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A systematic review examining the effect of vitamin D supplementation on functional outcomes post-stroke

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Abstract

Objective: The objective of this systematic review was to explore the effect of vitamin D supplementation on functional outcomes (motor function, mobility, activities of daily living and stroke impairment) among individuals post-stroke (PROSPERO CRD42022296462).

Data Sources: MEDLINE, PsycINFO, EMBASE, and CINAHL were searched for all articles published up to March 5, 2023.

Methods: Only interventional studies assessing vitamin D supplementation compared to placebo or usual care in adult stroke patients were selected. After duplicate removal, 2912 studies were screened by two independent reviewers. A total of 43 studies underwent full text review; 10 studies met inclusion criteria (8 randomized controlled trials and 2 non-randomized studies of intervention). Data were extracted by two independent reviewers using Covidence software. Motor function (Brunnstrom Recovery Stage, Berg Balance Score), mobility (Functional Ambulation Category), activities of daily living (Barthel Index, Functional Independence Measure) and stroke impairment (modified Rankin Scale, National Institutes for Health Stroke Severity, Scandinavian Stroke Severity) were the outcome measures of interest reported in the included studies.

Results: In total, 691 patients were studied for which 11 of 13 outcome measures showed improvement with vitamin D supplementation.

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Conclusions: The majority of studies showed a statistical improvement in motor function, mobility, and stroke impairment with vitamin D supplementation; however, the evidence did not support an improvement in activities of daily living with treatment. Despite this, there may not be clinical significance. Strong, methodologically sound, randomized controlled trials are required to verify these findings.

Keywords
vitamin D, stroke, mobility, activities of daily living, supplementation, systematic review

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Introduction

Serum 25(OH)D (vitamin D) has a clinically important role in skeletal and muscle function, cardiovascular diseases, autoimmune diseases, and some cancers.[1] Researchers have shown that individuals with vitamin D deficiency have an increased risk of stroke[2–5] including a systematic review and meta-analysis showing an association between vitamin D deficiency and incidence of ischemic, but not hemorrhagic, stroke.[6] However, it is actually unclear whether vitamin D deficiency may be a consequence of stroke or a causative factor.[4] A diagnosis of vitamin D deficiency after a stroke may be related to limited sunlight exposure and decreased oral intake of vitamin D-rich foods.[7] Other data suggests pre-existing vitamin D deficiency may lead to worse stroke outcomes, rather than be a sequela of the stroke itself. For example, in recent studies of acute ischemic stroke patients, lower serum vitamin D levels on admission to acute care were inversely associated with stroke severity, as measured by the National Institute of Health Stroke Scale and infarct volume.[2,8,9] Further, low vitamin D levels have been linked to poor outcomes, as measured by the modified Rankin Scale, at discharge,[10] 3 months[8,10,11] and 6 months post-stroke.[2]

The scientific literature suggests an important role for vitamin D status on various outcomes post-stroke; however, it is currently unknown how vitamin D supplementation, as a treatment, rather than just presence of deficiency, may affect outcomes. A recent meta-analysis assessing vitamin D supplementation to prevent initial stroke did not show a reduction in these events.[12] There is no current synthesis of the literature describing the relationship between vitamin D supplementation and functional outcomes among those after stroke. The findings from such a study may provide insight into treatment protocols addressing vitamin D deficiency. Thus, the objective of this systematic review was to determine the effect of vitamin D supplementation on remediation of deficits (including motor function, mobility, activities of daily living, and stroke impairment) in adults' post-stroke.

Methods

Literature search strategy

The review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[13]

MEDLINE, PsycINFO, EMBASE, and CINAHL were searched for journal articles published from database inception to March 5, 2023. Clinicaltrials.gov was also searched for ongoing or completed relevant trials. The search strategy was developed with the assistance of medical librarians. Search terms reflected two main constructs: stroke and vitamin D. No filters were applied to the search. The full search strategy is outlined in Appendix A. Reference lists of relevant articles were also reviewed to identify studies missed in the original search. The systematic review was registered with PROSPERO (CRD42022296462).

Study selection

Studies from the above searches were imported into Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne,

Australia), and duplicates were removed. Three researchers were involved in the refinement process (JF, MQ, RC) of the systematic search. The title and abstract of each study were independently screened by two reviewers. Similarly, two reviewers independently assessed all full texts for further inclusion. Any disagreements were resolved through consensus and input from the third reviewer if consensus was not reached.

Articles were included based on the following a priori inclusion criteria: they studied individuals post-stroke (either hemorrhagic or ischemic); at least 80% of participants were over the age of 18 years old (pediatric strokes typically do not have the same underlying etiology as stroke in adults[14]); it was an interventional design assessing the effect of vitamin D supplementation (both randomized controlled trials and non-randomized studies of interventions); and at least one functional outcome assessment was reported. All types of comparator groups were considered (e.g. placebo, usual care, physiotherapy, other types of rehabilitation, etc.). Functional outcomes could include motor function or activities of daily living or mobility or stroke impairment if the outcome was assessed using a validated outcome measure. No restrictions were placed on the setting in which the intervention was provided (i.e. hospital, community, long-term care) or on the administration of vitamin D in terms of route, dose, or formulation.

Studies that only assessed vitamin D status (i.e. comparing patients with vitamin D deficiency to those who are vitamin D replete), as well as those assessing vitamin D supplementation to prevent first stroke were excluded.

Data extraction, risk of bias, and quality assessment

Two reviewers (JF, MQ, and/or RC) independently extracted the following study data: author, year, country of origin, study design, sample characteristics, treatment and control protocols, outcome measures for function (i.e. motor function, activities of daily living, mobility, stroke impairment), adverse events, and results. If necessary, missing participant data was assumed to be missing at random and only reported, complete information was extracted.

Each study included in the systematic review underwent a full risk of bias assessment by two independent reviewers (JF, MS). The revised Cochrane Risk of Bias tool[15] was used for randomized controlled trials and the Risk of Bias in Non-Randomized Studies of Interventions tool[16] was used for non-randomized studies of interventions. These assessments evaluate level of risk (i.e. low risk, some concern, or high risk) for five domains: (a) randomization process, (b) deviation from intended intervention, (c) missing data, (d) measurement of the outcome, and (e) selection of reported results for randomized controlled trials. Additional domains of selection bias and confounding are included in the risk of bias assessment for non-randomized studies.

Each outcome measure also underwent an assessment of the quality of the evidence using the grading of recommendations assessment, development, and evaluation (GRADE) framework.[17] Based on the GRADE Working Group recommendations,[17] there are four levels of certainty for evidence: high, moderate, low, and very low. Each level indicates how likely future research is to impact the current results. Randomized controlled trials and non-randomized studies of intervention were assessed separately.

Data analysis

Extracted data were organized and tabled. Mean differences between the vitamin D and control groups were calculated (when not reported) using an unpaired *t*-test using GraphPad (GraphPad Software, San Diego, CA; https://www.graphpad.com/quickcalcs/ttest1/). We intended to undertake a random-effects meta-analysis for similar outcomes where the data permitted, however due to general under-reporting and missing data, significant heterogeneity, and few studies using the same outcomes scales, this was not possible.

Results

A total of 2912 studies were screened for title and abstract relevance after the automatic removal of

914 duplicates. Authors of five published abstracts were contacted; just one responded, indicating that there was no additional information available nor a fully published study. A search of ClinicalTrials.gov found one study that recently finished recruiting from Brigham and Women's Hospitals in the United States (ClinicalTrials.gov Identifier: NCT04070833), however, this study was excluded from the review as it is currently in-progress and results have not yet been reported.

A total of 43 articles underwent full text review of which 33 studies were subsequently

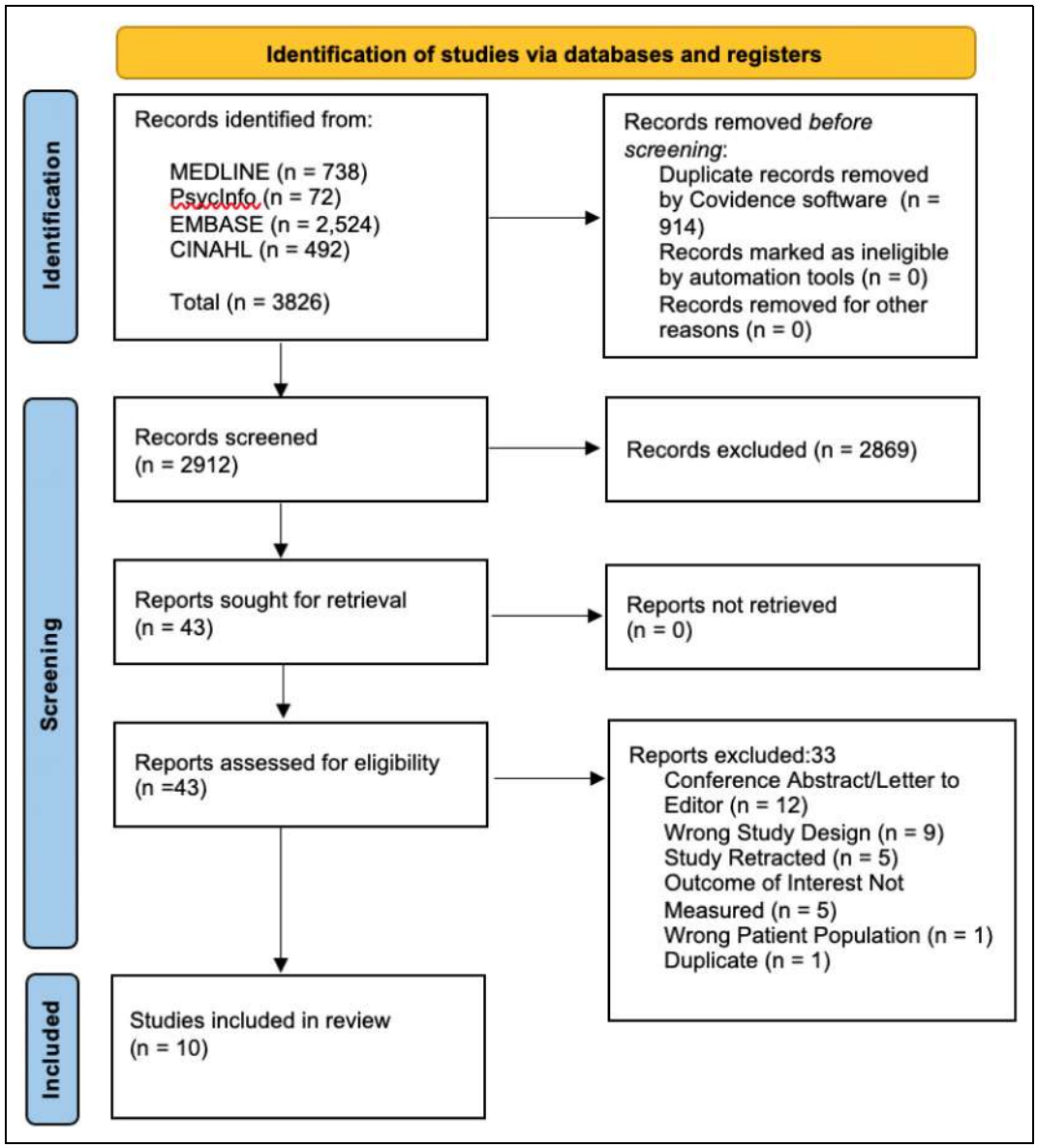

Figure 1. PRISMA flow chart of included studies.

excluded (Figure 1 and Appendix B for list of excluded studies at full text stage). Ten studies were included in this systematic review, including eight randomized controlled trials[7,18–24] and two non-randomized studies of intervention,[3,25] examining a total of 691 patients (Table 1).

Many validated outcome measures for each category exist; however, those described below were used in the included studies.

The Brunnstrom Recovery Stage assesses motor function post-stroke in the hand, arm, and leg, classifying recovery into six stages, where stage one is flaccid and stage six is approaching normal function.[26] The Brunnstrom Recovery Stage scale correlates well with other measures of motor function post-stroke, and has been shown to be responsive to clinically important changes in motor recovery.[27]

The Berg Balance Scale is a fourteen item scale assessing motor function through balance, with each item measured zero to four, where four represents ability to complete task independently.[28] This measure has been validated in the stroke population and a score of ≤44 indicates a high risk of falls.[29]

Table 1. Study and sample characteristics of all studies included for review ($n = 10$).

First author, year country	Sample size	Type of stroke	Vitamin D status	Mean age (Years)	% Female	Follow-up	Outcome measures
Randomized Controlled Trials							
Acharya, 2022	88	All types	Insufficient/ deficient	67.6	22.8%	3 months	SSS
Gupta, 2016 [7] India	53	Ischemic	Insufficient/ deficient	Not Reported	30.2%	6 months	mRS
Hesami, 2022 Iran	41	Ischemic	Deficient	Not reported	31.7%	48 hours 3 months	NIHSS BI
Kadri, 2020 [18] Indonesia	60	Ischemic	Any	64.5	58.3%	12 weeks	NIHSS
Momosaki, 2019 [19] Japan	97	Ischemic, ICH, SAH	Any	66.6	29.9%	8 weeks	BI BRS
Narasimhan, 2017 [20] India	60	Ischemic MCA	Insufficient/ deficient	Not reported	33.3%	3 months	SSS
Sari, 2018 [21] Turkey	64	Ischemic	Deficient	68.4	45.3%	3 months	BBS BRS BI FAC
Torrisi, 2021 [22] Italy	29	Ischemic or hemorrhagic	Any	60.6	51.7%	12 weeks	FIM
Non-Randomized Studies of Intervention							
Utkan Karasu, 2021 [25] Turkey	76	All Types	Any	Not reported	55.2%	Median 43 days	BRS FAC
Wang, 2021 [3] China	123	Ischemic	Deficient	Not reported	52.0%	3 months	mRS

Note: ICH, intracranial hemorrhage; SAH, subarachnoid hemorrhage; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; BI, Barthel Index; BRS, Brunnstrom Recovery Stage; SSS, Scandinavian Stroke Scale; BBS, Berg Balance Scale; FAC, Functional Ambulation Classification; FIM, Functional Independence Measure.

The Functional Ambulation Classification is a general assessment of mobility with scores ranging from zero to five. Zero indicates someone who is not able to ambulate at all or needs the help of two therapists, and five indicates someone who can ambulate in any capacity.[30] This score has been validated and shows high test–retest and inter-rater reliability, as well as good predictive validity to predict independent community ambulation.[30]

The Barthel Index is a 10-item, validated form of common activities of daily living, including toileting, grooming, bathing, feeding, and dressing. The original measure is totalled out of 100, with a higher score indicating better performance, however other variations also exist.[31,32]

The Functional Independence Measure is an 18-item ordinal scale used to gage functional status by assessing the level of assistance an individual requires to complete activities of daily living. Each item is scored from one to seven, where seven is independent, and one requires total care. The Functional Independence Measure has been validated in the post-stroke population.[33]

The modified Rankin Scale is a six-item scale primarily indicating level of physical disability, indicative of stroke severity or impairment. Scores range from zero to six, where zero indicates no symptoms and six indicates death.[34] The

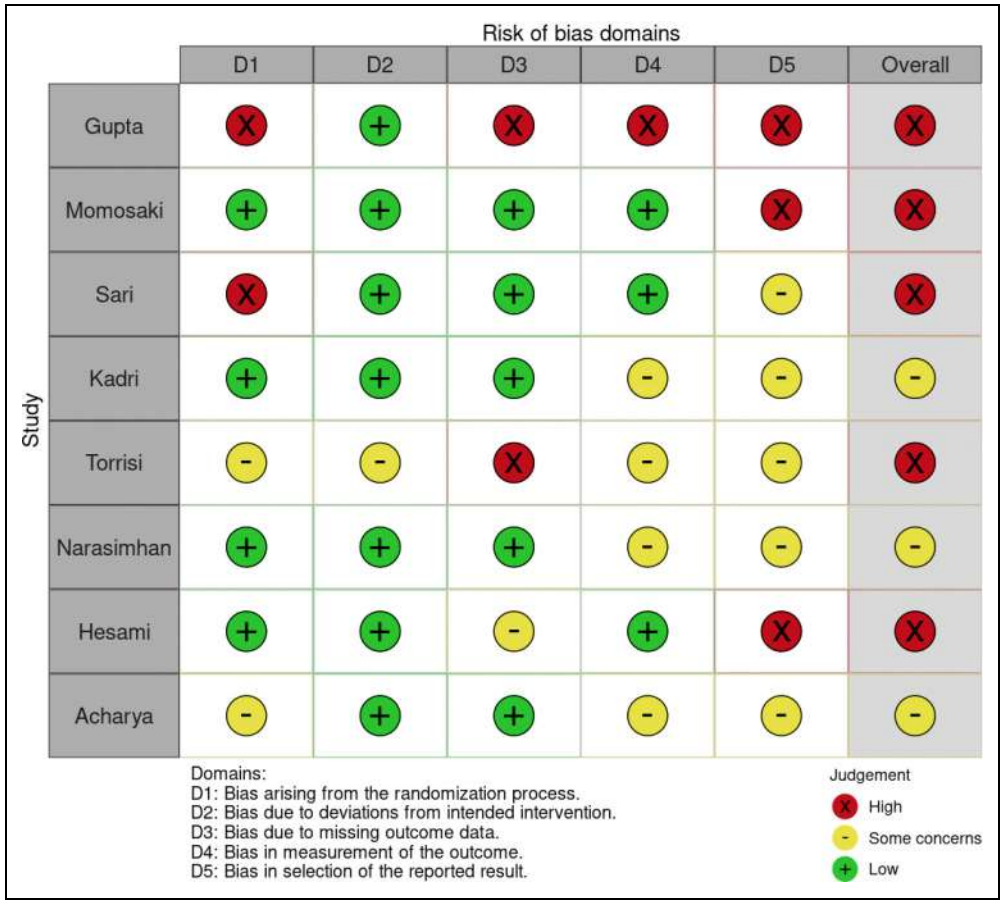

Figure 2. Risk of bias of randomized controlled trials using the revised cochrane risk of bias tool.

Table 2. Summary of treatment and control protocol(s), outcome measure(s), result(s), and certainty of evidence for all studies included for review ($n = 8$).

Author	Treatment group	Control group	Outcome measure	Effect measure (95% CI)	*P* value	Results	Certainty of evidence
Motor Function							
Sari et al. [21]	300,000 IU IM × 1	Placebo	BBS	MD 13.97 (6.75–21.19)	<0 .001	+	*Low* due to high risk of bias, imprecision
			BRS (Leg)	MD 0.47 (0.05–0.89)	0.027	+	*Very Low* due to high risk of bias, imprecision, inconsistency
Momosaki et al. [19]	2000 IU PO daily	Placebo	BRS (Leg)	20 vs 18[@]	0.740	-	
[**]Utkan Karasu et al. [25]	50,000 IU PO weekly	Usual care	BRS (Leg)	Median (IQR) improvement 1 (0–5) vs 0 (0–2)	0.018	+	*Very Low* - no large effect size or dose response effect
Mobility							
Sari et al. [21]	300,000 IU IM × 1	Placebo	FAC	MD 0.74 (0.12–1.36)	0.020	+	*Low* due to high risk of bias and imprecision
[**]Utkan Karasu et al. [25]	50,000 IU PO weekly	Usual care	FAC	Median (IQR) improvement 1 (0–4) vs 0 (0–3)	0.005	+	*Very Low* as no large effect size or dose response effect
Activities of Daily Living							
Sari et al. [21]	300,000 IU IM × 1	Placebo	BI	MD 17.31 (6.66–27.96)	< 0.001	+	*Very Low* due to high risk of bias, imprecision, and inconsistency
Momosaki et al. [19]	2000 IU PO daily	Placebo	BI	MD −0.50[#] (−6.14–5.14)	0.860	-	
Hesami et al. [24]	600,000 IU IM × 1	Usual care	BI	Median (IQR) 8 (7.5–8.5) vs 9 (8–9)	0.03	+	
Torrisi et al. [22]	2000 IU PO daily	Usual care	FIM	MD 15.44 (−6.67–37.55)	0.163	-	
Stroke Impairment							
Kadri et al. [18]	50,000 IU PO weekly	Placebo	NIHSS	MD −1.35 (−2.00 to −0.70)[*]	< 0.001	+	*Low* due to high risk of bias and imprecision
Hesami et al. [24]	600,000 IU IM × 1	Usual care	NIHSS	Median 6.5 (5.5–7) vs 8 (7–8)	0.008	+	
Narasimhan et al. [20]	600,000 IU IM × 1	Usual care	SSS	MD 3.89 (2.04–5.74)	< 0.001	+	
Acharya et al.	600,000 IU IM × 1	Usual care	SSS	12.59 vs 3.25[^]			
Gupta et al. [7]	600,000 IU IM × 1 then 60,000 IU PO monthly	Usual care	mRS	[a]OR 1.2 (0.4–3.6) [b]OR 1.9 (0.6–6.4)	[a]0.730 [b]0.310	-	

(Continued)

Table 2. (Continued)

Author	Treatment group	Control group	Outcome measure	Effect measure (95% CI)	*P* value	Results	Certainty of evidence
**Wang et al. [3]	600 IU PO daily	Usual care	mRS	Median (IQR) 1 (1–2) vs 2 (1–2)	< 0.010	+	*Very Low* as no large effect size or dose response effect

Note: NRSI, non-randomized study of interventions**; IU, international units; IM, intramuscular; PO, per oral; BRS, Brunnstrom Recovery Stage; BBS, Berg Balance Scale; IQR, interquartile range; FAC, Functional Ambulation Classification; BI, Barthel Index; FIM, Functional Independence Measure; NIHSS, National Institute of Health Stroke Scale; SSS, Scandinavian Stroke Scale; mRS, modified Rankin Scale; MD, mean difference; RR relative risk; OR odds ratio.
@Only the number of individuals that improved in each group was reported.
#Mean BI gain.
*A lower score on NIHSS indicates better function, therefore a negative mean difference in this case suggests better function in the vitamin D group.
^ Difference in SSS scores between the vitamin D and control group, however no standard deviations were presented to complete a *t*-test.
+, indicates improvement in vitamin D group; –, indicates no difference between experimental and control group.

modified Rankin Scale has been validated in several studies and demonstrates good correlation between size of stroke lesion, acute impairment scores, and other disability scores such as the Barthel Index, as well as high inter-rater and test–retest reliability.[34]

The Scandinavian Stroke Scale is a nine-item measure of stroke impairment which assesses level of consciousness, motor function, orientation, and speech, with a maximum score of 58, indicating no neurologic deficits.[35] It also correlates well with the National Institute of Health Stroke Scale and has high inter-rater reliability.[35]

Lastly, the National Institute of Health Stroke Scale is a relatively easy, 11-item score often used as an indication of stroke severity or impairment at onset, but has also been proven reliable for post-stroke outcomes.[36] The score considers weakness, sensory changes, level of consciousness and other exam findings, to give a maximum score of 42, which indicates very severe stroke deficits.

Among the randomized controlled trials, five were deemed to have a high risk of bias whereas the other three had only "some concerns" (see Figure 2). For both non-randomized studies of intervention, the risk of bias was deemed serious (see Figure 3). Certainty of the evidence for the randomized controlled trials ranged from low to very low, often due to high risk of bias and imprecision from small sample sizes. Certainties around the two non-randomized studies of interventions were both very low due to lack of large effect or any dose response effect.

Table 2 summarizes treatment and control protocols, outcome measures, results, and certainty of evidence for all studies included for review. A meta-analysis was unable to be conducted due to insufficient overlap in outcome measures, limited data reporting, and clinical heterogeneity.

Two randomized controlled trials[19,21] and one non-randomized study of intervention[25] assessed motor function using the Brunnstrom Recovery Stage. After vitamin D supplementation, both Sari et al.[21] and Utkan Karasu et al.[25] demonstrated improvement on the Brunnstrom Recovery Stage of the leg after a one time and weekly doses of vitamin D, respectively. On the other hand, Sari et al.[21] did not find significant changes in the Brunnstrom stages of the hand or arm (mean difference −0.07, 95% confidence interval −0.43 to 0.29, $P = 0.70$ and 0.41, 95% confidence interval −0.02 to 0.84, $P = 0.063$, respectively). Sari et al.[21] did however note improvement on the Berg Balance Scale.

One randomized controlled trial, by Momosaki et al.[19] did not find an improvement on Brunnstrom Recovery Stages of the leg, however the authors only reported patients that improved

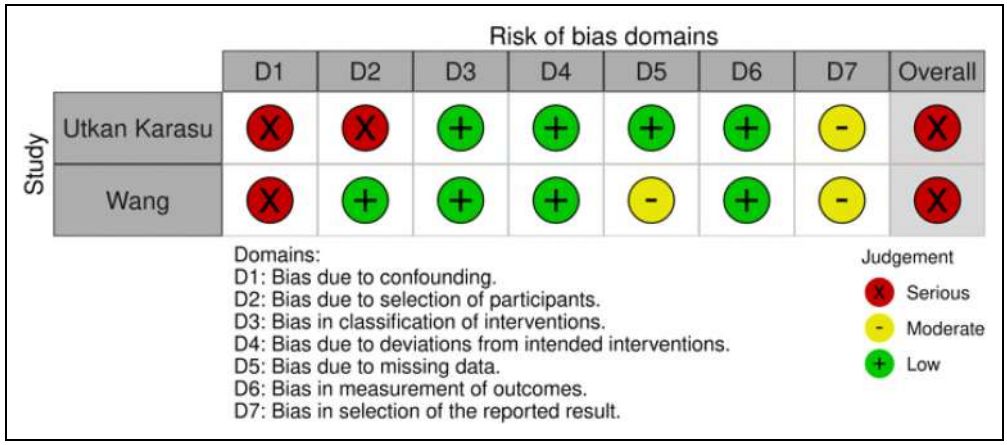

Figure 3. Risk of bias of non-randomized studies using the risk of bias in non-randomized studies—of intervention tool.

on Brunnstrom Recovery Stage without providing any additional information on by how much. Momosaki et al.[19] also assessed the Brunnstrom Recovery Stage scores in the hand and arm between groups but again did not find a significant difference in the amount of people who improved post-supplementation (relative risk 1.04, 95% confidence interval 0.77–1.41, $P = 0.77$ and relative risk 0.91, 95% confidence interval 0.66–1.27, $P = 0.59$, respectively).

Two studies—one randomized controlled trial by Sari et al.[21] and one non-randomized study of intervention by Utkan Karasu et al.[25]—assessed mobility using the Functional Ambulation Classification. Both noted a significant improvement compared to placebo and usual care, respectively.

The effect of vitamin D supplementation on activities of daily living was examined in four randomized controlled trials[19,21,22]: three[19,21,24] used the Barthel Index and one[22] used the Functional Independence Measure. Sari et al.[21] and Hesami et al.[24] both assessed the Barthel Index and found a significant improvement in the vitamin D supplementation group compared to placebo and usual care, respectively. However, two other randomized controlled trials by Momosaki et al.[19] and Torrisi et al.,[22] found no significant between group difference on ability to perform activities of daily living after vitamin D supplementation.

Six studies assessed stroke impairment: five randomized controlled trials and one non-randomized study of intervention. Overall, five studies showed an improvement in stroke impairment. Kadri et al.[18] and Hesami et al.[24] both found improvements on the National Institute of Health Stroke Scale in the vitamin D supplementation group. Narasimhan et al.[20] and Acharya et al.[23] used the Scandinavian Stroke Scale, and while Narasimhan et al.[20] noted statistical improvement, in the study by Acharya et al.[23] an improvement was suggested, however only within group comparisons were reported (mean improvement in scores 12.59 in vitamin D group vs 3.25 in control group), with no standard deviations so between group differences could not be calculated.[23]

When looking at stroke impairment assessed by the modified Rankin Scale, Wang et al.[3] found a significant improvement in the modified Rankin Scale at three months in the vitamin D group compared to usual care. Conversely, Gupta et al.[7] did not find an improvement. Unfortunately, they only presented patients with a "good" outcome, defined as a score of 0–2 on the modified Rankin Scale, without further breakdown on mean improvement or individuals at each level of the modified Rankin Scale at the end of the study. No significant difference between the

two groups on number of individuals that achieved a good outcome were reported.[7]

The reporting of adverse events by included studies was poor, with none explicitly outlining a plan to collect adverse events that occurred. Only one study reported any adverse events post-vitamin D supplementation, namely mortality. Gupta et al.[7] reported that 16% of individuals in the vitamin D group died compared to 39.3% of those in the control group (adjusted odds ratio 0.26, 95% confidence interval 0.08–0.90, $P = 0.030$). They do not report on cause of death among these individuals.

Discussion

This systematic review aimed to evaluate the effectiveness of vitamin D supplementation in adults' post-stroke on functional outcomes. Ten studies were located from the literature search, including eight randomized controlled trials and two non-randomized studies of intervention. Results were mixed regarding effectiveness of vitamin D supplementation on outcomes overall, but most suggest statistically significant improvements in motor function, mobility, and stroke impairment.

Unfortunately, the clinical significance of the results is not clear. Only the post-vitamin D supplementation improvements reported by Sari et al.[21] (Berg Balance Scale, Barthel Index) and Wang et al.[3] (modified Rankin Scale) surpass previously documented minimal clinically important differences.[37–39] Some outcomes such as Brunnstrom Recovery Stage do not have documented minimal clinically importance differences as they are ordinal scales. Overall, certainty of the evidence is very low, based on the high risk of bias and small sample sizes demonstrated. Therefore, it is difficult to reliably draw any clinical conclusions from the current scientific evidence base.

There are several potential explanations for functional improvements with vitamin D supplementation. In addition to the effect on bone health, vitamin D deficiency is associated with muscle weakness and atrophy, as well as worse physical performance, suggesting that supplementation may mitigate these negative sequelae.[40] In stroke specifically, one area of research has indicated that vitamin D may enhance the inflammatory response post-stroke, and exert a protective effect on the blood-brain barrier,[41] however, to date, most studies in this area have been performed in vitro or in animal models.[42,43] Vitamin D may also decrease reactive oxygen species that contribute to further damage after stroke.[44,45] Another potential mechanism to improve post-stroke outcomes is in preventing cerebral vasospasm, a complication after hemorrhagic stroke, that can lead to further stroke deficits.[41,46] Lastly, vitamin D deficiency may be associated with mental health concerns after stroke which can lead to overall worse stroke outcomes.[41] Several of the studies did not comment on the post-supplementation vitamin D levels, and Momosaki et al.[19] did not measure levels either pre- or post-intervention. Because of this, it is unclear if normalizing vitamin D levels is related to the potential functional improvement noted in some of these studies.

Only Gupta et al. reported on mortality as an adverse effect.[7] it seems adverse effects were not actively sought out in any study. Additionally, while Gupta showed lower mortality in the vitamin D supplementation group, they state this may be due to residual confounding or the small sample size (53 patients total) that could lead to a spurious association that warrants further exploration.[7]

Overall, the findings are encouraging, however, they should be interpreted with caution. It is worth highlighting the limitations of included studies. First, there is limited representation from diverse post-stroke geographic and cultural populations, sample sizes were small, and sociodemographic and clinical health characteristics were generally underreported. As well, the reporting of study outcomes was problematic with missing elements to calculate effect sizes and undertake a meta-analysis. This impacts the ability to understand the findings clearly and to generalize to other areas. Second, there was wide variability in treatment protocols, with some providing vitamin D once (300,000–600,000 international units),[20,21,23,24] whereas others delivered the treatment on a daily (2000 international units),[3,19,22] weekly (50,000 international units),[18,25] or monthly (60,000 international units)[7]

basis. Because of this, it is still unclear what the optimal dose of vitamin D for supplementation may be. Additionally, inclusion criteria varied, with some studies appearing to include anyone regardless of vitamin D status,[18,19,22,25] while others only included those who were insufficient or deficient in vitamin D.[3,7,20,21,23,24] Overall, this variability limits the ability to draw conclusions on if and how individuals post-stroke should be supplemented. Third, although each study evaluated functional outcomes using common, validated outcome measures, there was little overlap between them, and results were often poorly reported, precluding combination for a meaningful meta-analysis. Further, while the Barthel Index was used as an outcome measure in several studies, at least four variations of this measure exist,[32] making comparison difficult, especially as not all studies explicitly mention which version was used. Lastly, bias and imprecision in the randomized controlled trials, as well as inclusion of non-randomized studies of intervention, reduced the overall certainty of the evidence.

This systematic review itself also has its limitations. Several databases were searched systematically; however, it was not possible to search all available medical databases and therefore it is possible some articles were missed. All studies included for review originated from non-native English-speaking countries. Therefore, it is possible that there are other non-English trials that have been published which were not uncovered in our literature search, despite our search not limiting by language.

In summary, this systematic review highlights the paucity of high-quality studies for vitamin D supplementation for improving functional outcomes post-stroke. While most studies show an improvement with vitamin D supplementation, this may not be clinically important. Additionally, the evidence is uncertain and based on a limited number of studies overall. Future trials should aim to overcome the methodological, protocol, and bias difficulties observed in the existing literature, including assessing if there is a difference in outcomes in those who are vitamin D deficient versus vitamin D replete while undergoing rehabilitation. Specifically, randomized controlled trials should be performed with larger samples, consistent vitamin D dosing over longer periods of time, and with adequate follow-up. Studies should also aim to use comparable outcome measures that are reported transparently and consistent with the Consolidated Standards of Reporting Trials (CONSORT) framework.[47]

Clinical messages

- Vitamin D supplementation shows statistical improvement on outcomes post-stroke such as motor function, mobility, and stroke impairment, while clinical relevance is not clear.
- More high quality studies are needed in this area to confirm results.

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Author contributions

JF and AP devised study idea; JF completed search strategy; JF, MQ, RC completing screening and data extraction; JF and MS completed risk of bias assessments; JF, AM, SJ, and MS analyzed and interpreted results; all authors participating in drafting manuscript.

Declaration of conflicting interests

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Appendix A. EMBASE Search Strategy

1. brain ischemia/ or brain infarction/ or brain stem infarctions/ or lateral medullary syndrome/ or cerebral infarction/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or intracranial hemorrhages/ or cerebral hemorrhage/ or intracranial hemorrhage, hypertensive/ or subarachnoid hemorrhage/ or stroke/ or hemorrhagic stroke/ or ischemic stroke/
2. (brain ischemia or brain infarction or brain stem infarctions or lateral medullary syndrome or cerebral infarction or infarction, anterior cerebral artery or infarction, middle cerebral artery or infarction, posterior cerebral artery, or intracranial hemorrhages or cerebral hemorrhage or intracranial hemorrhage, hypertensive or subarachnoid hemorrhage or stroke or hemorrhagic stroke or ischemic stroke).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
3. 1 or 2
4. (vitamin D or 25-hydroxyvitamin D or vitamin D3 or 25-OH or vitD or vitD3 or calcitriol or ergocalciferol or cholecalciferol).mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 176,593
5. exp Vitamin D/
6. 4 or 5
7. 3 and 6

Appendix B. List of Excluded Studies

Reference	Reason for exclusion
Andole S. Primary prevention and bone protection in post stroke, post-menopausal women: an observational study. *Cerebrovasc Dis*. 2012; 33(Suppl 2):842–843	Conference abstract
Ashouri R, Fangman M, Brielmaier J, et al. Nutritional supplementation of naturally occurring vitamin D to improve hemorrhagic stroke outcomes. *Front Neurol*. 2021;12:670245	Wrong study design
Bejot Y, Giroud M, Jacquin A, et al. Vitamin D and stroke prognosis. *Neuroepidemiology*. 2013;41(3–4):235–236.	Conference abstract
Bird ML, Williams S, Gahan L, et al. The role of vitamin D in injurious falls for people in the first year after stroke; ongoing clinical trial. *Int J Stroke*. 2018;13(2 Suppl 1):175.	Conference abstract—authors contacted for additional information with no response
Brennan M, Cassidy T. Assessing bone health protection in a stroke rehabilitation unit: are we doing enough? *Int J Stroke*. 2018;13(3 Suppl 1):30.	Conference abstract
Fang Y, Ji W, Zhou H, et al. Low serum levels of 25-hydroxyvitamin D are associated with stroke recurrence and poor functional outcomes in patients with ischemic stroke. *J Nutr Health Aging*. 2017;21(8):892–896.	Wrong study design (no vitamin D supplementation)
Foley NC, Meyer M, Janzen S, et al. Identification and treatment of vitamin D insufficiency/deficiency following stroke: current practice at a single inpatient rehabilitation facility in Ontario. *Stroke*. 2012;43(11):e137.	Conference abstract (authors contacted—confirmed no additional manuscript or information)
Greenberg, JA, Roth EJ, Wuermser L, et al. Grand rounds. Osteoporosis treatment for patients with stroke. *Topics Stroke Rehab*. 2007;14(2):62–67.	Wrong outcomes (use of osteoporosis medications)
Hassine A, Naija S, Ben Amor S, et al. Effect of vitamin D supplementation on anxiety-depressive disorder at six months of stroke: a randomized clinical trial. *Eur J Neurol*. 2021;28(Suppl 1):864.	Conference abstract—authors contacted for additional information with no response
Iwamoto J, Kanoko T, Satoh K, et al. Low dose vitamin D prevents muscular atrophy and reduces falls and hip fractures. *Cerebrovasc Dis*. 2005;20(3):187–192.	Study retracted
Jacks B. Vitamin D update. *Alive*. 2016;399:67–69.	Opinion piece
Judd S, Le A, Gutierrez O, et al. Vitamin D intake: a novel neuroprotectant? *Neurology*. 2012; 78(1 Meeting Abstract)	Conference abstract
Kamal A, Majeed F, Naqvi I. Vitamin D supplementation for preventing recurrent stroke and vascular events in patients with stroke or transient ischemic attack. *Cochrane Datab Syst Rev*. 2017;2017(2):CD009762.	Study retracted (published protocol since been withdrawn from publication as authors did not complete full review—authors contacted with no response)
Khan SU, Khan MU, Riaz H, et al. Effects of nutritional supplements and dietary	Wrong study design (review article)

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Reference	Reason for exclusion
interventions on cardiovascular outcomes: an umbrella review and evidence map. *Ann Intern Med*. 2019;171(3):190–198.	
Makariou S, Tzoufi MS, Challa A, et al. Vitamin D and stroke: promise for prevention and better outcome. *Curr Vasc Pharmacol*. 2014;12(1):117–124.	Wrong study design (review article)
Missaoui M, Naija S, Ben Amor S. Effect of vitamin D supplementation on cognitive function at six months after a stroke: a randomized clinical trial. *Eur J Neurol*. 2021;28(Suppl 1):676–677.	Conference abstract—authors contacted for additional information with no response
Myint PK, Poole KES, Warburton EA. Hip fractures after stroke and their prevention. *Quart J Med*. 2007;100(9):539–545.	Wrong study design (review article)
Pilz S, Tomaschitz A, Drechsler C, et al. Vitamin D supplementation: a promising approach for the prevention and treatment of strokes. *Curr Drug Targets*. 2011;12(1):88–96.	Wrong study design (review article)
Sato Y, Kuno H, Kaji M, et al. Effect of ipriflavone on bone in elderly hemiplegic stroke patients with hypovitaminosis D. *Am J Phys Med Rehab*. 1999;78(5):457–499.	Study retracted
Sato Y, Maruoka H, Oizumi K, et al. Amelioration of hemiplegia associated osteopenia more than 4 years after stroke by 1 alpha-hydroxyvitamin D3	Study retracted

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Reference	Reason for exclusion
and calcium supplementation. *Stroke*. 1997;28(4):736–739.	
Sato Y, Honda Y, Iwamoto J. An open label trial comparing alendronate and alphacalcidol in reducing falls and hip fractures in disabled stroke patients. *J Stroke Cerebrovasc Dis*. 2011;20(1):41–46.	Study retracted
Shishkova V. Prevention of bone loss after stroke. *Osteoporosis Int*. 2013;24(1 Suppl 1):S190.	Conference abstract
Thiele, I, Linseisen J, Meisinger C, et al. Associations between calcium and vitamin D supplement use as well as their serum concentrations and subclinical cardiovascular disease phenotypes. *Atherosclerosis*. 2015;241(2):743–751.	Wrong patient population (not stroke—subclinical cardiovascular disease patients)
Tomosevic-Todorovic S, Savic M, Boskovic K, et al. Vitamin D deficiency and bone density in patients after stroke. *Osteoporosis Int*. 2016;27(Suppl 1):S166.	Conference abstract
Verheyden GSAF, Weerdesteyn V, Pickering R, et al. Interventions for preventing falls in people after stroke. *Cochrane Datab Syst Rev*. 2013;5.	Wrong study design (review article)
Verheyden GSAF, Weerdesteyn V, Pickering R, et al. Interventions for preventing falls in people after stroke. *Cochrane Datab Syst Rev*. 2013;5.	Duplicate
Wei Z, Kuang J. Vitamin D deficiency in relation to the	Wrong study design (no intervention—

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Reference	Reason for exclusion
poor functional outcomes in nondiabetic patients with ischemic strokes. *Biosci Reports*. 2018;38(2): BSR20171509	assessing vitamin D status only)
Witham MD, Dove FJ, Sugden JA, et al. Does vitamin D supplementation improve markers of vascular health in stroke patients? A randomised controlled trial. *Int J Stroke*. 2009;4(Suppl 2):21	Conference abstract
Witham MD, Dove FJ, Sugden JA, et al. The effect of vitamin D replacement on markers of vascular health —a randomised controlled trial. *Nutr Metab Cardiovasc Dis*. 2012;22(10):864–870.	Wrong outcomes (no functional outcomes —blood pressure, endothelial function, cholesterol, B-type natriuretic peptide, heart rate turbulence)
Xie X, Ji F, Wang M, et al. Combined application of salmon calcitonin see calcimar, alpha vitamin D3 and calcium carbonate for prevention of osteoporosis after limb paralysis in senile patients with stroke. *Chin J Clin Rehab*. 2005;9(33):10–12.	Wrong outcomes (no functional outcomes —bone mineral density)
Yalbuzdag SA, Sarifakioglu AB, Afsar SI, et al. Inme ve Vitamin D. *J Phys Med Rehab Sci*. 2015;18(2):129–135.	Wrong study design (review article)
You X, Zhou Y, Zhang J, et al. Effects of parathyroid hormone and vitamin D supplementation on stroke among patients receiving peritoneal dialysis. *BMC Nephrol*. 2020;21(1):1–10.	Wrong outcomes (no functional outcomes —incident stroke)
Yousefian M, Sadegi SRGP, Sakaki M. Vitamin D supplements' effect on expediting the weaning process in patients with stroke. *Electron J Gen Med*. 2019;16(2):1–5.	Wrong outcomes (no functional outcomes —weaning from mechanical ventilation)

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