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SYSTEMATIC REVIEW

Primary Care

Vitamin D recommendations in clinical guidelines: A systematic review, quality evaluation and analysis of potential predictors

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Abstract

Background: Vitamin D has been widely promoted for bone health through supplementation and fortification of the general adult population. However, there is growing evidence that does not support these strategies. Our aim is to review the quality and recommendations on vitamin D nutritional and clinical practice guidelines and to explore predictive factors for their direction and strength.

Methods: We searched three databases and two guideline repositories from 2010 onwards. We performed a descriptive analysis, a quality appraisal using AGREE II scores (Appraisal of Guidelines Research and Evaluation) and a bivariate analysis evaluating the association between direction and strength of recommendations, AGREE II domains' scores and pre-specified characteristics.

Results: We included 34 guidelines, 44.1% recommended, 26.5% suggested and 29.4% did not recommend vitamin D supplementation. Guidelines that scored higher for "editorial independence" and "overall quality score" were less likely to recommend or suggest vitamin D supplementation (median 68.8 vs 35.4; $P = .001$ and 58.3

vs 37.5; $P = .02$). Guidance produced by government organisations and those that reported source of funding were associated with higher AGREE II scores. Unclear role of source of funding was associated with recommending or suggesting vitamin D supplementation ($P = .034$). Editorial independence was an independent predictor for recommending or suggesting vitamin D supplementation (OR 1.09; CI95% 1.02 to 1.16; $P = .006$).

Conclusions: Policymakers, clinicians and patients should be aware that lower quality guidelines and those reporting conflicts of interest are more likely to promote vitamin D supplementation. Guideline organisations should improve the quality of their recommendations' development and the management of conflicts of interest. Users and editors should be aware of these findings when using and appraising guidelines.

1 | INTRODUCTION

Vitamin D plays a vital role in several physiological processes.[1-4] The best understood function is calcium regulation, counter-regulating parathyroid hormone secretion to maintain calcium serum levels[5] and calcium absorption. It is predominantly synthesised via sunlight exposure,[6] as it is limited to only a few natural sources[7] in the human diet. Deficiency has been associated with low bone mineral density (BMD),[8] an increased risk of fractures[9] in adults, and severe cases may lead to rickets in children and osteomalacia in adults.[10]

The association between vitamin D supplementation and fracture risk is controversial.[11] Supplementation recommendations were initially formulated for populations with low sun exposure, particularly in northern latitudes.[12] Despite, early systematic reviews[13-15] showing a decrease in fractures among older institutionalised women, no beneficial effects have been reported in more recent reviews.[16-22] Randomised clinical trials evaluating fracture risk in the general population are lacking, with studies usually reporting surrogate outcomes, such as BMD or 25-hydroxycholecalciferol (25-OH-D) levels.[23] Moreover, vitamin D supplementation has not been shown to prevent other outcomes, such as cardiovascular outcomes or cancer,[24-26] and high doses (500,000 UI of cholecalciferol) have been associated with an increased risk of falls.[27-29]

Another subject of debate is what constitutes vitamin D deficiency. While some studies declared epidemic proportions of deficiency,[30] others have not confirmed these claims.[31] Typically assessed by 25-OH-D levels, the threshold to maintain adequate bone health remains controversial.[31] Some authors have also expressed concerns about the rigour of clinical guideline (CG) development process.[32]

Public health concerns about suboptimal vitamin D intake have led to the development of dietary and supplementation recommendations.[31] The Institute of Medicine (IOM) defines guidelines as "statements that include recommendations, intended to optimise patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options".[33] In this context, they allow discerning of which patients or populations may require vitamin D supplementation, in case of evidence of benefit.

Despite the relevance of this public health topic, there are no evaluations of the quality of vitamin D guidelines. Our aim is to review recommendations on vitamin D supplementation, assess their quality and explore predictive factors.

Review criteria

- In our systematic review, we analyse vitamin D clinical guidelines targeted at general adult population for primary prevention of fractures and/or general health.
- We searched three databases and two guideline repositories from 2010 onwards.
- We performed quality appraisal using the AGREE II tool and evaluated the association between direction and strength of recommendations, AGREE II scores and reporting of conflicts of interest.

Message for the clinic

- Lower quality guidelines, and those with unclear reporting of conflicts of interest, are more likely to recommend vitamin D supplementation.
- End-users should remain cautious of vitamin D recommendations, especially those recommending wider population supplementation, unclear methods or reporting of conflicts of interest.
- Guideline developers should adhere to rigorous methods, including the reporting and management of COI. Stakeholders should adopt a cautionary approach when recommending interventions aimed at the general population.

2 | METHODS

2.1 | Protocol and registration

We previously published the protocol.[34] We have adhered to the PRISMA checklist.[35] See File S1.

2.2 | Eligibility criteria

We included CGs, following the definition of the Institute of Medicine (IOM): "*statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*.".[33] We included CGs that included recommendations for vitamin D supplementation and/or screening of vitamin D. We included those targeted to the general adult population, defined as individuals who are healthy and have no pre-existing conditions or comorbidities. CGs for the general population that included thresholds or definitions of vitamin D deficiency were also included.

We excluded CGs for prevention of osteomalacia and rickets in children, those targeting specific conditions only (eg, chronic corticoid users) and CGs focused only on secondary prevention of osteoporotic fractures. We also excluded nutritional guidelines if they only formulated daily reference intakes and that did not provide specific advice on how to achieve the recommended nutrient intake.

2.3 | Search methods

We searched Medline (via PubMed), EMBASE and CINAHL from January 2010 to January 2020. We also searched the Guidelines International Network (G-I-N) and the guidelinecentral.com libraries. Search strategies are provided in File S2. We also searched the references of included CGs.

2.4 | Study selection and data extraction

Title and abstract, full-text screening and data extraction were performed independently by two reviewers. We resolved disagreements through discussion or with the help of a third reviewer.

2.5 | Data extraction

We extracted details on institution, region, year of publication, type of organisation, target population, purpose of supplementation, vitamin D status, recommendation of vitamin D supplementation, thresholds for deficiency or insufficiency, screening advice, monitoring, sun exposure, method to obtain vitamin D, vitamin D and calcium supplementation. We used the GRADE framework to classify recommendations into three categories. The first is "Recommends" (for unequivocal, strong recommendations, in favour of supplementation). The next is "Suggests", which is for weak or conditional recommendations (either for or against). Lastly, "Does not recommend", which is for guidelines which do not recommend in favour of supplementation or recommended against supplementation.[36]

We also collected information concerning authors' conflicts of interest (COI). We evaluated COI reporting process and the potential role of the source of funding.[37,38] We collected five dimensions of COI; transparency of the reporting process, reporting of authors' affiliations, financial and intellectual COI and the role of the source of funding of the CG. Transparency of the reporting process and role of the source of funding were classified as "clear", "unclear" or "not reported", depending on how explicit these were in the CG or accompanying documents. For analysis, "not reported," or "unclear" were combined into one category, as underreporting has been previously considered a potential source of COIs or bias.[39]

2.6 | Quality appraisal

We assessed the quality of the CGs using the AGREE II (Appraisal of Guidelines Research and Evaluation version 2) instrument.[40] AGREE II is a well-established tool to evaluate the methodological rigour and transparency through which a guideline is developed and has been used previously in systematic reviews of CGs.[41] After initial calibration, four reviewers evaluated all included CGs independently. We calculated the percentage of the maximum possible score for each domain, and its standardised range (from 0% to 100%). To ensure inter-rater reliability, we compared the item scores of each appraiser. We considered there to be a low discrepancy if there were less than 1.5 standard deviations (SD), using the McMaster's AGREE II concordance calculator.[42] If there was large discrepancy, it was resolved with the help of a fifth reviewer. The AGREE II tool does not set a threshold for defining the quality of a CG. However, we considered a CG to be acceptable if a threshold of 60% in the "Rigour of development" domain and at least two additional domains was achieved for, in line with previous AGREE II evaluations.[43-45]

2.7 | Analysis

We performed a descriptive analysis of the main characteristics of included CGs. For each AGREE II domain, we calculated the mean score after converting them to percentages (being 0% the minimum possible score for the domain and 100% the maximum one). We calculated the mean, median, percentile 25, percentile 75 and SD. We conducted a bivariate analysis to evaluate the potential association between vitamin D supplementation recommendations with the following factors: AGREE II scores, region, type of organisation, target population, suggested method to obtain Vitamin D, advice on sun exposure, advice on food and COI reporting. We also analysed how these factors were associated with the AGREE II scores. After initial analysis and given the asymmetry on the distribution of AGREE II

scores, we used non-parametric tests to explore associations (Mann-Whitney U and Kruskal-Wallis tests). After performing a bivariate analysis, the statistically significant variables ($P < .05$) were incorporated into a multivariate logistic regression model using a forward-stepwise method. Our dependent variable in the logistic regression model was vitamin D supplementation recommendation. We used IBM SPSS Statistics® version 27 for running the analysis.

3 | RESULTS

3.1 | Guidelines characteristics

The initial search yielded 561 references, 60 CGs were selected for full-text review and 34 guidelines[46-79] were included in the final analysis (Figure 1). These included 12 (35.3%) guidelines from Europe, 10 (29.4%) from North America, five (14.7%) from Asia, two (5.9%) from Oceania, two (5.9%) from South America and three (8.8%) from international organisations. The majority (23, 67.6%) of guidelines were developed by scientific societies, nine (26.5%) by governmental organisations and two (5.9%) from other types of organisations. Eighteen (52.9%) guidelines targeted elderly populations, 15 (44.1%) were the general population and one (2.9%) targeted women exclusively (Tables 1 and 2).

3.2 | Recommendations of Vitamin D supplements for general population

Almost half of the included CGs (15, 44.1%) recommended in favour of vitamin D supplementation, nine (26.5%) suggested supplementation, ten (29.4%) did not recommend or recommended against supplementation and none of the included CGs provided weak recommendations, "suggesting" against supplementation. Most CGs (33, 97.1%) targeted the elderly people, 22 (64.7%) targeted women, 18 (52.9%) targeted the general population and seven (20.6%) targeted children. Regarding vitamin D status for recommending supplementation, 13 CGs (38.3%) did not specify it, 11 (32.4%) recommended supplementation when risk factors and/or established deficiency were present and seven (20.6%) only recommended supplementation in those with established deficiency. CGs thresholds used to define vitamin D sufficiency and maintain adequate bone health, ranged from 25 to 125 nmol/L. In thirteen CGs (38.2%), values over 75 nmol/L were suggested, over 50 nmol/L in seven (20.6%), over 25-30 nmol/L in four (11.8%) and in ten (29.4%) the threshold was not specified. The daily dose suggested for supplementation ranged from 400 International Units (IU) to 2000 IU (SD 555, mode = 800 IU). There was no specific information in the documents analysed regarding the specific laboratory method used to calculate vitamin D deficiency. Thirteen CGs (38.2%) supplemented for general health, a further 12 (35.3%) for prevention

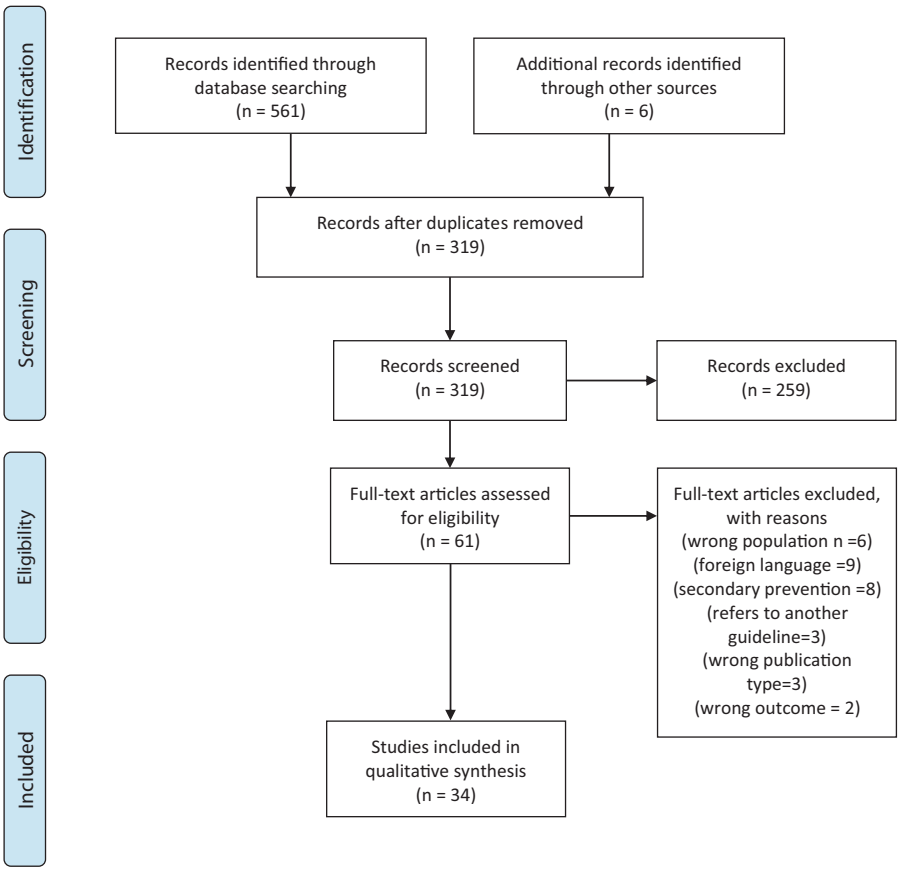


FIGURE 1 PRISMA 2009 flow diagram

TABLE 1 Characteristics of the included guidelines

Region	Frequency	%
International	3	8.8
Europe	12	35.3
North America	10	29.4
South America	2	5.9
Asia	5	14.7
Oceania	2	5.9
Type of organisation		
Scientific society	23	67.6
Government organisation	9	26.5
Other	2	5.9
Target population		
General population	15	44.1
Older population	18	52.9
Women	1	2.9
Vitamin D supplementation		
Does not recommend	10	29.4
Suggests	9	26.5
Recommends	15	44.1
Vitamin D status for recommendation		
Any	13	38.3
With risk factors and/or deficiency	11	32.4
Deficiency	7	20.6
Total	31	91.2
Non-Applicable	3	8.8
Vitamin D screening advice		
No	20	58.8
Yes, with risk factors	12	35.3
Yes	2	5.9
Favoured method for Vitamin D obtention		
No method favoured	5	14.7
Supplementation	24	70.6
Sun exposure	4	11.8
Fortification	1	2.9
Food advice		
No	22	64.7
Yes	11	32.3
Unclear	2	5.9
Sun exposure advice		
No	23	67.6
Yes	11	32.3

of falls or osteoporotic fractures and nine (26.5%) for preventing osteoporosis (Tables 1-3, Table S1).

Eleven CGs (32.3%) highlighted the importance of sun exposure to achieve vitamin D requirements, whereas 11 CGs (32.4%) advised on dietary sources. The preferred method to achieve adequate vitamin D levels was supplementation in most CGs (24, 70.6%) in four (11.8%) sun exposure was favoured and only in one (2.9%) fortification was suggested[79] (Tables 1 and 2). Five CGs (14.7%) did not provide a specific method to obtain vitamin D. Concurrent calcium intake advice was provided in 21 (61.8%) of the CGs. (Table 3).

3.3 | Recommendations for Vitamin D screening and monitoring

Most CGs recommended against screening for general population (20/34, 58.8%). Twelve (35.3%) CGs recommended vitamin D screening for individuals with risk factors for fractures or osteoporosis. Only two (5.9%) CGs recommended general screening for their target population. With respect to the monitoring of Vitamin D levels, it was recommended in eight (57.1%) of those recommending screening. (Tables 1 and 2).

3.4 | Quality appraisal

In the domains of AGREE II evaluated (Figure 2A, Table S2), the mean score was 59.4% (SD 18.3%) for "scope and purpose", 39.4% (SD 21.1%) for "stakeholder involvement", 32.3% (SD 20.2%) for "rigour of development", 59.3% (SD 18.2%) for "clarity and presentation", 27.4% (SD 18.7%) for "applicability", 42.5% (SD 23.5%) for "editorial independence" and 44.5% (SD 17.5%) for the "overall rating". As part of the AGREE II appraisal, the reviewers recommended four of the guidelines analysed (11.8%),[57,63,66,80] 12 (35.3%)[47-51,55,59-61,71,75,76] were recommended with modifications, and 18 (52.9%)[46,52-54,56,58,62,64,67-70,72-74,77-79] were not recommended for use. Only three guidelines (8.8%) scored over 60% in "Rigour of development domain" and are considered high quality. See Table S1 for the detailed AGREE II scores.

4 | CONFLICTS OF INTEREST REPORTING

Reporting of the COI management process was unclear in 18 CGs (52.9%), in ten (29.4%) it was not reported and in six (17.6%) guidelines, the process was clear. Twelve (35.3%) reported panellists' affiliations, whereas 22 (64.7%) did not. Sixteen (47.1%) reported financial ties, nine (26.5%) did not report them clearly and nine (26.5%) did not report them at all. Intellectual COIs were reported in five (14.7%), with 29 (85.3%) not providing any information. The role of the source of funding was not reported in just over half of the CGs (18/34; 52.9%), in nine (26.5%) it was unclear and only in seven (20.6%), it was considered clear. (Table 4).

4.1 | Associations between supplementation recommendations and predictors

Guidelines that did not recommend vitamin D supplementation (compared with those that suggested or recommended it) scored significantly

TABLE 2 Guideline characteristics

Guideline name	Institution	Region	Year
Vitamin D for Prevention of Falls and their Consequences in Older Adults	American Geriatrics Society	North America	2014
Building healthy bones throughout life an evidence-informed strategy to prevent osteoporosis in Australia	Australia and New Zealand bone and mineral society & osteoporosis Australia	Oceania	2013
Osteoporosis: diagnosis, treatment and fracture prevention	British Columbia Medical Association	North America	2011
Taiwan osteoporosis practice guidelines	Bureau of Health Promotion Taiwan	Asia	2011
Dutch dietary guidelines 2015/Evaluation of dietary reference values for vitamin D	Health Council of the Netherlands	Europe	2015
Evaluation, treatment, and prevention of Vitamin D deficiency: An Endocrine Society Clinical Practice Guideline	Endocrine Society	North America	2011
Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations	European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO)	Europe	2013
IOF position statement: vitamin D recommendations for older adults	International Osteoporosis Foundation	International	2013
Osteoporosis screening, diagnosis, and treatment guideline	Kaiser Permanente	North America	2019
Evidence-based guidelines for fall prevention in Korea	Korean Association of Internal Medicine	Asia	2017
Calcium and Vitamin D Supplementations: 2015 Position Statement of the Korean Society for Bone and Mineral Research	Korean Bone Society	Asia	2015
Assessment and prevention of falls in older people	National Institute for Health and Care Excellence (NICE)	Europe	2013
Clinician's guide to prevention and treatment of osteoporosis	National Osteoporosis Foundation	North America	2016
Osteoporosis clinical guideline for prevention and treatment executive summary	National Osteoporosis Guideline Group	Europe	2016
Nordic nutrition recommendations 2012: integrating nutrition and physical activity	Nordic nutrition recommendations	Europe	2012
Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada	Osteoporosis Canada	North America	2010
Preventive activities in women PAPPS (preventive and promotional ACTIVITIES PROGRAM health)	Spanish Society of Family Medicine (SEMFyC)	Europe	2018
Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men and treatment of osteoporosis in postmenopausal women and older men	Royal Australian College of General Practitioners	Oceania	2010
Clinical practice guidelines for vitamin D in the United Arab Emirates	United Arab Emirates[a]	Asia	2016
Vitamin D and calcium supplementation to prevent fractures in adults: US Preventive Services Task Force recommendation statement	United States Preventive Services Task Force	North America	2018
Vitamin D supplementation in pregnant women	World Health Organisation	International	2012

Type of organisation	Target population	Purpose of supplementation	Vitamin D status for Supplementation	25-OH-D threshold for deficiency or insufficiency[a]
Scientific Society	Population older than 65	Prevention of falls and fractures	Not specified	75 nmol/L
Scientific Society	General population with risk factors of deficiency	Overall Health	N/A	50 to 75 nmol/L
Governmental Organisation	General population	Prevention of osteoporosis	Not specified	30 to 50 nmol/L
Governmental Organisation	General population with risk factors of deficiency	Prevention of osteoporosis	With risk factors or deficiency	75 nmol/L
Governmental Organisation	General population with risk factors of deficiency	Prevention of fractures	With risk factors or deficiency	30 to 50 nmol/L
Scientific Society	General population with risk factors of deficiency	Prevention of falls and fractures	With risk factors or deficiency	50 nmol/L
Scientific Society	Population older than 50	Prevention of osteoporosis	Not specified	75 nmol/L
Scientific Society	Population older than 60	Prevention of falls and fractures	Deficiency / Insufficiency	75 nmol/L
Other	Population older than 50 and women	Prevention of osteoporosis	Cloudy months	Not specified
Scientific Society	Older population	Prevention of falls and fractures	With risk factors or deficiency	Not specified
Scientific Society	Population older than 50	Prevention of fractures	Not specified	75 nmol/L
Governmental Organisation	Population older than 65	Prevention of fractures	N/A	Not specified
Scientific Society	Recommendations apply to postmenopausal women and men aged 50 and older.	Prevention of osteoporosis	Not specified	75 nmol/L
Scientific Society	Older population	Prevention of osteoporosis	N/A	Not specified
Governmental Organisation	General population	Overall Health	Not specified	50 nmol/L
Scientific Society	General population	Prevention of osteoporosis	Not specified	75 nmol/L
Scientific Society	Women older than 65	Prevention of osteoporosis	Deficiency	Not specified
Scientific Society	Postmenopausal women and older men	Prevention of osteoporosis	Deficiency	60 nmol/L
Governmental Organisation	General population	Overall Health	Not specified	30 to 50 nmol/L
Governmental Organisation	Population older than 65	Prevention of falls and fractures	Deficiency	Not specified
Governmental Organisation	Pregnant women	maternal and infant health outcomes	Deficiency	50 to 75 nmol/L

(Continues)

Guideline name	Institution	Region	Year
Vitamin D recommendations in general population *(Recomendaciones de vitamina D para la población general)*	Spanish Society of Endocrinology and Nutrition (SEEN)	International	2017
Nutritional guidelines for older people in Finland	Finnish National Nutrition Council	Europe	2014
Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice.	Vitamin D Summit Meeting	Europe	2010
2012 Guidelines for diagnosis, prevention and treatment of osteoporosis	Argentinian society of osteoporosis and Argentinian society of osteology and mineral metabolism. Sociedad Argentina de Osteoporosis y la Asociación Argentina de Osteología y Metabolismo Mineral	South America	2013
Polish guidelines for the diagnosis and management of osteoporosis: a review of 2013 update	Polish Associations of Orthopaedics and Traumatology, Rehabilitation, Gerontology, Rheumatology, Family Medicine, Diabetology, Laboratory Diagnostics, Andropause and Menopause, Endocrinology, Radiology, and the STENKO group	Europe	2014
Preventing falls in older persons	American Association of Family Physicians	North America	2017
Recommendations of the Brazilian Society of Endocrinology and Metabology (SBEM) for the diagnosis and treatment of hypovitaminosis D	Brazilian Society of Endocrinology and Metabology (SBEM)	South America	2014
The use of vitamins and minerals in skeletal health: American Association of clinical endocrinologists and the american college of endocrinology (AACE/ACE) position statement	American association of clinical endocrinologists and the American college of endocrinology (aace/ace)	North America	2018
The Asia-Pacific clinical practice guidelines for the management of frailty	Society for Post-Acute and Long-Term Care Medicine	Asia	2017
Prevention of fall-related injuries in the elderly: An eastern association for the surgery of trauma practice management guideline	Eastern Association for the Surgery of Trauma Injury Control and Violence Prevention	North America	2016
Position statement: clinical management of vitamin D deficiency in adults	Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE)	Europe	2018
Vitamin D and bone health: a practical clinical guideline for patient management	Royal Osteoporosis Society (ROS), previously National Osteoporosis Society (NOS)	Europe	2020
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 Calcified Tissue Society	Europe	2019

[a]As defined by guideline authors as either target status to maintain adequate general or bone health, threshold for starting supplementation, or to define deficiency or insufficiency.

higher in the "overall score" (median 57 vs 39 ($P = .02$), and in "editorial independence" median 62.9. vs 34.5 ($P = .001$)) domains of the AGREE-II tool (Figure 2B). We did not find significant differences (post-hoc analysis) between the "suggest" and "recommend" categories in both domains.

4.1.1 | Types of organisation

Regarding the type of organisation, governmental sponsored guidelines scored significantly higher than scientific societies and other organisations in three domains ("scope and purpose", $P = .038$; "stakeholder involvement" $P = .039$ and "rigour of development" $P = .015$) and the overall score ($P = .009$).

4.1.2 | Role of funding source and Conflicts of Interest reporting

When comparing the role of the source of funding, guidelines that reported this aspect scored significantly higher in "Overall score"

Type of organisation	Target population	Purpose of supplementation	Vitamin D status for Supplementation	25-OH-D threshold for deficiency or insufficiency[a]
Scientific Society	General population	bone and non-skeletal health outcomes	With risk factors or deficiency	75 to 125 nmol/L
Governmental Organisation	Population older than 65	Overall Health	Not specified	Not specified
Other	General population	musculoskeletal health, cardiovascular disease, autoimmunity and cancer	With risk factors or deficiency	75 to 100 nmol/L
Scientific Society	Population older than 65	Prevention of fractures	insufficiency	75 nmol/L
Scientific Society	General population	Prevention of osteoporosis	Not specified	75 nmol/L
Scientific Society	Older population	preventing falls in older people	Not specified	Not specified
Scientific Society	General population	treatment of deficiency	High risk for deficiency	75 nmol/L
Scientific Society	General population	Skeletal Health	Deficiency	50 nmol/L
Scientific Society	Older Population	Frailty prevention	Deficiency	Not specified
Scientific Society	Population older than 65	prevention of falls	Not specified	Not specified
Scientific Society	General Population	treatment of deficiency	Deficiency or with risk factors	75 nmol/L
Scientific Society	Population older than 65	Overall Health	At risk for deficiency or insufficient sun	25 to 50 nmol/L
Scientific Society	General Population	Overall Health	At risk for deficiency	Not specified

(P = .032). Guidelines that reported intellectual COI scored significantly higher in "Rigour of development" (P = .011), "Clarity and presentation" (P = .02), "Editorial independence" (P = .002) domains and overall score (P = .031). Guidelines that did not report financial COI scored significantly lower in the "Editorial independence" domain (P = .001). Guidelines in which the role of the funding source was unclear or not reported were also associated with recommending or suggesting supplementation (P = .034). Associations between COI reporting and Editorial Independence would be expected given that these measurements overlap between the AGREE-II and the additional COI evaluation we performed.

4.1.3 | Other analysis

In the forward stepwise logistic regression model, "Editorial independence" remained an independent predictor for recommending vitamin D supplementation (Odds Ratio: 1.091; CI 95%, 1.02-1.16; P = .006); the lower the score, the more likely supplementation was

TABLE 3 Vitamin D and related recommendations in guidelines

Guideline name	Vitamin D supplementation	Vitamin D screening advice	Vitamin D monitoring advice	Food advice	Sun exposure advice	Favoured method for obtention	Suggested vitamin D dose (ui)	Calcium advice
Vitamin D for prevention of falls and their consequences in older adults	Recommends	No	No	Yes	Yes	Supplementation	1000	No
Building healthy bones throughout life an evidence-informed strategy to prevent osteoporosis in australia	Does not recommend	With risk factors	No	No	Yes	Sun exposure N/A		Yes
Osteoporosis: diagnosis, treatment, and fracture prevention	Recommends	No	No	Yes	No	Supplementation	Different doses	No
Taiwan osteoporosis practice guidelines	Recommends	Yes	Yes	No	No	Supplementation	800-1000	Yes
Dutch dietary guidelines 2015/evaluation of dietary reference values for vitamin D	Suggests	No	No	Yes	Yes	No method favoured	400-800	Yes
Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline	Suggests	With risk factors	Not reported	Yes	No	Supplementation	2000-6000	No
Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations	Recommends	With risk factors	Not reported	Unclear	No	Supplementation	800-1000	Yes
IOF position statement: vitamin D recommendations for older adults	Recommends	With risk factors	Yes	Not clear	No	No method favoured	2000	Yes
Osteoporosis/fracture prevention national guideline summary	Suggests	No	No	yes	No	Supplementation	1000-2000	Yes
Evidence-based guidelines for fall prevention in Korea	Suggests	No	No	No	No	Supplementation	Not reported	Yes
Calcium and vitamin D supplementations: 2015 position statement of the Korean Society for Bone and Mineral Research	Recommends	No	Yes	No	No	Supplementation	800	Yes
Falls: assessment and prevention of falls in older people	Does not recommend	No	No	No	No	Supplements	N/A	Yes
Clinician's guide to prevention and treatment of osteoporosis	Suggests	With risk factors	Yes	Yes	No	Supplementation	800 to 1000	No
Osteoporosis clinical guideline for prevention and treatment executive summary	Does not Recommend	No	Not reported	No	No	Supplementation N/A		Yes
Nordic nutrition recommendations 2012: integrating nutrition and physical activity	Recommends	No	Not reported	yes	Yes	Supplementation	800	Yes

(Continues)

TABLE 3 (Continued)

Guideline name	Vitamin D supplementation	Vitamin D screening advice	Vitamin D monitoring advice	Food advice	Sun exposure advice	Favoured method for obtention	Suggested vitamin D dose (ui)	Calcium advice
Vitamin D in adult health and disease: a review and guideline statement from osteoporosis canada	Recommends	With risk factors	Not reported	yes	Yes	Supplementation	Different doses	Yes
Preventive activities in women PAPPS (preventive and promotional activities program health)	Does not recommend	No	Not reported	yes	Yes	Sun exposure/diet	800	Yes
Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men and treatment of osteoporosis in postmenopausal women and older men	Does not recommend	No	No	no	Yes	Sun exposure	800	Yes
Clinical practice guidelines for vitamin D in the United Arab Emirates	Recommends	With risk factors	yes	no	No	Supplementation	400 - 2000	No
Vitamin D and calcium supplementation to prevent fractures in adults: U.S. preventive services task force recommendation statement	Recommends against	No	No	No	No	Supplementation	N/A	Yes
Vitamin D supplementation in pregnant women	Recommends against	No	No	No	No	No method favoured	200	No
Vitamin D recommendations in general population *(recomendaciones de vitamina d para la población general)*	Suggests	With risk factors	yes	No	No	Supplementation	600-1000	No
Nutritional guidelines for older people in finland	Recommends	No	No	No	NO	Supplementation	800	No
Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice.	Recommends	Yes	yes	No	No	Supplementation	800	No
2012 guidelines for diagnosis, prevention and treatment of osteoporosis	Suggests	No	yes	No	Yes	Sun exposure	800 –2000	Yes
Polish guidelines for the diagnosis and management of osteoporosis: a review of 2013 update	Recommends	No	yes	No	No	Supplementation	800 –2000	Yes
Preventing falls in older persons	Recommends	No	No	No	No	Supplementation	>800	Yes

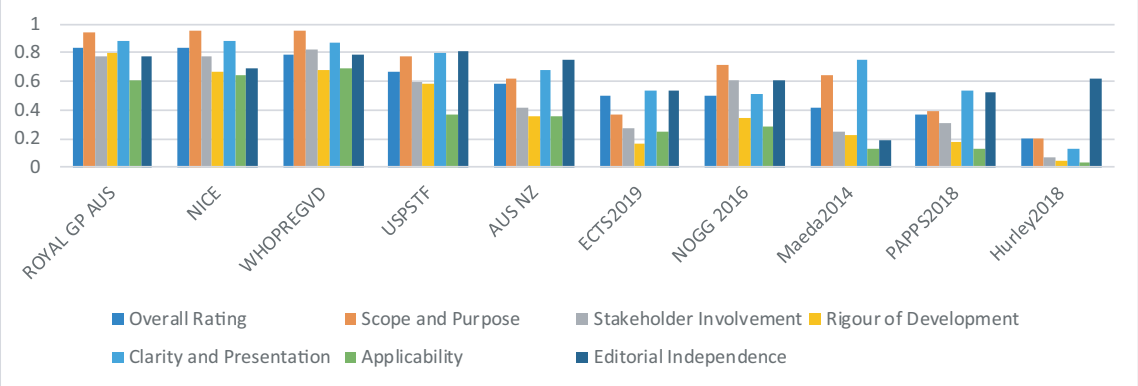
(Continues)

TABLE 3 (Continued)

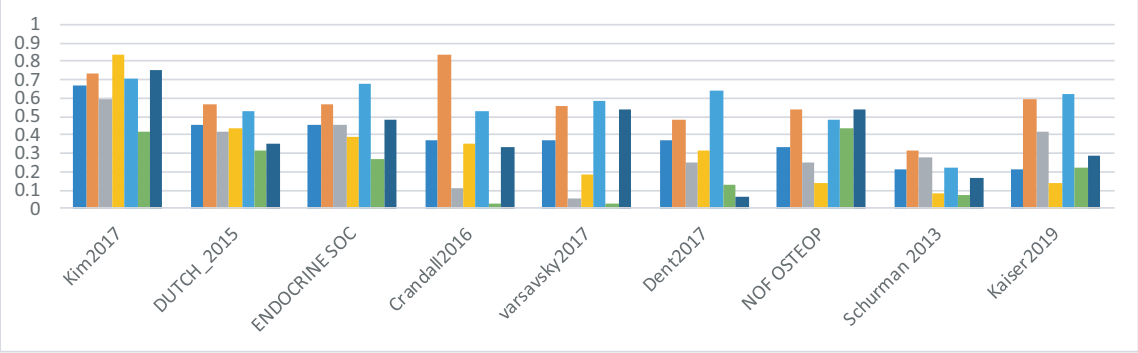
Guideline name	Vitamin D supplementation	Vitamin D screening advice	Vitamin D monitoring advice	Food advice	Sun exposure advice	Favoured method for obtention	Suggested vitamin D dose (ui)	Calcium advice
Recommendations of the brazilian society of endocrinology and metabology (SBEM) for the diagnosis and treatment of hypovitaminosis D	Does not recommend	No	yes	Yes	Yes	No method favoured	1000-2000	No
The use of vitamins and minerals in skeletal health: American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) position statement	Does not recommend	With risk factors	No	No	No	No method favoured	1000	Yes
The Asia-Pacific clinical practice guidelines for the management of frailty	Suggests	No	No	No	Yes	Supplementation	800-1000	No
Prevention of fall-related injuries in the elderly: an eastern association for the surgery of trauma practice management guideline	Suggests	No	no	No	No	Supplementation	400-800	Yes
Position statement: clinical management of vitamin D deficiency in adults	Recommends	With risk factors	No	No	Yes	Supplementation	2000	No
Vitamin D and bone health: a practical clinical guideline for patient management	Recommends	With risk factors	Yes	No	No	Supplementation	400	Yes
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	Does not recommend	With risk factors	No	Yes	No	Fortification	400-800	No

(A)

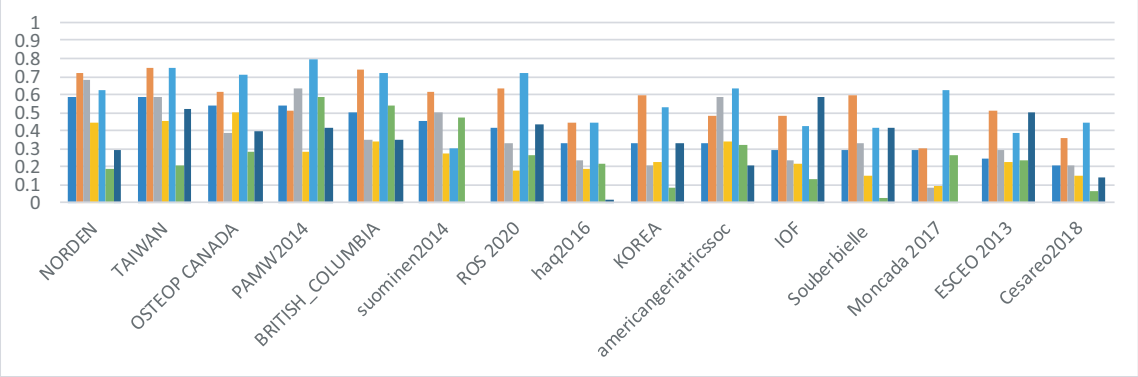
Does not recommend



Suggests



Recommends



(B)

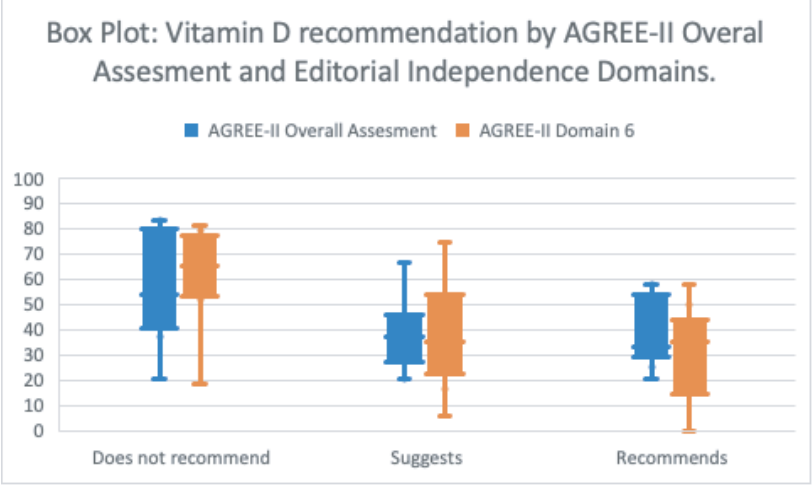


FIGURE 2 A, AGREE II mean domain scores by type of Vitamin D supplementation recommendation. B, Vitamin D recommendation by AGREE-II overall assesment and editorial independence domains

recommended. The rest of the predictors explored (AGREE Overall score, COI reporting process, Intellectual COI reporting, Funding source reporting and Screening for Vitamin D) were not included in the final model. No differences were observed when comparing CGs with a higher deficiency threshold vs low threshold with respect to supplementation recommendations.

5 | DISCUSSION

5.1 | Main findings

Our systematic review shows that, with only a few exceptions, CGs were rated as low quality. Those with lower quality scores, unclear COI reporting and management processes, or where the role of the funding source was unclear or not reported, were more likely to recommend or suggest vitamin D supplementation. Governmental guidelines also scored significantly higher compared with those produced by Scientific Societies. There was also substantial variability in the recommendations for the general population, with the majority of organisations recommending in favour but some recommending against. Most of the guidelines recommended against screening for vitamin D deficiency. We also collected calcium advice and recommendations when they were provided. However, calcium advice was unspecific, which precluded an analysis of calcium recommendations with an adequate level of detail.

5.2 | Our results in the context of previous research

The results of our review are in line with previous AGREE II evaluations in which low scores were reported for nutritional guidelines[41,81] as well as for other topics.[82-87] Previous studies detected methodological flaws when appraising evidence to formulate recommendations in nutritional guidelines.[81] Our evaluation also shows that renowned osteoporosis organisations do not fulfil basic criteria in the guideline development process, such as rating the quality of the evidence or grading the strength of the recommendations in the guideline development process. Furthermore, they made no distinction between populations with very different baseline risks.

Our results are in agreement with previously reported ties between industry, advocacy and academia in this field.[32,88] However, we provide empirical evidence that COI are associated with more interventionist recommendations. In a systematic review on COI in CGs, the authors could not identify studies informing the link between COI and recommendations.[89]

Vitamin D supplementation or dietary fortification may be justified in northern latitudes, especially in higher risk subpopulations, such as dark-skinned individuals, people who do not spend enough time outdoors and women who fully cover themselves for religious or cultural reasons.[31] Most guidelines that we identified acknowledge these issues but do not make specific recommendations for these subgroups. Certain countries have opted for fortification of dietary products with vitamin D[60]; however, only one of the included guidelines suggested fortification of dietary products over other methods of vitamin D obtention.[79]

In 2011, the IOM published a landmark report that aimed to establish dietary reference intakes for vitamin D.[31] To date, it is still considered the most comprehensive and extensive study on vitamin D effects. This review recognised the low quality of available evidence about vitamin D supplementation, favouring supplementation only in specific situations where there is inadequate sun exposure.[31] Paradoxically, this report is cited in most of the guidelines evaluated to support strong recommendations in favour of supplementation. GRADE details some exceptional situations in which a strong recommendation may be warranted in the face of low-quality evidence.[36] However, none of these situations applies here. Finally, the IOM report acknowledged that the thresholds proposed by some organisations are exacerbated by an "epidemic of deficiency that does not correlate with epidemiological data".[31] In addition to the IOM, the European Food Safety Authority (EFSA) and the UK Scientific Advisory Committee on Nutrition (SACN) produced as well updated reports on vitamin D.[90,91] Although the EFSA takes a stance similar to the IOM, the SACN recommends that the government gives consideration to strategies for the UK population to achieve the RNI of 10 μg/d (400 IU/).[91]

Recommendations for vitamin D supplementation in wide population groups were based primarily on the use of surrogate markers, such as bone mineral density or serum levels of 25-OH-D.[92] This is particularly problematic given that the correlation between intake, desirable serum levels and preventive effects remains unclear.[31] Despite a potential benefit of supplementation of vitamin D and calcium in specific subgroups, such as institutionalised older women,[13] extrapolating this supplementation to the general population is inappropriate. Additional concerns have been raised regarding how representative of the overall population are the participants included in vitamin D trials.[93] Although calcium has not been the focus of our review, the absence of clear calcium recommendations is also worrying, given the fact that there is a lack of benefit in bone health outcomes when vitamin D is supplemented alone without calcium.[94] Finally, there are economic implications for wide-spread testing[95] and supplementation, including the risk for over-medicalisation. For instance, in our local context of the Madrid region (Spain), there was an increase of 1154% (from € 535,807 to € 6,719,710) in the prescription of vitamin D, and a 2456% increase in the laboratory testing of 25-OH-D blood levels, in the period of 2009-2018.[96] However, during the same period, the incidence of hip fracture has not varied.[96]

TABLE 4 Conflicts of interest reporting in guidelines

Guideline name	Institution	COI process reporting	COI affiliation reporting	COI financial reporting	COI intelectual reporting	ROLE of funding source reporting
Vitamin D for prevention of falls and their consequences in older adults	American Geriatrics Society	Unclear	Clear	Clear	Unclear	Unclear
Building healthy bones throughout life an evidence-informed strategy to prevent osteoporosis in Australia	Australia and New Zealand Bone and Mineral Society & Osteoporosis Australia	Clear	Unclear	Clear	Unclear	Unclear
Osteoporosis: diagnosis, treatment, and fracture prevention	British Columbia Medical Association	Not reported	Unclear	Unclear	Unclear	Not reported
Taiwan osteoporosis practice guidelines	Bureau of Health Promotion Taiwan	Unclear	Unclear	Clear	Unclear	Unclear
Dutch dietary guidelines 2015/evaluation of dietary reference values for vitamin D	Health Council of the Netherlands	Not reported	Not reported	Not reported	Not reported	Not reported
Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline	Endocrine Society	Unclear	Clear	Clear	Clear	Not reported
Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations	European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (esceo)	Unclear	Clear	Clear	Unclear	Unclear
IOF position statement: vitamin D recommendations for older adults	International Osteoporosis Foundation	Unclear	Unclear	Unclear	Unclear	Not reported
Osteoporosis/fracture prevention national guideline summary	Kaiser Permanente	Not reported	Not reported	Not reported	Not reported	Not reported
Evidence-based guidelines for fall prevention in Korea	Korean Association of Internal Medicine	Unclear	Unclear	Unclear	Unclear	Not reported
Calcium and vitamin D supplementations: 2015 position statement of the korean society for bone and mineral research	Korean Bone Society	Unclear	Unclear	Unclear	Unclear	Not reported
Falls: assessment and prevention of falls in older people	National Institute for Health and Care Excellence (NICE)	Unclear	Unclear	Unclear	Unclear	Clear
Clinician's guide to prevention and treatment of osteoporosis	National Osteoporosis Foundation	Unclear	Clear	Clear	Unclear	Unclear
Osteoporosis clinical guideline for prevention and treatment executive summary	National Osteoporosis Guideline Group	Not reported	Unclear	Unclear	Unclear	Clear
Nordic nutrition recommendations 2012: integrating nutrition and physical activity	Nordic Nutrition Recommendations	Not reported	Not reported	Not reported	Not reported	Not reported
Vitamin D in adult health and disease: a review and guideline statement from osteoporosis Canada	Osteoporosis Canada	Clear	Clear	Clear	Clear	Unclear

(Continues)

TABLE 4 (Continued)

Guideline name	Institution	COI process reporting	COI affiliation reporting	COI financial reporting	COI intelectual reporting	ROLE of funding source reporting
Preventive activities in women papps (preventive and promotional activities program health)	Spanish Society of Family Medicine (SEMFYC)	Unclear	Unclear	Unclear	Unclear	Not reported
Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men and treatment of osteoporosis in postmenopausal women and older men	Royal Australian College of General Practitioners	Clear	Clear	Clear	Clear	Clear
Clinical practice guidelines for vitamin D in the United Arab Emirates	United Arab Emirates[a]	Not reported	Not reported	Not reported	Not reported	Not reported
Vitamin d and calcium supplementation to prevent fractures in adults: U.S. preventive services task force recommendation statement	United States Preventive Services Task Force	Unclear	Clear	Clear	Clear	Clear
Vitamin D supplementation in pregnant women	World Health Organisation	Unclear	Clear	Clear	Clear	Unclear
Vitamin D recommendations in general population *(recomendaciones de vitamina d para la población general)*	Spanish Society of Endocrinology and Nutrition (SEEN)	Clear	Unclear	Unclear	Unclear	Clear
Nutritional guidelines for older people in finland	Finnish National Nutrition Council	Not reported	Not reported	Not reported	Not reported	Not reported
vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice.	Vitamin D Summit Meeting	Unclear	Unclear	Clear	Unclear	Unclear
2012 guidelines for diagnosis, prevention and treatment of osteporosis	Argentinian Society Of Osteoporosis and Argentinian Society of Osteology and Mineral Metabolism. Sociedad Argentina de Osteoporosis y la Asociación Argentina de Osteología y Metabolismo Mineral	Unclear	Clear	Clear	Unclear	Not reported
Polish guidelines for the diagnosis and management of osteoporosis: a review of 2013 update	Polish Associations of Orthopedics and Traumatology, Rehabilitation, Gerontology, Rheumatology, Family Medicine, Diabetology, Laboratory Diagnostics, Andropause and Menopause, Endocrinology, Radiology, and the Stenko Group	Unclear	Unclear	Unclear	Unclear	Unclear
Preventing falls in older persons	American Association of Family Physicians	Unclear	Unclear	Clear	Unclear	Not reported

(Continues)

TABLE 4 (Continued)

Guideline name	Institution	COI process reporting	COI affiliation reporting	COI financial reporting	COI intelectual reporting	ROLE of funding source reporting
Recommendations of the brazilian society of endocrinology and metabology (sbem) for the diagnosis and treatment of hypovitaminosis d	Brazilian Society of Endocrinology and Metabology (SBEM)	Unclear	Clear	Clear	Unclear	Not reported
The use of vitamins and minerals in skeletal health: american association of clinical endocrinologists and the american college of endocrinology (AACE/ACE) position statement	American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE)	Clear	Clear	Clear	Unclear	Not reported
The Asia-Pacific clinical practice guidelines for the management of frailty	Society for Post-Acute and Long-Term Care Medicine	Not reported	Not reported	Not reported	Not reported	Not reported
Prevention of fall-related injuries in the elderly: an eastern association for the surgery of trauma practice management guideline	Eastern Association for the Surgery of Trauma Injury Control and Violence Prevention	Not reported	Not reported	Not reported	Not reported	Not reported
Position statement: clinical management of vitamin D deficiency in adults	Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE)	Unclear	Not reported	Not reported	Not reported	Not reported
Vitamin D and bone health: a practical clinical guideline for patient management	Royal Osteoporosis Society (ROS), Previously National Osteoporosis Society (NOS)	Not reported	Not reported	Not reported	Not reported	Clear
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 Calcified tissue Society	Clear	Yes	Yes	Not reported	Clear

[a]Referred as a guideline for the country in the paper, but no specific institution mentioned.

5.3 | Limitations and strengths

We performed a search in three relevant medical databases and the G-I-N database; however, since the closure of guidelines.gov, there is no specific source that systematically compiles guidelines. To minimise this limitation, some of the guidelines analysed were retrieved after snowballing. We have only included guidelines published in English or Spanish. However, we captured guidelines from all continents and not only from Spanish or English-speaking countries. We only excluded a small number of guidelines not published in these languages, and it is unlikely that these guidelines would be inconsistent with our results.

This review had several strengths. To our knowledge, it is the first systematic assessment of vitamin D recommendations in published CGs. We also explored for the first time the effect of COI reporting on vitamin D recommendations. We performed our analysis using rigorous and transparent methods. Evaluation of several pre-specified factors with more interventionist recommendations provides relevant information for stakeholders.

5.4 | Implications for practice and research

Vitamin D is one of the most widely studied topics in medicine. However, its use in the general population remains controversial, and this is reflected in the variability of recommendations. We encourage end-users to remain cautious of vitamin D recommendations, especially those developed with unclear methods reporting, or management of COI, or those recommending wide general population screening or supplementation. Guideline developers should adhere to rigorous methods, including the reporting and management of COI. Finally, we urge scientific societies and government organisations to adopt a cautionary approach when recommending preventive or screening interventions aimed at the general population.

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CONFLICT OF INTERESTS

RZC has received a grant been hired by the Health Research Institute of the Balearic Islands (IdISBa) thanks to the joint financing of four enteral nutrition companies (Nestlé, Abbot, Fresenius and Nutricia) between September 2018 and July 2019. Also, she received a travel payment to attend a day long course by Nutricia on 2019. ALG and PAC are authors of one of the guidelines analysed in this review.[62] To maintain objectivity in the data extraction and quality appraisal process, they did not participate on this part of the study or in any other that implied analysing the guideline they authored. They do not declare any financial conflict of interest regarding this subject. The rest of the authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

We confirm that all listed authors met ICMJE authorship criteria and that nobody who qualifies for authorship has been excluded. **(DFN) David Fraile Navarro:** Conceptualisation, Investigation, Data curation, Formal analysis, Methodology, Project administration, writing original draft, writing review and editing. **(ALG) Alberto López-García-Franco**: Conceptualisation, Methodology, writing review and editing. **(ENG) Ena Niño de Guzmán:** Conceptualisation, Investigation, writing review and editing. **(MR) Montserrat Rabassa:** Methodology, Investigation, writing review and editing. **(RZC) Rocio Zamanillo Campos:** Conceptualisation, Investigation, writing review and editing. **(HPH) Héctor Pardo-Hernandez:** Investigation, writing review and editing. **(IRC) Ignacio Ricci-Cabello:** Investigation, writing review and editing. **(CCA) Carlos Canelo-Aybar:** Investigation, writing review and editing. **(JFME) Jose Francisco Meneses-Echavez:** Investigation, writing review and editing. **(JJYN) Juan Jose Yepes-Nuñez:** Investigation, writing review and editing. **(JK) Jesse Kuindersma:** Investigation, writing review and editing. **(IGS) Ignasi Gich-Saladich:** Formal analysis, writing review and editing (equal). **(PAC) Pablo Alonso-Coello:** Supervision, Methodology, Conceptualisation, writing review and editing.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article (and its supplementary information files).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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