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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Vitamin D Supplementation for the Prevention of Falls and Fractures in Residents of Long-Term Care Facilities: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	April 30, 2019
Report Length:	26 Pages

CADTH

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Cite As: Vitamin D Supplementation for the Prevention of Falls and Fractures in Residents of Long-Term Care Facilities: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa: CADTH; 2019 Apr. (CADTH rapid response report: summary with critical appraisal).

Acknowledgments:

ISSN: 1922-8147 (online)

Abbreviations

AEs	Adverse events
AIMSS	Australian Institute for Musculoskeletal Science
AGREE	Appraisal of Guidelines for Research & Evaluation
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AGS	American Geriatrics Society
AU$	Australian dollars
CI	Confidence interval
ED	Emergency department
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IRR	Incidence rate ratio
IU	International unit
JBI	Joanna Briggs Institute
MA	Meta-analysis
NHMRC	National Health and Medical Research Council
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALYs	Quality-adjusted life-years
RCT	Randomized controlled trial
RaR	Rate ratio
RR	Risk ratio
SACOC	Scientific Advisory Council of Osteoporosis Canada
SR	Systematic review

Context and Policy Issues

Falls among the elderly are major source of fatal and non-fatal injury that results in loss of quality of life and increase in financial burden to individuals, family and society.1 Compared to those dwelling in the community, older people living in residential care, also known as long-term care, nursing homes, or complex care, tend to have more complex health problems and therefore fall more frequently.1,2 Among Canadians, aged 65 years or older, approximately 50% of long-term care residents and 30% of community dwellers fall each year.2,3 Many risk factors for falls and fall prevention among the elderly have been studied including frailty, impaired sensorium, multi-morbidity, polypharmacy, house hazards, and vitamin D deficiency.4-6

In Canada, over 90% of long-term care residents had inadequate micronutrient intakes for vitamin D, E, K, magnesium and potassium, and more than 50% consumed amounts of folate, vitamin B6, calcium and zinc that were below the Estimated Average Requirement or Adequate Intake.7 Among micronutrients, only Vitamin D supplements were effective in improving this inadequacy.7

Vitamin D and calcium plays an important role in maintaining musculoskeletal health in older people.8 It can be endogenously synthesized by the skin from exposure to sunlight or it can be acquired exogenously from foods or supplements.8 With the same amount of sunlight exposure, the capacity to synthesize vitamin D in older adults aged 65 years or over has been estimated to be about 25% of that in younger adults aged 20 to 30 years.8 Calcium intestinal absorption is vitamin D-dependent, and thus decreases with age due to reduced vitamin D production.8 Deficiency of vitamin D and calcium is associated with risk of developing osteomalacia, osteoporosis, and muscle weakness, leading to increase chance of falls and fall-related fractures in older adults.8

Studies on vitamin D supplementation in the prevention of falls and fall-related fractures in older adults have yielded mixed results. A recent review of meta-analyses of randomized controlled trials investigating the impact of various interventions including vitamin D supplementation on falls in older adults living in long-term care facilities and hospitals by Stubbs et al., 20159 found that only one of six pooled analyses reported a significantly reduced rate of falls. The authors concluded that the evidence did not support vitamin D supplementation to reduce falls in long-term care residents. However, some meta-analyses cited in the review by Stubbs et al., 20159 had included trials conducted in community settings or trials with mixed populations of community dwellers and long-term care residents.10 Indeed, vitamin D plus calcium supplementation has been shown to reduce fall-related hip fractures in institutionalized older adults, but not in non-institutionalized older adults.11,12 Thus, it appears that some differences may exist between care facility settings and community settings regarding the impact of vitamin D supplementation in prevention of falls and fall-related injury.

The aim of this report is to review the clinical effectiveness, cost-effectiveness, and evidence-based guidelines on the use of vitamin D supplementation for the prevention of falls and fractures in residents of long-term care facilities.

Research Questions

1. What is the clinical effectiveness of vitamin D supplementation for the prevention of falls and fractures in elderly patients residing in long-term care facilities?

2. What is the cost-effectiveness of vitamin D supplementation for the prevention of falls and fractures in elderly patients residing in long-term care facilities?
3. What are the evidence-based guidelines regarding vitamin D supplementation for the prevention of falls and fractures in elderly patients residing in long-term care facilities?

Key Findings

Moderate quality evidence suggested that vitamin D supplementation may reduce the rate of falls (i.e., number of falls), but not the risk of falling (i.e., number of individuals who fall) in older adults residing in long-term care facilities. Economic evaluations revealed that vitamin D supplementation dominates “no intervention” (i.e., less costly and more effective than “no intervention”) in preventing falls and fall-related injuries. Vitamin D supplementation at a dose of at least 1,000 IU daily is recommended by the guidelines. High daily doses (> 4,000 IU daily) or high load doses of vitamin D may result in higher fall rates than standard doses, and are therefore not recommended.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2014 and March 29, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Seniors residing in long-term care facilities
Intervention	Vitamin D supplementation, all formulations, all doses
Comparator	Q1-2: No Vitamin D supplementation; different dosing of vitamin D
Outcomes	Q1: Effectiveness (e.g., fall reduction, fracture reduction, etc.); safety (e.g., adverse events or adverse health outcomes related to supplementation, etc.) Q2: Cost-effectiveness for preventing falls and fractures or other outcomes. Q3: Guideline on optimal use of vitamin D supplementation; optimal vitamin D supplementation; optimal dosing; guidelines regarding who should and should not be supplemented.
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2014. Systematic reviews, in which their included studies were overlapped with another SR published at a later date, were excluded. Primary studies were excluded if they had been included in the identified SRs. Guidelines with unclear methodology or that were not clearly evidence-based were excluded.

Critical Appraisal of Individual Studies

The AMSTAR-2 checklist was used to assess the quality of SRs.[13] The critical appraisal checklists of the Joanna Briggs Institute were used to assess the quality of the included RCTs[14] and economic studies.[15] The quality of the evidence-based guidelines was assessed using AGREE II instrument.[16] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 169 citations were identified in the literature search. Following screening of titles and abstracts, 151 citations were excluded and 18 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of the 19 potentially relevant articles, 13 publications were excluded for various reasons, while 6 publications including one SR, one RCT, one economic study, and three guidelines met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The characteristics of the identified SR,[10] (Table 2) RCT,[17] (Table 3) economic study[18] (Table 4) and guidelines[19-21] (Table 5) are presented in Appendix 2.

Clinical Studies

Study Design

The identified Cochrane SR[10] updated its previous reviews first published in 2010 and in 2012. Of a total 95 RCTs included, eight RCTs examined vitamin D supplementation. The literature search results of major databases were limited from 2012 onwards.

One additional double-blinded, parallel, phase II RCT[17] was identified.

Country of Origin and Publication Year

The SR[10] was conducted by authors from Australia and was published in 2018. The RCTs that were cited in the SR evaluated the effect of vitamin D supplementation on fall prevention, and were conducted in developed countries such as Switzerland, USA, France, Australia, Japan, Canada and USA.

The additionally identified RCT[17] was conducted by authors from USA and was published in 2017.

Population

The eight primary studies cited in the SR[10] included a total of 9,278 older people in long-term care facilities with a mean age of 83.5 years. There were more females (73.5%) than males.

The additionally identified RCT[17] also included older residents with mean age of 81 years and 58% females.

Interventions and Comparators

One of the interventions assessed in the SR[10] was vitamin D supplementation (vitamin D or vitamin D + calcium) compared with usual care or placebo. The dose of vitamin D ranged from 400 IU to 800 IU vitamin D3 daily, or 800 IU to 1,100 IU vitamin D2 daily.

The additional identified RCT[17] compared high dose vitamin D3 supplement (100,000 IU monthly) with standard dose vitamin D3 supplement (i.e., a monthly placebo for participants taking 400 to 1,000 IU daily, or a monthly supplement of 12,000 IU for those taking less than 400 IU daily).

Outcomes

The outcomes evaluated in the SR[10] were rate of falls, risk of falling (i.e., number of individuals who fall), risk of fracture (i.e., number of individuals having fall-related fractures) and adverse events.

The primary outcome investigated in the additional identified RCT[17] was incidence rate of acute respiratory infection. The secondary outcomes were falls, fractures, 25-hydroxyvitamin D levels, hypercalcemia, hypervitaminosis D, kidney stones, all-cause hospitalizations and death. Adverse events were also recorded.

Treatment Duration

Treatment duration of RCTs cited in the SR[10] varied from 12 weeks to 24 months. Participants in the additionally identified RCT[17] were treated for 12 months.

Quality Appraisal Tools

The authors of the SR[10] assessed the quality of the included RCTs using the Cochrane Risk of Bias tool. In the SR,[10] the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to evaluate the quality of the body of evidence for each outcome on the basis of the following considerations: risk of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, and dose-response gradient.

Data Analysis and Synthesis

The authors of the SR[10] quantitatively synthesized data from included studies using a meta-analysis approach. Treatment effect for rate of falls was reported as rate ratio and 95% confidence interval. A risk ratio was reported for number of of individuals who fell and number of participants having fall-related fractures.

The additionally identified RCT[17] analyzed data using the intention-to-treat approach. Although sample size calculation was applied, the studies population did not reach the

recruitment goal. The incidence rate ratio and 95% confidence interval was reported for rate acute respiratory infection, rate of falls and rate of fall-related fractures.

Funding

Both the authors of the SR[10] and the additionally identified RCT[17] received public funding for their work.

Economic study

Study design

The economic study[18] was conducted based on the Australian healthcare perspective with a time horizon of one year. A decision analytic model incorporated with a Markov model of individuals assigned to four health states (i.e., low risk of falling, medium risk of falling, high risk of falling, and death) was used to evaluate the cost-effectiveness of interventions including vitamin D in fall prevention and fall-related injury in older adults of long-term care facilities.

Effectiveness

Treatment effects were rates of falls or risks of fall-related injury obtained from two previous SRs conducted by the Cochrane Collaboration. The primary outcome was incremental cost-effectiveness ratio (ICER) with benefits expressed as quality-adjusted life-years (QALYs) and utility including population norms, emergency department decrement, hospitalization decrement, patients in residential aged care, previous fracture in year following a fall, and fear of falling decrement. A discounted rate of 5% per year was applied for all costs and outcomes.

Costs

Costs incorporated in the model included intervention costs and healthcare-related costs (e.g., emergency department attendance, hospital admission, attendance to other medical services). All costs were adjusted to 2015 Australian dollars.

Population

The studied population was older people living in long-term care facilities with a mean age of ≥ 71 years.

Interventions

The investigated interventions were vitamin D, medication review, multifactorial interventions, hip protectors and “no intervention”.

Sensitivity analysis

One-way sensitivity analysis and probabilistic sensitivity analysis were undertaken using confidence intervals, standard errors, best estimates of ranges around the means or adjusting the parameter by 25%.

Funding

The economic study[18] was publically funded.

Guidelines

Country of Origin

The 2016 Australian Institute for Musculoskeletal Science (AIMSS) Consensus Statement,[19] the 2015 Scientific Advisory Council of Osteoporosis Canada (SACOC) guideline, [20] and the 2014 American Geriatrics Society (AGS) Consensus Statement[21] were from Australia, Canada and USA, respectively.

Objectives

One of the objectives of the included guidelines[19-21] was to provide recommendations regarding vitamin D supplementation for the prevention of falls and fall-related injury in older people residing in long-term care facilities or community.

Target Users of the Guidelines

The guidelines[19-21] were targeted to healthcare professionals who are involved in providing healthcare for older adults.

Methods Used to Formulate Recommendations

The SACOC guideline[20] used systematic methods to search for evidence, while the AIMSS Consensus Statement[19] and the AGS Consensus Statement[21] did not. Quality of evidence was assessed in all guidelines, and strengths of recommendations were provided in the SACOC guideline[20] and the AGS consensus statement.[21]

In the AIMSS Consensus Statement,[19] participants in the expert panel, who were selected on the basis of their practice in long-term residential care facilities, received topics randomly and had to propose a statement on each topic for approval after a short, evidence-based presentation, when possible. The SACOC guideline[20] was developed using the GRADE approach, and the recommendations were made by a panel including authors, multidisciplinary healthcare providers and researchers, and representatives from residents and family councils. In the AGS consensus statement,[21] the working group members (not specified) reviewed all meta-analyses and RCTs published up to February 2009.

Summary of Critical Appraisal

The SR[10] provided appropriate research questions, an *a priori* protocol, explanations for selection of the study designs for the inclusion, used comprehensive literature search strategies, performed study selection and data extraction in duplicate, provided a list of included studies, described the included studies in adequate detail, used satisfactory techniques for assessing the risk of bias in individual studies included in the review, performed meta-analysis using appropriate methods, assessed the potential impact of risk of bias in individual studies on the results of the meta-analysis, provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results, carried out appropriate investigation of publication bias, and reported the sources of conflict interest and funding. Sources of funding for included studies were not reported in the review. Evidence of each outcome was rated using GRADE. Overall, the quality of the SR was high, as its research methodology was rigorous.

In the additionally identified RCT,[17]participants were truly randomized to treatment groups, treatment groups were similar at baseline, participants and treatment providers were blinded to treatment assignment, study groups were treated identically other than the

intervention of interest, intention-to-treat analysis was applied, outcomes were measure in the same way for both groups using reliable methods, and appropriate statistical analysis was used. It was unclear if allocation to treatment was properly concealed, and whether or not outcomes assessors were blinded to treatment assignment. Although calculation of sample size was provided, this trial was underpowered as the studied population did not reach the recruitment goal. The quality of this RCT was considered as moderate.

The included economic study[18] provided an appropriate research question, comprehensive description of alternatives, identified all important and relevant costs and outcomes for each alternative, established clinical effectiveness, accurately measured and credibly valued costs and outcomes, adjusted for a discount rate, conducted an incremental analysis of costs and consequences and sensitivity analysis, study results included all issues of concern to users, and findings were generalizability to the setting of interest in the review. The quality of this study was considered as high.

The SACOC guideline[20] was explicit in terms of scope and purpose, stakeholder involvement, and clarity of presentation, but not fully explicit in terms of rigour of development, applicability and editorial independence. The AIMSS Consensus Statement[19] and the AGS consensus statement[21] were explicit in terms of scope and purpose and clarity of presentation, but not in terms of stakeholder involvement, rigour of development, applicability and editorial independence. For stakeholder involvement, it was unclear if the view and preference of the target population have been sought in the AIMSS Consensus Statement[19] and the AGS consensus statement.[21] For rigour of development, systematic methods used to search for evidence was not reported in AIMSS Consensus Statement[19] and the AGS consensus statement,[21] it was unclear if the AIMSS Consensus Statement[19] underwent external review prior to its publications, and it was unclear if an updating procedure was provided in all three guidelines.[19-21] For applicability, cost was not considered in the recommendations of all guidelines.[19-21] For editorial independence, it was unclear if the views of the funding body had any influence to the content of the guidelines.[19-21] Overall, the two Consensus Statements by AIMSS[19] and AGS[21] had more methodological limitations compared to the SACOC guideline.[20]

Summary of Findings

The main findings and conclusions of the SR[10] (Table 10), additional RCT[17] (Table 11), economic study[18] (Table 12) and guidelines[19-21] (Table 13) are presented in Appendix 4.

Clinical Effectiveness

Rate of falls (i.e., number of falls)

Pooled data from four trials cited in the SR[10] revealed that vitamin D supplementation at range of 800 IU to 1,100 IU daily significantly reduced the rate of falls by 28% (Rate ratio [RaR] 0.72; 95% CI 0.55 to 0.95; *P* = 0.02) compared to usual care or placebo. The quality of evidence was graded as moderate.

The identified RCT[17] found that high dose (100,000 IU) vitamin D3 administered monthly significantly increased the incidence rate of falls by 133% (incidence rate ratio [IRR] 2.33; 95% CI 1.49 to 3.63; *P* < 0.001) compared to standard dose (400 to 1,000 IU) vitamin D3.

Risk of falling (i.e., number of individuals who fall)

Pooled data from four trials cited in the SR[10] revealed that there was no significant difference in the risk of falling between vitamin D supplementation groups and control groups (usual care or placebo). The quality of evidence was graded as moderate.

Risk of fracture (i.e., number of individuals having fall-related fractures)

Pooled data from three trials cited in the SR[10] showed that vitamin D supplementation had no significant effect on risk of fall-related fractures. The quality of evidence was graded as very low.

Rate of fractures (i.e., number of fractures)

There was no comparison between vitamin D supplementation and placebo or usual care for this outcome.

The identified RCT[17] found that high dose (100,000 IU) vitamin D3 had no significant effect on the incidence rate of fractures compared to standard dose (400 to 1,000 IU) vitamin D3.

Adverse events

Two trials cited in the SR[10] reported no observed adverse events. One trial in the SR found two cases of increased constipation in the vitamin D group and no case of hypercalcemia in either group. One trial in the SR found no significant difference in gastrointestinal disorders between groups.

The identified RCT[17] found no significant differences in adverse events recorded as overall or by MedDRA categories (Medical Dictionary for Regulatory Activities) between high and standard dose vitamin D3 groups.

Other outcomes

In the identified RCT,[17] safety outcomes such as hypercalcemia, kidney stones and hypervitaminosis D were not observed in either high or standard vitamin D3 group. The rates of all-cause hospitalizations and death were similar in both groups.

Cost-effectiveness

The results from the identified economic study showed that vitamin D supplementation dominated “no intervention” or hip protectors, in terms of incremental cost per fall avoided, or in terms of incremental cost per QALY gained (i.e., vitamin D was less costly and more effective). Among the investigated interventions, vitamin D supplementation was the most cost effective option at a threshold of AU$0 to AU$20,000 per QALY.

Guidelines

All three identified guidelines[19-21] unanimously recommend vitamin D supplementation for fall and fracture prevention in older people living in long-term care facilities. Recommended daily dosage of vitamin D supplementation is 1,000 IU in the AIMSS Consensus Statement,[19] 800 IU to 2,000 IU in the SACOC guideline,[20] and at least 1,000 IU with calcium in the AGS Consensus Statement.[21] The AIMSS Consensus Statement[19] does not recommend high daily doses (> 4,000 IU) or high load doses of vitamin D.

Limitations

The quality of clinical evidence derived from primary studies cited in the SR was considered as moderate as the included studies may contain some risk of bias. The sample size of the

additional identified RCT did not reach the recruitment goal which may have impacted the power and precision of the trial. Although the methodology of the economic study was robust, its economic evaluations were not conducted alongside with RCTs to determine the cost-effectiveness of each intervention being tested. Instead, the effectiveness data on vitamin D supplementation were derived from a previous Cochrane SR published in 2012. It is unclear if the cost-effectiveness results could be replicated with the results of the current updated Cochrane review identified in this report. Unlike the Canadian guideline,[20] two consensus guidelines from Australia[19] and USA[21] were limited in terms of collection, selection and synthesis of evidence and development and evaluation of recommendations.

Conclusions and Implications for Decision or Policy Making

This review includes one SR, one additional RCT, one economic study and three guidelines. Evidence of moderate quality on clinical effectiveness suggests that vitamin D supplementation at a dose of 800 IU to 1,100 IU daily may reduce the rate of falls (number of falls), but may have little effect on the risk of falling (number of individuals who fall) in long-term care residents. It remains uncertain about the effect of vitamin D supplementation on the risk of fall-related fractures or adverse events as the quality of evidence was low. Vitamin D supplementation was found to be a more cost-effective intervention than no intervention in preventing falls and fall-related injuries. All identified guidelines recommend vitamin D supplementation for long-term care residents with a daily dose of at least 1,000 IU. High daily doses (> 4,000 IU daily) or high load doses of vitamin D may result in higher fall rates, and are therefore not recommended. Further trials evaluating the effect of vitamin D supplementation on fall-related fractures are needed. The overall findings in this review regarding vitamin D supplementation and fall prevention in long-term care residents are likely to be generalizable to the Canadian context.

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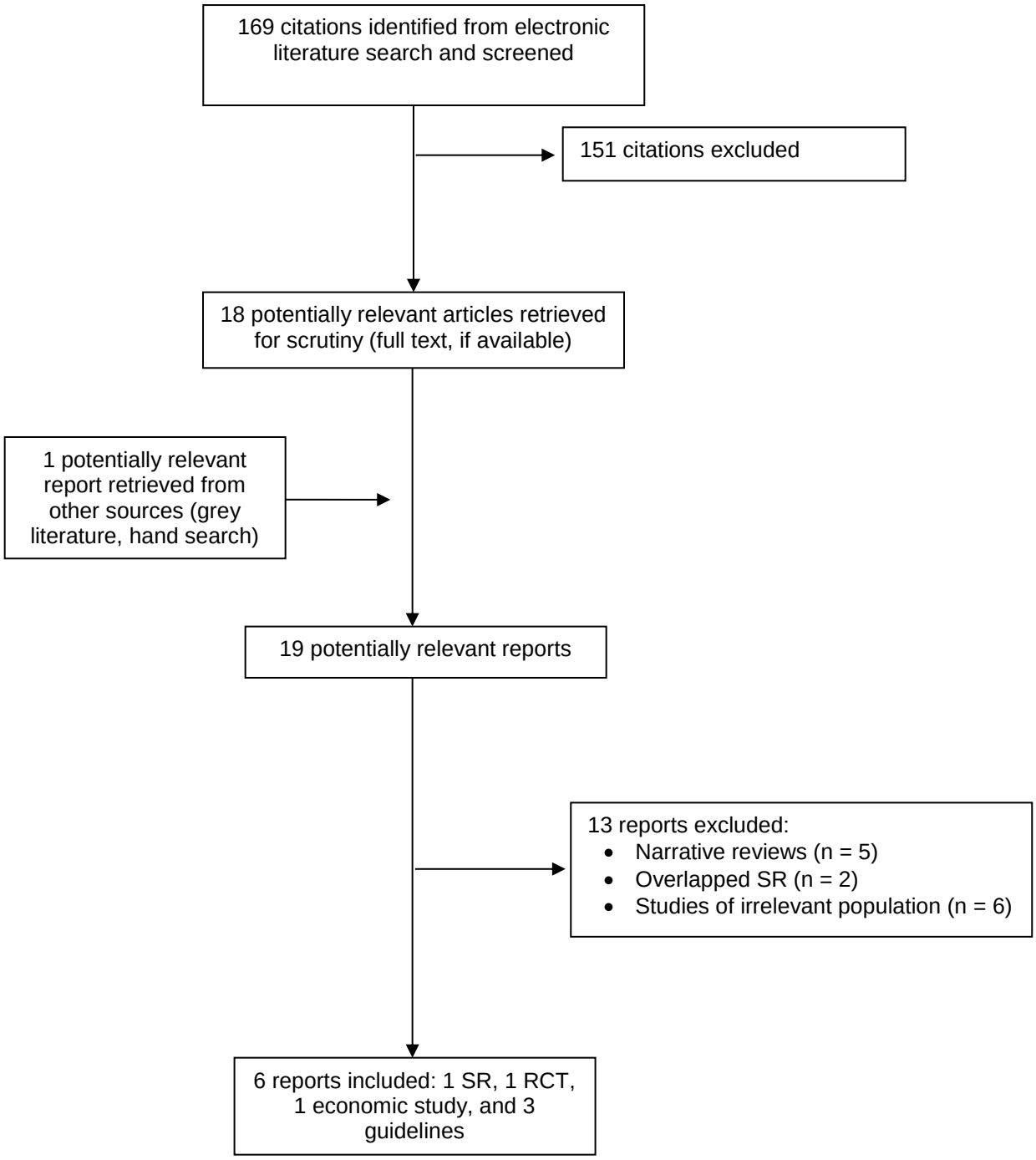
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Types of Comparisons, Treatment Setting, Dose, Duration of Treatment	Outcomes
Cameron et al., 2018[10] Australia Funding: Public	Objectives: To assess the effects of interventions designed to reduce the incidence of falls in older people in care facilities and hospitals Total 95 RCTs; 8 RCTs (n = 9278 participants) examined vitamin D supplementation Risk of Bias tool for assessing the quality RCTs; GRADE for assessing the quality of the body of evidence for each outcome Databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, CENTRAL, MEDLINE, Embase, World Health Organization's ICTRP search Portal and ClinicalTrials.gov Search date: As this review is an update of a Cochrane Review first published in 2010, and later updated in 2012, the search results were limited from 2012 onwards	Older people (≥ 65 years) in care facilities and hospitals Mean age: 83.5 years in care facilities; 77.6 years in hospitals Gender: 73.5% women in care facilities; 51.6% women in hospitals	Vitamin supplementation (vitamin D or vitamin D + calcium) in some form administered in care facilities was compared with usual care or placebo. In hospitals, multifactorial interventions were compared with control group. Dose of vitamin D, comparator and duration of treatment from 8 RCTs: – 800 IU vitamin D3 + 1200 mg calcium vs. 1200 mg Ca (daily for 12 weeks) – 800 IU vitamin D2 vs. control (daily for 5 months) – 800 IU vitamin D3 + 1200 mg calcium vs. placebo (daily for 24 months) – 10,000 IU oral vitamin D2 weekly or 1000 IU oral vitamin D2 daily + 600 mg calcium daily vs. placebo + 600 mg calcium daily (24 months) – Multivitamin tablet containing 400 IU vitamin D3 and 360 mg calcium vs. placebo (daily for 6 months) – Oral vitamin D (900 IU daily) as Isocal jelly PCF (500 IU) and a supplement of 400 IU vitamin D3 vs. usual care (3 months intervention; follow-up 9 months) – ViDOS multifaceted KT intervention vs. usual care – 2.5 mg oral vitamin D2 every 3 months (equivalent to 1,100 IU daily) vs. usual care (median length of follow-up 10 months)	– Rate of falls – Risk of falling – Risk of fracture – Adverse events

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; IU = international unit; NR = not reported; RCT = randomized controlled trial

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Clinical Outcomes
Ginde et al., 2017[17] USA Funding: Public	Double-blinded, parallel, phase II RCT Intention-to-treat analysis Sample size calculation: Yes, but population did not reach recruitment goal	Older residents aged ≥ 60 years Mean age: 81 years Sex: 58% female Length of stay: 26 years Co-morbidities: balanced between groups	High dose (100,000 IU) vitamin D3 supplement administered monthly for 12 months	Standard dose vitamin D3 supplement: Either a monthly placebo (for participants taking 400 to 1,000 IU/day) or a monthly supplement of 12,000 IU (for those taking < 400 IU/day)	Primary: – Incidence of acute respiratory infection Secondary: – Falls/fractures – 25-hydroxyvitamin D levels – Hypercalcemia – Kidney stones – Hypervitaminosis D – All-cause hospitalizations – Death Adverse events

IU = international unit; RCT = randomized controlled trial

Table 4: Characteristics of Included Economic Studies

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions	Costs included
Church et al., 2015[18] Australia Funding: Public	Cost-effectiveness 1º outcome: ICER Benefit: QALYs Decision analytic model incorporated with Markov model of individuals assigned to	Perspective: Australian healthcare perspective Time horizon: 1-year Currency: 2015 Australian dollars Discount rate: 5% per year	Older people living in long-term care facilities Age: ≥ 71 years	– Vitamin D – Medication review – Multifactorial intervention – Hip protectors – No intervention	– Intervention costs – Healthcare-related costs (emergency, other medical services, hospital admission)

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions	Costs included
	four health states (i.e., low risk of falling, medium risk of falling, high risk of falling, and death) Treatment effects: Rate of falling or risk of injury from two previous Cochrane SRs Utility: Population norms, ED decrement, hospitalization decrement, patient in residential aged care, previous fracture in year following a fall, fear of falling decrement Sensitivity analysis: 1-way, probabilistic				

ED = emergency department; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life-years

Table 5: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
AIMSS Consensus Statement, Duque et al., 2016[19] Australia Funding: Public	Intended users: Healthcare professionals involving in the diagnosis and treatment of older residents with osteoporosis in residential aged care facilities Target population: Older people living in residential aged care facilities	Non-pharmacological: – Fall prevention (Screening for fall risk, medication review, multifactorial intervention) – Hip protectors Pharmacological: – Calcium and vitamin D supplementation – Antiresorptives Other treatments: – Strontium ranelate – Teriparatide	Fall and fall injury prevention	Systematic methods used to search for evidence were not reported. Levels of evidence: based on the NHMRC criteria	Participants in the expert panel were selected on the basis of their practice in long-term residential care facilities. Participants received topics randomly and had to propose a statement on each topic for approval after a short, evidence-based presentation, when possible.	Guideline validation was not reported
SACOC, Papaioannou [20] et al., 2015 Canada Funding: Public	Intended users: Inter-professional teams caring for frail older adults in long-term care facilities Target population: Older residents in long-term care facilities who are high risk or not at high risk of fracture	– Calcium and vitamin D – Pharmacologic therapy for individuals at high risk of fracture – Hip protectors – Exercise – Multifactorial intervention	Fracture prevention	Systematic methods used to search for evidence were reported. The level of evidence and grade of recommendations were assessed using GRADE	The guideline was developed using GRADE approach. Panel including authors, multidisciplinary healthcare providers and researchers, and representatives from residents and family councils.	Peer-reviewed

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
AGS Consensus Statement, 2014[21] USA Funding: Public	Intended users: Healthcare providers involved in providing healthcare for older adults Target population: Older residents in long-term care facilities or community-dwelling older adults	Vitamin D	Fall and fall injury prevention	Systematic methods used to search for evidence were not reported. Evidence was assessed using GRADE	Working group members (not specified) reviewed all meta-analyses published before 2008 and RCTs cited in the meta-analyses. A supplement search was conducted for RCTs published between January 2006 and February 2009.	Peer-reviewed

AGS = American Geriatrics Society; AIMSS = Australian Institute for Musculoskeletal Science; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NHMRC = National Health and Medical Research Council; RCTs = randomized controlled trials; SACOC = Scientific Advisory Council of Osteoporosis Canada

Appendix 3: Quality Assessment of Included Studies

Table 6: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[13]	Cameron et al., 2018[10]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

AMSTAR = Assessing the Methodological Quality of Systematic Reviews

Table 7: Quality Assessment of Randomized Controlled Trials

JBI Critical Appraisal Checklist for RCT[14]	Ginde et al., 2018[17]
1. Was true randomization used for assignment of participants to treatment groups?	Yes
2. Was allocation to treatment groups concealed?	Unclear
3. Were treatment groups similar at the baseline?	Yes
4. Were participants blind to treatment assignment?	Yes
5. Were those delivering treatment blind to treatment assignment?	Yes

JBI Critical Appraisal Checklist for RCT[14]	Ginde et al., 2018[17]
6. Were outcomes assessors blind to treatment assignment?	Unclear
7. Were treatment groups treated identically other than the intervention of interest?	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes
9. Were participants analyzed in the groups to which they were randomized?	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes
11. Were outcomes measured in a reliable way?	Yes
12. Was appropriate statistical analysis used?	Yes
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes

JBI = Joanna Briggs Institute; RCT = randomized controlled trial

Table 8: Quality Assessment of Economic Studies

JBI Checklist for Economic Evaluations[15]	Church et al., 2015[18]
1. Is there a well-defined question?	Yes
2. Is there comprehensive description of alternatives?	Yes
3. Are all important and relevant costs and outcomes for each alternative identified?	Yes
4. Has clinical effectiveness been established?	Yes
5. Are costs and outcomes measured accurately?	Yes
6. Are costs and outcomes valued credibly?	Yes
7. Are costs and outcomes adjusted for differential timing? (Discount rate)	Yes
8. Is there an incremental analysis of costs and consequences?	Yes
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	Yes
10. Do study results include all issues of concern to users?	Yes
11. Are the results generalizable to the setting of interest in the review?	Yes

Table 9: Quality Assessment of Guidelines

AGREE II checklist[16]	AIMSS Consensus Statement, Duque et al., 2016[19]	SACOC, Papaioannou [20] et al., 2015	AGS Consensus Statements, 2014[21]
Scope and purpose			
1. Objectives and target patients population were explicit	Yes	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes	Yes
3. The population to whom the guidelines is meant to apply is specifically described	Yes	Yes	Yes
Stakeholder involvement			
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes	Yes
5. The views and preferences of the target population have been sought	Unclear	Yes	Unclear
6. The target users of the guideline are clearly defined	Yes	Yes	Yes
Rigour of development			
7. Systematic methods were used to search for evidence	No	Yes	No
8. The criteria for selecting the evidence are clearly described	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Unclear	Yes	Yes
14. A procedure for updating the guideline is provided	Unclear	Unclear	Unclear
Clarity of presentation			
15. The recommendations are specific and unambiguous	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes	Yes

AGREE II checklist[16]	AIMSS Consensus Statement, Duque et al., 2016[19]	SACOC, Papaioannou [20] et al., 2015	AGS Consensus Statements, 2014[21]
Applicability			
18. The guideline describes facilitators and barriers to its application	Not applicable	Not applicable	Not applicable
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Yes	Yes	Yes
20. The potential resource (cost) implications of applying the recommendations have been considered	No	No	No
21. The guideline presents monitoring and/or auditing criteria	Yes	Yes	Yes
Editorial independence			
22. The views of the funding body have not influenced the content of the guideline	Unclear	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes	Yes

AGS = American Geriatrics Society; AIMSS = Australian Institute for Musculoskeletal Science; NHMRC = National Health and Medical Research Council; SACOC = Scientific Advisory Council of Osteoporosis Canada

Appendix 4: Main Study Findings and Author's Conclusions

Table 10: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Cameron et al., 201810	
Vitamin D supplementation (800 IU to 1,100 IU daily) versus placebo or usual care – Rate of falls, i.e., number of falls (moderate quality evidence) – Pooled data from 4 trials (4,512 participants): RaR (95% CI) = 0.72 (0.55 to 0.95); I^2 = 62%; P = 0.02 – Risk of falling, i.e. number of individuals who fell (moderate quality evidence) – Pooled data from 4 trials (4,512 participants): RR (95% CI) = 0.92 (0.76 to 1.12); I^2 = 42%; P = 0.41 – Risk of fracture (very low quality evidence) – Pooled data from 3 trials (4,464 participants): RR (95% CI) = 1.09 (0.58 to 2.03); I^2 = 63%; P = 0.80 – Adverse events ○ No AEs observed (2 trials) ○ Two cases of increase constipation in the intervention group and no case of hypercalcemia (1 trial) ○ No significant difference in gastrointestinal disorders between groups (1 trial; very low quality evidence) **Multivitamins (including vitamin D3 + calcium) versus placebo** – Rate of falls (very low quality evidence) 1 trial (51 participants):): RaR (95% CI) = 0.38 (0.20 to 0.71); P = 0.0024 – Risk of falling (very low quality evidence) 1 trial (51 participants):): RR (95% CI) = 0.82 (0.40 to 1.66)	*"Vitamin D supplementation probably reduces the rate of falls but not the risk of falling."*[10] p.2

AEs = adverse events; CI = confidence interval; IU = international unit; RaR = rate ratio; RR = risk ratio

Table 11: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Ginde et al., 2017[17]	
High dose (100,000 IU monthly) versus low dose (400 to 1,000 IU daily) of vitamin D3 One RCT (107 participants) – Incidence of ARIs: 0.67 versus 1.11 per person-year IRR (95% CI) = 0.60 (0.38 to 0.94); *P* = 0.02 – Incidence of falls (rate of falls): 1.47 versus 0.63 per person-year IRR (95% CI) = 2.33 (1.49 to 3.63); *P* < 0.001 – Incidence of fractures: 0.10 versus 1.19 per person-year IRR (95% CI) = 0.56 (0.18 to 1.71); *P* = 0.31 – Safety outcomes such as hypercalcemia, kidney stones and hypervitaminosis D were not observed in either group. – All-cause hospitalizations: 46% versus 43% – Death: 22% versus 21% – Adverse events: No significant between groups	*"Monthly high dose vitamin D3 supplementation reduced the incidence of ARI in older long-term care residents but was associated with a higher rate of falls without an increase in fractures."*[17] p.2

ARI = acute respiratory infection; CI = confidence interval; IU = international unit; IRR = incidence rate ratio

Table 12: Summary of Findings of Economic Studies

Main Study Findings	Author's Conclusions
Church et al, 2015[18]	
Vitamin D supplementation *Cost-effectiveness* Expressed as incremental cost per fall avoided – Vitamin D dominated "no intervention" and hip protectors (i.e., vitamin D was more effective and less costly through healthcare cost saving) Expressed as incremental cost per QALY gained – Same results *Sensitivity analysis* One-way – Vitamin D supplementation still dominated "no intervention" when fear of falling was excluded, or still dominated hip protectors when hip protectors were limited to medium- and high-risk populations. Probabilistic – Vitamin D was most cost-effective option at a threshold of AU$0 to 20,000 per QALY	*"The model suggests that vitamin D supplementation and medication review are more cost-effective interventions that reduce falls, provide health benefits and reduce health care costs in older adults living in residential aged care facilities."*[18] *p.1301*

AU$ = Australian dollars; IU = international unit; QALY = quality-adjusted life-year

Table 13: Summary of Findings of Included Guidelines

Recommendations
AIMSS Consensus Statement, Duque et al., 2016[19]
"Vitamin D • Vitamin D supplementation should be universal (level V). • Vitamin D supplementation is an effective intervention in fall prevention (level I). • Adequate 25(OH)D concentration is >50 nmol/L (level I), with optimal levels >75 nmol/L (level II). • Dose equivalent to 1000 IU/day (25 mcg/d) necessary to achieve this target (level I). • High daily doses (>4,000 IU/d) or high load doses are not recommended (level II)."[19] p.18 Quality of evidence: Level I: A systematic review of level II studies Level II: A randomized trial Level V: Consensus expert opinions
SACOC, Papaioannou [20] et al., 2015
"For residents at high risk of fractures, we recommend daily supplements of 800 IU to 2000 IU vitamin D3 (strong recommendation; moderate-quality evidence). *For residents not at high risk of fractures, we suggest daily supplements of 800 IU to 2000 IU vitamin D3 to meet the recommended dietary allowance, depending on resources and their (or their carers') values and preferences (conditional recommendation; moderate-quality evidence)."*[20] p.3 Quality of evidence: Moderate: Moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Type of recommendation: – Strong: Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Most individuals should receive the intervention. – Conditional: The majority of individuals in this situation would want the suggested course of action, but many would not. Clinicians recognize that different choices will be appropriate for each individual patient and that clinicians must help each individual arrive at a management decision consistent with his or her values and preferences.
AGS Consensus Statement, 2014[21]
"STATEMENT 1b: There are insufficient data at this time to support a recommendation for increased vitamin D supplementation without calcium for older persons residing in the community or in institutional settings."[21] p.148 *"STATEMENT 2: Clinicians are strongly advised to recommend vitamin D supplementation of at least 1,000 IU/day with calcium to older adults residing in institutionalized settings in order to reduce the risk of fracture and falls."*[21] p.148 Type of recommendation: – No recommendation: Due to very low availability and quality of evidence. – Strong recommendation: Based on a high level of evidence from meta-analyses and RCTs, and a strong preponderance of benefit over harm

AGS = American Geriatrics Society; AIMSS = Australian Institute for Musculoskeletal Science; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NHMRC = National Health and Medical Research Council; RCTs = randomized controlled trials; SACOC = Scientific Advisory Council of Osteoporosis Canada