Studies examining other psychological, metabolic or neurological conditions were excluded. Data extraction involved retrieval of authors, study design, population characteristics, vitamin D measurement and assay, neuropsychological test, covariates and statistical methods. Both authors reviewed abstracts and full text and conflicts were resolved accordingly.

Methodological quality

Methodological quality was assessed using the modified Newcastle-Ottawa Scale [NOS (0-3 pts.)] for observational studies (Table S6). This scale rates studies on four domains; selection bias (participants), performance bias (sample size and confounders), detection bias (statistical analyses) and information bias (measurement of the dependent variable). For interventional studies the Physiotherapy Evidence Database (PEDro) Scale (0-10 pts.) assessed five domains; group allocation, blinding, attrition,

116 statistical analyses and data variability (Table S7). This scale is based off the Delphi list
117 for quality assessment of interventions and randomized control trials.[24]

118 *Statistical analyses*

119 Studies categorizing vitamin D into low and high groups were included in the meta-
120 analysis. Studies reporting means (SD) and odds ratios (OR) or containing sufficient
121 data to calculate these parameters were included. All studies reporting cognition as a
122 continuous variable were converted to ORs using Comprehensive Meta-Analysis V
123 3.0.[25] This allowed for the combining of studies reporting cognition both continuously
124 and dichotomously, avoiding a systematic loss of information and potentially bias
125 sample of included studies.[25] Sensitivity analysis was then performed to assess the
126 effect size for only the longitudinal studies measuring cognition dichotomously (i.e. non-
127 converted studies). Positive values represented worse neuropsychiatric test scores with
128 low compared to high vitamin D.

129 The majority of studies administered multiple neuropsychological tests. As the same
130 participants performed all tests within a study, the effect size for each individual test are
131 not independent of each other.[25] Therefore to obtain a single effect size for each
132 study, all effect sizes within that study were averaged using a weighted mean.[25]

133 Based on previously published methods,[19] for studies categorizing vitamin D into
134 quintiles, quartiles or tertiles, the lowest versus highest vitamin D categories were
135 compared. Where data was presented for multiple models, fully adjusted results were
136 used. If publications reported data from the same population study, data was checked to
137 ensure different samples were reported and where appropriate, the most recent
138 publication was included.

139 For interventions, means and SD's for the control and vitamin D supplementation
140 groups were extracted to compute a standardized mean difference ([SMD] hedges g).
141 Positive values favored improved cognition with vitamin D supplementation and
142 negative values favored the control. As systematic distributions of the true effect size
143 were predicted, a random effect model was used for all meta-analyses.[25]

Heterogeneity was assessed using the I^2 statistic with percentage cut-offs 25, 50 and 75% corresponding to low, moderate and high heterogeneity respectively. Funnel plots assessed publication bias using Egger's regression test of asymmetry. Where funnel plots suggested publication bias, Duval and Tweedie's trim and fill plot was used to estimate the adjusted effect size with imputed studies.

A-priori subgroup analyses included; study design (cross-sectional vs. longitudinal), age (<65 vs. ≥65 vs. mixed), adjustments (partial vs. multivariate), blood measurement (plasma vs. serum), vitamin D assay (radioimmune, liquid mass spectroscopy or ELISA) and cognitive abilities. The neuropsychological tests were grouped per cognitive ability in accordance with the Carroll et al.1993 framework (table 1).[26]

Vitamin D measurements are expressed in International System (SI) of units. For reported conventional values (ng.mL) we used the conversion 2.496. Statistical significance was alpha <.05 (two-tailed) and confidence intervals are reported as 95%. Statistical analyses were performed using Comprehensive Meta-Analysis (V3.0, Biostat, Englewood, USA).

RESULTS

Study characteristics

Study characteristics are outlined in Tables' S1-S5. Of the 41 studies, 18 were cross-sectional, 20 were longitudinal and three were interventional (Figure 1). Five longitudinal studies also reported cross-sectional associations.[7, 15, 17, 27, 28] Sample sizes ranged from 19 to 9,556 and 63 to 128 for observational and interventional studies respectively. Follow-up durations ranged from four months to 10 years; however only five studies conducted follow-up's greater than five years.[7, 11, 17, 27, 29] Intervention durations ranged from a single dose to six weeks of daily vitamin D supplementation and administration varied from an intramuscular ergocalciferol injection,[30] to ergocalciferol[31] and cholecalciferol[32] oral capsules. Two studies included vitamin D deficient participants[30, 31] and two studies used a placebo-controlled group.[30, 32]

Most studies were mixed gender, two included only women[13, 33] and five were male only.[16, 18, 34-36] While the majority (*n*=25) of studies recruited older adults, five investigated middle aged adults[14, 29, 32, 34, 35] and 11 included both.[5, 7, 8, 16, 27, 36-41] Eight studies reported vitamin D as a continuous variable[5, 6, 10, 27, 29, 36, 39, 42] and 27 as a categorical variable, whilst three reported both. Seventeen studies used a-priori cut offs[6, 8, 14, 15, 16, 28, 34, 35, 37, 41, 43-49] and 13 categorized into tertiles[9, 17, 38, 50, 51], quartiles[7, 12, 18, 33] or quintiles.[13, 40, 52, 53] The majority of studies analyzed serum 25OHD with four analyzing plasma 25OHD.[12, 13, 29, 47] The most commonly reported vitamin D assays were the Dia Sorin radioimmune (*n*=12) and liquid chromatography-tandem mass spectrometry (*n*=10).

Ten studies classified cognition dichotomously (e.g. decline vs. no decline)[9, 11, 12, 17, 18, 33, 43, 45, 51, 53] and 28 reported cognition as a continuous score. Overall, 52 neuropsychological tests were used (table 1). Twenty-three studies measured general cognition, with the Mini-Mental State Examination (MMSE [*n*=16]) being the most commonly administered. Three studies measured reasoning and language with Ravens Colored Progressive Matrices, Boston Naming Test and Wide Range Achievement Test respectively. Ideas and figural creations were measured in 12 studies with verbal fluency being the most common. Ten studies measured visuospatial abilities using Clock Drawing, Block Design, Matrix Reasoning, Hooper Visual Organization, Rey-Osterrieth Copy and CANTAB-One Touch Stockings of Cambridge. Mental speed/attention (*n*=12 tests, 25 studies) and memory/learning (*n*=20 tests, 26 studies) were the most commonly tested abilities, with the Trail Making (*n*=11), Digit Symbol Substitution (*n*=9), Word List Recall (*n*=7) and Digit Span (*n*=9) being the most common tests.

Methodological quality

Overall, studies were deemed good quality (low-moderate bias; Tables' S6 and S7). The most common source of bias in observational studies was a lack of power analysis, although most studies had large sample sizes (*n*>100). Most studies didn't report handling of missing data; however participant characteristics for attrition were well

documented. When considering selection bias, only one study reported on socioeconomic status (SES).[14] The authors demonstrated no difference in SES in high and low vitamin D groups.[14] For the studies that presented education across vitamin D groups, the majority (*n*=10)[9, 13, 14, 18, 37, 44, 48-50, 52] also observed no difference in level of education between high and low vitamin D, while seven studies[7, 11, 12, 15, 28, 33, 51] did report lower education in participants with low vitamin D. Two studies[34, 35] performed no covariate adjustment. Most studies (*n*=32) performed multivariate adjustments and four studies performed partial adjustments for at least age and education.[18, 46, 49, 52] Common covariates included age, gender, education, season of blood collection, physical inactivity, smoking, alcohol, comorbidities and depression. Only three studies adjusted for vitamin D supplementation.[17, 33, 41] For intervention studies the main source of bias was lack of concealed allocation.

Meta-analysis

Observational studies

Twenty-six observational studies were included in the meta-analysis. Two cross-sectional studies[34, 35] were excluded as they performed no adjustments. Three authors were contacted[5, 36, 45] however did not respond or could not retrieve sufficient data to compute an effect size and seven studies[6, 10, 16, 27, 29, 39, 42] measured vitamin D as a continuous variable without a comparative group.

The summary effect combining 26 studies (*n*=20,750) showed individuals with low vitamin D status (*n*=9,590) had poorer cognition (OR=1.24, CI=1.14-1.35, P<.001) compared with high vitamin D (*n*=11,033, Figure 2). In the sensitivity analysis including only longitudinal studies measuring cognitive decline, the likelihood of cognitive decline with low vitamin D (OR=1.26, CI=1.09-1.23, P<.001) was similar to the overall summary effect. There was heterogeneity (I^2=74.7%) between the study effect sizes and Egger's regression (t(24)=5.68, P<.001) indicated the possibility of publication bias. The trim and fill plot revealed an adjusted effect size (OR) of 1.15, indicating a true effect of vitamin D and cognition (Figure S1).

Mixed-effect analyses revealed a stronger effect for cross-sectional (OR=1.50, CI=1.23-1.83) compared with longitudinal (OR=1.14, CI=1.06-1.23) studies (P=.01). For cognitive abilities, general cognition (OR=1.21, CI=1.10-1.33, P<.001), visuospatial abilities (OR=1.32, CI=1.03-1.68, P=.03) and mental speed/attention (OR=1.23, CI=1.07-1.42, P=.004) showed stronger effects than idea production (OR=1.21, CI=0.97-1.52, P=.09) and memory (OR=1.10, CI=0.96-1.24, P=.19). No other subgroup analyses were significant.

Interventions

The summary effect for three interventional studies (*n*=314) showed no benefit for vitamin D supplementation on cognition (SMD=.21, CI=-0.05-0.46, P=.11; Figure 3). These studies had moderate, non-significant heterogeneity (Q(2)=3.06, P=.22, I^2=34.5%) and no publication bias (Egger's t(2)=0.20, P=.86).

DISCUSSION

Our meta-analyses (*n*=26) support the relationship between low vitamin D, poor cognition and cognitive decline in observational studies. Much of the heterogeneity was accounted for by the range of neuropsychological tests administered. There have only been a small number of interventional studies, employing short therapy durations. Current knowledge on dementia pathophysiology indicates that disease develops over decades of aging[22] and observational studies indicate early exposure is a stronger predictor of later-life cognition.[22] The optimal, necessary duration of repletion is in excess of currently available intervention studies. The optimal age for treatment in individuals at risk of cognitive decline and dementia also remains unidentified. A better understanding of therapeutic windows and timing of repletion is crucial to translate observational associations into preventive therapy.

Vitamin D and cognitive abilities

Previous meta-analyses demonstrating the relationship between vitamin D and cognition have included only the MMSE,[4] verbal episodic memory and executive

functioning tests.[19] The use of narrow selection criteria may represent fewer than 30% of the published neuropsychological tests, creating bias within the literature. Our findings expand previous literature by synthesizing all available evidence on cognition and vitamin D in individuals prior to the onset of dementia. When including all neuropsychological tests, despite added heterogeneity, we also demonstrate a significant association between low vitamin D and poor cognitive performance.

Evidence suggests psychomotor and executive functions are most susceptible to fluctuations in vitamin D physiology during aging.[27] In line with a previous meta-analysis[19] and observational studies,[15, 27, 39, 41, 47] we revealed a stronger effect for general cognition, mental speed and visuospatial abilities compared with memory. While many previous studies preference associations with different cognitive domains, they also represent different age brackets when specific neuropsychological tests were used. It is essential we develop greater standardization in methods and coverage of cognitive domains to draw firm conclusions on the differential effects of vitamin D on specific cognitive abilities.

The mechanisms by which vitamin D modulates cognitive processes in aging and the neuro-pathophysiology of dementia are complex. Vitamin D has been shown to elicit neuroprotective properties, through calcium homeostasis and maintaining the integrity of nerve conduction.[54] Vitamin D may also be indirectly related to cognitive decline and dementia, through its effects on cardiovascular health and known vascular risk factors for dementia.[55] This evidence for the involvement of vitamin D in vascular health may further elucidate the preferential effect observed for executive function and psychomotor speed in this meta-analysis and previous studies.[19, 27, 47]

Longitudinal evidence

There have been numerous longitudinal studies published in the last four years to better examine vitamin D status and cognitive decline in aging. However the majority of studies only provide follow-up of less than 10 years. Our results revealed a significant, but weaker effect for longitudinal compared with cross-sectional studies in relation to

low vitamin D. This less powerful association is likely attributed to age and gender differences, as well as follow-up durations between different studies.

When considering the neurophysiological effects of vitamin D in the brain, it is important to examine gender differences. Studies[16, 18, 35, 36] or sub-samples[38, 52, 53] conducted in males reported non-significant or weaker associations between vitamin D and cognition than mixed gender or women only studies. Gender specific cognitive decline has been related to vitamin D receptor polymorphisms and expression of the Megalin gene[56] which may differentially modulate vitamin D physiology in women and men. There is also evidence that the expression of the vitamin D receptor protein is estrogen dependent,[57] which further justifies the different involvement of vitamin D in women. It is therefore important that future studies perform gender stratified analyses.

While it is accepted that vitamin D levels decline with age, only one study[27] measured time-course changes in cognition and vitamin D concurrently. Therefore, age-related fluctuations in vitamin D may influence cognition at follow-up. Further, only three studies adjusted for vitamin D supplementation[17, 33, 41] and only recorded usage at baseline. Given the relationship between aging, declining vitamin D and increased use of supplementation, future studies should control for supplement use across all points of neuropsychological testing.

Of the studies greater than five years,[7, 11, 17, 27, 29] only three performed multiple neuropsychological tests to allow modelling of cognitive decline.[11, 17, 27] Most of these studies are also performed in older adults (>65years), which show more consistent associations[11, 27] than studies in midlife.[14, 17, 29] These findings may however represent the co-existence of low vitamin D and cognitive decline in older adults, rather than causation across the lifespan. In midlife adults (45years), vitamin D was not associated with cognition five years later.[14] However in healthy middle-aged adults, cognitive reserve may prevent decline over a short duration. It would be of greater interest to see the association with follow-ups at an age where clinical symptoms of cognitive decline begin to manifest.

In a 10 year follow-up (age range 45-65 at baseline), no association between vitamin D and subsequent risk of dementia or cognitive decline was observed.[17] Although this study included middle-aged adults, the average baseline age was still greater than 60 years. Only one study has provided longitudinal data from midlife through to later-life.[29] The authors found a positive association between midlife vitamin D and cognitive function 13 years later, only for low educated older adults. Unfortunately this study did not measure baseline cognition and results may be confounded by reverse causality. It is essential we examine longer duration studies with time-course cognitive testing to determine the importance of midlife vitamin D on cognitive decline in aging.

Given the prolonged prodromal stage of cognitive decline,[22, 23] lifespan cohort studies are needed to determine the correct timing, duration and therapeutic window for this potential therapy. Further investigation into the effect of midlife vitamin D and later-life cognition will help determine the potential to prevent cognitive decline, through supplementation of an inexpensive and readily available therapy which carries low toxicity.

Interventions

While the three included intervention studies did not demonstrate a benefit of vitamin D therapy, it is important to examine these in the context of the observational literature, which now indicates that preventative therapy should begin earlier[22] and for significant duration.[2] As these studies were performed in either young or older adults, the age window for vitamin D supplimentation may have been overlooked. While the development of cognitive decline occurs over decades and the pathological antecedents of dementia occur 20-30 years before diagnosis, the interventional studies to date, demonstrating no clear improvements in cognition, have only been performed for a maximum of six weeks. There is current incongruity of the timing and duration for preventative treatments, in which longitudinal studies indicate is important.[17] A return to lifespan observational studies to provide empirical evidence as to the optimal timing and duration is essential to inform therapeutic interventions towards delaying or preventing cognitive decline in aging.

342 *Limitations*

343 When interpreting these findings, heterogeneity amongst the studies should be
344 considered. The included studies differed in the neuropsychological tests and diversity
345 in categorizing low (ranging from <25 to <50 nmol) and high (ranging from >50 to >100
346 nmol) vitamin D. Five studies[8, 33, 43, 44, 53] also had marginally unequal sample
347 sizes between low and high vitamin D categories. As our summary effect was
348 significant, these factors are also notable strengths in our review, allowing for greater
349 clinical application and generalizability of results for the effect of low vitamin D on
350 overall cognition. Lastly, while we excluded studies with baseline dementia, the
351 possibility of undiagnosed or unreported dementia in elderly participants included in the
352 study samples cannot be disregarded.

353 *Conclusions*

354 Our findings support the relationship between low vitamin D, poor cognition and
355 cognitive decline. However given disease development and pathology are measured in
356 decades, the majority of the available evidence conducted less than five years, and
357 primarily in the elderly, may be subjected to reverse causation. Lifespan cohort studies
358 are needed to inform clinical trials, regarding the optimal therapeutic window and
359 duration of supplementation for prevention of cognitive decline in later-life.
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365 advisory committees for the Australian Commonwealth Scientific and Industrial
366 Research Organisation, Alzheimer's Australia, University of Melbourne and other
367 relationships which are subject to confidentiality clauses. She has been a named Chief
368 Investigator on investigator driven collaborative research projects in partnership with
369 Pfizer, Merck, Bayer and GE. She may accrue revenues from patent in

pharmacogenomics prediction of seizure recurrence. AG has no conflict of interest to declare.

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Table 1 Neuropsychological test and cognitive abilities measured in each study

Cognitive abilities	Neuropsychological test used in assessment
General cognition	Mini Mental State Examination,[6, 9-12, 15, 27, 42-45, 47-51] Modified Mini Mental State Examination,[18, 28, 33] Montreal Cognitive Assessment,[8] Cognitive Telephone

	Screening Instrument,[13, 52, 53] Short Blessed Test.[48]
Reasoning	Ravens Colored Progressive Matrices.[15]
Mental speed and attention	Stroop color-word,[9, 42, 44, 50] Digit Symbol Coding,[7, 15, 47, 49] finger tapping,[7] Symbol Digit Modalities Test,[8, 9, 46] Trail Making Test A[9, 11, 27, 34, 42, 47, 49] and B,[9, 11, 18, 27, 29, 33, 34, 42, 44, 47, 49] Best Symbol-Digit Substitution Test,[16, 17, 27, 28, 34, 36, 39, 40, 42] serial reaction time,[32, 40, 42, 50] choice reaction time,[42, 30] switch-cost reaction time,[32] letter cancelation,[14] Go-no-Go.[44]
Memory and learning	Ray Auditory Verbal Learning Test,[5, 9, 15] California Verbal Learning Test,[27] WAIS-Logical Memory delay,[40-42] East Boston Memory Test,[13] Wechsler Memory Scale-recall,[47] immediate and delayed word list recall,[7, 14, 17, 39, 42, 43, 50] Rappel indice-48 items,[29] Rey-Osterrieth Complex Figure-recognition,[8] CANTAB-Paired Associate Learning,[46] Camden Topographical Recognition Memory, [16, 36] WAIS-Visual Reproductions,[41,42] Wechsler Memory Scale-Logical Memory Recognition,[47] Digit Span-forward,[9, 27, 29, 34, 37, 42, 46, 47] Digit Span-back,[9, 13, 27, 29, 34, 37, 42, 46, 47] Serial-Digit Learning Test,[39, 40] CANTAB-verbal recognition,[37, 46] CANTAB-spatial working memory,[37, 38, 46] Rey-Osterrieth Complex Figure-delay,[8, 16, 27, 36] N-back.[32, 35, 44]
Language	Boston Naming Test,[27, 42] Wide Range Achievement Test.[27, 42]
Visuospatial perception	Rey-Osterrieth Complex Figure-Copy,[8, 16, 27, 36] Clock Drawing (copy and command),[27, 31] Block Design,[42, 47, 49] Matrix Reasoning,[47] Hooper Visual Organization,[41]

	CANTAB-One Touch Stockings of Cambridge.[37, 46]
Ideas, abstraction, figural creations and mental flexibility	WAIS:similarities,[27, 41] Controlled Oral Word Association [47], Trail Making Test (B-A),[41] Verbal Fluency,[9, 13, 17, 27, 29, 31, 37, 42, 46, 50] Isaacs Set Test.[6]

LEGENDS

Figure 1 PRISMA flow diagram of study screening and selection.

Figure 2 Forest plot of effect sizes for observational studies. The diamonds represent the overall effect for each study design (cross-sectional and longitudinal) and overall pooled summary effect (odds ratio [OR]). The sizes of the symbols are relative to each studies weight.

Figure 3 Forest plot of effect sizes for intervention studies. The diamond denotes the pooled summary effect (standardized mean difference [SMD]). The sizes of the symbols are relative to each studies weight.

Supplementary material

Supplementary Table S1 Characteristics of cross-sectional studies (partially adjusted models).

Supplementary Table S2 Characteristics of cross-sectional studies (fully adjusted models).

Supplementary Table S3 Characteristics of longitudinal studies (partially adjusted models).

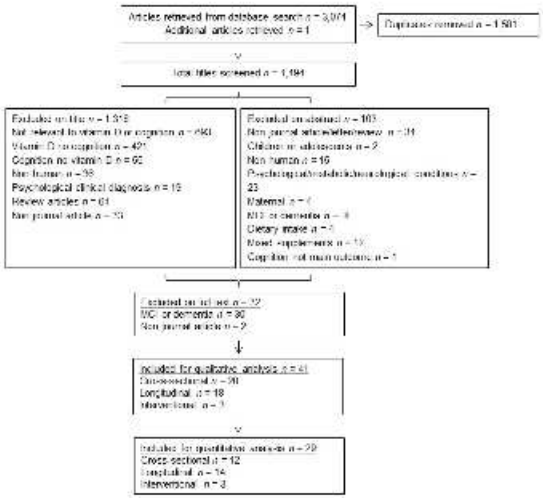
Supplementary Table S4 Characteristics of longitudinal studies (fully adjusted models).

561 Supplementary Table S5 Characteristics of interventional studies.

562 Supplementary Table S6 Modified Newcastle-Ottawa Scale (NOS) for quality
563 assessment of observational studies.

564 Supplementary Table S7 Physiotherapy Evidence Database (PEDro) rating scale for
565 quality assessment of interventional studies.

566 Supplementary Figure S1 Funnel plot of log odds ratios against the studies precision
567 (standard error). Open circles and open diamond represent
568 the observed studies and summary effect respectively. Dark
569 circles and diamond represent the imputed studies and
570 adjusted summary effect respectively.



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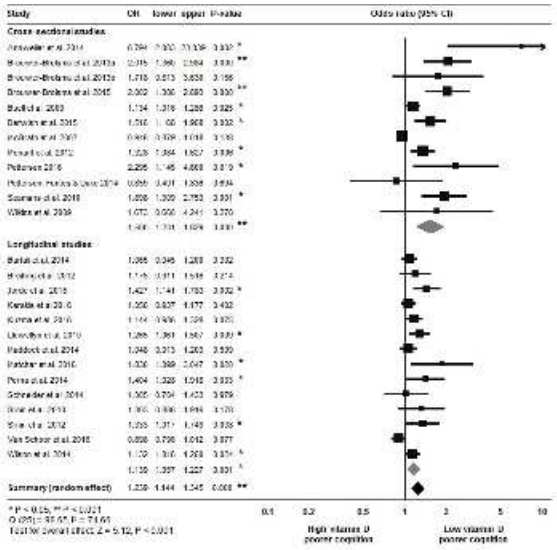

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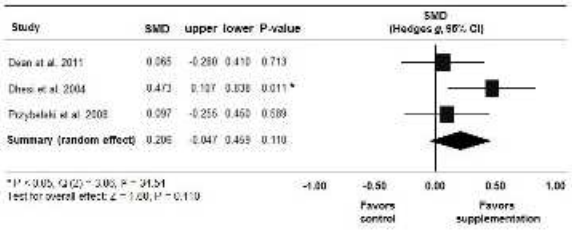

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