Vitamin D Supplementation and Fractures in Adults:
A Systematic Umbrella Review of Meta-Analyses of Controlled Trials

Marlene Chakhtoura, Dani S. Bacha, Charbel Gharios, Sara Ajjour, Mariam Assaad, Yara Jabbour, Francesca Kahale, Aya Bassatne, Stephanie Antoun, Elie A. Akl, Roger Bouillon, Paul Lips, Peter R Ebeling, Ghada El-Hajj Fuleihan

Calcium Metabolism and Osteoporosis Program, WHO CC Center for Metabolic Bone Disorders, American University of Beirut Medical Center, Beirut, Lebanon M Chakhtoura MD, MSc; D S Bacha MD, C Gharios MD, S Ajjour MSc, M Assaad MSc, Y Jabbour MD, F Kahale MD, A Bassatne MD, S Antoun PhD, G El-Hajj Fuleihan MD, MPH.

Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon, Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton (ON), Canada EA Akl MD, MPH, PhD.

Department of Chronic Diseases, Metabolism and Ageing, Katholieke Universiteit Leuven, Leuven, Belgium R Bouillon MD, PhD

Department of Internal Medicine, Endocrine Section, Amsterdam University Medical Center, location VUMC Amsterdam, Netherlands P Lips MD

Department of Medicine, School of Clinical Sciences, Monash University, Clayton, Victoria, Australia P Ebeling MD

© The Author(s) 2021. Published by Oxford University Press on behalf of the Endocrine Society.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Correspondence to:

Marlene Chakhtoura, MD, MSc
Calcium Metabolism and Osteoporosis Program
WHO Collaborating Center for Metabolic Bone Diseases
American University of Beirut Medical Center
Beirut, P.O. Box: 113, 6044/C8, Lebanon
mc39@aub.edu.lb

Disclosure Summary:

Drs M. Chakhtoura, D. Bacha, C. Gharios, Y. Jabbour, F. Kahale, A. Bassatne, S. Antoun, E. Akl and G. El Hajj Fuleihan, and Ms S. Ajjour and M. Assaad have no conflict of interest.

Dr. P. Ebeling reports grants and other from Amgen, grants from Eli-Lilly, grants from Alexion, other from Sanofi, outside the submitted work. Dr. R. Bouillon reports receiving small lecture fees from FAES (Spain), Proctor & Gamble (Belgium), Abiogen (Italy), and support for attending meetings and/or travel from FAES (Spain), Abiogen (Italy). Dr P. Lips reports receiving travel cost for vitamin D workshop from Abiogen.

Sources of Funding and Support:

This project is in part supported by internal institutional funds from the Medical Practice Plan, at the American University of Beirut Medical Center.

Research reported in this publication was in part supported by the Fogarty International Center and Office of Dietary Supplements of the National Institutes of Health under Award Number D43 TW009118; PI Ghada El-Hajj Fuleihan. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Role of the Funder/Sponsor

The funder had no role in the design and conduct of this project, interpretation of the results, manuscript write up and submission for publication.
ABSTRACT

Context: The growing number of systematic reviews/meta-analyses (SR/MAs) on vitamin D (±calcium) for fracture prevention has led to contradictory guidelines. This umbrella review aims to assess the quality and explore the reasons for discrepancy of SR/MAs of trials on vitamin D supplementation for fracture risk reduction in adults.

Evidence Acquisition: We searched 4 databases (2010-2020), Epistemonikos, and references of included SR/MAs, and we contacted experts in the field. We used AMSTAR-2 for quality assessment. We compared results and investigated reasons for discordance using matrices and sub-group analyses (PROSPERO registration: CRD42019129540).

Evidence Synthesis: We included 13 SR/MAs on vitamin D and calcium (Ca/D) and 19 SR/MAs on vitamin D alone, compared to placebo/control. Only 2 from 10 SR/MAs on Ca/D were of moderate quality. Ca/D reduced the risk of hip fractures in 8/12 SR/MAs (relative risk (RR) 0.61-0.84), and any fractures in 7/11 SR/MAs (RR 0.74-0.95). No risk reduction was noted in SR/MAs exclusively evaluating community-dwelling individuals or in those on vitamin D alone compared to placebo/control. Discordance in results between SR/MAs stems from inclusion of different trials, related to search periods and eligibility criteria, and varying methodology (using intention to treat, per-protocol, or complete case analysis from individual trials). Vitamin D alone has no protective effect on fracture risk.

Conclusions: Ca/D reduces the risk of hip and any fractures, possibly driven by findings from institutionalized subjects. Individual participant data meta-analyses of patients on Ca/D with sufficient follow-up period, and subgroup analyses, would unravel determinants for a beneficial response to supplementation.

Key Words: Vitamin D, Fractures, Adults, Umbrella Review
INTRODUCTION

Vitamin D plays a critical role in musculoskeletal health through its effects on mineral homeostasis and bone metabolism (1, 2). Vitamin D deficiency is common among the elderly due to reduced cholecalciferol synthesis in the skin, reduced intestinal calcium absorption, and changes in lifestyle favoring lower exposure to ultraviolet radiation (3). This deficiency may contribute to the observed steep rise in the risk of fractures with older age, particularly at the hip (4). This is of particular importance given that the estimated one-year mortality following hip fracture is around 30% (5).

The benefit of vitamin D supplementation on fracture prevention has been extensively assessed, with an exponential rise in the number of systematic reviews/meta-analyses (SR/MAs) reporting discordant conclusions (6). A recent review in 2017 identified more than 40 international vitamin D guidelines with highly variable recommendations (7). There is still conflicting evidence with regards to the extent of vitamin D’s benefit in fracture prevention, the target population likely to benefit the most, the desirable serum 25-hydroxyvitamin D [25(OH)D] concentration, the optimal vitamin D dose, and the need for co-administration of calcium (7-9).

We therefore conducted an umbrella review of SR/MAs of vitamin D supplementation RCTs evaluating fracture risk reduction in adults, to assess the quality of each SR/MA, explore similarities and differences between them, investigate the reasons for any discrepancy, and formulate a reliable conclusion on the topic. Such an approach would bring clarity to much confusion, pave the path for the formulation of informed population-tailored conclusions regarding the benefit of vitamin D supplementation in preventing fractures.
METHODS/LITERATURE SEARCH

We followed the guidance provided by Pollock et al (10) to develop the protocol for this umbrella review. We registered the protocol on PROSPERO (CRD42019129540) (11). We included SR/MAs of RCTs on adults aged ≥18 years evaluating the risk of hip and any fracture, with vitamin D supplementation, alone or in combination with calcium, compared with placebo/control.

We searched MEDLINE, PubMed, Embase, Cochrane and Epistemonikos databases, without language restriction, from January 1st, 2010 until October 23rd, 2020, with the help of a medical librarian (AF), in order to cover the reviews published following vitamin D guidelines issued by 2 major societies, the Institute of Medicine in 2009 (9) and the Endocrine Society in 2011 (8). We used MeSH terms and keywords relevant to vitamin D, fractures, meta-analysis, systematic review, and randomized controlled trials. We reviewed the citations of included SR/MAs and of narrative reviews on the topic, and contacted experts in the field (Appendix 1 (12)).

Pairs of reviewers (CG-FK, DB-SA, YJ-MA, AB-SA) completed title/abstract and full text screening, and data abstraction in duplicate and independently, after a calibration exercise. Disagreement was resolved through discussion with a content expert (GEHF or MC).

We collected information on study population, intervention(s), comparator(s), and outcome(s), in addition to the methodology of each SR/MA. We constructed, for each of hip and any fractures, figures displaying the effect size estimates derived from each SR/MA, 95% confidence intervals (CIs), and degree of heterogeneity using I². We constructed matrices to compare and contrast the SR/MAs’ respective results, included RCTs and respective data, and quality ratings. We calculated the “corrected covered area” (CCA) for each of hip and any fracture, as suggested by Pieper et al (13), using the following formula: CCA=(N-r)/[rc-r], where N is the total number of included publications (including double counting) as
displayed in the matrix for all the SR/MA, r is the number of RCTs included at least once in the matrix, and c is the number of SR/MAs. We also collected data on sub-group analyses by baseline serum 25(OH)D concentration (pre-specified), and on other sub-groups as available in each SR/MA.

We assessed the quality of SR/MAs independently in triplicate using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR-2)(14).

RESULTS

The search strategy retrieved 14,357 citations. We reviewed 1,375 full text papers. We identified 81 SR/MAs of RCTs on vitamin D supplementation, 25 of which assessed fractures (n=21)(15-35) or fall-related fractures (n=4)(36-39), all in English language. We included SR/MAs on vitamin D with concomitant calcium supplementation (Ca/D) (13 SR/MAs(15-17, 19, 22-24, 28-31, 37, 39)), or vitamin D alone (19 SR/MAs(15, 16, 19-21, 23-28, 30-32, 34-37, 39)), compared to placebo/control, while 9 SR/MAs included other comparisons(15, 17, 18, 20, 21, 33, 37-39), which are beyond the focus of this manuscript (Figure 1).

1. Results on Ca/D supplementation vs. placebo/control:

We identified 12 SR/MAs assessing hip fracture risk and 11 assessing any fracture risk, with Ca/D supplementation compared with placebo/control, including one individual participant data meta-analysis (IPD-MA)(23). The mean age of participants ranged between 62-85 years. The vitamin D dose was 400-800 IU/day, and six SR/MAs included one trial providing a high dose of 300,000 IU once(15, 16, 19, 24, 31, 37). The calcium dose was 500-1,200 mg/day. The included trials extended from 1-7 years. Five SR/MAs reported on baseline 25(OH)D concentration (20.9-83.8 nmol/L)(15, 19, 24, 31, 37), and the achieved concentration (15-112.3 nmol/L)(19) (Table 1).
**Hip Fractures:** Most SR/MAs had the same direction, but were discrepant in both magnitude of effect and statistical significance. Eight of 12 SR/MAs reported a significant reduction in hip fracture risk when combining institutionalized and community dwelling individuals (15, 16, 19, 22, 28-30, 39) (Figure 2A). Only one Cochrane SR/MA, by Avenell et al., was of moderate quality, and was the only one evaluating the quality of evidence, reported as high, with a 16% relative risk reduction (RRR) in hip fracture, with Ca/D supplementation compared with placebo/control (15). The other seven SR/MAs, of critically low quality, showed a 16-39% RRR in hip fracture (16, 19, 22, 28-30, 39). Two other SR/MAs (17, 23), including one IPD-MA (23), and the two SR/MAs that exclusively evaluated RCTs in community dwelling individuals (24, 31) failed to show any significant fracture reduction. They were of low (31) to critically low quality (17, 23, 24) (Appendix 2 (12)).

Nine SR/MAs on hip fracture were included in the matrix, as they provided the needed information (Table 2). The population consisted of older women and/or men, with or without a history of fracture (45-49). The WHI trial (N=36,282, Ca/D dose/d 1,000 mg/400 IU) (48) and the RECORD trial (N=5292, Ca/D dose/d 1,000 mg/800 IU) (41) contributed the largest weights for the findings in the community. The two trials by Chapuy et al. were the only trials on institutionalized subjects included in all SR/MAs (N=3,847, Ca/D dose/d 1,200 mg/800 IU) (45, 46) (Table 2).

There was a substantial overlap in the RCTs conducted in community dwelling subjects, included in the SR/MAs by Avenell and Bolland (15, 19), Zhao and Hu (24, 31), Yao and Barrionuevo (16, 30), thus explaining their very similar effect size estimates. Conversely, the overlap varied across other SR/MAs. One study (Porthouse 2005) (44) was included in all SR/MAs, whereas another one (Larsen 2004) (43) was only included in the most recent one (22). This is explained by differences in either the search period or the eligibility criteria. Some SR/MAs included RCTs with a relatively large sample size (>500 (30) or >1,000...
participants(23), or exclusively from the community(23, 24, 31), or exclusively women(16, 17), or excluded specific trials or trial arms if the intervention was a single high vitamin D dose(22, 27), calcium only, vitamin D only(15, 19, 24, 30, 31), or hormone replacement therapy(17)(Appendix 3(12)). One SR/MA included duplicate data from the WHI trial(22) (primary(48) and post-hoc analyses(50)). The CCA for SR/MAs on hip fracture was 57%.

For the same RCTs, the derived effect size estimates varied across SR/MAs. For instance, for Chapuy 1992, the sample size in the intervention and the control varied, 877-1634, and 888-1636, respectively. Similarly, the number of hip fractures considered ranged between 21-137 in the intervention arm, and 37-178 in the control arm. Therefore, the effect size was also variable of 0.57-0.77 (Table 2). Such findings are related to the data abstraction methods, targeting intention to treat(17, 22), per protocol analyses(29), complete case analyses(15, 16, 19, 30), or excluding deaths(15, 16, 22, 29, 30). Furthermore, the methods used for pooling data were also heterogeneous; while the majority used a traditional meta-analysis, few conducted a network(16, 24, 27, 28, 39) or an IPD-MA(23) (Appendix 3(12)).

Sub-group analyses

Residency status as a predictor of response was scrutinized in two SR/MAs. Although the CI of the effect size estimate in the sub-group of institutionalized subjects in the Cochrane SR/MA(15) did not cross 1.0, subgroup effect by residency was not significant, p-interaction 0.15 (Table 2). Similarly, another SR/MA reported no significant heterogeneity across residence sub-groups(15, 30), without providing an interaction p-value (Table 2). The Cochrane SR/MA reported an overall 16% RRR in hip fractures(15). The absolute risk reduction therefore varied depending on the baseline risk. It was 1/1,000 (0/1,000-2/1,000) for a lower risk population derived from the community (baseline hip fracture risk of 8/1,000), while it was 9/1,000 (2/1,000-14/1,000) for a higher risk population derived from institutional residence (baseline risk of 54/1,000)(15). Age ≥ 80 years and a baseline serum
25(OH)D concentration ≤ 50 nmol/L approached significance, as modifiers. Conversely, sub-group analyses based on sex(31), osteoporotic fracture history(15, 30), and vitamin D dose(23, 31) did not (Table 3).

**Any Fracture:** Eleven SR/MAs assessed the benefit of Ca/D on any fractures(15, 17, 19, 22-24, 29-31, 37, 39). They had the same direction but were discrepant in both magnitude of effect and statistical significance. Seven SR/MAs reported a significant reduction in any fracture risk in analyses combining institutionalized and community dwelling individuals(15, 19, 22, 23, 29, 30, 39) (Figure 2B). Only two SR/MAs, by the Cochrane Group, were of moderate quality(15, 37). The first on fall-related fracture included exclusively RCTs from the community and showed no effect(37). The second combined institutionalized and community-dwelling subjects and was the only one evaluating the quality of the evidence. It reported high quality of evidence for a 5% RRR in any fractures(15). The remaining six SR/MAs, of a critically low quality, reported an RRR ranging between 6-29% (19, 22, 23, 29, 30, 39), one of which was a network MA(39) and one an IPD-MA(23). Three other SR/MAs on community dwelling individuals, were of critically low quality, and did not show evidence of fracture reduction(17, 24, 31).

Ten SR/MAs were included in the matrix (Table 4). The population consisted mostly of older women and/or men with(40-44, 49, 51) or without(45-48, 52) a history of fracture. The RCTs with the largest weights were the community-based WHI and RECORD trials(41, 48). The two trials by Chapuy et al. were the only ones on institutionalized individuals included in SR/MAs(45, 46). The overlap of included RCTs from the community was variable. As reported for the hip fracture, the variability in the inclusion of RCTs and the discrepancy in their individual effect size estimates across SR/MAs are explained by the difference in the search period, eligibility criteria, and analysis methods. The CCA for any fracture was 39%.
Sub-group analyses

Two SR/MAs conducted sub-group analysis by residency (15, 30). Although there was a trend for a higher effect in institutionalized individuals, none of the SR/MAs found a sub-group effect (15, 30). The Cochrane SR/MA reported a 5% RRR in any fracture and an absolute risk reduction varying from 1/1,000 for a lower baseline risk population (of 26/1,000), to 4/1,000 for a higher baseline risk population (of 74/1,000) (15). Weaver et al conducted 2 primary analyses according to residency and the effect size CIs were overlapping (29). There was a sub-group effect by age in one SR/MA; p-heterogeneity 0.02, p-interaction not reported (30). Other sub-group analyses did not show any significant effect (Table 4).

2. Results of SR/MA on Vitamin D alone vs. Placebo

Out of the 19 SR/MAs on vitamin D alone vs placebo/control, only three were of moderate quality, published by the Cochrane group (15, 36, 37), 15 evaluated the effect on hip fractures (15, 16, 19, 20, 23-28, 30-32, 35, 39), 13 on any fractures (15, 19, 21, 23, 24, 27, 30-32, 34, 36, 37, 39), and two on fall-related fracture (36, 37). They were all concordant in direction and statistical significance. They showed a trend for an increased risk of hip (RR 1.10-1.30) and any fracture (RR 1.01-1.09), but none reached statistical significance.

DISCUSSION

In this umbrella review, we synthesize, compare and contrast methodological quality and findings, and investigate reasons for discordance of SR/MAs of RCTs evaluating the efficacy of vitamin D supplementation, with or without calcium supplementation, on fracture risk. Importantly, the majority of the identified SR/MAs were rated of low to critically low quality, secondary to the lack or insufficient data in one or more of the critical AMSTAR-2 domains, specifically limitations in the search strategy, the lack of a list for excluded trials, the absence of an appropriate bias assessment or accounting for it in the interpretation of results, and the lack of investigation of publication bias.
Several of these items were added to the AMSTAR-2 tool, but were not available in AMSTAR-1, which was available when many of the included SR/MAs were conducted/published (14).

Most of the included SR/MAs showed a protective effect of Ca/D compared with placebo/control. The discordance in results stemmed from differences in the magnitude of the effect size and statistical significance, for both hip and any fracture. SR/MAs that exclusively considered RCTs in community dwelling individuals failed to show any significant reductions in fractures. We identified only one SR/MA of moderate quality, pooling data from institutionalized and community dwelling individuals, and that evaluated the quality of evidence (15). It reported a high-quality evidence of a small RRR in hip fracture by 16% and any fracture by 5% with vitamin D dose of 400-800 IU/d, co-administered with calcium, compared with placebo/control. Fracture risk reduction in institutionalized individuals was derived from two RCTs, included in all SR/MAs except those exclusively targeting the community (31, 38). These two RCTs enrolled older women (mean age 85 years) living in nursing homes, with mean serum 25(OH)D concentration 22.5-40 nmol/L, randomized to daily Ca/D 1,200 mg/800 IU or placebo, for 18-24 months (45, 46). Each of these RCTs demonstrated a beneficial effect of Ca/D in reducing the risk of hip and non-vertebral fractures (45, 46).

Subgroup analyses by residency status were performed in 2 SR/MAs. The first revealed a RR of 0.75[0.62,0.92] (15), and the second of 0.69[0.53,0.90] (30), in institutionalized individuals, but the interaction term was not significant for the former, thus ruling out an effect of residency on risk reduction, and was not provided for the latter. The lack of evidence for a sub-group effect by residency may be due to the imprecise effect size estimates, with large CIs, despite a large number of trials and sample sizes (2,000-3,500 (41, 44, 56), and >36,000 participants in the WHI trial (48)), explained by the very low baseline fracture risk (<1%) in this population (47-50). Indeed, the neutral results of sub-group analyses could imply a lack of effect, or it may be also affected by the evaluation...
of subgroup effect within versus between trials, and pre-specifying subgroup analysis before the conduct of the SR/MA, among others(57).

Vitamin D alone does not appear to protect against fractures when compared with placebo, and this is consistent with findings of a previous umbrella review(58). Concomitant calcium supplementation is needed(59), as the combination has a synergistic effect on intestinal calcium absorption(60), on reversal of secondary hyperparathyroidism, especially if 25(OH)D< 25 nmol/L(61), and on reducing body sway and falls’ risk(62).

The discordance in results between SR/MAs is multifactorial(63), including the clinical question investigated, the search period, the eligibility criteria, the intervention, the co-intervention, and the outcome. For the hip fracture outcome, few SR/MAs aimed to assess interventions that reduce fracture risk in individuals with osteoporosis or at risk for osteoporosis or fragility fractures(16, 25, 28), while for others the population consisted of post-menopausal women and older men. Despite this variability in the population of interest, there was a significant overlap (CCA >15% for both hip and any fracture) of the included RCTs, many of which had patients with previous fractures(15-17, 23, 24, 26, 29-31, 37). Fracture definition varied across SR/MAs. Some SR/MAs included proximal femoral fractures as hip fractures(15, 19, 24, 31), while others did not(29). “Any fracture” included fall-related fractures(36, 37), or non-vertebral fractures(15, 20), or fractures defined at specific sites (hip, spine or wrist)(21), or fractures at any site(30), or without site specification(31). None of the SR/MAs targeted fragility fractures per se, and few excluded non-osteoporotic fractures (skull, carpal, metacarpal, tarsal, or metatarsal bones)(61-66). There was heterogeneity in the measure of association used. While the majority of studies used RR, the preferred tool, few studies used hazard ratio (HR) or odds ratio (OR); the latter
tends to inflate the association(67). Similarly, there was variability in the methods used for pooling of effect sizes and in the data derived from each trial(6, 63). Although all SR/MAs used a complete case analysis, which is the appropriate analysis method to deal with missing data at the trial level in the primary analysis(68), some used intention to treat or per protocol analyses for one or more RCTs.

There are two previous umbrella reviews on vitamin D supplementation. Theodoratou et al included observational and interventional SR/MAs until 2013, addressed 137 health outcomes(58). Stubbs et al assessed interventions preventing fall in the community, among which the efficacy of vitamin D supplementation on fall-related fractures(69). The first concluded there was no evidence, and the second commented on conflicting evidence, for a fracture risk reduction. Neither delved into critical appraisal of quality of SRs/MAs, and importantly into sources for any discrepancy in results from various SR/MAs, and their heterogeneity leading to conflicting conclusions.

Pollock et al has recognized several methodologic challenges in the overview of reviews (70). When a meta-analysis of SR/MA is conducted, overlap between reviews is a major consideration, as it is associated with the risk of “double counting” of studies included in more than one SR/MA(70). Therefore, some experts select only one SR/MA when several ones are eligible, such as the most recent one, or the one conducted by the Cochrane group(70). We have quantified the overlap between the SR/MAs included in our umbrella review. However, we did not pool their results, and therefore, we do not expect an amplification of the related bias in the interpretation of the results.

We have used the AMSTAR-2 tool to evaluate the quality of the included SR/MAs. Given that this tool implies some subjectivity, the assessment was done by 3 reviewers (including a content expert, MC, GEHF), and the rational for the decision was detailed in Appendix 3(12), as it was previously suggested(70). We did not use the GRADE approach to summarize our findings, since to-date, there is no clear guidance on how to apply the GRADE principles in an umbrella review (70, 71).
assess for publication bias as this remains one of the challenges of umbrella reviews without a validated tool to assess it (70).

The limitations of our findings are in large part due to the limitation of the evidence available. Baseline vitamin D status was reported only in 14 SR/MAs (15, 19, 21, 24-26, 30-32, 35-37), and fewer reported on follow-up status (19, 21, 30, 32, 35). The large variation in 25(OH)D assays was not addressed. Several SR/MAs on vitamin D alone compared with placebo/control included trials extending over 1-10 months (15, 17, 19, 21, 30-32, 35), an insufficient period to demonstrate any significant effect on fractures. For SR/MAs on Ca/D, a narrow range of vitamin D dose was used in the included trials, and therefore a dose effect cannot be investigated. Some discrepancies in SR/MAs might be related to human errors (60, 69); however, we did not investigate this possibility as verifying trials’ data was beyond our aim.

To our knowledge this is the only umbrella review on a controversial topic, that is exclusively focusing on SR/MAs analyses of RCTs, and solely on fractures. Our umbrella review fulfills the Joanna Briggs Institute (JBI) guidance on conducting umbrella reviews (73) (Appendix 4)(12). Furthermore, the quality assessment of SR/MAs, the matrices to dissect their similarities and differences, and important subgroup analyses allow a better understanding of the evidence available, contradicting results, and provides a path forward.

There is a wide variability in the development methods of the current vitamin D guidelines (74) and in their recommended vitamin D doses. Despite the lack of a solid evidence on a protective effect of vitamin D supplementation in the younger adults (50-65 years) and the non-institutionalized subjects, the majority of the guidelines recommend vitamin D supplementation for adults (8,9, 75-81). Only few guidelines target older adults, >60-70 years (82-84), or older institutionalized individuals (85-86), or recommend a higher dose in older individuals (9, 79-81), populations in which
the evidence is most convincing, namely institutionalized subjects, or most suggestive (age as a high risk).

Therefore, there is a need to improve on the methodologic rigor of vitamin D guidelines in order to issue recommendations that are evidence-based(74).

CONCLUSIONS

Vitamin D with concomitant calcium supplementation reduces the risk of hip and any fracture, in analyses combining institutionalized and community dwelling individuals. High risk individuals, such as those older, institutionalized or with low vitamin D status, may benefit most, although this could not be unequivocally demonstrated in the few SR/MAs that evaluated such predictors, most likely due to low power. An IPD-MA, using individual patient data, restricted to subjects with sufficient follow-up, rather than pooled data will be more powerful to evaluate treatment efficacy, and predictors of fracture reduction. These would include age, residency status, baseline vitamin D level, and regimen used (daily, weekly or monthly vitamin D).
Acknowledgements:

We would like to thank the investigators who replied to our emails and provided information whenever available: Drs B. Abrahamsen, A. Avenell, H. Bischoff Ferrari, L. Kahwati, L. Renjmark, and C. Weaver.

We would like to thank Miss Aida Farha, senior librarian at the American University of Beirut who has provided advice of the search strategy and Mrs Nariman Chamoun who built the search strategy.

Data Availability: Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References.
References:

1. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev. 2008;29(6):726-76.
2. Christakos S, Li S, De La Cruz J, Bikle DD. New developments in our understanding of vitamin metabolism, action and treatment. Metabolism. 2019;98:112-20.
3. Cesari M, Incalzi RA, Zamboni V, Pahor M. Vitamin D hormone: a multitude of actions potentially influencing the physical function decline in older persons. Geriatrics & Gerontology International. 2011;11(2):133-42.5.
4. Kanis JA, Oden A, McCloskey EV, Johansson H, Wahl DA, Cooper C, et al. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012;23(9):2239-56.
5. Lund CA, Møller AM, Wetterslev J, Lundstrøm LH. Organizational factors and long-term mortality after hip fracture surgery. A cohort study of 6143 consecutive patients undergoing hip fracture surgery. PLoS One. 2014;9(6):e99308.
6. Bolland MJ, Grey A. A case study of discordant overlapping meta-analyses: vitamin D supplements and fracture. PLoS One. 2014;9(12):e115934.
7. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. Nature Reviews Endocrinology. 2017;13(8):466-79.
8. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30.
9. Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D, Calcium. The National Academies Collection: Reports funded by National Institutes of Health. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US) Copyright © 2011, National Academy of Sciences.; 2011.
10. Pollock M, Fernandes RM, Becker LA, Featherstone R, Hartling L. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev. 2016;5(1):190. doi:10.1186/s13643-016-0367-5
11. Chakhtoura M, Ajjour S, Assad M, Bacha D, Gharios C, Kahale F, Jabbour Y, Akl EA, Saad R, El Hajj Fuleihan G. The impact of vitamin D supplementation on fractures, falls and mortality: an umbrella review of systematic reviews and meta-analyses of randomized controlled trials April, 2019. Available from (accessed in May 2021): https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019129540
12. Chakhtoura M. Vitamin D Supplementation and Fractures in Adults: A Systematic Umbrella Review of Meta-Analyses of Randomized Controlled Trials. Appendices. 2021; doi: https://doi.org/10.6084/m9.figshare.16595090.v2
13. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol. 2014;67(4):368-75. doi:10.1016/j.jclinepi.2013.11.007
14. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
15. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014(4):CD000227.
16. Barrionuevo P, Kapoor E, Asi N, Alahdab F, Mohammed K, Benkhadra K, et al. Efficacy of Pharmacological Therapies for the Prevention of Fractures in Postmenopausal Women: A Network Meta-Analysis. J Clin Endocrinol Metab. 2019;104(5):1623-30.
17. Bergman GJ, Fan T, McFetridge JT, Sen SS. Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis. Curr Med Res Opin. 2010;26(5):1193-201.
18. Bischoff-Ferrari HA, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med. 2012;367(1):40-9.
19. Bolland MJ, Grey A, Gamble GD, Reid IR. Vitamin D supplementation and falls: a trial sequential meta-analysis. Lancet Diabetes Endocrinol. 2014;2(7):573-80.
20. Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al. Calcium intake and risk of fracture: systematic review. BMJ. 2015;351:h4580.
21. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2011;155(12):827-38.
22. Eleni A, Panagiotis P. A systematic review and meta-analysis of vitamin D and calcium in preventing osteoporotic fractures. Clin Rheumatol. 2020;39(12):3571-3579.
23. Group D. Patient level pooled analysis of 68,500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010;340:b5463.
24. Hu ZC, Tang Q, Sang CM, Tang L, Li X, Zheng G, et al. Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomised controlled trials. BMJ Open. 2019;9(10):e024595.
25. Kahlwati LC, Weber RP, Pan H, Gourlay M, LeBlanc E, Coker-Schwimmer M, et al. Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018;319(15):1600-12.
26. Lai JK, Lucas RM, Clements MS, Roddam AW, Banks E. Hip fracture risk in relation to vitamin D supplementation and serum 25-hydroxyvitamin D levels: a systematic review and meta-analysis of randomised controlled trials and observational studies. BMC Public Health. 2010;10:331.
27. Li S, Xi C, Li L, Long Z, Zhang N, Yin H, et al. Comparisons of different vitamin D supplementation for prevention of osteoporotic fractures: a Bayesian network meta-analysis and meta-regression of randomised controlled trials. Int J Food Sci Nutr. 2020;71:1-11.
28. Murad MH, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA, et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. J Clin Endocrinol Metab. 2012;97(6):1871-80.
29. Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int. 2016;27(1):367-76.
30. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019;2(12):e191789.
31. Zhao JG, Zeng XT, Wang J, Liu L. Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. JAMA. 2017;318(24):2466-82.
32. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol. 2018;6(11):847-58.
33. LeBlanc ES, Zakher B, Daeges M, Pappas M, Chou R. Screening for vitamin D deficiency: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015;162(2):109-22.
34. Thanapluetiwong S, Chewcharat A, Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Susantitaphong P. Vitamin D supplement on prevention of fall and fracture: A Meta-analysis of Randomized Controlled Trials. Medicine (Baltimore). 2020;99(34):e21506.
35. Van Nguyen T, Zheng YT, Cui QQ, Hong YM, Yao WG. A Meta-Analysis of High Dose, Intermittent Vitamin D Supplementation among Older Adults. Plos One. 2015;10(1):e0115850.
36. Cameron ID, Dyer SM, Panagoda CE, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev. 2018;9:CD005465.
37. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012(9):CD007146.
38. Michael YL, Lin JS, Whitlock EP, Gold R, Fu R, O'Connor EA, et al. Interventions to Prevent Falls in Older Adults: An Updated Systematic Review. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Rockville (MD)2010.
39. Tricco AC, Thomas SM, Veroniki AA, Hamid JS, Cogo E, Strilfer L, et al. Comparisons of Interventions for Preventing Falls in Older Adults: A Systematic Review and Meta-analysis. JAMA. 2017;318(17):1687-99.
40. Avenell A, Grant AM, McGee M, McPherson G, Campbell MK, McGee MA, et al. The effects of an open design on trial participant recruitment, compliance and retention—a randomized controlled trial comparison with a blinded, placebo-controlled design. Clin Trials. 2004;1(6):490-8.
41. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet. 2005;365(9471):1621-8.
42. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ, Nottingham Neck of Femur S. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. Age and Ageing. 2004;33(1):45-51.
43. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res. 2004;19(3):370-8.
44. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ. 2005;330(7498):1003.
45. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med. 1992;327(23):1637-42.
46. Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int. 2002;13(3):257-64.
47. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997;337(10):670-6.
48. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354(7):669-83.
49. Salovaara K, Tuppurainen M, Kärkkäinen M, Rikkonen T, Sandini L, Sirola J, et al. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial--the OSTPRE-FPS. J Bone Miner Res. 2010;25(7):1487-95.
50. Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int. 2013;24(2):567-80.
51. Xue Y, Hu Y, Wang O, Wang C, Han G, Shen Q, et al. Effects of Enhanced Exercise and Combined Vitamin D and Calcium Supplementation on Muscle Strength and Fracture Risk in Postmenopausal Chinese Women. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2017;39(3):345-51.
52. Liu BX, Chen SP, Li YD, Wang J, Zhang B, Lin Y, et al. The Effect of the Modified Eighth Section of Eight-Section Brocade on Osteoporosis in Postmenopausal Women: A Prospective Randomized Trial. Medicine (Baltimore). 2015;94(25):e991.
53. Inkovaara J, Gothoni G, Halttula R, Heikinheimo R, Tokola O. Calcium, vitamin D and anabolic steroid in treatment of aged bones: double-blind placebo-controlled long-term clinical trial. Age and ageing. 1983;12(2):124-30.
54. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Arch Intern Med. 2006;166(4):424-30.
55. Bolton-Smith C, McMurdo ME, Paterson CR, Mole PA, Harvey JM, Fenton ST, et al. Two-year randomized controlled trial of vitamin K1 (phyloquinone) and vitamin D3 plus calcium on the bone health of older women. J Bone Miner Res. 2007;22(4):509-19.
56. Kärkkäinen MK, Tuppurainen M, Salovaara K, Sandini L, Rikkonen T, Sirola J, et al. Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS). Maturitas. 2010;65(4):359-65.
57. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. CMAJ. 2020;192(32):E901-E6.
58. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. 2014;348:g2035.
59. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab. 2007;92(4):1415-23.
60. Heaney RP. Vitamin D and calcium interactions: functional outcomes. The American Journal of Clinical Nutrition. 2008;88(2):541s-4s.
61. Lips P. Interaction between vitamin D and calcium. Scandinavian Journal of Clinical and Laboratory Investigation Supplementum. 2012;243:60-4.
62. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res. 2000;15(6):1113-8.
63. Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. CMAJ. 1997;156(10):1411-6.
64. FitzGerald G, Boonen S, Compston JE, Pfeilschifter J, LaCroix AZ, Hosmer DW, Jr., et al. Differing risk profiles for individual fracture sites: evidence from the Global Longitudinal Study of Osteoporosis in Women (GLOW). J Bone Miner Res. 2012;27(9):1907-15.
65. Morin SN, Lix LM, Leslie WD. The importance of previous fracture site on osteoporosis diagnosis and incident fractures in women. J Bone Miner Res. 2014;29(7):1675-80.
66. Delmas PD, Marin F, Marcus R, Misurski DA, Mitlak BH. Beyond hip: importance of other nonspinal fractures. Am J Med. 2007;120(5):381-7.
67. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ. 2012;184(8):895-9. doi:10.1503/cmaj.101715
68. Akl EA, Kahale LA, Agoritsas T, Brignardello-Petersen R, Busse JW, Carrasco-Labra A, et al. Handling trial participants with missing outcome data when conducting a meta-analysis: a systematic survey of proposed approaches. Syst Rev. 2015;4:98.
69. Stubbs B, Brefka S, Denkinger MD. What Works to Prevent Falls in Community-Dwelling Older Adults? Umbrella Review of Meta-analyses of Randomized Controlled Trials. Phys Ther. 2015;95(8):1095-110.
70. Pollock A, Campbell P, Brunton G, Hunt H, Estcourt L. Selecting and implementing overview methods: implications from five exemplar overviews. Syst Rev. 2017;6(1):145.
71. Lunny C, Brennan SE, McDonald S, McKenzie JE. Toward a comprehensive evidence map of overview of systematic review methods: paper 2-risk of bias assessment; synthesis, presentation and summary of the findings; and assessment of the certainty of the evidence. Syst Rev. 2018;7(1):159.
72. Khamis AM, El Moheb M, Nicolas J, Iskandarani G, Refaat MM, Akl EA. Several reasons explained the variation in the results of 22 meta-analyses addressing the same question. J Clin Epidemiol. 2019;113:147-58.
73. Aromataris E MZE. JBI Manual for Evidence Synthesis. JBI 2020; Available from (accessed in September 2021) https://doi.org/10.46658/JBIMES-20-01
74. Dai Z, McKenzie JE, McDonald S, et al. Assessment of the Methods Used to Develop Vitamin D and Calcium Recommendations-A Systematic Review of Bone Health Guidelines. Nutrients. 2021;13(7)
75. Hanley DA, Cranney A, Jones G, et al. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. CMAJ. 2010; 182(12):E610-8.
76. German Nutrition Society. New reference values for vitamin D. Ann Nutr Metab. 2012; 60(4): 241.
77. Płudowski P, Karczmarewicz E, Bayer M, et al. Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe—recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol. 2013; 64(4): 319-27.
78. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). Scientific opinion on the tolerable upper intake level of vitamin D. european food safety authority; 2012. Available from (accessed in September 2021): http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2813/epdf
79. Haq A, Wimalawansa SJ, Płudowski P, Anouti FA. Clinical practice guidelines for vitamin D in the United Arab Emirates. The Journal of Steroid Biochemistry and Molecular Biology. 2018;175:4-11.
80. Lötscher KQ, l'Allemand D, Bischoff-Ferrari HA, Burckhardt P. Vitamin-D deficiency: Evidence, safety, and recommendations for the Swiss population. 2012; Available from (accessed in September 2021) https://www.zora.uzh.ch/id/eprint/73029/
81. Weggemans RM, Kromhout D, van Weel C. New dietary reference values for vitamin D in the Netherlands. European Journal of Clinical Nutrition. 2013;67(6):685
82. Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. Jul 2010;21(7):1151-4.
83. National Institute For Health And Clinical Excellence. 2008; Available from (accessed in August 2021) https://www.nice.org.uk/guidance/ph56/documents/implementing-vitamin-d-guidance-final-scope-2
84. National Osteoporosis Society. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. 2013; Available from (accessed in September 2021) http://www.aub.edu.lb/fm/cmop/downloads/Vitamin-D-Bone-Health.pdf
85. Lips, P, Cashman, K.D, Lamberg-Allardt, C, Bischoff-Ferrari, HA, Obermayer-Pietsch, BR, Bianchi, M, Stepan, J, El-Hajj Fuleihan, G, Bouillon, R. Management of Endocrine Disease: Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency; a position statement of the European Calcified Tissue Society. European Journal of Endocrinology. 2019; 180(4):P23-P54.
86. Judge J, Birge S, Gloth F, et al. Recommendations abstracted from the American Geriatrics Society consensus statement on vitamin D for prevention of falls and their consequences. J Am Geriatr Soc. 2014; 62(1): 147-52.
Figure Legends:

**Figure 1**: Flow diagram of the included studies

* List of excluded articles is available upon request.

* These will be included in separate manuscripts.

**Figure 2**: Effect size estimates and 95% confidence interval for hip (A) and any (B) fracture risk with CaD supplementation vs. Placebo/control. Quality assessment using AMSTAR-2 tool: (A): moderate quality, (B): low quality, and (C): critically low quality.

* Abbreviations: RR: Risk Ratio, OR: Odds Ratio, HR: Hazard Ratio.

* Meta-analyses that included institutionalized trials.

* Network meta-analyses.

* Not available
Table 1: Characteristics of the populations and interventions in the included systematic reviews/meta-analyses on Vitamin D and concomitant calcium supplementation compared to placebo/control.

| Characteristics of population & interventions | N (%) or Range |
|-----------------------------------------------|----------------|
| **Mean Age (years)**                           | 62-85.2        |
| **Gender**                                     |                |
| • Men and women                                | 9 (69)         |
| • Women only                                   | 2 (15)         |
| • Not reported                                 | 2 (15)         |
| **Residency Status**                           |                |
| • Community-dwelling only                      | 3 (23)         |
| • Institutionalized only                       | 0 (0)          |
| • Both                                         | 8 (62)         |
| • Not reported                                 | 2 (15)         |
| **Mean serum 25(OH)D concentration at baseline (nmol/L)** | 11.9 – 84      |
| • Reported                                     | 5 (38)         |
| • Not reported                                 | 8 (62)         |
| **Mean serum 25(OH)D concentration at follow-up (nmol/L)** | 15.0 - 112     |
| • Reported †                                   | 1 (8)          |
| • Not reported                                 | 12 (92)        |
| **Vitamin D dose frequency**                   |                |
| • Daily (IU/day)                               | 400 – 1,600    |
| • Once (IU)                                    | 300,000        |
| **Calcium dose (mg/day)**                      | 500 – 1,200    |
| **Vitamin D route of administration**          |                |
| • Oral supplementation only                    | 1 (8)          |
| • Oral and parenteral supplementation          | 4 (31)         |
| • Administration mode not mentioned            | 8 (62)         |
| **Individual trial duration**                  |                |
| • SR including ≥1 trial < 12 months            | 0 (0)          |
| • SR including all trials ≥ 12 months          | 9 (69)         |
| • Not reported                                 | 4 (31)         |
| **Fracture site**                              |                |
| • Hip                                          | 12             |
| • Total / Any / Other                          | 11             |
| • Vertebral                                    | 6              |
| • Non-vertebral                                | 5              |
| **SR/MAs with trials on individuals at high risk of fracture** | 9              |

Abbreviations: 25(OH)D: 25-hydroxyvitamin D; IU: International units

† Yao reported change rather than follow up 25-hydroxyvitamin D concentration (30). Some MAs may include more than one fracture site. Previous fracture or osteopenia/osteoporosis.
Table 2 - Comparison of individual trials included in traditional systematic reviews/meta-analyses\(^a\) and reasons for exclusion\(^b\) of trials by some systematic reviews/meta-analyses investigating hip fracture risk with Ca/D supplementation.

|                | Bergman(17) 2010 | Avenell(15) 2014 | Bolland(19) 2014 | Weaver(29) 2016 | Zhao(31) 2017 | Barrionuevo(16) 2019 | Hu(24) 2019 | Yao(30) 2019 | Eleni(22) 2020 |
|----------------|------------------|------------------|------------------|-----------------|---------------|----------------------|-------------|-------------|---------------|
| **Pooled RR**  | 0.72(0.32, 1.40) | 0.84(0.74, 0.96) | 0.84(0.74, 0.96) | 0.61(0.46, 0.82) | 0.81(0.71, 0.93) | 0.84(0.72, 0.97) | 0.61(0.40, 0.92) | |
| **Institutionalized RR** | 0.75(0.62, 0.92) | 0.84(0.74, 0.96) | 0.84(0.74, 0.96) | 0.61(0.46, 0.82) | 0.81(0.71, 0.93) | 0.84(0.72, 0.97) | 0.61(0.40, 0.92) | |
| **Community RR** | 0.91(0.77, 1.09) | 1.09(0.85, 1.39) | 1.09(0.85, 1.39) | 1.09(0.85, 1.39) | 1.15(0.81, 1.62) | 1.15(0.81, 1.62) | 0.92(0.77, 1.10) | |
| **AMSTAR Quality Assessment** | Critically Low | Moderate | Critically low | Critically low | Low | Critically low | Critically low | Critically low | Critically low |
| **Included Trials** | Chapuy(45) 1992 | NA | 38.24% 137/1634 178/1636 0.77(0.62, 0.95) | 38% 137/1634 178/1636 0.57(0.34,0.97) | NA 21/877 37/888 | Excluded institutionalized trials | 42.77% NA NA 0.77(0.62,0.95) | Excluded institutionalized trials | 25.5% 80/1634 110/1636 0.72(0.53, 0.96) | 15.2% 21/1387 37/1403 0.57(0.34, 0.98) |
|                | Chapuy(46) 2002 | NA 273/393 21/190 NA | 6.02% 27/389 21/194 0.64(0.37, 1.10) | 6% 27/389 21/194 NA | NA 27/393 21/190 0.62(0.36,1.07) | Excluded institutionalized trials | 6.50% NA NA 0.64(0.37,1.10) | Excluded institutionalized trials | 5.5% 27/393 21/190 0.58(0.31,1.08) | 15.0% 27/393 21/190 0.62(0.36,1.07) |
|                | Dawson-Hughes(47) 1997 | Excluded trials including men | 0.31% 0/187 1/202 0.36(0.01, 8.78) | 0.2% 0/187 1/202 NA | NA 0/170 1/148 0.29(0.01,7.08) | Excluded trials including men | 0.6% 0/187 1/202 0.36(0.01,8.78) | Excluded trials with <500 participants | 1.5% 0/187 1/202 0.36(0.01,8.78) | |
|                | Larsen(43) 2004 | NA | “No treatment group received vitamin D & calcium alone” | NA | NA | “No treatment group received vitamin D and calcium” | NA | NA | “Not randomized (cluster randomized factorial” | 18.6% 87/4957 114/2116 0.33(0.25,0.43) |
| Study (ref) | Year (Type) | Design Exclusion | Hip Fracture | Odds Ratio (95% CI) | Exclusion Reason | Design Exclusion |
|------------|-------------|------------------|--------------|---------------------|-----------------|------------------|
| Bergman (17) 2010 | Avenell (15) 2014 | Excluded trials including men | 0.21% 1/35 1/35 1.0(0.07,15.36) | “Doesn’t qualify as an RCT of Calcium and vitamin D” | Excluded trials including men | 0.8% 1/35 1/35 1.0(0.07,15.36) |
| Bolland (19) 2014 | Weaver (29) 2016 |  | 0.2% 1/35 1/35 | | | |
| Zhao (31) 2017 | Barrionuevo (16) 2019 | Excluded trials including men | 0.26% 1/75 1/37 0.49(0.03,7.67) | | Excluded trials with <500 participants | |
| Hu (24) 2019 | Yao (30) 2019 | Excluded trials with <500 participants | 0.8% 1/75 1/37 0.49(0.03,7.67) | | | |
| Eleni (22) 2020 | | | NA | | Excluded trials with <500 participants | |
| Harwood (NoNOF) (42) 2004 | Excluded trials on post-hip fracture | 0.29% 1/75 1/37 0.49(0.03,7.67) | | | Excluded trials including men | |
| Grant (RECORD) (41) 2005 | Included in sensitivity analysis | 8.73% 46/1306 41/1332 1.14(0.76,1.73) | No data on hip fracture as per the SR/MA definition | | Excluded trials including men | |
| Porthouse (44) 2005 | | 2.91% 8/1321 17/1993 0.71(0.31,1.64) | NA | | | |
| Jackson (WHI) (48) 2006 | Excluded interventions incorporating hormone therapy | 42.86% 175/18176 199/18106 0.88(0.72,1.07) | | | | |
| Salovaara (OSTPRE-FPS) (49) 2010 | Excluded Search Period | 0.43% 4/1586 2/1609 2.03(0.37,11.0 6) | | | | |
| Prentice (50) | Beyond | | | | | |

**Notes:**
- “It assessed the open trial design and not explicitly the combination of Ca & vitamin D”
- Excluded trials including men
- Excluded trials with <500 participants
- NA: Not applicable (no data available)
- NA: Not applicable (no data available)
- NA: Not applicable (no data available)
- NA: Not applicable (no data available)
- NA: Not applicable (no data available)
- NA: Not applicable (no data available)
|          | Bergman(17) 2010 | Avenell(15) 2014 | Bolland(19) 2014 | Weaver(29) 2016 | Zhao(31) 2017 | Barrionuevo(16) 2019 | Hu(24) 2019 | Yao(30) 2019 | Eleni(22) 2020 |
|----------|-----------------|-----------------|-----------------|----------------|----------------|---------------------|----------|------------|----------------|
| 2013     | Search Period   |                 |                 | 19/7530 35/7406 | 0.53(0.31,0.93) | analysis of WHI trial |          |            | 19/7530 35/7801 0.56(0.32 0.98) |

Abbreviations: RR: relative risk; NA: Not available.

Yellow: Institutionalized population; Green: Community-dwelling population

Individual rows within cells are filled with the following: % is weight of each trial taken from the forest plot of the corresponding SR/MA, Number of fractures/total number of participants in the treatment group, Number of fractures/total number of participants in control group, Effect size estimate of the trial taken from the forest plot of the corresponding SR/MA.

---

a MAs not included in the matrix: Abrahamsen 2010: IPD without details about individual RCTs(23); Murad 2012: Network MA without details about Ca/D vs placebo(28); Tricco 2017: Network MA without details about individual RCTs(39).

b Reasons for exclusion of some trials by systematic reviews/meta-analyses either as exactly reported or derived from inclusion/exclusion criteria.

c “The test for subgroup differences was not significant (P value 0.15)”.

d “P for heterogeneity: 0.07”, p value for interaction term was not provided.

e This RR is for high vitamin D (≥800 IU/day) + high Ca (≥800 mg/day) vs placebo. RR for low vitamin D (<800 IU/day) + high Ca (≥800 mg/day) is 1.13(0.78,1.63). RR for low vitamin D (<800 IU/day) + low Ca (<800 mg/day) is 0.36 (0.01, 8.81).

f Avenell excluded Larsen because participants in each of the three treatment clusters received one or more co-interventions designed to reduce falls (medication review, environmental hazard and health assessment, and osteoporosis/fall prevention leaflets) but the control group received no intervention. No treatment group received vitamin D and calcium alone.

g Confidence interval for “equally allocated” subgroup.
Table 3 - Subgroup analyses of vitamin D with calcium vs. placebo on the risk of hip and any fracture.

|                        | Hip Fracture                                                                 | Any fracture                                                                 |
|------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
|                        | **Yao, 2019(30):**                                                          | **Yao, 2019(30):**                                                          |
|                        | **<80:** 0.92 (0.77, 1.10)                                                   | **<80:** 0.96 (0.90, 1.02)                                                   |
|                        | **≥80:** 0.69 (0.53, 0.90)                                                   | **≥80:** 0.76 (0.62, 0.92)                                                   |
|                        | **P (interaction): NA**                                                     | **P (interaction): NA**                                                     |
|                        | **P (heterogeneity): 0.07**                                                  | **P (heterogeneity): 0.02**                                                  |
| **By Age (years)**     |                                                                              |                                                                              |
|                        | **Zhao, 2017(31):**                                                         | **Zhao, 2017(31):**                                                         |
|                        | **Women only:** 1.07 (0.79-1.46)                                             | **Women only:** 0.88 (0.71-1.08)                                             |
|                        | **Both:** 1.12 (0.75-1.68)                                                   | **Both:** 0.83 (0.48-1.42)                                                   |
|                        | **P (interaction): 0.86**                                                   | **P (interaction): 0.84**                                                   |
| **By Gender**          |                                                                              |                                                                              |
|                        | **Zhao, 2017(31):**                                                         | **Zhao, 2017(31):**                                                         |
|                        | **Yes:** 1.12 (0.75-1.68)                                                   | **Yes:** 0.92 (0.76-1.11)                                                   |
|                        | **Other a:** 1.07 (0.79-1.46)                                                | **Other a:** 0.88 (0.71-1.09)                                                |
|                        | **P (interaction): 0.86**                                                   | **P (interaction): 0.78**                                                   |
|                        | **Avenell, 2014(15):**                                                      | **Avenell, 2014(15):**                                                      |
|                        | **Yes:** 1.02 (0.71, 1.47)                                                  | **Yes:** 0.93 (0.79, 1.10)                                                  |
|                        | **No:** 0.82 (0.71, 0.94)                                                   | **No:** 0.95 (0.90, 1.00)                                                   |
|                        | **P (interaction): 0.26**                                                   | **P (interaction): 0.84**                                                   |
| **By History of**      |                                                                              |                                                                              |
| **Osteoporotic Fracture** | **Zhao, 2017(31):**                                                                    | **Zhao, 2017(31):**                                                                    |
|                        | **Yes:** 0.92 (0.76, 1.10)                                                  | **Yes:** 0.92 (0.76-1.11)                                                   |
|                        | **Other a:** 0.88 (0.71-1.09)                                                | **Other a:** 0.88 (0.71-1.09)                                                |
|                        | **P (interaction): 0.78**                                                   | **P (interaction): 0.78**                                                   |
| **By baseline**        |                                                                              |                                                                              |
| **serum 25(OH)D**      |                                                                              |                                                                              |
| **concentration (nmol/L)** | **Zhao, 2017(31):**                                                      | **Zhao, 2017(31):**                                                      |
|                        | **≥50:** 0.36 (0.01-8.78)                                                   | **≥50:** 1.87 (0.32-11.02)                                                  |
|                        | **<50:** 1.14 (0.88-1.48)                                                   | **<50:** 0.90 (0.76-1.05)                                                   |
|                        | **P (interaction): 0.48**                                                   | **P (interaction): 0.42**                                                   |
| Study | Vitamin D Dose | ≥50 (nmol/L) | <50 (nmol/L) | P (interaction) |
|-------|----------------|--------------|--------------|----------------|
| Bolland, 2014 (19) | ≥50: 0.36 (0.02, 8.79) | <50: 0.84 (0.74, 0.97) | 0.82 |
| | ≥50: 1.50 (1.02, 2.19) | <50: 0.75 (0.43, 1.31) | 0.24 |
| By Vitamin D Dose | Zhao (with Ca), 2017 (31) | ≥1 g & ≥800 IU: 1.06 (0.74-1.51) | Another dose: 1.12 (0.80-1.57) | 0.83 |
| | ≥1 g & ≥800 IU: 0.90 (0.78-1.04) | Another dose: 1.15 (0.28-4.74) | |
| Abrahamsen, 2010 (23) | 10 ug: 0.74 (0.60, 0.91) | 20 ug: 1.30 (0.88, 1.91) | |
| | 10 ug: 0.91 (0.85, 0.99) | 20 ug: 0.95 (0.80, 1.14) | |
| Other sub-group analyses: | Yao, 2019 (30): region, open label, Ca dose (1000 mg, 1200 mg), treatment difference in 25(OH)D (<50 nmol/L, ≥50 nmol/L) | Bolland, 2014 (19): achieved 25(OH)D (nmol/L), duration of trial | Zhao, 2017 (31): Ca dose (<1 g, ≥1 g), dietary Ca intake (<900 mg, ≥900 mg), dose frequency | Weaver, 2016 (29): use of personal supplements, adherence to assigned study pills in the WHI |

Abbreviations: I: Institutionalized; C: Community-dwelling individuals. NA: not available. Units listed as reported; to convert from nmol/L to ng/ml, divide by 2.496.

*Other: includes no fracture, partial fracture, or missing fracture data.
Table 4 - Comparison of individual trials included in traditional systematic reviews/meta-analyses a and reasons for exclusion b of trials by some systematic reviews/meta-analyses investigating any fracture risk with Ca/D supplementation.

| Trials | AMSTAR Quality assessment | Total Fx Definition: | Annual Fx | Excluded institutionalized trials |
|--------|---------------------------|----------------------|-----------|-----------------------------------|
| Chapuy(45) 1992 | NA 80/1387 115/1403 NA | Excluded institutionalized trials | 10.67% 255/1634 308/1636 0.83(0.71,0.96) | 19% 255/1634 308/1636 NA |
| Chapuy(46) 2002 | NA 70/393 30/190 NA | Excluded institutionalized trials | 1.57% 69/389 34/194 1.01(0.71,1.47) | 4% 69/389 34/194 NA |
| Inkovaara(53) 1983 | NA | Excluded trials not reporting on fall outcome | “Unclear whether the data represent fractures or participants with fractures” | NA |
| DawsonHughes(47) | Excluded trials | Excluded trials not reporting on fall outcome | 0.87% 11/187 1% 11/187 | NA 11/170 |

Notes: a: Pooled RR; b: Institutionalized RR; c: Community RR; d: AMSTAR Quality assessment; e: Total Fx Definition: Any fx excluding hip & NV fx; f: Fall-related fx at any site; g: Any fx excluding hip, V, & NV fx; h: Any fx excluding hip fx; i: Any fx excluding hip, V, & NV fx; j: Any fx including hip fx²; k: Any fx excluding hip & V fx.
| Year | Authors | Trials Excluded | Reason for Exclusion | Trials Included | Sample Size | Mean Age | Mean Duration | Mean Follow-up | Fracture Events | Event Rate | Odds Ratio (95% CI) | Notes |
|------|---------|-----------------|----------------------|----------------|-------------|----------|-------------|---------------|----------------|-------------|-------------------|-------|
| 1997 | Bergman (17) 2010 | Including men reporting on fall outcome | | | 26/202 | 0.46 (0.23, 0.9) | 26/202 | 0.37 (0.19, 0.72) | | | | |
| 2004 | Larsen (43) | NA | “The outcome is only ‘severe’ falls leading to acute hospital admission” | | | | | | | | | |
| 2004 | Avenell (40) | Excluded trials including men | Excluded trials not reporting on fall outcome | | | | | | | | |
| 2004 | Harwood (NoNOF) (42) | Excluded trials on post-hip fracture | | | | | | | | | |
| 2005 | Grant (RECORD) (41) | Excluded trials including men | Excluded trials not reporting on fall outcome | | | | | | | | |
| 2005 | Porthouse (44) | NA | | | | | | | | | |
| 2006 | Jackson (WHI) (48) | Excluded interventions incorporating | Excluded trials not reporting on | | | | | | | | |

**Notes:**
- "No treatment group received vitamin D & calcium alone"
- "No treatment group received vitamin D and calcium alone"
- "Doesn't qualify as an RCT of Calcium and vitamin D"
- "It assessed the open trial design and not explicitly the combination of Ca & vitamin D"
|                          | Bergman(17) 2010 | Gillespie(37) 2012 | Avenell(15) 2014 | Bolland(19) 2014 | Weaver(29) 2016 | Zhao(31) 2017 | Hu(24) 2019 | Yao(30) 2019 | Eleni(22) 2020 |
|--------------------------|------------------|-------------------|------------------|------------------|----------------|-------------|-----------|-----------|-------------|
| hormone therapy          |                  |                   |                  |                  |                |             |           |           |             |
| fall outcome             | 0.97(0.92,1.03)  | NA                | NA               | instead          | definition     |             |           |           |             |
| Bischoff-Ferrari(54) 2006| NA               | 3.75%             | 0.46(0.23,0.91)  | NA               | NA             |             |           |           |             |
| Bolton-Smith(55) 2007    | NA               | Excluded trials not reporting on fall outcome | 0.07% 2/62 2/61 0.98(0.14,6.76) | 0.2% 2/62 2/61 NA | NA | No data on any fracture as per the SR/MA definition | NA | Excluded trials with <500 participants | Excluded because “confounded by the use of vitamin K1 in the therapeutic regimen” |
| Salovaara(49) 2010       | Beyond search period | 11.63% 2/62 2/61 0.89(0.65,1.21) | 2.82% 71/1586 82/1609 0.88(0.64,1.2) | 6% 78/1586 94/1609 0.84(0.63,1.13) | NA | 23.9% 78/1586 94/1609 0.83(0.62,1.11) | NA | 3.7% 86/1586 103/1609 0.84(0.63,1.13) | 11.0% 78/1586 94/1609 0.84(0.63,1.13) |
| Prentice(50) 2013        | Beyond search period | Beyond search period | NA | NA | NA | NA | NA | NA | NA |
| Liu(52) 2015             | Beyond search period | Beyond search period | Beyond search period | Beyond search period | NA | 0.4% 1/50 2/48 0.48(0.04,5.12) | NA | 0.4% 1/50 2/48 NA | Excluded trials with <500 participants | NA |
| Xue(51) 2017             | Beyond search period | Beyond search period | Beyond search period | Beyond search period | NA | 0.7% 3/139 2/173 1.87(0.32,11.0) | NA | 0.7% 3/139 2/173 NA | Excluded trials with <500 participants | NA |

Individual cells are filled with the following: % is weight of each trial, Number of fractures/treatment group, Number of fractures/control group, Effect size estimate.

Yellow: Institutionalized population; Green: Community-dwelling population

32
Abbreviations: RR: relative risk; V: vertebral; NV: non-vertebral; Fx: fracture; NA: Not available.

\(^a\) MAs not included in the matrix: Abrahamsen 2010: IPD w/out details about individual RCTs(23); Tricco 2017: Network MA w/out details about individual RCTs(39).

\(^b\) Reasons for exclusion of some trials by systematic reviews/meta-analyses either as exactly reported or derived from inclusion/exclusion criteria.

\(^c\) “The test for subgroup differences was not significant (P value 0.13)”.

\(^d\) Not a sub-group analysis; community and institutionalized were each analyzed separately.

\(^e\) “P for heterogeneity: 0.02”.

\(^f\) This RR is for high vitamin D (≥ 800 IU/day) + high Ca (≥800 mg/day) vs placebo. RR for low vitamin D (<800 IU/day) + high Ca (≥800 mg/day) is 0.48 (0.04, 5.16). RR for high vitamin D (≥800 IU/day) + low Ca (<800 mg/day) is 1.87 (0.31, 11.13).

\(^g\) Any fracture is defined as a fracture occurring at any site, but if an RCT only reported hip fracture, these were also counted as any fracture.

\(^h\) Only total number available (number of events per treatment/control is not available).

\(^i\) Confidence interval for equally allocated subgroup.
Figure 1

11,808 potentially relevant citations identified by initial search until July 2018

14,357 total relevant citations identified.

1,375 full text articles assessed for eligibility.

81 Systematic Reviews/Meta-Analyses Included

25 Systematic Reviews/Meta-Analyses on Fractures:
- 21 on fractures
- 4 on fall-related fractures

13 Systematic Reviews/Meta-Analyses on the vitamin D and calcium vs. placebo/control:
- 12 on hip fractures
- 11 on any fractures

19 Systematic Reviews/Meta-Analyses on the vitamin D alone vs. placebo/control:
- 15 on hip fractures
- 13 on any fractures

1,294 full text articles excluded:
- 744 Other study designs
- 160 Narrative reviews
- 166 Intervention is not vitamin D
- 46 None of the outcomes of interest assessed
- 37 Systematic reviews of RCTs
- 19 Age <18
- 14 Systematic reviews of observational studies
- 14 Cancer patients
- 12 Chronic renal failure
- 9 Pregnant women
- 9 Comparator is a bone active agent
- 4 Intervention is active vitamin D
- 5 Co-intervention differs across arms
- 4 Chronic steroids
- 2 HIV patients
- 1 Chronic heart failure
- 39 Duplicates

12,082 citations excluded after title and abstract screening.

56 articles on other outcomes:
- 25 Systematic Reviews/Meta-analyses on Falls
- 31 Systematic Reviews/Meta-analyses on Mortality
Figure 2

A. Vitamin D+Ca Supplementation vs Placebo/Control

| Study | RR   | 95% CI  |
|-------|------|---------|
| Eleni  | 0.84 | (0.70-0.99) |
| Yang  | 0.85 | (0.71-0.99) |
| Hu  | 0.99 | (0.83-1.10) |
| Berrevoet | 1.03 | (0.81-1.30) |
| Zhao  | 1.07 | (0.85-1.33) |
| Tricco  | 1.10 | (0.92-1.29) |
| Vowinkel  | 1.14 | (0.92-1.40) |
| Dalland  | 1.19 | (0.93-1.51) |
| Almqvist | 1.23 | (1.00-1.51) |
| Bergmark  | 1.26 | (1.04-1.53) |
| Abrahamsson  | 1.28 | (1.05-1.54) |

B. Any Fracture

| Study | RR   | 95% CI  |
|-------|------|---------|
| Eleni  | 0.75 | (0.59-0.97) |
| Yang  | 0.95 | (0.76-1.20) |
| Hu  | 0.95 | (0.77-1.17) |
| Zhao  | 0.80 | (0.63-1.00) |
| Tricco  | 0.81 | (0.66-0.99) |
| Vowinkel  | 0.80 | (0.64-0.99) |
| Dalland  | 0.82 | (0.65-1.02) |
| Almqvist | 0.89 | (0.69-1.15) |
| Bergmark  | 0.95 | (0.72-1.25) |
| Abrahamsson  | 0.92 | (0.70-1.22) |

Quality Assessment Using the AMSTAR 2 Tool:
- (A) Moderate Quality
- (B) Low Quality
- (C) Critically low Quality

Abbreviations: RR: Risk Ratio; OR: Odds Ratio; HR: Hazard Ratio

A: Meta-Analysis including institutionalized trials
B: Network Meta-Analysis
d: not available

d: not available