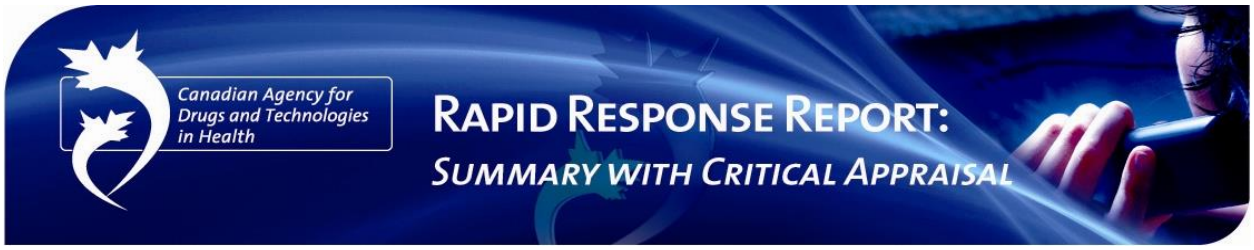

TITLE: Vitamin D Supplementation for the Prevention of Falls and Fractures in Residents in Long-Term Care Facilities: A Review of the Clinical Effectiveness, Cost-Effectiveness, or Guidelines

DATE: 15 April 2016

CONTEXT AND POLICY ISSUES

Vitamin D, the major circulation form being 25(OH)D, plays an important role in bone mineralization in the human body.[1] Low values of vitamin D are associated with osteopenia, osteoporosis and subsequent risk of fractures.[2,3] Seniors living in long-term care (LTC) facilities are reported to have low 25(OH)D values,[4] and, keeping in mind that fall vulnerability in elderly is a consequence of multiple factors such as poor bone health, impaired sensorium, and multimorbidity,[5] have a higher average rate of falls (1.5 to 1.7 per person per year) than community-dwelling seniors (0.65 per person per year).[1,6]

Despite evidence from systematic reviews/meta-analyses showing that vitamin D alone does not appear to be effective in preventing hip fractures in post-menopausal women and older men,[7,8] vitamin D use has been on the rise in LTC facilities,[9] with more than half of general practitioners systematically prescribing vitamin D to their patients living in nursing homes according to a recent survey.[10] A previous CADTH Rapid Response review, which included literature from 2005 to 2010,[11] found that "*Overall, the identified evidence supports vitamin D supplementation at a dose of at least 800 IU daily in residents of long-term care facilities to reduce the rate of falls. The impact on fracture and risk of falling was not definitive. Given that calcium (600 mg to 1200 mg daily) was also supplemented in a number of studies in the included systematic reviews, it is not clear whether vitamin D alone would achieve the same result.*" (p. 1)

This Rapid Response report aims to review the clinical and cost-effectiveness of vitamin D supplementation for the prevention of falls and fractures in residents in LTC facilities. Guidelines associated with the use of vitamin D supplementation in residents in LTC facilities will also be examined.

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

Current evidence does not support vitamin D supplementation in elderly residents living in long-term care facilities. A systematic review of meta-analyses (MA) identified five MAs, four of which did not report a statistically significant reduction in the rate of falls. Data from one Australian cost study (which used clinical effectiveness data from the one MA that reported a statistically significant reduction in the rate of falls in long-term care facilities with vitamin D supplementation) found that the costs were lowest with vitamin D supplementation compared to other types of interventions and that vitamin D supplementation is cost-effective for older adults living in residential aged care facilities. The American Geriatric Society Consensus Statement did not recommend vitamin D supplementation alone for the prevention of falls and fractures in elderly patients residing in long-term care facilities. The Scientific Advisory Council of Osteoporosis Canada recommended daily supplements of vitamin D for residents identified as being at high risk of fracture, and daily supplements of vitamin D to meet the recommended dietary allowance for non-high-risk residents.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, 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. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and March 17, 2016.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria	
Population	Frail adults in long term care facilities
Intervention	Vitamin D supplementation
Comparator	No vitamin D supplementation, different dosing of vitamin D
Outcomes	Fall reduction, fracture reduction, safety, adverse events or adverse health outcomes related to supplementation Cost-effectiveness for preventing falls and fractures or other health outcomes. Optimal use of vitamin D supplementation, optimal vitamin D supplementation, optimal dosing, guidelines regarding who should and shouldn't be supplemented.
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), economic evaluations, guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2011, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included systematic review, cost evaluation, and guidelines was assessed using the AMSTAR,[12] Drummond,[13] and AGREE[14] checklists, respectively. Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 173 citations. After screening of abstracts from the literature search and from other sources, 13 potentially relevant studies were selected for full-text review. Four studies were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included study is provided in Appendix 2.

Study design

One systematic review of meta-analyses (MA),[15] one cost-effectiveness study,[16] and two guidelines published by the American Geriatric Society (AGS) in 2014[17] and by the Scientific Advisory Council of Osteoporosis Canada in 2015,[18] were included. The systematic review included five MA published from 2010 to 2014 which included only RCTs.[15] The economic study used clinical outcomes derived from two Cochrane systematic reviews published in 2010 (for the effectiveness of hip protectors) and 2012 (for the effectiveness of vitamin D supplementation; this review was included in the systematic review of meta-analyses[15]), performed Markov modelling based on one-year cycle length and included sensitivity analyses.[16]

Population

The systematic review of systematic reviews[15] included RCTs on older adults dwelling in long-term care facilities regardless of vitamin D status. The cost-effectiveness study[16] evaluated residents of aged care facilities. The guidelines[17,18] were for older persons residing in long-term care facilities.

Interventions and comparators

The systematic review of systematic reviews[15] compared vitamin D supplementation to no supplementation. The cost-effectiveness study[16] compared the cost of vitamin D supplementation to other types of interventions such as medical review, hip protectors, multifactorial intervention, or no intervention.

Outcomes

The systematic review of systematic reviews[15] evaluated the rate of falls. The cost-effectiveness study[16] evaluated the costs of vitamin D supplementation (health care costs and fall-related intervention costs), incremental cost-effectiveness ration (ICER) and quality-adjusted life-years (QALY) gained. The guidelines[17,18] provided recommendations on the use of vitamin D supplementation in older residents of long-term care facilities.

Summary of Critical Appraisal

The included systematic review provided an a priori design and performed a comprehensive literature search.[15] The review included MAs of RCTs. Procedures for the independent duplicate selection and data extraction of MAs were in place, a list of included MAs and characteristics were provided, and quality assessment was used in formulating conclusions. Heterogeneity was present in a number of pooled analyses. The review did not assess publication bias, and did not include a list of excluded studies.

The included cost study had an economic evaluation that is likely to be usable, and outcomes and costs were assessed and compared appropriately.[16] A sensitivity analysis and an incremental cost-effectiveness analysis were performed. The study used clinical effectiveness data from a MA that reported that vitamin D supplementation significantly reduced the rate of falls in long-term care facilities. The MA was included in the systematic review of MAs,[15] but the remaining four analyses in that review did not find a statistically significant reduction in falls with vitamin D supplementation. The model assumed that the benefits and costs of the intervention

are incurred each year; this assumption may overestimate the cost effectiveness of the intervention if the results of the clinical trial cannot be replicated in subsequent years. The generalizability of the results to a Canadian context may not be strong since the study was conducted in Australia, and the delivery of the multifactorial intervention may vary across jurisdictions.

The included guideline had specific and unambiguous recommendations, with a systematic and clearly described method of searching for and selecting the evidence. Clearly described methods were used to formulate the recommendations.[17,18] Health benefits and risks were stated, and procedures to update the guidelines were provided. It is unclear whether the guideline was piloted among target users, or whether patients' views and preferences were sought. Potential cost implications of applying the recommendations were not included.

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

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?

The review included five MAs of RCTs on the clinical effectiveness of vitamin D supplementation for the prevention of falls and fractures in elderly patients residing in long-term care facilities.[15] One MA (5 RCTs; n = 4603) reported a significant reduction in the rate of falls (relative risk [RR] 0.63; 95% confidence interval [CI] 0.46 to 0.86). The remaining four MAs reported a non-significant reduction in the rate of falls from vitamin D supplementation with or without calcium. The authors concluded that current evidence does not support vitamin D supplementation in elderly residents living 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?

The cost study evaluated the costs and cost-effectiveness of vitamin D supplementation for the prevention of falls and fractures in elderly patients residing in long-term care facilities.[16] The study used the clinical effectiveness data from a 2012 Cochrane systematic review that reported that vitamin D supplementation statistically reduced the rate of falls in long-term care facilities. The Cochrane review was captured in the systematic review of MAs[15] included in this report, however that report also identified four additional analyses that did not find a statistically significant reduction in the rate of falls in long-term care facilities with vitamin D reduction. The study compared the costs of vitamin D supplementation, medication review, hip protectors, a multifactorial intervention (a combination of risk assessment, medication review, vision assessment and exercise), and no intervention. The study found that the costs were cheapest with vitamin D supplementation and medical review (AU$2289 for vitamin D supplementation, AU$2321 for medication review, AU$2937 for hip protectors, AU$4991 for multifactorial intervention, and AU$2925 for no intervention).

Vitamin D supplementation lead to 1.260 quality-adjusted life-year (QALY) gained, multifactorial intervention lead to 1.276 QALY gained. Vitamin D is less costly and more effective than other

options at threshold of AU$0 - 20000 per QALY. The authors concluded that vitamin D supplementation and medical review are cost-effective interventions in older adults living in residential aged 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?

The AGS Consensus Statement[17] recommended for the prevention of falls and fractures in elderly patients residing in long-term care facilities: *"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. (No recommendation is made due to very low availability and quality of evidence.)"* (p. 11) The guideline recommended, however, vitamin D supplementation with calcium to prevent falls and fractures in that population.

The Scientific Advisory Council of Osteoporosis Canada[18] recommended: *"For residents at high risk of fractures, we recommend daily supplements of 800 IU to 2000 IU vitamin D_3 (strong recommendation; moderate-quality evidence). For residents not at high risk of fractures, we suggest daily supplements of 800 IU to 2000 IU vitamin D_3 to meet the recommended dietary allowance, depending on resources and their (or their carers') values and preferences (conditional recommendation; moderate-quality evidence)."* (p. 3)

"*Residents identified as being at high risk of fracture include those with prior fracture of the hip or spine, those with more than one prior fracture and those with one prior fracture and recent use of glucocorticoids."* (p. 1)

Limitations

The evidence on the clinical effectiveness of vitamin D supplementation was based on a review of five MAs that recognized the limited number of MAs included and the heterogeneity of the pooled estimates. The vitamin D status and fall risk of patients included in the reviewed studies was unclear. It is possible that there are specific subgroups that may benefit from supplementation, but this remains unclear based on the currently available evdience. The cost-effectiveness study of vitamin D supplementation was conducted in Australia, thus limiting the generalizability of the results to a Canadian context.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Current evidence does not support vitamin D supplementation in elderly residents living in long-term care facilities. A systematic review of meta-analyses (MA) identified five MAs, four of which did not report a statistically significant reduction in the rate of falls. Data from one Australian cost study found that the costs were lowest with vitamin D supplementation compared to other types of interventions and that vitamin D supplementation is cost-effective for older adults living in residential aged care facilities. This cost study was based on clinical effectiveness data from the one MA that reported a statistically significant reduction in the rate of falls in long-term care facilities with vitamin D supplementation, while other MAs have reported fall reductions which are not statistically significant.

The AGS Consensus Statement did not recommend vitamin D supplementation alone for the prevention of falls and fractures in elderly patients residing in long-term care facilities. The

Scientific Advisory Council of Osteoporosis Canada recommended daily supplements of vitamin D for residents identified as being at high risk of fracture, and daily supplements of vitamin D to meet the recommended dietary allowance for not high-risk residents.

A study conducted in Ontario, Canada (ViDOS or Vitamin D and Osteoporosis Study) looked at barriers for the implementation of osteoporosis and fracture guidelines in long-term care.[19,20] The study identifies several barriers, citing *"lack of educational information and resources prior to the ViDOS intervention, difficulty obtaining required patient information for fracture risk assessment, and inconsistent prescribing of vitamin D and calcium at the time of admission"* (p. 1) A study looking at vitamin D prescription trends for residents of long-term care in Ontario before and after implementing the Ontario Osteoporosis Strategy which emphasized outreach activities to increase awareness about fracture prevention specifically in long-term care[21] found knowledge translation activities improved vitamin D prescribing rates.

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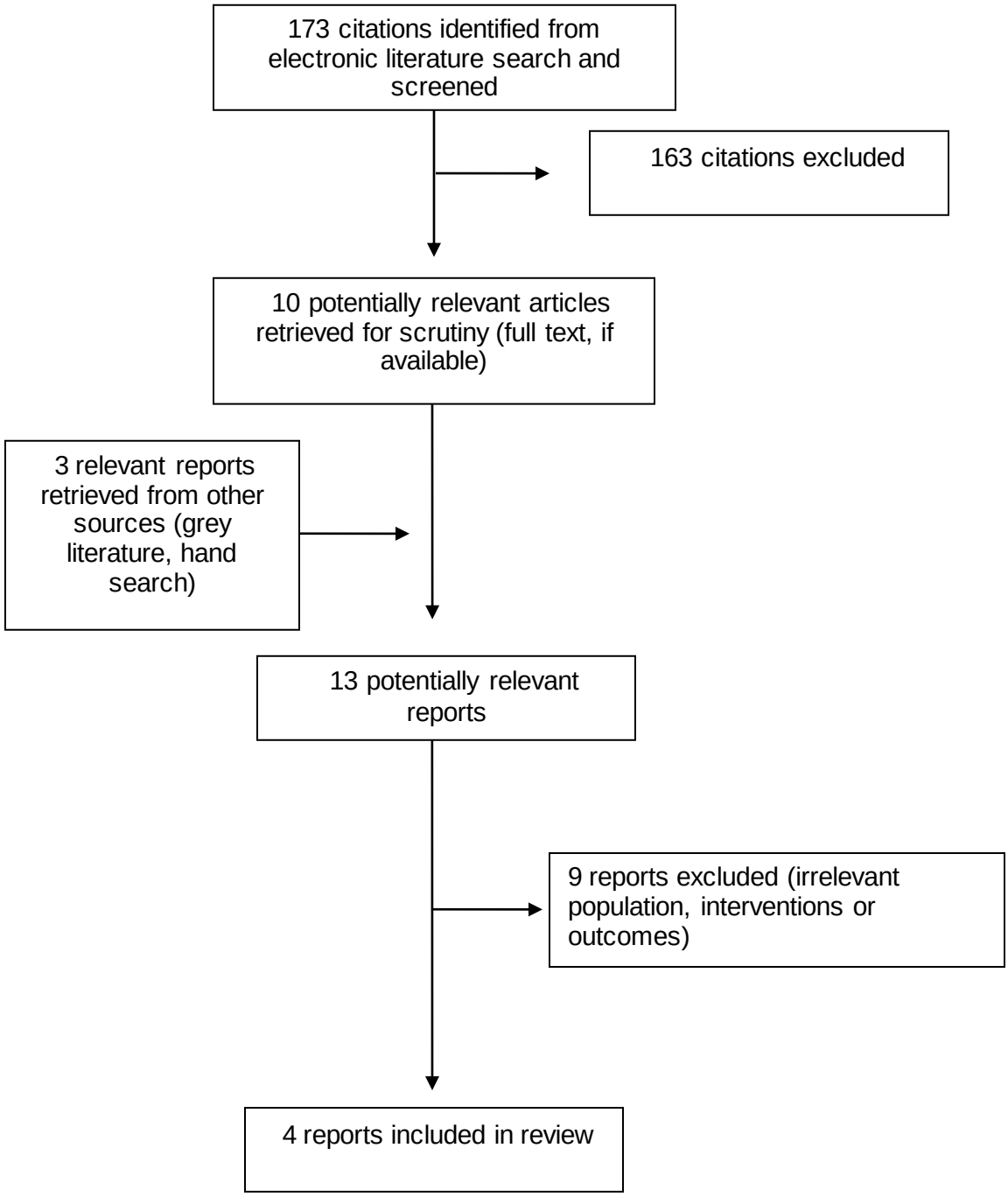
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included studies				
First Author, Year, Country	**Literature Search Strategy**	**Inclusion Criteria**	**Exclusion Criteria**	**Studies included Main outcomes**
Systematic reviews				
Stubbs,[15] 2015, UK, Germany	*"We conducted an umbrella review of MA of randomized controlled trials (RCTs) of falls prevention interventions in long-term care facilities (LTCF) or hospitals"* (p 335)	*"Meta-analyses of RCTs that investigated any intervention that sought to reduce falls in older adults dwelling in LTCF or delivered in hospitals were included"* (p 336)	*"Studies conducted in community dwelling older adults were excluded. We also excluded reviews focusing solely on specialist populations (e.g. stroke, Parkinson's disease, dementia) in order to increase homogeneity"* (p 336)	Five meta-analyses on vitamin D supplementation in LTC facilities were included. Rate of falls
Cost studies				
First Author, Year, Country	**Study Objectives**	**Interventions/ Comparators**	**Patients**	**Main Study Outcomes**
Church,[16] 2015, Australia	*"To evaluate the cost effectiveness of interventions designed to prevent falls and fall-related injuries among older people living in residential aged care facilities (RACFs) from an Australian health care perspective."* (p 1301)	Vitamin D supplementation (1000 IU daily plus 600mg calcium daily) Multifactorial intervention (a combination of risk assessment, medication review, vision assessment and exercise) Annual medication review (general practitioner, pharmacist) Hip protectors No intervention	Residents of aged care facilities	Cost (adjusted to 2015 AU$): - Health care-related costs (emergency department, admission, and inpatient hospital costs) - Intervention costs Economic evaluation (Markow model) - ICER - QALY

ICER : incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

Appendix 3: Summary of Critical Appraisal of Included Study

Table A2: Summary of Critical Appraisal of Included Study

First Author, Publication Year	Strengths	Limitations
Critical appraisal of included systematic reviews (AMSTAR[12])		
Stubbs,[15] 2015	• a priori design provided • all included meta-analyses included studies that are randomized controlled trials • independent meta-analyses selection and data extraction procedure in place • comprehensive literature search performed • list of included meta-analyses, meta-analyses characteristics provided • quality assessment of included meta-analyses provided and used in formulating conclusions • conflict of interest stated	• no assessment of publication bias performed • heterogeneity present in a number of pooled analyses • list of excluded meta-analyses not provided
Critical appraisal of included cost study (Drummond[13])		
Church,[16] 2015	• the economic evaluation is likely to be usable (a well-defined question posed in an answerable form; a comprehensive description of the competing alternatives given; evidence for the programme's effectiveness established) • outcomes and costs assessed and compared appropriately (all the important and relevant outcomes and costs for each alternative identified; outcomes and costs measured accurately in appropriate units prior to evaluation; outcomes and costs valued credibly; outcomes and costs adjusted for different times at which they occurred) • an incremental analysis of the outcomes and costs of alternatives performed • a sensitivity analysis performed • the presentation and discussion of study results include all issues of concern to users	• The study used clinical effectiveness data from the only MA that reported that vitamin D supplementation significantly reduced the rate of falls in long-term care facilities, while there are data from four additional MAs that reported that vitamin D supplementation did not lead to a statistically significant reduction • The assumption that costs and benefits of the interventions are incurred each year the Markov model is run may overestimate the cost effectiveness of interventions if the result of the clinical trial cannot be replicated in subsequent years • The generalizability of the results for multifactorial interventions may not be strong since the delivery of the intervention varies across jurisdictions
Critical appraisal of included guidelines (AGREE[14])		
AGS Consensus Statement,[17] 2014	• scope and purpose of the guidelines are clear • the recommendations are specific and unambiguous • the method for searching for and selecting the evidence are clear • methods used for formulating the recommendations are clearly described • health benefits, side effects and risks were stated in the recommendations • procedure for updating the guidelines provided	• unclear whether the guideline was piloted among target users • unclear whether patients' views and preferences were sought • potential cost implications of applying the recommendation not included

Table A2: Summary of Critical Appraisal of Included Study		
First Author, Publication Year	**Strengths**	**Limitations**
	• target users of the guideline are clearly defined	
Scientific Advisory Council of Osteoporosis Canada Recommendations,[18] 2015	• scope and purpose of the guidelines are clear • the recommendations are specific and unambiguous • the method for searching for and selecting the evidence are clear • methods used for formulating the recommendations are clearly described • health benefits, side effects and risks were stated in the recommendations • procedure for updating the guidelines provided • target users of the guideline are clearly defined	• unclear whether the guideline was piloted among target users • unclear whether patients' views and preferences were sought • potential cost implications of applying the recommendation not included

AGS: American Geriatrics Society

Appendix 4: Main Study Findings and Authors' Conclusions

Table A3: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical effectiveness of vitamin D supplementation for the prevention of falls and fractures in elderly patients residing in long-term care facilities)		
Stubbs,[15] 2015	Rate of falls Five meta-analyses (MA) reported the effect of vitamin D supplementation on falls in elderly living in LTC facilities. One MA (5 RCTs; n = 4603) reported significant reduction in the rate of falls (relative risk RR 0.63 [95% CI 0.46-0.86]. The remaining MAs reported a non-significant reduction in the rate of falls from vitamin D supplementation with or without calcium.	*"The current evidence does not support vitamin D supplementation"* (p 337)
Research question 2 (cost effectiveness of vitamin D supplementation for the prevention of falls and fractures in elderly patients residing in long-term care facilities)		
Church,[16] 2015	*Costs* Vitamin D supplementation: AU$2289 Multifactorial intervention: AU$4991 Medication review: AU$2321 Hip protectors: AU$2937 No intervention: AU$2925 *Cost-effectiveness* Vitamin D supplementation: 1.260 QALY gained Multifactorial intervention: 1.276 QALY gained ICER: Vitamin D is less costly and more effective than other options at threshold of AU$0-20000 per QALY	At threshold of AU$0-20000 per QALY, vitamin D is the most cost-effective option
Research question 3 (evidence-based guidelines for vitamin D supplementation for the prevention of falls and fractures in elderly patients residing in long-term care facilities)		
AGS Consensus Statement,[17] 2014	*"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. (No recommendation is made due to very low availability and quality of evidence.)"* (p 11) *"STATEMENT 2: Clinicians are strongly advised to recommend vitamin D supplementation of at least 1,000 IU/d with calcium to older adults residing in institutionalized settings to reduce the risk of fracture and falls. (Strong recommendation for this intervention, based on a high level of evidence from meta-analyses and RCTs, and a strong preponderance of benefit over harm)"* (p 12)	Not applicable
Scientific Advisory Council of Osteoporosis Canada Recommendations,[18] 2015	*"For residents at high risk of fractures, we recommend daily supplements of 800 IU to 2000 IU vitamin D_3 (strong recommendation; moderate-quality evidence)* *For residents not at high risk of fractures, we suggest daily supplements of 800 IU to 2000 IU vitamin D_3 to meet the recommended dietary allowance, depending on resources and their (or their carers') values and preferences (conditional recommendation; moderate-quality evidence)"* (p 3)	Not applicable

AGS: American Geriatrics Society; LTC: long-term care